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PRINCIPLES OF CLINICAL CANCER RESEARCH

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Principles of Clinical Cancer Research

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*To Mom, who conceived me
To Dad, who catechized me
To Jean and Bus, who crafted me
To Jared, who sings to me
To Jaime, who inspires me
To my patients, who treat me
To Ryan, who keeps me in tempo
To Elliot, who enriches me
And above all to Gina, who makes me want to dance*

May this book accomplish one of the above for everyone else.—Loren K. Mell

The inspiration for this work was and is from my brave and gracious patients who elect to enroll on clinical trials and was only made possible by the immense support of my family (DJ, CDT, LTT, and QNT) and trainees (HW, AS, JD, KT, RM, and AM). Lastly, to my fearless and timeline-driven coeditor and friend who was the impetus for this project and for saving my father's life (LKM). Thank you.—Phuoc T. Tran

For Brenna.—James B. Yu

This book is dedicated to my family, especially my sons, H.G. Zhang (Columbia University) and his twin brothers R.G. Zhang and W.G. Zhang.—Qiang (Ed) Zhang

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Foreword

Drs. Mell, Tran, Yu, and Zhang have written a readable yet comprehensive textbook on various aspects of clinical cancer research. They cover valuable information relating to clinical research in cancer. Important aspects, such as basic science in the context of translational research, principles of molecular biology, cell cycle, metastasis, mechanisms of resistance, preclinical models, and prognostic and predictive biomarkers, are introduced in a comprehensive way. They then move on to describe population and outcomes research in the context of statistical modeling, cancer epidemiology with a focus on longitudinal and observational analysis, time-to-event models, and machine learning, followed by two important chapters on health disparities and cost-effectiveness analysis. Toward the end of the book they deal with clinical trials, including early and late phase trials, quality of life analysis, screening and prevention, imaging, adaptive trials, noninferiority trials, and finally meta-analysis. The conclusion of the book leads into “omics” research, an exciting area at the forefront of clinical cancer research.

It is unusual to find such diverse topics covered in depth for a book focused on clinical research. Usually wide searching is required to bring each of these important topics into a specific, concentrated research focus. Although this book is geared toward trainees and junior investigators, this senior investigator found the book highly informative, covering topics that were no longer familiar and I needed to reacquaint myself with. The general organization of the chapters proceeds from simplicity to complexity as appropriate to the topics under investigation. The wide range of topics covered under this book is extremely valuable, with comprehensive coverage of nearly all aspects of clinical cancer research.

I plan to keep this book handy as I assist junior faculty in designing and implementing clinical research, especially those with translational aspects. I particularly enjoyed the first chapter, which focuses on careers in clinical cancer research, elements of running a lab, writing protocols, and obtaining funding. Many diagrams throughout the book assist the reader in following the more complex concepts. I congratulate the authors on an outstanding book, with its unification of many diverse topics. I am sure it will find a place in many investigators' libraries.

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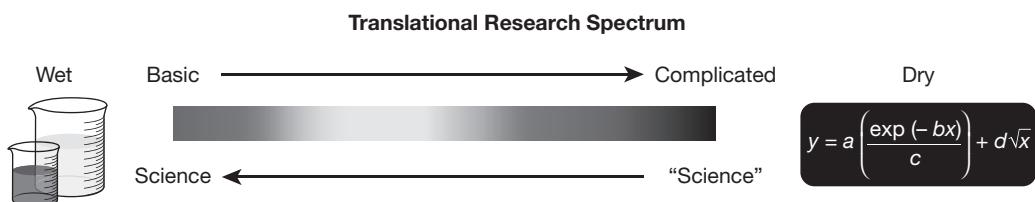
Preface

In the long run men hit only what they aim at. Therefore, though they should fail immediately, they had better aim at something high.

—Henry David Thoreau

Clinical cancer research is the scientific discipline concerned with advancing knowledge to benefit cancer patients. The field encompasses a broad spectrum of subdisciplines and methods, including wet and dry laboratory sciences, controlled and uncontrolled experiments, and retrospective and prospective study designs. The cohesive bond these subdisciplines share is their common quest. What makes “clinical cancer research” different from other kinds of research is the meaning we attach to its purpose—a quest that is not simply for our, or even knowledge’s, own sake, but for the sake of patients afflicted with the insidious assortment of diseases we collectively call cancer.

Stemming from this motivation, we proffer this book, which endeavors to address a gap in the existing tertiary literature. Although several textbooks about clinical research exist, few have specifically and simultaneously addressed the needs of both clinicians and physician-scientists in oncology. Other popular textbooks have predominantly focused on either a broad range of disciplines not specific to oncology, or on technical statistics of clinical research, or solely on issues related to cancer clinical trials. Clinical cancer research, however, involves much more than clinical trials, encompassing branches ranging from developmental or translational preclinical and retrospective modeling studies, to clinical trials, to population-based studies and meta-analyses designed to answer questions that clinical trials cannot. In that sense, it represents a set of interwoven and integrally dependent physical and humanitarian sciences, uniting to form the translational research spectrum¹:



¹ Readers can view the color version of this figure in the free ebook that accompanies the purchase of the print version of this book.

In this book, we provide a wider perspective on the clinical oncologic sciences. We have written this book primarily for trainees and junior faculty interested in careers in clinical and translational research. It has three principal aims. The first is to introduce readers to the fundamentals of clinical cancer research, including the basic methodologies used in our field, and, in doing so, arm them with the skills to recognize, produce, and disseminate quality clinical science in oncology. The second is to guide trainees who aspire to careers in this field, by offering a mix of practical advice and analytical tools, and references to resources that address areas falling outside the scope of our handbook. The third is to assist educators, by providing them with an organizational structure and a set of practical examples upon which they can build an effective curriculum. In short, this is a book by clinical scientists, for current and future clinical scientists. However, we also hope that general medical professionals will find this book helpful in navigating the vast and often bewildering nomenclature used in clinical cancer research, and that it will facilitate their application of evidence-based medicine, ultimately benefiting the patients they treat.

The translational research spectrum exists, representing the trade-off between idealized models with controlled experimental conditions and real-world implementation in patients, where ideals may fall short and pure experimentation becomes infeasible, with increasing reliance on mathematical representations of biologic processes. At its best, clinical cancer research marries the extremes of this spectrum to produce advances in knowledge that benefit patients.

Loren K. Mell, MD

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Principles of Clinical Cancer Research



9

Working With Industry

SWAN LIN ■ YAZDI K. PITHAVALA ■ SANDIP PRAVIN PATEL

Historically, academic researchers have been major drivers of basic science research in molecular pathways and targets and have contributed to a better understanding of cancer biology. Conversely, discovery efforts and testing of candidate compounds in preclinical and clinical studies have largely been carried out by pharmaceutical industry scientists. The intersection of academia and industry research generally occurred at the clinical development stage of phase 1 through phase 3 trials. Over the past few decades, innovations for molecularly targeted therapies and cancer immunotherapy driven by collaboration between researchers from public and private sectors have blurred the traditional roles of academia and industry. This chapter highlights examples of successful collaborative efforts, discusses the evolving roles of academia and industry in discovery and development particularly with translational research, and provides insight into the training programs for future collaborative opportunities in oncology research and drug development.

