

Exploring Complexities of Cell Death As a Trigger for Lupus

The innovative work of **Douglas Green, PhD**, St. Jude Children’s Research Hospital, probes the minute inner workings of the world of cells: their functions, their deaths — and their inextricable link to lupus.

Every day billions of cells die within the human body. The balance between cell survival and cell death is crucial to all of the body’s intricate systems. Nowhere is this equilibrium more critical than the immune system.

Cells called macrophages (big eaters) do the important job of eating and digesting dead cells — essentially removing debris from the body — in a process called phagocytosis. Much like the way amoebas eat, macrophages completely engulf the dead cells into a little vesicle — a sort of bubble inside the cell.

But the death of human cells is far more complex than this.

In the 1990s scientists made a key observation. They discovered that a process where a cell removes bits of itself as a source of energy, and as a way to clean up cell damage. *“This is the process of autophagy,”* said Dr. Green. *“It is a self-eating process.”*

Why is this crucial? Dr. Green revealed the connection: *“Part of the reason why this is so significant is that a lot of diseases — including lupus — have been linked to polymorphisms, differences in the genes, for proteins in that autophagy pathway.”*

With Lupus Research Alliance funding, Dr. Green and his team have explored a new pathway that involves some of the same autophagy surface molecules. *“We started studying it,*

and using genetic manipulations we were able to remove this process we called LC3-associated phagocytosis (LAP),” shared Dr. Green.

In murine models, animals developed human-like lupus when Dr. Green removed LAP. The implications of this discovery are weighty. In the 1950s, a cell that contains an undigested cell, the LE cell, was discovered as a marker for lupus but the connection was unknown.

Dr. Green’s work may be that connection. When there are defects in LAP, dying cells are eaten but are not digested. This may be a significant link to lupus.

Going forward, Dr. Green’s investigation will focus on how to manipulate LAP in cells — how to change the tendency of a cell to engage LAP or not, depending on the setting.

Learning more about LAP may help prevent lupus and develop ways to restore the control of cells with LAP defects. Dr. Green’s exciting study may help pave the way to novel treatment strategies for lupus.

In talking about his relationship with the Lupus Research Alliance, Dr. Green has nothing but praise for the organization and the individuals who support it.

“Scientists are passionate about making discoveries and applying them to human disease,” said Dr. Green. *“And the Lupus Research Alliance enables us to bring our ideas to fruition. It allows us to move forward.”*

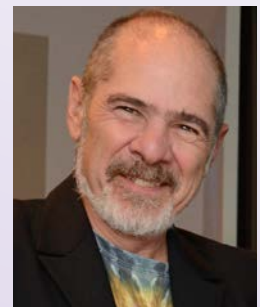
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Dr. Douglas Green

Dr. Green is the Peter C. Doherty Endowed Chair of Immunology at St. Jude Children’s Research Hospital and a grant awardee of the Lupus Research Alliance.

After receiving his PhD from Yale University, Dr. Green has focused his career on the processes of active cell death and cell survival. This work began with his discovery of activation-induced apoptosis in T lymphocytes, the role of c-Myc in this process, and the finding that Bcl-2 cooperates with Myc in oncogenesis by blocking apoptosis. These are themes that he continues to study.

More recently, Dr. Green discovered the process of LC3-associated phagocytosis, which links the autophagy pathway to phagosome maturation.

Dr. Gerald Nepom Bringing Expertise and a Fresh Perspective

The future of the Lupus Research Alliance is bright with **Dr. Gerald Nepom, MD, PhD**, in the critical role of Co-Chair of our Scientific Advisory Board.

Over the past three decades, his work has focused on the underlying principles of autoimmunity, biomarkers, and therapy for autoimmune diseases.

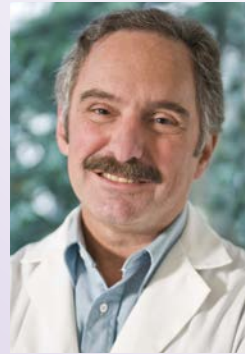
In the 1980s, Dr. Nepom was a major player in outlining the immunogenetics (the relationship between the immune system and genetics) of autoimmune disease. He concentrated mostly on identifying the structure and function of key cells. Later, his lab focused on the structure/function actions, in order to discover what these genes do and how to control the T cell response.

