Ulrich A. K. Betz *Editor*

Curious2018

Future Insights in Science and Technology

Springer

Curious2018

Ulrich A. K. Betz
Editor

Curious2018

Future Insights in Science and Technology

Springer

Editor
Ulrich A. K. Betz
Vice President Innovation
Merck KGaA
Darmstadt, Germany

ISBN 978-3-030-16060-9 ISBN 978-3-030-16061-6 (eBook)
https://doi.org/10.1007/978-3-030-16061-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Not many institutions, let alone pharmaceutical companies, are able to celebrate a 350th anniversary. But Merck was in the enviable position to do just that. The Curious2018—Future Insight Conference, held in Darmstadt, Germany, to commemorate Merck's 350th anniversary, brought together a special group of scientists under the leadership of Ulrich Betz with the challenge to think about the future of medical science and how to innovate for a better future. Three and a half centuries of successfully developing therapies to benefit humankind provide a unique background to ponder the future. I was honored to participate in the conference and to provide some of my ideas on using genomics and advanced phenotype screening for early detection and even prevention of diseases. I am pleased to see that Ulrich has brought much of the flavor of the forward-looking presentations into this book so that many can better understand the challenges of pharmaceutical development from cognitive diseases to neglected parasitic infections in Africa.

May 2019

J. Craig Venter
Founder, Chairman and CEO
J. Craig Venter Institute
La Jolla, CA, USA

Preface

2018 was an outstanding milestone for the world's oldest pharmaceutical and chemical company, Merck, which celebrated its 350th anniversary in that year. It was also an outstanding year for all involved in the science and technology workstream of the corresponding special anniversary activities which among several other projects involved the inauguration of Curious—Future Insight, one of the world's most renowned conferences around the future of science and technology. This book gives the details on how it came about and provides an overview on the background, content, and outlook of this initiative, including chapters written by many of its keynote speakers. The project was started to contribute to securing another 350 years of success for the company, being aware of the key trends that influence our world, being in contact with the people that shape the future of science and technology and to become a part of it. But now today what is Curious—Future Insight? It is much more than a conference, it involves a new research prize, the Future Insight Prize, that helps to make visionary dream products important for the future of humanity a reality, it is a special project involving bright young talent from innovation hotspots all over the world brainstorming with retirees in a meeting of the generations for new breakthrough ideas, and it is, with the Darmstadt Science Declaration, a call to all nations, societies, and organizations to dedicate more resources to the advancement of science and technology to solve the global challenges of today and to enable the dreams of a better tomorrow. It is an initiative open for other partners to join. It is a bright positive utopian view of the future, a belief that together we can create a better world for everybody, it is a call to action.

Darmstadt, Germany — Ulrich A. K. Betz

Contents

Part I

Creating a Better World with Science and Technology

Further Pushing the Boundaries of Possibility

1

Stefan Oschmann

It's been quite some time since I worked in a laboratory as a scientist. Since then, my professional career has taken me on a very interesting journey. Yet, even after decades in executive management positions, I still enjoy leaving office and conference rooms behind to interact directly with researchers, whether in their laboratories or at conferences. Science still fascinates and amazes me. That is why the Curious 2018 Future Insight Conference was truly special for me.

In July 2018, around 1000 bright minds gathered in our home town of Darmstadt for the Curious 2018 Future Insight Conference to discuss the latest trends in science and technology. The topics and projects presented were cutting-edge. They showcased what humanity can achieve. I am very proud of the fact that we were able to welcome some of the world's most distinguished scientists and entrepreneurs, among them six Nobel laureates, including Frances Arnold, the winner of the Nobel Prize in Chemistry in 2018.

Curious 2018 was one of the highlights of our company's 350th anniversary celebrations. At the conference and on many other occasions throughout our anniversary year, people I met asked me two questions. How has Merck managed to survive over such a long period of time? And how do you plan to continue this legacy? Even though our anniversary is now over, I want to take this opportunity to address these two questions.

1.1 What Has Allowed Merck to Thrive for 350 Years?

So what are the factors that have enabled Merck to grow for more than three and a half centuries? There is no silver bullet answer to this question. Certainly, many factors have contributed to our company's longevity. However, two stand out.

First, there's family ownership. In 1668, the aspiring pharmacist Friedrich Jacob Merck acquired a pharmacy in Darmstadt. That was the time when scientists such as Isaac Newton and Gottfried Wilhelm Leibnitz were revolutionizing the world of mathematics and science. The first thinkers of the Enlightenment were challenging the divine world order and embracing the concept of human self-determination. Ever since this era, the Merck family has controlled our company's development. They successfully steered it through three and a half centuries, including several major political and economic crises. This is a great entrepreneurial accomplishment that the Merck family can be very proud of.

The original version of this chapter was inadvertently published as non-open access. It has now been changed to open access with the copyright holder name "The Author(s)". The correction to this chapter is available at [https://doi.org/10.1007/978-3-030-16061-6_18]

S. Oschmann (✉)
Chairman of the Executive Board and CEO of Merck, Darmstadt, Germany

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_1

The second factor that has greatly contributed to the longevity of Merck is curiosity. The desire to learn and discover and to explore the new and unusual is a core part of our DNA. Hardly anyone embodies this as well as Emanuel Merck. He played a central role in the history of our company. Emanuel Merck took over the Merck pharmacy in 1816. He not only learned the pharmacy craft, as was common at the time, but also received extensive scientific training. His research focused on the field of phytochemistry, particularly on alkaloids. Scientific interest in these highly effective active plant ingredients increased considerably after Friedrich Wilhelm Sertürner had discovered morphine as an active substance in opium. Compared with the herbal preparations that were standard at the time, isolated alkaloids offered a decisive advantage: Physicians could dose them precisely; their effect in patients became calculable. Emanuel Merck succeeded in producing highly pure alkaloids that he provided to pharmacists, scientists, and physicians for further research. His products were well-received and demand grew, and soon he started supplying them to many European countries. Thanks to Emanuel Merck's passion for research and discovery and thanks to his curiosity, the pharmacy grew to become a research-driven industrial company.

Another prime example of the importance of curiosity is the story of liquid crystals. They were first discovered by an Austrian botanical physiologist in 1888. By the early twentieth century, Merck had already offered substances with liquid crystalline properties. Yet, demand was very low since apart from research, no one could conceive of any technical, large-scale applications. Eventually, the business was ended altogether and the story could have ended as well, but it didn't. Fast forward some decades to the 1960s, when a Merck scientist attended a scientific conference on liquid crystals in the USA. He returned convinced of the technology's economic potential. Together with a few colleagues, he started to work on this topic. The team encountered many skeptics who had doubts about the technology's potential. Protected by senior management, they carried on with their work. With tenacity and expertise, our scientists brought a first product line to market in 1969. This early technology was far from perfect. To function properly, these liquid crystals required a temperature of 80 °C.

Eventually, Darmstadt-based researchers succeeded in mixing liquid crystals that worked at room temperature—an enormous advance. With this development, the technology was perfected for mobile applications. And in the 1990s, the market was ready: A huge order of 100 kg of liquid crystals came in from Japan. The reason for this? Tamagotchis! These handheld digital pets were very popular back then. Today, liquid crystals are the central technology in the displays of smartphones, computers, and TVs. Merck is the market leader—a position that we owe to a large degree to the curiosity of our scientists who pursued their passion for research and discovery over decades.

1.2 A Vibrant Science and Technology Company

Today, Merck is a vibrant science and technology company with around 52,000 employees in 66 countries around the world.

Our company comprises three distinct business sectors, each of which ranks among the technology leaders in its respective industry.

Our Healthcare business sector helps to create, improve, and prolong life. We deliver personalized treatments for serious diseases such as cancer and multiple sclerosis and enable people to achieve their dream of becoming parents. Our research activities focus on oncology, immuno-oncology, and immunology.

Our Life Science business sector empowers the scientific community. Our tools and solutions make research simpler, more exact, and help to deliver breakthroughs more quickly. Our discoveries have far-reaching impact, such as assuring people around the world that the food they eat is safe and the medicines they take are effective.

Our Performance Materials business sector helps to literally brighten the world around us with technologies such as the aforementioned liquid crystals and OLED materials. Our science is inside technologies such as semiconductor

materials that are changing the way we access and display information and that are making future mobility safer, homes and devices smarter, and technology more sustainable.

Our business sectors engage in very different industries and markets. Yet they are firmly united by one single factor: science. That's at the heart of everything we do. Science drives the discoveries we make and the technologies we create.

1.3 Curious Minds Dedicated to Human Progress

We are curious minds dedicated to human progress. We believe in science as a force for good, a force that can help us to make a lasting difference in the lives of millions of people around the world.

Curiosity is a fundamental part of our identity. Yet we know that in order to make a positive difference in many people's lives, it must be firmly anchored in strong values. As majority owners, the Merck family has always ensured that Merck is a values-based company. Courage, achievement, responsibility, respect, integrity, and transparency shape our daily work, the way we engage with all our stakeholders and how we tackle future challenges.

With that in mind, how do we intend to ensure that our entrepreneurial legacy continues in the years to come?

Taking a step back and looking at the fundamental developments that are shaping our world, we see that science is having a great impact on people's lives. Over the past decades, mankind has achieved a lot through science. On average, we now live longer than ever before, global average life expectancy stands at 72 years. We are making good progress in fighting HIV, malaria, and some neglected tropical diseases. The proportion of people living in extreme poverty has fallen dramatically over the past decades—even though the world's population is growing steadily. Hundreds of millions of people have been lifted out of poverty. I see absolutely no reason why science and technology should not continue to further improve human life. In fact, I am convinced that there has never been a more exciting time for research than today.

Precision medicine can fundamentally change the way we not only treat but also prevent and intercept disease. Our understanding of the fundamental biological mechanisms of diseases is growing. Combining new molecular biological methods with technologies like artificial intelligence (AI) will help us to better understand disease and to develop entirely new ways of treating it. Very soon, physicians will be able to tailor medicines to patient needs even more precisely, eventually making the "one-size-fits-all" approach obsolete.

At the same time, we are seeing emerging players, for example, from the digital world, entering the healthcare sector. New technologies, for example, those that connect biological systems, such as those found in the human body, with the digital world hold great promise. They will permit much better monitoring and management of health.

At the same time, the way R&D works is changing as well. Equipment costs are falling. Knowledge is broadly available. The so-called crowd can be both a congenial co-researcher and financier. All of this will empower smaller players who will increasingly have the means to transform their ideas into real products.

A big driver of this is the fact that more and more devices are connected with one another and to the Internet. Thanks to new generations of microchips and sensors, we are just starting to feel the impact of the Internet of things (IoT). It will not only make scientific work easier and faster, but also transform many more aspects of our daily lives. It will boost the electronics industry. And it will help us to generate new data which we can use to build entirely new business models.

1.4 Pushing the Boundaries of Possibility

At Merck, we are shaping all these trends and developments. Our more than 7000 curious researchers are pushing the boundaries of what's

possible. Hardly any other company unites so many disciplines and such broad scientific expertise under one roof.

In our Healthcare business sector, we are aiming to become a global specialty innovator. We want to deliver innovative specialty medicines that make a lasting difference in patients' lives, for example, new and very precise therapies to fight cancer.

In our Life Science business sector, we seek to further empower researchers and biotech companies by developing new technologies, for instance, genome-editing tools. These will give researchers around the world entirely new ways to further enhance their understanding of biology.

In our Performance Materials business sector, we want to excite our customers with innovative high-tech solutions. Our technologies enable the electronics industry to produce faster and smaller microchips—for instance, specialty chemicals that allow manufacturers to apply insulating material and metal layers with the thickness of a single atom to semiconductor wafers.

We are working hard to drive new technologies. Yet to ensure lasting entrepreneurial success in an era of exponential technological change, we know that we cannot simply rely on our established business sectors. We must and we will go further. Given the very diverse set of competencies and scientific expertise, we aim to develop groundbreaking new technologies at the interfaces of as well as beyond our three business sectors.

That's the mission of our new Innovation Center. Here, we are helping ideas to grow and turning them into viable new businesses. Merck employees from all business sectors can team up with external entrepreneurs to develop innovations beyond our current boundaries. The focus of our activities lies on three innovation fields: "Biosensing and Interfaces" focuses on the interface between the biological and the digital world. "Clean Meat" is about alternative ways of meat production that require less resources and are more sustainable. And "Liquid Biopsy Technologies" aims to develop new technological solutions to overcome unresolved challenges in the liquid biopsy workflow as well as new applications beyond cancer.

Another important way to drive innovation is through partnerships. As a science and technology company, we want to be part of the global scientific community. This is why we are collaborating with leading research institutions such as the Weizmann Institute in Israel.

But partnerships extend beyond the academic sector. We are also working closely and developing new technologies with other leading technology companies. A prime example is Syntropy, a new joint venture which we plan to establish together with Palantir Technologies. Its goal is to unlock the potential of data in cancer research to facilitate scientific collaboration. Much of the vast amount of data that we generate every day is inaccessible to the researchers who might benefit from it the most. With Syntropy, we want to overcome this problem and develop a new platform that allows scientists to access and work with other scientists' data in a secure and transparent manner. At the same time, scientists will always have control over their data.

1.5 Making Curiosity Thrive

Curiosity always has and will continue to play a major role at Merck. As a science and technology company, we must ensure that it can thrive and that our researchers have the best possible work environment.

Therefore, to define curiosity more precisely, we have developed a model consisting of four key pillars. According to this model, curiosity comprises "joyous exploration" or the pleasure of seeking out new information and of learning and growing. It also encompasses "deprivation sensitivity," the unpleasant state of uncertainty which persists until we have closed the gap between what we know and what we want to know. The third pillar is "stress tolerance," the willingness to accept the distress that arises from exploring uncertain terrain. And lastly, curiosity of course implies an openness to other people's ideas, an appreciation of different perspectives.

Since curiosity plays a critical role in today's fast-paced environment, we surveyed over 3000 workers from China, the USA, and Germany across five industries. The aim was to gain insights that will help further unlock the potential of curiosity to drive innovation. You can find the detailed results in our "2018 State of Curiosity" report on our Web site (curiosity.merckgroup.-com). Our study showed that curiosity is malleable; it can be taught and cultivated. If actively encouraged and nurtured throughout an organization, curiosity can accelerate idea generation and enable us to address global challenges and change with efficiency and precision. In my view, that's good news.

So what are we specifically doing to make curiosity thrive and provide our R&D staff with the best possible work environment?

There is no doubt that the days of the genius working on an idea in solitary confinement in a laboratory are long gone—if that was ever the case in the first place. Science is teamwork, and a company's duty is to provide scientists with an environment that allows them to focus on what matters most: research.

We want scientists to see Merck as a great place to work. Therefore, we are continuously looking at ways to help our researchers to deliver their very best. The steps we have taken in recent years include measures such as adapting feedback mechanisms to the specific environment of R&D units, opening new career paths for scientists and establishing a company-wide "science network" to help our researchers collaborate and share ideas.

Pushing the boundaries of possibility in our industries, creating new technology ventures beyond our current scope and providing our scientists with the best possible work environment are key in making sure that Merck successfully continues its more than 350-year history. But as a values-based company, we know that our responsibility extends beyond the boundaries of our business activities. We are convinced that science and technology will greatly help us to tackle some of humanity's greatest challenges in the years and decades to come.

1.6 Helping Tackle Global Challenges

These threats are evident. We need to prepare ourselves for global pandemics. Antimicrobial resistance poses one of the most pressing global health challenges. We need to ensure safe and sufficient nutrition for a world that, according to the United Nations' estimates, will be home to almost 10 billion people in 2050. And of course, we are in desperate need of finding new clean sources of energy. None of these are core business areas for Merck. Yet as a science and technology company, we hold a special responsibility to encourage research in these fields, which can lead to the breakthrough technologies we urgently need.

This is why we decided to launch the Future Insight Prize, which we publicly announced for the first time at Curious 2018. With the prize, we want to stimulate innovative solutions to help solve the global challenges described above. We intend to grant up to one million euros annually for the next 35 years. The first Future Insight Prize will be awarded in summer 2019 to researchers who have made important contributions in the field of pandemic preparedness. Potential award recipients will be selected by a high-ranking jury of internationally renowned scientists and executives from Merck and our cooperation partners worldwide.

1.7 Let's Unleash the Potential of Science and Technology

We have every reason to believe that science and technology will further drive human progress. At Merck, we want to help shape this change. We believe that scientific exploration, driven by curiosity, and responsible entrepreneurship are key to technological advances that will benefit us all. Therefore, we will continue to push the boundaries of what's possible and to create opportunities for everyone. This is what drives us. This is what we work for. So let's unleash the potential of science and technology—as curious minds, dedicated to human progress.

2 Building a Better World with Science and Technology: Curious Future Insight

Ulrich A. K. Betz

The original version of this chapter was inadvertently published as non-open access. It has now been changed to open access with the copyright holder name "The Author(s)". The correction to this chapter is available at [https://doi.org/10.1007/978-3-030-16061-6_18]

Electronic supplementary material The online version of this chapter (https://doi.org/10.1007/978-3-030-16061-6_2) contains supplementary material, which is available to authorized users.

U. A. K. Betz (✉)
Vice President Innovation Merck,
Darmstadt, Germany
e-mail: ulrich.betz@merckgroup.com

When I was given the chance to lead the science and technology workstream of Merck's 350th anniversary, it was immediately clear that the overall theme of the activities should not be to primarily look back on what great things the company did in the past 350 years, but rather to look ahead and to help ensure a bright future for the organization if not for the next 350 but at least for the next 35 years. In addition to a clear future orientation, at the occasion of the 350th anniversary and being the world's oldest pharmaceutical and chemical company, the program should contain some major aspects going beyond

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_2

boosting the company business but helping address key challenges of humanity and giving something back to the world at the occasion of this phenomenal birthday. And third, the highlight of the entire program should be a big science conference with global impact that brings together some of the world's best scientists and most accomplished entrepreneurs to explore the future of science and technology what then later materialized as the Curious2018—Future Insight Conference. The overall ambition of the science and technology workstream was summarized in the following mission statement: "Working with the best minds in science and entrepreneurship to realize the dreams of a better tomorrow!".

The program that was finally put together and endorsed by Merck management and the Merck owner family consisted of three consecutive phases.

The main goal of phase one, the conceive phase, was to start the thought leadership process and to define the challenges and dreams of today and tomorrow. Together with the journals Nature, Science/AAAS, Harvard Business Reviews and Technology Forecasting and Social Change, in total more than 2000 scientists and business leaders were surveyed. The results were published via Harvard Business Reviews Analytical Services (Breakthrough Innovation in the twenty-first Century, https://hbr.org/sponsored/2018/03/breakthrough-innovation-in-the-21st-century) and in Technology Forecasting and Social Change (in press 2019).

Contributing to this phase, additional papers were published such as a review summarizing technological progress in the past centuries combined with an outlook into the future (Is the force awakening? https://www.sciencedirect.com/science/article/pii/S0040162517309733/pdfft?md5=cf000fcaf784353d1db25cc231e1e944&pid=1-s2.0-S0040162517309733-main.pdf) or a special Nature Outlook on the future of medicine (The future of medicine, https://www.nature.com/collections/zfnjwhjjct) as well as a special edition of Angewandte Chemie (https://onlinelibrary.wiley.com/toc/15213773/2018/57/16) and a special Merck advertorial along with presentation of the Technology Breakthrough of the year 2017 in Science Magazine (Boldly imagining the next 350 years, http://www.sciencemag.org/advertorials/boldly-imagining-next-350-years) and last but not least a review article about the Merck Innovation Cup that had run successfully for seven years (An innovators midsummer dream come true, http://www.europeanbusinessreview.com/an-innovators-midsummer-dream-come-true/).

Phase number 2, the convene phase, had the goal to assemble the brightest scientific and entrepreneurial minds to shape the future. It involved the flagship science conference Curious2018—Future Insight along with the Anniversary Edition of the Merck Innovation Cup. In total, about 1500 people were coming together at the occasion of these meetings.

Last but not least, the goal of phase 3, the realize phase, was to move from curiosity to action and to set in place the infrastructure, processes and resources to start implementing the best ideas and partnership proposals worked out during the two preceding phases and to initiate activities to lay the foundation for a successful future.

At the end of 2018, the 350th anniversary year, we can now look back at an extremely successful track record of the science and technology workstream, and the main key achievements are:

(1) Curious2018—Future Insight Conference with > 60 top speakers incl. six Nobel Laureates, 1300 participants, was established as top global scientific flagship conference on the future of science and technology.
(2) The Merck Future Insight Prize (http://futureinsightprize.merckgroup.com http://futureinsightprize.emdgroup.com) with impact for the next 35 years was rolled out pioneering the dream product concept.
(3) The Darmstadt Science Declaration—Make Science Not War (http://make-science-not-war.org) was rolled out and initiated a global movement to create a bright future with science and technology.

(4) The Anniversary Innovation Cup (http://innovationcup.merckgroup.com, http://innovationcup.emdgroup.com) for young talent achieved an all-time high new record number of applications from all over the world 2200 and resulted in 15 innovative project ideas worked out, and 13 of these at the end of 2018 are being implemented.
(5) The 350th Anniversary Research Grants achieved the highest response ever from the scientific community in the history of Merck (with >1300 research project proposals incl. from elite universities such as Harvard or Stanford). Ten grants of up to more than 1 million € each were awarded covering all Merck businesses (health care, life science, performance materials and digital).
(6) Ten publications in top journals such as Nature, Science, Harvard Business Reviews and Angewandte Chemie were published covering the 350th anniversary activities.
(7) Surveys with >2000 scientists and business leaders on future game changers were performed.
(8) Two international business awards (Stevie Gold Awards) were won: Manager of the Year, Innovator of the Year.

As stated before, the Curious2018—Future Insight Conference was the crown jewel and flagship of the entire 350th anniversary science and technology workstream. Together with a team of Merck internal and external scientists and managers, a series of key paradigms for the conference were agreed. First of all, the key goal was to assemble the best scientists and most accomplished entrepreneurs from all over the world based on top achievements and with a high chance to further shape the progress of science and technology in the future. The conference should explore the future of science and technology with a timeframe of 35 years ahead. A broad range of topics should be covered, largely inspired by Merck's business areas. In the field "Healthy Lives – new breakthrough therapies and diagnostics," scientific topics around pathophysiological mechanisms, disease biology, new breakthrough drugs and diagnostics should be elucidated. The field "Live reimagined – synthetic biology and beyond" should look at topics such as synthetic biology, gene editing and the biological revolution ahead. The area "Materials & solutions – chemistry and more" should mainly focus on new innovative materials and their applications. The field of "Digitalization – the power of in silico" should cover the most disruptive game changer currently talked about, and last but not least the field of "Bright future – new ways of working together" should provide space for speakers covering topics on how an ideal innovator organization should look like, deal with new open innovation approaches up to completely new areas of science and the further development of society. Within all activities, we wanted to clearly focus on a bright future, a utopian not a dystopian view and on the power science and technology can exert to create a bright future. This positive and utopian outlook, the ambition to connect people from all over the planet with this unifying mission statement of building a better world and a bright future with the help of science and technology, was more or less the red threat for all our activities, and it even manifested itself in the key visual that was chosen for the conference, the bright supernova spreading its light into the darkness of space!

Rather than just providing a compilation of lectures, we wanted the conference to also comprise interactive modules and to provide ample time and space for networking and discussions. In the end, the following modules were implemented:

(1) Plenary keynote lecture
These were the absolute highlights of the conference. 45 min (incl. Q&A) speaking slots in front of all attendees (∼1300). Usually, such speaker slots were only given to Nobel Laureates or other famous top scientist such as the genome pioneer Craig Venter or the CRISPR researcher Emmanuelle Charpentier. Speaking slots were given by invitation only.

(2) Keynote lecture
These were speaking slots of the same length, but distributed over three parallel workstreams. Speaking slots were given by invitation only.
(3) Barcamp sessions
This innovative module provided speaking slots of 10 min length and was open for application.
(4) E-Poster sessions
Electronic posters display sessions around the conference's main topic fields, and also these slots were open for application.
(5) Exhibition
Exhibition booths could be booked/purchased.
(6) AI-workshop
Together with the Fraunhofer Institute for Intelligent Analysis and Information Systems and the Fraunhofer Institute for Applied Information Technology, three interactive workshops were run around the topic of artificial intelligence.
(7) Partnering Meetings
Dedicated partnering meetings were organized with each keynote speaker and panelist of Curious2018 together with Merck scientists and managers in order to explore potential collaboration opportunities.
(8) Evening events
Two different evening events were organized comprising ample networking opportunities as well as exhibition of top innovative technologies and gadgets.
(9) Curiosity circle
The curiosity circle was comprised of a round theater seating setup and was mainly used for so-called ask-me-all sessions where keynote speakers made themselves available to answer general questions going beyond topics covered in their keynote lecture.

A three-day duration of the event was considered optimal with a start in the afternoon of day 1 allowing for travel to the location in the morning, a full-day program at day 2 and an afternoon end at day 3 to facilitate travel arrangements back home.

The most important prerequisite to create a top conference was to motivate top keynote speakers to come. First invitations for keynotes were already sent out in December 2017. For that purpose, an invitation card with an embedded screen playing a video was distributed. The second wave then consisted of a printed paper invitation card with special Merck pigment. With only a single exception, all keynote speakers were not paid a speakers fee but full coverage of business travel and accommodation was provided. In that regard, it was of utmost importance that Curious2018—Future Insight was an independent science conference sponsored by Merck at the occasion of its 350th anniversary, but not in a strict sense a corporate event!

The well-being of keynote speakers was always a key priority for the entire organization committee. This involved full reimbursement of all travel and accommodation costs as well as booking of pickups and transfers for airport and conference transportation. In addition, each keynote speaker was allocated a personal caretaker. Caretakers were Merck scientists that were available to accommodate the keynote speaker at all times and were available not only for all help and support required but also acted as personal capable guides for the conference including being able to conduct stimulating scientific discussions with the guests and making contact to other key guests of interest. All caretakers were volunteers from the company and were trained in multiple sessions prior to the event.

In addition to top keynote speakers also having capable moderators was a key success criterion for Curious2018.

The full conference program is attached as an appendix to this chapter.

The conference was also supported by a welcome address from the Germany Federal Minister of Education and Research, Anja Karliczek, with the following letter message read at the Curious2018—Future Insight Conference:

> Life is full of challenges and opportunities. For centuries, science and research have been producing new developments to make the world a better place. Experience has shown that innovations are generated exactly where people from

> different disciplines, companies, institutions and countries come together and exchange ideas and knowledge. This diversity can also be found at Merck where an international team is continuously trying new paths – whether by using intelligent materials to improve electronic equipment, monitoring the quality of food and medicines, exploring the possibilities of genetic engineering or treating cancer. Merck's 350 years of work are proof of the good performance of German companies in the field of research and development. I wish all the participants a successful 2018 conference with inspiring discussions and the possibility to further enhance international cooperation.

The event was also supported by an event app that allowed participants to communicate and network. The app also provided an overview of the agenda, location and special events as well as organizational messaging.

Key for the success of the conference and its image as an independent science conference were clearly also the partnerships with Nature and AAAS/Science that both organized a panel discussion at the Curious2018—Future Insight Conference. The roundtable discussion done together with AAAS/Science revolved around the Technology Breakthrough of the year that is annually elected by Science. Topics covered were: CRISPR/synthetic biology, artificial intelligence, material sciences, astrobiology and solar system exploration. The roundtable organized together with Nature was an extension of the Nature Outlook published earlier in the year and focused on the Future of Medicine, covering new therapeutic modalities such as the microbiome, personalized medicine and biomarkers as well as big data, AI and machine learning.

For operational excellence and top logistics, the collaboration with the event management agency VOK DAMS was of key importance. The project team of Merck and VOK DAMS met weekly for more than 1.5 years to prepare the event.

All tickets for Curious2018—Future Insight were given out for free, around one half via a direct invitation and the other half after an application process. Overall 50% of attendees had an academic background from around 150 different institutions, 50% were from a corporate background, and 40% of attendees were female. Regional distribution was 78% from Europe, 16% from America, 5% from Asia and 1% from Africa/Middle East.

The speakers panel consisted of more than 60 top speakers and panelists from all over the world, including six Nobel Laureates: Frances H. Arnold, Nobel Prize in Chemistry 2018; Fraser Stoddart, Nobel Prize in Chemistry 2016; Jean-Marie Lehn, Nobel Prize in Chemistry 1987; Joachim Frank, Nobel Prize in Chemistry 2017; Bruce Beutler, Nobel Prize in Physiology or Medicine 2011; Harald zur Hausen, Nobel Prize in Physiology or Medicine 2008. Frances Arnold has actually been allocated the Nobel Prize in 2018 a few weeks after speaking at the conference!

Another key highlight of the event was the rollout of the Future Insight Prize (http://futureinsightprize.merckgroup.com and http://futureinsightprize.emdgroup.com), by the CEO of Merck Stefan Oschmann at day 2 of the conference. The Future Insight Prize was initiated and designed by Ulrich Betz and will be awarded annually from 2019 onwards to honor and enable outstanding achievements in science and technology toward a groundbreaking innovation, enabling the later realization of a dream product, important for the future of humanity in the areas of health, nutrition and energy with a research grant of up to 1 million € sponsored by Merck. The Future Insight Prize is covered in detail in the following chapter of this book. The prize will be given out for the first time in 2019 for work enabling the later realization of the dream product Pandemic Protector, to protect humanity from the outbreak of a new viral pandemic. In the following years Future Insight Prizes will be given out on the topics of antibiotic resistance, food generation and clean energy.

Already at day 1 of the conference, the Darmstadt Science Declaration was rolled out. The Darmstadt Science Declaration is a global call to action to devote more resources to the advancement of science and technology with the task to enable humanity to solve the challenges of today and to realize the dreams of a better tomorrow. Everybody is cordially invited to sign this declaration at http://darmstadt-science-

declaration.org). The call was later also given the subline "Make Science not War." Further details are described in an article in Angewandte Chemie (https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201811929).

The Darmstadt Science Declaration reads in detail:

> We, the signatories, are people of different national origins, creeds and convictions. We all firmly believe that human progress is deeply linked to further advances in science and technology. We are truly convinced that science is a force for good which enables us to solve many of mankind's most pressing challenges. We believe that huge opportunities will arise from future science and technology efforts. Yet we are also very well aware of the responsibility and accountability we bear for the new technologies that are realized. We call on all nations, societies and organizations to devote more resources to the advancement of science and technology. We encourage the international community to join forces in battling debilitating diseases, ensuring sufficient food for a growing world population, stopping the destruction of our environment, and engaging in joint endeavors to elucidate the secrets this fascinating universe holds. Nothing shall be impossible.

The Curious2018—Future Insight Conference has received enthusiastic feedback. A participants' survey resulted in 98% of participants agreeing that the event has increased Merck's reputation as leading science and technology company. 97% of all participants rated the overall experience of the conference as excellent or very good. In terms of the most important conference topic, 36% voted for healthy lives—new breakthrough therapies and diagnostics, 19% for live reimagined—synthetic biology and more, 19% for bright future—new ways of working together, 15% for materials and solutions—chemistry and beyond and 12% for digitalization—the power of in silico.

The following participants' statements that were shared via the survey give a good impression on the spirit of the event:

> I will never see such a line-up of speakers anymore in my entire life
> This was the Woodstock of science.
> It will leave a lasting legacy.
> The quality of the program was outstanding.
> Impressive inspiring scientific community and talks. Perfect organization and ideal venue
> One of the best Conferences I have ever participated! Should become an annual event
> Probably the next step up in quality is the Nobel Price Ceremony!
> This conference has shown the world, this 350 years old company has recharged with the future inspiration and driven with curiosity for future success.
> The speaker line-up was unbelievable.
> Of the impact that goes beyond the conference: the Darmstadt science declaration, the future insight prize, the plan to do the conference ongoing.
> It is a groundbreaking conference making you feel the love, excitement and potential of science and technology everywhere!
> Amazing talks. Never visited a comparable conference.
> This was the best conference I have ever attended. Congrats to you and your team for organizing such an amazing, star-packed, thought-provoking and landmark event in history.
> I am seriously thrilled that the event went so well. The feedback has been incredible.
> You were a superstar at Curious2018.
> A once in a lifetime event.
> This was the best organized conference I have ever attended.
> The best event I have ever attended.
> Grandios event, perfectly organized, huge impact, congratulations.
> Curious2018 was brilliantly designed and executed.
> Very impressive in all aspects.
> Thank you for the most amazing conference I have attended in recent times. As a recap I have written a poem to summarize.
> I am at a lot of conferences and I can say that this was by far the most interesting, energetic and diverse I have witnessed in a long time.
> What a stimulating event, it was truly fantastic.
> You did an amazing job, I think everyone will remember it for another 350 years.
> Truly a marvelous event. Thanks to Merck, Uli Betz and the entire team.
> Congratulations on both the Curious2018 and the Innovation Cup. They both were absolutely first class all the way, brilliantly planned and executed. The Merck team should be so proud of the event against so many metrics – not just logistical, but as a pivotal boost to the culture of multi-disciplinary collaboration and long term human-centered scientific endeavor, which I personally think marks Merck out as a very special organization, and very different in mindset to other big pharmas.
> Thank you Uli, it was a great conference and lots of fun.

> You hosted an amazing event in Darmstadt.
> You and your colleagues deserve to be lauded and praised for your service to science. Please keep up the good work.
> To mobilize such a large number of high quality on such international base I have not seen yet in my career, excellent job.
> A conference of the highest standards.
> The Curious2018 conference paired with the innovation cup were easily the most stimulating and exciting experiences of my scientific career thus far. I really cannot thank you enough.
> Such days let us hope for the world and also for Germany.
> It was indeed the most unique event I have attended in my 20 years on the circuit.
> I had a great time there, such an incredibly well organized meeting!
> Congratulations to you Dr. Betz for organizing an event of such epic proportions. It was definitely one of the best experiences of my life.
> It was truly an amazing experience and one that I will always remember

Beyond official surveys, the feedback gathered in one-on-one discussions from participants directly was outstandingly positive too. People were enthusiastic, inspired by the positive outlook into the future, by the great science presented, the presence of so many people that had provided outstanding contributions to the advancement of science and technology and by the enthusiasm of all attendees. My personal experience from Curious2018—Future Insight was incredible. Never before in my live have I been approached by and received congratulations from so many amazing people. To see the top presenters on stage, the high-quality science, the stimulating discussions during the breaks and at the evening events, the top performance and enthusiasm of my team as well as the enthusiastic feedback was just phenomenal, it was a once-in-a-lifetime experience that I will certainly cherish for the rest of my life.

The conference together with the associated Future Insight Prize has received considerable echo in the media including TV, radio, print and social. Also Nature magazine has published a summary: https://www.nature.com/articles/d42473-018-00168-z.

In addition, most of the presentations given at Curious2018 were videotaped and are available in a media library: https://curious2018.com/media-library/.

Directly following the Curious2018—Future Insight Conference the Anniversary Edition of the Merck Innovation Cup (http://innovationcup.merckgroup.com and http://innovationcup.emdgroup.com) was conducted, and 15 teams consisting of 5–6 top graduate students plus one coach (alumni of previous editions of the Innovation Cup) were working over a week to come up with new ideas for innovative products solving key unmet challenges of humanity. The topics covered were the same as during the conference, and three teams each were working on healthy lives, live reimagined, materials and solutions, digitalization and bright future. Students received lectures and coaching from experienced professionals and retirees in a meeting of the generations. Teams presented their project plan at the last day of the Innovation Cup in front of a jury consisting of Merck researchers, managers and Merck-external experts, delegates from venture funds and accelerators as well as academic scientists. The presentation in front of the jury is considered a publication, and all worked-out ideas and project plans are released in the public domain for implementation. The winning team was awarded the Merck Innovation Cup along with 20,000 Euro for a project idea on synthetic biology: "Plastics to Biologics," involving a concept to turn plastics into biologics using engineered *E. coli* to produce methionine from PET.

As the Curious2018—Future Insight Conference was so successful, it will from now on be conducted bi-annually as an independent science conference, and the next event will take place in Darmstadt on July 13–15, 2020. Innovation-driven organizations from all over the world are invited to partner and join the initiative. Invited partners are: corporations, NGOs, scientific organizations, philanthropists and in general all interested individuals.

We have the ambition to grow the conference into the world's most renowned gathering on the future of science and technology covering a broad range of topics such as health care, drug

discovery, synthetic biology, nutrition, material sciences, digitalization, mobility, energy, human mind and bright future—new ways of working together, it will be the "Davos" of science and technology.

Curious2018—Future Insight is bringing the world's best scientists and most accomplished entrepreneurs together to explore the future of science and technology, to solve the challenges of today and to enable the dreams for a better tomorrow, creating a bright future for humanity. You are invited to be a part of it.

Acknowledgements Special thanks go to Stefan Oschmann, the Merck board and the Merck ownership family that have made the budget available to run this outstanding event. The Curious2018—Future Insight organization team consisted of: Beate Moch, Brendan Monks, Brigitte Alexander, Heike Schwarz-Schlenger, Ines Kahlert, Katharina Lenz, Kathrin Hackenberg, Kerstin Weber, Lea Flöring, Maike Kober, Melanie Heumann, Sarah Knick, Seline Wagner, Sonja Hatz, Tamara Engels, Timm Wutzler, Ulrich Betz plus many others that contributed substantially to the success of this endeavor.

Future Insight Prize—From Dream to Reality

3

Ulrich A. K. Betz

Merck is the world's oldest pharmaceutical and chemical company and a leading player in science and technology. When the company celebrated its 350th anniversary in 2018 among other activities a comprehensive future-oriented program around science and technology was set up with the overall goal not only to support the further long-term prospering of the company but also to help boost the further advancement of science and technology in general and particularly to help applying it to solve some of humanities biggest problems.

To support that goal a 350th anniversary science and technology program was set up consisting of three consecutive phases. The main goal of phase one, the conceive phase, was to start the thought leadership process and to define the challenges and dreams of today and tomorrow. Together with the journals Nature, Science/AAAS, Harvard Business Reviews and Technology Forecasting and Social Change, in total more than 2000 scientists and business leaders were surveyed and more than 10 publications resulted. Phase number 2, the convene phase, had the goal to assemble the brightest scientific and entrepreneurial minds to shape the future. It involved the flagship science conference Curious2018—Future Insight along with the Anniversary Edition of the Merck Innovation Cup. In total, about 1500 people were coming together at the occasion of these meetings. Finally, the goal of phase 3, the realization phase, was to move from curiosity to action and to set in place the infrastructure, processes and resources to implement the best ideas and partnership proposals worked out during the two preceding phases and to initiate activities to lay the foundation for a successful future. For that purpose, the Merck 350th Anniversary Research Grants and the Future Insight Prize and were designed and rolled out. While the main purpose of the 350th Anniversary Research Grants was to perform mid- and long-term research to benefit the Merck product pipeline, the main goal of the Future Insight Prize is to boost scientific and technological progress globally and to help solve some of humanities most pressing issues.

What are these problems? Think tanks all over the world have compiled lists and performed assessments of the greatest threats to humanity as we know it such as the Future of Humanity Institute of Oxford University (https://www.fhi.ox.ac.uk/), the BBC (http://www.bbc.com/future/story/20170815-the-greatest-threats-to-humanity-as-we-know-it) or the Global Challenges Foundation (https://globalchallenges.org/). Main topics are: war (nuclear armageddon, bioterrorism, new

The original version of this chapter was inadvertently published as non-open access. It has now been changed to open access with the copyright holder name "The Author(s)". The correction to this chapter is available at [https://doi.org/10.1007/978-3-030-16061-6_18]

U. A. K. Betz (✉)
Vice President Innovation Merck, Darmstadt, Germany
e-mail: Ulrich.betz@merckgroup.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_3

nano-weapons), global pandemic threat via a newly emerging likely viral pathogen, ecological collapse/climate change/global warming associated with overpopulation and food production issues, a flawed artificial intelligence, emergence of the next ice age (natural climate change), eruption of a super-vulcano or a major asteroid impact. A recent survey conducted with 50 Nobel Laureates by the Lindau Nobel Laureate Meeting and Times Higher Education listed as the three biggest threats: (1) environmental degradation/overpopulation, (2) nuclear war and (3) infectious diseases (https://www.dailymail.co.uk/sciencetech/article-4838392/50-Nobel-laureates-reveal-greatest-threats-mankind.html).

A key question in prioritizing the areas where additional stimulation via a special research prize makes most sense and is able to create the highest impact, and it is important to sort out the fields where prospected commercial benefit alone and market forces are not sufficiently stimulating progress and where additional incentives and support structures are required.

In collaboration with Harvard Business Reviews Analytical Services, we conducted a survey with 1000 readers of Harvard Business Reviews which were asked about the anticipated social and business impact of certain technological advances. Interestingly, the top five gap areas in which social impact is greater than business impact were: curing cancer, pandemic preparedness, genetic modification of humans, food for the world and reversing climate change.

To explore the area further, we organized a series of scientific advisory boards to elucidate topics potentially suitable as focus areas for the planned Future Insight Prize. Finally, after thorough evaluation and assessment, it was decided that at the occasion of its 350th anniversary, Merck will sponsor the Future Insight Prize to stimulate innovative solutions to solve some of humanities greatest problems and to realize the dreams for a better tomorrow in the areas of **health**, **nutrition** and **energy** (Figs. 3.1 and 3.2).

In the area of health, the key issue on how to achieve a rapid protection from a newly emerging likely viral infectious disease with pandemic potential should be addressed. Emergence of a new, potentially lethal infection that is easily transmitted from person to person is among the greatest threats to humanity. The risk is increasing due to global urbanization, ease and speed of travel, climate change and the possibility of bioterrorism. Using current technology, development of medical countermeasures would be too slow to prevent many millions, or even billions, of deaths.

Fig. 3.1 Future insight prize logo

Fig. 3.2 Future insight prize trophy

Another field to be tackled in the health area is combating the problem of multi-drug resistant bacteria. Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections. CDC estimates that in the USA, more than two million people are sickened every year with antibiotic-resistant infections, with at least 23,000 dying as a result. There are already high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multi-drug-resistant gram-negative bacteria.

In the area of nutrition, new innovative technologies to feed a growing world population should be the field of focus. The projections show that feeding a world population of >9 billion people in 2050 would require raising overall food production by some 70% between 2005 and 2050. This will only be possible by applying unconventional highly innovative new technology.

Finally, in the area of energy the problem of rising CO_2 levels leading to pronounced climate change should be addressed via production of fuel from atmospheric CO_2. The reduction of CO_2 to useful chemicals has received a lot of attention as an alternative to the depletion of fossil resources without altering the atmospheric CO_2 balance. As the chemical reduction of CO_2 is energetically uphill due to its remarkable thermodynamic stability, this process requires a significant transfer of energy. Achievements in the fields of photocatalysis during the last decade sparked increased interest in the possibility of using sunlight for photocatalytic reduction of CO_2 for the production of solar fuels.

Rather than just providing a general stimulus and research funding in the respective areas, we felt that a vision should be developed for an ideal outcome that would stimulate creativity worldwide on how to make it a reality. For that purpose, the "dream product" concept was developed. A dream product is a product that cannot be realized with the current state of science and technology, but whose existence would be extremely desirable and which is required to ensure the long-term survival of humanity. Who is finally developing, manufacturing and selling the dream product is not of relevance as long as it is made available in sufficient quantities and to a reasonable price worldwide. The Future Insight Prize will put the vision for ambitious dream products of global importance for humankind into the world and will trigger curiosity and creativity worldwide on how to make this vision a reality. The timeframe given for such a realization was set to 35 years, as a resemblance to the 350th anniversary of the company. The prize should be given to people whose work enabled a significant progress toward making the vision a reality via discovering new groundbreaking science or via development of enabling technologies.

In that sense, the work to be conducted can be termed "**visearch**" visionary research, focusing on areas whose further investigation promises to lead to avenues toward technologies that can then be utilized to make the visionary dream products a reality. It is important to note that this can be basic and applied research! In that sense, it especially has to be kept in mind that breakthroughs very often originated from the so-called Pasteur's quadrant according to the four-quadrant scheme introduced by Donald Stokes (*Stokes, Donald E. (1997).* Pasteur's Quadrant—Basic Science and Technological Innovation. Brookings Institution *Press. p. 196.* ISBN 9780815781776), seeking fundamental understanding of scientific problems, while also having immediate use for society.

Working together with scientific advisory boards, definitions for dream products were compiled covering all four focus areas.

The dream product to achieve a rapid protection from a newly emerging infectious disease with pandemic potential is called "Pandemic Protector" with the following properties: "*The dream product starts with a clinical sample of a person infected with an unknown pathogen and*

produces an agent to cure the infected person or to prevent infection of others within a clinically relevant timeframe."

The pandemic protector advisory board consisted of Christopher Milne, Daniel Bausch, James Le Duc, Michael Jacobs and Ron Fouchier (Fig. 3.3).

Already at the Curious2018—Future Insight Conference, the topic of pandemic preparedness and the pandemic protector as the first installment of the Future Insight Prize was covered in a panel discussion and received outstandingly positive assessments. The following panelists were participating: Christopher Milne (Tufts Center for the Study of Drug Development), Eileen Farnon (Head Outbreak Investigation Task Force Institute Pasteur), Justin Sanchez (Director Biological Technologies Office DARPA), Lothar Wieler (Director Robert Koch Institute), Nadia T Tornieporth (University of Applied Sciences and Arts Hannover, Coalition for Epidemic Preparedness Innovations), Sir Michael Jacobs (Clinical lead in infectious diseases, Royal Free London NHS Foundation Trust), Stefan Oschmann (CEO Merck), Subhanu Saxena (Bill & Melinda Gates Foundation).

The dream product to combat the problem of multi-drug resistant bacteria is called "multi-drug resistance breaker" with the following properties: "*The dream product is a series of novel narrow-spectrum antibacterial agents that are able to cure any bacterial infection without induction of drug resistance, empowered by a one hour diagnostic test to select the appropriate agent from this series for an infected patient.*"

The multi-drug resistance breaker advisory board consisted of Deborah O'Neil, Hans-Joachim Zeiler, Harald Seifert and Stewart Cole (Fig. 3.4).

The dream product to help feed a growing world population is called "Food Generator" with the following properties: "*The dream product converts any non-edible biomass into readily edible fully nutritional food within one day without any biohazard.*"

The food generator advisory board consisted of Camille Delebecque, Isha Datar, Kara Bren, Lolke Sijtsma and Martin Jonikas (Fig. 3.5).

Finally, in the area of sustainable energy and stopping further climate change the dream product should have the following properties: "*The dream product generates a high-energy-density fuel from renewable energy, water and atmospheric carbon dioxide with an overall negative carbon dioxide balance.*"

The CO_2-to-fuel converter advisory board consisted of Clifford Kubiak, Daniel Nocera, Ferdi Schüth and Michele Aresta (Fig. 3.6).

The Future Insight Prize will be awarded annually from 2019 onwards to honor and enable outstanding achievements in science and technology toward a groundbreaking innovation, enabling the later realization of a dream product, important for the future of humanity in the areas of health, nutrition and energy. The prize will be given out for the first time in 2019 for work enabling the later realization of the dream

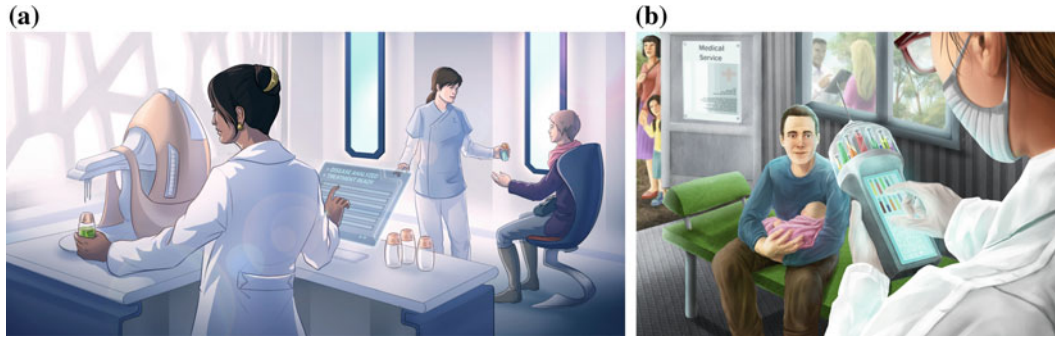


Fig. 3.3 Artist's view of dream product pandemic protector

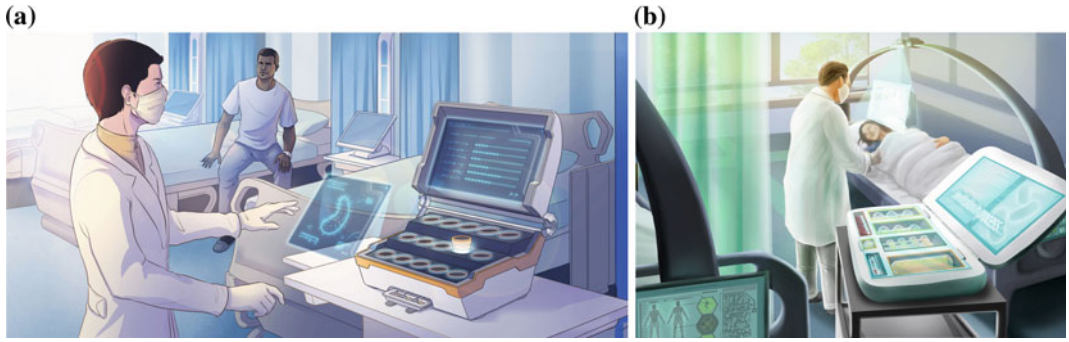


Fig. 3.4 Artist's view of dream product multi-drug resistance breaker

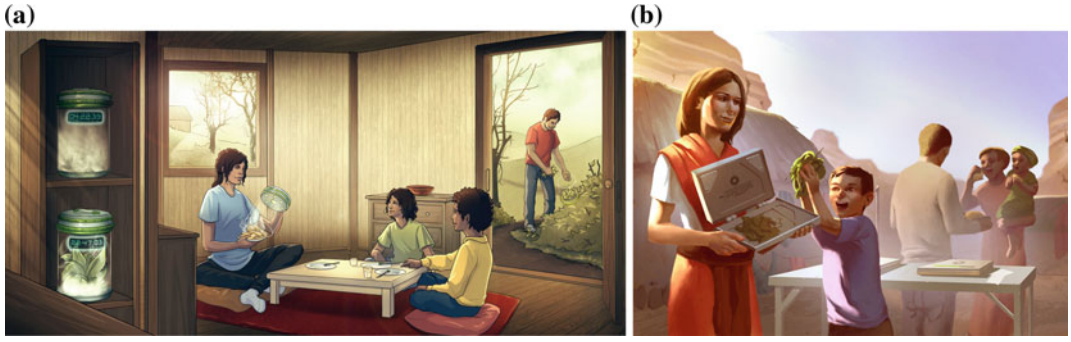


Fig. 3.5 Artist's view of dream product food generator

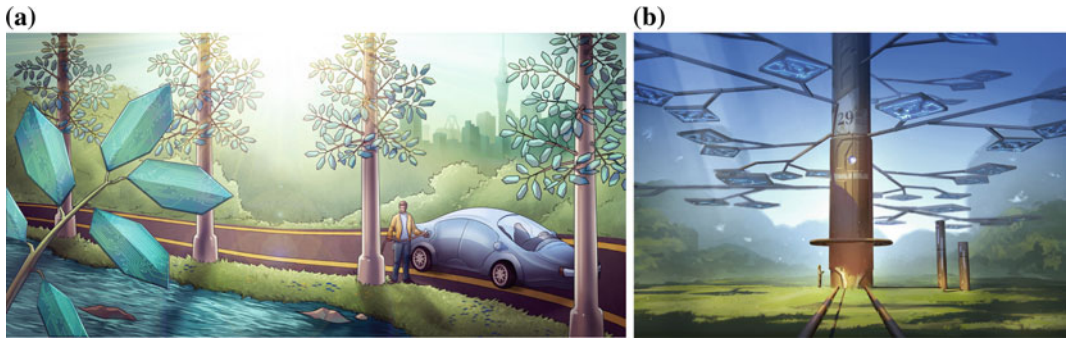


Fig. 3.6 6 Artist's view of dream product CO_2-to-fuel generator

product pandemic protector, to protect humanity from the outbreak of a new viral pandemic. In the following years, Future Insight Prizes will be given out on the topics of multi-drug resistance, food generation and CO_2-to-fuel conversion.

The Future Insight Prizes consists of a research grant of up to 1 million €, the Future Insight Prize trophy, a keynote lecture at the annual Future Insight Prize Winner Event plus a plenary keynote lecture at the Curious—Future Insight Conference. The research grant can be used by the recipient for research located in an area that will provide important input to making the dream product a reality down the road. Ownership of developed intellectual property is not affected by the research grant.

A jury composed of independent international experts will screen the global landscape and identify potential candidates for the Future Insight Prize. In addition, scientists from all over the world can propose suitable candidates to the jury. The jury will then select the final candidates that will be contacted and encouraged to send in an application. The jury will then screen all received applications and select the winner. The winner will be publicly announced and present their research at the Future Insight Prize Winner event and at the Curious—Future Insight Conference.

The winner will be selected according to the following criteria:

(1) Has the recipient's work provided important breakthroughs to enable a later realization of the dream product?
(2) Is the recipient's work of utmost scientific quality recognized by top peer review journals?
(3) Is there reason to believe that the recipient will be able to make good use of the prize money to advance research in this area further?

