Progress in Translational Research:
Examples and Thoughts from the Dermatologic Research Community
# Progress in Translational Research:
Examples and Thoughts from the Dermatologic Research Community
January-December 2015

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The twelve cover stories were written by BA Gilchrest, who also selected the cover images.
This reprint of the editorials, cover images, and cover stories on the theme of “Progress in Translational Research” and published throughout Volume 135 of the Journal of Investigative Dermatology is made possible by funding from Advancing Innovation in Dermatology (AID). AID is a not-for-profit organization committed to catalyzing the development of new dermatologic solutions for patients and healthcare providers by bringing together stakeholders who can enable, encourage and support new products for skin conditions. The cover image, representing careful inquiry, is composed of photographs obtained at the AID-organized 2014 Dermatology Summit meeting in San Francisco. The organization was founded in 2011 by a group of like-minded medical professionals and thought-leaders in the field who saw a need for an increased commitment to new scientifically-based solutions in dermatology. AID’s goal is to facilitate meaningful interactions and create an ecosystem among a broad range of constituencies with a common interest in bringing innovative products to market that will substantially improve dermatologic health.

For more information about AID visit www.advancing-derm.com

BACK COVER
Pictured on the back cover are Advancing Innovation in Dermatology members (from top left to bottom right):

Rox Anderson MD, FAAD
Professor, Department of Dermatology, Director of the Wellman Center for Photomedicine, Massachusetts General Hospital, Professor of Health Sciences and Technology at MIT

Frederick Beddingfield, MD, PhD
Chief Medical Officer, Kythera

Douglas Canfield
Founder and President of Canfield Scientific

Albert Cha, MD, PhD
Managing Partner, Vivo Capital

Brian Cunningham, MD
Founder, Chief Business Officer, and Senior Vice President, Finance, Madrigal Pharmaceuticals and Venture Partner, Bay City Capital

John Doux MD, MBA
Analyst, Palo Alto Investors

William Eaglstein, MD
Chairman Emeritus, Department of Dermatology, University of Miami

William Ju, MD
President, Advancing Innovation in Dermatology

Seth Orlow, MD, PhD
Chairman and Professor, Department of Dermatology, New York University

Neal Walker, DO, MBA
CEO and President, Aclaris Therapeutics

Patty Walter, MD, PhD
President and Chief Scientific Officer, Brickell Biotech

Ken Washenik, MD, PhD
Medical Director of Bosley and CEO of Aderans Research Institute

Lee Zane, MD, MAS
Senior Vice President and Chief Medical Officer, Anacor Pharmaceuticals
When I was asked to compose an editorial for this monograph, presenting my perspective as an entrepreneur in dermatology within the context of translational research, I wanted to understand how translational research was defined and learn how it was viewed by other stakeholders. After all, “translational research” is often (or typically) viewed either through a “clinical lens,” that is, translating research “from bedside to bench”—or through a “laboratory lens,” that is, translating “from bench to bedside” (and back)—as described by Eugene Bauer in his editorial from this series (Bauer, 2015). Much less often it is viewed through the lens of an entrepreneur whose translation must be from idea, clinical concept, “interesting” lab study, or “unexpected result” to a commercial product with value not only as a treatment for patients in need but for financial partners who must fund the “translation.” Reading the prior editorials in this series and obtaining an understanding of the lens through which the other “stakeholders” view the concept of translational research has been both pleasurable and enlightening.

In the editorial that introduced this series, Barbara Gilchrest articulated that translational research is a vague term that can mean different things to different people. “To me, the critical elements include conceptualizing an improvement in patient care, identifying a potential means of achieving that improvement through one’s own research or recognizing that means in the work of another, demonstrating proof of principle, and then assembling the team that will be required for commercialization” (Gilchrest, 2015). Although she describes translational research as a potentially “vague term,” I think her characterization of such research resonates beautifully and highlights critical concepts that were also elucidated in a similarly themed paper, “The Meaning of Translational Research and Why It Matters” (Woolf, 2008). First, at its core, translational research embodies innovation in all forms and at all stages. Second, success as defined by producing new drugs, devices, and treatment options for patients is dependent on a team approach. Third, a continuum exists that extends well beyond the traditional view of “translational research,” bridging the gap between the proof of principle and the commercialized product.

Most are aware of the team requirements in the early stages of innovation, which typically include relatively straightforward collaborations between scientists and clinicians. However, if the innovation is to move through the continuum, additional team members with relevant expertise in preclinical development, clinical drug development, regulatory affairs, chemistry manufacturing and controls, intellectual property (IP), finance, and commercialization must be added. Additionally, financial partners—ideally, ones with an understanding of the process and the “space”—must work in concert with the developing team to fund the personnel and activities. The insight, expertise, and value that each of these individuals or groups brings to the project cannot be overestimated. Each member’s insights and contributions can not only greatly enhance the original concept—often in unexpected ways—but also increase the probability of success. Failure to recognize the need for and value of team members with these additional and specialized skill sets can quickly leave the innovation languishing without a clear path forward. Quite often the decisions made early, such as those involving IP, may have long-
lasting consequences (positive or negative) that can have a profound effect on the commercial viability of the innovation. There are many of us who operate in this critical part of the continuum, with many hard lessons learned, and are willing and able to provide the expertise, guidance, and financing to help inventors and founders move their innovations to the next level.

Although initially I trained as a dermatologist (and continued to practice one day a week until about two years ago), I now consider myself a full time entrepreneur. I have worked in the pharmaceutical industry for 19 years and have been fortunate to start and sell a number of companies. One of the most rewarding aspects of entrepreneurship is working with inventors and founders as they navigate through the complex fund-raising and business aspects of the process. A great example is the journey Stuart Shanler and I embarked on several years ago.

Stuart Shanler and Andrew Ondo collaborated on the initial discovery that α-adrenergic agonists could be used topically to treat the erythema of rosacea (Shanler and Ondo, 2007). After filing IP around the discovery, Dr Shanler needed to determine how to get his invention into formal development, clinical trials, and, ultimately, the hands of patients. Dr Shanler was a full-time practicing Mohs surgeon with little exposure to the pharmaceutical industry or the business world. Knowing he needed assistance, Dr. Shanler asked me to advise and assist him as he contemplated his next steps. Although we both agreed that there was an unmet need and that this represented a real innovation in the field, we needed to determine the path through the continuum to the patient. This involved crafting a development plan and budget, building a team around the asset, forming a company, and negotiating with each other to establish a value for the asset and the relative ownership in the company.

After many months of discussions and planning, we were ready to secure funding for the company. During the fund-raising part of the process, we pitched the idea to investors (venture capitalists) who conducted extensive diligence on the asset and newly assembled team. After a few months, we secured a term sheet from a lead investor and then set about navigating the complex fund-raising and business aspects of the process. A great example is the journey Stuart Shanler and I embarked on several years ago.

Once we secured financing, we had to execute the plan that we promised to our investors. This involved establishing the appropriate regulatory path, interfacing with the US Food and Drug Administration, developing a formulation, conducting preclinical studies with the formulation, filing an investigational new drug application to study the new drug in humans, conducting the clinical studies, and much, much more. At each point in the process, there were a multitude of variables to consider and balance. As an example, a topical formulation must meet several criteria across a matrix of variables: stability parameters, aesthetic quality, and penetration and release characteristics, to name a few. Any major issues identified with any of these variables could result in significant delays and increased costs. Even if everything goes perfectly, drug development is a multi-year process costing millions of dollars with no guarantee of success. Fortunately, we had the right team, coupled with a great innovation, which enabled us to successfully navigate the asset from the preformulation stage up through a successful phase II program. Ultimately, we passed the baton: Vicerpt was sold to Allergan in 2011. Drs. Shanler’s and Ondo’s invention is well on its way to being available for patients suffering with facial erythema.

I have been fortunate to have been through this process several times, and the story above is rather typical. To successfully progress through this continuum requires constant rebalancing, which necessitates close collaboration among scientists, inventors, practicing dermatologists, investigators, drug developers, business executives, entrepreneurs, and investors. Innovation is truly a product of each of the constituencies of the value chain. In fact, if orchestrated appropriately and well executed, the separate components are self-reinforcing. In business, the value chain is defined as the full range of activities that companies go through to bring a product or service to their customers (Porter, 1985). Value-chain analysis relies on the basic economic principle of “advantage” in that companies are best served by operating in sectors where they have a relative productive advantage compared with their competitors (Porter, 1985; Meyer and Mathonet, 2005).

If one applies this analysis within the continuum of translational research, several similarities immediately become apparent: The way to optimize the value chain in translational research is to ensure that the appropriate team members, i.e., those with a relative productive advantage in terms of the knowledge and skill set they bring to the continuum, are layered in at the appropriate points of the process. Similarly, translational research must be viewed as a much broader collaboration, encompassing not only the people (or entities) who contribute to the innovation at its earliest stages but also those who deliver their contribution to the value of the product further downstream.

One way to help facilitate translational research and replicate the success described above is to build, support, and extend the dermatology ecosystem. Continuous evolution requires continuous adaptation, and the landscape in both clinical practice and industry is changing rapidly. As dermatologists, we all have a stake in translational research and innovation. To continue to foster growth in our specialty, we must move outside our comfort zone and engage more broadly with the other constituencies. When considering entrepreneurship, it is important to understand the
complex decision matrix that must be navigated regarding the identification, nurturing, operationalizing, and ultimately commercialization of a compound (asset). Often this process can be as complex and difficult to traverse as the basic-science discovery itself. The breadth and intensity of the process can seem daunting because the continuum of innovation and translational research requires a dizzying array of skills and resources, and even those well equipped are challenged on a daily basis. But, although occasionally rough, with the right partners the seas are navigable.

Fortunately, there are more resources then ever at the innovator’s disposal. One is Advancing Innovation in Dermatology (AID), a group formed by William Ju, Rox Anderson, Bill Eaglstein, and Brian Cunningham in 2011. AID is a not-for-profit organization committed to catalyzing the development of new dermatologic solutions for patients and health-care providers by bringing together the various stakeholders who, together, can help enable, encourage, and support the development of new products and technologies for skin conditions. The organization is now guided by a group of like-minded medical professionals and thought leaders in the field who recognize the need for an increased commitment to new, scientifically based solutions in dermatology. AID’s goal is to facilitate meaningful interactions and create an ecosystem encompassing a broad range of constituencies, all with the common interest of bringing innovative products to market that will substantially improve dermatologic health. The organization’s members believe that an interconnected community is a strong one, and each year it hosts the Dermatology Summit at the JP Morgan Healthcare Conference in January and the Dermatology Entrepreneurship Conference in conjunction with the annual American Academy of Dermatology meeting in order to provide a venue to learn, meet people, and exchange ideas about the next generation of dermatology products. In the past two years, the attendance at these conferences has clearly demonstrated the latent demand and the enthusiasm for entrepreneurship and innovation in our specialty.

All members of our community can and must play an important role in ensuring that we have a continuous pipeline of new and impactful products for our field. Dermatology research centers, clinician and scientist entrepreneurs, investors, corporate partners, and many others each bring with them important and complementary talents and resources. Building and maintaining a successful ecosystem will help sustain a vibrant continuum for translational research. As we continue to advance our understanding of the pathophysiology of many skin diseases, it is incumbent on all of us to engage and make a difference to support the specialty.

ACKNOWLEDGMENTS
The author recognizes Stuart D. Shanler for his insights, assistance, and contributions to our field. In addition, I thank my fellow board members of the Dermatology Summit and Dermatology Entrepreneurship Conference: William Ju, John Doux, Albert Cha, Seth Orlow, and Frederick Beddingfield. This group’s dedication and drive have helped create a renewed energy and ultimately a more robust ecosystem to cultivate the next great innovations in dermatology.

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REFERENCES


Edward Jenner Performing the First Vaccination in 1796
Edward Jenner Performing the First Vaccination in 1796 (ca. 1895, Gaston Mélingue).

In this issue, we introduce the JID theme for 2015, “Progress in Translational Research” (see the Editorial on page 1), with the story of Edward Jenner's demonstration that cutaneous inoculation with purulent material from a patient's cowpox lesion—a procedure he termed “vaccination,” from the Latin vacca for “cow”—confers immunity to the similar but far more deadly disease variola, or smallpox. Beginning in the Middle Ages, wave after wave of smallpox epidemics decimated the population of Europe and later the New World. It had been noted that patients who survived smallpox were subsequently immune to the disease. By the early 1700s, Europeans became aware of a practice in Turkey and other parts of the world of intentionally inoculating healthy people with purulent material from a smallpox lesion (“variolation”). This led in most, but not all, cases to a mild transient disease with little scarring, followed by long-term immunity. Because the fatality rate was about 2–3%—no more than one-tenth that of naturally acquired smallpox—many physicians and their patients opted for this procedure. At this time, it was also recognized by cowherds, although not by learned physicians, that contracting cowpox, a mild disease common in cows, seemed to protect workers from smallpox.

Jenner, working as a physician/surgeon in rural England, made the intellectual leap that purulence from a cowpox lesion might be substituted for purulence from a smallpox lesion to provide immunity to smallpox with virtually no risk. In 1796, he used the purulent drainage from a cowpox lesion on a dairymaid's hand to “vaccinate” the arm of a healthy 8-year-old boy, James Phipps, who developed a mild fever and axillary adenopathy but was soon completely well. Two months later, Jenner “variolated” the boy, who developed no smallpox lesions or symptoms. Jenner carefully wrote up his observations and interpretation and submitted the paper to the prestigious Royal Academy—which rejected it. The following year he self-published a booklet setting forth his hypothesis and supporting data based on young Phipps and several other vaccinated patients. Acceptance of Jenner’s approach was not immediate, but he persevered and provided inoculant to numerous physicians, who replicated his observations. Within 40 years, vaccination became the standard of care in Europe and the United States, leading to virtual eradication of the deadliest disease of the time.

There are several lessons in this story. (i) Jenner was observant and open-minded. (ii) Based on the available information, he made a reasonable deduction about the potential benefit of vaccination and then performed and documented proof-of-principle experiments. (iii) It is highly unlikely that any institutional review board would have approved his experiments. (iv) His learned peers initially rejected his hypothesis and supporting data. (v) Without any knowledge of virology or cutaneous immunology, Jenner almost single-handedly eliminated the world’s deadliest and most disfiguring disease. In the 1700s, the “bench” in bench-to-bedside translational research was underdeveloped, but the approach of harnessing astute observations for patient care, epitomized by Edward Jenner, remains central to successful translational research.

When I began training in dermatology in the 1970s, I was impressed with the rapidly increasing depth and breadth of cutaneous research and eager to participate in what I imagined would soon be a revolution in the diagnosis and management of skin disease. I was fortunate to train in a department in which recent progress in human photobiology was being translated rapidly into an effective new therapy for psoriasis, mycosis fungoides, and other T cell–mediated dermatoses (Parrish, 2012). I even had the good fortune to spend one year of my residency as the photobiology fellow, participating in clinical research and developing new therapies that became immediately available to patients (Gilchrest et al., 1976, 1977, 1979). The experience was highly gratifying and motivated me to obtain laboratory-based training following my residency to prepare for a career bridging basic discoveries at the cellular and molecular level with improvements in patient care. Limited only by my imagination and work capacity, I embarked on just such a career.

My story could not happen today. The inability of dermatology residents to immerse themselves in translational research at the most formative time in their careers is a great loss, not only to aspiring physician–scientists and clinical investigators but also, and more importantly, to dermatology as a discipline and to our many patients whose diagnostic and therapeutic needs remain unmet.

With the best of intentions, our government, certifying agencies, and academic institutions have imposed numerous hurdles on the preparation for and conduct of translational research. Cumulatively these regulations and requirements deter all but a handful of exceptionally determined individuals from attempting to translate discoveries from bench to bedside.

Consider the typical dermatology trainee who may have participated in laboratory-based research as a medical student, in some cases in the context of an MD–PhD program, suggesting a strong intent to mature into a physician–scientist. Upon entry into a dermatology residency program, he or she is likely to be informed that devoting any substantial time during the three-year residency to research—whether clinical or laboratory-based—is virtually impossible. In addition to the extensive and detailed certification requirements of the American Board of Dermatology, hospitals require a full complement of residents in patient care roles. Dermatology departments also rely on this clinical manpower to meet their patient-care obligations. As teaching hospitals and dermatology departments become ever more reliant on high patient volumes to make ends meet financially, the time and money required to encourage resident participation in research disappear.

Should the resident be willing to work nights and weekends on a clinical research project (knowing that laboratory-based or animal research is usually even less compatible with the obligations of dermatology residency), it soon becomes apparent that delays are to be expected. First, the trainee must take a formal course to qualify as a clinical investigator and thereafter must maintain certification, usually with monthly reading assignments and quizzes. Submission of the project proposal to the institutional review board and the inevitable revisions require months—in my own experience up to a year (a long time in the context of a three-year residency program). Once the project is approved and under way, meticulous and time-consuming HIPAA (Health Insurance Portability and Accountability Act)-compliant data storage is required. Of course, it is impossible to argue against the intent of these safeguards or the necessity of covering institutional costs by maximizing residents’ patient-care roles. However, it appears that little attention has been paid to cost–benefit ratios or to the lost opportunity that results from discouraging trainees from participating in research early in their careers. I believe the cost is huge—both to the trainees, who will forfeit many years of professional challenges and accompanying rewards, and to the patients who will never benefit from their potential discoveries.
To trainees, such impediments must seem the inevitable way of the world, integral to conducting safe, ethical research. They may deduce that meaningful participation in research is incompatible with obtaining a solid foundation in the practice of dermatology, at least during a three-year residency. But none of these requirements existed 30 years ago! Research-oriented residents, many of whom are today's department chairs and accomplished career-long investigators, as well as highly regarded clinicians, routinely spent a year or more of their three-year dermatology residency at the bench, seeing patients under faculty supervision for perhaps only half a day per week during that time. Their research, including human-subjects research, was discussed in an ongoing manner with appropriate faculty supervisors but did not require lengthy applications or approval by committees unfamiliar with the disease being studied or the specific techniques employed. In the “old days,” mistakes may have been made and study designs may occasionally have been flawed, but I suspect such errors still occur today. Importantly, however, in the absence of extensive regulation, a critical number of physician–scientists and clinical investigators-to-be emerged from their residencies fully committed to translational research, their enthusiasm and curiosity intact.

Over the past 30 years, a second phenomenon has discouraged translational research, although happily it is now being addressed constructively. I refer to the core belief by many academics that product development is ethically and intellectually inferior to “basic” research. Related beliefs include the ideas that involving physicians in bringing their intended treatments or diagnostic procedures to the clinic creates an insurmountable conflict of interest (Stell and Stossel, 2011); that money is the major incentive for physicians or anyone else becoming involved in such projects; and that encouraging pharmaceutical or biotechnology companies to participate in research meetings reduces meeting quality, introduces bias, and detracts from physicians’ learning. The consequence of such beliefs was for many years a dysfunctional separation between leading physician–scientists and clinical investigators and those best able to harness their discoveries for improving human health.

The 1984 Bayh–Dole Act was enacted in response to Congress’s realization that surprisingly little US government–funded research resulted in new disease treatments or better public health. This legislation directed academic institutions to promote commercialization of discoveries made by their federally funded investigators. Motivated by the potentially lucrative provision of this act that institutions—the owners of any intellectual property created by their faculty—could generate income from this process, academic medical centers gradually developed “technology transfer offices” to assist investigators with patent protection and then licensing their discoveries to companies wishing to commercialize them. Although often inefficient and underfunded, these offices did provide assistance to already savvy investigators. More recently, these offices have also attempted to educate students and faculty in relevant matters. In tandem with a more progressive view of the product-development process by the professoriate, such efforts are slowly bearing fruit.

As will be described in a series of invited editorials to be published in JID throughout 2015, several dermatologic investigators have successfully participated in the creation of new drugs and devices based on their own laboratory work or are working to facilitate the translation process through creation of new structures or paradigms. As well, the Society for Investigative Dermatology (SID) and many other dermatologic research organizations have begun to reach out to industry representatives and venture capitalists. The SID now solicits their membership, invites them to annual research meetings, welcomes sponsored symposia, and has even initiated “speed dating” sessions to promote dialog between individual investigators and those who might commercialize their work. All these efforts have great potential to accelerate progress in translational research.

