Chapter 1
Getting Started

Daria Mochly-Rosen and Kevin Grimes

In recent decades, we in academia have focused on advancing scientific understanding through basic research and counted on the biopharmaceutical industry to translate promising discoveries into new therapeutics. Given the recent developments, however, this paradigm needs to change. Pharmaceutical companies have drastically cut their research budgets and basic research staffs to decrease costs and improve short-term profits. Additionally, the number of biotechnology venture funds has contracted, especially those that invest in new biotechnology start-up companies. As a result, we can expect that fewer novel drug programs will originate in the biopharmaceutical sector. Academic inventors can and should step in to fill this gap in the discovery pipelines. But we often lack the expertise and resources to advance our projects through this applied science stage of drug discovery and development. This chapter introduces the process of drug development and highlights some of the important first steps: understanding the clinical needs, developing a target product profile (which defines the new drug's essential characteristics), and adopting a project management approach. These essential steps not only increase the likelihood of success, but can also help decrease both the cost and time required to accomplish our goal. Translating discoveries from bench to bedside is a challenging, but incredibly rewarding process, allowing us to advance scientific discovery and ensure that our government-funded research translates into improved health for our society.

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1.1 Advancing New Treatments to the Clinic Within Academia

Daria Mochly-Rosen

In 2000, our laboratory demonstrated that a rationally designed inhibitor of the delta isozyme of protein kinase C (δPKC) reduced infarct size after heart attack by 70% in a rat model. The basic research that led to this result began more than a decade earlier. Our laboratory had studied protein–protein interactions and their specific role in PKC-mediated signal transduction. Because we needed tools to probe these protein–protein interactions, we discovered a methodology to design selective peptide inhibitors and activators of the individual members of the PKC family of enzymes (isozymes). After confirming the effect of these modulators *in vitro*, we replicated these effects in cultured cells.

How did our lab begin studying heart attack? In 1997, I presented our data at the American Heart Association Meeting. Using the peptide regulators of protein–protein interactions, we found that two PKC isozymes activated by adrenaline in the heart caused opposite effects: one increased and the other decreased the rate of contraction of cardiac muscle cells in culture. I thought that regulating contraction rate of the heart would interest cardiologists. To my dismay, my report triggered no response whatsoever.

Box 1.1: Key Terms and Abbreviations

PKC: protein kinase C
Isozyme: family of closely related enzymes that catalyze similar reactions
OTL: Office of Technology Licensing; the university group responsible for managing intellectual property
IND: Investigational New Drug application; document filed with the FDA prior to initiating research on human subjects using any drug that has not been previously approved for the proposed clinical indication, dosing regimen, or patient population
FDA: US Food and Drug Administration
Repurposed drug: an FDA-approved drug with a new indication, formulation or route of administration

Dr. Joel Karliner, the Chief of Cardiology at the University of California at San Francisco, was kind enough to point out the problem. He stopped me as I was leaving the lecture hall and told me that regulation of contraction rate is of limited clinical importance. He advised, “Focus instead on determining the role of PKC in heart attack.” He also suggested that I take a cardiology fellow into my laboratory “just to keep us informed.” I invited Mary Gray, M.D., to join my group as we set out to examine the potential clinical uses for our basic research tools. In less than three years, we had shown that we could substantially reduce the infarct size of

heart attacks *in vivo* by treating animals with the δPKC inhibitor. Surely, the pharmaceutical industry would now be pounding on our doors!

Box 1.2: Recommendation

Having a clinician as part of a basic research team can provide a real advantage when considering translational opportunities. When a basic discovery is made, the team has an opportunity to consider whether it also has clinical relevance. Understanding a clinical need is not necessarily intuitive; why not engage clinicians early to help identify how our discoveries may be put to clinical use? *–DM-R*

With the help of the Office of Technology Licensing (OTL), we secured our intellectual property through patent filings. To our surprise, the pharmaceutical companies were not remotely interested in our findings. We heard an assortment of reasons: "Rats are easy to cure"; "Peptides are not drugs"; "Kinases are poor drug targets." Out of complete frustration that a potentially life-saving treatment garnered absolutely no interest from the industry, I founded KAI Pharmaceuticals together with my student, Dr. Leon Chen. We visited scores of venture groups over 18 months attempting to raise funding for KAI. Finally, after a successful pre-IND meeting with the Food and Drug Administration (FDA) in 2003 with our clinical advisor, Dr. Kevin Grimes, and a handful of other consultants, we convinced investors to fund us. In 2004, I took a leave of absence from Stanford to serve as the chief scientific officer of the company for its first year.

1.1.1 SPARKing Translational Research in Academia

During my year at KAI, I became interested in creating a program that would help drug and diagnostic development in academia. It was clear to me that there were many clinically valuable discoveries at Stanford's OTL that were not licensed. These inventions may be considered less attractive for many reasons including: (1) lack of proof-of-concept data in animals; (2) poorly characterized new chemical entity or drug that the industry has no or little experience with (e.g., our peptide inhibitors); (3) addresses a clinical indication that is known to be difficult (e.g., expensive clinical trials, like Alzheimer's disease and/or indications where pharma had prior failures, such as stroke); or (4) a therapeutic target (e.g., a particular receptor) without a drug that modifies its activity. Even something as promising as an entirely new therapeutic platform is now considered unattractive (although these were preferred in the 1990s) because of the long development time.

In other words, academic inventions are generally deemed to be premature and therefore too risky for pharma and/or investors. I believe that academic institutions must develop these discoveries further within academia if they are to attract commercial interest. We can also advance some of our discoveries directly to the

clinic without commercial support, particularly when developing diagnostics or "repurposed" drugs. It is our social responsibility to step into this gap so that our discoveries will benefit patients.

1.1.2 What is SPARK?

SPARK is a hands-on training program in translational research that I founded in 2006 and now co-direct with Dr. Kevin Grimes. Each cycle of training lasts 2 years and we are now in our seventh cycle.

SPARK's mission is to accelerate the transition of basic discoveries in biomedical science to FDA-approved drugs and diagnostics. SPARK provides training opportunities in translational research to faculty members, postdoctoral fellows and students. Our goals are to move five to ten new discoveries each year from the lab to the clinic and/or to commercial drug and diagnostic development.

Each autumn, we select approximately 15 new projects to participate in SPARK. We first assemble a selection committee of representatives from Stanford and the local biotechnology community. OTL provides us with disclosures of unlicensed discoveries from the prior year that may be developed into drugs, biologics, or diagnostics. We also solicit proposals from across the university. SPARK selection criteria are quite simple:

1. The invention addresses an important unmet clinical need
2. The approach is novel
3. Two years of SPARK support will increase the likelihood that the invention will enter clinical trials and/or be licensed

Finalists are invited to compete for funding from the program. (Although access to the funding is limited to ~15 new projects each year, any university member can attend the meetings and obtain advice.) When preparing their presentation, the inventors follow a SPARK template that requires information beyond the background science. After presenting a scientific introduction, presenters focus on the clinical benefits and basic requirements of their product (Target Product Profile, discussed in Sect. 1.4) and propose a development plan with specific funding requests and milestones. In other words, the inventor is asked to plan from the product back to the experiments that will generate it. We encourage this project management mindset—a thinking process that is more prevalent among industry scientists than academic researchers—because novel discoveries can only advance towards a clinical therapeutic by following a disciplined path of applied science during development.

