

Bringing Epigenetic Therapy to the Forefront of Cancer Management

Dream Team Leader:

Stephen B. Baylin, M.D., Deputy Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

Co-Leader:

Peter Jones, Ph.D., Distinguished Professor of Urology and Biochemistry & Molecular Biology, University of Southern California

BACKGROUND:

Scientists have known for years that genetic changes contribute to the growth and spread of cancer. Genes can be either turned on or off inappropriately leading to abnormal cell growth. Recently, researchers have determined that there is a second layer of genetic information that is not contained in the DNA, but rather embedded in the proteins that surround or package DNA. These epigenomes control access to genes allowing each cell type to activate its own genes while blocking the rest.

This field of epigenetics is rapidly becoming the focus of how scientists view molecular causation in cancer. The Dream Team Leaders have defined a key epigenetic process known as DNA de-methylation that inactivates or “silences” involved genes. They have also shown how this abnormality drives the malignant process, both in terms of causing cancer and allowing cancer cells to renew themselves on a long term basis.

This work is very important both in understanding how and why cancers occur and in developing new targeted therapies for a wide range of cancers. Unlike mutations in the DNA, epigenetic changes are reversible, meaning that there is great potential for developing new treatments that would block or re-activate silenced genes.

The primary goal of this Dream Team Project is to bring the promise of epigenetic therapy to clinical practice. The project will focus on breast, colon and lung cancers as well on leukemia and another blood disease, myeloid dysplastic syndrome. The specific goals include developing biomarkers that can predict and monitor the efficacy of cancer epigenetic therapies. The Dream Team will also conduct clinical trials that will bring epigenetic therapy to the forefront of cancer management.

One area of very high interest for researchers are self-renewing cancer cells, often called cancer stem cells. These cells are often missed or become resistant to currently available cancer drugs. Many researchers believe that it is essential to develop new therapies that target these cancer stem cells in order to improve the long-term outcomes of cancer treatment. This Dream Team will build on intriguing preliminary data suggesting that reversal of gene silencing leads to a loss of cancer stem cells.

Finally, this Dream Team will work to develop a clinical trial that utilizes a new second generation epigenetic drug that may be able to more effectively inhibit the epigenetic changes involved in cancer causation.

SIGNIFICANCE:

Cancer epigenetics is a burgeoning field, and scientists have gained a greater understanding of how these processes help make a malignancy develop and grow. Researchers are poised to apply these research findings into clinical applications. This Dream Team will move the field forward by demonstrating the effectiveness of epigenetic cancer therapies in several different cancer types and thus bring significant patient benefit.

RESEARCHER QUOTE (ATTRIBUTE AS NOTED):

“What has really happened over the last few years is we have gained an ability to look at cells, both normal cells and cancer cells in their entirety, and note the sorts of molecular changes that occur in the formation of a cancer cell. This will allow us to think more clearly about prevention and therapeutic strategies.

“What we find happens in cancer cells is that the packaging gets messed up so the genes get mispackaged. Some of them get closed up into boxes where they cannot be used and others get activated where they shouldn’t be used. Importantly, we have drugs that we think can undo the bows and open the boxes and allow the appropriate genes to get out and do their thing. This is a completely novel way of looking at cancer therapy.”

Peter Jones, Ph.D., D.Sc.

“Your DNA is like a hard drive. You’ve got all the information in it to read out and do everything you can do with it, but without packaging and without sufficient software you can’t instruct that DNA when to do X and when to do Y and Z. Cancers mutate the DNA and can thus corrupt the hard drive; but the package can also go wrong. Fortunately, the packaging is more reversible than trying to do something about an actual mutation. We can do things to bring that cell back into normal balance.”

Stephen Baylin, M.D.