TransTech Alert
Transformational Technology

Mutant-Fungus Attack on Biologics Industry Could Make Investors Rich

Issue: 6.03 • March 2018

In This Issue

01 Mutant-Fungus Attack on Biologics Industry Could Make Investors Rich

08 From the Analysts

Dear TransTech Reader,

Drugs fall primarily into two categories, small-molecule drugs and larger biological molecules like proteins. Small-molecule drugs can usually be synthesized in a lab because they are simpler. Biologics, however, must be grown. These organic molecules are larger, far more complex, and must be synthesized in a cell. As it stands today, what can be done in the biotech lab doesn't even come close to the biosynthetic abilities of cells.

The biologics industry essentially consists of huge cell farms that harvest biologics synthesized by mammalian or bacterial cells, or—in the case of Dyadic International (OTCQX: DYAI)—fungal cells.

In the last two decades, Big Pharma has mass-produced biologics by using an oddly specific line of mammalian cells called Chinese hamster ovary (CHO) cells. Chinese researchers started working with hamsters in 1919 when studying pneumonia. Eventually, these hamsters made it over to the US and were bred in US laboratories as well.

In 1957, when American geneticist Theodore T. Puck was looking for an optimal line of mammalian cells for research, he eventually settled on CHO cells because of their rapid growth in suspension and robust protein expression. The protein biosynthesis industry is using them to this day.

However, this industry standard is being challenged by this month's recommended company, Dyadic International, which has developed an even more efficient cell line originating from fungi.

Led by CEO Mark Emalfarb, Dyadic has capitalized on mutations to develop fungal cells that can secrete biological drugs more efficiently than CHO cells—but the company got its start in an entirely different industry. As unlikely as it sounds, Dyadic's CEO started out as a rock salesman.

From Jeans to Genes

Dyadic was founded in 1979 as an industrial supplier of pumice stones used in the manufacturing of stone-washed blue jeans. Emalfarb helped develop the process of "stone washing," which creates the familiar faded color and softer feeling.

Pumice stone https://en.wikipedia.org/wiki/Pumice#/media/File:Teidepumice.jpg

Big brand-name denim manufacturers such as Levi, Lee, Guess, and Wrangler adopted this manufacturing process and used it throughout the 1980s. As Mark Emalfarb told me, in that heyday, Dyadic sold $15 million in pumice stones per year to these companies. The process of stone washing is still in use, but to a lesser extent due to alternative processes.

Those innovative processes were indeed a biotechnological development that changed the shape of the jean manufacturing and stone washing industry.

While pumice stone washing worked well, it had a few drawbacks: a lack of control and specificity, as well as chemically tainted pumice residue that needed to be disposed. Scientists discovered that biologically sourced enzymes could be used to pre-stress jeans more precisely and at the same time solved the disposal problem. Specifically, enzyme washing utilizes cellulase, which breaks down cellulose, the main component of the cell walls of plants, like the cotton used to make denim.

In nature, cellulase can be found in fungi, the third kingdom of multicellular organisms alongside plants and animals. Although we often think of mushrooms as vegetables, they are no more a plant than they are a cow. In many ways, fungi are actually more similar to animals. For instance, whereas plants can convert photons from sunlight into glucose, both animals and fungi must find nutrients in their habitats and consume them to survive.

For the most part, fungi sustain themselves by absorbing nutrients held inside the cells of other cells—whether they come in the form of fruit that's fallen on the forest floor, the decomposing carcass of an animal, or bacteria cells. Fungi are efficient scavengers and dutiful janitors helping recycle organic matter. They typically accomplish this by secreting digestive enzymes into their environment and then absorbing the dissolved nutrients.

The two largest industrial enzyme companies at the time, Novozymes and Genencor, had around 70% market share combined. They used fungal cells to produce their cotton-digesting enzymes, a process that would come to be known as *biostoning*.

So cellulase was the target enzyme needed, and fungi naturally produce it best. Fungi are also attractive from an industrial perspective because, as I said, they are natural secretors. At this point, the race was on to find a fungus that expressed exactly the right enzyme.

A Search for Scientists and Fungi Leads Dyadic to Russia

By the 1990s, the denim industry had switched over to enzymes for treating blue jeans, forcing pumice stone sellers like Emalfarb to adapt or walk away. Instead of abandoning the industry, Dyadic decided to adapt to the new field of enzyme production.

