# Research Collaboration

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

DoubleStrand Foundation has been collaborating with and has funded top researchers at Massachusetts Institute of Technology and Harvard-Massachusetts General Hospital for the past 2 years on a research project that with the proper funding will dramatically improve the treatment for Central Nervous System (CNS) Hemangioblastomas and many Cancer Metastasis.

The project will reach human clinical trials in 5 time blocks from cell line to genetically engineered mouse models and ultimately to human clinical trials. The anticipated budget is $919,000 of which 30% has already been attained. As proof of concept emerges, grant applications will be completed to help fund the remaining phases of the project.

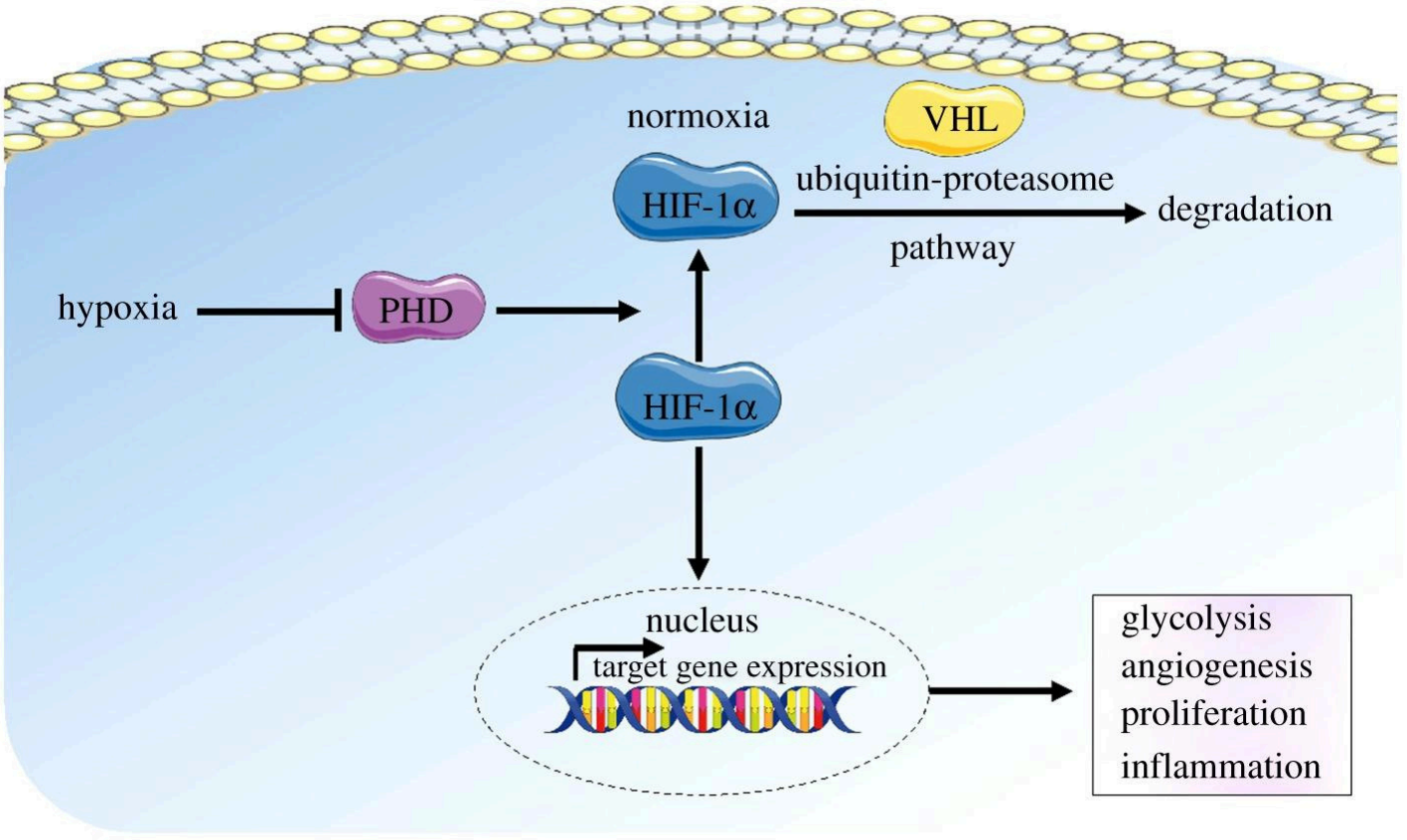
This research project is designed to validate transcription activators Hypoxia Inducible Factors 1α and 2α (HIF1α/2α) as therapeutic targets for human hemangioblastoma (HB), using cutting edge nanoparticle technology tailored to specifically deliver cargo siRNA against both HIF2α, HIF1α to sufficiently suppress and eliminate HB tumors. These studies will validate pre-clinically, the HIF-targeting nanoparticles for treatment of human VHL-related HB.

