DISCOVERY

Transforming lives through innovation.

Lupus Research Institute

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LRI's Unwavering Commitment to Innovation Keeps the Discoveries Coming

Two important Novel Research Grant discoveries exemplify why LRI's proven scientific strategy works: give talented researchers worldwide opportunities to take some risks and pursue bold, creative, novel research. LRI grant winner Dr. Jeffrey Rathmell notes, "We are moving on to bigger and bigger questions; that's how we know the original question in our LRI grant was a good one!"

Read about how his results and those of Dr. Mariana Kaplan, another LRI Novel Research grant recipient, are advancing new lupus treatments to transform patients' lives.

What if the Lupus Immune System Ran Out of Energy?

Like any athlete, the lupus immune system needs large amounts of glucose for the energy to keep going. But could this high-energy demand be its downfall? Immunologist and LRI Novel Research Grant recipient Dr. Jeff Rathmell at Duke University recently published new insights on how to stop harmful immune cells in their tracks by cutting off their energy supply.

In pursuing this idea, Dr. Rathmell took a cue from cancer research. When healthy cells turn cancerous they rely on glucose as fuel to allow them to divide and spread. A potential new type of drug that prevents cancer cells from getting energy from glucose is now in clinical trials. Knowing that active immune cells have the same need for energy as cancer cells, Dr. Rathmell is exploring if a similar treatment strategy could deprive the immune system of the energy it needs to attack in autoimmune diseases like lupus.

Zeroing in on B cell metabolism

Dr. Rathmell's LRI grant focused on white blood cells called B cells which cause damage in lupus by producing antibodies that attack the patient's own cells and organs. His recent results published in the *Journal of Immunology*, show how autoimmune B cells switch their metabolism to use large amounts of glucose. The genes and molecules he identifies are potential novel targets for lupus drug discovery.

In fact, a drug that inhibits one of those new targets (an enzyme called PHK) has been developed and is in clinical trials for cancer. Future studies can determine if this drug should be tested in lupus.

Exploring new treatments

Dr. Rathmell is currently on sabbatical from Duke, working alongside researchers at Swiss pharmaceutical company Novartis to explore early-stage ideas on how the immune system's metabolism can be manipulated to treat autoimmune disease.

"Many traditional immunosuppressant drugs [like methotrexate and azathioprine] work by inhibiting cell metabolism. Those drugs were found by chance and have many unpleasant and toxic side effects because of their broad effects on metabolism. Our goal is to pick out new molecular targets and develop new drugs that are more precise, more effective, and less toxic," explains Dr. Rathmell.

Back in the lab at Duke, new research paths initiated with his LRI grant are accelerating thanks to over $800,000 in follow-on funding awarded by the National Institutes of Health and private-sector non-profit organizations.

"Our LRI funding was essential to open up a new avenue of research and show that this new

metabolic approach has promise."

How Lupus Strikes the Heart - Turns "Good" Cholesterol Bad

Dr. Mariana Kaplan's recently published results show the power of innovation to drive new treatments. Building on earlier LRI studies, her work is getting to the heart of why lupus causes cardiovascular damage.

Neutrophils are the immune system's superheroes – the first white blood cells on the scene when your body comes under attack from bacteria or fungus. These cells trap and kill the microbes in webs (called neutrophil extracellular traps or NETs) containing toxic chemicals. But in lupus, rogue neutrophils release NETs indiscriminately into the blood stream.

Now, new research by Dr. Mariana Kaplan shows the powerful chemicals in NETs that attack the molecule that carries 'good' cholesterol called high density lipoprotein (HDL), which could explain why lupus patients are at risk of premature heart disease. The study was initiated with LRI funding and further developed with support from the National Institutes of Health.

Why Good Cholesterol Goes Bad

Damage to the heart and blood vessels caused by atherosclerosis (hardening of the arteries) is a common and life-threatening complication of lupus. But scientists have not understood why or how to prevent it. Earlier LRI-funded work by Drs. Bevra Hahn and Maureen McMahon had shown that in lupus, HDL is converted to a form that promotes rather than protects from atherosclerosis. With an LRI research grant awarded in 2012, Dr. Kaplan, then at University of Michigan, set out to explain what causes HDL to turn bad in lupus.

Her results recently published in the journal *Arthritis & Rheumatism* prove her theory, showing that NETs from lupus patients convert good HDL to the harmful form.

And when lupus mice were treated with an experimental compound to prevent the release of NETs, normal levels of HDL were restored. They also found that antimalarial drugs often used to treat lupus inhibit NET formation – which might explain epidemiological studies suggesting that lupus patients on antimalarials have less cardiovascular disease.

"Our idea that the NETs attack HDL in lupus was just a theory; we had limited data to back it

up. But LRI saw the potential and allowed us to do the critical experiments to prove our hypothesis."

Moving Toward New Treatments for Heart Disease in Lupus
Now working at the National Institutes of Health, Dr. Kaplan and her team are delving deeper into how NETs impact the cardiovascular system of lupus patients.

"Our work has revealed new drug targets, and with NIH funding we are moving forward new strategies for therapeutics to protect lupus patients from cardiovascular disease."

About the Lupus Research Institute
The world's leading private supporter of innovative research in lupus, the LRI champions scientific risk-taking in the hunt for solutions to this complex and dangerous autoimmune disease.

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