RACE TO ERASE MS

Content
2018

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25th Anniversary, Race to Erase MS

Siedah Garrett leading Finale "Lean on Me"

Elle King

Flo Rida

On Friday, April 20th, Multiple Sclerosis (MS) advocate and Center Without Walls founder, Nancy Davis, welcomed guests to the Beverly Hilton for its historic 25th Anniversary Race to Erase MS Gala. The event raised over $1.7 million to benefit the Race to Erase MS and its Center Without Walls program, a collaboration of top MS research centers working together as a team on ground-breaking research with the goal of treating and, ultimately, finding a cure for MS.

Host Scott Rogowsky (HQ Trivia) welcomed guests to the event and introduced the Fall 2018 runway show from Hollywood-favorite fashion brand alice + olivia by Stacey Bendet. The looks were showcased by a variety of models and actors, including Victoria Justice, Serayah, Paris Sanders, Francesa Capaldi, and Ajiona Alexus. Race to Erase MS founder Nancy Davis took the stage next, thanking guests for being in the room to celebrate the momentous 25th Anniversary Gala. She shared a special video highlighting the incredible accomplishments of the organization over the past quarter century, including raising over $47 million for the Center Without Walls program.

Peter Facinelli introduced the first performer of the evening, Grammy Award-nominated artist Elle King, who had the crowd on their feet with her hit song "Ex's & Oh's" and a cover of Tom Petty's "American Girl." Brother and sister duo Kelly

(GALA continued on Page 14)

American Academy of Neurology
2018 Conference Recap By Erin Longbrake, MD, PHD, Yale

The 2018 AAN meeting was held in Los Angeles April 21-27, 2018. Highlights of the meeting included the emergence of neurofilament light chain (NfL) as a promising new biomarker for disease activity and effectiveness of treatments. Other highlights were updates on B-cell therapies for MS and on therapies for progressive MS that are in development.

Neurofilament light chain: a new biomarker for MS? For decades, clinicians and researchers have recognized the need for an easily tested biomarker to monitor whether patients with MS are responding to treatment or not. Now, neurofilament light chain (NfL) is emerging as an exciting new candidate biomarker. Neurofilament is a protein expressed by neurons, which is released into the spinal fluid and the blood when the nerve cells are damaged. New technology has allowed NF-L to be detected in the blood, as opposed to the spinal fluid, and this makes it much more feasible to routinely use this biomarker for MS research and in clinical practice. Numerous posters and platform talks at AAN centered on whether NfL could be used to help monitor the severity of MS and to determine whether medications are being effective. The data demonstrated that NfL levels correlated with the number of enhancing brain lesions on MRI as well as with numerous other metrics including clinical disability and brain atrophy. Blood levels of NfL were reduced in response to many types of disease modifying therapies, including both established medications (natalizumab, ocrelizumab, fingolimod) and new medications under development (siponimod, ozanimod).

B-cell therapies for MS: Last year, the MS community was re-energized by the groundbreaking disease modifying therapy ocrelizumab, which was approved by the FDA in March, 2017. Ocrelizumab depletes one type of circulating immune cell, called B-cells. At this year's AAN

(AAN continued on Page 14)

Message from Nancy Davis

President and Founder

2018 marks the 25th year of our Race to Erase MS, our silver anniversary. What an amazing milestone we all have reached together as a team. I feel so blessed to know so many incredible role models and supporters and have each and every one of you as an empowering and important piece of this intricate puzzle that is truly finding a cure for Multiple Sclerosis. What started out 25 years ago as the "impossible dream" has materialized into a reality which is no longer a dream.

When we started this journey 25 years ago, I was newly diagnosed with MS. I was a young mom with three young sons feeling very alone and scared. I was told I would never walk again and the most I would get to look forward to in my life was operating the remote control on my TV. There was no known cause, no drugs on the market, and literally no hope. Through much soul searching, I came up with my impossible dream, The Center Without Walls.

Today, we have seven of the best MS centers in the country who work together as a team from Harvard, Yale, Johns Hopkins, USC, UC San Francisco, Oregon Health Science University and Cedars-Sinai. They are the best and brightest minds in MS research who follow our motto of constantly communicating and never duplicating research to develop the next generation of treatments for MS as well as training the next generation of researchers.

We are committed to our mission to fund research grants to Young Investigators as we strive to support the most highly advanced and most innovative research to lead us to a cure for MS. Ground-breaking basic science is at the heart of our Young Investigator program.

Thank you to everyone who has supported our mission for 25 years. Thank you for 15 therapies, for hope and tomorrow a cure for MS.

Peace and Love,

Nancy Davis

RACE TO ERASE MS

Scientific Advisory Board

Dr. Andrew Goodman joins our stellar review team to help lead us to finding a cure for multiple sclerosis!

We are thrilled and honored to welcome Dr. Andrew Goodman to our prestigious Center Without Walls Scientific Advisory Board (SAB). Dr. Henry McFarland, Dr. Monica Carson, Dr. Anne Cross and Dr. Daniel Reich are truly the most stellar team of brilliant minds who will continue to lead our foundation in supporting ground breaking research initiatives.

We congratulate our team on helping to break down barriers and create excellent communication with no duplication of basic science research, bringing us one step closer to finding a cure. We are so appreciative of our brilliant doctors who will continue to lead our foundation in funding only the highest quality of research to expedite our mission to Erase MS.

Andrew D. Goodman, MD is Professor of Neurology, Chief of the Neuroimmunology Division, and Director of the Multiple Sclerosis Center at the University of Rochester. He completed a research fellowship in the Neuroimmunology Branch at the National Institutes of Health, Bethesda, Maryland under the mentorship of Drs. Dale McFarlin and Henry McFarland. Dr. Goodman's interests include clinical and experimental therapeutics research. Visit our website to read Dr. Goodman's most impressive and extensive biography.

ALEX AND ANI®

With the start of summer, there's always a reason to celebrate! ALEX AND ANI has donated over $1.2 million to Race to Erase MS, helping to support 16 research grants though our Center Without Walls program. Every day we move closer to finding a cure for MS.

