Accelerated Cure Project for MS

January 2018

Accelerating research towards a cure for multiple sclerosis

Dear Friends,

Our January newsletter focuses on the main tenets of ACP – collaboration, open science, and liberal sharing to accelerate MS research. The ACP Repository was developed on the premise of collaboration. Researchers studying MS and other demyelinating diseases obtain samples and associated data from the Repository with the understanding that research data generated by their studies will be returned to the database and shared with other researchers. Read our first article to learn more about ACP's collaboration with BC Platforms to manage and grow the Repository. This represents a major step toward making valuable data available to the research community in an organized, readily accessible way that can be easily analyzed, and will further facilitate collaboration between ACP and researchers!

Since its inception, ACP Repository samples have enabled new innovations in MS research. Our Repository Spotlight, a new addition to the newsletter in 2018, highlights a recent study that is using ACP Repository samples and returned data in their research. This month features the work of Dr. Doug Feinstein at the University of Illinois. In addition, Dr. Mireia Guerau, a scientist at the Ohio State University who is working with our Repository samples, also plans to access our returned research data in order to accelerate her research. Our second article explains the important work she is doing to investigate the mechanisms that drive inflammation and autoimmunity in MS. The data from Dr. Guerau's research will also be returned to our database for future researchers to build on!

We also pay homage to the late Dr. Ben Barres, an acclaimed Stanford neuroscientist, who shared ACP's collaborative approach to research. An early user of ACP Repository samples, his pioneering research revolutionized our understanding of the brain.

Dr. Farren Briggs' column this month discusses modifiable dietary factors and MS. He looks at two studies that see if altering portions of your diet can change the current and future state of your MS.

In addition to reporting on advances in MS research, we'd also like to introduce you to a partner and friend of ACP, Marc Stecker. Diagnosed with progressive MS in 2003, Marc is the author of the popular blog Wheelchair Kamikaze. Marc's purpose is to share with, educate and entertain his readers. Marc's posts are a wonderful mixture of facts and feelings, delivered with humor and bluntness. Whether you have MS or not, they leave you wanting to read more!

We hope you enjoy our newsletter and encourage you to share it with anyone you think may be interested in learning more about ACP. As the New Year begins, we are excited at new possibilities that lie ahead as we forge forward in collaboration with our many partners and constituents, and all of YOU, to improve diagnosis, optimize treatments and find a cure for MS!

The Accelerated Cure Project Team

Driving MS Research Forward with BC Platforms

The ACP Repository was developed to be a readily available source of biospecimens and associated patient-reported and clinical information for the research community. Working with a network of 10 leading neurology clinics throughout the US, samples and data were collected from over 3,200 participants, with and without demyelinating disease. To date, Repository samples and data have been used by investigators in over 100 studies in Multiple Sclerosis, Transverse Myelitis, Neuromyelitis Optica, and Clinically Isolated Syndrome. These studies have been conducted on a wide variety of topics, including genetics, identifying biomarkers to improve diagnosis, immune system responses, and disease risk. Other studies have focused on the explanation of how treatments under development actually work within the body. Researchers who use samples from the ACP Repository must agree to return their research results back to ACP for sharing with other researchers and for inclusion in the Repository database. The diverse collection of genomic and other research data generated by scientists using ACP Repository samples can be analyzed in its entirety, enabling the ACP Repository to be a rich "open source" resource that can be mined by researchers. To date, the challenge in realizing this vision for the ACP Repository has been finding a data management system that can be used to store and curate all of these diverse data sets in an easily accessible and searchable manner.

BC Platforms is a world leader in providing genomic data management and analysis solutions for large-scale collaborative research projects, whose expertise is in integrating clinical phenotype[1] data (such as data collected for the ACP Repository) with genetic data. Founded in 1997, BC Platforms has operations around the world with its headquarters in Switzerland, research and development operations in Finland, and sales and marketing offices in London, Boston, and Vancouver. Their HIPAA compliant data management platform offers flexible data integration, data security, and scalability. With it, clinicians and researchers are able to easily combine and use datasets, perform analyses, and share their results in a secure manner. BC Platforms has also established a global network, BCRQUEST.COM, which combines the datasets of biobanks around the world. This facilitates collaboration and makes it easy to determine sample/data availability across biobanks.

