

## Innovations

# Elixir Pharmaceuticals: Targeting Molecular Sources of Aging

Its name may initially provoke images promising the fountain—or medicine—of youth. But the daily business of Cambridge, MA-based Elixir Pharmaceuticals could not be more current and high tech. According to Peter DiStefano, PhD, Elixir's Chief Scientific Officer, "The mission of the company is to identify the molecular targets involved in the aging process and to manipulate those targets pharmacologically to prevent and treat a variety of age-related diseases." Elixir is a 30-person company of highly qualified scientists with serious reputations in the fields of biology, genetics, aging, and longevity, focused on identifying key pathways involved in the diseases usually associated with aging. "But, we are not about creating an anti-aging pill," explains Alan Watson, PhD, the company's Chief Business Officer. "We are in the drug discovery business, pursuing established disease indications with discrete clinical endpoints."

### **An Evolved Partnership**

"Elixir came into being focused on the aging angle, and we now have a very cogent disease-focused perspective," says DiStefano. The company's initial technology platform was contributed by its two scientific founders, Cynthia Kenyon, PhD, from the University of California, San Francisco, and MIT's Leonard Guarente, PhD. Dr. Kenyon works mainly in studies of *C. elegans*; Dr. Guarente studies yeast molecular genetics. These two researchers provided much of the model organism work wherein important conserved pathways involved in the diseases of aging have been discovered and are now being mined for pharmaceutical targets at Elixir. In February 2003, Elixir merged with a sister company in the world of aging studies, Centagenetix, Inc., also of Cambridge, MA. The key drivers behind Centagenetix were Louis Kunkel, PhD, a renowned geneticist who is currently director of the Genetics Program at Children's Hospital in Bos-

ton, Alli Puca, MD, a Kunkel post-doctoral fellow and protégé, and Thomas Perls, MD, MPH, the founder of the New England Centenarian Study, charged with collecting DNA samples from hundreds of 100-year-old individuals.

Elixir had a model organism genetics technology platform, whereas Centagenetix had a human genetics technology platform it used to conduct genetic population association studies. That was the core difference, although both companies were ultimately pursuing drug discovery. "It was the origins of the sources of targets and biochemical pathways that were different," says Watson. Representatives from both first-generation companies are on board at Elixir, originally incorporated in 1999.

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### **Conventional, though Novel, Druggable Targets**

"We are focusing on conventional druggable targets like cell surface receptors, enzymes, and the like," says DiStefano. But he acknowledges he came to these from the early "aging platform" days at Elixir. "A lot of the model organisms work performed early on identified some orthologous human targets in these lower animals—worms, flies, and yeast—as being critically involved in controlling the aging process." It turns out that almost all those genes, pathways, and targets are found in

organisms like bacteria all the way up to man. "These targets play critical roles in cellular function in all species," says DiStefano. The company has taken that founding biology, looked at those pathways existing in lower organisms, and asked if they operate similarly in humans. "The short answer is that yes they do quite a bit, and they modulate cell division, the redox state of the cell, oxidative damage, apoptosis, and metabolic functions within the cell," says DiStefano. "And we've looked at various targets in those pathways and started small molecule drug discovery programs around those targets." The theory is that, gone awry, these pathways could give rise to many diseases with increased prevalence in older people: cancer, cardiovascular disease, neurodegenerative disease, Alzheimer's Disease, diabetes, and other metabolic disorders. "These molecules or targets affect a lot of these cellular processes that go haywire in these diseases—that's what's really exciting," adds DiStefano.

One of those pathways is the DAF-2 pathway, partially drawn out by Dr. Kenyon in her study of *C. elegans*. "DAF-2 happens to be the ortholog of the IGF-1 receptor/insulin receptor in man," explains DiStefano. It is a highly conserved pathway found in several organisms. Kenyon discovered that altering a single nucleotide in the DAF-2 gene in the worm more than doubles its usual life span. "The DAF-2 pathway has a similar function in many different species, and we have mined that pathway, looked for key intervention points in mammalian organisms, identified targets, and mounted drug discovery programs around those targets," DiStefano says. In particular, Elixir is interested in further investigating the recently discovered association between diabetes and neurodegeneration, such as that in Alzheimer's disease, in terms of the DAF-2 insulin/diabetes pathway.