Thank you to this incredible company and their founder, Carolyn Rafaelian, for supporting our quest to find a cure for multiple sclerosis.

Our Cupcake charm bangle that exclusively benefits Race to Erase MS can be purchased at alexandani.com/cupcake-charm-bangle-cbd17ccsg.html. ALEX AND ANI will donate 20% of the purchase price with a minimum donation of $25,000 between January 2018 and December 2018!

25 Years of Racing to Erase MS

Center Without Walls program accomplishments

The Race to Erase MS was founded in 1993 and over the last two decades our esteemed Center Without Walls program has been involved in many of the cutting-edge discoveries in the MS field in the last 25 years. We are now so much closer to putting most relapsing patients into long-term remissions and starting to develop real therapies for people with progressive MS.

The brilliant team of doctors representing the Center Without Walls program have broken down scientific barriers and made incredible discoveries in MS. The foundation's core focus is funding Young Investigator Awards ($75,000 each) and Innovation Awards ($75,000 each). Race to Erase MS is the only foundation that actively supports Young Investigators. We are the niche leader in funding these promising young investigators during the critical time of their career, developing their independent research programs and keeping them in the MS research sector. Without the Race to Erase MS Young Investigator award, these doctors would likely leave MS research and pursue a private practice. The program also creates a collaborative environment to interact with senior investigators.

Our strategy is to fund important studies at the basic science level when they are just an idea or in their infancy. When they show promise or efficacy, drug companies come in and take this research all the way to getting FDA approval. Our program has been able to foster research on several approved drugs for MS including Ocrevus, Tecfidera, Gilenya, Tysabri, Copaxone, Rebif, Avonex, Betaseron, and Novantrone. The Center Without Walls scientific contributions have helped bring these drugs to the market but have also identified how these drugs work, in order to maximize their benefit.

Our foundation makes a huge impact in the research arena by supporting innovative research projects that would not ordinarily receive funding through government or other foundation sources. We create opportunity for daring projects to come to life, out of the box concepts, that could potentially lead to a cure. The Race to Erase MS Center Without Walls program fosters a collaborative research community among the 7 participating academic institutions which are MS centers of excellence. Scientists share their research results within the program to accelerate progress and have expeditated discoveries because of this unique platform of team work. Ground-breaking concepts have germinated through the program and ultimately made it to patients to improve their lives. Some of these include:

•We have identified the genes that can make someone susceptible to developing MS. We know now that there are over 200 genes. This knowledge should lead us to developing new treatments to prevent MS.
•Low vitamin D levels and diet can influence the likelihood of developing MS. 25 years ago no one believed that lifestyle affected the course of this disease, which we now know is not true.
•Responsible for the NAIMS project which is the internationally renowned Imaging program. This brings together MRI MS researchers from multiple academic research programs. This is the only definitive tool to diagnose and treat MS.

We are proud of the tremendous strides that have been accomplished in our Race to Erase MS and the advances that have been made towards finding a cure. We thank everyone who has supported our vision and to all those who "race" with us in unwavering generosity in our journey to find a cure for MS. There are now 15 drugs with FDA approval to help stop the progression of MS and more on the horizon. The future is bright for the person being diagnosed today with multiple sclerosis.

WE RUN THE GROVE

for Race to Erase MS - June 3, 2018

The Grove and Race to Erase MS hosted its 3rd Annual WE RUN THE GROVE 13.1 mile run, 10K and 5K with charity partner Race to Erase MS on Sunday, June 3rd. The morning was kicked-off with an enthusiastic warm up sponsored by Nike.

Race to Erase MS founder Nancy Davis welcomed runners at the start line and then introduced Honorary Chair Lauren Paul who inspired the crowd before the run. Lauren's father Tom was diagnosed with MS 13 years ago and she spoke of his tremendous spirit and determination to not let MS define his life.

Siedah Garrett, Nancy Davis, Lauren Paul, Tom Parsekian

Grammy award winning songwriter Siedah Garrett sang the National Anthem. Just last year, at our 24th Gala event, Siedah announced for the first time to the world that she herself has been battling MS.

Runners and walkers took off down First Street in a staggered start and proceeded to run/walk the local streets, wearing The Grove branded tees. Race to Erase MS dedicated supporter Matt Rosler captured the event through our Facebook Live for everyone in the world to enjoy. Runners returned through a balloon arch near the trolley barn and enjoyed an after-party in The Park with a health expo, treats, music and a photo opportunity. Thank you to our water sponsor Core Hydration and to our photo sponsor, The Green Screen. Thank you to all of our vendors; doTerra, Kind, Noosa Yoghurt, Organic Valley, Pasta Chips, RX Bars, Vita Coco. We are thrilled to be partnering once again with "We Run The Grove" for a spectacular morning of inspiration and health.


Left to Right: Siedah Garrett joins the Nike warm up; Runners get ready at the start line; Lauren Paul welcomes participants with Nancy Davis and Siedah Garrett; Everyone is off on the course!

RACE TO ERASE MS

CENTER WITHOUT WALLS
Collaborating Physicians

Dr. Katerina Akassoglou, UCSF
Dr. Lilyana Amezcua, USC
Dr. Lisa Barcellos, UCSF/Berkeley
Dr. Dennis N. Bourdette, OSHU
Dr. Peter A. Calabresi, Johns Hopkins
Dr. Rob Bakshi, Harvard
Dr. Michele Cameron, OHSU
Dr. Tanuia Chitnis, Harvard
Dr. Margarita Dominguez-Villar, Yale
Dr. Ben Emery, OHSU
Dr. Wendy Gilmore, USC
Dr. Jennifer Graves, UCSF
Dr. David Hafler, Yale
Dr. Roland Henry, UCSF
Dr. Adam Kaplin, Johns Hopkins
Dr. Eve Kelland, USC
Dr. Vijay Kochroo, Harvard
Dr. Brett Lund, USC
Dr. Kelly Monk, OHSU
Dr. Ellen Mowry, Johns Hopkins
Dr. Gopal Murugaiyan, Harvard
Dr. Kevin O'Connor, Yale
Dr. Dan Ontaneda, NAIMS Project
Dr. Daniel Pelletier, USC
Dr. Samuel Pleasure, UCSF
Dr. William Rooney, OHSU
Dr. Nancy Sicotte, Cedars-Sinai
Dr. Jack Simon, OHSU
Dr. Rebecca Spain, OHSU
Dr. VJ Yadav, OHSU
Dr. Emmanuelle Waubant, UCSF
Dr. Howard Weiner, Harvard
Dr. Leslie Weiner, USC
Dr. Katie Whartenby, Johns Hopkins
Dr. Don Zack, Johns Hopkins
Dr. Scott Zamvil, UCSF

