Annual Gala Event Highlights

On April 15, 2016 we celebrated our 23rd Annual Race to Erase MS at the Beverly Hilton. We were so grateful to be able to honor the very generous Carolyn Rafaelian, the founder and CEO of ALEX AND ANI®, who has a remarkable commitment to charity and has contributed to Race to Erase MS in ways we never thought possible.

Presenters for the evening were LL Cool J, Jaime Pressly, Ashley Tisdale and Randy Jackson. The evening also included a live auction, during which lucky bidders walked away with items including a stay on the Illusions Yacht, an African Safari, a trip to Abu Dhabi, Dubai, and The Maldives with two roundtrip business class tickets on Etihad Airways, and the chance to have afternoon tea with Sharon and Kelly Osbourne at The Peninsula Hotel in Beverly Hills. Race to Erase MS continued its legacy of incredible musical performances this year with the iconic band KISS who performed hit songs including “Deuce”, “Calling Dr. Love” and fan-favorite “Rock and Roll All Nite”. Jordan Smith gave an incredible performance that included his original song “Stand in the Light” and our Musical Director the talented David Foster, brought Eric Benet onstage for a moving tribute to a longtime supporter of the cause, the late Natalie Cole, with a rendition of “Unforgettable”.

Guests could not stop talking about the spectacular floral arrangements generously donated by Mark’s Garden. Everyone commented on their extraordinary beauty. Mindy Weiss, well known event designer, created a lively auction atmosphere. Guests couldn’t leave without picking up the amazing Race to Erase MS gift bag so generously donated by Tiger J. Sweet E’s Bakeshop spoiled guests with scrumptious treats to top off the evening. We would like to thank our amazing presenting sponsors The Beverly Hilton, Associated Television International and ALEX AND ANI® for their generous support. Our event sponsors were truly instrumental in making the Race to Erase MS an electrifying evening. Thank you to Bianchi Winery, Svedka Vodka, Neo North America, New Belgium and Nice Guy Limo for their incredible support. Thank you to Cristophe Salon and MAC, who created the amazing hair and makeup for our celebrity presenters. Save the date for May 5, 2017 at The Beverly Hilton.

ECTRIMS 2016 Update

By Pavan Bhargava, M.D., Johns Hopkins University

The annual European Consortium for Treatment and Research in MS (ECTRIMS) meeting was held in September 2016 in London, UK. This meeting had several interesting results from trials of non-disease modifying therapies including studies of vitamin D and lipoic acid supplementation. There was also information about the effects of off-label B-cell targeting therapies and new information about the role of the gut microbiota (bacteria) and biomarkers in MS.

Non-DMT therapies: Vitamin D: While we have known for several years that vitamin D deficiency increases the risk for developing MS and the risk for more disease activity in people with established disease, the role for vitamin D supplementation in reducing MS disease activity was unknown. At ECTRIMS two trials of vitamin D supplementation reported results, the SOLAR trial of vitamin D supplementation in RRMS patients on treatment with interferon beta, reported a 32 % reduction in new MRI lesions in those on high-dose vitamin D group (14,000 IU daily) compared to no supplementation. Another pilot trial from France which compared high-dose vitamin D (100,000 IU every two weeks) also reported a similar result with reductions in new MRI lesions and in new disease activity in those who were compliant with medication. A drawback of the second study was that a large proportion of participants dropped out of the trial making the results hard to interpret. Overall these results are suggestive that addition of

(ECTRIMS continued on Page 15)
Twenty-four years ago I dared to dream the impossible dream of finding a cure for MS. What an incredible place we are with 2017 bringing promise of the fifteenth and possibly sixteenth drug with FDA approval for MS. There are now many different drugs for the many different types of MS, with results and safety improving quality of life. We are all anxiously awaiting the FDA approval of Ocrelizumab, a drug that we have been heavily involved with in pilot studies for many years. The promise of so many new drugs and how it could affect the course of this complicated disease gives me so much hope as we reach for our biggest goal of putting an end to MS.

In October, our Center Without Walls doctors met for their semi-annual symposium and we felt tremendous validation from our dedicated research doctors that we are making a significant impact towards finding a cure. Dr. Monica Carson, a member of our esteemed Scientific Advisory Board, commented on how incredibly unique and special our Center Without Walls program is and that there are no other groups that exists like the cohesive collaboration of our team. We feel extremely honored by her compliment to our program which we pride ourselves in only funding the best of the best basic science research.

We are thrilled to be honoring Jamie-Lynn Sigler with our Race to Erase MS “Medal of Hope” Award at our 24th Race to Erase MS gala on May 5, 2017. She is an incredible role model and we admire her courage of sharing her MS diagnosis with the world. I am even more honored to announce Jamie-Lynn’s acceptance to our Race to Erase MS Board of Directors. We welcome her contribution of new and innovative ways of raising funds to win this Race and find a cure for multiple sclerosis. Make sure to also save the date of May 6th for our MS Forum and Expo. Visit our website and social media platforms for more details.

Wishing everyone love, health and happiness in the new year!

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Race to Erase MS and ALEX AND ANI have raised a landmark $1 million and counting together, announced in October 2016. Funds are raised through the ALEX AND ANI philanthropic CHARITY BY DESIGN® division and are dedicated to Race to Erase MS’ “Center Without Walls Program” — a unique collaboration of the world’s leading MS research scientists who are on the cutting edge of innovative research and therapeutic approaches to treat Multiple Sclerosis.

