New Melanoma Drugs
and the role of the
Melanoma Research Foundation

The Melanoma Research Foundation issued its first research grant in 1998, the same year a new drug was approved by the FDA for the treatment of metastatic melanoma. That drug has brutal side effects and 85% of patients who take the drug derive no benefit from it. Given the challenges of this treatment, no-one in their darkest nightmare would have anticipated that 13 years would pass before another drug would be approved. On March 25, 2011, the FDA approved Yervoy (ipilimumab) for use in metastatic melanoma. It is likely that a second new drug will be approved by the end of 2011. The Melanoma Research Foundation (MRF) is playing a pivotal role in the development of these drugs.

Ipilimumab

In June, 2010, the melanoma community saw significant press with the announcement of a breakthrough in melanoma treatment using a new drug known as ipilimumab. This is a monoclonal antibody that blocks CTLA-4, a compound released by melanoma cells that masks them from the body’s T-cell immune response. By blocking CTLA-4, the drug allows the immune system to “see” melanoma cells and attack them.

The therapeutic potential of an anti-CTLA4 antibody was reported in 1993 by James Allison, Ph.D. while at UCLA. Subsequently, the monoclonal antibody was co-developed with Medarex/BMS. The first in-human Phase 1 study reported at ASCO in 2002 showed responses in heavily pretreated patients with melanoma. This led to rapid clinical development of the antibody known as ipilimumab.

While the MRF did not play a role in the early development of the single agent, as our grant program launched in 1996, we are closely collaborating with its continued development in the following ways:

- Dr. Jedd Wolchok from the Memorial Sloan Kettering Cancer Center, the co-lead (co-PI) of the Phase 3 study of ipilimumab submitted to the FDA to support approval, was a MRF grant recipient for the experimental work underlying the immunotherapy of melanoma.
- Drs. Steve Hodi and Jedd Wolchok (co-PIs) are continuing to develop ipilimumab and wrote a next generation concept for a Phase 3 clinical trial combining ipilimumab with PLX 4032, a selective BRAF inhibitor. Leadership of the MRF Breakthrough Consortium (MRFBC), along with Drs. Hodi and Wolchok, has met with leadership of BMS and Genentech/Roche to explore a tripartite partnership for the conduct of this pivotal trial. The discussions are confidential but can be summarized as proceeding very well.
- The lead people involved in the ipilimumab trials are, almost without exception, working with MRF as members of the Scientific Advisory Committee (SAC) to the
board and/or are members of the MRFBC, developing strategies prospectively and collaboratively around future translational research and clinical trials.

- The principal investigator (PI) of the Phase 3 study, Dr. Steve Hodi of Dana Farber, is one of the founding members of the MRF Breakthrough Consortium and co-chair of its Immunotherapy Subcommittee.
- A major contributor to the clinical development of anti-CTLA antibodies in the therapy of melanoma, Dr. Jeffrey Weber, has not only been an advisor since 2001 but he also led the grants program of MRF for three years.

Four additional investigators have been funded by MRF to conduct research in immunology related to stimulating the immune response in melanoma patients:

- Dr. Patrick Hwu at M.D. Anderson Cancer Center, who is one of the leading clinical trialist for the development of ipilimumab has received an MRF grant. He is a member of the SAC and the MRFBC.
- Antoni Ribas, at University of California in Los Angeles, has received an MRF grant and is now a member of the MRFBC.
- Paul Antony, a junior investigator at the University of Maryland in Baltimore, received an MRF grant to develop new strategies combining antibodies and cytokines, which follows a related approach to anti-CTLA4 therapy.
- Alexander Krupnick at Washington University in St. Louis, MO, has received an MRF grant to characterize in detail the target cells for ipilimumab.

Ipilimumab is the first drug that has shown an overall survival benefit in melanoma in a Phase 3 trial. Yet, only 24% of patients on drug were still living after 2 years, compared to 12% on the control arm.

**PLX4032**

About 50% of melanoma patients have a mutation in a gene known as BRAF. This mutation allows the tumor cell to grow and divide out of control. PLX4032 is a BRAF inhibitor; it shuts down the function of that mutated gene and prevents the tumor cell from growing. Genentech/Roche, who own PLX4032, have launched an international Phase 3 trial to demonstrate an overall survival benefit, but will likely approach the FDA with their Phase 2 data for accelerated approval in the near future.

This selective inhibitor can induce responses in up to 90% of those patients who have the BRAF mutation. This work was cited by the American Society of Clinical Oncology as one of the major clinical cancer advances of 2009. The MRF has been involved in exploring BRAF through grants and clinical trials.

- The BRAF mutation was discovered by Dr. Michael Stratton’s group of the Sanger Centre in the UK in 2002. The MRF was the first foundation to fund research related to the preclinical development of anti-BRAF therapy in a grant to Dr. Meenhard Herlyn, of the Wistar Institute.
- Dr. Martin McMahon received an MRF grant to support development of a mouse model of BRAF-induced melanoma. Animal models that can mimic the specific
biology in humans, e.g., BRAF-driven melanoma, accelerate development of the best combination therapies, as this research takes months rather than years. This model has been successfully commercialized and is available to researchers internationally.

- Dr. Roger Lo at the University of California in Los Angeles received an MRF grant to develop new insight into optimal combinations of drugs to eliminate BRAF tumors.

- Dr. Keiran Smalley from the Moffitt Cancer Center received an MRF grant to investigate the mechanisms of resistance to BRAF inhibitors, so that a strategy can be built for those patients whose response to treatment is short.

While early responses to PLX4032 are very encouraging, the duration of the response is limited. On average, patients show recurrence of tumor growth after 7 months. The newly formed MRFBC is negotiating with two companies to launch 2 clinical trials of combinations that have the potential to extend response to PLX4032.

**Other Milestone Grants**

MRF has a history of funding pivotal research. In particular, three major discoveries have received MRF support:

- Dr. Boris Bastian discovered that some melanomas, predominantly those arising from mucosal surfaces, palms, soles and nail beds, have c-kit mutations. This biologic discovery led to successful treatment of patients whose tumor harbors that mutation, using existing, commercially available targeted therapeutics. This was the first time a targeted therapy was used in melanoma, and was the first time a truly effective approach was found for mucosal melanoma.

- Dr. Sean Morrison’s work on the nature of melanoma stem cells and its implication for treatment, published in Nature 2008, has been heralded as a major breakthrough in understanding the ability of melanoma to spread or metastasize.

- Dr. Gavin Robertson from the Hershey Medical Center is studying the signaling of mutant BRAF and of AKT. His laboratory has developed a novel delivery system, nanoparticles, that may more effectively carry drugs specifically to the tumor site.

**MRF Breakthrough Consortium**

MRF is committed to continuing its long-standing support of basic research that unravels the biology of melanoma. The recent advances in biology have led to therapeutic agents that now offer an opportunity to translate these basic science discoveries into novel clinical treatments. For this reason, MRF has launched the MRF Breakthrough Consortium, a collaboration of top clinical and basic scientists who have agreed to work cooperatively to design and conduct clinical trials of combinations. This goal requires initiatives in the laboratory (animal modeling of combinations, sequencing of tumors, etc.) as well as in the clinic. The MRFBC has formed 5 subcommittees that meet regularly to set goals across centers of excellence. We are convinced that this Breakthrough Consortium is consistent with the mission of the MRF to accelerate research for a cure.