The Molecular Medicine Investigation Unit: Linking Patient Care and Scientific Inquiry in Physician-Scientist Training

Amy Berger, MD, PhD
Mehrdad Matloubian, MD, PhD
Neil P. Shah, MD, PhD
Robert M. Wachter, MD
Joseph L. DeRisi, PhD
Mark Anderson, MD, PhD

ABSTRACT

Background Medical innovation depends on translation, the process of applying clinical insights to solve biological problems, and vice versa, yet existing training programs provide few opportunities for physician-scientists to integrate their clinical and research training.

Objective We developed and determined the feasibility and acceptability of a rotation on the Molecular Medicine Investigation Unit (MMIU), a novel program that engages trainees in the deliberate linkage of patient care and scientific inquiry to cultivate their interest and skills in translation.

Methods Between July 2017 and January 2019, fourth-year medical students and internal medicine residents were offered a 4-week elective rotation on the MMIU. Supervised by 2 part-time faculty, trainees evaluated patients with unusual and perplexing presentations with the goal of generating hypotheses and a research plan to elucidate the underlying mechanisms of disease. We tracked the development of research hypotheses and resulting projects and surveyed participants about their satisfaction with the program.

Results Over 18 months, 21 trainees (11 medical students and 10 residents) participated in the program and evaluated a total of 70 patients. Trainees generated a mechanistic hypothesis in 45 (64%) cases, and this resulted in a patient-centered research project in 38 (54%) cases. Trainees unanimously agreed that the program gave them an opportunity to integrate their clinical and research training, and many expressed that it reinforced their interests in translational research.

Conclusions With modest funding support, it was feasible to deliver authentic experiences of translational inquiry for medical students and internal medical residents, and these experiences were valued by trainees.

Introduction

Physician-scientists are uniquely equipped to catalyze medical innovation by transforming puzzling clinical observations into tractable research questions and translating basic insights about disease pathogenesis into new clinical practices and treatments.[1–3] It is important to note, however, that this process of translation requires unique skills that are not routinely taught during medical or scientific training.[4,5] Furthermore, as the day-to-day practice of both medicine and science has become more technically complex and administratively demanding, the process of translation has also become more challenging.[6–8] It is not surprising that the number of young physicians choosing to pursue research has declined steadily over the past 3 decades[9,10] or that, of those who do take up the mantle of physician-scientist, a shrinking number choose to pursue patient-oriented translational research.[1,6]

Leading research organizations have responded to these trends with calls to intensify recruitment, mentorship, and financial support for physician-scientist trainees and faculty.[2,10–13] Of these efforts, MD-PhD programs and similar programs for residents and clinical fellows have been the most widely adopted, because they offer opportunities to integrate clinical and research training.[11,14–16] The nature of this integration, however, is frequently superficial and limited to curricular structure.[4] For example, MD-PhD students may complete graduate coursework during their preclinical years, but unless it is intentionally cultivated, they will not develop the habit of mind of relating clinical concepts to fundamental scientific principles.

To address this gap in training, we have developed an innovative rotation on the Molecular Medicine Investigation Unit (MMIU) to help aspiring physician-scientists build skills in "bedside-to-bench" and "bench-to-bedside" translation.

Methods

Setting and Participants

The MMIU is based in a large urban academic medical center with undergraduate and graduate physician-

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scientist training programs, the Medical Scientist Training Program (MSTP) and the Molecular Medicine Residency Program (MMRP), respectively. The MSTP enrolls on average 12 MD-PhD students out of approximately 150 medical students each year; the MMRP enrolls on average 8 residents out of approximately 60 internal medicine residents each year. Both of these programs include opportunities for independent scholarly projects and physician-scientist–specific curricula on career development, focusing on academic careers in basic and translational research.

We piloted the MMIU rotation for 1 resident per month between July 2017 and January 2019 and 1 to 2 fourth-year medical students per month between March 2018 and January 2019. Residents of all years were permitted to rotate; however, because interns in our program have little to no elective time, the majority of participants were second- or third-year residents. Participants were strongly encouraged to have prior basic research experience, but the program was not limited to members of the MSTP and MMRP.

What was known and gap
Applying clinical insights to solve biological problems is vital to biomedical discovery, but the skills to translate this knowledge are not routinely taught during scientific or medical training.

What is new
A rotation that engages medical students and internal medicine residents in the deliberate linkage of patient care and scientific inquiry in order to cultivate their interest and skills in translation.

Limitations
This rotation was offered to residents within a single residency program at a single institution, limiting generalizability. The end-of-rotation satisfaction survey lacked validity evidence, and follow-up did not occur.