The Future Insight Prize Jury is composed of renowned international scientists and managers, and currently (status December 2018), it has the following members:

Angela Belcher, MIT
Benjamin List, Max-Planck-Institute for Coal Research
Camille Delebecque, Afineur
Carolyn Aldige, Prevent Cancer Foundation
Christina Smolke, Stanford University
Christopher Milne, Tufts
Clifford P. Kubiak, UC San Diego
Daniel Bausch, LSHTM
Daniel Nocera, Harvard University
Daniel Zajfman, President Weizmann Institute of Science
David Solit, Memorial Sloan Kettering
Dean Radin, California Institute of Integral Studies
Deborah O'Neil, Novabiotics
Donald Cleveland, UCSD
Eileen Farnon, Pasteur Institute
Ernst-Ludwig Winnacker, LMU München
Ferdi Schütz, Max-Planck-Institute for Coal Research
Hans-Joachim Zeiler, Creative Therapeutics
Harald Seifert, University of Cologne
Isha Datar, New Harvest
Jake Yeston, Editor AAAS/Science
James Le Duc, UTMB
Jef Boeke, NYU Langone Health
Jean-Marie Lehn, College de France, Strasbourg
Jeremy Nicholson, Imperial College London
Joao Monteiro, Editor Nature Medicine
John Gyapong, University of Health and Allied Sciences, Ghana
Kara Bren, University of Rochester
Kenneth Drazan, President GRAIL
Lolke Sijtsma, University of Wageningen
Martin Jonikas, Princeton University
Mary Voytek, NASA
Matthew Rosseinsky, University Liverpool
Michael Jacobs, RFL NHS
Nadia Tornieporth, CEPI
Nancy Cox, Vanderbilt University
Nicholas M. Donofrio, IBM Fellow
Peidong Yang, UC Berkeley
Peter Hotez, Baylor College of Medicine, Texas
Peter Piot, LSHTM, London
Ron Fouchier, Erasmus University
Ross Maclean, Precision Value & Health
Rudi Balling, University of Luxembourg
Rudolf Aebersold, ETH Zürich
Scott Spangler, IBM
Shinichi Akaike, NISTEP Japan
Shyam Sankar, Palantir Technologies
Stefan Oschmann, CEO Merck
Stewart Cole, EPFL
Subhanu Saxena, Bill & Melinda Gates Foundation
Toby Bloom, New York Genome Center
Tom Knight, Ginkgo Bioworks
Ulrich Betz, VP Innovation Merck
Ulrich Wiesner, Cornell University
Yang Shao-Horn, MIT

The Future Insight Prize was initiated and designed by Ulrich Betz and officially announced by the CEO of Merck, Stefan Oschmann, at the second day of the Curious2018—Future Insight Conference (http://curious2018.com) and in an official press release published July 17th:

> Darmstadt, Germany, July 17, 2018 – Merck, the vibrant science and technology company, today announced a new research prize. The company will award the "Future Insight Prize" of up to € 1 million annually for the next 35 years. The prize will be presented to researchers who will make outstanding contributions to enable innovations important for the future of humanity in the categories of health, nutrition and energy.
> "As we are discussing the future of science and technology at the 'Curious2018 – Future Insight' conference, this is the right place to announce the 'Future Insight Prize'. With this award we aim to stimulate groundbreaking science and innovative development of key products or technologies, to bring meaningful visions to life for the benefit of humanity," Stefan Oschmann, Chairman of the Executive Board and CEO of Merck, said when he announced the prize today at the conference. This event in Darmstadt, of which Merck is the main sponsor, is currently being held for the first time and brings together globally renowned scientists, among them five Nobel Price laureates.
> The new award will be issued for the first time at next year's "Curious2019" conference. It will relate to the health category and a 'Pandemic Protector' – a visionary dream product enabling an accelerated protection against newly emerging pathogens. The 'Pandemic Protector' should make it possible to swiftly analyze emerging pathogens, to generate an agent for disease treatment or prevention, and in doing so protect humanity against the outbreak of a new, global plague.
> A scouting team will monitor scientific activity worldwide with a view to selecting potential candidates for the award. Experts in the relevant fields are likewise free to propose candidates of their own. The chosen scientists will be approached and asked to submit their entry to a jury of distinguished scientists and managers, drawn both from Merck and beyond. The winner of the respective award should use the prize for further research on the specific topic.
> The Future Insight Prize for the years thereafter will be awarded for the following three topics:
>
> - 2020: Multi-Drug Resistance Breaker - solving the problem of antibacterial resistance to multiple antibacterials (category health)
> - 2021: Food Generator – Technology to help feed the world's growing population (category nutrition)
> - 2022: CO_2-to-Fuel Converter – Generating fuel by photocatalytic conversion of atmospheric CO_2 (category energy)
>
> All future research projects receiving this award should contribute to laying the scientific and technological basis for the later realization of so-called "dream products", in the first year the 'Pandemic Protector'. The products envisaged are visionary products which the prize will catalyze to become reality. The same principle applies to the dream products Multi-Drug Resistance Breaker, Food Generator and CO_2-to-Fuel Converter. None of the awarded projects is meant to be in connection to or to directly contribute to any of the three business sectors of Merck. More information and illustrations are available at http://futureinsightprize.merckgroup.com or http://futureinsightprize.emdgroup.com.
> The science conference "Curious2018 – Future Insight" (http://curious2018.com), where the award was announced today, brings together some of the world's most accomplished scientists. The new conference is one highlight of the 350th anniversary year of Merck. More than 35 internationally renowned scientists – including five Nobel Prize laureates – are presenting their work and discussing the future of science and technology from July 16 to July 18, 2018 in Darmstadt, Germany. The speakers are presenting to an audience of around 1000 guests from all over the world topics oriented to the main focal areas of the three Merck business sectors (Healthcare "Healthy Lives – new breakthrough therapies and diagnostics", Life Science "Life Reimagined – synthetic biology and beyond", and Performance Materials "Materials & Solutions – chemistry and beyond"). Other conference topics address questions regarding digitalization ("Vibrant Digital – the power of in silico") and new forms of collaboration ("Bright Future – new ways of working and collaborating").
> Merck is fighting cancer, multiple sclerosis and other serious diseases. With our Life Science products we are helping other companies to conduct research even more quickly and efficiently. And we are developing high-tech materials with which autonomous driving or foldable displays are becoming reality. We are doing all this in close partnership with top researchers around the globe. Therefore, we are very much enjoying this huge celebration at 'Curious2018 – Future Insight' conference of research with the best of the best," is how Stefan Oschmann described the concept behind this new conference.

The Future Insight Prize is open for expansion and partners (other corporations, NGOs, academic research institutions, governments, philanthropists etc.) are invited to join the concept and sponsor additional prizes stimulating the realization of dream products of their choice. At a "dream board" positioned at Curious2018—Future Insight conference participants could propose dream products of their choice, also in a survey with readers from Nature, Science and Harvard Business Reviews proposals were collected with some examples given here: Material to grow food in every kind of environment - some kind of intelligent soil, a robotic pill that can target infections and tumor cells, clean up trash and man-made debris from the oceans, stay young and healthy for the entire life, smart drugs, living in our bodies and self-applying according to individual needs, self-cleaning rooms, a dinner plate that can analyse and guide your daily intake of vitamins and nutrients, a tool to collect water from the air, a human knowledge repository to restart civilization after a catastrophe and an in silico predictor to create a drug against each human genome encoded target.

The Future Insight Prize has received considerable echo in the media and also triggered enthusiastic statements, and some are given here as examples:

> The Future Insight Prize is great because it sets a grand challenge and seeks a solution to societies greatest future needs.
> Merck's idea to launch the Future Insight Prize is an excellent idea to celebrate the anniversary. In particular for the 'pandemic threat' topic. The Future Insight Prize is great because it will allow blue sky research in an area where this type of research rarely happens but major innovations are desperately needed.
> The Future Insight Prize in Pandemic Protection is great because it is a clear expression of Merck's commitment to society and global health.
> The Future InSight Prize is great because it shows a 350-year old company is thinking about the next 350 years.
> The Future InSight Prize is great because it will foster scientific innovation in areas critical to humanity's future.
> The Future InSight Prize is great because it sets a grand challenge and seeks a solution to societies greatest future needs.
> I applaud your Future InSight prize.
> The Future InSight Prize is great because it tackles issues that matter to us all.
> The Future InSight prize is great because with no/little commercial agenda it is a vehicle to highlight the importance of the best research endeavors in key areas that could greatly impact the future of humankind!
> The Future InSight Prize is great because it will inspire researchers to develop solutions to the major challenges that humanity will face over the coming decades.
> The Future InSight prize is great because it will stimulate and acknowledge out of the box thinking in an effort to cope with one of the most serious threats i.e. infections caused by multi-drug or more recently even pan-drug resistant bacterial pathogens.
> I applaud you and your colleagues at Merck for proposing the Future InSight Prize and specifically for your interests in global pandemic preparedness. The threat of a new pathogen arising from nature, or through genetic mutations or intentional creation, is very real. The Future Insight Prize will stand alone as recognition of technical excellence in a field that historically has not received the attention it so justly deserves.
> I am certain that this new Prize will be warmly welcomed by leaders in global health from around the world.
> Merck's idea to launch the Future Insight Prize is an excellent idea to celebrate the anniversary. In particular for the 'pandemic threat' topic. The Future Insight Prize is great because it will allow blue sky research in an area where this type of research rarely happens but major innovations are desperately needed.
> The Future Insight Prize in Pandemic Protection is great because it offers scientists an incentive to work towards a long-term vision in an area that cannot be stimulated by traditional market forces. It is a clear expression of Merck's commitment to society and global health.
> The Future InSight Prize is great because it shakes the core assumptions behind food sustainability, autonomy and security by rewarding technologies that will empower most humans on the planet to have access to affordable, plentiful and nutritious food.
> The Future Insight Prize is great because it shows a 350-year old company is thinking about the next 350 years.

The ambition is not only to get insights into how the future will look like but to actively shape it to be bright and peaceful. You can be a part of it!

Acknowledgements Special thanks go to Stefan Oschmann, the Merck board and the Merck ownership family

that have made the budget available to make the Future Insight Prize a reality. I am also grateful to the team that worked with me on the implementation of the Future Insight Prize: Brendan Monks, Maike Kober, Melanie Eckardt, Peter Rupprecht, Seline Wagner, Sophia Münkel, Thomas Tresper and Timm Wutzler.

Curious2018—Future Insight

4

Ulrich A. K. Betz

"This is the first meeting of its kind", said Ulrich Betz, vice-president of innovation at Merck Biopharma in Darmstadt, Germany, as he opened Curious2018 in July. The conference is one of a number of celebrations of Merck's 350th birthday, all with the theme "Always curious—imagine the next 350 years" (see "350 years young").

Betz was the driving force behind the conference, which welcomed delegates and speakers from around the world and across the scientific disciplines, and was attended by around 1300 participants. Among the speakers were five Nobel Prize winners, several world-renowned scientists including Craig Venter, and representatives of the European Space Agency (ESA) and the US Defense Advanced Research Projects Agency (DARPA) among others.

The conference covered topics including Healthy Lives—new breakthrough therapies and diagnostics; Life Reimagined—synthetic biology and beyond; Materials and Solutions—chemistry and more; Vibrant Digital—the power of in silico; and Bright Future—new ways of working and collaborating. Sessions dealt with humanity's move from the Stone Age (Society 1.0) to today's Information Age (Society 4.0) and looked forward to Society 5.0—a human-centred technological age. And visitors pondered not just how the future might look, but also on the best way to get there (Figs. 4.1, 4.2 and 4.3).

4.1 Sometimes no Strategy Is the Best Approach

Scientific research, particularly within companies, is often strategy focused; that means researchers tend to find only the "known unknowns".

In contrast, many major discoveries have been "unknown unknowns", found through fundamental research, an open mind and an ability to recognize opportunities, said physicist Daniel Zajfman of the Weizmann Institute of Science in Rehovot, Israel. Examples include liquid crystals that today power smartphone displays, X-rays now routinely used in imaging, and the physics that led to the global positioning system (GPS).

"Strategy should provide direction, not control the process", said Zajfman. "Beyond strategy, we need knowledgeable, curious, passionate scientists—and we need to give them freedom to think and the ability to take risks and fail".

The work of biotechnologist Craig Venter exemplifies the ethos of curiosity-driven research. His institute, with laboratories in La

This chapter is a reprint from the previously published advertisement feature on nature.com https://www.nature.com/articles/d42473-018-00168-z

U. A. K. Betz (✉)
Vice President Innovation Merck,
Darmstadt, Germany
e-mail: ulrich.betz@merckgroup.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_4

CURIOUS2018
FUTURE INSIGHT CONFERENCE

Fig. 4.1 Credit Merck KGaA, Darmstadt, Germany

Fig. 4.2 Credit Merck KGaA, Darmstadt, Germany/Eva Speith

Jolla, California, and Rockville, Maryland, has always valued basic research, and as such has been involved in a series of firsts—sequencing the genomes of a free-living organism, a person and a human microbiome, and creating a self-replicating synthetic organism.

Venter described how such exploratory research could still lead to practical applications. "We can now interconvert genetic and digital code, and make phages and vaccines", he said. "This could mean creating better seasonal flu vaccines with two or three updates in a year, 'printing' off vaccines at home or even DNA 'transportation' to Mars within minutes".

4.2 Small Questions Are Good Too

Curiosity is driven by questions, and the biggest is how matter became complex, from the elementary particle to the thinking organism. To answer it, humans created science, where "Chemistry bridges physics' general laws and biology's rules of life", said 1987 chemistry Nobel Prize winner Jean-Marie Lehn of the University of Strasbourg in France. "Chemistry is to science what music is to acoustics".

The development of technologies such as cryo-electron microscopy has given chemists and

Fig. 4.3 Stefan Oschmann, Merck's Chairman of the Executive Board & CEO, announces the Future Insight Prize. Credit Merck KGaA, Darmstadt, Germany/Eva Speith

biologists extraordinary resolution, down to the side chains of amino acids in a protein molecule, to help answer many of life's difficult questions. "We can now see distinct species of molecules in the same sample", said 2017 Nobel Prize winner Joachim Frank, a biophysicist at Columbia University in New York. "This is a new era in structural biology".

Biological chemistry and the manipulation of living cells have been major drivers in health care and biotech, which leads Frances Arnold, a chemical engineer at Caltech, to another question: "Evolution wrote DNA, through a process of mutation and natural selection", she said. "We have altered biology through artificial selection and genetic modification—but what about chemicals not found in biology?" Arnold has used evolutionary biology techniques to create novel chemicals. Enzymes and whole organisms synthesize non-natural molecules with an efficiency far greater than traditional chemical laboratories.

Angela Belcher, a materials chemist at the Massachusetts Institute of Technology (MIT), has also captured the power of biology. She uses modified bacteriophages to create nanomaterials, such as carbon nanotubes for use in cancer imaging and theranostics, and flexible materials for wearable electronics.

Also working in the nanosphere is 2016 Nobel Prize winner Fraser Stoddart, head of the Stoddart Mechanostereochemistry Group in the Department of Chemistry at Northwestern University, who is employing new chemistry to create nanoscale molecular machines including motors, rotors, switches and pumps. Stoddart has advice for the next generation of curious and creative scientists: "Tackle a big problem—and do your own thing".

350 Years Young

Looking to the Future

Starting as a single pharmacy in Darmstadt in 1668, Merck has grown into an international company with a focus on health care, life science, and performance materials. During this time, it has seen pharmacy shift from an art to a science and been part of the move to industrial production, driven always by curiosity.

Merck will support the development of creative solutions over the next 35 years with a new Future Insight Prize. It will bestow its first award of up to €1 million in 2019, with the goal of pandemic preparedness against emerging viral diseases.

Future prizes will tackle antibacterial resistance, technology to feed the world's growing population, and fuel generation by photocatalytic conversion of atmospheric carbon dioxide.

Directly after the conference, Merck conducted an anniversary edition of its Innovation Cup, which was contested by around 80 students from all over the world who spent a week to learn from Merck professionals and to develop an idea of their own into a business plan. The €20,000 team prize went to the Life Reimagined team who presented a concept to turn plastics into biologics using engineered *E. coli* to produce methionine from PET.

4.3 Humans, Microbes, and Medicine

Tropical diseases have historically received scant attention from biomedical science, despite the fact that they collectively affect more than a billion people. Parasitic diseases such as Chagas disease, schistosomiasis, and leishmaniasis are spreading across Latin America, and many preventable diseases are resurging in developed nations as vaccination rates fall. Antimicrobial resistance is rising, and climate change is driving tropical parasites into temperate zones.

Curiosity can play an important role in what are otherwise strategic and goal-driven projects, such as making affordable versions of vaccines against diseases linked with poverty; developing better formulations of existing disease targets; predicting and preventing the spread of disease; and in considering the interactions of the genome, microbiome, metabolome, and environment. What is required is that researchers work together, across disciplines, using international networks to exchange data.

And we should not forget the role of education and communication, said Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston, Texas. Hotez urged scientists "to engage with the public more, and build scientific literacy into science and medical training" (Figs. 4.4, 4.5 and 4.6).

4.3.1 Society 5.0

As humans live longer, societies are ageing. And nowhere is this more apparent than in Japan, which has the highest proportion of centenarians on top of a falling birth rate. Shinichi Akaike, senior fellow, National Institute of Science and Technology Policy (NISTEP), and Naohiro Shichijo, director of the Centre for Institutional Research, Tokyo University of Technology, proposed Society 5.0 to meet these challenges. Society 5.0 aims to integrate advances in artificial intelligence (AI), big data processing, and the Internet of Things (IoT) to resolve societal challenges such as health care and support for older people within a human-centred society.

Yoshiyuki Sankai, of robotics company Cyberdyne, takes a creative approach to realizing Society 5.0: "Imagine yourself standing in the future, looking at the present, then create the technology to make this future". Sankai's cyborg-type HAL (hybrid assistive limb) uses the "intention signal" derived from the brain to realize the intended motion of the wearer while inducing functional regeneration; another version of HAL provided is Single Joint Type, which is a

Fig. 4.4 Ulrich Betz, VP of innovation at Merck, opening the conference. Credit Merck KGaA, Darmstadt, Germany/Eva Speith

compact and easy to use device that could be attached on both upper limb and lower limb. Cyberdyne also develops Lumbar Type which reduces the stress applied on the lumbar region of manual workers during lift and carry to mitigate the risk of back injury.

In Society 5.0, AI will also be an important part of drug discovery and development, said Scott Spangler of IBM Watson Health. In research, AI can provide confidence scoring, validate reasoning and data, and help scientists to interrogate existing knowledge for new connections. This can aid target identification, prediction of gene function, and selection of drug indications.

However, AI's biggest role isn't simply to provide answers—it's going to be to drive curiosity by helping researchers ask better questions. "AI isn't an oracle", said Spangler. "It's an annoying collaborator that constantly says, 'what about…?'".

4.3.2 The Final Frontier

For the really curious scientist, there are extra-terrestrial questions, starting with our nearest celestial neighbours. "The Moon is a history book of our own planet", said ESA astronaut Thomas Reiter. "And we might find proof of past or current life on Mars in the next few years".

ESA's planned space missions include the BepiColombo spacecraft, which will head to Mercury in October 2018 to investigate the Sun's closest planet; and the ExoMars lander, which will land on Mars in November 2018 to study the crust, mantle, and core of the planet.

Curious2018 was also the birthplace of the Darmstadt Science Declaration, a global call to action to devote more resources to the advancement of science and technology to enable humanity to solve the challenges of today and to realize the dreams of a better tomorrow. The declaration can be signed online at make-science-not-war.org.

Fig. 4.5 Credit Merck KGaA, Darmstadt, Germany/Eva Speith

Fig. 4.6 Credit Merck KGaA, Darmstadt, Germany/Eva Speith

The story from Curious2018—Future Insight is a varied one, picking a route through chemistry, biology, physics, and technology. From the hugeness of outer space to the minutiae of molecular machines, from the history of pharmacy to health care in Society 5.0, and like the drone-powered balloons, with their curious three-dimensional flight and ethereal internal light that were present during the official welcome ceremony, ideas from the conference will follow the attendees out of the lecture theatre and into the laboratories to inspire the next generation of breakthroughs.

The Darmstadt Science Declaration—Make Science not War

5

Ulrich A. K. Betz

Over the centuries and millennia, humanity has made tremendous progress in science and technology—just compare the complexity of a stone-age wedge to that of a silicon computer chip. Without the advancements in food production, hygiene, and medicine, we would have never been able to grow the world population to 7.7 billion people as of September 2018. The achievements are incredible: Modern technologies allow more or less each person to communicate with each and every other human being on the planet at all times, we have available the entire knowledge of humanity at our fingertips, antibiotics have tamed the threats of bacterial infections that haunted us for so long, man-built machines have left our solar system, we understand the secrets of our genome and the composition of matter and energy, and we engineer organisms and create new species. Nevertheless, despite all this progress, significant challenges remain to be solved such as fighting debilitating disease, preventing new global pandemics, stopping climate change, feeding a growing world population, achieving access to clean water for all, stopping global pollution of the oceans, satisfying the needs for a clean and sustainable energy source, achieving proper education and housing for everybody and ensuring a peaceful coexistence of all humans on this planet. We will only be able to solve these challenges with further progress in science and the development of new superior technologies applied to the benefit of humanity with strong ethical values of mutual love and respect. It is the purpose of the Darmstadt Science Declaration to underline the importance of this mission and to create a global movement to make these dreams a reality.

This chapter is adapted from *Angewandte Chemie International Edition* https://doi.org/10.1002/anie.201811929.

U. A. K. Betz (✉)
Vice President of Innovation Merck KGaA, Darmstadt, Germany
e-mail: Ulrich.betz@merckgroup.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_5

Ulrich A. K. Betz
Vice President
Merck KGaA, Darmstadt,
Germany

And rapid action is necessary. Despite convincing analysis showing that the world has become a bit better each day, there are signs that this trend will not go on forever without our strong continuous efforts. We might have overstretched the utilization of the available resources. There are signs that humanity on earth is approaching the limits to growth, as first predicted in a report to the Club of Rome in 1972 that caused worldwide attention. The project that produced this report officially titled *The Limits to Growth* was conducted by D. H. Meadows, D. L. Meadows, J. Randers, and W. W. Behrens at the Massachusetts Institute of Technology (MIT), commissioned by the Club of Rome, and funded by the Volkswagen Foundation (Germany). Despite a lot of criticism that the first book received, mainly based on the perceived simplicity of the used computer simulations, it could be shown in the regular updates published since then that the "business-as-usual scenario" described in the report unfortunately aligns well with historical data so far. Continuing unchanged, this would finally result in collapse of the global economy and environment in the first half of the twenty-first century because of a combination of increased pollution and exhausted natural resources, with signs of economic decline becoming visible some time before. We might only have a short time window left to discover the required technologies required to avoid global collapse, and the time to act is now.

Worldwide R&D expenditures in Organisation for Economic Co-operation and Development (OECD) countries totaled an estimated $1.1 trillion in 2016 and have continuously risen in the past, apart from a dip after the financial crisis in 2008. Nevertheless, in its last report the OECD raised serious concerns about recently declining public funding for R&D and innovation, indicating that the situation could deteriorate further with aging societies. In many OECD countries, public research funding in 2015 was already below the level determined for 2000 (e.g., Australia, Finland, France, UK, Italy, Spain, and the USA). In the USA for example, government funding flatlined after the 2008 crash and has declined as a percentage of gross domestic product from 0.88% in 2009 to 0.62% in 2015. There are growing pressures on the developed societies from ageing, global migration, and climate change issues, and we need to ensure that these pressures are not making R&D funding suffer, as it is our only hope to solve these problems in the future.

Especially in times when we hear dominant voices asking for an increase in military spending, it should be clear that more weapons cannot avoid the outbreak of conflicts for the remaining resources of our planet. To avoid such conflict altogether and to enable a great life for each and every human, new science and technology is required to fight the root causes and sources of conflict. What we also urgently need is a positive outlook, a force countering the increasingly dystopic views of the future we encounter daily not only in the news but also in art and literature, where a utopian view of our future has largely been replaced by dystopic visions.

With around 1300 participants from all over the world, a lineup of more than 50 top speakers and panelists including six Nobel Laureates, the Curious2018—Future Insight Conference (http://curious2018.com) brought together in the Science City in Darmstadt (Germany), some of the world's greatest scientists and most accomplished entrepreneurs to jointly explore the future

of science and technology and to create this positive and utopian future mindset. Both the conference and a new research prize (http://futureinsightprize.merckgroup.com) were sponsored by Merck KGaA Darmstadt, Germany, the world's oldest pharmaceutical and chemical company, on the occasion of its 350th anniversary. On the first day of the conference, the Darmstadt Science Declaration was rolled out. The Darmstadt Science Declaration is a global call to action to devote more resources to the advancement of science and technology to enable humanity to solve the challenges of today and to realize the dreams of a better tomorrow. Everybody is cordially invited to sign this declaration (http://darmstadt-science-declaration.org).

The declaration reads: "We, the signatories, are people of different national origins, creeds and convictions. We all firmly believe that human progress is deeply linked to further advances in science and technology. We are truly convinced that science is a force for good which enables us to solve many of mankind's most pressing challenges. We believe that huge opportunities will arise from future science and technology efforts. Yet we are also very well aware of the responsibility and accountability we bear for the new technologies that are realized. We call on all nations, societies and organizations to devote more resources to the advancement of science and technology. We encourage the international community to join forces in battling debilitating diseases, ensuring sufficient food for a growing world population, stopping the destruction of our environment, and engaging in joint endeavors to elucidate the secrets this fascinating universe holds. Nothing shall be impossible."

The declaration has in the meantime been signed by thousands, including Nobel Laureates Frances Arnold, Bruce Beutler, Joachim Frank, Harald zur Hausen, Avram Hershko, Louis Ignarro, Jean-Marie Lehn, James Rothman, Jean-Pierre Sauvage, J. Fraser Stoddart and other famous scientists such as Craig Venter, Emmanuelle Charpentier, or the President of the Weizmann Institute of Science, Daniel Zajfman as well as other celebrities such as for example Wolfgang Ischinger the chairman of the famous Munich Security Conference. It will be widely published and brought to the attention of decision-making bodies all over the world. The goal is to shape public opinion, to create a global movement resulting in a change in the allocation of resources toward research and development, in an increased attraction of bright young talent to science and technology and in general in an optimistic, utopian outlook to ensure the technologies required for a bright and sustainable future are made available in time.

It has been argued that the growth of the human population in a closed ecosystem as our planet must necessarily come to an end and that no new technologies can overcome these physical limits. This, however, is not true, there are no limits to human growth and new science and technology will enable us to spread into space and colonize new planets, the universe is huge.

The movement supporting the Darmstadt Science Declaration is synergistic with other global movements that were recently emerging, such as the "March for Science" (www.marchforscience.com) or "Fridays for Future" (www.fridaysforfuture.org).

The Science Declaration is now going across the world and should be rolled out in all major cities (e.g., we already did a Paris Science Declaration, Jerusalem Science Declaration, London Science Declaration) all linking to the central site for collecting signatures http://make-science-not-war.org. Activists for science all over the world are encouraged to launch the science declaration in their city, link it to the site, and communicate about it in the social and print media all over the world.

The universe is an incredible place that holds endless secrets waiting to be uncovered. With all progress in science and technology, we have just scratched the surface of what is out there waiting to be known. What more noble an endeavor could one imagine than proudly advancing into the unknown, increasing the understanding of the universe we are living in and using this

knowledge to solve the challenges of today, to enable the dreams of a better tomorrow and to create a good and peaceful life full of love and achievement for everybody on this planet and beyond.

Nothing will be impossible.

Join the movement, spread the news, share it with you friends all over the world, and sign the declaration today at: http://make-science-not-war.org.

Part II

Science and Technology at Its Best—Examples from Curious2018 Future Insight Conference Keynote Speakers

Integrating Modern Immunology into Medicine

6

Mark M. Davis and Robert M. DiFazio

6.1 Introduction

Manipulating the immune system to produce health benefits for human beings has had many successes, from the first vaccines of Jenner and Pasteur to most recently the use of checkpoint inhibitors in cancer. The promise of even more significant health benefits has been tantalizing, but elusive. This is because while inflammation and other types of immune involvement are evident in many diseases, we lacked a detailed enough understanding of this system to intervene with therapeutics other than generic treatments (e.g., steroids) that have limited effectiveness. Thus, it became apparent that convenient animal models were needed in order to understand the principals of immunity. Many were investigated—rabbits, guinea pigs, goats, sheep, rats—but the clear winner was the inbred mouse, which was already in widespread use by the 1950s and was the workhorse of the field by the 1980s and 1990s.

With the critical development of recombinant DNA methods in the seventies, then later transgenics and knockouts, mice became the go-to species for in-depth studies of the immune system (as well as other important mammalian biological systems). Since the turn of the last century, they have been instrumental in elucidating much of basic immunology and allowed for seminal discoveries governing what we know about the immune system, its many components, cell types and unique mechanisms. These discoveries include gene rearrangement to create vast reservoirs of diversity in antibodies and T cell receptors, the ability of MHC molecules to capture peptide antigens from degrading proteins and present them to T cells, and the many signaling pathways that are key for initiating or blocking these processes. Almost all we know of basic immunology therefore has been derived from inbred mouse studies, but where those models have been less successful is allowing us to create accurate models of disease that can be studied for the development of therapeutics. There are many models of disease, and many ways to cure or prevent these diseases have been developed, but the ones that are feasible to do in humans and lead to successful treatments have been remarkably few. It has been reported, for example, that papers describing methods to prevent type 1 diabetes in the major mouse model (NOD) are in excess of 300, but we have yet to prevent this disease in a single human being [1]. Similar successes were reported regularly in immunological treatments of

M. M. Davis (✉) · R. M. DiFazio
Institute for Immunity, Transplantation and Infection, Stanford, USA
e-mail: mmdavis@stanford.edu

R. M. DiFazio
e-mail: rdifazio@stanford.edu

M. M. Davis
Stanford University School of Medicine, Howard Hughes Medical Institute, Stanford, CA 94305, USA

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_6

tumors in mice, for decades, but human trials invariably failed and many dismissed the possibility that such treatments would ever work [2]. Fortunately, the pioneering work of Allison et al. showing that anti-CTLA4 had promise in treating mouse tumors by their very novel mechanisms of attenuating natural tolerance mechanisms does carry over enough to benefit a significant fraction of people with certain cancers [3], but the road to achieving this remarkable success was not straightforward and benefits only a fraction of people.

Why have mouse models of disease been so poor at developing useful clinical treatments? We don't know, but there are a number of possibilities including evolutionary distance, the utilization of inbred versus outbred mice, and the way models are designed to yield relatively quick, reproducible results. But whatever the reasons, it is quite clear that inbred mice have not been a great success as disease models that lead easily to human treatments [4]. This is unfortunate, especially as these models have occupied a large fraction of scientists interested in translation. This has had the effect of diverting the attention of the most talented researchers away from direct human studies to focus on more tractable mouse models. The situation is now changing dramatically, if slowly, due to the fact that studies performed directly in humans are now much more feasible with the introduction of new technologies and have more and more appeal to both translational and basic science questions. We are therefore poised for a revolution in human immunology. This will expedite the use of immunology in the clinic, because now instead of having to 'translate' results from mouse studies, we will more and more have direct patient data to guide existing treatment options and develop new ones. Here, we briefly outline what has changed and what we can look forward to.

6.2 New Paradigms

While the existing paradigm of mouse models of disease is still useful, its relatively low yield and the ability to get high-quality data from patient cohorts mean that there could be substantial improvements. Chances are there will be significant differences between murine and human data, or perhaps they are completely different. In the former case, it may be that the mouse model represents only a fraction of patients, which will help in understanding what it may be good for, and in the latter case, it would say we need to look for a new model entirely. A more sweeping and very different paradigm is the concept of 'systems immunology,' [5–7] which starts from the fact that since most of what we can do in murine studies cannot be done in human beings, we should develop an entirely new scheme, built around the advantages of human studies. What are the advantages? The ready availability of blood samples, for example, and the fact that there is a potential wealth of immunological information in them in the form of the circulating cell types and communication molecules of the immune system. While not an 'immunological organ' *per se*, these cells and molecules in the blood represent a real-time snapshot of both the steady state of a person's immune system as well as a window on the dynamics that occur after an intervention. For example, a week after a flu vaccination B and T lymphocytes specific for flu antigens surge through the circulating system [8]. Similarly, six days after gluten challenge in patients with Celiac disease particular T cells (including gluten specific ones) also mobilize into the blood and can be analyzed in that time period [9]. These represent part of the natural immune response whereby specific lymphocytes proliferate in localized lymph nodes and then between six–ten days exit into the circulation to populate a broader spectrum of lymphoid organs. In chronic diseases such as MS, the release of pathogenic T cells seems to be relatively continuous, as judged by the effectiveness of drugs such as fingolimod that inhibit egress from lymph nodes [10]. Another example of how we might 'read the blood' was described recently with a report showing that depressed levels of circulating B cells is characteristic of subjects with a latent *M. tuberculosis* (Mtb) infection and especially the finding that a drop in NK cell levels presaged a descent into active tuberculosis

(TB) disease [11]. Studies of gene expression patterns in blood cells have also identified important indications of other types of infections and stages on the way to sepsis [12], or the likely success or failure of a vaccine [13]. But these studies are just the tip of the iceberg compared to what we could learn if we were at all systematic about interrogating patients' blood across the whole spectrum of health and disease. The fact that complete blood counts (CBCs) are still the standard assay for white blood cells in medicine, which was introduced in 1959 [14], should be an embarrassment to the profession, since we now know that there are hundreds if not thousands of different cell types [15]. To correct this, we must have very focused efforts to discover and validate immune biomarkers that are accurate predictors of disease trajectories and especially treatment options in patients. Only data that meets these criteria will be widely adopted. Especially, valuable would be a goal we have here at Stanford to develop a cholesterol test-like panel for immunological health. If achievable, this immune health panel could identify who is at risk for a serious infection or even cancer. We have also seen, in a number of studies, a close correlation between certain inflammatory markers and cardiovascular diseases [16, 17]. Even disease risks and related factors that are not typically thought of immunological may come up in 'systems immunology' studies.

6.3 Technological Advances

For many years, there were numerous technological advances in mouse immunology, but very few for human work. This was because most of the advances in immunology came in murine systems. This then became a self-perpetuating 'loop' which drew most of the research talent in the field, even those with medical training, toward mouse studies. Fortunately, the past ten years has seen an explosion in new technologies that have revolutionized the study of human immunology. Particularly important are those technologies that can be applied to blood cell analysis at the single cell level, since individual cells are the principal effectors of an immune response, and so it is important to know both the variety of cell types and the distribution of cellular activity. For example, earlier work in the Davis lab showed that most T cells could recognize a single peptide-MHC on another cell [18], and later studies showed that this could result in a full-blown release of cytokines by a CD4+ T cell [19]. But it was an 'all or none' response, meaning that one or two or three peptide-MHC ligands all gave the same response. So how do you 'scale' a T cell response? By recruiting more cells with that specificity [19]. This means that in evaluating a response, you need to know how many cells are not responding as well as how many are. So, what are these new technologies?

6.3.1 'Deep' Phenotyping of White Blood Cells

The development of mass cytometry has been a key development, and while fluorescence-based methods have been a mainstay of immunology (developed by the Herzenbergs here at Stanford [20]), they reached an effective plateau of 12 or so colors from about 2000 because of overlapping spectra. Mass cytometry analysis (pioneered by Garry Nolan also here at Stanford) improved upon this limitation fundamentally since it relies on metal labeled antibodies with little or no overlapping spectra, allowing the use of now 45–50 different labels, giving vastly more information and revealing studies of stem cells [21], T cells [15, 22], NK cells [23], and B lymphocytes [24] have all revolutionized our understanding of cellular complexity in human immunity. The fluorescence-based cytometry industry may be fighting back by introducing the next generation of analyzers that can detect ~28 colors, a major leap over the status quo; this bar though is still lower than what the latest mass cytometry instruments can do. Single cell RNA-seq is also coming up quickly, and although it is not capable of cataloging every gene in a given cell, the

technique can still provide a wealth of information on thousands of genes and is clearly superior to mass cytometry in defining cell types [25, 26].

6.3.2 B and T Cell Responses

B and T cell lymphocytes have a variety of functions and phenotypes, and thus have benefitted from the above innovations, but special mention should be made of methods that have been developed recently to analyze their specificity and general response repertoire. The ability to analyze specificity and repertoire first benefitted from high-throughput sequencing methods, currently dominated by instruments from Illumina and PacBio, which enable routine sequencing of millions of immunoglobulin and T cell receptors very economically. These technologies then enabled high-throughput single T or B cell receptor sequencing [27, 28], which revealed major clones that were responding to tumors or a vaccine. The sequences allowed both a snapshot of a response, but also an ability to immortalize the specificity in a cell line or in case of immunoglobulins to make specific antibodies recombinantly. In the case of T cell receptors, the main drivers of T cell specificity are often a mystery, and thus the yeast display method pioneered by Garcia and colleagues [29, 30], whereby up to a billion randomized peptides bound to a given MHC molecule can be used to discover antigens, has been a major resource to discover antigens in cancer and in any disease involving T cells. An additional problem with T cells is the fact that a given peptide-MHC specificity could have thousands of different T cell receptors that bind to it. They often though have sequence motifs in common and here the analytical solutions developed by the Davis lab [31], or that of Paul Thomas [32], are enormously useful in focusing on the ability to group sequences by antigen specificities versus sequence diversity.

6.4 Conclusion

These new technologies, and others too numerous to list here, are bringing important hope to studies of the human immune system and will soon give us 'actionable intelligence' that will allow us to assess a person's immune health accurately and assess possible disease risks—before they develop a disease or succumb to a common infection like influenza or pneumonia. We also see persistent signs of a close linkage between inflammatory pathways and diseases not previously linked to the immune system [16, 17, 33, Pickman et al., Nat. Med. 2019, in press], suggesting that immune biomarkers could greatly improve our ability to detect cardiovascular disease, pre-term birth, and other health-related problems earlier than now possible.

References

1. von Herrath M, Nepom GT. Animal models of human type 1 diabetes. Nat Immunol. 2009;10(2):129–32.
2. Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. Am J Transl Res. 2014;6(2):114–8.
3. Page DB, et al. Immune modulation in cancer with antibodies. Annu Rev Med. 2014;65:185–202.
4. Wagar LE, DiFazio RM, Davis MM. Advanced model systems and tools for basic and translational human immunology. Genome Med. 2018;10(1):73.
5. Furman D, Davis MM. New approaches to understanding the immune response to vaccination and infection. Vaccine. 2015;33(40):5271–81.
6. Brodin P, Davis MM. Human immune system variation. Nat Rev Immunol. 2017;17(1):21–9.
7. Davis MM, Tato CM, Furman D. Systems immunology: just getting started. Nat Immunol. 2017;18(7):725–32.
8. Wrammert J, et al. Rapid cloning of high-affinity human monoclonal antibodies against influenza virus. Nature. 2008;453(7195):667–71.
9. Han A, et al. Dietary gluten triggers concomitant activation of CD4+ and CD8+ alphabeta T cells and gammadelta T cells in celiac disease. Proc Natl Acad Sci USA. 2013;110(32):13073–8.

10. Brinkmann V, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat Rev Drug Discov. 2010;9(11):883–97.
11. Roy Chowdhury R, et al. A multi-cohort study of the immune factors associated with M. tuberculosis infection outcomes. Nature, 2018;560(7720):644–48.
12. Sweeney TE, et al. A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. Sci Transl Med. 2015;7(287):287ra71.
13. Team, HCSP, Consortium HI. Multicohort analysis reveals baseline transcriptional predictors of influenza vaccination responses. Sci Immunol. 2017;2 (14).
14. Verso ML. The evolution of blood-counting techniques. Med Hist. 1964;8:149–58.
15. Newell EW, et al. Cytometry by time-of-flight shows combinatorial cytokine expression and virus-specific cell niches within a continuum of CD8+ T cell phenotypes. Immunity. 2012;36(1):142–52.
16. Shen-Orr SS, et al. Defective signaling in the JAK-STAT pathway tracks with chronic inflammation and cardiovascular risk in aging humans. Cell Syst. 2016;3(4):374–84 e4.
17. Furman D, et al. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. Nat Med. 2017;23(2):174–84.
18. Irvine DJ, et al. Direct observation of ligand recognition by T cells. Nature. 2002;419(6909): 845–9.
19. Huang J, et al. A single peptide-major histocompatibility complex ligand triggers digital cytokine secretion in CD4(+) T cells. Immunity. 2013;39 (5):846–57.
20. Hulett HR, et al. Cell sorting: automated separation of mammalian cells as a function of intracellular fluorescence. Science. 1969;166(3906):747–9.
21. Bendall SC, et al. Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum. Science. 2011;332 (6030):687–96.
22. Newell EW, et al. Combinatorial tetramer staining and mass cytometry analysis facilitate T-cell epitope mapping and characterization. Nat Biotechnol. 2013;31(7):623–9.
23. Horowitz A, et al. Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. Sci Transl Med. 2013;5 (208):208ra145.
24. Bendall SC, et al. Single-cell trajectory detection uncovers progression and regulatory coordination in human B cell development. Cell. 2014;157(3): 714–25.
25. Sade-Feldman M, et al. Defining T cell states associated with response to checkpoint immunotherapy in melanoma. Cell. 2018;175(4):998–1013 e20.
26. Azizi E, et al. Single-cell map of diverse immune phenotypes in the breast tumor microenvironment. Cell. 2018;174(5):1293–1308 e36.
27. Han A, et al. Linking T-cell receptor sequence to functional phenotype at the single-cell level. Nat Biotechnol. 2014;32(7):684–92.
28. Robinson WH. Sequencing the functional antibody repertoire–diagnostic and therapeutic discovery. Nat Rev Rheumatol. 2015;11(3):171–82.
29. Birnbaum ME, et al. Deconstructing the peptide-MHC specificity of T cell recognition. Cell. 2014; 157(5):1073–87.
30. Gee MH, et al. Antigen identification for orphan T cell receptors expressed on tumor-infiltrating lymphocytes. Cell. 2018;172(3):549–63 e16.
31. Glanville J, et al. Identifying specificity groups in the T cell receptor repertoire. Nature. 2017;547 (7661):94–8.
32. Dash P, et al. Quantifiable predictive features define epitope-specific T cell receptor repertoires. Nature. 2017;547(7661):89–93.
33. Aghaeepour N, et al. An immune clock of human pregnancy. Sci Immunol. 2017;2(15).

7 The Changing Landscape for New Drug Development: Medical Countermeasures (MCMs) as a Case Study

Christopher-Paul Milne

7.1 Introduction

The prospects of a new medicine making it from the laboratory bench to the pharmacy shelf are daunting. For each drug that makes it into the clinic for testing in humans, thousands do not, for myriad reasons ranging from easy-to-understand ones such as toxicity in animals to more esoteric ones such as "druggability" (i.e., simply put, the likelihood of being able to modulate a target with a drug). Once in the clinic, the odds are a little better that a lead compound will emerge as the target product of a new drug application or biologics' license application and be approved by National Regulatory Agencies (NRAs)—those odds are typically calculated to be about 1 in 10. Still this is not good news for drug sponsors, who may spend as long as two decades and over $1 billion USD out-of-pocket to get a new drug to market. But over the last decade, the news has become even more daunting. Risks associated with drug and biologics research and development (R&D) have only grown over time, while rewards are diminishing. Average time before follow-on competitors chase a first-in-class drug into the marketplace shrink each decade by several fold, and the percentage of prescriptions filled by generics doubles decade by decade (now reaching as high as 90% in many developed country markets). More telling for the demise of the traditional blockbuster strategy for achieving a sustainable return-on-interest (ROI) is that average sales for new launches were lower by 40% in 2010 from what they were just 5 years earlier [1] and declined to 2% from the 10% achieved in 2010 as of 2018 [2]. This new reality is often heralded as a healthy development for healthcare cost containment, even though drugs typically comprise a relatively minor share of the total bill for health care, for example, 10% in the USA [3]. However, for those concerned with not only controlling the escalation of healthcare costs but also curtailing health risks, these circumstances represent a different set of perils. Drugs that present too difficult a development challenge or too uncertain a market will not be able to compete successfully for resource allocation internally within companies or externally in the capital marketplace. These perils are particularly acute in new fields of product development like regenerative medicine or even a new sub-sector derived from several existing fields of product R&D—such as Medical Counter Measures (MCMs), which are products that may be used in the event of a potential public health emergency stemming from a terrorist attack with chemical, biological, or radiological/nuclear (CBRN)

C.-P. Milne (✉)
Tufts University School of Medicine, Boston, USA
e-mail: sirenlim@gmail.com

C.-P. Milne
University of Edinburgh, Edinburgh, Scotland, UK

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_7

agents or a naturally occurring, emerging or re-emerging infectious disease.

The product sector case example for this overview of the shifting landscape for new drug development (including both small molecule and large molecule drugs, respectively of chemical or biological origin) will be MCMs, and the regional focus will be primarily on the USA. Fully half of new active substances (NASs) approved globally each year, ownership of the extant R&D pipeline worldwide (for MCMs and in general), as well as the end-market for all medicines occur within the purview of the USA. So as the USA goes, so goes biopharma world. For example, historically most of the regulatory innovations of the twentieth century, such as the Orphan Drug and Fast Track programs, were first introduced in the USA and soon emulated by Europe and Japan, while in the twenty-first century, a number of emerging market countries (especially those in the Asia-Pacific region) base their regulatory and reimbursement evaluations on those conducted in the USA, especially for breakthrough products, for which the resources and expertise for developing the evidence base to make such decisions (e.g., regulatory science tools and/or real-world data) are limited in emerging market countries. In addition, the US National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) lead their respective fields of research and regulation due to the number and expertise of their staff, the size of their budgets, as well as global influence and interest.

The remainder of this chapter is comprised of materials adapted from previous publications authored by the Center for the Study of Drug Development at Tufts University School of Medicine (Tufts CSDD) over a ten-year period from 2010 through 2019. In addition, there are occasional infusions of updated commentary to "connect the dots" of how we got to where we are today. These publications may be requested from Tufts CSDD (if originally published in-house) or through the usual channels for requesting articles published in the public domain (permission to reprint the articles having been granted, where required). The text of the chapter is structured basically in a chronological fashion beginning with Tufts CSDD analysis of the early era of MCM evolution as a sub-sector from various extant therapeutic areas. It then chronicles the changes to the R&D paradigm in response to the challenges that emerged for both MCMs and biopharma in general. Finally, it ends with an exploration of the devolution of the MCM sub-sector back into its roots in the infectious disease area as an increase in actual outbreaks as well as other signals of global vulnerability to pandemic threats have minimized the MCM emphasis on biodefense against a wide range of CBRN agents in favor of public health tactics to address humankind's maladaptation to a world in which it is constantly assailed by its microbial competitors and symbionts, or to novel public health crises of its own making.

7.2 Early Evolution of a New R&D Sub-sector [4]

Historical Background—Historically, in the USA, even though the "war on cancer" had been declared in the early 1970s, awareness of the chasm between risk and reward in biopharmaceutical R&D first became a political issue in the 1980s, initially through advocacy efforts on behalf of victims of rare diseases. In aggregate, rare diseases comprise a large "special patient" population of 20–30 million each in the USA and European Union and perhaps as many as 400 million worldwide, but this population is spread over approximately 7000 small disease markets, and so became therapeutic "orphans" due to the lack of incentives for product developers willing to foster R&D programs for these rare conditions. Close on the heels of the economic epiphany revealed by the orphaning of rare disease due to business reasons, the AIDS epidemic struck. In true epidemic fashion, AIDS quickly fomented a crisis for a healthcare system in the USA that had no weapons with which to stem the bewildering tide of morbidity and mortality, whereas cancer and HIV were rampant killers in the 1980s and 1990s, and budget thieves for healthcare systems as well; today scores of new medicines have blunted some of their public

health impact and often have commuted imminent death sentences to chronic disability—with variable levels of quality of life, but life nonetheless. Other diseases have now emerged to take their place; some, such as antibiotic-resistant infections, are as lethally inexorable as AIDS once was. Others, such as depression and obesity, kill more slowly but in great numbers across the spectrum of age ranges, just as cancer once did, unchecked and with little medical recourse. The difference over the years was that AIDS, rare diseases, and cancer developed a vocal and organized advocacy that affected political change, which in turn laid the statutory groundwork on which the USFDA built the designation programs to address the unmet medical needs of these special patient populations.

In the early 2000s, a frightening new public health reality dawned, as it became clear in the wake of 9/11 that terrorist attacks are a very real threat that could cause a large number of civilian casualties. Incidents involving anthrax, a commonly occurring bacterium, and sarin, a chemical toxin from a commonly used family of pesticides, demonstrated the potential for bioterrorists to use a wide range of CBRN agents in future attacks. Awareness of naturally occurring pandemics has also been increasing. The range of infectious threats include: emerging infectious diseases like severe acute respiratory syndrome (SARS) and avian flu (H5N1); re-emerging diseases like measles, pertussis, and Ebola; "neglected diseases" like tuberculosis, dengue, and water-borne parasites; and bioterror agents such as smallpox and anthrax. SARS was the first severe newly emergent infections of the twenty-first century and also demonstrated two significant characteristics of the new plagues: The first is their potential for significant direct (i.e., medical and government program costs) and indirect economic impacts (e.g., Asia-Pacific economy lost nearly $40 billion); and second, even relatively quick-kill infections can spread rapidly due to modern travel and the global nature of business (i.e., approximately 250 cases of SARS in 10 countries spread within a few days from a professor, who had been treating SARS patients in the Chinese countryside and then traveled to a popular hotel in Hong Kong).

In response to these threats, it became imperative that a biodefense system of pandemic and bioterror medical countermeasures (collectively, MCMs) had to be developed. Many of the identified threats, even from pathogens known to be highly lethal and transmissible, did not have optimal or, even sometimes, any treatment options at all, beyond supportive care. At this time, however, the research and development of MCMs was typically viewed as "stagnant or non-existent" among major biopharma firms. As a consequence, what little R&D that took place was at small companies funded by venture capital with little institutional memory for managing a product from discovery through licensing to the marketplace. To this end, the US government (USG) passed a series of laws to stimulate countermeasure development that encompassed programs and funding for basic research, advanced development of technology, and acquisition of product for stockpiling in emergencies or prophylactic use by the military and first responders.

Roles of the Public and Private Sectors—The shape-shifting of the biodefense industry in the USA began in 2002, with the Bioterror Act, which called for development and monitoring of a stockpile of bioterror countermeasures. Several years later, BioShield I was passed in order to create a market for MCMs by setting up a special reserve fund for the purchase of medical countermeasures to be stored in the strategic national stockpile (SNS) and available for quick distribution in the event of an attack. This was soon followed by the Pandemic and All-Hazards Preparedness Act (also known as BioShield II), which brought both pandemic and bioterrorism legislation into one bill with the intent of generating incentives for entry into the business of biodefense. BioShield II established the Biomedical Advanced Research and Development Authority (BARDA) within the federal department of Health and Human Services (HHS). BARDA is the central authority in countermeasure development and administers the Biodefense Medical Countermeasure Development Fund,

which expands the options for procurement funding to include milestone payments, awarding exclusive supplier status, establishment of domestic manufacturing capacity, and dosing and administration studies.

Yet even by FY2010, the entire biodefense allocation comprised only 0.1–1% of the budgets for the main USG departments responsible for protecting the public—Health & Human Services (HHS)—which includes FDA, the Department of Homeland Security (DHS), and the Department of Defense (DoD). Biotech and pharmaceutical companies read the "tea leaves" of these relatively small numbers as indicating that the US Congress was not serious about investing in the development of medicines and vaccines against bioterror threats.

But the USG did want to encourage more interest from the private sector but was at odds how to do it. Consequently, it took only tentative baby steps in that direction. HHS proposed pilot studies to promote a more synergistic working relationship among government scientists at NIH, CDC, FDA, and BARDA. Predictably, the response from industry and investors was ho-hum. Guidance on cell-based vaccine production was finalized by FDA, but during drafting failed to elicit even a single industry comment despite being "advertised" in an HHS press release. With a few exceptions, there was almost no interest by private investment firms and funds in biodefense due to its perception as defense contracting with lower margins, smaller markets, and one-off product sales. The basic problem was laid out by Chuck Ludlam, former top staffer for BIO and Senator Joe Lieberman (I-Conn) at an Institute of Medicine (IOM) meeting in 2010[1]:

> …firms need "goal line" incentives such as "cash, tax benefits, patent benefits and liability protections."

Near the end of the 2000s, the private sector MCM pipeline was comprised by somewhat over a hundred, but less than two hundred companies, mostly start-ups and small/medium-sized enterprises (SMEs). As seen in Fig. 7.1, for Big Pharma companies with any MCMs in their pipelines, the total number of products in development approached 1000, but well short of 10% could be categorized as MCMs. Among start-ups and SMEs combined, there were approximately an equal number to Big Pharma of products in the R&D pipeline overall, but 42% and 25% respectively were MCMs. Although the majority of start-up and SME MCM pipelines were at Phase 1 or earlier, Big Pharma had a considerable number in later stage development (over 40%). Thus, although Big Pharma players in the MCM field were small in number, they were large on impact. However, even early in the evolution of the MCM sector, its fortunes as a whole appeared to be more likely to wax and wane in sync with the fortunes of the start-ups and SMEs based on their greater dependence on and resource commitment to MCMs. The paramount question that loomed in the background was whether MCMs would emerge as a new business sector under a traditional pharmaceutical business model or evolve into something similar to what was at the time still a shape-shifting biotech business model?

Business Models: Old Paradigm—Under the traditional market model, there were two basic strategies for MCMs: the "One drug, one bug," or so-called "fixed defenses" approach versus the development of multi-purpose countermeasures, so-called "flexible defenses," such as immunomodulators, better delivery systems, or prototype vaccines that can be easily tailored to emerging noxious agents. The flexible defense strategy is more functional given the unpredictable nature of the threat but also more economically attractive because flexible broad-spectrum products will have markets beyond government purchases.

The MCM product range consisted of: vaccines, therapeutics, diagnostics, immunomodulators, platform technologies (e.g., including some current or back-burner technologies such as new methods of drug delivery, specialized enzymes for decontamination, technologies for faster design and production of vaccines or antibodies against new strains or new microbes and

[1]As reported in the Pink Sheet (Informa subscription newsletter) on April 12, 2010 at 24.

	Big Pharma	SMEs	Start-Ups
Total number of products in pipeline	833	591	104
Percent of products that are MCMs	6.8%	25.2%	42.3%
Percent of products in phase 1 or earlier	56.1%	89.3%	100%

Fig. 7.1 MCM pipeline snapshot in 2008

products that create molecular barriers to infection at vulnerable sites like mucous membranes), as well as antidotes, chemoprotective agents, ancillary treatments, or prophylactic measures to mitigate, prevent or treat illness resulting from intentional bioterrorist attacks with CBRN agents or naturally occurring pandemic disease.

Traditional Business Models—"Biotech Business Models," an article by L. Paveras,[2] discusses the business models being utilized at the time for biotech R&D:

(1) FIPCO (fully integrated pharmaceutical company)—brings a product to market after early identification of lead or acquisition of promising compound;
(2) RIPCO (royalty income pharmaceutical company) identifies and takes lead compound through proof-of-concept, then sells off or partners with other firm, usually Big Pharma/Biotech;
(3) Technology Platform—develops new technology and creates specialty line of products or exploits it through licensing, partnering, etc.
(4) NRDO—"no research, development only"—firms that usually acquire or license-in leads that Big Pharma/Biotech is not interested in commercializing in-house;
(5) Product development partnerships (PDPs) or private–public partnerships (PPPs);
(6) Virtual R&D (e.g., Battelle)—U.S. Department of Defense (DoD) preferred providers who sub-contract out.

The major operational features of the traditional models were government push and pull incentives, mainly the USG (but also the EU Innovative Medicines Initiative—IMI) as well as risk-sharing opportunities through Cooperative Research & Development Agreements (CRADAs in the USA) and consortia. Much of the fundamental impetus from push incentives derive from increased funding for basic research to develop intellectual property (IP) that can be transferred to private sector companies. Other push incentives were cost-sparing measures such as liability protection under vaccine compensation laws as well as tax credits.

While government expedited development and review programs can get a product to market quicker (i.e., push incentive) and market protection awards can keep it on the market longer (i.e., pull incentive), for MCMs the most significant of the pull incentives was procurement contracts. Procurement contracts guarantee companies that countermeasures developed from promising candidates will be purchased by government agencies. Other incentives for companies to enter biodefense apply mostly to SMEs, as explained by AVI Biopharma President and COO Alan Timmins[3]:

> "While we're working with the government on some specific viruses that are very lethal, we're learning a lot about our own technology: how to apply it, where it works best, where it might not work so well," said Timmins. "So we get a lot of benefit at no cost to us. And we get enhanced credibility within the marketplace for drugs and

[2]See Paveras, L. "Biotech Business Models," http://www.healthonomics.org/2008/01/biotech-business-models.html.

[3]AVI Biopharma President and COO Alan Timmins as quoted in the trade magazine Bioexecutive International (April 2007 at 22–27).

> within the stock market because there's cachet in having the government as a partner."

