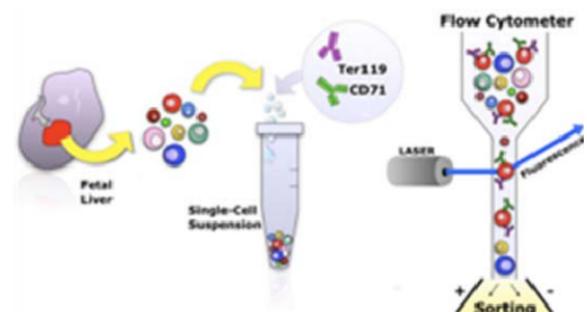




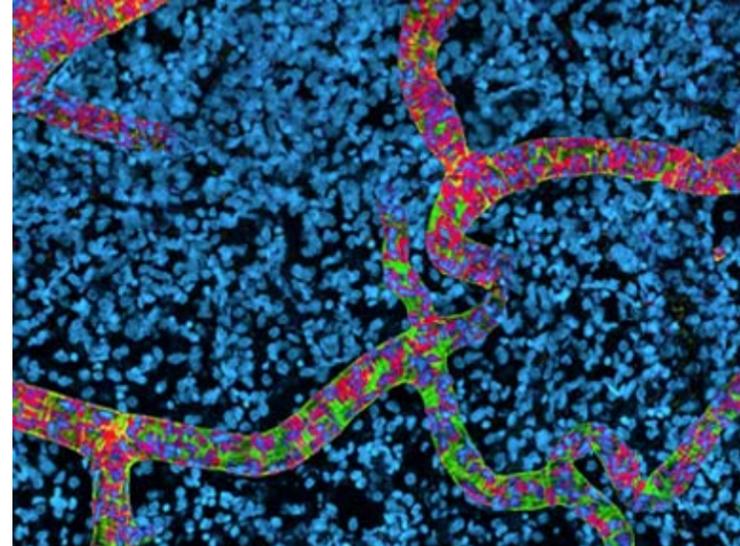
## THE BCRF WISHLIST

Advances in medicine start in the lab and new equipment is helpful as we continue to make strides in Blood Cancer research. While it may not look that impressive, the BD FACSARIA III (pictured above) is a high-priority item we would like to add to our lab's arsenal of research equipment this year. This addition will allow us to further expand our research capacity.

Dr. Laura Rassenti, senior project scientist and the director of the Tissue Core/biorepository for the Chronic Lymphocytic Leukemia Research Consortium, also hopes to acquire a ThermoFisher PCR machine—the Verti 96-Well Thermal Cycler—along with a small bench top centrifuge.



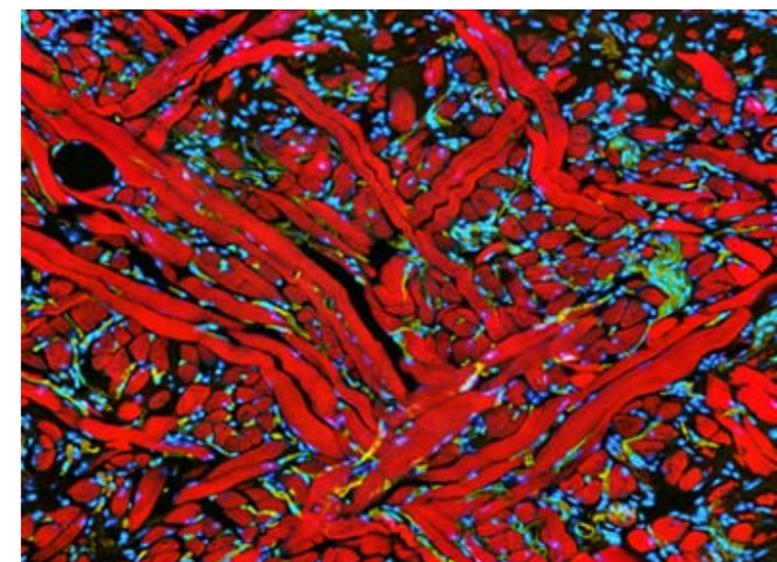
Using a six-color flow cytometry, the FACSARIA III analyzes the physical and chemical characteristics of particles in a fluid as it passes through at least one laser. Cell components are fluorescently labelled and then excited by the laser to emit light at varying wavelengths.



