# Researchers use zebrafish to identify new gene linked to melanoma

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Thanks to the zebrafish, there is new hope for people with melanoma, an aggressive skin cancer that is responsible for approximately 8,700 deaths each year in the United States.

In a study that was published in the March 24th issue of the journal *Nature*, and featured on the cover, researchers identified SETDB1 as a new gene that promotes the growth of melanoma and may play a role in up to 70 percent of malignant melanomas.

"We hope our discovery will ultimately lead to better therapeutic strategies for patients with melanoma," says study co-first author Dr. Yariv J. Houvras, assistant professor of medicine in the Departments of Surgery, Medicine, and Cell and Developmental Biology at Weill Cornell Medical College.

Although melanoma accounts for less than 5 percent of skin cancer cases, it causes a large majority of skin cancer deaths. The American Cancer Society estimates that about 68,000 were diagnosed in the United States last year -- 39,000 in men and 29,000 in women. The incidence of melanoma continues to increase at a rate faster than that of the seven most common cancers; according to the National Cancer Institute, between 1992 and 2004 the melanoma incidence increased 45 percent.

The report in *Nature* originated in the laboratory of Dr. Leonard Zon, director of the Stem Cell Program at Children's Hospital Boston, where Dr. Houvras worked prior to joining Weill Cornell earlier this year. Dr.

Houvras and colleagues created "MiniCoopR," a transposon-based vector to deliver candidate human test genes into a specially engineered strain of zebrafish that harbors a mutated BRAF gene. The researchers screened more than 3,000 zebrafish and found one gene that dramatically accelerated melanoma formation: SETDB1, which encodes a histone methyltransferase enzyme. Fish melanomas with elevated levels of SETDB1 are highly invasive and have a set of deregulated genes that are present in human tumors with high levels of SETDB1.

The discovery that SETDB1 accelerates melanoma formation in zebrafish is important because SETDB1 appears to be frequently overexpressed in human melanomas. "SETDB1 is an enzyme, so it may be a good drug target," explains Dr. Houvras. In a second report from Dr. Zon's lab led by first author Dr. Richard White, researchers found that the combination of leflunomide, a drug used to treat arthritis, and a BRAF inhibitor in clinical development was effective in blocking the formation of stem cells in zebrafish that give rise to melanoma.

Dr. Houvras, who joined the faculty of Weill Cornell in January 2011, is a physician-scientist with a focus on cancer genetics. He received his M.D. and Ph.D. degrees from the Mount Sinai School of Medicine in New York City. He received his residency and fellowship training in internal medicine and hematology-oncology at the Massachusetts General Hospital and the Dana-Farber Cancer Institute, both in Boston. He was an instructor in medicine at Harvard Medical School and an assistant attending physician at Massachusetts General Hospital in hematology-oncology. Dr. Houvras has co-authored articles in *Nature* and the Journal of Biological Chemistry. His honors include a Young Investigator Award from the American Society of Clinical Oncology. Dr. Houvras is the recipient of a mentored physician-scientist training award from the National Institutes of Health.

Dr. Houvras has set up a laboratory at Weill Cornell to expand on the

research in zebrafish on SETDB1 and cancer. "People are surprised when I tell them I use zebrafish to do cancer research. It is still amazing to me that the same genes that cause cancer in humans also cause cancer in fish. The zebrafish is an amazing organism because we can do complex genetic studies, and the fish has many of the same organs and tissues that we have," Dr. Houvras says.

He explains that the zebrafish is becoming a popular method for investigating malignancies, including melanoma, leukemia and sarcoma. "The melanoma model allowed us to integrate data from human genomic studies with the zebrafish. This made it possible to create thousands of transgenic animals and look for animals with more aggressive disease," Dr. Houvras says. "The zebrafish is an emerging organism in cancer biology. It has been an important organism for developmental biology and now we want to demonstrate that it has a unique set of attributes that we can use to discover new genes and treatments for patients with cancer."

Research with zebrafish has a practical side as well. The small, translucent embryos help make some processes, such as angiogenesis or genomic instability, more transparent. "For the melanoma studies, we designed and executed a study with more than 3,000 adult animals. It would have been very hard to do this kind of research with mice. I'm very excited about finding the right niche for zebrafish in cancer research. There are certain questions in cancer research that zebrafish are perfectly suited toward addressing. There is a great environment at Weill Cornell in the Departments of Surgery and Medicine for cancer research, and I am grateful that they provided me with a lab and a zebrafish facility to continue my research," Dr. Houvras says.

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