



Scientific Abstract

Van Andel Research Institute-SU2C Cancer Epigenetics Dream Team:

“The Epigenetics Dream Team II”



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

The VARI-SU2C Epigenetics Dream Team has been in existence for over three years. It has made exceptional progress toward its **Overall Goal** of selecting the most promising laboratory concepts to bring to clinical trials for patients with cancer. We think of our trials in three categories: **Immune Sensitization, Chemo Sensitization, and Novel Targeting Strategies**. Further, and crucially, all of our trials involve the collection of samples of normal and tumor cells from patients, in hopes of learning why some treatments work and why certain patients respond and others do not.

The longest standing of our **Immune Sensitization** trials is the **Legacy Lung Cancer Project**, which is a carryover from the 2009 SU2C Epigenetics Dream Team. The early studies strongly suggested that epigenetic therapy could provide a major breakthrough by synergizing with immune checkpoint therapy. Therefore, we began a trial in which we evaluate how epigenetic therapy may sensitize patients having non-small-cell lung cancer (NSCLC) to immune checkpoint therapies. This work fostered concepts for additional clinical trials, including the following.

The **MDS Project**, is built upon Dr. Grønbæk's laboratory studies of myelodysplastic syndrome (MDS), which predisposes patients to leukemia. This Phase I/II clinical trial combines the DNMT inhibitor (DNMTi) guadecitabine with the immune checkpoint inhibitor atezolizumab. Phase I of this trial at University of Southern California (USC) is nearly complete and will continue on to phase II with additional sites at Fox Chase, and University of Maryland.

The **Multiple Solid Tumor Trial Project** is a Phase I/II trial in advanced hepatocellular, biliary, and pancreatic cancers, all of which have limited therapeutic options and poor outcomes. It tests whether a DNMTi can enhance the immune response of these tumors and thus increase the effectiveness of anti- PD-1 therapy. This trial is anticipated to start in Jan/Feb 2018 at USC and Johns Hopkins University (JHU).

Another project, based on both our early clinical observations and recent laboratory work involving **Chemo Sensitization**, i.e., that epigenetic therapies can sensitize patients to other drugs and/or reverse drug resistance. The **Colorectal Cancer (CRC) Project** trial tests whether an epigenetic drug can restore a treatment response in patients with advanced colon cancer who have developed resistance to treatment with irinotecan, which is an almost universal problem of this chemotherapy. The trial is now well into Phase II using a DNMTi plus irinotecan. The trial also tests whether epigenetic therapy will work better to reverse resistance than the current FDA-approved drugs such as





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regorafenib or TAS-102. In Phase II, 67 patients have now been enrolled at the sites: JHU, MSK, USC, and VU Amsterdam (Netherlands).

The final set of trials involves **Novel Targeting Strategies**. The **AML Project** is a collaboration between Drs. Feyruz Rassool, Maria Baer, and Stephen Baylin, testing whether DNMTi's plus a polymerase inhibitor (PARPi) can kill acute myeloid leukemia (AML) cells and thus enhance tumor response. This trial is based on extensive studies from the Rassool lab that were published in *Cancer Cell* in 2016. This Phase I/II trial is now enrolling to test the combination of talazoparib (PARPi) plus decitabine (DNMTi) in advanced AML. Phase I has accrued 15 participants and is anticipated to move Page 4 to phase II in early 2018 with additional sites at Fox Chase and USC.

The **EVITA Project** is based on key findings from the Jones lab (PNAS, 2106). A pilot trial is testing whether vitamin C can enhance response to DNMTi's in AML and MDS patients who have low vitamin C levels. The pilot trial involves 40 patients receiving standard-of-care DNMTi therapy who receive either a vitamin C daily supplement or placebo over two cycles. Also, enrollment has begun for a cohort of subjects who have clonal cytopenia of undetermined significance, a precursor to MDS.

In all of our trials, we place particular emphasis on the collection and study of specimens from participants—such as tumor biopsies, blood, or bone marrow—in hopes of learning why treatments work in some patients but not in others.