Chapter 3
Translational Research in Drug Discovery and Development

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Abstract Translational research facilitates the application of basic scientific discoveries in clinical and community settings to prevent and treat human diseases. The translation of knowledge and innovations from basic laboratory experiments to point-of-care patient applications; production of new drugs, devices, and healthcare products; and promising treatments for patients is referred to as benchside to bedside transition. Numerous opportunities encompass translational research. However, there are several obstacles involved in the process that make the translational journey quite challenging. The major challenges that hamper the growth of translational research include insufficient resources, inadequate funding and infrastructure, shortage of qualified researchers, and lack of sufficient experience in essential techniques. Translational drug discovery and development is an exceedingly difficult, expensive, time-consuming, and risky process. Despite thousands of pharmaceutical companies working to develop and get new drugs to market, and billions of dollars spent every year, only a few new molecular entities (NMEs) receive marketing approval from the FDA per year. Translational drug discovery demands both the need for cooperation between clinical and pharmacological research and the significance of the role of academia in target identification and drug discovery, design, and development. This chapter highlights an overview of translational research in a drug discovery and development perspective. We further discussed associated opportunities and challenges, as well as possible strategies that could be used to overcome the challenges. Certain strategies like prioritizing research area,

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D.-Q. Wei et al. (eds.), *Translational Bioinformatics and Its Application*, Translational Medicine Research, DOI 10.1007/978-94-024-1045-7_3

clearer vision on the project, committed team of researchers, established infrastructure, sufficient funding, and meaningful collaborations could be highly beneficial in accelerating the hunt to discover new drugs and for the establishment of successful translational drug discovery process.

Keywords Translational research • Drug discovery and development • Opportunities • Challenges • Drug repurposing

List of Abbreviations

BrIDGs	Bridging Interventional Development Gaps
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
GWAS	Genome-wide association study
ITHS	Institute of Translational Health Sciences
MHRA	Medicines and Healthcare Products Regulatory Agency
NCATS	National Center for Advancing Translational Science
NCI	National Cancer Institute
NIH	National Institutes of Health
TRWG	Translational Research Working Group
CRC	Colorectal cancer
ALL	Acute lymphoblastic leukemia

3.1 Translational Research

Translational research is basically translating knowledge obtained from laboratory science into clinical practice in order to improve human health. It involves the process of applying ideas, insights, and discoveries unveiled through basic scientific researches for the welfare of mankind. The knowledge acquired, mechanisms devised, and techniques developed using basic science researches are effectively translated into new approaches for prevention, diagnosis, and treatment of diseases (Fang and Casadevall 2010). The applications of such basic scientific discoveries in clinical and community settings thereby are instrumental in bridging the gap between biomedical science and medical practice (Zerhouni 2005).

3.1.1 How Is It Different from Traditional Research?

Basic and translational research can be considered as complementary areas of human endeavor that differ primarily in integration and practicality, respectively. Whereas basic science contributes in deriving deeper knowledge in the desired

Table 3.1 Difference between basic and translational research

Terms of comparison	Basic research	Translational research
Research orientation	Also referred to as traditional research wherein the motivation lies in acquiring knowledge. This type of research is mostly exploratory and often leads to great discoveries	Also referred to as advanced research wherein the motivation is to get results. This research is more of practical approach that refines the discoveries into useful products
Scientific approach	It is the style of scientific inquiry which is bottom-up	The scientific inquiry is top-down
Organization	It is generally performed by academia constituting scientists and biologists involved in benchwork	Generally performed largely by engineers employed by industries and/or by government organizations
Type of invention	Basic research is revolutionary	Translational research is evolutionary
Research application	The results and findings of basic research are sometimes shelved without an obvious immediate use	As this type of research is goal oriented, its results are of immediate use to be used outside of academia

field, the significance of translational science lies entirely in its practicality (Koshland 1993; Selep 2013). Some of the differences in approach and goals of the two kinds of researches are summarized in Table 3.1.

3.1.2 Translation Continuum from Benchside to Bedside

Since basic and translational researches are complementary to each other, they assist each other in their further development. While basic research takes up the task of unveiling promising novel ideas for their use in translational research, the translational research on the other hand raises new questions for the researchers of basic sciences to address. Thus, basic research generally plays the part of generating new ideas, and applied research conveys these ideas in the more refined and applicable form to the market so as to be implemented for the betterment of the population (Drolet and Lorenzi 2011). This translation of the nurtured research ideas going long way till their application in more elaborate, productive, valuable, profitable, and promising manner to enhance human health and well-being is often referred to as benchside to bedside transition (Keramaris et al. 2008). Translational research helps turn early-stage innovations starting from basic laboratory experiments progressing through the several rounds of clinical trials to point-of-care patient applications (Tufts 2015); production of new drugs, devices, and healthcare products; and promising treatments for patients, thereby advancing the innovation to make it attractive for further development and commercialization by the medical industry or healthcare sectors (Woolf 2008).

3.1.3 Translational Research Phases

Translational research has often been described in phases of translation, also known as "T-phases" that revolve around the development of evidence-based guidelines. The Institute of Translational Health Sciences (ITHS) has adopted a model of five phases (T_0–T_4), which is adapted from the Khoury et al.'s (2007) description of four phases. T_0 phase is characterized by the identification of opportunities and approaches to health problems that need to be addressed, whereas T_1 phase attempts to translate basic discovery into a candidate health application. T_2 phase assesses the value of application for health practice leading to the development of evidence-based guidelines which are moved into health practice through dissemination and diffusion research in T_3 phase. The final evaluation of the health outcomes of the health practice is then performed in T_4 phase. An outline of the transformation of basic research from benchside to translational research till bedside progressing through different research phases is illustrated in Fig. 3.1.

3.1.4 Translational and Clinical Science

Biomedical research community in today's world has taken up the task of translating the remarkable scientific innovations into health benefits. For realizing this objective and developing the ideas and strategies, the US National Institutes of Health (NIH) initiated a series of consultations with the research community in order to define major scientific trends collectively, with the goal of identifying thematic areas that the whole of the NIH needed to address. This initiative led to the development of the NIH road map for medical research, which is based on three fundamental themes (Zerhouni 2003):

(i) *New Pathways to Discovery*: This theme is aimed at the identification of the need to stimulate the development of novel approaches to unravel the complexity of biologic systems and their regulation. Implementation groups in this area are Molecular Libraries and Imaging; Building Blocks, Biological Pathways, and Networks; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine.

