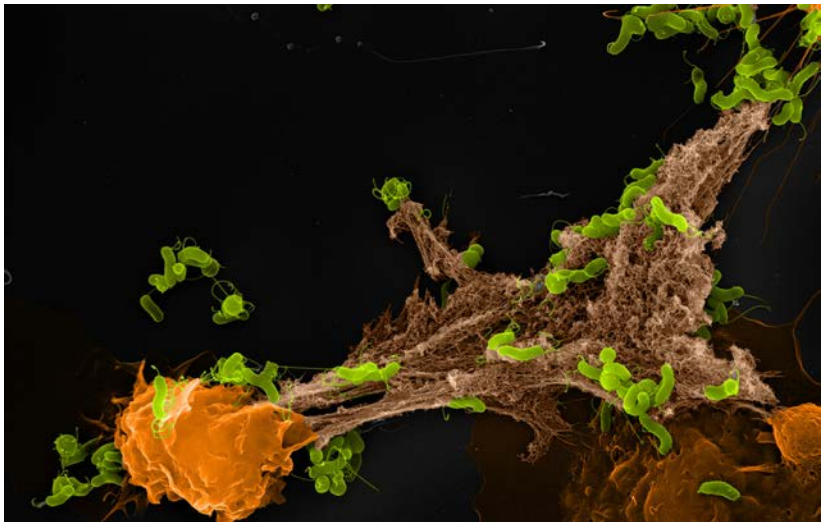


Thank you for being ambassadors for Michigan Medicine. We value your partnership and appreciate your commitment. Together, we are improving and saving lives.

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Antiphospholipid syndrome is an unpredictable autoimmune disease that can cause dangerous blood clots to form in blood vessels. Roughly 200,000 people in the United States have APS, which can lead to very serious and sometimes life-threatening health complications, including stroke, pulmonary embolism, and pregnancy loss. Unfortunately, most patients with APS do not receive a diagnosis until one (or often more) frightening health issue has occurred, which makes the search for more precise medical diagnostics and interventions all the more urgent.

At University of Michigan Health, the Department of Internal Medicine's Division of Rheumatology is deeply invested in creating personalized treatment options for our patients. Precision medicine for all is the next frontier in health care. To achieve this for APS, we are constantly pursuing new cross-disciplinary and synergistic collaborations with molecular biologists, geneticists, biomedical engineers, vascular biologists, neuroscientists, and whoever else is needed to tackle the problems we see everyday in the clinic. Our mission is to always be the leaders and best for our patients and their families, and donor support helps us stay the course.

KNIGHT LABORATORY

Jason S. Knight, M.D., Ph.D., is the Marvin and Betty Danto Research Professor of Connective Tissue Research. His laboratory focuses on APS research with the goal of identifying avenues for more precise, customized therapeutic interventions. **Currently, his team works with many collaborators across the University of Michigan to create a deeper and more nuanced understanding of the APS disease process so they can help patients earlier than ever before.**

The team is also building what they anticipate will soon be the largest APS biospecimen repository in the world. The goal is to deeply understand every APS patient's unique genetic, epigenetic, gene expression, and autoantibody signatures and how they relate to disordered inflammation and blood clotting. The prediction is that over the next decade, this resource will bring disruptive diagnostics and therapeutics from the laboratory to the clinic. Our goal is to utilize the biorepository to discover the strategic immune system reprogramming that will be necessary for a viable cure.

UNFORESEEN COLLABORATIONS

Part of the work of the Knight laboratory focuses on understanding NETs, or neutrophil extracellular traps. **Dr. Knight's lab was the first to connect the presence of these NETs to APS — a field-changing discovery that provided researchers with new avenues for research and therapeutics. NETs are released by a flurry of overactive immune cells that release toxic tangles of proteins and DNA in what is sometimes referred to as a spider web-like response.** For patients with APS, the presence of NETs can lead to blood clots and inflammation, so developing treatments to slow down the production of NETs has been a primary focus. The goal for physician-researchers like Dr. Knight is to learn how to target NETs with FDA-approved drugs in order to prevent serious health complications from happening. Recent preclinical studies in the Knight lab have shed light on the potential benefits of drugs like colchicine, dipyridamole, and defibrotide – and even ginger supplements – and the next step is to test these strategies in the clinic.

As descriptions of COVID-19 cases began emerging in

2020, Dr. Knight was one of the first researchers in the United States to see a potential link between blood clotting and severe COVID-19 symptoms. Along with University of Michigan Health rheumatologist Yu (Ray) Zuo, M.D., Dr. Knight questioned whether NETs could be behind some of the clotting and severe respiratory issues characteristic of the earliest reports of COVID-19 out of China. When he posed this question on social media, other researchers reached out, and a team of experts from across the country began pouring over case studies, publications, and any information they could get their hands on. They hypothesized that NETs were likely to be present in the most severe cases of the virus, but they needed to be sure.