In related fashion, government incentives are sufficient to stimulate interest from biotech companies, for whom an inflow of tens or hundreds of millions of dollars will have a significant impact. Nevertheless, Senator Lieberman explains in his testimony before a US Congressional Committee that there are other "benefits" to USG funding as well[4]:

> The only companies that are likely to accept a defense contractor model are companies with no approved products, no revenue from product sales, and no other source of capital to keep the lights on. For them government funding is "non-dilution" capital, meaning it's a form of capital that does not dilute the ownership shares of its current shareholders. Many biotech companies have stock trading in the low single digits, so they cannot issue another round of stock that would enrage the current shareholders. For them this government funding might validate the scientific platform of the company, generate some revenue, and hype the stock.

As a market, MCMs have many weaknesses. For example, antimicrobials have a shorter product life cycle due to the development of resistance. Vaccines are typically administered to healthy people and so have a higher risk-benefit threshold, and thus greater litigation exposure. Overall, MCMs are typically not treatments for chronic diseases, which offer a repeat sale market. In addition, generally speaking there is dependence on a single customer, often a government agency, and as with all large volume purchasers, margins are lower. Also, the government can be a difficult and sometimes unreliable business partner. For example, there was the well-publicized Cipro incident when the government was seen as extorting a low ball price, while another major problem is cancellations of request for proposals (RFPs).

In order to expand the government market and attract additional institutional purchasers, developers must optimize product characteristics such as: durable storage properties, convenient "kit" packaging with attached patient/prescriber information and supplies for administration, minimal need for boosters, as well as a manageable expiration and replacement cycle. Getting products approved and into the medical armamentarium does not mean that the challenges are over. In January 2003, the Bush Administration had a goal of immunizing 500,000 health workers for smallpox within 30 days and 10 million emergency response personnel within a year, but five years later only 40,000 were actually vaccinated due to problems with unexpected side effects, worker compensation issues, and liability concerns. Of the 95 patients who contracted measles during the 2008 outbreak in the USA and were eligible for vaccination, 63 were unvaccinated because of their parents' philosophical or religious beliefs.

Business Models: New Paradigm—In his 2006 text on the future of biotech, Harvard Business School professor and economist Gary Pisano describes various types of technological innovation (e.g., novel research methods and tools, novel targets or mechanisms and novel compound types/treatment modalities/markets), and the factors that companies with different types of innovation must consider when planning a business model.[5] Pisano explains that there are four factors that determine whether "a market for know-how" will succeed or fail: information asymmetry; specialized assets; tacit (not easily transferable) knowledge; and intellectual property (IP) protection. Continuing IP legal battles aside, when markets for know-how work, business models that involve out-licensing technology increase efficiency and can create handsome returns. When markets for know-how fail, business models with vertical integration may be the most effective strategy, if enough capital is available and attainable. Is there a market for know-how in MCMs?

The MCM sector is built on new technology platforms to identify novel pathogens in the

[4]As quoted by Gronvall, G. K. et al., Flexible Defenses Roundtable Meeting, http://igcc.ucsd.edu/pdf/1ALiebermanTestimonyOctober6.pdf.

[5]Pisano, G. P. Science Business: The Promise, the Reality, and the Future of Biotech; Harvard Business Press, Boston, MA, USA. November 2006; ISBN 13:978 1591398400.

laboratory and in the field, discover novel target pathways to neutralize or prevent illness as well as to improve existing ones, and apply this knowledge to the development and production of MCMs, i.e., a market for know-how. This is a new market for know-how different from the one in which Big Pharma is the acknowledged leader, like cardiovascular or GI disease markets, where numerous drugs have been developed and an infrastructure is in place. Most government grants for civilian biodefense awarded to the private sector have gone to biotechs. This has engendered something akin to a working relationship between government and the biotech sector, albeit more like a mutual dependency. However imperfect, it is a better relationship and thus more valuable than what had previously existed between Big Pharma and governments. In addition, most biotechs in the biodefense field have specific platform technologies and research expertise that extends farther upstream in the R&D continuum than the clinical focus of most Big Pharma. This results in both information asymmetry and a disparity of tacit knowledge between biotech firms and Big Pharma (a potential competitor and/or buyer) on the one hand, and between biotech and government (a potential buyer) on the other.

Some of the work in MCMs could also be considered specialized assets. These are assets that are not easily applied to alternative uses. Once invested in a specialized asset, it is very difficult to switch gears. The market for know-how generally does not highly value the prospects of being locked into an investment for specialized and limited applications. Indeed, while some companies with a biodefense core focus are developing very specialized technology, many are working with multi-purpose platforms applicable to various therapeutic areas and are able to spread risk through collaborations (now increasingly with Big Pharma and Big Biotech).

If there is a functioning market for know-how with the government as the buyer as well as Big Pharma, but the market is limited, at least as far as the biodefense MCM space is concerned, there is a role for integrated business models, such as FIPCO, that SMEs with a core MCM focus may utilize to reach their goals. The MCM market is complicated by the influence of the government intervention in the market dynamics by supporting a market for know-how to a limited extent as well as being a source of capital for SMEs that adopt a vertical integration approach, but again to a limited extent. Since the market for know-how is limited to a cadre of SMEs (and start-ups that evolve into emerging SMEs) with a core focus on MCMs (mostly vaccines and technology platforms), this leaves room for other business models and sector players to address the remaining market needs. For fixed defenses, such as MCMs for some CBRN and known pandemic threats (e.g., antibiotics, antivirals, and treatments for acute radiation sickness (ARS) and chemical poisons), it would be Big Pharma, employing a FIPCO or NRDO model, using incremental innovation within their existing portfolios. For diagnostics, specialty pharma or biotechs are the likely players using FIPCO, or RIPCO involving partnering or out-licensing to Big Pharma/Biotech. For flu vaccines, it would be Big Pharma/Biotech and specialty pharma/biotech, perhaps in partnership. In addition, there is a significant role to be played by the government in both fixed and flexible defenses. For fixed defenses, the government's role would be as purchaser, and a lesser role as provider of R&D funding, and a limited role as the player of last resort in product development and manufacture. For flexible defenses, the government would have to play all three roles in order to generate an effective capacity.

By the end of the 2000s, a US presidential commission of influential leaders and experts came to appreciate three crucial realities.[6] The first is that "… efforts to address biodefense and emerging infections are mutually supportive and that compartmentalizing these efforts is arbitrary and counterproductive." The second is an extension of the first, i.e., the recognition that the ends and thus the means must go beyond even pandemics and WMDs (i.e., weapons of mass

[6]As reported in National Health Security Strategy for the U.S., Objective 6, December 2009, at 13–14.

destruction). Among HHS recommendations for action were that investments should focus on new technologies or MCMs that could also have uses in non-public health emergency situations, and should address the continuum from research to delivery. Investments should be prioritized to effectively pursue those countermeasures that have the greatest potential to improve national health security, prevent or limit the spread of disease, limit the clinical impact of a health incident, and have elements with potential widespread application even in the absence of a catastrophic event. Third, somebody has to take charge.

Update and Commentary—Looking back in 2018, some of what these government and industry experts proposed actually happened and improved the overall funding environment for MCMs, if not the actual performance of the sector. President Obama implemented a strategy that combined efforts aimed at addressing both deliberate and accidental threats to US (and global) public health and BARDA more or less became the go-to agency for this initiative. While it is unclear what exactly was expected in terms of somebody taking charge, start-ups and SME biotech companies were recognized as the most promising candidates to foster development of new medical countermeasures, and the USG began to focus its funding and assistance on these companies. They face serious challenges related to manufacturing capacity and negotiating the regulatory labyrinth, according to Battelle's Senior Market Manager for Medical and CBRN Products Russell Coleman. Examples of initiatives in place to address these challenges include: Advanced Development and Manufacturing capabilities (ADMc), which provides both development and manufacturing resources to smaller biotech companies as needed; and the Medical CBRN Defense Consortium (MCDC), an organization that aims to help smaller companies who wish to work with the DoD navigate the process of becoming an approved federal contractor [5].

Meanwhile, even as Big Government's attitude toward SMEs began to change, Big Pharma was undergoing its own change of direction, becoming more willing to consider specialty markets and increasingly investing in historically unattractive markets like orphan drug development and vaccines, and subsequently in MCMs. Industry formed consortia with the public sector to address some of the R&D problems inherent in the field, exemplified by the work of the Alliance for Biosecurity (formed in 2005, consisting of approximately 15 member companies to foster private–public partnerships for MCM development) such as the development of appropriate animal models. In contrast to the field of countermeasures for emerging and little known pandemic threats, populated mostly by biotech start-ups and SMEs, the market for known pandemic countermeasures, i.e., for various forms of flu, has been so far supplied primarily by Big Biopharma. And business is good! The estimated global flu market for therapeutics and vaccines (20% and 80% of the market respectively) is estimated to be worth $10.2 Billion by 2022 [6].

7.3 Impact Factors for Sector Building in the Twenty-Teens [7]

7.3.1 Facilitated Regulatory Pathways (FRPs)

Broadly speaking, special designation programs such as those implemented by the USFDA—orphan, priority review, accelerated approval, fast track, breakthrough therapy designation (BTD)—have been to expedite and sustain development and facilitate authorization of new medicines for unmet medical needs through so-called push–pull incentives. Although generally successful over time, their success has been confined to certain therapeutic areas and, within those areas, certain diseases. Times have changed. The research and development (R&D) burdens and public health urgency that acted as an impetus for the FDA to intervene more actively for certain disease areas are now broadly experienced across many disease areas. This betokens the need for the FDA to make designation and implementation decisions with a view that reaches beyond

the immediate horizons of political expediency and patient advocacy to encompass the broader expanse of factors that now influence R&D decisions—public and private sector prioritization, new players in the paradigm, and patient-focused drug development.

Orphan Designation—Among the FRPs, the Orphan Drug Act was the first "push–pull" incentive (early 1980s in the USA, 1990s in Japan, and 2000s in the EU) and has been arguably the most successful. The push incentives lower the logistical and financial barriers for entry into the field of R&D for rare diseases (i.e., those with a prevalence of 200,000 patients or less, or unlikely to recoup R&D costs from market returns) and include waiver of user fees, technical and administrative assistance by the FDA's Office of Orphan Products, and clinical research grants. Pull incentives increase the likelihood that if the products reach the market, there will be sufficient return on investment. Pull incentives encompass tax credits for as much as 50% of clinical development costs and, most importantly, the so-called orphan exclusivity that prohibits the FDA from approving a marketing application for the same drug that treats the same condition or illness for 7 years from the date of approval of the first orphan application, even in the absence of a patent.

If the measure of success for FDA special designation programs was the orphan drug program, one would have to say that they have worked very well. Some form of the program has been adopted worldwide in the major geographic loci of medicines R&D, and elements of the push–pull approach have informed incentive programs for other unmet needs right up until the present time. The program broke new ground before the ground was even recognized on a number of fronts: patient-focused drug development, targeting subsets of diseases, and proving that there was a viable economic model in small markets—giving birth to the term of niche blockbusters (i.e., the number of orphan drugs in the top 200 for US sales increased fourfold over the 2000s).

Accelerated Approval was another early special program in the USA for expedited development. Accelerated approval regulations were promulgated on December 11, 1992. The law stipulates that drugs must be intended for patients with serious illnesses. Moreover, the data used for the accelerated approval must show an independently corroborated effect on an as yet unvalidated surrogate end point that is reasonably thought to be predictive of clinical benefit. Upon completion of Phase 4 trials that confirm a clinical benefit (i.e., that the "new" surrogate was indeed predictive of clinical benefit), a traditional full approval may be awarded. If the confirmatory trial does not show that the drug provides clinical benefit for patients, the FDA has regulatory procedures in place that could lead to removing the drug from the market. If a company seeks accelerated approval based on restricted distribution, then it must have clear distribution restriction practices and provider/user education programs for the drugs to gain approval.

Priority Review introduced the concept of a premium for novelty. In 1992, the FDA agreed to specific goals for improving drug review time by creating a two-tiered system of review times: standard and priority reviews. Standard review is applied to a drug that offers, at most, only minor improvement over existing marketed therapies. A priority review designation is given to drugs that offer major advances in treatment or provide a treatment for which no adequate therapy exists. Designation of a drug as "priority" alters neither the scientific/medical standard for approval nor the quality of evidence necessary but simply the amount of time (6 months) that FDA has to review (i.e., take first action: accept, reject, needs more work) the marketing application as opposed to 10 months for an application given a "standard" review.[7] The distinction between priority and standard review times is that additional FDA attention and resources will be directed to drugs that have the potential to provide significant advances in treatment, prevention, or diagnosis,

[7]In the mid-2000s a two-month filing review period was added to priority and standard review time goals.

including expansion of indications to a new subpopulation, such as children.[8]

Fast Track Designation—can be requested by the drug sponsor at any time during development. It allows sponsors to increase their scientific interaction with the FDA through more frequent meetings and written correspondence, as well as to submit completed sections of the new drug application to the FDA for "rolling review" rather than having to wait until the entire application is complete. In addition, as the FDA notes on its Web site, most drugs eligible for fast track designation are likely to be considered appropriate to receive a priority review. Therefore, the designation can act as a push incentive by expediting the development and review process, lowering the cost burden upfront for bringing a product to market. It can also act as a pull incentive by providing the product earlier access to the market, thus allowing more of the patent life to run while the product is actually on the market earning returns rather than during the development period when investment funds are being "burned" without replenishment from sales. Fast track was the most significant factor in a recent study of 20 variables affecting the likelihood of first-cycle approvals, with 78% of fast tracks achieving this milestone. Investment boost seems to be a significant result of being awarded a fast track designation—an analysis by a consulting firm showed an 18% increase in stock valuation on the first day after designation announcement. A study by the Tufts Center for the Study of Drug Development confirmed this effect by demonstrating a statistically significant percentage of change in stock price ($P = 0.03$) and upward difference in stock price ($P = 0.04$) after designation was publicized.

Breakthrough Therapy Designation (BTD)—The FDA Safety and Innovation Act of 2012 (FDASIA) was the congressional response to stakeholders' calls for an upgrade and update to FDA special designation programs. FDASIA changes focused on accelerated approval in particular and, to a lesser degree, on priority review and fast track, as well as adding a new program, the Breakthrough Therapy Designation (BTD). The FDA's response in turn was the 2014 publication of a draft guidance on expedited programs for serious conditions. In the guidance, the scopes of priority review and fast track were expanded to include qualified infectious disease products (QIDP) as directed under the Generating Antibiotic Incentives Now (GAIN) Act.[9]

The guidance also broadens the use of accelerated approval to "cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but clinically important improvement from a patient and public health perspective." At the same time, the guidance broadens the scope of the empirical evidence of clinical benefit from surrogate end points, or intermediate clinical end points (e.g., ones reasonably likely to predict an effect on irreversible morbidity and mortality), to include evidence that may be provided by such evolving technology as biomarkers and "other scientific methods or tools." Like fast track and accelerated approval, the first level of eligibility for the BTD is that the drug (or biological drug product) treats or intends to treat a serious condition. BTD distinguishes itself somewhat in the second eligibility criteria by requiring clinical evidence as the quantum of proof, as opposed to fast track, for instance, in which non-clinical data (or clinical data) may be used. Similarly, the third arm of eligibility for the BTD is that the drug demonstrates substantial superiority over available therapies on a clinically significant end point, whereas fast track requires only a demonstration of the potential to address unmet medical need and accelerated approval requires that it provides

[8]Subsequently, priority review was expanded into the Priority Review Voucher (PRV) program adopted to incentivize drug sponsors by awarding an obligation on the part of the USFDA to consider a drug for priority review if its sponsor had received a product approval for another disease indication listed as important to global health (in three categories: neglected tropical diseases, rare pediatric diseases, or medical countermeasures). How much of an incentive it is remains to be seen, especially for medical countermeasures? Although MCMs were added to PRV program in 2016 under the twenty-first century Cures Act, as of the end of FY 2018 only one PRV has been awarded to Siga Technologies.

[9]With dramatic results—74 QIDP designations awarded in the first 5 years of the program according to the General Accounting Office (GAO) of the US Congress.

both meaningful advantages over available therapies and evidence that reasonably predicts clinical benefits. The benefits of the BTD are more expansive than fast track and in fact subsume its features, as well as providing for "intensive guidance on efficient drug development … beginning as early as Phase 1," with specific recognition of advances in clinical trial design, such as adaptive clinical trials, as well as evolving technology, such as companion diagnostics. Most notably, the BTD offers the sponsor "organizational commitment involving senior managers," which has been likened to an "all hands on deck" call for collaborative, cross-disciplinary engagement by the FDA, not just at the division level but across all levels of management.

7.3.2 Prioritization and Access to FRPs

Cancer, AIDS, and orphan diseases were intentionally the focal point of the FDA's special programs in the 1980s and 1990s. However, as the public health emergency status of these diseases has been addressed to some degree in the 2000s, indeed AIDS and to some degree cancer have become "chronic diseases," others have surged to the forefront, including type 2 diabetes, depression, heart disease (especially in women), pandemic flu, and drug-resistant bacteria. For example, the threat level that AIDS represented in the 1980s and 1990s now confronts the USA in the 2000s in a different guise: flu pandemics, severe acute respiratory syndrome (SARS), and Clostridium difficile-associated diarrhea. For example, the cost to the US healthcare system of infections caused by antibiotic-resistant pathogens is $21 to $34 billion per year, with more than 8 million additional hospital days, whereas the medical costs of providing lifetime care for the 1.1 million people living with AIDS are $20 billion per year.

How have the therapeutic areas that represent these diseases—anti-infective, central nervous system (CNS), CV, and metabolic/endocrine—been served by the FDA's special designation programs in the 2000s? It is a very important question not only for the USA but for the world as well. Together with oncology, these four therapeutic areas comprise 75% of the pipeline in the USA from which 50% of global new active substances will flow, and they also encompass 13 of the 16 diseases and conditions identified by the World Health Organization as being global priorities for public health where there are pharmaceutical gaps. Yet, while oncology (and, to a lesser degree, HIV/AIDS) has been well served in the 2000s, with 38–71% of the FDA's special designations (depending on which of the programs is being considered), the other four major therapeutic areas noted above have not benefited to anywhere near the same degree, with only 24–47% of FDA's designations being awarded to them.

7.3.3 Emerging Sponsors and Paradigm Shift

An analysis of drugs discontinued during development from 2001 to 2011 showed that financial and strategic factors were responsible for 56% of the discontinuations and safety, efficacy, and quality considerations for the remainder. This highlights an important change in the 2000s. In earlier years, it would have been anathema for the USFDA to take into consideration the impact of its programs on the investment community. In the wake of the new economic reality of limited resources for drug R&D from both public and private sources, and the recognition that an increasing proportion of approved drugs are owned by venture-backed "emerging sponsors," that has all changed. An emerging sponsor is defined as the sponsor listed on the FDA approval letter who, at the time of approval, was not a holder of an approved application. Sponsors are still classified as "emerging" even if they have partnership or parent relationships with sponsors of a currently approved product. Of recent new molecular entity/new biological entity approvals approximately 40% belonged to emerging sponsors. We know that small companies are more likely to have multi-cycle

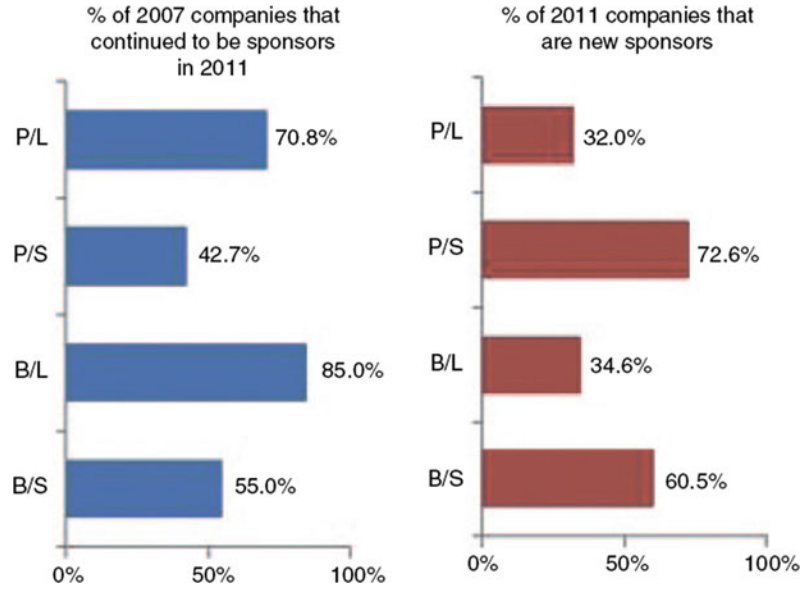


Fig. 7.2 Fate of orphan product companies from 2007 to 2011

review, and less likely to garner approvals, with a 50% approval rate as compared with 80% for medium/large companies, according to an FDA study. Thus, emerging sponsors need more FDA assistance, and they benefit from a more structured process to ensure that discussion of prospects for special designation occurs early in the development program. A lack of predictability makes it difficult for sponsors to manage their portfolio and for small companies, in particular, to raise additional funds to bring those trials forward.

It has been shown in studies by the Tufts Center for the Study of Drug Development and others that priority review is important to investors, and consequently fast track is important because it is a harbinger of likely priority review and FDA flexibility on risk–benefit at a time closer to the "valley of death" (i.e., the time period from late discovery into early clinical development during which the flow of funds often dries up). During the congressional testimony on the Advancing Breakthrough Therapies for Patients Act, it was specifically noted that the legislation was supported in particular by the National Venture Capital Association. As with predecessor incentives, the real benefit of the BTD may be perceptual. One small company commenter said that the BTD may provide the certainty that investors want, whereas an investment commenter stated that the incentive structure is changing, moving away from incrementalism, and that breakthrough therapies are consistent with what insurers are looking for. In some critical areas, even in the face of daunting "push" hurdles, "pull" rewards can often be a sufficient incentive to sustain investment support, as novel antibiotics may now be considered an attractive opportunity due to the GAIN Act. According to a recent newsletter for investors, the new drug research and development paradigm shifted rapidly from traditional Big Pharma to venture capital-backed small companies, with emerging sponsors becoming increasingly crucial to the future of innovation, particularly in challenging areas of R&D. Although smaller companies are often the seedbeds of new products and platforms for unmet medical needs, the example of orphan product R&D indicates that emerging sponsors come and go quickly, and much of their pipeline is at an early stage of development.

For example, Fig. 7.2 details how dramatic a change orphan drug sponsorship experienced from 2007 to 2011, losing ~150 companies that were in business at the time of the 2007 baseline accounting, but gaining ~200 new companies by 2011. The greatest change occurred among smaller companies as pharma/small (P/S) and biotech/small (B/S) have considerably lower percentages of companies that remained "in the game" from 2007 to 2011, and yet comprised the lion's share of companies new to orphan product R&D in 2011.

7.3.4 Patient-Focused Drug Development (PFDD)

Patient-focused drug development is an important new construct in the emerging paradigm for drug development. According to Theresa Mullin, the FDA's Center for Drug Evaluation and Research's Associate Director for Planning and Informatics, patient-focused drug development is a term used by the FDA in describing its efforts to ensure that the review process benefits from a systematic approach to obtaining patient perspectives on disease severity or unmet medical need. Expediting development for unmet medical needs will require a change in philosophy, one that can be undertaken only with the help of patient advocates themselves, in line with the new appreciation for patient-focused (also called patient-centered) drug development. The threshold for acceptable risk—the stumbling block for advancing HIV drugs decades ago—must again be re-evaluated and tailored to the willingness of patients to enable developers to make drugs (and of the FDA to review them) that have a narrower margin between risks and benefits. To this end, FDASIA allows: patients to participate in "appropriate agency meetings"; conflict-of-interest caps to be removed to make eligible a broader swath of stakeholders, such as patient advocates and consumer representatives; and pilot programs for patient participation to be put in place at the Center for Drug Evaluation and Research's divisions of oncology, gastroenterology, and antivirals; the Center for Devices and Radiological Health's offices dealing with in vitro diagnostics and cardiac devices; and selected units within the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research.

Update and Commentary—A recent Tufts CSDD/DIA (Drug Information Association) study examined patient-centric activities implemented by pharmaceutical, biotechnology, and contract research organizations, as well as activities being piloted or in the planning stages. A global industry survey was conducted across pharmaceutical, biotechnology, and contract research organizations, assessing 25 patient-centric activities within clinical research. Some of these initiatives involve the use of social media to engage with patients, or the use of social listening to monitor study activity. Twenty-two unique companies responded to the survey, representing a mix of large, mid-sized, and small organizations. The most widely adopted patient-centric initiatives, including activities both implemented and piloted across organizations, were patient advisory boards (17 companies), professional panels (16 companies), lay-language clinical trial results summaries (13 companies), assessment of the patient-organization landscape (10 companies), and the use of home nursing networks (9 companies). The results suggest that organizations have a varied approach to the adoption and implementation of patient-centric initiatives, with more activities occurring in the planning stages than are being piloted or implemented. Many factors affect implementation and adoption, including buy-in by senior management, organizational vision, resources, and level of investment [8].

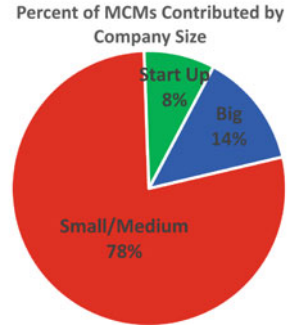
7.4 What Happened to the MCM Sector from 2008 to 2016? [9]

Beginning in 2008, the Tufts CSDD has routinely explored the R&D landscape of Medical Countermeasures, which encompasses biologics, drugs, devices that may be used for biodefense against biological, chemical, and radiological bioweapons, or in the event of naturally

(a)

	Big	Small/ Medium	Start Up
Total # of Products in Pipeline	2310	1682	175
% MCMs	3.3%	26.5%	28%
% MCMs at Early Stage (Phase 1 or Earlier)	64.9%	84.5%	100%

(b)



(c)

Indication	# Products	% MCM Pipeline
Influenza virus infection (Universal vaccines or Pandemic threats)	125	21%
Ebola virus infection	76	13%
Dengue virus infection	50	8%
Zika virus infection	41	7%
Rabies virus infection	40	7%
Total	**332**	**56%**

Fig. 7.3 MCM company, pipeline, and top 5 indications in 2016

occurring emerging and re-emerging diseases, or natural disasters. CSDD's most recent review (see Fig. 7.3) reveals that while some aspects of the field remain unchanged, there have been some significant changes as well. Broadly speaking, companies in the MCM field are typically privately owned, small to medium-sized enterprises (SMEs), with a biotechnology focus. While more than half of these companies are headquartered in the USA, there are now more non-US companies than in the past (48%). China with 33 companies, the UK with 12, and Canada and Switzerland, both with 10 companies, together with the USA's 144 companies, round out the top five countries.

The most significant change in the landscape is the size of the MCM pipeline. In 2008, there were roughly 263 countermeasures in development. By 2016, that number had reached 592. Similarly, in 2008 there were around 133 companies working on MCMs. In 2016, there were 303. Continued, steady pipeline growth seems to indicate a positive impact from programs intended to encourage and support the development of MCMs, such as Project BioShield. It was established in 2004, with an initial budget of $5.6 billion through FY2013, and since 2006 has been managed by the Biomedical Advanced Research & Development Authority (BARDA), the overarching MCM authority within the U.S. Department of Health & Human Services. BARDA and Project BioShield budgets have grown steadily, with budget increases in 2016 totaling more than $400 mil USD over their 2015 budgets, signaling to biopharma companies that MCM development is of continuing interest to the US government (USG). Much of the USG's support for SMEs comes in the form of Broad Agency Announcements (BAA) and Funding Opportunity Announcements (FOA), which allow smaller companies to compete for grants, awards, and contracts by conducting specified research projects.

This support for SMEs is vital as they are developing 78% of all MCM products currently in the pipeline. Looking at the numbers a little differently is also telling. Out of the 2310 total products in development by Big Pharma (i.e., top 25 biopharma companies), only 3.3% of them are MCMs. SMEs and start-ups, in contrast, have a much greater focus on the MCM arm of their portfolios at 26.5% and 28%, respectively.

Another aspect of the Medical Countermeasure landscape worth examining is the relative role played by Big Pharma, SMEs, and start-ups in moving products from early development to later stages. Of the 592 products in development, 488 (82%) are in early stages (Phase 1 or earlier), but among Big Pharma only 65% of MCMs are in early development, while among SMEs that figure rises to almost 85%, and among start-ups the figure is 100% (almost by definition as start-ups are typically described as relatively new, small, privately-funded companies with no products on the market). Hence, Big Pharma is important for getting products through later stage development on the way to market, but the

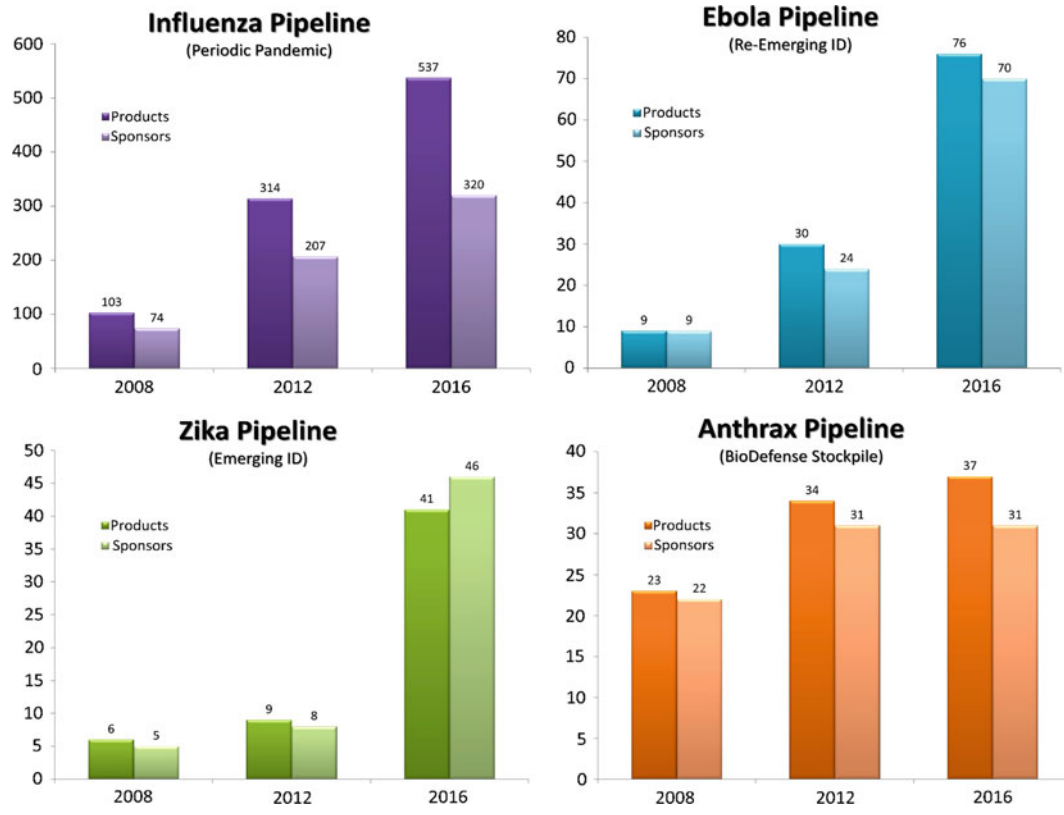


Fig. 7.4 Pipeline landscape snapshots for MCM category exemplars

seedbed for discovery to early development translation resides in SMEs and start-ups.

The five most prevalent indications in the MCMs pipeline provide some insight into a strong driving factor behind how a company decides the indications for which they will develop countermeasures. All five of the most common countermeasures have applications other than biodefense. Influenza MCMs are by far the most prevalent; there are 125 universal vaccines or vaccines for potential pandemic threats in production. These countermeasures alone make up 21% of the MCM pipeline. A broader look at all influenza products in development shows rapid growth from 103 products in 2008, to 314 in 2012, to 537 in 2016. Frequent influenza outbreaks make this rapid and sustained growth within the pipeline unsurprising. Periodic pandemics of various strains such as avian flu, swine flu, and H1N1 and their associated economic impacts have spurred interest in universal vaccines that protect against multiple strains of flu and avoid the need to respond to the current flu du jour by rushing to create a new vaccine.

Similar, though less dramatic, trends can be seen among other top countermeasures which have also seen recent outbreaks (see Fig. 7.4). Ebola countermeasures increased from 9 in 2008, to 30 in 2012, to 76 in 2016. Zika countermeasures increased from 6 in 2008, to 9 in 2012, to 41 in 2016. In 2014, Ebola had the largest outbreak in its 40-year history, and similarly in 2015/16, there was the first large outbreak of Zika. These events demonstrated the urgent and unmet medical needs for treatment and prevention presented by emerging and re-emerging infectious diseases (ID) that are naturally occurring, sporadic, and non-biodefense, yet potentially profitable as future outbreaks of these or

similar diseases are very likely. On the other hand, biodefense-only countermeasures tend to be purchased in bulk by governments and placed in readiness in something like the USG's Strategic National Stockpile. Ideally, such MCMs are rarely or never used, eventually reaching a target plateau in terms of "market" growth determined by the requirement to replace expired stock or expansion in the populations at-risk. Bacillus anthracis infection (Anthrax) illustrates this point very well. In 2008, there were 23 countermeasures being developed. In 2012, there were 34, and by 2016 that number had essentially plateaued at 37.

Considering the fact that the top five indications on the list (influenza, Ebola, dengue fever, Zika, and rabies) comprise over half of all of the MCMs in development, it is clear that industry efforts are concentrated on a relatively narrow stream of the potential threat bandwidth. These five indications have a total of 332 products currently in development and average 66 countermeasures per indication. The remaining 57 indications, however, on the U.S. National Institute of Allergy and Infectious Diseases (NIAID) list of Emerging Infectious Diseases and Pathogens have a total of only 289 products currently in the pipeline, averaging 4.5 MCMs per indication (ranging from 0 to 37 per indication). Some very deadly diseases are in this group. Marburg virus, a virus related to Ebola, currently has only 12 countermeasures in development, 9 of which are still in discovery. Eastern Equine Encephalitis, which sees small but recurring outbreaks in the USA, and whose mortality rate of up to 75% makes it the deadliest mosquito-borne disease in North America, has only four MCMs in development.

Taken as a whole, it appears that while the budgets and prioritization schemes of government departments such as NIAID and BARDA affect the overall size of the Medical Countermeasure pipeline, it is current and recent world events—particularly in the form of emerging and re-emerging ID and pandemic outbreaks—that determine which countermeasures experience pulses in pipeline growth.

7.5 Key Factors for the Future: Proving and Paying for Value [10]

After surviving the "valley of death," the precarious period that exists between late discovery and early clinical trials, the next critical juncture for an innovative product is getting buy-in from USFDA to award it special status in one of its facilitated regulatory programs (FRPs), which expedite development and regulatory review. At that point, however, the imprimatur of the USFDA only goes so far to predict future success after launch. The path to commercial success can certainly be delayed by obstacles during the technical process of getting a product through the hurdles of proving safety, effectiveness, and product quality, but the last hurdle is always proving value—to physicians, patients, and especially third-party payers, both private and public. A study by Tufts CSDD in the early 2000s showed that technical success and commercial success do not always go hand-in-hand. That seminal study reported that of 15 major companies, there was a wide range of correlations between technical and commercial success. That gap has only become more challenging over time. Even though the time of development has remained somewhat static over the last decade, the cost of development has doubled, and overall success rates have declined. Thus, the ramifications of a market failure are much more daunting than in the previous decade, when only 3 out of 10 marketed products earned enough to pay their own freight (and generally the sunk costs of the other products on the market as well).

While the number of "Big Pharma" companies decreased by half in the 2000s, emerging sponsors are now responsible for close to half of novel approvals in the USA as well as ownership of 80% of the R&D pipeline. For these small, start-up companies, reaching the market only to be thwarted by difficult reimbursement conditions or outright rejection for formulary inclusion can be disastrous for the company as a whole. Yet, these very companies are often where the seedbeds of innovation are most fertile, as mid-sized companies often have limited their

portfolios to a few therapeutic areas and some larger companies over time have been abandoning certain therapeutic areas (such as CNS disease) after experiencing a lack of success or portfolio realignment due to merger and acquisition or new leadership.

On the commercial side what has to happen to balance the prospects of success for novel products generated by innovative platforms? Two concepts must become mainstream precepts—patient access schemes, more commonly referred to in the literature as risk-sharing agreements (RSAs), and real-world evidence (RWE). These concepts are intertwined and must be integrated to provide a solution for moving therapeutic options forward at the speed of science.

Risk-sharing entails agreements in which the buyer and seller believe that a product is sufficiently promising that it warrants the taking of certain risks by all parties because of the likelihood of potential benefits, i.e., value to the patient and thus to the healthcare system responsible for care and coverage, even if that benefit may be as barebones as "it's better than nothing." The first fundamental factor involved in risk-sharing is that all parties actually share the risk. This is where payers have often been found wanting, either by requesting too much proof too early (i.e., pre-approval) or by an unwillingness to accept any risk at all for an untried product without regard to regulatory approval or patient need. As counterproductive as this seems, there are many examples of this being the case with urgent medical needs in orphan drugs, personalized medicines, and most recently, abuse-deterrent formulations (ADFs) for opioids. In a 2014 study by Tufts CSDD of orphan drugs approved from 1983 to 2013, 9 out of 10 drugs had at least one condition restricting reimbursement, whereas for the 11 most expensive orphan drugs, patient cost-sharing ranged from 20 to 35% for drugs costing on average $400,000 annually. For an early cohort of ten personalized medicines in 2013, Tufts CSDD found that payers reimbursed all drugs with variable and relatively high payer co-insurance and formulary restrictions, but reimbursement for the companion diagnostics was limited and highly variable. By 2015, product developers still considered reimbursement to be a 4 out of 5 on an index of the most challenging factors facing personalized medicine. The problem is not confined just to private insurers. For example, the opioid abuse epidemic in the USA sounded the clarion call for ADF products. There has been a laudable response by manufacturers with 25-30 new applications pending review, 10 approved, and 4 launched by mid-2017, despite the fact that two years earlier 96% of prescribed opioids were not ADF products. Nonetheless, coverage by the US government under the Medicare program ranges from only 8 to 54% for these four critically needed products.[10]

Payers would say, in their defense, that they must see proof of clinical utility, i.e., that the drug, drug–diagnostic combination, or formulation demonstrate statistically robust evidence of positive outcomes for the patients for a sufficiently high proportion of patients. The problem is a Catch-22 (i.e., a difficult circumstance from which there is no escape because of mutually conflicting conditions). You cannot provide the quantum of evidence necessary for comparative effectiveness that payers demand until there are a sufficient number of patients who have experienced a therapeutic trial of the product in real-world settings. For this to happen, payers must assume certain risks a priori. It is a hard lesson. One that FDA has struggled to learn, but has finally become reconciled to it as a necessary regulatory paradox—accepting a certain amount of uncertainty in order to advance promising new technologies. Now payers have to "walk a mile" in the shoes of patients, care-givers, and regulators and take this same "leap of faith."

Arguably, faith is not a strong point among public or private payers, and probably we don't

[10]Opioid mismanagement is a worldwide problem—although 80% of the global supply of opioids is currently consumed in the USA, it is a growing threat to global public health. In the EU, prescription opioids cause three-quarters of overdose deaths of teens and young adults, aged 15–39 years old. Often unheralded among the problems related to opioids is that half of all deaths that occur across the globe each year happen among people without access to pain medications.

want it to be. We do want them to be able to make decisions on the best available evidence at the earliest point in time to meet an unmet need as soon as possible. This is where real-world evidence (RWE) comes into play. RWE is defined as data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized controlled clinical trials, such as observational studies, registries, insurance claims databases, electronic medical records, wearable devices as well as patient-centered outcomes studies. The regulators are beginning to accept that RWE can be a telling source of evidence to assess the value over time in the life cycle of a marketed drug, and perhaps even answer questions that hadn't been asked yet, but should have been. However, there is some reticence to substitute RWE for randomized controlled trials (RCTs) as the gold standard for providing the necessary quantum of proof for initial approval, although it is gaining credence as a supplement to pivotal RCTs in this regard. In fact, FDA's premier regulatory science experiment—the Oncology Center of Excellence—now just a year old, works to incorporate RWE among just a handful of key advances in regulatory decision-making along with revamping trial design to eliminate the arbitrary phases 1, 2, 3 structure, employing master protocols, re-defining trial eligibility criteria in conjunction with patient advocacy organizations to ensure representativeness, and reaching out to professional colleagues outside the agency as well as external stakeholders to generate better patient-reported outcomes metrics and instruments. Payers, for their part, have to shake off the shackles that bind them to a decision process that requires upfront proof of clinical superiority or rejection as the only two options for whether or not to reimburse a new drug (or a sliding scale of incremental cost-effectiveness that purports to implement a public health rationale of "greatest good for the greatest number of people" but is really thinly disguised rationing). Real-world evidence in its simplest terms is evidence from the patient, by the patient, for the patient. If the system is serious about becoming more patent-centric—as it should be since regulators serve the people, and patients are the end-customer for manufacturers and payers—then the experience of the broadest swath of patients in the widest range of practice settings should inform payer decisions. Who will pay and how is a different question, and depends on individual, familial, community, and nation-state support as well as cultural norms, but the first threshold is to establish whether a product has sufficient value to bring this next set of considerations into play.

Through a panoply of government, private, and individual payer systems, the ingredients exist to craft fair pricing and coverage solutions worldwide as much or even more rapidly than in the USA. Many nation-states in developed regions have nascent infrastructure or even burgeoning programs to provide for a system of real-world data collection that could provide an adequate source of RWE. At the same time, RSA models are not confined to any one global region but are ongoing initiatives in many countries (including in China and South Korea according to a recent ISPOR workshop summary). With the judicious implementation of RSAs and RWE, access to novel medicines and a conducive environment for innovative technology can be a reality on the short-term horizon not just for a few countries but many emerging markets, and from there the rest of the world.

7.6 Global NAS Launches 2013–2017: Trends and Implications [11]

The term new active substances (NASs) originated with the European Medicines Agency (EMA) and is defined as a new product that contains an active substance that was not previously authorized, is not related to any other previously authorized substances, and differs significantly in safety and/or efficacy. NAS launches serve as a surrogate measure for evaluating innovation trends in chemical and biological discovery and development in addition to patent and clinical trial data and generally in place of other forms of sourcing data such as the

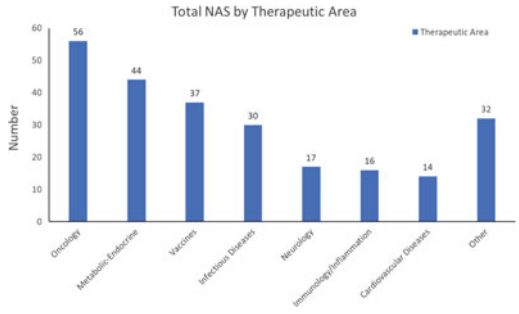


Fig. 7.5 Global NAS launches by therapeutic area 2013–2017

country in which the sponsor company is headquartered because globalization of the industry and the marketplace have rendered such data unreliable for such evaluations. NAS launch data is a reliable indicator of the sponsor's target country and indication because nearly half of all new drugs are launched in ten or fewer countries, often with long lags from first launch to subsequent launches.[11]

NAS output during 2013–2017 was quite variable, ranging from 40 to 60, and averaging 49, a yet substantial increase over the average for the twenty-oughts at 32 and even the teens overall at 46. The current cornucopia of NAS reflects the favorable economic environment as well as the expansive number of companies and compounds in the field, over 4000 companies and over 15,000 drugs in the pipeline. The US share of first launches worldwide remains dominant at 60–65% during 2013-2017, having increased steadily from a low point of 45% in 2010 according to FDA. Nonetheless, Asia is a fast comer. As shown in Fig. 7.5, the NAS output of Japan alone (30) is equal to the entire output of the EU (33). And when the output of Japan is added to that of the rest of the Asia-Pacific region, it is nearly half that of the USA (65 vs. 74/148, respectively).

Oncology currently makes up 34% of the global industry pipeline and 23% of NAS from 2013 to 2017. Although the metabolic–endocrine category appears in this Figure to be the second most common therapeutic area for NASs, it is really a composite category comprised of drugs for endocrine diseases such as type 2 diabetes and a broad array of metabolic drugs for congenital enzyme deficiencies (i.e., orphan drugs for rare conditions). Infectious disease represented by both columns 3 and 4 in Fig. 7.5 is the second most common therapeutic area among NAS—a positive trend. However, the fact that neurological disease (including Parkinson's and Alzheimer's diseases) and cardiovascular diseases trail oncology by a considerable margin is a negative trend and brings into question the prioritization agenda of both the private and public sectors. During 2013–2017, oncology, diabetes, and orphan drugs comprised from 37 to 54% of the NAS launched worldwide, indicating that nearly half (46%) of all new drug approvals worldwide addressed a limited set of the most significant threats to global public health. For example, according to the WHO Global Burden of Disease study published in 2012, they recorded the following Global Death Ranks respectively in 1990 and 2010:

Ischemic heart disease	1st	1st
Stroke	2nd	2nd
Respiratory disease	3rd	4th
Top four cancers	8–24th	5–19th

The USA produces the majority of NAS overall at around 60%, but the vast majority of oncology drugs at 82% and infectious disease

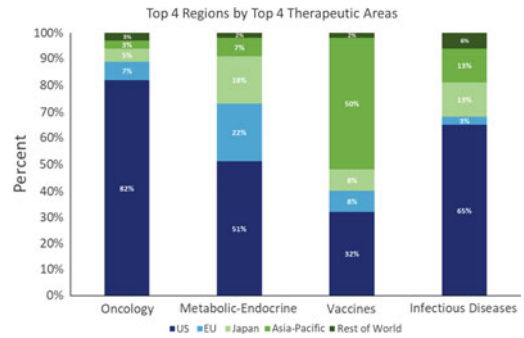


Fig. 7.6 Global NAS launches by region and ta 2013–2017

[11]Cockburn, I. et al. Patents and the Global Diffusion of New Drugs. American Economic Review 2016, available at http://eprints.lse.ac.uk/65415/.

treatments at 65% (see Fig. 7.6). The metabolic–endocrine field is more evenly divided among the USA (at just over 50%), Europe and Japan (at about 20% each), with Japan emphasizing endocrine drugs for diabetes type 2 and the EU focusing on enzyme replacement treatments for orphan conditions.

Significantly, the Asia-Pacific region, in particular China and India, are the major sources of vaccines for the worldwide market at 50%. In sum, the report highlights that while the USA remains dominant as the source of NAS and oncology remains the dominant therapeutic area, change is coming. We see evidence of such changes, the challenge of infectious disease to the hegemony of the oncology therapeutic area, as well as the new role of Asia-Pacific emerging market powers in R&D and the upsurge of the metabolic–endocrine therapeutic area worldwide due to new treatments for diabetes and rare diseases.

7.7 What the MCM Experience Portends for Drug Development in 2020 and Beyond

Taking an overarching perspective at what happened in the years encompassed by our review of the MCM experience reveals how the industry evolved and de-evolved in response to a web of economic, political, and public health events. Economically, specialty markets such as targeted cancer drugs and orphan drugs are outcompeting generalist disease markets like CVD, respiratory, and GI because investment dollars respond to the new shibboleth of "personalized medicine," and innovative approaches for serious disease are better-received by private payers and meeting unmet medical needs by public payers. Diabetes is beating the trend inveighing against the generalist market because it is widespread, well-covered, and cost-effective. Infectious disease therapeutics are currently beating the headwinds of the past because of the push from low comparative R&D costs along with high success rates due to recent regulatory incentives. Meanwhile, emerging markets' countries in the Asia-Pacific region are picking up the slack in vaccines by building on their capital investment in manufacturing equipment and facilities and institutional expertise in generics production.

Politically, industry and the public health community realized by this time the power that patient advocacy through groups such as the American Cancer Society and NORD (National Organization for Rare Diseases) wielded and the impact they had had in a few short decades to focus not only government but industry priorities. This generated a public health lobby from a consortium of 50 or so mostly public health and employer groups that successfully stumped for the GAIN Act with dramatic results. So, what changed over time from the twenty-oughts to the twenty-teens was a very real series of pandemic threats from Swine flu and Bird flu in 2009, H1N1, Ebola, antimicrobial resistance, etc., and a diminishing of bioterror concerns, which became subsumed into a background impetus for MCM prioritization. Coincident with this and in part because of it, MCMs devolved from an emerging stand-alone biodefense sub-sector to merge instead into the more generalized expansion of infectious diseases R&D for therapeutics, diagnostics, and preventatives.

In terms of public health, there is a growing realization that HIV/AIDS and many forms of cancer are now "chronic diseases" and not the death knell that once sounded such alarm among both the public and private sectors. While cancer is still a major priority, heightened attention to visible threats to the public health such as diabetes among an increasingly "older" population and the vulnerability of the general population to pandemics in the "global village" have begun to swing the pendulum back toward a focus on the unmet needs of the broader population. The challenge is that the "quick fix" of regulatory incentives is only a partial fix as it affects only the middle third of a typical drug's several-decade life cycle. It is certainly useful to shorten development and approval time on average from approximately 10 years to 7 years for prioritized products, but those 7 years are preceded by 7–10 years in discovery and

followed by 7–10 years of marketing. FRPs are better than nothing, but oncology has a competitive advantage in corporate decision-making for resource allotment because it benefits from decades of previous basic research that have created an expansive and expanding knowledge base on which to build future directions and reassess current ones. Diabetes on the other hand derives its favorable competitive position versus other therapeutic areas in the post-launch period because of the familiarity among providers and prescribers with the basics of the disease and a rising prevalence (fast approaching the certainty of death and taxes), as well as the pharma industry ROI "comfort level" of addressing a long-term chronic disease affected by both metabolic and behavioral factors.

What has to change to enhance our prospects for a future not driven by commerce and caprice, but foresight and forbearance? We have been faced with rumblings for a long time that something is going to "rock our world." These premonitory tremors have been cataclysmic events whose impact was limited or long ago, but now loom again as the primary threat to the future of civilization, if not, humankind's continued dominance of its environment. There are, however, some who believe that we cannot continue to depend on the defenses of time, distance…and luck forever, or even for the foreseeable future. Just consider how long mankind has been dealing with the nemesis of pain—the primary antagonist of quality of life with only variable success. And even now that success is threatened anew by the epidemic of opioid addiction, now being recognized as a double-edged Sword of Damocles—a threat to the teens and young adults of the developed world due to addiction and overdosing while fast-becoming a threat to the developing world as control measures and liability concerns exacerbate an already dire lack of access to pain medications.

Concern and concerted effort for our health and prosperity is considered to be the responsibility of our government as well as each individual. Yet, our responses to threats that are novel or widespread so far have been too little, too late. We can no longer afford such nonchalance. We must recognize that we are faced with a growing panoply of threats to public health—some at least of an unknown nature, size, and imminence. We know there are significant unmet medical needs, but we don't know exactly where they are and when they will reach critical mass…or the "point of no return." We do know, however, that if we don't begin to hammer together a network of fixed and flexible countermeasures, our only defenses will be draconian public health programs such as triage and quarantine for infectious disease (or rationing of pain medications in a mostly symbolic attempt to control addiction).

We have another choice. We can work on products to identify, treat, and prevent the harmful agents that we know, as well as accelerate and expand our capacity to identify and combat the ones we don't know. It will, however, require much more commitment, coordination, funding, and accountability than we have shown so far. This sounds easy in concept, but the reality is hard. There is the vexing problem of the tension between the long-term need for MCMs and the short-term horizon of our political systems. The likelihood of an event happening within any one person's working (or voting) lifetime is low, but the likelihood that the consequences of such an event would be extremely unpleasant is high. It is a basic paradox inherent in public health preparedness. If you are really good at it…nothing bad happens! But then complacency and second-guessing seep in and weaken the resolve and resource commitment. The way out of this conundrum is to put people in charge who have a clear vision of what needs to be done and provide them the independent authority, resources, and infrastructure to do it right the first time. We do not know when the time may come that we will not have a second chance to avoid cataclysmic casualties from a contagious super-spreader like pandemic flu or to play catch-up in a race with an insidious dealer of death like opioid mismanagement that should never have been a contest at all! The ancient Greeks framed the challenge eloquently and ineluctably: "A society grows wise only when old men plant trees under whose shade they will never sit!"

References

1. Whalen J. Hurdles multiply for latest drugs. Wall Street J 1 August 2011.
2. Deloitte Consulting, 2018 report, "Unlocking R&D Productivity: Measuring the return from pharmaceutical innovation 2018," available at www2.deloitte.com. Last accessed 6 Jan 2019.
3. U.S. Centers for Medicare & Medicaid (CMS) report, National Health Expenditures 2017 (Highlights), available at www.cms.gov. Last accessed 6 Jan 2019.
4. Milne, C.-P. Is there a business in medical countermeasures for bioterror and pandemics? (White Paper, 2010). *Tufts Center for the Study of Drug Development (Tufts CSDD)*; Boston, MA, USA.
5. Alex Murtha, Homeland Prep News, Friday, September 1, 2017. http://webcache.googleusercontent.com/search?q=cache:YtWOf3fpbkgJ, https://homelandprepnews.com/stories/24000-battelles-coleman-small-companies-key-new-cbrn-medical-countermeasures/&hl=en&gl=us&strip=1&vwsrc=0. Last accessed 26 Nov 2018.
6. Industry Experts Fall 2018, Global Influenza Market—Vaccines and Therapeutics (Report Code PH015) at industry-experts.com. Last accessed January 6, 2019.
7. Milne C-P Clinical Pharmacology & Therapeutics 2013;95(1):98–109 advance online publication 30 October 2013. https://doi.org/10.1038/clpt.2013.155.
8. Lamberti MJ, Awatin J. Mapping the landscape of patient-centric activities within clinical research. Clin Ther 39(11):2196–2202. https://doi.org/10.1016/j.clinthera.2017.09.010. Epub 2017 Oct 9. https://www.ncbi.nlm.nih.gov/pubmed/29032849. Last accessed 26 Nov 2018.
9. Milne C-P, Smith ZP, Chakravarthy R. Landscape for medical countermeasure development. Nat Rev Drug Devel 2017; 16:448–449.
10. Milne C-P. Reaching a New Innovation Threshold. *Pharma Focus Asia (editorial), Ochre Media Pvt. Ltd.*, Issue 30, 2018. Available at https://www.pharmafocusasia.com/archives-magazine/81. Last accessed 26 Nov 2018.
11. Kaitin KI, ed. U.S. continues to lead new drug R&D, but Asia-Pacific is starting to rise. *Tufts CSDD Impact Report* (January/February 2019), vol. 21, number 1. Tufts University School of Medicine, Center for the Study of Drug Development, Boston, MA, USA, 2019.

8 In the Face of Global Health Challenges—Let's Redefine Innovation

Subhanu Saxena and Ian B. Wilcox

Expanding the Scope of Innovation

Exactly 100 years ago, the 1918 influenza pandemic grabbed headlines as the deadly effects of the outbreak devastated the world for a full year. The CDC reports that "an estimated one-third of the world's population (or ≈500 million persons) were infected and had clinically apparent illnesses during the 1918–1919 influenza pandemic. Total deaths were estimated at ≈50 million" or about 1 out of every 40 people in the world population [16].

