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Graduate students bring clinical know-how into their lab work through the HHMI Med into Grad program

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The launch of the National Institutes of Health (NIH) roadmap in 2004 increased the biomedical community's focus on translational research by designating significant funding for discoveries in basic research that could lead to changes in patient care. Scientists who once lived at the bench are increasingly asked to support the clinical significance of their work. To demonstrate their bench-to-bedside applicability, researchers now feel encouraged to include patient sample analysis to complement a mechanistic study or in vitro mechanistic data to support a population study. As a result, basic research papers bring together evidence from multiple disciplines, although gathering such evidence often falls outside of the traditional training and experience of most individual laboratory researchers.

The Howard Hughes Medical Institute (HHMI) recognized the need for a more 'cross-cultural' curriculum to give graduate students beneficial clinical exposure along with their research training, and created the Med into Grad training program. Simultaneously, Baylor College of Medicine (BCM), also aware of the lack of clinical experience in graduate training programs, developed its own Interdepartmental Program in Translational Biology and Molecular Medicine (TBMM). Because of its clearly aligned goals, TBMM became one of the first programs to be funded through the HHMI's Med into Grad initiative. This program is now in its fifth year and has 48 graduate students; members of the first class will begin graduating this spring. As students of the inaugural TBMM class, we find many of our unique training experiences useful in our development as translational researchers.

Dual mentorship

Each graduate student in the TBMM Med into Grad program receives dual mentorship and is advised by both a basic science and a clinical mentor, most commonly one PhD and one MD, throughout their dissertation work. Students first choose a basic science mentor and laboratory, and outline the clinical and translational potentials of their project. Next, students choose a clinical mentor, who plays an active role in shaping the student's project, meets regularly with the student and thesis committee, and helps to provide access to valuable patient samples. The early marriage of a basic and clinical scientist on each student's advisory team sets the stage for fruitful collaborations and a truly translational experience.

Some of the best learning opportunities take place through informal coffee shop meetings where a student discusses, with both mentors, the details and direction of a project that will simultaneously address a basic research question and have diagnostic or therapeutic potential. The program puts graduate students at the interface between basic science and the clinic, and brings them together to close the divide between the research laboratory and patient care. Dual mentorship attracts many students to the Med into Grad program and provides them with a unique understanding of translational medicine.

Image created by Conrad Russell Young Cruz.

Clinical rotations

Unique terminology and distinct day-to-day experiences prevent fluid communication between basic science and clinical research. To help bridge this gap, TBMM students attend clinical rotations that introduce students to clinical nomenclature, and give names and faces to the diseases that they study. The benefits are threefold: (1) practical experience in the clinic can identify new scientific questions or reveal obscure roadblocks to the translation of relevant basic research; (2) relationships develop with clinicians, which may lead to future collaborations; and (3) patient interactions personalize research for students, providing strong inspiration and motivation. Their research no longer consists of just test tubes and tissue culture; rather, they are now ultimately trying to improve care for real people.

Regulatory procedures

A major barrier to translational research is the difficulty in finding access to clinical samples. Many institutions have established tissue banks, so the availability of samples is not the problem. Instead, basic researchers may not know how to traverse the regulatory hurdles that are necessary to obtain them. The increasing emphasis on patient-oriented research demands a new type of researcher who can negotiate the paperwork and red tape effectively, correctly and quickly.

To this end, students in the TBMM program receive specific training on the regulatory processes protecting clinical samples. Students attend Institutional Review Board (IRB) meetings, witness the informed consent process, and often write the IRB protocols that are used for their own research. These opportunities give TBMM Med into Grad students practical experiences, allowing them to ask and answer more clinically oriented research questions.

Translational curriculum

The TBMM Med into Grad program has a curriculum that is designed specifically for translational researchers. Unlike more traditional biomedical science curricula, the TBMM program

includes courses in human physiology, pathophysiology and animal models of disease. These courses give students a broader view of human health and disease, and reinforce the idea that, even when studying a specific protein-signaling pathway, it is crucial to consider the implications for the disease process and the organism as a whole. The program also requires a course in biostatistics for translational researchers to prepare students to calculate sample sizes for animal studies and design clinical trials to accurately compare the effectiveness of distinct treatments.

TBMM Med into Grad students participate in journal clubs developed specifically for them, such as the Bench to Bedside series, which reinforce the translational mindset. Students study articles where a research question moves beyond the lab to clinical observations. Together, basic science and clinical faculty lead Bench to Bedside discussions and guide students to understand the unique challenges of doing translational research.

Leadership and team science

Translational research, by definition, requires researchers to cross disciplines. Some can do this as individuals, but usually this involves collaborations. Successful researchers in this field must therefore be able to forge collaborations and work as a team. In addition, leading a successful research lab requires management skills, which are even more important in multi-lab, collaborative science. To address these needs, students in the TBMM program participate in a leadership training course taught by BCM community leaders, which covers topics such as team building, communication skills, conflict resolution and time management.

