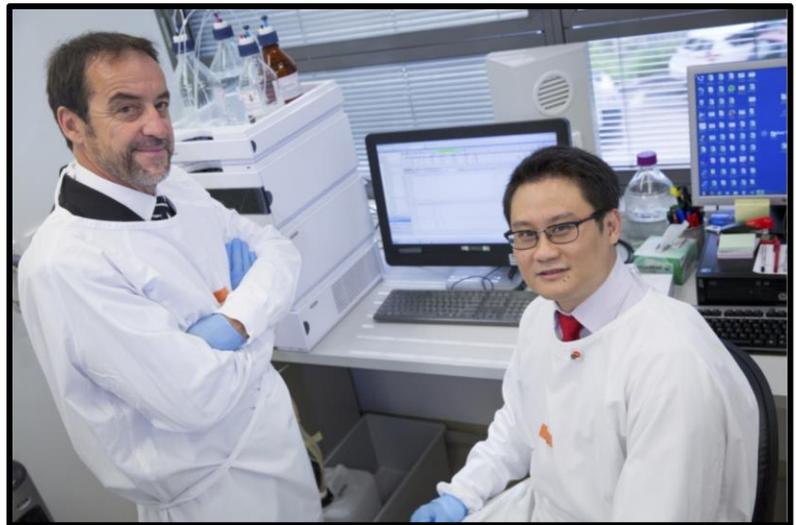# ACP Resources Help Scientists Gain New Insights Into MS Progression

As we have reported in previous issues of the newsletter, ACP accelerates MS research by distributing samples and data from the Repository that many of you helped to create, to scientists studying MS. At the heart of ACP's mission is providing resources that enable scientists to do important work that positively impacts the lives of people affected by MS. What sets us apart from other MS organizations is that we partner with hundreds of scientists, in a wide array of institutions, literally all over the globe. We think it's impossible to predict where the next great discovery in MS treatment will be found. Accordingly, our resources are "open source," meaning that we're willing and able to invest in *every* MS researcher, wherever they may be.

This is the story of one investigation, conducted by a team of nine scientists from four Australian universities and a French biotechnology company, led by Dr. Gilles Guillemin of the Faculty of Medicine and Health Sciences, Macquarie University, New South Wales, Australia. Guillemin and his team used ACP samples and data, to discover the existence of possible biomarkers for MS. Their discovery may help physicians to diagnose MS, while providing new insight into a mechanism that could determine the transition from relapsing remitting MS (with its characteristic inflammatory attacks) to secondary

Photograph by Carmen Lee

progressive MS (defined by lasting loss of neural function). It may also have revealed novel drug targets. Their work was detailed in an article published earlier this month, in the online journal Nature Scientific Reports (http://www.nature.com/scientificreports),[1] from which the information that follows was taken.

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[1] Lim, C. K. *et al*. Kynurenine pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. *Sci. Rep.* **7**, 41473; doi: 10.1038/srep41473 (2017).

The story begins with the essential amino acid, tryptophan (a breakdown product of dietary protein), which the body metabolizes at higher levels when activated by inflammation, such as occurs in people with MS. When tryptophan is metabolized, it activates a pathway known as the kynurenine pathway (KP). Activation of the KP is one way the body blunts the force of acute inflammation, such as occurs during relapsing episodes of MS. In progressive forms of MS where inflammation is longer term, chronic activation of the KP occurs and may explain some symptoms of MS such as mood changes, reduced cognition and fatigue. It also produces a molecule, which, at elevated levels, causes neuronal death and is associated with the progression of neurodegenerative disease.

The Use of ACP's Repository Samples and Data

To gain insights into the links between inflammation, the KP and the progression of multiple sclerosis, Guillemin's team investigated the presence of substances formed in, or necessary for, the metabolism of tryptophan via the KP in MS patients. To do so, they obtained serum samples and data from patients with RRMS, SPMS, primary progressive MS (PPMS) and healthy controls from ACP's Repository. The samples were primarily derived from blood donations collected between 2006 and 2010. Data consisted of demographic and medical information, as well as information about the donors' observable physical or biochemical characteristics and the results of common diagnostic and monitoring tests they had undergone. All in all, there was a total of 136 "ACP participants," consisting of 50 with RRMS, 20 with SPMS, 17 with PPMS and 49 healthy controls.

The ACP Repository had an insufficient number of longitudinally collected samples (samples collected from the same people, over a period of time), to meet the scientists' requirements. Accordingly, they obtained those blood samples from an Australian study known as the Tasmanian MS Longitudinal Study, which was conducted between 2003 and 2005.