THE IMPACT OF  
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## AN UPDATE ON BLOOD CANCER RESEARCH FUND

WINTER 2015



## BCRF BIOMEDICAL SCIENCES HIGH SCHOOL INTERNSHIP



This summer the BCRF hosted five High School students for biomedical research training and career development.

We expect the students to gain skills in basic lab techniques, research planning, logistics of clinical research, biomedical informatics experience, and to



have a deeper understanding of the complex field of oncology.

Each of the interns has volunteered between 12-18 hours per week. One other aspect—and perhaps the most important—is that we help the interns learn how to increase their career skills. We stress the importance of resumes, cover interview skills, where to look for jobs, and building a network of references and employers.

ADDRESS LABEL HERE



Blood Cancer  
Research Fund

Post-Doctoral Researchers:

Dr. Yun Chen

Dr. Han Zhang

Visiting Graduate Scholars:

Shuangyue Xu

Swati Kumar

Undergraduate Interns

Stephanie Badaro Garcia

## NEW RESEARCHERS

[BCRF.UCSD.EDU](http://BCRF.UCSD.EDU)

UC San Diego  
MOORES CANCER CENTER

# VENETOCLAX (ABT-199)



Venetoclax (ABT-199) kills cancer cells by a unique mechanism, by interfering with BCL-2 (B-cell lymphoma/leukemia 2). BCL-2 is a protein that ordinarily prevents cell death by binding to and disabling cell-death proteins (called BAX and BAK)—which when freed from channels within the cells that release chemicals that trigger the cell death cascade.

defective, such as typically seen in CLL cells that have deletions in the short-arm of chromosome 17, or del (17p). Such defects in p53 makes CLL cells resistant to the effects of chemotherapy.

Altogether, our impression is that venetoclax is an active drug, capable of inducing deep remissions, including a high rate of complete responses in which there is no evidence for minimal residual disease (or MRD). This differentiates it from the oral tyrosine kinase inhibitors. With caution when starting treatment (close laboratory monitoring during dose ramp-up) tumor lysis syndrome has not been an issue.

Based on the results of these studies, an international Phase 3 trials are underway comparing venetoclax + obinutuzumab versus chlorambucil + obinutuzumab involving patients here at the UCSD Moores Cancer Center.

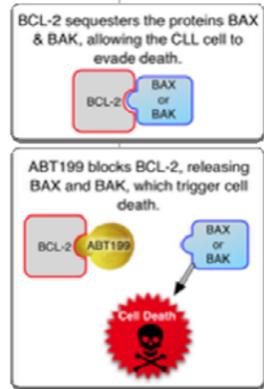
We have also initiated laboratory studies on venetoclax, focusing on those cases that have a small amount of residual disease after treatment, and evaluate how some CLL cells might survive venetoclax treatment.

—By Dr. Michael Choi

Normally, the grasp of BCL-2 on these cell-death proteins is released when the cells are damaged. For instance, conventional chemotherapy (eg. with fludarabine or bendamustine) or radiation therapy work by activating an important protein, called p53, which can induce the so-called “BH3-only proteins” that block BCL-2; this in turn keeps BCL-2 from inhibiting BAX or BAK, Venetoclax binding to BCL-2 and mimics the BH3-only proteins to release the cell

death proteins BAX and BAK. For that reason, it is also referred to as a BH3-mimetic.

By doing this, it also bypasses p53 to directly trigger the death of the cell without needing DNA damage. This is particularly useful in cases where p53 is absent or



## CELL PROCESSING CENTER

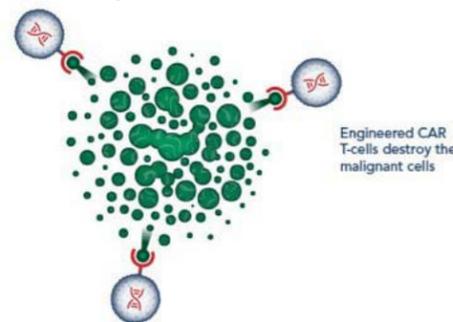
A necessary precursor to the conductance of human clinical trials requires that we develop and validate methods required for the manufacture cell-based therapeutics. The BCRF and several other collaborators are actively developing a new Cell Processing Center at UC San Diego to enable clinical trials of novel, genetically engineered immune cells

A goal of the translational immuno-therapy laboratory is to develop a generation of chimeric antigen receptor modified T-cells

(CARs), which will be created to target tumor specific antigens such as ROR1 expressed on the surface of patients’ cancers. CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells. These engineered CAR T cells are then grown in the laboratory until they number in the billions.