Just 20 years later, with the invention of the first influenza vaccine, the fears of another pandemic began to wane, and they have continued to do so over the last 60 years as pharmaceutical innovations have made the seasonal vaccine safer, more effective, more affordable, and more available. A similar story can be told of other illnesses that once grabbed headlines for their capacity to kill with impunity.

Pharma is deservedly celebrated for innovation. In rare diseases, for example, the advances are astonishing. In 2016 alone, the Food and Drug Administration received a record 582 requests for orphan drug designation—110 more than the previous year's record-setting request. The agency designated 333 drugs in development as orphans in 2016, approving 39 products—both novel medications and new orphan uses of already-approved treatments. Both numbers were dramatically higher than just a decade ago. Nearly 40% of the new molecular entities approved over the past five years have initially been for orphan indications [15]. In oncology, to take one high-profile therapeutic area, advances like immunotherapy are giving new hopes to patients.

This scientific vanguard grabs attention for its sheer novelty, the cures it delivers and, rightly, the potential returns it offers investors.

To take a few examples, immunization has led to the obliteration of smallpox, a 74% reduction in childhood deaths from measles over the past decade, and the near-eradication of polio. As funding for treating malaria has increased tenfold over the past 12 years, the number of new cases has declined by 25% globally, and deaths are down by 42% [2].

HIV is another example. It is a global pandemic, with nearly 37 million affected people around the world—25 million of them in

S. Saxena (✉)
Melinda and Bill Gates Foundation, 500 Fifth Avenue North, Seattle, WA 98109, USA
e-mail: Subhanu.saxena@gatesfoundation.org

S. Saxena
New Rhein Healthcare Investors, LLC, Two Logan Square, 110 N. 18th St., Suite 1930, Philadelphia, PA 19103, USA

I. B. Wilcox
Adjunct Faculty, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032, USA
e-mail: Ian.wilcox@cogitariadvisors.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_8

Sub-Saharan Africa [3]. But with the help of existing therapies, it has become a manageable disease.

We are proud to say that Subhanu's former company, Cipla, played a role in this achievement. In 2001, Cipla introduced the world's first recommended 3-in-1 fixed-dose combination (Stavudine + Lamivudine + Nevirapine) to fight AIDS. It was made available at less than $1 per day. The result? The global incidence of HIV has declined by nearly 40% since 2001, and 17 million people worldwide are receiving antiretroviral treatment.

We have also seen reductions in vaccine-preventable diseases, infectious diseases, and infant mortality [10]. Innovation, when paired with dire global health needs, yields immense social good. Clearly, when we invest in confronting even the most fundamental global health challenges, the entire world benefits.

What the Headlines Aren't Telling Us

At a time, when the pharmaceutical industry consistently delivers headline-grabbing medical advances that cure rare diseases and bring previously unimaginable treatments to many in need, millions of people around the world continue to suffer and die from "old" illnesses because they have no access to these innovations. For example:

- One in five children worldwide is not fully protected by even the most basic vaccines. As a result, about 1.5 million children die each year—one every 20 s—from vaccine-preventable illnesses such as diarrhea and pneumonia [4].
- An estimated 207 million people suffered from malaria in 2012, and about 627,000 died. About 90% of the deaths were in Sub-Saharan Africa, and 77% were among children under age 5 [2].
- Influenza, considered a seasonal annoyance in the developed world, continues to kill as many as 646,000 people per year. The greatest rates of flu deaths are seen in sub-Saharan African countries, along with Eastern Mediterranean and Southeast Asian countries. Despite World Health Organization recommendations to use flu vaccination to help protect people in high-risk populations, few developing countries have seasonal flu vaccination programs or the capacity to produce and distribute seasonal or pandemic vaccines [6].

Our Vision for Innovation and Global Health

In the face of such realities, we can no longer overlook fundamental health needs in our global community as we (and our boards and shareholders) pursue the latest in medical innovation. In fact, the human and economic burden of disease in the developing world is now a two-tailed adversary—infectious diseases *and* non-communicable diseases: heart disease, stroke, and COPD are among the top ten causes of death in the developing world, along with preventable communicable infections [5].To address these burdens, we need to transform the industry from a center for developing innovative products into an engine of global well-being.

As Steven Morgan et al. have argued, "To describe a product as innovative implies that it has properties that are worthy of recognition and reward. The term suggests that the product has a unique value. However, notions of value are a matter of perspective… *Pharmaceutical products have no intrinsic value to patients or to society; rather, their value lies in the health outcomes they generate*" ([11], emphasis ours). Put simply, without universal patient access to these innovative products, they have no value because their ability to generate positive health outcomes is restricted.

For this reason, to truly fulfill our mission, we need to commit to a parallel track of innovation in access. Such a track would require us to:

- Redefine "access" as a "none will be denied approach" that gets both prevention *and* treatment to as many patients in need globally as possible, in contrast to the current

approach of making medicines available (but not always patient-accessible) in as many markets as possible.
- Find sustainable ways to deliver medicines for prevention and treatment to the patients that need them most.
- Simplify the process of gaining access to medicines for patients.
- Provide education for providers and patients about whom these medicines benefit and why and how patients can get access to them.
- Expand the measures of success across the industry: Currently, we ground our metrics in shareholder returns, so the industry cannot afford to provide broad access to therapies, nor can it pursue development in areas that will not yield a reasonable return. Our boards must instead measure our success not simply in revenue and market share growth, but by assessing the breadth of reach and access to our products. (See Appendix A: *Access Scorecard*).
- Create a pricing structure that aligns with financial realities in each location.
- Advocate for policy incentives for the industry to allocate resources/investment in therapeutic areas that will address diseases in developing nations—for example, extending patents on drugs developed in therapeutic areas that are under-served.

Let us explore this type of innovation in more depth.

Innovation in the Face of Global Health Challenges

Despite the progress we noted earlier, substantial challenges remain. The most pressing health challenges today include such non-communicable diseases as strokes and heart disease [14]. They also include dangers like the looming threat of drug-resistant infections that kill around 700,000 people each year [12]. Infectious diseases like influenza, Zika, and Ebola present challenges as well, especially in parts of the world that lack first-rate treatment centers. Many parts of the developing world still lack basic sanitation. Worldwide, 36.9 million people were living with HIV/AIDS at the end of 2017. That same year, 940,000 people died of AIDS [17].

As we have seen, pharma, endowed with financial resources and an abundance of brainpower, can play a role in addressing these global challenges. Many companies are already taking action as more organizations have created global health units that are shaping decision making.

For example, in 1999, The Bill & Melinda Gates Foundation's pledged US $750 million in seed money to launch Gavi, a global Vaccine Alliance, bringing together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries. Gavi's mission is to create access to life-saving vaccines in the countries that need them the most by pooling demand for vaccines from the world's poorest countries, securing long-term funding, and shaping vaccine markets [7].

Additionally, leading industry corporations have launched efforts focused on increasing access to health care for those who are not getting the vaccines and treatments they need, either because they cannot afford them, they cannot get them locally, or they simply do not exist. Such programs as GSK's Health for All initiative, The Novartis Malaria Initiative, and Merck's Access to Health Statement of Guiding Principles, among others, have established a foundation of access-focused global corporate citizenship that we can now build upon.

However, to generate the needed health outcomes, we need to adopt a more access-oriented approach to innovation.

What are the Next Steps to Innovation?

An access-oriented approach to generating innovative health outcomes will require progress in four key areas:

1. **We need to redouble our efforts in infectious diseases**. Some companies are making strides. Two recent examples: In 2017, GlaxoSmithKline announced it will allocate

80% of its R&D budget to respiratory and HIV/infectious disease [9]. And this year, Novartis committed $100 million over five years toward the elimination of malaria. Importantly, Novartis CEO Vasant Narasimhan made clear that access was integral to that commitment: "At the same time, we need to work to ensure that our innovation reaches those most in need." [13] These are good examples of investments that will yield a robust return in the form of global health and social well-being. We need more such commitments to reduce the impact of infectious diseases on global morbidity and mortality. For example, multidrug-resistant (MDR) infections are rapidly increasing worldwide, and, unfortunately, few new antimicrobials capable of treating these infections are under development [8]. And while researchers are actively engaged in developing treatment and prevention for viruses with recent outbreaks, like Zika and Ebola, infections with pandemic potential will continue to emerge. Moreover, vaccine-preventable infections like seasonal flu continue to kill because countries lack the resources and infrastructure for a vaccine program. All of these are critical areas that demand our attention.

2. **We need to adopt a partnership mindset**. Building partnerships within and outside the industry is essential to expanding access. These partnerships can take many forms. For example, when global health is at stake, companies should share data to promote life-saving collaboration. They could also begin to view generic makers as allies in bringing down costs to developing-world governments and NGOs. Finally, companies can partner with other pharma companies, NGOs, and developing-world governments to facilitate treatment distribution and access.
To illustrate: When in 1987 Merck pledged to provide Mectizan, its River Blindness drug, free of charge to patients in Africa, it was not acting in isolation. It was a member of the River Blindness Partnership, along with the WHO, World Bank, African governments, and other pharma. (That pledge remains in force today.) And when Merck today makes its Ebola vaccine available pre-licensing to fight a new flare of the disease in the Congo, it's partnering with both the WHO and GAVI, the vaccine alliance (which has pre-purchased more than 300,000 doses of the vaccine) [1].

In a more recent example, supported by the Gates Foundation, nearly 200 countries around the globe have endorsed a shared vision—known as the Decade of Vaccines—to extend the benefits of vaccines to every person by 2020 and thereby save more than 20 million lives. This international collaboration has generated the Global Vaccine Action Plan (GVAP), a framework for preventing millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. Partners in the program include civil society organizations, the World Health Organization (WHO), UNICEF, and the GAVI Alliance. This kind of partnership is a model for what we can do to achieve positive healthcare outcomes.

3. **We need to examine our business models to account for global health requirements**. The first two goals cannot be reached without this radical step. Both innovation *and* access come out of an ecosystem in which many stakeholders participate. These stakeholders include the companies themselves (their leaders, boards, private investors, and shareholders). They also include governments (both where the companies operate and where they market), as well as research institutes and academia, payers and HTAs, NGOs, philanthropic foundations, and others. It is time to talk about ways in which pharma can work with those stakeholders most effectively to promote global health *and* a sustainably profitable pharmaceutical industry. Our companies, and the public, will be better off if we create our own industry-wide consensus.
4. **We need to redefine our thinking about how corporations measure the success of a product**. Historically, we have measured availability and profitability. For true innovation to occur, that success must now be

measured in terms of *overall accessibility* to a product. Specifically, the outcome is not only one of measuring the extent to which we have distributed the product, but quantifying the contribution the product/therapy is making to reducing the overall cost of care and/or improving health outcomes globally.

Implications for Pharma Leadership

The industry that has brought us cures for small pox, Hepatitis C, and some of the greatest advances in health and is working tirelessly toward cures for cancer, heart disease, Parkinson's disease, and other leading causes of death, has the opportunity to take the lead in shaping a path forward of innovative solutions to access that are affordable and address both acute needs and growing markets. But as leaders of this industry, we need to ask ourselves, "What do we want our legacy to be?"

For decades, our focus has been on our bottom line. We now need to commit our companies to convene a conversation around our business model. When we do, we will see that investing in innovation and providing equitable access for people all over the world are *not* mutually exclusive. This is not a zero-sum situation. It is not "or." It is "and."

Leaders in the pharma industry are now and have always been deeply committed to the well-being of patients. To borrow the mission statement of the Gates Foundation, we need to be "impatient optimists working to reduce inequity." We *can* work together to continue to deliver shareholder value as we also ensure that the benefits of innovation accrue to as many people as possible, because, as they say at the Gates Foundation, all lives have equal value.

References

1. Branswell H. WHO readies to test Merck's experimental Ebola vaccine in Congo outbreak. In: STAT, 11 May 2018. https://www.statnews.com/2018/05/11/who-merck-ebola-vaccine-congo/. Accessed 13 Mar 2019.
2. Bill & Melinda Gates Foundation [1]. What We Do: Malaria. https://www.gatesfoundation.org/What-We-Do/Global-Health/Malaria. Accessed 13 Mar 2019.
3. Bill & Melinda Gates Foundation [2]. What We Do: HIV. https://www.gatesfoundation.org/What-We-Do/Global-Health/HIV. Accessed 13 Mar 2019.
4. Bill & Melinda Gates Foundation [3]. What We Do: Global Vaccine Delivery. https://www.gatesfoundation.org/What-We-Do/Global-Development/Vaccine-Delivery. Accessed 13 Mar 2019.
5. Booth O. Top 10 Causes of Death in Developing Countries. In: The Borgen Project: the blog. https://borgenproject.org/causes-of-death-in-developing-countries/, 31 Mar 2018. Accessed 13 Mar 2019.
6. Center for Disease Control. Seasonal flu death estimate increases worldwide (press release), 13 Dec 2017. https://www.cdc.gov/media/releases/2017/p1213-flu-death-estimate.html. Accessed 13 Mar 2019.
7. GAVI: The Vaccine Alliance. https://www.gavi.org/ (2019). Accessed 13 Mar 2019.
8. Hersh LB, Newland JG, Beekmann SE, Polgreen PM, Gilbert DN, Unmet Medical Need in Infectious Diseases. In: Clinical Infectious Diseases 2012; 54(11):1677–8. https://doi.org/10.1093/cid/cis275, https://www.researchgate.net/publication/223986634_Unmet_Medical_Need_in_Infectious_Diseases. Accessed 13 Mar 2019.
9. Hirschler B. GlaxoSmithKline's new boss streamlines R&D, axes slew of drugs, Reuters, 26 Jul 2017. https://www.reuters.com/article/us-gsk-results/glaxosmithklines-new-boss-streamlines-rd-axes-slew-of-drugs-idUSKBN1AB1BH. Accessed 13 Mar 2019.
10. Koppaka R. Morbidity and Mortality Weekly Report, 20 May 2011. Center for Disease Control and Prevention. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm. Accessed 13 Mar 2019.
11. Morgan S, Lopert R, Greyson D. Toward a definition of pharmaceutical innovation. Open Med 2008;2(1): e4–e7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3091590/. Accessed 13 Mar 2019.
12. Nathe M. 7 Global health issues to watch in 2017. In: Humanosphere 23 Jan 2017. http://www.humanosphere.org/global-health/2017/01/7-global-health-issues-to-watch-in-2017/. Accessed 13 Mar 2019.
13. Novartis. Novartis renews commitment to malaria elimination, investing USD 100 million to research and develop next-generation antimalarials (press release), 17 Apr 2018. https://www.novartis.com/news/media-releases/novartis-renews-commitment-malaria-elimination-investing-usd-100-million-research-and-develop-next-generation-antimalarials. Accessed 13 Mar 2019.
14. Office of Disease Control and Health Prevention, HealthyPeople.gov. https://www.healthypeople.gov/2020/topics-objectives/topic/global-health (2019). Accessed 13 Mar 2019.
15. Pagliarulo N. 5 trends shaping rare disease drug development. In: Biopharmadive, 10 Apr 2017.

https://www.biopharmadive.com/news/trends-rare-disease-orphan-drug-development/439866/. Accessed 13 Mar 2019.
16. Taubenberger JK, Morens DM. 1918 Influenza: the Mother of All Pandemics. Emerg Infect Dis. 2006;12 (1):15–22. https://doi.org/10.3201/eid1201.050979. Accessed 13 Mar 2019.
17. UNAIDS, Global HIV & AIDS Statistics—2018 Fact Sheet, 2019. http://www.unaids.org/en/resources/fact-sheet. Accessed 13 Mar 2019.

9 Neglected Parasitic Infections and the Syndemic Anemia Vaccines for Africa

Peter J. Hotez, Ulrich Strych and Maria Elena Bottazzi

9.1 Introduction

Neglected parasitic infections represent a subset of the world's neglected tropical diseases, which are highly prevalent and mostly chronic and debilitating infectious diseases that promote poverty through their harmful effects on both children and adults [1]. In the early 2000s, the leading neglected parasitic helminth (worm) infections affecting sub-Saharan Africa, including schistosomiasis, the three major soil-transmitted infections (ascariasis, human hookworm infection, and trichuriasis), lymphatic filariasis, and onchocerciasis were targeted for intervention through a program of integrated mass drug administration, using donated drugs from the major pharmaceutical companies [2]. This program was accelerated through donations of praziquantel from Merck in order to target schistosomiasis, and triggered efforts to develop a new pediatric formulation of praziquantel, scheduled to become available in 2022 [3]. Through these interventions, over the last decade, there have been significant public health gains for most of Africa's neglected parasitic helminth infections, especially in terms of partial reductions in their prevalence, although the impact has been much more modest for human hookworm infection [4]. In parallel, through anti-malaria drugs and the use of bed nets and other vector control approaches, there have been roughly equivalent gains in reducing the prevalence and incidence of malaria, Africa's leading neglected parasitic infection in terms of the magnitude of disease incidence and deaths [5]. Ultimately, these gains represent a key component for achieving global goals in the area of sustainable development [6].

A key issue is how to leverage these initial gains in order to accelerate disease prevalence and incidence reductions or even to achieve potential elimination goals and targets? Shown in Table 9.1 are the most recent estimates for the prevalence (helminth infections) or incidence (malaria) of the leading neglected parasitic infections in sub-Saharan Africa. These estimates are based on studies conducted by the Global Burden of Disease Study (GBD) 2016 [7, 8].

It is clear that neglected parasitic infections remain widespread on the African continent and especially in sub-Saharan Africa. Indeed, today

P. J. Hotez (✉) · U. Strych · M. E. Bottazzi
Texas Children's Hospital Center for Vaccine Development, Departments of Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA
e-mail: hotez@bcm.edu

U. Strych
e-mail: strych@bcm.edu

M. E. Bottazzi
e-mail: bottazzi@bcm.edu

P. J. Hotez · M. E. Bottazzi
Department of Biology, Baylor University, Waco, TX, USA

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_9

Table 9.1 Leading neglected parasitic infections in sub-Saharan Africa

Rank	Disease	Prevalence or *Incidence* in sub-Saharan Africa
1	Malaria	*213 million*
2	Schistosomiasis	162 million
3	Ascariasis	133 million
4	Hookworm infection	132 million
5	Trichuriasis	111 million
6	Onchocerciasis	15 million
7	Lymphatic Filariasis	14 million

Prevalence and incidence figures from healthdata.org [8]

malaria, schistosomiasis, ascariasis, hookworm infection, and ascariasis still represent some of the most common afflictions affecting people living in poverty in this region.

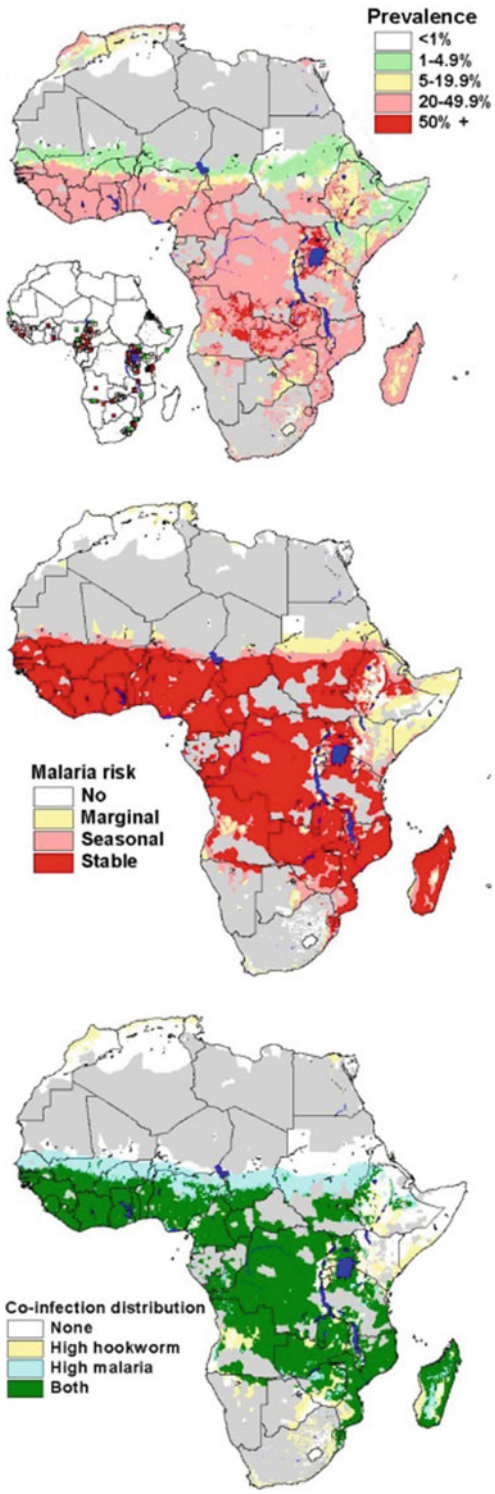
9.2 Rationale for Linking Malaria with Helminth Control

Shortly after the launch of the 2000 Millennium Development Goals, the studies showing the geographic overlap and co-endemicity of malaria and major parasitic helminth infections, prompted calls to integrate the control of all of these diseases in Africa in a larger and expanded framework (Fig. 9.1) [9, 10]. Thus, it would be feasible to link the mass treatments using anthelminthic drugs with antimalarial drugs and bed nets, with resultant synergies in the delivery of these interventions [11]. For example, mass treatment for parasitic helminth infections can be combined with intermittent preventive therapy (IPT) for malaria, in which a full dose of an antimalarial drug is given as a mass treatment to a vulnerable target population, such as infants (IPTi), older children (IPTc), or pregnant women (IPTp), whether or not they are currently infected with malaria [9, 11, 12]. In some African settings, it has been shown that combining mass treatments for worms with IPT can result in improved clinical outcomes [13]. Similarly, the use of insecticide-treated bed nets for malaria control has the potential to reduce transmission of mosquito-transmitted helminth infections in Africa such as lymphatic filariasis [14]. There are still additional synergies for simultaneous deliveries of interventions for parasitic infections and HIV/AIDS, as well as bacterial infections and trachoma [9, 11].

Beyond the convenience of co-delivery, there are also potential and actual public health benefits for combining the control of parasitic worm infections and malaria. For example, in areas where schistosomiasis and malaria are co-endemic, the former can result in increases in malaria incidence, so that mass treatment with praziquantel can result indirectly in the reduction of malaria transmission [17].

It has been further noted that malaria, schistosomiasis, and hookworm infection each can cause anemia via independent pathways—with hookworm causing intestinal blood loss, schistosomiasis causing both blood loss and inflammatory anemia, and malaria causing red blood cell lysis, splenic sequestration, and dyserythropoiesis (Table 9.2) [9, 10, 18, 19]. In some areas of sub-Saharan Africa, these infections can combine to produce severe reductions in host hemoglobin [18–22], which is sometimes referred to as syndemic anemia [2, 9], with one example being the "agriculture-related anemias" due to the expansion of the agriculture and the related increased parasite transmission [23].

The impact of anemia on the health of developing countries, especially in sub-Saharan Africa, is tremendous. According to the GBD 2016, iron deficiency anemia alone is responsible for almost 35 million disability-adjusted life years, more than double the global disease burden from breast cancer, and four times the global disease burden from cervical cancer [24]. Another measurement of global anemia from the GBD 2010 found that it was responsible for more than 68 million years lived with disability, with malaria, schistosomiasis, and hookworm accounting for a significant percentage of the anemia in Africa [25].



◀ **Fig. 9.1** (top) Predicted prevalence of hookworm based on relationships between observed prevalence of infection among school-aged children (insert) and satellite-derived environmental data; (middle) map of climatic suitability for *P. falciparum* malaria transmission based on Snow et al. [15], adjusted for urbanization [16]; and (bottom) map of geographic overlap of moderate–high hookworm (prevalence >20%) and *P. falciparum* transmission. Gray indicates population density <1 km^2. Figure and Figure Legend reproduced from Ref. [10] (open access source)

Table 9.2 Parasitic disease causes and mechanisms of anemia in sub-Saharan Africa

Disease	Major etiologic agent	Major mechanisms of anemia
Malaria	*Plasmodium falciparum*	Hemolysis Splenic sequestration Dyserythropoiesis
Human Hookworm infection	*Necator americanus*	Intestinal blood loss
Schistosomiasis	*Schistosoma mansoni* *Schistosoma haematobium*	Chronic inflammation Blood loss

9.3 Syndemic Anemia Vaccines

Since 2008, we have proposed the concept of reducing the global burden of anemia through the development of a multivalent vaccine against hookworm and schistosomiasis [26–28]. But the possibility exists of also simultaneously vaccinating against these two human helminth infections, together with malaria in a "pan-anemia" vaccine.

The feasibility of developing a vaccine to prevent anemia in Africa is based on three independent lines of evidence, namely the development and testing of individual and specific vaccines against malaria, human hookworm infection, and schistosomiasis, respectively (Table 9.3). Ultimately, these vaccines could be combined as a trivalent anemia prevention strategy, possibly then embedded into ongoing preventive African chemotherapy programs.

Table 9.3 Current state of neglected parasitic disease vaccines in clinical development

Disease	Vaccines in clinical development
Malaria	YES, licensed as Mosquirix in 2015
Schistosomiasis	YES, completing Phase 1 and advancing to Phase 2
Ascariasis	NO, undergoing preclinical development
Hookworm infection	YES, completing Phase 1 and advancing to Phase 2
Trichuriasis	NO, undergoing preclinical development
Onchocerciasis	NO, undergoing preclinical development
Lymphatic Filariasis	NO

9.3.1 Malaria Vaccine

Progress in the development and licensing of the first malaria vaccine, known as Mosquirix, has been reviewed previously [29]. Briefly, the failure of a World Health Organization (WHO)-led initiative to control or eliminate malaria by mass treatment with chloroquine and DDT insecticide due to emerging resistance led to multiple studies to develop first-generation malaria vaccines. The fundamental work showing how irradiated *Plasmodium* sporozoites could elicit protective immunity started several lines of investigative work, now leading to whole cell experimental malaria vaccines using either irradiated—or genetically—modified sporozoites [30]. In parallel, the work led by Ruth and Victor Nussenzweig on the cloning and expression of a major sporozoite surface antigen ultimately led to the development of a recombinant polypeptide-based vaccine, known as RTS, S [31]. Much of the development of the RTS, S malaria vaccine was led by the United States Army and Walter Reed Army Institute of Medical Research, prior to downstream development by GlaxoSmithKline and the Bill & Melinda Gates Foundation [29]. Safety and proof-of-concept trials for efficacy for the RTS, S malaria vaccine continued throughout the 1990s and early 2000s, until a multicenter phase 3 trial in Africa began in 2009 [29]. The vaccine was shown to be partially protective and approved for use in African young children in 2015 under the trade name of Mosquirix [29]. Since then, changes in clinical development, including the age of first vaccination and delayed fractional dosing, have been shown to improve vaccine immunogenicity and possibly protective efficacy of the vaccine [32, 33]. Accordingly, additional trials of Mosquirix are planned, some in combination with other childhood vaccinations.

9.3.2 Human Hookworm Vaccine

Since 2000, the human hookworm vaccine initiative has been developing a recombinant protein-based vaccine that targets *Necator americanus*, the major hookworm of Africa and elsewhere globally. The initial approach toward hookworm vaccine development followed a somewhat similar path to the RTS,S malaria vaccine, namely building on scientific evidence that found immunization with the infective stages—but in this case third-stage infective hookworm larvae—is highly protective if the larvae were first attenuated through ionizing radiation [34]. This finding led to the discovery and development of an immunodominant antigen linked to larval immunization, known as *Na*-ASP-2 [34, 35]. In a randomized phase 1 clinical trial in healthy adult volunteers in the USA, immunization with recombinant *Na*-ASP-2 on alum was found to be both safe and immunogenic [36]; however, immunization among adult volunteers in a hookworm-endemic area of Brazil was shown to be associated with allergic responses, due to circulating IgE present in adults previously exposed to infective *N. americanus* larvae [37]. Therefore, an alternative approach was undertaken to directly interfere with adult *N. americanus* blood loss at the site of attachment [26, 38], leading to the development of a bivalent vaccine comprised of two recombinant hookworm antigens, known as *Na*-GST-1 and *Na*-APR-1, again adjuvanted with alum, but also additional immunostimulants [39–41]. To date, there do not appear to be concerned about

pre-vaccination IgE among endemic populations, and phase 1 trials have shown that human vaccines prepared from these recombinant antigens (on alum together with a Toll-like receptor [TLR] agonist) are both safe and immunogenic [42]. Therefore, there is optimism that this approach will lead to the development of the first human vaccine to prevent hookworm-associated blood loss and anemia [43], which in modeling studies has been shown to be highly cost-effective and cost savings compared to annual deworming depending on the length and level of protection of the vaccine [44]. The human hookworm vaccine is now entering advanced clinical testing led by the nonprofit product development partnership (PDP) based at Texas Children's Hospital Center for Vaccine Development (Texas Children's CVD) in partnership with George Washington University, the Oswaldo Cruz Foundation (FIOCRUZ) and a consortium of European and African organizations through the HOOKVAC consortium and partnership [45, 46].

9.3.3 Schistosomiasis Vaccine

There are two vaccines that target human schistosomes currently in clinical development, while a third vaccine is scheduled to begin phase 1 testing. One of these vaccines, the *Sm*-TSP-2 schistosome vaccine includes a recombinant extracellular loop of a major tetraspanin surface antigen from *Schistosoma mansoni*, the major cause of intestinal and biliary schistosomiasis in Africa [26]. It was discovered through an immunomics approach that paired the proteomic analysis of the schistosome surface with immunological screening using pooled sera from putatively immune individuals living in an endemic area of Brazil where *S. mansoni* is endemic [47, 48]. Texas Children's CVD has scaled up production of the recombinant *Sm*-TSP-2 antigen formulated on alum (together with a TLR-4 agonist) [49, 50], which is now completing phase 1 clinical trials in collaboration with the NIAID-NIH—supported Vaccine Trial Evaluation Unit (VTEU) based at Baylor College of Medicine, George Washington University and FIOCRUZ. It is projected that the *Sm*-TSP-2 schistosomiasis vaccine will advance to phase 2 clinical trials in Uganda shortly. In parallel, a Brazilian-led effort based at FIOCRUZ is testing the recombinant *Sm*-14 schistosome vaccine formulated in a stable emulsion with a TLR-4 agonist [50], while a third vaccine comprised of the recombinant *Sm*-p80 enzyme known as calpain has undergone extensive testing in non-human primates and is expected to soon enter the clinic [51, 52]. These vaccines are currently being tested separately, although there is a downstream possibility of evaluating these vaccine antigens in combinations.

9.4 Maternal–Child Target Product Profiles of an Anemia Vaccine

As vaccines for malaria, schistosomiasis, and human hookworm infections are developed and introduced across Africa, there will be a requirement to shape parallel and synergistic target product profiles (TPPs) for each of these vaccines. Conceivably, a vaccine may have more than a single indication. For example, if the goal is to target anemia, then efforts could be made to focus on two of the human populations most susceptible to anemia—children and women of reproductive age—due to their lower underlying iron stores relative to other populations (Fig. 9.2). Following licensure, plans are already underway to introduce Mosquirix into infant and preschool-aged populations, while similar plans

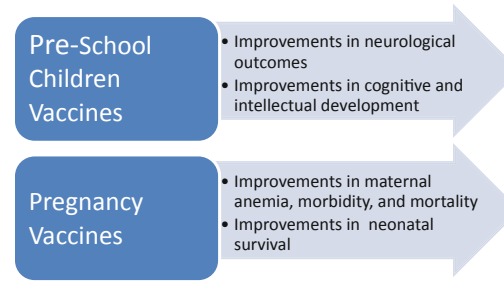


Fig. 9.2 Potential Maternal–Child TPPs for Syndemic Anemias

are in discussion for the human hookworm infection and schistosomiasis vaccines.

Furthermore, a pediatric anemia vaccine would be most needed for young children, since this population has the greatest vulnerability to long-term cognitive and intellectual deficits from iron deficiency anemia [53]. In many instances, young (preschool-aged) children also suffer the greatest risk of death and other serious sequelae from parasitic infections [54–56].

A second highly vulnerable population in terms of anemia is pregnant women, especially in developing countries, where up to 80% of pregnancies are complicated by anemia [57]. Anemia in pregnancy results from the high iron demands of the fetus, together with malaria, hookworm, and schistosomiasis coinfections [18, 58–61]. In many cases, the anemias from these diseases are syndemic and result in profound reductions in host hemoglobin [18]. Yet another clinical consequence is higher maternal morbidity and mortality, as well as in poor neonatal survival and other outcomes [61]. From the above analysis, it would be particularly worth accelerating vaccine development for both of these highly vulnerable populations.

9.5 New Public–Private Strategic Alliances

Fundamental to the success in advancing Mosquirix through advanced clinical development and licensure in Africa was the involvement of major strategic alliances including a multinational pharmaceutical company (GSK), with expertise both in conducting and coordinating phase 3 trials, as well as in the capacity for industrial-scale manufacture suitable for advanced development and vaccine introduction. To date, there are no major vaccine Pharma partners for anthelminthic vaccines, such as hookworm and schistosomiasis. However, the Darmstadt, Germany-based Merck and its Life Sciences Division, MilliporeSigma, have taken a major interest in the development of the *Sm*-TSP-2 schistosomiasis vaccine advanced by Texas Children's CVD. The collaboration includes training and the exchange of technical know-how in process development and formulation, as well as filling knowledge gaps that exist from research and development to manufacturing. The essential components of Merck's involvement include: (1) Revision of chromatographic processes to improve yields and purity of the final drug substance (the recombinant protein); (2) revision of formulation processes to stabilize the recombinant protein molecule by altering key buffers and excipients in the final formulation; and (3) overall optimizations in processes to improve cost-effectiveness and cost savings. This final component is essential to ensure that the vaccine is produced at the lowest possible price and safeguard access for the poorest people living in sub-Saharan Africa now at risk for schistosomiasis and other parasitic diseases.

The strategic alliance between Merck and Texas Children's CVD represents an important step toward advancing the *Sm*-TSP-2 schistosomiasis vaccine through advanced development and licensure. The scientific knowledge exchange from this partnership is catalyzing and accelerating product development of this much-needed vaccine and should serve as a framework for capacity building and the establishment of self-reliance in vaccine development and manufacturing around the globe. Interestingly, it also affords a unique opportunity to assess the feasibility of combining the vaccine with Merck's pediatric formulation of PZQ in a vaccine-linked chemotherapeutic approach during early childhood. One potential scenario for the schistosomiasis (and the human hookworm vaccine) would be to administer the priming vaccine doses around the time a preschool-aged child receives their first dose of an anthelminthic drug—PZQ in the case of schistosomiasis, and albendazole in the case of human hookworm. Still another scenario is the administration of both schistosomiasis and human hookworm vaccines around the time of Mosquirix immunization during infancy or preschool-aged years.

Finally, another consideration is the administration of the anthelminthic vaccines in young women of reproductive age in order to achieve

protective immunity against schistosomiasis and hookworm infections during pregnancy. This approach has been used successfully for immunizing against tetanus, diphtheria, and pertussis in what is known as the Tdap vaccination [62]. By immunizing against hookworm and schistosomiasis, however, such an approach could both reduce maternal morbidity and improve neonatal survival. Downstream it would be worth examining the possibility of combining Mosquirix with the *Sm*-TSP-2 schistosomiasis vaccine and the human hookworm vaccine in a multivalent syndemic anemia vaccine for Africa, for use during pregnancy.

9.6 Next Steps and Future Directions

There are some formidable hurdles to bring both the schistosomiasis and human hookworm vaccines up to the same point in development as Mosquirix. Both anthelminthic vaccines are only now entering phase 2 trials for the proof of concept of their efficacy at either preventing burden of disease in endemic settings or using controlled human challenge models of infection. Success in further development will require the expansion of strategic public–private alliances including committed industrial and governmental partners and investors for phase 3 trials, licensure, and vaccine introduction. It is worth noting that the public health consequences of simultaneously preventing all three syndemic anemias of young children and pregnant women are potentially enormous. Together the anemia from these neglected parasitic infections represents perhaps the most significant causes of pediatric malnutrition in Africa and one of the most common serious complications of pregnancy. Success in the creation of innovative business models and the application of novel vaccine development strategies, therefore, represent a highly cost savings approach to both improve maternal and child health and save lives of both pregnant women and their infants.

References

1. Hotez PJ. Forgotten people, forgotten diseases: the neglected tropical diseases and their impact on global health and development. 2nd ed. Washington, DC: ASM Press; 2013. xviii, 255 p.
2. Molyneux DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med. 2005;2(11):e336. https://doi.org/10.1371/journal.pmed.0020336 (PubMed PMID: 16212468; PMCID: 1253619).
3. Reinhard-Rupp J, Klohe K. Developing a comprehensive response for treatment of children under 6 years of age with schistosomiasis: research and development of a pediatric formulation of praziquantel. Infect Dis Poverty. 2017;6(1):122. https://doi.org/10.1186/s40249-017-0336-9 (PubMed PMID: 28768535; PMCID: PMC5541653).
4. Hotez PJ, Fenwick A, Ray SE, Hay SI, Molyneux DH. "Rapid impact" 10 years after: The first "decade" (2006-2016) of integrated neglected tropical disease control. PLoS Neglected Trop Dis. 2018;12(5):e0006137. https://doi.org/10.1371/journal.pntd.0006137 (PubMed PMID: 29795551; PMCID: PMC5967703).
5. Nkumama IN, O'Meara WP, Osier FHA. Changes in malaria epidemiology in Africa and new challenges for elimination. Trends Parasitol. 2017;33(2):128–40. https://doi.org/10.1016/j.pt.2016.11.006 (PubMed PMID: 27939610).
6. Hotez PJ, Herricks JR. Helminth elimination in the pursuit of sustainable development goals: a "worm index" for human development. PLoS Neglected Trop Dis. 2015;9(4):e0003618. https://doi.org/10.1371/journal.pntd.0003618 (PubMed PMID: 25928617; PMCID: PMC4415765).
7. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211–59. https://doi.org/10.1016/S0140-6736(17)32154-2 (PubMed PMID: 28919117; PMCID: PMC5605509).
8. Institute_for_Health_Metrics_and_Evaluation. Global Health Data Exchange 2013. Available from: http://ghdx.healthdata.org/gbd-data-tool.
9. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med. 2006;3(5):e102. https://doi.org/10.1371/journal.pmed.0030102 (PubMed PMID: 16435908; PMCID: 1351920).
10. Brooker S, Clements AC, Hotez PJ, Hay SI, Tatem AJ, Bundy DA, Snow RW. The co-distribution of

Plasmodium falciparum and hookworm among African schoolchildren. Malaria J. 2006;5:99. https://doi.org/10.1186/1475-2875-5-99 (PubMed PMID: 17083720; PMCID: 1635726).
11. Hotez PJ, Mistry N, Rubinstein J, Sachs JD. Integrating neglected tropical diseases into AIDS, tuberculosis, and malaria control. New Engl J Med. 2011;364 (22):2086–9. https://doi.org/10.1056/NEJMp1014637 (PubMed PMID: 21631320).
12. Greenwood B. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. Malaria J. 2010;9(Suppl 3):S2. https://doi.org/10.1186/1475-2875-9-S3-S2 (PubMed PMID: 21144082; PMCID: PMC3002144).
13. Opoku EC, Olsen A, Browne E, Hodgson A, Awoonor-Williams JK, Yelifari L, Williams J, Magnussen P. Impact of combined intermittent preventive treatment of malaria and helminths on anaemia, sustained attention, and recall in Northern Ghanaian schoolchildren. Glob Health Action. 2016;9:32197. https://doi.org/10.3402/gha.v9.32197 (PubMed PMID: 27633035; PMCID: PMC5025525).
14. Kelly-Hope LA, Molyneux DH, Bockarie MJ. Can malaria vector control accelerate the interruption of lymphatic filariasis transmission in Africa; capturing a window of opportunity? Parasites Vectors. 2013;6:39. https://doi.org/10.1186/1756-3305-6-39 (PubMed PMID: 23433078; PMCID: PMC3599698).
15. Snow RW, Craig M, Deichmann U, Marsh K. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. Bull World Health Organ. 1999;77(8):624–40 (PubMed PMID: 10516785; PMCID: PMC2557714).
16. Robert V, Macintyre K, Keating J, Trape JF, Duchemin JB, Warren M, Beier JC. Malaria transmission in urban sub-Saharan Africa. Am J Trop Med Hyg. 2003;68(2):169–76 (PubMed PMID: 12641407).
17. Ndeffo Mbah ML, Skrip L, Greenhalgh S, Hotez P, Galvani AP. Impact of Schistosoma mansoni on malaria transmission in Sub-Saharan Africa. PLoS Neglected Trop Dis. 2014;8(10):e3234. https://doi.org/10.1371/journal.pntd.0003234 (PubMed PMID: 25329403; PMCID: 4199517).
18. Brooker S, Akhwale W, Pullan R, Estambale B, Clarke SE, Snow RW, Hotez PJ. Epidemiology of plasmodium-helminth co-infection in Africa: populations at risk, potential impact on anemia, and prospects for combining control. Am J Trop Med Hyg. 2007;77(6 Suppl):88–98 (PubMed PMID: 18165479; PMCID: 2637949).
19. Hotez PJ, Molyneux DH. Tropical anemia: one of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. PLoS Neglected Trop Dis. 2008;2(7): e270. https://doi.org/10.1371/journal.pntd.0000270 (PubMed PMID: 18665256; PMCID: 2474697).
20. Matangila JR, Doua JY, Linsuke S, Madinga J, Inocencio da Luz R, Van Geertruyden JP, Lutumba P. Malaria, schistosomiasis and soil transmitted helminth burden and their correlation with anemia in children attending primary schools in Kinshasa, Democratic Republic of Congo. PloS One. 2014;9(11):e110789. https://doi.org/10.1371/journal.pone.0110789 (PubMed PMID: 25372029; PMCID: PMC4220949).
21. Njunda AL, Fon SG, Assob JC, Nsagha DS, Kwenti TD, Kwenti TE. Coinfection with malaria and intestinal parasites, and its association with anaemia in children in Cameroon. Infect Dis Poverty. 2015;4:43. https://doi.org/10.1186/s40249-015-0078-5 (PubMed PMID: 26445484; PMCID: PMC4595138).
22. Zeukeng F, Tchinda VH, Bigoga JD, Seumen CH, Ndzi ES, Abonweh G, Makoge V, Motsebo A, Moyou RS. Co-infections of malaria and geohelminthiasis in two rural communities of Nkassomo and Vian in the Mfou health district, Cameroon. PLoS Neglected Trop Dis. 2014;8(10):e3236. https://doi.org/10.1371/journal.pntd.0003236 (PubMed PMID: 25329479; PMCID: PMC4199518).
23. Fleming AF. Agriculture-related anaemias. Br J Biomed Sci. 1994;51(4):345–57 (PubMed PMID: 7756942).
24. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1260–344. https://doi.org/10.1016/s0140-6736(17)32130-x (PubMed PMID: 28919118; PMCID: PMC5605707).
25. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, Regan M, Weatherall D, Chou DP, Eisele TP, Flaxman SR, Pullan RL, Brooker SJ, Murray CJ. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615–24. https://doi.org/10.1182/blood-2013-06-508325 (PubMed PMID: 24297872; PMCID: PMC3907750).
26. Hotez PJ, Bethony JM, Diemert DJ, Pearson M, Loukas A. Developing vaccines to combat hookworm infection and intestinal schistosomiasis. Nat Rev Microbiol. 2010;8(11):814–26. https://doi.org/10.1038/nrmicro2438 (PubMed PMID: 20948553).
27. Hotez PJ, Bethony JM, Oliveira SC, Brindley PJ, Loukas A. Multivalent anthelminthic vaccine to prevent hookworm and schistosomiasis. Expert Rev Vaccines. 2008;7(6):745–52. https://doi.org/10.1586/14760584.7.6.745 (PubMed PMID: 18665774).
28. Hotez PJ, Van Leeuwen R. Vaccinating against iron-deficiency anemia: a new technology for maternal and child health 2015. Available from: https://www.healthaffairs.org/do/10.1377/hblog20150219.044524/full/.

29. Chauhan VS. Development & licensing of first ever vaccine against malaria. Indian J Med Res. 2015;142 (6):637–9. https://doi.org/10.4103/0971-5916.174535 (PubMed PMID: 26831410; PMCID: PMC4774058).
30. Jongo SA, Shekalaghe SA, Church LWP, Ruben AJ, Schindler T, Zenklusen I, Rutishauser T, Rothen J, Tumbo A, Mkindi C, Mpina M, Mtoro AT, Ishizuka AS, Kassim KR, Milando FA, Qassim M, Juma OA, Mwakasungula S, Simon B, James ER, Abebe Y, Kc N, Chakravarty S, Saverino E, Bakari BM, Billingsley PF, Seder RA, Daubenberger C, Sim BKL, Richie TL, Tanner M, Abdulla S, Hoffman SL. Safety, immunogenicity, and protective efficacy against controlled human malaria infection of Plasmodium falciparum sporozoite vaccine in tanzanian adults. Am J Trop Med Hyg. 2018;99(2):338–49. https://doi.org/10.4269/ajtmh.17-1014 (PubMed PMID: 29943719).
31. Cohen J, Nussenzweig V, Nussenzweig R, Vekemans J, Leach A. From the circumsporozoite protein to the RTS. S/AS candidate vaccine. Human vaccines. 2010;6(1):90–6 (PubMed PMID: 19806009).
32. Chaudhury S, Regules JA, Darko CA, Dutta S, Wallqvist A, Waters NC, Jongert E, Lemiale F, Bergmann-Leitner ES. Delayed fractional dose regimen of the RTS, S/AS01 malaria vaccine candidate enhances an IgG4 response that inhibits serum opsonophagocytosis. Sci Rep. 2017;7(1):7998. https://doi.org/10.1038/s41598-017-08526-5 (PubMed PMID: 28801554; PMCID: PMC5554171).
33. Witte D, Cunliffe NA, Turner AM, Ngulube E, Ofori-Anyinam O, Vekemans J, Chimpeni P, Lievens M, Wilson TP, Njiram'madzi J, Mendoza YG, Leach A. Safety and immunogenicity of seven dosing regimens of the candidate RTS, S/AS01E malaria vaccine integrated within an expanded program on immunization regimen: a phase II, single-center, open, controlled trial in infants in Malawi. Pediatr Infect Dis J. 2018;37 (5):483–91. https://doi.org/10.1097/INF.0000000000001937 (PubMed PMID: 29432383).
34. Loukas A, Bethony J, Brooker S, Hotez P. Hookworm vaccines: past, present, and future. Lancet Infect Dis. 2006;6(11):733–41. https://doi.org/10.1016/S1473-3099(06)70630-2 (PubMed PMID: 17067922).
35. Goud GN, Bottazzi ME, Zhan B, Mendez S, Deumic V, Plieskatt J, Liu S, Wang Y, Bueno L, Fujiwara R, Samuel A, Ahn SY, Solanki M, Asojo OA, Wang J, Bethony JM, Loukas A, Roy M, Hotez PJ. Expression of the Necator americanus hookworm larval antigen Na-ASP-2 in Pichia pastoris and purification of the recombinant protein for use in human clinical trials. Vaccine. 2005;23(39):4754–64. https://doi.org/10.1016/j.vaccine.2005.04.040 (PubMed PMID: 16054275).
36. Bethony JM, Simon G, Diemert DJ, Parenti D, Desrosiers A, Schuck S, Fujiwara R, Santiago H, Hotez PJ. Randomized, placebo-controlled, double-blind trial of the Na-ASP-2 hookworm vaccine in unexposed adults. Vaccine. 2008;26 (19):2408–17. https://doi.org/10.1016/j.vaccine.2008.02.049 (PubMed PMID: 18396361).
37. Diemert DJ, Pinto AG, Freire J, Jariwala A, Santiago H, Hamilton RG, Periago MV, Loukas A, Tribolet L, Mulvenna J, Correa-Oliveira R, Hotez PJ, Bethony JM. Generalized urticaria induced by the Na-ASP-2 hookworm vaccine: implications for the development of vaccines against helminths. J Allergy Clin Immunol. 2012;130(1):169–76 e6. https://doi.org/10.1016/j.jaci.2012.04.027 (PubMed PMID: 22633322).
38. Ranjit N, Zhan B, Hamilton B, Stenzel D, Lowther J, Pearson M, Gorman J, Hotez P, Loukas A. Proteolytic degradation of hemoglobin in the intestine of the human hookworm Necator americanus. J Infect Dis. 2009;199(6):904–12 (PubMed PMID: 19434933).
39. Goud GN, Deumic V, Gupta R, Brelsford J, Zhan B, Gillespie P, Plieskatt JL, Tsao EI, Hotez PJ, Bottazzi ME. Expression, purification, and molecular analysis of the Necator americanus glutathione S-transferase 1 (Na-GST-1): a production process developed for a lead candidate recombinant hookworm vaccine antigen. Protein Expr Purif. 2012;83 (2):145–51. https://doi.org/10.1016/j.pep.2012.03.013 (PubMed PMID: 22503665).
40. Curti E, Seid CA, Hudspeth E, Center L, Rezende W, Pollet J, Kwityn C, Hammond M, Matsunami RK, Engler DA, Hotez PJ, Elena Bottazzi M. Optimization and revision of the production process of the Necator americanus glutathione S-transferase 1 (Na-GST-1), the lead hookworm vaccine recombinant protein candidate. Human Vaccines Immunotherapeutics. 2014;10(7):1914–25. https://doi.org/10.4161/hv.28872 (PubMed PMID: 25424799; PMCID: PMC4186034).
41. Seid CA, Curti E, Jones RM, Hudspeth E, Rezende W, Pollet J, Center L, Versteeg L, Pritchard S, Musiychuk K, Yusibov V, Hotez PJ, Bottazzi ME. Expression, purification, and characterization of the Necator americanus aspartic protease-1 (Na-APR-1 (M74)) antigen, a component of the bivalent human hookworm vaccine. Human Vaccines Immunotherapeutics. 2015;11(6):1474–88. https://doi.org/10.1080/21645515.2015.1036207 (PubMed PMID: 25905574; PMCID: PMC4514214).
42. Hotez PJ, Strych U, Lustigman S, Bottazzi ME. Human anthelminthic vaccines: rationale and challenges. Vaccine. 2016;34(30):3549–55. https://doi.org/10.1016/j.vaccine.2016.03.112 (PubMed PMID: 27171753).
43. Diemert DJ, Freire J, Valente V, Fraga CG, Talles F, Grahek S, Campbell D, Jariwala A, Periago MV, Enk M, Gazzinelli MF, Bottazzi ME, Hamilton R, Brelsford J, Yakovleva A, Li G, Peng J, Correa-Oliveira R, Hotez P, Bethony J. Safety and immunogenicity of the Na-GST-1 hookworm vaccine in Brazilian and American adults. PLoS Neglected

Trop Dis. 2017;11(5):e0005574. https://doi.org/10.1371/journal.pntd.0005574 (PubMed PMID: 28464026; PMCID: PMC5441635).
44. Bartsch SM, Hotez PJ, Hertenstein DL, Diemert DJ, Zapf KM, Bottazzi ME, Bethony JM, Brown ST, Lee BY. Modeling the economic and epidemiologic impact of hookworm vaccine and mass drug administration (MDA) in Brazil, a high transmission setting. Vaccine. 2016;34(19):2197–206. https://doi.org/10.1016/j.vaccine.2016.03.018 (PubMed PMID: 27002501).
45. Diemert DJ, Bottazzi ME, Plieskatt J, Hotez PJ, Bethony JM. Lessons along the Critical Path: Developing Vaccines against Human Helminths. Trends in parasitology. 2018. https://doi.org/10.1016/j.pt.2018.07.005 (PubMed PMID: 30064902).
46. HOOKVAC. The human hookworm vaccine 2018 [8/20/2018]. Available from: http://hookvac.eu/project/.
47. Tran MH, Freitas TC, Cooper L, Gaze S, Gatton ML, Jones MK, Lovas E, Pearce EJ, Loukas A. Suppression of mRNAs encoding tegument tetraspanins from Schistosoma mansoni results in impaired tegument turnover. PLoS Pathog. 2010;6(4):e1000840. https://doi.org/10.1371/journal.ppat.1000840 (PubMed PMID: 20419145; PMCID: 2855321).
48. Tran MH, Pearson MS, Bethony JM, Smyth DJ, Jones MK, Duke M, Don TA, McManus DP, Correa-Oliveira R, Loukas A. Tetraspanins on the surface of Schistosoma mansoni are protective antigens against schistosomiasis. Nat Med. 2006;12(7):835–40. https://doi.org/10.1038/nm1430 (PubMed PMID: 16783371).
49. Cheng W, Curti E, Rezende WC, Kwityn C, Zhan B, Gillespie P, Plieskatt J, Joshi SB, Volkin DB, Hotez PJ, Middaugh CR, Bottazzi ME. Biophysical and formulation studies of the Schistosoma mansoni TSP-2 extracellular domain recombinant protein, a lead vaccine candidate antigen for intestinal schistosomiasis. Human vaccines Immunotherapeutics. 2013;9(11):2351–61 (PubMed PMID: 23880663; PMCID: PMC3981844).
50. Curti E, Kwityn C, Zhan B, Gillespie P, Brelsford J, Deumic V, Plieskatt J, Rezende WC, Tsao E, Kalampanayil B, Hotez PJ, Bottazzi ME. Expression at a 20L scale and purification of the extracellular domain of the Schistosoma mansoni TSP-2 recombinant protein: a vaccine candidate for human intestinal schistosomiasis. Human Vaccines Immunotherapeutics. 2013;9(11):2342–50 (PubMed PMID: 23899507; PMCID: PMC3981843).
51. Siddiqui AA, Siddiqui SZ. Sm-p80-Based Schistosomiasis Vaccine: Preparation for Human Clinical Trials. Trends Parasitol. 2017;33(3):194–201. https://doi.org/10.1016/j.pt.2016.10.010 (PubMed PMID: 27865740; PMCID: PMC5328854).
52. Siddiqui AJ, Molehin AJ, Zhang W, Ganapathy PK, Kim E, Rojo JU, Redman WK, Sennoune SR, Sudduth J, Freeborn J, Hunter D, Kottapalli KR, Kottapalli P, Wettashinghe R, van Dam GJ, Corstjens P, Papin JF, Carey D, Torben W, Ahmad G, Siddiqui AA. Sm-p 80-based vaccine trial in baboons: efficacy when mimicking natural conditions of chronic disease, praziquantel therapy, immunization, and Schistosoma mansoni re-encounter. Ann New York Acad Sci. 2018. https://doi.org/10.1111/nyas.13866 (PubMed PMID: 29888790).
53. Georgieff MK. Iron assessment to protect the developing brain. Am J Clin Nutr. 2017;106(Suppl 6):1588S–93S. https://doi.org/10.3945/ajcn.117.155846 (PubMed PMID: 29070550; PMCID: PMC5701704).
54. WHO. Malaria in children under five 2018 [08/17/2018]. Available from: http://www.who.int/malaria/areas/high_risk_groups/children/en/.
55. Blouin B, Casapia M, Joseph L, Gyorkos TW. A longitudinal cohort study of soil-transmitted helminth infections during the second year of life and associations with reduced long-term cognitive and verbal abilities. PLoS Neglected Trop Dis. 2018;12(7):e0006688. https://doi.org/10.1371/journal.pntd.0006688 (PubMed PMID: 30052640).
56. Lo NC, Snyder J, Addiss DG, Heft-Neal S, Andrews JR, Bendavid E. Deworming in pre-school age children: a global empirical analysis of health outcomes. PLoS Neglected Trop Dis. 2018;12(5):e0006500. https://doi.org/10.1371/journal.pntd.0006500 (PubMed PMID: 29852012; PMCID: PMC5997348, which is an organization that promotes prevention and treatment of soil-transmitted helminthiasis. The remaining authors declare no conflicts of interest).
57. Sun D, McLeod A, Gandhi S, Malinowski AK, Shehata N. Anemia in pregnancy: a pragmatic approach. Obstet Gynecol Surv. 2017;72(12):730–7. https://doi.org/10.1097/OGX.0000000000000510 (PubMed PMID: 29280474).
58. Brooker S, Hotez PJ, Bundy DA. Hookworm-related anaemia among pregnant women: a systematic review. PLoS Neglected Trop Dis. 2008;2(9):e291. https://doi.org/10.1371/journal.pntd.0000291 (PubMed PMID: 18820740; PMCID: 2553481).
59. Ajanga A, Lwambo NJ, Blair L, Nyandindi U, Fenwick A, Brooker S. Schistosoma mansoni in pregnancy and associations with anaemia in northwest Tanzania. Trans R Soc Trop Med Hyg. 2006;100(1):59–63. https://doi.org/10.1016/j.trstmh.2005.06.024 (PubMed PMID: 16219330).
60. Tay SC, Nani EA, Walana W. Parasitic infections and maternal anaemia among expectant mothers in the Dangme East District of Ghana. BMC Res Notes. 2017;10(1):3. https://doi.org/10.1186/s13104-016-2327-5 (PubMed PMID: 28057071; PMCID: PMC5217638).
61. Christian P, Khatry SK, West KP Jr. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. Lancet. 2004;364(9438):981–3. https://doi.org/10.1016/S0140-6736(04)17023-2 (PubMed PMID: 15364190).

62. Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, Kudish K, Cieslak PR, Lewis M, Shang N, Martin SW. Impact of the US maternal tetanus, diphtheria, and acellular pertussis vaccination program on preventing pertussis in infants <2 months of age: a case-control evaluation. Clin Infect Dis: Official Publ Infect Dis Soc Am. 2017;65(12):1977–83. https://doi.org/10.1093/cid/cix724 (PubMed PMID: 29028938; PMCID: PMC5754921).

Out of Curiosity from Blue Sky Research to Medical Innovation

10

Rudi Balling

10.1 Introduction

Curiosity, the intrinsic urge to know and to find out more about whatever has caught our mind, seems to be laid down in our DNA. Much has been written about the evolution and the forces that drove human evolution. We cannot repeat the experiment, but try to imagine human mankind without the trait called "Curiosity"? This trait seems to be closely associated with genes related to the dopamine and the dopamine receptor system, which in turn we know is connected to personality traits such as novelty-seeking, exploration behavior, risk-taking, or reward-expectancy and, on a more darker side, addiction [10].

At the "*Curious*" Conference 2018, there was a plenty of opportunity to witness the phenotypic spectrum related to curiosity. During the 3-day conference held on the occasion of the 350th birthday of the Merck Company in Darmstadt, Germany, the fruits and prospects of curiosity unfolded in a stunning way. We are living in an age of scientific acceleration, if not revolution, be it the genomic revolution, the resolution revolution or the revolution in artificial intelligence. Interestingly, they all seem to come together at or around the same time, and one is entangled with the other. Just a decade ago, it was not possible to apply powerful machine learning algorithms since we were lacking both computational power and sufficient capacity and infrastructure for data storage. Moreover, without super-resolution microscopy or affordable whole-genome sequencing, we would not have the required data to look into the architecture and dynamics of living systems.

In 2012, Eric Topol published his bestseller "The creative destruction of medicine" describing the dramatic changes that come along with the application of smartphones and other digital devices in clinical medicine and health care [21]. Topol borrowed the term "creative destruction" from Joseph Schumpeter who, in [19], had described economic transformations that accompany radical innovation. He even called the process "Schumpeterization." At the Curious Conference, one could inhale "Schumpeterization." The talks from the leaders in the field spanned an incredible breadth, from chemistry and physics to biology and medicine to artificial intelligence and robotics. As mentioned, these disciplines now come together. And they challenge not only the traditional way of "doing science" but also the training and education of the next generation of scientists. We need experts and we need generalists. We need detail and we

R. Balling (✉)
Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Campus Belval, Belvaux, Luxembourg
e-mail: rudi.balling@uni.lu

Scripps Translational Science Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_10

need abstraction. But foremost, we need cooperation between scientists from this wide spectrum of disciplines. The conference was a marvelous demonstration of how interdisciplinarity will transform scientific discovery and innovation.

This paper is not about a comprehensive and fully inclusive report about the Curious 2018 conference. It is about the spirit and some of the impressions that the conference conveyed. The choice of the conference title was certainly "Spot on."

10.2 The Resolution-Revolution

The progress in science always hinges upon progress in technology. It was the increased optical resolution that transformed astronomy, cosmology, and later biology and medicine. But it wasn't just the higher resolution that made the difference. It was the necessity to develop new mathematical tools or new hypotheses following puzzling observations after the introduction of new instruments or technologies, particularly when new data did not fit old paradigms. Examples are calculus, non-Euclidian geometry, or the theory of relativity, all of which had their roots in attempts to explain abnormalities in planetary motion. One can only speculate how Anton van Leeuwenhoek must have felt in 1674 when he first observed bacteria in his microscope. At *Curious 2018*, the report of Joachim Frank about the latest version and state of the art of single-particle cryo-electron microscopy felt like a "Leeuwenhoek Moment". Seeing is believing. With a routine resolution of now 3–4 Angstroms, and in many cases of even 2 Angstroms, drug design will enter a new phase.

However, there is more to it. A repeating theme during the conference was the very rapid miniaturization and automation that takes place almost immediately following the establishment of a proof of principle for new technologies. This is also the case for single-particle cryo-EM. Powerful new algorithms now extract at once many, if not all, realized configurations of a molecule. It allows us to analyze large ensembles of molecules that often go into the millions, and even detect rare states which would otherwise almost never be encountered. This permits us to measure states in a continuum and see how they are connected. A continuum of density distributions will eventually lead to detailed maps of entire energy landscapes.

Single-particle cryo-EM offers new opportunities and stimulus for the development of new statistical and mathematical approaches. Frank, for example, described "Manifold embedding", where by projecting these manifolds into low-dimensional subspaces, we get distributions of the images of the molecules that can be transformed into Boltzmann relationships and free energy landscapes [7]. Looking at the example of a Ca^{2+}-release channel with and without ligands, one can infer how to get from one energy state to another and then look at the dynamics and trajectories taken in response to an activation signal.

Makoto Fujita gave a nice example about a technical innovation that overcomes the traditional limitation of X-ray crystallography, where the target molecules must be obtained as single crystals The recently developed "Crystalline sponge method" does not require crystallization of the sample [12]. Instead, tiny crystals of porous complexes are provided as a host framework. The solution of a target is soaked in the porous complex host crystal in a way that the complexes can absorb the target molecules. Due to the tiny size of these crystals, the required sample amount is only in the nano- to microgram range. Efforts are now underway for high-throughput automation that eventually turn crystal-free X-ray crystallography into a machine.

10.3 Pushing the Dimension Frontier: From Temporal to Spatial to Distributions

To fully understand the biological systems and their perturbations in disease, we must develop multiscale mathematical and computer models to study the dynamics of the biological systems. These scales range from the atomic to the

molecular and cellular scale all the way to the whole organism. Garry Nolan introduced us into the new era of multiscale pathology, using multi-dimensional single-cell antibody or transcription readouts [6]. For the first time, we are able to span from a molecular level all the way up to the 3D architecture of the spatial organization of a cell. Nolan's urge to "get away from Western Blots" led him to pave the way for the simultaneous measurement of thousands of transcripts, dozens, and soon hundreds of proteins and an entire metabolome, initially in tissue sections, and now in entire 3D reconstructions. The development of CYTOF already marked a major shift in cell biology analytics, and now newly developed technologies move without too much effort from tissue to atomic scales and back. And we see the same driving forces: miniaturization and automation. The newly obtained insight into subcellular architectures of cells and corresponding temporal and spatial information will inform us about new strategies for drug development and other medical applications. This was another "Leeuwenhoek moment" at the conference.

As was described for single-particle-cryo-EM, it was again the possibility to upscale and parallelize the measurements that opened the door to identify, count, and order the continuum of single microstates. At this point of time, the focus is still on the transcriptional level, but this will certainly change in the future with improved analytic methods for single-cell proteomics or metabolomics. We are moving the average values of these microstates to probabilities or frequency distributions. The huge amount of data produced in this process motivates the development of new mathematical and statistical tools in order to deconstruct the data and extract the relevant information. The "Wanderlust" algorithm, based on the concept of pseudotime [16], is one example of mutual synergistic relationships between data production and data analysis. B-cell leukemias were used as an example for the power of the high-resolution, high-throughput, and high-dimensional data analysis. The objective was to order B-tumor cells along the path of B-cell differentiation, all the way from stem cells to mature B-cells. Despite the fact that tumors represented different genetic disorders, it was possible to order the tumor cells according to their best fit on the differentiation trajectory. Interestingly, all B-cell diseases clustered at a couple of places in this trajectory with surprisingly tight distributions. The hope is to infer whether this ordering can help predicting relapses.

From a translational medicine perspective, the key question is whether this information will predict the best therapies for patients. And probably even more important, what underlying molecular mechanism determines the developmental arrest in different B-cell tumors. It appears that differentiation is a continuous trajectory not a chain of discrete stages. The race is on to start looking at dynamics of molecular assemblies, molecular machines, and entire temporal and spatial trajectories of biochemical and cellular pathways. However, without the powerful toolbox of machine learning and AI, none of this will be possible. And, as mentioned already, we need the data to provide machine learning with its power. Large data meets smart algorithms.

We also heard about exciting developments to combine temporal with spatial scales. Using DNA-based barcoding combined with single-cell subcellular antibody staining, one can not only follow distributions and migrations within cells during differentiation or disease processes, but also trace the binding of proteins to specific regions of the genome. Gene expression markers define the niche and the expression of specific proteins, which reflect the postal codes and addresses within cells.

We will be able to follow in 3D over time the movement of single cells and deduct where cells might be in tissues. The first validation and proof of principle studies used melanomas, and we can expect that the integration of temporal and spatial information, moving from 1D to 5D, will soon be applied for other diseases and many biological processes. Cell biology will be studying molecular machines, how they are put together and how they are integrated into an assembly line. Cells are looked at as factories with an ensemble

of assembly lines, workflows, and underlying control systems. It took quite some time to move from the invention of the steam engine to the construction of steamships or the electric generators. We might be in a similar phase of cell biology and bioengineering. The difference is the acceleration. Whereas it took decades to build iterative generations of steam engines, it is now a question of years or months to catapult technologies in life sciences from proof of principle to reduction to practice.

The next target of even higher resolution is to go down to single-atom sensitivity, being able to read every atom in a protein. The necessary tools are also already at the horizon, with Atomic Microscope by Projection (AMP) being one of them [8]. It will still take weeks to read every molecule in a cell, but it will not come as a surprise that AMP is already motivating the development of new machine learning algorithms. Hence, we can expect that eventually we will move the past this roadblock.

10.4 From Chemistry to Biology and Back Again

Chemistry can be exciting, as clearly seen by a number of talks that presented highly innovative new ways of chemical synthesis. New combinations and successions of chemical reactions and intriguing catalysts are developed that require a deep understanding of chemical bonds, down to the level of quantum chemistry. One of the fields that exploded in recent years is organo-catalysis. Benjamin List presented new catalysis concepts that allow enantio-selective- and complement bio- and transition metal catalysis. Insight was given into new catalysts, such as proline, and important progress in the synthesis of natural products and pharmaceuticals. His group was also at the origin of a new approach to asymmetric catalysis, now known as asymmetric counter-anion-directed catalysis (ACDC) [14].

Again, as seen before, once a proof of concept has been obtained, and the objective is to upscale it to a technical scale. For example, in the field of Lewis acid catalysis, it was clear that considerable progress has been made on this front. Varrinder Aggarwal described assembly lines for asymmetric synthesis that are able to create molecules with tailored shape and talked about the power of organic borane chemistry [4]. This allows the synthesis of highly efficient and specific natural product at a level that was thought impossible just a few years ago.

An equally exciting area is the exploding field of nanomaterials that can be used for new applications in life sciences and clinical medicine. Ulrich Wiesner gave us an idea of what to expect and presented some of the latest development in the design and synthesis of completely new nanomaterials based on silicon [3]. Nanomaterials from silicon can be made with an extremely small size, even smaller than the renal cutoff. This then allows their application as delivery vehicles or when combined with imaging technologies as reporter molecules for high-resolution clinical imaging. Because of their small size, silica-based nanoparticles are taken up by lymph nodes to visualize individual cancer cells. The objective is to use this resolution to differentiate, for example, lymph nodes that may need to be removed within the context of tumor surgery. The new generation of reporters should also allow a better molecular-based stratification of tumors. Apparently, the path to using silica nanoparticles for drug delivery is more difficult, but major efforts are also put into this direction. The extremely small size of nanoparticles apparently has another advantage. In most cases, one has to go to micromolecular drug concentrations. However, the use of this new generation of nanoparticles might allow up to 4000 times less of a drug compared to traditional treatment regimes.

A lot of efforts are put into the design and development of new materials that have entirely new or improved properties such as increased strength, deformation behavior, or the ability for self-healing. In many cases, the design of new materials is inspired by properties found in natural materials. One such example is human cartilage that allows virtually frictionless mechanical motion within joints, even when they undergo strong compression. Whereas many

activities in material design so far had a focus on attractive interactions. Takuzo Aida presented new composite hydrogels with anisotropic mechanical properties [22]. They harnessed the concept of embedding anisotropic electrostatic repulsion between negatively charged titan nanosheets and obtained a hydrogel that deforms easily under shear forces if applied parallel to the embedded nanosheets and resists compression forces that are applied orthogonally. He gave a number of examples of materials with other fascinating new properties. One was the development of new materials with optical properties of aqueous colloidal dispersions. This allowed the introduction of anisotropic magnetic susceptibility of titan-based nanosheets, which might serve as an optical switch that can be remotely operated by magnets and light.

One of the world's most famous engineer of molecular machines is Fraser Stoddard. He developed fascinating artificial molecular machines on the basis of the "mechanical bond" [5]. His concept of the development of mechanically interlocked molecular architectures utilize molecular recognition and molecular self-assembly processes and has led, for example, to new catenanes and rotaxanes. These new molecular machines can serve as molecular pumps, sensors, actuators, amplifiers, or switches. He compared his efforts to improvements that took place in the performance of the steam engine. These went from catalyzing the development of electric internal combustion to diesel engines and all the way up to jet rockets. He pointed out that often the different phases of improvements were overlapping.

10.5 Chemistry of the Biological World

The conference was a wonderful demonstration where chemistry is heading and the exciting developments that are underway at the interface of chemistry and biology. Frances Arnold laid down her view on how we can learn from the chemistry of the biological world [1]. No rational design will ever be possible to come up with the innovative solutions that nature produces with the combination of mutation and selection. Enzymes can look at as genetically encoded machines that self-replicate, self-assembly, and self-correct. She called this a "sustainable chemistry", and she clearly spelled out the objective: build a new chemistry as a central science using the platform of biological chemistry. At the core of these developments are nature's most powerful tools, mutation, and selection. Equally important is the transformation of the biological code into a digital code. Craig Venter described life as a DNA software system and the billions of natural gene sequences as a great library for new proteins and protein functions that might be useful for applications [20]. Frances Arnold called it the "Recoding of life." However, she also wanted to go one step further.

Geneticists sometimes say: "The art is in the assay." This also holds for setting up new and innovative screens to select for completely new functions that even nature did not come up with and that will expand the horizon and the space of chemistry of the biological world. It is now possible to synthesize any DNA that we want, send the code around in the world, and get the DNA quickly by mail. The challenge however is still to anticipate or design the function of new proteins. This composition problem can be partially circumvented by the design of smart selection assays that enforce onto the space of possible proteins and protein function-specific constraints. Jef Boeke extended this view by talking about genome writing. His goal is to develop *Sacharomyces cerevesia* 2.0 as a testing ground for building entire new genomes [17]. The strategy is not starting from scratch but always begins with a living cell and a natural chromosome. Then step by step the natural genome is substituted. This overwriting uses a stepwise substitution of chromosomal regions walking along each and every chromosome until the entire genome is replaced.

The heroic effort became clear when he explained that it took an entire year just to plan the design. In the meantime, the first fruits are getting harvested, for example, new insight into the function of repeats, introns, or other components, which they partially or totally removed

from a genome and the resulting consequences were analyzed. The comparison of natural and synthetic chromosomes already pays off. New yeast strains with different temperature ranges have been produced. Interspecies diploids with boosted resistance traits were obtained, and the chromosome was transferred to completely new places in the nucleus. We can expect that this kind of building a synthetic genome will teach us a lot of new biology. And, similar to the other areas of new technology development, the power of automation and miniaturization will become important. Today we have DNA synthesizers. Tomorrow we will have cell synthesizers.

10.6 Understanding Diseases—The Prerequisite for Translation into Clinical Medicine

Data needs to be transformed into information, and information needs to be transformed into knowledge. Despite all the progress in technology, our understanding of the complexity of biological systems, and therefore the real underlying mechanisms of disease pathogenesis, is much more sobering. Jeremy Nicholson gave us an idea about the current state of the art of clinical phenotyping [13]. We are still struggling with the integration of heterogeneous data sets that can be produced based on the latest omics or imaging technologies or that consider the wide spectrum of clinical records. Intelligent knives and endoscopes capable of analyzing tissue at the molecular level at the same time that they cut through it herald the next generation of diagnostics. However, a clinical phenotype, be it an omics signature or a high-resolution image, is a snapshot and representation of a high-dimensional underlying molecular network. It does not give us an explanation for the mechanisms involved. In addition, information such as whole-genome sequencing might not be as informative, particularly if used in a clinical setting. Furthermore, we will need to develop translational technologies for real-world applications that allow to accompany and optimize patient's journeys. We are still far away from reliable predictive disease modeling, and we urgently need better tools for data visualization. According to Nicholson, precision medicine requires precision metrics, a goal which we have not yet reached.

Whereas a major trend can be observed by looking at patients and patient material, even in preclinical settings, a deep mechanistic understanding of biological processes and of disease pathogenesis does require animal models. Bruce Beutler described his efforts to carry out genome saturation using chemical mutagenesis in mice [2]. He reminded us that point mutations are not the same as gene knockouts, since most of them do not lead to complete loss of function alleles. His approach of phenotype-driven mutagenesis already provides us with a treasure trove for functional studies and complements nicely with the work of Emmanuelle Charpentier [11]. She gave her view on the development and potential of RNA-programmable CRISPR-Cas9 technology that can only be described as transformative. It is now possible to obtain precise and efficient engineering or correction of mutations, modulation of gene expression, and marking of DNA in a wide variety of cell types and organisms. The uptake within the scientific community and industry was fulminant and the translation into clinical applications is underway in full swing. CRISP-Cas9 technology, however, also raises a new dimension of ethical questions, which are not only of a scientific nature. They do require a scientific understanding of the technology and a dialogue with society.

10.7 Medicine—Quo Vadis?

There are very high expectations that progress in new technologies, new materials, and new insight into biological systems will translate into clinical medicine. How close are we in our efforts to improve diagnosis, therapy, or prevention of diseases? How long does it take curiosity-driven research to improve patient's lives? One of the most successful clinical areas is immunotherapy. Crystal MacKall described her effort in leveraging the power of immune systems to fight cancer

by using checkpoint inhibitors, one of the hottest frontiers in clinical oncology [15]. Despite the excitement, there are still main challenges ahead, mostly related to therapeutic resistance and remission of tumors. One strategy to overcome therapy resistance is to use bispecific CAR combinations. However, complete eradication, or at least limiting the growth of tumors, is still not there. Tumors still kill, and we have to admit that we do not yet understand molecular and cellular mechanisms that underlay the development of complex biological systems. Diseases can be looked at as either perturbations of biological systems or compromised feedback regulations, with many components and interactions that are highly nonlinear and operate far from thermodynamic equilibria. Maybe we have to proactively adopt tools of statistical physics and thermodynamics to better understand the development and behavior of tumor cells. Or maybe we have to invest much more time in first answering the question that was put forward by Schrödinger in the 40s: "What is life?" [18]. A large part of this is about emergence and self-organization—questions of fundamental research.

10.8 AI and Robotics Will Transform Medicine

Medical research and health care have to a large degree developed into data science. Scott Spangler made clear that artificial intelligence and machine learning have had the biggest impact of all developments. He stressed that integrating machine learning and AI is no more an option but a requirement and that it is essential to use all the data available. Machine learning has been around for quite some time, but only with the availability of large amounts of data, of increased computational power and data storage capacity, could impact we witness today be reached [9]. He also pointed out the fine balance, with respect to the development of new machine learning algorithms, in terms of being very general or very specific. The goal should be to develop deep approaches that might not be the most specific complex algorithms, but are able to be more broadly applicable and generalizable. We need to use what we know to extract what we don't know. New approaches like graph diffusion will be important to move into the territory of the known unknowns and eventually the unknown unknowns. One of the limitations of machine learning is that although many of the classifications and corresponding predictions are becoming much better, machine learning does not come up automatically with a mechanistic model. Mechanistic models need validation. With the increasing availability of data, that eventually spans longer time periods, we can use older data to gain confidence in our predictions. From a medical point of view, we need to have a good understanding about false positive or false negative error rates. Information technology and biotechnology converge.

10.9 Interdisciplinarity

Technology is exciting, but we should not forget that the Achilles tendon is still the necessity to relate the results, for example, high-resolution temporal and spatial information, to clinical outcome. This is where interdisciplinary cooperation comes in again. Interdisciplinarity is easier said than done. Going out of one's comfort zone and crossing the boundaries of the discipline, we were initially trained and require curiosity. It also needs a certain amount of risk-taking, and the rewards often need a long incubation time, with a highly uncertain return of investment. It needs a blue sky.

References

1. Arnold FH. Directed evolution: bringing new chemistry to life. Angew Chem Int Ed. 2018;57:4143–8. https://doi.org/10.1002/anie.201708408.
2. Beutler B. Innate immunity and the new forward genetics. Best Pract Res Clin Haematol. 2016;29:379–87. https://doi.org/10.1016/j.beha.2016.10.018.
3. Chen F, Ma K, Madajewski B, Zhuang L, Zhang L, Rickert K, Marelli M, Yoo B, Turker MZ,

Overholtzer M, Quinn TP, Gonen M, Zanzonico P, Tuesca A, Bowen MA, Norton L, Subramony A, Wiesner U, Bradbury MS. Ultrasmall targeted nanoparticles with engineered fragments for imaging detection of HER2-overexpressing breast cancer. Nat Comm 2018;9:4141. https://doi.org/10.1038/s41467-018-06271-5.

4. Collins BSL, Wilson CM, Myers EL, Aggarwal VK. Asymmetric synthesis of secondary and tertiary boronic esters. Angew Chem Int Ed. 2017;56:11700–33. https://doi.org/10.1002/anie.201701963.
5. Stoddart JF. Mechanically interlocked molecules (MIMs)-molecular shuttles, switches and machines (Nobel Lecture). Angew Chem Int Ed Engl. 2018;56(37):11094–125. https://doi.org/10.1002/anie.201703216.
6. Duckworth AD, Gherardini PF, Sykorova M, Yasin F, Nolan GP, Slupsky JR, Kalakonda N. Miltioplexed profiling of RNA and protein expression signatures in individual cells using flow or mass cytometry. Nat Protoc 2019. https://doi.org/10.1038/s41596-018-0120-8.
7. Frank J, Ourmazd A. Continuous changes in structure mapped by manifold embedding of single-particle data in Cryo-EM. Methods. 2016;100:61–7. https://doi.org/10.1016/j.ymeth.2016.02.007.
8. Gavara N. A beginners guide to atomic force microscopy probing for cell mechanics. Microsc Res Tech 2017; 80:75–84. https://doi.org/10.1002/jemt.22776.
9. Goodfellow I, Bengio Y, Courville A. Deep Learning. Cambridge, MA; The MIT Press; 2016, ISBN 9780262035613.
10. Gruber MJ, Gelman BD, Ranganath C. States of curiosity modulate hippocampus-dependent learning via the dopaminergic circuit. Neuron. 2014;84:486–96. https://doi.org/10.1016/j.neuron.2014.08.060.
11. Hille F, Richter H, Wong SP, Bratovic M, Ressel S, Charpentier E. The biology of CRISPR-CAS: backward and forward. Cell. 2017;172:1239–59. https://doi.org/10.1016/j.cell.2017.11.032.
12. Hoshino M, Khutia A, Xing H, Inokuma Y, Fujita M. The crystalline sponge method updated. IUCrJ. 2016;3:139–51. https://doi.org/10.1107/S2052252515024379.
13. Hoyles L, Fernandez-Real JM, Federici M, Serino M, Abbot J, Charpentier J, Heymes C, Latorre LJ, Anthony E, Barton RH, Chilloux J, Myridakis A, Martinez-Gili L, Maria Moreno-Nasvarette J, Benhamed F, Azalbert V, Blasco-Bacque V, Puig J, Xifra G, Ricart W, Tomlinson C, Woodbridge M, Cardellini M, Devato F, Cardolini I, Porzio O, Gentileschi P, Loez F, Foufelle F, Butcher SA, Holmes E, Nicholson JK, Bureelin R, Dumas ME. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat Med. 2018;24:1070–80. https://doi.org/10.1038/s41591-018-0169-5.
14. Mahlau M, List B. Asymmetric counteranion-directed catalysis: concept, definition and applications. Angew Che Int Ed. 2013;52:518–33. https://doi.org/10.1002/anie.201205343.
15. Brown CE, Mackall CL. CAR T cell therapy: inroads to response and resistance. Nat Rev. 2019;19:73–4.
16. Reid JE, Wernisch L. Pseudotime estimation: deconfounding single cell time series. Bioinformatis. 2016;32:2973–80. https://doi.org/10.1093/bioinformatics/btw372.
17. Richardson SM, Mitchell LA, Stracquadanio G, Yang KY, Dymond JS, DiCarlo JE, Lee D, Huang CLV, Chandrasegaran S, Xai Y, Boeke JD, Bader JS. Design of a synthetic yeast genome. Science. 2017;355:1040–4.
18. Schrödinger E. What is life? The physical aspect of the living cell. Cambridge: Cambridge University Press; 1944. ISBN 0-521-42708-8.
19. Schumpeter, Joseph A. Capitalism, Socialism, and Democracy. 3d ed. New York: Harper and Brothers; 1942 (1950).
20. Telenti A, Pierce LCT, Biggs WH, Di Jiulio J, Wong EHM, Fabani MH, Kirkness WF, Moustafa A, Shah N, Brewerton SC, Bulsara N, Garner C, Metzker G, Sandoval E, Perkins bA, Och FH, Turzpaz Y, Venter JC. Deep sequencing of 10,000 human genomes PNAS 2016; 113:11901–11906. www.pnas.org/cgi/doi/10.1073/pnas.1613365113.
21. Topol E. The creative destruction of medicine. How the digital revolution will create better health care. New York: Basic Books; 2012.
22. Yanagisawa Y, Nan Y, Okuro K, Aida T. Mechanically robust, readily repairable polymers via tailored nonovalent crosss-linking. Science. 2018;359:72–6. https://doi.org/10.1126/science.aam7588.

From Diagnosing Diseases to Predicting Diseases

11

Rudi Balling, Jorge Goncalves, Stefano Magni, Laurent Mombaerts, Alice Oldano and Alexander Skupin

11.1 Introduction

Within the last 100 years, the spectrum of diseases has dramatically changed [1]. In the past, infectious diseases dominated the scene. Today, a remarkable increase in life expectancy has led to a surge of chronic diseases in the general population, many of them associated with long periods of morbidity [2]. As a consequence, early diagnosis has become more important in today's medicine. Often, clinical signs of a chronic disease are preceded by changes in preclinical parameters that can be detected by blood analysis, imaging techniques or by the measurement of other biomarkers or surrogate markers that are indicative of pathophysiological developments.

Despite the enormous progress that has been made in genomics, in non-invasive imaging and in the corresponding data analytics, the key challenge for anticipating disease onset is still the large heterogeneity between individuals in disease manifestation, disease progression and therapeutic response. Major efforts are therefore underway to identify meaningful general biomarkers that allow the early detection and a mechanism-based stratification of upcoming diseases on an individual basis. Unfortunately, the validation of personalized highly predictive biomarkers has not yet achieved satisfactory standards [3]. Single parameter biomarkers show large individual variation and most of the time have a limited predictive value in terms of clinical outcome [4, 5]. Multifeature biomarkers, such as gene transcription or metabolomic signatures are currently being tested. Whereas it is typically not difficult to discriminate between a healthy and a fully developed diseased state, the differentiation between a healthy and a pre-disease state is much harder. High glucose levels, e.g., can be easily measured and are indicative of diabetes. However, it is much harder to detect pre-diabetes when fasting glucose levels are still in the normal range.

11.2 Diseases as Perturbations of Networks

Biological systems are extremely complex and can be described as dynamic networks. Networks are in fact a powerful way to describe complex systems in terms of their parts (the nodes of the network) and the interactions among these parts (the links of the network). These networks are often composed of a very large number of

R. Balling (✉) · J. Goncalves · S. Magni · L. Mombaerts · A. Oldano · A. Skupin
Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Campus Belval, Belvaux, Luxembourg
e-mail: rudi.balling@uni.lu

R. Balling
Scripps Translational Science Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_11

components, which are interacting in a highly non-linear manner and often operate far from their thermodynamic equilibrium. However, biological systems are also highly adaptive as a result of a multitude of positive and negative feedback loops that lead to some of the most fascinating and important characteristics of life, self-organization and emergence [6]. Adaptation requires the sensing, identification, integration and reaction to external and internal stimuli across many scales. The time scales in which biological systems operate and react can range from seconds and minutes to hours, days or years. In analogy to the description of biological systems as networks, diseases and their development can be described as perturbations of networks loosing resilience over time and eventually tipping into undesired disease states [7].

11.3 Theoretical Background and Conceptual Framework of Critical Transitions

A major impetus for the study of complex biological and disease systems has been derived from physics, particularly from non-equilibrium dynamics. Of particular interest are critical transitions or catastrophic shifts, where a so-called tipping point is reached and the system rapidly shifts from one stable state to another qualitatively different state. The switch from one state to another can be a result of either their intrinsic dynamics, of external forcing and perturbations or combination of both. Critical transitions occur when a critical threshold is crossed and reflect the long-lasting re-organizations of a complex system that can subsequently lead to a sudden and rapid change and a qualitatively different system state [8, 24].

One of the first models used to unravel potential universalities of critical transitions was the 2D—"Ising model". This model describes phase transitions of ferromagnetic material at a critical temperature [9, 10]. The Ising model is an idealized statistical-physics model of ferromagnetic material based on simple interacting magnetic spins that nevertheless leads to basic insights and features of real magnets such as phase transitions at a critical point. While mathematically simple, this model captures fundamental characteristics of phase transitions and is widely used to model transitions in very diverse systems like crises in financial markets [11].

External forces like environmental perturbations or changes in the underlying network structure [7] can lead to a continuous or rapid shift from one stable state to another. Well-functioning feedback processes typically ensure a rapid adaptation response to such changing environmental conditions in a way that the system can quickly and reversibly shift within certain boundaries [12]. Such a region of resilience indicates a basin of attraction of the system. However, once a tipping point has been crossed and a critical transition occurred, the system state might reach a new qualitatively different attractor that is rather stable and might even become irreversible. Reversing to the previous attractor often requires more energy than was required in the forward reaction—a phenomenon called hysteresis.

A first biological metaphor used by Conrad Waddington describes cell differentiation as an energy landscape in which the relative strengths of attractors are represented as valleys and hills, and the trajectory of the development of a system (or cell) state is considered as the rolling of a ball from the top to the bottom of this landscape. Jumping from one valley, or attractor, to another, requires energy and occurs with a certain probability [13]. The corresponding probability function is influenced by a change in the local or global landscape such as the shape of a valley. A transition between attractors can occur by putting more energy into the system either in an inductive way such as by specific transcription factors or in a stochastic manner like in spontaneous differentiation. The landscape metaphor explains why small external perturbations can be sufficient to change a trajectory from one attractor to another when a system moves closer to a tipping point, which corresponds to a summit or branching valleys in the landscape.

The existence of alternative stable system states and their sudden and dramatic changes has

also been observed in a wide range of complex systems such as in ecosystems, climate, financial markets or in diverse biological systems [14–21]. Such regime shifts can have serious consequences, e.g., for the environment or the health of a person. Bifurcation theory can be used to describe the structural changes that occur in the development of a dynamic system. Based on system parameters, bifurcation analysis can identify regimes of unique or multistable attractors, classify their underlying dynamics into oscillatory or damped relaxation and predict transition between them. Dependent on the response of the system after moving beyond a tipping point, different classes of bifurcations have been defined that can lead to multiple equilibria and attractor states, e.g., saddle-node-, trans-critical- or Hopf-bifurcations [22, 23].

11.4 Early Warning Signals of Critical Transitions in Complex Systems

While bifurcation theory is applicable for systems that are fully defined by a complete set of dynamic equations, such a description for high-dimensional, complex real-world systems is typically lacking. However, comparisons of the response of different complex systems have led to the conclusion that certain generic features of the underlying network structure might still indicate whether such a critical threshold exists [25]. Interestingly, recent investigations suggest the existence of certain generic indicators that can be used as an "Early warning signal" (EWS) that indicates if the system is moving close to a tipping point [24–27]. The identification of early warning signals could help to develop risk management strategies and initiate compensatory measures or in an ideal scenario allow the prevention of an upcoming critical transitions. For this reason, understanding the theoretical and mechanistical basis of early warning signals and the identification of generic parameters that indicate such shifts are an intense area of research in many disciplines like in climate research, ecology, economics or sociology [20, 26, 27]. Although it is now recognized that dynamics of many complex systems exhibit some universal properties near critical transition points (Fig. 11.1), accurate predictions of catastrophic shifts remain a challenge.

Empirical and theoretical studies suggest that the recovery rate at which a system returns to its initial equilibrium state after a small perturbation is reducing when a critical transition is approached [26]. The stability of the attractor (corresponding to the depth of a valley in the energy landscape) shrinks, and as a result the resilience of the system decreases. The increased time needed for recovery might then be used to estimate the distance of the system to a tipping point. This phenomenon is called "Critical Slowing Down" (CSD). Critical slowing down might only apply for systems around their equilibrium point under conditions of small stochastic fluctuations [28]. Nevertheless, evidence for CSD has been found in paleoclimate records in the context of logistically growing resources such as excessive grazing, fishing or biomass harvesting [29]. Critical slowing down has also been shown to indicate the transition of spiking in neurons of the mammalian cortex [30] and the self-termination of human seizures [31].

If a system approaches an underlying bifurcation, critical slowing down can also be measured by an increase in the autocorrelation of its dynamic observables. Larger and stronger correlations are observed between successive states of the system over time. This increase in autocorrelation reflects a longer memory for perturbations because it takes more time for the impact of the external forcing to dissolve [26]. In addition to the increased recovery time and the increased autocorrelation, the variance of the fluctuations of the system is going up due to the decreased stability of the attractor. In some critical transitions, the system exhibits flickering when the intermediately decreased separation of attractors allows for stochastic back and worth transitions until the alternative attractor is eventually gaining stability and becoming the new stable state [32]. Therefore, flickering can be

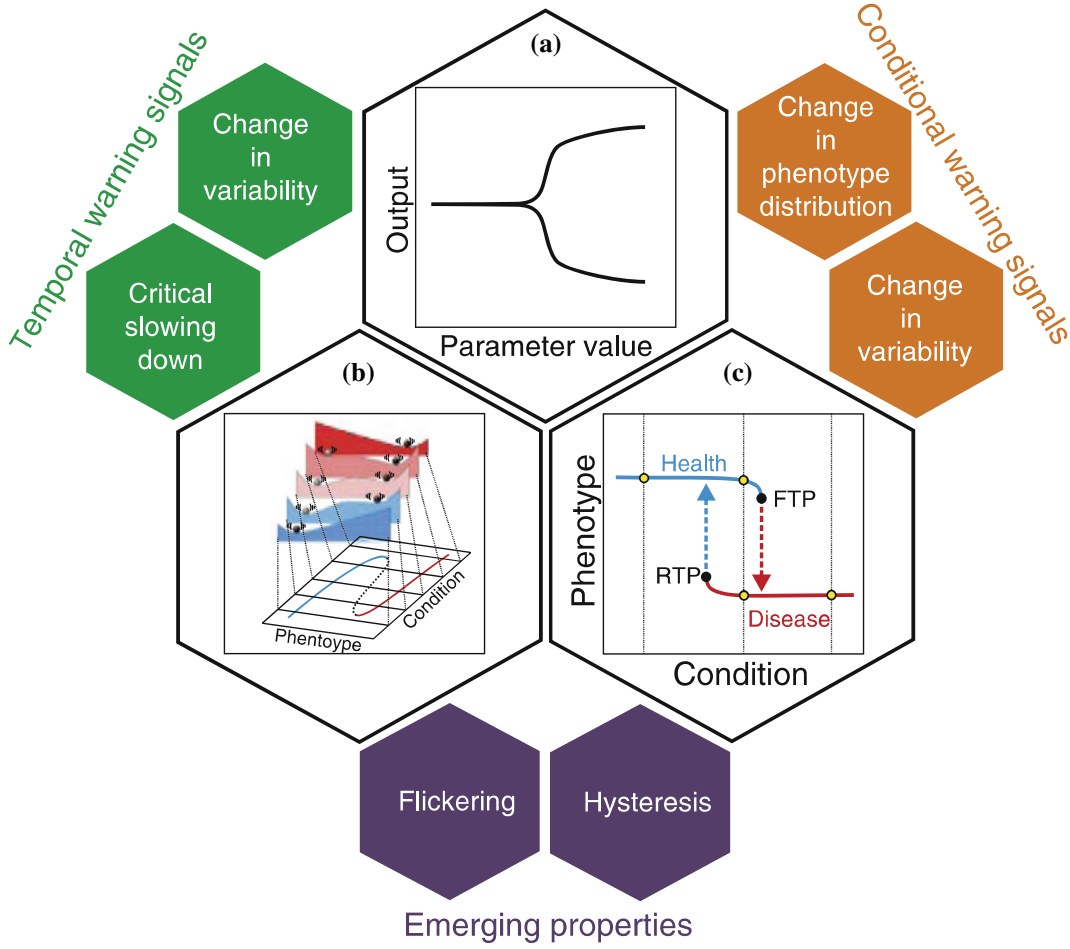


Fig. 11.1 Temporal and conditional warning signals

considered as an extreme mechanism captured by an increase in variance. Since both autocorrelation and variance measure rates of change, it is not surprising that also higher moments, which quantify the properties of fluctuations, like skewness and kurtosis, change [33].

11.5 From Physics and Ecology to Clinical Medicine

So far, research on early warning signals and critical transitions was mainly carried out in applications related to theoretical and practical physics and ecosystems. However, many aging and chronic diseases are also characterized by a loss of resilience and a sudden transition from a healthy to a preclinical disease state and finally to a clinical state with overt disease symptoms arising. Catastrophic shifts can, e.g., be observed during the progression trajectories of acute or chronic diseases, such as cardiovascular events, epilepsy or diabetes [34–36].

Key contributions to the study of complex biological systems were made by Stuart Kauffman and his collaborators. They proposed that cell differentiation can be described as dynamical attractors of gene regulatory networks and the development of specific cell types as transitions between cell fate attractors [37]. Transcript profiling was used to describe the state of a cellular system as a "Waddington type landscape" with

the valleys representing attractors. A differentiation process is therefore dependent on its current state, the architecture of the surrounding landscape, but it is also a stochastic process with Markov-like processes of transition probabilities reflecting the inherent molecular noise [38]. Disruption of regulatory networks by genetic or environmental perturbation can lead to changes in the network topology by rewiring and induce different cell types or abnormalities in cell differentiation as it is seen, e.g., in cancer [37]. The ability to follow the expression-trajectories of individual genes during differentiation and diseases processes has opened new opportunities to identify critical transitions and potential corresponding early warning signals.

A "thermodynamically inspired" approach, known as surprisal analysis, has been introduced by Remacle et al. [39] and applied by Zadran et al. [40] to monitor global miRNA expression in glioblastoma patients. Instead of using fold-changes and cutoffs of transcripts, thermodynamic weights that are proportional to the transcript abundance were used, a concept borrowed from information theory. In this approach, the most stable balanced transcript distribution is identified at every stage of the disease, in addition to the less stable transcriptional networks that maintain cells away from the balanced state. The authors were able to identify a glioblastoma-specific signature that allowed the discrimination of healthy and glioblastoma patients. Kravchenko-Balasha et al. [41] extended the thermodynamic-based approach to proteomic data.

11.6 Dynamic Network Biomarkers

While in many physical and some biological systems, few quantities can be monitored with high temporal resolution, complex biological networks can be typically only characterized at a few time points but therefore with high-dimensional omics readouts. To address this challenge, Chen et al. [42] developed the concept of "Dynamical network biomarkers (DNB)" as a means to identify early warning signals for an imminent phase transition in the development of diseases [43]. Whereas it is generally possible to identify a disease state from a healthy state, it is much more difficult to discriminate a pre-disease state from a healthy state. DNB explores the information of molecular fluctuations as well as the correlations between molecules in high-dimensional gene expression data. Within the transcriptome of a patient, a subset of transcripts undergoes significant changes that are indicative of an imminent phase transition. A specific group of transcripts can be identified whose average Pearson's correlation coefficients (PCC) is drastically increased in absolute value. When comparing the average PCC of transcripts between this group and transcripts that are outside of this group, PCC drastically decreases in absolute value. In addition, the average standard deviations of transcripts in the inner core group drastically increase, reflecting their higher fluctuation. This group is called by the authors the "dominant group of the system." It is a change in correlation as well as variation of the members of the dominant group in relation to other subgroups that is monitored and integrated as a single composite "critical index" [42, 44]. The elements of the dominant group behave dynamically in a strongly collective manner with respect to the fluctuation as well as the correlation of elements in a molecular network, which is the basis for calling the approach "Dynamic network biomarkers." Using microarray data from a range of diseases such as lung injury, liver cancer or lymphoma cancer, they were indeed able to detect the critical transition from a healthy to a pre-disease state [45].

The group of L. Chen was also able to identify tissue-specific dynamic network biomarkers in liver, adipose and muscle during type 2 diabetes development and progression [45]. Recently, the concept was extended to the analysis of single-sample dynamic network biomarkers by integrating the expression from an individual sample with information on the expression of every gene from a reference population data set from which the potentially modified dynamics is inferred [46].

A major step forward in the attempt to use transcriptome or proteome data for the analysis

of diseases progressions is the analysis of single-cell transcriptomics and proteomics. Mojtahedi et al. [47] described cell fate decisions between the myeloid and the erythroid blood cell lineage as high-dimensional state transitions. Using single-cell RNA-Seq data analysis, they were able to demonstrate that the differentiation of blood progenitor cells to the erythroid or myeloid cell lineage is preceded by a destabilization of their high-dimensional gene expression configuration. The differentiating cells undergo a critical transition, which was characterized by a new gene expression attractor state. A quantitative index based on a decrease of correlation between cells and a concomitant increase of correlation between genes was established and found to be a suitable early warning signal associated with the underlying critical transition. So-called rebellious cells were discovered to make the transition into a new attractor in a stochastic manner. Because of the high inter-individual variation and because each patient might have their specific individual disease trajectory, dynamic network biomarkers could overcome the problems related to the loss of the signal in averaged group measurements.

11.7 Extracting Early Warning Signals from Electronic Health Records

Within the next years, we can expect that electronic medical records will become an established component of modern healthcare provision. The information contained in statewide or nationwide electronic medical records bears a tremendous potential to obtain an improved understanding of disease processes. Electronic medical records might also be used for the identification of early warning signals of critical transitions. The first study of this kind has recently been published by Jin et al. [48]. Using electronic health records from the entire state of Maine, the authors collected a comprehensive historical longitudinal electronic health record data set of a cohort of more than 7000 type 2 diabetes patients. Applying a "transition-based network entropy methodology" to the cohort's clinical records, they succeeded in showing the existence of a critical transition between a pre-disease and a type 2 diabetes state.

11.7.1 A Note of Caution

Despite the optimism that critical transitions might become predictable, there are a number of caveats that need caution and further research [49]. For critical transitions in complex systems, such as the development of a disease, an ice age or the development of a desert, it is often difficult to obtain sufficient high-resolution time-series data that allow a robust prediction of the future trajectory with currently available methods. In most cases, the mechanistic process that is responsible for generating the observed data is unknown and we cannot describe the underlying system dynamics to analyze whether one or several critical or bifurcation points exists at all or whether past transitions were purely noise induced and the result of a rare event that pushed the system over a tipping point [50]. These issues lead to an inherent uncertainty of tipping point predictions based on our current understanding [51] and demonstrate the need to analyze different classes of bifurcations and their behavior in the vicinity of tipping points for the development for robust EWS.

The complexity of high-dimensional and often non-linear systems has given rise to some skepticism whether disease-trajectories can be predicted. This pessimism might be somewhat warranted in ecological, social or financial systems. However, we should be much more optimistic for organisms and disease systems. Biological systems operate within the constraints of the genome inherited from one generation to the other and are less free to fill the space of potential system states as it is the case in the aforementioned areas. While currently adequate data sets are still rare, this situation is rapidly changing. We will be able to extract from millions of patients generalities and common paths that guide potential trajectories. At least, we will have individualized risk scores that have a much

higher predictability than what is currently available.

A major challenge in the study of complex non-linear systems is the heterogeneity in terms of the underlying systems architecture and the major external or internal constraints that act on the complex system under study. We cannot expect that different complex systems behave in a similar way and will show system specific characteristics and behavior close to tipping points. For a systematic understanding of EWS, it will be therefore essential to develop a systematic classification of critical transitions, similar to a "Catalogue of abrupt shifts" that has been assembled for climate change models [52] and contrast this with relevant biomedical data. For disease prediction, dynamical systems theory strongly suggests the use of personalized longitudinal data that will support the establishment of more robust individualized risk scores by compensating inter-individual heterogeneity.

11.8 The Next Challenge: Beyond Correlation—Causal Inference

There is evidence that, in order to achieve an optimal balance between robustness and flexibility, biological systems operate at the edge of a critical transition [53]. This "criticality" might not only allow for the flexibility in responding to environmental stimuli, but might also be the basis for the development of the system toward a pathogenic disease state. Transferring concepts from physics and ecology to biomedical applications might be a powerful approach and give us new insights into the pathogenesis of diseases.

A major goal of modern precision based medicine is the identification of early risk markers that help to prevent or ameliorate a disease long before the disease manifests itself. The challenges involved, such as the uncertainty of external forces or the lack of an understanding of the underlying systems structure, are very similar to many multi-dimensional adaptive and complex ecosystems. However, in contrast to many ecological, social or financial complex systems, the potential trajectory space of biological systems is genetically constrained. Once we understand the genetic circuitry and regulation of a biological system, we might be in a better position to predict the future development of the disease trajectory and progression.

For thousands of years, doctors made diagnostic and therapeutic decisions on the basis of their individual and collective experience. Outstanding doctors were able to recognize specific symptoms and features in patients and associate them with the most likely future trajectories of a disease. The quality of a doctor was depending on the accuracy and the precision of their diagnosis combined with their ability to use diagnostic features as an input for their medical and clinical decisions. The better the input, the better the output or the outcome for the patient. The revolution in molecular biology and genetics has now opened the path not only for a better classification of diseases but also for a mechanistic understanding of disease pathogenesis. Time has come to go beyond correlation analysis of, e.g., genes and phenotypes and tackle the much more difficult frontier of causality. Data-driven approaches such as machine learning and artificial intelligence are very successful in classification but at the current time do not provide us with mechanistic insight. The application of graphical inference methods, e.g., those developed by Judea Pearl [54, 55] to biomedical data might provide us with useful mathematical and modeling tools to move from correlation to causality in medicine.

References

1. Jones DS, Podolsky SH, Greene JA. The Burden of Disease and the Changing Task of Medicine. N Engl J Med. 2012. https://doi.org/10.1056/nejmp1113569.
2. World Health Organization (WHO). Global Burden of Diseases. 2017.
3. Voskuil J. How difficult is the validation of clinical biomarkers? F1000Research. 2015;101(MAY):1–10. https://doi.org/10.12688/f1000research.6395.1.
4. Engel J, Pitkanen A, Loeb JA, et al. Epilepsy biomarkers. Epilepsia. 2013;54(SUPPL.4):61–69. https://doi.org/10.1111/epi.12299.
5. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: A

clinical review. Eur Heart J. 2013;34(20):1475–80. https://doi.org/10.1093/eurheartj/eht024.
6. Tu Y, Rappel W-J. Adaptation in living systems. Annu Rev Condens Matter Phys. 2018. https://doi.org/10.1146/annurev-conmatphys-033117-054046.
7. Bascompte J. Disentangling the web of life. Science (80-) 2009. https://doi.org/10.1126/science.1170749.
8. Rinaldi S, Scheffer M. Geometric analysis of ecological models with slow and fast processes. Ecosystems. 2000. https://doi.org/10.1007/s100210000045.
9. Ising E. Beitrag zur Theorie des Ferromagnetismus. Zeitschrift für Phys. 1925. https://doi.org/10.1007/bf02980577.
10. Onsager L. Crystal statistics. I. A two-dimensional model with an order-disorder transition. Phys Rev. 1944. https://doi.org/10.1103/physrev.65.117.
11. Smug D, Ashwin PA. Generalized 2D-dynamical mean-field ising model with a rich set of bifurcations (inspired and applied to financial crises). 2018;28(4). https://doi.org/10.1142/s0218127418300100.
12. Karin O, Swisa A, Glaser B, Dor Y, Alon U. Dynamical compensation in physiological circuits LINEAR INTEGRAL FEEDBACK. 2018:1–7.
13. Zhou JX, Aliyu DSM, Aurell E, Huang S. Quasi-potential landscape in complex multi-stable systems. J R Soc Interface. 2012. https://doi.org/10.1098/rsif.2012.0434.
14. Dai L, Vorselen D, Korolev KS, Gore J. Generic indicators for loss of resilience before a tipping point leading to population collapse. Science (80-). 2012. https://doi.org/10.1126/science.1219805.
15. Drake JM, Griffen BD. Early warning signals of extinction in deteriorating environments. Nature. 2010. https://doi.org/10.1038/nature09389.
16. Hirota M, Holmgren M, Van Nes EH, Scheffer M. Global resilience of tropical forest and savanna to critical transitions. Science. 2011;334(6053):232–5. https://doi.org/10.1126/science.1210657.
17. Kéfi S, Rietkerk M, Alados CL, et al. Spatial vegetation patterns and imminent desertification in Mediterranean arid ecosystems. Nature. 2007. https://doi.org/10.1038/nature06111.
18. Rietkerk M, Dekker SC, De Ruiter PC, Van De Koppel J. Self-organized patchiness and catastrophic shifts in ecosystems. Science (80-). 2004. https://doi.org/10.1126/science.1101867.
19. Scheffer M, Carpenter S, Foley JA, Folke C, Walker B. Catastrophic shifts in ecosystems. 2001;413(October).
20. Scheffer M, Carpenter SR. Catastrophic regime shifts in ecosystems: Linking theory to observation. Trends Ecol Evol. 2003. https://doi.org/10.1016/j.tree.2003.09.002.
21. Veraart AJ, Faassen EJ, Dakos V, Van Nes EH, Lürling M, Scheffer M. Recovery rates reflect distance to a tipping point in a living system. Nature. 2012. https://doi.org/10.1038/nature10723.
22. Ashwin P, Wieczorek S, Vitolo R, Cox P. Tipping points in open systems: bifurcation, noise-induced and rate-dependent examples in the climate system. Philos Trans R Soc A Math Phys Eng Sci. 2012. https://doi.org/10.1098/rsta.2011.0306.
23. Strogatz SH, Shafer DS. Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering. Westview Press. 1994. https://doi.org/10.1137/1037077.
24. Chang W-C, Kudlacek J, Hlinka J, et al. Loss of neuronal network resilience precedes seizures and determines the ictogenic nature of interictal synaptic perturbations. Nat Neurosci. 2018;21(12):1742–52. https://doi.org/10.1038/s41593-018-0278-y.
25. Jirsa VK, Stacey WC, Quilichini PP, Ivanov AI, Bernard C. On the nature of seizure dynamics. 2014:2210–30. https://doi.org/10.1093/brain/awu133.
26. Scheffer M, Bascompte J, Brock WA, et al. Early-warning signals for critical transitions. Nature. 2009. https://doi.org/10.1038/nature08227.
27. Scheffer M, Carpenter SR, Lenton TM, et al. Anticipating critical transitions. Science (80-). 2012. https://doi.org/10.1126/science.1225244.
28. Lenton TM. Early warning of climate tipping points. Nat Clim Chang. 2011. https://doi.org/10.1038/nclimate1143.
29. Dakos V, Carpenter SR, Brock WA, et al. Methods for detecting early warnings of critical transitions in time series illustrated using simulated ecological data. PLoS One. 2012. https://doi.org/10.1371/journal.pone.0041010.
30. Meisel C, Klaus A, Kuehn C, Plenz D. Critical slowing down governs the transition to neuron spiking. 2015:1–20. https://doi.org/10.1371/journal.pcbi.1004097.
31. Kramer MA, Truccolo W, Eden UT, et al. Human seizures self-terminate across spatial scales via a critical transition. Proc Natl Acad Sci. 2012;109(51):21116–21. https://doi.org/10.1073/pnas.1210047110.
32. Wang R, Dearing JA, Langdon PG, et al. Transition to a eutrophic lake state. Nature. 2012;492(7429):419–22. https://doi.org/10.1038/nature11655.
33. Trefois C, Antony PMA, Goncalves J, Skupin A, Balling R. Critical transitions in chronic disease: transferring concepts from ecology to systems medicine. Curr Opin Biotechnol. 2015. https://doi.org/10.1016/j.copbio.2014.11.020.
34. Dahlem MA, Kurths J, Ferrari MD, Aihara K, Scheffer M, May A. Understanding migraine using dynamic network biomarkers. Cephalalgia. 2015. https://doi.org/10.1177/0333102414550108.
35. Olde Rikkert MG, Dakos V, Buchman TG, et al. Slowing down of recovery as generic risk marker for acute severity transitions in chronic diseases. Crit Care Med. 2016.

