



Team Progress Updates

SU2C Epigenetics Dream Team:

“Bringing Epigenetic Therapy to the Forefront of Cancer Management”



While it is now well established that cancer is a consequence of genetic alterations, it is becoming increasingly clear that disruption of epigenetic mechanisms is also a hallmark of the disease. Those epigenetic mechanisms help control the expression of genes—whether they are turned on or off—without affecting the genes' DNA sequences themselves.

Thus, whether a cell becomes cancerous depends not only on its genome (whether key genes are mutated), but also on its epigenome (whether these genes are expressed appropriately). These epigenomes have become the focus of a rapidly emerging and important new area of cancer research.

Unlike DNA mutations, which are permanent, epigenetic changes can be reversed. This means that it may be possible to find a way to regulate inappropriate activity or to get a gene that is improperly expressed, due to epigenetic changes, to begin functioning normally again.

The Dream Team is using a combination of two drugs (a DNA-demethylating agent and a histone deacetylase inhibitor) to reverse the epigenetic modifications that have inappropriately turned genes on or off in cancer cells. The overarching goal of this project is to bring the promise of epigenetic therapy to clinical practice.

The team reported the following progress:

December 2014

- During this final reporting period, the Dream Team continued their work on two key clinical trials assessing the ability of epigenetic therapy to prime non-small cell lung cancer (NSCLC) to be more sensitive to subsequent chemotherapy or immunotherapy.
- Through the work supported by the SU2C grant, this team has shown that approximately 3% of patients will respond robustly to epigenetic therapy alone, with almost full disease regression which can last for years. For approximately 20% more patients, epigenetic therapy appears to potentially sensitize to subsequent therapies, including standard chemotherapy and new forms of immunotherapy. While all of the above data are from a small number of patients, clinical trials are currently underway to expand these observations.
- Also, they are enrolling patients in a trial with an immunotherapy drug to formally test the paradigm that epigenetic therapy may sensitize the patients with advanced NSCLC to immunotherapy. These trials will be conducted in the next 1-2 years and could bring a new form of therapy to robustly change management for patients with advanced NSCLC.





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- In addition, the promising results from early clinical trials of a new DNA demethylating agent (SGI-110) in patients with acute myelogenous leukemia (AML) has prompted an advanced phase 3 trial that will open in March of 2015.

June 2014

- During this period, the Dream Team continued their work on two key clinical trials assessing the ability of epigenetic therapy to prime non-small cell lung cancer (NSCLC) to be more sensitive to subsequent chemotherapy or immunotherapy. Those two trials have accrued 5 and 15 patients, respectively.
- The relatively low accrual for the epigenetic therapy followed by chemotherapy trial is partly due to patient preference for the other study; the epigenetic therapy followed by immunotherapy. This latter study was amended to remove the arm testing the oral formulation of azacitidine due to safety concerns.
- The Team also continued with their follow-up studies for patients in the clinical trials for advanced colon cancer and advanced breast cancer. For all these trials, pre- and post-treatment biopsies are collected to allow in-depth follow-up studies. The Team has continued accrual for their clinical trial for patients with intermediate or high risk myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML). Partial responses are observed which are more robust when epigenetic therapy is given as frontline therapy. The Dream Team efforts to identify candidate biomarkers of response, as well as predictive biomarkers for all their clinical trials are still ongoing.

December 2013

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June 2013

- During the first half of their fourth year of funding, the Dream Team focused on initiating two key clinical trials that were designed based on strong pre-clinical and clinical data accumulated during the initial grant term.
- The first clinical trial is a phase II study that is assessing the ability of epigenetic therapy to prime non-small cell lung cancer (NSCLC) to be more sensitive to subsequent chemotherapy. It opened at Johns Hopkins University and is pending approval at the University of Southern California.
- The second clinical trial is a phase II study that will assess the ability of epigenetic therapy to prime NSCLC to be more sensitive to subsequent immunotherapy. It is pending approval at Johns Hopkins University.
- In addition, the Dream Team continued the clinical trials they had previously initiated in breast and colon cancers, as well as leukemia. They persisted with their follow-up studies for patients in the clinical trial for advanced colon cancer, while the clinical trial for advanced breast cancer became fully enrolled. For all these trials, pre- and post-treatment biopsies are collected to allow in-depth follow-up studies.
- They also initiated the dose-expansion segment of their clinical trial for patients with intermediate or high risk myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML), which will evaluate the safety and efficacy of the new epigenetic therapy SGI-110 at the biological effective dose (BED) or maximum tolerated dose (MTD), as defined in the dose-escalation segment of the trial.
- Last, the Dream Team continued to identify candidate biomarkers of response, as well as predictive biomarkers for all their clinical trials.

