DOUBLE STRAND
VHL CANCER RESEARCH FOUNDATION

Research Collaboration

"Smart Bomb" Nanoparticles Loaded With Targeted Precision Therapeutics to Successfully Treat VHL Hemangioblastomas and Metastatic Cancer

Dr. Othon Iliopoulos
Harvard Mass General

Dr. Paula Hammond
MIT

Othon Iliopoulos, MD, PhD

Clinical Director, Von Hippel-Lindau Disease/Familial Renal Cell Cancer Program
Massachusetts General Hospital Cancer Center

Associate Professor of Medicine, Harvard Medical School
Medical Oncology, American Board of Internal Medicine

Dr. Iliopoulos, MD, PHD, is the Clinical Director, Von-Hippel Lindau Disease/Familial Renal Cell Cancer Program Massachusetts General Hospital, an Associate Professor of Medicine Harvard Medical School, and Center for Cancer Research, Massachusetts General Hospital, Boston, MA. He is the Director of the Iliopoulos Research laboratory with focused work on understanding the biochemical mechanisms of cancer angiogenesis and cancer metabolism in order to identify and validate new targets for treatment of Renal Cell Carcinoma (RCC) and a board member and chair of the VHLA Research Council. Dr. Iliopoulos published several seminal papers in *Science* and *Nature Medicine* demonstrating the role of the VHL protein in kidney cancer and its mechanism of action and collaborated with Nobel prize winners Drs. Kibel and Kaelin on some of the early research into the von Hippel-Lindau (*VHL*) tumor suppressor gene, which was initially named for its link to von Hippel-Lindau syndrome. Mass General is the #1 Research Hospital in America and the only hospital to be recognized in all 16 specialties assessed by U.S. News & World Report.

CONTACT INFORMATION

Iliopoulos Laboratory
Phone (617) 724-3404
Email: iliopoul@helix.mgh.harvard.edu

Massachusetts General Hospital, Grj 904
Hematology/Oncology
55 Fruit Street #148
Boston, MA 02114-2696
Phone (617) 724-1971

Paula T. Hammond, PhD

Koch Professor of Engineering, Department Head of Chemical Engineering, Koch Institute of Integrative Cancer Research, MIT

Professor Paula T. Hammond is the David H. Koch Chair Professor of Engineering at the Massachusetts Institute of Technology, and the Head of the Department of Chemical Engineering. She is a member of MIT's Koch Institute for Integrative Cancer Research, the MIT Energy Initiative, and a founding member of the MIT Institute for Soldier Nanotechnology. The core of her work is the use of electrostatics and other complementary interactions to generate functional materials with highly controlled architecture. Her research in nanomedicine encompasses the development of new biomaterials to enable drug delivery from surfaces with spatio-temporal control. She also investigates novel responsive polymer architectures for targeted nanoparticle drug and gene delivery, and has developed self-assembled materials systems for electrochemical energy devices. Professor Hammond serves as an associate editor of the American Chemical Society journal *ACS Nano*. She has published over 250 scientific papers and holds over 20 patents based on her research at MIT. She has been named a fellow of the National Academy of Sciences in 2019, the National Academy of Engineering in 2017, the National Academy of Medicine in 2016 as one of only 25 distinguished scientists elected to all three national academies and additionally was elected to the American Institute of Chemical Engineers, and the American Academy of Arts and Sciences, among others.

CONTACT INFORMATION

Paula T. Hammond, PhD
room 76-553
phone (617) 258-7577
email hammond@mit.edu

Hammond Lab
phone (617) 258-7577
fax (617) 258-5766
https://hammondlab.mit.edu/

“Smart bomb” Nanoparticles Loaded With Targeted Precision Therapeutics to Successfully Treat VHL Hemangioblastomas and Metastatic Cancer.

DoubleStrand Foundation has collaborated with top researchers at Massachusetts Institute of Technology and Harvard-Massachusett’s General Hospital (see attached bios of both researchers) on a research project that with the proper funding will dramatically improve the treatment for Central Nervous System (CNS) Hemangioblastomas and many Cancers.

The duration of the project is expected to be 30 months to reach human clinical trials in 5 time blocks from cell line to genetically engineered mouse models to clinical trials. The anticipated budget is $1.4 million of which 20% has already been attained. At its conclusion, treatment for VHL Hemangioblastoma tumor patients and many cancer patients will be forever changed with multiple repeated major surgeries replaced by periodic IV treatments at infusion centers with improved quality of life and survival.