2018-2019 Young Investigators
Dr. Michael Kornberg, Johns Hopkins
Dr. Erin Longbrake, Yale
Dr. Nikolaos Patsopoulos, Harvard

Project Update

By Dr. Nancy Sicotte, Cedars-Sinai

NAIMS
North American Imaging in MS Cooperative

Meetings: The 10th NAIMS meeting was held in February 2018. A full day workshop entitled "Deep Gray Matter Injury in MS" took place at the Hilton Bayside Hotel in San Diego, CA. A group of international experts in the fields of immunology, neuroimaging, informatics and statistics presented their latest updates in a highly informative and productive meeting led by Drs. Christina Azevedo and Daniel Ontaneda. The proceedings of this meeting will be published in the coming months. Four more sites (UTSW, Univ of Maryland, Univ of Pittsburgh, UC Irvine) were approved for NAIMS membership, bringing our current total to 31 centers in the US and Canada.

Grants/Projects: Thanks to the generosity of the Race To Erase MS contributors, we are now able to expand the pilot study to validate the Central Vein Sign (CVS) from 6 to 10 sites, and to increase enrollment to 100 subjects. The findings from this study will be critical in establishing the usefulness of a new type of MRI scan that will allow an earlier and more accurate MS diagnosis. Plans are underway to use the pilot study data to obtain funding for a definitive study to establish the role of CVS in MS diagnosis. NAIMS is working with MRI scanner manufacturers to incorporate the software for CVS in all scanners in the future.

Manuscripts: A total of 5 manuscripts from the NAIMS cooperative have been published, one is submitted and one is in preparation.

Upcoming events in October 2018: The NAIMS cooperative will join our European counterparts in Berlin, Germany for the second joint NAIMS/MAGNIMS social hour. The first event was a great success and forged new projects and collaborations. We are looking forward to another exciting and productive year ahead!

What is NAIMS? The North American Imaging in Multiple Sclerosis Cooperative (NAIMS) was established in 2012 with the support of the Race to Erase MS. The goals of the NAIMS group are to: (1) develop reliable imaging-based measures for disease-progression in multiple sclerosis (MS); (2) accelerate the pace of MS research in North America by creating standardized imaging protocols for use in clinical research; and (3) bring together a range of imaging expertise focusing on the study of MS.

Uncovering Myelin

By Jennifer Orthmann Murphy, Johns Hopkins

Myelin, a specialized structure formed by oligodendrocytes in the brain, wraps around the output portion of neurons (or "axons") providing insulation, protection, and support to the neuron so that it may send signals to other neurons throughout the brain and body.

The goal of this project was to determine whether life experience could change myelin. We used a cutting-edge technique called in vivo two-photon microscopy, which is an approach that allows for long-term monitoring of living cells, and their individual features, in the intact brain. We studied the cortex of the brain, an area that contains more neurons than oligodendrocytes and myelin. In particular, we examined the area that receives whisker sensory information, called the barrel cortex. We found that new oligodendrocytes were born over the full course of an animals' life, with half of the population of cells born after early adulthood. The oligodendrocyte precursor cells, which normally populate the adult brain and are a natural source of new oligodendrocytes, are able to make new oligodendrocytes well past "middle-age" in a mouse. However, we also found that most of the precursor cells that attempt to change into oligodendrocytes do not survive. The new oligodendrocytes that are successfully formed in the cortex are highly stable, and their myelin sheaths rarely change once established. Interestingly, we found that, even in aging mice, there are long stretches of axon "cables" without myelin, indicating that intermittent myelination is an important feature of cortical neurons, but we do not yet know why these sparse bits of myelin are required by neurons.

Last, we tested how constant whisker stimulation might affect oligodendrocytes and myelin in the barrel cortex. We found that mice exposed to hanging beads for 3 weeks had a dramatic increase in the production of new oligodendrocytes, together forming hundreds of new myelin sheaths. This "sensory enrichment" experiment demonstrates that changes in life experience can change how much myelin is present in neuronal circuits. Therefore, even in what may be considered a "mature" brain, myelination patterns are still flexible and subject to change. In addition, the low probability of new oligodendrocytes being successfully made by the precursor cells suggests that in order to develop effective remyelination therapies, we must better understand the mechanisms that stabilize these cells attempting to become mature oligodendrocytes. Dr. Orthmann-Murphy is addressing the mechanisms of remyelination in her current project, environmental factors.

photo gallery: 2017 Annual Race to Erase MS


Kenny, Mariella and Isabella Rickel with Nancy Davis


Stacy Bendet and Nancy Davis


Kelly and Jack Osbourne

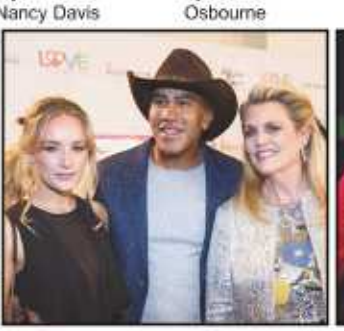

Aaron and Lauren Paul


alice + olivia Fall collection preview


Nancy Davis and Avril Lavigne


Elle King


Greg Phillinganes and Randy Jackson


Lara Sebastian with Bill Perkins and Nancy Davis


Flo Rida


Jerry and Tawny Sanders, Guest and Kelly Day


Victoria Justice


Kathy and Rick Hilton


Scott Rogowsky, Nancy Davis, Lance Bass, Siedah Garrett


Guests with Pouneh Amini, Deb MacMillan, Lynn Palmer and Brandy Navarre


Peter Facinelli and Guest


David Yocum, Laura and David McKenzie, Nicole Yocum


Nancy Davis, Guest and Frances Fisher, Nile Rodgers


Paul and Lynn Palmer


Heather Boschke, Heather Hall, Mark Locks, Bob Rosenblatt, Nancy Davis, Mishawn Ring, Matthew Lubkeman, Brenda Richie


