

## HHMI-NIH Scholar Aims Stem Cells at Multiple Sclerosis

by Trisha Gura



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*Editor's Note: This feature is reprinted with permission from the June 2002 issue of the Howard Hughes Medical Institute Bulletin. Dan Refai, who was selected as an HHMI-NIH research scholar, returned to the University of Chicago in July 2002 to complete his fourth and final year of medical school. Anticipating graduation in June 2003, Refai plans to enter a neurosurgical residency and become an academic neurosurgeon, focusing on tissue engineering and regeneration in the central nervous system. Meanwhile, he plans to continue his research this year and expand on it while in residency. An unprecedented five Chicago students have followed in Refai's footsteps as HHMI-NIH scholars this year. (See related story on next page.)*

**D**an Refai, 26, is panning the human bloodstream for stem cells — those biological nuggets that have the potential to develop into virtually any type of body cell — with a specific goal in mind. He wants to help reverse the destruction suffered by patients with multiple sclerosis, a nerve-wasting disease that afflicts an estimated one million people worldwide and 350,000 people in the United States.

“There’s been a shift in the thinking about MS,” said Refai, a Howard Hughes Medical Institute-National Institutes of Health research scholar. Scientists have long recognized the autoimmune component of the illness, in which the patient’s own immune system mysteriously attacks the myelin that insulates basic nerve circuitry. Researchers now are learning that MS has a second phase — a chronic, intermittent degeneration of nerve tissue. This erosion is what causes the worst effects of MS, such as loss of coordination, paralysis and eventual death.

Some drugs have achieved partial successes against the autoimmune aspects of the illness, but “those treatments are more or less useless during later, chronic phases of the disease,” said neuroimmunologist Roland Martin, Refai’s mentor at the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Md.

Refai’s entry into the MS arena was serendipitous. “When I came to the NIH, the last thing I thought I’d ever do was immunology,” recalled the fourth-year University of Chicago medical student, who wants to pursue neurosurgery.

In October 2000, however, he happened to pick up a current issue of *Nature Neuroscience* and come across an article by Angelo L. Vescovi’s group at the Stem Cell Research Institute in Milan, Italy. He was fascinated to read that the team had isolated stem cells from the brains of adult mice and from tiny ball-shaped human embryos and kept the cells alive in petri dishes for months. The researchers also had coaxed the stem cells to mature in vitro into skeletal muscle cells. Moreover, it appears that both the mouse and human stem cells could “walk the walk” in vivo: When transplanted into a group of muscle-injured rodents, the cells eventually made their way to the damaged sites and transformed themselves into muscle cells within regenerating fibers — the first step toward restoring muscle function. In short, the researchers were potentially developing a whole new way to treat muscle-wasting illnesses.

Impressed as he was, Refai had no connection with such work, so he filed away the information until the following March, when he overheard Martin discussing a vague idea with colleagues about using stem cells to treat MS. Martin proposed to repair the nerve deterioration by recruiting the

patients' own stem cells under the right conditions. To avoid the ethical and political tangles of using stem cells from human embryos, he would try to coax adult hematopoietic (blood-forming) stem cells into becoming neural stem cells, which could then go on to produce neurons, glia and other cells of the central nervous system. Those, in turn, might repair the nerves' frayed outer sheaths or build new connections within the central nervous system.

Refai immediately jumped in. "I want to do this," he told Martin, who gave him a month to read up on the subject and put together a proposal. It was a convincing proposal, which blossomed into a plan that won a two-year, \$170,000 grant from NINDS for Martin's laboratory and five collaborating labs.

Refai obtained blood samples from healthy human donors who had been injected with a factor that helps enrich their blood supply of CD34-positive stem cells. He then fished out that scant supply (only 1 percent) of candidate cells with the help of a magnetic tag and grew the cells in petri dishes.

As with most first-time investigators, Refai's early months were slow going. He lost all the stem cells on the first try because of a fluke in the isolation procedure, but by the second try, he was up and running. He can now get the cells to stay in culture for up to a week and is tinkering with conditions to see whether he can trick the cells into maturing into neural stem cells, which the team eventually hopes to inject into the central nervous systems of mice.

Refai resumes his medical training in June, but he is so taken with the project that he wants to return to it periodically over the next eight years as he completes neurosurgery training. That plan pleases Martin, who characterizes his protégé as the kind of young physician who is much needed in the research community.

"It is actually a sad development," Martin said, "that fewer and fewer students who have chosen MD paths are eager to venture into the very difficult but very rewarding career of physician-scientist."

## The Chicago Five

This year, five University of Chicago third-year medical students applied to the Howard Hughes Medical Institute-National Institutes of Health Research Scholars Program. All five were selected — an unprecedented number.

**Todd Casese** of Port Jefferson Station, N.Y., is studying virology during his year at HHMI. After graduation, he's planning a combined medical/pediatrics residency, followed by an infectious disease fellowship.



"This program is a great opportunity to explore the forefront of biomedical research and to learn how I might apply this basic science research to improve patient care," Casese said.

**Jason Elinoff** of Orlando, Fla., is studying structural biology and its applications in immunology while at HHMI, but plans to specialize in general surgery after graduating medical school.



"I became really interested in research and the possibility of a career in academic medicine after participating in the University of Chicago Summer Research Program," he said. "I thought that it would be helpful to take a year off and dedicate more time to research so that I could better evaluate whether research was something that I really enjoyed."

**Danielle M. Hari** of Bethlehem, Penn., also plans a career in general surgery. While at HHMI, however, in order to better understand the mechanisms that



regulate tissue remodeling and fibrosis, Hari is using DNA microarray technology to "fingerprint" fibrotic liver genes of mice infected with the helminth parasite *Schistosoma mansoni*.

"Research provides a forum to develop new treatments, procedures and other methods of patient care," Hari said. "The HHMI-NIH program will grant me the unique opportunity to enhance the research skills I want for my residency program."

**Amy Jost** of St. Louis, Mo., who plans to specialize in pediatrics, is studying *Plasmodium falciparum*, the parasite that infects more than 400



million people with malaria each year and is one of the most lethal infectious diseases, third only to TB and AIDS.

"My project will enable me to learn how basic science research can be applied to gain an understanding of the molecular mechanisms of a socially relevant and clinically devastating disease," she said.

**Bruce Tan**, originally from Singapore, is studying gene expression profiling of leukemias and lymphomas.



"I wanted to strengthen my understanding of the biomedical sciences and gain research experience," Tan said. "The

HHMI program has given me the opportunity to achieve these goals at the NIH with an intellectually stimulating group of peers."

— Catherine Gianaro