Emalfarb wasn't going to leave the industry he pioneered. Since he had taught the denim companies to use pumice stones, he figured he could teach them how to use cellulase as well. He hired scientists to find the best organism to produce cotton-digesting enzymes for the biotech equivalent of stone washing.

This was soon after the dissolution of the Soviet Union, and the wall between Russian and US research had been torn down. Soviet funding for research had dried up, but scientists were now crossing over and working together.

Emalfarb saw this as an opportunity to work with brilliant researchers. Dyadic was able to hire high-caliber Russian scientists for far less than their US Ivy League counterparts, and they began looking for a superior source of cellulase.

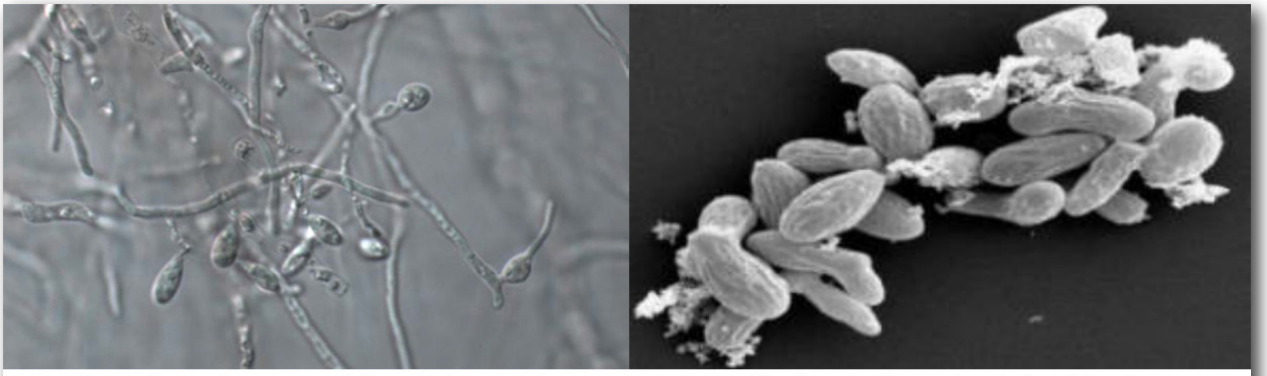
It is worth noting that not just any old cotton-digesting enzyme would suffice. While there are many fungi that synthesize cellulase, premium biostoned denim required an enzyme that would be stable at neutral pH levels and at the temperatures being used by the stone-wash laundries.

The logical thing to do was to look for an environment with similar conditions to those in the denim industry. The scientists' search for an appropriate fungus eventually led them to the *Myceliophthora thermophila* fungus in the alkaline soil of a forest in the far east of Russia.

The problem was that Myceliophthora thermophila, like most wild microorganisms, secreted cellulase in relatively small amounts, so Dyadic's scientists took the fungus back to their labs and started selectively breeding it for higher expression of the desired cellulase protein.

To propagate new characteristics in the fungal cells, they exposed them to ultraviolet light in a process called *UV mutagenesis* and expanded and reinforced beneficial mutations in a line of cells designed for lower-cost, large-scale manufacturing that the company named C1.

During this process, two serendipitous mutations occurred. One of them was a drastic change in the shape of C1, from long, spaghetti-like, filamentous strands to short, grain-sized sections. This profound change in morphology resulted in multiple unexpected benefits in terms of industrial production of proteins.



Long, filamentous pre-mutation C1 fungal cells *Short, grain-like post-mutation C1 cells*

This transformation mattered because C1 fungal cells secrete enzymes from the ends of the filaments. With the much shorter, grain-like filaments of the post-mutation C1, there would be more secreting ends, multiplying total yield.

Second, due to its new geometry, C1 became easier to grow in large tanks. Imagine a tangled-up mess of spaghetti versus a pot of short-grain rice. The less viscous nature of the smaller C1 cells made them easier to stir. Additionally, it allowed the scientists to grow C1 in small microliter-sized wells for more efficient testing and breeding. Previously, long filaments would stick and get in the way, making testing slower and more difficult.

At this point, Dyadic realized that the true potential of C1 as a protein biosynthesis platform lay far beyond that of washing blue jeans. By creating recombinant C1 cells, they could mass produce a seemingly endless number of proteins, or biologics.