The Accelerated Cure Project will be using BC Platforms' data management system and BCRQUEST.COM to manage and grow its Repository. This represents a major step toward realizing the vision for the ACP Repository, and will further facilitate collaboration between ACP and researchers. All collected and returned data will be integrated into one easily accessible data management system, which will allow the analysis of combined returned research data along with the information collected from Repository participants and the information provided by clinicians. This information will further assist researchers in understanding what factors may cause or influence multiple sclerosis and other demyelinating disorders.

The research results flowing into the database are anticipated to increase dramatically as ACP initiates new projects. These include the planned sequencing of the full exome of all of the patient DNA samples. Exome sequencing of all of the ACP Repository DNA samples will result in a massive amount of data. The BC Platforms system is ready, willing, and able to handle the anticipated large quantity of data. The BC Platforms data management system will also allow ACP to streamline the process of selecting samples based on investigators' specific research requirements. Being able to service more requests for Repository samples means more studies can be done -- accelerating the research needed for better treatments, diagnoses, and cures.

When asked about the collaboration between ACP and BC Platforms, Robert McBurney, CEO of the Accelerated Cure Project, said "MS affects at least 2.3 million people worldwide. BC Platforms' technology provides an efficient way to manage the growth of our data repository, increases its visibility to the research community, and offers a simple way for researchers to collaborate and test hypotheses, especially those involving genetic data. As a result of this relationship with BC Platforms, ACP can have an even bigger impact in driving research that will improve the health, healthcare and quality of life of people affected by MS."

[1] The observable physical characteristics of an individual resulting from the interaction of its genotype with the environment.

Repository Spotlight – Dr. Doug Feinstein

Dr. Doug Feinstein, University of Illinois – Genetic factors are known to influence the risk of developing MS. Dr. Feinstein's research is focused on genetic variations as risk factors for MS. Specifically, he is studying changes in a specific gene called SNPs (single nucleotide polymorphisms) that show a significant association with MS in women. Interestingly, cells in the immune system with this gene are more sensitive to Metformin (a drug commonly used to treat type II Diabetes). This research will shed light on a genetic risk factor for RRMS in women, and provide a biomarker for possible treatment with Metformin for female MS patients who have this gene to reduce their immune response.

Collaboration in Research – Dr. Mireia Guerau

The mission of ACP is to accelerate research with the objective of understanding disease mechanisms and providing better diagnostics, treatments, and cures for MS. Our strategy includes an "open source" model where the resources we've developed, like the ACP Repository and iConquerMS™, are made broadly available to investigators and that these resources are used in ways that foster collaboration and learning from the work of others. One of our requirements of the investigators, to whom we provide samples and data, is that any newly generated research results are returned to us in order to be made available to other scientists. Thus a significant aspect of the acceleration of research is the use, by scientists, of ACP's returned data to add value to their research programs.

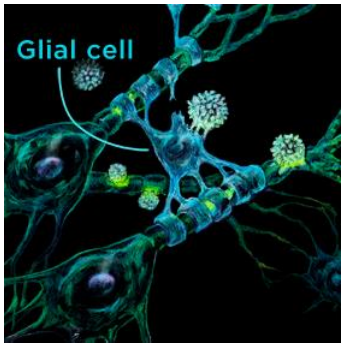
Dr. Mireia Guerau at the Ohio State University is an example of a scientist who is working with our Repository samples and also plans to access our returned research data in order to accelerate her research. The mission of the Guerau Laboratory is to identify blood biomarkers linked to disease activity that could help diagnose, predict and/or monitor MS therapy responsiveness. Such biomarkers may optimize therapy thereby reducing long-term disability, and may also provide new targets for therapeutic intervention as part of a larger objective of investigating mechanisms that drive inflammation and autoimmunity in MS.

