RESEARCH UPDATES

Project 1: Inhibitor Master Oncogene Function
Gregory Lanza, MD, PhD, Professor of Medicine
& Biomedical Engineering
Washington University School of Medicine
Co-Leader of Project 1

From this research foundation, Project 1 strives to screen and select a translatable VLA-4-targeted micelle nanotherapeutic incorporating the most effective small-molecule c-Myc-Max inhibitors.

The reference prodrug, MI1-PD, based on the 10058-F4 is being compared with a second-generation 10074-G5 (MI2-PD) prodrug analogue. 10058-F4 and 10074-G5 bind to distinct regions of Myc’s bHLHZIP domain and affect its ability to interact with Max. A third generation compound (10074-A4, MI3-PD) binds to the Myc-Max heterodimer to distort its structure diminish DNA binding without disrupting protein-protein interaction. The bioactivity of each prodrug versus free drug counterpart was confirmed using an adherent human cMyc-inhibitor sensitive melanoma cell line (C-32). The biopotency of the prodrugs uniformly exceeded the free drugs, with the best results achieved with MI2-PD and MI3-PD.

The compounds incorporated into VLA-4 cMyc-inhibitor-PD micelles are currently being studied in the 5TGM1 C57BL/KaLwRij mouse model. As anticipated, mouse survival with VLA-4 MI1-PD micelles essentially doubled with treatment. However, survival responses with VLA-4 micelles incorporating the MI2-PD or MI3-PD were not improved. Reanalysis of all chemical components revealed no anomalies. Testing of the prodrugs in human and mouse myeloma are ongoing with modifications in technique required given the nonadherent nature of myeloma. Given the activity of these prodrugs against human melanoma, the newer prodrugs may be specific to human cMyc, but other differences are being considered. A second block of animals will be initiated with newly prepared materials to further replicate the assessments. As alternatively planned, Celastrol which has potent anti-Myc-Max activity, will be synthesized as a prodrug if needed.

From a translational perspective, further replication of the initial VLA-4 MI1-PD micelles in the next block of animals will constitute enough confidence to move toward a start-up company. When an improved cMyc-PD is identified, bridging studies will be pursued to bring forward the superior product candidate as needed. Also, initial claims for the prodrug patent, US Patent Application Serial Number 15/179,626 Entitled: “Prodrug Compositions, Prodrug Nanoparticles, and Methods of Use Thereof” were allowed. Serial continuation applications that will expand the breadth the IP are underway.

NEWS

Pilot Projects Awarded
The CMMN Pilot Project Funding Committee chose two proposals for awards in the amount of $30,000 each, to begin on September 1, 2016.

Hong Chen, PhD, serves as principal investigator on a project titled, “Focused Ultrasound-Enabled Delivery of Theranostic Liposomes for Cancer Treatment.” Working with Kareem Azab, PhD, Dennis Hallahan, MD, and Dinesh Thotala, PhD, the group will explore theranostic medicine as the next-generation platform for cancer therapy. The goal of this project is to develop a new therapy for brain cancer by delivering novel targeted theranostic liposomes using focused ultrasound (FUS).
Investigators Monica Shokeen, PhD, and Pratim Biswas, PhD, are working with co-investigators Ramesh Raliya, PhD, and Deep Hathi, PhD candidate, on a project titled, “Dual Modality Nanoparticle Contrast Agent for Imaging Multiple Myeloma.” This research focuses on addressing critical clinical ambiguities associated with multiple myeloma using progressive biomedical imaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI).

2017 CMMN Pilot Funding Available
The 2017 Cycle 1 CMMN pilot project call for applications will be announced in late fall, 2016, with funding expected to begin in spring, 2017.

CMMN External Advisory Committee Meeting
The CMMN External Advisory Committee (EAC) will meet on December 13-14, 2016, in St. Louis. The EAC will make recommendations on the scientific direction of research projects, cores and development programs, as well as identify innovative areas of nanotherapeutic agents and commercialization projections, and provide guidance in new pilot/auxiliary projects to enhance the CMMN’s mission. We are pleased to welcome EAC members James R. Baker, Jr., MD, Director of the Michigan Nanotechnology Institute for Medicine and Biological Sciences; Tayyaba Hasan, PhD, Massachusetts General Hospital, Harvard Medical School; and patient advocate, James Omel, MD.