The Investigation

Most significantly, the scientists found aberrant levels of *two key substances* that are present when the KP is activated, one that is neuroprotective and the other that is neurotoxic. Kynurenic acid (KA) is a brain compound that is neuroprotective. Quinolinic acid (QA) has a

potent toxic effect on the nervous system, leading to acute neuronal death and hence to chronic dysfunction.

The KP is the major route that breaks down tryptophan. Within the brain and central nervous system, when the KP is activated, QA is produced by microglia (a type of glial cell that is prevalent throughout the brain). These cells act as the first and main form of active immune defense in the central nervous system (CNS). KA blocks the toxic effects of QA.

An important aspect of this study is that when the scientists looked at blood samples of people with MS and found KP metabolic "signatures," these metabolite patterns were very similar to the patterns seen in the fluid that bathes the brain and spinal cord. This bodes well for the development of a tractable blood test. Using these biomarkers, the scientists observed a strong correlation of marker levels with disease severity and were also able to distinguish between the MS subtypes, RRMS, and SPMS, with an accuracy rate of 85% in a blinded test. Their studies suggest that abnormalities in the KP may be associated with the transition from earlier stage MS to debilitating progressive forms of the disease.

Although we think that inflammation contributes to neurodegeneration and is linked to MS progression, we still don't know why approximately 50% of relapsing remitting MS patients progress to secondary progressive MS, while 50% do not. This study sought to better understand the mechanisms that drive one course of the disease versus the other. Since the kynurenine pathway (KP) is induced in inflammatory environments, and the amino acid tryptophan was previously known to have decreased in MS patients, the investigators wondered whether changes in the KP might have some relationship to the progressive "switch" in MS.

They asked the question: is there a causal relationship between this metabolic shift in the KP and the transition in people with RRMS to SPMS or other more debilitating forms of the disease? Currently, there are no biomarkers that can identify this transition, and a reliable biomarker could be useful to assess the prognosis for people with MS, and could even lead to the discovery of new therapeutics to limit, slow or halt the transition.

All the samples of people with MS (of all types) revealed significantly higher concentrations of KA vs QA, compared with people in the healthy controls group. They also showed that changes in the KP could potentially lead to well documented MS symptons, including abnormalities in mood, behavior and sleep, as well as to neurodegeneration and both physical and cognitive fatigue. KA levels were highest in the RRMS group, compared with healthy controls and progressive MS groups. The production of QA increased uniformly in concert with disease severity and was particularly elevated in the PPMS group.

All the data generated by the study supported the scientists' hypothesis that toxic KP metabolites fuel neurodegeneration in MS. They also observed that the KP leans towards production of KA, but not QA, during the early course of MS, whereas in the later stages of the disease, the KP is shunted differently, favoring production of QA over KA. The mechanism of

this differential shunting remains unclear, but understanding it better could well lead to new therapeutic options for people with progressive MS.

The data provided by ACP's Repository donors revealed a direct correlation between KP variables and donors' scores on the Expanded Disability Status Scale (EDSS), presenting additional evidence that heightened KP metabolism reflects the progression of the disease. Notably, the KA/QA ratio correlated strongly with EDSS results, underscoring the significance of these key parameters to the disability and severity of MS.

Conclusions

The investigators described the significance of their work as follows:

"To our knowledge, this is the first study using targeted KP metabolomics as a blood-based prognostic biomarker capable of distinguishing MS subtype. Previously, decreased tryptophan was found in MS patients and described as a potential biomarker. However, this study only detected tryptophan and was not capable of detecting other downstream KP metabolites. This study also failed to distinguish between MS subtype. We showed that tryptophan and 3 other metabolites of the KP were important predictors of MS subtype and correlated to disease severity scores. Indeed, the four KP predictors accounted for approximately 90% of the predictive power of our built model with the two inflammatory mediators only adding 10% predictive power. This suggests that tryptophan metabolism is more relevant to MS pathology than general inflammation.

In conclusion, our results demonstrate that KP parameters have a strong association with MS subtype, correlating with disease severity scores. The changing levels of KP metabolites we observed also provides a mechanistic insight that may explain the transition from the milder RRMS form to the more debilitating SPMS disease form. KP profiling is likely to be relevant to the pathogenesis of other diseases characterized by inflammation and neurodegeneration, like Alzheimer's disease, Parkinson's disease and ALS, where aberrant KP metabolism has been reported. Our results also suggest that strategies aimed at rebalancing the KP, particularly in terms of QA/KA levels, could be useful therapeutic approaches in slowing neurodegeneration in MS."

If you are one of the thousands of people who contributed blood and data to create ACP's Repository, then YOU have contributed to a critical discovery about MS. It may point the way to faster, more precise diagnoses, as well as to future treatments for MS, including treatments for progressive forms of the disease. At ACP, we are thrilled to partner with you and members of the scientific community on this journey.

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