For this process, we are creating a third-generation CAR constructs produced by retroviral packaging systems. These chimeric vector systems will then be used to transduce the donor patient T-lymphocytes, which will then be activated in the presence of the targeted cancer. We expect CAR based clinical studies to be initiated in the fourth quarter of 2016.

—By Charles Prussak



## SPLICEOSOME STUDIES

Recently, there have been studies reporting the role of gene mutations associated with spliceosome. We know that RNA splicing plays a fundamental role in human biology. Its relevance in cancer is rapidly emerging as demonstrated by spliceosome mutations that determine the prognosis of patients with hematological malignancies.

Drs. Manoj Kumar Kashyap, Deepak Kumar, James La Clair carried out the study led by Dr. Castro, Dr. Burkart, and Dr. Kipps reporting targeting of the spliceosome using FD-895 and pladienolide-B macrolides in primary leukemia cells derived from CLL patients and leukemia-lymphoma cell lines.

They found that FD-895 and pladienolide-B induce an early pattern of mRNA intron retention – spliceosome

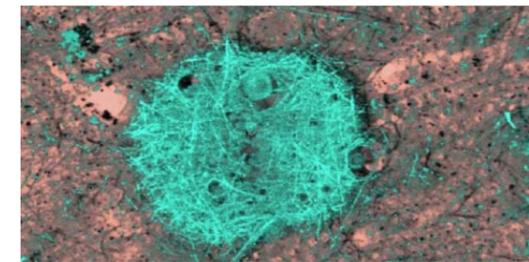
inhibition. This process was associated with apoptosis preferentially in cancer cells as compared to normal lymphocytes. The pro-apoptotic activity of these compounds was observed regardless of poor prognostic factors such as Del(17p) or SF3B1 mutations and was able to overcome the protective effect of culture conditions that resemble the tumor microenvironment.

These findings show evidence for the first time that drugs directed against the spliceosome have clinical activity in patients with CLL. Further, these findings provide the rationale for the development of spliceosome modulators for cancer therapy.

—Dr. Manoj Kashyap and Dr. Deepak Kumar

**A spliceosome is a large and complex molecular machine found primarily within the splicing speckles of the cell nucleus of eukaryotic cells.**

## BIOLOGY OF ROR1 AND CIRMTUZUMAB INSIGHTS



ROR1 and ROR2 are each considered a distinct receptor for Wnt5a, implicated in non-canonical Wnt-signaling involved in organogenesis or cancer metastasis.

We have shown that Wnt5a induces ROR1 to complex with ROR2 and recruit guanine exchange factors (GEFs) that activate Rac1 and RhoA, which enhance proliferation and migration of chronic lymphocytic leukemia (CLL) cells; such effects could be inhibited by siRNA-silencing of either ROR1 or ROR2 or treatment with an anti-ROR1 mAb (UC-961), which also had activity against leukemia cells in vivo.

With funding from the Blood Cancer Research Fund, Dr. Yu and his collaborators found the ROR1 intracellular

domain was required for recruitment of GEFs and its Kringle domain was necessary for it to complex with ROR2 in response to Wnt5a.

This study reveals a previously-unrecognized interaction between ROR1 and ROR2 for Wnt5a signaling in CLL.

Furthermore, additional studies demonstrate that the anti-ROR1 mAb cirmtuzumab can block the formation of such complexes and impair the capacity of ROR1 to enhance leukemia cells migration and proliferation in vitro and in vivo, providing rationale for ongoing clinical evaluation of this antibody in patients with CLL or other cancers that are complemented by ROR1-dependent, non-canonical Wnt5a signaling.

—By Dr. Jian Yu