(ii) *Research Teams of the Future*: Under this theme, the main objective is to explore out ways to reduce the cultural and administrative barriers that often hamper the research which is done at the interface of preexisting disciplines and to invoke an era in which scientists can cooperate in new and different ways. NIH also developed an innovative program called as the Pioneer Award, wherein unprecedented intellectual freedom is provided to highly creative thinkers who are engaged in investigating problems of biomedical and behavioral importance. Implementation groups in this area are Interdisciplinary Research; Interdisciplinary Health Research Training: Behavior, Environment

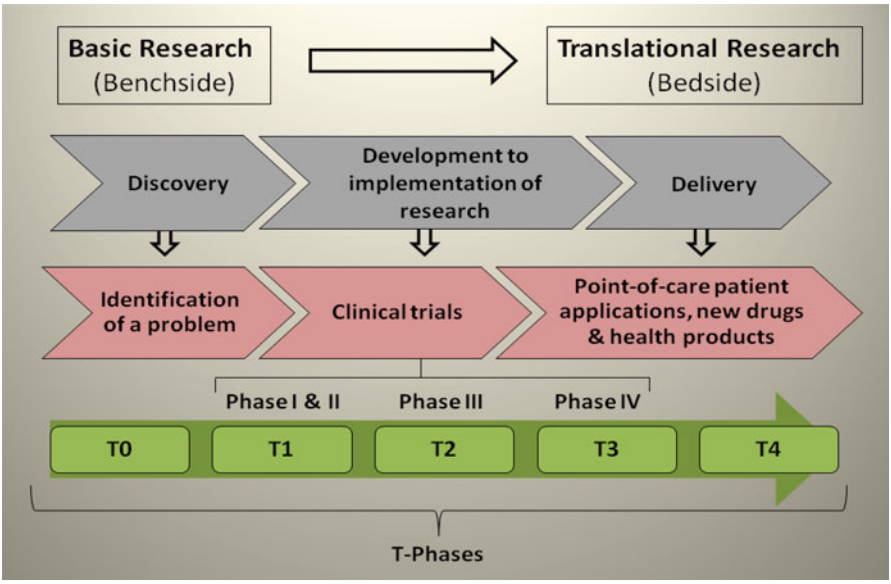

Fig. 3.1 Translation of basic science from benchside to bedside

and Biology; High-Risk Research; NIH Director's Pioneer Award (NDPA); and Public/Private Partnerships.

(iii) *Reengineering the Clinical Research Enterprise*: There have been concerns to bring together the basic, translational, and clinical researchers for better and fruitful interactions. Moreover, the new investigators are lesser interested in clinical research which is preventing the scientists to go on for patient-oriented research. This has called for an immediate need for instigating renovations in translational and clinical science by the NIH, which is the main objective of this theme. Implementation groups in this area are Harmonization of Clinical Research Regulatory Processes, Integration of Clinical Research Networks Clinical Research Informatics: National Electronic Clinical Trials and Research System (NECTRS), Regional Translational Research Centers, Enabling Technologies for Improved Assessment of Clinical Outcomes, and Dynamic Assessment of Patient-Reported Chronic Disease Outcomes.

3.1.5 Reengineering Translational Science

Due to immense economic stresses and patent expirations, pharmaceutical companies are turning down their investments in research (Wilson 2011). Furthermore, biotechnology companies are finding it very difficult to obtain venture capital for projects that need many years of support for achieving long-term profitability (Ernst and Young 2010). Realizing the need to pursue opportunities for disruptive

translational innovation and reengineering the process of developing diagnostics, devices, and therapeutics across a wide range of human diseases through translational research, the NIH has established a National Center for Advancing Translational Science (NCATS). The mission of this center is to catalyze the generation of innovative methods and technologies for the development and implementation of diagnostics and therapeutics (Ferrell 2009). The long timelines, steep costs, and high failure rates in the translational pathway compel the initiation of revolutionizing the science of translation through comprehensive, systematic, and creative approach. NIH aims to shape and sharpen this new vision through a transparent scientific environment, via NIH-based online resources, thereby ensuring the proper and wider dispersal of complete information about the successes and failures in research swiftly to all the stakeholders (Zerhouni 2003). NCATS aims to offer unparalleled opportunities to researchers for intense focus on the reengineering of the translational process, beginning from the initial target identification to first-in-human application of small molecules, biologics, diagnostics, and devices (Collins 2011). Besides NCATS, there are various other research institutes and centers all over the world that are dedicated toward performing translational research in different fields of scientific advancement (Table 3.2).

3.1.6 Opportunities in Translational Research

Translational research is a new area of investigation that involves the integrated application of advanced technologies that include multiple disciplines of science like physiology, pathophysiology, natural history of disease, genetics, and proof-of-concept studies of drugs and devices (Zerhouni 2005). Recent research breakthroughs, most importantly, completion of the Human Genome Project, offer a pool of nonending opportunities for basic investigators to work and make further advancements in these areas. Other accomplishments like advances in information technology; biocomputing; high-throughput technologies for screening, identifying, and studying compounds of interest; and novel imaging capabilities also tend to provide direct and immediate rewards for individual investigators and the institutions that support their work (Hobin et al. 2012).

3.1.6.1 Opportunities for Researchers

For basic researchers, engaging in translational research benefits them in contributing to the understanding and treatment of human diseases and participating in the development of solutions to medical and public health problems that serves as a source of intellectual inspiration and stimulation. On personal front, translational research provides opportunities to researchers to develop their own science and learn new methods that paves way for initiating new projects, gives directions for existing projects, and increases publication rates. Furthermore, it helps in

Table 3.2 Partial list of dedicated translational research institutes and centers across the globe

Institute	Weblink	Country	Comments
Translational Research Institute Australia	www.tri.edu.au/	Australia	Aims at comprehensive medical research and biopharmaceutical facility. The institute currently hosts four flagship programs: (1) immunotherapy, (2) diagnostic imaging, (3) microbiome, and (4) gynecological cancer
The Centre for Drug Research and Development	www.cdrd.ca/	Canada	Alliance of Translational Research Centres established to accelerate global drug development. Their project portfolio includes 13 technologies commercialized till date in the wider area of immunotherapy, neuroscience, anti-infective, oncology, fibrosis, inflammation, and regenerative medicines
National Research Center for Translational Medicine	www.natureindex.com/institution-outputs/china/national-research-center-for-translational-medicine/556d6532140ba05c398b4570	China	First of five institutions meant to bridge the gap between basic research and clinical application by putting researchers, doctors, and patients under one roof
Translational Health Science and Technology Institute	www.thsti.res.in/	India	The emphasis is on fast-tracking healthcare solutions that would meet the needs of a rapidly developing economy in need of healthcare intensity for its large population
Translational Research Informatics Center	www.tri-kobe.org/	Japan	The center is supported by the Ministry of Education, Culture, Sports, Science and Technology. The center's aim is to develop methods for improved prognosis in important disease areas

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Institute	Weblink	Country	Comments
European Infrastructure for Translational Research (representative organization)	www.eatris.eu/	Multiple European countries	One-stop access to over 70 academic research centers in Europe. Their research services are focused around the following technologies: (1) ATMP and biologics, (2) biomarkers, (3) imaging and tracing, (4) small molecules, and (5) vaccines
Centre for Translational Research and Diagnostics	https://www.csi.nus.edu.sg	Singapore	The center is equipped with three major facilities: (1) the NUHS Tissue Repository, (2) the Translational Interface molecular pathology facility, and (3) the Diagnostic Molecular Oncology Centre with excellence in clinical sample and data management, translational research and clinical trial support, and the development and deployment of novel diagnostics into the clinic
National Center for Advancing Translational Sciences	www.ncats.nih.gov/	USA	Centers at the NIH; established to transform the translational process so that new treatments and cures for disease can be delivered to patients faster
Center for Comparative Medicine and Translational Research	https://cvm.ncsu.edu/research/centers/ccmtr/	USA	Promotes scientific discovery and facilitates its clinical application to achieve the goal of improving the health of animals and humans
Translational Research Institute for Metabolism and Diabetes	http://www.tri-md.org/	USA	Joint venture between Florida Hospital and Sanford-Burnham Medical Research Institute; dedicated to the study of obesity, metabolism, diabetes, and the