Importantly, unlike regular seed grants that go directly to the lab's account, SPARK funding (averaging ~$50,000/year for 2 years) is managed centrally and is paid only for pre-agreed upon milestones; money that has not been used in time reverts to the general fund pool and may end up supporting another SPARK project.

Experts from local biotechnology and pharmaceutical companies join our inventors each Wednesday evening. The success of SPARK is dependent on these experts

who volunteer their time and who agree not only to complete confidentiality, but also to assign any inventions resulting from their advising activity at SPARK to our university.

1.1.3 I Love Wednesdays

This is a comment that we often hear as people are reluctantly leaving the room at the end of our SPARK sessions. Between 80 and 100 people join us every Wednesday night throughout the year in a room that is bustling with energy and excitement. During the two hour meeting, SPARK inventors (aka SPARKees) either present progress reports on their project or listen to an interactive lecture by an industry expert on a topic related to drug or diagnostics discovery and development. (The book that you are holding introduces briefly the topics of these lectures.) Each inventor presents a progress report every 3 months or so, and the amount of progress often surprises even the most experienced SPARK advisors. The benefit of the meetings comes from the strong commitment of the advisors to share their knowledge and experience in real-time. This feedback is invaluable in helping the SPARKees to overcome challenges and find a path forward to achieving their goals.

1.1.4 SPARK Track Record of Success

SPARK is in its 7th year of existence. The educational value of the program is substantial for graduate students, postdoctoral fellows and faculty. The experience is particularly helpful for trainees who are seeking positions in industry. However, a more quantitative measure of SPARK's success can be assessed by four parameters:

1. Licensing of projects (to a funded company)
2. Entry into clinical trials
3. Publications
4. Research funding awarded to SPARKees that they attributed to the work they carried out in SPARK

As of summer 2013, a total of 32 projects have completed their participation in SPARK. Of these, 19 were either licensed and/or moved into the clinic; a *success rate exceeding* 50%! We also collected information on grants enabled by SPARK participation. To our surprise, based on participants' reports, the return was about $5 for every $1 invested by the school. Although SPARK is a relatively young program, we are on track to maintain a similar success rate in the future. As SPARK establishes a history of valuable projects, we are seeing more industry interest in collaborating or licensing—even for our early discovery-stage projects.

Box 1.3: Recommendation

Translational research is complementary to basic research, but should not be conducted at the expense of basic research. Medical schools will weaken themselves if the pendulum swings too far in favor of translational research. *–DM-R*

What is lacking in this analysis is the economic impact of new product sales on the academic institution. This is not an accidental omission; the impact can be measured only many years later. It takes 10–15 years for commercialization of a new drug. If academic institutions invest in translational research hoping for revenues, there is a risk that their programs will become risk-averse, focusing on low-hanging fruit with limited impact on patient care, or on indications that have large markets (e.g., another anti-erectile dysfunction drug) rather than a true novel therapeutic for an unmet clinical need. If SPARK is rewarded for innovation, for getting programs to the clinic regardless of the commercial value, and for impact on the drug and diagnostic development process in general, we may be able together to have a true impact on patients' health and health care costs.

1.1.5 Should Academia be Engaged in Advancing Early Inventions?

You might believe the answer is obvious. However, during my many years of discussions with colleagues, I have learned that perhaps not all arguments in favor of translational research efforts in academia are apparent. Here are some that I find compelling.

- It is our social responsibility: Most of our research is supported by public funds and therefore we should make an effort, if our work can be translated to novel therapeutics or diagnostics, to make it attractive and useful for development by industry.
- It fits our education mission: The majority of our graduates who do not land academic positions are likely to work in industry. It is therefore an opportunity to educate them on the development process and through them, educate the industry on what academia's contribution can be.
- It is pure fun: Academicians often hold the opinion that industry's work is applied science, and therefore less intellectually demanding or gratifying. My 1 year in industry and the years that followed taught me that this is an incorrect notion. The work of drug and diagnostic development is intellectually challenging and a really exciting and worthwhile activity.
- It is an opportunity: The success rate of drug discovery and development is still dismal and the consequences of failures greatly impact our health care costs. There is a special role and advantage for academicians in improving public health through drug and diagnostic development. First is the cultural difference

between industry and academia. While industry by nature is risk averse, academia gives higher rewards to risk takers—innovation and impact on the field are key components in faculty promotion and awards. In addition, academics are not burdened by knowledge of what can fail and has failed in industry; there is little published work on the topic, so we are free to apply new ideas to old problems. Further, academia can rely on the enthusiasm and brilliance of our students who are the major engines of our research and innovation. Finally, there is a disincentive in industry to share information. On the other hand, in academia, all that we learn is passed on through teaching and publications and thus can positively impact industry, which can translate into better health and lower health care costs.

Box 1.4: What Surprised an Academician?

Good science is important for raising funds from venture capitalists. But equally important are a clear and logical plan to develop a product, a strong team to run the company, and a positive attitude. We can't allow our egos to stand in the way. Rejection rates in drug development for funding or licensing are even higher than those for paper submissions or grant applications. *–DM-R*

Without a doubt, basic research is essential for our mission and should remain the main focus of academic research. However, I strongly believe that it is our responsibility as academic institutions to contribute to the development of leads for drugs and diagnostics to benefit society.

Box 1.5: The Bottom Line

SPARK's mission is to accelerate the transition of basic discoveries in biomedical science to FDA approved drugs and diagnostics.

1.2 Overview of Drug Discovery and Development

Kevin Grimes

Drug discovery and development is not for the faint of heart. The bar is indeed high for a new molecule to receive regulatory approval for widespread clinical use—and appropriately so. As patients, we want our drugs to be both safe and effective. The failure rate in drug development is quite high. Only 20% of drugs entering clinical study receive regulatory approval and the failure rate is even higher during the preclinical phase of development. Given the complex array of drug-like behaviors that the new molecule must exhibit and the large number of interdependent tasks that must be successfully accomplished during development, this high rate of attrition is not unexpected.

The development cost for each successful drug is staggering, ranging from several hundred million to several billion dollars. The latter figure typically includes the cost of failed programs and the cost of capital. While an exceptionally well-executed program may be completed within 7 years, the norm is closer to 12 years and often much longer. Since patent protection for a new compound is granted for 20 years, the period of exclusive marketing after regulatory approval is typically in the range of 7–8 years, leaving a relatively short time for recovery of costs and generation of profit.

1.2.1 The Shifting Landscape

We are currently in a time of transition in the biopharmaceutical sector. The number of pharmaceutical companies has contracted through mergers and acquisitions as larger companies seek to fill their pipelines. Many profitable drugs are facing their "patent cliff." The "blockbuster" business model, which favored development of drugs for very large markets (statins, antihypertensives, drugs for type 2 diabetes, etc.), is falling into disfavor as advances in "omics" allow for more tailored patient therapies. The previously ignored orphan diseases (<200,000 patients in the USA) recently became more attractive for several reasons: (1) regulatory incentives effectively guarantee a period of marketing exclusivity, (2) clinical development costs can be substantially lower, and (3) "designer drugs" can command a premium in pricing.

