

A Root Cause of Pediatric Lupus: Dysfunctional Red Blood Cells

It takes extraordinary skill and determination to make headway against an elusive disease process—exactly the qualities that **Virginia Pascual, MD** and her colleague **Simone Caielli, PhD** bring to the field of lupus research.

These brilliant scientists have achieved a breakthrough that promises a potential yield of new targets for lupus therapies. Working with a team at Weill Cornell Medicine in New York, they have identified an important link between red blood cells (RBCs) that don't function properly and pediatric lupus. Their research—partially funded by the **Lupus Research Alliance** (LRA)—is groundbreaking.

To fully appreciate the scope of Dr. Pascual's discovery, we must start with the function of mitochondria—the “powerhouses” inside cells that convert energy from food into fuel. Her research strategy was built on growing evidence that mitochondrial dysfunction is connected to the development of many diseases, including lupus.

Previously, Drs. Pascual and Caielli had studied mitochondrial dysfunction in children with lupus in relation to two types of immune cells, neutrophils and CD4 T cells. Next, they wanted to extend their work to see if mitochondrial dysfunction in other cells, specifically those found in the blood stream, also contribute to the development of lupus or its progression.

Normally, RBCs, which carry oxygen, shed mitochondria as they mature in the bone marrow. The study compared the RBCs of pediatric patients with active lupus to those of healthy children and discovered a new piece in the lupus puzzle.

“We found that a significant number of children with lupus had mature red blood cells which still contained mitochondria. In fact, the presence of RBCs containing mitochondria was linked to higher lupus disease activity,” said Dr. Pascual.

Mitochondrial removal is essential to healthy RBCs—and the investigators pinned down the defective mechanism that leads these cells to retain mitochondria. Macrophages tightly control the production and clearance of RBCs by eating and destroying any cellular

debris—a process that has an important downstream effect in lupus. Ingestion by macrophages of RBCs that still contain mitochondria cause a flood of type I interferons.

Interferon proteins are essential to the body's natural defenses—but high interferon levels have the negative effect of promoting autoimmune inflammation.

Dr. Pascual believes it's possible to fix the RBC mitochondria pipeline, stop the overproduction of type I interferons and, thereby reduce disease activity in patients carrying abnormal RBCs. *“Our findings support the idea that we need to separate patients according to the dysregulated pathways that lead to increased interferon production,”* said Dr. Pascual.

She went on to graciously acknowledge the critical role the Lupus Research Alliance played in the success of her investigation: *“Thanks to the funding support from the LRA, we identified a new defective pathway, which could help us classify lupus patients more effectively. We hope this discovery will also lead to new modalities of treatment for lupus and other autoimmune diseases.”*



Dr. Virginia Pascual

Dr. Simone Caielli

In 2017, Dr. Pascual was the recipient of the **LRA's Lupus Insight Prize**, which recognizes major, recent breakthroughs in lupus research. Dr. Caielli is the current recipient of the LRA's **Lupus Innovation Award**, which provides support for high-risk, high-reward approaches to major challenges in lupus research.

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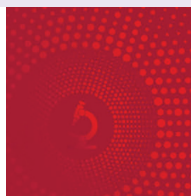
NEW GRANT MECHANISM SEEKS ADVANCES IN LUPUS HETEROGENEITY

The LRA's new grant mechanism—**The Global Team Science Award (GTSA)**—will support interdisciplinary, collaborative, and highly synergistic projects that push the boundaries of innovation, bridging research and clinical efforts in lupus.

GTSA will focus on unraveling human lupus heterogeneity by applying cutting-edge technologies to address critical questions that could bring about breakthroughs in lupus care, research, or drug development.

The recipients of this year's GTSA awards are **Virginia Pascual, MD** and **Ignacio Sanz, MD**. You can read more about their previously supported LRA research in the main articles on pages 1 and 2.

GLOBAL TEAM
SCIENCE AWARD



Finding Key Answers Through Clinical Research

Why does lupus affect women more than men? Why are Black women more susceptible? Why are there such highly individualized, multiple, and varied symptoms of this heterogeneous disease?

These are some of the questions that **Ignacio Sanz, MD** is looking to answer with a grant from the LRA—and he will be concentrating on the diversity that is particularly prominent within immune cells called B cells and plasma cells (PC).

"These cells are responsible for the generation of antibodies that ultimately attack the patient's organs in lupus," said Dr. Sanz. "We found that lupus B cell signature is particularly accentuated in Black patients with severe disease, but there are still major gaps in knowledge to understand the different types of lupus."

