Bio·IT World
January 12, 2004

High-Tech Search for the Fountain of Youth

Dramatic advances may help biotechs develop drugs that slow aging

By Karen Hopkin

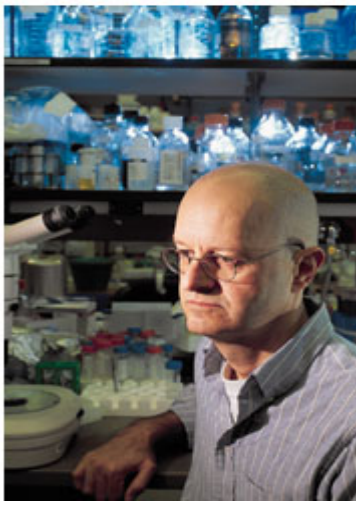
THROUGH THE AGES, the quest for perpetual youth has driven otherwise normal people to ingest, inject themselves with, and immerse themselves in a variety of unpleasant and unusual substances. Englishman Roger Bacon touted the rejuvenating powers of the breath of young virgins, while physicians turned to dog testicles — or extracts therefrom — for invigoration.

But if Ponce de León were to set out in search of the Fountain of Youth today, he would surely trade in his seamen for a bevy of gene chips and a fistful of worms. Now, scores of researchers have signed up with fledgling biotech companies that are racing to identify compounds that will delay the onset of aging-related diseases and perhaps put the brakes on aging itself. Unlike the hucksters of yore, these anti-aging warriors are backed by a decade of scientific research that suggests that the rate of aging is not immutable — and that simple interventions might one day allow us to live longer and healthier lives.

Although the risks are significant, the rewards are almost unimaginable. The chronic conditions that accompany aging — such as cardiovascular disease, cancer, and diabetes — account for 75 percent of healthcare costs each year. And these costs will continue to rise, as the number of Americans over 65 is expected to double by 2030.

"Consumer demand for a drug that could retard aging would be enormous," says Paul Watkins, vice president of business development for BioMarker Pharmaceuticals in Campbell, Calif.

With any luck, such an anti-aging nostrum would also stave off the physical deterioration and cognitive decline associated with growing old.



SNAKE CHARMER: Despite concerns about the quackery of products promoting longevity, Elixir co-founder Leonard Guarente says his company's name is not "huckstery." According to Elixir CEO Ed Cannon, some skeptics have said, "Why don't you just call it Snake Oil Inc.?"

Although such revitalizing remedies are still far in the future, researchers are hoping that their investigations will lead to novel ways to treat aging-related diseases.
At the very least, the methods they develop for cataloging the physiological changes that occur with age should provide a marketable means for studying a broad range of complex biological processes.
In the meantime, the challenge for these young companies remains finding and testing their anti-aging compounds — and staying afloat long enough to do so.

http://www.bio-itworld.com/archive/011204/youth.html

Borrowing the Bathwater

The corporate quest for age-retarding tonics has been fueled by findings over the past 10 years that aging is under genetic control in a variety of creatures, including yeast, worms, flies, and mice. Mutations in individual genes can boost the life span of these laboratory organisms anywhere from 25 percent to 500 percent. But the discovery of these genes does more than suggest that aging can be manipulated. It has provided druggable targets for anti-aging interventions.

Elixir Pharmaceuticals in Cambridge, Mass., for example, licensed patents based on the work of company co-founders Leonard Guarente and Cynthia Kenyon. Working independently, these molecular biologists have identified genes that influence aging in yeast and worms, respectively. The company's mission is to find drugs that reproduce the longevity-enhancing effects of these genes.

To speed the process, Elixir, which last year received $40 million in financing, has partnered with Evotech, a Hamburg, Germany-based company with expertise in medicinal chemistry. Evotech provides a library of druglike compounds from which Elixir scientists will search for compounds that will interact with their target proteins — a process Guarente likens to "going through bathwater to find the baby." Elixir will then hand the baby back to Evotech for lead optimization and testing for toxicity, oral availability, and side effects.

"If we had tried to do this five or six years ago, it wouldn't have worked," says Ed Cannon, Elixir's CEO. "We wouldn't have had access to the quantity or quality of novel compounds." And developing the drug in house would cost time and money. "We would have had to hire a couple dozen chemists and buy a big compound collection. And we wouldn't have been able to do much else."

Being able to outsource the chemistry gives today's anti-aging companies a leg up on the road to the marketplace. "Ten years ago, you could not have been a drug development company that doesn't do chemistry," says Siegfried Hekimi, a McGill University biologist and founder of Chronogen, a biotech studying longevity in worms.

The Toll Road

After identifying potential lead compounds, the next task is to determine whether these molecules can buy organisms extra time. Elixir will start by seeing whether its proto-drugs extend life span in worms or in yeast.

After that, things get complicated. Longevity studies in simple organisms such as yeast or worms take days or weeks. Similar experiments in a mouse would take three or four years. "That's one-tenth of one's career," notes Richard Weindruch, a researcher at the University of Wisconsin-Madison and co-founder of LifeGen Technologies. And when it comes to testing an anti-aging drug in humans — as would be required for FDA approval — the original investigators would be long dead before the study was complete. "Doing a clinical trial with longevity as the endpoint is not something that anyone is anxious to do," Cannon concedes.

