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Alabama's Genetics Pioneers

Genetics-based research puts companies in the fast lane of potential biotech breakthroughs. Five Alabama companies exemplify the exciting promise and hard won gains of genomics research and investment.

By Verna Gates

Once the long-awaited news that the human genome project was complete and we found out only a handful of genes separated us from the fruit fly, we had more dismaying news. We had mapped the genome but had hardly begun exploring it.

Five companies in Alabama are among those working to begin making the leap from microbiology to practical, profitable therapy. Each is using genomics in promising and different applications. They now employ only a handful of highly skilled workers, but their research and market goals are profound—from breakthrough research techniques to cancer treatments to flu vaccines.

Applied Genomics, Inc.
If you have just been diagnosed in stage IV cancer, the last thing you want is for your doctor to be wasting time trying out drugs that may or may not be effective. If the doctor could send off a sample of a patient's malignant tissue and have it further evaluated to specify, for example, one of four or five recognized types of breast cancer, then more specific chemotherapy drugs could be chosen to target the diseased tissue and leave other tissues unharmed.

"You can waste precious time," says Rob Seitz, CEO of Applied Genomics Inc. in Huntsville. His company is working with 30,000 old biopsy samples to sort out the genes that subdivide cancer to give us more accurate diagnoses.

Using genetic information from Stanford that looks at genetic patterns of cancers, Seitz's group is translating that information into practical tools that physicians can use to test drugs on tumors, rather than patients.

"The difference between people isn't so much the genes that we have, but the genes that we use. Cancer itself can be defined as a wrong subset of genes turned on and exhibiting uncontrolled growth," explains Seitz.

The technology for testing uses antibodies for diagnosis. The best example of this type of testing is the rabbit test for pregnancy. The advantage to using antibodies is that they are very specific to certain types of cells and they work on preserved tissue, which is a key for biopsies sent to labs. And antibodies are simpler and cheaper to use than other types of testing.

"We have generated more than 680 antibodies just to test cancer and 50 just to test breast cancer," says Seitz.

One application that is being marketed successfully is to screen candidates for clinical trials. Antibody testing can be used to narrow the sample group to include only trial candidates with the specific type of cancer targeted by the trial drug.

"It can keep a pharmaceutical company from making an $800 million mistake," says Seitz, citing the tremendous expense of bringing a new drug to market. "Finding the nugget from among all the fool's gold is what is so costly."

The company should be profitable by 2005, predicts Seitz, who says there is a $25 million market per diagnostic tool. They also are investigating the possibility that some of the antibodies themselves could turn into effective therapies. The company already has its first major partnership with one of the top 10 pharmaceutical companies in the U.S. The company was thought up in 1997 by Seitz and Jim Hudson, founder of Research Genetics and then founded in 2000 by Seitz and Doug Ross, M.D., Ph.D, out of Stanford who now serves as the chief scientific officer. Seitz founded the antibody department at Research Genetics and decided to stay in Huntsville when the company was sold. Today, 13 people work for Applied Genomics, which also has a research and development office in Sunnyvale, Calif.

Genomics is proving to be one of the great revolutions in healing, according to Seitz. “By 2015, cancer will be a manageable disease,” he believes.

Expression Genetics, Inc.

The introduction of a foreign species into the human body in genetic therapy unleashes reactionary gasps like you might hear in an audience watching the old horror movie “The Fly.” Let’s just say that in the movie, it turns out bad.

The lessons of science fiction aside, many of today’s modern genetic-based drugs are planning to introduce viruses into our systems as a means to deliver drugs and vaccines. And the admonitions of some critics are loud and clear.

Who knows what could happen? Is it worth the risks?

Those are the questions asked by Expression Genetics Inc. in Huntsville, which offers a polymer as an alternative for delivering genetic material. Even though the researchers know that using polymers as carriers is less effective than viral approaches, still they believe the biodegradable polymer is easier for the body to get rid of than a virus once the drug is delivered. It is their assertion that polymers are less toxic and have fewer side effects.

“If you use a virus as a carrier, the virus might integrate with your genes and modify them,” says Byung Geon Rhee, Ph.D., president and CEO of Expression Genetics.