TRADITIONAL ROLES OF ACADEMIA AND INDUSTRY

The ultimate goal of cancer research is to find treatments and cures; however, the driving forces and approach by which academia and industry scientists conduct cancer research differ. Academic research seeks to gain an understanding of the basic science of the pathophysiological mechanisms that drive tumor growth through deductive experimentation. Research is generally motivated by intellectual curiosity and there is often more freedom for exploration of theoretical ideas without the constraints of strict timelines. Although there is often more flexibility in selecting the work, obtaining resources is usually a major hurdle in academia.

In contrast, industry scientists are able to efficiently and effectively move a drug candidate into clinic through conducting more structured and well-defined experiments and trials. Product development and profit are the main drivers of private sector research. Particularly in large pharmaceutical companies, the financial resources and personnel expertise are comparatively more plentiful, which allows for more strategically planned research with the caveat of needing to meet tight timelines to ensure competitive advantage.

Not only do the drivers for research in academia and industry differ, the collaboration approach within these sectors is often different as well. In an academic laboratory, the team is generally limited to the principal investigator (PI) and those who work with the PI. In some instances, the collaborative effort may extend to other colleagues in the department. In industry, each drug

candidate has an extensive team of experts who help guide the candidate from discovery to the market. The interdisciplinary work often extends beyond the research itself with involvement of team members with regulatory, supply chain, or even commercial marketing expertise. Thus, academic researchers often need to wear many hats, whereas industry researchers can hone in and become specialists in their own functional lines.

DRUG DISCOVERY AND DEVELOPMENT

The process from first understanding a pathway or target for cancer drug development to marketing of a drug is long and complicated. Figure 9.1 illustrates the chronological processes and

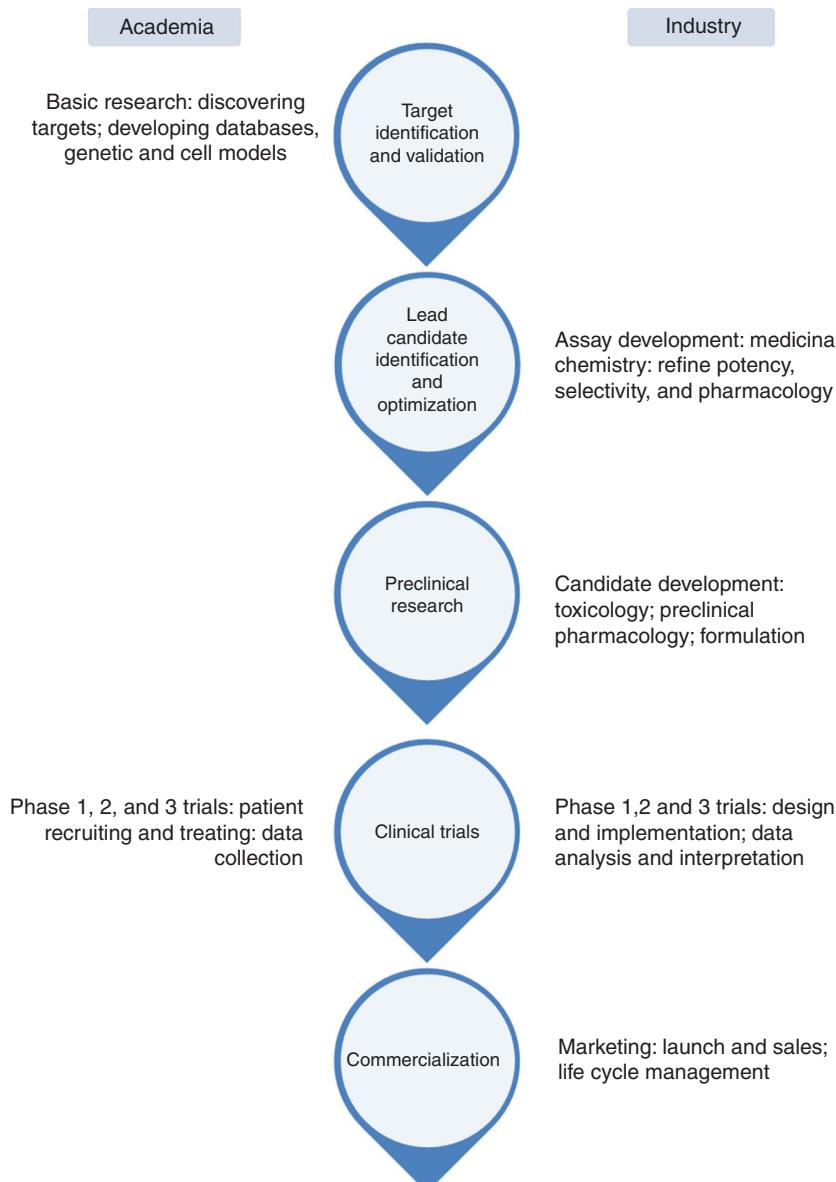


FIGURE 9.1 Relationship between academia and industry.

activities of drug discovery and development and summarizes the traditional roles that academic and industry researchers play at each step.

Academic researchers play a critical role in target identification and validation through their early discovery, basic science research efforts. Discovery research often leads to important publications about the target and creation of large databases that house this information. The lead drug candidate identification and optimization step often occurs in industry. The activities involved in this step are often part of a well-defined and regimented process, including assay development to optimize the medicinal chemistry, potency, selectivity of the candidate to the target, and pharmacology. Preclinical proof-of-concept, toxicology, and pharmacology studies are also often carried out in industry subsequent to the identification of a lead candidate. Simultaneously, efforts to develop a formulation of the lead candidate into drug form occur at this step. The crossroads for collaboration between academia and industry occurs in the clinical trial step of the process, where the industry partner often provides the funding and design for the studies and the academic partner helps with the recruiting of patients and data collection. Data analysis and interpretation are often done by the industry partner to support regulatory filing. With regulatory approval, commercialization of the drug is generally done in the private sector, along with conducting postmarketing trials and other life cycle management studies for the drug.

TRADITIONAL ROLES OF RESEARCHERS IN ACADEMIA AND INDUSTRY

“Translational research” and “personalized medicine” are hot phrases in the world of oncology. The idea of applying the progress in basic science research to development of new drugs or procedures that can readily benefit patients is the essence of translational research. Therefore, rather than taking the traditional, stepwise approach as outlined in Figure 9.1, it is necessary for academic and industry researchers to collaborate earlier on in the discovery and development timeline. *Translational research* can also refer to utilization of patient tissues or specimens collected from clinical research to then drive more basic science research in an effort to further the understanding of the nature of the disease. Thus, the paradigm for collaboration between academia and industry partners is ever evolving to allow for the fluid dialogue and in-parallel research from both sectors.