One of Dr. Guerau's projects involves the expression of genes that may serve as disease biomarkers in relapsing remitting MS vs. healthy donors. Her lab looks at both ribonucleic acid (RNA) and protein molecules, both outcomes of gene expression, and their consequences on T cells and macrophages that promote MS. Dr. Guerau is using frozen blood cells (which include immune system cells) and RNA samples from the ACP Repository in order to achieve her research objectives.

Dr. Guerau has a specific interest in whether certain MS-risk SNPs are linked to biomarkers in MS vs. healthy donors. In order to gain insights into these links, Dr. Guerau will also be accessing genetic data that has been returned to ACP. This data was generated by the International MS Genetics Consortium (IMSGC), a project that included ACP patient DNA samples in a large, multinational study on genetic markers that are associated with MS. Through access to this returned data set, Dr. Guerau will be able to gain further insights into how genes impinge on MS pathogenic mechanisms and biomarkers. Dr. Guerau's approach of building upon the work of others to complement and enhance her work is a perfect example of the value of the open-source and collaborative model at the heart of ACP's mission.

Changing the Course of Neuroscience

Ben Barres, MD PhD 9/13/54 – 12/27/17



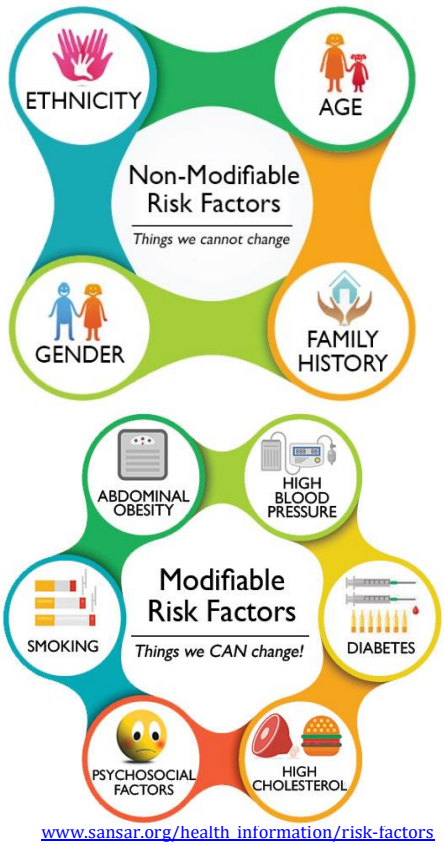
We, at ACP, and the scientific community are saddened by the loss of Dr. Ben Barres, who recently lost his fight with pancreatic cancer. Dr. Barres

was an acclaimed Stanford neuroscientist whose research revolutionized our understanding of the brain. Frustrated at physicians' inability to provide cures or even to understand the causes of complex degenerative brain diseases, his main focus was determining the molecular and cellular causes of brain tissue degeneration. In his early work, Dr. Barres used samples from the ACP Repository for a study that focused on the role of the blood brain barrier in both the cause and progression of MS. He shared ACP's collaborative approach to research and went to great lengths to make his methods and data widely available to others working in the same area. He was known by many in the neuroscience community as the "godfather of glia" for his pioneering research into the roles played by the brain's glial cells. Glial cells make up about 90 percent of the brain's cells and, interestingly, are not nerve cells. Earlier researchers thought that glia merely supplied stability and nutrients to the brain's neurons. Dr. Barres pioneered the idea that glia play a central role in the "wiring" of our brain and are integral for maintaining the brain's network of synapses, through which neurons pass signals to one another. Dr. Barres' research demonstrated that inflamed or "reactive" glial cells play an causal role in neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's diseases, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and glaucoma. In 2011, Dr. Barres co-founded a biotechnology company, Annexon Biosciences, to translate these findings into drugs that could someday succeed in retarding or preventing the progression of neurodegenerative disorders. Dr. Barres not only changed the course of neuroscience, but he also cared deeply about other people and touched many lives. He was devoted to his students and trainees, and was beloved for his efforts to promote equity and diversity in science.

