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 way to knock out genes. Two years later, they reported that RNAi, a technique that uses small interfering RNA molecules to turn off gene expression, is essential for the survival of the worm.

RNAi—abbreviated for RNA interference—is a natural process that cells use to silence foreign RNA molecules, such as those from viruses, and to maintain gene expression patterns. The technique has been widely used in research to study gene function because it allows researchers 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 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 interesting results for about 240. “It seems like they are on the verge of understanding how neoblasts work,” says Richard Behringer, a genomicsist 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 stem 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.

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