New Zealand Company, Innate Immunotherapeutics, Explores Treatment for Progressive MS

Since 2006, when ACP created the Repository of biological samples, over 90 requests for samples from researchers working on multiple sclerosis (MS) have been fulfilled. The significance of this is that every day, somewhere in the world, scientific research on MS is being done using this valuable resource. As we noted in our January newsletter, wherein we traced the international journey of just one biological sample from "Patient 221," by supplying this critical resource to MS researchers, ACP achieves global reach and impact.

A central tenet of the ACP Repository is that we supply resources to a wide variety of scientists around the globe, because we believe that *scientific advances can come from anywhere.* None of us has the power to predict where the next blockbuster drug or possible cure will be hatched.

Whether far away or close to home, a particular challenge that MS researchers face is that they don't fully understand the causes of MS. In their search for causes, scientists typically focus their attentions on specific pathways or biological targets that underpin disease pathology. Biological samples from patients play an important role in these investigations. Drug discovery efforts are then focused on modifying the functions of identified targets and pathways and observing the impact of these modifications on disease symptoms, first in animal models of disease, then in humans.

One such example of promising MS drug discovery occurring on the other side of the globe is the work being done by a small innovative company based in Auckland, New Zealand. Innate Immunotherapeutics is developing a drug that modifies the function of the immune system in order to interrupt a pathological process that occurs in progressive multiple sclerosis (MS). Innate sought out ACP's repository samples to help them understand how their drug works. Given the fact that there are no approved treatments for progressive MS, Innate's drug, MIS416, could have a significant impact on the treatment of that form of MS.

To understand their work, it helps to know that our immune system has two complimentary wings that work in tandem. The innate wing serves to provide rapid, non-specific anti-infective immunity and also coordinates repair to the body following damage due to injury or disease. The adaptive wing is slower to develop and is specific for each individual infection. The development of adaptive immunity depends on the instructions given by the innate wing.

In diseases such as multiple sclerosis, there is a breakdown in communication and cooperation between the innate and adaptive wings and adaptive immunity specific for the central nervous system develops, resulting in progressive degeneration of the central nervous system. To date, therapies for multiple sclerosis have focused on targeting the adaptive biology to treat this disease. However, more recently it has become apparent that the innate wing contributes to disease progression as well, through ongoing contribution to destructive inflammatory pathways that occur within the central nervous system. There are currently no approved therapies that target innate-associated inflammation.

Innate Immunotherapeutics derives its name from the innate immune system and is leveraging the powerful immunoregulatory features of the innate wing that are associated with anti-inflammatory activity and the establishment of effective neuro-repair pathways. Innate's drug, MIS416, is composed of two distinct potent stimulators of the innate immune response that are of bacterial origin. These stimulators are formulated as a microparticle, which further assists in targeting the appropriate innate immune cells that are particularly associated with anti-inflammatory activity.

The drug has shown efficacy in early clinical studies to test safety and efficacy in secondary progressive MS; study participants showed that the drug was well tolerated, along with early evidence of neurological improvements over the 12 week trial. Many of these early clinical trial patients remain on therapy to-date under a compassionate use program accessible in New Zealand, with no evidence of disease progression and persistence of the neurological improvements seen during the clinical trial. These early studies underpin the current Phase 2b "efficacy" clinical trial, which is designed to formally demonstrate that MIS416 therapy leads to neurological improvement in secondary progressive MS patients. This trial is placebo controlled and also "blinded" to both the patient and treating clinician, and follows the patients over a 12-month treatment period.

Innovative pre-clinical research has provided an understanding of the mechanism underpinning the efficacy of MIS416 in MS. This work has shown that the drug suppresses not only the development of adaptive immunity more relevant to the earlier relapsing-remitting phase of MS, but more importantly, suppresses the innate immune inflammatory pathways that drive the progressive stage of disease, which are independent of adaptive immunity.

Innate Immunotherapeutics is using specific samples from ACP's repository to further examine the mechanism of action of MIS416. There are two therapies approved for relapsing-remitting MS (interferon beta and Copaxone), which do not work in secondary progressive MS (SPMS). However, they may overlap with MIS416 in some of the immune pathways they stimulate. ACP has immune cells from the blood of (SPMS) patients who are still being treated with these relapsing remitting therapies, in spite of their demonstrated lack of efficacy. The goal is to

compare blood immune cells from MIS416 treated patients with these samples to assist with the further identification of the unique pathways that MIS416 drives.

Samples with these characteristics are not available in New Zealand (and many other parts of the world) because people with SPMS are not approved to receive treatment with relapse remitting drugs (the treatment is not covered by the public health system). Innate's Chief Scientific Officer, Dr. Gill Webster, called it a "Good day at the office," as she recalled learning of ACP's Repository from Marie Wesselhoft of Tucson-Based MSDx (profiled in our July, 2015 newsletter), a company with which Innate is collaborating on the search for SPMS biomarkers.

Blood serum from the same patients has also been obtained and is being analyzed for levels of key signaling molecules associated with MIS416 therapy such as interferon gamma. Says Webster, "This work will contribute to the improved understanding of key immune mechanisms that may be able to inhibit progressive MS, and also these findings are important for the clinical development of MIS416 as a therapy for progressive MS." Asked what she would like to communicate to people with SPMS, Dr. Webster replied, "MIS416 is the first drug of its kind. It halts the smoldering inflammation in your brain. How we accomplish that feat is novel. We do it by stimulating the repair wing of the immune system to put out the fire and encourage repair."

The groundbreaking work at Innate Immunotherapeutics is just one of many examples of the use of the ACP Repository accelerating MS drug discovery in new and novel ways. If you are one of the thousands of people who donated your blood sample to ACP, take a moment to pat yourself on the back for the contribution you are making to science. And, if you are not among them, but you want to impact MS research going forward, **please consider becoming a registered member of iConquerMS™ (www.iconquerms.org), our growing patient-powered research network, today**. Stay tuned in the coming months for more articles about the MS research frontier and the ways that ACP is impacting progress.