Update on Drug Discovery Programs to Identify Novel Treatments for Duchenne Muscular Dystrophy

PTC Therapeutics and Parent Project Muscular Dystrophy (PPMD) are collaborating to discover novel drugs to treat Duchenne muscular dystrophy (DMD). The PTC-PPMD collaboration has been a productive partnership focused on identifying and developing new therapies for Duchenne and Becker muscular dystrophy. Our commitment to finding new DMD treatments started over a decade ago when we initiated our nonsense suppression program. From this work ataluren (also known as PTC124®) was identified and is currently in a pivotal clinical trial in patients with Duchenne and Becker muscular dystrophy caused by nonsense mutations. Along the way we worked with investigators to pioneer the regulatory ataluren clinical development plan that paves the way for the development of future treatments.

Once ataluren is approved, it will be for Duchenne boys harboring nonsense mutations. We are also currently developing treatments for those boys with DMD that do not have nonsense mutations. Our work is aimed at identifying new drugs to treat DMD by tackling three important aspects that we think could change the course of the disease. These include: muscle growth and regeneration, muscle membrane integrity, and cardiac function. We have screened for hit compounds and have identified lead scaffolds and analog molecules that are active against each of these targets and have advanced these molecules into different stages of development (Figure 1). Each of these targets will be described in more detail below.

Myostatin and the muscle-specific isoform of insulin-like growth factor 1 (mIGF1) were selected as targets to increase muscle growth and regeneration. These drugs are expected to increase muscle mass. As muscles in DMD boys are fragile and break easily, there is continued regeneration that ultimately exhausts the muscle stem cells. Since myostatin and mIGF1 are regulators of cell growth, drugs that alter their levels would prevent or slow the loss of muscle mass in DMD boys.

Utrophin was selected as a target in the search for compounds that promote membrane stabilization. In the absence of dystrophin, membranes are more fragile and are disrupted easily. Utrophin is analogous to dystrophin’s “little brother,” and can substitute for dystrophin and help strengthen the muscle’s membranes. Drugs that increase utrophin levels in cells would allow utrophin to compensate for dystrophin loss and strengthen the muscle membrane.

SERCA2a was selected as a target to identify new drugs that can help address the cardiac issues that arise in DMD boys. DMD boys have cardiac issues as a consequence of defective calcium signaling. SERCA2a is a pump that can help repair this defect by...
pumping calcium across the sarcoplasmic reticulum membrane. The goal of this program is to identify compounds that increase the amount of SERCA2a in the heart so that defective calcium signaling is corrected.

In this report, the progress for all of our programs will be described. However, in order to rapidly progress the programs towards clinical development, the majority of our efforts are currently focused on myostatin and utrophin.

We have expanded these efforts to include prioritizing the compounds synthesized based on their activity in the \textit{mdx} mouse, an animal model of DMD, as well as using cell culture assays. We are performing extensive pharmaceutical characterization of the scaffold analog compounds in order to improve their drug-like properties. These analyses include determining the amount of compound that reaches the bloodstream for each drug tested when orally administered to the animal. In addition we monitor how effective that level is in altering the biological activity that we are testing. This analysis is a critical part of the drug discovery process.

We have made significant progress in the first half of this year. Through our extensive medicinal chemistry and pharmacology efforts we have shown that we can affect the biological levels of myostatin, mIGF1 and utrophin in animals treated with our compounds. In the myostatin program, we demonstrated that treating \textit{mdx} mice with our scaffold analog compounds results in a 50% decrease in myostatin in the diaphragm. In the mIGF1 program, we demonstrated that treatment with our analog compounds selectively increases mIGF1 in skeletal muscle by 50%, and importantly, did not increase IGF1 in the liver or plasma.

In the utrophin program, we identified analog compounds that increase utrophin up to 4-fold in muscles from \textit{mdx} mice. This is an important milestone for the program because these data demonstrate that the exciting results obtained in cell culture anticipate those obtained when animals are treated with our compounds. In the second half of the year we will expand these efforts to characterize compounds at multiple doses in order to determine the optimal dose for efficacy of our most advanced compounds.

The SERCA2 program is at an earlier stage in the drug development process. Through our screening efforts, we have identified compounds that increase SERCA2a levels in cell culture. The next step for this program will be to continue characterization of the compounds and to perform additional medicinal chemistry to understand the structure-activity-relationship of these compounds so that we can begin a lead optimization program.
We will continue our intensive chemistry and pharmacology efforts and continue to work to improve both the efficacy and safety of the lead compounds through the lead optimization phase of our program. This process involves synthesizing compounds that are structurally similar to the core of each parent compound with systematic alterations made that we anticipate will precisely define the important parts of the compound that impart biological activity. This effort, while time consuming and laborious, is required in order to identify a single compound that has the desired properties of potency, efficacy, and safety in animal studies with the appropriate pharmaceutical properties.

The results summarized above are a culmination of the efforts of a team of scientists dedicated to moving these programs rapidly forward. We are truly excited about the potential of the lead scaffolds and molecules identified for each target. Our efforts in the 2nd half of 2009 will focus on pushing the myostatin and utrophin programs so that we can rapidly identify development candidates. The next phase of this program is designed to demonstrate the efficacy of our compounds in altering the expression of myostatin or utrophin in mdx mice.

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