New Pilot Projects

Understanding the Role of Ca2+ Signaling in the Pathogenesis of Sjögren’s Syndrome
Principal investigators: Stefan Feske, MD, and Rodrigo S. Lacruz, MSc, PhD

In Sjögren’s syndrome, a condition affecting as many as 4 million people in the United States, the moisture-producing glands of the body are impaired, which leads to symptoms including excessive dryness of the saliva and tear ducts, profound fatigue, chronic pain, major organ involvement, and neuropathies and lymphomas. Approximately 50 percent of patients develop complications including non-Hodgkin’s B-cell lymphoma. While Sjögren’s syndrome is considered an autoimmune disease, it’s long been unclear whether the disease is caused by a malfunction in the autoimmune system, or whether it’s caused by the autoimmune system responding to factors such as a viral infection. Recent discoveries, however, have indicated that genetic and environmental factors precipitate Sjögren’s syndrome, and that subsequent activation of the adaptive immune system starts the vicious cycle of inflammation and gland destruction.

In preliminary data, Drs. Feske and Lacruz found an unexpected link between the onset of Sjögren’s syndrome and the way that T-cells process calcium ion signals. Calcium ions are crucial to the biological processes of all cell types; in T-cells, calcium ions flow into the cell through a channel that’s regulated by several proteins, ORAI1, STIM1, and STIM2. When any of these proteins is deleted, T-cells cannot properly process calcium ions, which leads to the autoimmune inflammation of the salivary glands that characterizes Sjögren’s syndrome.

Spotlight on Timothy Niewold, MD, director of the Colton Center and the Judith and Stewart Colton Professor of Medicine
Since joining as director earlier this year, Dr. Niewold has started to prepare the Colton Center for the next stage of its growth while continuing to conduct his own research, which focuses on finding the causal molecules and pathways that lead to lupus and other autoimmune diseases. Dr. Niewold’s latest collaboration, with Jef D. Boeke, PhD, director of the Institute for Systems Genetics, marks an important step forward both for his own research and for the Colton Center’s growth. Drs. Niewold and Boeke will apply pioneering genetic engineering technology to gain insights into the function of a gene linked to lupus, and this project will also serve to launch the Colton Collaborative Project, Dr. Niewold’s vision for taking the Colton Center’s research in new directions. We interviewed Dr. Niewold to learn more about his collaboration with Dr. Boeke, and about his plans for the Colton Center’s future.

Researchers have discovered a lot of risk genes that predispose to lupus and other autoimmune diseases, which is good news, but the problem is trying to understand what they do. In lupus, the variant of the IRF5 gene is located in a fairly large region of the genome, and we usually find at least a few things within that region that could be causal. One of the limits in studying these natural variants is you can’t split them up. If you try to design a medicine against one of those gene variants and you pick the wrong one, it wouldn’t work. Dr. Boeke’s approach is groundbreaking, and we’re excited to apply it to lupus and other autoimmune diseases. Dr. Boeke has done path-breaking work in making artificial chromosomes; using the techniques he’s developed, we can make combinations that can’t be found in nature, and do the scientific tests that we need to do. If we have four different risk genes we’re interested in, we can make a chromosomal stretch that has just one of those four, put it in a cell, and see if that’s enough to cause perturbation in the cell’s biology. The fascinating thing is that we can also test combinations, so that we can be very systematic and find the exact variant or combination where we see a change in function. What’s the potential long-term impact of the findings that might come from this collaboration?

Both Dr. Boeke and I are excited about this collaboration because this could give us a new way to target lupus. If we can understand the biological process that the risk gene is causing, we can hopefully counter the risk of disease and actually be proactive about prevention. Aside from prevention, it might also lead to better therapeutics for people who develop the disease; if there’s a patient with lupus and we know what risk genes they have and know the molecular function of those genes, it would give a much better idea of how to treat that person. I think we’re getting enough tools in terms of immune system medications that work in fairly specific ways that we could envision this as so far off. For example, if there are drugs that target a particular cytokine molecule, or a particular immunological pathway, we could envision matching the molecular profile of a given person’s lupus with a drug tailored for that profile. Aside from what would mean for lupus, the method that we’re using is very broadly applicable to many different diseases. We’re going to start with this pilot grant that will support work on lupus and the IRF5 gene, and we’ve already been drafting a proposal to do this more broadly that we’re sending to the National Institutes of Health to study larger numbers of genes.

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Our lab is focused on applied genetics in lupus, where we really want to understand the mechanisms of the disease, whereas Dr. Boeke is more about the big-picture challenges in the field of genetic engineering. It’s a great synergy; we provide a route for Dr. Boeke’s technology to be used in human disease and to serve as proof-of-principal to apply it to many complex human diseases. Also, the genetics of autoimmune diseases really lends itself to Dr. Boeke’s approach. In cancer, for example, the genes in a person’s tumor are drastically different from the normal cells from that person, and it’s relatively easier to discern the mutations. Autoimmunity is not like that. A cell taken from a person with autoimmune disease and a cell taken from a healthy person might look very similar, so you need a well-designed system, like Dr. Boeke’s, to study them and see the differences.

The collaboration with Dr. Boeke is part of the Colton Center’s new approach to research, called the Colton Collaborative Project. Can you briefly explain what this model is? How will it accelerate progress?

The Colton Collaborative Project model involves assembling a team of researchers to work on a defined problem, as opposed to asking researchers to submit their own unrelated projects for funding. When we look back at the first few years of the Colton Center, there have been a lot of successes. The pilot program is working well, but the next step is finding synergy between the different people the Colton Center is supporting. It’s a balancing act—we want people to present their best science, for sure. That’s a model that’s worked forever in science. The Colton Collaborative Project is all about creating some synergy, but without being too prescriptive so that people can contribute their best ideas and strongest areas of work.

Do you feel like being part of the Colton Center is pushing you to work and think in a different way?

That’s one of the exciting things about changing institutions and taking up leadership of the Colton Center. My laboratory is working on new and different questions than we would have if we hadn’t come here, and so the Colton Center director, I’m integrated with so many activities across the university. We’ll keep up the ongoing work in my own group, and via the Colton Center I’ll be able to support the things others are doing, and as a whole we’ll get a lot more done, and I’m excited about that. The great geniuses of our time were great geniuses because they were brushing up against other great geniuses, and I think that’s a crucial part of the scientific method—we’re all much better when we connect with each other and help each other along. I brought with me a number of junior faculty members, and I think the environment is much richer for them as well. Whichever direction their research may take them, they’ll find good support from other people here at NYU Langone. If their work takes them into a new area, we’ll be able to connect them with the right people to make sure they succeed in that area and push on with their question.