CLASSIC SUCCESSFUL COLLABORATIONS

The ever growing knowledge of molecular pathways and genetic alterations driving cancer cell proliferation and survival has generated a plethora of potential antitumor targets. The need to further evaluate and validate these targets to ultimately develop new therapeutic strategies in historically unassailable tumors is too great for academia, government, or industry to meet alone. In order to move novel targeted small-molecule inhibitors and biologics from bench to bedside more quickly and efficiently, collaborations between public and private sector researchers in complementary areas of expertise have grown. Case studies 1 and 2 describe the unique collaboration of researchers and clinicians from academic and industry sectors leading to the development of targeted therapies: trastuzumab and axitinib.

CASE STUDY 1

DEVELOPMENT OF TRASTUZUMAB (HERCEPTIN)

One of the classic academia and industry collaboration stories is the development of trastuzumab (Herceptin) for the treatment of breast cancer (1). This collaborative effort followed some aspects

(continued)

CASE STUDY 1 (*continued*)

of the traditional roles of academia and industry, in that target identification and discovery were first characterized by academic researchers and subsequent clinical development of a candidate compound was carried forward by the pharmaceutical industry. This case study describes the story of Herceptin, the evolving relationships and roles between academic researcher-oncologists and Genentech, and the challenges in development that eventually led to the approval of the first monoclonal antibody targeted against human epidermal growth factor receptor 2 (HER2) for breast cancer.

The breast cancer target discovery of *neu* gene in rats was first described by the laboratory of academic researcher Robert Weinberg from the Massachusetts Institute of Technology (2). The subsequent discovery that the human homolog of *neu*, HER2, could oncogenically transform normal cells was led by Dennis Slamon (University of California, Los Angeles [UCLA]) and Bill McGuire (University of Texas at San Antonio) and was instrumental in characterizing the clinical relevance of HER2 in breast cancer (3). At the time, Slamon was a junior faculty member at UCLA and divided his time between patient care and academic research. He collected excised tumors of a variety of cancers from surgeons and pathologists with the hope of finding oncogenes from these tumors.

The industry counterpart was Genentech, which in the late 1970s was a small biotechnology company in the Bay Area. Axel Ullrich was a postdoctoral fellow at the University of California, San Francisco (UCSF), before being recruited to join Genentech for his highly regarded work with isolating the gene for insulin from rats and producing the protein in bacteria. At Genentech, Ullrich's research was first focused on epidermal growth factors (EGFs) and he was part of the effort that discovered the oncogene called erb-b that leads to unrestrained cell growth and division (4). From there, Ullrich successfully isolated the gene for HER2 and purified the protein.

Dennis Slamon and Axel Ullrich first met at an airport in 1986 following a scientific conference. A few months after this chance meeting, Ullrich was in UCLA giving a seminar when Slamon approached him with the suggestion to collaborate: Ullrich had a rich collection of cloned growth factor genes and Slamon had his human tumor samples from a variety of different cancers. It naturally made sense to investigate whether there were any links between growth factor genes and specific cancer types. This collaboration yielded the important finding that the HER2 mutation in breast and ovarian cells produced normal HER2 proteins, but in abnormally high amounts. In order to characterize the type of breast cancer with this HER2 mutation, Slamon reached out to McGuire, who had a sizable collection of frozen breast tumors with detailed medical histories. In evaluating the number of cancerous lymph nodes before mastectomy in McGuire's breast tumors, Slamon discovered that HER2 breast cancers were generally faster spreading, more apt to recur, and deadlier than other breast cancers (5). In subsequent studies and exploration of the basic science, Slamon and Ullrich demonstrated that using a monoclonal antibody to block breast cancer cells that overexpress HER2 resulted in stopping the growth and division of the cancer

(*continued*)

CASE STUDY 1 (*continued*)

cells *in vitro*. This was further corroborated with remarkable tumor shrinkage in mouse xenograft models of human breast cells treated with monoclonal antibodies against HER2. Although these initial collaborative efforts on HER2 in breast cancer were instrumental in understanding the fundamental biology of breast cancer and revolutionizing oncogene research, a series of challenges in developing a therapy for HER2 breast cancers followed.

Genentech, being a small company, depended on Activase for its profits; additionally, Roche's acquisition of Genentech lent some uncertainty to the HER2 program. Having had unsuccessful trials in the development of alpha interferons in a broad range of cancers, there was hesitation within the upper management about investing in oncology programs. Moreover, developing antibody therapeutics at the time was novel and risky, as all monoclonal antibodies in the 1970s to 1980s were developed from genes in mice or other animals and could result in severe immunologic responses when administered to humans. The turning point came in late 1989, when the HER2 project found its champion in the vice president for manufacturing at Genentech, Bill Young, whose mother was coincidentally diagnosed with breast cancer. With the backing of senior management, the HER2 program had new life. To tackle the potential problem of severe immunologic responses with antibodies from mice or other animal species, Genentech hired Paul Carter to "humanize" monoclonal antibodies. In a short 10 months, the humanized HER2 antibody was developed and ready for evaluation in phase 1 studies, which were done at UCLA with Slamon, Sloan Kettering, and UCSF. At UCLA, Slamon tested the humanized HER2 antibody in combination with cisplatin and at Sloan Kettering and UCSF, HER2 antibody was given as monotherapy in breast cancer.

The development of a HER2 antibody seemed finally to be gaining steam. This was helped along by a large endowment to UCLA and Slamon from Revlon, the cosmetic company. Between 1989 and the end of 1997, the total contribution from Revlon to UCLA's work on women's cancer totaled \$13 million. This money helped to set up phase 1 and phase 2 trials at UCLA. Throughout the years, Slamon continued to advocate for and champion the development of the HER2 antibody, trastuzumab, even in the volatile landscape of his industry partner at Genentech.

The initial trials of the humanized HER2 monoclonal antibody enrolled patients who had advanced, relapsed breast cancer. Even with the first phase 1 study of trastuzumab, Slamon saw remarkable response in some of his patients and the phase 2 trials had promising results as well; not only did trastuzumab shrink tumors, some patients even experienced cancer remissions (6). Soon, the promise of trastuzumab in treating women with breast cancer who otherwise had limited options was spreading publicly and widely. It was at this time that patient advocate groups Breast Cancer Action and the National Breast Cancer Coalition took to the media and government agencies to advocate for a compassionate use program for trastuzumab. It was apparent that collaborating with patient advocate groups in drug development would be important and soon these groups were involved in providing feedback on the inclusion/exclusion criteria of the

CASE STUDY 1 (*continued*)

phase 3 protocols and in participating on Data Safety and Monitoring Boards. The data from women treated through the compassionate use program, along with its pivotal phase 3 studies (trials 648, 649, and 650) would later support the approval of trastuzumab.

The pivotal phase 3 study, trial 648, was initially designed as a double-blind, placebo controlled study of trastuzumab plus Cytoxin and Adriamycin (CA) in 450 women with newly diagnosed metastatic breast cancer. The selection of CA chemotherapy to be combined with trastuzumab had not previously been studied in earlier phases and went against many of the treating oncologists' preferences—Slamon had advocated for cisplatin, while other key opinion leaders had advocated for Taxol. The two other trials were smaller and conducted in 200 women each. Trial 649 evaluated trastuzumab monotherapy in women whose metastatic disease had failed to respond to one or more rounds of chemotherapy. Trial 650 evaluated trastuzumab monotherapy in newly diagnosed metastatic disease without prior chemotherapy treatment.