Biopharmaceutical companies have drastically cut their basic research staffs because of pressures to decrease costs in order to improve profits. The number of biotechnology venture funds is contracting, especially those that will invest in new biopharmaceutical start-up companies. As a result, we can expect that fewer novel drug programs will originate in the biopharmaceutical sector.

Academics are well positioned to step into the breach, especially if there is institutional support for translational activities. This support can come through funding, the creation of core service centers (e.g., high throughput screening centers, medicinal chemistry units, animal imaging centers, phase 1 units, etc.), and a culture that values bringing new treatments to patients. By advancing our promising basic research discoveries towards novel therapies for unmet clinical needs, we academics will maintain our social contract with our fellow citizens who pay for our research and hope for better health in return. In addition, we will contribute to our economy when successful academic programs enter the commercial sector as either start-up companies or new programs in existing biopharmaceutical companies.

1.2.2 The Critical Path

In order to obtain market approval for a new drug, a number of complex steps must be successfully navigated (Fig. 1.1). While many of the steps must be accomplished sequentially (e.g., demonstration of safety in animals before study in humans), drug

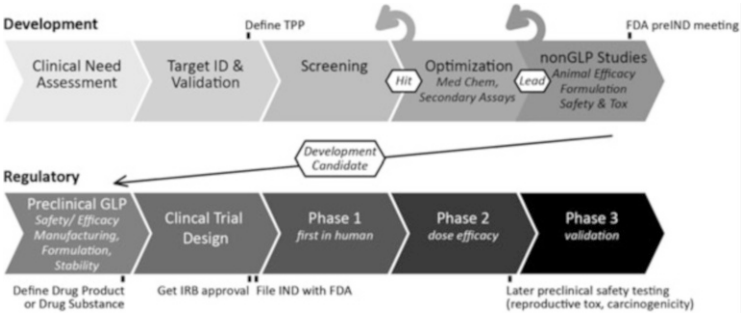

Fig. 1.1 General drug development pipeline. *TPP* Target Product Profile, *Med Chem* Medicinal Chemistry, *GLP* Good Laboratory Practice, *Tox* Toxicology, *FDA* Food and Drug Administration, *IND* Investigational New Drug application, *IRB* Institutional Review Board

development is very much an iterative process where a given step may be informed by or contingent upon many others. The following paragraphs provide an introduction to some of the critical steps in the development process. The timing of the handoff from academia to industry depends upon several factors, including cost of development and commercial attractiveness. For example, a repurposed drug may be fully developed within academia, whereas a more costly monoclonal antibody program may necessitate an earlier handoff in order to advance.

Box 1.6: Key Terms and Abbreviations

mAb: Monoclonal antibody
HTS: High-Throughput Screening
Hit: Molecules that display the desired activity in an assay
Lead: Most promising early-stage molecule(s) identified through *in vitro* and *in vivo* testing
Development candidate: Molecule selected for clinical development after meeting criteria established in the TPP for efficacy, pharmacokinetics, and safety
TPP: Target Product Profile; a document outlining desired characteristics of the final drug product
SAR: Structure–Activity Relationship
ADME: Absorption, Distribution, Metabolism, and Elimination; pharmacokinetic parameters
API: Active Pharmaceutical Ingredient
Drug Product: API and inactive components such as binders, capsule, etc. that compose the final drug formulation
Excipient: Inactive material added to the formulation to control drug dissolution, absorption, stability, etc.

(continued)

Box 1.6 (continued)

IND: Investigational New Drug application; document filed with the FDA prior to initiating research on human subjects using any drug that has not been previously approved for the proposed clinical indication, dosing regimen, or patient population
GLP: Good Laboratory Practice; extensive documentation of each procedural step to ensure high quality, reproducible studies
CRO: Contract Research Organization
FDA: US Food and Drug Administration
GMP: Good Manufacturing Practice; exacting procedures and documentation of quality assurance carried out at a certified facility (sometimes referred to as "cGMP" for "current" practice)
CMC: Chemistry, Manufacturing, and Controls
NDA: New Drug Application; FDA paperwork to obtain approval for the sales and marketing of a new drug in the USA
BLA: Biologics License Application; FDA paperwork to obtain approval for the sales and marketing of a new biologic in the USA

1.2.2.1 Identifying the Opportunity/Target

Academics have discovered promising new drugs through a variety of approaches. Serendipity has played a role, as when Alexander Fleming combined critical observation with scientific acumen to discover penicillin. Unexpected side effects in early clinical studies have also been used to therapeutic advantage. This is how the anti-angina/antihypertensive drug sildenafil was repurposed as the first drug in the lucrative erectile dysfunction market. More typically, however, academic drug discovery is biology-driven—the result of hard work at the research bench. Novel associations are uncovered between specific proteins (or protein mutations) or pathways and one or more underlying diseases. The causality must then be proven through target validation studies using gene knockout/knock-in models, siRNA gene silencing, or tool molecules that modulate the activity of the protein of interest.

1.2.2.2 Selecting the Therapeutic Approach

Once confidence in your target is established, it is time to consider the therapeutic approach. Most often, intracellular targets will require a small molecule approach, whereas cell surface targets (e.g., CD20) and circulating bioactive molecules (e.g., tumor necrosis factor) may be amenable to monoclonal antibody (mAb) approaches as well. Some advantages to mAb therapeutics include the more predictable safety profile, less frequent dosing, and premium pricing. Disadvantages include the need

for parenteral (intravenous) dosing and the higher early development costs, a major drawback for academic researchers. Some diseases are best addressed by replacing deficient hormones (e.g., thyroxin for hypothyroidism) or bioactive proteins (e.g., glucocerebrosidase in Gaucher's disease or erythropoietin for anemia associated with kidney failure).

1.2.2.3 Assessing Clinical Need

Before embarking on an expensive and time-consuming development plan, it is important to ensure the therapy will provide a clinical benefit. Take an unbiased look at clinical need, the suitability of the approach, and the feasibility of clinical development. This is best accomplished by a comprehensive review of the relevant literature and by extensive discussions with clinical experts and disease advocacy groups. The goal is to develop an outline of the clinical development plan, including route of administration, dosing regimen, efficacy endpoints, and duration of the trials. Obtaining help from a clinical trial design expert and a regulatory consultant can ensure that the team is on the right path.

Once you have determined your clinical indication and therapeutic approach, it is imperative that your team establish a Target Product Profile (TPP). This critical document defines the essential characteristics of the final drug product and will serve as an important guide throughout the development process.

Box 1.7: What Surprised an Academician?

We—as academics—are often under the impression that drug development, unlike our own basic research, is a rather mundane and straightforward process. In fact, those of us who have spent time in the biopharmaceutical industry have found that drug discovery and development lies at the intersection of basic research and applied science and requires a great deal of creativity and rigor. Exceptional scientists populate both the biopharmaceutical industry and the regulatory agencies. Drug development can be every bit as challenging and require even more persistence than traditional academic research. *–DM-R*

1.2.2.4 Determining the Preclinical Animal Model

Unfortunately, rodents are much easier to cure than humans. A critical step in predicting the efficacy of the drug under development will be to select an appropriate animal model for the clinical indication. While animal models are only imperfect approximations of the clinical disease, some models are more analogous than others. We might recognize that the administration of a neurotoxin to produce acute Parkinsonism in rodents has little similarity to chronic Parkinson disease, which progresses over many years in patients. But we currently do not have better

models. We might predict that occlusion of the middle cerebral artery in a rat would closely approximate a stroke in humans caused by acute occlusion of the same vessel. But multiple new drugs that showed efficacy in rodent stroke models failed to show benefit in humans.