The relationship between Race to Erase MS and ALEX AND ANI developed organically after the Senior Vice President of CHARITY BY DESIGN was introduced to the organization by someone who had lost a family member to the disease. Carolyn Rafaelian, the brand’s Founder, CEO and Chief Creative Officer, was moved by her story, and shortly thereafter, the two organizations collaborated on a bracelet for the ALEX AND ANI | CHARITY BY DESIGN Collection. Since May 2012 when it first launched, a portion of the proceeds from the sale of the Cupcake Bangle has been donated to Race to Erase MS. Additionally, ALEX AND ANI | CHARITY BY DESIGN continually supports the annual gala in Los Angeles, where Race to Erase MS most recently honored Rafaelian for her incredible contributions and dedication to the cause.

“Carolyn has created a charitable force in the community with her Charity by Design program, empowering so many organizations to make a difference in their individual missions,” said Race to Erase MS founder Nancy Davis. “We are so blessed to be an Alex and Ani Charity by Design partner. On behalf of the millions of people living with multiple sclerosis, words cannot express the deep gratitude and hope that you have given to our community with a contribution of over a million dollars to help us win this Race to Erase MS.”

The partnership between Race to Erase MS and ALEX AND ANI continues to grow. On November 17, 2016, ALEX AND ANI celebrated their Irvine store location opening with a kick-off event in collaboration with Race to Erase MS. Guests received a sneak peek of the new store and 15 percent of sales from the event benefited Race to Erase MS. “MS affects more than 2 million people worldwide, most often between the ages of 20 and 40, and nearly three times as many women as men. Finding new ways to treat and hopefully cure this disease is a daunting task, and ALEX AND ANI is proud to be a supporter,” said Rafaelian. “The ALEX AND ANI Irvine grand opening event provided an opportunity for new customers and change makers to connect, support, and learn more about this important cause in a new and exciting atmosphere.”
Race to Erase MS 2017 “Medal of Hope” Honoree
Jamie-Lynn Sigler

On May 5, 2017 we will celebrate our 24th Race to Erase MS at The Beverly Hilton. I am so honored and proud to recognize Jamie-Lynn Sigler with our Race to Erase MS “Medal of Hope” Award at this very special event. She has made a profound statement in the community by bringing multiple sclerosis into the limelight with her public diagnosis. She has also just recently joined our Board of Directors, so we welcome her passion and ambition to help find a cure for MS.

We hope that you can join us in our Race to Erase MS and help us celebrate Jamie-Lynn’s courage and inspiration as a role model to so many millions that suffer with this autoimmune disease. See below a brief synopsis of her work and visit our website for her complete biography: Jamie-Lynn Sigler first captured audiences when she appeared on HBO’s critically acclaimed drama “The Sopranos” as mafia daughter, ‘Meadow Soprano.’ Now the extraordinary talent is lighting the screen displaying her vast range of acting chops. Sigler recently wrapped production on the independent western “Justice” opposite Stephen Lang, Jackson Rathbone and Robert Carradine. The film centers around a U.S. Marshal seeking justice for his brother's murder defends a small town from a corrupt Mayor and his henchmen with intents to revive the civil war. A native of New York, Sigler divides her time between New York and Los Angeles.

WE RUN THE GROVE!
Jamie-Lynn Sigler and The Grove support MS

The Grove hosted its 5th Annual WE RUN THE GROVE 13.1 mile run and 10K with charity partner Race to Erase MS on Sunday, June 12, 2016. This run was The Grove’s most successful to date with 1,400 participating runners, an increase of 500 runners from last year.

Actress Jamie-Lynn Sigler welcomed the runners who started on First Street in a staggered start and proceeded to run/walk our local streets, many wearing their Grove branded tees.

Race to Erase MS dedicated supporters Kurt Knutsson and Matt Rosler spoke about the foundation’s mission to find a cure and inspired the audience with hope. Runners returned through a balloon arch near the trolley barn and enjoyed an after-party in The Park with treats, music and a photo opportunity.

Save the date: Sunday, June 4th 2017 for the 6th annual event! We are thrilled to be partnering once again with “We Run the Grove” for a spectacular morning of inspiration and health. Follow us on social media for updates. Help us win our Race to Erase MS and join us next summer!

SAVE THE DATE: June 4, 2017
We Run the Grove to Erase MS
Ocrelizumab UPDATE
By Dr. Emmanuelle Waubant and Dr. Bardia Nourbakhsh, UCSF

Early MS medications such as interferons and Copaxone decreased modestly the risk of MS flares, while newer medications may have a more dramatic benefit. In the past few years, new technology has allowed making monoclonal antibodies from cell cultures that can target and even deplete a specific group of immune cells. One example includes B-cells that participate to demyelination and tissue damage in patients with MS. A decade ago, investigators performed a clinical trial to investigate the effects of B-cell removal from the blood of patients with MS using the first generation of monoclonal antibody that targets B-cells called rituximab. Rituximab decreased dramatically new brain lesions in MS patients. Although the drug was never tested in larger clinical trials, newer generations of anti-B cell therapies such as ocrelizumab and ofatumumab were recently tested in large trials in patients with relapsing and primary progressive MS.

