Biotech Finds a Growth Industry

Young developmental biology firms have high hopes of treating disease with model organisms and the regenerative power of the embryo, but they face many commercial and scientific growing pains

The first time Spyridon Artavanis-Tsakonas went to Wall Street to argue that the lowly fruit fly *Drosophila melanogaster* may hold the key to biotechnology's future, financiers all but laughed him out of their offices. "The moment I said the word 'fly,' I would see a kind of curtain falling over their eyes," the Yale University developmental neurobiologist recalls. Three years later, however, it's Artavanis-Tsakonas and his partners who are laughing all the way to the bank. Exelixis Pharmaceuticals, the Massachusetts biotech firm they co-founded in 1995, has licensed a powerful technique for manipulating fruit fly DNA to ferret out key developmental genes. And in a round of private financing that raised $12.5 million this spring, so many venture capitalists wanted a dram of *Drosophila* in their portfolios that the company had to turn several potential investors away.

The investors eager for a piece of Exelixis are betting that developmental genetics, which relies on *Drosophila* as one of its premier experimental organisms, may revolutionize drug discovery. Because organisms from flies to humans turn out to have similar developmental genes, young firms hope to transform the biotech industry's largely scattershot search for human genes into a systematic dissection of developmental signaling in lab organisms. The potential payoff: drugs that rejuvenate damaged tissues by re-creating a bit of the embryo in the adult.

Companies are exploring ways to regenerate bone, muscle, and other tissue, and coax damaged brain tissue to again produce vital neurotransmitters, all to treat conditions ranging from Parkinson's disease to skin cancer. "In the developed world the greatest number of diseases are degenerative, where the challenge is to restore normal function and repair," says physician and neurobiologist Doros Platika, CEO of Ontogeny Inc., a 2-year-old developmental genetics firm in Cambridge, Massachusetts. "The best way to identify the genes responsible for that is to look at the system when it's being built. That way, instead of fishing in the ocean, you're fishing in a stocked pond with sonar."

But for the moment, developmental genetics' commercial promise is far from a sure bet. Exelixis, for example, has jumped one hurdle—the need for capital—but like other young start-ups faces a maze of other scientific and financial obstacles before it can mature into a commercially successful company. Even more established firms, such as Regeneron Pharmaceuticals of Tarrytown, New York, have yet to get a single drug to market. Companies that rely on patents for families of genes or proteins run the risk that their proprietary molecules won't provide ideal keyholes for drug design, and some face cutthroat competition on similar molecules. Exelixis skirts these dangers by offering a method rather than a molecule, but runs a scientific risk of its own: The company is gambling that the similarities between fly and human genes are deep enough that plumbing the fly will yield therapies in people.

All these hazards keep developmental genetics "a niche area" for the biotechnology industry, says David Molowa, a biotechnology analyst at the investment firm Bear Stearns in New York City. Yet despite the risks, investors are willing to pump in money. "When very bright scientists speak, you listen," says Stelios Papadopoulos of New York's PaineWebber investment firm, one of Exelixis's earliest backers.

Payoffs and perils

Long an obscure corner of academic biology, developmental genetics gained worldwide attention last year with the capture of the Nobel Prize in medicine by three researchers who uncovered the genes and proteins that form the first specialized structures in a fruit fly body (*Science*, 20 October 1995, p. 380). And over the past decade, researchers have been astonished to find that these genes have counterparts in species across the animal kingdom—including *Homo sapiens*.

This cross-species similarity offers a new tool for understanding a question the biotech industry has been working on for years: how to regulate cell differentiation, the creation of specialized cell types from uncommitted cells. Indeed, the most successful biotech product in history, Amgen Inc.'s Epogen, is a genetically engineered version of the protein erythropoietin, which is produced by the kidneys and stimulates blood stem cells to mature into red blood cells. Approved by the FDA in 1989, Epogen can reverse the severe anemia often suffered by patients with kidney disease. Biotech executives often say they want their firm to be "the next Amgen," and with good reason: Amgen's sales of Epogen and Neupogen, a recombinant version of a protein that directs blood stem cells to become bacteria-fighting neutrophils, totaled $1.8 billion in 1995.