"The other pathway we are working on came from Lenny Guarente's yeast work involving the SIR2 pathway, or the 'Silent Information Regulator' pathway," explains Watson. "This is an entirely novel target involved in a number of bioenergetic and potentially cancer-regulating pathways." He further explains that there are seven human homologs of the SIR2 gene in yeast, known as the SIR-T family. Adds DiStefano, "We have identified small molecule modulators of targets in both of these pathways and tested them in cell-based assays, and we have begun looking at them in rodent-based in vivo models." The company has identified near lead-stage compounds in its DAF-2 program. "It is a medicinal chemistry approach now to further identify those leads and come up with clinical candidates," says DiStefano.

#### **Centenarian Genetics**

##### **Analysis Secondary**

Centagenetix contributed highly publicized tantalizing work on a particular area of human Chromosome 4. Researchers had identified a gene in that region as being critical to longevity: the MTTP (microsomal triglyceride transfer protein) gene. "The good news was that it was known to be involved in triglyceride regulation, something you would expect to be central with respect to aging and longevity," explains Watson. But the bad news for Centagenetix was that this known target had been well trodden by about a dozen large pharma companies and so was not an exclusive novel target. More importantly, Centagenetix's own centenarian genetic association studies showed that other genes aside from those on Chromosome 4 must be involved in the human longevity phenotype. "This is one of the reasons we are not aggressively pursuing the Chromosome 4 findings," says Watson, even though Elixir recently received a U.S. patent on the use of the conserved area of Chromosome 4 implicated in human longevity.

It should be noted that Kunkel and Perls remain dedicated to the field of identifying single-nucleotide polymorphisms (SNPs)—bits of genome sequences—and other longevity genes associated with aging. Kunkel published a recent paper on the topic in the November 25, 2003 issue

of the *Proceedings of the National Academy of Science*. In addition, Elixir continues a research collaboration with Dr. Francis Collins, director of the National Human Genome Research Institute at the National Institutes of Health, who is studying the genetics of Hutchinson-Gilford progeria syndrome, a disease of accelerated aging. In May 2003, Dr. Collins published results identifying the Lamin A gene as a central causative factor in progeria (*Nature* 423: 293–298). "He is interested now in comparing his Lamin A gene with our centenarians as a gold standard control group," according to Watson. That collaboration will likely continue throughout the remainder of this year.

##### **Treatment, Not Prevention**

"We are focused on treatment: things we can do to affect various ongoing pathological processes involved in a disease," says DiStefano. The company has a big push in the metabolic disease arena, pursuing type II diabetes, obesity, and the metabolic syndrome. "We are looking to see if modulation of these pathways with our compounds will tip things in the right direction so that we can alter lipid profiles or insulin sensitivity and improve glucose metabolism," he says of a few key examples.

Elixir is firmly pathway driven rather than therapeutic-area focused. Instead of looking at longevity genes, as Centagenetix was, they are searching for disease-based genes. "What is tantalizing about the genetics is the inherent pleiotropy it predicts across different disease indications, potentially treatable with a single small molecule," says Watson. "We are starting to see glimmers of that in one of our programs, obesity and feeding disorders, as a preliminary first indication. You automatically begin looking at a whole range of clinical chemistry indicators including glucose levels, insulin levels, IGF-1, and growth hormone levels." He hopes that if the small molecule starts shifting patterns in the right direction, they might have a compound with efficacy not only in obesity but also for diabetes and possibly even neurodegeneration. "We can basically start to get to grips with that pleiotropy advantage early on in the drug

development process," according to Watson. To take advantage of the clinical opportunities of this pleiotropy, Elixir welcomes partnerships with pharmaceutical companies. Says Watson, "This way we can quickly get beyond the limitations of a small company like ours to do the breadth of clinical programs required to exploit what compounds like this could do for the treatment of a range of age-related diseases."

**Chemistry & Biology invites your comments on this topic. Please write to the editors at [chembiol@cell.com](mailto:chembiol@cell.com).**

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