

INTERVIEW

A Big Voice for Science

A conversation with Leonard Zon.

With his enthusiasm and booming voice, Leonard I. Zon, an HHMI investigator at Children's Hospital in Boston and Harvard Medical School, can be persuasive. Those traits are useful in his roles as leader and advocate.

Zon helped turn a tiny tropical fish—the zebrafish—into one of the key model organisms for geneticists. And last year, Zon became the founding president of the International Society for Stem Cell Research (ISSCR).

When we met with him in December at Children's, he had just moved into a new zebrafish facility.

What are you and your colleagues doing with zebrafish?

Zon: Many things. [HHMI investigator] Mark T. Keating and his associates are studying how damaged organs regenerate, which the limbs of zebrafish do very quickly. Other scientists are looking at angiogenesis—the growth of blood vessels—which is important in cancer. Some people from [HHMI investigator] Louis M. Kunkel's lab are doing research on muscle disorders such as muscular dystrophy.

In my own work, I use zebrafish in lots of ways, but what got me started was my search for the genes that control the gene *GATA-1*, which directs the development of red blood cells. This was around 1992, and I had heard through the grapevine that Janni [Christiane Nüsslein-Volhard, a German geneticist and recipient of the 1995 Nobel Prize for Physiology or Medicine] had started to work with zebrafish, which are fantastic models for developmental studies because they are fertilized externally and their embryos are completely transparent. You can see all the organs in the zebrafish blood system, which forms within 24 hours. We used this system to study the genes required for blood formation.

1992 was still a prehistoric era with respect to zebrafish in research, wasn't it?

Zon: Yes, almost nothing was known about these fish at the time. In 1996, I began a collaboration with Janni, who had found 50 zebrafish that had independent mutations affecting their blood. I sent a postdoctoral fellow and a graduate student to her lab to work on these blood mutants. Ultimately, they found that 17 genes were involved, because in some cases the same gene had been mutated in several different places. A lot of critics said it would be impossible to isolate the genes that were responsible for these mutants. We had no physical map of the zebrafish, no gene libraries, no reagents, and very few gene markers for a genome roughly the size of the mouse genome. So I took a role in getting the zebrafish community to think about tackling the zebrafish genome, and we finally got a genome initiative. By the end of 1998, we had fantastic resources for zebrafish that actually made our system go very fast!

So that took care of the doubts?

Zon: No, not even when we developed the first animal model of a human disease—congenital sideroblastic anemia, in which patients have trouble making hemoglobin. The critics said, "We already knew about this gene. Can zebrafish be used to define something new?" Well, in 2000, we published a paper on a gene, *weissherbst*—that's the name of a wine—which encodes a novel iron transporter protein, ferroportin, a key regulator of iron biology. Janni and I had a few glasses of weissherbst to celebrate. For years, people had been looking for an iron transporter gene in the gut of humans. It turned out to be the *weissherbst* gene product. Humans diverged from fish about 300 million years ago, but the process of iron metabolism is conserved in vertebrates. Two years ago, we and others found human

patients with problems in iron metabolism and mutations in ferroportin.

Did you ever find the gene you were originally looking for that regulates *GATA-1*?

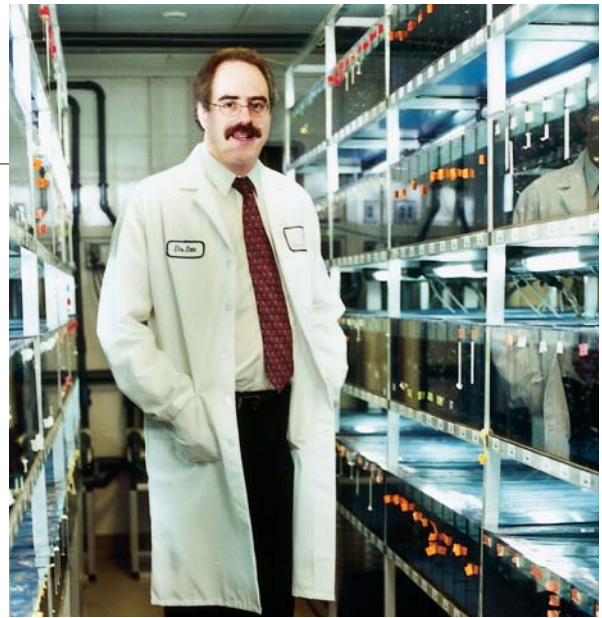
Zon: We did find a gene upstream of *GATA-1*, just recently. It's *cdx-4*, and it participates in the generation of blood stem cells during embryogenesis. That's very exciting because it may lead to ways of regulating blood stem cell development in the treatment of patients.

What prompted you to become a stem cell activist?

Zon: Well, I needed to study how stem cells become blood. And people who are trying to understand the biology of stem cells clearly need to band together. Four years ago, at a Keystone meeting on stem cells, people who don't usually interact with each other—they work on different organisms, for example, or different problems—realized they had a lot in common. So Irving Weissman, Douglas Melton, and I decided it would be a good idea to start a society. [An HHMI alumni investigator, Weissman is at Stanford University School of Medicine. HHMI investigator Melton is based at Harvard University.] Our group, the ISSCR, is now 700 members strong and will hold its second annual meeting in Boston in June. We just launched a Web site (www.isscr.org).

In the past, stem cell biologists didn't have a voice; now we do. Stem cell biology is in its infancy. We hope the ISSCR will help to move the field at a faster pace.

—MAYA PINES



Zebrafish advocate Leonard Zon, in Children's Hospital's new fish facility.

