BREAKTHROUGH TECHNOLOGY ALERT

FEBRUARY 2011 VOL. 5 ISSUE 04

How You Can Profit From Zinc Finger Technology

By Patrick Cox

This month, I'm going introduce you to one of the most important companies in the world today, and that's saying a lot.

This company is bringing a brand-new therapeutic platform to the world.

Moreover, it is the principal intellectual property holder for this incredibly powerful form of genetic engineering. Afterward, I'll also tell you about a pre-public company that holds the keys to a transformational breakthrough in the semiconductor industry.

Rewriting the Language of Life to Cure Disease

This month's company is **Sangamo BioSciences (NASDAQ: SGMO)**. Ray Blanco and I had the privilege of interviewing Edward Lanphier, the founder, CEO and president. We also benefited from extensive and patient tutoring from Dr. Elizabeth Wolffe, Sangamo's director of communications.

I'm not going to pretend that Sangamo's technology is easy to understand, or even to explain. I do want you to grasp the basics of their platform, however. The science behind this company will play an increasingly larger role in our economy and personal health care, so those who understand what is really happening in this field are going to have a real advantage over those who do not.

Today, almost nobody gets it. That includes the typical Wall Street analyst who does not understand the power of genetic engineering, and, therefore, the real value of an early-stage biotechnology company like Sangamo. To quote Arthur C. Clarke: "Any sufficiently advanced technology is indistinguishable from magic."

Let's try to dispel these magical mists by first giving an overview of Sangamo's breakthrough technology and history.

The core science Sangamo is built upon involves the use of "zinc finger protein transcription factors" (ZFP-TFs). As you know, transcription factors are the tools our bodies use to activate the programming code of our DNA. Transcription factors are protein molecules that can bind to a single sequence of DNA. Once it has bound, a transcription factor acts on a specific gene, typically at the center of the sequence it has bound to.

The word "transcription," incidentally, refers to the gene's process of "transcribing" a sort of mirror image copy of DNA code. Unlike DNA, this mirror image protein, called RNA, is mobile. It carries out the master program's commands.

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Sangamo, as I've already said, is focused on a primary type of transcription factor. Not surprisingly, these molecules contain zinc ions.

As you learned in high-school chemistry class, or from reading Wikipedia, "An ion is an atom or molecule in which the total number of electrons is not equal to the total number of protons, giving it a net positive or negative electrical charge." In the ultra-precise world of organic chemistry, ions act somewhat like magnetic hinges. They allow molecules to take different and stable shapes under different conditions, which determines how they behave. The "finger" part of the term "zinc fingers" was coined by the original discoverers because transcription factors "grab" the DNA like molecular hands.

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This, in fact, is a pretty good metaphor for "zinc finger protein transcription factors." I liken them to molecular hands that search the double helix of DNA for a single unique sequence of genes. When they find these unique attachment points, they grab them. Usually, it is the gene between those binding points that the transcription factor acts upon.

I asked CEO Edward Lanphier how he describes his technology to nonscientists. Using an analogy even his children can understand, Lanphier likens engineered ZFPs to Lego toy bricks:

> Zinc fingers are a lot like those little bricks, but they bind to three little bricks. Those three little bricks represent three pieces, or three base pairs of DNA.
>
> If you can imagine the various permutations and combinations of three base pairs of DNA, you have about 64 of them. What Sangamo has are 64 different Legos. With these mixed and matched Legos, we can target a gene. There are about 3 billion of those individual base pairs, or little bricks, in the genome. However, if you can bind 18 contiguous base pairs, you can target a single site in the genome with singular specificity.
>
> Since Sangamo has built all of the possible engineered zinc finger proteins, we can literally go to a computer terminal and type in the gene sequence that we want, and then robotically assemble zinc finger proteins that exactly target that gene.

The History of ZFP Discovery

The Lithuanian-born British scientist Aaron Klug discovered the zinc finger structure of these transcription factors while working at Cambridge. He did so using his own revolutionary combination of X-ray diffraction and electron microscopy. In fact, Klug was awarded the 1982 Nobel Prize in Chemistry a few years later, "For his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes."

To commercialize his discoveries, Klug founded Gendaq.

AGORA FINANCIAL

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In the early 1990s, Lanphier came across ZFP research at Klug's Cambridge laboratory. This led him to related research performed at an MIT lab headed by Carl Pabo, who was MIT's Howard Hughes professor. Pabo has subsequently served as Sangamo's chief scientific officer.

At about the same time, Lanphier also integrated ZFP discoveries made in the laboratory of Jeremy Berg, the chairman of biochemistry and biochemical physics at Johns Hopkins University.

