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From Artist to Immunologist

Gladstone's Shomyseh Sanjabi wasn't always set on being a scientist, but her work in immunology could revolutionize our understanding of how our bodies fight disease.

BY ANNE D. HOLDEN, PHD

Our immune system protects us. It fights dangerous pathogens and builds defenses to block future infections. But it is extraordinarily complex, and scientists are still unraveling the inner workings of how this system attacks potentially deadly diseases.

As an immunologist and Gladstone Investigator since 2010, Dr. Shomyseh Sanjabi has spent her career defining how this highly sophisticated system is controlled. But she did not start out to be an immunologist—or even a scientist.

"Actually, I was more interested in art and thought that one day I would become a famous painter," said Dr. Sanjabi. "But when I was 12, my family emigrated from Iran to the United States. I was good at math and science, I think, because they required the least proficiency in the English language."

Perhaps her first exposure to science occurred during her undergraduate studies at UCLA, when she worked as a laboratory assistant for Dr. Jeff Miller.

"Jeff is one of the most enthusiastic scientists I have ever met," she said, "and he made it seem like being a scientist was just the best thing in the world. I ended up falling in love with science, and completing my honors thesis in his lab."

Armed with her newfound interest, she continued her studies at UCLA's PhD program in the laboratory of Dr. Stephen Smale. Dr. Sanjabi quickly found that his lab offered the perfect environment to learn molecular immunology. There, she focused on how the so-called '*innate* immune system' becomes activated and responds to these pathogens.

An All-Natural Defense

Work performed by Dr. Sanjabi and other immunologists around the world over the last several years has helped piece together how the innate immune system fights infections. In essence, pieces from cells damaged by pathogens are picked up by this system, which then alerts other immune systems to destroy them. But the innate immune system is not specific to a particular disease, nor can it adapt and learn from previous infections.

For that, a secondary defense, the '*adaptive* immune system,' kicks in. And it's this second wave of attack that intrigued Dr. Sanjabi as she began her postdoctoral training with Dr. Richard Flavell at Yale University.

"It would have been more natural if I had continued my postdoctoral training in innate immunity," she explained. "But I decided to explore a new area of immunology by learning about adaptive immunity. I joined Richard's lab at Yale for my postdoctoral training. His lab is like immunology heaven, and I was exposed to all aspects of immunology. It was an incredible experience for me, and I'm glad I took the chance to learn a whole new field."

The adaptive immune system differs from innate immunity in that it provides a more tailored immune response. It also employs immunological memory, a process by which a specific pathogen is 'remembered' by a particular set of immune cells. These memory cells allow the body to quickly generate an effective immune response if it ever shows up again. The body's adaptive immune response is the basis behind vaccinations.

Survival of the Fittest

Later on in her postdoctoral training, Dr. Sanjabi studied how TGFb—a protein involved in a variety of cellular functions—controls a specific set of immune cells called cytotoxic T cells, or CD8 T cells. In so doing, she uncovered an important aspect of immunological memory.

These cells protect us by killing other cells that can be harmful, such as tumor cells or cells that are infected with viruses and bacteria. And while most of the CD8 T cells are short-lived, a select few live for a very long time. And there has been much debate as to what controls survival and death of these cells.

Dr. Sanjabi and her colleagues showed that TGFβ actually controls the number of these short-lived CD8 T cells that are generated in response to infection. They further found that TGFβ specifically kills off the short-lived cells, while another protein complex called IL-15 helps keep the cells alive. The cells that survive form the core of the memory pool that will help the body defend against future infection.

"Pharmacological agents are being developed that, if administered as vaccines, can block TGFβ signaling and boost the expansion of CD8 T cells," said Dr. Sanjabi. "This would help create more long-lasting memory cells and accelerate their ability to fight disease."

Modifying the Models

There are many more questions left to be answered about the human immune system—but current animal models have their own limitations. For example, the immune system of a mouse is different from that of a human. But Dr. Sanjabi and the team at Yale—led by Dr. Flavell—found a solution.

These 'humanized mice' are advantageous models of human disease, because their natural immune systems have been replaced with a human one. In recent years, humanized mice have been developed to study a whole host of human diseases, including cancer, blood diseases and HIV/AIDS.

In her lab at Gladstone, Dr. Sanjabi hopes to use these mice together with the latest iPS cell technology to mimic the immune system of HIV elite controllers—individuals whose immune systems can naturally control HIV infection. Studying how elite-controller immunity can protect the host promises to teach us a great deal about what kind of immune response humans have to generate during vaccination, in order to establish protection from this deadly virus.

"My work at UCLA and Yale prepared me to tackle some of the most fundamental questions surrounding the human immune system," said Dr. Sanjabi. "And importantly, they have allowed me to use my knowledge to study HIV's harmful effects on the human immune system."