Debbie and Jimmy Lustig


Mason and Camille Grammer with Derek Warburton


Casey Kramer, Cammy MacMillan and Steve Ponce


Richard and Karen Levine


Brenda Richie, La Toya Jackson, Nancy Davis, Lynn Palmer, Marcy Taub


Melissa Beyeler, Lou Elsey, Julie Finnerty, Beth Preece, Silvia Baker, Robin Correll, Debra Eaton, Sherry Corday, Judy Angel, Debbie Abascal


Logan Browning

Jason, Nancy
and Brandon Davis

Lance Bass
and Randy Jackson

Nancy Davis, Ken Rickel,
Richard and James Lovett

Paris Sanders
alice + olivia

Vanna White
and John Donaldson

La Toya Jackson, Flo Rida,
Nancy Davis

Barbara Davis
and Maureen McCormick

Ron Rosenbloom, Caryn Alpert, Avril Lavigne,
Cheryl Alpert and Gina Furth

Nancy Davis
and Cammy MacMillan

Guest with Michael
and Jane Eisner

Debbie Eaton
and Sherry Corday

Dorothy Lucey, Teri Hausman,
Russ Fluter

Victoria Justice
alice + olivia

Sandra Truelove,
Kristi Cook, Mary Jo Hausman

Rumer Willis

Robert Morton and Family with
Scott Rogowsky and Ken Rickel

Codi Wiggins, Lara Sebastian
and Bill Perkins

Kechi Okwuchi
and Nancy Davis

Heather Hall, Nancy Davis, Ken Rickel,
Matthew Lubkeman

Anne Heche

Greg and Jory Phillinganes

Jennifer Rebello
with Richard David

Cheryl Burke
and Matthew Lawrence

Harriet Sternberg, Andrew Zucker,
Lyndi Hirsch

Mark Held and Roberta Karsh

Matt Rosler, Paul Berman,
Michael Runyan, Josh Rosenzweig

highlights from the lab

Center Without Walls Program 2018-2019 Research Update

Our mission is to fund cutting-edge, innovative research programs in our quest to find a cure for MS. Below are the 2018-2019 grantee research summaries from our newly awarded Young Investigators and Innovation Awards as well as updates from our second year Young Investigator grant awardees that began their basic science research in 2017.

1st Year YI Grant Recipients:

Michael Davin Kornberg, M.D., Ph.D., Assistant Professor of Neurology, Johns Hopkins

Bryostatin-1 as a potential modulator of the innate immune system in progressive multiple sclerosis: Progressive MS, which lacks satisfactory treatments, is characterized by chronic activation of so-called "innate" immune cells (macrophages and microglia) in the nervous system. These chronically activated innate immune cells cause ongoing injury and prevent repair processes such as remyelination, but thus far no treatments targeting these cells have been developed. Recently, we found that bryostatin-1, a brain-penetrant, naturally occurring drug known to be safe in humans, specifically targets innate immune cells to prevent inflammatory activation and favor a repair-promoting cell type. Bryostatin-1 also showed significant benefit in an animal model of MS.

The project funded by Race to Erase MS aims to further characterize the precise targets of bryostatin-1 in innate immune cells of the central nervous system and to examine whether the drug's actions promote remyelination in animals. The goal of the work is to determine the therapeutic potential of bryostatin-1 in progressive MS and to identify additional targets for drug development. The established safety of bryostatin-1 suggests it could be rapidly advanced into studies in MS patients.

Erin Longbrake, MD, PhD Assistant Professor, Department of Neurology, Yale University

Interactions between gut microbiome and B-cell depletion in MS: MS is a heterogeneous disease which at times causes minimal disability and at other times is neurologically devastating within years, despite appropriate treatment. No predictive algorithms or biomarkers currently exist to stratify risk at the time of diagnosis and to help guide treatment decisions. The mechanisms behind this heterogeneity is not known. MS develops when environmental exposures trigger autoimmunity in a genetically susceptible person. Changes in the gut microbiota represent one possible mechanism by which this interaction occurs. The gut is home to trillions of microbes which are critically important for the normal development and function of the immune system. These microbiota are sensitive to environmental changes and are affected by the same environmental triggers that are linked to developing MS. We propose that changes in the gut microbiota contribute to the differences in MS severity and effectiveness of disease modifying therapy that are observed on a person-to-person basis.

Ocrelizumab is an exciting new medication used to treat both relapsing and progressive MS. Ocrelizumab is designed to specifically eliminate B-cells, a specific subtype of immune cells. However, because the immune system is highly inter-related, loss of B-cells leads to many other changes in the immune system. These downstream changes may be an important part of the reason that ocrelizumab works so well. We hypothesize that administering ocrelizumab changes the composition and function of the gut microbiota and that this may be an important component of the drug's disease modifying effects in MS. With support from Race to Erase MS, we have begun to evaluate the composition and the function of the gut microbiota for patients newly diagnosed with MS compared to healthy individuals. We will simultaneously comprehensively evaluate the circulating immune cells in these patients. We will then re-evaluate the gut microbiota and circulating immune cells at multiple timepoints during the first year of ocrelizumab therapy. This study will lead to important information about the mechanisms behind ocrelizumab's effectiveness and may ultimately lead to valuable biomarkers that guide clinical decision making regarding how to prescribe this medication.

