



BEYOND THE BENCH

A publication of the Office of Graduate and Postdoctoral Studies at The Rockefeller University

Volume IV, Issue 1 February 1993

LOOKING FORWARD AND BACKWARD

The 1993 admissions season is well underway. Over 240 M.D.-Ph.D. applications have been under review since November and the Ph.D. admissions committee, headed by Associate Dean for Admissions Marjorie Russel, is sorting through this year's 337 applications for the graduate program. As the M.D.-Ph.D. admissions committee prepares to accept the program's third Tri-Institutional class, we thought it would be interesting to ask two recent biomedical fellows - Anne Hermanowski-Vosatka and Joseph Heitman - to assess their experiences.

LIFE AFTER THE PH.D.

By Anne Hermanowski-Vosatka

The transition between the second and third year of medical school is a daunting one...It is even more daunting when separated by three or four years. This is the plight of M.D.-Ph.D. students in their final year of clinical training.

I went back to the wards in January, 1992, with much trepidation. The last time I had used my stethoscope - not counting when I checked my new puppy for heart murmurs - was in July of 1988. The last time I had taken an exam was in June of that year. In the interim, I had been happily diverted from thinking about the clinical side of my chosen career by long hours in the lab. The hours were spent learning a variety of techniques, agonizing over finding a thesis project, and, finally, in pursuing a line of inquiry that would bring me to the ego boosting stage of completion of the requirements for the Ph.D. degree.

RETURN TO CORNELL: ANOTHER PERSPECTIVE

By Joseph Heitman

I joined the Rockefeller-Cornell M.D.-Ph.D. program in 1984. To put this in perspective, remember that since that time Rockefeller University has evolved through three presidencies, four deanships, an expansion of the junior fellows program, an increase in interlaboratory contacts through the tetra- and multi-lab meetings, and the construction of Scholars' Residence and the Howard Hughes Building. The M.D.-Ph.D. program is now unified between the tri-institutions. There are annual M.D.-Ph.D. retreats and students have the luxury of escaping the city with the Rockefeller vans.

Following my Ph.D. years, which were spent with Drs. Peter Model and Norton Zinder studying DNA repair and DNA-protein interactions, I took a somewhat unusual route. In 1989, I moved to the Biocenter in Basel, Switzerland, to pursue post-doctoral studies before returning in 1992 to finish my final clinical year of medical school.

In terms of research directions, I had been perhaps the least medically oriented of my M.D.-Ph.D. classmates. My Ph.D. years were spent learning the vagaries of *Escherichia coli* bacterial genetics and concentrating on problems which seemed to many, me included, far from the bedside. My plans for post-doctoral studies were to move up the evolutionary ladder to the yeast, *Saccharomyces cerevisiae*. Like *E. coli*, *S. cerevisiae* is a splendid microorganism to work with because of its well-defined genetics. My plan was to isolate mutants impaired in nuclear import and thereby study protein localization in the cell and the function of the nuclear pore.

However, after six months of hard work in Basel, I had managed to show that my genetic screen was not yielding the mutants I had expected. Instead, I had a collection of mutants that blocked the yeast pheromone response, whereby yeast cells of opposite mating type respond to peptide pheromones secreted by the mating partner. This signal transduction pathway is similar in many ways to those from multicellular eukaryotes: cell membrane receptors with seven transmembrane domains, coupled heterotrimeric G-proteins, a kinase cascade, and finally transcription factor machinery that activates gene expression in the nucleus. All this intrigued me so I decided to embark on a side project. It soon became my major research focus and brought my interest back to the bedside. Since many others were working on signal transduction and concentrating on membrane-linked receptors or nuclear transcription factors, I decided to concentrate on the intermediate steps that carry signals from the membrane to the nucleus. My approach was to look for chemical inhibitors of these intermediate signal transduction steps.

Fortunately, there were a few such inhibitors that were already known to block intermediate signal transduction steps in multicellular eukaryotes. One is the well-known immunosuppressive compound cyclosporin A, which has brought about a revolution in transplantation through its widespread application to prevent or treat graft rejection and graft-versus-host disease following organ and tissue transplants in humans. Two novel immunosuppressive macrolides, FK506 and rapamycin, are currently in clinical trials, most notably in the liver transplant center at the University of Pittsburgh headed by Dr. Thomas Starzl.