(OCRELIZUMAB continued on Page 15)

2017: Save the Date May 6, 2017

Don’t miss our MS Forum and Expo in the Spring, May 6, 2017. The event 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 forums this past year covered topics including emotional wellness, remyelination and repair, promising therapies for MS, clinical trials, brain atrophy and progressive MS. Photos are from both forums this year. Make sure to follow us on our social media platforms or check our website to obtain updates on our topics for 2017.
Can a Nutritional Schedule Help People with MS?
By Ellen M. Mowry, M.D., M.C.R. Johns Hopkins University

Multiple Sclerosis (MS) is a common neurological disorder. Despite advances in treatment, it remains the top cause of non-traumatic disability in earlier phases of adulthood. Studies from several parts of the world suggest an increase in the number of people who are developing MS, which is occurring at a rate too fast to be explained by genetic factors. Thus, changing factors in the environment that influence MS risk are the likely culprits. One environmental MS risk factor that has recently been identified is obesity, which is also on the rise globally. Since the food we eat plays an important role in biological processes relevant to MS, such as inflammation, the balance of bacteria in the gut, and others, we became very interested in studying how changing the diet may influence people with MS. The identification of obesity as a risk factor for MS made evaluating weight loss through dietary modification an attractive option. Furthermore, intriguing research led by the Center Without Walls’ Scientific Advisory Board member, Dr. Anne Cross, and others showed that modifying the amount of food fed to mice changed their susceptibility to, or the severity of, the mouse version of MS. In particular, when mice are subjected to intermittent calorie restriction or fasting (i.e. a dramatic reduction in the amount of food provided, or even abstaining from food altogether, on a periodic basis), they either don’t seem to get the MS-like illness or they have fewer signs of it, both in terms of things like motor strength but also nervous system damage visualized by a microscope.

Based on all of this evidence, we decided to perform a two-part, small trial of calorie restriction in people with MS. For the first 8 weeks, participants receive one of three types of diets: one group eats the same amount of food as always (control), another receives the same amount of food five days a week but eats only 25% of their normal food amount two days a week (intermittent calorie restriction), and the third has the same percentage of calories taken out as the previous group, but the reduction is spread out over the course of seven days (continuous calorie restriction). In this phase of the study, the food is standardized based on a “typical” American diet and shipped to participants so that everyone is eating the same foods. After the eight weeks are over, participants receive training in how to monitor calories, and everyone is asked to try to follow the intermittent calorie restriction diet using their own food for another 40 weeks. We are evaluating several outcomes as part of the study, including its feasibility not only during the phase in which food is provided, but also over a longer period of time when they have to make their own food choices. We are also assessing if the intermittent calorie restriction reduces blood markers of inflammation or processes indicating the kinds of stress in cells that is damaging to neurons. Through a previous Center Without Walls grant, we showed that such cellular stress markers in people with MS were not improved by vitamin D supplementation, while people without MS did have a benefit from vitamin D. Thus, we’re very interested to see if intermittent calorie restriction can reduce these stress markers. We have just completed enrollment for the study and thus expect to have some results as early as late 2016, with more complete results in the fall of 2017.

Fatigue and Multiple Sclerosis
By Bardia Nourbakhsh, MD MAS, University of California San Francisco

Fatigue is one of the most common symptoms of MS. Unlike normal persons, many patients with MS feel tired and exhausted all the time (even without or with minimal physical or mental exertion) and require prolonged rest and frequent naps. Fatigue negatively affects the quality of life and can be a major cause of disability and unemployment among patients with MS. It is more common among patients with progressive types of MS. MS fatigue can interfere with daily activities, is more severe later in the day and can be worsened by heat and hot and humid environments. It is unknown why MS patients develop fatigue. Previous studies have suggested that damage to certain areas and structures of the brain or production of some harmful proteins due to inflammation might be contributing to the development of fatigue in MS.

However, conditions other than MS might be the cause of fatigue and treating those conditions can improve or eliminate fatigue. For example, depression, which is commonly seen among patients with MS, can be a cause of fatigue in some patients. It is not uncommon for patients to have bladder problems, pain and muscles spasms that interfere with their sleep and cause daytime sleepiness and fatigue. These other causes of fatigue should be evaluated with the primary care physician or neurologist. Anemia and thyroid problems should also be investigated. Most of the medications that are used to treat MS (the so called disease-modifying therapies) have no beneficial effect on MS fatigue. Some of these medications may actually worsen the fatigue in some patients. So, it is important to talk about fatigue with the treating neurologist. The initial evaluation will include searching for secondary causes of fatigue, such as depression and sleep disturbance. Exercise, rehabilitation strategies and medications have been used to alleviate fatigue in patients with MS. Studies have shown positive effects of aquatic exercise, resistance training and aerobic and inspiratory exercises in relieving fatigue. Educational activities, such as energy conservation courses and tele-conference delivered fatigue management programs are shown to be effective in reducing fatigue in MS. Physical therapist specialized in neurological disorders can guide patients regarding available local resources. Occupational and physical therapists can teach patients how to simplify their daily tasks and save

(FATIGUE continued on Page 14)
photo gallery: 23rd Annual Race to Erase MS

Nancy Davis, Ken, Isabella and Mariella Rickel
Eric Benet and Jordan Smith
Randy Jackson
KISS with Joe Triangelo, Ani and Carolyn Rafaelian, Lynn Palmer, Nancy Davis, Ken Rickel
Jaime Pressly

Lynn Palmer, Nancy Davis, David Foster, Carolyn and Ani Rafaelian
LL Cool J
Dorothy Lucey, Teri Hausman and Richard Hausman
Kathy and Rick Hilton
Lean on Me Finale

Barbara Davis
Beth Preece, Debbie Easton, Sherry Corday, Judith Angel
Gene Simmons
Jimmy and Debbie Lustig
Tracy Danza, Jerry and Tawny Sanders

Ross Mathews and Garcelle Beauvais
Nancy Davis and Ally Hilfiger
Larry and Shawn King
Dove Cameron
Dana Davis and Guests

Jeff Gurthie with Ghada Irani
Steve Ponce, Kiki Anderson, Brett Hagan, Addrine Carter, Drew Anderson
Paget Brewster
Steve Ponce, Cammy and Jim MacMillan, Meredith Johnson, Shayna and Benny Baltrotsky
Ashley Tisdale

2016-2017
Young Investigator Research Update

Center Without Walls Program
Young Investigator Research Update

Our mission is to fund cutting-edge, innovative research programs in our quest to find a cure for MS. Below are the 2016-2017 grantee research summaries from our newly awarded Young Investigators and Pilot Studies as well as updates from our second year Young Investigator grant awardees that began their basic science research in 2015.