In 1995, Lanphier founded Sangamo BioSciences and licensed ZFP technology and intellectual property rights from all these labs. Then, in the late 1990s, he raised private funding from several prestigious institutional biotechnology investors. In 2000, Sangamo went public. Aaron Klug's company, Gendaq, was purchased by Sangamo in 2001. Today, Sir Aaron, who has been knighted for his contributions to science, serves on the Sangamo BioSciences scientific advisory board.

The ZFP Potential

The human DNA molecule contains the data for tens of thousands of genes, which are encoded on about 3 billion DNA base pairs. In their totality, these genes are called the human genome. Every cell, from your cornea to your little toe, contains the same entire master genome. These cells are different, however, because different genes are active in different cell types.

Our bodies encode several thousand different zinc finger proteins, the most common transcription factor in nature, to act on the genes as needed. ZFPs regulate the function of individual genes, and therefore the state of the cell.

Moreover, this is an ever-changing process because internal and external factors require them to change. Our ZFP transcription factors adapt the activity of genes to changing conditions.

Since genes all have different codes, the zinc fingers must have the ability to find and act on a specific gene in the enormous DNA strand.

Previously, I described ZFP as molecular hands, but it is just as useful to think of them in terms of computer software. DNA is, in fact, the most complex code ever written. If we think of DNA as the master database, ZFPs can be thought of as a "search" mechanism capable of accessing the right data or specific DNA sequence within the genome.

In nature, these ZFP search modules also contain specific commands. Sangamo's breakthrough is twofold. They can duplicate the function of natural ZFPs. They have also, however, extended the functionality of zinc finger transcription factors beyond those that are naturally available.

This provides the company an extraordinary genome engineering toolbox. Its modular ZFP library can bind to any DNA sequence in any organism, plant or animal. The specificity of Sangamo's technology allows it to go to the desired DNA sequence while ignoring the others. In doing so, Sangamo's platform has the power to regulate, rewrite, disrupt or insert any gene. Sangamo can make a gene more or less active, just as nature does. It can also, however, attach regulatory molecules to the ZFP to accomplish other ends.

Sangamo can disrupt genes using nuclease technology. This process can be used to repair errors or mutations that have developed in the DNA. By attaching nucleases — DNA-cutting

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enzymes — to the ZFPs, they can cut the DNA strand at an exact site. This process occurs continually, incidentally, because DNA is constantly repairing itself due to events such as exposure to naturally occurring gamma radiation.

When a break is repaired, the DNA machinery draws on its own genetic materials for a repair template. Sangamo uses this mechanism to actually change a gene.

If they deliver, along with the ZFP, snippets of DNA that resemble the disrupted gene, the cellular machinery will use them to make repairs. Those snippets can be coded differently from the original gene. The end result is a rewritten gene. This technology can be used to insert whole new genes into the DNA sequence.

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Sangamo's ZFPs are the first new class of engineered molecules that function at the DNA level. Moreover, ZFP technology works across different species. If an organism uses DNA to encode its genetic information, ZFP can be used to modify it. When genes are faulty, or are incorrectly expressed within cells, the result is disease. Zinc finger transcription factors can be used to change them.

Therapeutic Pipeline

Hopefully, you now have an inkling into the science behind Sangamo's platform. So we can move on to the human therapeutics being advanced by the company.

One of Sangamo's most clinically advanced programs is in the area of peripheral diabetic neuropathy. This form of neuropathy causes patients with long-term diabetes to lose nerve function. Diabetes destroys the small blood vessels in the extremities that feed and deliver oxygen to nerve cells. Nerve damage and a cascade of cell damage follow. This is why advanced diabetes often leads to amputations. With millions of diabetics and a total population projected to rise, this is a huge and extremely expensive problem.

Currently available drugs mask some symptoms, but do not attack the disease. Sangamo's candidate, SB-509, uses zinc finger technology to increase the activity of the vascular endothelial growth factor A (VEGF-A) gene. This gene has properties that protect, regenerate and help nervous tissues grow. Upregulating VEGF-A stimulates the growth of new blood vessels, restoring oxygen supply when there is inadequate blood circulation.

The ZFP drug candidate has shown good results to date. In Phase I trials, the drug demonstrated good tolerability along with improvements in nerve health. In a completed Phase II trial, called SB-509-601, the candidate demonstrated increased blood vessel growth in the area of the nerves. This led to an improved regrowth of epidermal nerve fibers. In a second Phase II, SB-509-701, the ZFP drug was administered to patients that had at least one nerve in which electrical function was so low as to be unmeasurable. In this study, SB-509 delivered a substantial improvement in nerve function.

