hibit even more complex behaviors, including choice of fish with which to shoal, circadian rhythmicity of locomotion, and right-eye dominance in the decision to bite.

Most human genes studied so far have orthologs in the zebrafish. In fact, large regions of human and zebrafish chromosomes show synteny (conservation of gene order) that has been conserved for more than 420 million years (the approximate date of the last common ancestor). However, within these large gene blocks, the order of genes may be transposed or inverted (*9*). This conserved synteny has promoted our understanding of genome evolution, including the relative contributions of chromosomal translocations and inversions. For example, there is a genome duplication at the base of the teleost radiation about 100 million years ago, and about 20% of these duplicated genes are believed to have been retained in the zebrafish. Interestingly, where evaluated, the duplicated genes are not redundant in function, but rather subdivide the function of the ancestral gene. Thus, mutations in one of the duplicated genes may give rise to a more discrete phenotype than mutation of the ortholog in a species, such as the mouse, where gene duplications have not been found. In addition to identifying new genes, the complete zebrafish genome sequence will reveal noncoding sequences shared through evolution, thereby pinpointing important candidate regulatory elements.

The zebrafish will undoubtedly be key to understanding human disease. First, mutations in orthologous zebrafish genes have provided models for several human genetic disorders. For example, mutations in genes encoding enzymes of the heme biosynthetic pathway cause the porphyrias. These diseases are characterized by a constellation of hematological, hepatic, and skin abnormalities. Mutations in orthologous zebrafish genes cause similar phenotypes, dramatically illuminated by fluorescent porphyrins visible in the transparent embryo. The otic vesicle defects in the *mariner* zebrafish mutant are caused by mutations in the myosin VIIA gene; this is the gene disrupted in human Usher 1B deafness syndrome (*10*). Second, the conservation of body plan among all vertebrates means that the phenotype of a zebrafish mutation may resemble a human disease in search of a molecular explanation. This applies both to congenital and adult-onset human diseases. For example, in the *gridlock* zebrafish mutant, the aortic branch point is blocked, which suggests that mutations in the *gridlock* gene (*11*) or other components of its signaling pathway may contribute to congenital malformations of the aortic arch in the human fetus. Even characteristic combinations of organ systems affected in certain genetic disorders, such as craniofacial and pigmentation defects, are mimicked by single-gene defects in zebrafish. Complex diseases in the adult, such as heart failure, often have a clear genetic predisposition but are refractory to standard gene mapping techniques. Dozens of mutations in zebrafish yield a phenotype characterized by inefficient contraction of cardiac muscle; identifying the mutated genes may yield candidates involved in human heart failure. Third, zebrafish mutations that result in loss of stem cell populations, for example, those of gut or blood, or that perturb regeneration of injured fins, will be valuable for designing drugs for use in regenerative medicine.

Limited only by the imagination of the investigator and by the precision of the phenotype, the zebrafish is turning out to be a species for all genomic seasons.

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NOTA BENE: PROTEIN FUNCTION

Clockedout—an Archetype of a Functionless Protein

Proteomics is set to revolutionize our knowledge of protein function. But is the assumption that all proteins are functional really valid? A recent study indicates that at least one protein does not do anything useful—for all practical purposes, it merely comes along for the ride. Skumway *et al.* have studied the function of Missingear (Mr), initially believed to be a clock protein in *Drosophila*. Mr was always coexpressed with Tic, Toc, and Buzzer. However, no change in clock dynamics could be discerned at any level of expression of Mr, leading to the speculation that the protein had some other function. After an extensive functional, genetic, and structural survey, Skumway *et al.* now conclude (*1*) that Mr does not do anything. They have tentatively renamed the protein as clockedout.

Clockedout has no distinctive structural motif but appears to have borrowed elements from several other protein families. Enzymatic pockets are turned inward, and binding sites are tagged with odd lipids and saccharides so that the protein gives the appearance of a molecular junk pile. All ubiquitination sites are inactivated, as if the protein had made a deal with these enzymes to take five and leave it be.

How does the cellular economy deal with a deadbeat like clockedout? If evolutionary niches—even molecular ones—can be thought of as "jobs," then clockedout has hit upon an ideal strategy: If one's niche is doing nothing, how can a competitor do more than nothing? It is not clear whether clockedout is unemployed or whether it is like one of the mythical cubicle dwellers who serve no function but still get paid. The latter may in fact serve a function, in that they allow headcount to be reduced without any loss of overall productivity (the "bait and switch" strategy).

Those looking for the true null of background signal in functional assays will find clockedout invaluable as a control. It binds to no known chemical or other protein, turns over no substrate, and undergoes neither import nor export. Whether clockedout is fully optimized to do nothing or, like some designed enzymes, simply does everything badly is still open because of its limited homology with the protein incompetent. Perhaps its true function lies in a symbiotic relationship with the recently evolved *Homo sapiens* ssp. *sleepless*, that is, the molecular biologist.

Homologs are being found across the evolutionary spectrum (*2*), including *nodoff* in the dormouse, *kickback* in *Xenopus*, *wormedoutofit* in *Caenorhabditis elegans*, *flatbread* in *Saccharomyces*, *float* in zebrafish, *DORMANT* in *Arabidopsis*, and *lazy* in the rat. Studies in the human are still in progress, but tentative evidence for the gene *layabout* is being gathered—slowly.

—CHIP READER

References and Notes

1. H. S. Skumway *et al.*, *J. Overinterpret. Res.* **2**, 449 (2001).
2. H. S. Skumway *et al.*, in perpetration.

3. The author is currently between industrial positions. He can be reached through Phil Szuromi, a Supervisory Senior Editor at *Science*.