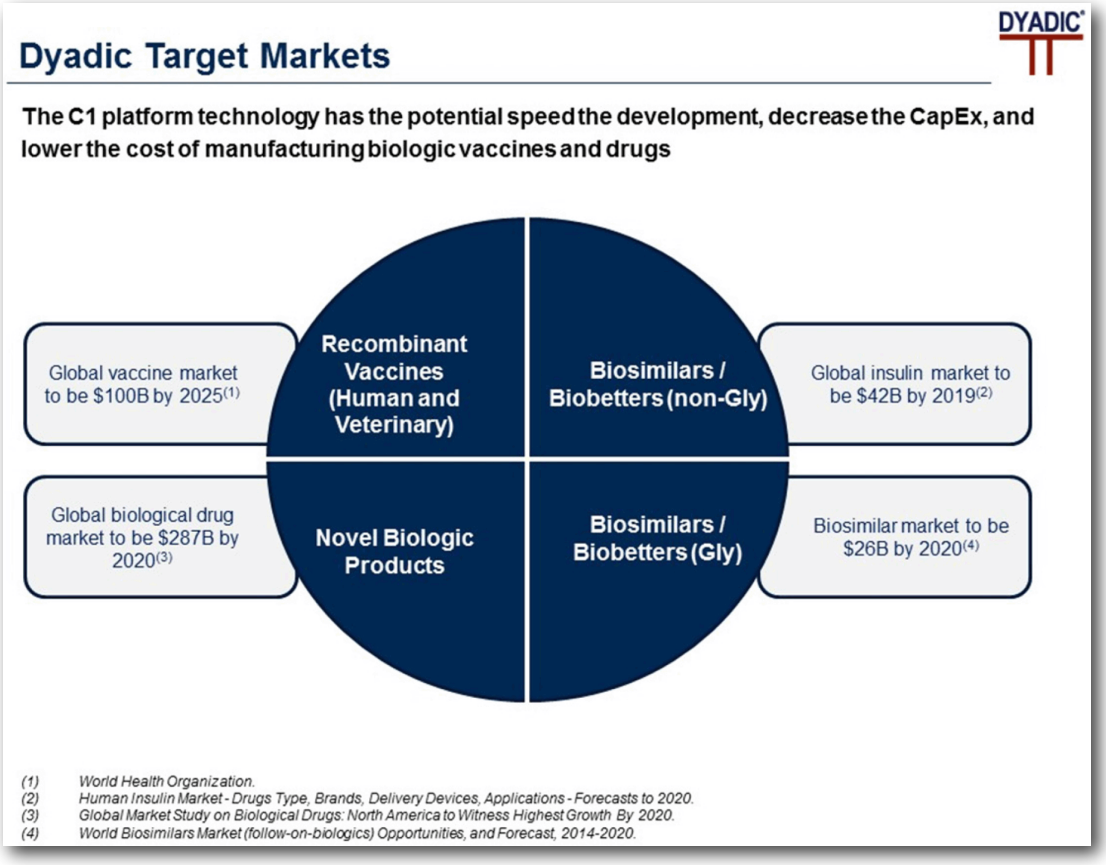
Recombinant, in this context, means a cell with an inserted foreign gene. After a new gene is inserted, the C1 cells' own protein synthesis machinery then turns out the desired protein.

Gene kits are commercially available for the cell lines most commonly used in labs, but using fungal cells for biosynthesis was such a new development that Dyadic was the only company that possessed the novel C1 fungal cells. For that reason, it had to develop its own fungal gene kits from scratch.

From Washing Jeans to Saving Lives—Moving into Biologics and mAbs

The company realized that it could synthesize vaccines, antibodies, and theoretically any biologic on the market. Its C1 production platform was far more efficient than the pharmaceutical industry's standard of CHO cells.

Dyadic therefore began moving away from biosynthesis of proteins for industrial applications and set its sights on pharmaceutical applications. It further developed C1 into a safe and efficient expression system designed to speed up development, lower production costs, and improve the performance of biologic vaccines and drugs at flexible commercial scales.