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 Cancers Metastasis.

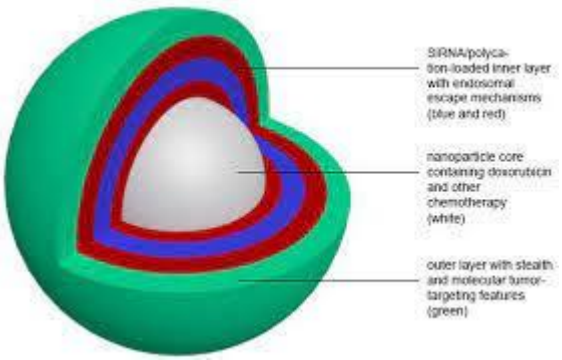
Central nervous system (CNS) HBs are tumors, which develop in patients with germline mutations in the Von

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.

Inactivation of VHL gene is the earliest and only genetic lesion known to occur in both sporadic and VHL disease-related HBs. The VHL gene was first identified in 1993 and is currently studied by multiple research labs globally. 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.



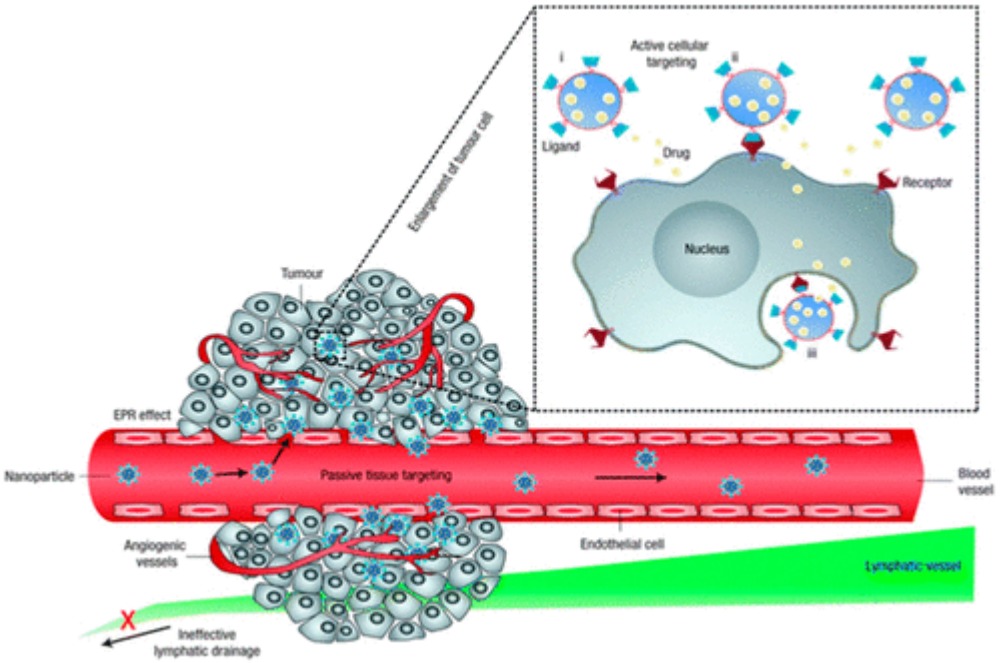
We propose here to take advantage of the hallmark properties of the HB tumor microenvironment mediated by HIF expression, in order to specifically direct therapeutic nanoparticles to HB tumor.




Researchers at MIT have developed nanoparticles (NPs) with specific surface binding receptors for VHL hemangioblastomas. These nanoparticles (NPs) have 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

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.

The next steps of the project will validate the NP surface receptor binding to Hemangioblastomas in vitro and development of a mouse model for testing. This will be followed by drug loading of the NPS and treatment efficacy studies in vitro and in the murine model. 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.

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