There are many reasons for this lack of predictive value. In preclinical *in vivo* studies, the strains are typically inbred. The study animals are relatively young and frequently of one sex. They are fed the same food and follow the same sleep-wake cycles. Human subjects have diverse genetic backgrounds, and come from a wider range of ages (often older) of both genders. Furthermore, human patients eat a varied diet, follow varied lifestyles, and may be taking a number of concomitant medications that could interfere with the new drug's absorption, metabolism, mechanism of action, or apparent treatment effect.

1.2.2.5 Defining the Drug Candidate

In the case of small molecules, this typically requires designing a chemical or cell-based assay to identify activators or inhibitors of a target, and then optimizing the assay for use in a high throughput screening (HTS) facility. Most HTS centers have libraries containing between 10^5 and 10^6 compounds. Generally, a successful HTS will identify a few families of related molecules that have activity against the target of interest at low micromolar concentrations. An experienced medicinal chemist can help exclude certain *hits* as false positives that either interfere with the reporter in the assay or exhibit exceptional promiscuity in targets. Those compounds that appear to be true hits can then be validated in a secondary screen. The most promising of these will become the *lead* molecule.

Once the team is satisfied that the lead compound truly modulates the target, a medicinal chemist can suggest chemical modifications to help optimize the desired molecular features, including potency (ideally activity in low nanomolar concentrations), selectivity for the desired target, solubility, bioavailability, duration of action, protein binding, plasma half life, etc. This SAR analysis is an iterative process involving new chemical modifications and biologic testing to identify the most promising compound. The goal is to identify a drug that meets acceptable standards for efficacy, toxicology, pharmacokinetics/ADME (absorption, distribution, metabolism, and excretion); as well as a wide therapeutic window (ratio of toxic dose/minimally efficacious dose). This process should culminate in designating a *development candidate*, or active pharmaceutical ingredient (API) that meets pre-defined advancement criteria in the TPP.

The final *drug product* will include not only the API but also excipients to help maintain stability (shelf life), control dissolution rate, and otherwise optimize performance of the drug. Certain salts of the API may provide better solubility characteristics than others. Once the optimized formulation that we intend to bring forward into clinical studies has been identified, we can proceed with the more expensive IND-enabling preclinical studies.

1.2.2.6 IND-Enabling Preclinical Studies

Once the drug product has been finalized, it is time to begin to design and execute a series of rigorous preclinical studies that will characterize the safety, pharmacokinetics, ADME, and interactions with drugs that will be given concurrently in the clinic. These studies must be carried out under Good Laboratory Practice (GLP) and are typically conducted at a GLP contract research organization (CRO). GLP entails a good deal of quality control and documentation to ensure that the studies are carried out in exactly the manner as stated. The FDA provides guidance documents on its Web site regarding these studies, which must be completed before filing an Investigational New Drug application (IND) in order to begin a human clinical study. Because of the scope of work and documentation required, IND-enabling studies may cost in excess of 1 million dollars.

Prior to embarking on these expensive studies, it is prudent to arrange for a pre-IND meeting with the FDA. The goal is to obtain general concurrence on the development plan and to ask specific questions regarding the drug product, proposed clinical studies, and preclinical development plan. Since the animal toxicology studies must predict safety for the human studies, they must be similar in route of administration, dosing regimen, and duration. Therefore, seek some assurance that the proposed series of preclinical studies will be acceptable to the FDA.

During GLP toxicology studies, animals must be dosed for at least as long as the intended clinical studies, so the animal studies can only be designed after formalizing the clinical study design. The drug product used in preclinical studies must also be prepared according to GLP standards. Ideally, this GLP drug should be less pure than the clinical grade drug product that will eventually be dosed in patients. If the contrary were true, then animal toxicology studies would not adequately reflect safety for patients, because the increased impurities in the clinical drug will not have been tested in animals.

More expensive GLP reproductive toxicology, carcinogenicity, and long-term stability studies can often be deferred until before initiation of phase 3 clinical studies.

1.2.2.7 Obtaining GMP Drug Product

Drug product that will be used in the clinic must be manufactured and quality tested according to Good Manufacturing Practice (GMP). GMP manufacturing requires exacting procedures and documentation and must be carried out at an experienced and certified facility. In addition to the manufacturing procedures, strict quality testing is performed at set intervals (e.g., every 3 months) under a variety of conditions to ensure that the drug is of highest quality. The drug product is tested to ensure that the API has not degraded and that new impurities have not appeared. Parenteral formulations are also tested for sterility and for the presence of endotoxins. The GMP manufacturing process and quality testing are resource intensive and quite expensive, so it makes sense to obtain several quotes and enlist a

Chemistry, Manufacturing, and Controls (CMC) expert to evaluate the facilities under consideration. The FDA will often audit GMP facilities to ensure compliance.

1.2.2.8 Filing the IND

The IND contains three major sections. The clinical section contains the clinical protocol for the phase 1 clinical trial as well as the investigator's brochure, which describes the drug in detail and reports possible safety issues based upon the preclinical animal safety studies. The preclinical section reports the results of the GLP studies and any additional information that may be relevant to safety. The CMC section contains information regarding the API, formulation, manufacturing process, and quality control studies. Once the IND has been submitted, the FDA has 30 days to respond with concerns, or clinical studies in humans may commence.

1.2.2.9 Clinical Development

Phase 1 studies are *first in human* studies primarily conducted to characterize the pharmacokinetics and determine the safety in people. Most often, phase 1 studies are conducted in healthy volunteers. Occasionally, they are carried out in patients who stand to possibly benefit if the drug carries significant risk of adverse effects (e.g., neutropenia) or must be administered in an invasive manner (e.g., intracoronary or intraventricular). For example, cancer patients are often the subjects of phase 1 studies of chemotherapeutic agents since these drugs typically produce serious side effects.

Phase 2 studies are performed to explore the effective dose range or dosing regimen and to demonstrate efficacy. Often, the primary endpoint in phase 2 proof-of-concept studies is a surrogate biomarker associated with disease progression rather than a clinical endpoint, since the latter would require a much larger study to reach statistical significance. For example, when studying a new drug for chronic heart failure, the study might be powered to demonstrate a difference in ejection fraction on serial echocardiograms rather than a change in the composite of hospitalizations and death. Once adequate efficacy is demonstrated for surrogate endpoints and the best dose(s) determined, the drug is ready for the pivotal phase 3 studies.