With 99 sites in the United States, 7 in Canada, and 33 in Europe, the phase 3 trials got under way in 1995. Even with 150 oncologists ready to enroll the 450 patients required for trial 648, enrollment ticked along slowly, although trial 649 accrued more rapidly. In trial 649, patients had few other alternatives for treatment, whereas trial 648 was in newly diagnosed patients. The biggest hurdles for enrollment in the key 648 trial were the placebo arm and the selection of the chemotherapy. With a placebo arm, physicians were concerned about withholding a possibly effective treatment from their patients. The selection of CA limited enrollment for physicians who would have otherwise chosen that regimen for their patients. About a year later, as the enrollment in trial 648 continued to lag, the protocol was amended to an open-label study of trastuzumab and added Taxol as an alternative to CA. With this change and the help of the patient advocate groups to advertise the revised protocol, enrollment in trial 648 was completed less than a year later. In September 1998, Herceptin received approval from the Food and Drug Administration (FDA) for use in women with metastatic breast cancer that overexpresses HER2 as first line in combination with chemotherapy or as monotherapy in patients who had failed one or more lines of chemotherapy.

The story of Herceptin is unique and highlights the importance of the partnership between academia, industry, and even patient advocate communities. Though the rationale for HER2 as a target for breast cancer stemmed from early academic researcher efforts, industry backing of Genentech in the development of humanized monoclonal antibodies and clinical development program proved to be crucial. However, given the many players in Genentech over the development course of trastuzumab, there were many setbacks along the way. With the persistence of researcher-oncologists, including Slamon and his UCLA–Revlon financial backing, the stalemate and near-failure of the pivotal phase 3 trial was averted, paving the way for Herceptin's approval in the treatment of breast cancer.

(*continued*)

CASE STUDY 1 (continued)

The development of Herceptin extends beyond breast cancer. Since its first indication in breast cancer, there have been other studies evaluating the use of Herceptin in patients with HER2-driven cancers arising from other anatomical sites. One such example is the *Trastuzumab for GAstic cancer* (ToGA) study, which was an open-label, international, phase 3, randomized controlled trial in patients with gastric or gastroesophageal cancer whose cancers expressed HER2 (7). In total, 594 patients were randomized in the study with $n = 298$ treated with trastuzumab plus chemotherapy and $n = 296$ in the control chemotherapy alone arm. The median overall survival was 13.8 months compared to 11.1 months in the chemotherapy group (hazard ratio 0.74, $p = .0046$), leading to its approval in this population in 2010. More recently, Roche/Genentech has an ongoing nonrandomized phase 2 open-label study, *My Pathway*, consisting of six treatment arms for patients with advanced solid tumors and expression of one of six targets for any cancer (trastuzumab and pertuzumab, erlotinib, vemurafenib plus cobimetinib, vismodegib, alectinib, and atezolizumab) (8). The approach to enroll patients based on biomarker expression and without regard to anatomic location of the primary tumor is revolutionizing the treatment approach and expanding options to oncology patients. This certainly will continue to drive increased collaborative efforts between academia and industry to coordinate such studies.

CASE STUDY 2**DEVELOPMENT OF AXITINIB (INLYTA)**

The clinical development of axitinib (AG-013736, Inlyta) began in May 2002 with the First In Human study initiated in patients with solid tumors (9). Three clinical sites, University of Wisconsin Comprehensive Cancer Center, University of Texas MD Anderson Cancer Center, and UCSF, enrolled patients on this trial sponsored by Pfizer (9). Axitinib is a substituted indazole derivative that was developed using structure-based drug design as a potent small-molecule tyrosine kinase inhibitor of all known VEGF receptors (VEGFRs) at subnanomolar concentrations (9). Using the standard 3+3 design for safety-based dose finding, and based on real-time evaluation of patient tolerability by the three PIs and Pfizer, the 5 mg twice daily (BID) dose was identified as the maximum tolerated dose for axitinib and also the recommended dose for further clinical development (9).

Increase in blood pressure and proteinuria were two of the major class effects and it was important to characterize the drug exposure and side effect relationship in order to identify safe and efficacious doses. Results from dynamic contrast-enhanced MRI (DCE-MRI) employed in all patients on the study as a pharmacodynamic (PD) marker of antiangiogenic effect indicated

(continued)

CASE STUDY 2 (*continued*)

that near maximal reduction in permeability and blood flow was associated with axitinib mean steady-state plasma exposures (AUC_{tau}) associated with the 5 mg BID dose (10). Hence, the dose identified based on intended mechanism of action dovetailed nicely with the dose suggested by safety criteria. From the first cohort of patients enrolled in the study, high intersubject variability in axitinib plasma exposure was noted, with coefficient of variation ranging from 30% to 98% in the doses evaluated in the trial (9). Flat dosing had been routinely applied for small-molecule, tyrosine kinase inhibitors until that point. Additional analysis with axitinib pharmacokinetic (PK) data that was subsequently published indicated that the intersubject variability in plasma exposures was not related to common demographic parameters such as age, body weight, body surface area, gender, or ethnicity (11). Hence, dosing based on body surface area or weight would not be helpful.

Subsequently, a phase 2 study was initiated in cytokine-refractory renal cell carcinoma patients, in which 44.2% objective response rate (ORR; 95% confidence interval [CI]: 30.5–58.7) was observed with the use of the flat 5 mg BID dose in the majority of patients (12). This demonstrated that a robust clinical response could be achieved with axitinib at a flat 5 mg BID dose. However, the high intersubject variability in pharmacokinetics suggested that a subset of patients with lower than typical drug concentrations at the 5 mg BID dose were likely getting subtherapeutic exposures. In order to maximize the likelihood of clinical response in the majority of patients, axitinib dose titration was proposed as a way of allowing patients who are able to tolerate the 5 mg BID starting dose to increase their dose. A specific dose algorithm was developed in collaboration between the industry sponsor and the key academic investigators participating in the axitinib clinical trials. If a patient was not already on hypertensive medications, did not have an increase in blood pressure, and did not have ≥ grade 2 drug-related toxicities after at least 2 weeks of dosing at the 5 mg BID starting dose, they were allowed to have their dose increased to 7 mg BID. After at least 2 weeks of dosing at the 7 mg BID, and applying the same criteria as before, the patient dose could be increased again to a final maximum dose of 10 mg BID. Investigator discretion was always to be applied prior to implanting this dose titration algorithm in individual patients (13).

With the agreement from investigators participating in axitinib trials at the time, this dose titration scheme was then implemented in a study in sorafenib-refractory renal cell carcinoma patients, and another study in Japanese cytokine-refractory patients with renal cell carcinoma (13,14). Additional guidance was provided to investigators participating in these trials regarding the logistics of the dose titration algorithm, and feedback was received on the challenges with implementing the individualized dosing strategy.