1st Year YI Grant Recipients:

**Jae Kyu Ryu, Ph.D. Staff Research Scientist, Gladstone Institute of Neurological Disease, University of California, San Francisco**

Determining mechanisms and therapeutic strategies for neurodegeneration in CNS autoimmunity:

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, associated with myelin damage and degeneration of neurons. Although neuronal damage is a major cause for disability in MS, current disease modifying therapies do not directly protect from degeneration of neurons. This proposal aims to determine the cellular and molecular mechanisms that induce inflammatory-mediated neurodegeneration with the ultimate goal to develop neuroprotective therapies for MS. Our prior studies and preliminary data suggest a novel mechanism linking blood-brain barrier disruption with oxidative changes and axonal damage in neuroinflammation. We propose to determine how the innate immune cells in the CNS contribute to neurodegeneration, discover novel molecular mechanisms for oxidative damage, and test the efficacy of novel therapeutics in protecting from neurodegeneration in MS animal models. Our study is based on an innovative experimental design that integrates cutting-edge proteomic approaches, high resolution two-photon microscopy of inflammatory and neurodegenerative processes in the living mouse, and novel pharmacological approaches. This proposal has the potential to discover novel mechanisms of oxidative damage and provide the basis for transformational neuroprotective MS therapies.

**Tarun Singhal, M.D.**

**Associate Neurologist, Brigham and Women’s Hospital, Harvard Medical School**

Microglial activation PET imaging in multiple sclerosis: With support from Race to Erase MS, we are pursuing this research study to investigate if an advanced brain scanning technique called Positron Emission Tomography (PET) can identify active injury to the brain in Multiple Sclerosis better than MRI scans. PET scanning is otherwise used for cancer imaging or cardiac imaging and sometimes for brain imaging by assessing the activity of the brain using a radiolabeled sugar molecule. For our study, we intend to use novel molecules called PB R06 or PR28 for PET imaging of the brain in MS patients. PB R06 and PB R28 can be thought of as a colorless radioactive ‘dye’ that labels cells called ‘microglia’ in the brain that are activated to cause injury to the brain. We use a PET scanner in order to see this ‘dye’. We plan to enroll total 45 subjects for this study including 15 healthy controls, 15 patients with relapsing remitting multiple sclerosis and 15 patients with secondary progressive multiple sclerosis who will undergo PET and MRI scans at baseline and after 1 year. We will first compare PB R28 with PB R06 in a subset of MS patients to determine if PB R06 is as good as PB R28, which is considered the current gold standard but is difficult to use on a widespread basis because of its short half-life. If PB R06 is at least as good or better than PB R28, we will pursue the rest of the study with PB R06 given its longer half life and potential for widespread use. Otherwise, we will continue with PB R28. Further, our study aims to compare PET and MRI with respect to their sensitivity in detecting ongoing injury to the brain in MS patients. Also, we aim to compare PET and MRI in terms of their correlation with clinical parameters, such as disease severity, fatigue and cognitive disabilities. If this study demonstrates that PET imaging can identify ongoing injury to the brain in MS patients beyond what is seen on MRI scans, that will establish a new method to study brain injury in MS and its response to treatment.

**Pavan Bhargava, MD. Assistant Professor of Neurology, Johns Hopkins University**

Targeting Leptomeningeal Inflammation for Progressive Multiple Sclerosis: While multiple treatment options exist for relapsing remitting MS, there is a lack of effective therapies for people with progressive MS. Inflammation in the meninges (coverings of the brain) has been noted on autopsy in people with MS and is associated with a more severe disease course and greater damage to underlying brain tissue. Recent studies have shown that it is possible to detect regions of inflammation in the meninges using certain magnetic resonance imaging (MRI) techniques. Efforts are underway to target meningeal inflammation using drugs that deplete immune cells involved in this process. However, the lack of an animal model of meningeal inflammation is an obstacle to screening treatments and...
identifying new targets to eliminate meningeal inflammation. With funding from the Race to Erase MS, we are in the process of developing a model of meningeal inflammation that is seen in people with MS. We have noted in preliminary studies that in an existing model of MS, called experimental allergic encephalomyelitis (EAE), we can detect areas of contrast enhancement in the meninges on MRI at late stages of the disease. These areas of enhancement on pathological examination correspond to collections of inflammatory cells (B and T lymphocytes). During this project we will perform MRI at multiple time points on mice with EAE to detect meningeal lesions and to track their evolution over time. We will also obtain brain tissue from mice that undergo MRI at various time points to confirm that the MRI lesions correspond to areas of inflammation in the meninges. We will then perform staining of these tissues to determine the various cells making up the meningeal lesions. We will also determine other molecules that may be important for the formation and maintenance of these lesions, and the effect that meningeal inflammation has on the brain tissue adjacent to it. This will help us better characterize this model of meningeal inflammation. We will then utilize this model to test potential therapies that could target meningeal inflammation. These treatments could then be transitioned into clinical trials in people with MS, especially those with progressive MS. Thus, this project has the potential to identify new targets and treatments that could impact meningeal inflammation in people with MS.