2nd Year YI Grant Recipients:

Nikolaos A. Patsopoulos, M.D., Ph.D. Assistant Professor, Department of Neurology, Brigham & Women's Hospital, Harvard

Personalizing the MS genetic risk in the presence of environment: It is well established that MS has a strong genetic contribution. Recent technological advantages and large-scale studies have led to the discovery of more than 200 robustly associated genetic risk factors. The vast majority of these genetic differences are very common in the population, and having one of them does not imply that an individual will develop MS. One does not also need to have all of the 200 genetic

highlights from the lab

culprits to develop the disease. It is more plausible that some of them need to be present to increase the susceptibility to the disease. However, there is no working model of how the MS associated genetic variants cluster together to predispose to the disease. Furthermore, one potential explanation of why the genetic variants are so common in the population is that some other, non-genetic, factors are needed to trigger the disease. A lot of the identified genetics variants alter the way that specific cells respond to external factors, i.e. their environment. Thus, the inability of immune cells to respond properly to the wrong environment could be a mechanism via which these genetic variants predispose to MS. Unfortunately, a system to systematically interrogate the genetically programmed responses of immune cells to environmental changes does not exist. With the support from Race to Erase MS 1) we are building mathematical models to identify the combinations in which these MS genetic variants cluster together, and 2) we are creating a system to test environmental changes in immune cells isolated from individuals with specific genetic background.

In the first year of this award, we were successful in optimizing a platform to systematically measure the response of human immune cells to environmental changes. In the second year, we are optimizing algorithmic approaches in order to personalize one's risk to develop MS given their genetic background. We will use these mathematical models to prioritize individuals with MS that have a unique combination of genetic risk factors. We will then isolate specific immune subpopulations from these prioritize individuals and measure the response of these cells in different microenvironments, using the platform development in year 1. Our research will create a systematic approach to translate an individual's genome response to environmental changes, paving the way to precision medicine approaches for MS.

Innovation Grant Summaries 2018-2019

Peter Calabresi, M.D.
Professor of Neurology and Director of the Johns Hopkins MS Center

Transcriptomic and Functional Profiling of Human iPSC Derived Oligodendrocyte Precursor Cells: Our ability to study MS has been limited by the fact that we rarely have access to brain cells from people with the disease. Stem cell technologies now allow the generation of brain cells from people's own blood cells. Using this approach, we have made myelin producing precursor cells from people with different types of MS, and can now study why these cells sometimes fail to repair myelin. We have found that specific inflammatory proteins reprogram the myelin precursor cells to become part of the problem (inflammation) rather than repairing the damage (remyelination). By interrogating the cell programming pathways, we may better understand what goes wrong and develop strategies to fix the problem.

Jennifer Graves, MD, PhD, MAS
Assistant Professor of Neurology and Ophthalmology, UCSF

Association of Biological Age and Senescent Cells with MS progression:The most critical objective facing MS research today is stopping disease progression and accumulation of neurological disability. While we have fifteen medications to prevent relapses, there are no current therapies proven to stop the insidious worsening of function as observed in primary and secondary progressive MS. To fill this treatment gap, we need to better understand the pathological processes driving progression. One patient characteristic has been consistently associated with rate of non-relapse related disability accumulation – age at onset. Chronological age has been associated with time to disability milestones independent of disease duration, with older patients experiencing shorter time intervals to ambulatory dysfunction. In addition, the average age at diagnosis of progressive MS in adults is 10 years older than that of relapsing-remitting (RR) disease. Despite these intriguing observations, there has been little study of the role of biological aging or its markers in MS progression. We propose to consider progressive MS as an aging-related disease. Establishing that robust markers of biological aging are associated with disability will support leveraging large studies of human aging to identify new types of treatment for progressive MS. One of the most robust ways to assess overall "biological age" as opposed to chronological age determined by birthdate is to measure the function of multiple organ systems at once (heart, lungs, liver, kidney and immune system). In the first part of this project we will measure the biological age of both very young and older patients with MS. We will accomplish this by taking blood pressure and breathing measurements in patients with MS as well as measuring factors in their blood related to liver, kidney and immune function. Using a well-established mathematical equation, we will calculate participants' biological age and compare this to the severity of their MS.

An exciting advance in the study of human aging is the concept of a senescent cell. These cells accumulate in normal human aging, but importantly their accumulation and the products they secrete are associated with chronic disease. In animal models removing these cells decreases the development of aging-related disease. Many of the chemicals secreted by these cells have strong impact on the immune system and would be expected to have a potential effect on MS. In the second aim of this innovation award we propose to measure the number of senescent cells in participants with MS and compare the burden of these cells to MS severity.

Linking MS progression to biological age

CWW continued on Page 10)

highlights from the lab continued from page 9

and the accumulation of senescent cells would be a paradigm shift in understanding this phase of the disease. Studies are already under way in humans to try to manipulate the function of senescent cells to decrease age-related illness. The wealth of resources being developed in the human aging field could be leveraged to identify new therapeutic targets for primary or secondary progressive MS.

David A. Hafler, M.D.
Professor of Neurology and Immunobiology
Chairman, Department of Neurology
Yale School of Medicine

Histopathology of the MS lesion at single-cell resolution: Relapsing remitting multiple sclerosis (MS) is a genetically-mediated, neuroinflammatory autoimmune disease that is thought to arise from a breakdown of immunological tolerance leading to the activation of myelin-autoreactive T cells. There is recent striking evidence that B cells are crucial drivers of MS with the remarkable efficacy of B cell depletion therapy, demonstrating ~95% reduction in gadolinium-enhancing lesions after B cell depletion treatment with Ocrelizumab.

However, the underlying mechanism of its effectiveness in MS is not understood. The role of B cells in MS suggests critical T-cell-extrinsic factors in what had classically been considered a T cell-mediated disease. We propose a novel, longitudinal, single-cell assessment of the immune system to interrogate the immune state after Ocrelizumab treatment in cohorts we have collected and continue to enroll for studies. Integrating detailed unbiased characterization of myelin-reactive T cells with an unbiased perspective on immune cell architecture will allow us to understand the immunological shifts that promote the dramatic response to therapy.