The proposed dose titration scheme was based entirely on individual patient tolerability; it did not take into account patient responses to treatment, nor did it involve therapeutic drug monitoring based on measured plasma concentrations of axitinib. Hence, in order to ascertain if the

CASE STUDY 2 (continued)

implemented dose titration scheme did result in dose escalation in the right patients, a retrospective analysis was conducted using data from the three phase 2 studies in patients with renal cell carcinoma. The results from this analysis were presented by Dr. Brian Rini in an oral presentation at the American Society of Clinical Oncology Genitourinary (ASCO GU) Annual Meeting in 2012 (Table 9.1) (15).

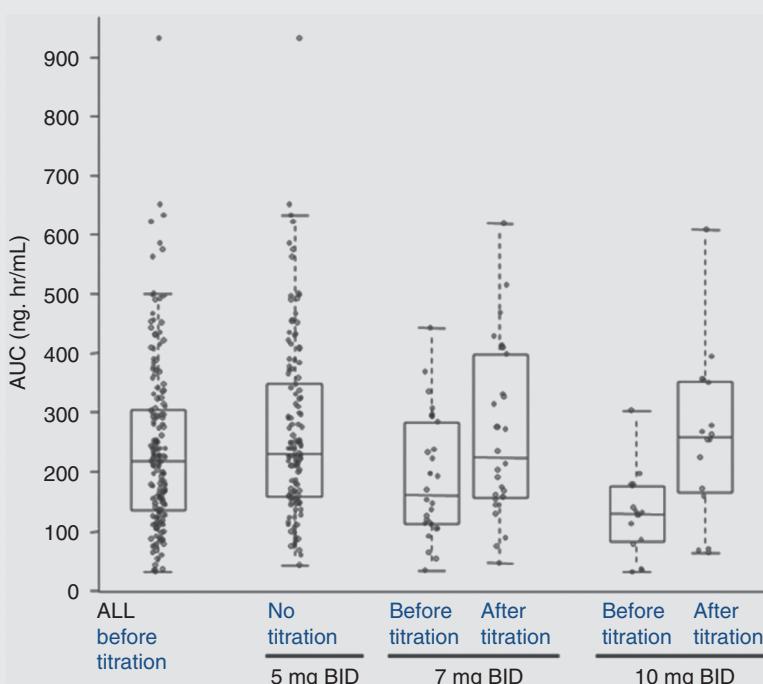
TABLE 9.1 AXITINIB STEADY-STATE PLASMA EXPOSURES BEFORE AND AFTER TITRATION			
Median AUC ₀₋₁₂ ng × h/mL (range)	5 mg BID N = 129	7 mg BID N = 30	10 mg BID N = 16
Before titration	231 (42–931)	160 (32.8–443)	129 (31.9–304)
After titration		225 (45.9–620)	258 (63.9–608)

AUC, area under the curve.

In Figure 9.2, the individual steady-state plasma exposures are provided from the pooled data from the three clinical studies *prior to* dose titration. The data are divided into subgroups based on the highest dose that the patient dose was eventually increased to. It is evident that *prior to* dose titration, patients who eventually had their dose increased to 7 mg BID and particularly those whose dose increased to 10 mg BID had lower than typical plasma exposures, that is, 160 ng × h/mL mean area under the curve (AUC) for 7 mg BID group and 120 ng × h/mL compared to 231 ng.h/mL in patients not requiring dose escalation. Moreover, *after dose titration*, patients in all dose groups had normalized plasma exposures, as noted visually in Figure 9.2 and by similar mean AUC values of 231, 225, and 258 ng × h/mL in the three dose groups. This retrospective analysis therefore confirmed that dose titration implemented based on individual patient safety did in fact result in bringing all patients to similar plasma exposures. Also, this analysis confirmed that patients whose doses are increased from the 5 mg BID starting dose to the 10 mg BID maximal dose do not have higher than typical exposures; rather, this allows patients who had lower than typical exposures at the starting dose to catch up with the remaining patients at the 5 mg BID starting group.

Based on this analysis, the dose titration scheme was implemented for the phase 3 AXIS registration study comparing axitinib with sorafenib in 723 patients enrolled from 175 sites in 22 countries (16). This large study, conducted collaboratively across academic and treatment centers around the world and in conjunction with the sponsor, led to the approval of axitinib in second-line renal cell carcinoma.

(continued)

CASE STUDY 2 (*continued*)**FIGURE 9.2 Axitinib plasma exposures before and after dose titration.**

AUC, area under the curve; BID, twice a day.

Source: Rini BI, Escudier BJ, Michaelson MD, et al. Phase III AXIS trial for second-line metastatic renal cell carcinoma (mRCC): effect of prior first-line treatment duration and axitinib dose titration on axitinib efficacy. *J Clin Oncol.* 2012;30(5 suppl):354–354. doi:10.1200/jco.2012.30.5_suppl.354

Because the prior analysis justifying the basis for dose titration of axitinib was based on retrospective analysis of data from three phase 2 studies, there were concerns that the results might be prone to bias. Hence, a prospective study was designed to unequivocally evaluate the benefit of dose titration. The design for this study was developed jointly by Pfizer and key academic research investigators in renal cell carcinoma (17). In this phase 2, randomized, double-blind study that enrolled 213 patients, all patients were initially given the 5 mg BID starting dose. Based on individual patient tolerability, patients eligible for titration were randomly assigned to either active axitinib titration or placebo titration. For the primary end point of objective response there was a statistically significant higher response rate in the axitinib titration group compared to placebo titration; 54% versus 34% respectively ($p = .019$) (17). More mature data from the same study eventually demonstrated higher overall survival as well for the axitinib titration group compared to the placebo group; 42.7 months versus 30.4 months, respectively (18). This study provided prospective evidence in support of the benefit of the applied dose titration scheme for axitinib. This individualized dosing scheme is on the axitinib (Inlyta) label in all countries where the drug is

(continued)

CASE STUDY 2 (*continued*)

approved. Continued efforts are ongoing to further refine the dose titration scheme for axitinib to achieve even better patient tolerability.

Additional clinical studies are being conducted in collaboration with investigators in a variety of clinical settings. This includes single-agent use in neoadjuvant renal cell carcinoma, glioblastoma, hepatocellular carcinoma, neurofibromatosis type 2 and progressive vestibular schwannomas, soft tissue sarcomas, salivary gland cancers, adenoid cystic carcinoma, neuroendocrine carcinomas, melanoma, prostate cancer, and head and neck cancer. Axitinib is being tested in combination with a variety of agents including the PD-L1 inhibitor avelumab (Bavencio), the PD-1 inhibitor pembrolizumab (Keytruda), dalantercept, and temsirolimus, indicating the benefits of continued interaction between industry and academia, particularly in this unique case of the need to individualize dosing for axitinib.