Modifiable Dietary Factors and MS

By Farren Briggs PhD, ScM

Within the last several years, there has been a steady stream of scientific publications focusing on modifiable factors, whether behavioral or lifestyle, on the pathoetiology of MS. Modifiable factors are things we can change, and therefore research on these agents is



www.sansar.org/health_information/risk-factors

exceptionally important and particularly of interest to everyone affected by chronic conditions – we all want to know what we can personally do to improve our health. However, understanding the role of non-modifiable factors is critical to understanding the biological mechanisms contributing to onset and outcomes (i.e. genetic analyses to uncover biological processes involved in rapid disability accrual – which may eventually lead to improved screening tests and interventions for those with the greatest risk of severe disability). This month two papers related to diet, which is becoming a popular avenue of research in MS, were published.

The first study, by Tankou et al, published in the *Multiple Sclerosis Journal*, was a pilot study on the influence of probiotics in MS.[1] This study compliments several studies investigating the gut microbiome (e.g. those reported on in the September 2017 Newsletter). There is enough gathering evidence suggesting the microbiome plays a role in MS risk and progression, but the *how* and *why* are still fuzzy. We also do not know if we can sufficiently alter our microbiome in order to affect some sort of change. For example, can we take a probiotic to alter our gut microbiome? This pilot study of 9 MS subjects and 13 unaffected controls adds to the beginning conversation in MS. All study participants were given a twice daily, oral dose of a probiotic cocktail VSL3 for two months. The daily dose included **3.6 trillion** cells of eight bacteria. Prior studies of VSL3 suggest it may have anti-inflammatory properties and promote neuroprotection, but little is known about the influence on circulating immune cells. First, administration of VSL3 did alter the composition of the gut microbiome (detected in fecal samples) in unaffected controls, and a similar (though not statistically significant trend) was observed in the MS subjects. Upon discontinuation of the VSL3 probiotic, the gut microbiome shifted back to baseline patterns in all study participants. Second, the researchers looked at the composition of circulating immune cells at baseline, during probiotic supplementation, and a few months after the study had stopped. The frequency of several different immune cells were influenced – generally, there were fewer inflammatory cells during supplementation. For a study of 22 individuals, these interesting results beg further investigation in a larger sample size, as well as if other strains of probiotics show similar results, whether disease modifying therapies influence gut microbiomes, and so forth.

Grapefruits are one of my favorite fruits. As a child, I would slice a grapefruit in half and top it with sweetened condensed milk… it's a Caribbean thing, but I haven't done this in decades ¯_(ツ)_/¯. The second study, by Wang et al, published in the *Journal of Nutritional Biochemistry*, focused on the effect of naringenin in the mouse model of MS (experimental autoimmune

encephalomyelitis [EAE]). Naringenin is a common flavonoid in tomatoes, and citrus fruits, including grapefruit. Up to **10%** of a grapefruit is naringenin. Prior research in animals and immune cells suggests naringenin may influence the immune system. For this study, there were two groups of EAE mice: 1) fed a normal diet, and 2) fed a normal diet supplemented with a low dose of naringenin. The first result was to determine if naringenin influenced the onset of EAE/MS in the mice – and it did! Only 63% of mice on naringenin developed EAE, while 100% not on naringenin developed EAE. Also, for the mice on naringenin that did develop EAE, their onset was delayed and the disease course was milder than the untreated counterparts (Figure 1). Naringenin also reduced the development of autoreactive T-cells – those pesky immune cells that attack myelin. In addition, the research showed that treated mice had less inflammation and myelin destruction in their central nervous tissue, as well as less invasion of immune cells into the central nervous system. And lastly, the research showed that naringenin slowed the disease course in mice treated **after** the onset of EAE (Figure 2). For an animal study, this is very exciting. Now we need to study naringenin in humans. Key questions would be: Does it work in humans? If so, what is a safe dose? What does it do in a human body? What genes are activated? Nonetheless, it was a very cool mouse study.