Source: Dyadic International

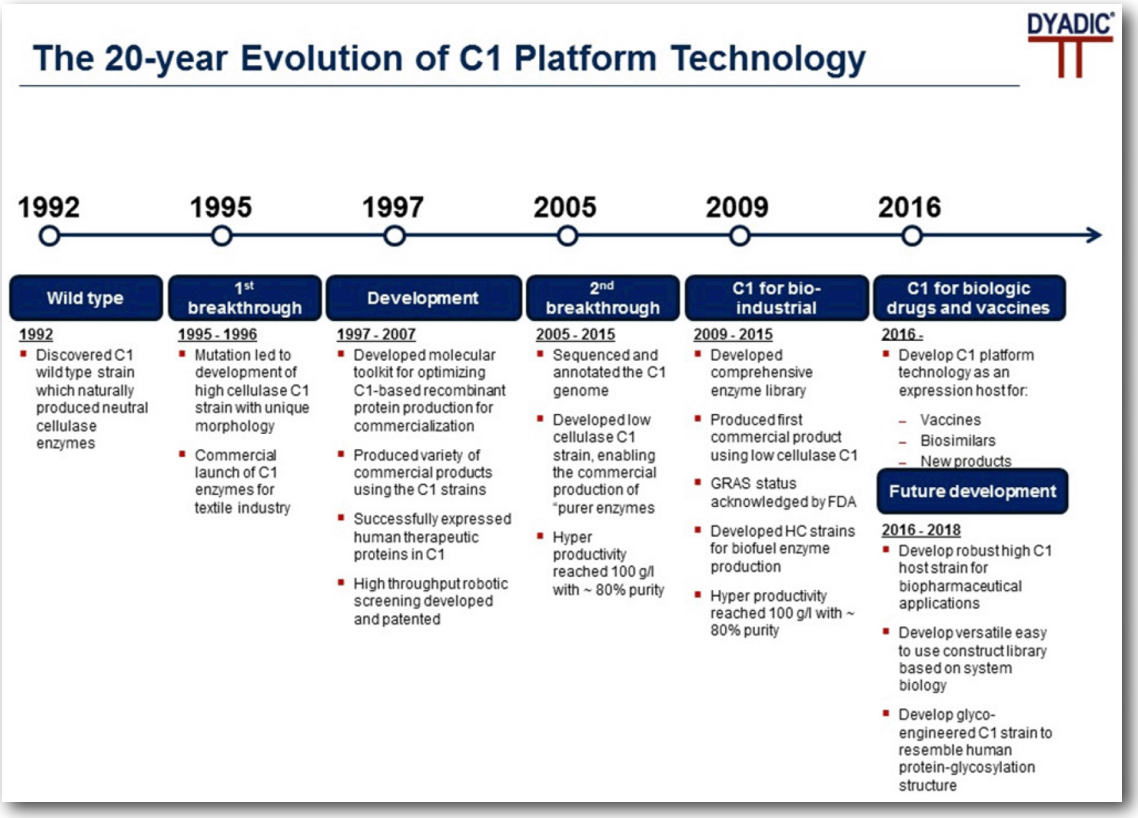
Dyadic can use its C1 production platform to move into various animal and human pharmaceutical applications. This is particularly valuable because of high demand for biologics and the company's ability to make current biologics at lower prices.

Dyadic's industrially proven hyper-productive C1 Gene Expression Platform has already shown that it can produce industrial enzymes at up to 100 grams per liter and about 80% purity. The cell platform can express a monoclonal antibody (mAb) at 8 grams per liter in half the time it takes to produce mAbs using CHO cells. CHO cells' protein expression slowly increased over the decades of their use, but has plateaued at an average of only around 4 grams of drug per liter.

Dyadic has reduced the production time as well. Each batch of C1 cells takes one week less compared to CHO cells—that's a 50% shorter production cycle. Antibodies produced by Dyadic's C1 cells have virtually indistinguishable binding kinetics—meaning the degree to which they can bind to their targets—to those produced using the more expensive CHO platform.

Because of this efficiency and shorter cycle time, Dyadic could make biologics out of smaller 2,000-liter bioreactors compared to the standard 12,000-liter tanks used by CHO cell manufacturers and still produce the same yield. That means if the company did scale up, it would blow alternative means of production out of the water.

With these advantages, Dyadic has first targeted the monoclonal antibody and vaccine market, one of the largest biologics sectors. And while I believe other medical fields will eventually become less important due to anti-aging therapeutics, infectious diseases are likely to remain an important field for innovation.



