



**SU2C–Melanoma Research Alliance Melanoma Dream Team:  
“Personalized Medicine for Patients with BRAF WildType (BRAFWt) Cancer”**

*[This abstract was provided by the scientists when their application was accepted.]*

Melanoma patients broadly fall into two groups: Those whose genome harbors an oncogenic mutation in BRAF (BRAFMut), and those who don't (BRAFWt). Currently, patients who develop metastatic melanoma (MM) have a dismal prognosis, with a median survival of 6-9 months and a 3 year survival rate of 10-15%. Recently developed inhibitors have demonstrated clinical efficacy in patients with metastatic melanoma who have mutations to the BRAF gene, but little progress has been made in identifying therapeutic targets to treat patients with BRAFWt tumors, that comprise half of all metastatic melanomas. Better therapies, and more efficient means of identifying those therapies, are needed to make a major impact in treating BRAFWt metastatic melanoma.

We are in a new era of genome-based treatments and “personalized medicine”, which represents a paradigm shift in how therapeutic decisions are made, relative to the conventional approach that generically treats without consideration to underlying tumor genomics and biology.

Patients with BRAFWt metastatic melanoma represent an ideal population for investigating the utility of personalized target/therapy identification. The proposed Dream Team has expertise in complementary areas, including experts in the medical management of patients with metastatic melanoma, drug development, genomics research, biostatistics, bioinformatics, and patient advocacy.

The Team hopes that an individualized medicine approach to the treatment of BRAFWt metastatic melanoma will not only lead to therapeutic benefit for this patient population, but may also be beneficial to many other tumor and disease types.

#### SUMMARY OF SPECIFIC AIMS

**Aim 1.** The investigators will perform a small clinical trial (n=15) of BRAF wild-type (wt) melanoma patients to determine if it is feasible to collect tumor tissue, perform extensive genomic studies, and arrive at a molecularly informed treatment decision within the first 4 weeks after patient enrollment. Patients will be randomized 2:1 to “molecularly guided therapy” vs. Standard of Care (SoC). The former will be chosen from FDA-approved drugs and from a list of approximately 12 investigational agents (primarily kinase inhibitors including drugs that target MEK, AKT, and different RTKs). It is anticipated that this list will grow over time.

**Aim 2.** Seven BRAFWt and 3-BRAF mutant cell lines will be extensively molecularly profiled (including genomic DNA sequencing, RNA sequencing, copy number analysis, and mRNA profiling). These



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same cell lines will also be tested for their sensitivity to 100 “prioritized” compounds in a variety of cell-biological assays that might translate into therapeutic utility (e.g. induction of apoptosis or inhibition of migration). The data from these studies will be used to generate models that predict the sensitivity of BRAFwt melanomas to specific drugs. These predictions will be tested using xenografts of the melanoma lines described above as well as primary tumors obtained from biopsies in aim 1 and aim 3. This aim will certainly generate a rich and useful dataset for the community.

**Aim 3.** This aim will bring together the findings from specific aims 1 and 2 in the conduct of a clinical trial to determine whether this personalized approach significantly improves clinical outcome. This will be a randomized clinical trial of 96 BRAFwt melanoma patients who will be randomized 2:1 to molecularly-guided therapy versus standard of care. The goal of this aim is a 30% improvement in tumor response relative to standard-of-care therapy.