Phase 3 studies are larger studies that are powered to clinical endpoints that are acceptable to the FDA. Typically two separate studies with an efficacy p-value of <0.05 are required for final drug registration. If the drug addresses a serious unmet need, the FDA might allow a single study with a lower p-value (e.g., <0.01). Assuming phase 3 studies demonstrate both safety and efficacy, it is now time to compile the data into a New Drug Application (NDA) or Therapeutic Biologic Application (BLA) and submit to the FDA. Review of this final submission may take up to 18 months. If the project has Fast Track designation for a drug that addresses a serious unmet need, the review may be completed in 10 months. The FDA may request that an Advisory Committee comprised of external experts make

a recommendation regarding final market approval, although the FDA may concur or disagree with the Advisory Committee's recommendation. Once an approval is granted, we are free to market our drug in compliance with FDA regulations.

Box 1.8: The Bottom Line

Drug discovery and development is a complex process involving many interdependent disciplines. Success requires creativity, persistence, some degree of luck, and a willingness to enlist the aid of experts in various fields.

1.3 Assessing Clinical Need

Kevin Grimes

As academic drug developers, we hope to translate our ideas into effective new therapies that will save lives, improve health and quality of life, and/or lower the costs of health care. We arrive at our therapeutic approaches in different ways. We may be basic research scientists who have discovered a promising new cellular target or pathway that plays a critical role in one or more serious diseases of which we have only a superficial clinical knowledge. Or we may be physician scientists or basic researchers who have dedicated our career to finding a cure for a specific disease with which we are intimately familiar. In either case, we need to call upon the collective wisdom of our peers, disease experts, and experts in drug development to ensure that our therapeutic approach will address the unmet needs of the patients in an optimal manner; and the unmet needs are great.

Despite impressive advances in drug therapy over the past 50 years, tremendous numbers of patients are in desperate need of effective new therapies for a wide variety of medical conditions. The list of diseases with inadequate or no treatments is daunting. Consider the following examples: pediatric diseases such as sickle cell disease, inborn errors of metabolism, bullous skin diseases, and autism spectrum disorders; obstetric disorders including premature birth and preeclampsia; global health challenges such as multi-drug resistant tuberculosis, chronic Chagas' disease, and newly emerging viral diseases; autoimmune conditions including progressive systemic sclerosis (scleroderma), systemic lupus erythematosis, and multiple sclerosis; neurodegenerative conditions such as amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease; and a wide variety of intractable malignancies. These examples are just the tip of the iceberg.

1.3.1 Starting with the End in Mind

Before we embark on a lengthy and costly campaign to develop a new drug, it is imperative that we understand why patients and providers will use our proposed product. What clinical problem are we solving? What specific unmet medical need

will our product address? How will patients or the health care system be better off once our new drug is available? Are there known or predictable risks involved with modulating our drug's molecular target, and if so, is the risk-to-benefit ratio acceptable to our intended patient population? Will our drug delivery and dosing approach be acceptable to patients and providers? Will payers (insurers, health plans, Medicare, Medicaid) agree to pay for our new therapy?

1.3.2 Understanding Clinical Need

The first step is to understand the unmet clinical need. There are numerous reasons why a new therapeutic might be needed for a given condition. The following categories provide a framework for analyzing the necessity for a new drug for a clinical indication.

1.3.2.1 No Therapies Currently Available

Clinical need is most apparent when there are no effective treatments for a serious disease. Amyotrophic lateral sclerosis and advanced pancreatic adenocarcinoma are clear examples where current drug therapy has little to offer except palliation.

1.3.2.2 Need to Reverse or Arrest the Disease Process

For other serious diseases, we have therapies that reduce symptoms temporarily and even prolong life, but do not arrest disease progression. For example, current drugs for Parkinson's disease improve neurologic symptoms and improve quality of life, but do not prevent the relentless downhill course of the disease. Similarly, current therapies for idiopathic pulmonary artery hypertension are vasodilators that do not arrest progression of the underlying pathology. Although therapies are available for such diseases, there is a tremendous need for novel drugs that will modify the progression of the disease.

1.3.2.3 Severe/Unacceptable Side Effects

For many other diseases, current treatments may be effective, but cause serious or unwanted side effects. A few illustrative examples follow: (1) Hodgkin lymphoma was once a fatal disease, but can now be cured in the majority of cases using a combination of chemotherapy and radiation therapy. Despite this success, patients frequently develop delayed, but life-threatening cardiac toxicity from doxorubicin, one of the first-line chemotherapy drugs. (2) Corticosteroids can be life-saving treatments for a wide variety of autoimmune, allergic, or inflammatory diseases.

Yet they cause a litany of very harmful side effects. (3) The calcineurin inhibitors cyclosporine and tacrolimus, important components of immunosuppressive regimens following organ transplantation, can cause nephrotoxicity. Unfortunately, these drugs often damage the transplanted kidneys that they are protecting from the host immune system.

Many other very commonly prescribed medications cause unwanted side effects that affect the patient's health, quality of life, and even willingness to adhere to the drug regimen. Selective serotonin reuptake inhibitor (SSRI) and serotonin–-norepinephrine reuptake inhibitor (SNRI) antidepressants commonly cause sedation, weight gain or loss, and sexual dysfunction. Metoclopramide, the most commonly prescribed drug for diabetic gastroparesis (delayed gastric emptying), can cause extrapyramidal movement disorders including irreversible tardive dyskinesia. Clearly, patients would benefit tremendously from effective drugs that lack such undesirable side effects.

1.3.2.4 Patient Preference/Convenience/Cost

In general, oral drugs that require less frequent dosing are preferable and improve patient adherence. Physicians rarely prescribe oral erythromycin (dosed four times daily for 7–10 days) since the FDA-approved azithromycin (dosed once daily for 5 days). Some drugs must be administered intravenously at an infusion center, which is both inconvenient and costly. Alternative treatments that a patient can dose at home would be preferable.

Many new therapies, especially biological drugs, are prohibitively expensive. Less costly drugs would be a terrific boon to patients, insurers, and the health care system. New platforms for biological drug discovery, development, and manufacturing might increase the success, shorten the time lines, and lower the costs of new therapies.

1.3.3 Suitability of Approach

After studying the unmet clinical need, our second step is to determine whether our planned therapeutic approach will provide an acceptable solution. For example, a peptide therapeutic that is injected subcutaneously twice a day might be readily acceptable for treating cancer, but is a non-starter for male pattern baldness. Speaking with physician experts, patient advocacy groups, patients, and eventually the FDA (and other regulatory agencies) will help us identify the acceptable and ideal drug characteristics.

Box 1.9: What Surprised an Academician?

When we proposed developing a new treatment for the prevention of radiation dermatitis (the skin burn that occurs as a result of radiation therapy for malignant tumors), we were surprised when a potential investor insisted that there was no unmet clinical need in this indication. His dermatology expert reported that he never saw patients with this problem. But since dermatologists do not have any effective treatments, the radiologists no longer make referrals and instead prescribe emollients to try to alleviate this very debilitating condition. In fact, there is significant unmet need; the burns of radiation dermatitis cause substantial suffering and frequently require that further radiation be withheld. Our lesson: Cast a wide net—make sure you are speaking with the right experts, and with patients too. *–DM-R*

In the case of a serious or life-threatening disease that currently lacks an effective treatment, there will be a higher tolerance for side effects, patient inconvenience, and associated costs. Let us suppose our new drug is expected to arrest or reverse the progression of Huntington's disease. Patients would very likely be willing to accept an increased risk of serious side effects such as cardiac arrhythmias. They would probably also be willing to use the drug even if it required subcutaneous, intravenous, or even intrathecal administration in the doctor's office. And certainly, a drug that prevented the death and disability of Huntington's disease could command premium pricing.

