The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

The Clinical-Translational Physician-Scientist: Translating Bedside to Bench

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Translational research is often conceptualized with an implicit directionality, taking an idea generated in the laboratory (ie, the "bench") and applying it at the point of care (ie, the "bedside"). This role is often played by physician-scientists who work both in the laboratory and in the clinic. Less well appreciated is the valuable role a physician-scientist can play by using compelling observations from clinical research studies to guide basic scientists toward clinically important problems and even novel scientific concepts. The goal of this editorial is to highlight this often overlooked role that clinical-translational physician-scientists can play in translating observations at the bedside to efforts at the bench, highlighting their importance for scientific progress and discussing the type of research training and scientific environments that can help these individuals flourish. The importance of cohort studies and multidisciplinary team science in this context will also be highlighted.

Keywords. HIV; physician-scientist; translational research.

The physician-scientist is ideally suited to translate basic discoveries generated in the laboratory into life-saving therapies for individuals with disease and to improve the health of the general population. Indeed, translational research is often conceptualized with an implicit directionality, taking an idea generated during laboratory-based research (ie, the "bench") and applying it at the point of care (ie, the "bedside"). This role is often played by physician-scientists, who work both in the laboratory and in the clinic. The essential role of physician-scientists with expertise in conducting clinical research and clinical trials is also often acknowledged (although often underappreciated!), because they are critical to assessing the relevance of concepts emerging from experiments conducted in artificial cell culture systems and animal models in humans. Less well appreciated is the valuable role a physician-scientist can play by using compelling observations from clinical research studies to guide basic scientists toward clinically important problems and even novel scientific concepts. The goal of this editorial is to highlight this often overlooked role that clinical-translational physician-scientists can play in translating observations at the bedside to efforts at the bench, highlighting their importance for scientific progress and discussing the type of research training and scientific environments that can help these individuals flourish. The importance of cohort studies and multidisciplinary team science in this context will also be highlighted.

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The Journal of Infectious Diseases® 2018;218(S1):S12–5

DOI: 10.1093/infdis/jiy264

AN EXAMPLE OF BEDSIDE-TO-BENCH TRANSLATION

About a decade ago, I was working as part of a collaborative team to establish a gut biopsy protocol for the SCOPE study, a large cohort of human immunodeficiency virus (HIV)–infected individuals at the University of California–San Francisco that was focused on HIV pathogenesis studies. My own research focus had been on the persistence of abnormal immune activation despite effective antiretroviral therapy in HIV-infected individuals and how this process might contribute to morbidity and mortality. Gut barrier dysfunction and microbial translocation had recently been described as potentially important contributors to this process, so helping build a local gut biopsy program that might eventually address some of these questions seemed like a good idea at the time. To get the program off the ground, I worked with several laboratory-based investigators (eg, Drs Barbara Shacklett, Doug Nixon, and Mike McCune) who had funded research projects that were trying to understand how some individuals naturally control HIV replication in the absence of antiretroviral therapy (ie, "elite controllers"). They wanted to understand whether these rare individuals mounted a strong HIV-specific T-cell response in the gut mucosa, where reservoirs of HIV tended to be high. As I obtained informed consent from a potential participant in one of these studies, I highlighted how understanding the mechanisms by which they were able to control the virus might provide important insights about developing an effective HIV vaccine. He told me, "That's all fine, but I just want you to tell me why my CD4 counts are dropping." He was right. Despite controlling HIV replication to undetectable levels, his $CD4^+$ T-cell counts had been declining, and he was becoming progressively immunocompromised. That afternoon, I returned to my office and started probing data sets that we had been collecting on

HIV controllers. I noticed that other HIV controllers in our cohort also had experienced a $CD4^+$ T-cell decline like him, and another had even developed Kaposi sarcoma despite having an undetectable plasma HIV RNA level. I then compiled all the immune activation data in our cohort and noticed that the HIV controllers had abnormally high immune activation despite controlling viral replication and that this activation was even higher than that among HIV-infected individuals maintaining treatment-mediated viral suppression. The HIV controllers with the greatest level of immune activation also experienced the greatest depletion in $CD4^+$ T-cell count. This work, published in *The Journal of Infectious Diseases* [1] and later confirmed by other groups [2–6], suggested that there might be negative immunologic consequences to the natural control of viral replication in HIV infection. T-cell–mediated control of HIV replication, manifest in most HIV controllers, appeared to be insufficient to prevent pathological immune activation, a fundamental insight that affected the viability of T-cell–based vaccine strategies at the time. This basic insight started with a conversation with a research participant, something that might not have happened if I had been based solely in the laboratory and had relied on clinical colleagues less familiar with HIV pathogenesis concepts to obtain informed consent from potential participants.

TRAINING (AND RETAINING) CLINICAL-TRANSLATIONAL RESEARCHERS: THE KEY INGREDIENTS

There are several key ingredients to creating an academic environment conducive to the development and retention of impactful clinical-translational researchers. While the optimal scientific environment for training bench scientists is relatively straightforward, the optimal environment for clinical-translational researchers is less well defined and will be discussed here. Just as the bench scientist needs years of training in the laboratory under the guidance of a supportive mentor before becoming an independent principal investigator, the clinical-translational researcher also needs training in their craft to become an effective independent investigator. The key ingredients—in terms of both academic environment and training experiences—that are required to develop and maintain clinical-translational researchers will be described here.