Translational research is a vague term used by different individuals and groups to mean different things (Cripe et al., 2005; Rubio et al., 2010). To me, the critical elements include conceptualizing an improvement in patient care, identifying a potential means of achieving that improvement through one’s own research or recognizing that means in the work of another, demonstrating proof of principle, and then assembling the team that will be required for commercialization. It is an ambitious undertaking, easily derailed. It cannot thrive in an environment that is overly distrustful or disparaging of any of the required components. Translational research is best taken up as early as possible in one’s career because there is much to learn and many experts who need to be in the professional network of a successful translational researcher.

Not every dermatologist or cutaneous biologist wishes to participate in translational research or, indeed, research of any kind. I am comfortable in suggesting, however, that everyone in the larger dermatology community must be supportive of this effort. This includes those responsible for setting the parameters of dermatology training, those supervising residents, those referring patients for research projects, and those funding research proposals. At the institutional level, I urge consideration of the risk–benefit ratio when evaluating protocols that entail truly minimal risk to human subjects (e.g., a punch biopsy or completing a questionnaire). Benefits of rapid, hassle-free approval include not only conducting the research in a timely manner but also teaching young investigators that such research can involve them in a deeply gratifying process and yield interesting results after a tolerable investment of time. I predict that even a modestly enlightened application of federal institutional review board regulations at teaching hospitals would notably promote clinical and translational research among investigators at all levels of seniority.

However, the primary rationale for selecting “Progress in Translational Research” as the JID’s 2015 theme is not to emphasize current barriers. For many reasons, these barriers are unlikely to be mitigated in today’s medical envi-
ronment. Rather, it is to celebrate the impressive progress being made despite the obstacles described above. Such progress is manifest in every issue of the Journal and in day-to-day patient care. May this progress continue and accelerate.

**Barbara A. Gilchrest**
*Editor*

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Niels Finsen: The Birth of Modern Phototherapy
The accomplishments of Niels Finsen (1860–1904) are of particular interest to dermatologists and photobiologists, and he provides an inspiring example of translational research. Born in the Faroe Islands, Denmark, Finsen studied medicine at the University of Copenhagen but struggled with severe fatigue and anemia, symptoms of Niemann–Pick disease, which eventually confined him to a wheelchair and led to his premature death.

After graduating at age 30 and teaching at the university for three years, Finsen decided to devote all his limited energy to finding a treatment for his disease. Hypothesizing that sunlight might be of benefit, he systematically studied the effects on various microbes of ultraviolet light, which he called the sun’s “chemical rays,” as well as visible light and infrared (heat) energy. After recognizing the inherent limitations of his laboratory-based studies, he expanded his work to clinical trials using sunlight and a carbon arc lamp that he had developed (which was later termed the Finsen lamp). When a smallpox epidemic struck Copenhagen in 1894, he observed that scarring was aggravated by UV irradiation but reduced by red light exposure, which enabled many to escape the disease’s dread sequelae.

His greatest success, however, was with UV irradiation of lupus vulgaris, a superficial but often severely disfiguring skin infection that is a complication of tuberculosis and for which there was no previously effective treatment. Within a few years, this phototherapy breakthrough was acknowledged by the creation of the Finsen Institute in Copenhagen, soon expanded with philanthropic and government support. In 1903, Finsen received the Nobel Prize in Physiology or Medicine for this discovery, although his poor health prevented him from attending the award ceremony. Less than a year later, at age 43, he died of cardiac and hepatic failure.

From the perspective of translational research, there are several lessons to glean from Finsen’s lifework. First, he was passionate about his research. Motivated initially by a desire to reduce his own suffering and prolong his life, his discoveries led him in a tangential direction. Although Finsen clearly recognized this, he continued to pursue his findings with an intensity that was seemingly impossible in the face of his progressive illness. Second, the primitive nature of his research tools and limited understanding of photobiology and microbiology did not prevent Finsen from conceptualizing practical application of his discoveries and then pursuing them. Indeed, the mechanism by which phototherapy can cure lupus vulgaris remains incompletely understood today; it may include both UV-mediated microbial killing and visible light-mediated photodynamic effects attributable to low-level porphyrin synthesis by Mycobacterium tuberculosis. Third, lack of regulatory constraints at the turn of the twentieth century allowed virtually immediate introduction and widespread adoption of this much-needed new approach to a devastating dermatosis. Now, slightly more than a century later, a man of such modest means and very limited time and energy could almost certainly never make this important a contribution to human health.
Randomized controlled clinical trials (RCTs) and systematic reviews of RCTs serve a pivotal role in informing evidence-based practice through guidelines and shared decision making (Williams and Dellavalle, 2012). Although some innovations such as adaptive designs have emerged (Kunz et al., 2014; Parmar et al., 2014), the basic design of a clinical trial has remained largely unchanged since the first trials of streptomycin for tuberculosis in 1948 (Crofton, 2006), especially with regard to the fundamental methods designed to reduce bias. Thus, randomization that is truly random and concealed from investigators serves to reduce selection bias. Blinding the intervention and ensuring that each treatment group is followed up in the same way reduces performance bias. Assessing the outcome in a blinded fashion reduces detection bias, and analyzing all those that were originally randomized through an intention-to-treat principle minimizes attrition bias (Higgins and Green, 2011). Knowing how to critically appraise a clinical trial is a core competency for clinical dermatologists and scientists interested in evidence-based medicine (Williams, 2011).

Here, we provide some useful tips on how to play your cards right when submitting your trials to this journal. Although the Journal of Investigative Dermatology does not publish many RCTs compared to some clinical dermatology journals (Williams, 2014), our output has steadily increased (10 in the past five years compared with 6 in the five preceding years and two in the five years before that), and the JID has also published several systematic reviews dealing with methodological issues pertinent to designing good clinical trials (see, for example, Do-Pham et al., 2014). The RCTs that the JID does publish are well reported, thanks to our early adoption of the recommendations of the International Committee of Medical Journal Editors for prospective trial registration (Williams and Stern, 2005), structured abstracts (Williams and Bergstresser, 2010), and complete reporting (Williams and Goldsmith, 2006) according to the Consolidated Standards of Reporting Trials Statement (CONSORT) (http://www.consortstatement.org). These principles can seem to be annoying obstacles, so it is worth revisiting their purpose through analogies to the basic rules of playing cards (Figure 1).

**Rule 1: place your bet**

Sadly, despite the potential of clinical trials to minimize bias, history is replete with examples of distortion of the scientific record (Chalmers and Glasziou, 2009; Goldacre, 2012). A particular source of bias that besets clinical trials—and any experimental investigation, for that matter—is selective highlighting of results that look good and downplaying or not reporting those that look unimpressive (Chan and Altman, 2005). It was previously easy to get away with such selective reporting outcome bias because only the investigators knew what their original plan and primary outcome or definition of “success” were. This problem has been unearthed in all branches of medicine and surgery, including dermatology. In a survey of 109 RCTs of atopic dermatitis treatment identified through the Global Resource of Eczema Trials (GREAT), only 34 had been registered on an approved register, and only 19 of these had been registered properly, that is, before recruitment starts and by declaring their main success criteria beforehand (Nankervis et al., 2012). Only 5 of the 109 RCTs provided enough information to allow confidence that the main reported findings were consistent with the original registration. Prospective trial registration overcomes the problem of selective reporting outcome bias quickly and easily. Prospective means prospective. Specifically, you must register your trial and “place your bet” on one of the recognized trial registers before recruitment starts, not when submitting your trial report.
Rule 2: show us your hand
If you were buying a used car, you would not contemplate a purchase without inspecting the service record and viewing all the essential items such as applicable taxes, proof of roadworthiness, and ownership history (Williams, 2010). In the same way, you should not “buy” the results of a trial unless all of the essential basic items are reported. Complete reporting does not necessarily mean good quality, but it is difficult to say anything about study quality without seeing exactly what was done to whom and how. Not only does full reporting permit judgment of study quality and how the results might apply to the sorts of patients seen in everyday clinical care, but it also permits inclusion of that study in a systematic review of all relevant evidence. All trials have a second life in such systematic reviews. Systematic reviews of RCTs and appropriate meta-analysis of those trials are often considered the most informative study type in the evidence-based hierarchy of effectiveness studies, yet missing essential information, such as description of the intervention, participants, control group, and outcomes, frequently hampers the efforts of those who produce systematic reviews such as those in the International Cochrane Collaboration (http://www.thecochranelibrary.com). Thankfully, the CONSORT statement and its various extensions for pragmatic, noninferiority, and cluster trials offer a simple checklist for authors to which the JID adheres.

Rule 3: make it a good hand
Although the JID encourages submission of clinical trials that are prospectively registered and fully reported, competition to publish in our journal means that they also must be something special. Small, early, inconclusive proof-of-principle trials are less attractive to the JID unless they unlock some key insights into mechanisms of diseases. Such clinical trials must be truly translational in the way that they are integral to any mechanistic study (see, for example, Papp et al., 2012), rather than stuck in as an afterthought to pad out a submission. Clinical trials with built-in mechanistic components defining which patient groups respond best to treatment fit in very well with our journal’s theme of “Progress in Translational Research” for 2015. Not all JID trials need to elucidate mechanisms, however. Definitive phase III studies that are likely to change clinical practice or are newsworthy in some other respect are also welcome (see, for example, Joly et al., 2009). Clinical trials evaluating commonly used treatments in which for-profit organizations have little interest, such as a head-to-head comparison of prednisone and mycophenolate mofetil for pemphigus vulgaris, are also welcome (see, for example, Beissert et al., 2010). Such trials need not have a “positive” outcome; demonstrating equivalence or noninferiority in a planned way by estimating likely treatment effects using confidence intervals can be just as informative.

Conclusion
Comparing clinical trials to gambling with cards may sound superficial, yet placing a bet is exactly what happens when testing a hypothesis, and declaring the results fully and honestly is what every good trialist should do. Undertaking a clinical trial is a serious professional business that relies on the altruistic donation of time and informed risk from patient volunteers. Clinical trials are set to remain a backbone of experimental design to inform insights into the causes, mechanisms, and treatment of skin diseases. We welcome their inclusion in this journal.

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Sidney Farber with a Young Leukemia Patient
In the 1940s, childhood leukemia was uniformly fatal, usually within weeks after diagnosis. Sidney Farber (1903–1973), an assistant professor of pathology at Harvard Medical School and Children’s Medical Center in Boston, was aware that deficiency of folic acid (FA), a recently discovered metabolite, could lead to the appearance of leukemia-like cells in the blood and bone marrow, changes that normalized after folate repletion. Hypothesizing that acute leukemia represents FA deficiency, he began to treat children using FA. Unfortunately, this tended to accelerate the disease course, a now-foreseeable outcome. More than 90 children were treated unsuccessfully. He then became aware that Lederle Labs was creating FA antagonists that inhibited normal cell growth. Farber obtained several of these compounds and administered aminopterin to 16 children with advanced leukemia. Ten achieved temporary remissions, results reported in the New England Journal of Medicine in 1948. Today, the closely related FA antagonist methotrexate remains widely used for cancer chemotherapy, as well as for benign hyperproliferative disorders such as psoriasis.

Although Farber’s work was initially met with disbelief and resistance by the medical establishment, those caring for children with leukemia soon adopted this approach, testing various antimetabolites individually and in combination, leading in 1958 to the first systematic combination chemotherapy trials for childhood leukemia, a multicenter effort that eventually revolutionized patient care and prognosis. The survival rate for acute lymphoblastic leukemia (ALL), by far the most common childhood leukemia, rose from 0% in 1950 to 50% in 1980 to more than 90% today, reflecting the increasing success of chemotherapy regimens.

Sidney Farber went on to develop a successful chemotherapy protocol for Wilms tumor, and, critically, his personal efforts enormously expanded private philanthropic and federal funding for cancer research. He also conceived of a “total care” approach, integrating all aspects of a child’s and family’s experience to decrease their stress, another major contribution to pediatric oncology. He has been rightly lionized as the father of modern cancer chemotherapy. On the basis of his reading and observations made at his laboratory microscope, without prior patient-care experience, Farber initiated a clinical research program that within five years established the value of a previously untested approach to a fatal disease. However, as noted in regard to other celebrated translational researchers in this series (see the cover information for the January and February issues of JID), in today’s world this breakthrough would probably require decades, if it could be achieved at all. What institutional review board would sanction administration of a known toxin to severely ill children—especially after 90 consecutive children had died during a very similar intervention, many more rapidly than otherwise? Would the FDA or IRB ever allow a drug company to provide an unapproved drug for such a trial? As we celebrate the courage and vision of translational researchers such as Sidney Farber, we must ask ourselves these difficult questions.

Background for these comments was obtained from Wikipedia (accessed 6 November 2014) and two commentaries (D Ribatti D, Pediatr Hematol Oncol 29:299–302, 2012, and DR Miller, Br J Haematol 134:20–26, 2006). Photo courtesy of Dana–Farber Cancer Institute.
From the Bench to the Bedside and Back: An Essential Journey

Barbara Gilchrest, in her inaugural Editorial for this series on translational research, related that her clinical experiences kindled a desire to pursue laboratory-based training to bridge “basic discoveries at the cellular and molecular level with improvements in patient care” (Gilchrest, 2015). Her approach was bedside to the bench (…and back). My career had just the opposite genesis. I wanted principally to do fundamental biochemistry and cell biology and, indeed, embarked on a postdoctoral career studying tadpole metamorphosis under the tutelage of Arthur Eisen, then head of the Division of Dermatology at Washington University School of Medicine in St. Louis. That I found a career in dermatology, let alone one steeped richly in translational research, is due largely to consummately practical advice from two people.

Before I delve into the rest of that story, I want to set the stage. When she invited me to write an Editorial, Dr. Gilchrest asked me to review my career and the insights that fostered movement from fundamental research to academic administration and finally to industry. Reflecting on this challenge, I quickly realized that the assignment was not about my career, but rather about the plethora of challenges and opportunities that dermatology (writ large) offers to all of us. This commentary begins in the mid- to late 1960s, a scientifically fertile time for the deployment of nascent technologies, to bring them to bear on dermatologic diseases and to allow for observations that had theretofore been impossible.

Early in my postdoctoral career, one of the most stimulating descriptions of the scientific state of dermatology was offered in a 1967 New England Journal of Medicine review by Irwin Freedberg, then at Harvard Medical School and later chairman of the Department of Dermatology at New York University School of Medicine. In his article, entitled “Rashes and Ribosomes,” Freedberg stated, “The era of the rash is in the past, and the era of complete understanding of dermatologic problems is still in the future” (Freedberg, 1967). Not given to unsubstantiated generalities, Freedberg cited as an example the importance of correlating recent electron microscopic insights with fundamental protein-synthetic and nucleic acid labeling studies to probe mechanisms of diseases such as psoriasis and ichthyosis. He reviewed the extant thinking about psoriasis to be the result of a process that “is genetically determined with a positive family history.” He went on to say that, without proof, “I am certain that [psoriasis] is related to an abnormality in the control of either epidermal cell division or differentiation” and that data “have pointed to the existence of substances in skin ... that will control epidermal proliferation.” His prescience joined that of perhaps a dozen others in dermatology at the time to adumbrate subsequent decades of work that have elucidated the complex genetic underpinnings of psoriasis along with a mind-boggling array of cytokine interdependencies that are keys both to the pathogenesis of the disease and to our hopes for rational interventions. At the time, such examples represented for me the excitement of being part of a discipline undergoing a metamorphosis from the descriptive to the mechanistic.

While the 1960s saw the blossoming of dermatologic clinical scientists deeply interested in the fundamental underpinnings of cutaneous biology, Freedberg (1967) used the “Rashes and Ribosomes” report to review how emerging techniques could also be used to understand therapy. He showed that when the widely used topical coal tar and UV light therapy (the so-called Goeckerman regimen) produced clinical remission of psoriasis, there was a concomitant fivefold decrease in DNA and RNA synthesis, as well as a significant decrease in protein synthesis, in the psoriatic plaques. Again, the excitement for me was the articulation of a collective sentiment, among an impressive array of dermatologic clinical scientists and skin biologists,
that we were working at the dawn of a mechanism-based approach to fuel dermatologic therapeutics.

From our enlightened vantage point more than four decades later, we acknowledge—both intuitively and explicitly—that discovery of fundamental pathways will lead to better therapeutics. But acknowledgment also embodies a challenge: how do we maintain the flow of basic knowledge and what is the best way to ensure its translation into therapeutics? Now, as in the mid-1960s, dermatology remains ripe for innovation. Indeed, various waves of innovation have occurred over the past 50 years, including systemic and topical steroids for control of cutaneous inflammatory disorders; antimitabolites and immunosuppressive agents for control of psoriasis; systemic and topical antibiotics for the treatment of acne; systemic and topical retinoids for use in disorders of keratinization and in acne; novel forms of phototherapy, such as psoralen plus UVA and later narrow-band UVB, for amelioration of psoriasis and mycosis fungoides; calcineurin inhibitors for control of eczema; and biologics for the treatment of psoriasis. Each of these embodied the paradigm of bench to bedside to bench, as increasing efficacy and safety data impinged on product and/or regimen design. In a greater sense, as important as these advances have been to the lives of our patients, their emergence has been sporadic and stuttered at best.

My lifelong career conviction has been that maintenance of a flow of knowledge and discovery is crucial to survival, let alone a robust thriving, of dermatology. In 2000, I was deeply enshrouded in issues related to payment for services in a major academic medical center. I argued that, despite the fact that—from an intellectual standpoint—dermatology had never been more exciting, much of the public and many payer organizations considered dermatology the study of relatively trivial diseases requiring little expertise and deserving minimal investment (Bauer, 2000). I further argued that public perception of dermatologists as aestheticians reinforced the very trivialization that we wished to avoid. In the intervening almost 15 years, little has changed to alter those perceptions. Let me emphasize that I in no way denigrate the need for dermatology and dermatologists to be responsive to the quality-of-life issues driven by patients’ deep self-image needs. Rather, I argue that our value must rest on a solid scientific foundation and that we must, with one voice, articulate how science informs the needs—medical, surgical, and aesthetic—of patients.

Let me now return to advice given me by two wise mentors, both of whom counseled—not only with words but also by example. The first was Ruth Freinkel, who at the time was professor of dermatology at Northwestern University School of Medicine. As a medical student, I sought Ruth’s advice about where to begin my laboratory research career. She could have urged me to stay at Northwestern, but with great generosity of spirit Ruth suggested that I go the Eisen lab at Washington University in St. Louis. The basis for her advice rested with the excellence of the science being done by Eisen and his collaborators, although I believe her more subtle goal was to ensure that I would be compelled by the excitement of doing real science as it related to dermatology. In retrospect, she could not have been more right, because the second role model was Arthur Eisen himself. What I learned from Arthur was multifold:

- To recognize the importance of the unity of science (i.e., genetic principles, protein-synthetic mechanisms, and regulatory controls transcend species and are, in principle, the same in bacteria, in amphibians, and in humans)
- To allow trainees to follow their noses scientifically and to provide a nurturing environment not excessively fettered by superfluous structure
- To encourage broad thinking and appreciation that the applicability of a technique used in a different discipline might apply to dermatology and that curiosity, tenacity, and common sense can pay off
- To develop a trusted team of basic and clinical scientists to engender cross-fertilization for optimal movement of projects—both basic and clinical—to fruition

These same principles have continued to guide me in my stints as department chairman, dean, and entrepreneur.

Perhaps the best example of a transition from fundamental research to industry is that of my first encounters with Genentech. During my Washington University tenure, our fundamental research involved connective tissue biology and biochemistry—synthesis and degradation of collagen—in health and disease. Inevitably, this led us (Jouni Uitto, then at Washington University, now chairman of dermatology at Jefferson Medical College, and me) to an interest in scleroderma and an examination of collagen-synthetic and matrix metalloproteinase expression in scleroderma fibroblasts. Our patient-oriented research was not truly translational; rather, it employed patient-derived cells to probe mechanisms (Uitto et al., 1979). Upon my arrival at Stanford, Edward Amento, who at the time headed a connective-tissue/immunology group at Genentech, asked me to consider using recombinant human relaxin, an inducer of expression of matrix metalloproteinase I, as a possible therapy for scleroderma. We filed an investigator-initiated investigational new drug application with the US Food and Drug Administration (FDA) and treated one patient who suffered from moderately severe systemic sclerosis. The results were sufficiently encouraging to allow us (Amento at Genentech; Brian Seed, professor of genetics at Harvard Medical School; and me) to outlicense the relaxin technology and form our first company, at the time known as Connective Therapeutics and later renamed Connetics Corporation. We had come at least half-circle from bench to bedside. What we learned from later scleroderma patients would take us full-circle, i.e., from the bedside back to the bench. We learned that the amelioration of tissue fibrosis was seen in only some patients, and even in them it was not durable. The lesson was an important one—not to have tried would have guaranteed failure. To have tried for a solid-cell biologic/biochemical rationale at least informed future therapeutic avenues. Sadly, scleroderma remains one of the greatest challenges of dermatologists and rheumatologists.
Generally, however, there remains great cause for hope and enthusiasm. Dermatology, as a clinical-scientific discipline, has been a leader in elucidating genotype-phenotype correlations. The reason is obvious: we can, literally, see the phenotype. The addition of the powerful tools of the genomic revolution offers the basis for understanding hereditary diseases of the skin, such as epidermolysis bullosa (Fine et al., 2014), and further offer the promise of not only symptomatic but also corrective therapy (Woodley et al., 2013; Cogan et al., 2014; Siprashvili et al., 2010; Sun et al., 2014). Novelty continues to drive the industry side of dermatologic therapeutics as well, with the founding of several new companies, including our own, palpably focused on innovation.