Bottom line
The program, which was feasible and valued by trainees, may provide a model for how to foster interest and skills in translational inquiry among clinical trainees planning research careers.

Development

The MMIU was originally proposed by a group of internal medicine residents (including A.B.) and championed by a group of key stakeholders, including the directors (N.P.S. and M.A.) of the MSTP and MMRP. An advisory board of physician-scientist faculty has been instrumental in establishing relationships with investigators across the University of California, San Francisco (UCSF) community.

The project has been funded by a combination of medical education and translational research grants and departmental support, which together provided an annual budget of approximately $150,000, including 20% salary support for 2 faculty members as well as funding for a part-time clinical research coordinator, biobanking, and research services, such as next generation sequencing.

The Program

The goals of the MMIU are to build skills that support translation and to promote an integrated physician-scientist identity that is more than the sum of its parts. These goals are achieved through hands-on experience in patient-inspired scientific inquiry. In addition, because new technologies have created new prospects and challenges for translational researchers, we sought to create opportunities for trainees to apply cutting-edge tools to patient-inspired research questions.

The core experience of the rotation is the evaluation of real patients with rare and unusual phenotypes who are referred to the program by their health care providers. This can include both patients who lack a diagnosis and patients with atypical presentations of known diagnoses or molecular test results of uncertain significance. From all of the referrals received, program faculty select cases with the greatest potential to discover clinically meaningful biological insights through the thoughtful study of a single patient or family. Trainees working individually or in pairs are assigned 2 to 4 cases to evaluate during their month-long rotation.

The clinical evaluation of such complex cases frequently adheres to a top-down, systems-based framework. In contrast, MMIU trainees are coached by physician-scientist mentors (A.B. and M.M.) to take an alternative, bottom-up approach, and to focus on the potential mechanisms of disease rather than diagnostic labels. During this process, they review relevant literature, consult with scientific experts, and iteratively correlate their learning with the patient's clinical data in order to generate hypotheses about the underlying pathophysiology and a research plan to differentiate or refine these possibilities. Trainees' personal expertise is also valued, and many contribute important skills (eg, in bioinformatic analyses) and knowledge (eg, of relevant disease models) to the process.

MMIU trainees meet 2 to 3 times a week with faculty mentors and their fellow rotators to share learning and receive feedback on their developing hypotheses. At the culmination of each month, trainees present their hypotheses and research proposal at a case conference for the broader physician-scientist community. Trainees also discuss their plan and the biologic rationale with members of the clinical team who referred the patient to the MMIU.

Patient-Inspired Research Program

In parallel to the rotation elective, we have also developed a research program to advance the investigation of mechanism in MMIU cases. This not only provides an opportunity for trainees to learn about state-of-the-art tools, but also creates the potential for tangible scientific impact that trainees find uniquely motivating.

We have established a research protocol that permits the collection of blood, noninvasive specimens, and remainder clinical samples from patients and their relatives following informed consent. In addition, we have developed collaborations with technology pioneers across the UCSF community, through which trainees are able to leverage experimental tools (eg, whole exome sequencing, metagenomic sequencing, single cell transcriptomics) that are applicable to a wide range of questions. In specific cases that require more targeted expertise, we also attempt to establish new patient-centered research collaborations.

Outcomes and Assessment

The goals of the pilot study were to demonstrate the feasibility of delivering authentic experiences of translation and proof-of-value of such experiences for physician-scientist trainees. For the former, we tracked trainee engagement in a range of translational activities. For the latter, we developed an 8-item, end-of-rotation survey that consisted of Likert-type (scale 1–5) and open-ended questions that were not tested for validity.

The research protocol of this work was approved by UCSF Institutional Review Board.

Results

Participation

Between July 2017 and January 2019, 10 residents participated in the MMIU rotation. Between March 2018 and January 2019, 11 fourth-year medical students completed the rotation. Of these 21 participants, 14 (67%) were members of our physician-scientist training programs, and 18 (86%) stated that they were interested in pursuing a career in basic or translational research.

Engagement in Translational Activities

During their MMIU rotations, trainees engage in the intentional linkage of patient care and scientific inquiry in the context of real clinical cases. In the best-case scenario, they first correlate clinical findings with pathophysiologic concepts in order to develop hypotheses about disease mechanisms. Then, they use these hypotheses as a roadmap to guide patient-inspired experimental studies and biologically grounded clinical reasoning. Although the full spectrum of translation is not expected in every case, it provides a useful framework to evaluate trainees' depth of engagement (see the FIGURE).

