



Progress Updates

SU2C Colorectal Cancer Dream Team:

“Targeting Genomic, Metabolic, and Immunological Vulnerabilities of Colorectal Cancer”



This Dream Team is focusing on three areas of research that have the potential to impact the treatment of all stages of colorectal cancer.

The first two areas of research examine the potential of immunotherapy and targeted therapy to revolutionize the treatment of colorectal cancer. The team will determine the mechanisms of resistance to immunotherapies and targeted therapies and devise new strategies to overcome resistance.

The third area of study evaluates strategies to target different colorectal cancer subtypes. Specifically, two major subgroups of colorectal cancer—those with a mutation in the KRAS/BRAF gene, and those with a mutation in the PIK3CA gene—are susceptible to high doses of vitamin C combined with depletion of a nutrient called glutamine.

In animal studies, drugs developed to target these vulnerabilities were able to slow down or cure colorectal cancers of the two subgroups. This team is evaluating whether these promising findings can be transposed to patients with similar genomic abnormalities.

The team has reported the following progress:

January 2019

- The team has worked to build better combinations of targeted drugs for colorectal cancer.
- Promising laboratory results have prompted a clinical trial of the B-Raf inhibitor dabrafenib + MEK inhibitor trametinib + the anti-PD1 inhibitor PDR001.
- The team has completed a Phase I clinical trial and has shown safety for combination therapy with the glutaminase inhibitor CB-389 and capecitabine for patients with PIK32CA-mutant metastatic colorectal cancer.
- The team is exploiting the vulnerability of colorectal cancers with mutant KRAS or BRAF to ascorbate. Of the subjects treated so far, two have exhibited disease stabilization.
- Initial analyses of six patients enrolled in their vitamin C trial suggest that high-dose vitamin C increases DNA damage repair pathways, as well as ROS cellular regulation pathways.





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- The team also designed a new clinical trial arm that will combine the DNA damage effects of vitamin C with therapeutic doses of liver directed radioembolization (Y90 therapy).

June 2018

- The team has identified two genes involved in DNA repair that are highly mutated in colorectal cancer patients.
- The team has found that activation of the WNT/ β -catenin signaling pathway may help cancer cells evade the immune system. Drugs that block this pathway may help a patient respond better to immunotherapy.
- The team has opened a clinical trial testing a combination of vitamin C and phenformin (a drug that can increase the uptake of vitamin C) with the hope of inhibiting tumor growth.
- Based on promising results from its phase I study, in March 2018 the team opened a phase II clinical trial that combines a new drug called CB-389 with capecitabine, a chemotherapeutic drug used in CRC treatment.

December 2017

- The Team found potential parameters that can be used to predict how effective a patient's immune system can be, in fighting cancer cells.
- The Team has developed a tool that can help them tell if Vitamin C is taken into tumor cells. This tool would be very helpful as they conduct the clinical trial with Vitamin C.
- The Team is conducting 5 clinical trials and is planning 9 clinical trials that tests different kinds of treatment strategies: chemotherapy, targeted therapy, and immunotherapy. In these trials, they are particularly paying attention to the mutations in the tumors of the patients that they treat so that they can determine which drugs can be more effective to treat different groups of patients depending on the kind of mutations that their cancer cells have.
- The Team has shown that circulating DNA in the blood can be used to identify the mutations that a patient's cancer tissue has. By using DNA in the blood, the response of a patient's tumor to treatment can be more easily monitored than having to get a tumor biopsy frequently.