Pair Pursue Promise of Proteomics

If you haven't heard of "proteomics," you're not alone. But expect to begin hearing more about this technique for analyzing all the proteins expressed by a cell, tissue, or organism. Proteomics, which was nominated by *Science* magazine as a "breakthrough" story for 2001, is now offering new directions in cancer research for VIMS scientists Drs. Peter Van Veld and Wolfgang Vogelbein.

Van Veld and Vogelbein are using proteomic techniques in collaboration with researchers at the Eastern Virginia Medical School to identify cancer biomarkers in wild fishes, with intriguing early results. Their study focuses on cancer-bearing mummichogs from a highly contaminated site on Norfolk's Elizabeth River called Atlantic Wood.

Proteomics is perhaps best explained in reference to the more familiar field of genomics. Researchers expended vast effort in the 1990s to sequence the human genome—the complete set of genes required to build a functional human being. The genome provides a "DNA blueprint" for building an organism, whether human, mouse, or fruit fly.

But the genome is only the start of the story, just as a blueprint is only the start of a house. The actual construction of an organism from its genetic blueprint is accomplished through the creation and action of proteins. And unlike the genome, which remains basically unchanged from cell to cell and throughout an organism's life, the organism's proteome—its full complement of proteins—is remarkably dynamic. The proteome can differ from adult to juvenile, diseased to healthy individuals, and from cell to cell.

All these possibilities result in a proteome estimated to be an order of magnitude more complex than the genome. Whereas scientists now think the human genome comprises 30,000 to 40,000 individual genes, the human proteome likely contains hundreds of thousands of proteins.

Efforts to develop technology for identifying all human proteins first began in the 1970s. However, the work was put on hold in the 1980s with the advancement of DNA technologies. Now that scientists have successfully charted the genome of humans, mice, and other organisms, they have renewed their focus on proteins and are applying technological advancements from DNA research to the study of proteomics. These advancements are allowing them to move beyond their previous focus—on characterizing the structure and function of proteins already known to be associated with cancer—to an analysis of an organism's full proteome, thus promising discovery of many new cancer markers.

Van Veld and Vogelbein chose the Atlantic Wood site for their study because it holds a population of mummichogs with significantly elevated levels of liver, pancreatic, and vascular cancers. The site is heavily contaminated with polycyclic aromatic hydrocarbons, a class of known carcinogens that derive largely from treatment of marine pilings and other wood products with creosote. A second site, King Creek, provides a "standard" of fish living in a healthy environment.

"Being able to study a natural population of vertebrates that are continuously exposed to known human carcinogens provides an ideal arena for cancer research," explains Van Veld.

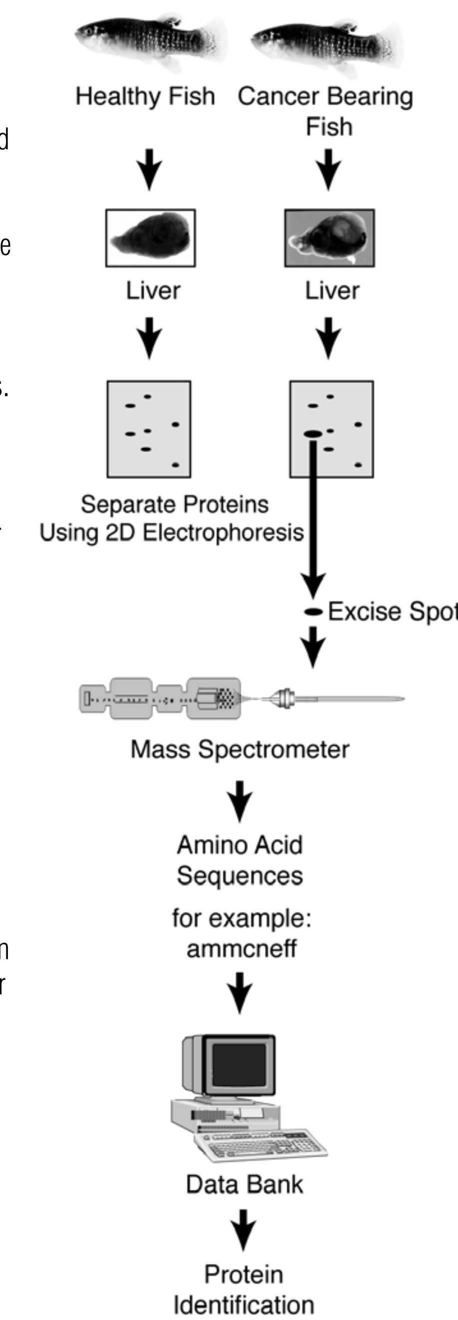
Although fish at the Atlantic Wood site eventually develop cancer, they remain resistant throughout their lives to the acute toxicity associated with exposure to creosote-contaminated sediments. In contrast, fish from King Creek die within days or weeks of exposure to this sediment. The resistance to toxins observed in the tumor-bearing fish supports a theory proposed by renowned cancer expert Emmanuel Farber that chemically induced cancer is an adaptation to a harsh chemical environment.