SB-509 is currently in Phase IIb studies for diabetic neuropathy. However, its neuroprotective, neuroproliferative and neuroregenerative effects make it an ideal drug for other nervous system diseases. For this reason, it is also in clinical trials for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

ALS causes a progressive loss of motor function as motor neurons die off, and is ultimately fatal. The disease starts as a weakness in the ability to control the limbs of the body. It progresses to the point where breathing and swallowing are impaired. Advanced cases often end with asphyxiation.

SB-509 has demonstrated clinical benefits for ALS patients. Phase II results announced in November 2010 show that it delays deterioration in the strength of muscles in the lower legs and feet in 40% of trial patients. Rounding out Sangamo's nerve regeneration efforts, it is currently engaged in preclinical evaluations of ZFP therapies for spinal cord injuries, neuropathic pain and Parkinson's disease.

In Parkinson's disease, which is also a degenerative disorder of the central nervous system, there have been good data. Just before this writing, Sangamo announced publication of preclinical findings in animal models for Parkinson's. The data show neuroprotective effects and improvements in motor function. The study was funded by the Michael J. Fox Foundation for Parkinson's Research.

Another item in the Sangamo clinical pipeline that is generating real excitement is a ZFP-based HIV therapeutic called SB-728. Rather than acting by gene regulation, this ZFP therapeutic actually rewrites a gene. In the last several years, a population of individuals has been discovered to possess a natural immunity to HIV. Unlike the vast majority of HIV sufferers, these individuals do not develop a large viral population after exposure. This is because they have a natural mutation of a gene known as CCR5 in the immune system's T cells.

The CCR5 gene codes for a protein receptor on the surface of these T cells. The most common HIV strain, HIV-1, actually uses the CCR5 protein receptor as a gateway for entry into T cells. In effect, it hijacks and takes over the killer T cell that should be attacking the HIV infection. If this receptor is not present, however, the virus cannot gain entry to infect the cell. To date, no observable deleterious effects have been observed in individuals with this natural CCR5 mutation.

It was recently announced that Timothy Ray Brown, a leukemia patient that had received a stem cell transplant, has apparently been cured of HIV. The stem cell allograft essentially rebooted his immune system with new, genetically different killer T cells. Since the stem cell donor had the mutated CCR5 gene, the recipient received the immunity as well.

Unfortunately, finding tissue-matched stem cell donors with the right mutation is not a practical way to treat HIV.

Genetically reengineering T cells is what Sangamo is doing with SB-728. This ZFP is designed to actually rewrite the "code" of the CCR5 gene. It gives it the same mutation that exists in those with the natural immunity. A single patient Phase I trial at the University of Pennsylvania has given evidence of tolerability.

Additionally, the modified helper T cells remained at stable levels in the bloodstream for the duration of the study, which was 20 weeks. T cells are known to live in the body for longer than 18 months, and they do divide and multiply. After cessation of standard antiviral therapies, the patient was found to have a significant delay in the return of the virus to detectable levels.

A second Phase I trial is under way in San Francisco. A population of nine patients organized in three cohorts will receive increasing doses of ZFN-modified T cells. The study is currently in the data collection phase.

Finally, Sangamo is pursuing highly lethal brain tumors called glioblastomas. Here, zinc finger technology is also being used to modify T cells. This functionalizes them to seek out and attack the tumors. The trial started earlier this year and is ongoing.

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Profiting From Nontherapeutic Applications

I've mentioned the species-generality of ZFP technology. Its broad applicability in many species creates profitable opportunities outside of just human therapeutics. Sangamo has been successful in taking ZFP science and applying it to nontherapeutic fields through partnerships.

In agriculture, for example, zinc finger transcription factors can be used to modify plant genomes in order to create desirable traits such as disease and drought resistance. To accomplish this, Sangamo is collaborating with the Dow AgroSciences division of Dow Chemical Co. (NYSE:DOW) for plant agriculture.

"Recommendation: Buy Sangamo BioSciences (NASDAQ: SGMO) up to $8.00."

Dow Agro has an exclusive agreement with Sangamo to use its ZFP technology to improve crops. Called EXZACT Precision Technology, it enables Dow to precisely target plant genomes in order to develop desirable traits. According to the Dow site:

> Because the technology is flexible, precise, highly specific and relatively simple — and because it can delete or edit existing plant genes — EXZACT creates the potential to define a regulatory path that is different from the current route for biotech products.

