SUMMARY OF THE PATIENT ADVOCACY PRE-MEETING

Spinal Muscular Atrophy: A Test Case for Drug Development in Orphan Diseases

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Spinal muscular atrophy (SMA) is an inherited neuromuscular disease and the leading genetic killer of infants and toddlers. The human toll of this disease, combined with its unique genetic profile, has focused attention from the National Institutes of Health, industry, academia, and advocacy organizations on making a treatment available by 2010. Indeed, SMA was selected in 2003 by the National Institute of Neurological Disorders and Stroke (NINDS) for a model translational research program aimed at accelerating drug discovery efforts against neurodegenerative diseases through a collaborative process involving all stakeholders. This program responds to the need for an increased focus on treating rare diseases. About 10% of the 6000 to 7000 recognized rare diseases are neurological, yet of the more than 200 drugs and biological products for orphan diseases that have been introduced since 1983, only a handful were for neurological diseases. Spinal muscular atrophy was chosen as the prototype because scientists believe it is one of the closest to a cure and because of a belief that research aimed at finding treatments for SMA will shed light on treatments for other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Parkinson's, Alzheimer's, and Huntington's disease.

Advocacy groups such as the SMA Foundation have joined forces with NINDS and industry to accelerate progress in finding a treatment for SMA. In March 2006, the Foundation held a satellite symposium in conjunction with the annual meeting of the American Society for Experimental NeuroTherapeutics, which brought together stakeholders in an effort to share information and describe efforts underway to accelerate progress in drug discovery for SMA. Speakers provided an overview of the disease, including drug development considerations, and discussed drug development for orphan drugs, how philanthropy is making an effort to drive progress, and

the efforts of industry to move the scientific process forward in developing treatments for SMA.

SMA: READY FOR DRUG DISCOVERY

Darryl C. De Vivo, M.D., professor of neurology and pediatrics at Columbia University, provided an overview of the biology and clinical aspects of SMA. The disease is caused by an autosomal recessive mutation in the gene for the survival motor neuron-1 (SMN1) protein, which results in degeneration of motor neurons in the spinal cord, muscle weakness, and in most cases, premature death. Humans have a second SMN gene, called SMN2, which can partially compensate for the loss of SMN1. An increased number of SMN2 gene copies results in decreasing severity of the disease.

De Vivo described the three major types of SMA. Type 1 is the most common and the most severe, manifesting during infancy and preventing the baby from sitting independently. These babies usually die of respiratory failure before reaching their second birthday, although they may live longer with ventilatory support. Type 2 is an intermediate form of the disease. Although affected children achieve certain developmental milestones, they generally experience such profound weakness that they never gain the ability to walk independently and are at high risk for developing musculoskeletal and respiratory complications. About 70% of people with Type 2 SMA live 25 years after onset of symptoms. Type 3 SMA is a milder form, associated with nearly normal life expectancy. This form of the disease progresses slowly and is marked by intervals of stabilization, with many patients progressing to severe disability.

Neuropathological features of the three types of SMA also differ. Type 1 is associated with severe denervation and little evidence of collateral sprouting or reinnervation. Type 2 patients show some evidence of collateral sprouting and reinnervation. Type 3 patients show sig-

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nificant reinnervation but subtle impairments of neuromuscular transmission. In all three forms, the disease affects the entire motor unit, with disturbances in the cell body, axon, neuromuscular junction, and muscle fiber; thus all represent candidate therapeutic targets.

Because genetically increased amounts of SMN2 can mitigate the loss of SMN1, several therapeutic approaches have focused on either upregulating SMN2 gene expression, for example with histone deacetylase (HDAC) inhibitors, or otherwise modifying the amount of functional SMN2 available, for example by stabilizing the *SMN2* transcript. A third therapeutic approach being pursued is the use of neuroprotectants and neurotrophic factors. Several drugs are currently under study through cooperative groups such as the Pediatric Neuromuscular Clinical Research Network, American SMA Randomized Trials, Project Cure SMA, and at Stanford University; many more compounds are in the pipeline. However, reliable and validated outcome measures are needed in order to conduct these trials. Outcome measures being evaluated for use in these trials include measures of muscle mass, strength, and function; pulmonary function; motor unit integrity, SMN abundance (as a surrogate marker); and pediatric quality of life.

Dr. De Vivo predicted that rapid progress in SMA research seen over the last decade will culminate with an effective treatment by 2010. The role of SMN was defined, and clinical trials began, within ten years of when the genes for SMN1 and SMN2 were identified in 1995. And it was only 5 years earlier that the genes were localized to chromosome 5 and other types of the disease were shown to be allelic variants. With research continuing on multiple fronts to identify treatments and develop better ways of assessing effectiveness, the outlook appears extremely promising.

DRUG DISCOVERY FOR ORPHAN DISEASES

Katherine Klinger, Ph.D., senior vice president for genetics and genomics at Genzyme Corporation, provided her perspective on the obstacles to developing treatments for SMA and other rare diseases; and on how researchers, industry, and the advocacy community can work to overcome these obstacles. "Drug discovery and development is hard," she said. "Orphan drug development and discovery is even harder."