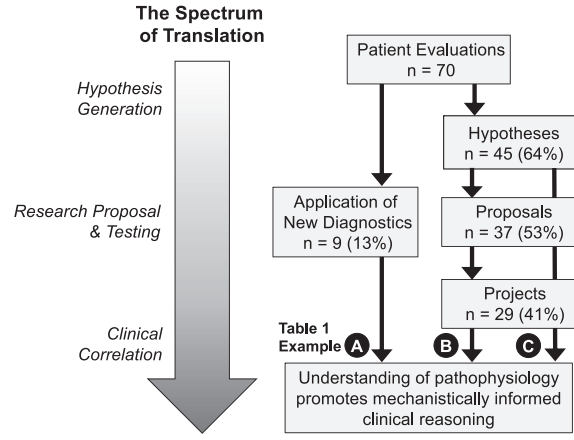

FIGURE
Trainee Engagement Across the Spectrum of Translation

Trainees participated in the evaluation of 70 patients. In 45 (64%) cases, they successfully developed mechanistic hypotheses. No hypothesis was developed in the remaining cases for a variety of reasons, such as a lack of objective or specific findings. Although no novel hypothesis was developed, trainees still proposed the use of research-based technologies (eg, metagenomic sequencing for pathogen detection) to probe the existing differential in 9 (13%) cases (TABLE 1, example A).

Beyond hypothesis generation, trainees also developed a research proposal in 37 cases (53%), and this proposal has resulted in a collaborative research project in 29 (41%). Thirteen (19%) cases have resulted in the establishment of new patient-centered research collaborations (TABLE 1, example B), and the remaining projects are being conducted through existing technology partnerships.

It is difficult to isolate the impact of mechanistic insights on clinical reasoning, as MMIU trainees are not a part of the treatment team responsible for clinical decision-making. However, we have observed that simply reframing the clinical problem in mechanistic terms was sufficient to refine the differential diagnosis in some cases (TABLE 1, example C). Anecdotally, multiple referring physicians have also reported that having a better understanding of the potential pathophysiology increased their diagnostic certainty. Going forward, we hope to support these observations with longitudinal surveys of referring providers.

TABLE 1
Case Examples

Clinical Scenario	Clinical Framework or Hypotheses	Mechanistic Framework or Hypotheses	Translational Implications
A. *Suspected culture-negative infection:* A young woman presented with necrotizing pneumonia complicated by empyema.	Infection was suspected; however, pleural fluid cultures were negative, and the patient's symptoms persisted despite drainage and antibiotics.	No change from the clinical differential of infection.	The MMIU trainee proposed use of experimental metagenomic sequencing, which revealed Streptococcus pyogenes.
B. *A molecular finding of uncertain significance:* An elderly man was hospitalized 8 times for fever of unknown origin associated with cytopenias.	An extensive work-up for infection, malignancy, and rheumatologic disease was negative. A bone marrow biopsy revealed isolated Trisomy 8 (T8) without dysplasia or neoplasm, which was thought to reflect clonal hematopoiesis of indeterminate potential (CHIP), a common condition in the elderly.	The MMIU trainee suspected that the potential of CHIP to cause immune dysregulation is underappreciated and hypothesized a paraneoplastic-like autoinflammatory syndrome related to T8. She found evidence of a similar syndrome associated with T8 in the context of congenital mosaicism and myelodysplastic syndrome.	Collaborative research revealed that the patient shares an IL-1-dependent inflammatory signature with children who have fever caused by T8 mosaicism. Additional studies of the genetic and cellular mechanisms are underway. The patient's symptoms resolved following treatment with an IL-1 receptor antagonist.
C. *An extreme presentation:* A middle-aged man with HIV, Hodgkin's lymphoma, and recent treatment with anti-CD30 presented with new onset diabetes and diabetic ketoacidosis that was refractory to massive doses of insulin, up to 600 units/hour.	The treating team suspected a paraneoplastic process related to Hodgkin's lymphoma, an adverse effect of anti-CD30, or a parainfectious process related to HIV.	Reframing the clinical problem as insulin resistance led to a mechanistic differential, including rapid insulin degradation, downregulation of the insulin receptor, and antibodies to insulin or its receptor.	These biochemical processes can result from paraneoplastic or parainfectious processes; however, framing them mechanistically was more amenable to testing (eg, measuring antibodies) and treatment (eg, IVIg and plasmapheresis).

Abbreviation: MMIU, Molecular Medicine Investigation Unit.

Attitudes and Perceptions

In post-rotation surveys, all 21 participants (100%) agreed or strongly agreed that the MMIU rotation "gave [them] an opportunity to integrate [their] basic science and clinical training" (mean score 4.7 [SD = 0.47] on a 5-point Likert scale). Seventeen (81%) agreed that it "improved [their] ability to apply pathophysiological concepts to clinical decision making" (4.3 [0.78]), and 16 (76%) agreed that it "improved [their] ability to teach about basic science concepts in a clinical setting" (4.1 [0.75]).