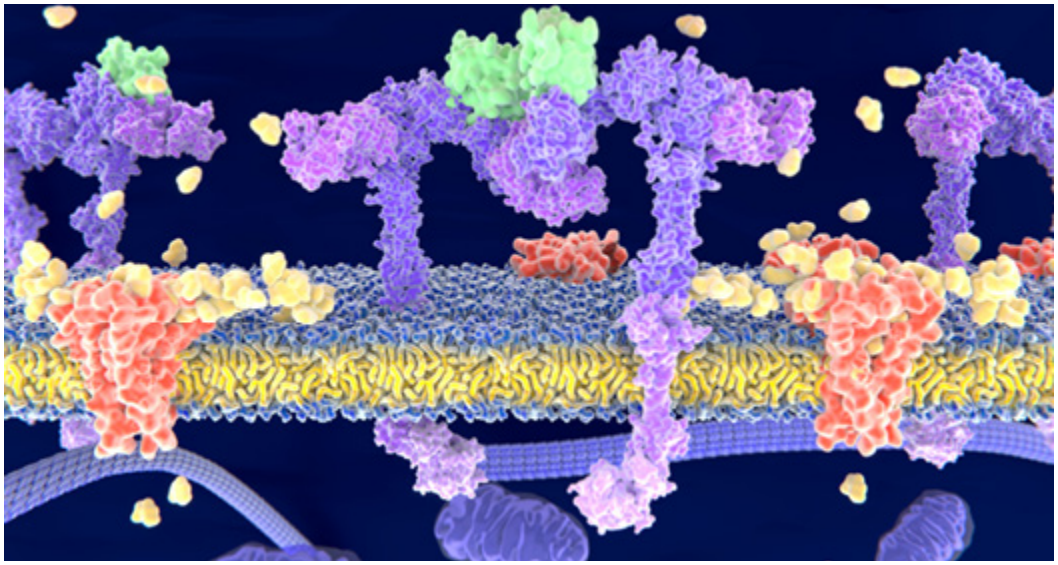
Due to the potential benefits of this research, University of Michigan Health approved an emergency petition to reopen Dr. Knight's laboratory in April 2020 at the height of the pandemic so the researchers could test their theory about the presence of NETs. They also received special approval to obtain blood samples from patients diagnosed with COVID-19. They gathered almost 200 samples for their study and found that over half of the patients hospitalized with complications from the virus had the presence of APS-like antibodies in their blood. They believe the presence of these antibodies triggers NETs to be released into the bloodstream, explaining why some patients have more severe cases. This finding continues to give physicians and researchers potential targets for treatment of coronavirus patients.

THE FUTURE OF APS RESEARCH

Donor funding makes a significant, measurable difference to our researchers — especially for diseases like APS, which is just beginning to receive national attention and awareness. In addition to Dr. Knight's projects, three other projects helped highlight the impact donor generosity can have on research. Within the last 6 months, incredible progress has been made within the APS program, and each of these projects is now benefiting from federal grant money

Dr. Yu (Ray) Zuo was drawn to the University of Michigan because of Dr. Knight's mentorship and the outstanding basic and translational research environment of the APS program. He reached out to Dr. Knight with a new and bold idea to characterize "anti-NET autoantibodies" in APS, and with initial support from donors, Dr. Zuo was able to put his hypothesis to the test. He discovered a new class of clinically actionable autoantibodies, and this donor-funded discovery made him eligible for large grants from the Arthritis National Research Foundation, the Rheumatology Research Foundation, and the National Institutes of Health. He will now be able to undertake a comprehensive examination of the role of anti-NET autoantibodies in APS and beyond using cutting-edge technology. **Fascinatingly, the APS program believes that this work has revealed an entirely new aspect of pathophysiology in APS, lupus, and COVID-19 that has significant translational potential.**

Ajay Tambralli, M.D., is a clinical research fellow with the Knight laboratory. His project examines how the metabolism of neutrophils is altered in APS and lupus with the goal of identifying smarter, more personalized targets for therapeutic interventions. **Using donor funding, Dr. Tambralli realized that neutrophils in APS were especially adept at using sugars to generate energy. This is, in part, what makes neutrophils hyperactive in the APS bloodstream.** With his project now supported by



the Rheumatology Research Foundation, Dr. Tambralli will use several high-tech approaches to investigate how various metabolic pathways are altered in APS and lupus. The hope is to eventually tailor treatment to the individual through key supplements, special diets, or other lifestyle changes that can free patients with APS from the consequences of active disease and medication toxicities.

Jacqueline Madison, M.D., is a clinical assistant professor in the University of Michigan Health Department of Internal Medicine's Division of Rheumatology. Because of her dual certifications in adult and pediatric rheumatology, Dr. Madison often serves as a bridge between the APS program and C.S. Mott Children's Hospital as she tries to help identify and care for pediatric APS patients. At first blush, pediatric APS cases seem relatively rare. However, Dr. Madison believes that APS is actually going unreported and undiagnosed because pediatric-specific criteria need to be more widely developed. **Donor funding helped Dr. Madison enroll pediatric patients in a U-M APS study examining inflammation that underlies their disease. Pediatric patients with APS often do not know where to turn for care, and Dr. Madison is grateful to donors for the opportunity to develop a pediatric arm within the APS program.** Additionally, donor support has enabled Dr. Madison to have protected time dedicated to participating in U-M's clinical trial academy, a specialized curriculum that prepares researchers for the rigors of clinical trials.

WITH GRATITUDE

APS research at University of Michigan Health is shaping our understanding of the relationship between autoantibodies, neutrophil extracellular traps, and blood clotting — and thereby revealing numerous avenues that should help us prevent serious medical complications from arising in the first place. **Recent events have proven the significant impact medical research can have when we work together.** Thank you for supporting our work and for enabling us to improve the lives of our patients and their families.

For more information, please contact the Michigan Medicine Office of Development:
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