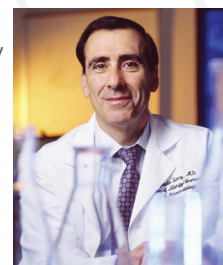
Dr. Sanz's goal is to understand how different types of B cells and PCs contribute to clinical heterogeneity in Black patients with SLE. Heterogeneity is key because it points to the complexity of lupus ... its many possible triggers ... and the need to target the underlying disease pathways specific to each patient.

Working with a cohort of Black patients who receive care at Emory

University, the University of Alabama at Birmingham, and the Medical University of South Carolina, Dr. Sanz has three objectives.

He seeks to **1)** determine the precise contribution of various B cells and PCs to the clinical heterogeneity of lupus, **2)** establish B cells and PCs as biomarkers of different manifestations of disease, and **3)** identify new pathways for treatment.

Dr. Sanz is a leading authority on lupus and the LRA has recognized his extraordinary contributions to research.

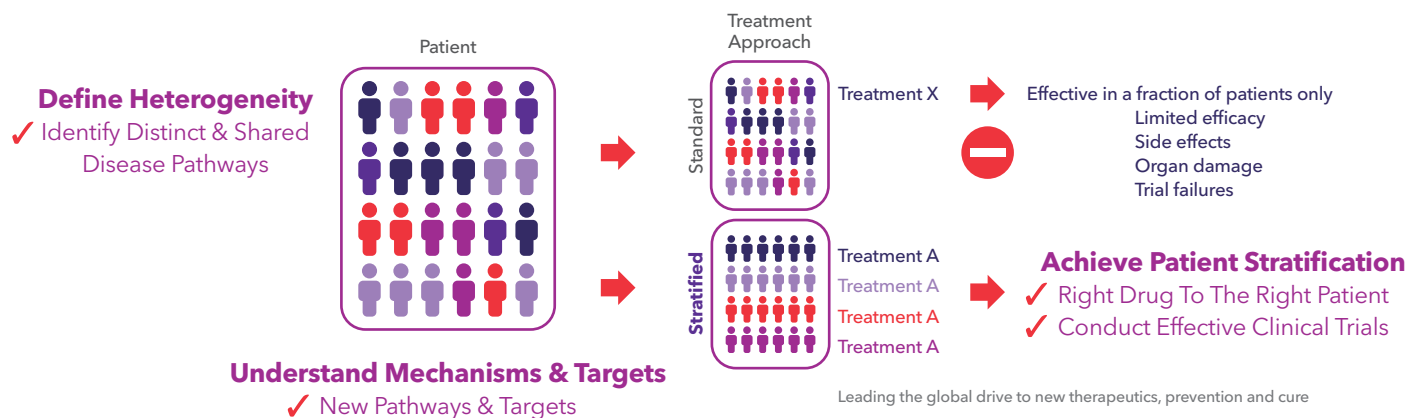


Dr. Ignacio Sanz

Dr. Sanz was awarded the LRA's **2019 Lupus Insight Prize** and our **2020 William E. Paul Distinguished Innovator Award in Lupus and Autoimmunity**.

Dr. Ignacio Sanz serves as Mason I. Lowance Professor of Medicine and Pediatrics and Chief, Division of Rheumatology, Department of Medicine at Emory University School of Medicine as well as Director of The Lowance Center for Human Immunology at the Emory University/Children's Health Care of Atlanta.

DEFINING HETEROGENEITY WILL REVOLUTIONIZE LUPUS THERAPIES



Two Stories of Resilience and Hope

One Family ... Twice Impacted by Lupus

—When **Michelle Lederman** was diagnosed with lupus in 2007—it came as a complete surprise because she showed no signs. They wouldn't appear until 11 years later.

That's when she was seeing a neurologist for severe headaches, an orthopedist for joint pain, and a dermatologist for a continuously red face.

When Michelle's dermatologist mentioned her face looked like a lupus butterfly rash, everything clicked. *I was lucky,* she said. *"My symptoms are managed, and I have no major organ damage."*

But Michelle's second brush with lupus came as an absolute shock.

*"At the end of 2020, which was an already horrible year, my son, **James**, was diagnosed with lupus nephritis,"* shared Michelle. James

would spend the week of his 15th birthday undergoing his first round of chemotherapy. *"The nephritis caused some permanent kidney damage, but fortunately we caught it early,"* Michelle said with relief.

This mom, author, and speaker wasted no time in learning all she could about the disease. *"The exact cause of lupus is unknown, and it is very difficult to diagnose,"* Michelle shared online. *"That's where the LRA is bridging the gap."*

And in the short months from James' diagnosis to today, Michelle has become a great fundraiser for the LRA—raising \$18,000 through her **2021 ManyOneCan. Walk with Us to Cure Lupus** fundraising page.