Vijay K. Kuchroo, DVM, Ph.D.
Professor of Neurology,
Harvard Medical School and Brigham and Women's Hospital

Derivation of T regulatory cells from MS patient-specific induced pluripotent stem (iPS) cells for autologous cell therapy: In Multiple Sclerosis, the immune system attacks the protective myelin sheath around nerve fibers in the brain and spinal cord leading to many neurologic deficits including loss of sensation, difficulty to walk and cognitive decline. With time, the there is increasing axonal resection with development of neurodegeneration. Current therapies inhibit the immune system very broadly, however, this may also limit the ability to fight infections or lead to other severe adverse reactions. Furthermore, none of the current therapies can inhibit the degenerative process that sets in.

In addition to pathogenic T cells that mediate autoimmune attack, there is a class of T cells that regulates immune responses and maintains tissue health. In multiple sclerosis, there is either decrease or loss of function in these cells. Therefore, it is envisaged that restoring the balance of regulatory T cells may greatly benefit not only relapsing-remitting but also chronic progressive disease, by promoting tissue health. In this pilot grant, we propose to generate for the first time T regulatory cells from the patient's own stem cells. This has the tremendous advantage that these patient specific T regulatory cells would not be rejected as they came from the patient's own stem cells. In the proposed pilot grant, we will (1) differentiate stem cells derived from MS patients to protective regulatory T cells and (2) study their ability to suppress pro-inflammatory immune responses in the culture dish. Our long-term research goal is to transfer these regulatory T cells back in MS patients to specifically inhibit the self-myelin reactive T cells but also inhibit degenerative process that get in the chronic progressive disease.

Kelly R. Monk, Ph.D.
Senior Scientist and Co-Director
Vollum Institute
Oregon Health & Science University

Glial-glial interactions in CNS myelination: In the healthy nervous system, a specialized structure called myelin ensheathes specific regions of neurons much like insulation materials ensheathe electric wires. In the brain and spinal cord, cells called oligodendrocytes make the myelin sheath, and these cells are also required to provide neurons with key nutrients and energy supplies. In multiple sclerosis (MS), myelin is attacked and destroyed by the body's immune system, which harms neurons and causes many of the symptoms associated with the disease. In the healthy nervous system, immune cells called microglia constantly survey the environment to promote homeostasis so that neurons and other cells can function properly. Our studies are focused on mutant animals in which the relationship between oligodendrocytes and microglia is dramatically altered. We will determine the identity of the gene that is defective in our mutants and define interactions between oligodendrocytes and microglia during both normal development and in the mutant nervous system. Our work can provide new insight into myelin development and oligodendrocyte-immune cell interactions by uncovering fundamental mechanisms that regulate these processes. These new players may represent novel targets to therapeutically manipulate in myelin repair in the future.

Daniel Ontaneda, M.D. MSc
Assistant Professor of Neurology/Medicine, Cleveland Clinic

Central Vein Sign in Multiple Sclerosis: The diagnostic criteria for multiple sclerosis (MS) are sensitive (many suspected cases are detected) but not entirely specific (not all cases meeting the criteria have MS). Misdiagnosis of MS is

highlights from the lab

a common problem occurring in up to 1 of 10 patients diagnosed with MS. A more specific marker of the disease is needed. Recent advances in magnetic resonance imaging (MRI) have enabled researchers to identify small central veins within MS lesions. The presence of central veins may help differentiate MS from other diseases that also have white matter lesions, where the central vein is absent. In this study, we aim to test a novel protocol for detecting central veins. The protocol involves a fluid-attenuated inversion recovery T2*-weighted image, also known as FLAIR*. We have received initial funding to validate the use of FLAIR* across 6 sites in North America by measuring the relative intensity of lesions, veins, and white matter with comparisons among the different sites. We will also study the best method for selecting/counting a number of central veins to diagnose MS as compared with the more traditional McDonald MS criteria. The data obtained in this pilot study will be used to design a larger study, where patients will be followed over 2 years to determine how the central vein can be used as part of the formal MS diagnostic criteria.

With additional pilot funds we will add 4 sites to our initial study and recruit a further 40 patients (10 per site) in whom there is a suspicion of MS. Patients will have a single MRI of the brain conducted with contrast and the FLAIR* protocol for determination of central veins. Subjects will also have a detailed neurological exam, walking speed test, hand function test, brief cognitive screening test, and visual testing. The data will be collected and analyzed looking at the intensity of the lesions, vein, and normal-appearing white matter. The variability of these measures between the sites will be tested. The presence of central vein will be compared with the traditional McDonald criteria for a diagnosis of MS. The results will be used to plan the larger definitive study and the total sample of 100 subjects in this pilot study will form part of the larger prospective study.

Rebecca Spain, MD, Assistant Professor, Department of Neurology Oregon Health & Science University

Optimizing gastrointestinal tolerability and absorption of racemic lipoic acid and R-lipoic acid in progressive multiple sclerosis: a randomized cross-over trial: There are many treatments available for relapsing MS but few for progressive MS. Lipoic acid has excellent potential to be a disease modifying treatment for progressive MS. Lipoic acid is an antioxidant that releases other powerful antioxidants in the body, boosts mitochondrial health, reduces inflammation and is easily available over the counter in capsules. Dr. Rebecca Spain and colleagues recently completed 2 year pilot clinical trial of lipoic acid in 51 people with secondary progressive MS found that people taking 1200mg daily of oral lipoic acid had a remarkable 68% reduction in their rate of brain atrophy, or shrinkage, and a tendency for preservation of walking speed compared to people on placebo. Unfortunately, more than half of the participants taking the lipoic acid complained of stomach upset, and the lipoic acid used was poorly taken up into the bloodstream. We therefore need to find a better tolerated and absorbed form of lipoic acid. Lipoic acid comes in two types, R and S.

Dr. Spain's pilot study used an equal mix of R and S, known as a racemic mixture. We think that the R form is likely to be better tolerated and absorbed because it is the form found in nature and in the human body, and because the S form may block absorption. In this project, we will compare the tolerability and absorption of lipoic acid in the racemic mixture form and the R form in people with progressive MS. The results of this study will help guide what form of lipoic acid to use in future studies examining and developing lipoic acid as a treatment for progressive MS.