Academic Environment Supportive of Team Science

In many ways, physician-scientists are primed for multidisciplinary team science through their medical training. For example, the practice of consultation has a long and deep tradition in medicine, with physicians tacitly acknowledging that they do not have all the answers and welcoming ideas and advice from specialists in other disciplines in the care of patients. While such multidisciplinary environments are traditionally less common in the training of basic scientists, they are essential for the success of clinical-translational researchers. To effectively translate clinical observations into bench research or to translate discoveries from the laboratory into clinical interventions, the clinical-translational researcher needs at least modest fluency in both clinical and laboratory-based research. This is ideally developed and nurtured by ongoing interactions and collaborations within a team of multidisciplinary researchers with expertise spanning laboratory-based and clinical research. Frequent research seminars and conferences that bring clinical and laboratory-based investigators together are critical for exchanging ideas and developing new collaborations. Ultimately, however, ongoing mutually beneficial scientific collaborations resulting in high-profile publications and grant support keep a community of multidisciplinary investigators together. When both clinical and laboratory-based investigators receive support, through authorship and grant funding, for their independent creative contributions to multidisciplinary work, the multidisciplinary team thrives, allowing ideas to be freely exchanged and for the team to work together to rapidly address important scientific goals that may be impossible to accomplish by an investigator working alone. This type of environment is particularly critical for the clinical-translational researcher, as they need to become a jack-of-all-trades, with fluency in a variety of different disciplines to be most effective. Ongoing interactions within a multidisciplinary team of investigators facilitates this scientific fluency in the same way that fluency in a foreign language is facilitated by spending time in a country where the language is natively spoken.

Academic institutions can help promote environments conducive to multidisciplinary team science (and, by extension, clinical-translational researchers) in important ways. For example, contributions to team science (eg, serving as a coinvestigator on a grant or as a middle author on an article) are often not valued as highly as individual contributions (ie, serving as a principal investigator on a grant or as a first or last author on an article) in the academic promotion process of many institutions. This serves as a systematic disincentive to participate in team science. Given the increasing importance of team science across the spectrum of research from basic (eg, systems biology) to clinical (eg, multicenter clinical trials) investigations, many institutions are revising their promotions criteria, specifically highlighting the importance of team science contributions. My institution's department of medicine, for example, recently revised its promotions guidelines in this regard. In addition to specifically highlighting the importance of contributions to team science, it provides a mechanism to highlight specific independent and creative contributions made by middle authors on articles (with a brief attestation from the senior author), to help promotions committees better understand the value of those contributions as opposed to only assigning value to first and last authorship.

These were important changes my institution took to value team science in the promotions process, but they did not come about without advocacy. Several leading physician-scientists passionate about this topic, including one of my mentors (Mike McCune), formed a task force to draft the new proposed promotions guidelines for our department of medicine. I am told that my experience was used as one of the examples cited to support promotions guidelines changes, because I had been passed over at my first opportunity for promotion to associate professor. Those recommendations were accepted by the promotions committees and chief of medicine and were subsequently adopted. A working group (which I subsequently joined) focusing on promoting team science within the Clinical and Translational Science Institute was then formed to encourage other departments within the university to adopt similar promotions criteria, working through the vice dean of academic affairs. Similar advocacy efforts have helped support team science at the National Institutes of Health, as well. One tangible result of this is the allowance of grants that have multiple principal investigators, which has helped facilitate collaborative team science. Such progressive policies help remove the disincentives for multidisciplinary teams of investigators to work together and help create academic environments where clinical-translational researchers can thrive.

Cohort Studies

Cohort studies (or clinical trials) are the glue that enable fruitful, mutually beneficial collaborations between clinical and basic scientists and provide opportunities for the clinical-translational researcher to develop independent lines of scientific inquiry. Ultimately, successful collaborations result when all participating investigators derive benefit, and the collection of biologic samples from highly characterized participants in cohort studies or clinical trials creates opportunities for both clinical and basic scientists. For example, the basic scientist may want to test whether a biomarker of a process they have been studying in ex vivo systems or in animal models predicts disease in humans or is altered by a given disease state. Biologic samples from clinical studies provide such opportunities for the basic researcher. The collaboration with the basic scientist also provides opportunities for the clinical scientist to learn about novel scientific insights emerging from the laboratory that might help explain clinical riddles that remain unsolved. This was certainly the case in my experience working on studies of HIV controllers. As such multidisciplinary collaborations mature and trust builds between investigators, the next generation of clinical research studies may start addressing the needs of the basic scientist as opposed to simply answering a set of narrow clinical questions. For example, a clinical-translational researcher may invest in storing the optimal type of biologic samples with optimal processing methods and sampling frequency and/or may specifically target participants with rare extreme phenotypes that may be particularly valuable to the basic scientist. Linking data generated by the bench scientist to clinical variables may also generate novel research opportunities for the clinical-translational researcher. All of this activity provides opportunities for multidisciplinary publications and grants, through which both the basic and clinical-translational researcher thrive.