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Institute	Weblink	Country	Comments
			metabolic origins of cardiovascular disease
Center for Translational Injury Research	http://cetir-tmc.org/	USA	The goal of the center is to lead research and development of next-generation medical technologies in the areas of hemostasis, resuscitation, and computerized decision support for trauma patients
Translational Genomics Research Institute	https://www.tgen.org/	USA	Primary focus is to discover the genetic cause of disease. The institute's thrust areas include disorders in the areas of oncology, neurogenomics, and metabolic diseases
Center for Translational Medicine, the University of Texas Southwestern Medical Center	http://www.utsouthwestern.edu/research/translational-medicine/index.html	USA	CTM is a member of the national Clinical and Translational Science Award (CTSA) consortium, a group of 62 medical research institutions, funded by the National Institutes of Health (NIH), that work together to improve the way biomedical research is conducted across the country, to reduce the time it takes for laboratory discoveries to become treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers
The Institute for Translational Medicine and Therapeutics	http://www.itmat.upenn.edu/	USA	ITMAT includes faculty, basic research space, and the Clinical and Translational Research Center (CTRC), which now includes the former

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Institute	Weblink	Country	Comments
			General Clinical Research Center (GCRC) of both Penn and the Children's Hospital of Philadelphia (CHOP). It supports research at the interface of basic and clinical research focusing on developing new and safer medicines
Duke Translational Medicine Institute	https://www.dtmi.duke.edu/what-we-do/translational-medicine-at-duke/	USA	DTMI strives to overcome the obstacles to developing discoveries into devices, drugs, or therapies to improve health. The major areas of research are as diverse as ophthalmology, cancer screening, and a device for screening blood for transfusions
Center for Translational Medicine, the University of Minnesota	http://www.researchservices.umn.edu/services-name/center-translational-medicine/	USA	The center solicits and evaluates promising research leads; identifies necessary resources; provides expertise for the preclinical evaluation and testing of novel reagents, GMP manufacture of clinical products, and IND/IDE development and submission; and supports phase I clinical trial design and implementation

promoting interdisciplinary collaborations between clinicians, clinical researchers, and basic investigators that can provide exposure to new areas of science and also can generate new ideas. The basic researchers in this way also can mentor clinical colleagues in basic science methods.

3.1.6.2 Opportunities for Institutions

Besides researchers, the institutions facilitating and encouraging translational research also benefit from these programs. They have ample opportunities to provide unique training experiences to undergraduates, graduate students, and postdoctoral fellows, thereby motivating them and encouraging new talent to enter biomedical research. Moreover, due to the promotion of the development of new drugs, devices, and other medical interventions, they are able to accomplish their biomedical research missions, attract more and more patients, and enhance their status and repute. Translational research opportunities help institutions and organizations to facilitate their investigators with easy and affordable access to resources, collaborators, and expensive shared equipment and facilities. They are also able to attract public-private partnerships, leverage federal and nonfederal resources, and attain support from funding agencies in new and lucrative projects.

3.1.7 Challenges in Translational Research

Although there are numerous opportunities encompassing translational research, there are several obstacles as well involved in the process that makes the translational journey more and more challenging. The major challenges that limit professional interest and hamper the translational enterprise are insufficient resources, inadequate funding and infrastructure for developing research programs, shortage of qualified investigators, and lack of sufficient experience with essential methods and techniques as well as with complex regulatory requirements (Hait 2005). Other issues that have been repeatedly debated include academic cultural differences between basic scientists and clinicians that hinder collaboration. These differences arise due to communication gap, differences in education and training, and different goals and targets. The culture of valuing clinical care over research sidelines the basic researchers who tend to show little interest in the research.

Moreover, lack of incentives and rewards for the researchers discourage them to take initiative in novel research. Regulatory and ethical issues that are involved in human research, tissue banking, intellectual property rights, and toxicology and manufacturing regulations have become more gruesome with expanding work in the fields of cell and gene therapies and tissue engineering. Getting approvals from regulatory agencies like the Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA) has become much more difficult and complicated. All of these issues contribute to several checkpoints in translational research phases including the "valley of death" that exists between preclinical research and clinical trials (Butler 2008). The Federation of American Societies for Experimental Biology (FASEB) has made recommendations to deal with these challenges by emphasizing upon the roles and responsibilities of

institutions, professional societies, funding organizations, and individual scientists (http://www.faseb.org/Portals/0/PDFs/opa/TranslationalReportFINAL.pdf).

3.1.8 Controversies in Translational Research

Since the establishment of the NCATS, there have been a lot of controversies within the research community on the purpose, structure, and funding of the center. The mission of this center is to experiment with innovative approaches to reduce, remove, or bypass the bottlenecks often associated with the translational pipeline. Although efficient implementation of the translational research process is an important step in the emergence of an advanced research scenario, however many basic research scientists raised the concerns on the development of NCATS as it would take off the focus away from basic research entirely to the translational research (McClure 2012). This debate by the basic researchers is apt and reasonable as advances in the treatments that are being made at present are the result of enormous efforts made by the basic researchers over the decades that laid the foundation for further discoveries. Therefore, this calls for an understanding of the significance of the basic research and considering the investments made in basic research, for all intents and purposes, as an investment in translational research.

3.2 Translational Drug Discovery

The past decade has witnessed an increased emphasis on laboratory-based translational research which has been instrumental in enabling clearer understanding of the disease mechanisms and in the development of novel approaches to varied scientific areas like in gene therapy, RNA interference, and stem cells (Littman et al. 2007). The increasing adoption of translational research is leading to novel integrated discovery nexuses that may change the landscape of drug discovery. Drug discovery is the first step in the creation of new drugs that takes place in academic institutions, biotech companies, and large pharmaceutical organizations. These sectors, though, used to operate independently with minimal collaboration between those at the forefront of discovery research and those with experience in developing drugs, but with the emergence of translational research, have come closer for seeking collaboration to pool the expertise required to generate new therapies by linking laboratory discoveries directly to unmet clinical needs (Fishburn 2013). However, despite the huge investments made in drug discovery process in the past decade, there still remains a shortage of new drugs. The reasons behind this could be attributed to the continued existence of a standard drug development model that has not attuned to changes in science and public perception

of drug companies. Furthermore, the pace of drug development process lags behind in the USA due to a high profit margin that prevents reform in the absence of economic pressures (Fitzgerald 2005). The World Health Organization report on "Priority Medicines for Europe and the World" (WHO Geneva 2004) specifies several "high-burden" diseases for which no active treatment is currently available, including infectious diseases, a range of chronic diseases of the central nervous system and the cardiovascular system, autoimmune disorders, and cancer. The number of patients with these chronic diseases is continually growing in the aging population.

