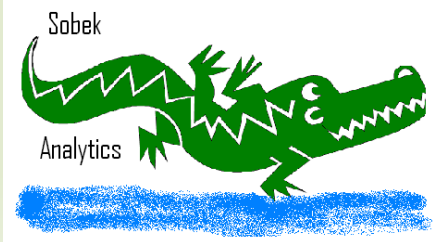

Sangamo (SGMO) Playing with a Deep Bench

Sangamo: A Deep Bench

Sangamo's (SGMO) recent presentation at the 10th Annual Needham Conference highlights two important strengths of the company. First, while the diabetic neuropathy and HIV programs are the most advanced, there is a lot of research being done that is building a deep pipeline. Second, one could argue that the real strength and elegance of the technology is best seen in its pre-clinical work in monogenic diseases.

This is important from an investor perspective because it creates an added layer of security in that the failure of any compound does not crush the company. While any failure would be a disappointment, the fact is that the depth of the pre-clinical pipeline allows these setbacks to be replaced with a new compound. Of course, if the lead compounds succeed, then the pipeline becomes a source of additional investment and further increases the growth prospects. Rather than focus on all of the pre-clinical programs, this report focus on Sangamo's efforts in Parkinson's disease. I focus on this because some of the research has been published in The Journal of Neuroscience in 2010, and it is likely to be one of the next compounds to make it into the clinic. In the next report on Sangamo, I will take a look at the monogenic diseases.

Contents

Sangamo: A Deep Bench 1

Sangamo and Parkinson's Disease: A Novel Approach 1

Cracking Parkinson's Disease Estimating the Current Net 2

GDNF and Neuroprotection 2

Disclaimer 3

Sangamo and Parkinson's Disease: A Novel Approach

Loss of dopaminergic neurons drives the onset and progression of Parkinson's Disease. As such, modern therapeutic approaches attempt to protect these neurons. A prime target for this approach is glial cell-derived neurotrophic factor (GDNF). Sangamo has engineered a ZFP TF that stimulates the production of GDNF provides functional neuroprotection in the rat 6-OHDA model of Parkinson's disease.

Cracking Parkinson's Disease

Parkinson's Disease is a degenerative and chronic neurological disease. The current standard of care is to treat patients early in the process with Levodopa, which only offers symptomatic relief. Aside from only providing symptomatic relief, long-term use of Levodopa is additionally limited given its side effects. As such, there is clearly a need for a treatment that (a) can provide more of a disease modifying effect and (b) can be taken over the long term.

The limits of Levdopa provide insight into the ultimate utility of Sangamo's approach. As noted earlier, the loss of the dopaminergic neurons is a key characteristic of Parkinson's Disease. This loss ultimately decreases the amount of dopamine in the brain. The decrease in the levels of dopamine has a series of effects as dopamine plays an important role in behavior and cognition. Levdopa is important as it is able to cross the blood-brain barrier. Once through that barrier, Levdopa is converted into dopamine thereby counteracting the loss of dopamine from the dopaminergic neurons. Unfortunately, Levdopa is also converted into dopamine in the peripheral nervous system causing a series of side effects. To counteract this, Levdopa is often administered with carbidopa or benserazide. Even with these additional drugs, however, Levdopa is not a long-term solution.

One of the main issues with Levdopa is its ability to generate dopamine in the body. The problem is that it floods the system with too much dopamine. The key, then, would be to have a therapeutic dose that raises the levels of dopamine back to normal levels in the brain without flooding the rest of the system with supra-normal levels.

It appears that the administration of ZFP can stimulate the production of a physiologically relevant level of GDNF and provide neuroprotective benefits leading to clinically relevant changes in behavior in a rat model.

GDNF and Neuroprotection

A key therapeutic approach would be to stimulate the production of or protect the dopaminergic neurons. If a treatment were to re-establish normal levels of dopaminergic neurons, then they would properly regulate the level of dopamine and hopefully provide a disease modifying effect for Parkinson's Disease patients. Glial cell-derived neurotrophic factor (GDNF) is a neurotrophin in the basic fibroblast growth factor superfamily. Of most interest is the ability of GDNF to promote the in vitro survival of embryonic dopaminergic neurons. As such, there has been intense interest in using GDNF to treat Parkinson's Disease but clinical studies have thus far failed to provide encouraging results. Arguably the lack luster results could have been driven by either the lack of an efficient delivery method or the high focal levels of the therapeutic factor delivered.

Sangamo's approach is different in that it does not attempt to deliver GDNF; rather, it seeks to activate GDNF expression from its endogenous gene. In other words, Sangamo uses a ZFP TF to get the body to produce GDNF by itself. Why should this be any different than simply injecting GDNF? The key is that by using the endogenous gene the Sangamo treatment will get a clinically relevant increase in GDNF but not a supra-normal level as the endogenous gene will provide a physiological upper limit on the level of gene expression from each allele. This approach should then circumvent the two problems seen with previous GDNF treatments: delivery and high focal levels. In addition, since the body is not receiving supra-physiological levels, there should be less of a problem with side effects.

Sangamo has tested this treatment in a number of animal models. In particular, in a rat model the treatment with the ZFP increased the levels of GDNF by about 60% after four weeks. To see if the treatment actually protected the dopaminergic neurons, the rats were infused in the right stratum leading to the loss of dopaminergic neurons in the ipsilateral substantia nigra that is manifested by a series of behavioral abnormalities. The rats were then given a series of tests to determine if the ZFP treatment was able to provide any prophylactic benefit. In particular, the rats received a corridor test, cylinder test, and rotations test. The non-ZFP treated rats showed the predicted behavioral abnormalities that one would expect with the loss of dopaminergic neurons in the ipsilateral substantia nigra. In contrast, the ZFP treated rats had significantly statistically significant fewer behavioral abnormalities in all three tests indicating that treatment with the ZFP not only increased the GDNF but that this protected the dopaminergic neurons. After the behavioral tests, the rats were euthanized and their brains were analyzed. These additional analyses showed that treatment with the ZFP had " significant local effects on maintaining the terminals of the dopaminergic neurons and/or dopaminergic neurons that are intrinsic to the striatum" (Laganiere, et al 2010: 16473). Ultimately, then, it appears that the administration of ZFP can stimulate the production of a physiologically relevant level of GDNF and provide neuroprtoective benefits leading to clinically relevant changes in behavior in a rat model.

Of course, all of the normal caveats apply to pre-clinical research. Other approaches to using GDNF to treat Parkinson's Disease did well in animal testing only to fail in the clinic. If these previous failures were driven by delivery or the stimulation of supra-physiological levels of GDNF, then Sangamo's approach has a chance to succeed where the others failed.

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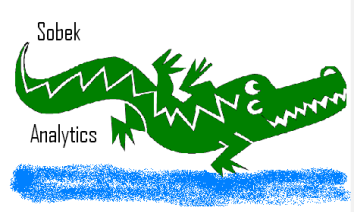

Disclaimer

I am not a certified financial analyst. All the information provided in this report is my interpretation and may contain errors. Please, do not invest based solely on my opinions as it is critical for all investors to conduct their own due diligence and invest in ways that best fit their own needs. In addition, I am long SGMO shares and April calls.