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
unknowningness. 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.”