CANCER

# One Foundation's Strategy to Accelerate Drug Discovery Through Genomics

**Louise M. Perkins,[1] Anne Quinn Young,[1]* Kathy Giusti[1]***

**The Multiple Myeloma Research Foundation (MMRF) has the principal goal of accelerating development of next-generation drugs for treating multiple myeloma. By making targeted investments in key research areas such as genomics and epigenetics, the MMRF is helping to elucidate the basic biology of multiple myeloma, to drive promising new treatments into clinical development, and ultimately to link the right treatment to the right patient.**

Multiple myeloma is an incurable cancer of mature B lymphocytes (plasma cells; Fig. 1) affecting 60,000 individuals in the United States (*1*). This heterogeneous disease shows great diversity in molecular features, including several chromosomal translocations involving genes aberrantly juxtaposed to the immunoglobulin heavy chain locus. The pathogenesis of multiple myeloma is poorly understood compared with solid tumors such as breast and colon cancer, and disease progression in individual patients follows an unpredictable course. Four new drugs developed over the past decade have improved patient outcomes, but new treatments are needed to drive the disease into long-term remission.

The Multiple Myeloma Research Foundation (MMRF) was established in 1998 by one of us (K.G.) to accelerate the development of next-generation treatments. In 2004, the MMRF created an affiliate organization, the Multiple Myeloma Research Consortium (MMRC), to address specific critical challenges in drug development. Through an integrated collaborative network of initially four and now 16 North American academic and community centers, the MMRC has built a critical mass of banked tissue samples and has facilitated the conduct of early-stage clinical trials.

Given the rarity and heterogeneity of multiple myeloma, the MMRF has faced enormous scientific and practical challenges, not to mention costs, in driving forward research on this disease and getting new drugs into clinical trials and patients. Here, we discuss some of the strategies we have taken that may be useful for other disease foundations facing similar hurdles.

[1]Multiple Myeloma Research Foundation and Multiple Myeloma Research Consortium, Norwalk, CT 06851, USA
*Corresponding authors. E-mail: QuinnYoungA@themmrf.org (A.Q.Y.); giustik@themmrf.org (K.G.)

## DRIVING TARGET DISCOVERY WITH GENOMICS

Believing that rigorous and thorough genomic analyses will yield new molecular targets to inform drug discovery and development, the MMRF launched the multimillion dollar Multiple Myeloma Genomics Initiative (MMGI) in 2005. The MMGI is the single largest financial research commitment our organization has ever undertaken, and it has recently borne fruit with the report in *Nature* two weeks ago of the genome sequences of myeloma tumor cells from 38 patients (*2*). Working with bone marrow aspirates from myeloma patients containing malignant cells matched with normal peripheral blood samples from the same patients, Todd Golub and his team at the Broad Institute in Cambridge, Massachusetts, used whole-genome and whole-exome sequencing to identify an abundance of new mutations. They highlight mutations in genes associated with protein translation, epigenetic regulation (histone methylation), and blood coagulation. The tumor genome sequences also confirm the importance of the NF-κB) and Ras/Raf signaling pathways in myeloma development: 50% of myeloma patients had activating mutations in NRAS or KRAS, and 4% had oncogenic mutations in BRAF kinase.

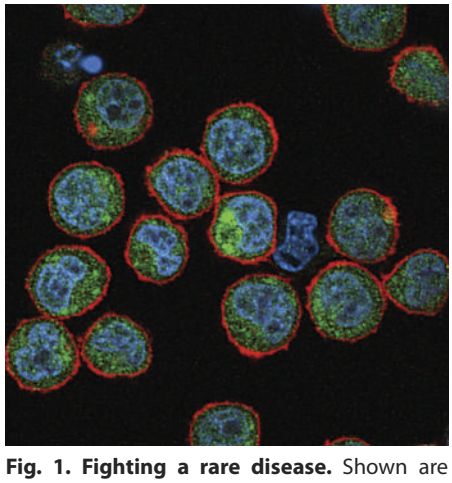

**Fig. 1. Fighting a rare disease.** Shown are multiple myeloma cells (malignant mature B lymphocytes) adhering to fibronectin (red, actin; blue, nucleus; green, phosphorylated focal adhesion kinase).