In addition to Dow, Sangamo also has a partnership with Sigma-Aldrich Corp. for using ZFPs as research reagents. Sigma-Aldrich has been able to use Sangamo's computer-programmed, algorithmic process for designing ZFP transcription factors for any genome, no matter what species. A researcher can send Sigma-Aldrich a gene sequence and what they want to do with it and in a matter of weeks, receive a custom ZFP for the job.

The technology, called CompoZr, has recently been awarded second place in *The Scientist* for 2010's top 10 innovations. By the way, Sangamo has royalty rights for any therapeutics developed using the ZFP technology developed through Sigma-Aldrich. I recommend a visit to the CompZr site. It gives an excellent overview of the power of zinc finger technology.

From a balance sheet perspective, Sangamo is in good shape for an early-stage biotech. It has zero debt and ends 2010 with $63 million in cash. For Sangamo, this represents close to three years of working capital. It has strong nontherapeutic partnerships with huge players and ZFP therapies in the pipeline (and more to come). Those relationships have to date brought in over $75 million to Sangamo. It is using that capital to drive forward its therapeutic platform.

This is a great, relatively undiscovered, technology that should be part of your core long-term transformational portfolio.

Recommendation: Buy Sangamo BioSciences (NASDAQ: SGMO) up to $8.00.

The Next Big Thing in Circuit Miniaturization

The semiconductor-based transistor is one of the greatest inventions of the last century. Its impact has profoundly influenced the quality and even the length of our lives. Science, including the path-breaking research taking place at Sangamo BioSciences, would not be possible without semiconductor technologies.

Early prototypes were assembled in AT&T Bell Labs in the late 1940s. Commercial transistors were first mass-produced by Texas Instruments in 1954. The previous state-of-the-art technology was, as you know, vacuum tubes.

Bulky and expensive, vacuum tubes could not be used in small consumer applications. The cheap little transistor changed this, however. Early on, for example, they enabled the most successful consumer product of the era: transistor radio. By the end of the 1960s, billions of these radios were quite literally in the hands of consumers.

Progress didn't stop there. These early transistor products were manufactured by placing discrete components on circuit boards. By 1958, Texas Instruments engineer and Nobel Prize winner Jack Kilby integrated multiple transistor components on a single substrate of semiconductor material. Thus, the integrated circuit was born. Fairchild Semiconductor's founder Robert Noyce further improved the technology by substituting inexpensive silicon for Kilby's germanium.

Over time, relentlessly improving fabrication techniques allowed semiconductor manufacturers to advance from a few components on a single silicon wafer to hundreds and then thousands. Today, billions of components fit on a few square centimeters of silicon real estate. Without the integrated circuit, we could never have all the electronic goodness we enjoy today. The invention of the integrated circuit has transformed every single economic activity we engage in.

That is all history, of course.

One of the most significant properties of the transistor is that it can be miniaturized to nanometer sizes while still reliably maintaining a performance that adheres to tight tolerances. This is not necessarily the case for other electronic elements, sometimes called passive components. Unlike the transistors in what are called active components, these attempts at aggressive miniaturization and integration at commercial scales have failed.

You can see this for yourself. If you have the temerity to open your computer case and look at the system board, you will see several integrated circuits. The most obvious of these is the microprocessor, or the "brains" of the computer. It packs over a million transistors per square millimeter. If you crack open the microprocessor, the individual elements will be too small to see with the unaided eye.

However, socketed throughout the board, you will see many dozens of passive components such as inductors, resistors, capacitors or transformers. Like the vacuum tubes of yesteryear, these are comparatively bulky and can't be manufactured at super-small scales.

Today, passive components have to be mounted on the surface of the circuit board because the electrical properties cannot be controlled enough to integrate onto a chip. Current ceramic component manufacturing processes use powders, and the chemical properties of the product are not sufficiently precise.

The resistance of a resistor, for example, would vary too much to be a reliable component using current technology at the scales needed to realize integration. If a single resistor was out of specification on a chip, the value of the entire circuit would be ruined. You can't simply replace a single component on an IC. More importantly, even if you could build a reliably precise small-scale resistor, its properties would change with temperature. It might work fine at 70 degrees Fahrenheit, but be out of spec at 90 degrees.

"One of the most significant properties of the transistor is that it can be miniaturized to nanometer sizes while still reliably maintaining a performance that adheres to tight tolerances."

> *"Frontier NanoSystems is a startup with a disruptive technology that proposes to completely change the industry."*

This problem is even worse in devices that push the envelope of size and portability, such as mobile phones. Consumers demand more and more features in their smartphones and manufacturers have to find ways to satisfy the demand. This means more components.