EVOLVING COLLABORATIVE EFFORTS

Oftentimes, the overall goals of oncology drug development for academia and industry sectors are not aligned; this stems from the different lenses of the researchers in these sectors. For the academic researcher who is also the treating physician, the individual patient presenting in the clinic is the primary focus. For the industry researcher, demonstrating the efficacious and safe use of a candidate compound in a population of patients is desired. These intrinsic differences in vantage points and goals can lead to very different approaches in trial design and patient selection for clinical studies. For example, many industry sponsored trials have strict inclusion/exclusion criteria in an effort to generate cleaner and more interpretable data. Additionally, study protocols may be filled with assessments that may not be medically necessary for the patient, but may generate important scientific and clinical data for the industry researcher. For academic-treating physicians carrying out industry sponsored trials, the strict eligibility criteria may preclude their patients from receiving medications that may be beneficial to the patients. Similarly, the long list of additional assessments required in study protocols may prove to be too logistically cumbersome for physicians and patients to buy into enrolling in industry sponsored studies versus selecting a standard of care treatment. Therefore, there is a role for **investigator initiated trials (IITs)** to bring potentially effective therapeutics to their patients through differently designed studies that may allow for patients who would not otherwise be eligible or able to join traditional clinical studies, to potentially benefit from drugs in development. Research conducted through the use of IITs has changed much about the traditional collaborative roles held in the industry and academic sectors.

ROLE OF IITs: CASE STUDY WITH DART

IITs are studies proposed and conducted by academic researchers who are not affiliated with the biopharmaceutical company, but are studying the company's drug product or disease area of interest (19). All potential uses of the study medication cannot be explored through industry sponsored trials alone. Therefore, IITs can help to expand the knowledge of the drug product, including identifying new ways of using existing medications, optimizing dosing strategies, or better characterizing safety. Much of the work stemming from IITs has led to further development efforts by the industry partner and has contributed to expanding the labeling indications for existing therapies.

One area in which IITs are often most fruitful is investigating a rare tumor type (either by a histological or biomarker definition) for which the biology of the agent may be an ideal fit, but the overall market is likely smaller, limiting commercial opportunities. Both IITs and cooperative group studies play a key role in this space. One example of an ongoing study of rare tumors is Southwest Oncology Group (SWOG) 1609 (S1609), DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (20). This clinical trial is studying the combination of two immunotherapy agents, ipilimumab and nivolumab, across more than 30 rare tumor histologic subtypes, and as of September 2017 had more than 700 sites and treated more than 120 patients in over 9 months.

DART was initially an investigator initiated study designed to more rationally investigate the utility of immune checkpoint blockade in rare tumors. Historically, these patients were seen often in phase 1 clinics and treated in dose escalation phase 1 clinical studies. However, while the rare tumor cancer patient may help inform dosing and toxicity of the novel agent, little clinical information related to the efficacy of that agent in that rare tumor type is gleaned from this approach. Thus, DART was devised as a study among a couple of phase 1 units to formally test the efficacy of ipilimumab and nivolumab across rare solid tumors in a basket design as part of a research collaboration with Bristol-Myers Squibb. However, increasing interest within SWOG and an opportunity to join National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH) as a rare tumor “arm” led to the formal launch of the protocol within the NCI-National Clinical Trials Network (NCTN) network.

The study utilizes a Simon’s two-stage design across each of the 30-plus rare histologic cohorts to investigate the overall response rate of ipilimumab with nivolumab across rare cancer subtypes, including cancers of unknown primary. Of note, a “not otherwise classified” (NOC) cohort was established to ensure that ultrarare cancers that were not classified among the 30-plus existing cohorts could also enroll. Finally, the translational medicine objectives of this study, which include whole-exome sequencing, RNAseq, cfDNA, proteomics, and immune-cell immunohistochemistry (IHC), will in many cases be the first of its kind for many of the tumor types in DART. With the potential for clinical efficacy in rare tumors and the further refinement of biomarker signatures across tumor types, the robust accrual of DART, despite being a rare tumor study, may open the door to other future rare tumor studies within the NCI-NCTN network. Another example of early phase clinical trials translating into a promising immunotherapeutic strategy involves pembrolizumab in microsatellite-unstable cancers.

EXPANDING THE USE OF THERAPIES WITH IITS: AN EXAMPLE WITH PEMBROLIZUMAB IN MICROSATELLITE INSTABILITY-HIGH (MSI-H) CANCERS

Pembrolizumab (Keytruda) is the first therapy that has been granted accelerated approval by the FDA for tissue- or site-agnostic indication. In May 2017, the FDA granted pembrolizumab accelerated approval for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or mismatch repair deficient (dMMR) solid tumors that have progressed on a prior treatment. This approval was based on data from five uncontrolled, single-arm clinical trials in 149 patients with 15 different cancer types who were prospectively determined to have MSI-H or dMMR cancers. The accelerated approval was based on an ORR of 39.6% (95% CI: 31.7–47.9) where responses lasted 6 months or more in the 78% of patients who responded to pembrolizumab. The ORR was similar whether the patients were diagnosed with colorectal cancer (which made up 90 of the 149 patients) or the other 14 cancer types at 36% versus 46% (21).

The main dMMR colorectal trial was initiated by researchers (Luis Diaz and Dung Le) from Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (22). Although the use of anti-PD-1 antibodies has led to remarkable clinical responses in a number of cancers, including melanomas, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and more, its use in colorectal cancer has not turned out to be particularly promising. However, Diaz et al. hypothesized that patients with dMMR cancers with 10 to 100 times more somatic mutations would have prominent

lymphocyte infiltrates, which would be susceptible to immune response. The inspiration for Diaz's study was a previously published study that enrolled patients with multiple cancer types reported by fellow Johns Hopkins researchers, Suzanne Topalian and Drew Pardoll, in 2012 where a single colorectal cancer patient responded well to treatment with nivolumab, another anti-PD-1 antibody (23,24). The difference with this colorectal patient who responded versus other colorectal cancer patients was that this patient also had Lynch syndrome, which is an inherited form of dMMR. From there, Diaz conducted the phase 2 study that evaluated the efficacy of pembrolizumab in 41 patients with dMMR colorectal cancer, mismatch repair proficient colorectal cancer, and dMMR cancers that were not colorectal. The results were striking: ORR was 40% in dMMR colorectal patients versus 0% in mismatch repair proficient colorectal patients. Patients with dMMR colorectal cancer had progression-free survival rates comparable to those of the dMMR noncolorectal cancer patients (78% vs. 67%).

This initial trial led by Hopkins researcher Diaz eventually led to the enrollment of other patients with different cancer types that shared this genetic trait, as reported earlier in 2017 in *Science* (22). The expansion led to the inclusion of 86 patients with 12 different tumor types with evidence of dMMR disease and progressive disease prior to enrollment. In this group of patients, 53% had objective radiographic responses with 21% achieving complete response. With even the positive results from the initial trial in dMMR colorectal patients by Diaz, Merck, the industry sponsor of Keytruda, conducted four clinical studies (NCT02460198, NCT01848834, NCT02054806, and NCT02628067) in multiple tumor types that are dMMR or MSI-H that led to the landmark tumor site and age agnostic approval of pembrolizumab. This example of an IIT that led to further industry sponsored studies and the eventual accelerated approval of the therapy based on the existence of a biomarker rather than the organ defining the disease has dramatically shifted the paradigm for collaboration between academia and industry partners, and more importantly the approach to oncology research and drug development that will, it is hoped, expand treatment options to previously difficult-to-treat cancers.