Repeating Amgen's coup in new tissues, however, won't be easy. The roles of both these proteins were well known long before the company developed its products, and there was no question about transspecies similarities; the main difficulties in bringing the molecules to the clinic were cloning key genes and inserting them into host cells. Today's geneticists, by contrast, can clone new genes with ease but may spend

SOME DEVELOPMENTAL VENTURES

Company	Date Est.	Projects—Disease Targets	Stage
Amgen	1980	Epogen—dialysis-induced anemia Neupogen—replenishing neutrophils after chemotherapy	Approved Approved
Genetics Inst.	1980	Bone morphogenic protein-2—bone fracture repair	Phase I and II trials
Creative BioMolecules	1987	Osteogenic protein-1—bone fracture repair	Phase III trials over
Regeneron Pharmaceuticals	1988	Nerve growth factors—ALS, peripheral neuropathies	Phase II, III trials
SyStemix	1988	Blood stem cell purification—stem cell transplants after chemotherapy	Approved
Progenitor	1992	Human yolk sac cells—cancer, blood vessel growth	Research
Idun Pharmaceuticals	1993	Cell-death inhibitors—ALS, Parkinson's, stroke	Research
Ontogeny	1994	Hedgehog proteins—cell replacement	Research
Exelixis Pharmaceuticals	1995	Pathfinder screen—gene identification and function	Research

years uncovering their functions and developing drugs. Says Fu-Kuen Lin, the Amgen biologist who first cloned the erythropoietin gene in 1983: "To discover a molecule and to make it useful are two totally different things."

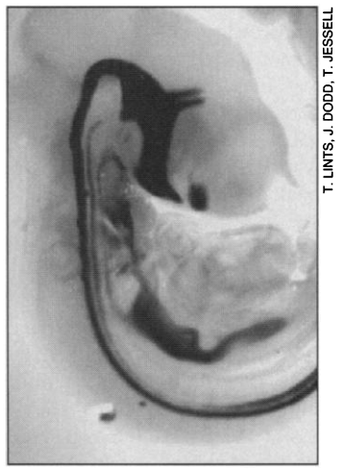
For example, Regeneron, which is working to regenerate nerve tissue to treat diseases such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), has cloned half a dozen mouse and rat genes encoding proteins and receptors that regulate nerve cell growth and survival. In 1991, only 3 years after its founding, the company went public in a spectacularly successful initial offering that raised $91.6 million. But in 1994 Regeneron canceled clinical studies of one promising molecule, ciliary neurotrophic factor, because it had proved ineffective against the loss of muscle control that eventually causes ALS patients to suffocate. (The company does have ongoing clinical tests of two other growth factors, neurotrophin-3 and, in a partnership with Amgen, brain-derived neurotrophic factor.) To further lessen the risks of focusing on only a few proteins, Regeneron scientists are now branching out, using their expertise to study proteins that regulate inflammation, the formation of blood vessels, and muscle growth and differentiation, hoping to develop therapies for a range of vascular and muscle diseases (*Science*, 24 May, p. 1100).

Other companies are betting that the proteins they study are consequential enough to have some important medical uses—even if the proteins' precise roles aren't worked out yet. For example, Ontogeny, founded by developmental geneticists Doug Melton and Andrew McMahon of Harvard University, Tom Jessell of Columbia University, and Eduardo Mitrani of Hebrew University in Israel, owns commercial rights to the recently discovered hedgehog family of vertebrate regulatory proteins. These three secreted proteins (whimsically named Sonic hedgehog, Desert hedgehog, and Indian hedgehog) bind to the surfaces of cells and activate a variety of developmental changes, depending on the cellular context. For example, when cells from the future midbrain region of chick embryos are exposed to Sonic hedgehog, the cells develop into various kinds of neurons, including those that produce the neurotransmitter dopamine. Researchers hope that the protein can be used to grow cells for implantation into the brains of Parkinson's patients, who lack dopamine.

