

# Hints from Wnts

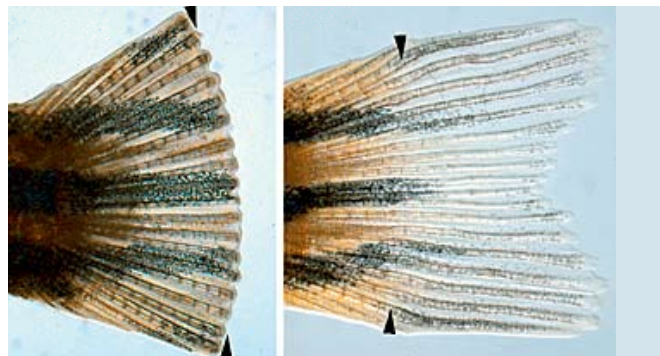
THE SECRET TO REBUILDING BODY PARTS MIGHT BE FOUND IN A FISH FIN.

When it comes to replenishing lost body parts, some of our distant cousins can teach humans a thing or two. Zebrafish, for example, have no problem regenerating perfect tailfins after being nipped by an aquarium mate—or snipped by an inquisitive doctoral student, like the University of Washington's Cristi Stoick-Cooper.

She and her colleagues in the laboratory of HHMI investigator Randall T. Moon recently coaxed a few secrets from zebrafish on how they regrow their tails. Specifically, the researchers discovered a critical ingredient in the creatures' regeneration potion—a group of signaling molecules called Wnt proteins (pronounced “wint”). Although Wnts are well-known regulators of many cellular processes, their role in organ regeneration had never been examined.

Wnt proteins typically respond to extracellular signals by prompting another protein, called  $\beta$ -catenin, to enter the nucleus and activate specific genes. In particular, Stoick-Cooper, University of Washington postdoc Gilbert Weidinger (now at the Technical University of Dresden), and colleagues found that Wnt/ $\beta$ -catenin activity rises in zebrafish undergoing tailfin regeneration, but the fish were unable to regrow snipped tailfins when researchers disabled the Wnt/ $\beta$ -catenin pathway. Zebrafish engineered with elevated Wnt signaling levels regenerated their tailfins with added haste.

Surprisingly, zebrafish that overproduced a different Wnt—Wnt5b—failed to regenerate tailfins altogether, but mutant fish lacking a functional *Wnt5b* gene replaced their tailfins at an



One day after trimming the edges of a zebrafish tail fin (left), things look a little too neat. Never fear: by ten days post amputation, the tail fin has regenerated.

accelerated pace, indicating that this Wnt protein normally inhibits regeneration.

These experiments, reported in the February 1, 2007, issue of *Development*, reveal that Wnts are central to the regeneration process in zebrafish, says Moon. Moreover, he cites his team's observation that Wnt activity in mice increases during liver regeneration, suggesting that the same pathways may be at work—and potentially extendable—in mammals. “Manipulating Wnt signaling could hold the key to regenerating damaged organs and limbs in humans,” says Stoick-Cooper. “It's just a dream right now, but we're getting closer to understanding how this might be possible.” ■ -PAUL MUHLRAD

## IN BRIEF

people working on skin biology described hair follicles in the dermis as basically like telephone poles stuck in cement,” Nathans says. The studies were published December 15, 2006, in the online early edition of the *Proceedings of the National Academy of Sciences*.

### ANCIENT DNA-REPAIR MECHANISM AIDS IN ANTIBODY SELECTION

New research by HHMI investigator Frederick Alt of Harvard University and colleagues shows how the immune system slices and dices genes so that B cells can program antibodies to seek out and destroy invaders. Their work, published December 14, 2006, in *Science Express*, suggests that an ancient DNA-repair mechanism designed to repair broken chromosomes may have evolved to play this role.

B cells are the immune system's armories, where antibodies that attack viruses, bacteria, and other invaders are produced. To take on specific pathogens, B cells first tailor antibodies to recognize the invaders. Called class switch recombination, the process entails cutting and joining two widely separated switch regions on the

genomic immunoglobulin heavy chain (IgH) locus so that one type of antibody constant region gene is cut out and replaced with another.

The team replaced very large switch regions with short DNA sequences that would be recognized not by the usual DNA-altering enzyme, activation-induced cytidine deaminase, but by endonuclease, a yeast DNA-cutting enzyme. The IgH class switching still functioned, albeit at a lower-than-normal frequency.

The findings also have implications for understanding the types of chromosomal rearrangements that underlie some cancers. “This mechanism might act as a sort of ‘glue’ to hold chromosomes together so that breaks are not allowed to migrate and be joined to other chromosomes,” Alt says.

### SCIENTISTS DISCOVER A NEW RISK FACTOR FOR ALZHEIMER'S

Researchers have identified a gene called *SORL1* that is implicated in late-onset Alzheimer's disease.

In a January 14, 2007, advance online publication of *Nature Genetics*, HHMI international research scholar Peter St George-Hyslop at the University of

Toronto and colleagues connected the gene to the disease in six groups of people by using a database that listed single nucleotide polymorphisms (SNPs), or single-letter changes in a gene's sequence. The researchers looked at more than 6,800 people, including groups of Caucasians, one group of African Americans, one group of Hispanics from the Dominican Republic, and a group of Israeli Arabs. The team used the SNP databases to track the *SORL1* gene in the populations studied but did not actually pinpoint the precise changes in the gene that contribute to disease.

After linking *SORL1* to late-onset Alzheimer's, the team investigated the gene's function. Using cell culture studies, they discovered that decreasing the amount of *SORL1* increased cells' production of amyloid-beta, a toxic protein fragment that is a key event in the progression of Alzheimer's disease.

A new player has been found among the mechanisms causing Alzheimer's disease, St George-Hyslop says. “This will lead to the real endgame, which is to see how to exploit the findings as a new diagnostic or therapeutic target.”