So what are the key components of the MMGI that made it successful, and what did we learn along the way? In early MMGI planning discussions, the director of the Broad Institute, Eric Lander, stressed that three elements would be needed for success: access to large numbers of high-quality, clinically annotated tissue samples; multiple myeloma clinical experts who could help correlate research findings with the clinical manifestations of the disease; and substantial funding. Together with the Broad Institute and the Translational Genomics Research Institute (TGen) in Phoenix, Arizona, we developed a collaborative project studying a reference collection of 250 myeloma patient samples from the MMRC tissue bank using gene-expression profiling, array comparative genomic hybridization, and, initially, kinome resequencing of these samples. As sequencing technology improved dramatically, the Broad Institute suggested embarking on a more robust program of whole-genome and whole-exome sequencing of myeloma tumor genomes. This adjustment required the collection of additional patient samples to meet the demands for high-quality DNA, which we were able to provide through the MMRC tissue bank.

A critical component of our success has been the availability through the MMRC tissue bank of a large number of clinically annotated, high-quality tissue samples collected from myeloma patients across North America. The MMRC tissue bank now has amassed more than 3,000 patient samples, a tremendous response from a small patient population and a testament to the commitment of our MMRC members. Overcoming what has been a significant challenge to a number of tumor genomic programs, we benefited from having relatively ready access to multiple myeloma cells through bone marrow aspiration and the ability to easily isolate >90% pure, viable tumor cells. To maximize the use of all tissues contributed by MMRC member institutions and to maintain tight consistency and quality, a centralized processing laboratory was established under good laboratory practice (GLP) standards.

Importantly, we and our collaborating researchers are committed to sharing the results of our work freely and to making MMGI genomics data open access. To that end, we provided funds to the Broad Institute to create the Multiple Myeloma Genomics Portal in 2007, which remains the world's only myeloma-specific repository of genomics information (*3*). The portal hosts summary mutation tables from the MMGI sequencing project as well as MMGI gene expression profiling data and copy number variation datasets. The portal, now used by 600 researchers worldwide, also hosts datasets from other multiple myeloma researchers and provides cutting-edge bioinformatics tools to help researchers analyze and interpret their own data. Privacy concerns relating to DNA sequence information prevent unrestricted open access to the whole-genome and whole-exome sequence data; however, consistent with the spirit of open access, qualified researchers will have the opportunity to obtain controlled access to the data through the dbGaP database.

## PURSUING LEADS THROUGH TARGETED RESEARCH INVESTMENT

A principal goal of the MMRF is to act quickly to capitalize on new research data and genomics information to guide strategies for drug discovery and development. For example, last year Carpten and colleagues at TGen reported CpG methylation patterns in multiple myeloma samples from the MMGI reference collection at different stages of the disease. The investigators reported a systematic pattern of DNA hypomethylation in myeloma cells, suggesting that epigenetic dysregulation may contribute to tumor formation and progression (*4*). This work complements the new findings of Golub and colleagues, who discovered in the sequenced tumor genomes evidence of somatic mutations in genes encoding the KDM6A histone demethylase and the MLL and WHSC1 histone methyltransferases that regulate the methylation of histone proteins. The observation that WHSC1 is mutated in multiple myeloma fits with the t(4;14) chromosome translocation in 15% of multiple myeloma patients, which is predicted to boost WHSC1 expression.

Analysis of individual gene expression alterations in the MMGI dataset identified the protein HOXA9 as a potential new therapeutic target. HOXA9 is normally silenced by histone methylation as hematopoietic stem cells differentiate into more mature blood cells, and the enzymes responsible for this silencing are the MLL histone methyltransferases. Based in part on these findings, the MMRF is now investing more than $5 million to investigate how epigenetic changes promote growth of myeloma cells. Last year, we provided $1 million each in funding to two biotechnology companies that are developing drugs to modify the activity of different epigenetic targets. This year, the MMRF is launching a three-year, multimillion-dollar collaborative program project to validate some of the most promising epigenetic targets in multiple myeloma. Specific areas of emphasis include functional validation of histone modifying enzymes such as KDM6A and WHSC1, as well as elucidating the role of DNA methylation and microRNAs.

The new tumor genome sequencing data have identified oncogenic mutations in BRAF kinase, opening up intriguing clinical possibilities. Building on the observation of a noncanonical but known activating mutation (G469A) in the sequencing data, Golub's team has identified activating mutations in a set of 161 multiple myeloma samples, including four V600E and three K601N mutations in BRAF. Although rare in myeloma, these BRAF mutations can be targeted by investigational drugs like PLX4032 (Plexxikon/Roche), currently in clinical trials for treating melanoma. The MMRF is now devising clinical strategies to explore the use of BRAF inhibitors to treat a subset of myeloma patients. Strategies could include inclusion of multiple myeloma patients in an "all comers" trial involving other cancer patients, or focusing efforts specifically on the small subset of myeloma patients carrying BRAF mutations. Such fine subsegmentation of an already small disease population highlights the challenge for the future, which is how to maximize the use of targeted therapeutics consistent with molecular drivers of pathology regardless of the tissue of origin of any given tumor.