Now let us suppose we are developing a novel therapeutic for a less serious condition—a new drug that prevents cataract formation. Since cataract surgery is effective, safe, and quite inexpensive, our new drug must have minimal side effects, convenient oral or topical dosing, and low cost if we expect patients, providers, and payers to support its use. We should also recognize that ophthalmologists might be less likely to champion our drug since it will severely undercut the number of surgeries they perform.

1.3.4 Feasibility of Development

Our next step is to determine whether it is feasible to develop our new drug. Is there a straightforward clinical development path? What is our target subject (patient) population? What are the primary and secondary endpoint(s)? How long must we follow the subjects to show efficacy for this endpoint? Are there predictive surrogate endpoints that we can follow? How large is our anticipated effect size? How many subjects must be enrolled? Can we afford to conduct this trial? To answer

these questions, we should start with a comprehensive review of the medical literature regarding clinical trials in our indication. We should then speak with physician experts in our chosen disease as well as clinical trial design experts and biostatisticians.

Lastly, we should try to understand the competition in our therapeutic area. What new therapies are in the development pipeline for our chosen indication? What are their mechanisms of action? Do they target the same patient population? If a pharmaceutical company has a 2 year head start using our same approach, perhaps we should move on to another clinical indication or another research project. We can explore the competition by doing the following:

1. Search the clinicaltrials.gov Web site for ongoing clinical trials in our clinical indication.
2. Search the pharmaceutical industry trade journals for novel drugs in our therapeutic area—these periodicals may be readily available through your university's business school library.
3. Search the internet for similar activity.
4. Speak with health care investors and other members of the biotechnology/pharmaceutical community to obtain non-confidential information about potential competitors.

On occasion, we may find that it is feasible to develop our drug for a number of clinical indications. In this case, we should not necessarily pursue the indication with the largest market size. Rather, we should determine which clinical development path has the surest and fastest route to regulatory approval. Once our drug is on the market, we can expand to other indications as part of the "life-cycle management" of the drug.

Box 1.10: The Bottom Line

Abraham Lincoln, arguably the greatest leader in the history of the United States, once said, "If I had eight hours to chop down a tree, I'd spend six sharpening my axe." Before spending our valuable time and resources executing a new drug development project, we must be certain that:

1. We are advancing an optimized product that addresses the needs of patients
2. We have a clear path forward
3. Our approach will still be valued by patients, physicians, and payers when it is finally ready for clinical adoption

1.4 Target Product Profile (TPP)

Robert Lum

A Target Product Profile, or TPP, is a list of attributes and minimum acceptable criteria that a project team should strive to meet when developing a new drug. The TPP provides a general set of goals for the project, but the more specific it can be made, the more useful it becomes. TPPs can and should be refined over time as new information becomes available, thus allowing the profile to be used as a guidance document, driving the research effort and keeping the team focused on the program's ultimate goals. The examples given below are not complete TPPs, but present relevant parts of a profile. Since each project is different, each TPP will have specific criteria that are tailored to each individual development program.

Box 1.11: Key Terms and Abbreviations

TPP: Target Product Profile; a document outlining desired characteristics of the final drug product
mAb: monoclonal antibody
PK/ADME: pharmacokinetics/absorption, distribution, metabolism, elimination; studies of how the body processes drugs
SI: sensitivity index
IC_{50}: drug concentration required to inhibit a process by half its full activity
ip: intraperitoneal (within the abdominal cavity)
po: oral administration
hERG: ion channel cell-based screen for cardiac toxicity
IP: intellectual property
PFS: progression free survival

TPPs are refined at various stages of the drug development process. At the onset of a project, the criteria can be general, and the TPP is used to guide the overall direction of the project and set "go/no go" decision points to continue project development. Defining a TPP also forces the team to think about attributes outside of their area of expertise. General characteristics of therapeutics include the clinical indication, route and frequency of administration, medical need, competition, current therapy, cost of intended therapy, stability, clinical development path, regulatory path, and IP position. This can be a daunting list of categories to consider, but it is important to remember that the team will refine broad characterizations into narrow specification windows as development progresses. SPARK uses a general template to get the process started (Table 1.1).

Table 1.1 SPARK target product profile template

Category	Final characteristics (ideal and acceptable ranges)
Product description	– Type of agent (small molecule, peptide, mAb) – Proposed target
Indication and usage	– Clinical Indication(s)—if more than one, specify intended lead indication – Intended patient population – Current available treatment options (including surgical, lifestyle, and homeopathic options)
Development candidate	– Target specificity – Efficacy (*in vitro*, cell-based, and *in vivo*)
Preclinical work	– Animal model(s) of disease – Safety/toxicity profiles
Clinical pharmacology	– Absorption, distribution, metabolism, excretion – Half-life in plasma or serum – Pharmacodynamics (extent of target inhibition or activation) – Protein binding, etc.
Dosage and administration	– Dosing amount, frequency, etc. – Route of Administration – Formulation (excipients) – Estimated shelf life, required storage conditions, etc.
Safety and toxicity in humans	– Known on-target or off-target predicted safety concerns – Therapeutic window
Regulatory considerations	– Presumed clinical path forward – Eligibility for Orphan drug status, Fast Track, Subpart H, etc. – Precedents set by previous trials in indication/patient population
Intellectual property	– Freedom to operate evaluation (competing patents, opportunities to write new patents) – Desired licensing outcome (license to company vs. start-up)
Financial considerations	– Cost of goods – Projected pricing and affordability compared to current options – Cost to develop – Estimated return on investment

Considering these attributes ahead of time allows the project team to map the path to meet the goals, determine additional expertise that may be needed, and prioritize what needs to get done in the context of the overall program. Example 1 provides a brief TPP that defines the general goals of a program.

Example 1: General TPP for Uncomplicated Falciparum Malaria

Adapted from Frearson et al. [1]:

1. Oral dosing (ideally once, but not more than 3 times per day)
2. Low cost of goods (~US $1 per full course of treatment)
3. Effective against drug resistant parasites (e.g., those that have developed resistance to chloroquine or sulfadoxine–pyrimethamine treatment)
4. Fast acting and curative within 3 days
5. Potential for combination with other agents

6. Pediatric formulation should be available
7. Stable under tropical conditions
8. IP: requires freedom to operate; composition of matter patent would be ideal

When developing a new chemical entity, the team uses the TPP to guide their efforts to optimize the characteristics of the lead molecule. The TPP document might include, for example, minimum acceptable criteria for the biochemical assays, cell-based assays, functional assays, selectively assays, solubility, size (molecular weight), chirality, toxicity profile, formulation, genotoxicity studies, safety pharmacology assays, maximum tolerated dose, efficacy in certain animal models, pharmacokinetic parameters, and intellectual property position. As the program matures, additional criteria may be added, such as pharmacokinetics/pharmacodynamics relationships, metabolic profile, frequency of dosing, number of animal models needed to be tested, and additional toxicity studies. The team has to define the desired parameters for each attribute. Once all of the criteria are met, a final set of compounds can be compared and the lead compound selected as a clinical development candidate. Example 2 provides a research-oriented TPP, with specific criteria for preclinical testing.