FUNDING STUDIES WITH INDUSTRY

Many companies fund extensive internal and external research and development (R&D) programs through partnerships with investigators in academia. This is a common method for funding IITs that are either directly **sponsored** by the company or sponsored by the investigator's institution with financial support from the company (see more in what follows). Often such research collaborations are facilitated through a **Medical Science Liaison (MSL)**. These are individuals employed by the company to help shepherd new ideas and proposals through the funding process. It is a good idea to try to identify whether a company has a local MSL you can contact to initiate funding applications for research concepts.

Often companies will partner with academic investigators on research they wish to sponsor, either through subcontracts for laboratory work, or to engage in clinical trials. In many cases, companies will sponsor trials they are conducting in order to seek federal regulatory approval (e.g., through the FDA) to permit labeling and marketing of their product. Academic investigators also frequently function as study chairs or local PIs, or as medical monitors, or through scientific advisory boards and steering committees. It is important when establishing research relationships with industry—particularly those that involve remuneration—to be open in declaring them, as they may generate conflicts of interest that can affect scientific objectivity (25).

In addition, many government agencies, such as the National Institutes of Health (NIH), offer **Small Business Innovation Research (SBIR)** funding mechanisms for the express purpose of facilitating research collaborations between small or start-up companies and academic investigators. Other research collaborations between companies and government agencies may involve establishing a **Cooperative Research and Development Agreement (CRADA)**, which is an agreement on the part of a federal government laboratory to provide resources, such as facilities, equipment, staffing, drugs, and so on, rather than funding, to support certain R&D efforts. The industry CRADA partner would contribute necessary funding and additional resources to support the

project. A CRADA allows the nonfederal collaborating party the option to negotiate licensing for any invention or intellectual property developed through a collaborative research project.

Many oncology clinical trials are also funded through partnerships between industry, the NCI, and the NCTN. The NCTN consists of several major cooperative groups: Alliance, SWOG, NRG Oncology, Eastern Cooperative Oncology Group (ECOG)—American College of Radiology Imaging Network (ACRIN), and the Children’s Oncology Group (COG). In addition, NCI of Canada (NCIC) is a frequent participant in supporting U.S. federally sponsored clinical trials, especially phase III trials. The NCI principally supports cooperative group trials through two agencies: the **Cancer Therapy Evaluation Program (CTEP)** and the **Division of Cancer Prevention (DCP)**, which respectively address trials either designed primarily to improve clinical outcomes or to reduce morbidity/improve patients’ quality of life. Industry partners often support such trials by providing funding and/or drug supply to support the costs of running large clinical experiments. For example, the NRG HN004 trial (<https://clinicaltrials.gov/ct2/show/NCT03258554>) represents a partnership between CTEP, NRG Oncology, the FDA, and Astra-Zeneca to test the PD-L1 inhibitor durvalumab in head/neck cancer patients who are medically unfit for standard therapy with radiation and cisplatin.

Finally, several NCTN groups also have established research **foundations** to operate clinical trials that are not expressly sponsored through the NCI but rather through a partnership directly between a company and a cooperative group. Examples include the Alliance Foundation, Radiation Therapy Oncology Group (RTOG) Foundation, and Gynecologic Oncology Group (GOG) Foundation. The mechanism for procuring support for such trials typically involves trilateral partnership among the investigator(s) initiating the proposal, the potential industry sponsor, and the respective cooperative group committee leadership, in order to advance a trial concept.

INVESTIGATIONAL NEW DRUG (IND) APPLICATIONS

In order to evaluate a drug or biological product in human patients, an IND application is required of all sponsors (i.e., the individual or institution who is considered the **IND holder**) and sponsor-investigators (e.g., academic or industry) by the FDA (26). Generally, for the IITs that evaluate an existing drug that is approved and marketed, it is important to first understand whether the investigation can occur without an IND. If the investigation is not exempt from the IND process, an existing IND may be used to evaluate the marketed drug for a different indication; alternatively, a new IND may be submitted to support the study.

Any IIT where the intent of the findings would support a new indication or any labeling or advertising changes to an existing, commercially approved drug would require an IND (26). The FDA has issued a draft guidance document that provides guidance on when to submit an IND application and the components of the IND application for sponsor-investigators (27). An individual is considered a sponsor-investigator if he or she both initiates and conducts a study—in most cases with IITs investigating existing drugs as new regimens or for new indications, the academic researcher would be considered a sponsor-investigator and would need an IND prior to initiating the research.

There are six main components of a new IND application: information on the qualifications of the sponsor-investigator, the drug’s Investigator’s Brochure, a clinical trial protocol, chemistry manufacturing and control (CMC) information, pharmacology and toxicology information, and a summary of previous human experience. If the sponsor-investigator has the permission to initiate a study using an existing IND from the industry sponsor, then a letter of cross-reference authorization from the industry partner (e.g., commercial sponsor) can be submitted. In the event a new IND application is needed, some of the six required components may be pulled from other applications (e.g., CMC and pharmacology and toxicology information usually are available from the industry sponsor in the previous application). To determine whether an existing IND can be used for a new IIT, it is important for the academic researcher to work with the industry sponsor and its regulatory team to determine the best course of action.

FDA REGISTRATION

Positive results from IITs that can potentially expand the use of existing drugs or treatment regimens to other indications should be considered for regulatory **registration**. The decision and process for filing a Supplemental New Drug Application (sNDA) or Supplemental Biologics License Application (sBLA) to the FDA depend on the legal agreements between the academic researcher and his or her institution and with the industry partner. This often becomes a complicated process for navigating the cosharing of patent rights.

An example is the recent approval of Mylotarg (gemtuzumab ozogamicin) for the treatment of newly diagnosed CD33-positive acute myeloid leukemia (AML) (28). The basis for this approval was the IIT study ALFA-701 (NCT00927498), a multicenter, randomized, open-label phase 3 study conducted in 271 patients with newly diagnosed de novo AML (29). Patients received induction therapy consisting of daunorubicin and cytarabine with or without Mylotarg. Mylotarg had been previously withdrawn from the market, and the reintroduction of the drug occurred via the exploration of lower fractionated doses of Mylotarg in the IIT study. The New Drug Application submission was conducted by the sponsor (Pfizer Inc.) in collaboration with the investigators, and utilized data from the IIT study. Of note, two additional IIT trials enabled additional indications for Mylotarg. The AML-19 (NCT00091234) was an IIT study conducted in 237 patients with newly diagnosed AML unsuitable for intensive chemotherapy (30). MYLOFRANCE-1 was a phase 2, single-arm, open-label study IIT trial of Mylotarg in adults with CD33-positive AML in first relapse (31). This is an example of three separate indications gaining registrational approval based on data from IIT studies that were jointly submitted with the sponsor.

WORKING WITH TECHNOLOGY AND DEVICE COMPANIES

In addition to food and drugs, the FDA also regulates medical devices, which are approved through a similar but slightly different mechanism compared to drugs (510(k) clearance). Medical devices fall under several different classes (e.g., Class I, II, or III), depending on the degree of regulatory requirements, risk, and the potential for regulatory exemption. A description of this process is beyond the scope of our chapter; more details can be acquired via the FDA website (www.fda.gov/MedicalDevices/default.htm).