Trainees were also asked to comment on which aspects of the rotation they found most valuable, and their responses were combined into themes by the authors. A repeated theme was the unique opportunity to practice the application of basic science thinking to clinical problems. In addition, many expressed that this opportunity inspired or reinforced their interest in patient-oriented inquiry. Illustrative examples are shown in TABLE 2.

Discussion

Our experience suggests that the MMIU provides authentic experiences of patient-inspired translational inquiry that are highly valued by physician-scientist trainees. The project was feasible with internal and external funding support.

Although cases were typically referred to the MMIU after an exhaustive clinical evaluation had been performed, trainees generated a novel hypothesis and seeded collaborative research projects in the majority of cases. During this process, trainees perceived that they gained valuable experiences in relating clinical observations to fundamental scientific principles, interpreting molecular data in light of the appropriate clinical and biological context, and communicating the translational implications of their work to clinical and scientific audiences. Such cross-disciplinary experiences are uncommon for most physician-scientists-in-training; however, we are aware of at least one other institution that has developed a

TABLE 2
Examples of Trainee Feedback

Theme	Trainee Comments on Educational Value
Opportunity to take a deep dive	"[W]e see interesting cases on the wards. . .but often don't have the time or bandwidth to ask *why* patients have unique problems. . .This rotation challenged us to ask and answer the *why* question. It made me a better scientist and also a better clinical doctor."
Integrated physician-scientist identity	"[This rotation was] definitely the time when I felt most valued for being a physician-scientist. I've never before had a chance to put both my basic science and clinical science hats on at the same time, and found it really inspiring. I always wondered what it would mean to help "translate" between these worlds, and feel like I was given the chance to actually do so on this rotation."
Impact on clinical practice	"[This rotation] provided me a model of how one can incorporate basic science principles to complex clinical problems. I will use this experience to guide future clinical practice."
Impact on research interests	"Wonderful opportunity to experience the intersection between clinical medicine, advanced diagnostics, and research questions. The most enlightening thing for me was just how much the patients are able to teach us."

similar program in response to trainee advocacy.[17] Programs like these can cultivate the skills needed to link patient care and scientific inquiry and sustain trainees' interest in translational research during long periods of intense clinical training.

Sustainability remains a challenge for these programs. The process of developing mechanistic hypotheses can feel overwhelming to clinical trainees who are used to a more algorithmic approach, and further work is needed to determine common best practices. In addition, the type of small scale, patient-centered collaborative research that is required to investigate mechanism in unique cases is unlikely to be sustained by traditional grant funding and may require new models of support.

This work is limited by the focus on a single internal medicine residency program at a single institution; thus, the ability to transfer the MMIU experience to other sites is unclear. Without follow-up, it is not known whether trainees participating in this experience continued to participate in research or develop research-intensive careers after graduation. The end-of-rotation satisfaction survey was not tested, so respondents may not have interpreted all questions as intended.

This study has also identified potential improvements to the MMIU. Scientific inquiry involves an iterative process of hypothesis generation and testing, and trainees have consistently expressed that this process is cut short by the short duration of the rotation. Trainees also have requested structured training in bioinformatic tools commonly used to study gene disease relationships, a fundamental issue in many MMIU cases. In response to this feedback, we are working with the leadership of the MSTP and MMRP to develop longitudinal scholarly projects and an associated curriculum based on MMIU cases.

Conclusions

The MMIU, an elective experience focusing on complex patient cases with unclear diagnoses, may provide a model for how to foster interest and skills in translational inquiry for medical students and internal medicine residents planning research careers. The MMIU was feasible, with institutional and grant support, and highly acceptable to trainees.

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All authors are with the University of California, San Francisco. **Amy Berger, MD, PhD,** is Assistant Professor of Medicine; **Mehrdad Matloubian, MD, PhD,** is Professor of Medicine; **Neil P. Shah, MD, PhD,** is Director, Molecular Medicine Residency Program, and Professor of Medicine; **Robert M. Wachter, MD,** is Chair, Department of Medicine, and Professor of Medicine; **Joseph L. DeRisi, PhD,** is Professor of Biochemistry and Biophysics and Co-President, Chan Zuckerberg Biohub; and **Mark Anderson, MD, PhD,** is Director, Medical Scientist Training Program, and Professor of Medicine.

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Corresponding author: Amy Berger, MD, PhD, University of California, San Francisco, 533 Parnassus Avenue, Suite U127, San Francisco, CA 94143, 415.502.3693, fax 415.514.2094, amy.berger@ucsf.edu

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