Translational drug discovery covers the entire spectrum from target identification to the evaluation of the efficacy and safety of novel medicines in clinical practice. It requires data generated from molecular investigations, healthcare, and clinical research. A vast and diverse amount of data thus produced pose various challenges like integrating fragmented databases, facilitating secondary usage of patient data in clinical research, and generating information systems for easy and immediate use to clinicians and biomedical researchers. Hence, for the management and integration of clinical and molecular data, a large number of web-based user-friendly databases and tools are being designed that are available online (Table 3.3).

Translational drug discovery demands both the need for cooperation between clinical and pharmacological research and the significance of the role of academia in target identification and drug discovery, design, and development. In the past decade, an important trend has been observed wherein an increasing proportion of innovative new drugs emerge from small biotech companies typically working in close collaboration with academia. An example of one such drug is the peptide vaccine for HPV-induced cervical cancer.

Discovery and development of safe and effective new drugs is an exceedingly difficult, expensive, and time-consuming process. Despite thousands of pharmaceutical companies working to develop and get new drugs to market, and approximately $50 billion spent every year, only 23 new molecular entities (NMEs) per year (on average) have received marketing approval from the FDA during the last 10 years. The most concerning fact is that, while expenditures have increased steadily since the mid-1990s, the number of drugs reaching the market has declined to a relatively low plateau (Fishburn 2011).

Although the developmental process of new drugs has been slow, the overall research and development investment has yielded important breakthroughs in basic cellular and molecular biology and in producing novel technologies to advance drug development. These advancements include the identification of all the genes in the human genome (the Human Genome Project), the use of microchip-based robotics for rapidly testing large numbers of potential new drug compounds, and the creation of cell-based systems for large-scale synthesis of protein and antibody therapeutics. The mismatch between scientific progress and poor productivity of drugs has led many scientists to reexamine the existing strategies for creating new

Table 3.3 Partial list of databases and tools dedicated for accelerating translational research in drug discovery

Databases		
Name	**Contents**	**References**
Neuroblastoma patients (NeuPAT)	An intranet-based database integration for neuroblastoma patients	Villamon et al. (2013)
Diet, Genomics, and Immunology Laboratory (DGIL) Porcine	Contains functional information on genes commonly studied in humans, pigs, and rodents	http://www.ars.usda.gov/Main/docs.htm?docid=6065
Stanford Translational Research Integrated Database Environment (STRIDE)	A Stanford project which consists of three components: clinical data warehouse, research data management applications, and biospecimen data management system	Lowe et al. (2009)
Cancer Survivors Against Radon (canSAR)	Database that integrates data from biology, chemistry, pharmacology, structural biology, cellular networks, and clinical annotations. A tool is also built that applies machine learning methods for several useful drug discovery predictions	Bulusu et al. (2014)
Repository of Molecular Brain Neoplasia Data (Rembrandt)	A cancer clinical genomic database and a web-based data mining and analysis platform aimed at facilitating discovery by connecting the dots between clinical information and genomic characterization data	Madhavan et al. (2009)

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Table 3.3 (continued)

Research Electronic Data Capture (REDCap)	It is a free web-based application designed to support data capture for research studies. It is a metadata-driven EDC software solution and workflow methodology for designing clinical and translational research databases	Harris et al. (2009)
Tools		
Name	**Purpose**	**Reference**
PRISYM CLINTRIAL	Clinical trial management and patient stratification system	http://www.prisymid.com/solutions/clinical-trials/prisym-clintrial/
GenetRx	Patient stratification based on gene expression biomarker	http://www.genebiomarkers.com/applications/patient-stratification.php/
HLA Twin	It is a dual-algorithm genotyping software	http://www.omixon.com/hla-twin/
RANDI2	It is a web-based application that supports many randomization algorithms, free configurable patient properties, stratification, and definition of inclusion criteria for easy management of multicenter clinical trials	Schrimpf et al. (2010)
HERMES	It is a free simulation software used for taking the key decisions of minimization or stratification using various modeling parameters	Fron Chabouis et al. (2014)

drugs. Presently, it takes an average of 12–15 years to bring a new drug to the market because the process involves sequential stages of discovery, preclinical development, clinical trials (phases I, II, III), and FDA review (Fishburn 2011). Moreover, the successful development of a single drug often starts with the synthesis and testing of thousands of different candidate drug molecules.

3.2.1 Translational Drug Development for Diseases

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified during drug discovery process. Across all diseases, translational drug discovery and development are lengthy, costly, and risky processes. The average cost for the development of new drug has been estimated to be greater than $1 billion. There are several challenges in neuroscience drug development such as target identification and validation, significant disillusionment with the use of animal model to evaluate efficacy, lacking biomarkers, and stratification of populations for clinical trials (Lally and MacCabe 2015). Various challenges in drug discovery and development for diseases are summarized in Fig. 3.2 and Table 3.4.

3.2.1.1 Nervous System Disorders

The prevalence and burden of neurological disorders impel the leadership within industry, academia, and government to take initiative for curing these disorders. Despite intensive research over many years, the treatment of brain disorders remains a major health issue (Morinet 2014). In spite of high prevalence, enormous contributions to disability worldwide, and substantial economic burden, there are no disease-altering therapies for neurodegenerative disorders (Karnati et al. 2015). Compared with other disease areas, failure rates in late-stage clinical trials are disproportionately high for neurodegenerative disorders. Many drug companies

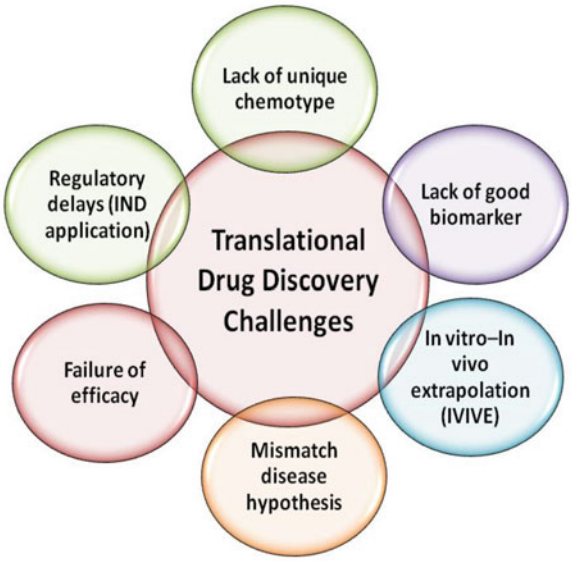

Fig. 3.2 Some of the major challenges in drug discovery and development

Table 3.4 List of important diseases and challenges associated with their drug discovery and development projects

