devo, biologist at the University of California, Berkeley.

The work has already yielded some bizarre results, and the draft genome is helping the researchers home in on the genes responsible. At the meeting, Kondoh described one mutant, called totoro, in which

Piscine genomics. The new medaka genome and thousands of mutants make these fish a useful tool for discovering gene function.

both males and females have abdomens filled with immature eggs. Another, called finless, lacks a tail and swims by thrusting its body from side to side. "And this is just the tip of the iceberg," says Amemiya. He's quite pleased with these results, noting that "all these kinds of [mutants] that are available for medaka will absolutely complement [studies] of zebrafish."

RNAi Takes Evo-Devo World by Storm

In 1998, geneticists working on the worm *Caenorhabditis elegans*, one of the first beasts to have its genome sequenced, struck gold. They discovered a simple way to find out the functions of many of its 20,000 sequenced genes. A stampede ensued, with researchers racing to try the procedure, called RNAi, in their favorite study organisms. "Here you had a technique that you could use on nonmodel organisms," for which no other good methods exist for knocking out genes, points out Nipam Patel, an evo-devo biologist at the University of California (UC), Berkeley. At the meeting, at least a half-dozen evo-devo biologists reported new results made possible through RNAi. From planaria and jellyfish to beetles and crickets, RNAi is unearthing the roles of certain genes in development and evolution—information that can also help illuminate human genes.

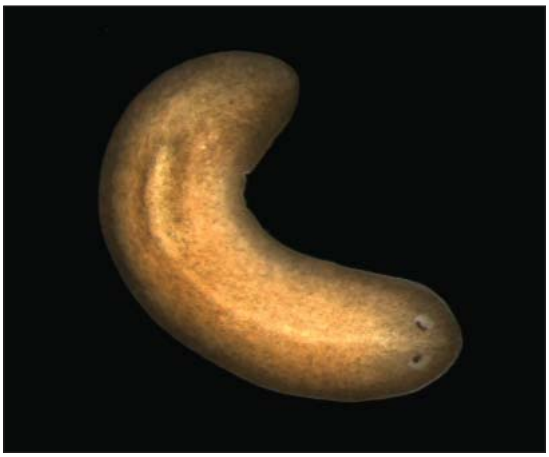
RNAi—the "i" stands for interference—works by neutralizing specific RNAs, essentially shutting down the gene that generated them. It's like using a mutation to knock out a gene, but easier. By observing how this shutdown affects an organism, researchers can deduce the gene's purpose.

Using this technique, Alejandro Sánchez Alvarado, a developmental biologist at the University of Utah School of Medicine in Salt Lake City, has zeroed in on a gene shared by many plants and animals, showing that in the planarian worm it can make or break the ability of stem cells to regenerate heads and other parts of the body. Others have discovered differences in the location and function of developmental genes shared by fruit flies, beetles, crickets, and spiders—differences that likely played a role in the evolution of these invertebrates. RNAi "has really opened new avenues of investigation of genes whose functions we think we know and genes whose functions we don't know," says Sánchez Alvarado.

For years Sánchez Alvarado has been painstakingly tracking down genes involved in planaria regeneration. These small worms can regrow a head in a matter of days and a whole body in not much longer. They depend on stem cells called neoblasts not only to build new body parts but also to maintain status quo in their tissues.

"Before the introduction of [RNAi], no functional assays were available to study the molecular biology of neoblasts," he recalls. But already his group has used RNAi to study 1200 genes, and it's gotten intriguing results for about 240. "It seems like they are on the verge of understanding how neoblasts work," says Richard Behringer, a genomicist at the University of Texas M. D. Anderson Cancer Center in Houston. He hopes the research on planaria can help elucidate human stem cells, those highly coveted cells that give rise to many different types of tissue.

A gene called *piwi* suggests that the planaria studies can do just that. Scientists already knew that stem cells use this same gene in other organisms—evidence that stem cells are evolutionarily quite old and so essential that their genes haven't changed much. The *piwi* gene is active in stems cells, and signs of its activity disappear when the stem cells are destroyed by radiation. Utah's Peter Reddien put RNA in the planaria's food. Although the stem cells continued to function, "regeneration failed once *piwi* was disabled," he reported.



Surrogate stem cell. Cells that generate the planaria's head could prove useful stand-ins for studying stem cells of more complex organisms.

Other RNAi work presented last week is helping demonstrate the role developmental genes played in reshaping organisms as they evolved. Susan Brown, a geneticist at Kansas State University in Manhattan, has been examining the activity and function of genes that help define the segments of the *Drosophila* embryo. In this fruit fly, segmentation happens early in development, and all segments form at the same time. In other insect species, however, such as the red flour beetle, most segments form one at a time, each one helping elongate the embryo's body. At the meeting, she reported that one common segmentation gene called *runt* may help explain the different developmental pathways observed in these two insects.

In fruit flies, *runt* plays a role in early, simultaneous segmentation, as mutant embryos lacking that functional gene are half the normal size and are missing every other segment. When Brown gave beetles low concentrations of RNAi against *runt*, their embryos looked just like these mutant fly embryos. But when she upped the dose of RNAi, "we got unexpected results," she reported. Very few segments formed, suggesting that because this beetle and the fruit fly diverged from a common ancestor, the function of this gene, and perhaps others, diverged along with developmental pathways. She's not sure how the difference in RNAi dosage works, however.

Some development genes seem to work the same in both fruit flies and evolutionarily divergent insects. Studies reported by Taro Mito of the University of Tokushima in Japan suggest that crickets use genes such as one called *eve*, which is involved in patterning the anterior part of the body, in much the same way as *Drosophila* does.

RNAi is not a panacea for functional studies, however. Sometimes the inserted RNA disrupts the function of genes other than its target, says UC Berkeley's Patel. Other times, it fails to turn off the target gene. Nonetheless, the use of this technique is sure to grow, says UC Berkeley's John Gerhart: "It's almost become a requirement if you are going to do evo-devo."

—ELIZABETH PENNISI

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