Box 1.12: What Surprised an Academician?

At first, we did not understand the value of establishing explicit criteria in a TPP. After all, we knew where we were going. Why waste time stating the obvious? But defining essential characteristics in a TPP has proven to be essential; it mapped our path, identified whom we needed to engage, and established optimal attributes for our product. *–DM-R*

Example 2: Hit-to-Lead TPP for Protozoa and Helminth Disease

Adapted from Nwaka et al. [2]:

1. *In vitro* activity in antiprotozoan screens:
   Plasmodium falciparum: IC_{50} <0.2 μg/mL
   Trypansoma cruzi: IC_{50} <1.0 μg/mL.
2. Antihelminthic screens:
   Schistosoma mansoni: 100% adult worm motility reduction, IC_{50} <2 μg/mL
   Onochocerca lienalis, *O. ochengi*, or *O. volvulus*: 100% inhibition of microfilarial motility at 1.25×10^{-5} M or 10 μg/mL.
3. Established selectivity for a molecular target or differential sensitivity between parasite and host enzymes should be > ten-fold.
4. Pre-toxicity screen in non-infected mice using up to 100 mg/kg ip or po.
5. *In vivo* activity in mouse or hamster models: significant reduction in parasitemia and/or increase in life span at 4×50 mg/kg either through ip or po route with no overt signs of toxicity.
6. Metabolic stability determined in microsomes in at least two species, including humans.

7. hERG binding >10 μM.
8. Low CYP450 inhibition profile.
9. IP: should be novel and be able to file for composition of matter patent.

During clinical development, the TPP should be modified to help define more clinically relevant attributes. This includes the primary indication, patient subtypes, dosing regimens, clinical pharmacokinetics, numbers of patients needed, clinical endpoints, cost of goods, and marketing or commercial strategy. The TPP can also define regulatory strategy, research into companion diagnostics, and alternate therapeutic indications or formulations. Example 3 provides a TPP for a compound in clinical development that may be used to guide the program team during the clinical development phase.

Example 3: Clinical Development TPP for a Clinical Stage Glioblastoma Cancer Drug

Adapted from unpublished program

1. Population: Seek approval alone or in combination with bevacizumab for the treatment of glioblastoma multiforme which has progressed after treatment with radiation plus temozolomide.
2. Efficacy: Median Progression Free Survival (PFS) >6.3 months compared with 4.2 months for bevacizumab alone; Median overall survival >9 months for combination.
3. Safety: Grade 3 or 4 neutropenia assumed in majority of patients; manageable with growth factor support. Neuropathy Grade 3 or 4 in <10% of patients. Other toxicities manageable, predictable, and reversible.
4. Dosing: 120 mg/m^2 IV once every 3 weeks until disease progression or 6 cycles.
5. IP: seek patent protection for novel combination therapy with bevacizumab.
6. Sustainable supply chain with cost of goods: <$50 per vial.

Box 1.13: The Bottom Line

The TPP should define the desired attributes of the novel therapeutic under development and should be edited and refined as the product moves further through the development pipeline. An effective TPP includes: clinical indication and medical need; route and frequency of administration; current and future competition; cost of intended therapy; intellectual property position; and all other advantages over current treatments. Other possible attributes include clinical development path; regulatory path; and metabolic and safety profiles.

1.5 Project Management and Project Planning

Rebecca Begley and Daria Mochly-Rosen

As academics, we take for granted that we know how to staff and manage our laboratories and/or clinics. Most members of our research teams are fairly junior and are trained in similar disciplines. The principal investigator is the leader and sets the research agenda. Progress is not usually tracked against a formal timeline and the research plan can rapidly change direction to pursue new and interesting observations. Little attention is given to actively managing the research enterprise per se.

But in industry, project management is a highly valued function that substantially increases the likelihood of a successful outcome and saves both time and money. Project teams bring together individuals with varying levels of seniority and widely divergent areas of expertise, such as pharmacology, toxicology, regulatory science, drug manufacturing, and clinical trial design (referred to as cross-functional teams). Team members are committed to advancing their project in a timely and collaborative manner. They are also encouraged to kill a project as soon as possible if the research indicates that the project is unlikely to succeed or will incur unacceptable costs or delays.

Box 1.14: Key Terms and Abbreviations

Gantt chart: development plan tracking tool listing critical tasks, timelines, and dependencies
Cross-functional team: project team comprised of individuals with expertise in different areas (e.g., pharmacology, ADME, manufacturing, regulatory science, clinical) required for successful completion of the project
TPP: Target Product Profile; a document outlining desired characteristics of the final drug product
CRO: Contract Research Organization
IND: Investigational New Drug application; document filed with the FDA prior to initiating research on human subjects using any drug that has not been previously approved for the proposed clinical indication, dosing regimen, or patient population

1.5.1 Project Leadership

Project management requires strong leadership, a committed team with the necessary complement of skills, and a well thought out development plan. The project team works together to identify the project's strategy (vision), goals (tactics), and a detailed plan of execution. The project leader then helps keep the team on task at the budget and timeline that were predetermined.

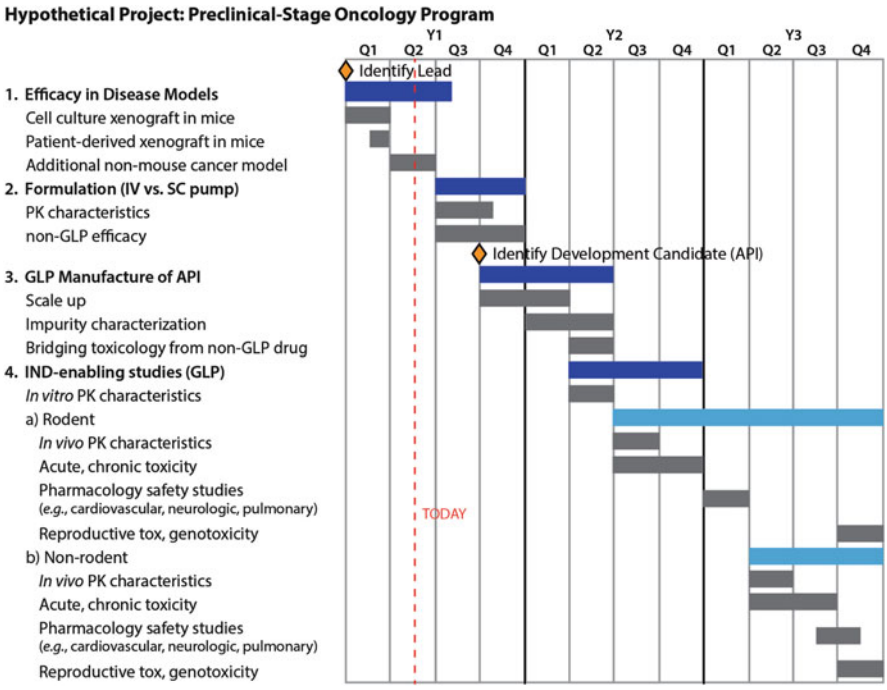

Fig. 1.2 Theoretical Gantt Chart for a preclinical-stage oncology program. This project Gantt Chart outlines possible tasks and predicted timelines for a hypothetical development program. *Q* Quarter, *Y* Year, *IV* intravenous, *SC* subcutaneous, *PK* pharmacokinetic, *GLP* Good Lab Practices, *API* Active Pharmaceutical Ingredient, *IND* Investigational New Drug application, *tox* toxicology

Importantly, many of the tasks carried out by the team members are highly interdependent. For example, drug supply for a clinical study cannot be manufactured until the appropriate clinical dosing regimen(s) is worked out. Clinical dosing for a first-in-human trial is furthermore highly dependent upon the toxicology, pharmacokinetics, and efficacy found in animal studies.