A Legacy Donor ... with a Heart of Gold

—There is nothing cliché about about describing **Barbara Abrams** as a lupus warrior with a "heart of gold."

She's a straightshooter who possesses an uncanny ability to be honest and true to herself. Being able to face difficult situations came in mighty handy when she was diagnosed with lupus shortly after she left Jacksonville, FL, for New York City. At the time, Barbara was barely 20.

"I felt that I had to make it. I simply had to. I was in extreme pain—and I was extremely determined to find answers," Barbara said reflecting on that time just after diagnosis.

Fortunately, Barbara found the SLE Lupus Foundation, which merged with the Alliance for Lupus Research to form the LRA. *"I felt like Dorothy*

clicking her heels. I found home—a place where other people felt like me," she enthused. *"I found this organization and never left. It is the love of my life!"*

It shouldn't surprise anyone that Barbara is a loyal donor to the LRA—but recently she made the decision to increase her commitment by leaving the organization a legacy gift. By including the LRA in her estate plans, Barbara took a major step to secure the future of the LRA and critical scientific investigations designed to find answers for everyone in her shoes.

Barbara's reason for looking out for the LRA is heartfelt.

"The people in this organization make me feel that I matter—that I am loved. They are conducting the world's best lupus research for me, and others like me," Barbara said. *"How could I not want to do my best—when they are giving it their all?"*



DEEPEST GRATITUDE FOR THE TRUEST OF FRIENDS

A very big, heartfelt thanks goes to our friends at the **Lupus and Allied Diseases Association, Inc. (LADA)** for their recent generous donation of \$120,000.

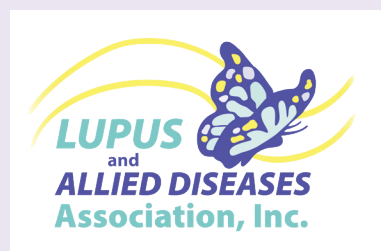


LADA President & CEO **Kathleen A. Arntsen** and Secretary **David L. Arntsen** presented the check August 19 during their 21st Annual Lupus Charity Golf Classic to staff members Jonathan Marks, Dorey Neilinger, and Albert Roy.

Over the past 20 years, LADA has funded LRA research with gifts totaling more than \$830,000!

"Beyond their steadfast show of support, everyone at LADA—and Kathleen, in particular—have been true allies to our organization and our pursuit of science," said **Andrea O'Neill**, Executive Director of the LRA. *"Always eager to lend a hand, Kathleen has frequently opened up about her own lupus in an effort to help others coping with the disease."*

Thank you, LADA! And thank you, Kathleen!

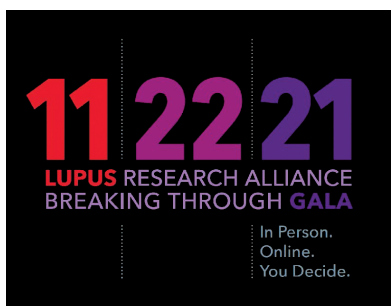


LRA in Action

Gala—Save the Date!

This year's **Breaking Through Gala** will take place in person and online the evening of Monday, November 22, 2021. Join us in NYC at the Ziegfeld Ballroom or watch our live broadcast. Either way you can support promising research that is breaking through the complexity of lupus to find the cure.

Featuring inspiring speakers and star-studded performances, the event will honor LRA Board Member and extraordinary lupus champion, **Nadeem Meghji**, Senior Managing Director, Head of Real Estate Americas at **Blackstone**.



Visit lupusresearch.org to make a donation, learn more about lupus and our funded lupus research, or find out about our *Walk with Us to Cure Lupus* program.



ManyOne Can.
walk WITH US
TO CURE LUPUS

100% of all donations goes to support lupus research programs because the Lupus Research Alliance Board of Directors funds all administrative and fundraising costs.

For the latest, up-to-date information about lupus you can join our online community on:



Calling Upon Federal Employees

Federal Government employees have a special chance to help transform the lives of people with lupus by contributing through the **Combined Federal Campaign**. Each year, thousands of federal employees pledge tens of millions of dollars to worthy causes including ours.

Please make your commitment by choosing the Lupus Research Alliance—**CFC #37283**—as the recipient of your CFC pledge!



CFC
#37283

Celebrating Walk Day, Every Way!

October 2nd was truly a day of celebration—that's when thousands turned out in support of LRA research programs at the New York, New Jersey, and individual virtual **ManyOneCan**.

Walk with US to Cure Lupus events.

Using the latest simulation technology, the Walk Day motivated participants with inspirational speakers and interactive activities, while encouraging everyone to walk—however they felt comfortable.

For more information on these successful events, please visit www.lupusresearch.org



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