2nd Year YI Grant Recipients:

Stephen P.J. Fancy, DVM PhD
Assistant Professor of Pediatrics and Neurology, UCSF

Remyelination in MS:

Permanent damage to white matter tracts, comprising axons and myelinating oligodendrocytes, is an important component of multiple sclerosis. In MS, myelin sheaths are lost through injury or death of mature oligodendrocytes (OL) as a result of autoimmune damage. In these conditions, myelin sheaths can be regenerated by oligodendrocyte progenitors (OPC) that are recruited to lesions and differentiate in a process called remyelination. But regulatory factors relevant in human myelin regeneration are unclear. Evidence suggests that myelin repair often fails in MS, and that this failure can result from failed OPC migration into lesions as well as their failed maturation into myelin forming OL once recruited to lesions. The inhibition of myelin repair contributes significantly to ongoing neurological dysfunction, axonal loss and disease progression in MS, and there are currently no treatments for promoting remyelination. During development OPCs migrate widely through the central nervous system (CNS) to achieve uniform distribution before halting migration and differentiating into oligodendrocytes that myelinate their target axons.

Despite decades of work on OPC migration, it has remained unclear how this highly migratory cell type distributes so rapidly around the developing CNS. We have identified this year how OPCs migrate during their developmental dispersal around the CNS using vasculature as the physical scaffold for their motility (Science 351, 379 (2016)). OPCs of embryonic mouse brain and spinal cord, as well as human cortex, emerge from progenitor domains and associate with blood vessels, crawling along and jumping between vessels like a jungle gym. OPCs utilize and require this vascular scaffold to migrate during development of the brain. This finding could have critical implications for understanding migration of these repair cells into lesions of MS, and understanding the failure of their migration in certain lesions which fail to repair.

Naila Makhani MD MPH
Assistant Professor of Pediatrics and Neurology, Yale University

Identification of Novel Biomarkers for Pediatric MS:

We now realize that the first symptoms of MS may present as early as in childhood. The challenge is that only some of the children who present with an MS-like first attack go on to develop MS, while most do not. In this study, we aim to identify novel markers for childhood MS. First, we are looking for patterns on brain and spinal cord magnetic resonance imaging (MRI) scans that are characteristic of MS using both standard and newer MRI methods. Second, we are using a recently developed laboratory test to look at the behavior of immune cells that are associated with MS. In this past year, we have optimized our MRI protocol to allow us to determine whether new MRI markers are associated with an increased risk of MS. We have also optimized our laboratory testing of immune cells and our preliminary data suggests a difference in immune cell behavior between children with MS and healthy children. We will use what we learn in the imaging and immune analyses to see if we can better predict which children truly have MS when they first present with possible symptoms. Identifying these children early will help us start MS treatments in a timely manner and in so doing, reduce long-term disability in our very youngest MS patients.

Pilot Study Summaries 2016-2017:

Laura Airas, David Pitt and David Hafler, Yale University

Towards personalized treatment of multiple sclerosis: It is unknown why some MS patients develop an aggressive progressive disease phenotype, and why some patients retain a benign disease course throughout their lives. We believe that genetic (CWW continued on Page 10)
regulation plays a role here. Our hypothesis is that a certain genetic signature predisposes patients to a more severe, progressive disease phenotype, which is associated with a higher tendency for microglial activation. Certain genetic variants of the NF-kB gene, a known activator of the innate immune system, are associated with likelihood for getting MS. We hypothesize that the NF-kB associated MS risk variants lead to unchecked NF-kB signaling and excessive activation of microglia, the resident innate immune system cells of the central nervous system. This dysregulation of the glial response may drive chronic central nervous system (CNS) inflammation, impair neuroprotective glial functions and ultimately lead to neurodegeneration and disease progression.

With support from Race to Erase MS, we will be able to evaluate the relation of the genetic variants to the activation status of microglial cells. We will first quantify the effect of the NF-kB risk variant on glial activation responses in cell culture with patient-specific macrophages and astrocytes. We will then evaluate in vivo in MS patients through 18kDa translocator protein (TSPO)-positron emission tomography (PET) imaging, whether the given NF-kB risk variant is also associated with more glial activation in situ within the brain. Ultimately, this will help us detect patients with highest risk for progressive disease, and it will teach us about the cellular pathways leading to harmful biopathology promoting disease progression. This will help us develop predictive biomarkers to identify patients most at risk of progression, and to develop new therapeutic approaches for progressive disease. Ultimately, we will be able to provide individualized therapies for MS patients tailored to their respective risk variants.

**Lisa F. Barcellos, PhD, MPH, Professor, Division of Epidemiology, School of Public Health and Graduate Program in Computational Biology, University of California, Berkeley**

Perinatal Epigenetic Changes and Pediatric MS Risk: MS onset typically occurs between the ages of 20 and 40; however, 5-10% of MS patients have symptoms before age 18. Pediatric MS (onset < age 18) affects 10-20,000 patients in the United States. The exact mechanisms that lead to developing MS are unclear; however, similar to adults, both genetic and environmental factors are involved. ‘Epigenetic’ factors are also important influences relevant to human health and disease; these factors include the addition of methyl groups to locations within the DNA sequence (or ‘DNA methylation’) which can affect the expression of certain genes in cells. Epigenetic changes in humans can result from environmental exposures such as toxins, infections or stress. In adult MS cases, we have evidence to support DNA methylation patterns in immune cells from MS patients are different from individuals without MS. The overall goal of this study is to identify and characterize epigenetic factors that are relevant to disease onset in pediatric MS. With support from The Race to Erase MS Foundation, our UC Berkeley-UC San Francisco team will perform comprehensive studies of DNA methylation patterns across the human genome derived from newborn blood spots in a sample of 50 pediatric MS cases and 50 healthy controls. We hypothesize that DNA methylation changes in important regions of the human genome detected at birth are associated with developing pediatric MS later in life. The results derived from this study will be among the first generated to investigate a role for causal epigenetic factors in pediatric MS. Results from the pilot study will lay a strong foundation for extending this important area of investigation to much larger numbers of patients and controls.

