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Dear Friends,

We may be in the dog days of summer, but there's plenty of activity here at ACP. In this issue we report on the promising research trend of hunting for biomarkers to easily and reliably diagnose, treat and predict the future course of MS, using samples from the ACP Repository. We announce the launch of a new long-term MS research project called REAL MS™, which aims to identify ways to personalize care across the heterogeneous population of people with MS. Finally, we give you an update on Kemp Jaycox's successful fundraising walk in Banff National Park last month.

The Search for Biomarkers to Diagnose, Treat and Predict the Course of MS

By David Gwynne and Katina Leodas

In recent months, we have reported on increased activity in ACP's Repository, which equates with increased distribution of samples to MS researchers around the globe. In a few issues, we've provided detailed descriptions of the work of particular scientists. For example, last April we profiled the work of Gillian Webster and her team of researchers at Innate Immunotherapeutics in Sydney, Australia, who are using blood samples from the ACP Repository to modify the function of the immune system in order to interrupt a pathological process that occurs in progressive MS.

We are in an excellent position to take a bird's eye view of MS research, and examine trends in the research being conducted with our samples, since they represent a microcosm of current frontiers in MS research. One notable trend is that in the last six months we have provided samples to a number of investigators who are focused on the discovery of molecular biomarkers in the blood of MS patients.

Molecular biomarkers are alterations in human tissue or body fluids that we can think of as “molecular signals” of biological activity. They provide a dynamic and powerful -- yet objective and measurable -- approach to understanding the spectrum of many diseases, with applications to screening, diagnosis and prognosis. Molecular biomarkers have been applied by generations of scientists to understand and manage a wide range of conditions including cardiovascular disease, infections and cancer, to name just a few.

The discovery of dependable MS biomarkers that are revealed in a simple blood test is very important. Neurologists can use the biomarker profiles of a person with MS to determine:

- Which patients will respond to what drugs. As any person with MS can tell you, there are currently few parameters to guide decisions on which of the twelve approved disease-modifying drugs should be prescribed, so people with MS are often switched from one drug to another as a result of a lack of efficacy or intolerable side effects.
- Which people with relapsing-remitting MS have a high likelihood of transitioning to chronic (secondary) progressive MS.
- Whether the current disease classification system (relapsing-remitting, primary progressive, secondary progressive) is appropriate with regard to patient-specific treatment.

In addition, drug-discovery scientists can use biomarker profiles to understand the specific biochemical processes, such as the immune response or neurodegeneration, that underpin MS. This can lead to the discovery of novel drug targets.

For those of us who are not scientists, it may help to review the basic biology behind the importance of molecular biomarkers. In all of us, a gene is a portion of a DNA molecule that encodes a functional RNA or protein product, and is the molecular unit of heredity. One type of RNA, known as a “messenger RNA,” serves as a temporary copy or template of the information found in DNA. These messenger templates are then read (“translated”) into proteins in the same way that computer code can be read by a 3-D printer, to manufacture a variety of specific shapes.

Proteins comprise most of the three dimensional molecules that support biological function. These include molecules that are secreted by certain cells of the immune system and have an effect on other cells, including growth factors and hormones (“keys"), which regulate biological processes and the molecules that they bind to, to signal changes in the activity of cells (“locks"). These biological keys and locks also include the molecules that regulate the reading of the gene code (gene expression).

Most diseases, including MS, are caused by defects in these “locks and keys.” The defects can be faulty proteins (defective keys or locks encoded by mutated genes) or caused by an abnormality in the way the gene code is read (keys and locks are not produced at sufficient levels or are produced in the wrong place or at the wrong time). In addition to proteins, a variety of different RNA molecules can also play a role as regulators of all of the steps from gene expression to protein production.

Mutated genes can be detected by “reading” the genetic code. Aberrations in gene expression can be detected by examining proteins and RNAs in blood. ACP’s Repository includes DNA that can be read to detect mutations. Its samples, which consist of whole blood that has been separated into component parts such as serum and plasma, can provide a “snapshot” in time of dysregulated gene expression in the form of protein and RNA profiles. Because we can provide detailed characteristics for each sample

donor, this research data can be correlated with each donor's profile (personal characteristics, such as ethnicity, observations by the patient's neurologist, lifestyle, etc.).

Each of the investigators who is using ACP samples to study biomarkers in MS is undertaking a slightly different blood-based analysis and studying a different category of molecules. Several have the objective of developing tools that can predict how disease will progress in individual patients (e.g. from relapsing to progressive disease). The RNAs that are being studied include fragments of messenger RNAs that encode proteins as well as regulatory RNAs that control gene expression. Changes in these RNAs could provide useful biomarkers that can be developed further to diagnose or predict the future course of MS.