A delivery system, or vector, has to be used to insert a desired gene for several reasons. The delivery system compresses the genes—typically several times larger than the pore of the cell—into a size suitable for cell penetration. It also protects genes from degradation inside the tissue and facilitates gene entry into the cell nucleus, which is the final destination of the gene delivery. Viruses are especially good at compressing and integrating with cells.

“Polymers are strings of repeating units of molecules with unique features that allow them to compress the genes into desired size using old fashioned positive/negative reactions,” says Khursheed Anwer, Ph.D., vice president, research and development.

While viral vectors are still leading the research on genetic drug development, more researchers are turning to alternatives owing to serious safety concerns with the viral systems.

“When we went to the American Society of Gene Therapy meetings two and three years ago, 90 percent used to be viral researchers. Last year, 30 percent were non-viral,” says Rhee.

If Expression Genetics can win the race to produce the first polymer vector solution, it stands to capture a multi-billion dollar market. So far, it has proved its concept in tests on animals and is preparing to move to a Phase I clinical trial next year. The therapy, which will be used to treat breast cancer, combines the delivery of a therapeutic gene with the administration of paclitaxel, a current chemotherapy treatment. The company also is working on anti-diabetic and cardiovascular drugs.

Expression Genetics originated in Salt Lake City, starting with $2 million in seed funding. It received an additional $4.5 million last year from Huntsville angel investors, and the company is currently seeking an additional $10 million.

“That is why we are in Huntsville,” explains Rhee.

It takes, on average, eight to nine years for biotechnology companies to get their first product after establishment. Expression Genetics is expecting their first product on the market in 2008-2009.

“We would like to see Expression Genetics become a $2 to $3 billion market capital company, have a five-story building and a parking space with my name on it,” says Rhee.

PNP Therapeutics, Inc.
Neighbors William Parker and Eric Sorscher were watching their babies play together in the back yard when they started talking about the problems with gene therapies for treating cancerous tumors. Instead of grabbing another hot dog off of the grill, these two Birmingham researchers got a $3.1 million grant from the National Institutes of Health in 1993, then another $4.9 million in 2000.

While there are a number of identified cancer killing agents, many of them are so toxic that they also are patient killers. Even traditional, long-refined therapies, such as chemotherapy, are highly toxic.

“The basic theory behind chemotherapy is to kill cells, and, hopefully, you kill more bad cells than good,” says Parker, Ph.D. vice president of PNP and senior research scientist at Southern Research Institute.

If a highly toxic agent can be safely delivered just to the tumor, then the tumor can be destroyed while sparing the rest of the body. The problem is slipping it past the rest of the system and into the tumor before it activates.

“It is a suicide gene therapy strategy. It is done by placing a gene in the tumor that makes it sensitive to the anti-tumor agent. Then the gene produces an enzyme in the tumor and the chemical reaction transforms a benign medication into a highly toxic killing agent,” explains Sorscher, M.D., president of PNP and professor of Medicine, Physiology and Biophysics at the University of Alabama at Birmingham.

The benign medication is called a pro-drug. It is what is administered to the patient and finds its way to the tumor. This drug can be revved up or down in toxicity to gain control over how much of the drug is delivered. In contrast, once chemotherapy enters a vein, there is no way to control its path inside the body.

One of their first pro-drugs is being paired with a promising carrier (vector) that targets prostate cancer tumors. The clinical trial should start within a year. It will be conducted by the Australian company Mayne Pharma.

There are a number of companies developing the gene delivery systems, called vectors, and many of these are looking for messages to slip into the envelops. With the pro-drugs to magnify the effect, PNP is already developing three partnering relationships, two national and one international.

“A lot of vectors have been put into humans already and none of them seem to be sufficient to stand alone to kill the tumor,” says Parker.

So far, the researchers have not found a type of cancer cell that is not sensitive to this approach. Prostate, lung and brain and neck tumors are currently being studied.

“We feel we have a strong anti-tumor strategy,” says Sorscher.

And then, again, medical breakthroughs are the stuff of overnight “Eurika!” As the two researcher/entrepreneurs have avidly pursued their dream, one of the toddlers from the back yard start-up is now driving.

Tranzyme, Inc.
Now that we are discovering which genes work, we also are figuring out that there are some genes we don’t want to work, such as the gene for Multiple Sclerosis. One of the hottest topics in genetic research today is gene silencing, named the Discovery of 2002 by Science Magazine. Tranzyme Inc. of Birmingham entered an agreement on Feb. 27 to work with an Australian company to develop gene silencing and delivery technologies.