A Gantt chart is a very useful tool that provides a detailed road map for executing and tracking the development project. It includes a comprehensive listing of each task that must be accomplished during the project, along with its anticipated timeline and its dependencies upon other parts of the project (see Fig. 1.2). The project manager can use the Gantt chart to track the progress of each task as well as overall progress of the project against the desired timeline. Similarly, team members representing different functional areas can track their tasks and see how slippage in their timeline might affect the overall timeline. For example, a delay in delivery of acceptable quality drug product will delay the start of IND-enabling toxicology studies and, in turn, delay the filing of the IND. That may seem obvious, but if we are late we also risk losing our time slot at the contract research organization (CRO) conducting the toxicology studies, which would cost us money in penalty payments to the CRO and further delay development. The costs and consequences of small delays can quickly snowball in drug development.

The Gantt chart is not set in stone and should be revised by the project manager to reflect reality as new information becomes available. Although complications invariably arise during drug development, the Gantt chart is an extremely useful instrument to help the development team complete the project on a timeline that fits the company's goals.

1.5.2 Project Management for SPARK

We include a section on project management because academics engaged in translational research must take on this function to ensure timely and successful completion of their aims. The project leader may be the faculty member, but can also be a student or a fellow. The team may include expert advisors, other research laboratories at the institution or elsewhere, as well as commercial research services (e.g., medicinal chemistry or toxicology). The team members in this case are not bound in the same way that they are in our own lab or in a typical project team in a company. Further, it is unlikely that the project leader will be able to assemble all the function heads for a meeting; therefore, a lot of the project planning relies on coordination and individual conversations with each expert and function. When possible, it is advisable to share the plan details with all the members of the team to confirm assumptions and coordinate progression. The following section and suggested references provide some practical advice on leading cross-functional teams; not all of it may apply to academic work [3, 4].

1.5.3 Leading a Cross-Functional Team

How to lead when you are not the expert or the most senior person in the team:

- Influence without authority depends on relationships and shared vision. Build the relationships before you need them.
- Stay flexible; adjust to new data or change in circumstances.
- Know enough about each functional area's activities to converse intelligently. You should understand where the key issues may arise and why. Ask questions early; establish mentors/go-to people to gain basic understanding.
- Use the cross-functional team meetings as a forum for holding the entire team accountable to the project and each other.
- Use cross-functional team meetings also to identify and address issues that arise from within each function as well as from an interface with another function (e.g., as discussed above, a delay in drug supply could impact the timing of a toxicology study).

- One way to gain agreement on contentious issues can be through pre-meeting discussions with key stakeholders, allowing them time to work through issues and voice opinions in advance of meeting.
- Written documentation can be useful for management of a team. Writing down goals and targets provides a common point of reference for communication, both internally within the team, as well as to external audiences. In addition, gaining team agreement on a written document can encourage more attention to the wording (written agreements can carry more weight than spoken ones) and subsequently can facilitate a greater degree of group buy-in, if the group feels involved in the process.
- Tools for communication can include the target product profile, the team goals and the team timelines/budget. Document assumptions as these will likely evolve over time.

Box 1.15: What Surprised an Academician?

A Gantt chart is rarely used in academia to identify specific goals and track progress towards them. Who can plan basic research with such detail? When asked to participate in this planning, I felt that it was a waste of time. I quickly realized that such detailed planning is an effective tool to create priorities, to know when to "kill a project" (e.g., it will be completed too late to impact the company's future, or the technical setback is so substantial that it is too expensive to complete), how to keep the project moving on track, and how to take corrective actions when budgets and/or timelines change. *–DM-R*

1.5.4 Aspects of Project Planning

Step 1: Plan with the end in mind—define the vision of the project.

We need to define a target product profile (TPP) with the team. This defines how our product will look and behave and will also define why a physician or patient would use our new drug by highlighting where it addresses unmet need. The "must-have" characteristics outlined in the TPP define the threshold below which the project would not be carried forwards and the project should be "killed." Published clinical trial data and product labels are resources for comparative information on related products.

Step 2: Outline a clinical development plan.

We need to hold an open discussion with the functional area leads to lay out a development plan. This is important even for an early stage project; broad strokes descriptions will suffice for the later stage activities. The development plan outlines decision points in the overall project development and details the activities needed to get from the current state to the next decision making point. In addition, the key risks and assumptions for the project are summarized. This activity is usually structured by starting with the TPP and working backwards to the current stage of development.

We start by asking the clinical lead to propose a clinical program that could support the desired indication laid out in the TPP. We should begin with the phase 3 studies, then ask what the preceding phase 2 and phase 1 studies would have to look like to support dose selection and study design for the phase 3 described. These discussions should help define variables such as endpoints, duration of treatment, number of doses, size of study, etc. As these are likely to change as the program evolves, test the boundaries of the proposed numbers. For example, if the clinician recommends that we treat this patient population for 1 month to see a significant change in a particular endpoint, we should query how likely it is that we would end up treating for 2 months or if it would be feasible to treat for 2 weeks instead. The rest of the team (toxicology, manufacturing, pharmacology, etc.) should be asked to propose activities that would be needed from their areas to support the clinical program as it is described. These activities should answer "key questions" that exist for the project.

Step 3: Lay out the project plan with all details to facilitate decision-making.

We need to place activities from the conversation in step 2 into a timeline, and include budget information. Many variables were likely discussed; it is best to pick a set that makes sense. Document the assumptions used to pull together this particular plan and ensure all envisioned activities needed to support the project are included.

Step 4: Define the activities needed to reach the next decision making point and set the goals accordingly.

As we review the overall project plan, inclusive of all proposed activities, we can prioritize the activities and determine which will add the most value to the project upon completion. For example, writing a clinical study protocol may add some value to the project, but completing a phase 1 study and having the data in hand will add significantly more value to the project. Then, we can evaluate the activities that could be done against the available budget.

We need to decide which activities the team will support moving forward (with a focus on the must-haves as first priority). These activities will comprise the goals (defined as things that add value) of the team. This list of goals becomes the project plan. We should revisit the plan upon receipt of new data or a change in the project environment (e.g., approval of a new agent in the disease indication, etc.)

Box 1.16: The Bottom Line

The development plan is an essential map for the team, navigating us through the many interdependent processes of drug development and defining critical "go/no go" decision points to continue or terminate the project. The plan is a living document without which we could wander off task, waste precious resources, and create delays in reaching our goal—to benefit patients.

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