Translating scientific discoveries into practical applications that can positively affect human health requires skills that are not taught in traditional graduate or medical school curricula. The HHMI Med into Grad initiative supports TBMM at Baylor, as well as several other similar graduate programs around the USA, to train a new generation of scientists to function more efficiently at the interface of science and medicine. Because of this unique training environment, TBMM graduate students undertake projects that they, or others, may not have attempted otherwise. Clinically oriented research forces students and mentors to think outside of their comfort zones and produce a project that will effectively bridge the gap between basic science and clinical research.

As with any change, the barriers can sometimes be difficult to overcome; however, our experiences in this program have convinced us that combining the two disciplines is invaluable to the progression of research impacting human health. We believe the unique skills acquired in the TBMM Med into Grad program will give us an advantage in our future endeavors as translational scientists.

Ryan J. Hartmaier and Donald R. Shaffer are based at Baylor College of Medicine, Houston, where, as students in Baylor's TBMM Med into Grad program, they investigate clinically relevant issues. Ryan is identifying single nucleotide polymorphisms (SNPs) that are associated with osteoporosis and how these small genetic changes influence disease. Donald is engineering T cells to target specific tumor antigens with immunotherapeutic potential.

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The Lasker Foundation celebrates medical advances made with help from model organisms

Biological similarities that extend from amphibians to mammals demonstrate the value of model organisms in disease-related discovery, which is highlighted by one of this year's most prestigious awards. This year's **Lasker Award for Basic Medical Research** went to two scientists whose work in model organisms, frogs and mice, led to the molecular definition of stem cells and the factors that allow cells to specialize into any cell type, including those as unique as a fat cell, a muscle cell or a neuron. The nuclear reprogramming discoveries of the winners, **John Gurdon** and **Shinya Yamanaka**, demonstrate that it is possible to reprogram mature adult cells. Cells reprogrammed in this way might someday promote regeneration of diseased or dysfunctional tissue in human patients.

John Gurdon's work was once hotly debated. At the time, it was generally believed that cells undergo permanent nuclear changes as they specialize, and that they lose the programming information that tells them how to become a different cell type during maturation. However, after inserting nuclei from fully differentiated cells from the skin or intestine of the frog *Xenopus laevis* into eggs that lacked a functional nucleus of their own, Gurdon was able to generate fully developed tadpoles. This technology of nuclear transfer was later used to clone a sheep, resulting in Dolly, and provides evidence that the entire array of developmental programs that a cell needs to differentiate are always present in its nucleus. How the cell activates the appropriate program, and how it might be reprogrammed to become a different cell type, remained a mystery in the early days of this work.

Shinya Yamanaka and his colleagues tackled the question of cell programming and discovered how to restore the pluripotent capacity to previously specialized cells. Yamanaka's lab generated a list of the genes that are activated in mouse embryonic stem cells and determined exactly which ones were necessary to make cells pluripotent. They showed that expression of just four genes (*Oct3/4*, *Sox2*, *c-Myc* and *Kif4*) together could turn a differentiated adult mouse fibroblast into a cell with the potential to become any cell type. They called these cells induced pluripotent stem cells or iPS cells, which are now known to be capable of generating whole fertile mice. This technology may lead to the ability to take mature cells from a patient and reprogram them into cells to replace dead tissue resulting from a heart attack, brain injury, cancer or a host of other diseases.

The work of Gurdon and Yamanaka is honored by the foundation for its amazing potential, while the Lasker Foundation recognizes scientists whose discoveries have already changed patient care with its **Lasker-DeBakey Clinical Medical Research Award**. This year, **Brian Druker**, **Nicholas Lydon** and **Charles Sawyers** were honored for creating Gleevec (imatinib), a drug that can be taken as a pill by patients with chronic myelogenous leukemia (CML). Before Gleevec, patients with CML often died within 5 years of diagnosis, but the drug has now boosted their 5-year survival rate to almost 90%.

The emergence of Gleevec onto formularies is testament to the resolve of the awardees and their colleagues. Many believed that the therapeutic strategy, to specifically target the aberrant Abl (BCR-Abl) enzyme that is characteristic to CML patients, would not offer the necessary specificity and would create significant side effects. They believed that the novel approach had fundamental flaws. Some executives at Novartis also worried about the cost recovery of pursuing a potential drug that might only affect a very small subset of cancer patients. The creators worked diligently to keep Gleevec moving forward.

As soon as the clinical trials began, however, the potential for Gleevec, the first molecular-based chemotherapeutic agent, was clear. The specific inhibition of BCR-Abl in cancer cells immediately improved survival and quality of life, with fewer side effects than the previously available treatments. In pursuit of more targeted and more effective cancer treatments, other scientists now copy the same strategy that was used to create Gleevec. The use of Gleevec now extends beyond CML and includes patients with gastrointestinal stromal tumors (GIST) and hypereosinophilic syndrome (HES). The story of Gleevec shows the translational power that can be achieved when creative minds bring clinical and laboratory experience together with strong determination.

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