AKASHI: DESIGNING COCKTAIL THERAPY FOR DMD

Akashi Therapeutics is a biopharmaceutical company with the mission to develop treatments for Duchenne muscular dystrophy (DMD) and other rare pediatric disease. NeuroInsights spoke with Akashi’s CEO Marc Blaustein about the unique model of the company and their multifaceted approach to treating DMD.

Akashi was formed as a result of support from two patient foundations, Charlie’s Fund and the Nash Avery Foundation. Five years ago, the foundations realized that in order to accelerate therapeutic development they needed to have a more active role and they became interested in finding promising molecules and creating a biotechnology company around those. Blaustein explains, “The real genesis was the compound that is the active ingredient in HT-100, halofuginone, was the subject of some research, including some publications in the mdx model of Duchenne, with some really profound findings.” The molecule was not being developed for DMD and Blaustein became involved in forming and leading a diligence team to evaluate the potential of halofuginone in DMD. The results of this diligence led to the creation of Halo Therapeutics in 2011, the predecessor of Akashi, to develop the compound for DMD. The company now has 12 team members, including Dr. Ernest Bush as the CSO and Dr. Diana Escolar as the CMO, who have been part of the effort since early in the formation of the company.

Blaustein believes that the treatment of DMD is going to be a cocktail of therapies attacking different pathways and pathologies to turn it into a chronic manageable disease. Akashi was built to leverage specific knowledge and expertise in terms of biology and pathology paired with drug development in a difficult disease, to develop multiple therapies that will be core components of the cocktail of therapies to manage DMD as a chronic disease.

The most advanced candidate in Akashi’s pipeline is HT-100. Blaustein explains why development of halofuginone had not previously advanced saying, “Probably the primary reason that the drug was never really developed as a human therapeutic was that it had a very consistent GI tolerability issue.” Initially, Akashi focused on developing an approach to address this issue. The scientific effort led to the development of HT-100, the enteric-coated formulation of halofuginone. The drug acts by reducing fibrosis and inflammation while promoting muscle fiber regeneration. Blaustein comments, “We think that the drug is so promising because each of these three activities work synergistically, in concert.” Up to this point, steroids have been the only drugs that have demonstrated efficacy and Akashi believes that this is due to their activity in many pathways, hence HT-100 activity in the different pathways reducing the inflammation, reducing the fibrosis and promoting the myotube fusion, may also demonstrate efficacy. In addition, Blaustein explains that there is a possibility that at different stages of the disease that the different effects may be more important. The ongoing HT-100 Phase I/II clinical program is investigating the effects on young and older patients, and hence will help understand the different drug effects in different disease states. Akashi has extended the treatment period in the Phase IIa extension study and will continue to gather data. By the middle of 2015 the next set of data, both biomarker and efficacy is expected.

A second compound in development is DT-200, a selective androgen receptor modulator working as a muscle-building drug. DT-200 is ready to enter proof-of-concept studies, as it has completed Phase I trials and there is an understanding of dosage, initial safety and tolerability. The proof-of-concept study for this type of drug is a short four to six weeks study in healthy volunteers investigating growth in lean muscle mass. Akashi intends to complete this study in 2015.

The last candidate in Akashi’s pipeline is AT-300, the only known inhibitor of stretch-activated calcium channels, which are specifically implicated in DMD pathology and the loss of cellular calcium homeostasis. Dystrophin has a structurally stabilizing activity in the muscle fiber and in DMD the damage and stress in the cell membrane leading to activation of the channels, leading to calcium overload and ultimately necrosis. The preclinical program for AT-300 will extend through 2015. Blaustein explains the reasons behind seeking the license for this compound, “Loss of calcium homeostasis is known as one of the drivers for pathology in DMD muscle and people had explored other calcium channel inhibitors without success, but these stretch-activated calcium channels were specifically implicated.”

Blaustein describes the candidates as “absolutely complementary” as the effects on fibrosis and calcium homeostasis are relevant to treating pathology regardless of the disease state. Akashi views HT-100 is a foundational drug in any therapy due to its effects on inflammation and fibrosis, with DT-200 and AT-300 complementing it.

At this time Akashi is not exploring other indications for their candidates but they remain open to this possibility, whether alone or in partnership with other companies. Although it is early in the
process, Blaustein comments that they will be looking for a partner that would help them achieve the goal of building the company and making the drugs available outside the US and for other indications.

Up to this point, Akashi's $15 million in funding has come from DMD and related foundations. The company is now actively planning a growth capital campaign to expand the company resources to move the pipeline forward and to have multiple candidates in the clinic at the same time. Blaustein is enthusiastic and shares, “There is a tremendous amount of interest in the DMD space and in our products both from investors and potential strategic partners.”

The work of the DMD foundations has been important for Akashi in other fronts beyond the financial. The foundations have led strong advocacy efforts on a political level and with the FDA, which has generated the interest to advance candidates for DMD. Blaustein comments on the positive interactions with the FDA saying, “We have found the agency incredibly willing to work with us. They have a strong interest in seeing good drugs for this indication move forward. We had a very positive and productive dialogue.”

Blaustein believes that this is a promising time with the success in orphan indications and previous value-building models, such as Genzyme’s, is leading biotech and pharma companies to be more comfortable working with smaller populations, whether these are orphan populations or specific subpopulations of larger diseases.