Let me extend the analogy: to the same degree that we can see the problems of skin diseases, there is also an elegant simplicity in being able to see and measure the responses to therapy. Admittedly to oversimplify, the regulatory pathway for approval of dermatologic therapies is predictable and straightforward. As a generality, both efficacy and safety observations made in an adequately powered proof-of-concept trial have a reasonable probability of being sustained in later stages of development. Unlike many trials for therapeutics in internal medicine, we are not generally burdened with measuring an evanescent surrogate marker before we assess efficacy in the “real” disease. Rather, with the approval of the FDA, we as dermatologists rely largely on three important parameters: an absolute change in number (or size) of lesions, a physician–investigator global assessment of change (improvement), and, increasingly, a patient-reported outcome instrument.

If our ultimate goal is to improve the lives of our patients, let me posit that there is not one perfect way to success. I do believe, however, that there are more, and less, efficient ways to bring fundamental insights to improved patient care. In a Commentary for this journal in 2012, David Cohen, professor of dermatology at New York University School of Medicine, and I discussed the changing roles of industry and academia. We observed that ancient silos are breaking down, that both industry and academic and research institutions are engaging in basic research and applications, and that there is an essential porosity between bench and bedside (Bauer and Cohen, 2012). However, the fact that such barriers are being eroded does not a priori mean that the blurring of functions will lead to the most efficient pathway for development of a new therapeutic. Several academic institutions are now initiating programs, not only to capture intellectual property but also to invest in early-stage development. During my tenure as dean, I, too, argued for such an approach, which subsequently was implemented at Stanford, albeit on a small scale. One advantage of this approach is that the physician–scientists who discover a possible therapy will often be the very ones to whom patients are referred. With appropriate oversight, they should indeed have an opportunity to engage in early-stage, proof-of-concept trials. However, having been in industry for the past 14 years as cofounder of two companies and as founding CEO of a third, I now have a somewhat more robust perspective, one first articulated to me by Paul Berg, Nobel Laureate and professor of biochemistry at Stanford University School of Medicine. Paul’s deep conviction is that the essential role of universities and research institutions is discovery, and the role of industry is application and development to commercialization. To follow this paradigm draws on the inherent strengths of each, ensures that scientific creativity will not be sidetracked by a focus on application, and places later clinical development (i.e., beyond proof of concept) in the hands of those who are best equipped to oversee the nuances of regulatory pathways and all the preclinical, pharmaceutical sciences, and manufacturing requirements.

As dermatologists, we exist in a specialty where we have a deep connection to our patients. We must be especially attentive on a daily basis to both the visual (i.e., the medical/surgical) and the psychosocial (i.e., the emotional) aspects of our patients’ diseases. We should be opportunistic and accept clinical challenges to think about, create, and participate in patient-oriented research. As Ruth Freinkel said in an interview published posthumously (Paller and Bauer, 2014), “If anyone is interested in research of the skin, it will be hard. But if you do it successfully, there’s nothing equal to the feeling of having accomplished something that is really important.”

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The 1950s: A Magic Time of Discoveries at the University of Chicago
The 1950s: a magic time at the University of Chicago

Stephen Rothman (at left in photo) introduced laboratory-based dermatologic research to the United States after emigrating to the University of Chicago from his native Germany in 1938 (see Burgdorf and Bickers’s article in this issue for an account of Rothman’s many contributions to American dermatology over the subsequent three decades). In 1948, Eugene Van Scott (at right in photo) joined Rothman as a dermatology resident, and with Rothman’s encouragement he soon began studies of cutaneous arginase activity and sulfhydryl content. His aptitude and enthusiasm for this work led only four years later to his appointment as head of the Dermatology Branch at the National Cancer Institute (NCI), where he stayed for 19 highly productive years before leaving to assume the chairmanship of the Department of Dermatology at Temple University, Philadelphia.

The 1950s and 1960s were a time of explosive growth in the sophistication of laboratory-based research techniques and in federal research funding, particularly for cancer. (See the March 2015 JID cover image and legend on Sidney Farber’s introduction of chemotherapy for childhood leukemia.) In the stimulating NCI environment, Van Scott began to study the effects of cancer chemotherapeutics and X-irradiation on cell proliferation in human epidermis and hair follicles. Based on his laboratory observations, he also began clinical studies of the emerging cancer therapies for benign hyperproliferative skin diseases such as psoriasis as well as for malignant skin diseases such as mycosis fungoides. Van Scott pioneered the use of methotrexate, cyclophosphamide, and topical nitrogen mustard for such disorders, establishing dosing regimens still employed today. During and after his time at the NCI, Van Scott’s example inspired many other physician–scientists to continue this work.

Would another dermatologist have perused the same studies or made the same observations? We can only be thankful that Eugene Van Scott was in the right place at the right time and used that opportunity to harness powerful new drugs to treat dermatologic diseases.

In the 1970s, after leaving the NCI, Van Scott’s interest turned to keratinization and eventually to the interesting moisturizing and antiaging effects of alpha hydroxy acids. These more recent translational research accomplishments have made Van Scott a very wealthy, as well as highly respected, member of the dermatologic research community. He has generously chosen to recognize and support others who aspire to employ discoveries at the bench to improve patients’ health and well-being. The dermatology community is truly grateful.

The cover photograph and biographical information were provided by Chris Shea, head of the Dermatology Division, University of Chicago.
On 23 October 2014, the α-melanocyte-stimulating hormone (α-MSH) analog afamelanotide (Scenesse) attained approval as a first-in-class drug for patients with adult erythropoietic protoporphyria (EPP) who are extremely intolerant of UV and visible light. This successful drug-development program is the consequence of a determined effort to translate extensive basic research efforts. α-MSH was originally characterized as a pituitary-derived inducer of pigmentation (Harris and Lerner, 1957). Notably, Lerner and co-workers were also the first to assess intradermally and intramuscularly injected α-MSH in patients with vitiligo. The clinical effect was limited to some perifollicular pigmentation, and subsequent attempts with adrenocorticotropin-like peptides were never encouraging enough to bring these melanocortin peptides into daily practice in dermatology (reviewed in Böhm, 2010). The reason for the limited clinical usefulness of α-MSH lies in its chemical structure—the tridecapeptide is too big for transcutaneous delivery; also, it rapidly degrades in the gastrointestinal tract when taken orally. In the presence of human plasma, the half-life of α-MSH is less than 30 minutes (Eberle, 1988). One possible strategy to overcome this problem is chemical modification of the peptide without affecting the message and signal sequences required for the melanotropic effect of α-MSH. Among the plethora of MSH peptides tested by Hruby and co-workers, Nle-D-Phe7-α-MSH (NDP-α-MSH) emerged as one of the most potent and long-acting pigment-inducing synthetic melanocortin peptides (Sawyer et al., 1980). The first clinical studies in the 1990s revealed that local subcutaneous injections of NDP-α-MSH increase skin pigmentation (Levine et al., 1991; Barnetson et al., 2006).

Interestingly, anti-inflammatory and immunomodulatory effects were soon recognized during the functional characterization of α-MSH and found to reside within its C-terminal-tripeptide sequence (reviewed in Catania and Lipton, 1993). However, pharmaceutical exploitation of KPV has been unsuccessful until now. The field of melanocortin research rapidly expanded on cloning of the MC-Rs by Cone’s group (Mountjoy et al., 1992). The five MC-Rs (MC-1-5R) belong to the superfamily of the G-protein-coupled receptors with seven transmembrane domains and differ with regard to their binding affinities for melanocortins. The human MC-1R binds α-MSH and adrenocorticotropin with similar affinity. Investigating various cell types and tissues with MC-R subtype–specific probes in combination with functional studies allowed identification of several novel targets of α-MSH within the skin and beyond.

The main function of α-MSH within the skin becomes most apparent during UV-induced tanning. Sun exposure is a prototypical environmental stressor and increases expression of the proopiomelanocortin (POMC) as well as secretion of α-MSH in the skin (Schiller et al., 2004). The mechanism behind this phenomenon is complex and involves on one hand UV-induced activation of the tumor suppressor gene product p53 that subsequently binds to the POMC promoter in keratinocytes and turns on α-MSH expression (Cui et al., 2007). On the other hand, proinflammatory cytokines and mediators, some of them also players of the classical hypothalamic–pituitary–adrenal axis, orchestrate UV-mediated POMC expression and α-MSH secretion within the skin (reviewed in Slominski et al., 2000). Melanocytes that express MC-1R most abundantly subsequently respond to UV-induced α-MSH expression with increased melanogenesis, proliferation dendrite formation, and melanin transfer to keratinocytes.

The physiological role of MC-1R in the context of UV-induced pigmentation is highlighted by the finding of polymorphisms in the MC1R gene that are responsible for red hair and pale skin type. Carriers of loss-of-function alleles of MC1R have a higher risk for the development of melanoma and nonmelanoma skin cancer. Interestingly, this appears to be only partially
dependent on the impact of MC-1R on skin pigmentation (Beaumont et al., 2009). Accordingly, α-MSH has been found to directly reduce the extent of UVB-induced genotoxic stress in melanocytes (for example, to reduce the amount of cyclopyrimidine dimers). In individuals with loss-of-function MC1R alleles, this cytoprotective effect of α-MSH is lost (reviewed in Abdel-Malek et al., 2008).

Our picture of α-MSH in the skin, however, would be incomplete when leaving out the majority of other cell types responding to this molecule (reviewed in Böhm et al., 2006). In many of the above cell types, α-MSH was shown to suppress the activation of the transcription factor NF-κB, α-MSH and thereby modulate production of proinflammatory cytokines and expression of adhesion molecules (reviewed in Brzoska et al., 2008). Among the most recently identified human target cells of α-MSH are basophilic granulocytes (Böhm et al., 2012) and T cells (Loser et al., 2010; Auriemma et al., 2012), both key players of the adaptive immune system that orchestrate allergic and inflammatory responses of the skin and mucosal membranes. Studies of these nonmelanocytic cells of the skin further extended our current view of the cytoprotective armamentarium of α-MSH. For example, α-MSH directly upregulates nuclear factor E2-related factor 2, a transcription factor crucially involved in cellular redox homeostasis and a regulator of antioxidative enzymes like heme oxygenase 1 (Kokot et al., 2009a, 2009b) (see Figure 1).

The pleiotropic cytoprotective properties of α-MSH provided the rationale for exploiting melanocortins as a new treatment in EPP. EPP is a rare autosomally inherited disease of porphyrin biosynthesis that is caused by mutations of ferrochelatase. As a consequence, the photosensitizer protoporphyrin IX accumulates in the skin, resulting in absolute sunlight intolerance. Upon sun exposure, EPP patients experience immediate, severe pain with subsequent erythema and edema. There is no effective therapy for this orphan disease, and often the only way that affected patients can prevent these symptoms is to strictly avoid daylight (Minder and Schneider-Yin, 2015). Using a sustained-release resorbable implant formulation that delivers 16 mg of NDP-α-MSH (afamelanotide), a pilot phase II trial was performed with five patients with EPP. The implant was administered subcutaneously, twice, 60 days apart. In all five patients, the time to provoke pain with an artificial xenon light source emitting UV light above 385 nm was significantly prolonged and associated with an increase in melanin density (Harms et al., 2009). Additional phase II trials indicated beneficial effects of afamelanotide in patients with solar urticaria, acne, and vitiligo and confirmed a good safety profile as well (Haylett et al., 2009; Böhm et al., 2014; Lim et al., 2015).

Importantly, the initially observed promising effects of afamelanotide in EPP patients have been extended in several phase II and III trials (http://www.clinuvel.com/erythropoietic-protoporphyria). The results of these trials were significant.
with consistent effectiveness, a favorable risk–safety profile, and a high compliance rate for afamelanotide (Minder and Schneider-Yin, 2015). A recently published longitudinal observational study in 115 EPP patients treated with more than 1,023 afamelanotide implants from 2006 to June 2014 confirmed good clinical effectiveness and safety as well as durably improved quality-of-life scores under these long-term conditions (Biocati et al., 2015).

The approval of afamelanotide by the European Medicines Agency in late 2014 can be regarded as a breakthrough for α-MSH in clinical medicine. This success is based on the year-long commitment of many scientists but also on the critical input of others (Clinuvel) at later stages. Indeed, EPP still cannot be cured by afamelanotide, and thus a long-term or even a lifelong management strategy for these patients is mandatory. Additional studies will be needed to further define the mode of action of afamelanotide in the skin of patients with EPP. For example, is the beneficial effect of afamelanotide in EPP patients due simply to increased epidermal pigmentation or is it related to reduced oxidative stress and nociception (Figure 1)? Is porphyrin metabolism perhaps directly targeted by α-MSH? It will be fascinating to answer these questions in the future and also to learn more about other possible indications for such α-MSH analogs.

**CONFLICT OF INTEREST**

T.A.L. is an advisor for Clinuvel; M.B. has been a principal investigator for a clinical trial sponsored by T.A.L.

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Douglas Lowy and John Schiller Recognized for their Work Leading to an Effective HPV Vaccine
The National Medal of Technology and Innovation was recently awarded to Douglas Lowy (2nd from left) and John Schiller (left), both of the National Cancer Institute (NCI), National Institutes of Health (NIH), by U.S. President Barack Obama for developing the virus-like particles and related technologies that led to the generation of effective vaccines that prevent cervical carcinoma and other cancers caused by human papilloma virus (HPV).

In the early 1980s Doug Lowy, now Deputy Director of the NCI of the NIH, recruited John Schiller as a post-doctoral fellow in his laboratory at the NCI, where Lowy had initiated basic research of papillomavirus genetics. Schiller's arrival began what is now a 30+ year partnership that has led to the much celebrated development of a vaccine that promises to eradicate a variety of cancers caused by HPV infection, including cervical cancer, which kills more than 250,000 women worldwide every year.

Their work progressed from an animal papillomavirus, from the bovine papillomavirus to HPV, following the identification of HPV16 or HPV18 (HPV16/18) in a high proportion of cervical cancers by Harald zur Hausen and his colleagues. In the late 1980s, Lowy and Schiller showed that HPV can immortalize human epithelial cells, a required step in carcinogenesis. Lowy and Schiller then started thinking about the possibility of developing a prophylactic vaccine against HPV, although they had no training in immunology or vaccinology. Together with Reinard Kirnbauer, a dermatologist from the University of Vienna who was a fellow in the Lowy/Schiller lab, they conducted a series of high-risk experiments, with BPV instead of with HPV, because the necessary reagents and assays were available for BPV, but not for HPV. Those studies led to development of a prototype BPV vaccine that could prevent infection of tissue culture cells and papilloma development in animals. They then showed the technology worked for HPV.

In 1995, the NCI Director encouraged Lowy and Schiller to initiate a clinical trial and thus participate in the further translation of their vaccine into clinical practice. At this point, in Lowy’s words, he and Schiller “embarked on yet more research for which (they) were not qualified.” Lowy took courses to learn clinical trial methodology, drug quality monitoring, and other aspects of vaccine development. They conducted early phase safety and immunogenicity trials of an HPV16 vaccine, showing it was well tolerated and highly immunogenic. The technology Lowy, Schiller, and Kirnbauer developed was licensed by the NIH to Merck and GlaxoSmithKline (GSK), which used the technology to develop commercial HPV vaccines that were licensed by the FDA in 2006 (Merck) and 2009 (GSK). The vaccines, which induce close to complete protection against the HPV types that they target, are the first successful vaccines against a local sexually transmitted disease.

In 2005, the NCI initiated a randomized controlled trial of GSK vaccine in Costa Rica, where cervical cancer has been the most common female cancer. The Costa Rica trial has provided key data not collected in the pivotal company trials. Although “proper” clinical trials collect and analyze data only for subjects who complete the study protocol, the Costa Rica trial followed up all enrolled subjects, whether or not they received all 3 intended doses of the vaccine. This unorthodoxy led to the critical observations that 1 or 2 doses were as effective as 3 doses – the regimen approved by the Food and Drug Administration for both vaccines - in preventing HPV infection and that the plateau serum antibody titers from 1 dose have been stable for several years, in contrast to antibodies induced by other subunit vaccines. These results have led Lowy and his NCI colleagues to propose a formal vaccine trial to determine whether 1 dose or 2 doses can induce long-term protection. In the developing world, where 88% of the worldwide cervical cancer deaths occur, demonstrating effectiveness from a single dose would be transformative for vaccine implementation.

There are important translational research lessons to be gleaned from this story. Among them: (1) Continuous stable research support for productive investigators is critical. (2) Investigators must be able to change or expand their research directions as dictated by their findings, even if they enter previously unfamiliar fields. (3) Interaction between researchers and industry is helpful and likely necessary to bringing laboratory discoveries to clinical implementation. (4) The research environment as well as the scientific problem needs to be well understood and optimized by the investigator. Lowy freely acknowledges that his group has tried to capitalize on being part of the NIH intramural program, drawing on its many resources and avoiding potential constraints, and that in another workplace a very different approach would probably have been required. (5) Vision and perseverance on the part of the physician-scientist are critical. After more than 30 years, Lowy and Schiller are still far from their ultimate goal of making oncogenic HPV an “endangered species” and preventing the vast majority of HPV-associated disease.

(Photo courtesy of the National Science & Technology Medals Foundation.)
Biologics for Psoriasis: A Translational Research Success Story

Psoriasis is a glowing example of collaboration between clinicians and scientists in an effort to find safe and effective therapies for this debilitating genetic disorder of the skin, joints, and immune system. In some instances, fortuitous clinical observations drove the laboratory work that explained the pathogenesis of this disorder; at other times, therapies were based on findings in the lab. The result has been a dramatic improvement in our understanding of the pathogenesis of this disorder and in our ability to treat psoriatic patients.

Psoriasis was first thought to be a primary disorder of the keratinocyte. In the 1960s, Weinstein, van Scott, and Frost demonstrated abnormal proliferation of keratinocytes in psoriasis (Weinstein and Van Scott, 1965; Weinstein and Frost, 1968). The turnover time of psoriatic epidermis was shown to be markedly faster than that of normal epidermis. Concurrently, van Scott, Auerbach, and Weinstein showed that methotrexate was effective in psoriasis, presumably by targeting those rapidly dividing epidermal cells (Van Scott et al., 1964). Shortly thereafter, Parrish, Fitzpatrick, and colleagues introduced the combination of psoralen and UVA (PUVA) (Melski et al., 1977). PUVA was thought to cross-link DNA strands, and the primary effect was again considered an inhibition of the proliferation of keratinocytes (Lerche et al., 1979).

It wasn’t until years later that we appreciated the impact of methotrexate and of PUVA on the immune system.

Involvement of the immune system in the pathogenesis of psoriasis was first appreciated as a result of the fortuitous observation that transplant patients who had psoriasis and were treated with cyclosporine exhibited remarkable improvement of their skin disease (Picascia et al., 1988). Griffiths and Voorhees were among the first to point out that cyclosporine’s beneficial effect on psoriasis was attributable to the drug’s impact on T lymphocytes. With co-workers, they showed that cyclosporine reduces numerous immune cells including T lymphocytes, monocytes, macrophages, and antigen-presenting cells (Griffiths and Voorhees, 1990; Gupta et al., 1989). Working with an illustrious group of scientists, they demonstrated many changes in the immune system from cyclosporine therapy and theorized that upon activation of T cells, lesional T cells released lymphokines that promote keratinocyte proliferation (Baadsgaard et al., 1990).