Source: Dyadic International

Currently, Dyadic is collaborating with the Israel Institute for Biological Research to develop vaccines and with the Zoonoses Anticipation and Preparedness Initiative (ZAPI). ZAPI is a research project funded by the European Union with the goal of combating epidemic zoonotic diseases (diseases transmitted from animals to humans).

Dyadic and Sanofi Pasteur, one of the world's largest influenza vaccine companies, have presented encouraging mice trial data showing hemagglutinin produced from C1 had excellent immunogenicity properties in mice without adjuvant, an agent that modifies or boosts the immune response of the vaccine.

This indicates that C1 may be able to shorten the time needed to develop and manufacture lower-cost flu vaccines that may also provide better protection. The C1 technology could also help combat some of the most common biological weapons like anthrax and botulinum.

At the end of February, Dyadic announced that it had entered into a collaboration with Mitsubishi Tanabe Pharma Corp. The Japanese pharmaceutical company will be funding proof-of-concept research using the C1 technology to produce "two vital therapeutic proteins for human health indications."

Mitsubishi Tanabe Pharma is the third pharma giant to provide funding to Dyadic to evaluate the potential of the C1 Gene Expression Platform, but due to confidentiality agreements, Dyadic has not disclosed the names of the other two.

In early January, Dyadic also announced a funded proof-of-concept research collaboration to explore the potential of its C1 technology to produce an important active moiety (part of a molecule) with an integrated, global biotech company.

According to Dr. Ronen Tchelet, Dyadic's VP of research, the research collaboration is about demonstrating the benefits of C1 "as a primary metabolite-producing host organism for producing an active compound."

Assets

Dyadic has 20 issued patents on the C1 cell line. Note that DuPont acquired the patents of C1 along with its purchase of Dyadic's Industrial Technology Business. However, Dyadic maintains the rights to use the C1 Gene Expression platform in all pharmaceutical applications, as well as the exclusive rights to sublicense those applications further.

Dyadic is well positioned to challenge the existing pharmaceutical order by providing fast, low-cost alternatives to some of the most valuable drugs on the market today. This fungal cell platform has enormous potential to alter the landscape of biologics as well as provide extraordinary returns for investors.

For transformational profits,

Patrick Cox

From the Analysts

Dyadic International (OTCQX: DYAI) has a unique background for a micro-cap biotech company. It's been in business since 1979, but it hasn't always focused on biotechnology.

The company has evolved from developing chemical enzymes to create "faded" jeans to its new focus on a fungus-based platform for creating enzymes with applications in the biopharmaceutical space.

The board made a strategic pivot to focus on leveraging its patented and proprietary C1 expression system to help speed up the development and production of biologic vaccines and drugs at a commercial scale. That may seem odd—but not when you consider that the board and management have a 20+ years of experience in the pharma industry.

Dyadic sold its industrial technology business to DuPont in December 2015 for $75 million. The agreement gives Dyadic co-exclusive rights to the C1 technology for use in human and animal pharmaceutical applications.

It also gives Dyadic the exclusive right to sublicense C1 for use in the development of biologics. Other C1-related licensing and equity deals with Abengoa Bioenergy, BASF, and Codexis/Shell have already brought in more than $110 million.

Dyadic also has a partnership with Biotechnology Developments for Industry in Pharmaceuticals (BDI Pharma). Last year, Dyadic paid €1 million to help develop C1-based product candidates. Additionally, Dyadic acquired a 16.1% equity interest in BDI Holdings and a 3.3% equity interest in its subsidiary VLPbio.

Dyadic is extremely well capitalized, with a fully funded development program in place. The size of the DuPont deal speaks to the upside potential of C1. It's so well funded, in fact, that management has already started returning money to shareholders. Last year, the company completed a total of $19 million in share buybacks and the board of directors authorized a new one-year stock repurchase program for $5 million more of its outstanding common stock.

Dyadic is still sitting on over $51 million in cash and investments, with no debt on the balance sheet. The quarterly cash burn has averaged just over $2 million over the last year. The end of the runway is not even close to being in sight.

Money won't be an issue as the company works on a potential game-changer for biologic drugs—the fastest-growing segment in the pharma industry. Approximately 18% or $235 billion of the $1.3 trillion spent on drugs annually is for biologics. And the segment is projected to grow at a 10.9% CAGR to over $479 billion by 2024.