**Peter Calabresi, M.D.**

Professor of Neurology at the Johns Hopkins School of Medicine, Director of the Johns Hopkins Multiple Sclerosis (MS) Center

Mitophagy and optic nerve degeneration in experimental autoimmune encephalitis (EAE): In progressive multiple sclerosis (MS), the chronic loss of myelin around the nerve wires called axons leaves them susceptible to injury and loss, which is thought to be how people become slowly disabled in MS. However, how this process happens is unclear and so it has been difficult to develop therapies for progressive MS. Recently, it has been described in progressive MS that the energy packs of the nerve cells, called mitochondria, become damaged over time and fail to keep up with the increased energy demands that occur when the myelin is lost. Normally there are mechanisms to repair and replace the mitochondria but these may fail in later stages of MS. In this study, we will examine whether there are changes in mitochondrial turnover pathways and will determine if recycling mitochondria can lead to better outcomes in an animal model of MS called EAE. This approach may allow us to better understand how this process happens in people and could lead to new avenues of treatment for patients with progressive MS.

**Ben Emery, Ph.D.** Assistant Professor, Junger Center for Neurosciences Research, Department of Neurology, Oregon Health & Science University.

Development of MyRF inducible conditional knockout mice as a model to study glial, immune and neuronal interactions during demyelination: Multiple Sclerosis is considered to be an autoimmune inflammatory attack against oligodendrocytes and the myelin that they produce. Although demyelination (loss of myelin) has long been known to be a key feature of MS, it is increasingly appreciat-
ed that MS is also associated with damage to neurons and their axons, with axonal loss playing a large role in the progression of the disease. Whether this loss of axons is a direct result of demyelination or whether they are damaged as “bystanders” to an inappropriately activated immune system remains unclear. Previous work from our laboratory has identified a gene, Myelin Regulatory Factor (MyRF) that is required for oligodendrocytes to produce, and also maintain, the myelin sheath. Making use of this finding, we have developed a genetically modified mouse in which the MyRF gene can be inactivated in adult mice, resulting in a highly reproducible demyelination throughout their nervous system. These mice provide us a highly simplified and reproducible animal model to investigate the direct effects that demyelination has on neurons and the immune system (in particular microglia, the brain’s resident immune cells). Unexpectedly, our preliminary findings with this model suggest that myelin breakdown in these mice may initially induce a protective rather than damaging program within the resident immune cells in the brain. In this project we will further investigate how a primary demyelinating event affects both the immune system and the health of neurons. This will set the groundwork for subsequent experiments aiming to discover ways to channel both the neurons and the immune system within the brain towards a more protective response to myelin damage.

Noah W. Palm, Ph.D. Assistant Professor of Immunobiology, Yale University

Oligoclonal bands in multiple sclerosis: a gut response? Oligoclonal immunoglobulin bands are a hallmark of Multiple Sclerosis (MS) and more than 95% of MS patients exhibit oligoclonal bands in the cerebrospinal fluid (CSF) that are not detectable in serum. Oligoclonal bands in CSF indicate the presence of an ongoing immune response in the central nervous system and, thus, the detection of oligoclonal bands in MS is considered a ‘gold standard’ in the diagnosis of MS in patients with clinical suspicion; however, despite considerable effort, the drivers and specificities of these antibody responses remain unknown. A number of recent studies suggest that the so-called ‘gut microbiota’—the trillions of bacterial, viral and fungal microbes that constitute the intestine—may play an important, and potentially even causal role, in MS. For example, MS patients exhibit a profound imbalance in the composition of the gut microbiota as compared to healthy controls. With support from Race to Erase MS, we will use a novel and unbiased approach to examine the hypothesis that oligoclonal bands are triggered by specific members of the intestinal microbiota, which may represent causal microbes in disease. These studies will provide insight into the etiology of MS and provide potential targets for the development of novel microbiota-focused therapies for the prevention or treatment of MS.

Daniel Pelletier, M.D. Vice Chair of Research, Department of Neurology

Professor of Neurology and Radiology Chief, Neuro-Inmunology Division and USC Multiple Sclerosis Center Director, Advanced Imaging in Multiple Sclerosis (AIMS) Laboratory myMST™: A Clinical Validation Study of a Mobile Technology for Multiple Sclerosis

In this proposal we are planning to validate the use of a novel iPhone application (app) for MS. The name of this new mobile app is myMST™. Our team at USC, in collaboration with a bioinformatics company, has developed an application using Apple’s latest technology ResearKit. In addition to surveys and demographic data collection, myMST™ will be able to monitor patients in the comfort of their home (“real world”) using MS-specific cognitive(COGapp™) and walking (6Mapp™) built-in applications. The overall aim of this study is to perform the first validation experiment of these active tasks and surveys against ‘gold standard’ and traditional clinical outcomes (EDSS, PASAT, SDMT, T25-FW) commonly used in MS research. We propose the following aims; (1) to test the reliability (in comparison with traditional measures) of COGapp™ and 6Mapp™ over 1 year in 75 MS patients followed at the USC MS Center; and (2) to test how sensitive myMST™ and its built-in applications are to detect differences between MS patients and healthy controls (n=50) and between MS patients with different disease severity status. The groundbreaking potentials of such tools used in patient’s homes throughout the nation could change the field of medical research, patient care, and accelerate breakthrough discoveries. The large sample size required in current MS clinical research studies, especially studies involving epidemiological and epigenetic components, is often cost-prohibitive and has prevented our ability to make robust discoveries associated with MS disease severity and progression. Thus, innovative ways such as mobile technology to investigate MS at a very large scale and track its evolution over time are greatly needed.