Independently, Gottlieb and Nickoloff and Griffiths espoused the same point of view, that is, that the T lymphocyte played a critical role in the pathogenesis of psoriasis and was an important target for psoriasis therapies (Gottlieb, 1988; Nickoloff and Griffiths, 1990). The role of the lymphocyte was convincingly confirmed when a group led by James Krueger successfully treated psoriasis using a lymphocyte-selective fusion protein consisting of interleukin-2 and fragments of diphtheria toxin (Gottlieb et al., 1995). The latter compound selectively blocks activated lymphocytes but has no effect on keratinocytes. Eight of 10 patients treated with two doses of this fusion protein had moderate to marked improvement, confirming the role of the lymphocyte.

With attention focused on the T cell, our knowledge about the pathogenesis of psoriasis was now poised to move forward quickly. It was known that activation of T cells requires not only antigen presentation to the T cells, but also costimulation with a number of possible signals. B7 molecules on the surface antigen-presenting cells were shown to provide an important costimulatory signal to their T cell–associated ligands, CD28 and CD152, also known as cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) (Abrams et al., 1999). CTLA-4 Ig, now known as abatacept, is a fusion protein consisting of the Fc portion of human IgG1 fused with the extracellular domain of CTLA-4. By binding to B7 molecules, abatacept prevents the second costimulatory signal, thereby blocking T-cell activation and resulting in improvement in psoriasis (Abrams et al., 1999). Abatacept, approved for the treatment of rheumatoid arthritis, is still...
being studied for psoriasis and psoriatic arthritis.

Soon the concept of a cytokine network in genetically predisposed individuals leading to abnormal keratinocyte proliferation in reaction to infectious or traumatic skin exposures began to emerge. The role of the Th1 cytokine, IFN-γ, was recognized early (Huang et al., 2001). In this cytokine network, activation of lymphocytes and T-cell trafficking were thought to play important roles. Two biologics that were constructed to block T-cell activation, alefacept and efalizumab, were briefly on the market for the treatment of psoriasis. Efalizumab also interfered with T-cell trafficking into inflamed skin (Krueger et al., 2002; Lebwohl et al, 2003).

The role of TNF-α was not appreciated until clinical efficacy had been anecdotally demonstrated (Chamian & Krueger, 2004). After clinical observations that TNF-α antagonists were effective, it was shown that these drugs result in rapid reduction of IL-1 and IL-8 followed by reductions in inflammatory gene expression including IFN-γ, Stat-1, and granzyme B (Gottlieb et al., 2005). The reduction in T-cell activation and decreased production of cytokines, chemokines, and growth factors by lymphocytes, neutrophils, dendritic cells, and keratinocytes stopped the vicious cycle of immune activation leading to keratinocyte proliferation and inflammation.

In the evolving cytokine network leading to psoriasis, Nestle and Conrad pointed out as early as 2004 that p40 was thought to play an important role in psoriasis (Nestle and Conrad, 2004). This led to the development of two antibodies targeting p40, ustekinumab and briakinumab (Lebwohl et al., 2012; Reich et al., 2011). Both biologic agents, which target the p40 components of IL-12 and IL-23, were dramatically effective but because of a small increase in myocardial infarctions in pivotal trials, briakinumab’s approval was not pursued.

As our understanding of the cytokine network response to psoriasis evolved, Nickoloff, Nestle, and colleagues pointed out the importance of the IL-23/IL-17 axis (Tonel et al., 2010; Di Cisare et al., 2009). We now know that IL-23 upregulates Th-17 cells to create more IL-17. At least three antibodies targeting IL-17 or its receptor have been studied clinically. The first of these, the recently approved secukinumab, targets IL-17A and has proven to be dramatically effective in the treatment of psoriasis (Langley et al., 2014). Ixekizumab, another antibody to IL-17A, is equally effective, as is brodalumab, an antibody to the IL-17 receptor (Leonardi et al., 2012; Papp et al., 2012).

In conclusion, for the past five decades, advances in our understanding and treatment of psoriasis have resulted from a close collaboration between scientists and clinicians, making psoriasis a model of a disease where basic laboratory scientists and clinicians benefit from interacting with one another. Advances in the laboratory have translated into new therapies that are more targeted, profoundly effective, and safer than older treatments. The next frontier in psoriasis is likely to involve pharmacogenomics or, in the distant future, even gene therapy. We already have a head start thanks to the extensive work identifying psoriasis-associated genes (Gudjonsson et al., 2010; Bowcock et al., 2001; Cargill et al., 2007).

**CONFLICT OF INTEREST**

Dr. Lebwohl is an investigator for and/or, prior to March 2014, was a paid consultant for AbGenomics, Amgen, Canfite Biopharma, Coronado Biosciences, Dermira, Dermisorp, Lilly, Forward Pharma, Janssen Biotech, LEO Pharmaceuticals, Meda, Merck, Novartis, Pfizer, Taro, and UCB Pharma.

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Editor's Note
Since beginning my term as JID Editor in 2012, the importance of unity among the many stakeholders in dermatologic research has become increasingly obvious. The interaction and mutual support of two of these communities—practicing dermatologists and investigators—are especially critical to the future of our specialty. It therefore gives me particular pleasure to see featured in this issue an editorial by the president of the American Academy of Dermatology, the elected representative and spokesperson for more than 10,000 dermatologists as well as one of the foremost clinical investigators and thought leaders in translational research. Dr. Lebwohl beautifully summarizes the advances in basic understanding of the disease psoriasis that have led to progressively targeted and effective therapies within a remarkably short time.

Barbara A. Gilchrest
Editor
Paul Janssen Discussing a Drug Candidate with His Chemists
JANSSEN PHARMACEUTICALS

Paul Janssen (1926–2003)

COVER IMAGE

The son of a moderately successful physician-pharmacist in a small Belgian town, Paul Janssen became the most productive drug inventor of all time, “the Thomas Edison of medicinal chemistry.” His story offers several lessons for those who aspire to impact patient care based on their research efforts.

Janssen first studied medicine, graduating from the University of Ghent magna cum laude in 1951. He then worked briefly with the Nobel Prize Laureate, Corneille Heymans, at the Institute of Pharmacy and Therapeutics. Although it was expected that he would join his father’s business, producing vitamins and organ extracts, Janssen had conceived a very different approach to pharmacy. In 1953, he conceived his father to provide him a garage on the company property with four assistants. In his first year, by modifying the core chemical motif phenylpropylamine that is widely present in nature, Janssen synthesized 500 new chemical entities, seven of which were developed into marketed drugs. One of them proved very useful for stomach pain and gastric ulcers, leading to “blockbuster” sales that allowed rapid growth of his laboratory. In 1956 he founded the company that became Janssen Pharmaceutica, later acquired by Johnson & Johnson and known to dermatologists for producing such drugs as miconazole and itraconazole.

Janssen's friend and collaborator of more than 40 years, Paul Lewi, noted that Janssen's ancestors were farmers with a stubborn character. To this heritage, he attributes Janssen's dictum, “You must not believe what people say or write….Sometimes it is better to do things differently.” Janssen's explicit goal was to use his sophisticated chemical knowledge to design and synthesize new drugs and to determine their pharmacologic properties by simple tests. He did not limit himself to any specific set of clinical indications and, as a result, over time created antipsychotics, anti-pyretics, anesthetics, the anti-diarrheal agent known as Lomotil, and many other first-in-class highly useful drugs still employed today.

Of course, Janssen did not accomplish all this alone. His prodigious success lay as much in the people he recruited and the work environment he created as in his personal genius. At the end of World War II, when independence was granted to the Belgian Congo, many Belgians returned home after years in the African jungle. Janssen offered employment to many veterinary workers, regardless of their academic credentials or prior experiences, so long as they seemed competent and passionate, as passionate as he, about their work. Janssen's biographer, Lewi, cites an example of how this practice, in combination with Janssen's independence of mind, led to important discoveries. One new employee was a parasitologist, committed to developing effective drugs for the debilitating diseases he had seen in the Congo. Janssen consulted his marketing group, who assured him there was no market for such drugs and that the project should not be undertaken. Given a free reign, nevertheless, within a year the man produced tetramizole and levamisole, the first highly active and safe anti-parasitic compounds. They were immediately commercially successful, revealing that the apparent lack of a market was attributable to the fact that previously available agents were so ineffective and highly toxic that no one wished to use them. Similarly, Janssen hired a mycologist determined to create highly effective treatments for fungal and yeast infections. Janssen was informed that this was folly, as the market was already saturated. Proceeding anyway, within 18 months the new program yielded miconazole and ultimately 12 more commercially successful anti-fungals, including intraconazole.

Recognizing and evaluating drug efficacy are at least as critical as creating candidate compounds. Among the simple but informative protocols developed by Janssen was a hot plate on which a mouse was placed. To test possible analgesics, the plate was slowly warmed and the delay time until the treated mouse began raising and licking its paws was recorded. Many effective analgesics were identified in this manner. On one occasion, however, the treated mice seemed blissfully unaware of the heat challenge. Janssen speculated that this might indicate a different non-analgesic therapeutic effect. He discussed the phenomenon with a prominent psychiatrist and gave him samples of the compound. When the psychiatrist was next referred an aggressive hallucinating patient, he injected Janssen's compound, which immediately calmed him. After one year or more formal clinical testing, haloperidol was approved as an anti-psychotic drug, greatly reducing psychiatric hospitalizations. It remains on the World Health Organization's list of “essential medicines.” Using the mouse hot plate screening test, the Janssen laboratory eventually developed 17 anti-psychotics.

Finally, Janssen drove his company's exceptional productivity by his personal involvement with the science and scientists. Unlike the vertical organization of conventional large pharmaceutical companies with many layers of management and relatively few people “at the bench,” Janssen created a horizontal organization with many hands-on scientists and sparse “management.” Throughout his career Janssen visited the laboratories daily, asking “What's new?” and discussing individual projects in depth, challenging the scientists. Having pioneered the molecular design approach to drug discovery, in the final years of his career Janssen established the Center for Molecular Design, where he introduced “super-computer” modeling for drug design and, working from the just-revealed 3D structure of the HIV reverse transcriptase, developed a first-in-class drug for AIDS.

Paul Janssen died at age 77 while attending a medical meeting, still passionately engaged in his work. His manifest love of science and of translational research, as well as the more than 80 new drugs he gave the world, are an inspiring legacy. Those wishing to imitate even a part of his success might consider the following: train with excellence, think “outside the box,” pursue your dreams, believe in yourself and when necessary act against conventional wisdom, share your passion to motivate others, be opportunistic, and be observant and curious.

Sources:
Facilitating Translational Research

Would a carpenter be asked to manage building a new housing development? Probably not. More likely, a real estate developer with the skills, experience and knowledge of the local market and trades, including carpentry, would manage such an undertaking. Good developers anticipate and address the challenges of building and selling homes. Delivering attractive, appropriately priced homes on time and on budget requires that developers use their knowledge, experience, and judgment to make numerous decisions that engage the right talent at the right time to balance development risks and costs.

Likewise, would musicians form an orchestra without a conductor? Again, probably not. Despite the considerable skills of even the very best musicians, they collectively create their best music when guided by a conductor.

If real estate developers and orchestra conductors are needed to facilitate their respective resources to get the best outcomes, why is the complex process of translational medical research in academia often led by a person with deep expertise in only one of, or at best a few of, the disciplines required to create viable solutions to important unmet medical needs?

Usually, the responsibility for managing translational research in an academic setting falls to a researcher designated as the “Principle Investigator” (PI). Academic healthcare institutions are very familiar with the role of PI as the responsible party for the conduct of all aspects of basic or applied research. A PI may be technically oriented and conceive of novel solutions, or be clinically oriented, with the savvy and commitment to appreciate the possible impact and champion the implementation of an innovation. Some PIs can do both and some can also raise venture funds and start a business, but they are the exceptions.

The traditional role of most PIs may not be ideal for translational research. Unlike the rigorous training they obtained in their specific discipline, PIs typically learn to conduct translational research by trial and error, inevitably making mistakes and experiencing failures along the way. Many failures are due to avoidable mistakes, such as not anticipating the potential consequences of decisions. Others result from the PI relying too heavily on his or her own, often limited experience. It is unusual for a PI to even consider taking work in a direction outside of their area of expertise if a major roadblock is encountered mid-stream. As the saying goes, “when the only tool you have is a hammer, everything looks like a nail.”

In contrast to the traditional approach, one strategy for overcoming the challenges in translational medical research can be adapted from the approaches taken by the successful developer and conductor: focusing responsibility on an experienced coach or facilitator. The facilitator’s role is to synergize, harmonize and synchronize the work of diverse professionals to achieve a shared vision of success through a journey with multiple, inter-related steps. This strategy should be even more valuable in translational medical research due to its complexity. It inherently entails more unknowns and risks, as well as unique requirements, such as adherence to strict constraints to protect animals from undue suffering or patients from harm. Even more than their counterparts on a housing project or in an orchestra, academic researchers often have very different motivations that can vary with the stage of their career, personal objectives and/or their institutional policies. In addition, while all industries are highly competitive, healthcare related businesses today face particularly difficult dynamic competitive and regulatory environments.

For over 15 years, the Consortia for Improving Medicine with Innovation and Technology (CIMIT) has learned, in essence, how to be the equivalent of a developer or conductor to create solutions to pressing unmet medical needs. CIMIT has learned to orchestrate the isolated pockets of expertise and misaligned incentives that impede translational research within academic medical centers to accelerate innovations to patient care.

CIMIT is a consortium of 13 academic medical centers and universities in the greater Boston area with a growing network of national and international affiliates. CIMIT focuses on products, procedures, and clinical systems (see www.cimit.org). It has supported the development of more than 250 potential solutions to important unmet needs through over 600 peer-reviewed projects. After identifying an important unmet medical need—perhaps the most critical of all potential. Rather than try to change existing motivations or incentives, an experienced facilitator can chart a path and show team members it aligns multiple objectives in such a way to meet everyone's needs and interests over time. Success requires constantly synchronizing the skills and composition of the team to meet the challenges at any point in the process, much like the accomplished developer and conductor.

Figure 1: Typical Issues Encountered in the Healthcare Innovation Cycle

The Cycle begins with a stakeholder, who may be a clinician, patient, administrator, supplier, or other participant, observing how care is actually delivered – the actual standard of care. From that observation, the individual can describe challenges to address and/or opportunities available to improve care. Inventors create potential solutions and attempt to demonstrate the feasibility of the underlying principles. Information on challenges and opportunities can also inform basic science and the development of enabling technologies that can later be incorporated into proposed solutions. Robust prototypes are then developed and tested to determine whether the solution will create sufficient value under practical considerations and constraints to attract commercial investment in a product or service, or a healthcare provider to implement a new procedure. Evidence is gathered to demonstrate that the product, service or procedure enables a “best practice” that should be replicated. At that point, the work is still not completed; the solution needs to be broadly disseminated and made widely available before it can become the new standard of care. When the cycle operates at its best, it is indeed a spiral, arriving at the end of each rotation at a higher standard of care, awaiting future medical insights and innovations for further enhancement.

For example, to share an insight or discovery with the world, a PI may describe results in an abstract or present them at a conference before properly protecting the underlying intellectual property (IP). While disseminating new knowledge is aligned with academic objectives, it needs to be coordinated with the commercial imperative to protect IP so that an economically motivated company or venture capitalist will be willing to invest. Further, many PIs have the misperception that a patent gives them broad rights to the invention it covers, whereas it only gives them the right to preclude others from using it. This possibly subtle distinction has huge potential ramifications— if decisions are made such that an invention requires the use of IP owned by others to work (i.e., no “freedom to operate” or “FTO”), investors will likely not even consider it unless a very robust license agreement is in place with those who control the other IP.

Unlike the immediate bad outcome if there is poor coordination between an electrician and a framer in building a house, an error in the healthcare innovation cycle may not come to light for years, wasting time and money. Even worse, the ramifications of a mistake may never be seen or appreciated by the responsible group, making “learning by doing” inefficient and arguably impractical. For example, in the case that IP is lost or there is no clean FTO, most investors will not even consider the opportunity. The team may only be told that an investor was “not interested”, but never know the reason.

The core approach behind the CIMIT Model is to find, fund, and facilitate multi-disciplinary teams through the innovation cycle to speed and maximize the impact of an innovation on patient care. The fact that CIMIT is multi-institutional increases the opportunities to access the ideal experts as team members. Like a developer or conductor, CIMIT facilitators enable team members to focus on what they do well in contributing to the process.

Effective facilitation is not cheap. It requires seasoned individuals with considerable experience who are seen by PIs as peers, at least. It also requires that the facilitators allocate the time needed to be actively involved in the project. Assigning junior people to manage a portfolio of projects is not sufficient. CIMIT facilitators usually commit at least 25% and often more than 50% effort to a single project. Just as an orchestra with world-class musicians invests in a world-class conductor, CIMIT has shown that it is a very good investment to engage a team of skilled facilitator to make the most of the available resources and teams.

The facilitator must understand and manage the different motivations and incentives that exist among members of the research teams. Clinicians are likely to focus on issues that most affect the care they can provide to their own patients, whereas scientists and technologists may value the potential novelty of solutions and entrepreneurs motivated by profit potential. Rather than try to change existing motivations or incentives, an experienced facilitator can chart a path and show team members it aligns multiple objectives in such a way to meet everyone's needs and interests over time. Success requires constantly synchronizing the skills and composition of the team to meet the challenges at any point in the process, much like the accomplished developer and conductor.
However, whereas a successful developer or conductor generally receives the acclaim for their work, the credit for success of the healthcare innovation goes to the research team and especially the designated PIs, not the individuals who facilitate the cycle. Therefore, finding people with the required skills and experience who are willing to facilitate the success of others can be a significant challenge. Further, finding sources of funding that understand the value that such facilitation brings is a challenge. Fortunately, the situation is changing in part due CIMIT’s track record of success and that of organizations adapting and using the CIMIT Model.

Substantial institutional investment is initially required to put the CIMIT model in place, including support for the facilitation team and seed grant funding to attract innovators and clinician researchers. CIMIT has documented its clinical, academic and commercial metrics of success to understand and improve the short and long-term value of the investment. In looking at just the financial return to member institutions, within a few years their investment is more than fully repaid through grants and associated overhead, with further downstream financial return in licensing fees and royalties. Since CIMIT entered a steady state, for every dollar CIMIT institutions invest in the infrastructure of CIMIT, they receive $3.50 directly back from CIMIT that year to fund potential solutions. In addition, each dollar of CIMIT-funded projects results in an additional $10 of funding to the institutions from outside sources, usually at full indirect cost. The result is more than a 35:1 multiplier of funds to advance solutions initiated with CIMIT support. Commercial investments are in addition and are of similar magnitude, and may generate licensing and royalty payments.

We conclude that translational medical research can be significantly enhanced through active facilitation and treating it as a learnable, dynamic process. It is enhanced by having the flexibility to assemble the most appropriate teams from many organizations to address the specific demands of a potential solution in each stage of its development. While some contend that academic institutions should eschew steps in the innovation cycle beyond pure discovery, we believe this approach is too wasteful of excellent clinical observations that would otherwise never lead to advancements in patient care. In fact, the CIMIT model imbeds business expertise throughout the innovation cycle.

The CIMIT Model works well in the resource-rich environment in Boston. It has also been shown to work well elsewhere when adapted, such as in Manchester, United Kingdom, and Singapore (ref IEEE article). It has the potential to create even more impact as the CIMIT network expands, linking medical innovation hubs across the world to enable enhanced access to assemble the best teams to address the ever-present critical challenges of improving patient care. Recent expansion of CIMIT’s scope to develop pharmacological solutions will reveal whether the same applies to therapeutics.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Judah Folkman (1933–2008): Pioneer in Angiogenesis Research
Judah Folkman, son of a rabbi, accompanied his father on visits to hospitalized patients, and at age seven decided to become a doctor so as to “cure as well as comfort.” He entered Harvard Medical School (HMS), where, still as a student, he developed one of the first cardiac pacemakers. During his surgical residency at Massachusetts General Hospital and his military service at the National Naval Medical Center, and upon his return to Boston and HMS, he pursued a variety of research interests. In 1968 he was appointed the Julia Dyckman Andrus Professor of Pediatric Surgery and Professor of Cell Biology at HMS, the youngest full professor in the school’s history. At Children’s Hospital Boston, his research evolved to become the basis of the Vascular Biology Program. For four decades, until his sudden death in 2008, the program virtually created the field of angiogenesis and trained generations of physician–scientists while forever changing the understanding and treatment of diseases as diverse as cancer and macular degeneration.

