Sobek Analytics

Report on Sangamo (SGMO) before the CROI presentation.

Report:

For general information about the company and its complete pipeline see the end of this report. The main purpose of this analysis is to provide a primer as to what to expect about its upcoming presentations at CROI (http://zika.retroconference.org/croi-2011-pocket-program.pdf). In particular, Sangamo has four presentations entitled:

Successful and Persistent Engraftment of ZFN-M-R5-D Autologous CD4 T Cells (SB-728-T) in Aviremic HIVinfected Subjects on HAART

Creating an HIV-resistant Immune System: Using CXCR4 ZFN to Edit the Human Genome

CCR5 Knock-out in Hematopoietic Stem Cells

Disruption of CCR5 in Zinc Finger Nuclease-treated CD4 T Cells: Phase I Trials

While one would generally not get too excited about the presentation of data from a couple of phase I trials, interest in these trials has recently been stoked by a Business Week article that talks about the Sangamo HIV program as a possible cure (http://www.businessweek.com/magazine/content/11_08/b4216018308281.htm).

My report is not meant to minimize the importance of Sangamo's work; rather, it is to focus investors on the proper ways to judge the upcoming results. Perhaps most importantly, these trials are **not** going to cure AIDS in the sense of eliminating viral loads. So why the excitement?

In many ways, HIV does not directly kill those infected with the virus but it eventually destroys the immune system to the extent that the individual becomes susceptible to co-morbidities. Current HAART treatments are fairly successful at keeping the virus under control but eventually the virus is able to compromise the immune system. In particular, the virus severely limits the body's ability of T-cells, which leads to immunodeficiency.

The virus, however, requires the CCR5 receptor to enter into the T-cells (http://en.wikipedia.org/wiki/CCR5). Some people, however, lack the CCR5 receptor making them essentially immune to HIV infection. Sangamo, in its trials, is able to remove T-cells from the patient,

eliminate the CCR5 receptor on those cells, and then re-infuse them back into the body. The new T-cells are now protected from the virus. If these new T-cells are able to traffic and reproduce in the body, then the treatment will have successfully created a compartment of the immune system protected from the virus.

Note, however, that this treatment will not eliminate the virus from the body; rather, it protects the T-cells from the virus. As such, the critical measures of success in the trails would be the persistence of the modified T-cells, i.e. do they traffic through the body, do they survive, and do they multiply. In addition, it is important to watch the CD4/CD8 ratio. If this normalizes, then it would indicate a reversal of the key immunologic defect seen with HIV infections.

Thus you can understand the excitement associated with this program and data. The ability to create a protected area of the immune system that could essentially allow it to function normally even though the patient is infected with HIV would be a tremendous breakthrough. Of course, the technology can do even more if it were able to modify the hematopoitic stem cells. This would be the equivalent of the "Berlin patient," whose body is now completely virus free (http://www.aidsmeds.com/articles/hiv_berlin_cure_1667_19563.shtml). Sangamo is actually working on this but it is still in pre-clinical development and is best left for another report. Sangamo has published its work on this in Nature Botechnology (http://www.nature.com/nbt/journal/v28/n8/full/nbt.1663.html) and the abstract of that article appears below after the pipeline slide.

So in sum, critical data will be presented at the CROI conference. Be sure to check out how the modified T-cells traffic in the system and the CD4/CD8 ratio. If these are both normal, then Sangamo's treatment would have successfully protected these patients from the key immunologic defect created by HIV infection.

If you have additional questions, please e-mail me at dsobek@sobekanalytics.com.
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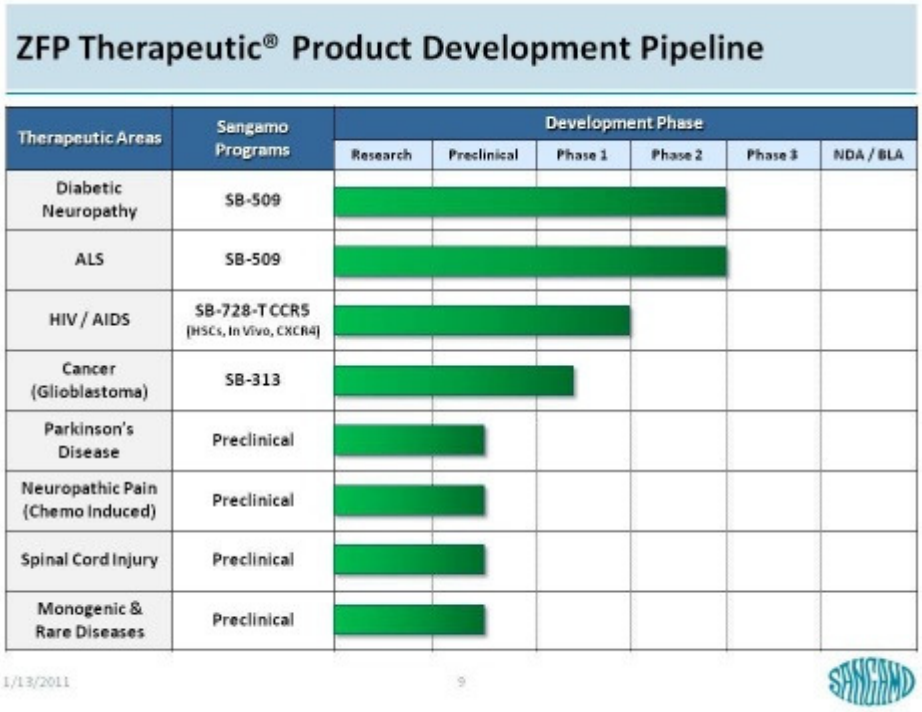
General company information:

Sangamo BioSciences, Inc.

http://www.sangamo.com/index.php

Sangamo Pipeline



Source: JPM 29th Annual Healthcare Conference

Abstract of the Nature Biotechnology article:

CCR5 is the major HIV-1 co-receptor, and individuals homozygous for a 32-bp deletion in *CCR5* are resistant to infection by CCR5-tropic HIV-1. Using engineered zinc-finger nucleases (ZFNs), we disrupted *CCR5* in human $CD34^+$ hematopoietic stem/progenitor cells (HSPCs) at a mean frequency of 17% of the total alleles in a population. This procedure produces both mono- and bi-allelically disrupted cells. ZFN-treated HSPCs retained the ability to engraft NOD/SCID/IL2rγ^{null} mice and gave rise to polyclonal multi-lineage progeny in which *CCR5* was permanently disrupted. Control mice receiving untreated HSPCs and challenged with CCR5-tropic HIV-1 showed profound $CD4^+$ T-cell loss. In contrast, mice transplanted with ZFN-modified HSPCs underwent rapid selection for $CCR5^{-/-}$ cells, had significantly lower HIV-1 levels and preserved human cells throughout their tissues. The demonstration that a minority of $CCR5^{-/-}$

HSPCs can populate an infected animal with HIV-1-resistant, *CCR5*$^{-/-}$ progeny supports the use of ZFN-modified autologous hematopoietic stem cells as a clinical approach to treating HIV-1.

Disclaimer:
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