Similar to pharmaceutical companies, most technology and device companies sponsor R&D programs with opportunities to fund research in conjunction with academic investigators. Research support may be provided in the form of direct grants or often as **in-kind loans**, which usually entail provision of special or proprietary equipment to conduct research at an academic institution. For example, Varian Medical Systems supports both individual investigator applications through a recurring grant cycle, in addition to Master Research Agreements with several university departments to fund coordinated research programs to advance innovations in medical physics. Because of the differences in regulatory approval processes for devices, however, these companies do not sponsor large clinical trials to the same degree as pharmaceutical companies. Therefore, larger questions regarding the clinical impact of new technologies are often taken up either through cooperative groups, or by alternative study designs to classic phase III trials (e.g., comparative effectiveness or registry trials).

TRAINING RESEARCHERS

As the line between traditional academia and industry research continues to blur, training budding researchers who can better bridge the two sectors is immensely important. Clinical researchers generally have one or more of three advanced degrees—MD/DO, PhD, or PharmD—and postgraduate training opportunities for these graduates differ depending on the degree.

For the physician (MD/DO), the typical path of postgraduate training involves more hands-on clinical experiences through residency programs and fellowships. For specialty therapeutic

areas such as medical or surgical oncology, completing a fellowship in clinical training is essential. Then, to enter the realm of clinical research, young physicians often may need formal training in research methodology, statistics, and patient-oriented outcomes research. Many academic institutions offer part-time courses or even master's programs in clinical research to provide more formal didactic training to enable physicians to gain these skills. Developing these skills can then help physicians become clinical researchers at academic institutions with an opportunity to be involved with clinical trials, including industry sponsored clinical trials. The experience of being an investigator physician in a clinical trial then allows the physician to gain access to industry opportunities as medical drug safety monitors or clinical development scientists. In essence, the exposure of physician researchers to academia and industry sectors is more sequential than in parallel.

Similarly, for the PhD graduate, postdoctoral research programs exist in academic institutions or private companies that are immediately available after conferral of the degree. Aside from the joint programs available with Rutgers University and various industry sponsors or University of North Carolina (UNC) with GlaxoSmithKline, there are very few postdoctoral programs that are jointly run by academic and industry partners. For PhD graduates, much of their experience has been in academia and most likely preclinical or basic science in nature. It is less common for PhD graduates to have direct clinical research experience through their graduate education, unless the PI was involved in clinical trials. Therefore, breaking into the clinical research space generally involves finding a postdoctoral program in industry in a clinical functional area to gain hands-on training in clinical research. It may be possible with some years of experience conducting clinical research in industry to then transition back into academia. In this case, introduction to clinical research in both sectors is also mostly sequential.

In contrast, more formal postdoctoral fellowship training programs for PharmD graduates exist that allow for immediate exposure to both academia and industry sectors. After graduation, there are often three routes available for PharmD graduates: retail or community pharmacy, pharmacy residency training, or postgraduate fellowship programs. A pharmacy residency helps to improve skills in patient care through experiences in both inpatient and outpatient settings, including general internal medicine, ambulatory care clinics, or specialty areas such as infectious disease and hematology/oncology. Conversely, a pharmacy fellowship is designed to prepare the PharmD graduate to become an independent researcher. In the United States, there are several major joint postdoctoral fellowships between well-known schools of pharmacies and industry sponsors, including: Rutgers, Massachusetts College of Pharmacy and Health Sciences (MCPHS), UNC, University of Southern California (USC), and University of California San Diego (UCSD). In these programs, the PharmD fellows focus on a functional area of practice and gain hands-on training with the industry sponsor while also having the opportunity to conduct academic research projects and participate in didactic courses in clinical research and professional/leadership development.

As an example, the UCSD oncology clinical pharmacology fellowship program is run jointly with Pfizer in La Jolla, California. The fellowship is 2 years in duration and aims to help the trainee develop skills in clinical pharmacology, including conducting clinical pharmacology studies and learning quantitative pharmacology to analyze and interpret PK and PD data. As the fellowship is oncology focused, it is necessary also to ensure that the fellow is clinically adept. Therefore, starting at the beginning of the fellowship, the PharmD trainee rotates through inpatient hematology/oncology service and outpatient oncology clinics at the UCSD Moores Cancer Center. After the full-time rotation experience, which lasts about 2 months, the fellow follows a medical oncologist outpatient in the phase 1 clinic longitudinally 1 day per week to continue to develop and practice clinical pharmacy skills, while also gaining exposure to phase 1 studies from an academic center point of view. In parallel, fellows also begin to take on projects at Pfizer, where they gain experience in clinical pharmacology study design, protocol writing, data analysis, and population PK and PKPD modeling. With the UCSD School of Pharmacy, the fellow has an opportunity to teach at the school, while also having opportunities to work on clinical pharmacology related IITs, usually also in collaboration with oncologists at Moores. For the duration of the fellowship program, the trainee is immersed in research projects both industry and academic, and thus gains invaluable

insight into the cultures of both sectors, which may help to better position the fellow for improved and more fruitful collaborative efforts in the future.

CONCLUSION

From the case examples with trastuzumab and axitinib, it is clear that academia and industry collaboration has long existed and proven to be necessary in the approval of these agents. In light of the rapidity of delivering new therapeutics in treating hematologic and solid malignancies, the work of academic and industry researchers is becoming more integrated and collaboration between the two entities is crucial to more efficiently bring novel treatments to patients, as evidenced by the use of IITs including DART and the story of pembrolizumab. With the ever evolving roles of academic and industry researchers, adequate exposure and training programs for future researchers are needed to aid in fostering stronger relationships and better collaboration. Although some postgraduate training programs that offer experience in both sectors already exist, more are needed to better prepare physician, PhD, and PharmD graduates for oncology clinical research.

GLOSSARY

investigator initiated trials (IITs): studies done to bring potentially effective therapeutics to patients through differently designed studies that may allow patients, who would not otherwise be eligible or able to join traditional clinical studies, to potentially benefit from drugs in development.

sponsored: underwritten.

Medical Science Liaison (MSL): person employed by an industry (drug) company to establish and maintain relationships with physicians and practitioners often at academic institutions.

Small Business Innovation Research (SBIR): a mechanism for funding offered by many government agencies, such as the National Institutes of Health (NIH), for the express purpose of facilitating research collaborations between small or start-up companies and academic investigators.

Cooperative Research and Development Agreement (CRADA): a research collaboration agreement on the part of a federal government laboratory to provide resources, such as facilities, equipment, staffing, drugs, and so on, rather than funding, to support certain R&D efforts.

Cancer Therapy Evaluation Program (CTEP): an NCI entity that supports cooperative group trials designed primarily to improve clinical outcomes.

Division of Cancer Prevention (DCP): an NCI entity that supports cooperative group trials designed primarily to reduce morbidity/improve patients' quality of life.

foundation: a research entity established to operate clinical trials that are sponsored through a partnership directly between a company and a cooperative group.

IND holder: the individual or institution who makes an Investigational New Drug Application to the FDA.

registration: regulatory submission made when the use of an existing drug or treatment regimen can potentially be expanded to other indications.

in-kind loan: research support that usually entails provision of special or proprietary equipment

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