In a seminal paper in the New England Journal of Medicine that was based on his already extensive studies of cultured tumor cells and in vivo tumor models, Folkman (1971) introduced the concept that in the absence of neoangiogenesis malignant tumors remain dormant, restricted to a small size by the very limited ability of oxygen to diffuse through tissue. He also postulated the existence of tumor-derived angiogenic factors that allow the malignant cell nests to create their own blood supply and predicted the use of antiangiogenic factors to restrict tumor growth. Folkman’s hypothesis was disregarded by most authorities in the field, but he persisted in his research. Within a few years, he and his colleagues identified diffusible angiogenic and antiangiogenic factors in vivo and further demonstrated that removing the angiogenic stimulus leads to regression of established vasculature.

Although Folkman’s early discoveries focused on the role of angiogenesis in malignancy, from the beginning he also pursued clinical implications for disorders as diverse as psoriasis (Folkman, 1972), endometriosis, congenital vascular malformations, and macular degeneration. When after nearly 20 years the skeptical academic community finally accepted the central role of angiogenesis in such diseases, based on his elegant laboratory-based research, Folkman expanded his efforts to translate these findings into clinical practice. This required that he convince pharmaceutical companies to develop antiangiogenic drugs—itself a major challenge and one not widely considered appropriate by his colleagues.

The first candidates approved by the US Food and Drug Administration (FDA) were for the indication of age-related neovascular macular degeneration: an aptamer of vascular endothelial growth factor (VEGF) and an anti-VEGF antibody. These drugs have restored useful vision to nearly 40% of patients classified as legally blind owing to this disease. In 2003 the FDA approved the first antiangiogenic drug for cancer therapy. By 2008, at least 10 additional antiangiogenic drugs had been FDA-approved and millions of patients in the United States and around the world had benefited from their use.

What lessons are inherent in Judah Folkman’s translational research career and accomplishments? They have been noted earlier in this series of JID cover commentaries (see the previous issues in 2015). First, to succeed it is helpful to be brilliant, but it is even more important to be highly creative and determined to make a difference to patients. Folkman never forgot his childhood pledge to cure and comfort. Second, he never doubted the importance of his research findings, and when others doubted his concepts, he simply worked harder to convince them. Third, he was the consummate mentor, welcoming and inspiring trainees from diverse backgrounds (including dermatology), thus establishing the broad field of angiogenesis almost single-handedly and ensuring that its impact was felt in many medical and surgical disciplines. Fourth, and perhaps most critically, he never gave up. When Avastin, the drug developed by Genentech to block VEGF, was approved by the FDA in 2004 and he was being widely acclaimed for this “overnight miracle,” Folkman wryly observed that it was an overnight miracle 40 years in the making.

Sources:
Recessive Dystrophic Epidermolysis Bullosa: Advances in the Laboratory Leading to New Therapies

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare, devastating, hereditary mechanobullous disease of the skin in which patients have marked skin fragility, widespread bullae, and erosions that characteristically heal with exuberant scarring and milia formation (Fine et al., 2014). Our laboratory and several others have long aspired to develop an effective treatment—a goal now seemingly far closer than we had dared hope only a few years ago. Here we summarize relevant laboratory-based advances in understanding RDEB pathogenesis as well as recent steps toward translating this knowledge into targeted therapies.

RDEB is attributable to mutations in the COL7A1 gene that encodes type VII collagen (C7). C7 forms large structures called anchoring fibrils (AFs) that localize to the dermal–epidermal junction (DEJ) and are required for epidermal–dermal adherence (Fine et al., 2014). In human skin, both keratinocytes and fibroblasts synthesize C7 α1 chains that form homotrimeric C7 molecules. The cells then secrete C7 molecules into the high extracellular space of the papillary dermis. It is not clear how C7 in the papillary dermis actually gets to the DEJ to form AFs, but we demonstrated that C7 has specific binding domains for type IV collagen and laminin 332 in the DEJ (Chen et al., 1997, 1999). Therefore, C7 likely binds to components of the DEJ, condenses into antiparallel dimers, and then forms AFs. Using normal mouse wound healing models and mouse RDEB models, we and others have learned that all one needs to do is get C7 into the high papillary dermis: it will then self-assemble and form correctly localized AFs (Chen et al., 2002; Ortiz-Urda et al., 2003; Remington et al., 2009; Wang et al., 2013; Woodley et al., 2003, 2004, 2007, 2013a).

The ultimate treatment for RDEB may be gene therapy, provided the RDEB patient’s skin cells have a normal COL7A1 gene and express normal, functional C7. The COL7A1 gene is quite large, more than 9 kb, which exceeds the gene-packaging capability of most viral vectors. Nevertheless, we used a fourth-generation lentiviral vector engineered to express full-length C7 and demonstrated that RDEB keratinocytes and fibroblasts, when infected with this vector, were then able to synthesize and secrete full-length C7 (Chen et al., 2002; Woodley et al., 2004). Therefore, one promising method of treating RDEB would be to take a biopsy from the patient, place the patient’s keratinocytes and/or fibroblasts into tissue culture in the laboratory, gene-correct the cultured RDEB cells such that they now express full-length C7, and then transplant the gene-corrected cells back onto the RDEB patient as a cultured autograft. Scientists in the Department of Dermatology at Stanford have taken this approach using gene-corrected cultured keratinocyte autografts and have achieved proof of principle for this approach in one RDEB patient. The Stanford team is now evaluating the safety and efficacy of this approach with other RDEB patients in a phase I clinical trial.

Using RDEB murine models and murine wound models, we (Woodley et al., 2003) and Ortiz-Urda and colleagues (Ortiz-Urda et al., 2003) demonstrated that cultured dermal fibroblasts (either from normal human subjects or from RDEB patients, engineered to express C7) can be injected into murine skin or transplanted RDEB skin equivalents and that the injected cells then secrete C7 into the papillary dermis. There, C7 incorporates into the DEJ, forms new AFs, and reverses the RDEB phenotype of poor epidermal–dermal adherence. Interestingly, we also showed that the cells could be administered intravenously (IV) and home to open wounds in the skin, promoting healing (Woodley et al.,


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2007). This suggests that such cells, injected IV into an RDEB patient, might localize within healing wounds and continually secrete C7 that can then incorporate into the DEJ and form new AFs that promote healing.

Along the lines of cellular therapy for RDEB, two studies attempted to treat RDEB patients with intradermal injections of normal cultured dermal fibroblasts obtained from closely related relatives (Wong et al., 2008; Venugopal et al., 2013). These injected cells did not persist in the skin very long, but the treated RDEB patients had increased C7 expression at their DEJ and improved skin fragility and blistering. The increased C7, however, was not produced by the injected normal fibroblasts. Rather, the allogeneic fibroblasts or perhaps even the process of creating an injection wound itself (Venugopal et al., 2013) stimulated the RDEB patients' endogenous skin cells to synthesize increased amounts of mutated C7. Although the C7 was mutated, it was partially functional. Therefore, increased endogenous mutated C7 improved the epidermal–dermal adherence of these RDEB patients, leading to clinical improvement.

Cell therapy for RDEB has also been demonstrated using another approach: delivery of allogeneic bone marrow/stem cells from normal relatives of RDEB patients who were closely HLA matched using a protocol similar to those used for the treatment of cancer and leukemia patients. This therapy requires immunosuppression and ablation of the patient's normal bone marrow prior to the administration of the donor bone marrow/stem cells and has substantial inherent risks. This therapy has been shown to have remarkably positive effects in some RDEB patients by increasing C7 at the patient's DEJ, with subsequent improvement in their skin disease and quality of life (Wagner et al., 2010), although there were also some deaths and untoward side effects. Nevertheless, the success rate appears to be improving with this therapy as investigators optimize their protocols, reduce the intensity of immunosuppression, optimize the selection of candidates, and identify the best population of stem cells and more closely HLA-matched donors.

Most collagens, if injected intravenously, activate platelets and the plasma clotting system and induce vascular apoplexy and death. C7 is different. C7 is soluble in neutral buffers and blood. Therefore, in addition to cellular therapy for RDEB, it might be possible to simply provide full-length functional C7 itself to patients, so-called “protein replacement therapy.” Our laboratory developed a method by which we could obtain milligram quantities of purified human recombinant C7 (rhC7) (Chen et al., 2002; Woodley et al., 2004). Using RDEB mouse models, we have shown that one can administer rhC7 intradermally (Woodley et al., 2004; Remington et al., 2009), topically to wounds (Wang et al., 2013), or even IV (Woodley et al., 2013a) to these animals, and it will incorporate into the DEJ and form new human AFs, improve epidermal–dermal adherence, and increase the survival of the animals. Importantly, the IV rhC7 only went to wounded skin and not to any internal organs (Woodley et al., 2013a). Because RDEB skin probably has widespread subclinical, microscopic wounds, conceptually, IV rhC7 could home to all of these skin sites and prevent frank skin blisters. We have completed toxicity studies in rats and minipigs with intradermal rhC7 and found no untoward side effects (unpublished data). IV administration is appealing because patients with RDEB characteristically have widespread skin lesions as well as lesions in areas that are less accessible, such as the upper third of the esophagus. Safe IV administration of rhC7 has been shown in several “preclinical” animal models (normal mice, RDEB mice, hypomorphic RDEB mice, and RDEB Golden Retriever dogs). Shire Pharmaceuticals (Dublin, Ireland) is currently exploring the possibility of developing IV rhC7 for use in RDEB patients. If IV rhC7 behaves in RDEB patients as it does in these preclinical animal models, it would home to the open or subclinical microscopic wounds, incorporate into the DEJ, generate new AFs, and improve, if not normalize, the epidermal–dermal adherence at that site. How often these patients would need to be treated with IV rhC7 to maintain improved epidermal–dermal adherence and prevent new blister formation remains unknown. Type I collagen injected into human skin for improvement in photoaging, however, persists for about 6 months. In RDEB mice and RDEB dogs, injected rhC7 persists for months, but the half-life of rhC7 in human skin may differ.

RDEB patients heal their skin wounds with severe scarring that leads to esophageal strictures and fusion of the digits on their hands and feet (so-called “mitten” deformities). The conventional wisdom is that this occurs because the blister cleavage plane in RDEB is below the lamina densa zone of the DEJ. We recently found, however, that RDEB skin and cultured fibroblasts exhibit upregulation of profibrotic isoforms of transforming growth factor-β and its downstream signaling pathways, suggesting that the reason RDEB patients have such horrible scarring is because the absence of C7 produces a proscarring microenvironment. Further evidence that C7 may play a role in wound healing includes experiments in which exogenous rhC7 was administered to wounds topically or IV and, surprisingly, wound closure was dramatically accelerated by promoting reepithelialization (Wang et al., 2013). Even more surprising, exogenously administered rhC7 to standardized murine skin wounds resulted in healed wounds with less scarring and an associated downregulation of fibrosis markers such as profibrotic forms of transforming growth factor-β, type I collagen, connective tissue growth factor, and α-smooth muscle actin–positive myofibroblasts (Wang et al., 2013).

Gentamicin, an aminoglycoside antibiotic, and its derivatives are old drugs traditionally used to resolve serious Gram-negative bacterial infections and are known to be otoxic and nephrotoxic in some patients. Interestingly, this class of antibiotics has been shown in some cases to have the ability to “read-through” premature stop codons generated by nonsense mutations in certain types of gene defects. Approximately 10–25% of RDEB patients have nonsense mutations resulting in a truncated C7 or no C7 at all. We recently identified, genotyped, and characterized clinically, histologically, immunologically, and by electron microscopy 22 bona fide RDEB patients (Woodley et al., 2013b), of whom two had nonsense COL7A1 mutations. We cultured their keratinocytes and fibroblasts with varying doses of ami-
noglycoside antibiotics. Without aminoglycosides, these cells synthesized no C7. By contrast, in the presence of non-cytotoxic doses of aminoglycosides, both the RDEB cultured keratinocytes and the fibroblasts synthesized and secreted full-length C7 at a level between 10 and 35% that of normal cells (Cogan et al., 2014). The C7 generated was structurally identical to normal C7 and incorporated correctly into the DEJ of a human skin equivalent in vitro. RDEB cells expressing C7 also exhibited a reversal of the abnormal cellular motility that is characteristic of RDEB cells. Finally, we generated 22 published RDEB nonsense mutations by site-directed mutagenesis and transfected these constructs into human 293 epithelial cells. Without aminoglycosides, these cells produced no C7. By contrast, treatment of the cells with aminoglycosides induced C7 expression between 10 and 80% of the level of C7 expressed in cells transfected with an expression vector for normal C7. These data suggest that aminoglycosides administered judiciously and cautiously may provide benefit for selected RDEB patients with nonsense mutations that create premature stop codons.

In summary, recent federally funded laboratory research has generated reagents and concepts that are currently being translated into therapies for the devastating disease recessive dystrophic epidermolysis bullosa.

CONFLICT OF INTEREST
Mei Chen, David Woodley and the University of Southern California hold patents for type VII collagen, which are licensed by Shire Human Genetic Therapies. Mei Chen and David Woodley have filed a conflict of interest declaration with Dr. Randall W. Hall, Vice Provost for Research Advancement at the University of Southern California.

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In 1972, after one year of dermatology residency, Dr Edelson went to the National Institutes of Health (NIH) as one of the draft-eligible generation of “yellow berets,” physicians who might never have sought in-depth research training had it not been the alternative to military service in Vietnam. At the NIH, he became involved in the care of patients with cutaneous lymphomas while participating in laboratory-based research to characterize the responsible cells. This experience led to four decades of applying discoveries—his and others’—in the rapidly evolving field of lymphocyte immunology to the treatment of the disease for which Edelson proposed the name “cutaneous T-cell lymphoma” (CTCL).

Initially Edelson reasoned that a combination of leukapheresis to remove circulating malignant lymphocytes and psoralen + UVA (PUVA), a topical treatment shown in the 1970s to clear CTCL skin lesions, might be more effective than either modality alone in advanced, otherwise fatal CTCL. In 1987 he and his colleagues reported the stunning, unanticipated, and unexplained success of this approach, which they termed ECP. One year later ECP was approved for this indication by the US Food and Drug Administration (FDA), becoming the first (by 20 years) FDA-approved cellular immunotherapy for any form of cancer.

This remarkable accomplishment, complemented by Edelson’s organization of a highly informative multicenter clinical trial and convincing a major pharmaceutical company to develop and market the photopheresis machine, revolutionized the care of CTCL patients. But this was only the beginning. His major contribution to translational research can be seen as “reverse-engineering” the usual paradigm, proceeding from the clinic to the laboratory. Over the ensuing 30 years he and his colleagues have continued to make unexpected clinical observations, inexplicable at the time by immunologic dogma, and then to painstakingly work out the underlying mechanisms in vitro. The group’s work has now amply documented that malignant CD4+ T cells subjected to PUVA-mediated DNA damage during their passage through the ECP tubing undergo “gentle” (gradual) apoptosis, and the resulting cell fragments are “presented” to the patient’s normal undamaged immunocompetent CD8+ T cells. Within weeks, patients are immunized against their CTCL, and even the malignant cells that are not DNA-damaged during ECP sessions are targeted. Critical to this process is the conversion of circulating blood monocytes to antigen-presenting dendritic cells (DCs) during their passage through the ECP tubing—itself a major step forward in understanding physiologic immune activation.

By starting with a patient’s unsolved clinical problem, and by never ignoring a clinical observation that failed to conform to prevalent dogma, Edelson’s group gradually explained not only the detailed mechanism by which ECP treats CTCL but also the distinct mechanism by which ECP unexpectedly treats GVHD and organ-transplant rejection. Briefly, by varying the UVA irradiation dose received by blood-borne monocytes in the ECP tubing, one can either generate minimal damage that allows the cells to mature fully into DCs that then immunize against processed antigens (and treat CTCL) or generate greater damage that impairs DC maturation and results in immune tolerance of foreign antigens (thus ameliorating GVHD or organ-transplant rejection). By elucidating these basic immunologic mechanisms, Edelson has also created an opportunity to fine-tune ECP to optimize the desired cellular responses in different disease settings, work that is still ongoing in his laboratory.

Edelson credits his success to dogged determination, noting that his ECP work has not always garnered the attention or approval of the immunology community, and especially to his perspective as a clinician. He suggests that clinicians, being responsible for the care of patients, resort to trial and error more often than “real scientists” do and are therefore more often confronted with observations for which there is no comfortable intellectual framework. In the best case, this may eventuate in a new framework, advances in understanding, and a new approach to addressing a previously intractable problem. (Photo courtesy of Yale University.)
Recent progress in melanoma drug development highlights the critical impact that translational research plays in advancing patient care. Prior to 2011, dacarbazine, IL-2, and IFNα-2b were the only US Food and Drug Administration (FDA)-approved treatment options for metastatic melanoma. These early therapies resulted in poor and inconsistent overall response rates (~10–15%; Eggermont and Kirkwood, 2004). A renaissance in melanoma therapeutics occurred with the recognition that molecular aberrations in the mitogen-activated protein kinase (MAPK) pathway (Figure 1) were present in a majority fraction of melanomas (Davies et al., 2002). These investigations resulted in the vigorous pursuit of small-molecule kinase inhibitors and the eventual FDA approval of three novel MAPK pathway inhibitors for the treatment of advanced melanoma (Figure 1). Although key insights into immune

**Figure 1.** Molecular targeting of the mitogen-activated protein kinase (MAPK), PI3K, and CDK4 pathways and the associated mutation rates of potential molecular targets in advanced melanoma (Hodis et al., 2012). Activation of a receptor tyrosine kinase such as c-KIT results in the propagation of signal via the MAPK pathway leading to activation of RAS, RAF, MEK, and ERK. This ultimately results in gene expression and promotes cellular proliferation and survival. Mutated BRAF bypasses this ordered pathway and stimulates constitutive signaling, making it a prime target for vemurafenib and dabrafenib. Trametinib targets the downstream effector molecule MEK. Dysregulation of the PI3K pathway promotes melanoma progression. Small-molecule inhibitors of the PI3K pathway are being clinically tested in combination with MAPK pathway inhibition. Similarly, CDK4 is an attractive candidate molecule to target in melanoma and is the focus of multiple clinical trials. Red, activated; gray, inactivated; green, normal function. Drugs (shown in boxes) that have been approved (boldface) or are in trial (italics) are indicated. Please note that trials and drug approvals are subject to change.

checkpoint blockade have generated a similar number of recent immunotherapeutic breakthroughs (Brahmer et al., 2012; Hamid et al., 2013; Hodi et al., 2010), this Editorial focuses on the development of molecular targeted therapies.

Melanoma arises from the activation, or inactivation, of genes that regulate critical cellular functions including proliferation, cell-cycle regulation, survival, angiogenesis, and cell migration. Efforts to systematically codify these changes have uncovered molecularly discrete subsets of melanoma (Curtin et al., 2005). For instance, melanomas arising in the context of non–chronic sun damaged skin are associated with BRAF and NRAS mutations, whereas lesions that arise from mucosal and acral surfaces are linked to KIT alterations (Curtin et al., 2005). Moreover, some melanomas that lack NRAS or BRAF mutations harbor deleterious lesions in NF1 or amplifications of CDK4 (Lin et al., 2008), which are downstream mediators of cell-cycle progression in the MAPK pathway (Figure 1). These data suggest that inasmuch as melanomas should be classified histologically, molecular subtyping may provide a more pragmatic approach as specific therapies targeting receptor tyrosine kinases, downstream kinases, and other signaling molecules become available. Table 1 highlights key clinical trials that have expanded the treatment landscape of melanoma with targeted therapies.

BRAF inhibition

The rationale for targeting BRAF is evident because the Val600-Glu mutation in the BRAF kinase domain is the single most common mutation in cutaneous melanoma (Davies et al., 2002). This substitution constitutively activates BRAF and its attendant downstream MAPK pathway effectors such as MEK (Figure 1). Although 50% of melanomas harbor the BRAF V600E mutation, nearly 80% of benign nevi also contain the identical mutation (Pollock et al., 2003). Thus, it is an early genetic lesion that is neither necessary nor sufficient to fully induce melanoma. Preclinical work demonstrated that BRAF knockdown reduced tumor formation in murine xenograft models, and selective small-molecule inhibitors of RAF suppressed BRAF-mutant melanoma cell lines (Hoefflich et al., 2006; Joseph et al., 2010). These translational studies show that BRAF is a well-validated target and set the stage for the development of BRAF inhibitors for clinical use.