Vijay K Kuchroo

Samuel L Wasserstrom Professor of Neurology, Harvard Medical School Associate Member, Broad Institute Director, Evergrande Center for Immunologic Diseases

High salt diet and MS: The prevalence of autoimmune diseases including multiple sclerosis in the western world is increasing, but the underlying cause for this unprecedented increase in incidence has not been elucidated. A number of environmental factors have been identified but none explains the massive increase in autoimmunity in western populations. We have made a surprising discovery that high salt diet is as a trigger for (CWW continued on Page 14)
2016-2017

Jessica and Clay Walker
Bette Smith and Nancy Davis
Jordan Cohen and Ken Rickel
David Foster, Eric Benet, Jordan Smith
Anna Trebunskaya

Megan Nicole and Guests
Lean on Me Finale
Jamie Winkler and Guest
Dina and Noel Cohen and Guests
Nancy Davis and Erica Tucker-Weinberg

Elena and Sydney Baca, Brandi Navarre, Alex and Chloe Amini
Olivia Sanabia and Guest
Carolyn and Ani Rafaelian
David Faustino and Guest
Christine Devine and Guest

Jen Rade and Guests
Artem Chigvintsev
Guests Rocking out to KISS
Kirsten Vangness
Dr. Emmanuelle Waubant and Dr. Henry McFarland

BC Jean
Modi Wiczky and Kate Wiczky-Phillips and Nancy Davis
Katherine McNamara
Guest and Gail Levine
Jenny and Jason Hochberg
inducing autoimmune disease. High salt intake enhances expansion pathogenic T cells in vivo leading to the development of autoimmune disease. This project will determine whether a high salt diet indeed is an environmental trigger for the induction of autoimmune disease in human and mice. Since salt concentration in the blood and tissues are strictly controlled, this raises the issue of how high salt diet enhances pathogenic Th17 cells and inhibits FoxP3 Tregs. We hypothesize that this high salt achieves this indirectly by regulating microbiome in the gut. As a part of the pilot grant, we will address the hypothesis that indeed high salt will change gut microbiome in both humans and mice. We will identify whether high salt diet changes some of microbial species that are represented in the microbiome of MS patients as well. These pilot studies will provide rationale for undertaking a full study on the microbiome and identify the microbial species that may affect the development of pathogenic and regulatory T cells and enhance susceptibility to EAE.

Emmanuelle Waubant, MD, PhD
Professor of Neurology and Pediatrics
University of California, San Francisco

A pilot study of oxidative pathways in MS fatigue: Fatigue is one of the most severe MS symptoms that can affect dramatically people with the disease and limit their quality of life. There are no FDA-approved medications to treat MS fatigue and the biological processes underpinning MS fatigue remain mysterious. We will study chemical imbalance related to oxidation pathways in patients with progressive MS with (n=10) and without (n=5) fatigue. We will use state-of-the-art brain imaging (with high-field spectroscopy) and novel blood markers of oxidation to identify chemicals that may explain MS fatigue. We will also study the effect of an antioxidant drug called N-acetyl cysteine on MS fatigue using questionnaires and chemical measurements from brain imaging and blood samples in 10 patients with progressive MS. N-acetyl cysteine is available on the market and helps prevent liver damage in patients who have taken too much Tylenol. The results from this pilot study will help understand MS fatigue mechanisms and possibly lead to new treatment for this disabling MS symptom. The results derived from this study will be among the first generated to investigate a role for causal chemical imbalance in oxidation for MS fatigue. Results from the pilot study will lay a strong foundation for extending this important area of investigation to a much larger clinical trial.

Donald J. Zack, M.D., Ph.D., Guerrieri Professor of Molecular Ophthalmology and Genetic Engineering, Wilmer Eye Institute
Johns Hopkins University School of Medicine

Screening for Molecules that Promote OPC Differentiation and Myelination in Human Cell Cultures: Multiple Sclerosis (MS) is the most common cause of neurological disability in young adults. There are approximately 400,000 MS patients in the US and 2.5 million patients worldwide. In MS, the immune system attacks and degrades myelin sheaths on axons in the central nervous system (CNS, brain and spinal chord), in a process known as “demyelination.” The myelin functions to provide an insulating sheath along the axons of nerve cells, and when it is damaged information transfer (“nerve conduction”) along nerves is impaired, resulting in motor and sometimes cognitive disabilities. Although most current MS therapies are directed at managing the immune process that leads to demyelination, we are working in collaboration with Dr. Peter Calabresi on a complementary approach, with generous support from Race to Erase MS, to develop drugs that can promote remyelination. Myelin in the CNS is formed by an interaction between specialized cells called oligodendrocytes and the neurons that they myelinate. Since immune-mediated processes in MS can lead to the death of oligodendrocytes, we are screening for small molecules (potential drugs) that would promote the survival and differentiation of oligodendrocyte precursor cells using CRISPR/Cas9 genome editing technology and a new process in which human stem cells can be differentiated in a tissue culture dish into OPCs. In addition, our lab has also established a protocol for differentiation of human stem cells into retinal ganglion cells (RGCs), the cells that transmit visual information from the eye to the brain, and whose axons form the optic nerve. RGCs are particularly relevant to MS, because demyelination of the optic nerve causes optic neuritis, which is one of the most common initial presenting conditions of MS. We plan to co-culture reporter OPCs and RGCs and generate a system where we can explore the ability of human OPCs to myelinate RGC neurons in vitro. Such a model system could be ideal for myelination studies as well as the above discussed efforts to identify potential drugs to stimulate remyelination, which we hope will lead to the development of new and improved treatment strategies for MS patients.

