

# The *C*rest

*Current Issues in Coastal Ocean and Estuarine Science*

## To B or Not to B: Pair Use Trout to Study Kidney's Role in Nurturing Fish Immune Cells

*Dave Malmquist*

When humans are exposed to infectious bacteria or other foreign invaders, our immune system fights back using an incredibly diverse host of cells and molecules—B cells, T cells, macrophages, cytokines, and antibodies, among many others.

As fellow vertebrates, fish produce and use the very same cells and molecules to confer immunity. But amazingly, fish generate their immune cells in a completely different organ than do humans. In fish, immune cells are thought to arise in the kidney. In humans and other mammals, it's the bone marrow.

This paradox intrigues VIMS immunologist Dr. Steve Kaattari. "What's fascinating about fish is that they don't have bone marrow," says Kaattari, "yet their immune system looks very similar to that of mammals. The same types of cells work in the same sort of way. So now we're asking, does the anterior kidney function in developing a mature immune system for the fish? How might it actually work?"

To help answer these questions, Kaattari has teamed with Dr. Patty Zwollo of the Biology Department at William and Mary. The pair recently submitted a 4-year proposal to the National Institutes of Health to continue their research into the genesis and activation of B cells in rainbow trout.

Zwollo notes that the collaboration provides "a great opportunity" to build on their shared interests and individual expertise. "We're both B-cell immunologists," says Zwollo, "but my focus has been on B-cell development in

mice, whereas Steve has focused on fish."

B cells are frontline scouts of the immune system. They recognize bacteria, viruses, parasites, and fungi, then produce antibodies to help the body rid itself of these and other foreign antigens. In fish, B cells are thought to arise in the anterior kidney, though this has yet to be proven. They develop from stem cells via a complex pathway whose many twists and turns are controlled by the presence or absence of growth-regulating chemicals. Bathe stem-cell progeny in one chemical and they differentiate into mature B cells. Bathe them in another, and they grow into T cells. Encounters with antigens cause mature B cells to

differentiate further—into plasma and memory cells. Plasma cells quickly flood infected tissues with antibodies. The longer-lived memory cells provide a means to recognize and rebuke an invader if it returns—whether tomorrow or years hence.

The intricacy of this process makes its occurrence within completely different organs in mammals and fish truly remarkable, says Zwollo. By studying basic immunological processes in trout, Kaattari and Zwollo believe they can ultimately shed light on how B cells differentiate in bone marrow and are activated to fight diseases in humans.



From right to left: Dr. Steve Kaattari, with Erin Bromage and Ilsa Kaattari.

Kaattari notes that activation of B cells to produce antibodies is a particularly promising area for this type of comparative immunological research. "In trout, we have some evidence that mature B cells from the anterior kidney may continue to produce antibodies

*Continued on page 4*

Virginia Institute of Marine Science  
School of Marine Science  
College of William and Mary  
P.O. Box 1346  
Gloucester Point, Virginia 23062

ADDRESS SERVICE REQUESTED

Non Profit Organization  
U.S. Postage Paid  
Glou. Point, VA 23062  
Permit Number 6

*To B or Not to B...*  
*continued from page 1*

long after their initial exposure to an antigen. We're really interested in why that is. There are some elements that seem very reminiscent of bone marrow."

Recent studies with mammals show that bone marrow sometimes holds long-lived plasma cells that constantly trickle antibodies targeted at previously encountered invaders. Traditional thinking holds that plasma cells are short-lived, dying off as soon as an invader is vanquished, and that memory cells in the spleen provide the long-term protection. But memory cells must be activated before they can respond. Retention of active plasma cells could thus help the immune system react more quickly to future invasions. "You save time doing it this way," says Zwollo.

If Kaattari and Zwollo's research shows that the anterior kidney is indeed the reservoir for long-lived plasma cells in trout, it would support the idea that this organ is where fish develop B cells. "That's the way it works in mammals," says Zwollo, "long-lived plasma cells reside in bone marrow, the same organ that nurtures young B cells."

The pair's B-cell research builds on Kaattari's previous advances in developing the rainbow trout as an alternative to mice as experimental animals. Researchers have historically relied on mammalian models—the proverbial "lab rat"—to explore biomedical questions. "In our lab," says Kaattari, "we're refining trout as another model of biomedical research, particularly in immunology."

Several traits favor fish, trout in particular, as biomedical models. For one, researchers can manipulate fish reproduction to quickly produce large numbers of identical offspring. Whereas it took hundreds of generations to produce genetically identical mice, collaborators at Washington State University created strains of identical trout in only two generations. Use of genetically identical animals ensures a consistent, statistically meaningful response to immunological challenges. Young trout are also small enough that thousands can be reared in a normal-sized laboratory, yet they grow large enough (10-15 pounds) for easy manipulation and use in long-term experiments. With mice, juveniles and adults vary little in size. Finally, trout care is relatively easy, particularly now that high-tech biofilters and chillers

ensure that fish in aquaria have the cold, clean water they need.

But the trout's big advantage is that it provides researchers with a model animal that is agriculturally important. Trout, and their near relatives the salmon, "are about the most important species in aquaculture," says Kaattari. "They are cultured around the world. In Virginia alone, there are at least 12 trout hatcheries."

Use of a trout model to increase basic understanding of the fish immune system thus promises significant economic return, particularly since farmed fish are crowded and therefore more prone to disease than their wild kin. Coupled with its basic scientific merits, the potential economic value of Kaattari's research makes it attractive to a wide range of funding agencies. To date, five different agencies have funded his trout work, including the National Oceanic and Atmospheric Administration, the US Fish and Wildlife Service, the US Department of Agriculture, the National Institutes of Health, and the Department of Energy.

In addition to trout, Kaattari is studying the immune response within another commercially important fish species—the striped bass.

In Chesapeake Bay, around 70% of these popular game fish are now

infected with mycobacteriosis, a chronic disease whose characteristic lesions first showed up in Bay stripers in 1994. The prevalence of this disease in the Bay's striped population has raised numerous questions concerning its origin and transmission.

To help answer these questions, Kaattari and fellow VIMS researchers are developing a suite of genetic tests to determine if a striped is infected with or has developed immunity to mycobacteriosis. The tests will require only a small sample of blood, which could be taken by VIMS' Juvenile Trawl Survey team during their monthly catch-and-release sampling of Chesapeake Bay fish and invertebrates. The Trawl Survey and other population and tagging studies provide a comprehensive view of the Bay's striped population. Correlating the blood-test results with abundance and distribution data from these surveys will "allow us to look at the dynamics of disease and its impact within a wild population, and that's virtually never been done before," says Kaattari.

For further information on fish immunity research at VIMS (including video clips from Steve Kaattari's laboratory), visit the VIMS web site at <http://www.vims.edu/env/research/immune.html>