Science at the Interface of Chemistry and Biology at the University of Texas Southwestern Medical Center

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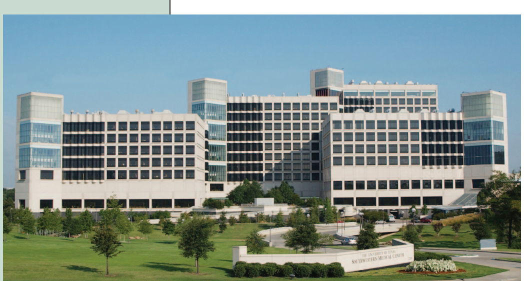

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Many of today's most exciting and pressing scientific questions lie at the interface of organic chemistry and biology. How can we design and synthesize biologically active small molecules *de novo*? What is the molecular basis for memory and sentience? How are inter- and intracellular communications regulated? By what mechanism do certain pharmaceutically relevant small molecules function? Answering these questions—and posing others yet unasked—requires expertise ranging from organic synthesis to molecular biology, from biophysics to clinical medicine. The Biological Chemistry Training Program at the University of Texas (UT) Southwestern Medical Center was established on this proposition and seeks to create an environment fostering excellence within disciplines to stimulate synergies between them.

Scientific departments across the world have recognized the potential of intercalating organic chemistry and biology. In fact, this recognition is more of a renaissance than a new revelation. Wohler created the field of organic synthesis while asking if biology was the sole provenance of natural products. Likewise, Watson and Crick, while memorably aware of the biological implications of their work, wrestled with a fundamentally chemical question as they gave birth to molecular biology. Nonetheless, a resurgent interest in this union has invigorated both communities. The origin of this excitement lies in the enabling advances witnessed by both molecular biology and chemistry over the last half century. Synthetic chemistry can create complex architectures by leveraging advances in catalysis, asymmetric synthesis, and reagent development. Similarly, biologists can manipulate proteins and genetic materials on scales ranging from *in vitro* reconstitutions to whole organisms. However, these are not simple tasks.

The challenge the chemical biology community must address is this: how can we create research and educational programs that maintain the rigor of traditional disciplines while benefiting from both chemistry and biology? The promise of chemical biology is to expand both chemistry and biology; the risk we seek to avoid is devolving to less than the sum of the parts. Our approach has been to build on UT Southwestern's strength in biochemistry, biophysics, and molecular biology by initiating a program in organic chemistry. Over the past 64 years, many areas of biomedical research at UT Southwestern have benefited from synthetic chemistry. For instance, the popularity of statins makes manifest the importance of their molecular target, HMGA coreductase, an enzyme discovered at UT Southwestern. Similarly, the pharmacopedia is replete with inhibitors of G-protein-coupled receptors. The prominence of these targets arose, in large part, from the pioneering studies of G-proteins at UT Southwestern. Indeed, synthetic chemistry groups have operated here since the 1980s. However, during the late 1990s, the administration recognized an opportunity to complement existing strengths in the biological sciences by expanding organic chemistry at the university.

Incorporating organic chemistry into a medical center involved four simultaneous initiatives: (i) Synthetic and natural product chemists established independent research programs at UT Southwestern. Currently, 10 research groups are focused primarily on the synthesis or isolation of biologically active compounds and the attendant mechanistic questions arising from such molecules. (ii) The university created the infrastructure necessary to support synthetic chemistry. New, modern laboratories for synthetic chemistry replaced existing biochemistry space. The university purchased and maintains instrumentation suitable for analysis of the structure and dynamics of small molecules. (iii) To help identify and promote collaborations between chemists and biologists, several core facilities were established for use by research groups across the UT Southwestern community. A high-throughput screening facility, a medicinal chemistry laboratory, and a structural biology core all support the mission of understanding and harnessing interactions between small molecules and proteins. (iv) Finally, we have established a graduate training program in chemistry alongside the educational tracks focused on biochemistry and biophysics.