To circumvent this problem, many of the companies in this field are pitting their compounds against individual diseases of aging, hoping to identify drug candidates that will reduce the onset or severity of these conditions. Studies that demonstrate efficacy against specific diseases can be done more expeditiously than longevity studies in animals — and eventually in humans.

The approach is scientifically sound, as animal studies indicate that critters engineered to live longer — through genes or through diet — are also resistant to a spectrum of age-related conditions: cancer, diabetes, neurodegeneration, and cognitive decline.

"This doesn't mean that in the end the compound could not modulate aging," Hekimi says. "But it's not necessary to market it that way."

Scientists at Juvenon, a company founded by University of California at Berkeley biochemist Bruce Ames, inventor of the Ames carcinogen test, are evaluating a mixture of compounds — acetyl-carnitine and lipoic acid — in a clinical trial on heart disease. The pair has been found to "promote cellular health" and improve mitochondrial function in old rats. Juvenon is currently marketing the combination as a nutritional supplement, and funneling the proceeds into running the clinical trials.

And researchers at Elixir are testing compounds that target the mammalian IGF-1 pathway in a mouse model of obesity and "seeing nice results," Cannon says. The proto-drugs reduce the activity of the pathway, regulating how much animals eat and how efficiently they use food to produce energy. Cannon has started work on the relevant patents, and Guarente says he hopes a compound will be ready for clinical trials within three years. Of course, a drug that combats heart disease or obesity is no small consolation prize. "If you find a drug that works on one disease, you've succeeded," Guarente says. The Elixir team, however, will probably go further. "For some people, the diseases are the end of the line," Cannon says. "For others of us, the diseases are just a toll we have to stop to pay before we continue down the road toward developing a drug to stop aging and maintain health."

Not every company in the aging field is studying model organisms, however. "We have nothing against nematodes, nothing against *Drosophila*, nothing against mice," says Kari Stefansson, CEO of deCODE Genetics. "But we prefer the company of men. Well, some men."

"We have nothing against nematodes, nothing against *Drosophila*, nothing against mice. We prefer the company of men. Well, *some* men."

Kari Stefansson,
DECODE GENETICS

Using its comprehensive database of the Icelandic population, deCODE is searching for genes that confer long life in humans. The researchers have narrowed their hunt to a couple of "very exciting" candidates within two chromosomal regions that appear to be linked to extended life span. "It would be fascinating if the genes made proteins that could serve as targets for drugs that could enhance the possibility of living healthy longer," Stefansson says.

Elixir, too, plans to pursue human genes for longevity and disease resistance. The company merged last year with Centagenetix, which has the world's largest repository of DNA samples from centenarians.

Enter Big Pharma

With a promising compound in hand, Cannon thinks it should be easy for Elixir to find a partner to commercialize its discovery. "If we get lucky and our compound pans out," he says, "there's not a single large pharma company that's not interested in obesity right now."

BioMarker has a similar plan, Watkins says. The company is developing a drug that will mimic the effect of calorie restriction (CR), a Draconian diet that stretches the life span of a variety of animals. Rodents that consume 30 percent fewer calories live 30 percent longer than those allowed to eat their fill.

Because few humans could stick to such a regimen, companies such as BioMarker and GeroTech are seeking compounds that will alter metabolism and hormone concentrations in ways that imitate CR. Should BioMarker succeed in developing a CR mimetic, Watkins imagines partnering with large pharma companies to develop and market the drug. "The pharma industry is looking to the biotech market to fuel their drug discovery, to continue to feed their pipeline," he says.

Pass the Proxies

Studying one disease at a time is not the only way to accelerate the evaluation of anti-aging compounds. Another pathway involves identifying biomarkers that serve as a proxy for aging, just as high cholesterol is an indicator of heart disease. Such markers would allow researchers to track aging in an individual organism, and to analyze interventions they hope would retard the process.

BioMarker has adopted this strategy in its search for drugs that mimic the effects of CR. Researchers first determine how CR changes the gene-expression profile of aging mice. Then they look for a drug that does the same thing.

Using this approach, researchers at BioMarker have reduced the time required to test a potential anti-aging compound from four years to four or five months. And they have identified a potential CR mimetic: Metformin, an off-patent drug used to treat diabetes, appears to tweak gene expression in a manner similar to CR. It's still early days, Watkins says, "but our track shoes are laced up, and we're in the race."

Other companies have gone straight to marketing their services to organizations that have compounds to test. LifeGen has signed an agreement with an "international pet food company" to look at various nutrient combinations for their ability to mimic the effects of CR on gene expression. Weindruch and his colleagues have patented the use of gene-expression profiling to determine the biological age of individual tissues.

"We might not hit a grand slam," Weindruch says, "but being able to get a read on the biological age of a specific tissue has major advantages." After all, aging manifests itself in the deterioration of these tissues.

Whether any of these approaches will ever yield a potion capable of slowing aging in pets or in people remains to be seen. "We can probably develop a drug," says Matt Kaeberlein of the University of Washington in Seattle, who co-founded a company called Longenity after finishing his Ph.D. in Guarente's lab. "But it's still a long road to show efficacy for aging or aging-related diseases," he says.

"Of course, if you can do that," Kaeberlein says, "you're golden"

Karen Hopkin is a contributing editor for Bio·IT World.
Illustration by Terry Miura; Photo of Guarente by Dana Smith