December 2012

- The Dream Team has now completed the three years of the initial grant term. They have been approved for a fourth year, no-cost extension to allow them to continue the clinical trials initiated (in breast and colon cancers, as well as leukemia). Supplemental funding has also been approved to allow the Dream Team to initiate two new clinical trials for patients with metastatic non-small cell lung cancer (NSCLC).
- The rationale for these new studies is supported by data obtained during the first three years of this grant: namely previous clinical trials that showed that patients with advanced NSCLC treated with low doses of 5-Azacitidine, a DNA methyltransferase inhibitor (Vidaza, from Celgene Corp.), and the histone deacetylase inhibitor Entinostat (from Syntax Pharmaceutical), undergo a “priming effect”, whereby they respond better to subsequent chemotherapy, or a new form of immunotherapy called immune checkpoint blockade.
- During this period, the Dream Team conducted studies to understand the molecular mechanisms underlying the priming effect of epigenetic therapy to subsequent



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immunotherapy. These data are reported in a manuscript currently under review. In addition, they continued to accrue patients in their active trials and to identify molecular markers of response.

June 2012

- In this period, the Dream Team continued to observe the robust sensitization to subsequent chemotherapy for patients with non-small cell lung cancer who have received one or more cycle of epigenetic therapy. The Dream Team also reported a strong sensitization to subsequent immunotherapy in this patient cohort.
- The majority of patients (18 of the 23) with chemo-refractory, metastatic colon cancer are still alive one year after their epigenetic therapy.
- Furthermore, the success obtained in the clinical trial testing the new generation DNA-demethylating drug in patients with leukemia has prompted the Dream Team to explore the possibility of conducting additional trials in solid tumors.

December 2011

- At the two-year mark, the Dream Team met their milestones for initiating and completing clinical trials, and are poised to observe how the potential of these trials will play out. The Dream Team further explored their "priming" hypothesis: that one of the effects of epigenetic therapy is to render cancer cells more sensitive to other subsequent therapies. They showed that a subpopulation of self-renewing, or "stem-like" cells, were particularly sensitive to treatment with the two epigenetic drugs, which would explain how epigenetic therapy might convert chemo-refractory cells into a more sensitive state.
- The Dream Team reported progress in the clinical trial evaluating a new DNA-demethylating drug, and showed that, indeed, it is more efficient than the existing drugs. They also reported promising results in terms of patient response in the early phase of this trial.

June 2011

- During this period, the Dream Team reported encouraging results in the clinical trial for non-small cell lung cancer, with median survival of 8.6 months among patients who completed at least one cycle of epigenetic therapy.
- More importantly, the Team made the intriguing observation that multiple patients who were required to stop therapy after only two to four cycles had long survival periods, with several alive years after completion of these courses. These findings suggest that very short courses of



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the two epigenetic drugs used may have a lasting effect and may “prime” cancer cells to better respond to cytotoxic chemotherapy.

- During this period, the Dream Team also initiated a phase I clinical trial to test a new generation DNA-demethylating agent that they predicted would be less rapidly metabolized by the body, hence more effective as an epigenetic therapy drug.

December 2010

- In this period, the Dream Team continued enrolling patients in all active clinical trials. They made great progress in their biomarker studies. Indeed, for stage 1 non-small cell lung cancer, they identified four genes that, when inappropriately turned off, seem to predict recurrence within 18 months of curative surgery.
- In addition, preliminary analyses of DNA isolated from the tumor of patients with myelodysplastic syndromes/acute myelogenous leukemia (MDS/AML) showed a correlation between DNA hypermethylation in a series of genes and positive responses to epigenetic therapy.

June 2010

- In the first six months, the Dream Team reported completion of a phase II clinical trial for patients with non-small cell lung cancer. Using a combination of two drugs (a DNA-demethylating agent, and a histone deacetylase inhibitor), they observed durable tumor ablation, regression, and stability in 30% of the patients enrolled, with one patient showing complete response for up to 3 years. More importantly, the treatment regimen used resulted in minimal patient toxicities.
- During this initial period, the Dream Team also initiated phase II clinical trials in colon and breast cancers. They also instigated important studies to identify biomarkers that can predict and monitor responses to epigenetic therapy.