INVESTMENT OUTLOOK
SECOND QUARTER 2016

First Quarter Review

	Close 3/31/16	Total Return First Quarter
Standard & Poor's 500 Index	**2059**	**+1.35%**
Dow Jones Industrial Average	**17685**	**+1.49%**
NASDAQ Composite Index	**4869**	**-2.43%**
Dow Jones Global (ex U.S.)	**208**	**-0.96%**
Barclays Aggregate Bond Index (LAG)	**58**	**+3.07%**

Some clients might wonder, but are too polite to ask, what do we do all day? Discuss Federal Reserve policy? Read Wall Street research reports? Listen to company investor calls? Screen financial databases? In truth, we do a little of all of the above. But the bulk of our time is spent looking for and researching investment ideas that just might make money for our clients. In this *Outlook,* we review our research progress on one of the ideas we have focused on during the past three months. We hope it provides more insight into how we spend our time.

Researching the "Biggest Biotech Discovery of the Century"

The MIT Technology Review recently called it the "Biggest Biotech Discovery of the Century." The front cover headline of the March *Nature* Magazine read "Dawn of the gene-editing age…CRISPR EVERYWHERE." The journal *Science* called CRISPR, "a genome editing system, the 2015 Science Breakthrough of the Year." "A revolution has seized the scientific community," noted Harvard's *SITN*, "research labs worldwide have adopted a new technology that facilitates making specific changes in the DNA of humans, other animals, and plants…it has changed the way basic research is conducted, but also the way we can now think about treating diseases."

So, with our curiosity piqued, is there money to be made from this new editing technique? Can we identify the best ways to invest in the technology? Are there new companies that are pure plays on the technique? Or, are there existing companies that will benefit materially? Finally, what are the odds that this is just another overhyped breakthrough that will take years to deliver and without a reasonable stream of profits?

So what is CRISPR? CRISPR is an acronym (Clustered Regularly Interspaced Short Palindromic Repeat). It is a sequence of DNA that can recognize invading viruses and naturally deploy an enzyme to precisely chop up the invading viruses into pieces to kill off the virus (layman's interpretation). It was actually first discovered in yogurt, but it works with some success in human cells to naturally trigger an effective immune response. The new technology, however, does even better. It allows scientists to direct, or program, CRISPR to very specific cells, or a multitude of cells, to virtually eliminate disease causing mutations. CRISPR has the potential to treat diseases by editing DNA -- turning genes on and off -- at precise DNA targets. [*For our biology buffs: the CRISPR technique actually has two components. One is the molecule RNA that functions as a precise guide (GPS) to an enzyme (Cas9) that acts as a genetic scalpel, or scissors, that cut out the mutated gene identified by an RNA molecule*]. CRISPR is easy and inexpensive compared to other gene editing techniques and also more targeted. **Scientists now believe that they have entered a new era of genomic medicine by using the CRISPR technology**.

From a therapeutic standpoint, the combination of understanding genetic mutations and now having the ability to attack diseases at their root cause is immensely exciting. There are over 6,000 diseases caused by genetic mutations, but very few have been addressed by approved therapies. CRISPR may eventually be used for the treatment of many forms of cancer, cystic fibrosis, sickle cell, Duchenne muscular dystrophy, Huntington's, liver diseases, eye diseases, autism, diabetes, Alzheimer's and Parkinson's. In addition to genetic based diseases it can also be used for infectious diseases, such as AIDs. Scientific researchers in labs all around the world are using CRISPR-Cas9 to create animal models (e.g. in mice, chickens, pigs, mosquitoes, fruit flies, fish, monkeys, et al.) of genetic diseases. In agriculture, the technology can be used to produce fungus resistant wheat as well as make soybeans and potatoes more drought resistant. It can also be used to make animals more disease resistant. Most important, this technology does not import DNA from other species, which is one of the critical issues surrounding genetically modified crops.

The Long and Winding Road from Exciting Technology Breakthrough to Investor Profits

Who discovered the CRISPR technique and who stands to benefit the most remains to be determined initially in the patent courts. The patent issues are as tangled as a strand of DNA. The following summary barely scratches the surface of the intriguing issues of who will prevail in court. There are two primary contestants claiming the patent rights and subsequent licensing fees that will accompany the winner of the patent suits. It is a Harvard/MIT versus University of California Berkeley et al. contest. It also involves some of the most celebrated scientists of our time. Dr. Jennifer Doudna and Dr. Emmanuelle Charpentier developed the CRISPR technique in 2012 and

were apparently the first to edit DNA. They represent the UC Berkeley et al group. Dr. George Church and Dr. Feng Zhang apparently were the first to use the technique in 2013 to actually edit human cells. Church and Zhang won the patent for CRISPR. The University of California et al are contesting the patent award.