Early studies targeting RAF employed sorafenib, a multi-kinase inhibitor that has activity against BRAF and CRAF, but resulted in little to no clinical activity as monotherapy (Eisen et al., 2006; Ott et al., 2010). Selective BRAF inhibitors (i.e., those agents that specifically target mutant BRAF over wild-type BRAF), however, demonstrated impressive results in melanoma. The small-molecule inhibitors vemurafenib and dabrafenib selectively bind the active conformation of BRAF and inhibit signal transduction between BRAF and MEK. A phase III trial, BRIM-3, of vemurafenib versus dacarbazine as first-line therapy for BRAF V600E–mutated metastatic melanoma demonstrated improved median progression-free survival (PFS; 5.3 vs. 1.6 months) and better overall survival (OS; 84% vs. 64%) at 6 months in the vemurafenib versus dacarbazine groups, respectively (Chapman et al., 2011). The most commonly detected toxicities of vemurafenib included cutaneous eruptions, arthralgias, photosensitivity reactions, and cutaneous squamous-cell carcinomas that were observed in 26% of patients. These results led to the FDA approval of vemurafenib (Zelboraf) in August 2011 for the treatment of unresectable BRAF V600E mutant melanoma.

Another phase III trial, BREAK-3, compared dabrafenib to dacarbazine in the treatment of patients with unresectable, metastatic, BRAF V600E mutation–positive melanoma. BREAK-3 demonstrated similarly impressive results as BRIM-3. Patients in the dabrafenib arm had improved median PFS when compared to those in the dacarbazine arm, 5.1 versus 2.7 months, respectively, with a hazard ratio (HR) for progression of 0.30 (95% confidence interval (95% CI) 0.18–0.51; P < 0.001) (Hauschild et al., 2012). However, one important dis-

Table 1. Key clinical trials in targeted melanoma therapy

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Experimental agent</th>
<th>Control agent</th>
<th>Tumor response (experimental; 95% CI vs. control; 95% CI)</th>
<th>PFS (experimental vs. control)</th>
<th>OS (experimental vs. control)</th>
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<tr>
<td>BRIM-3</td>
<td>Vemurafenib (N = 337)</td>
<td>Dacarbazine (N = 338)</td>
<td>48%; 42–55 vs. 5%; 3–9</td>
<td>5.3 vs. 1.6 months (HR 0.26; 95% CI 0.20–0.33; P &lt; 0.001)</td>
<td>84% vs. 64% (HR 0.37; 95% CI 0.26–0.55; P &lt; 0.001)</td>
</tr>
<tr>
<td>BREAK-3</td>
<td>Dabrafenib (N = 187)</td>
<td>Dacarbazine (N = 63)</td>
<td>50%; 42.4–57.1 vs. 6%; 1.8–15.5</td>
<td>5.1 vs. 2.7 months (HR 0.30; 95% CI 0.18–0.51; P &lt; 0.0001)</td>
<td>Not statistically significant (HR 0.76; 95% CI 0.48–1.21)</td>
</tr>
<tr>
<td>METRIC</td>
<td>Trametinib (N = 214)</td>
<td>Dacarbazine or paclitaxel (N = 108)</td>
<td>22%; 17–28 vs. 8%; 4–15</td>
<td>4.8 vs. 1.5 months (HR 0.45; 95% CI 0.33–0.63; P &lt; 0.001)</td>
<td>81% vs. 67% (HR 0.54; 95% CI 0.32–0.92; P = 0.01)</td>
</tr>
<tr>
<td>COMBI-d</td>
<td>Dabrafenib + trametinib (N = 211)</td>
<td>Dabrafenib (N = 212)</td>
<td>67%; 60–73 vs. 51%; 45–58</td>
<td>9.3 vs. 8.8 months (HR 0.75; 95% CI 0.57–0.99; P = 0.03)</td>
<td>93% vs. 85% (HR 0.63; 95% CI 0.42–0.94; P = 0.023)</td>
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<tr>
<td>coBRIM</td>
<td>Vemurafenib + cobimetinib (N = 247)</td>
<td>Vemurafenib (N = 248)</td>
<td>68%; 61–73 vs. 45%; 38–51</td>
<td>9.9 vs. 6.2 months (HR 0.51; 95% CI 0.39–0.68; P &lt; 0.001)</td>
<td>81% vs. 73% (HR 0.65; 95% CI 0.42–1.00; P = 0.046)</td>
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<tr>
<td>COMBI-v</td>
<td>Dabrafenib + trametinib (N = 352)</td>
<td>Vemurafenib (N = 352)</td>
<td>64%; 59–69 vs. 51%; 46–57</td>
<td>11.4 vs. 7.3 months (HR 0.56; 95% CI 0.46–0.69; P &lt; 0.001)</td>
<td>72% vs. 65% (HR 0.69; 95% CI 0.53–0.89; P = 0.005)</td>
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tinction between the two trials is that the primary endpoint for BREAK-3 was PFS, whereas the co-primary endpoint for BRIM-3 was PFS and OS. Dabrafenib also demonstrated remarkable efficacy in the treatment of intracranial metastases (Long et al., 2012). Although vemurafenib and dabrafenib appear to have similar efficacy with respect to overall response rates, patients in the vemurafenib trials had higher rates of cutaneous squamous-cell carcinomas, 18–25%, when compared to those in the dabrafenib trials, 6–11% (Chapman et al., 2011; Hauschild et al., 2012). BREAK-3 led to the FDA approval of dabrafenib (Tafinlar) in May 2013 for the treatment of unrespectable melanoma harboring BRAF V600E.

MEK inhibition

Solit et al. (2006) reported early preclinical results that melanoma sensitivity to MEK inhibition was also correlated with the presence of the BRAF V600E mutation. Thus, pharmacologic attenuation of MEK signaling represents another possible approach for BRAF-mutated tumors. Exome sequencing of metastatic melanoma specimens identified somatic mutations in MEK1 and MEK2 as potential clinically significant aberrations, characterizing MEK1 and MEK2 mutations in 8% of melanomas (Nikolaev et al., 2012). Moreover, pharmacological MEK blockade completely abrogated tumor growth in BRAF mutant xenografts (Solit et al., 2006). These data provided the rationale for a phase III trial, METRIC, which compared trametinib, a small-molecule selective MEK1/2 inhibitor, to chemotherapy (dacarbazine or paclitaxel) in the treatment of patients with BRAF V600E/K mutant–positive metastatic melanoma. Compared with patients receiving chemotherapy, patients treated with trametinib demonstrated significant improvement in median PFS (1.5 vs. 4.8 months; HR 0.45; 95% CI 0.33–0.63; P < 0.001) and 6-month OS (67% vs. 81%; HR 0.54; 95% CI 0.32–0.92; P = 0.01), despite being permitted to cross over to trametinib. Although cutaneous eruptions were observed as an adverse effect in 87% of patients, trametinib treatment was minimally associated with the development of cutaneous squamous-cell carcinomas. Other toxic effects such as diarrhea and peripheral edema occurred in 35% and 27% of patients, respectively (Flaherty et al., 2012b). Trametinib (Mekinist) gained FDA approval in May 2013 for the first-line treatment of patients with unrespectable BRAF V600E/K mutant–positive melanoma.

Combination BRAF and MEK inhibition

Despite the impressive levels of tumor shrinkage observed in BRAF mutant melanoma patients treated with small-molecule BRAF inhibitors, responses are typically short lived, with a PFS of approximately 7 months (Chapman et al., 2011; Hauschild et al., 2012). Importantly, molecular studies characterized a number of potential mechanisms of resistance and demonstrated that combined BRAF and MEK inhibition effectively abrogated resistance mediated by MEK1 mutations, BRAF truncation, and acquired NRAS mutations (Paraiso et al., 2010; Poulikakos et al., 2011; Wagle et al., 2011). To “oversuppress” MAPK signaling, a phase II/III trial demonstrated that combination dabrafenib and trametinib at full monotherapy doses improved response rate (76% vs. 54%, P = 0.03) and PFS (10.5 vs. 5.6 months; HR 0.39; 95% CI 0.25–0.52; P < 0.001) when compared to dabrafenib alone, respectively (Flaherty et al., 2012a). Based on these results, both dabrafenib and trametinib received accelerated FDA approval in January 2014 for use in the treatment of patients with metastatic melanoma with a BRAF V600E/K mutation.

Three recent phase III trials corroborated these early results. The combination of vemurafenib and the MEK inhibitor cobimetinib improved PFS (9.9 vs. 6.2 months; HR 0.51; 95% CI 0.39–0.68; P < 0.001) and OS (68% vs. 45%; P < 0.001) when compared to vemurafenib alone (Larkin et al., 2014). In another expanded study, the combination of dabrafenib and trametinib improved PFS (9.3 vs. 8.8 months, HR 0.75; 95% CI 0.57–0.99; P = 0.03) and OS (67% vs. 51%, P = 0.002) when compared to dabrafenib alone (Long et al., 2014). The much anticipated trial of the combination of dabrafenib and trametinib demonstrated improved PFS (11.4 vs. 7.3 months, HR 0.56, 95% CI 0.46–0.69; P < 0.001) and OS (72% vs. 65%, HR 0.69; 95% CI 0.53–0.89, P = 0.005) when compared to vemurafenib as monotherapy (Robert et al., 2015). Consistent with earlier studies, combination treatment led to lower rates of cutaneous squamous-cell carcinoma formation compared to BRAF monotherapy. Thus, at this juncture, dual BRAF and MEK inhibition is quickly emerging as a standard of care for BRAF V600E–mutated melanomas.

Looking forward

Indeed, molecular targeted therapy has proven successful in the treatment of melanoma. Future directions include optimizing the currently available drugs for maximal clinical benefit and also the identification of novel therapeutic targets in melanoma. The previous discussion highlights the significant clinical benefit of selective BRAF inhibitors and the eventual relapse that occurs in patients treated with this modality. Combination therapy targeting BRAF and MEK is one potential avenue to abrogate this resistance that has been explored clinically. Work in human melanoma xenograft models suggests another approach to delay BRAF inhibitor resistance. These studies demonstrate that vemurafenib-resistant melanoma cells maintain dependency on BRAF V600E signaling via BRAF V600E overexpression. Intriguingly, the vemurafenib-resistant tumors in this model demonstrate dependence on vemurafenib for continued proliferation, such that cessation of the drug leads to tumor regression (Das Thakur et al., 2013). This suggests that a pulsed dosing strategy may forestall eventual vemurafenib-resistant tumors. As novel targeted therapies for melanoma emerge, one key clinical challenge will be developing optimal therapeutic regimens or combinations of therapies that will provide the most durable clinical response.

Inasmuch as the ideal treatment regimens of the existing melanoma drugs are being investigated, therapies targeting novel melanoma targets are in development. Given the genetic diversity of melanoma cells, there exist other attractive therapeutic targets including PI3K, CDK4, ERK, NF1, PPP6C, BCL-2, HSP90, mTOR, PDGF, Notch, MITF, and RAC1. Preclinical studies have begun to lay a foundation for further efforts to confirm clinical relevance.
PTEN/PI3K

Molecular aberrations in the PI3K pathway play an important role in the pathogenesis of melanoma (Figure 1). The tumor suppressor PTEN negatively regulates PI3K signaling and has emerged as the dominant genetic target in the PI3K pathway for melanoma therapies. PTEN mutations were found in 40% of melanoma cell lines and 10% of primary melanomas (Guldberg et al., 1997; Tsao et al., 1998b). Moreover, forced expression of PTEN in PTEN-deficient melanoma tumor cells abrogates activation of the downstream PI3K effector molecule AKT and cell growth (Robertson, 2005). Mouse models have suggested that PTEN dysregulation acts in concert with BRAF V600E to promote melanoma tumorigenesis and that targeting both MEK and the PI3K pathway in these mice inhibits tumor growth (Dankort et al., 2009). These data strongly implicate PTEN and the PI3K pathway in the development of melanoma. Clinical trials targeting the PI3K pathway in combination with inhibiting the MAPK pathway in melanoma are currently underway (Table 2).

CDK4/6

Inappropriate CDK4/6 activity can result from rare activating mutations of CDK4 (Tsao et al., 1998a; Zuo et al., 1996) or, more commonly, loss of p16 (Figure 1). Knock-in mice expressing CDK4 mutations display enhanced melanoma in response to carcinogen exposure (Sotillo et al., 2001). Thus, small-molecule inhibitors targeting CDK4/6 may also be an effective strategy to target the cell cycle, and several agents are currently in clinical trials (Table 2).

The development of novel targeted therapeutic interventions in the treatment of advanced melanoma demonstrates the importance of translational studies. Characterization of the molecular aberrations present in different subsets of melanoma cells has driven the development of therapies targeted specifically at mutations proven to contribute to melanomagenesis. Preclinical and clinical efforts have led to the recent approval of a number of therapeutic agents that have improved the PFS and OS of advanced melanoma patients. Despite these successes, there remains much work to be done to characterize and exploit other molecular targets, to overcome resistance and adverse effects associated with the recently approved agents, and to evaluate how best to combine these new interventions to maximal benefit. The bench-to-bedside model provides an effective and efficient means to achieve these goals.

CONFLICT OF INTEREST
The authors state no conflict of interest.

ACKNOWLEDGMENTS
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Table 2. Combined melanoma targeted therapies in progress (trials subject to change)

<table>
<thead>
<tr>
<th>Clinical trial number</th>
<th>Description</th>
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<tbody>
<tr>
<td>NCT01512251</td>
<td>BKM120 (PI3K inhibitor) + vemurafenib in BRAF V600E/K advanced melanoma</td>
</tr>
<tr>
<td>NCT01616199</td>
<td>PX866 (PI3K inhibitor) + vemurafenib in advanced melanoma</td>
</tr>
<tr>
<td>NCT01363232</td>
<td>Safety and pharmacodynamics of BKM120 (PI3K inhibitor) + MEK162 (MEK1/2 inhibitor) in advanced solid tumors</td>
</tr>
<tr>
<td>NCT01673737</td>
<td>Phase I/ib trial of SAR260301 (PI3K inhibitor) + vemurafenib in advanced cancers</td>
</tr>
<tr>
<td>NCT01820364</td>
<td>LGX818 (RAF inhibitor) + MEK162, BKM120, LEE011, BGJ398, or INC280 in advanced BRAF melanoma</td>
</tr>
<tr>
<td>NCT02065063</td>
<td>Safety, anticancer activity, and pharmacodynamics of trametinib + palbociclib (CDK4/6 inhibitor) in solid tumors</td>
</tr>
<tr>
<td>NCT01777776</td>
<td>Safety and efficacy of LEE011 (CDK4/6 inhibitor) + LGX818 (RAF inhibitor) in BRAF melanoma</td>
</tr>
<tr>
<td>NCT01826448</td>
<td>Phase I trial of PLX3397 (Kit inhibitor) + vemurafenib in BRAF melanoma</td>
</tr>
<tr>
<td>NCT01929840</td>
<td>Japanese phase I/II trial of GSK2118436 (dabrafenib) + GSK1120212 (trametinib) in BRAF solid tumors and cutaneous melanoma</td>
</tr>
<tr>
<td>NCT01433991</td>
<td>E7050 (cMET + VEGF inhibitor) + E7080 (VEGF inhibitor) in glioblastoma or advanced melanoma</td>
</tr>
<tr>
<td>NCT01909453</td>
<td>LGX818 (RAF inhibitor) + MEK162 (MEK1/2 inhibitor) vs. vemurafenib in BRAF melanoma</td>
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<td>NCT01701037</td>
<td>Dabrafenib ± trametinib before surgery in advanced melanoma that can be removed surgically</td>
</tr>
<tr>
<td>NCT01562899</td>
<td>MEK162 (MEK1/2 inhibitor) + AMG479 (IGFR-1 mAb) in solid tumors</td>
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<tr>
<td>NCT01519427</td>
<td>Selumetinib (MEK inhibitor) + MK2206 (AKT inhibitor) in advanced melanoma that failed vemurafenib or dabrafenib</td>
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<td>NCT01271803</td>
<td>Vemurafenib + GDC0973 (MEK inhibitor) in BRAF advanced melanoma</td>
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<tr>
<td>NCT01380835</td>
<td>MEK inhibitor + PI3K/mTOR inhibitor in advanced solid tumors</td>
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<tr>
<td>NCT01781572</td>
<td>Phase Ib/II trial of LEE011 (CDK4/6 inhibitor) + MEK162 (MEK1/2 inhibitor) in NRAS melanoma</td>
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</tbody>
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Rox Anderson:
The Story of Selective Photothermolysis
Rox Anderson, MD, is an accidental physician-scientist. After an adolescence as a self-described minimally intellectually challenged ham radio aficionado, he studied physics at the Massachusetts Institute of Technology, but then left science for several years, working summers at a children’s camp. In time he was serendipitously recruited to work as a laboratory assistant at the Massachusetts General Hospital (MGH), by Dr. John Parrish, whose research involved use of lasers as high intensity sources of UVA and visible light. Soon he was encouraged to enroll at Harvard Medical School (HMS), where his 1984 honors thesis described a therapy now known as selective photothermolysis, a revolutionary refinement of laser technology that permits near-total scarless portwine stain (PWS) removal and eventually many other skin lesions.

Dr. Anderson reasoned that by choosing a wavelength of light absorbed most exclusively by intravascular hemoglobin, the “chromophore,” and adjusting the laser’s pulse duration the absorbed energy, converted to heat, would diffuse into the vessel wall and destroy it but not reach the surrounding dermis. Thus, the abnormal PWS vasculature would be eliminated without producing a clinically detectable scar. The next and critical step was building a laser to meet these theoretic criteria. There were two small candidate companies. The one initially expressing interest produced a prototype laser with the desired characteristics, but it proved quite unreliable, even bursting into flames on one occasion, so the effort was abandoned after six months. The president of the second company was eventually convinced to tackle the problem, financed the laser development by remortgaging his home, and within a short time obtained approval from the Food and Drug Administration for the pulsed dye laser for the indication of PWS treatment, based on clinical trials performed at MGH. Of note, Institutional Review Board (IRB) approval was not needed, as IRBs had not yet been invented; and no MGH or HMS patents were filed, as only the laser manufacturer was concerned with protecting this intellectual property. Dr. Anderson emphasizes, “For me, it is ALWAYS about the opportunity to help people,” adding, “Selective photothermolysis came about because I was pissed off that argon lasers were scarring children.”

After completing his medical school studies and clinical training in dermatology, Dr. Anderson was welcomed into the MGH Wellman Laboratories of Photomedicine by Dr. Parish, who continued for many years to nurture his creativity. For the subsequent three decades, with assistance of a highly interdisciplinary team, Dr. Anderson has continued to address unmet medical needs. Whether employing sophisticated laser technology, photodynamic therapy, or most recently cryolipolysis, however, his work always begins with a patient in need and involves reducing the medical problem to its most basic component parts, when necessary ignoring the current dogma that is unfortunately not always correct. This practice is perhaps best described as “beginner’s mind,” free from preconceived ideas. It also involves changing approaches when the first idea proves incorrect or impractical, as the focus must remain on solving the problem, not employing a specific technology. Finally, like every translational researcher highlighted in this year-long series of vignettes, Dr. Anderson identifies his critical requirements for success as passion for the work and perseverance in the face of the inevitable obstacles.
Twenty-four years ago, I first had the privilege of working in a research laboratory in dermatology for three years during medical school. It was my first exposure to immunodermatology, and I marveled at the extent to which the molecular culprits of various immunologic diseases had been systematically identified and cataloged—especially given the rudimentary nature to which the molecular mechanisms of diseases in other physiologic systems and specialties had been worked out.

Since then, having subsequently spent 15 years as a practicing clinician and 10 years concurrently as an investment professional, I have personally found it even more interesting that none of those discoveries was really ever carried forward for the development of targeted therapies. Having both witnessed and participated in the financing of companies whose business plans centered on treating rare diseases involving other organ systems—which were successful in both raising capital and developing treatments to help patients—the question that inevitably emerged was why did this phenomenon not happen with diseases in dermatology even though groundwork arguably had been laid to a greater extent than for many of the conditions that ultimately ended up as the basis for companies? We have begun to see interest from investors and companies in developing treatments for a rare disease such as epidermolysis bullosa, but there are many other diseases within dermatology that remain unaddressed—some represented within the ranks of the patient groups making up the Coalition of Skin Diseases, but countless others that are not.

Dermatology is indeed a specialty of a few very common afflictions, as well as many, many rare ailments, of which the aforementioned immunologic represent but a subset and for which the quality of research continues to advance and improve. Yet the focus of product development remains squarely centered on those few common diseases, to the detriment of the field. Many view dermatology as a medical specialty with few conditions affecting sufficient patient numbers to support a viable commercial enterprise; consequently, outside of those few entities, investment interest has historically been lukewarm. It seems almost necessary that, given the characteristics of the field, the orphan disease business model should be embraced as a means to both increase the breadth and depth of therapies within dermatology and reestablish the legitimacy of dermatology as a “serious” medical specialty.

