



On the Trail of Genomic Pioneers



Meet Catherine Lofton-Day, Ph.D.
VP Molecular Biology, Diagnostics
Epigenomics, Inc.

1) Would you tell us a bit about your educational background and research experience?

I received a PhD in Molecular Biology from the Medical University of South Carolina. My research interest at that time was to understand the molecular basis of blood homeostasis. I joined ZymoGenetics, a biotechnology company in Seattle to discover and develop biopharmaceuticals to aid in the alleviation of diseases and conditions of improper homeostasis. While there I was a member of the team that discovered, through targeted gene cloning, the gene for human thrombopoietin, a platelet growth factor. I then led a team of molecular biologists in the molecular cloning of numerous other growth factors and cytokines using nascent DNA sequence information. From ZymoGenetics I moved on to a start-up biotechnology company called Epigenomics and have been with them for almost 9 years. I was asked to join to set up the molecular research labs for the identification of DNA methylation markers associated with tumor DNA. Through this program we have successfully identified a number of biomarkers for colon, prostate, lung and breast cancer. My main focus has been on colorectal cancer markers and the development of a blood-based test for early detection of this disease.

Through our research and development efforts for early detection of colorectal cancer at Epigenomics we have identified a tumor marker that is detectable in the blood of individuals with early stage disease. This biomarker, mSEPT9, is now available as a CE-marked test in Europe called Epi

proColon. Since the assay is a blood test it can easily be integrated into an annual physical check-up at the family doctor's office. We believe that this test has the potential to address the fundamental dilemma in colorectal cancer management, that of lack of compliance to screening methodologies.

The mSEPT9 marker for the early detection of colorectal cancer in a simple blood sample has demonstrated continuously highest performance in eight clinical case-control studies with in total more than 3,250 individuals tested. To further support mSEPT9 as a screening marker we are currently conducting a clinical study to determine the performance of the marker in a screening population. This study, named PRESEPT, is a prospective multi-center, multi-national clinical research study expected to enroll around 7500 individuals, 50 and older, scheduled for routine screening colonoscopy. The goal is to identify 50 subjects in this population which harbor undetected colorectal cancer. Once completed, the PRESEPT Study will be one of the largest commercially sponsored colorectal cancer screening clinical studies ever conducted.

2) Your paper cites that you first used restriction enzyme based discovery methods to identify markers. Could you briefly explain the method?

The methylation markers were identified using a method called arbitrarily primed polymerase chain reaction (AP-PCR). In this method methylation specific restriction enzymes are used to distinguish between methylated and unmethylated DNA sequences. DNA is isolated from both tumor tissue and healthy tissue from the same organ. Methylation specific enzymes, which



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do not cleave their CpG- containing recognition site (cytosine followed by a guanine) are then added to the DNA samples. If the cytosine residues in a particular sequence are not methylated then the restriction site will be cleaved. If the cytosine residues are methylated, which is often the case in promoter regions of genes from cancer cells, then the DNA will not be cleaved. This is one of the fundamental tools for identifying DNA methylation. After restriction enzyme treatment, the DNA is then amplified using short, arbitrary primers that are CpG rich. Radioactive nucleotides are used in the PCR reaction. The DNA is then separated on sequencing gels to identify different banding patterns between healthy and cancer DNA. The presence of a band in the tumor DNA which is not present in the healthy DNA indicates that the DNA is methylated in the cancer cells but not the healthy cells.

3) To a broader audience, what is DNA Methylation and how it will help in determination of cancer biomarkers?

DNA methylation is a chemical modification of DNA that occurs naturally and functions to control normal gene expression. When DNA methylation occurs in the promoter region of a gene, can “turn the gene off”. If methylation happens in the promoter region of a gene that suppresses cancer cells – a so called “tumor suppressor” then this effect can be to promote aberrant growth of cells. DNA methylation is therefore believed to be an early step in tumor development.

4) Which study or research papers or work have strongly influenced your thought and research goals?

Dr. Peter Laird wrote a review article published in 2003 on the “Power and Promise of DNA Methylation Markers”. Although I was already actively working in the field, this article gave such a positive overall perspective of the potential of the new technology it gave me encouragement to pursue this course with a vengeance. Dr. Margaret Pepe’s article on “Phases of Marker Development for Early Detection of Cancer” helped guide me through the difficult process of tumor marker assay development.

5) Where do you see your research heading in the future ?

My research will most probably continue in the area of even earlier detection of cancer using DNA methylation markers. For colorectal cancer this means detecting the disease at a pre-cancerous stage known as an advanced adenoma. Detection of pre-cancerous disease will require improvements both in the tumor markers used and in the isolation and preparation of DNA from blood samples.

6) A great deal of your work focuses on cancer research. What do you think are the most important discoveries made in the recent years and what will be role of Genomics in cancer research in the near future?

This is the hardest question because there are so many areas of cancer research and so many important advances that are reported that it is difficult to keep up. One discovery that is greatly affecting both cancer treatment and the field of molecular biomarkers are the recent findings that



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mutations of certain genes can affect the response of a tumor to a particular drug therapy. This finding is starting to influence the way drugs are developed and how patients are treated. In line with this development is the constant improvement of DNA sequencing technologies. These technologies are moving toward fast, inexpensive sequencing of whole genomes which has the potential to provide individualized information for a patient's tumor and customized therapy based on the results.

7) Could you briefly tell us about Epigenomics and what are you into ?

Epigenomics is a molecular diagnostics company focused on the development and commercialization of in vitro diagnostic tests for cancer. The company specializes in the development of diagnostic assays for early detection of cancer which are carried out on body fluids such as blood plasma. Our lead test development program is in colorectal cancer with other tests in development for lung and prostate cancer.

Our diagnostic tests in development rely on detecting differences in DNA methylation patterns between healthy and sick individuals or between subgroups of patients for disease classification. We believe that we are an industry leader in DNA methylation technologies and biomarkers. The company has been a pioneer in DNA methylation marker discovery, methods for isolation of methylated DNA from body fluids and development of highly sensitive assays for methylated DNA detection.

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