This research project is designed to validate transcription activators Hypoxia Inducible Factors 1α and 2α (HIF1α/2α) as therapeutic targets for human hemangioblastoma (HB), using cutting edge nanoparticle technology tailored to specifically deliver cargo siRNA against both HIF2α, HIF1α to sufficiently suppress and eliminate HB tumors. These studies will validate pre-clinically, the HIF-targeting nanoparticles for treatment of human VHL-related HB and as Dr. Iliopoulos is the Director of the VHL Hemangioblastoma Center, will pave the way as a nodal point at that facility for their testing in a national clinical trial.

Many studies have shown that intra tumor hypoxia and HIF are integral to tumor metastasis in many cancer types and thus this work will provide treatment avenues to be broadly applied to not just VHL-related HBs but to a broad range of cancers1 .

Central nervous system (CNS) HBs are tumors, which develop in patients with germline mutations in the Von Hippel-Lindau (VHL) tumor suppressor gene, or may occur sporadically. They constitute 2.5% of all primary brain tumors. The majority (80%) of VHL protein deficient patients will develop multiple, synchronous or consecutive HBs in the cerebellum, spine, retina or hypothalamus. The age of onset starts at puberty and continues throughout life. HBs are refractory to radiation and there is no approved drug for their treatment. Repeated surgeries are the only treatment options for these tumors, but due to their location (cerebellum, hypothalamus, brain stem) surgery may be debilitating, technically dangerous or not even feasible.

As studied at the **Iliopoulos Research Laboratory**, Massachusetts General Hospital Cancer Center, Inactivation of VHL gene is the earliest and only genetic lesion known to occur in both sporadic and VHL disease-related HBs. Loss of function of the VHL protein results in stabilization of the Hypoxia Inducible Factors 1α and 2α (HIF1α/2α) and the overexpression of many HIF-target genes. HIFs dramatically reprogram cancer cell metabolism. Characteristically, HIF1a/2a expression blocks the transfer of glucose carbons into the Kreb’s cycle and diverts them into lactic acid. High production of lactic acid and lowering of the tumor microenvironment pH is a hallmark of VHL-driven tumors. In addition, HIF expression up-regulates the expression of the cell surface protein CD44. We propose here to take advantage of the hallmark properties of the HB tumor microenvironment mediated by HIF expression, in order to specifically direct therapeutic nanoparticles to HB tumor.

The Hammond research group, MIT Koch Institute of Integrative Cancer Research, has pioneered the development of nanoparticles (NPs) with unique physicochemical characteristics that tailor their specific delivery in targeted tumor microenvironments. They established the use of layer-by-layer (LbL) assembly of particles that

can shift their surface charge in a hypoxic tumor microenvironment due to lower tumor tissue pH2 . It is also possible to design the outer layer of these nanoparticles to specifically bind to CD44 receptors expressed at the tumor surface, and/or to attach specific targeting moieties such as antibodies or targeting peptides that bind to overexpressed receptors on the tumor cell surface. The core of the LbL nanoparticles can be loaded with chemiluminescent and fluorescent dyes that allow for in vivo tracking of their distribution and in vitro analysis of harvested tissues.

The experiments will be laid out such that monitoring of the pharmacokinetic and pharmaco-dynamic behavior of LbL treatment loaded nanoparticles, as well as their effects on the tumor growth and the tumor microenvironment is achieved. Thus experiment execution will garner information that may be critical in further optimization, if needed of the dose, schedule and physicochemical properties of the nanoparticles.

This research intends to demonstrate that 1) these hypoxia targeting nanoparticles can be tailored to act as highly specific “bullets” or “smart bombs” targeting selectively to HIF-expressing HB tumors without systemic side effects, and 2) encapsulation of siRNAs, silencing either HIF1α, HIF2α or both paralogs when delivered by LbL nanoparticles is a safe and effective treatment leading to HB tumor regression. We expect to confirm that the “hypoxia” responding nanoparticles are safe and effective in treating VHL-related HB tumors with broadening application in both the pre-clinical and clinical settings.

We anticipate that the completion of this work will introduce a sea change in the means of treating CNS hemangioblastomas and metatstatic cancers with breakthroughs in non surgical and targeted and precision therapies.