Dr. Baker is a professor in Biologic Nanotechnology and a professor of Internal Medicine at the University of Michigan. His research is in the area of immunology and host defense, evolving into nanomaterials and their applications in medicine. His work has produced new vector systems for gene transfer using dendritic polymers, which have the potential to revolutionize pharmaceutical therapy. Dr. Baker has also invented new forms of synthetic lipid and polymeric nanostructures, which have resulted in the development of nanoemulsions as a new approach to vaccines. He has founded five companies and spent two years as the worldwide head of vaccines at Merck.

Dr. Hasan is a professor of Dermatology at the Wellman Center for Photomedicine at Harvard Medical School and a professor of Health Sciences and Technology (Harvard MIT). Dr. Hasan’s scientific efforts are focused on photochemistry-based approaches (photodynamic therapy, or PDT) for treatment and diagnosis of disease. The overall strategy is to develop molecular mechanisms and optical imaging-based combination treatment regimens where one treatment arm involves light activation of certain near-infrared-absorbing chemicals.

Dr. Omel (Jim) is a retired family physician and a full-time cancer research advocate. He was diagnosed with myeloma in 1997 and was treated with VAD and radiation. At relapse in 2000, he had an ASCT, retired from active medical practice, and began a new role as cancer research patient advocate. Dr. Omel’s advocacy involves work with the NCI including the Myeloma Steering Committee, FDA as a myeloma patient representative, Alliance Cooperative Group as a member of PAC, and the Myeloma Committee, AACR, co-chair of CIBMTR (transplantation) CAC committee, Moffitt Cancer Center, and his local hospital cancer committee. Jim has also led the monthly Central Nebraska Myeloma Support Group since 2000.

SAVE THE DATE
December 13, 2016
Special Lecture: External Advisory Committee
3:30-5:00 pm, Erlanger Auditorium, Washington University School of Medicine; External Advisory speakers include James Omel, MD, and Tayyaba Hassan, PhD.

April 12, 2017
CMMN Mini Symposium
The invited distinguished speaker is Leaf Huang, PhD, from the University of North Carolina, Chapel Hill.

April 13, 2017
NCI Alliance for Nanotechnology in Cancer Site Visit

PUBLIC OUTREACH
Radio Talk Show:
Nanotechnology in Multiple Myeloma

On May 16, 2016, Drs. Samuel Achilefu, Ravi Vij and Monica Shokeen participated in a radio talk show hosted by the Myeloma Crowd to discuss nanotechnology and the
CMMN. The interview can be accessed on the Myeloma Crowd website.

**2016 Rock Docs**

Dr. Monica Shokeen will be honored as one of four 2016 “Rock Docs” at Siteman Cancer Center’s 11th annual CUREiosity event on September 30, 2016. This “party for a cure” celebrates research doctors making a difference in cancer research.

**INVITED LECTURES**

Samuel Achilefu, PhD, was the keynote speaker at the International Society on Oxygen Transport to Tissue (ISOTT), in Chicago, Illinois on July 11, 2016. His talk was titled, “Breaking the oxygen and tissue depth dependency of photodynamic therapy with nanophotosensitizers.”

Pratim Biswas, PhD, gave a talk titled, “The Life Cycle of Aerosol Particles: Enabling Energy and Environmental Technologies,” at the Environmental Research Center at the Missouri University of Science and Technology in Rolla, Missouri on April 22, 2016.

Ramesh Raliya, PhD, delivered a talk titled, “Nanotechnology-enabled bio-system engineering: applications and implications,” at the Indian Institute of Technology in Bombay, India on November 19, 2015.

**CMMN PUBLICATIONS**


**JOIN THE CMMN PEDAL THE CAUSE TEAM IN 2017**

Dr. Samuel Achilefu would like to announce the formation of a 2017 CMMN Pedal the Cause team in support of the Cancer Frontier Fund. This research fund was established in 2009 by Alvin J. Siteman, an emeritus Washington University trustee, chairman of Site Oil Company and president of Flash Oil Company. Since the fund’s inception, 134 awards for a total of $21.7 million have been granted to Washington University faculty focused on cancer research.

100% of the proceeds support cancer research at Washington University (WU) and St. Louis Children’s Hospital. Awards granted to WU faculty are managed by Siteman Cancer Center (SCC), a major contributor to CMMN. Participation by CMMN members shows our appreciation to SCC and demonstrates our commitment to both CMMN research and the community effort that raises local cancer research funds.

If you prefer swimming to biking, you have the option to participate in Swim Across America, a local event that also benefits the Cancer Frontier Fund. Proceeds from anyone who chooses to swim will contribute to the CMMN Pedal the Cause team effort.

Faculty, students, staff and families are more than welcome to join the team. For more information, contact Paige Isom, isom@wustl.edu.