Disease	Major challenges	References
Alzheimer's disease (AD)	Exact cause for AD onset is still unknown	Gu et al. (2015)
	Limited effectiveness of the cognitive tests	Wesnes and Edgar (2014)
	Problems associated with blood-brain barrier (BBB) penetration of drugs and its pharmacokinetic properties	Butini et al. (2013)
Schizophrenia (SZ)	Limitation in identifying, validating, developing, and clinically deploying new treatments	Millan et al. (2015)
	First- and second-generation antipsychotic drugs based upon the dopamine hypothesis are limited	Winchester et al. (2014)
Bipolar disease (BD)	Limitation in clinically deploying new treatments	Millan et al. (2015)
	Challenges in improving methods and tools to generate, integrate, and analyze high-dimensional data	Hoertel et al. (2013)
	Technical challenges related to the identification and validation of candidate genes and peripheral biomarkers	Le-Niculescu et al. (2011)
Major depressive disorder (MDD)	Limited efficacy and a pronounced delay to onset of action and provoke distressing side effects	Millan (2006)
Cancer	The sequencing of increasingly larger numbers of cancer genomes	McDermott et al. (2011) and Sellers (2011)
	Identification of key driver mutations and matching drug therapies	Greaves and Maley (2012)
	Heterogeneous populations in cancers are likely to include drug-resistant stem cells and a range of host cells that are involved in tumor progression	Jordan et al. (2006) and De Palma and Hanahan (2012)
	Selecting and validating the best targets	Benson et al. (2006)
	Druggability gap	Verdine and Walensky (2007) and Paul et al. (2010)
Diabetes	Safety concerns of GLP1 analogues	Drucker et al. (2010)
	Failure of antidiabetic medications like troglitazone, rosiglitazone, and pioglitazone	Henney (2000, Nissen and Wolski (2007) and Hillaire-Buys et al. (2011)
Cardiovascular disease (CVD)	Failure of translating good preclinical data into a safe and effective medicine (e.g., CETP inhibitor torcetrapib and vasopeptidase inhibitor omapatrilat)	Tall et al. (2007) and Ferdinand et al. (2001)
	Lower efficacy of the thrombolytic drugs (e.g., streptokinase and accelerated tissue plasminogen activator [tPA])	White and Van de Werf (1998)
	Lesser opportunities for young biotech companies	Katherine (2007)

have divested themselves almost entirely from neuroscience research program to other therapeutic areas.

Since pathophysiology of brain disorders is poorly understood, it is difficult to identify promising molecular targets and its validation (Feustel et al. 2012). It is also difficult to choose an animal model, because of poor understanding of disease mechanism. Brain disorders are associated with defect in synaptic communication and functional connectivity. Target identification is a critical factor in the drug discovery and development. Target validation is an iterative process of increasing confidence in a target, which can be conceptualized as continuing through phase III clinical trials. Along with target validation, it is critical to establish the therapeutic levels of a drug that can be reliably delivered to the brain and those levels at which the drug binds its target, thereby modifying the disease pathway in the desired direction. In the absence of this information, clinical trials are not eligible for testing the target validation hypothesis. Furthermore, failure of animal models to predict accurately the efficacy of drugs with new mechanism for neurological disorders has been a central problem in drug development. Owing to differences between animals and humans in cell types, transmitter function, and anatomy, the usage of animal models is not reliable.

Developing and integrating new approaches that utilize combination of animal and nonanimal models of disease mechanisms, along with new tools, technologies, and techniques, might illuminate the underlying biological mechanism of disease and improve target identification, validation, and therapeutic development. Current research paradigm might need to change, particularly for clinical studies. For the development of drugs, better understanding of disease mechanisms and improved ability to translate such discoveries into biomarkers and therapeutics is required. Several opportunities in translational drug discovery are illustrated in Fig. 3.3.

3.2.1.2 Psychiatric Disorders

Innovation is important for the identification and novel pharmacological therapies to meet the treatment needs of patients with psychiatric disorders including schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD) (Maurya et al. 2016). The process of drug discovery encompasses a period of intense research and development efforts that typically take 13–15 years. It involves search for target, optimization to allow candidate drug selection, and human testing to achieve proof of mechanism, principle, and concept, followed by regulatory approval. In the last decade, large-scale candidate gene and genome-wide association studies have generated a growing list of "risk" genes for psychiatric illness (Hess et al. 2016). Multiple risk genes were identified, each making a small contribution to such disorders. These human genome-based approaches of understanding the location and function of specific gene products and their relevance to disease pathophysiology have rewarded the field of biological psychiatry with some novel target ideas. New drug candidates can act in psychiatric disorders to show their effects by modifying certain pathways in the biological system, including

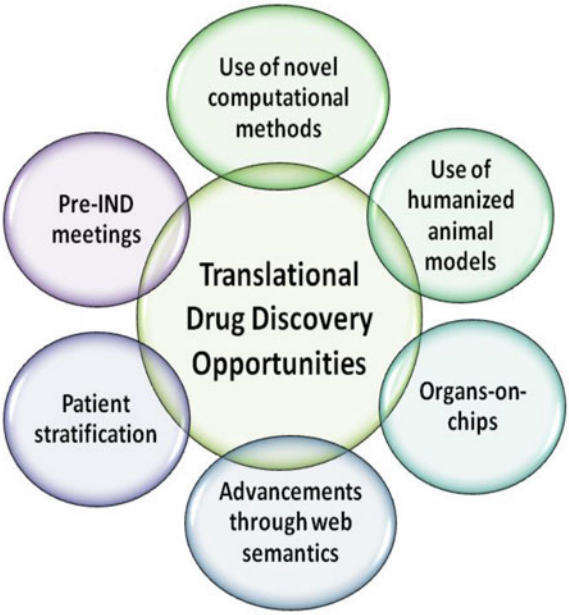

Fig. 3.3 Figure showing open opportunities with translational research in drug discovery

inflammatory pathway, cell-mediated immune (CMI) pathway, oxidative and nitrosative stress (O&NS) processes, antioxidant system (enzymatic and nonenzymatic), mitochondria, and neuroprogression (Table 3.5).

3.2.1.3 Cancer

Despite advances in diagnosis and therapies, cancer is still the leading cause of death worldwide. Genome-wide studies have been extensively used over the past decades as a powerful tool in defining the signature of different cancers and in predicting outcome and response to therapies.

