

BANK ON A CURE® UPDATE

Myeloma Today in conversation with Dr. Brian Durie

What is the status of the initial phases of the IMF's Bank On A Cure® project?

Bank On A Cure® is the world's first repository of DNA created to advance the understanding of myeloma. The initial phases of this research project, co-chaired by Drs. Gareth Morgan (Institute of Cancer Research, Royal Marsden Hospital, London) and Brian Van Ness (Institute of Human Genetics, University of Minnesota, Minneapolis), have been completed. We have developed a myeloma-specific single nucleotide polymorphism (SNP) chip. Once the custom chip was created, it took several months to get the Affymetrix machines (which run the chip) set up and standardized, both in the US and in the UK, and to get technicians familiarized with the process. Currently, the DNA samples collected from several large clinical trials in the US and in Europe are being analyzed.



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Can you briefly explain what SNPs are and how the custom chip works?

Single nucleotide polymorphisms (SNPs) are genetic variations in DNA sequences, which can affect how we develop diseases and respond to pathogens, chemicals, drugs, etc. Our Affymetrix machines are designed to process and analyze SNPs. While it is now possible to screen the human genome for half a million combinations of genes, such a process would be hugely cumbersome, so we have decided that it is much more efficient to target a smaller group of SNPs that is more likely to be relevant in myeloma. To proceed with a more focused and targeted approach, the Bank On A Cure research team helped select the 3,404 SNPs associated with gene functions that we think are most relevant to the regulation of myeloma growth, disease progression, response to treatment, drug metabolism, bone microenvironment, immune responses, DNA repair, and predisposition to side effects like neuropathy, mucositis, or deep vein thrombosis (DVT). Our custom chip includes all the major sequences where a change in the gene can relate to myeloma.

Can you give us an example of a discovery made from the data processed so far?

One of the Bank On A Cure projects sought to identify genetic pathways that may explain why an estimated 15% to 30% of myeloma patients treated with thalidomide suffer venous thromboembolisms (VTEs), or blood clots, as a major complication. We looked at data on 394 myeloma patients produced from three clinical trials, two performed in Europe and one in the US. We identified four gene clusters associated with the VTEs. It was discovered that the risk of developing VTEs while on thalidomide was mostly related to the genes that control inflammation, with IL6 and TNF shown to be the main cytokines to influence inflammation within blood vessels. Other genes related to drug processing and metabolism have also been linked to the risk of VTEs, which might relate to how quickly a patient responds to treatment. If a patient has a dramatic response to thalidomide, the rapid release of all of the products from the breakdown of the dying myeloma cells can promote clotting via inflammation. So, the

more rapid responses to thalidomide are associated with higher risk of VTEs. It is important to note that VTEs were not associated with any of the blood clotting genes, which supports the notion that aspirin can be helpful as a prophylactic treatment for VTEs.

These Bank On A Cure research findings were presented at the annual meeting of the American Society for Hematology (ASH) in December of 2006, and a manuscript is now being finalized for publication, with Gareth Morgan as the senior author. An update will be presented at the International Myeloma Workshop (IMW) in June of 2007. This will be one of two Bank On A Cure oral presentations to take place at the IMW meeting in Greece.

What is the focus of the second research project to be presented at the IMW meeting?

Dr. Van Ness is working on a paper about the development of our custom SNP chip evaluating the relationships to survival and outcome. He is looking for SNPs associated with event-free survival in patients

in two large clinical trials. Early analysis indicates that there may be detectable genetic differences between short- and long-term survivors, and that it may be possible to predict which patients will need more aggressive therapies when they start their treatment. He is also comparing SNPs of people who have myeloma with those who do not.

Can you tell us about the Bank On A Cure research projects you recently completed?

I looked at the impact of genetic variation on bone disease, focusing on SNPs that correlate with the likelihood that a myeloma patient would get bone disease. We analyzed genes related to various end points within the data set from the 256 myeloma patients who were enrolled in Total Therapy II (TT II), a clinical trial by Drs. Bart Barlogie and John Shaughnessy at the Myeloma Institute for Research and Therapy in Little Rock, AR. When it comes to accurately documenting the presence or absence of bone disease, the TT II data set is the strongest anywhere in the world because all 256 patients got whole body x-ray and MRI plus PET imaging studies performed as necessary. In this Bank On A Cure study, we found that there are several SNPs related to bone disease, four of them linked to the production of a peptide that enhances the formation of osteoclasts, MIP1-alpha. The SNP data analysis is now complete, and we have developed a prognostic tool to help evaluate whether a myeloma patient is likely to get bone disease. A paper on the subject is being prepared.

What's next for Bank On A Cure?

There are many exciting research projects emanating from the Bank On A Cure DNA repository. Readers of Myeloma Today should stay tuned for further developments, which will also be disseminated through the IMF's weekly email updates, Myeloma Minute, as well as the IMF website www.myeloma.org. **MT**