Katharine Whartenby, PhD Associate Professor, Neurology and Oncology, Johns Hopkins

Role of gut gammaherpesviral infection in CNS autoimmune pathogenesis: CD20+ B cells are the target of a class of therapeutic monoclonal antibodies in multiple sclerosis. Administration of the principal monoclonal therapeutics rituximab, ocrelizumab, and ofatumumab led to a dramatic drop in B cell number in perivascular spaces, the CSF, and a near complete depletion of B cells in peripheral blood. This large-scale B cell depletion remarkably reduces the number of new MRI lesions, the number of relapses and annualized relapse rate in phase II clinical trials. Although monoclonal antibodies demonstrate great promise for novel strategies to MS treatment their lack of specificity for the pathogenic subset of B cells has been accompanied by some undesired side effects. Thus, more specific identification of the nature of the B cells specific to MS pathology would enable more selective and thus less toxic therapies. Towards this end, the central hypothesis of the proposed studies is that EBV-infected IgA+ CD19+ B cells, which are a B cell subset purported to be involved in MS pathology, will provide a more specific target for B cell therapies. The primary goals of the study are to determine roles this subset may play in the development of disease. Targeting this subset could provide the necessary specificity for therapy. EBV infection has long been associated with MS development and has been considered as a trigger of the disease. EBV and its related murine viral relative, gamma murine herpesvirus-68 (MHV-68), infect B cells, drive polyclonal activation and proliferation, and eventually establish lifelong latency with periodic lytic reactivation and infection of new B cells. Gammaherpesviral latency is crucial to exacerbation of neuro-inflammatory autoimmune disease,. Because EBV tropism is limited to humans, MHV-68 is used in rodents as a model of EBV

(CWW continued on Page 14)

photo gallery, continued


Nancy Davis, Giacomo Mattioli and Clio Olaya


Jessica Holmes, Kurt Knutsson, Matt Rosler


Johnathon and Julie Schaech


Nancy Davis, Jennifer Garner and Guest


Guest with Michele Davis and Victoria Page


Jackie Plaza, Cassidy Macleod, Nick Belardo Melisa Lopez, Kimberlyn Kelly


Mr. and Mrs. Byron Allen


Brenda Richie, Debbie Lustig, Lynn Palmer, Nancy Davis, Camille Grammer


Francesca Capaldi
alice + olivia


Steven Cojocaru, Tracy Danza


Cade, Ryder and Chad Brownstein


Isabella Rickel
alice + olivia


Carmela and Ryan Giese


Jessica Lia, Corbin McCarthy Stephanie Perkins, Katarina Telerian and Melissa McWilliams


Mariella Rickel
alice + olivia


Hannah Zeile


Lianne, Richard and Ava Weintraub


Ajiona Alexus
alice + olivia


Charlotte Rosenzweig, Alexis and Michael Runyan


alice + olivia Fall presentation


Arianna Donnelly, Paris Sanders


Elena Pikor and Guest


Jordan Cohen with Guests and Dina and Noel Cohen


Pepi Sonuga


Flo Rida on stage with Guests


Danielle Savre


Bob Rosenblatt, Heather and Terry Dubrow


Olivia Sanabia


Nile Rodgers with Guest and Mark Barondess


Joan Collins


Ruby Modine and Guests

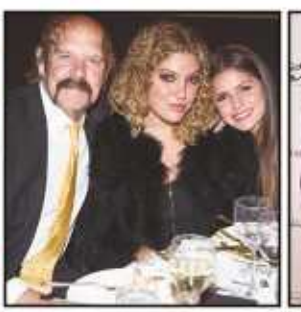

Greg, Jan and Lawrence Kelly


Nala Wayans


Hanna and Rachel Alansky


Graham and Kara Alloway


Elizabeth Stanton, Jacob Mayberry Garrett Clayton


Dr. Joel Geiderman and Guests


Bryan Greenberg


Christine Devine and Guests


Chandler Kinney


Nancy Davis, Brenda Richie and Guests


Mary Ellen Mitchell and Nicole Whitmore


Gina and Anthony Capaldi


Noel Cohen, Mark Locks, Jose Eber with Guests and Dina Cohen


Heather Hall, Nicole Ostoya and Stormi Simon


Serayah
alice + olivia


Nick Berman, Aron Hendin, Suzanne Berman, Shideh Miller


Miles Brown and Tabitha Bateman


Brandy Navarre, Pouneh and Chloe Amini


Natalie Alyn


Claudia Curry Hill (center) with guests including Peter Glecker, Matt Rosler, Kurt Knutsson, Dr. Nancy Sicotte, Dr. Emmanuelle Waubant


Ava Dash
alice + olivia


Scott and Lisa Arnold

(GALA continued from Page 1)

and Jack Osbourne, who himself was diagnosed with MS in 2012, announced the beginning of the evening's fast-paced auction, which featured one-of-a-kind opportunities and collector's items including a ski trip at The Little Nell in Aspen Colorado, a trip to New York Fashion Week with the alice + olivia team, an irresistible teacup puppy, dinner with the Osbourne family, and a Bahamas vacation aboard the Illusions yacht. The big item of the night was a 2018 Ferrari Portofino, one of the first of its kind to reach Los Angeles, which went for an incredible $250,000.

The next performer of the evening, Siedah Garrett, was introduced by actress Anne Heche. Garrett, who also has MS, sang her single "Carry On," which she wrote after meeting Nancy Davis last year and being inspired to do what she could to help Davis' cause. She also sang the song she co-wrote for Michael Jackson, "Man in the Mirror," and had the audience singing and dancing along. Randy Jackson introduced the night's headliner, music superstar Flo Rida, who brought down the house with a seven-song set that included hits "Right Round," "In The Ayer," "My House," and "Wild Ones."