The calculus to change the perception of investors has precedent and does not require extensive spreadsheet manipulation. Pioneered at Genzyme, which developed billion-dollar product franchises based on enzyme replacement therapies for genetic diseases affecting a handful of patients, the orphan disease model posits that a scarcity of affected individuals need not make a disease less lucrative as commercial opportunity. Indeed, it makes each of those individuals much more valuable and even more worthy of close attention and care. Annual courses of therapy cost not hundreds, but hundreds of thousands of dollars—and the regulatory exclusivity granted to such treatments (Seven years’ worth in the United States and 10 years’ worth in Europe) because of the presumed limitations of their scope of utility further buttresses this value. If suitably chosen and priced accordingly, a company with a single drug for an indication with a prevalence of one to five cases per million can generate well over a billion dollars in sales or more. According to Thomson Reuters, almost a third of orphan drugs currently generate more than a billion dollars of sales in a year, with more...
than $50 billion in global sales for the category. Moreover, there is always the potential for an unexpected upside from indications not previously considered at the time of initial development—both rituximab and recombinant erythropoietin, now mainstays of therapy in several medical specialties and bellwethers of biotechnology drug development, started out as orphan drugs.

Of course, positing pie-in-the-sky scenarios on the back of an investor’s napkin does neglect certain real-world considerations. The main requirement to achieve this rarefied status in the eyes of the regulatory agencies is simply the number of patients afflicted, but, of course, the social and commercial viability of such a model requires evidence that the investment in each patient is justified—that their lives are sufficiently transformed for the better to warrant the burden of cost, both to government and private payers and to society as a whole. Such an undertaking will necessitate comprehensive efforts to provide validation of outcome measures and documentation of natural histories, similar to the work done by the International Dermatology Outcome Measures group for psoriasis and as has been the case with other conditions outside dermatology, such as muscular dystrophies.

It is ultimately this demonstration of value—showing that diseases of the skin are as functionally debilitating to the individuals who are unfortunate enough to have them as those found with other specialties—that is required to compel reimbursement. If payers can be convinced to pony up for biologics costing tens of thousands of dollars a year for a condition as prevalent as psoriasis, then there is no reason why they cannot be swayed in similar fashion for treatments for isolated conditions within dermatology and at a higher per capita rate to make the rare disease business model feasible—opening up a heretofore largely unexplored vista of value creation to attract investors and help patients, as well as improve the stature of dermatology within medicine and society as a whole.

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The BCNS Clinical Trials Team Celebrates Together
In 2012 the first medical therapy was approved for treatment of advanced basal cell carcinoma (BCC), and an investigator-initiated study of this drug established its striking efficacy in patients with basal cell nevus syndrome (BCNS), a dominantly inherited disorder characterized by early onset of multiple BCCs, sometimes 100s to 1000s over a patient’s lifetime.

The BCNS study was spearheaded by Ervin H. Epstein Jr, Senior Scientist at the Children's Hospital Oakland Research Institute (CHORI), whose editorial describing this translational research journey appears in this issue. Pictured celebrating completion of their successful study at CHORI in May 2012 are (left to right) Joselyn Lindgren, Clinical Trials Coordinator; Dr Epstein; Kristi Schmitt Burr, Executive Director, BCNS Life Support Network; Bud Caruso, former Network Trustee and patient advocate; and Maria Acosta-Raphael, Clinical Trials Coordinator. The celebration is testimony to the critical role of collaboration among scientists, clinical investigators, patients, and patient advocates in translational research.

Photo courtesy of Children's Hospital Oakland Research Institute.
Three decades ago, near the end of a 30-hour, minimal-sleep, San Francisco–Cleveland round trip, I fell into a deep sleep at 36,000 feet, awakened refreshed somewhere over Wyoming, and was rested enough for once to read *Nature* with care. To my great good fortune, it was the issue that reported the identification of RB, the gene whose mutations cause the eye tumor retinoblastoma (Friend *et al.*, 1986). The approach that led to this discovery was two pronged: (i) searching tumor cell DNA for areas of recurrent loss of heterozygosity (i.e., loss of a portion of one of the two copies of a chromosome) that might include a putative tumor suppressor gene and (ii) doing family linkage studies on DNA gathered from kindreds with retinoblastomas. Because I have had a long-term interest generally in heritable disorders of the skin and identification of their molecular underpinnings and specifically in the basal cell nevus (Gorlin) syndrome (BCNS) (Aurbach *et al.*, 1970), the analogy between the clinical findings in retinoblastoma and basal cell carcinomas struck me as obvious—both came in two types: (i) the more common with a single sporadic tumor at a later age of onset and (ii) a rare variant, inherited as an autosomal dominant, often with multiple tumors and with an earlier age at onset. I thought that if Friend and colleagues could use their approach to identify the RB gene whose mutations underlie these tumors, we could use the same approach to identify the BCNS “gene,” and that might tell us something about the molecular aberration that causes the far more common sporadic basal cell carcinomas (BCCs).

I immediately embarked on a project to gather many, many blood samples from families with BCNS so that we could do family linkage analysis and lots of BCCs so that we could do many, many Southern blots to identify the locus of the putative tumor suppressor gene that is aberrant in BCNS patients. We then discovered that groups on several continents had already embarked on this quest. In fact, after we had struggled for several years, the group led by Alan Bale got there first and, using the same approach, localized the gene for which we had been searching to chromosome 9q (Gailani *et al.*, 1992). The next step was to find the actual gene, and we and the rest of the community focused our efforts on an increasingly small area that “must” contain the gene. We were, as Lyndon Johnson put it, knee deep in the Big Muddy—lost in a forest with impenetrable fog that got thicker by the moment when, fortunately, an aha moment came. Matt Scott at Stanford called in October 1995 to tell me he thought he “had” the gene for which we had been searching for nearly a decade. Matt is a superb developmental biologist with a long record of contributions to elucidating the hedgehog (HH) signaling pathway; he is now president of the Carnegie Institution for Science. His lab had cloned the human homolog of the Drosophila gene encoding *ptch*, the primary inhibitor of that pathway, and David Cox and Richard Myers, human geneticists at Stanford, localized it to 9q; sure enough, there was a human disease, BCNS, at that site. Fortunately, he called us. The collaboration cleared the fog in which we were searching for the gene, and eight months later we published our findings of inactivating mutations in *PTCH1* in BCNS patients and in DNA from sporadic and inherited BCCs (Johnson *et al.*, 1996). Oh yes, on the very same day in June 1996, a multicontinent con-
sortium, again led by Alan Bale, published their identification of the same gene, and they were smart enough to get there without needing a lucky phone call (Hahn et al., 1996).

The next lucky phone call was from Fred de Sauvage, at that time a young researcher and now vice president of Research Molecular Oncology at Genentech. His lab had cloned the human SMO gene, which encodes the protein that functions as the next step in the pathway, and together we found activating mutations in this gene (Xie et al., 1998), thus nailing the concept that it is elevated HH signaling that underlies all BCCs. Matt Scott’s lab made a Gorlin mouse (i.e., Ptc1-/-) to study more fully the role of hedgehog (HH) signaling in development. He graciously gave it to us for studies of murine BCC carcinogenesis; we now have produced untold numbers of these furry beasts, all descended from one genetically engineered mouse, and they have been the linchpins of all our lab’s work for the past 1½ decades.

But—except for enabling prenatal diagnosis—what was the utility of that discovery? At least theoretically, it opened the door to making a drug that might shut down the aberrant signaling pathway and thereby at least treat or, dare we hope, even cure BCCs. Scientifically, the way seemed clear, and Fred de Sauvage championed this project at Genentech. Alas, the company’s leadership, like that at most pharmaceutical companies, decided that BCCs were so well treated surgically that it was not worth the investment—better to pursue medical needs that seemed more unmet. Fortunately, data published in 2003 and 2004 suggested that enhanced HH signaling might be responsible for as many as 25% of all visceral cancers (e.g., Watkins et al., 2003; Berman et al., 2003), and after that Pharma became highly eager to develop an HH inhibitor. Genentech partnered and eventually absorbed the HH inhibitor program that had been undertaken with the leadership of Lee Rubin (now a Harvard professor of stem cell biology) at Curis using a high-throughput screen of small molecules.

The first such to be tested in vivo was Curis 61414, which has strong anti-BCC efficacy when applied to mouse skin but failed completely when applied to human skin (Tang et al., 2011). Although the reason for this disparity is not completely understood, at least in part it was because of the perhaps order-of-magnitude greater barrier function in human compared with mouse skin and the drug’s intrinsically stronger inhibitory effect on the murine than on the human molecular target. This failure encouraged Genentech to focus its efforts on developing an oral drug. The fruit of these efforts was vismodegib (Erivedge), which in 2012 became the first HH inhibitor to be approved by the US Food and Drug Administration (FDA) for marketing for treatment of “advanced BCCs,” an evolutionary term currently used to describe those BCCs for which surgery is at best a poor option. The good news is that it has remarkable antihuman BCC efficacy—approximately half of the very rare metastatic BCCs and the unusual but less rare locally advanced BCCs respond significantly (Sekulic et al., 2012; Basset-Seguin et al., 2015). Genentech entrusted us with funds and medication during their phase II development of the drug, unusually early for such entrustment, enabling us to prosecute an investigator-initiated, double-blind, placebo-controlled trial of vismodegib’s anti-BCC efficacy in patients with Gorlin syndrome. We found that Gorlin BCCs essentially all melt away, eventually completely, and no new BCCs develop while patients remain on the drug. While participating in our trials, no patient has required excision of a BCC (Tang et al., 2012). Unfortunately, vismodegib has systemic adverse effects that are class specific (hair loss that is likely due to the requirement for hedgehog signaling in anagen, taste loss that is likely due to the requirement for hedgehog signaling for taste bud development, and muscle cramps due to uncertain mechanisms).

These adverse effects have been seen with other clinically studied hedgehog inhibitors, including sonidegib (Odomzo), the Novartis HH inhibitor that was approved by the FDA in July 2015 for sale in the US. Because of these side effects, many patients stop taking the drug, and when Gorlin patients stop taking the drug, BCCs that are histologically and clinically cured recur in the same site covering the same skin surface. Fortunately, when the drug is restarted, the tumors remain sensitive, and we have not seen any nonadvanced BCC develop resistance to vismodegib in nearly six years of study. Unfortunately, all publicly reported clinical trials of the efficacy of vismodegib and of the other small-molecule HH inhibitors versus other cancers (e.g., colorectal, pancreatic, and ovarian cancers) have had disappointing results—BCCs and the subset of medulloblastomas that are hedgehog driven may be the only human tumors for which the current class of HH inhibitors has therapeutic efficacy.

I draw several lessons from my participation in the identification of the molecular target, testing a topical preparation on mouse BCCs, and testing the oral drug on humans:

1. Hillary’s speech writers were right—it takes a village, and in this case several villages—some with village elders such as J.B. Howell and other dermatologists who began describing patients with what now is termed BCNS in the 1950s; Robert Gorlin, who (like Columbus) was the “last” to describe the syndrome and therefore has the honor of having his name attached; Eric Wieschaus and Christiane Nüsslein-Volhard, the Nobel laureates who described the hedgehog signaling pathway in 1980; and hunter-gatherers such as the near dozen labs that worked collaboratively and competitively in the 1980s and 1990s to identify the gene whose mutations cause BCNS. Success also requires one or more of the near completely separate villages (such as Genentech or Novartis) that have the resources to fund the highly specialized armies of medicinal chemists, regulatory personnel, clinical trialists, and many others needed to move from concept and opportu-
nity to supplying an effective drug to the shelves of pharmacies around the world.

2. It takes a lot of money to feed and maintain even the last of these villages. The National Institutes of Health traditionally has supported the first villages. But these villages need enormous amounts of funds to develop new drugs—the estimates continue to climb from the hundreds of millions to more than a billion—and hence pharmaceutical companies need to invest in drugs that have at least a chance of returning large amounts of money.

3. Given that the former villages have produced and no doubt will continue to produce more targets whose “hitting” could significantly ameliorate various diseases of the skin, how can the interest of the latter villages be piqued sufficiently to unleash the large amounts of capital needed to bring such a drug to market? That’s really the big question. Two types of answers come to mind.

i. In the case of melanoma, and increasingly for psoriasis, the market opportunity is perceived as being large enough to develop drugs whose first indication is dermatologic, although many would consider melanoma once it has left the skin an oncologic rather than a dermatologic disease. Can we find more dermatologic markets (numbers of patients \( \times \) possible profit per patient) that are large enough that their targeting would justify the large amounts of capital that would have to be spent to develop new drugs specifically for those targets? In the case of the healing of chronic wounds and of the safe amelioration of eczema, the answer clearly would be affirmative. Perhaps this also might be the case for several orphan disease drugs with primarily skin manifestations because orphan diseases, at least for the time being, can command high prices per patient treated, and their path to approval may be less costly. But for the great majority of conditions to be found in any dermatologic text, the answer clearly is negative.

ii. In the case of hedgehog inhibitors for BCCs, it seems highly unlikely that the monies ever would have been spent were it to have been known that BCCs, and only a small subset of them (“advanced” or metastatic), would be the only market for the new drugs. The BCC drug came along on the coat-tails of anticipated indications for pancreatic, colorectal, and other cancers. This is a time-honored path for new dermatologic drugs (i.e., using a drug developed for some other indication for a skin problem)—consider aminopterin and methotrexate decades ago and etanercept and other tumor necrosis factor inhibitors more recently for psoriasis, bromodidine for a red face, and steroids for almost everything. Could we repurpose newer drugs (or even old standbys) developed and utilized for other ailments for skin problems? Presumably to do so we would need to think more seriously about identifying such drug–skin targets and to institute a more structured approach to the problem. One example comes from the hedgehog inhibitor field. An in vitro targeted assay by Philip Beachy, then at Hopkins, of a large number of FDA-approved drugs identified both in vitro and in vivo (at least in our Ptch1 \(^{−/−}\) mice) antihedgehog/anti-BCC activity of itraconazole unrelated to its antifungal activity (Kim et al., 2010, 2013). Investigation of its anti–HH efficacy in humans, including its anti–prostate cancer efficacy, is under way. Its potency is considerably less than that of vismodegib and other “professional” hedgehog inhibitors but if we did not have the latter, perhaps it could have served as an at least partially effective anti-BCC treatment. The regulatory and financial hurdles blocking repurposing of an old drug are far lower than are those blocking development of a new drug. Are there more such in vitro screens of already approved drugs that might unearth yet other, even more useful surprises?

4. I have been extraordinarily fortunate to have seen work that our lab has done actually lead to something useful for patients. How many people get to work on the identification of the molecular basis of a disease and then lead the clinical trial of the first drug to replace the function of the defective gene? What underlies that good fortune, beyond a very healthy dose of good luck? I could have skipped the Cleveland trip and not have read about RB; Matt could have called someone else; we could have worked on a disease for which the identification of the mutant gene did not lead so clearly to a drug. Indeed, our own findings of keratin gene mutations in epidermolysis bullosa simplex have not enabled a therapy. Part of it clearly depends on my having been surrounded from the start by very good individuals. Because of the example set by my family, I grew up expecting to become a clinical scholar in an era in which the phrase “balanced life” had not yet been coined and never felt that work was drudgery. And my lab at the San Francisco General Hospital for 35 years was adjacent to that of Y.W. Kan, a pioneer in applying molecular biology to clinical problems; he was kind enough to teach us the fundamentals of this then-arcane field. More broadly, being immersed even half-time in a vibrant research university gave me exposure to new ideas and the sense that if these guys could employ new approaches, maybe so could I. Part of it depended on having the freedom to travel. For many years I was not only a faithful attendee at the meetings of the Society for Investigative Dermatology but also the sole card-carrying dermatologist at the annual meeting of the American Society for Human Genetics. Because of this, in 1980 I was, along with Alain Hovnanian, one of the two persons on the planet who knew something about two particular fields of knowledge—family linkage analysis and Mendelian diseases of the skin. And part of it
was because I had both a clinical practice and a lab that allowed me to approach whatever problem I wanted so that I could fantasize about how wonderful it would be if someday I could go to some far off country and see on the druggist’s shelf a drug whose development I had touched, even peripherally. It happened, and the patients are even happier than I am. Now if only we can convert remission into cure!

CONFLICT OF INTEREST
The author states no conflict of interest.

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REFERENCES


Alice Gottlieb Examining a Psoriasis Patient while a Trainee Records her Observations
Alice Gottlieb was among the first women accepted into the MD/PhD program at Rockefeller University, intent on a laboratory-based career. While there she pursued the pathophysiology of psoriasis, then classified as a keratinocytic disorder. In one experiment that was forever to change our understanding of the disease, she selected psoriatic skin for use as a negative control in an immunofluorescence study of HLA-DR expression by keratinocytes. To her great surprise, the epidermis stained strongly, suggesting the presence of gamma interferon and/or other immunologic cytokines in plaques. With her laboratory colleague James Krueger she developed this observation into compelling evidence that psoriasis is an immunologic disease, driven by T cell abnormalities and responsive to a T cell-specific immunotoxin, work published in a seminal Nature Medicine paper.

Having completed her training and needing to stay in the New York City area for family reasons, Dr. Gottlieb worked briefly at Roche and then at the Robert Wood Johnson Medical School in New Jersey, seeing patients part-time as a double-boarded rheumatologist and dermatologist. One complex patient, followed for both Crohn’s disease and psoriasis, was prescribed an anti-TNF-α antibody for Crohn’s disease, followed by a dramatic response in both bowel disease and psoriasis. This chance observation led Dr. Gottlieb to design and obtain (with considerable difficulty) pharmaceutical support for the first randomized, placebo-controlled trial of an anti-TNF-α drug for the indication of psoriasis. In the studied group of moderate to severe psoriatics, 80% attained 75% clearing of their skin lesions (PASI 75) by weeks 6 and 10. This work opened a floodgate of interest by major pharmaceutical companies in testing their targeted immunotherapies, initially developed for rheumatoid arthritis, for the indication of psoriasis.

Dr. Gottlieb, the self-described “Jewish mother of biologics for psoriasis,” has since played a central role in the design and conduct of clinical trials for many drugs targeting specific cytokines implicated in the pathogenesis of psoriasis. She has tirelessly educated both industry leaders and practicing dermatologists about the risks and benefits of these agents. Critically, she has also championed development of clinically-meaningful outcome measures acceptable to regulatory groups and third-party payors, without which venture capitalists and the pharmaceutical industry cannot afford to invest in new drugs.
The policies of the US Food and Drug Administration (FDA) will affect the developmental course of any therapeutic, diagnostic, or preventative agent aimed at being marketed in the United States. As such, the FDA impacts almost all translational research. Put more bluntly, no research will be translated as a product to the US medical market until it is approved by the FDA.

I wrote a book entitled *The FDA for Doctors* (Eaglstein, 2014), which was recently published by Springer, said to be the largest academic press in the world. I had been working on the book episodically for some years and had a hard time finding a publisher. Several publishers of medical books declined, believing the book would not be of interest to doctors. The publishers explained that they succeed by publishing cardiology books for cardiologists, endocrinology books for endocrinologists, dermatology books for dermatologists, and so forth. They felt a book on the FDA, because it was not focused on a given specialty, would not be purchased by doctors. For specialists engaged in translational research, I strongly disagree.

My more-than-casual interest in the FDA first came through performing clinical studies aimed at FDA approval. I later helped with the FDA’s long-delayed review of the efficacy of drugs approved for marketing before efficacy was required, the so-called Drug Efficacy Study Implementation review. I have served as a member and ultimately the chair of FDA’s dermatologic drug advisory committee, and when I was a Robert Wood Johnson Health Policy Fellow, for a short time I was given the lead role in FDA oversight for the US Senate by way of the Labor Committee. During this time, I, too, decided that most doctors seem little interested in the FDA. I felt this disinterest was largely the result of doctors receiving limited formal training about the FDA while in medical school and then becoming overwhelmingly busy in the practice world.

Why wouldn’t doctors be curious about an agency that determines which drugs, biologics, and medical devices can be sold in the United States, an agency that mandates what can and must be on the labels of all therapeutics and what can be said to doctors and in advertisements? Few individuals realize that because of the FDA’s policies, the United States is one of only two countries that allow direct-to-consumer drug advertising. The FDA must approve even a drug’s name before it can be sold, and its authority actually covers 25% of the US economy, including foods, drugs, biologics, devices, cosmetics, and tobacco products. How many doctors know that the definitional difference between a drug and a device is that devices do not act chemically? And that more than 95% of new medical devices receive FDA approval without any required human testing? Although most doctors know that human clinical trials, phases I, II, and III, are required for drug approval, few realize that the clinical trials, especially phase III, are the most costly part of drug development. For completely new drugs, this cost is now estimated to be in the $2 billion range (Tufts Center, 2014).