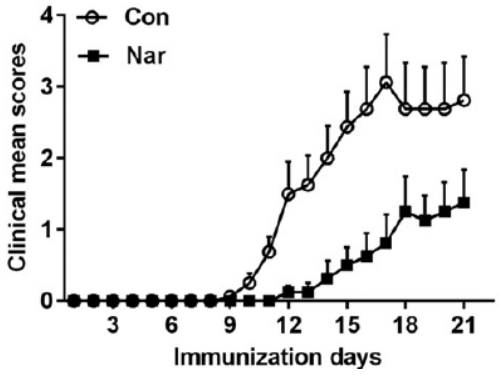


Figure 1: Early administration of naringenin delayed the onset of EAE and the severity in EAE mice.

In summary, both these studies address **potential** modifiable dietary opportunities in MS – they generate many intriguing questions, and will serve as a scientific foundation for many future studies.

(Grapefruits contain a compound, furancoumarins, that blocks an enzyme CYP3A4 needed to metabolize several drugs.[3] Speak to a health professional before you add grapefruit-condensed milk combos to your diet!)

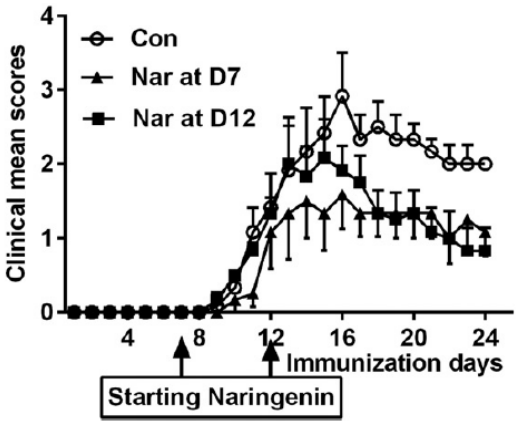


Figure 2: Dietary naringenin administered after EAE onset, on day 7 and day 12 and resulted in reduced severity.

1. https://www.ncbi.nlm.nih.gov/pubmed/29307299
2. https://www.ncbi.nlm.nih.gov/pubmed/29331869
3. https://www.drugs.com/article/grapefruit-drug-interactions.html

A Conversation with the Wheelchair Kamikaze

Marc Stecker, also known as the Wheelchair Kamikaze, has been sharing his perspective and experiences through his blog as he's navigated his life with MS since 2009. Ranging from heartfelt, to humorous, to candid, to persuasive, his posts are intended to share with, inform, and entertain his readers. With more than 3 million page views since its inception, the Wheelchair Kamikaze blog is interesting and compelling reading for anyone, whether you have MS or not. According to Marc, **"**The blog has put some method to the madness of my getting sick. I'm of mixed minds when it comes to subjects like fate, but the fact that Wheelchair Kamikaze may have, if even in the smallest of ways, helped some of my fellow members in this club that none of us ever wanted to join feel a little less overwhelmed by it all, then I am forever humbled and graced."

Marc grew up in New York City, where he currently resides. He studied film at Boston University and was the lead singer in a punk rock band in the 1980's. After school he lived in South Florida for about 10 years, during which he broke into the world of corporate video production and television. Eventually he followed his heart and returned to New York City. He was soon working freelance as a video editor and was eventually hired at Sony Music Studios as head of their DVD production department. It was an exciting place to work, with celebrities everywhere, but Marc wasn't content. He always had literary aspirations, and the administrative duties at Sony Music Studios weren't creative enough.

