The last time a drug was approved for metastatic melanoma was over a decade ago, and 85% of people who take that drug receive no benefit from it. Now that is changing, and it is likely that two new drugs 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 coverage with the announcement of a new breakthrough in melanoma treatment using a drug known as ipilimumab.

This new drug is a monoclonal antibody that blocks a 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.

Ipilimumab is owned by Bristol Myers-Squibb (BMS) and they have been granted expedited approval by the FDA. This means that approval for clinical use could be granted as early as mid-December, 2010.

The therapeutic potential of an anti-CTLA4 antibody was reported in 1993 by James Allison, Ph.D. while at UCLA. This was before the MRF's grant program launched in 1996. 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, we are closely collaborating with its continued development in the following ways:

- 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 (MBC) and co-chair of its Immunotherapy Subcommittee.
- Dr. Jedd Wolchok from the Memorial Sloan Kettering Cancer Center, the co-PI of the Phase 3 study on ipilimumab, was a funding recipient of MRF 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 concept for a Phase 3 combination trial with PLX 4032, a selective BRAF inhibitor. Leadership of the MBC, along with Drs. Hodi and Wolchok, has met
with leadership of BMS and Genentech/Roche to explore a partnership for the conduct of this pivotal trial. The discussions are confidential but 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 the MBC.
  - A major contributor to the clinical development of anti-CTLA antibodies in the therapy of melanoma, Dr. Jeffrey Weber formerly from UCLA and more recently from the Moffitt Cancer Center, has not only been an advisor since 2001 but he also led the grants program of MRF for three years.
  - Four additional senior or junior investigators have been funded by MRF conducting 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. He is a member of the SAC and the MBC.
    - Antoni Ribas, at University of California in Los Angeles is now a member of the MBC.
    - Paul Antony, University of Maryland in Baltimore, a junior investigator developing 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 characterized in detail the target cells for ipilimumab.

Ipiilimumab 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 patient 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 in several ways:
The BRAF mutation was discovered by Dr. Micheal 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 developed a mouse model of BRAF-induced melanoma. This model has been successful in supporting further research on the potential of combinations of therapeutics in this common type of melanoma.

Dr. Roger Lo at the University of California in Los Angeles has developed new insight into optimal combinations of drugs to eliminate BRAF tumors.

Dr. Keiran Smalley from the Moffitt Cancer Center has investigated the mechanisms of resistance to BRAF inhibitors.

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.

Other Relevant Milestones

MRF has a history of funding pivotal research. In particular, two major breakthrough discoveries were tied to MRF support:

- Dr. Boris Bastian discovered that some melanomas have c-kit mutations. This led to successful treatment of patients with that mutation, using existing 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 melanoma stem cells and implication for treatment, published in Nature 2008, has been heralded as a major breakthrough in understanding melanoma.

- Dr. Gavin Robertson from the Hershey Medical Center has made significant discoveries about the signaling of mutant BRAF and of AKT. He has developed nanoparticles that effectively carry drugs or other antagonists to the tumor.

MRF Breakthrough Consortium

MRF is committed to continuing its long-standing support of basic research relevant to melanoma. The recent advances in therapeutic agents 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 collaborative group of top clinical and basic scientists who have agreed to work cooperatively to further the drug development process.

Neither ipilimumab nor PLX4032 are the answer to metastatic melanoma. In fact, most doctors are convinced that real solutions will only be found by combining two or more drugs. The purpose of the MRF Breakthrough Consortium is to do exactly this—study
combinations of drugs. This is not easy, given that these are drugs still in development that have not been approved for general use. Nevertheless, we are convinced that this Breakthrough Consortium can accelerate the discovery process, and bring new, relevant therapies to patients months or even years sooner than would happen otherwise.