This work led Dr. Nepom to think about ways to modify and manipulate the T cell response. Currently, Dr. Nepom runs the Immune Tolerance Network, a collaborative network for clinical research funded by the National Institute of Allergy and Infectious Diseases, a part of the National Institutes of Health.

To this end, Dr. Nepom is looking at the ability of lymphocytes to sense their environment. *“They run around the body and look for dangers, damage, and infectious challenges. They also communicate in their environment what they have figured out,”* explains Dr. Nepom. *“The crux of my work has sought to understand the signals that T cells sense what they do with that information ... and how they communicate that information to the neighboring cells — whether there is a real threat or a false alarm.”*

But Dr. Nepom’s work doesn’t stop there. He has already had success in modulating the T cell response in other autoimmune diseases. Now, he is investigating that option for lupus.

Dr. Nepom received his bachelor’s degree in Biochemistry from Harvard in 1972 and doctorates from the University of Washington, receiving his PhD in Biochemistry in 1977 and his MD in 1978. After post-doctoral work in immunogenetics in the Department of Pathology at Harvard Medical School, he returned to Seattle to join the Fred Hutchinson Cancer Research Center and the University of Washington Medical School Faculty in 1982.



Dr. Gerald Nepom

Since 1985 he has been a Member of the Benaroya Research Institute at Virginia Mason (BRI) and served as Director of BRI from 1985 through 2015. In 2010, Dr. Nepom also became Director of the Immune Tolerance Network (ITN), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).

In speaking about his Co-Chair, Dr. Mary (Peggy) Crow, Dr. Nepom could not be more collegial. *“Peggy is a real pro, and the two of us cover the bases quite well. She has unrivaled experience in direct patient care, which complements my research and clinical trial experience.”*

Dr. Nepom will play a crucial role in helping the Lupus Research Alliance navigate the constantly evolving landscape of lupus research.

“In reviewing the proposals of grant candidates, Jerry’s knowledge will help us avoid duplication, false starts, and blind alleys,” said Kenneth M. Farber, Co-President of the Lupus Research Alliance. *“Having someone on board with such vast experience will greatly help our organization speed the process of discovery.”*

Supports Science in Style Luncheon Honors Two Lupus Warriors

They showed style. They showed grace. But more important, attendees of the **8th annual Lupus Handbag Luncheon and Silent Auction** showed awe for Women of Achievement honorees **Claudia Cividino** and **Alison Lee**.

Alison began battling lupus as a teenager. She worked in marketing for the beauty industry until, after enduring a lupus-related kidney transplant and cancer triggered by the transplant drugs, she realized that her health had become her full-time job.

With her cancer gone and her lupus at bay, she is deeply grateful and reflective. *“I’m recognizing that achievement comes in different forms,”* Alison says. *“I may not have built a career or have a fancy title, but I’ve fought and I’m continuing to fight a battle against lupus.”*

Our second Woman of Achievement, Claudia Cividino, oversees operations in the U.S., Canada, and South America for Bally, the 165-year Swiss luxury brand for footwear, fashion, and accessories.

Claudia, an active lupus advocate, revealed at the luncheon what she had long hidden from her colleagues



Women of Achievement honorees Claudia Cividino, Alison Lee

— she too suffers from lupus.

“Thanks go to the Lupus Research Alliance for creating a place where people with lupus go for hope,” Claudia says, *“the hope that lies in the innovative research that will deliver better, safer treatments, and a way to cure and even prevent this disease.”*

Held at the Plaza Hotel in New York City on April 4, 2017, the event was co-chaired by Matilda Raffa Cuomo, Former First Lady of New York State and Founder/Chair of Mentoring USA; opera legend Jessye Norman; and Brett Heyman, founder/designer for the home and fashion company, Edie Parker.