With Dr. Michael Hall at the Biocenter and our collaborator Dr. Rao Movva at

Sandoz Pharmaceuticals in Basel, my colleagues and I took a novel genetic approach to study the action of these immunosuppressants in yeast. Our studies concerned the role of a protein - the FK506 binding protein (FKBP), a proline isomerase which is highly conserved between man and yeast - that had been proposed as a candidate target for FK506 and rapamycin action in lymphocytes. FKBP is highly abundant and expressed in many tissues, thus raising the possibility that - although it binds both drugs - it might not be a relevant target. Our studies demonstrated that this protein is the target for rapamycin toxicity in yeast, and presumably also in lymphocytes, and that two other proteins, TOR1 and TOR2, cooperate with the FKBP protein during rapamycin action. Our work now focuses on the identification of human and mouse TOR1 and TOR2 homologs to further elucidate the mechanisms of immunosuppressive drug action and the roles of proline isomerases.

I left my post-doctoral studies at the peak of this work on FK506 and rapamycin action to return to Cornell and New York Hospital to complete the last year of medical school. Some colleagues questioned whether it was a good idea to leave an exciting scientific project to finish medical school. However, science, like medicine, largely moves forward with or without us. Why would someone want to return to medical school after success in science? Back at Cornell and New York Hospital, I found the question usually was reversed. Why would anyone want to spend four to six years studying for a Ph.D. instead of plunging faster ahead in medicine? Occasionally the question was compounded to: Why would anyone want to spend four years in medical school and four or more years in graduate school? Why?

In my case, I started the M.D.-Ph.D. program because I was genuinely interested in both medicine and science. However, I had long since realized that it might prove exceedingly difficult to succeed, let alone excel, in both fields. I decided to finish the last year of medical school and to consider a year as an intern. After seeing and hearing about the lives of interns, I could see little reason to continue for a year of apparent misery without the reward of progressing to the next steps. Thus, it was either an internship and residency or return to the

lab. In seeking advice, some hospital colleagues advised that if I did not apply for a five-year residency in general surgery, then I should at least complete a year of internship. I could then at least be licensed and write prescriptions for relatives. Those in whom I confided often found it curious that I considered this year of medical school clinical experience even more valuable and important because I was not planning to continue clinical training, and it would be all I would have. During this final year of medical school, while my medical school classmates were applying for internships and residencies and preparing for the match, I sometimes felt like an outsider as I applied for faculty positions to establish an independent lab.

Everywhere I traveled I found that many people were wondering about whether M.D.-Ph.D. programs have been successful. How could success even be measured in this sort of program? Should the program continue? People often asked me if I had the choice to do over again, would I go back and do the same? This always seemed an unfair question. Who, given the choice, would willingly return to third or fourth grade and repeat elementary school, junior high, and high school all over again? We are forced to look at the final products, the outcomes of all of this schooling, to decide if it has been worthwhile.

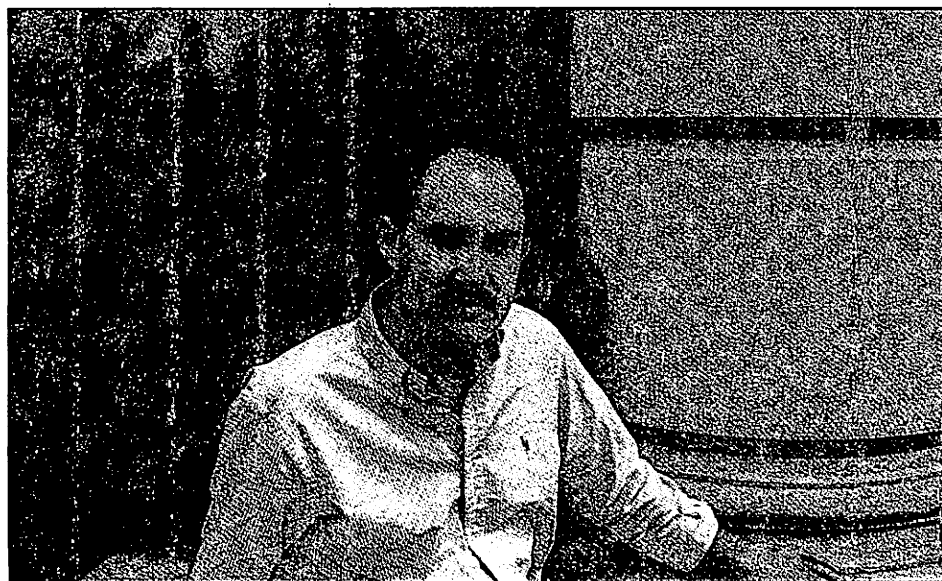
Increasingly, the outcome is that biomedical fellows are finding it necessary to decide between one world and the other. Medicine and science are both