MicroRNAs (miRNAs) are a contemporary class of tiny noncoding endogenous RNA molecules, only 18–25 nucleotides long. In human genome, the expression of each gene is tightly regulated to control the function and environment of each cell. In the nucleus, the template for genetic information is encoded in DNA segments, which are transcribed into RNA molecules. These molecules are transported from the nucleus to the cytoplasm, where they are translated into proteins. The activity of genes is controlled at the level of DNA, RNA, and protein. Different RNAs have different degrees of stability due to their unique interaction with cellular degradation machinery, which is regulated by cellular signals. The recent discovery of miRNAs, which alter RNA stability, ignited a growing interest in gaining further knowledge of gene regulation at the RNA level. About 5300 human genes have been implicated as targets for miRNAs, making them one of the most abundant classes of regulatory genes in humans. miRNAs recognize their target mRNAs

Table 3.5 Various drug candidates that can be used for psychiatric disorders in different modified pathways

S. No.	Pathways	Name of drugs (antidepressants)	References
1.	Inflammatory	Celecoxib, eicosapentaenoic acid (EPA), statins, acetylsalicylic acid, minocycline, interleukin-1 receptor antagonist (IL-1RA), etanercept, ketamine, curcumin	Maes et al. (2012), Najjar et al. (2013) and Lotrich et al. (2014)
2.	Oxidative and nitrosative processes, antioxidant defense	Zinc, N-acetylcysteine (NAC), coenzyme Q10, curcumin, liquiritin	Maes et al. (2011) and Doboszewska et al. (2016)
3.	Mitochondria	Minocycline, statins, celecoxib, eicosapentaenoic acid (EPA), N-acetylcysteine (NAC), coenzyme Q10, curcumin, resveratrol	Morel and Singer (2014), Pandya et al. (2013) and Ungvari et al. (2011)
4.	Cell-mediated immune (CMI) pathway	Indoleamine-2,3-dioxygenase (IDO) blockade, minocycline	Munn and Mellor (2013) and Dean et al. (2014)
5.	Neuroprogression	Neuronal cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), vascular growth factor (VGF), fibroblast growth factor receptor (FGFR), minocycline, ginseng, N-acetylcysteine (NAC), zinc, coenzyme Q10, curcumin	Nowacka and Obuchowicz (2012), Wędzony et al. (2013), Elsayed et al. (2012) and Berk et al. (2012)

based on sequence complementarity and act on +region of miRNA, important for mRNA target recognition, which is located at the end of the mature miRNA sequence from bases 2 to 8. This is often referred to as the "seed sequence" (Bartel 2004). Given the importance of miRNAs in regulating cellular differentiation and proliferation, it is not surprising that their misregulation is linked to cancer. In cancer, miRNAs function as regulatory molecules, acting as oncogenes or tumor suppressors. Amplification or overexpression of miRNAs can downregulate tumor suppressors or other genes involved in cell differentiation, thereby contributing to tumor formation by stimulating proliferation, angiogenesis, and invasion. Similarly, miRNAs can downregulate different proteins with oncogenic activity; i.e., they act as tumor suppressors. MicroRNA genes are evolutionarily conserved and are located within the introns or exons of protein-coding genes, as well as in intergenic areas. miRNA genes are transcribed by RNA polymerase II or III into pri-miRNAs. Pri-miRNAs are next cleaved into approx. 70 nucleotide-long precursor miRNAs (pre-miRNAs) by the nuclear microprocessor complex formed by the RNase III Drosha and DiGeorge syndrome critical region gene 8 (DGCR8). The average human pre-miRNA contains a 33-base-pair hairpin stem, a terminal loop, and two single-stranded flanking regions upstream and downstream of the hairpin. Pre-miRNAs are next transported by the exportin-5/Ran GTPase complex into the

cytoplasm, where miRNAs undergo maturation. In the cytoplasm, pre-miRNAs are cleaved by RNase III Dicer into B22 nucleotide-long miRNA duplex and are unwound by helicase. The passenger strand is degraded, and the selected guide strand together with Ago protein activates RISC (RNA-induced silencing complex), resulting in mRNA degradation or translational inhibition, depending on the percentage of sequence complementarity between the miRNA 50-seed and mRNA 30-UTR element.

Over the past few years, cancer death rates have shown an overall decrease compared with previous years. This trend is largely due to the development and implementation of improved cancer screening methods and treatment strategies (Gilliland et al. 2016; Matter 2015). Drug discovery is a risky, costly, and time-consuming process depending on multidisciplinary methods to create safe and effective medicines. Although considerable progress has been made by high-throughput screening methods in drug design, the cost of developing contemporary approved drugs did not match that in the past decade (Zhou et al. 2016). Despite these steps toward improving survival and reducing mortality rates, breast cancer still remains the leading cause of death among women younger than 85 years. As with many cancers, progress in early breast cancer detection has been inadequate, and methods for determining diagnosis and prognosis of breast cancer are still limited to invasive procedures, such as tissue biopsies for histological examination. Advances in understanding the cancer cell at the molecular level have enabled development of several targeted therapies that have advanced the treatment of relevant patient subgroups. In colorectal cancer (CRC), miRNAs have evolved in the regulation of chemoresistance to various CRC treatments and the stemness of CRC stem cells (CRSCs), sequentially modulating the sensitivity of CRC cells to anticancer treatments. Targeting miRNAs thus may be a novel plan for eradicating CRSCs, resensitizing drug-resistant cells to anticancer agents, improving drug competence, and developing novel biological agents for CRC treatments (Liu et al. 2016). Genomics-based predictors of drug response have the potential to improve outcomes associated with cancer therapy. Oncoproteomics is an important innovation in the early diagnosis, management, and development of personalized treatment of acute lymphoblastic leukemia (ALL). As inherent factors are not completely known, radiation exposure, benzene chemical exposure, certain viral exposures such as infection with the human T-cell lymphoma/leukemia virus-1, as well as some inherited syndromes may raise the risk of ALL – each ALL patient may modify the susceptibility of therapy. Shotgun proteomic strategies to unravel ALL aberrant signaling networks nowadays are very promising (López Villar et al. 2015). Osteosarcoma (OS), the most common primary bone cancer in dogs, is commonly treated with adjuvant doxorubicin or carboplatin following amputation of the affected limb. Literature shows that intra- and interspecies gene expression models can successfully predict response in canine OS, which may improve outcome in dogs and serve as preclinical validation for similar methods in human cancer research (Fowles et al. 2016). Solid tumors account for approximately 30% of all childhood cancers. An increased efflux rate of the antineoplastic drugs from

cancer cells by action of members of the ATP-binding cassette (ABC) transporters is one of the most important mechanisms of multidrug resistance (Fruci et al. 2016).

Epidemiological studies indicate that natural products are also used as anticancer agents. Agents targeting the genetic and/or epigenetic machinery offer potential for the development of anticancer drugs (Cho 2010). Accumulating evidence has demonstrated that some common natural products [such as epigallocatechin-3-gallate (EGCG), curcumin, genistein, sulforaphane (SFN), and resveratrol] have anticancer properties through the mechanisms of altering epigenetic processes [including DNA methylation, histone modification, chromatin remodeling, microRNA (miRNA) regulation] and targeting cancer stem cells (CSCs). These bioactive compounds are able to revert epigenetic alterations in a variety of cancers in vitro and in vivo. They exert anticancer effects by targeting various signaling pathways related to the initiation, progression, and metastasis of cancer (Wang et al. 2013).

The National Cancer Institute (NCI) has initiated the prioritization of cancer antigens so as to pave a way to a well-vetted, priority-ranked list of cancer vaccine target antigens based on predefined and pre-weighted objective criteria. By doing this, NCI also aims to test the new approach for prioritizing translational research opportunities based on an analytic hierarchy process. The elucidation and weighting of criteria for assessing cancer antigens would enable the immunologists to determine the characteristics and provide them with the experimental data needed to select the most promising antigens for further development and testing in clinical trials (Cheever et al. 2009). The NCI embarked on this new approach of identification, prioritization, and funding of translational cancer research due to the recommendations of the Translational Research Working Group (TRWG) (Old 2008). The focus is on evaluation of a method to select cancer antigens for subsequent development through the immune response modifier pathway, which is one of the six TRWG pathways leading from basic laboratory discoveries to final testing in clinical trials (Hawk et al. 2008; Cheever et al. 2008).

