

LE Magazine January 1999

## REPORT

The Key to New Treatments?

Genomics

Living longer and healthier may come from a variety of factors. One promising field is genomics, which uses new technologies to identify every human gene, and then develop precise drug "targets" that may, in turn, cure the diseases of aging.

By Pamela Tames

It's a given that anyone who wants to live longer wants to live healthier, too. You probably can increase your chances of doing both through good nutrition, nutritional supplements, regular exercise, stress management, and staying involved in life. But come a certain age, you might need a little help from pharmaceuticals, too.

Those kinds of drugs don't exist now, but in another decade they may, thanks to developments in genomics, an exciting new branch of biology that uses powerful technologies to identify every human gene, collectively known as the "genome." It may just be the key to discovering completely new, precise drug targets—that is, human enzymes, receptors and ion channels known to play a role in diseases, excluding those caused by pathogens.

No one has been watching the surge of genetic information coming out of genomics labs more closely than pharmaceutical executives. They've been cutting million-dollar deals with so-called genomics biotech companies fast and furiously. These companies believe genomics offers an efficient way to find new drug targets. That's no small feat in a world dominated by me-too drugs—improved versions of already existing drugs. (For more on how large companies and researchers are joining to produce anti-aging drugs, see *Life Extension* magazine, October and November 1998.)

If the genomics approach pans out, in a decade or so we could see novel treatments for age-associated diseases that are now "incurable." Right now, that possibility is hope enough for the pharmaceutical industry. Drug companies spend hundreds of millions of dollars and several years bringing a drug from lab bench to pharmacy shelf. Many companies set their sights on a growth rate of about 10% annually, but many don't have enough drugs in the pipeline to keep up that growth rate via the traditional methods of drug discovery. That is why genomics companies, making up about 5% of the biotechnology sector, are springing up everywhere.

Genomics companies are going at the concept from every conceivable angle. Some have focused on developing tests for genetic mutations associated with an increased disease risk, others, on finding gene-based diagnostics. At LifeSpan BioSciences, a Seattle, Wash.-based genomics company, the dream is bigger: To better understand the links between genes and disease, with the aim of generating leads for developing new drugs that could treat not just symptoms but possibly causes, too.

"When Glenna Burmer and I founded LifeSpan in 1995," says Dr. Joseph Brown, president and chief executive officer, "we were convinced genomics was the most efficient way to find new drugs. The human genome consists of about 100,000 genes. The top 200 drugs for sale today target about 50 of those genes. So there are many potential targets that haven't been discovered." The most exciting implication of genomics is the possibility of finding new, precise treatments for diseases that are now incurable. Compared to traditional techniques of drug discovery, genomics can do this faster, more efficiently and with a higher degree of predictability, explains Brown. "These are new kinds of drugs aimed at new targets. It's the difference between kicking your car and putting a diagnostic computer on it."

That genomics can do all this has already been borne out. The so-called protease-inhibitor drugs used in the treatment of AIDS were developed using genomics. "A novel gene for protease was found," explains Brown, "and in just seven years a whole new class of drugs was developed and has been very effective." At LifeSpan, researchers have already found a gene that is over-expressed in breast cancer tissue samples (as compared to normal controls). The company filed a patent on that gene and has done functional assays suggesting it is required for the growth of the breast cancer.

LifeSpan's ultimate goal is to find the top 1,000 genes that are attributable to disease. The company generates some of its revenue by selling to pharmaceutical companies these "gene leads" for possible drug targets.

When LifeSpan was founded three years ago, the focus was initially on diseases related to aging (it's since expanded to include other major diseases). The demographics were reason enough. In 1994, 34 million people in the U.S. were over the age of 65, with big numbers in Europe and Japan as well. And, there's a strong statistical association between disease and age. The incidence of such common diseases as arthritis, hearing loss, cataracts, cancer and cardiovascular diseases all rise exponentially after age 40.

Recent research findings increasingly show aging isn't just a random, wearing-out process. Rather, it appears to be controlled by specific genetic changes that affect underlying molecular mechanisms. "So my bias," says Dr. Burmer, chief scientific officer and executive vice president of LifeSpan, "is, that you won't affect human life span very much until you start treating the underlying genetic mechanisms causing disease."

Burmer and Brown believe that for certain specific diseases, the underlying genetic mechanism eventually converges into a common pathway leading to symptoms. Hypothetically, this common pathway could be blocked if you find the right gene to target with a drug, effectively throwing a wrench in the machine.

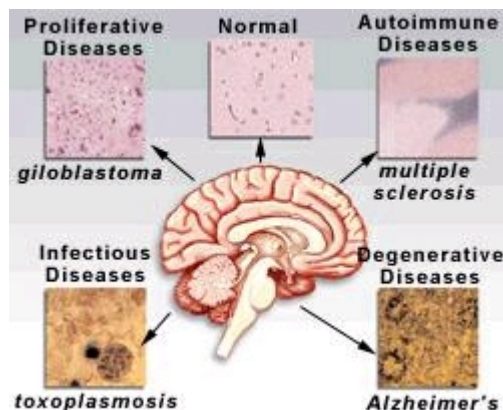
"The model we and others are following is to identify genes related to the progression of the disease," says Burmer. "This may not necessarily entail the primary cause of disease, although it might. But, it's somewhere in the common pathway. The principle is that, somewhere in the pathway, there's a target you can develop a drug against."

Not surprisingly, finding common pathways is not easy. No matter how you look at it, disease is very complex. For one thing, genes can act very differently. Some genes are risk factors for a disease; thus, when they're activated, you're at higher risk for developing the disease. In most cases of disease, though, no single gene can be isolated. "Even when you can isolate a single gene, it may only be involved in a few cases of the disease," adds Brown.

Such is the case with breast cancer. There are a number of risk factors for breast cancer, including the so-called BRCA-1 gene, age, X-rays (mammography), and estrogen levels. One or many risk factors may act on normal breast tissue, triggering a disease process, which-mediated through a common pathway-ultimately leads to cancer. Finding a "downstream target," such as an enzyme inhibitor, is potentially more effective than developing a drug to address the BRCA-1 gene (an "upstream target"), since the gene is a major cause of disease in relatively few women.

#### When Tissue is the Issue

Many investigators are tracking the genes in these common, multi-step disease pathways. But, like the blind men and the elephant, everyone may be somewhat correct but not have the whole picture yet. "We anticipate that companies like ours that focus on gene discovery will start seeing different parts of the picture," says Burmer. "In aging skin, for example, we see a whole cluster of genes that are up-regulated (turned on) or down-regulated (turned off) in coordinated fashion. So we're hoping to fill in many more pieces of the puzzle and put names to each step."



Analyzing changes in gene expression and identifying key genes at which to aim drugs isn't the same as finding a longevity drug. "When you think about a cure to aging," says Burmer, "what you're really talking about in technical terms is a form of controlled regeneration. That's a tough nut to crack. After a tissue undergoes regeneration, it's a question of the genetic code in the cells of that tissue being altered in such a way that it will, for example, double the number of stem cells being produced. If this could happen, it would be, in effect, the real cure to aging."

Even then, there are problems. Activating the "on switch" (if there actually is one) for continued stem-cell doubling in a tissue could increase the cancer rate in different organs. And how would you design a clinical trial to establish if a possible aging cure actually works? "You can design a therapeutic trial to measure a drug's effect on a disease," says Brown, "but how do you measure if a drug increases life expectancy? It's very difficult."

Continuation of article at "Which is why the goal..."

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.