In the meantime, the scientists are moving ahead of the courts. The CRISPR technique is being used in small labs and large pharmaceutical companies around the world. The smaller labs are raising money through grants and, if possible, venture capital investments. The larger institutions are self-funding these activities. Since this is such a transformative technology and biotechnology has been such a hot area for funding, there are a lot of dollars pouring into CRISPR related research. It is estimated that over $600 million has been raised in venture capital for CRISPR research that could ultimately lead to commercial applications and therapies.

The patent fight is not the only uncertainty in solving the investment issues. There are unusually complex regulatory issues when dealing with novel gene editing approaches that ultimately can lead to the controversial area of use in human embryos and human germline. These regulatory authorities are numerous, global in reach, bureaucratic by nature, and often times prone to reaching different conclusions at different times. There are also the developing intense competitive issues that will make predicting winners and losers difficult. There are already some enhancements to the technique (e.g. using CRISPR with a different enzyme than Cas9) as well as other gene editing platforms and techniques. Finally there are sure to be potentially therapeutic disappointments either from treatment side effects or editing mistakes.

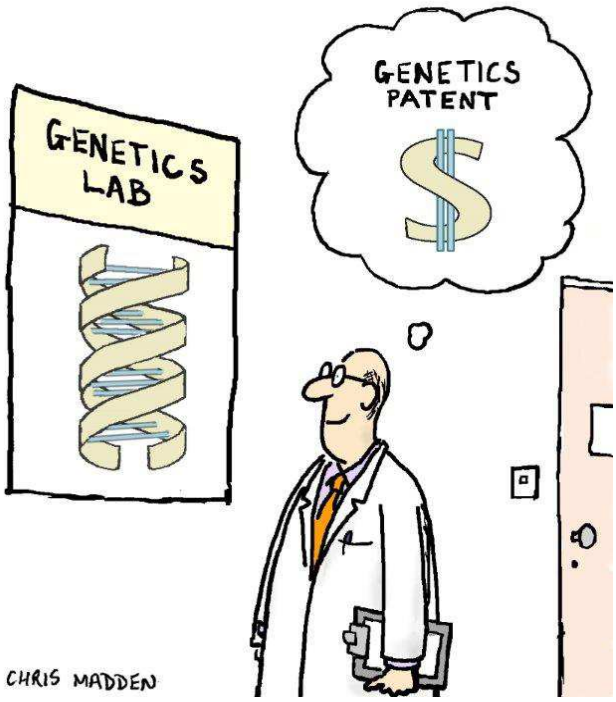
A Gene Editing Company Goes Public in February -- Editas Medicine

In the midst of the February stock market swoon, particularly in biotechnology stocks, Editas Medicine, a pure play "CRISPR" company, went public. It more than doubled in price within the first month. Investor enthusiasm was not affected by the lack of revenues, much less no prospects for profits for years. The company is facing patent and scientific challenges. Editas has licensed its technology from the Cambridge group. Other competing startups, associated with Dr. Doudna (Caribou Biosciences) and Dr. Charpentier (CRISPR Therapeutics), have licensed the technology from the UC Berkeley group. Each company, including Editas, has its own patent portfolio and many pending patent applications. At a value of $1 billion for Editas and no profits in sight, investors must be banking on the strength of the technology and that forthcoming patent decisions will not be so onerous as to eliminate access to the technology. In other words, it is most likely that whoever loses the patent contest will simply have to pay more to license CRISPR.

At the current time, Editas is furthest along on treating an eye disease (Leber congenital amaurosis -- LCA) that leads to blindness. LCA occurs in 2 to 3 per 100,000 newborns, and is the most common cause of blindness in children. It is thought to be caused by the mutations in at least 14 genes. Their work on LCA is expected to go into clinical testing next year. The company's current research is also focused on sickle cell, Duchenne muscular dystrophy, and cystic fibrosis. Editas is also

working with Juno Therapeutics to co-develop cancer therapies using gene editing technology. Juno is supplying much of the upfront money. The actual introduction of a product would certainly be many years off, accompanied by all the issues related to pricing and reimbursing new therapies.

On March 30th, Editas reported its first financial results as a public company for the quarter and year ended in December. The company highlighted their fund raising, the further development of their executive team, additional patent applications, and upcoming scientific meetings and abstracts. Financially, the company lost approximately $12 million in the quarter and $73 million for the year.



Those results lead to the original questions we asked above, is there money to be made at this time in this new technology? If Editas is the only pure play option at this point, do the risks outweigh the potential long term rewards? "Breakthrough, transformative" technologies do not come along very often, and CRISPR appears to be one. This is very tempting with one exception; there are slim prospects of actual profits for many years to come. From a portfolio perspective we are always spending time looking at new technologies that create younger, faster growing companies like Editas. If they can also create self-financing, profitable business models they become an excellent portfolio complement to more mature holdings. For the time being, CRISPR and all the companies associated with it remain in our research lab.

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