“We have been working on technology to deliver genes; now we can take genes away,” says Vipin Garg, Ph,D., president and CEO of Tranzyme.

The technology Tranzyme offers is a way to put genes into cells and see how they function. The official title is RNAi, which signifies RNA interference. When you can work with a gene in its natural setting and stop it from functioning, you can determine its therapeutic value.

“The future applications of this are endless,” says Garg. While actually addressing diseases is some time away, the ability to understand biology should rocket researchers into a new wave of discovery.

Another hot topic also is a subject of Tranzyme’s research: cloning. Their researchers have figured out a way to raise the success rate of cloning from 1 to 2 percent to nearly 60 percent, and they do it without puncturing the nucleus and destroying the embryo. They’ve also figured out how to break the species barrier. Currently, the company is creating specialty rats with human macular genes to study macular degeneration, a major cause of blindness. The company plans to study diseases associated with the neurosensory system, including taste, smell, vision and hearing. Many of these conditions are associated with aging.

“The most common drugs used for the ear are antibiotics for children’s ear infections. There are no drugs for hearing loss. Through the creation of these genetically altered animals, the quality of life of Americans and people around the globe can be enhanced with new therapies for diseases,” says Garg.

The company recently expanded into Research Triangle Park, opening laboratory facilities in September. The facility will focus on researching and developing drugs and therapies for neurosensory diseases. The company is based in Birmingham and employs 15.

One of Tranzyme’s first products was a tool that enables researchers to study compounds or genes within the simulated environment of the cell’s natural setting. One problem with research is that experimenting with a cell outside of the body system it lives in does not produce real-life answers.

With TranzAssay and other research products that enable the research of others to go faster and more smoothly, Tranzyme is a popular company to partner with. In the last 18 months, it has formed 12 partnerships with pharmaceutical and biotech companies from Australia to Israel. Currently it is seeking a Series B round of financing to continue its growth. It is looking to raise between $7 million to $8 million.

Vaxin, Inc.
People are working longer hours, spending more time indoors where the temperature is perfectly regulated, and the combination is making them sick. Stressed, sedentary workers laboring in artificial comfort climates are immune system weaklings begging to become victims. This simple demographic is one reason vaccines are an exploding industry.

Vaxin Inc. is one of the nation’s top contenders to capture a share of the $6.5 billion vaccine market—an industry yearly driven by the dreaded flu.

A Phase I clinical trial completed in October proved that Vaxin's needle-less, topically applied vaccine is not only safe, but also provokes an immune response in man. The influenza vaccine was applied to 18 participants who later demonstrated the right antibodies to the flu.

"The flu market is exploding. In an epidemic, thousands of people die. We hope to have a product on the market soon that will help save lives and prevent suffering without the pain and risks associated with the injectable vaccines," says Charles Defesche, M.D., CEO of Vaxin.

Other diseases being studied by Vaxin are cancer, anthrax, dengue fever, rabies and tetanus. With the proof of concept in hand, Vaxin is working steadily to expand its research base. It is trying out its topical, needle-less system with veterinary products and vaccines for other human conditions.

"We originally focused on infectious diseases. Now we are expanding into additional areas such as immuno-contraception. We are also expanding our targets, as well as our vectors," says Defesche.

The company recently expanded into a suite of offices in the World Business Center in Birmingham. It is looking for a second round of financing of $15 million, to be completed in May or early June. It will probably complete a Phase II trial next year. A major patent was issued last year and five expansions already have been filed.

"Our research continues to be very productive. We are increasing the value of the company. At the end of our Phase II, we will develop partners with companies to market our discoveries," says Defesche.

The vaccine technology is based on a simple premise: the largest and most effective immune organ we have is our skin. Yet, for a century, we have bypassed the skin to inject immune agents into deep tissue that has never seen a germ in its life. The resulting vaccine will be an affordable patch or cream that can even be mailed in an emergency.

Once their second round of financing is complete, Vaxin plans to target five top products.

"We expect to see the first commercialization to occur five years from now," Defesche says.

Verna Gates frequently covers biotechnology for *Business Alabama.* She is a freelance writer who lives in Birmingham.