Core Laboratories

The availability of core laboratories is also critical to provide opportunities for clinical-translational researchers to develop independent pathogenesis-oriented research programs. Without running a laboratory of their own, the clinical-translational researcher can still ask compelling pathogenesis-oriented questions that can be explored with stored biologic specimens from cohort studies or clinical trials by collaborating with core laboratories that perform research-level assays on a fee-for-service basis. Sometimes such core laboratories are supported by center grants within institutions or by multicenter research networks. As the clinical-translational researcher develops a maturing relationship with the core laboratory, they may become closely involved in assay development within the core laboratory, guided by the types of questions that are of most interest to the research program. To be sustainable, core laboratories need not just a critical mass of clinical-translational researchers to serve as a stable user base, but also require strong institutional support. Such institutional support needs to go beyond administrative and financial (eg, subsidies from center grants and divisions) efforts and include opportunities for career development and promotion for core laboratory leaders who may not necessarily have separate independently funded laboratories of their own. Clear career tracks need to be available for such individuals, with benchmarks for their promotion based on their facilitation of team science (measured by the articles and grants that they support but did not necessarily lead). This latter point cannot be overemphasized. Teams thrive when each member of the team is engaged, feels valued, and has ample opportunities for their own career growth.

Clinical Research and Data Analysis Training

Just as basic scientists need a solid foundation of training in bench research, clinical researchers also need training. Dedicated clinical research training programs did not exist at most institutions a few decades ago. Rather, clinical research was typically learned via mentorship, and the quality of the training varied widely. Over the last 15–20 years, however, there has been a proliferation of formalized clinical research training programs at universities across the country, with tuition often funded by T32 fellowship training grants and K-series career development awards.

Participating in a structured yearlong clinical research training program early on in my research fellowship had a major effect on my career trajectory. Those courses provided me not

only a solid foundation in epidemiology and clinical research methods so that I could design and interpret studies well, but also critical training in data management, analysis, and statistics, including a basic fluency in data analysis software. These latter skills allowed me to quickly analyze and explore clinical and laboratory data that were being generated in my studies.

I cannot emphasize enough how important performing analysis myself— as opposed to outsourcing all the analysis to a statistician—was to my career development as a clinical-translational researcher. First, I developed a healthy respect for the integrity of data, the importance of choosing the most appropriate analytic method for a given question, and the many ways an analysis can result in biased or invalid results. Just as the basic scientist needs to check the robustness of a given experiment, using multiple controls and ensuring reproducibility, the clinical researcher needs to make sure a given analysis is robust to a variety of sensitivity analyses and not simply driven by 1 or 2 influential outliers. Second and perhaps most importantly, learning to perform data analysis gave me the tools to probe data sets for clues that would help me generate or prioritize my next round of hypotheses. In observational human subjects research, we typically can never determine the causality of the associations that we observe. Multiple plausible causal relationships (and both measured and unmeasured biologic processes) might explain a given result, but the myriad of potential explanations are not necessarily all equally likely. Instead of pursuing all potential causal explanations in subsequent interventional trials (which would be impractical and too expensive), prioritizing the most likely explanations may help arrive at an answer more quickly and efficiently. Probing the data for clues that might be consistent with one causal explanation or another is one way of informing the likelihood of one explanation over another (eg, "If explanation *A* were true, I would expect *X*, *Y*, and *Z* relationships to exist in the current data set."). While such post hoc analyses are never definitive (and often not even publishable on their own), they can often help prioritize the next set of questions to pursue. This application of mechanistic thinking to data analysis also engages the curiosity of the clinical-translational researcher in a way similar a basic researcher's attempt understand an unexpected result by performing several follow-up laboratory experiments.

SUMMARY

In summary, I believe the clinical-translational researcher has an important role to play in science. While they use different tools, clinical-translational researchers often share the same type of scientific curiosity and mechanistic thinking as laboratory-based scientists, which can lead to unique insights that help inform basic science. Both laboratory-based and clinical-translational researchers can help enrich each other's work in a variety of ways, and an academic environment that rewards team science is optimal for these investigators to thrive. Nurturing such collaborative academic environments and providing young clinical-translational researchers with the skills and opportunities to conduct high-quality pathogenesis-oriented clinical research will be critical for training the next generation of these scientists. A career translating the observations at the bedside to efforts at the bench can be just as gratifying as translating observations at the bench to efforts at the bedside.

Notes

Acknowledgments. We are grateful to acknowledge the sponsorship of the Harvard University Center for AIDS Research and the Ragon Institute of MGH, MIT and Harvard.

Financial support. This work was supported by the National Institutes of Health (grants R01DK112304, R01AI116368, and R01AI110271).

Supplement sponsorship. This work is part of a supplement sponsored by the Ragon Institute of MGH, MIT, and the Harvard University Center for AIDS Research P30 AI060354.

Potential conflicts of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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