In what has become a Race to Erase MS tradition over the past 25 years, an uplifting rendition of "Lean On Me," was performed as the finale of the evening, led by Randy Jackson, who was joined on stage by Nancy Davis, Lance Bass, Siedah Garrett, La Toya Jackson, Kechi Okwuchi, A.R.T., Ajiona Alexus, and more. The Race to Erase MS Gala was generously sponsored by ALEX AND ANI, Ferrari Beverly Hills, alice + olivia by Stacey Bendet, Associated Television International, and The Beverly Hilton, with support from Evine, Mark's Garden, Carbonadi, Neo Water, and Bodvar House of Rosés. We look forward to celebrating with everyone in 2019. Make sure to save the date of May 10, 2019 at The Beverly Hilton.

(AAN continued from Page 1)

meeting, additional data was presented to further characterize the mechanisms of action, effectiveness and safety of this medication. Mechanistically, studies of spinal fluid from individuals treated with ocrelizumab revealed that patients taking the medication had not only reduced B-cells but also reduced T-cells in their spinal fluid. This suggests that the reason ocrelizumab works may depend on its interrupting the communication between B- and T-cells. This insight may be critical to understanding the biology behind MS. Another study reiterated the importance of early, effective treatment of MS. Patients who were treated with less effective, injectable medications during the clinical trials of ocrelizumab and subsequently switched to ocrelizumab after the conclusion of the study had rapid improvements in their relapse frequency and in the development of new brain lesions after switching medications. However, patients who were treated with ocrelizumab early (at the beginning of the trial) had less brain shrinkage (atrophy) over 4 years than patients who switched to ocrelizumab after being on less effective medication for two years.

No new safety concerns were raised based on ongoing analysis of the patients who participated in the clinical trials. Another study evaluated whether vaccines are effective among patients taking ocrelizumab. Patients on the medication had a weakened response to several common vaccines (tetanus, influenza), but the vaccines still provided protection against these diseases. Moreover, the vaccines appeared to be safe for treated patients.

Treatments for progressive MS: on the horizon. New treatments for progressive MS are sorely needed. Promising results from the two-year Phase 2 trial of ibudilast, an anti-inflammatory and possibly neuroprotective medication, were presented. In this study of 244 individuals with progressive MS, the investigators were able to show that rates of brain shrinkage (atrophy) were 48% slower in patients taking the medication. Side effects were minor and included gastrointestinal problems and fatigue. Larger trials are being planned to confirm these results and to establish whether measurable clinical improvements will also be seen.

(CWW Update continued from Page 11)

pathogenesis. Importantly, EBV is mainly transmitted orally and orally infected MHV-68 travels to and infects small intestinal epithelium. Our preliminary investigations into mechanisms of action show that MHV-68 infects Peyer's patches (PP) of the small intestine and establishes latency in this tissue. We found that MHV-68 alters the differentiation phenotype of IgA+ B cells and is associated with a significant reduction of CD19+ B cells in the PP. IgA+ CD19+ B cells are a B cell subset mainly generated in the PP and we hypothesize that these cells are the targets of oral MHV-68 infection in the PP, migrate into peripheral blood, and have the potential to seed the CNS with virus and participate in neuro-inflammatory autoimmune pathogenesis.

The importance of CWW funding for this is critical. This is a novel approach to a significant problem in MS, and the funding we obtain from the center will provide seed money to conduct the experiments necessary to apply for expanded future funding.

The project will also be a springboard for a post-doctoral fellow, who has been central to the development of the project, into a long-term career in MS to develop a research field that will form the basis of his future investigations. The funding from the CWW is absolutely critical to the ability to begin a novel project that tests an important paradigm in MS therapy and pathogenesis.

Pediatric MS Discoveries and Updates

By Jennifer Graves, MD, PhD, MAS, UCSF

Unfortunately, children can get MS, too. Between 3 and 10% of all MS patients have their first attack under the age of 18 years. When MS strikes during brain and immune system development, there are a number of unique features that emerge. The MRI may demonstrate more extensive brain lesions than in adult patients, but recovery from relapses is often better in children than adults. Cognition can be significantly affected in young people with MS and normal brain development is at risk of being interrupted. Children with MS often face entirely different social issues than adults with the disease and school can become a pediatric MS patient's biggest challenge.

Almost all children with MS have a relapsing form of the disease. Primary progressive MS is not observed in this age group. Treatment is directed toward controlling relapses and supporting families so that children with MS can lead as normal lives as possible with the disease. Although there has only been one clinical trial completed to date in pediatric MS, medications used in adult MS are prescribed for children and generally appear to work as well in children. No new side effects in children have been reported in the scientific literature.

Understanding why children exhibit better initial recovery from relapses than adults could lead to new neuroprotective strategies for all patients. Studying the biology of pediatric MS may shed light on how to promote re-myelination and repair. Children are also an important population to evaluate for the environmental causes of MS. Recent studies suggest the risk for MS may extend back as early as during pregnancy and the first few years of life.

The best approach to taking care of children with MS is to combine the expertise of a neuro-immunology specialist, social worker, and child psychologist. With a focus on individual child needs and expert use of available medications, young people with MS can meet their life goals including graduating from high school and pursuing college. New discoveries from the Center without Walls will help keep them healthy in adulthood.

MS Forum and Expo

Center Without Walls team speaks about latest advances

Our semi-annual Ms Forum and Expo is free and open to the public and we welcome you, your family, and friends to attend this unique opportunity to ask questions, receive resources and information, and to speak directly to top MS research doctors from around the country. Our past forums are available to view on our Facebook page at anytime and our future forums will always be accessible via Facebook Live. Below are a few pictures from our event this past April. Make sure to follow us on our social media platforms or check our website to obtain updates on our topics for October 28, 2018.

Guests enjoy the resources provided by our invaluable Expo Partners and Panelists

MS Forum and Expo Save the Date

FALL 2018
Sunday, October 28, 2018
1:00 pm
The Beverly Hilton

SPRING 2019
Saturday, May 11, 2019
10:00 am
The Beverly Hilton

Open forum with our top MS research scientists speaking on the latest advancements in multiple sclerosis research. Free to the public and no RSVP required. For more information please visit our website or follow us on social media.

RACE ERASE MS

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LOVE TO ERASE MS

RACE TO ERASE MS GALA

May 10, 2019 | The Beverly Hilton

6:30PM Silent Auction | Cocktail Reception | Dinner | Live Performances