Van Veld and Vogelbein have found that toxin-resistant Atlantic Wood fish exhibit altered protein profiles similar to those found in studies of drug-resistant mammalian tumors. The proteins identified in these mammalian studies are known to help break down and remove both chemical toxins and cancer drugs.

Van Veld says that he is "encouraged by early proteomic results and confident that proteomics will promote the discovery of new proteins, offer new ideas on the relationship between cancer and toxicity resistance, and help provide new warning signs for early cancer stages."

From "Fish to Gel"

A section of liver is taken from both the "control" or healthy fish and the fish known to have cancer. The proteins are separated onto a gel plate using 2D electrophoresis. The scientists then choose a spot that is over- or under-expressed, remove it from the plate, and find the amino acid sequence using a mass spectrometer. They can then access an on-line data bank to determine what the protein is (if known) or whether it is a new discovery.



Research Questions Environmental Safety of Flame Retardant

A study by VIMS graduate student researcher Mark La Guardia provides new evidence of the release and environmental accumulation of a common flame-retardant chemical. His findings come in light of a recent voluntary decision by the main U.S. manufacturer of two other closely related and widely used flame retardants to discontinue their production.

La Guardia is a graduate student under Professor Dr. Rob Hale in VIMS' Department of Environmental and Aquatic Animal Health. Hale is a leading expert on the environmental fate and effects of polybrominated diphenyl ethers (PBDEs), a class of chemicals added to many household foam and plastic products to reduce their flammability.

The Great Lakes Chemical Corporation will stop making the PBDE flame retardants known as Penta and Octa by December 2004, based on growing evidence that the chemicals are toxic, persist in the environment, bioaccumulate, and that people are being exposed. Scientists at VIMS and elsewhere have detected rising levels of these compounds in fish, sewage sludge, and human breast milk.

La Guardia's research deals with the third member of the PBDE family, known as Deca, which is the most widely used PBDE flame retardant in the world. Until recently, most researchers thought that Deca—unlike Penta and Octa—posed relatively little environmental risk. That's because they believed Deca was not in a form readily available to organisms, knew of no obvious pathways by

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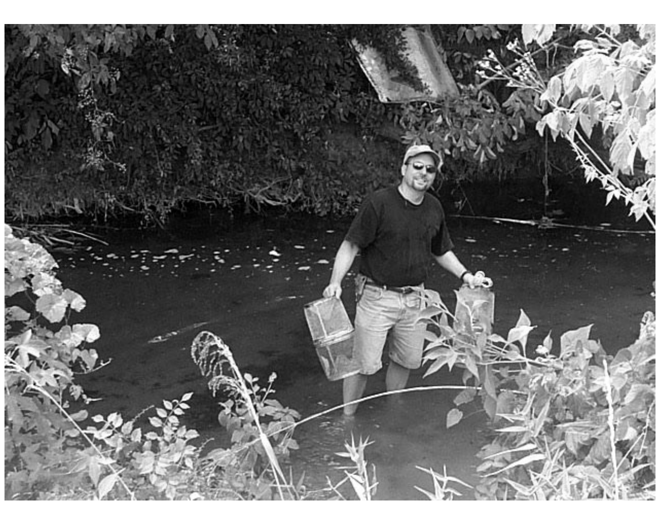

Mark LaGuardia collects samples from a freshwater stream for PBDE analysis.