

Gene Laboratory Ushers in New Research Paradigm

All diseases involve genetic variations, whether inherited or resulting from stressors like viruses or toxins. The traditional approach to identifying genes associated with a particular disease was to look for a promising candidate—an inherited gene involved in breast cancer, for example.

The problem with that approach is that most genetically mediated diseases involve changes in more than one gene, and the human genome is made up of 30,000 to 35,000 genes. But, with the success of the Human Genome Project (HGP), new technologies are being developed that make it possible for scientists to pinpoint a multitude of genetic variations that may cause or contribute to many diseases, including cancer.

by Affymetrix, called GeneChips®, to simultaneously monitor the expression of thousands of genes and identify those that show individual variations. Special software allows scientists to sift through and analyze vast amounts of data comparing their findings to information in public databases generated by the HGP.

new tools for diagnosing disease states.”

The only Miami Valley research facility with this technology, the GEL currently supports collaborative studies of gene expression in exposure to environmental toxins (funded by the Air Force), Gulf War Syndrome (funded by the Department of Defense), and cancer (funded by the National Cancer Institute). Dr. Berberich is assisted in the lab by Madhavi Kadakia, Ph.D., co-director; Tina Caserta, M.S., research associate; and Andrea Myers, B.S., research assistant.

Three collaborative projects now under way involve clinicians studying cancer of the ovary, brain, and colon.

Ovarian Cancer

Therapy for patients with ovarian and endometrial cancer has traditionally been guided by staging and the degree of residual disease following surgery. Using gene expression profiles from these tumors, a clinical collaboration with William Nahhas, M.D., professor and director of the

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Research scientists are using that technology at Wright State’s Gene Expression Laboratory (GEL) established in 2000 as a collaboration between the Air Force Research Laboratory at Wright-Patterson Air Force Base and the School of Medicine. New initiatives involve using the GEL’s facilities in both basic and clinical research, for example, with the Wallace-Kettering Neuroscience Institute.

The GEL uses DNA expression analysis microarrays manufactured

“Using gene arrays to determine global changes in gene expression represents a new research paradigm,” explains Steven Berberich, Ph.D., associate professor of biochemistry and molecular biology and GEL director. “No longer do scientists need to limit their investigations to genes previously shown to correlate with a given disease. DNA microarray technology provides a wealth of genetic data offering basic scientists new avenues of research exploration and clinicians

Gynecologic Oncology Center at Miami Valley Hospital, is aimed at improving treatment selection and patient outcome by identifying better prognostic indicators. The project focuses on determining the gene expression profiles of human ovarian and endometrial cancers and will attempt to use those profiles to identify gene expression patterns within tumor samples that may be predictive for tumor type, stage, metastatic potential, or treatment response.

Brain Cancer

Although surgery and radiation for patients with malignant cerebral gliomas can prolong survival for a few months, the long-term outlook is dismal. As part of a multi-center phase II clinical trial, researchers at the Wallace-Kettering Neuroscience Institute (WKNI) at Kettering Medical Center are evaluating a therapy that uses a glucose analogue (2-deoxyglucose) to make the tumors more sensitive, and the surrounding tissue less sensitive, to radiation. Although the therapy has shown promise, there is wide variation in tumor response.

GEL scientists are collaborating with WKNI researchers in a subproject to examine the molecular mechanisms underlying the differences in tumor sensitivity. They hope the gene profiling information they gather will be useful in future clinical trials investigating correlations between treatment-induced changes and clinical response in a large patient population. Establishing a significant correlation would lead to development of predictive assays for therapy response and individu-

alization of therapy for optimal benefit to the patients, according to Dr. Berberich.

Colon Cancer

The fact that U.S. residents are more than twice as likely to develop colon cancer as are residents of mainland China strongly suggests that environmental factors, especially diet, play a major role in its development. But, it is also clear from inconsistent findings in epidemiological studies that other factors must account for the wide variation within populations in the same environment.

The GEL is collaborating with Jianjun Zhang, Ph.D., M.D., a Hipple Cancer Research Center epidemiologist and an assistant professor in the Division of Cancer Prevention and Control, on an international collaborative case-control study of colon cancer to identify the role of diet and nutrient-gene interactions in the etiology of colon cancer in China, the United States, and Canada. "Our goal is to identify protective measures or factors against colon and other cancers in Asian diets that can be translated to diets in the United States and other western countries," Dr. Zhang says.

Dr. Berberich is enthusiastic about the collaboration between clinical and basic scientists in these research projects. "This is an opportunity for the GEL facility to develop clinically relevant data for potential biotechnology applications as well as an opportunity for the School of Medicine to become a regional leader in cancer diagnosis using DNA microarray applications." ■

—Robin Suits

Core DNA Microarray Grants

A seed grant initiative made possible by a grant from the Kettering Fund offers support to basic science faculty who want to incorporate gene expression profiling in new and ongoing research projects. The following investigators have been awarded support for 2002:

"Energy and Nutrient Sensing Through the Mammalian Target of Rapamycin and Their Effects on Transcriptional Patterning," Patrick Dennis, Ph.D., assistant professor of biochemistry and molecular biology

"Gene Expression in the Skin After Brief Treatment with Irritating Chemicals," James McDougal, Ph.D., professor of pharmacology and toxicology and director of toxicology research

"Gene Expression Studies of HIV-1-Infected Eosinophilic Cells," Dawn Wooley, Ph.D., associate professor of biochemistry and molecular biology.



Steven Berberich, Ph.D., at the Affymetrix Microarray, a system that can monitor the expression of thousands of genes simultaneously.