MS is a complex disease and research rarely produces instant insights. By its very nature, it is a slow, iterative process and it will likely be years before we understand or experience the benefits of these studies on biomarkers. But as Anita Williams, a member of iConquerMS™, wrote recently in describing her own journey of learning about her MS, "[With research], MS became less of a scary fog of unknowingness. Research stripped away the mystery and in its wake left the powerful gift of knowledge. We know what we know about MS because others heeded the call to contribute to the MS body of knowledge. Multiple sclerosis research has given me a treatment that enhances my life and a solid hope for a cure."[1]

REAL MS™: A Platform for Personalized Medicine Research in MS

In June, we reported on iConquerMS™, a 3,000-strong patient-powered research network for people with MS, which Accelerated Cure Project has been building for the past 18 months. This month, IConquerMS™ launched a pathbreaking MS research initiative. Called REAL MS™, the effort will be a longitudinal study of MS. It is intended to answer important questions about the heterogeneity of the experience of MS across the population of people living with the disease and to identify ways to personalize clinical care by identifying factors that affect progression and treatment outcomes. REAL MS™ (Research Engagement About Life with Multiple Sclerosis) will encompass a diverse population of thousands of individuals living with MS, who will participate by answering online questionnaires about their disease experience and by providing biosamples for molecular analysis. For each person living with the disease, REAL MS™ will be a very personal study about them and others like them living with the disease.

[1] Williams, Anita. "On the Shoulders of Giants." *MS Connection.* National MS Society, August 11, 2016.

REAL MS™ is modeled on the Framingham Heart Study, a longitudinal community-based research study launched in 1948, which has had a profound impact on our understanding of the causes of heart disease and how to treat and prevent it over the past 68 years. REAL MS™ emphasizes identification of personal characteristics and environmental factors that may interact with genetic predispositions to influence outcomes, and the discovery of molecular biomarkers of the disease through genomic and other biochemical profiling. Participation of a diverse population of those living with MS to provide their ideas on research conducted with their information, and a commitment on the part of the iConquerMS™ leadership to promptly and openly share research findings, are important aspects of the REAL MS™ study.

Current MS subtypes (relapsing and progressive) are broadly defined based on the presence or absence of disease relapses. "REAL MS™ may accelerate personalized approaches to MS by making it possible to classify individuals into new subtypes based on comprehensive personal characteristics and laboratory data and then to enable prediction of the likely course of disease based on such subtypes. The study could also provide people with MS and their physicians with new information on their likely response to particular disease-modifying therapeutics, and facilitate interventions early with treatment strategies to arrest, cure or prevent MS. In these ways, REAL MS™ has the potential to impact both short and long-term. By studying the patterns of many thousands of individuals living with MS, researchers may be able to discern patterns about factors that slow the disease or improve day-to-day functioning. Similarly, by identifying genomic and other biochemical factors, the study might provide biological pathways for new treatments that will arrest, cure or prevent the disease longer-term, including a new understanding of biological mechanisms of progressive MS for which there currently are no approved treatments.

"Those of us living with multiple sclerosis are very excited by the launch of the REAL MS™ study," noted Laura Kolaczkowski, Lead Patient Representative and Co-Principal Investigator of iConquerMS™. "We see it as the first-ever opportunity for active involvement of participants in determining which research questions will be studied and how research protocols are designed. Those of us who live with MS now have a voice in research, and if as a result, new knowledge emerges to guide our treatment choices based on individual characteristics, the impact will be tremendous."

Qualified researchers will be able to access the REAL MS™ dataset for their ongoing or new studies about causes and progression of MS. They will also have the opportunity to conduct special data collection activities via iConquerMS™ for specific research studies; to collect biosamples and conduct genomic and other biochemical analyses; and to seek individuals with certain characteristics for their research studies or clinical trials of targeted treatments. However, because REAL MS™ is not a study of a particular drug, FDA approval of the study design was not needed. Instead, REAL MS™ has been reviewed and approved by an IRB (that is, an Institutional Review Board), a special body that ensures that research subjects will not be exposed to unethical research practices.

In the coming months, we will be sharing more information and news about REAL MS™. In the meantime, to get started you must join iConquerMS™ by reviewing and signing a consent form located at www.iConquerMS.org/join. You will be asked to fill in detailed questionnaires online twice each year about your personal characteristics and background, your health history and your experience with multiple sclerosis.

Update on Kemp Jaycox and His Family's Walk for MS

In June, we told you about ACP-booster, Kemp Jaycox, and his plan to raise money for ACP by walking with his family while on vacation in Banff National Park in July. We're pleased to report that the event was a huge success. Kemp writes, " I want to give sincere thanks to all of you who have donated to the Accelerated Cure Project for my MS walk. We had a great vacation in Western Canada, including an amazing train ride through the Canadian Rockies. We hiked and scooted on a trail to lower Johnston Falls in Banff National Park. Costanza (my scooter) got a helluva workout! There were lots of small hills, bumps and divots and halfway through the walk a large boulder blocked the entire path. Thankfully a random person helped my wife, Cindy, lift the scooter over the boulder. It was like portaging a canoe in the Boundary Waters. If you haven't been to this part of the world, Banff and Lake Louise are amazing.

Together, we raised **$5,234.20** (and counting)! I am always grateful for your support, thoughts and prayers. I pray every day for medical breakthroughs that will help me and millions of other people!"