There are probably many reasons that doctors are not more interested in an agency whose policies and regulations control so much of what we need to prevent, diagnose, and treat disease. For one thing, the practice of medicine is controlled by the states, which issue licenses to practice medicine. The FDA is a federal agency whose powers derive from the federal control over interstate sales. That is, the FDA...
has no authority over the practice of medicine. As such, although science and medicine are often at the heart of FDA matters, the FDA’s powers, responsibilities, and actions derive mainly from laws and legal constructs that inherently reside in the legal rather than the medical purview.

I recognize that many of the JID’s readers are not medical doctors. However, like medical doctors, academic and other researchers have received little formal education about the FDA. Most investigators, even basic scientists, aspire to have their work result in clinical application, even if that occurs sometime in the distant future. The JID’s editor, Barbara Gilchrest, selected “Progress in Translational Research” as the journal’s 2015 theme “to celebrate the impressive progress” in translational research (Gilchrest, 2015). A subsequent editorial (Parrish et al., 2015) highlighted the need for academic investigators, physicians and nonphysicians alike, to be informed about the process of having their work translated to the clinic. The editorial gave as an example the need to forgo quick publication or presentation of findings to obtain patents, which are critical to incentivizing companies or venture capitalists to invest in the translational process.

In a similar manner, and realizing that almost all translation to the bedside in the United States is dependent on FDA marketing approval, knowledge about the agency—especially its regulatory categories and its preclinical as well as clinical requirements—will be useful in guiding researchers in directions that are most advantageous to the ultimate translation of their findings and technologies. For example, by knowing the difficulties of large-scale production and characterization of large protein molecules made by microorganisms (biologics), investigators might at the earliest possible stage seek small molecules able to mimic the effect achieved with large molecules to have a potential small-molecule drug. Recognizing the need for a stable molecule might dispose researchers to select this criterion at the earliest stage. Knowledge of the definition and approval pathways for devices might dictate the use of certain experimental approaches and an alertness to devices already on the market that might serve as predicates, thus greatly reducing the requirement for preapproval clinical testing. Similarly, knowledge of regulatory categories such as combination drug–device and device–drug can be useful early in the game. Of course, much of the work involved in ultimately obtaining FDA approval, especially the chemistry, manufacturing, and control requirements and long-term toxicology, cannot usually be done by academic investigators. However, the insights afforded by knowing more about the process might well help to shorten the “valley of death,” the period between the discovery of a potential drug and when the support for translational work is secured.

In summary, I believe that all medical scientists and physicians would not only help themselves but also ultimately help society by becoming more conversant with the FDA’s roles and its processes for carrying them out. It was with those beliefs in mind that my book was written. The book can serve as a primer for medical students, postdoctoral fellows pursuing medical research, and all those intrigued by translational research at any time in their careers. Information about the FDA and its goals, policies, and requirements can be found in many other places as well, including the agency’s websites.

CONFLICT OF INTEREST
The author states no conflict of interest.

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Brian Druker in His Laboratory
When Brian Druker was a first-year medical student in 1977, he read about Sidney Farber’s crusade to find an effective treatment for childhood leukemia (see the March 2015 JID cover story). He found the story inspiring but also depressing because the drugs employed were highly toxic, with both short-term and long-term potentially lethal side effects. Oncogenes were just being discovered, and he imagined dissecting the molecular mechanisms responsible for cancers, then developing a targeted therapy selective for the malignant cells.

Years later, during his medical oncology fellowship, Druker began laboratory-based research, studying tyrosine kinase signaling in animal tumor cells. In 1990, after five years in the lab, and now confident in his scientific as well as clinical acumen, he decided to focus his research on a human cancer: chronic myelogenous leukemia (CML).

Druker selected CML for development of a targeted therapy for several reasons. The Philadelphia chromosome had long been recognized as the hallmark of CML cells, and by the mid-1980s it was known to result from transfer of genetic material from chromosome 22 to chromosome 9, creating a fusion oncogene with tyrosine kinase activity—Druker’s area of expertise—that drove proliferation of the CML cells. Furthermore, the CML cells were apparently free of additional major genetic abnormalities, typically for 3–5 years after diagnosis, before the inevitable and rapidly fatal blast crisis.

Thought leaders in oncology dismissed Druker’s idea of inhibiting the CML-specific tyrosine kinase as a cancer therapeutic target, believing that inhibiting one kinase would inhibit all kinases, of which there are hundreds per cell. But Druker, aware of recent progress in the development of specific kinase inhibitors and armed with 4G10, an antiphosphotyrosine antibody he had generated at the Dana-Farber Cancer Institute, pursued his hypothesis.

He obtained experimental tyrosine kinase inhibitors from a biochemist acquaintance at Ciba-Geigy who was using Druker’s 4G10 to monitor their effectiveness in vitro. In 1993, Druker began treating CML cells obtained from his own patients. To his delight, one of the inhibitors killed the leukemia cells at a dose orders of magnitude lower than that required to kill normal cells. Determined to develop this inhibitor (imatinib, now known as Gleevec) into a drug for CML patients, Druker shared his results with Ciba-Geigy, which owned the small-molecule inhibitor, only to find that the scientist who had made imatinib—his “inside champion”—had left. In addition, the company was in the midst of a merger that eventually created Novartis. In that environment, it was extremely difficult to convince corporate management to fund the necessary drug development program. Moreover, Novartis’s financial analysis team concluded that CML was too rare a disease to justify the development costs. A clinical trial was looking unlikely.

Fortunately, in 1996 Druker received one of the first translational research awards from the Leukemia Lymphoma Society. This enabled him to collect additional preliminary data and ultimately to convince Novartis to conduct a phase I (dose escalation and safety) trial of imatinib in patients with CML.

That trial was a huge and unprecedented success: 98% of patients (nonresponders following conventional interferon therapy) who received a sufficient dose of imatinib experienced a normalization of their blood counts, while experiencing minimal side effects. In 2001—less than three years after the start of the first clinical trial—Gleevec was approved for CML by the US Food and Drug Administration.

Today Druker continues to care for CML patients, some diagnosed as long as 20 years ago, living normal, healthy lives on Gleevec, a blockbuster success for Novartis. In the laboratory he is studying the phenomenon of acquired drug resistance, how to extend targeted therapies to other cancers, and how tyrosine kinase inhibitors can be combined with immunotherapy to achieve true cures rather than disease control. Of note, the approach he pioneered in CML has proven highly relevant to the management of cutaneous melanoma, basal cell carcinoma, and many other malignancies.

Asked about the key to his success, Druker cites the importance of having passion for one’s work, persistence, and selecting one’s focus carefully, with an in-depth understanding: “You need to train to run a marathon.” He also notes the importance of risk-taking for both himself and his funding sources. His translational work with tyrosine kinase inhibitors to treat CML was never federally funded, being out of step with then-current research trends, and relied largely on the good faith of patient advocates whose desperate need for better treatment made possible the first clinical trial. Not all risks pay off, but those that do change the face of medicine.

Establishing an Academic–Industrial Stratified Medicine Consortium: Psoriasis Stratification to Optimize Relevant Therapy

Probably the most important change in dermatological care over the next quarter century will be the introduction of stratified medicine into routine clinical practice (Bell, 2014). This is a common goal of physicians, industry, and patients. Stratified medicine is not a new concept and is synonymous with the term personalized or precision medicine. It is best understood as a process that moves prescribing from its current “trial-and-error” basis to one that is targeted not only to the causes of disease but also to the needs of the individual patient, thereby fulfilling the premise of the right drug for the right patient. The ability to prosecute a stratified approach to prescribing has been led by the field of oncology in which most new therapies are released alongside a companion diagnostic. For instance, in the targeted management of breast cancer, trastuzumab is preferentially prescribed to those patients whose cancer expresses the human EGF receptor-2 (Slamon and Pegram, 2001).

The stratified medicine approach is beginning to percolate into the management of immune-mediated inflammatory disease. For instance, the anti-IL-13 biologic lebrikizumab is known to be far more effective for the treatment of asthma patients with high, as opposed to low, serum levels of periostin (Corren et al., 2011). In the management of inflammatory skin disease, the stratified approach is nascent but its successful prosecution will require close partnership among clinicians, scientists, patients, and industry. The development of the UK Medical Research Council (MRC)–funded stratified medicine consortium in psoriasis—Psoriasis Stratification to Optimize Relevant Therapy (PSORT)—is an excellent example of such partnership working, which is so vital to the concept of translational research whereby discovery and proof-of-principle testing can lead to improved patient care and commercialization. In December 2011, the British prime minister, David Cameron, announced a research initiative on stratification of disease to be implemented by the MRC. An application was made to this call for psoriasis to be recognized as an exemplar disease for stratification with an initial focus on biologic therapies. This Editorial provides the background and objectives to the PSORT consortium that commenced in September 2014.

The genesis of the consortium goes back 30 years, to the early 1980s, when the initial challenges to the dogma of psoriasis as primarily a disorder of epidermal keratinocytes were made and the concept of the central pathomechanistic role of T cells was introduced (Valdimarsson et al., 1986). This new paradigm was cemented by the observation that cyclosporine (a rudimentary T-cell-targeted approach) was an effective therapy for psoriasis—a consequence of an academic–industry collaboration with Sandoz, then the manufacturers of the drug (Griffiths et al., 1986). Further evidence of academic–industry collaboration arose from a number of sources, including Gottlieb, who reported that a lymphocyte-selective toxin, DAB389 IL-2, targeted to IL-2R-expressing cells (i.e., T cells as opposed to keratinocytes) was an effective therapy for psoriasis (Gottlieb et al., 1995). The biologic era for psoriasis dawned with the approval of alefacept (Ellis and Krueger, 2001), followed by efalizumab and cytokine-targeted therapies, primarily tumor necrosis factor (TNF)-α and then IL-12/IL-23 (ustekinumab). The approval of the first of the anti-IL-7 biologics, secukinumab, for the treatment of moderate to severe psoriasis in the United States and European Union.
occurred in early 2015 (Sanford and McKeage, 2015). A notable feature of this journey has been the close working relationship between clinicians, scientists, and industry—a necessary tripartite partnership in translational research.

Although biologic therapies have been transformational in the management of severe psoriasis, the known variability in both the short-term response and the persistence of that response to the drug is problematic. Such problems are tractable by a stratified approach. Psoriasis is a model disease for stratification because (i) unlike in other immune-mediated inflammatory diseases, such as rheumatoid arthritis, biologics are licensed for use as monotherapy; (ii) response to therapy is relatively easy to quantify and; (iii) the diseased tissue (skin) is accessible for sequential sampling by biopsy—a minimally invasive and patient-accepted technique. The MRC’s guidance specified that the consortium should embrace open collaboration rather than competition, with sharing of expertise across institutes and sectors with industry engaged as equal partners from the outset. The consortium is to be a dynamic platform and the programmatic support is milestone-driven.

In October 2012, key UK academics and clinicians with expertise in treating psoriasis and potential industry partners united by a strong research interest in the disease came together in a one-day scoping workshop in London, funded by the MRC and chaired by Sir John Bell. This invaluable meeting enabled active engagement among potential investigators, industry, and the Psoriasis Association of Great Britain and Ireland. Industry partners embraced the opportunities inherent in the stratified medicine approach to managing psoriasis and were generous in offers of support ranging from in-house expertise to data sets to finance. This formed the basis for the PSORT consortium application to the MRC in 2013. Using biologic therapies as the target for stratification, the main objective of PSORT is to use clinical, pharmacological, genetic, and immune biomarkers to predict and reproducibly stratify the response of psoriasis to biologic therapies. This could result in biologics being used at minimal effective doses and form the basis for an algorithm or stratifier scalable for clinical use with the potential for significant health-care savings.

The success of the PSORT application is founded on four pillars: (i) the main academic applicants have collaborated successfully for many years (in some cases, more than 20) on different aspects of psoriasis research and clinical management (Smith et al., 2009; Strange et al., 2010); (ii) the bioresource available to the consortium in the form of the British Association of Dermatologists Biologic Interventions Register (http://www.badbir.org (see Box 1); Burden et al., 2012) to test the clinical utility of biomarkers; (iii) the track record of the investigators’ collaboration with industry for many years; (iv) the involvement of expertise beyond basic science and dermatology, including bioinformatics, systems medicine, biostatistics, health economics, pharmacology, and research management; and (v) the involvement from the outset of patients in the planning and design of the studies that form the Work Strands of the consortium.

The work of PSORT is structured around a dynamic integrative platform of two related elements of research, or Work Strands: (i) Clinical and Pharmacology Studies; and (ii) Immune Biomarkers in Skin and Blood. The Work Strands move the research questions through the traditional discovery, refinement, and validation phases (Figure 1). An objective of the PSORT program is to identify and characterize psoriasis endotypes (endophenotypes). This terminology was first introduced into the asthma field to define subtypes of disease, both functionally and pathologically, by a molecular mechanism or by a treatment response (Anderson, 2008).

PSORT’s work will focus on adalimumab (anti-TNF), ustekinumab (anti-IL-12/23), and secukinumab (anti-IL-17A) in the first instance, but the dynamic aspect of the program allows inclusion of new biologics and small molecules as they become available for psoriasis. Work Strand 1 involves discovering disease endotypes associated with treatment outcome; assessing the influence of blood drug levels and antidrug antibodies on outcome; and assessment of adherence. Work Strand 2 concerns the discovery and

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**Box 1. The British Association Of Dermatologists Biologic Interventions Register (BADBIR)**

- Founded in 2007; funded until at least 2017
- Unique, long-term, Web-based pharmacovigilance register for psoriasis patients on biologic or conventional systemic therapies
- Viewed as international gold standard psoriasis registry
- 152 Dermatology Centres in the United Kingdom and Ireland recruiting to BADBIR
- 11,048 patients recruited: 7,102 on biologics and 3,946 on conventional systemic therapies
- High-quality phenotypic and quantitative disease severity data
- High-quality follow-up data on response to therapy and persistence of response
- More than 30% have serial serum samples and/or RNA and DNA banked

Source: http://www.badbir.org
validation of molecular and immune signatures (comprising disease and drug endotypes), in skin and blood, that stratify responses and assessment of key biomarkers for investigation of mechanisms of response.

The results of these investigations are stored in a tranSMART data warehouse (http://www.transmartfoundation.org), allowing seamless integration of PSORT multi-omic data and clinical phenotypes with a highly curated selection of preexisting public data. TranSMART offers the PSORT consortium and partners a unified, secure, and importantly sustainable research environment to apply a range of systems biological and machine learning methods for biomarker discovery. As the PSORT project scales in its data generation and integration, hosting of the PSORT–tranSMART will be transferred to the MRC-eMEDLAB, providing direct, secure access to substantial high-performance computing facilities. There is both the ability and the desire to add data from other resources (e.g., the European Molecular Biology Laboratory and ENCODE) as and when they become available, which will, in turn, help to ensure the durability of the consortium.

The consortium is composed of 18 partners, all of whom have signed a legally binding consortium agreement, a living document that determines, among other operational issues, the detail of intellectual property (both background and foreground) and commercialization of discoveries. There are currently 10 industry partners (7 pharmaceutical and 3 diagnostic companies; Table 1), but it is likely that this will change over the 4 years of the consortium as partners may, under the terms of the agreement, either leave or join PSORT. Examples of industry engagement in PSORT ranges from in-house expertise on development of the tranSMART data warehouse (Janssen), RNA Seq analysis (GSK-Stiefel), and embedding of PSORT Work Strand 2 objectives of sequential sampling for skin and blood transcriptomics in a subset of subjects in a UK commercial phase III trial of secukinumab in psoriasis patients deemed to have failed TNF-inhibitor biologics (Novartis). The diagnostic companies will engage more fully if and when a scalable stratifier for predicting response to biologics or a biologic is identified. Perhaps the crux of the MRC and the UK government’s strategic investment in this area is that industry wishes to be involved in PSORT and stratification of psoriasis is important to them. Such interest can be articulated thus: (i) taxonomic classification of psoriasis, based on mechanisms, will identify cohorts of patients suited to proof-of-principle testing of new molecules; (ii) stratification tools will facilitate accurate targeting of new molecules to patient/drug endotype; (iii) establishment of minimal effective dosing will inform best practice; (iv) PSORT will inform other IMIDs because psoriasis is the lead disease for new molecules (e.g., anti-IL-17 and anti-IL-12/23); and (v) value will be added through cross-referencing of data in other MRC-funded stratified medicine programs (e.g., rheumatoid arthritis–MATURA consortium) using tranSMART.

The PSORT consortium’s collaborators include those who curate databases, psoriasis patient cohorts, and registries in Europe and the United States. The management of the consortium places partnership with industry at its heart in that the steering committee is cochaired by the director
EDITORIAL

Table 1. Psoriasis Stratification to Optimize Relevant Therapy (PSORT) partners.

| The University of Manchester |
| King’s College London |
| University of Newcastle |
| Queen Mary University of London |
| University of Liverpool |
| Greater Glasgow Health Board |
| Centre for Addiction and Mental Health |
| Gay’s and St Thomas’ NHS Foundation Trust |
| AbbVie |
| Becton Dickinson and Company |
| Celgene Limited |
| Janssen Research and Development LLC |
| MedImmune Limited |
| Novartis Pharmaceuticals UK Limited |
| Pfizer |
| The Psoriasis Association of Great Britain and Ireland |
| Qiagen Manchester Limited |
| Sanquin Blood Supply Foundation |
| Stiefel Laboratories |
| GlaxoSmithKline |

(clinical academic) and the chair of the industry partner subgroup; both Work Strands have industry coleads and a separate intellectual property and commercialization subgroup is represented on the steering committee by its chair, as is the patients subgroup. The durability and future-proofing of the consortium beyond its initial 4 years of funding are dependent on additional industry and academic partners. For further information, please refer to the consortium’s website, http://www.psort.org.uk.

One may ask what the drive is for industry to collaborate so readily with PSORT. Industry participation in PSORT is driven strongly by the opportunity to be able to select the right patients to test new therapies definitively based on large, well-phenotyped patient cohorts and associated molecular tests. Ultimately, this will reduce the cost of development by eliminating failures early and accelerate clinical development of the best new entities. Industry also appreciates that obtaining regulatory and cost/benefit approval for expensive, potent biologic therapies in dermatology does, and will, require it to acquire a considerable body of positive evidence of efficacy, safety, health, economic, and patient outcome data. PSORT promises to create the leading “public sector/clinically led” stratified medicine development platform that will provide the optimal environment for it to create this body of data as efficiently as possible.

Stratified medicine is the great ambition of clinical translational research and will, in our opinion, change the landscape of dermatological practice in the next decade. To realize this requires big team science working in open collaboration with the commercial sector and with patient groups. That the MRC has selected psoriasis as 1 of only 12 diseases across the whole of medicine worthy of programmatic investment is a unique and exciting opportunity for those of us involved in psoriasis research and treatment. If successful, PSORT will benefit patients, health-care practitioners, and industry and will act as a platform for innovation, commercialization, and international research collaboration.

CONFLICT OF INTEREST
ADB receives paid consultancy, lectures, and/or research for Amgen, Abbvie, Celgene, Lilly, Novartis, Pfizer, Napp, Boehringer Ingelheim, and Janssen. JNWNB has received honoraria for advisory boards and lectures at sponsored symposia together with grants for research in the past 5 years from Abbvie, Amgen, Celgene, Janssen, Lilly, Novartis, and Pfizer. CEMG is in receipt of research grants and/or has received honoraria from AbbVie, Actelion, BMS, GSK, Janssen, Leo Pharma, MSD, Pfizer, Novartis, Sandoz, Eli Lilly, and UCB Pharma. FON is a consultant for Amgen, Lilly, Novartis, Pfizer, Janssen, Celgene, Sanofi, and GSK. NJR has been a consultant for Stiefel, a GSK company, Genentech, and Amgen and received sponsorship or grant funding from Novartis, Leo Pharma, Celgene, AstraZeneca, Stiefel, a GSK company, and BMS. RBW has received research funding from Abbvie, Novartis, Pfizer, and Leo (and GSK through pre-PSORT) and served as a consultant/speaker and or received honoraria from Amgen, Abbvie, Celgene, Pfizer, Novartis, Janssen, and Leo.

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