fast-paced fields. Each requires dedication and commitment to survive. To try and pursue both compounds the commitment. It is important to have individuals who can do both, or who are at least willing to try. This brings advances to medicine and gives impetus to science. However, one cannot escape the conclusion that something must suffer: if not one's attention to the science or to the medicine, it is likely to be one's family or personal life. If one decides to pursue only science or medicine, when should the decision be made: after graduate school, medical school, internship or residency? The choices are almost endless. Is someone who chooses one career over the other to be defined as a program failure? What if a biomedical fellow finishes a residency and then returns to science, never to see a patient again? Who is to judge and how?

Despite my decision not to pursue further clinical training, and rather to devote my energies to my laboratory, research interests, and family, I consider it an invaluable experience to have had the opportunity to go to both medical school and graduate school and to finish without a financial burden. The philosophies of graduate and medical education are entirely different. In medicine, one tries to become exposed to as broad an information base as possible as one never knows who will walk into the hospital next. Clinical education is driven by the patients to whom one is exposed and compelled to learn more about.

Continued on page 4, column 1

Joseph Heitman



Without this medical education, one is less likely to read *The New England Journal of Medicine*, less likely to think about the causes and treatment of inflammatory bowel disease, and less likely to know that myasthenia gravis often results from an underlying thymoma that fosters an autoimmune response to the acetylcholine receptor. This education serves as a strong background in human biology with which to approach almost any biological question. Medical education differs from clinical medicine at the bedside. The latter is akin to solving crossword puzzles day after day; often the questions are only partially answered. The next day one must move on to the next set. In contrast, graduate school trains one to think critically about a body of literature and to attack a question of defined scope day after day for a period of years. Many medical doctors cannot tolerate the pace of scientific research; it is to them too slow. Basic scientists are often frustrated by clinical medicine; the answers are frequently unclear and there are usually no controls. By exposing individuals to both approaches, the M.D.-Ph.D. program educates people to feel comfortable in both spheres.

In my opinion, the M.D.-Ph.D. program is still just beginning. We should give it at least another 20 or 30 years before we decide its fate. By then the sequence of the human genome will probably be nearing completion, and the impact of

molecular medicine will be in full stride. We will have educated a group of individuals who are comfortable thinking about the biology of whole organisms rather than at a purely cellular level. This will become increasingly important as mouse genetics evolves and allows us to model more and more human biology and disease in a genetically and experimentally manipulable organism. If there continue to be individuals who are brave or crazy enough to want to pursue both types of careers - with all the inherent problems - and we happen to think of or stumble upon something that is of interest to the scientific community, the medical community, or to both, then by all means I think our culture can afford to continue to support our education. In the end, however, we should leave it to these individuals to decide what is best to do with their education.

Joseph Heitman graduated from Rockefeller University in 1989 and Cornell University Medical College in 1992. He was an EMBO post-doctoral fellow at the Biocenter in Basel, Switzerland, from 1989 to 1990. He is now an Assistant Professor in the Section for Genetics, the Department of Pharmacology, and an Assistant Investigator in the Howard Hughes Medical Institute, at Duke University Medical Center in Durham, North Carolina.



BEYOND THE BENCH is published several times a year by the Office of Graduate and Postdoctoral Studies of The Rockefeller University. Dean: Bruce S. McEwen, Associate Dean for Admissions: Marjorie Russel, Associate Dean for Curriculum: Peter Model, Editor/photographer: Joanne Cunningham, Designer: Jody Miller



Volume IV, Issue 1, February 1993
THE ROCKEFELLER UNIVERSITY
1230 York Avenue, Box 270
New York, New York 10021

Non-profit organization
U.S. Postage
Paid
New York, N.Y.
Permit no 7619