## PARTNERSHIPS FOR ADVANCING CLINICAL DEVELOPMENT

Just as the MMRC has helped to build a critical mass of high-quality tissue samples for genomic analysis, we have been able to engage a critical mass of patients for rapid enrollment and completion of early-stage clinical trials. In collaboration with our 16 MMRC member institutions and our industrial partners, we have initiated several strategies that are making a difference. These include centralized contracting with the entire network of participating centers to speed trial startup, access to myeloma clinical experts, and the support of clinical trial project managers who facilitate more rapid IRB approvals and move the trials forward. For example, in 2006, the MMRC identified the proteasome inhibitor carfilzomib as a promising new treatment during its development by Proteolix, Inc. (which was acquired by Onyx Pharmaceuticals in late 2009), and entered into a collaboration to accelerate the drug's development for treating patients with relapsed/refractory multiple myeloma. The MMRC provided the company with strategic guidance and time-saving infrastructure to facilitate phase II testing of the drug in multiple myeloma patients. Centralized contracts and guidance on clinical site selection and protocol design all combined to accelerate the conduct of the trial, resulting in accrual of 60 percent of the required patient number through MMRC member institutions, which represented 36 percent of the total study sites. These efforts boosted rapid completion of patient enrollment in the trial and provided encouraging data on response rates and time to disease progression that we hope will enable filing for accelerated FDA approval for carfilzomib later this year (*5*).

To date, the MMRC has opened 30 clinical trials involving 18 new compounds; 16 of these compounds remain in development, with seven in phase III clinical trials. This underscores the importance of careful selection of research investments, which has been possible in collaboration with our MMRC member institutions. In terms of speed, recent data indicate that trials conducted through the MMRC open after approval of the final clinical protocol about 100 days (60%) faster than the published experience of one comprehensive cancer center (*6*). By applying standardized procedures, such as a standard protocol template, and by providing dedicated clinical project management resources, the MMRC is able to complete clinical trial enrollment two months (14%) earlier than the predicted timeline and enroll 25% more patients than the original MMRC commitment. These data are based on a retrospective review of 21 multiple myeloma trials conducted with MMRC project management resources from May 2006 to June 2010 (*7*).

## LESSONS LEARNED, AND WHERE TO GO NEXT

A key component of our strategy is the engagement and ongoing commitment of a sophisticated network of academic collaborators throughout each step of the process, from sample collection to leadership in ongoing clinical trials. Also, the continued close collaboration with partners in industry, who are drawn by the benefits provided by the MMRC in the form of faster trials and expert support, will remain crucial. Finally, we at the MMRF have made it clear that we are firmly focused on the rapid translation of research results into clinical benefits for multiple myeloma patients. To this end, we have funded preclinical and clinical research on more than 70 compounds and have supported the successful development in the past decade of four new treatments for multiple myeloma (bortezomib, thalidomide, lenalidomide, and pegylated liposomal doxorubicin), with a corresponding improvement in patient outcomes and a boost in median life expectancy by 4 years (*8*).

Moving forward, the analysis of additional multiple myeloma genomes will help to elucidate the complex dysregulation of many different signaling pathways, the frequency of individual mutations in the disease, and the identification of those mutations that are principal drivers of tumor development versus those that are simply passengers. The MMRF is investing another $2 million in the MMGI to increase the number of patient tumors sequenced to 250 and to undertake sequencing of the tumor transcriptome. An additional $5 million is being spent to expand our understanding of epigenetic dysregulation in myeloma pathogenesis and to yield targets for therapeutic intervention.

Despite these advances, many questions remain unanswered. Given the heterogeneity of the disease, is 250 a large enough number of samples to sequence? What are the genomic underpinnings of progression of disease from asymptomatic to symptomatic to drug-resistant? And what about the tumor microenvironment; are there subtle differences therein that support tumor progression? To begin to fully address these research questions to more quickly benefit patients, we need much more molecular and clinical data. We need to characterize the very earliest stages of the disease, track individual patients' drug regimens and their responses, and follow myeloma patients long-term to understand how the profile of the disease changes with time. This will require a longitudinal study over at least a decade, at the cost of tens of millions of dollars, which the MMRF is currently investigating. Such an effort is a key component of the MMRF's personalized medicine strategy and is expected to yield an improved ability to match today's treatments and the next-generation drugs of tomorrow to the individual patient, with improved outcomes for all.

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**Citation:** L. M. Perkins, A. Quinn. Young, K. Giusti, One foundation's strategy to accelerate drug discovery through genomics. *Sci. Transl. Med.* **3**, 78cm11 (2011).