And in her role as Mistress of Ceremonies, Emmy-winning TV newscaster, Brenda Blackmon touched those in attendance with a personal account of her own daughter’s struggle with lupus.

More than 400 prominent women and men from New York’s fashion, society, entertainment, philanthropic and lupus communities, raised crucial funds for lupus research — inspired in no small part by a silent auction of designer handbags.

With such a tour de force, defeating lupus is in the bag!



A bag by Bally as part of the Silent Auction

Meet the Awardees

The Lupus Research Alliance is delighted to announce the recipients of our Novel Research Grants.

These ten grantees continue a tradition of bold and innovative research that aims to discover safe, effective treatments and a cure for lupus

This grant mechanism allows new visions for lupus research and diagnosis — as demonstrated by these innovative investigations — to flourish.

Here are the 2017 Novel Research Grantees:

Mridu Acharya, PhD

Benaroya Research Institute at Virginia Mason
Dr. Acharya is investigating the inactivity of B cell-blocking proteins in lupus.

Shaun Jackson, MD, PhD

Seattle Children’s Hospital
Dr. Jackson is taking a deeper look at molecules that may promote immune system attacks.

Christian Lood, PhD

University of Washington
Dr. Lood is investigating possible links between improper disposal of cell mitochondria and excess lupus inflammation.

Zhiqiang Zhang, PhD

The Methodist Hospital Research Institute
Dr. Zhang is studying connections between APEX1 and overstimulation of defensive immune cells.

Guo-Ping Shi, DSc

Brigham and Women’s Hospital
Dr. Shi is developing a new treatment approach to maintain proper immune system control functions of T cells.

Natalia Giltiy, PhD

University of Washington
Dr. Giltiy is exploring how to retrain the immune system to stop its overreaction to normal body cells.

Anthony Rongvaux, PhD

Fred Hutchinson Cancer Research Center
Dr. Rongvaux is pursuing a possible lupus treatment that focuses on proteins that block the causes of lupus.

Vipin Kumar, PhD

University of California, San Diego
Dr. Kumar is examining a tropical parasite drug as a possible medication for lupus-related kidney damage.

John Zhang, DVM, PhD

Medical University of South Carolina
Dr. Zhang seeks to find a novel use for topotecan as a lupus therapeutic.

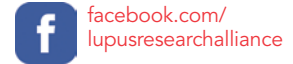
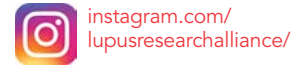
Andrea Knight, MD

The Children’s Hospital of Philadelphia
Dr. Knight is looking into more effective diagnosis of neuropsychiatric disorders in pediatric patients, such as those suffering from lupus.

Lupus News Corner



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



Plungers Freeze Out Lupus

Brrrrrrrr ... In mid-February, 200 friends, family, and co-workers of people affected by lupus plunged into the frigid Atlantic Ocean at Asbury Park, NJ to increase lupus awareness and raise money for lupus research.

They were freezing cold but their fundraising was red-hot: The **Lupus Research Alliance's first annual Plunge to Freeze Out Lupus** raised thousands to support research!

We want to thank all of our Plungers, Plunge Cheerleaders, Volunteers, Sponsors, and In-kind donors for helping to make the event such a success. To help us plan next year's Plunge, please email Sheri Kirkpatrick at skirkpatrick@lupusresearch.org



Lupus Research Alliance's Plunge to Freeze Out Lupus



Because our Board of Directors funds all fundraising and administrative costs, 100% of donations received support lupus research programs.

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WILLIE COLON GOLF OUTING

BENEFITING THE



LUPUS RESEARCH ALLIANCE

JEAN DAVIS RESEARCH GRANT

Willie Colon Tees-Off for Lupus

Fore! **The Third Annual Willie Colon Golf Outing** benefiting the Lupus Research Alliance and the Jean Davis Research Grant raised \$XXX crucial funds for lupus research programs—while increasing awareness of the disease.

Held at the Somerset Hill Country Club in Bernardsville, NJ, the outing is the premier golf event in the New York Metro Area — bringing together leaders from finance, banking and Major League Football.