Once our current technology hits the limits for passive component miniaturization, we will see a stagnation in innovative mobile telephony. We may already be seeing the limits today. For consumers, this will mean the technology will stall. There will be fewer and fewer new features. For manufacturers, this will create a commoditization of the product, along with falling profit margins.

This commoditization of a telecommunications terminal technology has happened before, by the way. Until the invention of push-button phone, consumers endured rotary dial technology for decades. It took a disruptive new technology to transform the market.

We are, therefore, essentially still stuck in a 1950s time warp where it comes to passive electronic components. This raises an obvious question: What if someone figured out a way to do for passive components what past pioneers did for active ones? The results would be revolutionary.

That revolutionary innovator is Frontier NanoSystems.

Frontier NanoSystems is a startup with a disruptive technology that proposes to completely change the industry. We had the pleasure of interviewing founder and CEO Pierre de Rochemont, as well as Juha Juhilla-Song, the director of marketing and supply chain coordination.

The heart of Frontier's invention is a flexible electroceramic lamination technology developed by de Rochemont. Using this technology, Frontier can mass-produce passive components with tight tolerances. Critically, their electrical properties do not appreciably change with temperature. What this means, in plain English, is that these components can now be vastly reduced in size and included on the same chips as the active components.

The technology uses a process called liquid chemical deposition (LCD). In LCD, the various ceramics are dissolved in a liquid that is sprayed in layers on a semiconductor wafer at temperatures lower than 400 degrees C. At these temperatures, there is no discernible grain structure. The laminate is like a glass.

Unlike powdered ceramic manufacturing techniques, the size in the grains of the deposited layers can be controlled with true nanometer-scale precision. This is accomplished by heating them for short periods of time. This precision is also the reason that component performance is so steady — despite changes in temperature.

Since the structure of the various amalgamated ceramics is so precisely controllable, the kinds of tolerances required to shrink passive components are also achieved. Incidentally, the world famous Argonne National Laboratory has attempted to quantify the precision of the ceramic mix inside the individual components. The variances, however, proved to be smaller than Argonne's ability to measure them.

This is a game change in more ways than one. Most cell phone components can enjoy economies of scale. Once a manufacturer designs subsystems like the interface or the microprocessor, it can choose to reuse these in other phones or variants of the original.

The big killer for reusability, however, is the radio antenna. Because the antenna reacts

to nearby components inside the phone, this makes its tuning sensitive to any changes in the material composition or layout. By way of analogy, think of structures precisely designed for acoustic properties, such as the Sydney Opera House. If you were to make a major change to the interior of such a facility, like removing carpeting or adding glass windows, the acoustics in the building could be seriously altered.

Similarly, any changes to the "electromagnetic acoustics" of a phone require that the antenna be custom engineered for every handset and any variant thereof. For example, if the antenna in your Blackberry were near the microphone and RIM decided to change the microphone design, it would take months of iterative redesign to get the radio to work the same as it did previously. Apple's embarrassment regarding the antenna design of its latest iPhone have made these issues better known among the general public.

Frontier NanoSystems' LCD technology allows radio circuits to be manufactured far smaller than they can be today. Smaller antennae have smaller "acoustic chambers." In other words, they are not as vulnerable to a phone redesign. Frontier can shrink the radio to a size at which it is no longer sensitive to nearby components. This creates reusability, and it also means that a cell phone fabricator can respond to market opportunities with much greater speed.

In addition, having tiny antennae allows a manufacturer to easily pack several into the same phone. Europe, the U.S. and Asia all use different wireless frequencies for cell phones. This means that for the same model phone, different antennae have to be used for various markets. Having all the antennae in the phone at the same time adds simplicity. The same model could work anywhere. For the first time, consumers could have the option of a true worldwide phone.

Frontier NanoSystems also reduces the number of manufacturing steps required to produce a usable electronic product. In the case of wireless handset manufacturers, this means a great deal. Cell phones require many assembly processes, usually carried out by several different subcontractors in the supply chain. The ability to build passive components on a single chip in one step shortens the chain. That is great for speeding up getting a new product to market, as well as cutting costs.

Frontier NanoSystems isn't publicly traded, but neither was Fairchild Semiconductor or Texas Instruments back when they were inventing the integrated circuit. It is, however, definitely a company to watch closely. Additionally, any companies that license its technology and put it to use are going to have a huge, disruptive edge on the competition, which creates transformational investment opportunities.

We will keep in touch with Frontier NanoSystems and keep you up-to-date on the business development of this astonishing new technology.

Yours for transformational profits,

Patrick Cox

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