36. Quail T, Shrier A, Glass L. Predicting the onset of period-doubling bifurcations in noisy cardiac systems. Proc Natl Acad Sci. 2015. https://doi.org/10.1073/pnas.1424320112.
37. Huang S, Ernberg I, Kauffman S. Cancer attractors: A systems view of tumors from a gene network dynamics and developmental perspective. Semin Cell Dev Biol. 2009. https://doi.org/10.1016/j.semcdb.2009.07.003.
38. Elowitz MB, Levine AJ, Siggia ED, Swain PS. Stochastic gene expression in a single cell. Science (80-). 2002. https://doi.org/10.1126/science.1070919.
39. Remacle F, Kravchenko-balasha N, Levitzki A, Levine RD. Information-heoretic analysis of phenotype changes in early stages of carcinogenesis. 2010;107(22). https://doi.org/10.1073/pnas.1005283107.
40. Zadran S, Remacle F, Levine R. Surprisal analysis of glioblastoma multiform (GBM) MicroRNA dynamics unveils tumor specific phenotype. PLoS One. 2014. https://doi.org/10.1371/journal.pone.0108171.
41. Kravchenko-Balasha N, Johnson H, White FM, Heath JR, Levine RD. A thermodynamic-based interpretation of protein expression heterogeneity in different glioblastoma multiforme tumors identifies tumor-specific unbalanced processes. J Phys Chem B. 2016. https://doi.org/10.1021/acs.jpcb.6b01692.
42. Chen L, Liu R, Liu ZP, Li M, Aihara K. Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers. Sci Rep. 2012. https://doi.org/10.1016/j.amjsurg.2003.12.037.
43. Liu R, Li M, Liu ZP, Wu J, Chen L, Aihara K. Identifying critical transitions and their leading biomolecular networks in complex diseases. Sci Rep. 2012. https://doi.org/10.1038/srep00813.
44. Yang B, Li M, Tang W, et al. Dynamic network biomarker indicates pulmonary metastasis at the tipping point of hepatocellular carcinoma. Nat Commun. 2018. https://doi.org/10.1038/s41467-018-03024-2.
45. Li M, Zeng T, Liu R, Chen L. Detecting tissue-specific early warning signals for complex diseases based on dynamical network biomarkers: study of type 2 diabetes by cross-tissue analysis. Brief Bioinform. 2014. https://doi.org/10.1093/bib/bbt027.
46. Liu X, Chang X, Liu R, Yu X, Chen L, Aihara K. Quantifying critical states of complex diseases using single-sample dynamic network biomarkers. PLoS Comput Biol. 2017. https://doi.org/10.1371/journal.pcbi.1005633.
47. Mojtahedi M, Skupin A, Zhou J, et al. cell fate decision as high-dimensional critical state transition. PLoS Biol. 2016. https://doi.org/10.1371/journal.pbio.2000640.
48. Jin B, Liu R, Hao S, et al. Defining and characterizing the critical transition state prior to the type 2 diabetes disease. PLoS One. 2017. https://doi.org/10.1371/journal.pone.0180937.
49. Boettiger C, Hastings A. Quantifying limits to detection of early warning for critical transitions. J R Soc Interface. 2012. https://doi.org/10.1098/rsif.2012.0125.
50. Rocha JC, Peterson G, Bodin Ö, Levin SA. Cascading regime shifts within and across scales. 2018;1383 (December):1–20. https://doi.org/10.1101/364620.
51. Brock WA, Carpenter SR. Early warnings of regime shift when the ecosystem structure is unknown. PLoS One. 2012. https://doi.org/10.1371/journal.pone.0045586.
52. Drijfhout S, Bathiany S, Beaulieu C et al. Catalogue of abrupt shifts in Intergovernmental Panel on Climate Change climate models. Proc Natl Acad Sci. 2015. https://doi.org/10.1073/pnas.1511451112.
53. Muñoz MA. Colloquium: criticality and dynamical scaling in living systems. Rev Mod Phys. 2018. https://doi.org/10.1093/ejcts/ezx068.
54. Pearl J. Causality. Cambridge university press;2009.
55. Pearl J. The book of why: the new science of cause and effect. Basic Books;2018.

Colloidal Quantum Materials for Photocatalytic Applications

12

Nir Waiskopf and Uri Banin

Beyond light emission, harnessing absorbed light energy to perform useful chemical work is an alternative route of utilization upon excitation of SCNC. This route is typically inefficient compared to other competing relaxation pathways, resulting in low photocatalytic activity in the absence of co-catalysts.

The capacity to grow a metal domain on the SCNCs, which forms a semiconductor–metal hybrid nanoparticle, laid the foundation to overcome the aforementioned low-efficiency limitation. Semiconductor–metal hybrid nanoparticles (HNPs) with various shapes, dimensions, and compositions have already been synthesized. These HNPs manifest intrinsic charge separation following the light absorption, which combined with the inherently reactive nanometal surface, increases their photocatalytic efficacy significantly. Recently, the photocatalytic functionality was realized for reactive species formation by HNPs, allowing their implementation in processes and systems which benefit from their tunable features, prolonged activity and the ability to produce reactive species in high spatiotemporal resolution on demand.

N. Waiskopf · U. Banin (✉)
The Institute of Chemistry, The Hebrew University of Jerusalem, 91904 Givst Ram, Jerusalem, Israel
e-mail: uri.banin@mail.huji.ac.il

N. Waiskopf
e-mail: nir.waiskopf@mail.huji.ac.il

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_12

Here, we introduce SCNC and their virtues, present the "all in one system" concept for semiconductor–metal HNPs, and summarize their emerging photocatalytic functions, including as photocatalysts for solar-to-fuel conversion and as photoinitiators for photo-curing and biomedical applications, such as phototherapy, sterilization, and diagnostics.

12.1 Introduction to Semiconductor Nanocrystals

Colloidal semiconductor nanoparticles are crystalline structures composed of tens to few thousands of atoms with all three dimensions in the nanometer scale (1–100 nm). In the nano-regime, semiconductor particles show unique and interesting size-dependent properties, dissimilar to those of their bulks, offering a new world of materials which are also broadly applicable in diverse fields.

Semiconductor materials are defined by having an energy band gap, which is small enough to allow the excitation of electrons from the highest full energy band (namely the valence band), to the lowest empty conduction band. Light excitation of the semiconductor results in the formation of an electron-hole pair, an exciton, which can recombine while emitting a photon with the characteristic nanocrystals band gap energy. Figure 12.1a schematically presents the

energy bands in bulk and in nanocrystals. Bulk materials possess continuous energy bands with band gap energy determined by the composition of the material. Nanocrystals, on the other hand, are characterized by dense discrete energy states. As the particles get bigger, the energy states become denser and the band gap gets smaller. In dimensions which are smaller than the excitonic Böhr radius of the material, strong quantum effects arise from the confinement of the charge carriers to the finite dimensions of the crystal. Similar to a particle in a box model, as the nanoparticle becomes smaller, the band gap increases. Figure 12.1b shows an example for the utilization of this phenomenon for controlling the emission spectra of semiconductor nanoparticles. During the growth of the nanoparticles, their band gap energy decreases and the emission spectrum is shifted to longer wavelengths. Therefore, the final characteristics of nanocrystals can be adjusted by altering their size, shape, and composition.

Another important aspect of nanocrystals is their surface coating. Nanocrystals are typically covered by organic ligands, which are used during their synthesis to control crystal growth, determine their shape and stabilize them. These ligands play a crucial role in the solubility, colloidal stability, and interactions of the nanocrystals with the surrounding milieu. Therefore, different ligand exchange and polymer-coating procedures have been developed. Figure 12.1c displays a selection of surface-coating approaches, for example, ligand exchange with hydrophilic thiolate ligands such as mercaptopropionic acid and dihydrolipoic acid which can be used for the phase transfer of nanocrystals into water.

In the last three decades, extensive research was directed to understand how the nanocrystals' nature, their ligands, and the environment affect their chemical, optical, and electronic properties. These studies revealed exceptional inherent properties of SCNC which give them significant advantages in specific applications over organic molecules. For example, Fig. 12.1d exhibits that nanocrystals have broad absorption with an onset that depends on their size allowing the excitation of several different nanocrystals using a single illumination source. In contrast, organic dye molecules have narrow absorption spectrum, which requires matching the light source's wavelength to the absorption spectrum of the specific dye. Such colloidal quantum materials have also shown very good photochemical stability allowing their use in harsh environmental conditions and in applications which require long-term excitation [3].

Another advantage of SCNCs stems from the gigantic absorption cross section of semiconductor nanocrystals in comparison with organic molecules which provides very high light sensitivity. The difference in the absorption cross section is even more pronounced for two-photon absorption, which depends quadratically on the excitation intensity [4–6]. Two-photon measurements exploit the absorption of two photons with lower energy, usually in the infra-red. This allows achieving reduced damage to the excited sample, higher resolution along the Z dimension, and increased penetration depth into tissues and solutions that scatter or absorb photons in the visible range. The outstanding compatibility of nanocrystals for two-photon modalities is specifically important for medical purposes, such as non-invasive imaging, and as will be elaborated in Sects. 2.3 and 2.4 also for phototherapy and for high-resolution 3D printing.

Besides these intrinsic traits of semiconductor nanocrystals, other particular advantages can originate from the use of nanocrystals with specific shapes and architectures. For example, semiconductor quantum rods present linearly polarized emission that was used to detect changes in the orientation of labeled biomolecules [7, 8], and was suggested to provide an interesting approach for energy savings in LCD display backlights [9].

12.2 Introduction to Semiconductor–Metal Hybrid Nanocrystals

The commercialization of nanocrystals as emitting materials for displays and as fluorescent markers for imaging along with the developments in their

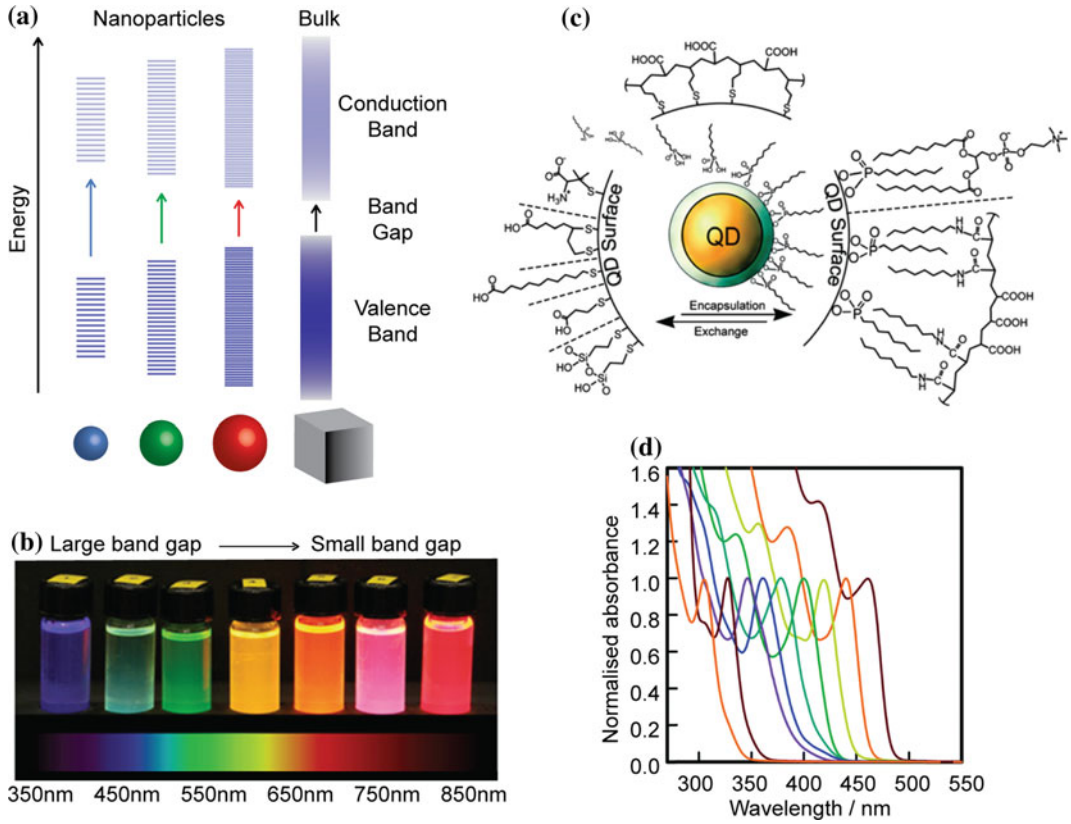


Fig. 12.1 **a** Schematic presentation of nanoparticles' discrete electronic bands and the continuous bands of bulk semiconductor. As the nanoparticles get larger, the discrete bands become denser and the energy band gap between the valence and conduction bands decrease. **b** CdSe SCNCs with different sizes exhibit emission in all the visible range. Smaller SCNCs have larger band gap and hence exhibit emission in shorter wavelengths and vice versa. **c** The organic surface coating of nanocrystals can be replaced by ligand exchange, polymer coating, or encapsulation to regulate their solubility, colloidal stability, interactions, and energy and charge transfer processes. **d** Absorption spectra of CdS quantum dots showing broad absorption covering both UV and VIS ranges. As the nanoparticles are larger, the absorption onset is shifted to longer wavelengths. Figure 1c, d are republished with the permission of The Royal Society of Chemistry and are taken from Tyrakowski and Snee [1] and Veamatahua et al. [2] respectively; permission conveyed through Copyright Clearance Center, Inc

syntheses pave the way for future nanocrystal-based applications. Here, we will present the concept of semiconductor–metal hybrid nanoparticles, introduce their photocatalytic activities, and overview their advantages for emerging utilizations.

In 2004, our group has shown a selective growth of a metal domain on the apex of semiconductor nanorods forming semiconductor–metal hybrid nanocrystals [10]. This was achievable by the reduction of metal salt, namely $AuCl_3$ by octadecylamine using the apex of the nanocrystal as a preferential reactive nucleation center. Interestingly, a unique feature of intrinsic charge separation upon light excitation was observed, with electrons moving to the metal tip and the holes residing in the semiconductor. This, combined with the catalytic nature of metallic nanocrystals, provide high photocatalytic activity as discussed in detail in Sect. 2.1.

The exceptional hybrid structure along with the combined and synergistic properties that stemmed from the nanoscale semiconductor–metal interface have led to the formation of a new

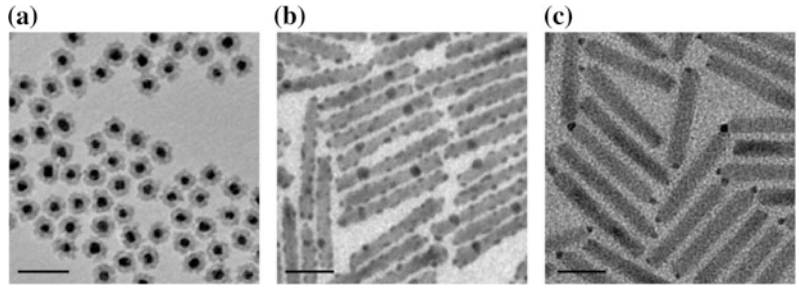


Fig. 12.2 Transmission electron microscopy images of **a** Au-CdS core/shell dots, scale bar 50 nm, **b** CdSe/CdS seeded nanorods with "body decoration" of small gold nanoparticles, scale bar 20 nm and **c** CdS nanorods with single gold metal tip, scale bar 10 nm. (**a**, **b**) Reprinted and adapted with permission from Chen Wei-Ta et al. [12] and Menagen et al. [13], Copyright 2008 American Chemical Society

research field in the nanomaterials world. To date, hybrid nanocrystals with various semiconductor and metal compositions, dimensions, and architectures (e.g., single tip, dumbbells, core/shell structures, and body decoration) have been synthesized (see few examples in Fig. 12.2), characterized for their optical and electronic traits and studied for their photocatalytic activities [11]. One of the main photocatalytic applications that were widely examined in the last decade is the green production of fuel by water splitting to produce hydrogen gas.

12.2.1 Solar Energy for Alternative Green Fuel

Environmental manufacturing of green fuels is one of the holy grails of the twenty-first century. One promising approach to achieve this is by harvesting solar energy for hydrogen gas generation via water reduction. The formed hydrogen can further be reacted in a controlled manner with oxygen in a suitable fuel cell to provide electricity while forming back water resulting in a zero-emission cycle.

Semiconductor–metal hybrid nanoparticles can be engineered to have band alignment that will provide sufficient over-potential to reduce water by photo-excited electrons. This, along with the possibility to have high light sensitivity in a wide range of wavelengths, covering the VIS and UV spectra, plus the high photochemical stability that can permit extended use of HNPs, make them good candidates for photocatalytic production of hydrogen gas.

The generation of hydrogen gas by HNPs, as well as all forms of their photocatalytic functionality, involves three main steps presented in Fig. 12.3a: (1) Absorption of light by the semiconductor component; (2) Rapid charge separation, with the electron transferring to the metal domain; (3) Participation of the charge carriers in redox reactions, which for H_2 formation includes a two-electron reduction of two water molecules on the catalytic metal. Additional examples of possible photocatalytic products, such as oxygen gas and reactive oxygen species, are given in Fig. 12.3b, c.

Various experiments have been performed to study how the properties of the HNPs affect their photocatalytic efficiency, in a search for the maximal quantum yield. This reductionist approach is enabled by the achievement of good control over various features such as the surface ligands, the metal tip size, its location, and others. The studies provide a basis to understand the role of the various characteristics on the photocatalytic functionality and have revealed three main pillars on which it depends: the HNP characteristics, their surface coating, and the environmental conditions.

For hydrogen generation, the semiconductor and metal compositions should be carefully selected to have band gap that will allow maximal coverage of the solar spectrum while

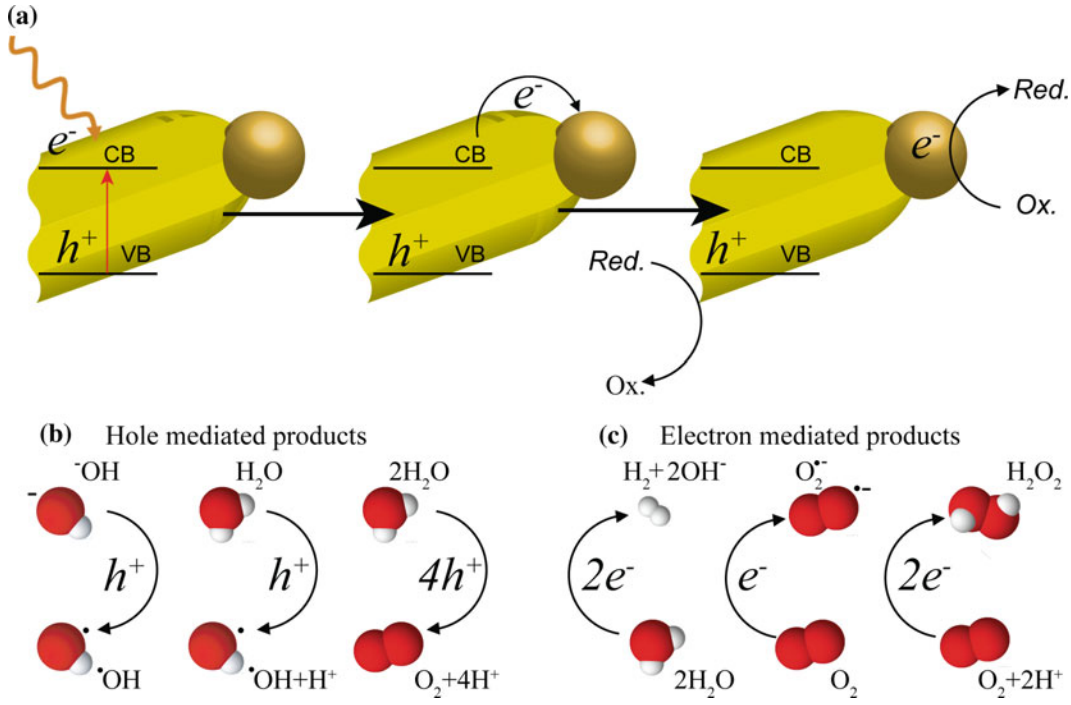


Fig. 12.3 Schematics of a general photocatalytic process. (**a**) Light excitation of the semiconductor component excites electron to the conduction band and leaves a hole in the valence band. Then, fast intrinsic charge transfer of the electron to the metal domain results in spatial charge separation allowing the charge carriers to participate in redox reactions. Products of hole mediated oxidized entities (**b**) and electron-mediated reduced entities (**c**). Republished with permission of John Wiley & Sons, Inc. Advance Materials 2018 30 (41), 1706697 [14]; permission conveyed through Copyright Clearance Center, Inc

providing sufficient over-potential above the water reduction potential. The work function of metal nanoparticles decreases as their size increases, and therefore the latter also depends on the size of the metal tip [15, 16]. This was suggested to result in an exponential decrease in the water reduction kinetics with decreased metal island radius. Yet, Fig. 12.4a shows a result taken from a recent experimental work supported by a theoretical model, with a non-monotonic photocatalytic behavior with the change in metal tip size [17]. This was explained by the presence of the charge separation step, which has an opposing size effect on account of increasing density of states that leads to enhanced charge separation for larger metal tip sizes.

Another set of experiments revealed the superiority of HNPs with the semiconductor in the shape of nanorods relative to spherical dot, resulting from the better charge separation in the former. Interestingly, also here a delicate balance was described for the optimal nanorods' length. For example, comparison of CdSe/CdS core/shell nanorods with Pt tip, wherein the holes tend to be localized to the core material have suggested that the photocatalytic activity of short nanorods is limited due to strong Coulombic interactions between the charge carriers, whereas the long nanorods reduce this effect but can have more surface defects which can be detrimental for the photocatalytic activity [18].

The surface of the nanocrystals is another important aspect affecting the photocatalysis. Figure 12.4b shows a comparison between Au-tipped CdS nanorods with diverse surface coatings showing outstanding photocatalytic performances for polyethyleneimine-(PEI)-capped HNPs with respect to the previously used thiolate

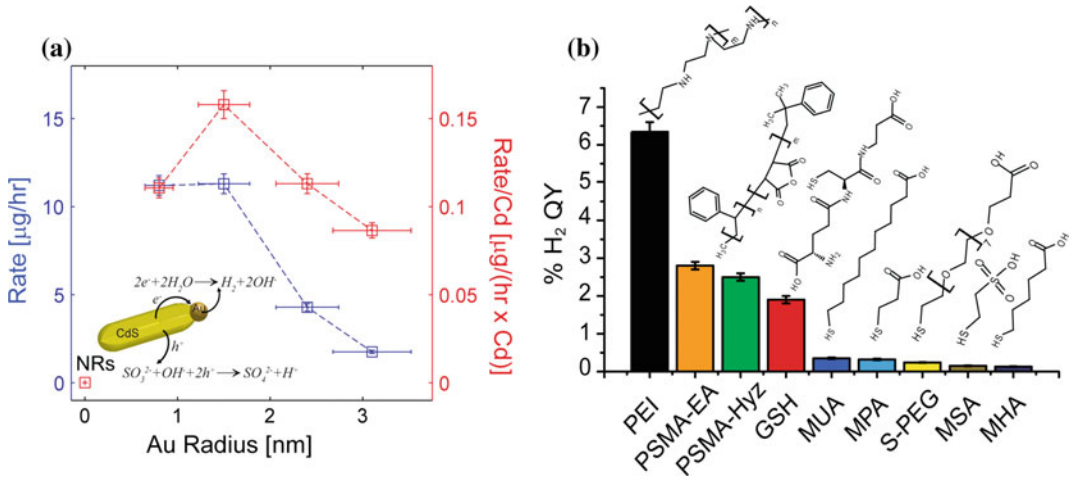


Fig. 12.4 Metal tip size and surface coating effect on hydrogen gas formation by HNPs. **a** An optimum size for gold metal tip on CdS nanorods was found resulting from two opposing observed trends; on one hand, larger metals enhance charge separation rate but, on the other hand, they reduce the over-potential required for efficient charge transfer from the metal for water reduction. In blue are the experimental results of the amount of hydrogen gas formation per hour and in red the data after normalization to the absorption of the semiconductor component on the HNPs. Reproduced with permission [17]. Copyright 2016 Nature Publishing Group. **b** HNPs coated with polyethylenimine (PEI) show the highest hydrogen gas formation compared to other examined surface coatings. This result was contributed to a better passivation of surface traps by this polymer. HNPs after ligand exchange with glutathione (GSH) or after encapsulation with amphiphilic polymer, poly-styrene-co-maleic anhydride (PSMA) opened with ethanolamine (EA) or hydrazine (Hyz) show moderate H_2 formation. The lowest photocatalytic activities were seen after ligand exchange with mercapto-alkyl ligands, including 11-mercaptoundecanoic acid (MUA), 6-mercapto hexanoic acid (MHA), 3-mercaptopropionic acid (MPA), 2-mercaptoethanesulfonic acid (MSA), and O-(2-carboxy ethyl)-O′-(2-mercaptoethyl)heptaethylene glycol (S-PEG). Republished with permission of John Wiley & Sons, Inc. Ben-Shahar Y. et al., Small 2014 [19]; permission conveyed through Copyright Clearance Center, Inc

ligand coatings [19]. This was attributed to a better passivation of surface traps by PEI which abolishes the main competing relaxation route of hole trapping that also localizes the electron due to the Coulomb interactions. As mentioned above, the surface coating also determines the colloidal stability of the nanocrystals, which again favors for polymer coating such as PEI which has multiple anchoring points to the nanocrystal and provides enhanced steric stability over the examined mono-dentate ligands. Moreover, the stability of PEI coated NCs in acidic pH is also improved in comparison with thiolate ligands, in which the thiol-anchoring group becomes protonated and dissociates from the NC surface [20].

The pH of the solution can also affect the photocatalytic activity in a reaction-dependent manner. For example, the redox potential of hydroxyl anion changes with the pH by −59 mV/pH unit, in agreement with Nernst equation. On the other hand, the valence and conduction bands energies were suggested to have different pH dependences. For example, for CdS coated with mercaptopropionic acid, it was measured to be −33 mV/pH unit, resulting in a crossover of the hydroxide oxidation potential and the CdS valence band energy [21]. This enables to extract the holes for the oxidation of hydroxide molecules, in strong alkaline conditions, yielding higher rates of hydrogen gas production. Even though this example works specifically for CdS and similar systems with energy bands which are relatively close to the redox potential [22], the generality of enhancing the catalytic activity by the introduction of sacrificial hole scavengers was widely demonstrated [23].

12.2.2 Light-Induced ROS Formation

The developments in the synthesis of hybrid nanocrystals along with their characterization and optimization toward photocatalytic hydrogen generation laid the basis for their utilization as efficient photocatalysts in additional redox reactions. One family of reactions that holds a great promise for a wide range of industrial applications is the light-induced formation of reactive species in general and of reactive oxygen species (ROS) in particular.

Electron paramagnetic resonance (EPR) measurements along with colorimetric and fluorescence assays have revealed the excitation of SCNC can lead to the formation of four main ROS [24]: Superoxide formed by one electron transfer from the conduction band of the semiconductor to molecular oxygen (Fig. 12.3c); Hydrogen peroxide formed by further reduction of superoxide in a process involving an additional electron and two protons (Fig. 12.3c); hydroxyl radicals produced by the oxidation of water and hydroxide by the valance band holes (Fig. 12.3b); and singlet oxygen formed by the oxidation of superoxide or by energy transfer to a triplet ground state of molecular oxygen. The different reactive species can further convert from one to the other on the surface of the nanocrystals or in solution. For example, hydrogen peroxide can thermally decompose to hydroxyl radicals or can be formed by dimerization of two hydroxyl radicals with opposite spins on the surface of TiO_2 [25].

In continuation of the characterization of the light-induced ROS formation by semiconductor nanocrystals, researchers have attempted to apply these photocatalytic activities. For example, the utilization of nanocrystals as photoinitiators for photo-curing or as photocatalysts for water purification and antibacterial applications were investigated. However, so far the realization of the semiconductor nanocrystals in these applications and others was limited mainly due to dominant competing relaxation modes that decrease the photocatalytic efficiency.

The introduction of HNPs with notable photocatalytic activity has opened the path for their investigation also for the production of ROS. Figure 12.5a shows that light excitation of CdS-Au in water has resulted in significant faster consumption of molecular oxygen in comparison with bare nanorods [26]. In-depth inquiry has revealed that the molecular oxygen was reduced, by both the CdS nanorods and HNPs, to produce superoxide. However, in comparison with the former, the HNPs also yielded a substantial amount of hydrogen peroxide.

Complementary experiments performed under argon flow, eliminated the formation of the reduction products, whereas experiments in the presence of hole acceptors showed an increase in their quantities. These indicated that the superoxide and hydrogen peroxide were indeed formed by the reduction of molecular oxygen. Figure 12.5b demonstrates that parallel investigation of the oxidation capacity has also shown enhanced production of hydroxyl radicals by HNPs in comparison with the bare nanorods. This was attributed to the cancelation of the radiative relaxation route due to the efficient charge separation in the HNP systems [26].

The catalytic activity toward reactive species production, in general, was found to depend, similar to hydrogen generation, on the composition of the semiconductor and metal, the dimensions of the nanocrystals and their surface coating. However, since, there are several parallel and competing catalytic pathways, the band alignment engineering, through the composition and dimensions of the nanocrystals, is also relevant for tuning the specificity of the produced ROS. For example, Niemeyer et al., showed that CdSe nanocrystals produce hydroxyl radicals, whereas CdS nanocrystals produce a higher amount of hydroxyl radicals and also superoxide [27]. These results were attributed to the larger band gap of CdS making it more compatible with the production of the two reactive species. Further experiments with HNPs showed that CdSe/CdS-Au core/shell-metal nanocrystals produce less hydroxyl radicals than CdS-Au NCs due to the localization of the holes in the CdSe seeds in the former [26].

Another important factor that is affected by the nanocrystal composition and, in turn, affects

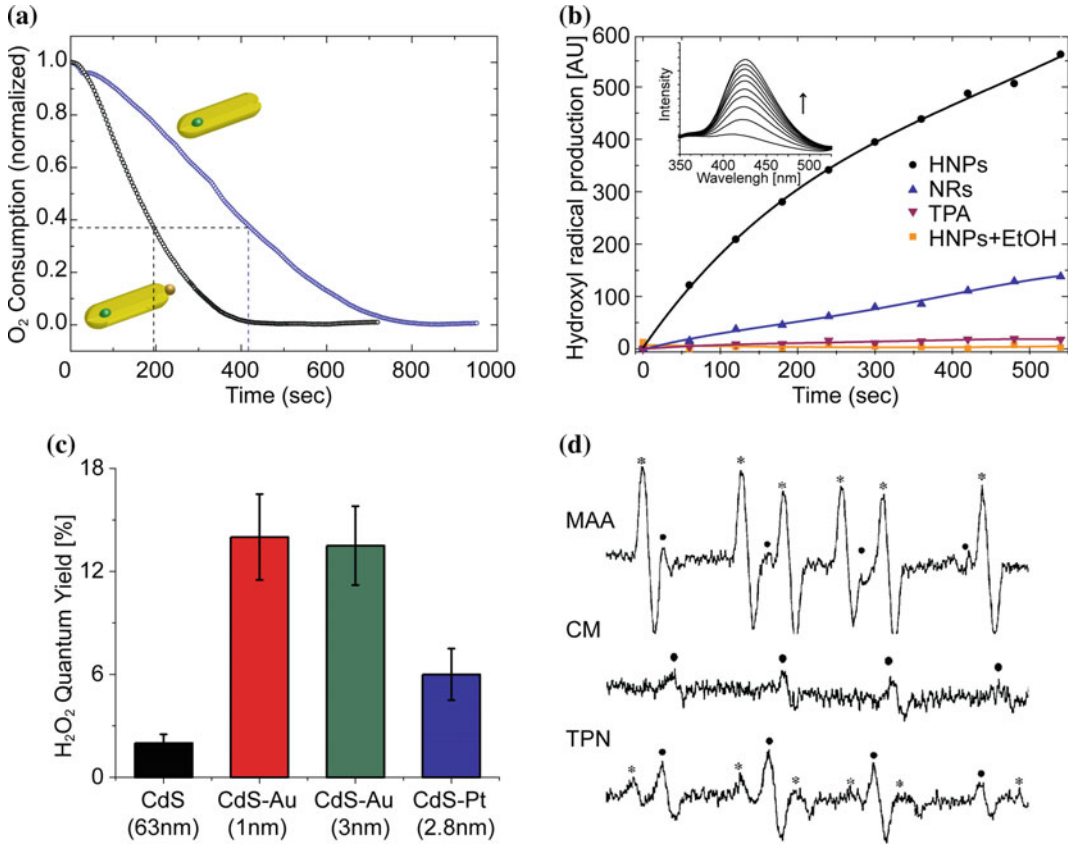


Fig. 12.5 Characteristics of ROS formation by semiconductor nanocrystals. **a** Enhanced molecular oxygen consumption by HNPs (black) in comparison with bare nanorods (blue). Reproduced with permission [26]. Copyright 2016, American Chemical Society. **b** Faster hydroxyl radical formation by HNPs (black) relative to nanorods (blue) is observed by terephthalic acid assay. Control experiments without nanocrystals (purple) or in the presence of ethanol which is hydroxyl radical scavenger (orange) showed negligible signals. Reproduced with permission [26]. Copyright 2016, American Chemical Society. **c** Selectivity dictated by the metal. The quantum yield for hydrogen peroxide production is higher for HNPs than bare nanorods. However, Au-tipped HNPs show significantly elevated QY over Pt-tipped HNPs. Republished with permission of John Wiley & Sons, Inc. D. Stone et al., ChemCatChem 2018 [28]; permission conveyed through Copyright Clearance Center, Inc. **d** EPR data, with 5,5-Dimethyl-1-pyrroline *N*-oxide (DMPO) as a radical trapping agent, obtained following the light excitation of CdS quantum dots coated with mercapto-acetic acid (MAA), cysteamine and 2-mercaptoethansulfonic acid (CM) and tiopronin (TPN), shows different spectra, indicating the surface coating affects the type and amount of the produced radicals. Sextet signal (marked with *) corresponds to DMPO adduct of superoxide radicals (a_N = 16 G, a_H = 23 G) or DMPO adduct of carbonyl radical for the TPN spectrum (a_N = 15 G, a_H = 23.25 G) and the quartet component, marked with a dot, represents hydroxyl radical signal. Reproduced with permission of The Royal Society of Chemistry, from Rajendran et al. [29]; permission conveyed through Copyright Clearance Center, Inc

the possible catalytic reactions is the adsorption energy of different molecular species to the reactive site. Comparison of the photocatalytic activities of CdS-Au and CdS-Pt, presented in Fig. 12.5c, has shown significantly higher H_2O_2 production by the former [28]. This result, which is opposite to the notion CdS-Pt produce more hydrogen gas than CdS-Au, was attributed to the stronger binding energy of molecular oxygen to the platinum surface resulting in dissociative adsorption and hence less H_2O_2 formation.

The surface coating of the particles also affects the efficiency and specificity through several routes. The effect of the surface coating on reactive species formation by passivation of surface traps is similar to that observed for hydrogen generation [26]. However, influences by other mechanisms such as the accessibility of the molecular species that participate in the reactive species formation and the ability of the reactive species to reach the solution through the surface coating without further interaction strongly depend on the specific surface coating and the involved molecular species. For example, as shown in Fig. 12.4b, Poly(styrene-co-maleic anhydride) (PSMA) as surface coating showed medium capacity for hydrogen generation in comparison with PEI and thiolate ligands. However, the production of hydrogen peroxide by PSMA-coated hybrid nanocrystals was negligible [26]. Another example is presented in Fig. 12.5d. EPR experiments done by Rajendran et al., showed that CdS nanocrystals coated with mercaptoacetic acid produce superoxide and hydroxyl radicals, whereas the same particles coated with tiopronin produce hydroxyl radicals and carbonyl radicals [29]. The latter was suggested to result from fast interaction of the superoxide with the capping ligands.

12.2.3 Photo-Curing and 3D Printing

One field that can benefit from the enhanced reactive species formation by HNPs is photo-curing in general and 3D printing in water in particular. Photo-curing is a technique that uses light to initiate polymerization. This process is widely used for industrial manufacturing of decorative and protective coatings, in adhesives and lately also for 3D printing. Traditionally, it involves a formulation containing monomers, additives, and organic photoinitiators that upon excitation in a narrow range of UV light break apart to produce reactive species that can attack the monomers and initiate the radical polymerization chain reaction. The available formulations are numerous and well established for specific applications. Yet, there is a need for new photoinitiators with better and/or distinctive capabilities. This is due to a combination of global trends and of technological advances, such as patents landscape, consolidation of companies, and the push for greener and safer processes and materials. For example, use of near-UV LEDs instead of traditional UV light sources can be much more efficient energetically and also avoids the use of harmful short wavelengths. Moreover, there is enhanced development of new applications, such as photo-curing in dental care and 3D printing of smart drug capsules or of scaffolds for tissue engineering that necessitates new materials and formulations.

One such new growing field, which lacks suitable photoinitiators, is photo-polymerization of water-based formulations. This kind of formulations can reduce the possible toxicity of polymerization in the presence of cells and tissues, and may reduce exposure to fumes that can carry various hazards, such as toxicity or bad odor, to name a few. The available commercial organic photoinitiators cannot address the needs of this field due to their unfavorable water solubility, limited absorbance in the near-UV–VIS range, and significant polymerization retardation by molecular oxygen in aqueous environments.

Recently, we have demonstrated the ability to overcome these restrictions and benefit from additional advantages in 3D printing by the use of semiconductor–metal hybrid nanocrystals as a new type of photoinitiators [30]. Water-soluble HNPs showed, in FTIR measurements, significantly higher polymerization capacity of acrylamide monomers during excitation at 385 nm in comparison with Igracure 2959. The HNPs were used successfully as photoinitiators for the printing of a 3D Buckyball structure in water using a commercial digital light processing (DLP) printer. The printed structure is presented in Fig. 12.6a, b. The superior two-photon absorption of the semiconductor nanorod component was also employed demonstrating the use of the HNPs as photoinitiators in high-resolution two-photon printing. Figure 12.6c shows a spiral structure with few microns width that was printed

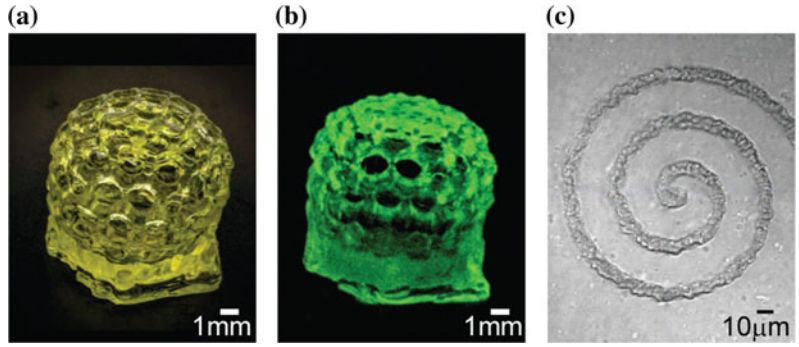


Fig. 12.6 HNPs as photoinitiators for radical polymerization. **a** Buckyball structure printed in a commercial digital light processing (DLP) printer in water using HNPs as the photoinitiators. **b** Post-printing fluorescence under UV light due to the addition of green-emitting quantum rods to the formulation. **c** High-resolution spiral structure printed with HNPs as photoinitiators in water through two-photon polymerization process using Nanoscribe printer. Reproduced with permission [30]. Copyright 2017 American Chemical Society

in water using a Nanoscribe printer. These were the first demonstrations for efficient 3D and two-photon printing with semiconductor-based nanocrystals as photoinitiators.

The impressive performances were found to rely on a unique mechanism of action of HNP as photoinitiators. First, instead of the stoichiometric production of reactive species by organic photoinitiators, the NCs continuously produce hydroxyl radicals in water in a photocatalytic manner. Second, in tandem, they consume the molecular oxygen which as mentioned above is a known retarder of polymerization processes. The NCs also present better flexibility in surface chemistry enabling to use similar NCs in several organic and water-based formulations. The large absorption cross section over a continuous absorption range with tunable onset residing in the near-UV–VIS range makes them suitable for excitation by both traditional UV and new energy-efficient LED illumination sources. Last but not least, the long-term stability of the NCs allows using them as multifunctional agents, for example, acting both as photoinitiators and as photocatalysts for post-printing functionalities.

12.2.4 Biomedical Applications

Biomedicine is another large industry that may significantly benefit from the new capabilities presented by HNPs. The significant leap toward the printing of complex structures, models, and scaffolds in the presence of tissues, cells, and biomolecules holds a great promise. However, this is just one implication and three additional examples from phototherapy, antibacterial application, and diagnostics will be given below to highlight the wide potential of the technology.

The initial studies for the use of colloidal quantum materials for imaging in living systems have revealed a possible trait in the nature of cytotoxicity. This was found to depend on the composition, size, shape, and surface coating of the nanocrystals which in turn affect their interactions with the surrounding biomolecules, the internalization pathways into cells and the release or accumulation in the body. The significant research that was done on this subject revealed ways to minimize and even eliminate the cytotoxicity, but more importantly, they also described the mechanisms that led to the observed toxicity. One particular mechanism which is of high relevance to our subject is ROS formation by the NCs. The cellular damage caused by ROS formation can turn to be of high value if carried out purposefully in a controlled manner, for example, to play a role in the battle against cancer.

The ability to kill cancer cells with HNPs was demonstrated *in vitro*. Twenty-four-hour incubation of HNPs with cells under dark conditions

did not show toxicity effects, indicating on the capacity to minimize undesired effects by suitable NCs engineering. However, samples of cells and HNPs exposed to 5 min of excitation during these 24 h resulted in significant cells death and showed much less live cells indicating it also stopped the cells proliferation [26].

Similar results have been shown, *in vivo*, with orthotopic tumor mouse model which were injected with HNPs conjugated to a peptide delivery agent that targets cancerous cells [31]. Histochemical staining along with measurements of tumor size in the succeeding days to the injection have shown significant cell death and smaller tumor sizes only in mice which were treated with HNPs conjugated to delivery peptides and were exposed to light, demonstrating the potential of HNPs for photodynamic therapy (Fig. 12.7a). Importantly, the examination of additional samples, taken from the liver, lungs, spleen, heart, and kidney exhibited insignificant systemic toxicity. Furthermore, the better compatibility of HNPs for two-photon excitation can allow their use for increasing the tissue depth possible for non-invasive treatments, giving them once again an important advantage in comparison with other photodynamic therapy agents.

Analogous to the idea of photodynamic therapy which kills cancer cells, ROS formation can be used for bacterial disinfection. This was demonstrated by incubating Gram-positive and Gram-negative bacteria, *(Escherichia coli* and *Staphylococcus aureus,* respectively) with ZnO-Au HNPs or ZnO. Figure 12.7b, c show that ten minutes exposure to simulated sunlight resulted in much more bacterial death for the HNP system [32]. This capability combined with the idea to use HNPs as multifunctional photoinitiators can lead to their use in the preparation of coatings and structures with antifouling properties.

The last two examples, phototherapy and antibacterial applications, can work well under conditions which result in non-specific ROS formation. However, there are others that require selectivity, to prevent non-specific effects by the alternative photocatalytic products. A family of applications that fall into this category is based on H_2O_2 formation by HNPs and the ability to activate with it peroxidase enzymes. Figure 12.7d shows turn on–off cycles of light stimulation of CdSe/CdS-Au HNPs resulting in distinctive staircase behavior of horseradish peroxidase (HRP) activity [26]. This enzyme is widely used in sensors, diagnostics, and biochemical kits, which detect molecules and processes in biological systems. For example, HRP secondary antibodies are commonly used in western blot, immunohistochemistry, and ELISA together with H_2O_2 and different substrates to form precipitates or produce colorimetric, fluorescent, or chemiluminescent signals. The resolution of the current assays is limited since the entire biological system is exposed at once to hydrogen peroxide and since the latter can harm the cells and tissues. These limitations can be alleviated by the local and time-controlled light-induced H_2O_2 formation as offered by HNPs. Another peroxidase enzyme, thyroid peroxidase, consumes hydrogen peroxide during the production of the thyroid hormones. The ability to produce H_2O_2 on demand by using HNPs might have a potential for cases in which physiological malfunctioning requires enhancing the production of hormones by thyroid peroxidase.

12.3 Concluding Remarks

The birth of new materials and their growth into applications is usually challenging and slow. It requires following a typically slow-learning curve for better synthesis and materials engineering, carefully characterizing their properties and then to bring them from the laboratory to the industrial scale. The commercial applications of semiconductor nanocrystals in displays and biomedical kits have already crossed this path, setting the stage with greater understanding of the possibilities and obstacles for the next generation of quantum materials and their applications. The emerging applications mentioned herein offer a glimpse to the possible photocatalysis processes. Novel photocatalytic and photo-redox reactions with quantum materials are becoming more and more common in research. These, alongside with continuous

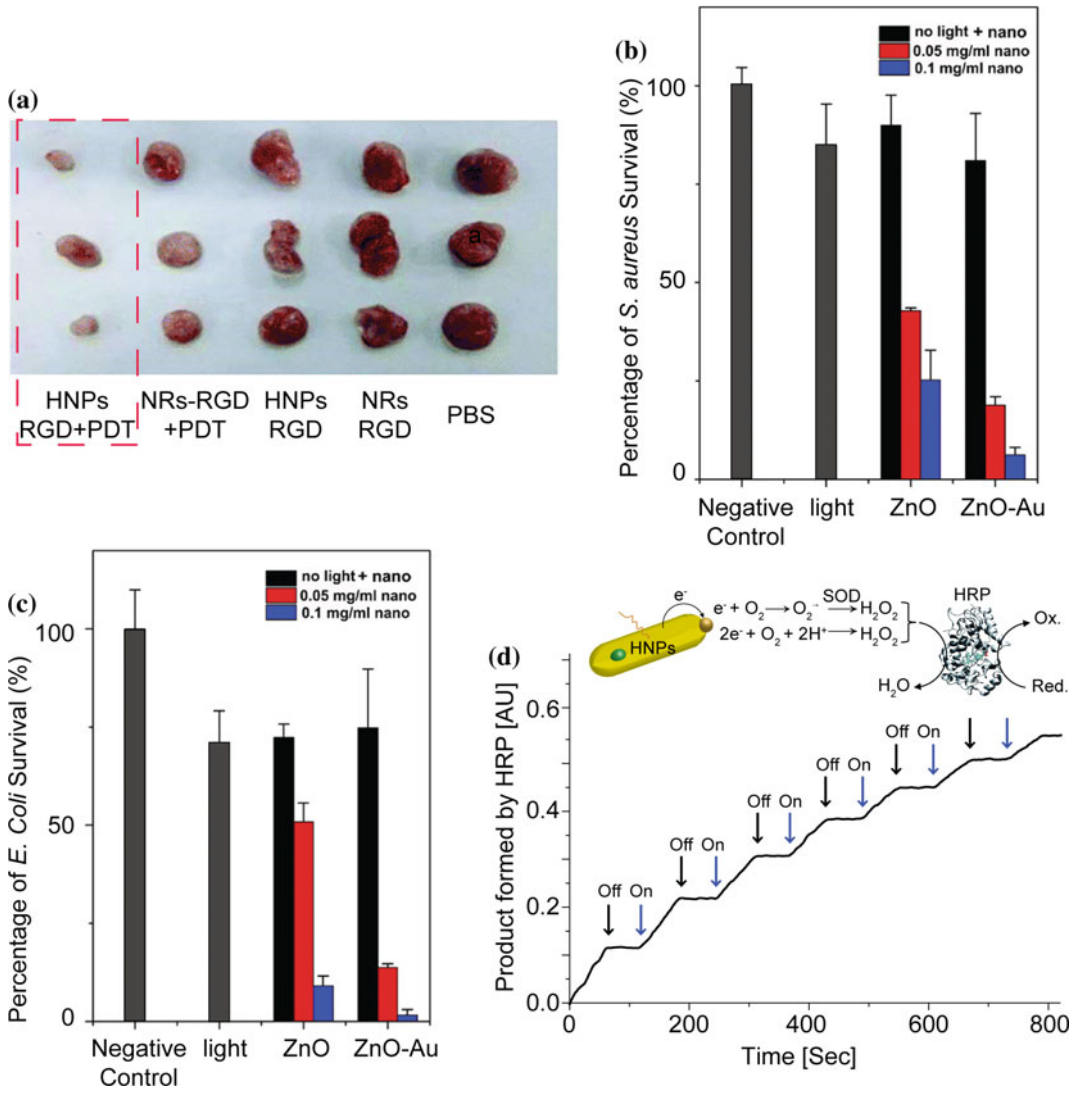


Fig. 12.7 Biomedical applications based on photocatalytic semiconductor nanocrystals. **a** Tumor mouse model injected with HNPs conjugated to delivery peptide (RGD) and their excitation with light (PDT) show significantly smaller tumor size in comparison with other treatments after 16 days. The results indicate the combination of the HNPs, delivery peptides, and light stimulation is required for the positive outcome. The other treatments showed tumor size similar to that seen in mice injected with phosphate buffer saline (PBS). Reproduced with permission [31]. Copyright 2017 The Royal Society of Chemistry. **b**, **c** Two lines of bacteria, *S. aureus* and *E. Coli*, grown in the presence of HNPs and exposed to 10 min of simulated light show significant mortality (red and blue in comparison to black bars). Reprinted with permission from He et al., J. Am. Chem. Soc., 2014, 136 (2), pp 750–757 Copyright (2013) American Chemical Society [32]. **d** Light-induced formation of hydrogen peroxide allows modulating horseradish peroxidase (HRP) activity, which follows the turn on and off light cycles. Inset—the hydrogen peroxide can be formed as a direct product of HNPs excitation or as a secondary product after the conversion of superoxide to H_2O_2 by superoxide dismutase (SOD). Reproduced with permission [26]. Copyright 2016 American Chemical Society

development of nanomaterials, and the introduction of formulations and compounds which can enhance the catalytic activity and selectivity bring us toward a greener future in which photocatalytic quantum materials may have a significant role.

Acknowledgements This work was supported by the Israel Science Foundation–Alternative Fuels Program Center of Excellence (grant #1867/17).

References

1. Tyrakowski CM, Snee PT. Phys. Chem. Chem. Phys. 2014;16:837.
2. Veamatahau A, Jiang B, Seifert T, Makuta S, Latham K, Kanehara M, Teranishi T, Tachibana Y. Phys. Chem. Chem. Phys. 2015;17:2850.
3. Wu X, Liu H, Liu J, Haley KN, Treadway JA, Larson JP, Ge N, Peale F, Bruchez MP. Nat. Biotechnol. 2003;21:41.
4. Resch-genger U, Grabolle M, Cavaliere-jaricot S, Nitschke R, Nann T. Nat. Methods 2008;5:763.
5. Maestro LM, Ramírez-Hernández JE, Bogdan N, Capobianco JA, Vetrone F, Solé JG, Jaque D. Nanoscale 2012;4:298.
6. Maestro LM, Rodríguez EM, Rodríguez FS, la Cruz MCI, Juarranz A, Naccache R, Vetrone F, Jaque D, Capobianco JA, Solé JG. Nano Lett. 2010;10(12):5109.
7. Ohmachi M, Komori Y, Iwane AH, Fujii F, Jin T, Yanagida T. Proc. Natl. Acad. Sci. USA. 2012;109:5294.
8. Watanabe TM, Fujii F, Jin T, Umemoto E, Miyasaka M, Fujita H, Yanagida T. Biophys. J. 2013;105:555.
9. Panfil YE, Oded M, Banin U. Angew. Chemie. Int. Ed. 2018;57:4274.
10. Mokari T, Rothenberg E, Popov I, Costi R, Banin U. Science 2004;304:1787.
11. Banin U, Ben-Shahar Y, Vinokurov K. Chem. Mater. 2014;26:97.
12. Chen WT, Yang TT, Hsu YJ. Chem. Mater. 2008;20:7204.
13. Menagen G, Mocatta D, Salant A, Popov I, Dorfs D, Banin U. Chem. Mater. 2008;20:6900.
14. Waiskopf N, Ben-Shahar Y, Banin U. Adv. Mater. 2018;30:1706697.
15. Jakob M, Levanon H, Kamat PV. Nano Lett. 2003;3:353.
16. Redmond PL, Hallock AJ, Brus LE. Nano Lett. 2005;5:131.
17. Ben-Shahar Y, Scotognella F, Kriegel I, Moretti L, Cerullo G, Rabani E, Banin U. Nat. Commun. 2016;7:10413.
18. Amirav L, Alivisatos AP. J. Phys. Chem. Lett. 2010;1:1051.
19. Ben-Shahar Y, Scotognella F, Waiskopf N, Kriegel I, Dal Conte S, Cerullo G, Banin U. Small 2015;11:462.
20. Aldana J, Lavelle N, Wang Y, Peng X. J. Am. Chem. Soc. 2005;127:2496.
21. Simon T, Bouchonville N, Berr MJ, Vaneski A, Adrović A, Volbers D, Wyrwich R, Döblinger M, Susha AS, Rogach AL, Jäckel F, Stolarczyk JK, Feldmann J. Nat. Mater. 2014;13(11):1013.
22. Kalisman P, Nakibli Y, Amirav L. Nano Lett. 2016;16:1776.
23. Berr MJ, Wagner P, Fischbach S, Vaneski A, Schneider J, Susha AS, Rogach AL, Jaeckel F, Feldmann J, Jäckel F, Feldmann J. Appl. Phys. Lett. 2012;100:223903.
24. Nosaka Y, Nosaka AY. Chem. Rev. 2017;117:11302.
25. Mtangi W, Tassinari F, Vankayala K, Vargas Jentzsch A, Adelizzi B, Palmans ARA, Fontanesi C, Meijer EW, Naaman R. J. Am. Chem. Soc. 2017;139:2794.
26. Waiskopf N, Ben-Shahar Y, Galchenko M, Carmel I, Moshitzky G, Soreq H, Banin U. Nano Lett. 2016;16:4266.
27. Ipe BI, Lehnig M, Niemeyer CM. Small 2005;1:706.
28. Stone D, Ben-Shahar Y, Waiskopf N, Banin U. ChemCatChem 2018;10:5119.
29. Rajendran V, Lehnig M, Niemeyer CM. J. Mater. Chem. 2009;19:6348.
30. Pawar AA, Halivni S, Waiskopf N, Ben-Shahar Y, Soreni-Harari M, Bergbreiter S, Banin U, Magdassi S. Nano Lett. 2017;17:4497.
31. Fan J-X, Liu M-D, Li C-X, Hong S, Zheng D-W, Liu X-H, Chen S, Cheng H, Zhang X-Z. Nanoscale Horiz. 2017;2:349.
32. He W, Kim HK, Wamer WG, Melka D, Callahan JH, Yin JJ. J. Am. Chem. Soc. 2014;136:750.