The hedgehog proteins are known to be crucial to many aspects of development, so they would seem to be a good bet as therapeutic targets. But Ontogeny still faces the danger that the hedgehog proteins might turn out to be the corporate vice presidents of developing tissues, too high up in the regulatory hierarchy to oversee the detailed clerical work of cell differentiation. Indian hedgehog can cause cells to differentiate into cartilage and bone, for example, but it may do so by activating genes with more specific effects. And while Ontogeny scientists are on the lookout for such genes and proteins in flies, mice, chickens, human tissue, and other model systems—and are keen to collaborate with academic scientists working on the hedgehogs and related molecules—other companies could strike oil first. Says Charles Cohen, chief scientist at Creative BioMolecules of Hopkinton, Massachusetts, a company working on bone regeneration: "It remains to be seen whether the hedgehogs or things 'downstream' of them are better points for pharmaceutical intervention" in processes such as bone growth.

But at least Ontogeny doesn't have to worry about direct competitors for medical therapies employing the hedgehogs. The firm has exclusive commercial rights to the known proteins, and no other members of the hedgehog family are thought to exist. Other companies—including Cohen's—aren't so lucky. The apparent redundancy of genes involved in vertebrate development means patent protection isn't always enough to fend off rival biotech firms. Creative BioMolecules, for example, has isolated two proteins that stimulate bone growth and has just finished clinical trials testing whether a collagen matrix impregnated with one, osteogenic protein–1 (OP-1), can substitute for grafts of living bone tissue in patients with severe tibial fractures. But another Boston-area firm, Genetics Institute, has discovered and patented 11 other members of the same protein family. The company is testing the ability of one of them, bone morphogenic protein–2 (BMP-2), to induce bone formation in jaw and spinal fractures.

As local bone repair agents, OP-1 and BMP-2 "appear to function about the same way," says Rod Riedel, a biologist at Genetics Institute. In the body, the two proteins may even form a "heterodimer," a paired molecule with OP-1 on one side and BMP-2 on the other. As a result, the two companies, like their Siamese-twin proteins, may find it hard to keep a step ahead of one another.



T. LINTS, J. DODD, T. JESSELL

Fetal futures. Sonic hedgehog protein expressed in chick embryo (dark areas) may one day help treat disease.

From fly to human

To avoid the commercial and scientific pitfalls inherent in the product-based approach, Exelixis—the name means evolution in Greek—took another tack. Artavanis-Tsakonas and the company's other two scientific founders, developmental geneticist Gerald Rubin and neuroscientist Corey Goodman, both of the University of California, Berkeley, chose to industrialize a technique, the "pathfinder screen." Rubin and Artavanis-Tsakonas have already used the method to identify all the molecules in two signaling pathways in fly eye development, from extracellular factors to cell-surface receptors and intracellular messengers, and the procedure should help to pick apart any genetic pathway.

Once a single protein in a pathway is known, the human or fly gene encoding this protein can be transferred into fruit flies using P elements, transposable DNA elements co-invented by Rubin and licensed for commercial biomedical uses exclusively to Exelixis. Researchers can then create descendants of these transgenic flies and examine them for mutations that alter the effects of the transgene. That should lead to genes encoding proteins upstream or downstream from the original protein in its pathway. The technique has the potential to take solitary genes, such as the human breast cancer gene *BRCA1*, and place them in the context of a biological signaling process that might be pliant to drug therapies. Says Artavanis-Tsakonas: "99% of biotechs focus on a particular product or two. ... We are rather using an approach that will allow us to have a hundred or a thousand fallback positions."

But Exelixis is taking its own gamble. For while there are numerous cases of homologous genes and proteins in flies and humans, there's no guarantee that a given *Drosophila* pathway will be so similar to the human one that the fly genes will have therapeutically relevant human counterparts. And if the pathfinder screen were to come up dry repeatedly, clients willing to pay for the service might also evaporate.

Such hazards are all part of growing up for young developmental genetics companies. The scientists and investors behind these firms are hoping that with a little help from hedgehogs and fruit flies, Ontogeny, Exelixis, and their kin won't end up contributing to the biotech industry's notoriously high rate of infant mortality. Says Ontogeny CEO Platika: "It may be demented, but I think we're going to be the Amgen of the future."

–Wade Roush