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Screening for Molecules that Promote OPC Differentiation and Myelination in Human Cell Cultures: Multiple Sclerosis

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Screening for Molecules that Promote OPC Differentiation and Myelination in Human Cell Cultures: Multiple Sclerosis

(fatigue continued from page 11)
North American Imaging in MS (NAIMS) UPDATE
By Dr. Nancy Sicotte, Cedars-Sinai

NAIMS has made great strides during the past year. The eighth NAIMS meeting took place on April 17, 2016 in conjunction with the American Academy of Neurology meeting in Vancouver, Canada at The University of British Columbia. A poster session featuring young investigators preceded a dinner meeting and general NAIMS meeting.

Several developments in the NAIMS group were discussed. Pilot Project: The first results of the pilot project were presented to the group. Three scientific abstracts derived from this study will be presented at ECTRIMS, the largest annual international meeting of the MS community, which will be held in London, England in September 2016.

Other Research Projects: the first draft of the NAIMS Consensus Statement on the Central Vein Sign (CVS) will be published soon. At least three new imaging projects utilizing NAIMS sites were discussed in detail. Membership: presentations from 6 new imaging sites were delivered, this brings the total number of NAIMS member sites to >20 across North America.

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.

(OCRELIZUMAB continued from Page 4)
These newer generation anti-B cell therapies are better tolerated than rituximab.

The results of those trials have not been published yet but presentations at scientific meetings suggest that ocrelizumab compared to high-dose interferon decreases the number of relapses and new brain lesions in patients with relapsing MS. Ocrelizumab also decreases modestly the risk of worsening disability in patients with primary progressive MS. The side effect profile of this medication appears overall very good over 2-3 years. Safety over longer periods of time remains to be defined. It is anticipated that ocrelizumab may gain FDA approval by the end of 2016 and therefore be the first approved medication for primary progressive MS. Although the addition of another drug to the growing list of MS medications is very exciting, it is important to discuss this option along with other MS therapies with treating neurologists.

(ECTRIMS continued from Page 1)
vitamin D to disease modifying therapy may be beneficial in MS patients, however there are still multiple ongoing trials that are likely to provide us with more information in the next year or two.

Lipoic acid: A two-year trial of 1200 mg daily lipoic acid vs placebo in secondary progressive MS patients, revealed a significant slowing the in the rate of brain atrophy in those taking lipoic acid. This was a very encouraging result and is likely to lead to a larger trial to assess whether lipoic acid can slow neurodegeneration in progressive MS patients.

News about Existing FDA-Approved MS Therapies and off-label MS therapies - Rituximab: Rituximab is a monoclonal antibody that targets CD20 a molecule found on the surface of B lymphocytes and leads to depletion of B cells in the peripheral circulation. A Swedish study utilizing data from their national MS registry compared almost 2000 MS patients on Rituximab to a similar number of patients on Fingolimod (Gilenya) or Natalizumab (Tysabri). They found that rituximab was better than both the other drugs as a first line therapy for RRMS patients and was better than Gilenya when switching from Tysabri. This is an interesting study and is reassuring since Ocrelizumab – another B-cell depleting agent is likely to be approved by the FDA later this year and would be expected to have a similar efficacy profile to rituximab given the results that were reported at ECTRIMS last year for this medication. Multiple studies also provided evidence from long term follow up studies or database studies that the early use of disease modifying therapies and the use of highly effective disease modifying therapies delays or prevents the accrual of disability in patients with RRMS.

More information about the role of the gut microbiota in MS: The role of the gut microbiota – bacteria, viruses and fungi that live in our gut in causing MS is gradually being understood. A study demonstrated that there were several bacterial classes that differed between MS patients and healthy individuals and that these bacteria could directly make human immune cells more inflammatory suggesting that the differences in the make-up of the gut microbiota could be a factor in the development of MS and perhaps in determining disease course. Another study also demonstrated that various disease modifying therapies can also change the gut microbiota and perhaps these changes may be part of their mechanism of action.

Hope for improved blood biomarkers of disease activity: Neurofilament light chain: Neurofilaments are structural proteins that are found in processes of nerve cells. When there is damage to nervous tissue these are released into the spinal fluid and can then leak into the blood. A study examining the effect of Tysabri treatment on levels of neurofilament light chains found that treatment reduced their level in both the spinal fluid and blood. The most encouraging result of this study was that the levels in the blood corresponded well to the levels in the spinal fluid. This suggests that in the future measuring levels of neurofilament light chain in the blood may help in tracking disease activity and assessing how well a therapy is working.
SAVE THE DATE

24th Race to Erase MS Gala  
“Love to Erase MS”

Friday, May 5, 2017  
The Beverly Hilton

For more information please call 310-440-4842 or visit www.erasems.org

2017 MS Forum and Expo  
Saturday, May 6th  
The Beverly Hilton

Free to the public. Open forum with our top MS research scientists speaking on the latest advancements in multiple sclerosis research.

We Run the Grove to Erase MS!

5K/10K Run/Walk and Half Marathon

June 4, 2017 at The Grove

For more information and updates, follow us on Instagram, Facebook and Twitter @racetoerasems @thegrovela

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