Vibrant Digital—A Personal Journey Navigating the Cognitive Era

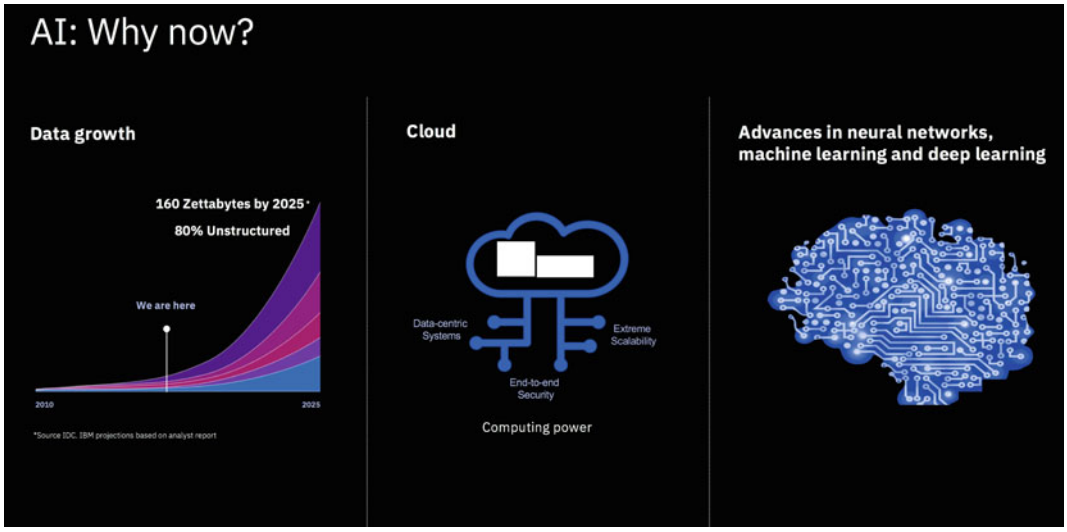
13

Scott Sprangler

There has been a seismic shift in the last decade in how we think about what computers are able to do in our everyday lives. Many tasks that we thought only humans could perform, such as those requiring specialized knowledge, sophisticated judgment, and advanced reasoning, we now see computers taking on more and more. There are many underlying causes for this shift, but three primary advances are driving the revolution.

13.1 Data Growth

The exponential growth in publicly available data has been the most important driver of the cognitive or artificial intelligence revolution now underway. The bulk of this data is in an unstructured format, making it challenging to utilize with traditional data analytics. But, a cognitive approach can leverage structured and unstructured data into a knowledge



S. Sprangler (✉)
IBM, 12840 Stevens Ct., San Martin, CA 95046, USA
e-mail: sprangles@us.ibm.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_13

representation that is flexible, extendable, and maintainable over time. Vast data availability is the fuel that powers the cognitive engine, allowing it to keep up with a rapidly changing environment and make sense of complex situations.

However, exponential data growth is in some ways problematic. Too much data can be confusing, overwhelming, and obfuscating. It can lead to greater and greater fragmentation of knowledge, as scientists and professionals become ever more specialized and disconnected in what each knows. This combination of both a great opportunity and a great human need makes data growth the most critical phenomenon explaining the sudden emergence of cognitive computing as a driver of progress.

13.2 Cloud Computing

The second-most important driver of cognitive computing today is the emergence of cloud computing as an architecture for deploying systems. Because data is constantly growing and changing over time, it would be impractical and expensive to deploy new models to every different end system each time the model changes. Cloud computing and Software as a Service make it possible to deploy changes rapidly with minimal cost. Cloud computing also makes it possible to more easily manage the vastly different computing requirements of training a model vs. execution of the trained model at runtime. The flexibility of this architecture makes it ideally suited to allow machine learning models to be scaled to whatever the data and runtime requirements are for each application.

With cloud computing, it is possible to combine local, company-specific learning with global, industry-wide models in a seamless way. This "hybrid" cloud architecture is critical when you want to utilize highly sensitive data and expertise to make critical decisions. Cloud computing allows us to quickly build and realize the kinds of systems that could only be diagrammed before.

13.3 Advances in Machine Learning

The least important of the three drivers of cognitive computing adoption today, in my opinion, is the latest advances in machine learning, often referred to as "deep learning". It is not the "new" algorithms themselves that have enabled their widespread application and adoption, but the realization that suitable data now exists with enough computation to make them practical. Models can only be as sophisticated as the richness of the data allow them to be. And if data is rich enough and the problem sufficiently complex, then models, or models of models, or models to the nth power, will be connected in such a way as to make it possible to simulate that complexity with a high degree of fidelity.

The so-called advances in machine learning that have occurred, while necessary, are entirely predictable and inevitable once data and computational power become readily available. But models follow from the data, not the other way around. The mistake that many practitioners and would-be practitioners make, is to assume that because a model worked to solve one problem it will work to solve a different challenge of equal difficulty. However, this will only be true if the data for the second problem is as extensive and as complete as it was for the first.

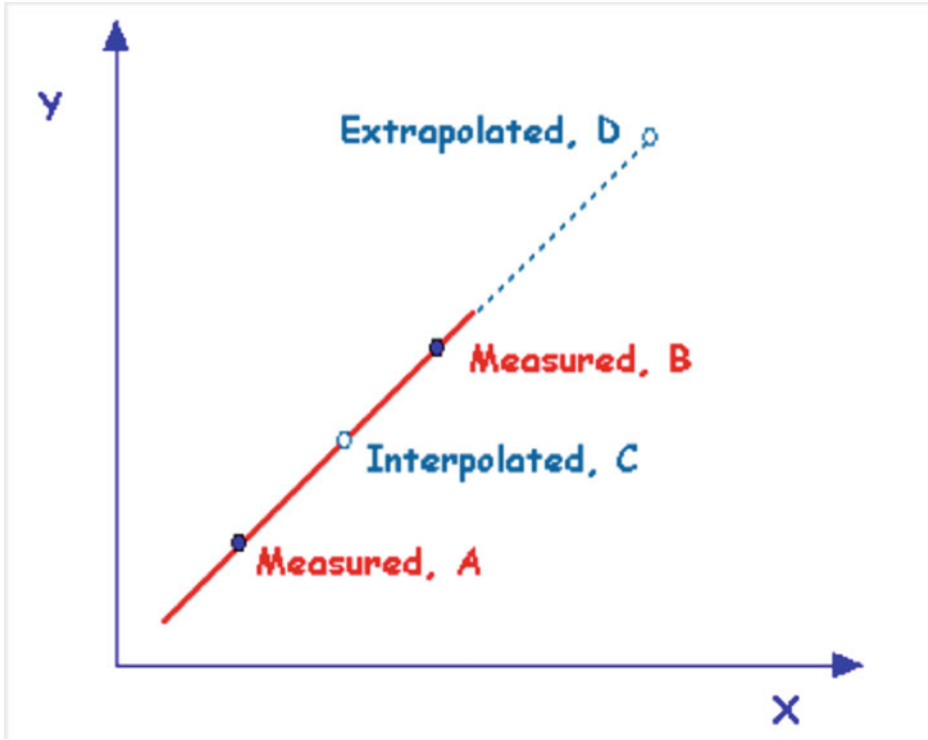
13.4 The Pitfalls of Complexity

> I feel so strongly that *deep and simple* is far more essential *than shallow and complex*.
>
> – Mr. Rogers

Applying cognitive approaches to solving real-world problems is seldom as straightforward as following a recipe. It requires, first and foremost, a fundamental understanding of the domain of the problem being solved. This means understanding the key concepts and the relationships between those concepts. It then requires a reasoning strategy that is only as complex as necessary to capture the relationship between the key-dependent variable and the independent features that drive the dependent response. A reasoning model that is more complex than

necessary is computationally wasteful and will be more brittle and less generally applicable as future data inevitably drifts away from the data used in training. Deep and simple is the only way to ensure a model will accurately reflect the best information available, while not concluding more than the data warrants.

13.5 Interpolation Versus Extrapolation



Once we generate a predictive model, there remains the question of where to apply it. Here, it is important to remember that a model is only as good as the context of the data used to generate it. The points we predict should be interpolations, not extrapolations. This means that if new vocabulary, new entities, or new relationships have been introduced since the last time our model was built, then we need to rebuild it. It also means focusing our discoveries on the implication of known facts as opposed to entirely new areas. The more we can rely on what is known, the more we can be confident that the predictions being made will bear fruit when actual validation experiments are performed.

Understanding interpolation as the goal helps us to pick the most appropriate problems for cognitive computing to solve. We need to stay away from areas of the universe that are poorly understood and sparsely charted. There are more than enough fruitful and significant discoveries to be made in the space between facts which are well known and verified.

13.6 Confidence Scoring—Knowing What to Believe

Not every fact that we can extract from existing knowledge sources will be of equal veracity. Being able to quantify the confidence, we have in the facts that make up our knowledge network is critical to trusting the conclusions we draw from it, and the models based on it. There are two primary sources of confidence: direct and indirect. Direct confidence refers to the substantiation of a fact from multiple information sources. The more sources repeat a fact, in general, the more confidence we have in that fact's truth.

Indirect confidence refers to the confidence we gain by the consistency of a fact with all the other facts in our knowledge network. If, for example, a fact represents a kind of connection between two different entities, we can observe other facts about these individual entities and measure the relative likelihood that the connection between them is what we would expect. One way to measure this quantitatively might be through collaborative filtering or matrix factorization approaches.

Principles for Calculating the Confidence of a Fact

- Frequency of Occurrence (higher frequency -> more likely to be true).
- Consistency, measured by collaborative filtering (higher matrix factorization score -> more likely to be true).
- At the limits:
  - Infinite support = 100% confidence
  - 1.0 MF = 100% confidence
  - 0.0 MF and 1 support = lowest confidence
- $P = a\mathrm{MF}^d - b/\mathrm{S}^e + c$.
- Need to determine *a, b, c, d* and *e* experimentally.
- Process: Sample facts with different levels of Su and MF and determine the observed *P* value.

The process shown above is one way to calculate the probability of a given fact observed in text. It combines two numbers in an equation: support (S) and matrix factorization score (MF). Coefficients for the equation are calculated by comparing the extracted facts with manually curated ground truth. By observing the accuracy rate at different levels of MF and S, it is possible to estimate the value of the coefficients and then use the equation for predicting the probability that any particular extracted fact is indeed true.

13.7 Explanation of Reasoning

In addition to making accurate predictions with cognitive approaches, it is also necessary to explain why the predictions are being made. An explanation of reasoning and a degree of transparency is necessary if scientists are to gain sufficient confidence in the results to make the effort to validate the hypothesis. Furthermore, the explanation itself must be grounded in the literature corpus from which the prediction was derived. This gives scientists a basis upon which to judge the underlying reliability of the information that was used to generate the hypothesis in the first place.

Bladder cancer example: evidence for top-ranked gene CD4

- The entities (**pathway, tumor, or condition**) in the rows are connected to the target **CD4**
- **Common genes** lists how many targets the entity shares with the targets or tumor in the known set of 70 genes associated with bladder cancer
- **Total genes** lists how many genes the entity is connected to in total
- **Probability** lists the p value of sharing that many common genes by chance (χ^2 test)

Pathway	Common genes	Total genes	Probability
Immune response	23	383	1.64E-78
T cell co-stimulation	6	80	5.46E-27
Positive regulation of interleukin-2 biosynthetic process	2	12	2.19E-21

(continued)

Pathway	Common genes	Total genes	Probability
Cell surface receptor signaling pathway	10	269	1.08E-20
Signal transduction	18	1071	6.78E-14
Positive regulation of calcium-mediated signaling	2	19	9.22E-14

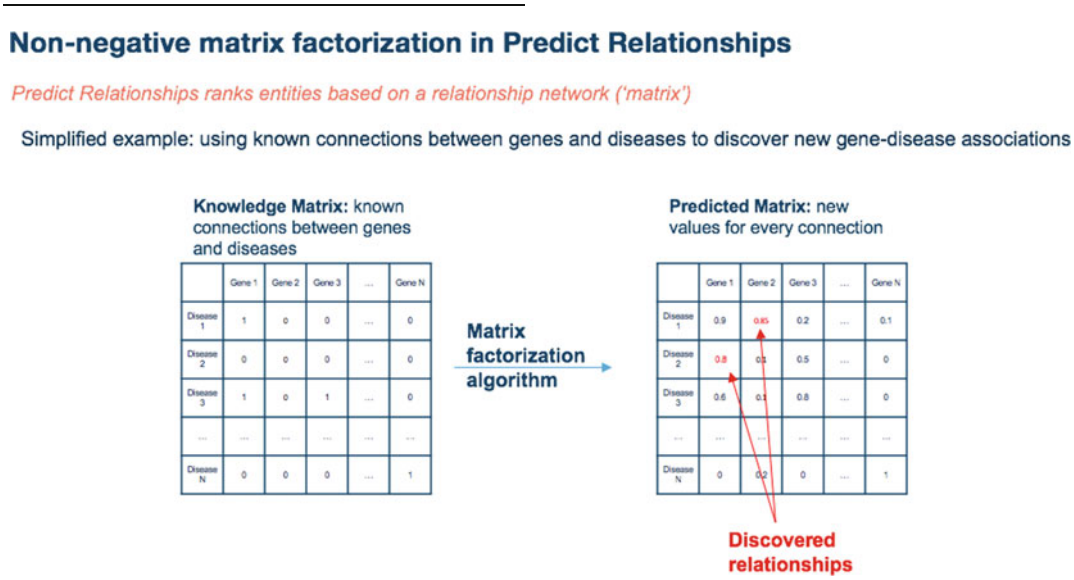
In this example, we seek to explain the predicted connection between the gene CD4 and bladder cancer. In this case, the total number of genes being ranked is $N = 19687$. The number of genes connected to bladder cancer in the knowledge network is $n = 70$. The matrix for prediction is made up of genes on one side and pathways/conditions/tumors on the other. For the most similar pathway, "immune response," the total number of genes is 383 and the number shared with bladder cancer is 23. This gives a χ^2 probability of $\chi^2(19{,}687, 70, 383, 23) = 1.64\text{E-}78$. And in fact, the immune response pathway is a very important pathway involved with this disease, so the result makes sense biologically.

In the example above, the cognitive system predicts that the gene CD4 has a connection to bladder cancer. It uses knowledge about genes and their connections to pathways, conditions, and tumors to make this prediction through matrix factorization. It then uses connections of the gene to key pathways known to be associated with genes connected to bladder cancer as an explanation for why the hypothesized connection is likely to be true. The scientist can then evaluate the relative strength of these connections to decide if the hypothesis is indeed valid.

13.8 Behavior Is Rational and Repeatable

Recommender systems collect the behavior of many users and use this to make recommendations based on similarity to the behavior of others. The basic assumption behind such a model is that behavior is a rational process that is relatively stable and consistent over time across many different individuals. To give a simplistic example—if most individuals who like A also like B, and you like A, you will probably also like B.

But we can apply this general principal beyond the realm of predicting individual preferences. In fact, we can use it to predict the behavior of any entity in our knowledge network, based on the behavior of entities that are similar in their overall behavioral pattern.



In the figure above, we show how this works, in practice, to predict new associations between genes and diseases. In the left matrix, a "1" in a cell indicates a known association of gene to a disease and a "0" indicates no known association. We then factor the input matrix into two product matrices that approximate it. The resulting approximation is shown in the right matrix. Those cells that were formerly zero and have a number near 1.0 are considered to be predictions of an association. In practice, this means we consider the overall behavior of those genes to be consistent with other genes that are associated with the disease. Such an approach can be used to find new targets for drug intervention or new biomarkers to identify patient populations.

13.9 The Past Is Validation for the Future

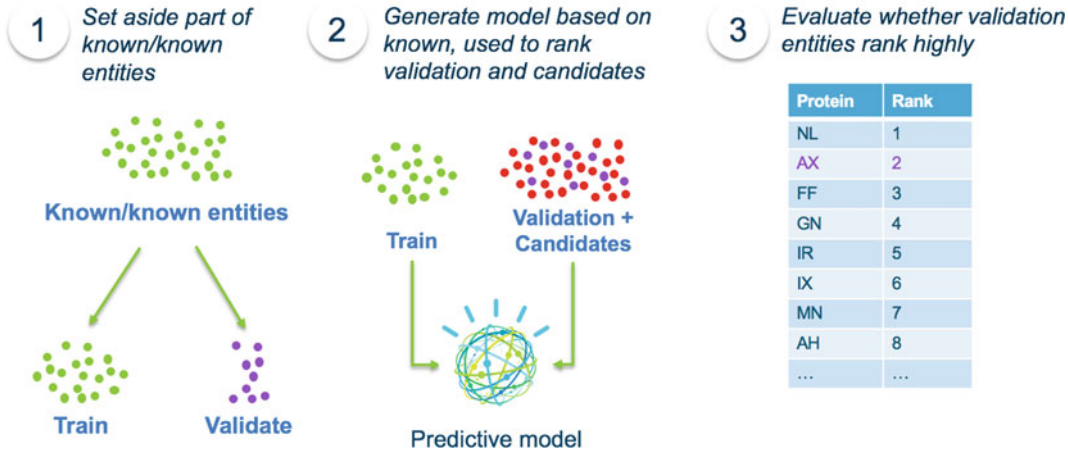
When we make predictions, such as the gene to disease prediction above, we often struggle to know how much faith to put in them. How reliable is an association based on similar genes? One way to measure this is by going back in time and seeing what we could have predicted at an earlier date and see how well that corresponds to what actually occurred.

The concept of "leaving-out" from a training set for validation is common in machine learning. It refers to the idea of removing some examples from the known, labeled, data set and including them with the unlabeled examples. We would then expect a model trained on the remaining training set examples to accurately label those that were left out. Since we know the correct labels for these excluded examples, we can gain insight into the accuracy of our model from this result.

To determine which labeled examples to validate with we can add information relating to the date of each labeled and unlabeled example (e.g., date of the first connection to a disease area of interest). This can then be used as the criteria for splitting examples into training and validation groups. Such an accuracy measurement is much more likely to provide a realistic estimate of the accuracy of future results because it has to deal with the problem that things change over time, and so models built in the past will naturally become more error prone which forced to predict the future.

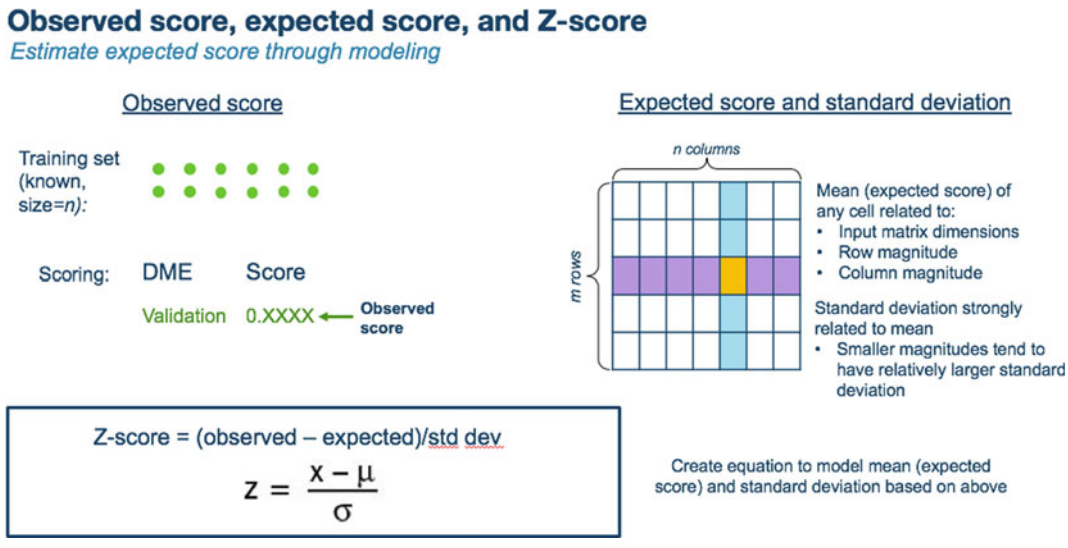
13.10 Unlikelihood Is a Measure of Interestingness

It is fairly easy to make predictions using models and data, and as we have shown above, we can even gain insight into the likely accuracy of a



Validation data sets

prediction. However, predictions, even accurate ones, are not always interesting. For example, if I predict that the gene P53, which is connected to many cancers already in the literature, is also connected to another cancer that has not yet been published, this may indeed be highly likely to be true, but is not necessarily valuable as a scientific hypothesis. This suggests we need a way to measure not just confidence, but also "interestingness".



knowledge network. It is possible to generate different matrices having the same overall structure and density, but a random distribution of 1's and 0's. We can then observe the mean and standard deviation of the cell corresponding to the disease/gene in question. If the Z-score of the prediction is zero or less than zero, it is uninteresting—even if the prediction confidence is large it is nothing more than we would expect. On the other hand, a large Z-score, even with a small prediction confidence, might turn out to be worth looking at more closely…keeping in mind that if both the disease and gene in question are quite rare in the network, there may be very little evidence to back up the prediction.

A good example of how to measure interestingness is through the concept of expected value. The mean (or average) of a distribution is its expected value. The standard deviation represents how much that expected value is likely to vary. By observing a number of network instantiations, we can detect the mean and standard deviations of the predictions, given the magnitude of the inputs. This can then be used to calculate a Z-score for the observed value (the actual prediction being made). The larger the Z-score, the more unexpected, and thus interesting, the prediction.

To say this in another way, suppose we have a gene that occurs with a certain frequency and a disease that occurs with another frequency in our

13.11 Don't Look for an Answer… Look for a (Better) Question

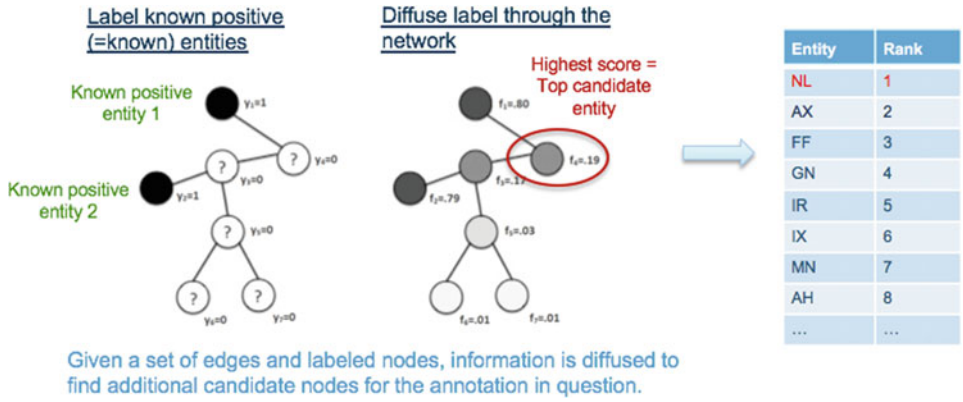
One of the common misconceptions about cognitive applications is that they make "better" decisions than humans because they are less biased or have access to more information. It turns out, there are only a very limited set of problems for which this is true. Problems which

are extremely well constrained and have all the rules and states completely determined ahead of time fall into this camp, for example, chess. If we were to limit ourselves to applications of this ilk, cognitive systems would be fairly useless to society.

But once we go outside these tidy boundaries, we must face the probability that models trained on messy and incomplete data will necessarily fail, and not always in predictable ways. This creates a dilemma if we want our cognitive system to be an oracle of truth. Eventually, it will let us down.

13.12 Use the Known to Map the Unknown

In discovery, we must always be pushing into uncharted territory. How do we do this effectively with machine learning models that only predict using models trained on what is already well known? This is the key paradox of Cognitive-Assisted Discovery. The solution is to use what is known as a map to the unknown.



Graph diffusion on a network

But there is another role that cognitive systems can play which allows them to be effective while still allowing them to be wrong. This is the role of collaborator with a human expert. Here, there is an ample opportunity for the human to benefit from machine capability with minimal risk of harm. Machines see, interpret, and reason over knowledge quite differently than humans, so a partnership allows each to benefit from the other. Human–machine partnerships are really the only effective way for cognitive systems to become capable of helping with the most important and complex decisions that we face. Indeed, it is becoming more and more necessary for humans to have cognitive assistance to navigate an increasingly complex knowledge environment.

In this example from our 2014 research into P53 [1], we use a similarity graph of entities as the basis upon which to explore. We fill in this map with landmarks based on the known kinases of P53, identified as "known positive entities." These are initially the hot nodes in our network. Next, we let heat diffuse throughout the rest of the graph. When we reach equilibrium, the "temperature" of each node is a measure of its similarity to the concept represented by the original known positive nodes. What is known has helped us discover which of the unknowns are most likely to be what we are looking for.

13.13 Training Sets Are Hard Work (Don't Take Shortcuts)

It should be obvious that to do any kind of machine learning you need training data. Usually a lot of it. And, the quality and quantity of the training data will largely determine how generalizable, how applicable, and how predictive your actual model becomes. Yet too often, how the data will be obtained, how it will be labeled, and how it will be utilized for training, testing, and validation over the long run is not adequately considered.

From time to time, techniques are invented and papers will be published about how training data can be automatically generated or otherwise obtained without much effort. Ignore this fool's gold. It cannot exist. You can only substitute human expertise for data; you cannot substitute pure computation for it.

The reason is that the data must capture all the key aspects of the thing you want to predict. To get that coverage you need rich data that is as varied as the data you expect to get in the real world. You also need enough of it to ensure the real world relevant to your prediction is captured in its entirety.

Effort spent in making the best possible training data should be 90% of any artificial intelligence project. The rest will have a negligible impact by comparison.

13.14 Persistence Is a Virtue

> Success is stumbling from failure to failure with no loss of enthusiasm.
>
> — Winston S. Churchill.

One key advantage of cognitive applications compared to human expertise is that they can persist indefinitely and continue to improve as more information and better models come to light. The ability to persist state and gradually improve models are critical to doing systematic discovery that applies the best approach to the best available data. But those who apply the technology need to be patient and expect failures along the way. Like their human counterparts, cognitive systems learn through failure, and a certain number of mistakes, especially in the initial phases, should be expected and planned for.

Too often in my experience, expectations for cognitive systems are for immediate perfection and rapid return on investment. When this fails to materialize, disillusionment follows. Often it is not that the technology has failed, but that expectations were unrealistically high and the patience to fix the problems, lacking.

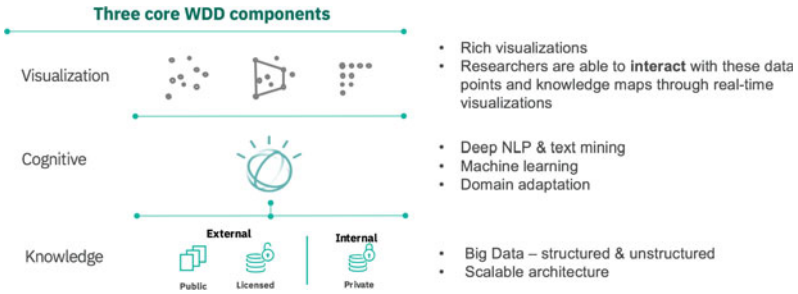
Those willing to put in the effort and measure progress realistically will usually find that the technology is capable of achieving its promise in the long run. The key is finding the right application, the right analytic approach, and the right data. These choices will probably need adjustment over time, but with patience and practice, the right configuration will eventually emerge and the benefits can be long-lasting and profound.

Reference

1. Spangler S et al. Automated hypothesis generation based on mining scientific literature. In: Proceedings of the 20th ACM SIGKDD international conference on knowledge discovery and data mining. ACM, 2014. p. 2623667.

14 Accelerating Discovery with Cognitive—An Example Cognitive Application for Discovery: Watson for Drug Discovery

Scott Spangler



Watson for Drug Discovery (WDD) is a cloud-based, end-to-end scalable platform that helps life science researchers discover new disease pathways, new drug targets, and additional drug indications. It ingests both structured and unstructured content from multiple internal and external heterogeneous sources. It then uses natural language processing and domain-specific ontologies to annotate this content so that the machine can read and understand the content more like the way a domain expert would. WDD can then use predictive machine learning technologies to identify potential new connections that are not explicitly represented in the input data or calculate the likely confidence of existing facts in the input data. Finally, the results are visualized to allow the user to see why the predictions were made, visualize the extracted entities and relationships, and trace back to the original publications and sources that generated the results. This interactive aspect of the approach is critical to making WDD work as a partner with, not an oracle for, with biological researchers.

14.1 Use Cases

WDD is designed to address three primary use cases: novel drug target identification, exploration of gene function and regulation, and the discovery of new therapeutic indications for existing drugs. WDD focuses on supporting scientists in the prediction, discovery, and mapping of the possible genes and diseases relevant for each use case so that research scientists can evaluate why identified connections exist.

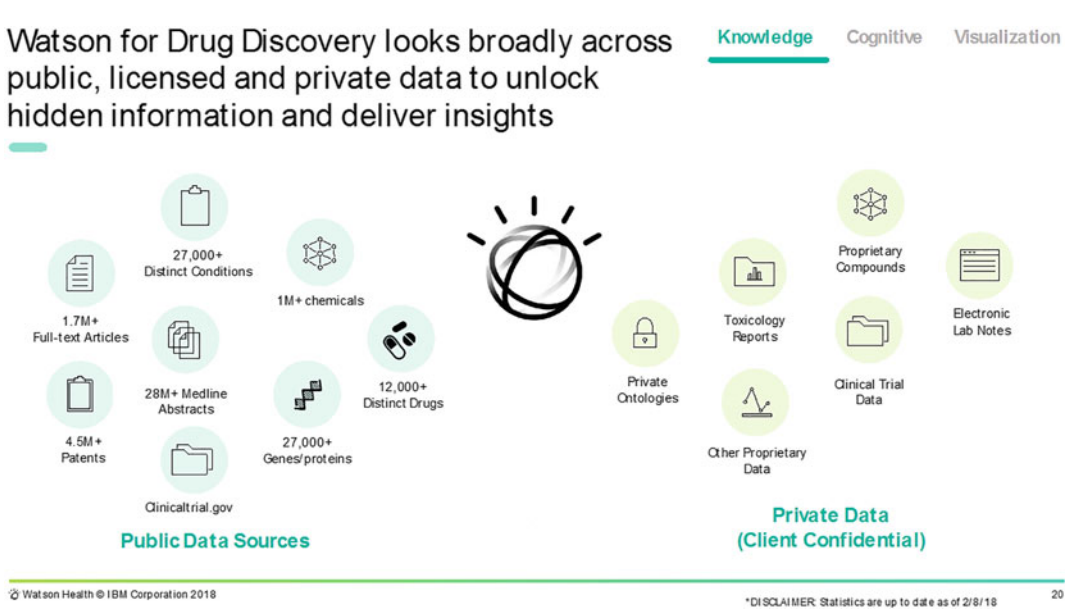
S. Spangler (✉)
IBM, 12840 Stevens Ct, San Martin, CA 95046, USA
e-mail: spangles@us.ibm.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_14

Depending on what information scientists have available and what decision they need to make based on this information, the knowledge graph has the capability to discover both existing and new connections derived from structured and unstructured data sources. In most cases, this capability comes from finding hidden similarities between different entities. For example, one disease might have many of the same gene associations as a very different disease, and therefore drugs that treat one might be useful in treating the other.

14.2 Ingested Content

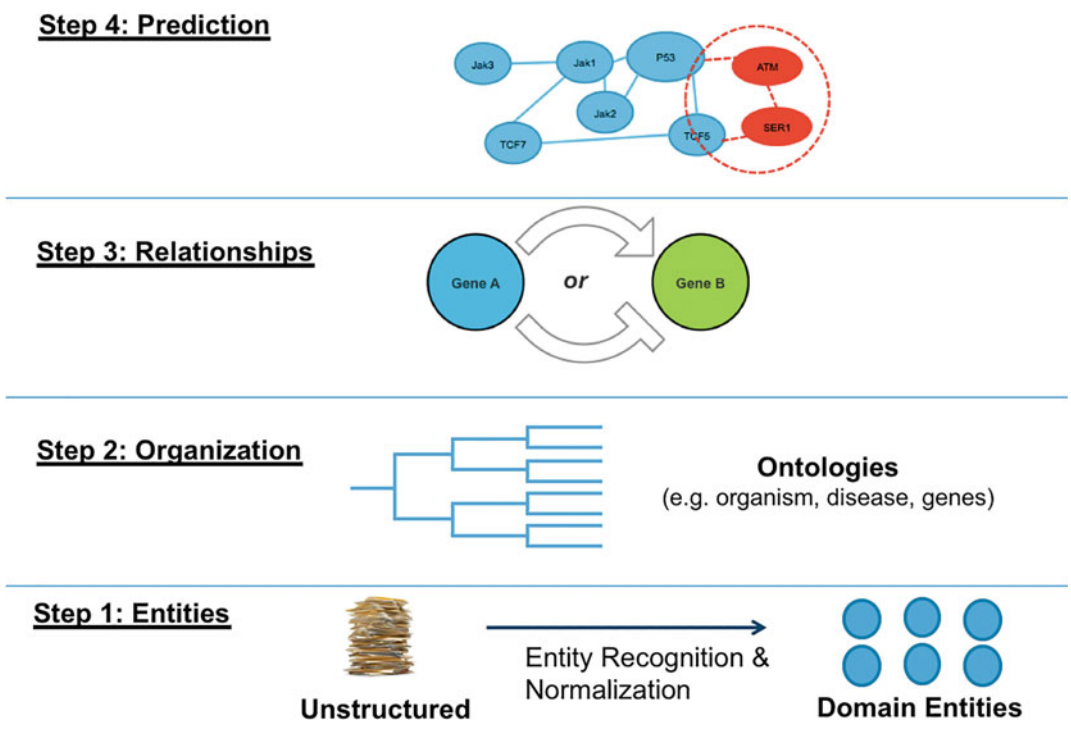
The WDD base corpus consists of publicly available scientific information relevant to drug discovery, including abstracts and full text scientific journal articles retrieved from Medline and PubMed Central (PMC) Open Access, patents from the USPTO, EPO, and WIPO, clinical trials from clinicaltrials.gov, and a variety of ontologies and databases such as the Gene Ontology Consortium, DrugBank, and ChEMBL. In addition to this base corpus, WDD can utilize structured and unstructured private content sources to enable analyses that reflect organization-specific knowledge or processes.



The ability to combine both public and private content into a seamless knowledge network is a key enabler for discovery in organizations today. While public content provides a wealth of relevant information about discoveries that scientists may not be aware of, private content provides key strategic and intellectual property insight that is only known and available within the organization. Leveraging both provides a distinct strategic advantage.

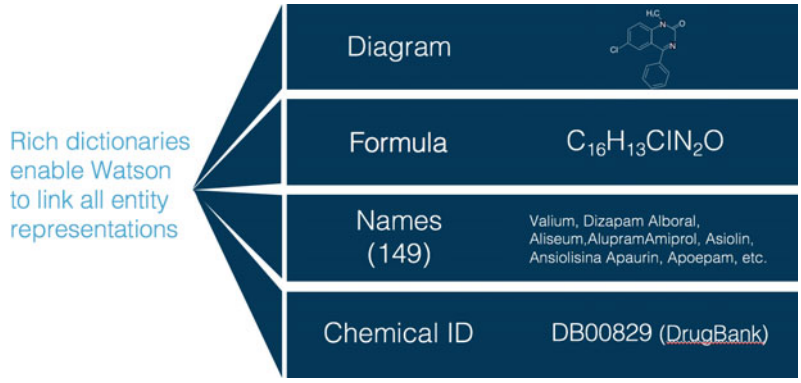
14.3 The Process for Accelerated Discovery

The accelerated discovery process moves step by step through layers of increasing complexity to build up the order from chaos. We begin with the most basic building block of order, the entity. The discovery and organization of domain-specific entities are the most fundamental task of the scientist, because if the entities do not exist there is no coherent way to think about the domain. Think of the periodic table of the elements in chemistry. Without this basic framework upon which to reason, chemistry (then called "alchemy") was a black art. With the framework of the periodic table of the elements, it became possible to make systematic progress. Data science is no different, and we must build up a systematic entity structure that mirrors the important domain concepts if we are to make any sustained progress.



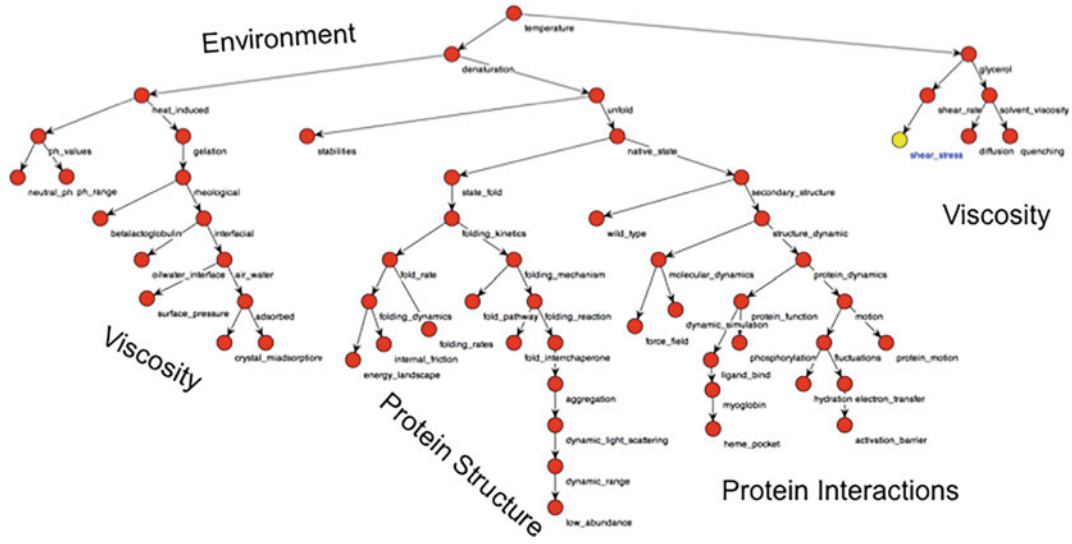
Watson for drug discovery accelerated discovery process

Two problems are usually present in entity detection: (1) What are the entities and (2) how do they appear? In some cases (such as the elements of the periodic table), this answer to #1 is obvious. In other cases (name the factor that influences protein viscosity), it is far less so. The answer to #2 is rarely certain at first. Human beings are individualistic creatures who love to express themselves originally and scientists are no different. There is never any certainty that two different scientists will describe the same thing in the same way. For this reason, entity detection and normalization will always remain one of the most difficult challenges in data science. But it is a key challenge to address because entity normalization makes it possible to summarize the results of many disparate sources and kinds of data into a coherent framework. It is also one of the chief ways that data science can further the impact of the past scientific research on future scientific discovery.



From individual entities, we begin to organize. Which entities belong together and which are separate? Can we create a type system that describes how entities go together? Is there an underlying structural framework that describes how one type of entity composes another type? Once again, the organization scheme may be clear-cut, or it may have to be inferred from what we see in the data, but either way, we must make sure that whatever organization scheme we infer is made to line up with physical reality. Domain expertise is a critical input to organizing the entity ontology. Ontologies then enable knowledge at many different levels and across many different but related areas of the domain to come together to create new insights.

The next step is the detection of relationships between entities. This transitions the focus of our process beyond form to function—how and why things happen. Typically, this will be a specific event observed to happen in a given context where one (or more) entity acts upon another to cause some change or subsequent reaction. As we shall see, the potentially complex nature of this kind of connection will require a much more fine-grained species of text analytics to recognize and classify the physical event. Similar to entities, relationships may also be normalized and have types and ontologies. And likewise, our representation must mirror physical reality as much as possible, with the aid of domain expertise.



Example of ontological structuring of data

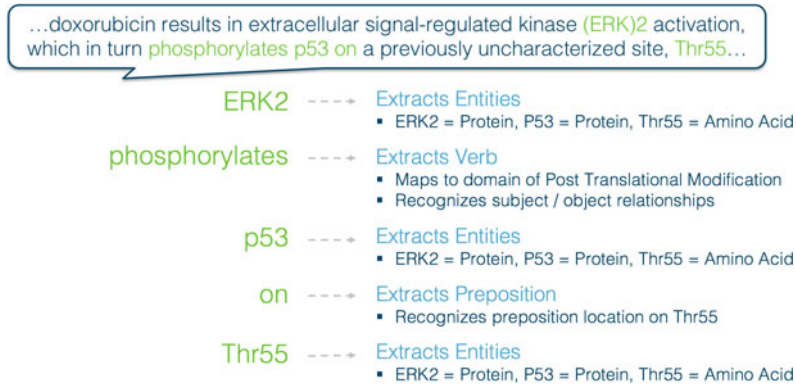


Illustration of Watson for drug discovery annotation

Combining entity and relationship recognition and ontologies we create a summary of how, in a given situation, all the relevant entities relate to each other. This summary can be a table, a map, a network, or anything you can think of, so long as it communicates at a macro-level what is occurring in the entity space. The challenge here is not to overwhelm scientists' minds with too much of a good thing. As we get better and better at detecting and representing the entities and relationships that exist in our knowledge corpus, we must also get better and better at highlighting interesting ones and filtering out extraneous information. Otherwise, we've only created a different kind of chaos.

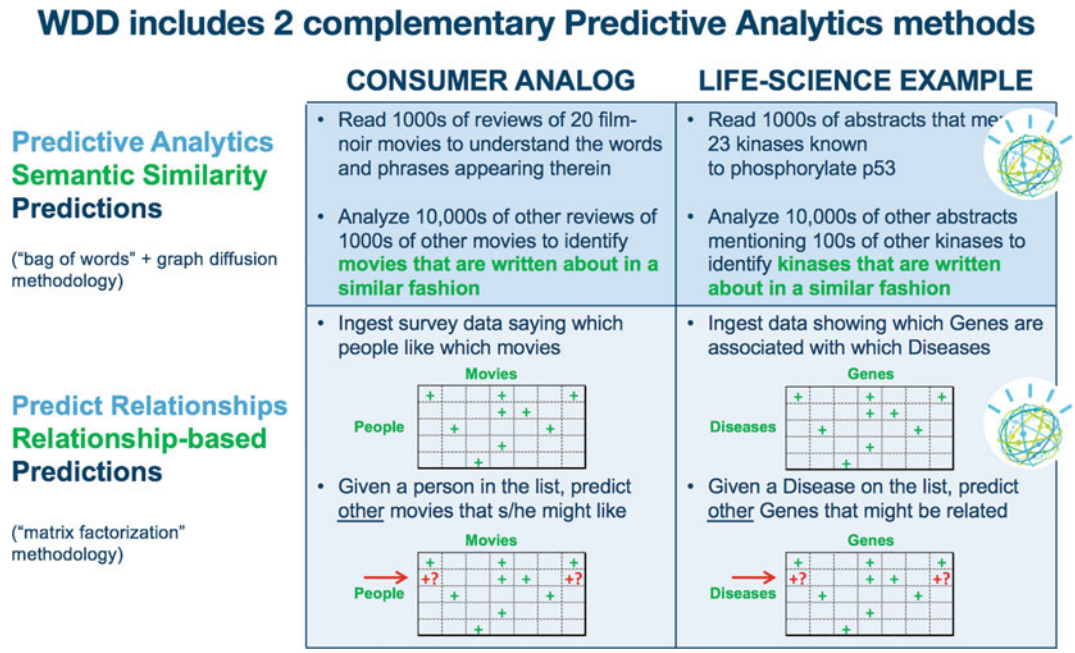
14.4 Hypothesis Generation

But how does the extraction and representation of form and function lead to hypothesis generation, a key goal of accelerated discovery? The answer is that the representation provides the means to evaluate and predict new properties of entities and new relationships between entities. The precise means of doing such prediction may vary from discipline to discipline and, for the most part, will necessarily lie outside the scope of this book. In the example chapters, we will show a few methods by which this may be accomplished, but this should in no way be considered a comprehensive representation of what is possible.

Some approaches to hypothesis generation include:

(1) Inferring properties of an entity based on similar entities using the documents that contain those entities and the text in those documents as a means of defining similarity.
(2) Inferring connections between entities based on relationships already found to exist between other entities in the network.
(3) Finding a potential pathway between two entities that predicts how one entity might affect another in a new situation.
(4) Building a classification model that predicts when an entity of type A may have a certain effect on an entity of type B based on the properties of A and B and the past examples of such effects.
(5) Look for areas of contradiction in the past research concerning entity relationships or entity properties. This might indicate a fruitful area for further experimentation.

Below we show two predictive strategies that are implemented in WDD. One is an example of #1, inferring properties of an entity based on similar entities, and the other is an example of #2, inferring new relationships based on existing relationships in the network. In each case, we use what is explicit in the literature to derive what is implied by the literature.

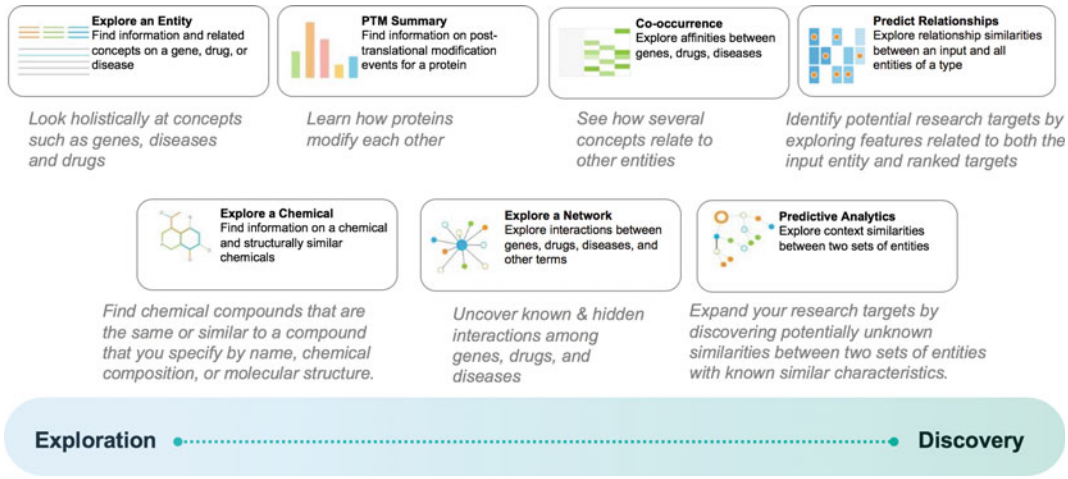


On the left, we see how recommender systems use these strategies in our everyday life to find movies we might like to watch. On the right, we see how the same strategy can be used to find a genes "preference" for a disease based on what is written about that gene in the literature.

Extracting and representing the form and function of entities in the physical world as they appear in documents leads naturally to new insights and hypotheses about how these entities might interact or behave in novel combinations and new experimental conditions. If done correctly, the document extractions from the past scientific results form a framework on which the next set of experiments can be reliably proposed. This is in theory how science has always been done. It is only the impossibility of having all past relevant knowledge in a scientific domain reside inside a single mind that makes it necessary, and indeed essential, to realize the knowledge framework of past discoveries in silico.

14.5 Discovery Is not One Thing, but Many

Extracted entities and relationships from literature can be utilized in many different ways throughout the discovery process. The range of capabilities extends from search-like features of exploration to the more predictive elements described above.



Watson for drug discovery applications

Each of these applications utilizes different kinds of inputs to produce different outputs from the same basic content, entities, and relationships. They help the user to see insights from whatever perspective they need for their situation. Explore a network is a way to visually see how entities are interconnected with directed relationships extracted from the literature. Post-translational modification summary maps all identified relationships of specific types to individual entities and predict relationships reinterprets entity relationship visualizations by predicting unknown connections based on matrix factorization of known relationships. Explore an entity and co-occurrence table allow users to see which entities are most often mentioned in the context of their entities of interest and analyze ontologies of mentioned entities as well as the expectedness of their co-occurrence. Explore a chemical provides users with a method to explore from a structural rather than textual viewpoint.

WDD also uses text mining and machine learning approaches to rank entities or text inputs that are the subject of the investigation with respect to entities that are known to have specific characteristics by using the predictive analytics application. Such an approach uses a list of entities that have a demonstrated relationship to the subject of interest; this list is referred to as a known set because it is used by Watson to determine what features in the text to look for.

The second list of entities—the list that we want to explore—is referred to as a candidate set. Watson ranks the candidates based on their semantic similarity to the known entities. The biological function of an entity is usually embedded in the language that scientists use to describe it in the literature. If a candidate entity shares numerous text features with the entities in a known set, it is predicted to have a higher probability of displaying the subject of interest.

Watson uses such cross-validation methods to provide a statistically based estimate of the validity of the predictive model. To do this, a subset of the known entities is “held out” and combined with members of the candidate entities to form a cross-validation set.

Watson ranks each entity in the cross-validation set and based on how highly the “hold out” set items are ranked, evaluates the model as having a high, medium, or low probability of being valid.

14.6 Case Studies

The following are a set of real-world examples of using Watson for Drug Discovery technology for the purpose of novel scientific discovery.

14.7 Example—Discovering New P53 Kinases

In 2013, a workshop took place that brought together data scientists from IBM who were creating accelerated discovery technology and molecular biologists at Baylor College of Medicine. They wanted to see if there was some way to accelerate discovery around the protein P53. The results of that effort were published in a paper in Knowledge Discovery and Data Mining 2014 [3]. Here we describe some of the back story behind how we arrived at the result, using the accelerated discovery methodology described in this book.

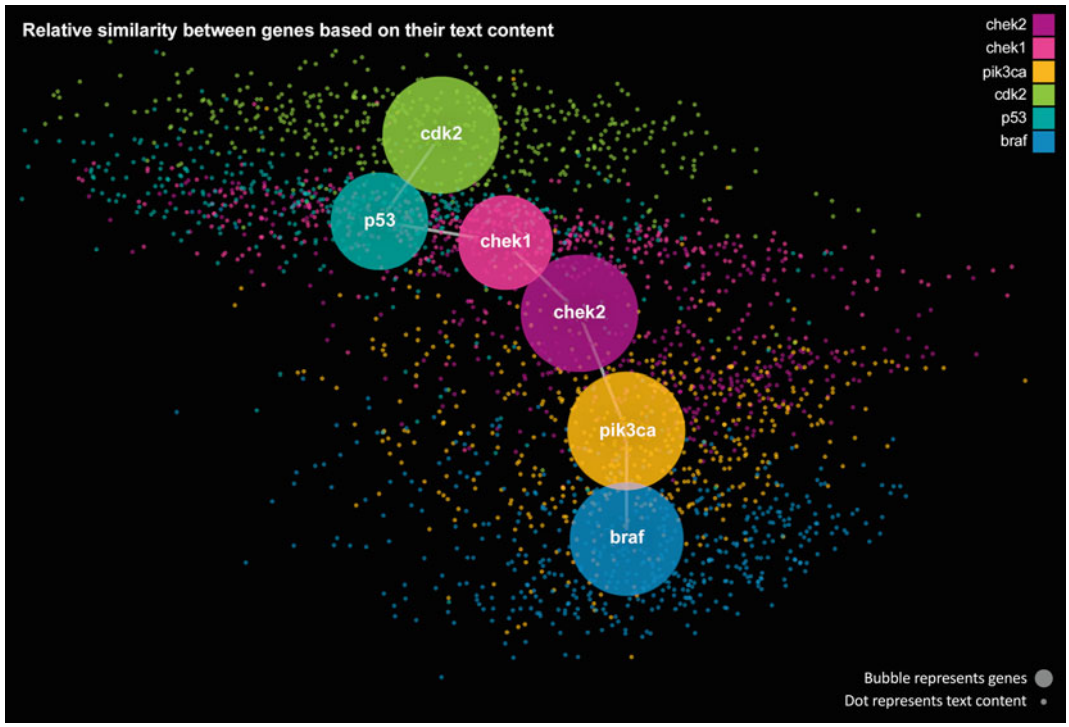
The first day of our two-day workshop was spent with the Baylor team explaining P53 biology to the data scientists from IBM. The content of this day can be roughly summarized as follows: all human cells in a body contain a nearly identical genome. This genome contains the information to create thousands of different proteins, which in turn perform cellular biological functions. One protein in particular, P53, is a kind of guardian of the genome and is involved in many kinds of cancer, since it helps to recognize genomic damage and prevent it from propagating. One of the ways in which P53 recognize cellular problems is through a set of messenger proteins called kinases. Kinases themselves are promising drug targets so knowing which kinases interact with P53 is an important area of discovery.

This background provided us with a well-formed problem: we had a space of entities (kinases) and we had the data to structure information from (published literature in the form of Medline abstracts). We also had some known entities that fit the pattern we were looking for (phosphorylate p53). With six months of funding, we needed to extract enough information to derive a prediction model that would extrapolate from the known p53 kinases to additional kinases that were not yet known to phosphorylate p53.

14.8 An Accelerated Discovery Approach Based on Entity Similarity

On the second day, I presented to Baylor our process for doing accelerated discovery. They immediately recognized what I was getting at. It was encouraging that they also remarked that it looked similar to the scientific methods they already used to uncover new properties of proteins.

Next, I showed them an example of how we could create a centroid representation of a protein that was based on all the published literature (Medline abstracts) that mentioned the protein. I showed them a scatter plot visualization of six proteins, with p53 being one of them. The large bubble indicates the location of a centroid, the small dots represent documents containing a protein, and the connected lines indicate similarity based on cosine distance.

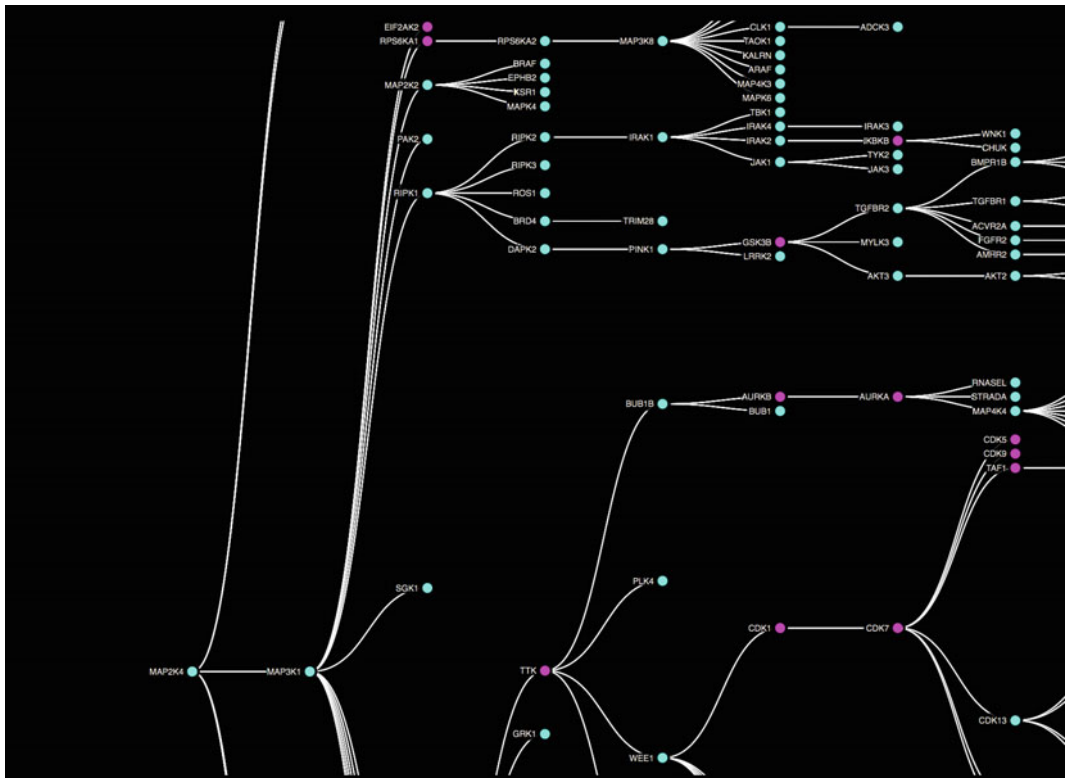


Scatterplot of proteins similar to p53

The biologists from Baylor immediately remarked that the associations I was indicating seemed reasonable. Their next question was could I do this same thing for protein kinases? I didn't see why not. To approach this, it helps to recognize that there are over 500 kinases and over 240,000 papers that mention at least one of them in the abstract. Fortunately, computers are not daunted by such numbers. We used queries based on kinase names and synonyms to collect the abstracts for each kinase. We then excluded kinases with fewer than 10 abstract mentions as being not well enough characterized. That left us with 259 kinases of which only 23 were known to be connected to P53.

