

# Accelerated Cure Project for MS

## February 2018



*Accelerating research towards a  
cure for multiple sclerosis*

### **ACTRIMS 2018 – Immune Response, Remyelination and Repair**

Two significant presentations at ACTRIMS 2018 in San Diego this month were the Kenneth P. Johnson Memorial Lecture (delivered by Dr. Suhayl Dhib-Jalbut of Rutgers University) and the NMSS Barancik Award Presentation (delivered by Dr. Robin Franklin of Cambridge University). Both presentations focused on disease mechanisms that are age-related.



Dr. Suhayl Dhib-Jalbut's presentation was entitled "Gut dysbiosis breaks immunological tolerance and contributes to multiple sclerosis". Diet and its effect on the gut microbiome are recognized as playing a significant role in health and disease, including MS. Dr. Dhib-Jalbut focused on the role that the gut microbiome may play in combination with genetic and environmental factors that trigger the immune system and elicit disease. He emphasized how gut bacteria can affect the mechanisms of immune tolerance, the "normal" condition where the immune system does not attack myelin.

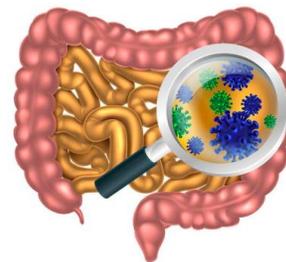
Fundamental to the disease process of MS is the immune response to myelin. Fragments of myelin generated by the tissue damage associated with the early phase of the immune response, cause specific myelin antibody-bearing cells (called T-cells) to elicit a later, specific immune response to myelin.

Dr. Dhib-Jalbut's work involved the creation of a new mouse MS disease model with a partially "humanized" immune system that was created by the transfer of specific sequences obtained from MS

patient DNA and transferred to the mouse genome. These sequences were derived from several disease-associated human genes that were identified by large-scale genetic studies performed several years ago by the International MS Genetics Consortium (IMSGC). The resulting “hybrid” mouse showed disease symptoms similar to those of MS.

MS is age dependent, with disease onset occurring in young to middle-aged adults. This new mouse disease model shows spontaneous disease (muscle paralysis) at a frequency of 25%. The symptomatic mice also show an age distribution of disease that is similar to MS in the sense that disease symptoms occur more frequently in young adult and middle-aged mice, and not in very young or old animals. Further analyses showed that young and aged mice were more “tolerant” to myelin basic protein (their “humanized” immune systems did not react as frequently to myelin). Myelin-reactive immune cell populations were also shown to be lower in young and aged mice than in “middle aged” mice.

The next step in the research examined the role of the gut microbiome in these disease susceptible mice. The mice can be made myelin-tolerant and disease free in the complete absence of gut bacteria (created by transplanting germ-free embryos to a germ-free surrogate mother). As an additional confirmation, antibiotic treated mice also did not develop disease. Further work showed that, because the gut is inflamed and leaky in the mouse disease model (as in MS patients) this condition allows specific microbe-derived molecules in the gut to access the immune system and to regulate mechanisms that increase myelin reactive immune cell populations. Additional experiments, where human feces containing gut bacteria were transplanted to germ-free mice, demonstrated that only MS feces, and not feces from a healthy human donor, induced symptomatic disease in mice. Gut bacteria were screened for their effect on the mouse immune system and predominantly one species was shown to most efficiently induce disease symptoms in the mouse model.

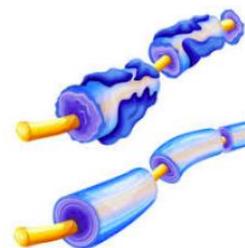


#### **In summary:**

- Gut dysbiosis triggers disease in a humanized mouse model of MS
- This is more likely to occur in young adulthood/middle age
- The mechanism involves the transfer of molecules from the gut which trigger an “autoreactive” immune response
- Gut dysbiosis may play a role in the initiation and progression of MS

Dr. Robin Franklin’s presentation focused on remyelination and repair. He has investigated the role that the progenitor cells of oligodendrocytes (OPCs, the cells that produce myelin in the brain and spinal cord) and specialized immune cells that clean up myelin debris, play in remyelination. He has investigated these mechanisms in the context of the decreased myelin regeneration capacity that is associated with aging. This work has led to the “repurposing” of existing cancer and diabetes drugs for the treatment of MS.

Dr. Franklin's research focuses on the interaction between myelin producing cells, their precursor cells and the cells that remove myelin debris (macrophages and microglia) in the brain and spinal cord. Central nervous system remyelination efficiency declines with age. This was previously discovered by Dr. Franklin's lab to be caused by a reduction in the effectiveness of removal of myelin debris, in both mouse disease models and in MS patients. When the circulatory systems of young and old mice are connected, efficient remyelination



can be restored in the old mice suggesting that “young” cells can restore remyelination. When the capacity of individual cell types from young mice to restore regeneration efficiency in old mice was tested, it was found that macrophages, not oligodendrocytes (nor oligodendrocyte precursors) stimulated this effect. This “young mouse regeneration” effect was discovered to occur via the removal of myelin debris by macrophages. The investigators went on to identify the mechanism that underpins the myelin debris removal in young mice and discovered that drugs that activate a specific molecule (the retinoid X receptor or RXR) could restore myelin debris removal in ageing mice. One of these RXR specific drugs was bexarotene, a cancer drug, which is now being tested in a MS clinical study. The RXR often functions in combination with the vitamin D receptor. In mice, vitamin D can also replicate the remyelination effect described above. This result is significant because a reduced level of vitamin D in the blood is a known risk factor for developing MS.

Dr. Franklin also presented some recent research focused on the regenerative capacity of oligodendrocyte precursor cells (OPCs) in aging mice and has opened the possibility of using type 2 diabetes drugs to treat MS.

OPCs from old mice fail to respond to drugs that normally induce remyelination. Gene expression analysis of young vs. old OPCs revealed that nutrient signaling pathways in OPC mitochondria (the energy producing “power packs” in cells) were involved in the drug-stimulated remyelination. If aging mice are calorie restricted (which affects mitochondrial function), OPCs can be “reprogrammed” to be remyelination capable. The research team went on to test known drugs that target mitochondria and are known to affect the calorie-restriction mechanism. Metformin, a commonly used type II diabetes drug that acts on mitochondria, was shown to “recalibrate” OPCs to be myelination capable. This opens up the possibility for metformin and other diabetes medications to be tested in MS remyelination.

### **In Summary:**

- The ability to remyelinate axons declines with age due to decreased efficiency of myelin debris clearance by cells (macrophages) that clear myelin debris as well as the decreased capacity of OPCs to produce myelin
- Retinoid X receptor pathway activators such as the drug bexarotene, mediate the age-related decline in myelin debris clearance and promote remyelination
- Metformin, a type 2 diabetes drug which can mimic the effects of calorie restriction, can recalibrate OPCs to remyelinate axons