3.3 Strategies to Accelerate Translational Research in Drug Development

With the ever-increasing number of unmet medical needs, researchers all around the world are striving for the cure. Not only the diseases that are coming to the scientific knowledge are new but also are complex. Many a times, these new diseases come as outbreaks and spread epidemically in no time (Stadler et al. 2003; Gostin et al. 2014). In such vulnerable situations, well-strategized translational research efforts can provide immediate hope for the cure. A prioritized research area, clear vision on the project, well-established infrastructure, strong team of committed researchers, sufficient funding, meaningful collaboration that can address the demand for extended project activity, and use of new scientific

Fig. 3.4 Figure showing some of the strategies that could be employed in translational drug discovery

methods can characterize successful translational research strategies (Khanna 2012). Some of the components of a good strategy helpful in accelerating the translational research in drug discovery and development are highlighted in Fig. 3.4.

3.3.1 Prioritizing Area of Research and Objectives

It is nearly impossible for any single organization to find a cure for every human disease known at any moment of time. Therefore, it is extremely important to prioritize the thrust area and the objectives. A loosely defined objective stating the definition of translational research will certainly not be helpful to lead an organization to a set destination (Sugarman and McKenna 2003). Objectives must be concise and focused to research area and must clearly address the research need with tentative road map and millstones. Understanding the importance of focused research, many centers around the world have been dedicated for specific diseases of the kidney, metabolic disorders, cancer, etc. Such dedicated centers have not only become the models for other scientific organizations but also have enhanced the scientific knowledge in terms of their contribution (Andrews 2013).

3.3.2 Meaningful Collaboration

Collaboration is the integral part of any drug discovery project. Many of the collaborations are actually seen based on their names or brand value (Butler 2008). However, in translational research, collaboration is the most important

thing. Collaboration should be made to further progress the discovery from one phase to another (Ioannidis 2004). If an organization is good in basic research (identification of new drug targets), then a fruitful collaboration with an organization competent in developing the new chemical moieties, which can synthesize and test the compounds against the target, would be beneficial (Watson et al. 2008). Small pharmaceutical companies should decide their limit of expanding research because at many times, with one or more lead discoveries, they invest a lot in clinical trials and such huge expenditures in a new assignment lead their initial discovery processes to suffer. Therefore, collaboration not only improves scientific research through knowledge sharing but also helps in maintaining the risk associated with any drug discovery project. A right collaboration in a drug discovery project is the best strategy in translational research (Pober et al. 2001).

3.3.3 Technology Upgradation

For successful translation of drug discovery project, it has to be ensured that quality and speed must go hand in hand. It is important to include the latest technology to produce high-quality results with speed and accuracy. One of the major bottlenecks in translational drug discovery is the limited extrapolation of results generated from preclinical studies as predicted clinical outcome. Therefore, in such instances, it is difficult to get confidence with the data produced with such preclinical experiments (Huh et al. 2010). Drug discovery phases, where the use of the latest technology such as tissue-on-a-chip and organ-on-a-chip could be beneficial to a greater extent, should be encouraged to produce reliable results speedily in a cost-effective manner (Ioannidis 2004).

3.3.4 Bridging Interventional Development Gaps (BrIDGs) Scheme

This is a special scheme under NIH-NCATS program (https://commonfund.nih.gov/raidoverview). The idea behind this unique concept is that certain critical resources are needed for the development of new therapeutic agents and it is difficult for an initial discovery to attract private sector partner to advance project with significant commercial potential. This is due to high risk associated with not-so-common disorders. Under BrIDGs, the investigator gets the chance to receive access to NIH experts and contractors who conduct preclinical studies free of cost for the investigator. At present, four services – synthesis, formulation, pharmacokinetic, and toxicology services – are available under this scheme. The success of this scheme is very encouraging as can be seen from data of 2014 published on the

BrIDGs website. Out of 15 supported projects, five BrIDGs-supported candidates have gone as far as phase II human clinical trials.

3.3.5 Drug Repurposing

Finding a novel indication for an existing drug is called drug repurposing (Issa et al. 2013; Law et al. 2013; Oprea et al. 2011; Buchan et al. 2011; Padhy and Gupta 2011; Ashburn and Thor 2004). This approach is gaining greater interest among the scientist around the world due to its direct market applicability and comparatively low financial risk. In this approach, since the starting point is mostly a molecule passed in clinical phase I, the risk associated with the toxicity becomes negligible. Drug repurposing approaches can be highly useful for orphan diseases and diseases for developing countries where pharmaceutical companies show lesser interest due to low financial returns. There are many instances where drug repurposing approaches have been successfully applied. A number of methods have been used to find alternative indication based on the same target or an alternative target (Sardana et al. 2011).

3.3.5.1 Computational Chemistry

Wide combinations of computational approaches can be utilized for identification of nonobvious indications for a given compound (Ekins et al. 2011; Hurle et al. 2013; Achenbach et al. 2011; Sanseau and Koehler 2011). Broadly, all these approaches can be divided into two methods: (1) ligand based (Gregori-Puigjane and Mestres 2008; Gong et al. 2013) and (2) structure based (Kharkar et al. 2014; Blondeau et al. 2010; Issa et al. 2015). Ligand-based methods are based on the notion that if compound C1 of target T1 significantly matches with a known compound C2 of target T2, then compound C1 could also work for target T2. A variety of sub-methods such as 2D fingerprint-based similarity, 3D shape similarity, scaffold matching, and comparison of ligand pharmacophore or atomic property fields can be utilized. The structure-based methods require the structural information of the target and its compound. Sub-methods such as high-throughput virtual target screening (Gfeller et al. 2014; Santiago et al. 2012), interacting pharmacophore (Liu et al. 2010), and active site similarity have been explored under this category (Haupt et al. 2013). A graphical overview of two computational chemistry methods is given in Fig. 3.5.

