

PUBLIC ABSTRACT (Blancafort, P & Strahl, B)

A subtype of breast cancer, named basal or triple negative, is characterized for being a genetically distinct type of breast cancer, very refractory to chemotherapy. Women affected with this type of breast cancer develop very aggressive tumors, able to metastasize very quickly. Since these tumors do not express receptor or proteins typically used for the breast cancer treatment, such as hormone receptors, current anti-hormonal treatments (such as tamoxifen) are typically not very effective in these patients. In addition, these tumors typically relapse upon chemotherapeutic treatments. Recent investigations revealed that these type of tumors are populated and enriched in special cells, named Cancer Stem Cells (CSCs). A CSC could be imagined as a “damaged” stem cell. In the normal breast, a small population of stem cells exist, and is very important for making all the breast tissue, for example upon every menstrual cycle the breast growth, and also during pregnancy. CSCs might be “corrupted” versions of normal stem cells. Because stem cells have the ability to self-renew or divide, their genes “stay” in the tissue for a life-time of an individual. These cells can then accumulate mutations (genetic defects) and develop growing abilities and potentially making a tumor. In addition, due to the fact that naturally stem cells are very resistant to drugs, and have abilities to divide and move in a tissue, it makes sense that basal breast cancer, enriched in these very dangerous cells, might be so difficult to treat. Given the fact that there are no presently efficient treatments for basal breast cancer, we need to develop novel approaches and methods. Since these tumors are enriched in CSCs, our laboratory seeks to investigate the development of novel therapeutic interventions to kill CSCs and also novel tools that will make CSCs more vulnerable to chemotherapy and radiation.

In this award we will develop a novel method to specifically kill CSCs. We will establish a collaborative interaction between my laboratory, that develops tools to recognize specifically damaged genes, and Dr. Strahl's laboratory, that studies novel ways to modify genes and DNA. With both expertises we aim to generate novel molecules, named Designed Epigenetic Remodeling Factors (DERFs). A DERF has a portion that we call zinc finger protein domains (ZFs), which have been developed in the Blancafort lab to bind specific sequences in a gene. These ZFs will be engineered with chromatin remodeling domains (generated and well characterized in Dr. Strahl's lab). The idea of a DERF is to target genes specifically damaged in CSCs, to kill CSCs and not normal cells. The ZFs will bind these genes, bringing the chromatin domains in these sites. The chromatin domains are engineered enzymes that will chemically modify these genes by adding what we call “epigenetic marks”. In a sense one can imagine the epigenetic marks like traffic signals (like traffic lights), which dictate if a gene will ON or OFF. In this project we want to artificially include many “red lights” in the genes that are expressed a way too much in the CSCs. Like red traffic signs, we expect that we will then stop or prevent these dangerous genes, involved in cell division, from being expressed in CSCs. The difference between our approaches and others, is that we indeed include (imprint) persistent marks in the “road” of the genes, making sure that these genes will shut down. The genes we have pick are very important controlling the division of CSCs, and by suppressing their expression, we hope to suppress the growth of these cells, thereby suppressing the growth of basal tumors in animal models.

First, we will develop the proof of concept by expressing these novel tools in basal cancer models of tumors in animals. Next, we will work with researchers in the UNC-CH to encapsulate these new tools in artificial particles (nanoparticles) that will be specifically delivered into the tumors and metastasis. In summary, in this project we propose a novel approach to suppress what might be the root of the basal breast cancer, with direct applications in the clinic for treatment of basal breast cancer.