The biological chemistry graduate program at UT Southwestern strives to prepare students to address emerging research opportunities at the crossroads of modern chemistry and biology. To this end, didactic teaching, student seminars, and invited lecturers create an educational experience that is both broad-based and rigorous. During their first semester of graduate school, students at UT Southwestern are not affiliated with a specific graduate program. Rather, all students participate in a course designed to build a foundation for all further studies. This course, the Core Course, connects principles of structure, thermodynamics, and kinetics within the context of catalysis, cellular function, and genetics. After this core training, students choose to enter a specific graduate program that encompasses their research interests. Students who desire rigorous training in chemistry or biochemistry choose to join one of the two parallel tracks within the Biological Chemistry Graduate Program. Graduate students join either the chemistry or biochemistry training tracks in December of their first year. Within these tracks, students receive instruction from members of the departments of biochemistry, molecular biology, pharmacology, and internal medicine. Students who enter the chemistry training track take a curriculum organized around four major classes: chemical synthesis, chemical reactivity, catalysis, and small-molecule structure elucidation. The goal of this combined coursework is to equip students to explore molecular structure, relate that structure to chemical reactivity, and harness chemical reactivity in the service of chemical synthesis. Likewise, the biochemistry training track features classes in physical biochemistry, enzymology, and metabolism.

Graduate class work is, of course, only a means to an end. The central objective is to perform meaningful research. Before joining a research group, graduate students rotate in three laboratories for six-week periods. The absence of undergraduates at UT Southwestern relieves graduate students (and faculty) of teaching burdens encountered elsewhere. For this reason, the rotation period can accommodate substantive laboratory work. During this period, students are exposed to different topics of inquiry, a range of styles and techniques, and various group dynamics. Upon choosing a principal adviser, students initiate their thesis research. Of note, several students have chosen two research advisers because their projects were collaborative in nature from the outset. Because teaching burdens are light at UT Southwestern, students and faculty alike are free to focus more completely on advancing science. Excellence in research is fostered further by the interactive nature of the training program. Students present advances and challenges of their research projects at a student seminar series, departmental retreats, and university poster sessions. These presentations foster a sense of community and provide forums for exchanging ideas.

Research within the biochemistry and chemistry training programs confronts some of the most challenging problems in their fields. However, questions at the interface of chemistry and biology present special opportunities for collaborative research and represent the motivation for incorporating organic chemistry into the broader UT Southwestern community. Several features of the training program bring diverse scientists together to foster interdisciplinary research. For example, because graduate programs function separately from the administrative departments, students and faculty interact frequently with research groups from multiple departments. This horizontal structure facilitates cross-pollination among disciplines. Furthermore, as research foci are only loosely correlated with departmental boundaries, synthetic chemistry functions within departments populated by biochemists, biophysicists, clinicians, pharmacologists, and cell biologists. Collaborative projects thus grow naturally out of shared excitement for complex problems coupled with expertise in diverse fields. Overall, the Biological Chemistry Graduate Program at UT Southwestern is designed to engender excellence in the individual disciplines of chemistry and biochemistry while providing ample opportunities for cross-discipline interactions. We hope that young scientists leaving the program will become leaders in their own fields who recognize the strengths and possibilities of complementary research approaches.

The measure of success of this endeavor must ultimately be the quality of research emerging from it. Within disciplines, UT Southwestern boasts an impressive litany of accomplishments, including four Nobel laureates and 17 members of the National Academy of Sciences. The quality of biological chemistry at UT Southwestern is unsurpassed—an opinion supported by *Science Watch*, an independent publication that recently ranked UT Southwestern's overall impact in biochemistry research first in the nation (*1*). Organic chemistry, too, has flourished here, with accomplishments that include the first total syntheses of multiple natural products, the structure determination of several others, and the development of general synthetic methods. Of special relevance to this article, however, is the research that impacts both biology and chemistry. Studies on the mechanism of action of natural products have pointed to new avenues for treating cancer; structural studies of proteins that regulate apoptosis likewise have led to novel inhibitors of cell proliferation; and non-natural polymers have been discovered with applications ranging from transcriptional regulation to disease diagnosis. We will never know whether these discoveries could have been made elsewhere, but the environment at UT Southwestern appears to nurture such interdisciplinary advances.

Chemistry and biology have always been kissing cousins. The graduate training programs in chemistry and biochemistry at UT Southwestern seek to prepare students for research at their interface. We have endeavored to provide students with classical training in their respective disciplines and foster collaborative research that builds on individual strengths. Success or failure of this enterprise will hinge on whether the interfacial research is more than the sum of its parts. We cannot yet predict the outcome, but the experiment is surely worth running.

REFERENCE

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