3.3.5.2 Literature Mining

A large amount of scientific findings are recorded in the form of publications. There are more than 25 million articles indexed alone in PubMed. It is practically

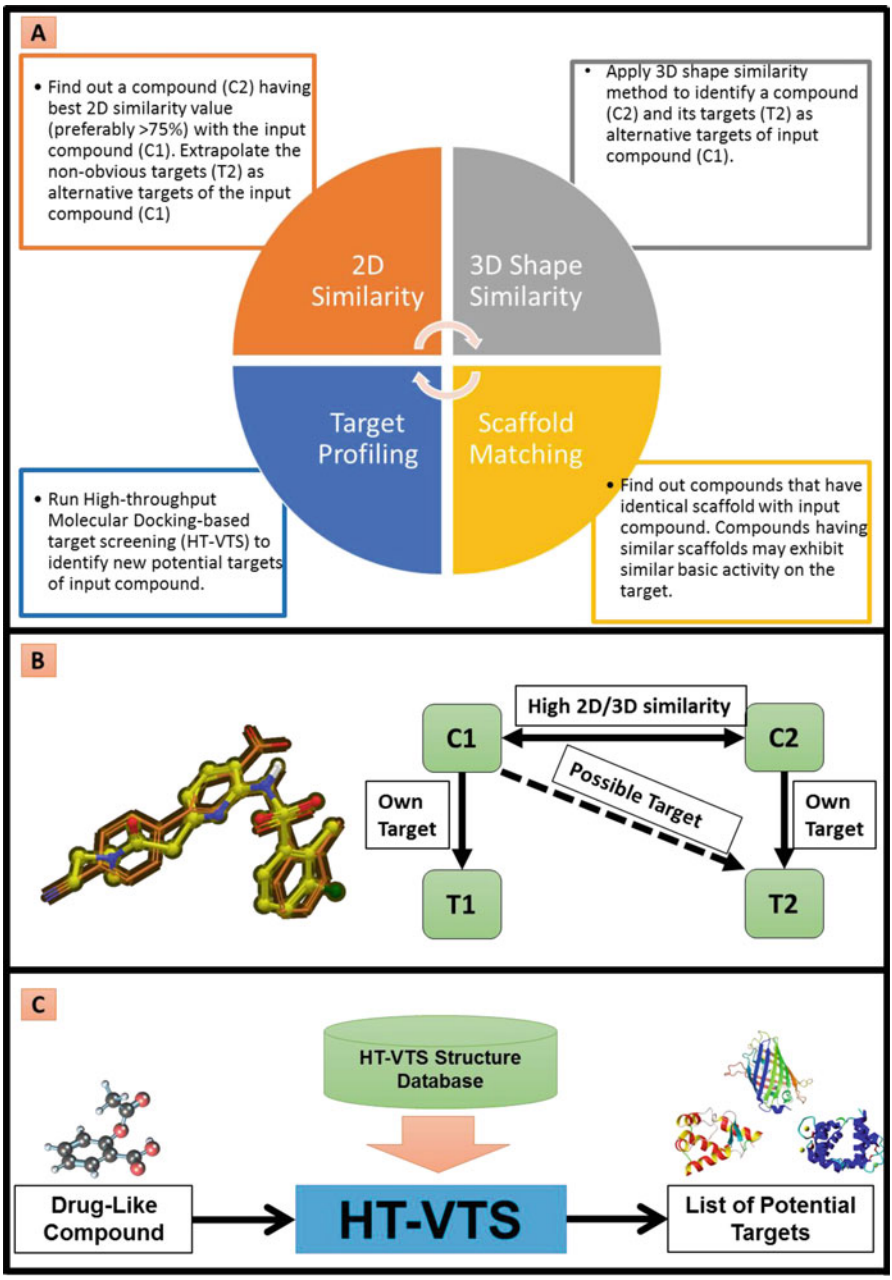

Fig. 3.5 Computational chemistry methods for drug repurposing. (**a**) An overview of four approaches. (**b**) 2D or 3D shape-based similarity method for drug repurposing. (**c**) High-throughput virtual target screening (HT-VTS) method for the identification of potential alternative target

impossible to manually scan all the articles related to a drug, disease, concept, or their associated combination. Therefore, a large number of literature mining techniques aiming to effectively extract the relation between keywords and present the biomedical interrelation have evolved (Frijters et al. 2010). In particular, ontologies have been extensively utilized in the biomedical domain either as controlled vocabularies or to provide the skeleton for mapping relations between concepts in biology and medicine (Andronis et al. 2011).

3.3.5.3 Genome-Wide Association Study (GWAS)

GWAS studies are not only limited to curate the biology of diseases but also provide translational opportunities for drug discovery and development through drug repurposing. In this approach, disease association for a given target gene is looked by means of single-nucleotide polymorphism (SNP) (Sanseau et al. 2012). Curated databases are available where information related to SNP and their association to pathologies is indexed. One of the extensively used databases is provided by the National Human Genome Research Institute (http://www.genome.gov/gwastudies/). Using this resource, Sanseau et al. (2012) performed an analysis to unveil potential new indications for protein targets through GWAS. The underlying concept behind the approach is that the association between a SNP and a trait from a GWAS can be extrapolated as a relation between a gene and a disease.

Other than the abovementioned methods, adverse events (Yang and Agarwal 2011), electronic health records (Xu et al. 2015), and web semantics (Chen et al. 2012) are also reported as useful methods for finding alternative indications.

3.4 Conclusion

Translational research, in recent years, has gained wide attention among the scientists across the globe. Traditionally, the industries were mostly considered as "product-driven" and academics as "knowledge-driven" centers. However, with the increasing burden of unmet medical needs, it becomes difficult and unfair for industries to be held responsible to sought solutions for all such medical urgencies. Therefore, understanding the need, governments across the globe have initiated to open nonprofit centers to conduct translational research. These centers have brought opportunities for professionals from multiple disciplines to come together, collaborate, exchange ideas, and focus their efforts to achieve the goal of having a disease-free world. However, like any other discipline, the field of translational research also comes with several challenges. Some of these challenges include wide coverage of chemical space around active ingredient to protect intellectual property, poor knowledge of disease pathophysiology, unknown differences in disease progression in animal vs. human, and regulatory delays, to name a few. The exceptionally large amount of scientific data are being generated on day-to-day

basis and being stored in central repositories such as databases and publications, which, in turn, again are accessed from all corners of the globe and have opened several avenues to retrieve data, develop tools, build analytics, and generate meaningful hypothesis to facilitate translational research. However, one has to understand that the tools and techniques being utilized conventionally have now become obsolete to process such data. High-end technology – driven by intelligent algorithms such as machine learning and natural language processing – is now being utilized not only to mine deeper into the information stack but also to establish scientifically meaningful relationship in a complex physiological network. Thanks for the enhancement of technology, several opportunities can also be seen to attain high success rate in translational research. Organ-on-chip is one of such technologies being used to reduce attrition at later stages of drug discovery campaign. Accurate knowledge of patient stratification would be a key in clustering the patient population and to ensure that investigational new therapy should be delivered to the right patient and produce optimum benefits. Pre-Investigational New Drug (IND) meeting can ease the understanding of the technicalities associated with lengthy documentation and therefore reduce the time for later revisions. Not limited to this, the strategies such as drug repurposing, more strategic collaborations could be highly beneficial in accelerating the hunt to discover new drugs. The field of translational research is still an evolving discipline which not only needs dynamic workforce but also requires significant amount of monetary investment to put the right and advanced technology in place. The challenges in finding new and better therapies would never be less, but courage of facing such challenges has certainly strengthened with translational research. The continuous rise of diseases and their outbreaks and complexity have made the translational research as a necessity and not mere a scientific concept. With the hope that translational research will come as a ray of hope by bringing better and more effective therapies to millions of patients in the form of novel and highly efficient drugs, we all wish to live in a better future in the years to come.

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