Biologic drugs are some of the most expensive treatments, costing tens to hundreds of thousands of dollars. This places an enormous financial burden on both patients and global healthcare systems.

The current CHO technology used to produce biologics is very capital intensive and requires costly manufacturing facilities. For instance, Samsung recently built a biologics plant in South Korea for $740 million.

Dyadic's C1 technology has the potential to significantly reduce upfront capital and operating expenditures. The potential to help bring vaccines and drugs to market faster, in greater volumes, at a lower cost, and with new beneficial properties is an easy value proposition for prospective customers.

Best of all, shares of Dyadic look very attractive right now. DYAI is trading near $1.41 as we go to press. That represents a 16% discount to its cash and investments of $1.68 per share.

The company's cash cushion limits the downside risk, while there is plenty of upside potential if the C1's proven success as a low-cost, highly productive gene expression host translates into the biopharma industry.

DYAI is thinly traded over the counter with an average volume of just 25,000 shares per day. With that in mind, **we recommend you allocate one-half of your planned capital to Dyadic International (OTCQX:DYAI) with a limit order of $1.41 per share**.

Read this letter online at https://www.mauldineconomics.com/tech/trans-tech/mutant-fungus-attack-on-biologics-industry-could-make-investors-rich

Use of this content, the Mauldin Economics website, and related sites and applications is provided under the Mauldin Economics Terms & Conditions of Use.

Unauthorized Disclosure Prohibited

The information provided in this publication is private, privileged, and confidential information, licensed for your sole individual use as a subscriber. Mauldin Economics reserves all rights to the content of this publication and related materials. Forwarding, copying, disseminating, or distributing this report in whole or in part, including substantial quotation of any portion the publication or any release of specific investment recommendations, is strictly prohibited.

Participation in such activity is grounds for immediate termination of all subscriptions of registered subscribers deemed to be involved at Mauldin Economics' sole discretion, may violate the copyright laws of the United States, and may subject the violator to legal prosecution. Mauldin Economics reserves the right to monitor the use of this publication without disclosure by any electronic means it deems necessary and may change those means without notice at any time. If you have received this publication and are not the intended subscriber, please contact service@MauldinEconomics.com.

Disclaimers

The Mauldin Economics website, *Yield Shark, Thoughts from the Frontline, Patrick Cox's Tech Digest, Outside the Box, Over My Shoulder, World Money Analyst, Bull's Eye Investor, Just One Trade, Connecting the Dots, Transformational Technology Alert, Rational Bear, The 10th Man, Stray Reflections*, *Street Freak, ETF 20/20, Macro Growth & Income Alert,* and *Conversations* are published by Mauldin Economics, LLC. Information contained in such publications is obtained from sources believed to be reliable, but its accuracy cannot be guaranteed. The information contained in such publications is not intended to constitute individual investment advice and is not designed to meet your personal financial situation. The opinions expressed in such publications are those of the publisher and are subject to change without notice. The information in such publications may become outdated and there is no obligation to update any such information. You are advised to discuss with your financial advisers your investment options and whether any investment is suitable for your specific needs prior to making any investments.

John Mauldin, Mauldin Economics, LLC and other entities in which he has an interest, employees, officers, family, and associates may from time to time have positions in the securities or commodities covered in these publications or web site. Corporate policies are in effect that attempt to avoid potential conflicts of interest and resolve conflicts of interest that do arise in a timely fashion.

Mauldin Economics, LLC reserves the right to cancel any subscription at any time, and if it does so it will promptly refund to the subscriber the amount of the subscription payment previously received relating to the remaining subscription period. Cancellation of a subscription may result from any unauthorized use or reproduction or rebroadcast of any Mauldin Economics publication or website, any infringement or misappropriation of Mauldin Economics, LLC's proprietary rights, or any other reason determined in the sole discretion of Mauldin Economics, LLC.

Affiliate Notice

Mauldin Economics has affiliate agreements in place that may include fee sharing. If you have a website or newsletter and would like to be considered for inclusion in the Mauldin Economics affiliate program, please go to http://affiliates.pubrm.net/signup/me Likewise, from time to time Mauldin Economics may engage in affiliate programs offered by other companies, though corporate policy firmly dictates that such agreements will have no influence on any product or service recommendations, nor alter the pricing that would otherwise be available in absence of such an agreement. As always, it is important that you do your own due diligence before transacting any business with any firm, for any product or service.