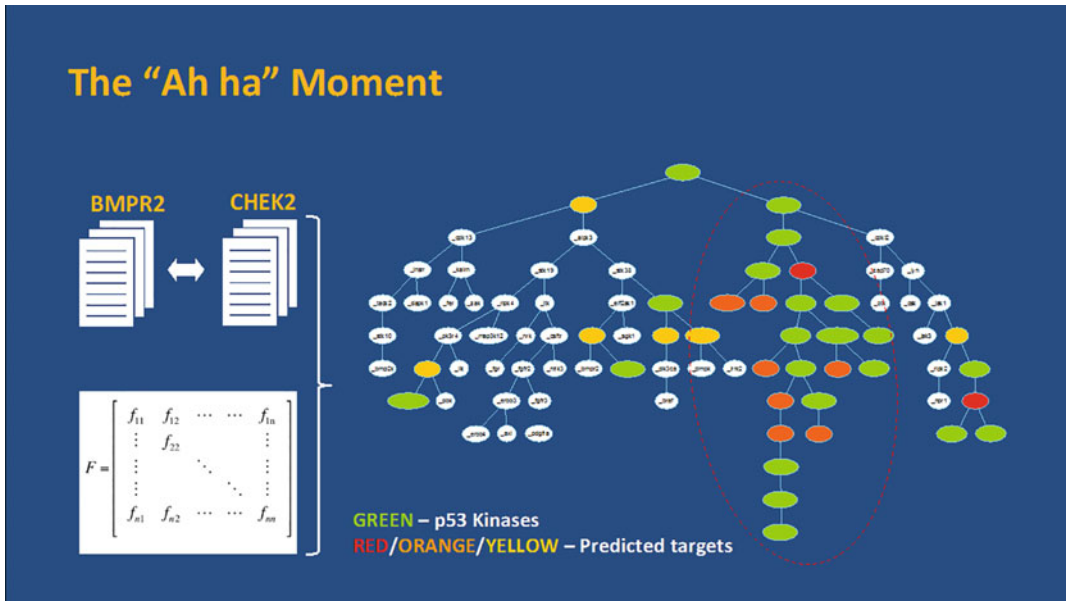
Next, we created a numeric vector representation of each kinase. First, each document is converted into a vector of words and phrases (unigrams and bigrams). The number of times each word or phrase occurs in the document is the value in the vector. Then after all words and phrases are counted, we normalize the vector to have unit Euclidean norm. The vector for the kinase is then the average vector for all documents that mention that kinase. After some experimentation, we weight the features in each centroid by term frequency-inverse document frequency, after determining that this provides the best overall prediction accuracy.

Centroids allow us to measure precisely how similar any two kinases are to each other, but we still need a way to visualize what that means. To help the domain expert, interpret these centroids In this specific instance, a pure network diagram would be mostly unhelpful. Instead, we create a simplified tree diagram that boils down the kinase centroid similarities to their most concentrated essence.



Simplified tree diagram of kinase similarity

Using this approach, we created a graph of all the kinases and then colored them by known P53 associations. The result was immediately striking. The known P53 kinases occurred together, and the other kinases were mostly in other areas of the kinase tree. Moreover, there were a few kinases not known to be P53 kinases that seemed to be in among those that were known. This was exactly what we hoped to find, because it gave us a ready list of potential candidate kinases to begin running experiments on.



In order to validate our predictions were reasonable, we needed to find a way to test whether the predictive approach we had in mind was indeed able to accurately foreshadow future discoveries. We did this through a time-based taxonomy, dividing the Medline data by date of publication—before and after January 1, 2003. This allowed us to analyze the data in the older publications in order to try to predict the discoveries that happened subsequently. The retrospective study section of our paper describes what happened.

14.9 Retrospective Study

Going back in time is difficult for people, but easy for machines. By simply hiding all the information after 2002, we could easily run our predictive approach and see how well it predicted actual discoveries. When we looked at a graph generated from 2002 data, we indeed found that subsequent later discoveries were very near to kinases known before 2003. What we needed though was a numeric way to assign a score to each kinase. To do this, we use graph diffusion to assign weights to each kinase based on its "nearness" to known P53 kinases. Using this approach, we found a ranking that produced an AUC of 0.84, much greater than random chance. This gave us confidence that we had a sound approach.

This type of retrospective study is an excellent way to gain confidence that the predictions we are making are not somehow artifacts of the way people write about P53 kinases. For example, it is conceivable (though very unlikely) that the only reason the P53 kinases clump together in the similarity tree is that the similarity is based primarily on this one property of being a P53 kinase. The retrospective study rules out this mechanism as an explanation for the clumping of the P53 kinases.

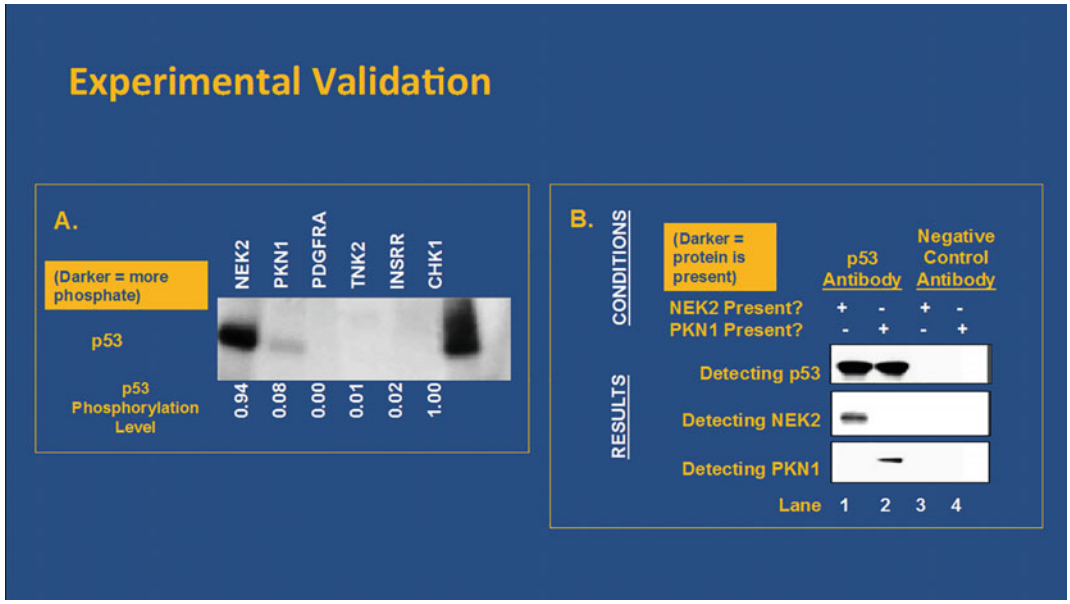
Now that we had some confidence that we had a mechanism for prediction, we selected two kinases to begin running experiments on. The next excerpt discusses what happened in these experiments.

14.10 Experimental Validation

Retrospective analysis is one thing, but only real discoveries of new facts are truly convincing. Therefore, the next step was to take five kinases that were not known to phosphorylate P53 and

test these by experiments for any sign of interaction with P53. We carefully chose two kinases from near the top of the list (PKN1 and NEK2), and as a control, we also chose other kinases from the bottom of the ranking (TNK2, INSRR, and PDGFRA). Two different assays were used.

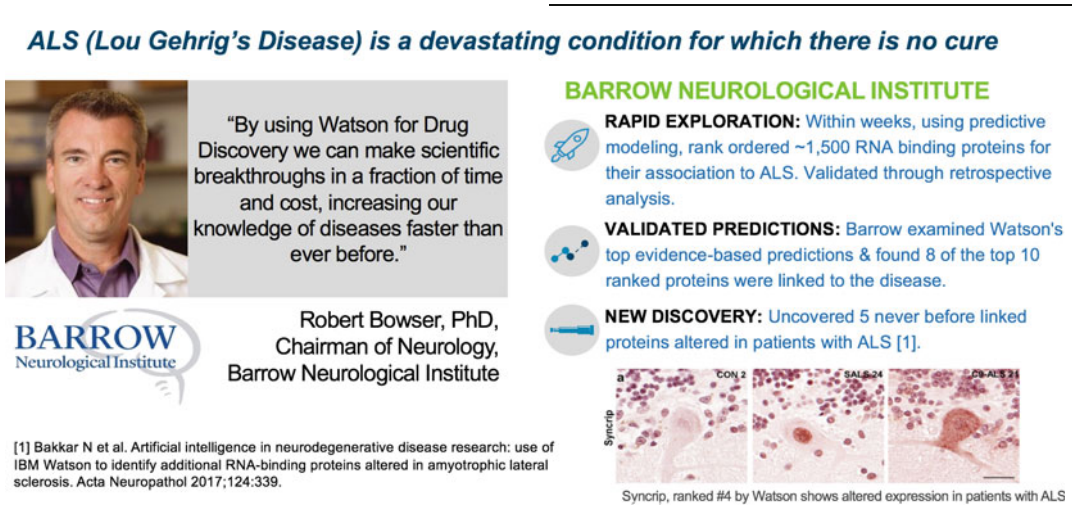
In the first assay, P53 is combined with a kinase and a radioactive phosphate and electrophoresis is used to separate the components. If there is a relationship present, we will see the kinase add radioactivity to P53. In the experiment, we see that NEK2 and PKN1 exhibit a P53 band, while in contrast, the other three kinases exhibit no such band.



In the second assay, cells containing P53 and the kinase are generated and analyzed. Proteins from the cell are isolated and a P53 antibody is introduced. An additional antibody is then used to test for the presence of each kinase. These results show that P53 was indeed bound to NEK2 and PKN1. These two experiments suggest strongly that PKN1 and NEK2 are true P53 kinases.

What's remarkable about this result is that no single paper or small set of papers could have made this prediction. Even the P53 expert at Baylor was unaware of the connections that were waiting to be discovered between these kinases and P53. If we can do this for P53, why not for other proteins and entities on a much larger scale? This is exactly the direction we are heading. And in fact, it can and must be the way science will be done in the future.

14.11 Finding New Targets for ALS



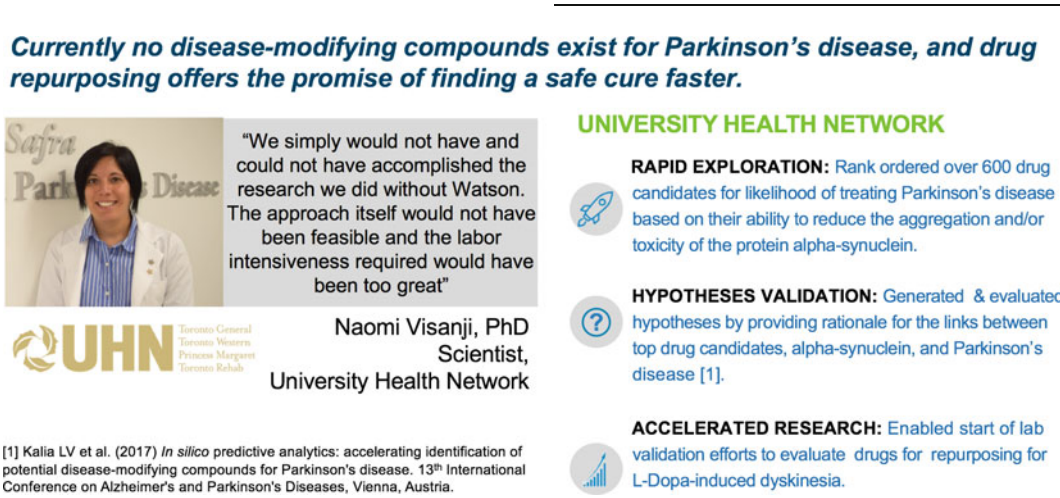
[1] Bakkar N et al. Artificial intelligence in neurodegenerative disease research: use of IBM Watson to identify additional RNA-binding proteins altered in amyotrophic lateral sclerosis. Acta Neuropathol 2017;124:339.

Another example of the accelerated discovery process is the use of WDD to identify new targets for amyotrophic lateral sclerosis (ALS). Various genetic factors are associated with ALS, but mutations in 11 RNA-binding proteins (RBPs) are clearly associated with disease. Furthermore, other non-mutated RBPs have been observed to present with distinct subcellular localization in ALS patients, suggesting RBPs are involved in disease pathogenesis.

To test this hypothesis, researchers at the Barrow Neurological Institute used WDD to rank nearly 1500 identified putative RBPs according to their text-based similarity to the 11 RBPs mutated in ALS [1]. Utilizing a method similar to that described in the example with p53, a retrospective analysis of the literature prior to 2013 was conducted to test WDD's ability to predict known RBPs. All four RBPs linked to ALS between 2013 and 2017 were ranked in the top 11% of WDD's predictions, including the 1st ranked result, validating Watson's predictive model.

Having validated WDD's model for predicting RBPs altered in ALS, the Barrow team turned to predicting novel RBPs that could be associated with ALS using this text-based method. To validate whether the top 10 results were actually altered in ALS, the Barrow team performed a series of in vitro assays ranging from gene, protein, and RNA expression analysis to immunohistochemistry. Eight of the top-ten WDD results were altered in ALS tissue by at least two of the validation methods used while none of the three control RBPs selected near the bottom of WDD's ranked list were altered, suggesting that the accelerated discovery method successfully identified, both retrospectively and prospectively, RBPs associated with ALS using a text-based analysis of the scientific literature.

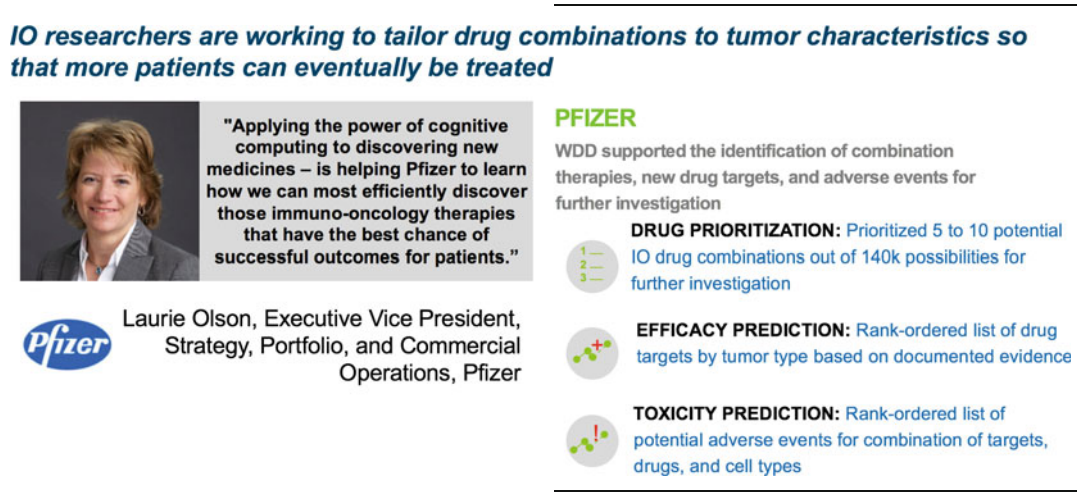
14.12 Drug Repurposing for Parkinson's Disease



Work by University Health Network (UHN) showcases how changing the inputs and outputs of the accelerated discovery method in WDD allows for exploration of even more types of questions. UHN researchers were interested in using WDD to determine which approved therapies might be useful to repurpose for the treatment of Parkinson's disease. To assess this, UHN created a list of 15 compounds with demonstrated ability to reduce L-DOPA-induced dyskinesia (LID) from which WDD analyzed text features to rank 3539 potential therapies from DrugBank, including small molecule, protein/peptide, nutraceutical, and experimental compounds [2].

Leave-one-out cross-validation and retrospective analyses were performed to confirm the model was able to successfully predict known therapies used in the treatment of LID. Cross-validation experiments resulted in an area under the receiver operator characteristics curve of 0.72 and the retrospective analysis predicting the three compounds discovered after 2013 yielded all three known compounds in the top 25% of results (two of the three in the top 5.5%). After validating the model retrospectively, analysis of WDD's top 50 prospectively ranked candidates identified the relationships of each predicted therapy to drugs in the set of 15 LID drugs to establish and verify the biological rationale for predictions. Top candidates from this list are being tested for antidyskinetic function using a variety of assays to confirm WDD's predictions are biologically relevant and understand which therapies may be most promising for treatment of LID.

14.13 Innovations in Immuno-Oncology



Immunotherapies, which modify a patient's immune system to recognize and target cancer cells using a combination of vaccines, immunomodulators, and small/large molecules, are reshaping the field of oncology. Oncology researchers at Pfizer use Watson for Drug Discovery to analyze massive volumes of disparate data sources, including licensed and publicly available data as well as Pfizer's proprietary data. With this tool, Pfizer researchers analyze and test hypotheses to generate evidence-based insights for real-time interaction. The customized technology can also support efficient safety assessments.

This example of applying the accelerated discovery method using WDD with a combination of scientific publications and proprietary Pfizer data demonstrates the potential for text-based analytics to be combined with other data types and methods to further accelerate insight generation. Using these methods, Pfizer has been able to prioritize five to ten potential immuno-oncology combination therapies from an initial list of 140,000 potential combinations. Furthermore, this combinatorial data approach has allowed for prediction of efficacy and toxicity —associations more detailed than those showcased in the UHN and Barrow examples.

In conclusion, we believe these examples illustrate the potential of cognitive technology to accelerate the pace of scientific discovery. We also feel that the general approach of mining literature to find hidden relationships between entities is not restricted to biology but has applications in nearly all sciences. This holds out the possibility of a dramatic acceleration of discovery leading to tremendous benefits for human health and societal progress in the coming years. Given the enormous challenges facing science today on a global scale, the acceleration of discovery is not only desirable, but indispensable for human flourishing.

References

1. Bakkar N et al. Artificial intelligence in neurodegenerative disease research: Use of Ibm Watson to identify additional rna-binding proteins altered in amyotrophic lateral sclerosis. Acta neuropathol. 2018;135.2:227–47.
2. Johnston TH et al. Repurposing drugs to treat L-Dopa-induced dyskinesia in Parkinson's disease. *Neuropharmacology* (2018).
3. Spangler S et al. Automated hypothesis generation based on mining scientific literature. In: Proceedings of the 20th ACM SIGKDD international conference on knowledge discovery and data mining. ACM; 2014.

Part III
Bright Future

Foresight Driven Policymaking: Society 5.0

15

Naohiro Shichijo and Shinichi Akaike

15.1 Overview

In this current turbulent and uncertain environment, societal issues are increasing their seriousness. At the same time, the speed of innovation is accelerating and it has great potential to answer those issues. Thus, STI (Science, Technology and Innovation) is attracting more attention and its importance is increasing. Under such circumstances, the National Institute for Science and Technology Policy (NISTEP) is executing Science and Technology Foresight Study (hereafter, S&T Foresight) for elucidating emerging signals in science, technology, and society. The analysis based on those signals is extensively used to facilitate discussion formulating STI policy in Japan to effectively incorporate possible potentials into STI policy in a proactive way. In this article, the brief history of S&T Foresight and its relationship with the S&T policy in Japan is described. Then, implications for future foresight and STI policy are mentioned as a conclusion.

15.2 Brief History of Foresight and STI Policy in Japan

Governmental forward-looking activity in Japan initiated in the late 1960s by the Science and Technology Agency (STA). Prior to this movement, the basic structure of science and technology policy had been establishing in Japan (1950–1970). During that period, starting with the establishment of STA in 1956, major national laboratories, science parks, and industrial clusters are also started to form its basic structure. It was a dawn of S&T policy in Japan (Table 15.1). Subsequently, the focus of S&T policy was set to further promote economic development in the long term, based on strategic actions, using information on the direction of S&T advancement, extracted by various forward-looking methodologies emerged in that period. Finally, in 1971, one of the earliest results is published as "Technology Forecast" [1].

The concept of "Technology Forecast" undertook in Japanese Government was strongly influenced by policy think tanks (RAND Corporation, Battelle Memorial Institute) and several futurists (Erich Jantsch and Theodore J. Gordon) who were leading future studies at that time. This study was organized by STA, but its influence was not limited to STA or even to the government as a whole. Since there was a strong backup from the industry sector (many major Japanese corporations joined the study), those companies

N. Shichijo (✉)
Tokyo University of Technology, Tokyo, Japan
e-mail: shichijonh@stf.teu.ac.jp

N. Shichijo · S. Akaike
National Institute for Science and Technology Policy, Tokyo, Japan

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_15

Table 15.1 History of Japanese Foresight and surrounding environment

	Societal issues related to S&T	Foresight	S&T policy
1970–	Catching-up Adapted methodologies used in forecast studies in US (Battelle, IFF) Bootstrapping science sector by establishing national research laboratories and science parks	Technology Forecast (1971, 1977, 1982, 1987)	General Guidelines for Science and Technology Policy (1985)
1990–	Transition phase Deepening usage of Technology Forecast in policymaking Technology Roadmaps were used in companies	Technology Forecast (1992, 1997) Outlook for Japanese and German Future Technology (1994)	General Guidelines for Science and Technology Policy (1992) Science and Technology Basic Law (1995) Science and Technology Basic Plan (1996–2000)
2000–	Prioritization Economic depression (Lost decade) Prioritization Forecast to Foresight Output of foresight surveys were used in shaping Basic Plan	Technology Foresight (2001) Science and Technology Foresight (2005)	Established MEXT due to ministry reform (2001) Established Council for Science and Technology Policy (2001) Science and Technology Basic Plan (2001–2005) Long-Term Strategic Guidelines "Innovation 25" (2007) Science and Technology Basic Plan (2006–2010)
2010–	Demand-driven Answering societal issues in aging society, global competition, and rise of Asia Integration of Science and Technology policy with Innovation Policy	Science and Technology Foresight (2010, 2015, 2019)	Science and Technology Basic Plan (2011–2015) Established Council for Science, Technology and Innovation (2014) Science and Technology Basic Plan (2016–2020)

actually used the output of the study to formulate their own long-term strategy. Such a deep involvement occurred because they had an increasing aspiration to establish a new corporate R&D strategy according to their new economic environment. The Japanese economy was experiencing a transition from "catching-up stage" (so-called the age of rapid growth in the 1960s) to the next level. Thus, in Japan, a special situation emerged: spontaneous integration of nation-wide STI policy, from government to industry, connected by the "Technology Forecast." As a result, corporate strategies of major Japanese companies were synchronized with and backed up by a national strategy. The study was continued in every five years and their results contributed further growth in technology competitiveness and economy during the 1980s and 1990s. This study initiated by STA and its surrounding environment was later analyzed [2] and described as "Technology Foresight," due to the characteristics surrounding Japanese "Technology Forecast" realized major characteristics of "Foresight" [3].

Aligned with forward-looking activities as above, Japanese STI policy had been gradually changing to incorporate "selection and concentration" by prioritizing strategic areas of research and development. In 1986, "General Guidelines for Science and Technology Policy" is approved by the cabinet (modified in 1992) as a response from report to Prime Minister prepared by

Council for Science and Technology of Japan (CST). In its 1992 edition, 16 areas (disciplines and missions) are selected as prioritized areas. The result of "Technology Forecasts" were utilized in the discussion at CST to select prioritized areas of scientific growth. This movement succeeded in the legislation of "Science and Technology Basic Law," enacted in 1995. After the legislation of Basic Law, the foresight activities are synchronously conducted to produce comprehensive information for the discussion of "Science and Technology Basic Plan." In 1988, NISTEP was established and continued Japanese National Foresight activities. According to the increase of interest in international collaboration is science policy in the 1990s, the first international collaboration in National Foresight started in 1993, when German Federal Ministry for Research and Technology (BMFT) conducted a survey identical with the Japanese fifth Technology Forecast Survey as a collaborative project with NISTEP and published its findings in August 1993 [4]. From its success, other foreign research institutes started international collaborations with NISTEP, including Finland, Korea, China, and APEC (Asia-Pacific Economic Cooperation).

15.3 Current Foresight Activities in Japan

The latest S&T Foresight study [5] was conducted during 2013–2015 employing multiple methodologies. The study consists of three stages: (1) visioning, (2) survey for scientist and engineers, and (3) scenario planning. In visioning stage, seven visioning workshops are conducted according to the societal issues. The outputs of workshops were analyzed to establish "Societal Visions" composed with societal issues that science and technology is supposed to address and its expected importance and relationship between issues. In the second stage, eight committee are organized according to scientific disciplines and selected around 100 topics for each committee that are expected to be realized within 30 years in order to contribute to solving societal issues addressed in the first stage. In total 932 topics are selected and further analyzed by 4309 scientists and engineers. In the final stage, several scenarios are compiled according to the societal issues utilizing the result of the survey in the second stage to create a comprehensive image of the future to realize societal visions.

The output of the tenth S&T Foresight was utilized in the discussion of the fifth Science and Technology Basic Plan [6]. Especially, during the discussion for elucidating the central concept of the fifth Plan, "Society 5.0," the result from tenth foresight is utilized extensively. The concept "Society 5.0," is going to add a fifth chapter to the four major stages of human development: hunter-gatherer, agricultural, industrial, and information. This new society is expected to be "ultra-smart," everything will be connected through IoT technology and not its network is only covered for "things," but all human and its knowledge will be integrated. As a result, dramatical improve of the quality of life is expected to be realized (see Fig. 15.1).

15.4 Further Development of Foresight

The 50 years history of national foresight system is exceptionally long for such nation level activities and following such tradition might have virtue on its own. However, it is necessary to introduce a new trial while following such tradition, since there is increasing need for the society for science to address societal issues, especially for aging, sustainability and globalization, and pace of that progress is ever accelerating. Therefore, we introduced visioning in order to consider the changing societal needs and to consider multiple options for its change. In the latest ongoing

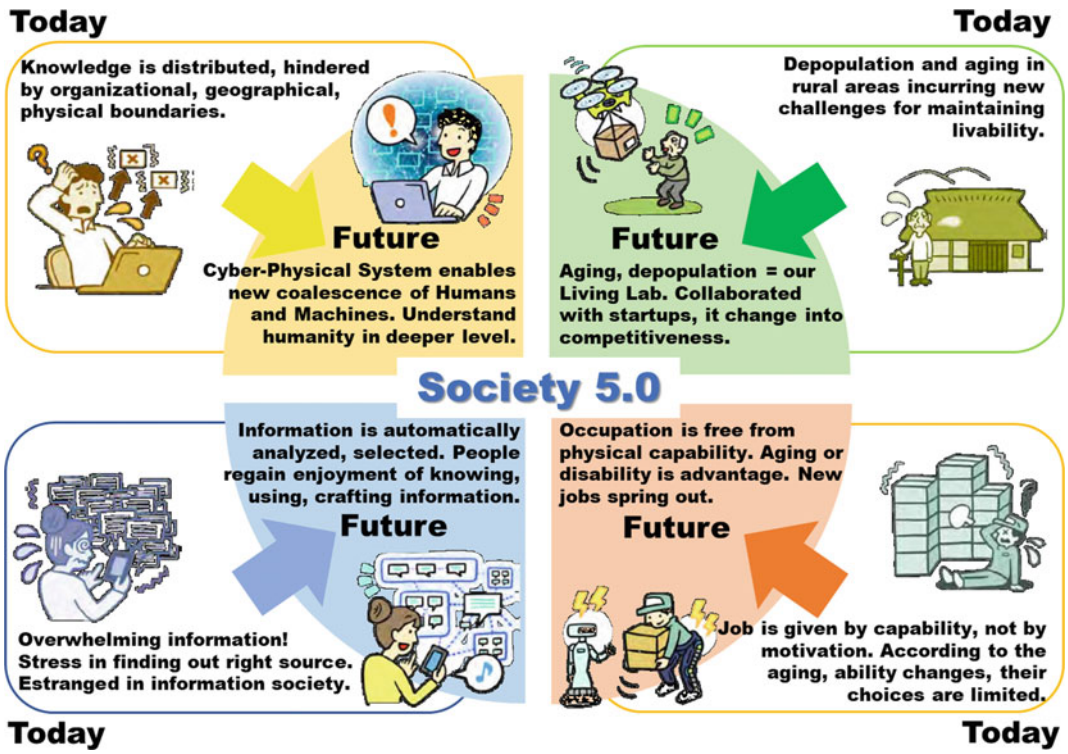


Fig. 15.1 Issues and its direction of solution addressed by Society 5.0

foresight study (the eleventh S&T Foresight), we are trying to enlarge consideration of societal visions as well as incorporating concurrency, by introducing new system "Horizon-Scan" (A semi-autonomous sense-making system from Web crawled open information, using mixed machine-learning algorithms). We also trying to seek other new foresight methodologies for further enriching the result. In order to do this, we believe the increase and deepening of international collaborations is one of the most important points. International joint Horizon-Scanning or joint sense-making (analyzing policy implications from various weak signals, megatrends, and indicators) are next breakthrough in government foresight. We hope such new foresight would contribute not only to STI policy, but to global harmonization and well-beings.

References

1. Makino N. Science and technology developments up to A.D. 2000. Tokyo, Japan: Japan Techno-Economics Society; 1972.
2. Martin BR. Foresight in science and technology. Technol Anal Strateg Manag. 1995;7(2):139–68.
3. Irvine J, Martin BR. Foresight in science: picking the winners. London: Frances Pinter Publishers; 1984.
4. Cuhls K. Changes in conducting foresight in Japan. In: Institutional and technological change in Japan's economy: past and present; 2005. p. 188–205.
5. Ogasawara A, Shichijo N. The 10th science and technology foresight: scenario planning from the viewpoint of globalization. In: NISTEP Report. Tokyo: National Institute for Science and Technology Policy; 2015.
6. Japan G.o. The 5th science and technology basic plan. Tokyo; 2016.

Curiosity—Fuel for Innovation

16

Carl Naughton

Findings from the Merck Curiosity Council show that workplace curiosity is a vital driver of organizational performance. This resonates well with general opinions about how curiosity fosters exploration, interest, and even creativity. But there is a small but vital difference hidden in plain sight in those first two sentences: curiosity does not necessarily equal workplace curiosity. While the former hinges on five dimensions including thrill-seeking, the latter is a construct with four dimensions that focuses on going on the hunt for information, looking for opposing world views, and not being distraught by insecurity or ambiguity that arises from new information and differing world views. Thus, workplace curiosity goes beyond just being interested and piqued to explore. Furthermore, the research done by Todd Kashdan and his team suggests that all four dimensions have to be present for a person or a team to act on their curiosity and in consequence be beneficial for organizational performance.

The researchers and innovations that are comprised in this book are living and tangible examples of the everyday potency of this multidimensional construct. Therefore, it pays to (a) look at the dimensions, (b) see how they play out, and (c) inquire whether they differ from culture to culture.

Curious individuals have a lot to offer in terms of motivational and behavioral contributions: they actively seek out new information, broaden their understanding, and thus accumulate new experiences and/or knowledge. While they pursue the paths of learning they tend to be more fascinated than frustrated by conflicting information, mystery, or ambiguity. When these people act on their curiosity in organizational settings they actively seek out feedback and see such feedback as a chance for communication rather than judgement regarding the quality of their work. That might be the reason why they actually enjoy getting better, they intuitively perceive such an information flow from their team leaders or supervisors as a possibility to grow. And while many readers and fellow scientists would agree to this at face value, very little research has been publicized to actually pin down what the behavior that is connected to workplace curiosity actually consists of. With the start of the Curiosity Council, digging deeper into workplace curiosity and filling this specific knowledge gap started to take shape. Now, in 2018, we have a revised, reliable, and valid construct which models workplace curiosity; among others, it can help predict curious behavior at the workplace, it can help find and hire those people who naturally bring this quality with them and can help develop the according

C. Naughton (✉)
Braincheck GmbH, Cologne, Germany
e-mail: cn@braincheck.de

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_16

strengths in people, and teams who look to increase the workplace curiosity scores.

16.1 Curious Individuals—Why Curious Minds Behave the Way They Do

Having synthesized existing research on curiosity into a single, synoptic measure, we bring together a range of dimensions that beforehand existed in isolation. Tying them together—via empirical research and rigorous statistical methods—we could correlate them with workplace performance indicators such as innovative work behavior or job performance.

The first dimension appears like the dictionary definition of curiosity. It centers on the joy of recognizing and seeking out new information and experiences at work. Learning is a joy to these people. Todd Kashdan refers to it as a pleasurable state, in which people revel in a kind of joie de vivre. A lot of times high scores on this dimension predict above-average innovative work behavior. Almost seeming like the flip-side of the aforementioned exploration part of the information gathering coin, the second dimension centers on feeling deprived due to a lack of information, a gap in the individual knowledge matrix. This then spurs the search for information in order to fill this gap. And while noticing the gap creates tension, filling it offers relief. As it appears, this kind comes with few feelings of joy, and in fact, it does not feel good. On the other hand, it is exactly this feeling, which drives people to keep on thinking about a solution to a problem until they have. So far the empirical results show that this dimension is not as strongly connected to innovation behavior as the other dimensions.

Once information is gathered or even during the process of procuring it, individuals interact with other people. People they ask for directions where to find information or people they ask in order to understand new information. Naturally, this works best when one mobilizes a certain degree of openness to those people. This implies valuing the diverse perspectives that come with the answers and being open to the different approaches that are associated with seeing the world—or the problem at hand for that matter—differently. New findings show that individuals who score particularly high in this dimension also display a high frequency of innovative behavior. More often than not workplace innovation equals team processes. So, it comes as no surprise that this dimension is strongly connected to innovative work behavior.

It may come as no surprise that both the hunt for new information as well as the encounter of differing opinions and approaches test the emotional stability of any individual. Thus, in order to deal with the ensuing thoughts and feelings, certain distress tolerance is needed. That is why the fourth dimension reflects the willingness to embrace the doubt, confusion, anxiety, and other forms of distress that arise from exploring new and uncertain terrain at work. The strength of the manifestation of this dimension very much relates to an individual's coping potential, i.e., everyone, when in a stress-inducing situation judges this situation on the basis of two questions: "Is it relevant to me and do I possess the means to cope with its effects?" Bridged over to curiosity these questions adapt to "Is it new and interesting enough to capture my attention and do I possess adequate mental resources to cope with any that stems from engaging this new information or situation?" People who are high in distress tolerance do display significantly higher degrees of innovative work behavior.

Looking at the four dimensions it becomes apparent why they all have to be present to a certain degree for workplace curiosity to work. During the initial workshop phase of a pilot program we designed to train the dimensions of workplace curiosity, we created a creative problem which had participants experience these almost in sequential order. Best suited for such experimental and experiential purposes are so-called insight problems. They are a kind of brain teasers dating back to the origins of gestalt psychology. They seem unsolvable at first but then, almost with a sudden burst of

understanding, a flash of inspiration, the solution appears in the problem solver's mind. One of the well-known examples is the nine-dot-problem, where people have to connect nine dots with a single line without crossing the line they draw. What normally happens is, that people either start drawing using what behaviorists would call trial and error or mentally probing different strategies. This joy of exploring can come to a sudden halt if the trial and error approach does not yield results after five to six attempts. Most of the times, this is when different information gathering scenarios are being contemplated, external advice sought, and alternative approaches taken into consideration. Then, after the next failed trial period, frustration, sometimes self-doubt, set in, and stress creeps up. There you have it: all four dimensions are present even when people are toying around with brain teasers.

16.2 Curious Teams—Why Curiosity Makes Teamwork Flourish

The times where individuals sit alone in office spacers and ponder over an innovative solution to a tricky problem are long gone. Teamwork has taken over. And with it a plethora of social and communication traps that keep teams from performing their best when dealing with their share of tricky problems. This tendency is supported by the general social inclination to feel a sense of belonging. Notwithstanding the importance of openness for others dimension when acting on curiosity individually, in this context, further aspects come into play when teams employ curiosity to achieve work-related goals. While Todd Kashdan points out that people's viewpoints and ideas are arguably their most important characteristic, it is essential for teams to synthesize these different vantage points in order to benefit from team synergies while solving problems. From personal experience, almost everyone working in an organization can recall countless examples where this synergy did not take place. Instead, defensive and tactical behaviors come to the forefront where team members aim to protect their ideas in negligence of a search for the best idea within the entire team. This stifles curiosity.

Most importantly, this hindrance does not only apply to the team members interactions but also to the perception of the team leader's behavior. In earlier research, the Curiosity Council found that team members experience barriers to asking questions and obtaining information outside of obvious sources. Thus, one could argue, allowing for more openness, leaders might increase the respect from their followers by being perceived as more susceptible to individual information gathering strategies.

The aforementioned leadership behavior also affects the two dimensions associated with information gathering: joyous exploration and deprivation sensitivity. From a leader's point of view, thinking outside the box may be viewed as valuable but at the same time exploring outside this said box is deemed as time and cost intensive. Also, people wandering off during the workday to go and hunt for new insights might even be viewed as weak leadership. From this point of view, the absence of von encouraging exploration would come as no surprise. But during our pilot-program, one team leader reported quite the opposite. He had his team come up with ideas about so far untried cake recipes and encouraged them to bring the results to the workplace. The workplace focus of this team was on lighting innovations, not kitchen experiences. But as far away from the mark as this cake challenge might seem at a first glance, as eye-opening becomes what happened in the wake of it. The playfulness opened up the team members to look for information that was focusing more on their innovation problems in unusual places. These actually were colleagues they had never spoken to before—although they resided in offices just down the aisle. Many people in organizations are familiar with this phenomenon called silo thinking. From a seemingly unrelated cake challenge to speaking with estranged colleagues might seem an unusual leap for an outsider, for the team it made perfect sense. Connect with aspects you did not connect with before and thus get the information you could not access before.

Apart from encouraging interaction with different departments in order to obtain new perspectives and approaches, this exploratory behavior falls in line with what IBM called T-knowledge. The letter serves as a visual metaphor. The vertical line of the "T" stands for the deeply rooted expert knowledge. It drives us deeper into any topic of our choosing. Like a vertical knowledge drill. At the same time, this "T" branches on the left and the right, becoming aware of related ideas and concepts, that are connected two our initial interest. And it normally does not stop there. It keeps on growing.

In addition to the team benefits of increased openness and inquisitiveness dimensions, the training of the distress tolerance dimension led to significant changes as well. A team of workplace security advisers who attended the pilot fed back that employing techniques that increased their psychological flexibility had a noticeable effect. The team leader reported that there was a feeling that the team members can share and talk about their problems and try to get to find solutions. With that he expressed his surprise that they did share stories, experiences, feelings in the most open way.

16.3 Curious Minds—Why a Belief in Oneself Is Important

So, curiosity appears to be a basic motif for creativity. Nearly everyone involved in research suspected this, but no one has been able to prove it yet. An indication of this appeared in 2006 with the novelty generation model. It links neuropsychological aspects to others related to personality and to the motivation to look for new things and think creatively. Here, curiosity is the primary factor in the search for novelty, which in turn translates into creativity. Unfortunately, it was merely a model and not evidence.

Polish psychologist Maciej Karwowski then tackled the subject in 2012. His results finally demonstrated that curiosity is essential for "the creative self". This is because the nature of curiosity appears to be essentially very close to so-called little c creativity, because it is perceived as a power that brings people to think and act in a new way. This has to do with creative thinking or such aspects of personality and self-concept as open-mindedness, vigor, or intellect. Now, we absolutely must make a somewhat finer distinction with respect to the different forms of creativity. One important differentiation seldom appearing in popular literature on creativity yet extremely important for the twenty-first century is between incremental creativity ("little c") and radical creativity ("big C"). This line of argumentation presupposes that intrinsic motivation, problem-driven, and abstract theory-related creative ideas are linked to radical creativity ("big C"), whereas extrinsic motivation and ideas that are solution-driven and developed on the basis of concrete practices are associated with incremental creativity ("little c"). In plain terms, this has to implications:

First: Curiosity, which is also strongly correlated to intrinsic motivation, plays a critical role in radical creativity—one study showed clear associations between intrinsic motivation (which is linked closely to curiosity) and radical creativity. In other words, we need curiosity to have big ideas. It appears that nothing at all would work in the world of creativity without curiosity, particularly if it is necessary to challenge paradigms! Second: What follows is a significant consideration for scientific practice. We have already spoken about how the labor force will get older and that you would be wise to come to terms with ways to foster creativity, especially these two special forms of creativity. Not only does each form represent a different process which occurs within us, but each is coupled with different preconditions and procedures. In its first step, a company therefore has to decide which form of creativity it is seeking. Does it need people with radical ideas, who think large scale, or rather employees who can bury themselves in an issue and put solutions on the table to tackle concrete tasks which arise?

The second step involves creating the right environment for these "creativity types," where they can settle in and flourish. This, in turn, has a lot to do with designing workflows, with task definition and with management in general,

though it also involves the company culture and open spaces. Or a company could try to think in situational terms and trigger the desired form of creativity in its employees. This is possible because generally every one of us has both forms within us. Here is an example: Depending on how you approach a project and how much space employees get for curiosity and freedom of thought, the results will be quite different solutions. This means that, when we work on a given problem and we start by looking for solutions, we will evince more incremental creativity. If it is preferred or even expected of us to first take a step back and examine and question the task definition, and perhaps even redefine it, this fits better to our radical creativity side.

From the perspective of the company as a whole, precisely this would be a beneficial approach—particularly when the task involves tackling the really big issues: restructuring the company, tapping into new markets etcetera. There are even other ways to support this "large-scale thinking." Perfectly in line with experiences that each of us has likely had at some point in our lives, it can be helpful to radical creativity to allow people to withdraw from the concrete work after an induction or briefing period so that they can go into reflective mode and get input from other sources, some of which may be abstract, to promote this consideration. Our minds then travel down pathways we are not even aware of—often with very successful results.

A person's core self-evaluation is very important for incremental creativity. Contemporary literature on creativity understands core self-evaluation or CSE as an individual's belief that they are capable of solving problems requiring creative thinking.

The results of one study show that curiosity and core self-evaluation are closely related. An individual's curiosity depends strongly on how much they see themselves as a creative person. Curiosity determines the allocation of personal resources and the energy dedicated to goal-relevant actions, which in turn yield intrinsically rewarding results. This also includes the learning of rules for an area of knowledge—through advanced learning and many hours of practice.

This is rather important news for those who would like to strengthen their creative personality—whether they be students, teachers, parents, or managers. However, there is one more thing they have to be mindful of: their mindset. Nowadays, everyone is talking about "passion," "commitment," and "leadership." Companies and institutions rely on dedicated employees, but these are demanding and in turn only want to work for dedicated companies. And what does dedication and passion have to do with curiosity? A lot! Carol Dweck of Stanford University showed the effect a specific mindset has on dedication at work. As expected, only employees who put their lifeblood into a task, whose mindset is aligned toward "growth" (and particularly the growth of their knowledge) are truly dedicated. Those whose mindset is "fixed," who are significantly less curious and stuck in a kind of stagnation, contribute less energy, that is, they are less dedicated—and consequently enjoy less success.

Studies prove that people who believe that creativity is malleable, that is, whether it can be developed and is not a fixed part of our personality rate themselves as more creative per se. After all, their own mindset is more aligned to growth! Logically, those with a fixed mind, who do not believe that creativity can be developed, are then the losers—oh well! Obviously, the question is whether these beliefs are also reflected in the quality of the creative solutions these individuals come up with. This can be tested by presenting the "affected" with a so-called insight problem. A simple insight problem might be a play on words by Groucho Marx: "Time flies like an arrow. Fruit flies like a banana." Get it? In point of fact, people who imagine that creativity is a fixed character trait do worse in such tests. In contrast, those who have a growth mindset toward their own creativity perform even better if the efficacy of their solution to insight problems is also measured. That is not so surprising when you think about it. We can do things when we feel they are possible. You can find quotes on that idea as far back as the inventor of the

Model T. "Whether you think you can or you think you can't – you're right." The new part is that this belief, this mindset, also determines whether people have more or fewer ideas.

This self-regulating and continuously self-actuating curiosity mechanism may very well be crucial for creating and fueling the link between personality, life experience, and the development of creativity skills and results. However, the central element is still mindset—very little works without it. Time and again it has been shown in educational psychology that individuals' mindset, whether it be fixed or growth-oriented, has an enormous impact on their well-being, locus of control (their explanatory model, as in "Did I do that, or did it just happen?"), and learning objectives.

How would this mindset affect individuals' creative performance, not only those of Nobel prize winners, but of everyone who sets his sights on contributing to innovation? It is down to a priming effect that paves the way for incremental creativity in those people's minds. And for that to work to its full effect, their mindset plays a major role, since it forms the source of our motivation or demotivation to think and act creatively. When people assume that creative prowess is a fixed character trait, for example, it is hard for them to find reasons to evince creative thinking.

There is an even more complex effect of mindset: People can actually display either a fixed mindset or a growth mindset depending on the situation or their mood. For example, many people think that the aforementioned "little c" or incremental creativity is normally distributed, as in the idea that "Everyone got a bit of it." And this little bit can be nourished and multiplied. Likewise, many people believe that the "big c" or radical creativity is based on talent and individuals are either gifted by nature or they are not. Now, an individual could easily believe both at the same time and, based on these beliefs, waste their "big c creativity" potential because they do not think it possible that they have it.

What is even more important is that this self-concept of one's own creative abilities can be promoted by the impulses one gets from organizational leaders. That is because this self-concept intervenes directly into the relationship between curiosity, core self-evaluation, and creativity. Research assumes that it is precisely the acceptance of complexity and the desire for novelty which allows people to test their abilities in practice. This is what yields the driving power of curiosity for the growth of our own core self-evaluation.

So, if there is one thing the presentations accumulated in this very book show us, it is that curiosity is not an optional extra, it is basic human feature allowing those of us who capitalize on it to foster and drive societal evolution. So, as long as there are people who say to themselves "Stay curious, be open, do what matters," there will be books like these allowing us to marvel at the performance of such curious and creative minds.

The Way Forward

17

Ulrich A. K. Betz

In this chapter, I would like to share some personal thoughts and ideas that developed in my mind while conducting the activities around the science and technology workstream at the occasion of Merck's 350th anniversary.

In the almost two years spent in preparation and operational execution of the various activities around science, technology and innovation, it was impressive not only to see the tremendous impact science and technology had over the millennia and what breakthroughs are ahead (Betz 2018, Is the force awakening? Technology Forecasting and Social Change 128, 296) but also how working on these fascinating topics can energize people to join forces and work on further advancement in highly motivated teams, across cultural, religious and national boundaries.

Advancements in science and technology however go hand in hand with ethical questions. We have seen from human history that new technologies often not only come with inherent risks and undesirable side effects but in general can be used for good and evil alike. Science and technology itself are ethically neutral, and we need to ensure that they are applied for the greater good.

Most important of all, science and technology remain silent on the essential question of live: For what purpose do we live and what should we do?

This question has been the domain of religion and philosophy and although there are wide differences between different religions and philosophies in regard to detailed rules and regulations, rites and believes, it is remarkable that there seems to be a set of fundamental principles that form the core, many of which are essentially identical on what constitutes ethical behavior, on how a good live should look like and what should guide our activities.

Just compare, for example, two moral codices that emerged independently in human history at two different locations, the Ten Commandments as described in the Bible (2. Mose, 20) and the Five Precepts of Buddhism (Sanskrit: pañcaśīla) (Table 17.1).

In the following, I delineate fundamental principles that could guide how we apply the benefits of science and technology:

Fundamental principle 1: **Truth**

Discovering and communicating the truth on what is, how the universe is working, is at the core of the scientific method. Science is the search for truth and the fundamental principle of truth is universally accepted in science (e.g., the

The original version of this chapter was inadvertently published as non-open access. It has now been changed to open access with the copyright holder name "The Author(s)". The correction to this chapter is available at [https://doi.org/10.1007/978-3-030-16061-6_18]

U. A. K. Betz (✉)
Vice President Innovation Merck,
Darmstadt, Germany
e-mail: ulrich.betz@merckgroup.com

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_17

Table 17.1 Agreement between the Ten Commandments and the Five Precepts

6. Commandment: Thou shalt not kill	1. Precept: Refrain from taking lives
7. Commandment: Thou shalt not commit adultery	3. Precept: Refrain from sexual misconduct
8. Commandment: Thou shalt not steal	2. Precept: Refrain from stealing
9. Commandment: Thou shalt not bear false witness against thy neighbor	4. Precept: Refrain from telling lies

motto of Harvard University is VERITAS). In his Metaphysics, Aristotle stated: "To say of what is that it is not, or of what is not that it is, is false, while to say of what is that it is, and of what is not that it is not, is true." The original meaning and essence of truth in ancient Greece ("aletheia") was the revealing of what was previously hidden into the open. Likewise, the 9th commandment and the 4th precept both underline the importance of communicating the truth.

Fundamental principle 2: **Love**

Love (agape, charity) as a fundamental principle affecting the relationship between ourselves and our fellow human beings is a key topic of all moral and ethical discourse. Christian/Jewish commandments 6–9 and Buddhist precepts 1–4 can basically be summarized as "do no harm to others." In the New Testament, all ethics is summarized by Jesus in one sentence (the great commandment as in Matthew 22:35–40 and Mark 12:28–34): "Love God with all your mind and with all your strength, love your neighbor as you love yourself. There is no commandment more important than these." Another statement in philosophy summarizing this principle is the "categorical imperative" from Immanuel Kant: "Act only according to that maxim whereby you can, at the same time, will that it should become a universal law." or the famous "Golden Rule." The Golden Rule is the principle of treating others as one's self would wish to be treated. It is a maxim that is found in many religions and cultures and appears prominently in Christianity, Judaism, Buddhism, Hinduism, Konfuzianism and Taoism. The concept of the Golden Rule is also codified in the Code of Hammurabi stele and tablets (1790 BC).

Fundamental principle 3: **Courage**

The virtue of courage (fortitude, valor or bravery) is an integral part of ancient western and eastern traditions. It is mentioned by ancient Greek philosophers Socrates, Plato and Aristoteles, the Roman philosopher and statesman Cicero lists it as one of the four virtues: courage, wisdom, justice and temperance. In Catholicism, courage is one of the seven gifts of the Holy Spirit (fortitude/courage, wisdom, understanding, counsel, knowledge, piety and fear of the Lord). In Hindu tradition, courage (shauriya) appears as the first of then characteristics (courage, patience, forgiveness, tolerance, honesty, physical restraint, cleanliness, perceptiveness, knowledge, truthfulness and control of anger). Courage is the basis for all action, linked with the strive to accomplish and willing to bear risk and sacrifice. It is the essence of entrepreneurship that is required to bring the benefits of science and technology to fruition to have impact in the world.

Fundamental principle 4: **Liberty**

Philosophers from earliest times have considered the topic of liberty. Roman Emperor Marcus Aurelius (121–180 AD) wrote: "a polity in which there is the same law for all, a polity administered with regard to equal rights and equal freedom of speech, and the idea of a kingly government which respects most of all the freedom of the governed." Aristotle put it: "This, then, is one note of liberty which all democrats

affirm to be the principle of their state. Another is that a man should live as he likes. This, they say, is the privilege of a freeman, since, on the other hand, not to live as a man likes is the mark of a slave. This is the second characteristic of democracy, whence has arisen the claim of men to be ruled by none, if possible, or, if this is impossible, to rule and be ruled in turns; and so it contributes to the freedom based upon equality." The first draft of liberty in continental Europe after the Roman Empire is the Twelve Articles as part of the peasants' demands of the Swabian League during the German Peasants' War of 1525 stating that "Christ redeemed all of us with his precious bloodshed, the shepherd as well as the highest, no one excluded. Therefore, it is devised by the scripture, that we are and that we want to be free." Finally and most famous, according to the 1776 United States Declaration of Independence, all men have a natural right to "life, liberty, and the pursuit of happiness." This then consequently would also involve the freedom to neglect the fundamental principles described here (Fig. 17.1).

Applying these fundamental principles can lead to a new way of working together, a new type of organization, that combines the strong cultural traditions of science (truth), religion (love) and entrepreneurship (courage) while at the same time being based on individual freedom (liberty). The four general principles of truth, love, courage and liberty can help us to find the right way forward and to apply further progress in science and technology for the benefit of all humanity. Keeping this in mind, we can combine constant change and innovation with never-changing eternal truths to a force of good that can change the face of the world.

And finally, there might be a fifth fundamental principle: spirituality. A notion that there is more than energy and matter, that there is spirit, that there is the "I am that I am," the alpha and the omega of all things, the end and the beginning.

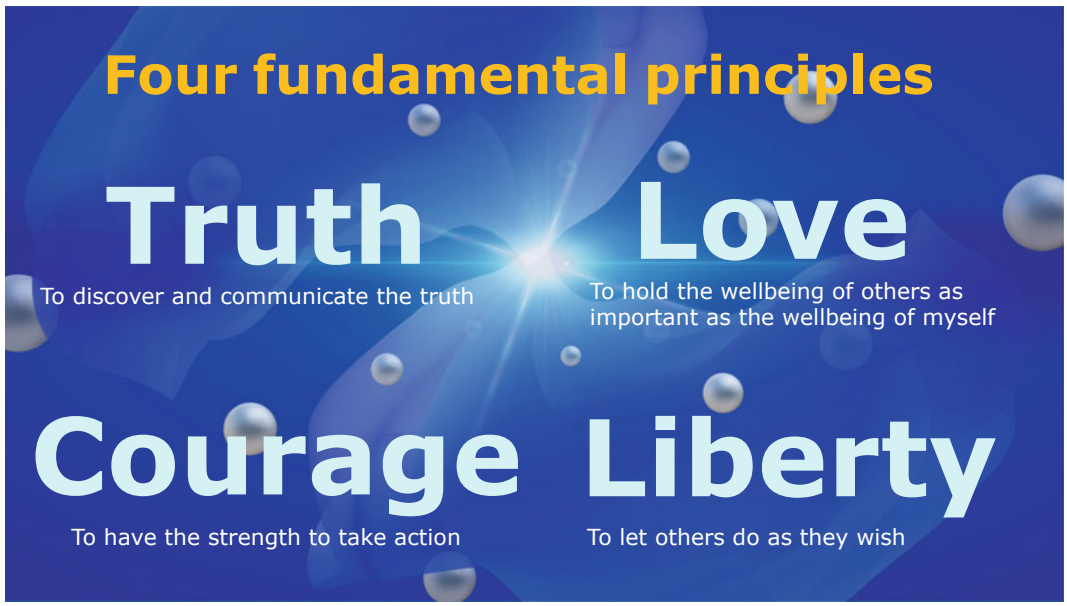


Fig. 17.1 Four fundamental principles

Correction to: Curious2018

Ulrich A. K. Betz

Correction to:
U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6

Due to a publisher error in the original version of the book, the following corrections have been incorporated:

The original versions of chapters 1, 2, 3, and 17 were inadvertently published as non-open access. They have now been changed to open access with the copyright holder name "The Author(s)". The book has also been updated with these changes.

The updated versions of these chapters can be found at:
https://doi.org/10.1007/978-3-030-16061-6_1
https://doi.org/10.1007/978-3-030-16061-6_2
https://doi.org/10.1007/978-3-030-16061-6_3
https://doi.org/10.1007/978-3-030-16061-6_17

U. A. K. Betz (ed.), *Curious2018*,
https://doi.org/10.1007/978-3-030-16061-6_18