Marc was diagnosed with primary progressive MS in 2003 and was forced to retire in 2007. At that time he was an active member of several online MS forums. As he learned more about MS, he tried to pass on what he was learning to other forum members, many of whom encouraged him to start blogging. Before his diagnosis, Marc was also an avid amateur photographer. However, his disability soon made it impossible for him to lift a camera to his eye. Encouraging him to continue to follow his passion, Marc's wife gave him a flexible tripod and a camera with video capabilities and a flip out view screen. This made it so Marc didn't have to lift the camera to his eye in order to take the pictures and movies that he enjoyed so much. Reluctantly at first, he hooked the tripod and camera up to his wheelchair, began taping videos of New York City excursions in his wheelchair (often while driving at full speed, hence the name "Wheelchair Kamikaze") and doing voiceover narration of them. He sent them to friends and family who, thinking they had viral potential, encouraged him to share them more broadly. According to Marc, "before I got the wheelchair I was so limited, I was housebound. I got the wheelchair very reluctantly and suddenly the whole world opened up to me and I spent countless hours exploring every nook and cranny of Central Park. I had unlimited time, and was taking pictures. Central Park became my muse. The wheelchair

awakened in me a lot of passions that had lain dormant for decades. I rediscovered who I was. It allowed me to follow passions I'd dreamed of until my disease became more invasive." Marc's blog started about 6 months after he got his wheelchair as a repository for his videos and photos. He never expected more than a dozen friends and family to ever look at them. He then started writing and the rest is history.

Marc's blogs are driven by the latest MS research and his own experiences with the disease. When he was less disabled, he was out interacting with people and taking pictures, which would also spur ideas. Wheelchair Kamikaze has a wide audience that includes MS patients, patients with other chronic illnesses, neurologists, as well as people that are healthy. Marc remembers being astounded by the first email from someone who read his posts. Around 2010, Marc blogged about a new, alternative theory of MS involving blood flow in MS patients. As interest in the theory grew, so did the number of page views on Wheelchair Kamikaze, going from a few dozen page hits per day to thousands. Marc received emails from people all over the world. The craze on the theory came and went, but the popularity of Marc's writing remains. Although he posts less frequently these days, he enjoys interacting with his readers and tries to answer as many emails as he can, as personally as he can. According to Marc, "The impact is far beyond anything I would have imagined. The hope is that it illuminates not only life with MS, but a little bit of the human condition."

As depicted in one of Marc's popular videos, Wheelchair Kamikaze: Dash Down Amsterdam, people with MS in wheelchairs face many physical challenges and obstacles while functioning in their daily lives. In our interview, he also shares his insight and perspective on some of the more psychological aspects of dealing with increasing disability, such as appreciating time as a gift that shouldn't be taken for granted. In addition, Marc shares some positives from his journey with MS. MS has helped him learn to forgive others (and himself), he's learned precisely where his passions and priorities lie, and to value the people that he loves. In facing the challenges of daily living with MS, Marc has learned he's much tougher than he ever imagined he could be.

Recent research results have often fueled Marc's posts. Recently, he is most passionate about research that is geared toward finding a cure for MS. Marc has never participated in a clinical trial, but has tried a number of alternative therapies. As described in his blog, Marc does a cycle of the Fast Mimicking Diet once every 6 - 8 weeks. He's also tried intravenous glutathione (an anti-oxidant) and acupuncture (both western and traditional Chinese). He sees a Naturopathic doctor who is a part of the neurology practice he goes to for his care. On her advice, he is taking a number of supplements, which help symptomatically. Of interest, Marc plans to post a 90-minute interview

with her on his website in the near future, containing many actionable items that people can take advantage of.

Marc has been involved with ACP for a long time, participating in both the Repository and iConquerMS™. With regards to iConquerMS, Marc states, "being able to take a look at data from thousands of patients and being able to analyze all of the data could lead to tremendous breakthroughs. It's a tremendously valuable project and is definitely on the right track…iConquerMS needs to get to critical mass that is truly indicative of a cross section of the entire MS population. Then it could be a game changer. The team they've assembled is incredible and dedicated. I'm confident we'll figure out a way to get there."

Marc generously allowed us to tape the interview for this article. If you're interested in listening to Marc share his experiences and perspective, please click here. Whether you have MS or not, stay tuned to Wheelchair Kamikaze. You will be entertained, touched, informed and left wanting to read more!

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