In any drug discovery effort, multiple iterative processes are required and each is associated with risks and attrition. Moreover, the process can be agonizingly slow; from the time a compound is identified in a drug screen as potentially interesting for the disease in question, at least three to four years of preclinical research are typically required to demonstrate whether the compound is worth pursuing in the clinic. Then another four to six years may be needed to conduct clinical trials. And de-

spite this painstaking process, most compounds still fail in the clinic, either for lack of efficacy, unacceptable toxicity, or for a variety of other reasons. Thus, there is a critical need for multiple development options, such as those being pursued by the SMA community.

Animal models are widely used in the preclinical drug discovery effort, but they also present challenges. Different species have different physiological and genetic characteristics. Rodents, for example, do not have gall bladders and metabolize drugs differently than do humans. There are also fundamental differences in the genetic organization of different species, often necessitating the development of complicated genetic models or multiple models that recapitulate various functional characteristics of the disease. In SMA, for example, several rodent models have been developed using varying genetic strategies; these are now being further validated and characterized by multiple SMA investigators.

Drugs for orphan diseases face additional hurdles, as there is often little information about the pathophysiology of the disease or appropriate targets. Moreover, the small number of affected people makes clinical trials even more difficult and may require different trial designs than those that would be used for more traditional drugs. For example there may be little known about the natural history of the disease or about the endpoints that indicate efficacy in a treatment trial, yet the choice of endpoint is critical as it will determine the number of patients required to achieve statistical significance. Surrogate markers may in some cases be used to help evaluate drug efficacy, but few have been validated for orphan diseases. Small populations introduce other factors as well that may impact trial design; for example, subjects may be geographically dispersed, necessitating a large number of trial sites. Thus, even while there is a push toward translational and clinical development, it remains imperative to support basic research to better understand the disease.

Orphan drug laws have partially mitigated these difficulties to some extent by providing incentives to drug makers, including tax breaks, extended exclusivity of patents, and an accelerated approval process for drugs against life-threatening diseases; but these laws do not, and should not, provide for a lesser degree of efficacy or safety.

Klinger concluded that because of the difficulty inherent in conducting preclinical and clinical studies for orphan drugs, it is imperative that investigators and advocacy organizations not wait until they have a drug in hand, but set up mechanisms and infrastructure in advance, so that when promising agents become available the structure is in place for beginning trials. As was in evidence from the presentations of other speakers at the symposium, the SMA community has heeded this call.

THE VIRTUAL MODEL: A NEW PARADIGM FOR TRANSLATIONAL DRUG DISCOVERY

Robert Pacifici, Ph.D., chief scientific officer for Cure HD Initiative (CHDI), Inc. and chair of the steering committee for the SMA Project, discussed the model his organization has been developing as a means to accelerate drug discovery for Huntington's disease (HD). The CHDI functions as a nonprofit virtual biotech company, said Pacifici: biotech because they are in the business of drug discovery, filling the gap between basic exploratory science and the medical, clinical, and regulatory aspects of drug development; virtual because they have no laboratories of their own but outsource all of the drug development work to contract research organizations and other biotechnology companies. The CHDI staff itself consists of individuals with a wealth of experience in the pharmaceutical industry across all of the necessary core competencies: business operations and strategies, information technology, medicinal chemistry, and quantitative biology. The idea is to set up a collaborative environment that leverages and focuses the experience of these individuals on finding a treatment for HD.

Although CHDI has an explicit focus on HD, Pacifici said that the model is equally applicable to SMA. These disorders, he said, are "ripe" for drug discovery for a variety of reasons. Both are progressive, fatal, and relatively rare, and no therapies are available for either. Both have a monogenic cause, although HD is autosomal dominant while SMA is autosomal recessive; and in both diseases genetic modifiers play important roles. In HD, genetic factors modify age of onset, while in SMA they modify severity. According to Pacifici, "genetics tells us that there is a way of modulating this disease in humans." Moreover, because they are monogenic diseases, genetic testing can predict who will get the disease and when. The monogenic nature of these diseases also may point the way to the discovery of biomarkers and to the development of cell-based assays, both of which will be of extreme benefit in downstream applications.

Some of the other commonalities between the two diseases relate to what is not known; i.e., the function of the normal protein, why some cells survive in the presence of the mutant protein, and whether the cells that die are the ones targeted by the mutant protein or are bystanders to the primary pathogenic insult. Animal models are available in both cases, although each has strengths and weaknesses. Until a drug is available that works in humans, it will be unclear which animal models are most useful, said Pacifici.

The CHDI has established a large and diverse drug portfolio that is modality agnostic, including compounds in different target classes and at different stages in the pipeline. Recognizing that discoveries that enable a cure may come from many sources,

CHDI has created a system that accepts candidate compounds from many sources, including companies, academia, and other organizations that are evaluating potential treatments for HD. For compounds that may require more time for a thorough evaluation, they also provide the resources to move them from an earlier to a later stage of drug development. They have established metrics to objectively validate different targets, and follow that with analysis by medicinal chemists. Each portfolio is guided through a flow scheme using a series of go/no go decision points to enable objective prioritization of the projects. Through this process, they have identified some 500 compounds that they are making broadly available, with known purity and concentration, to the HD research community. Data are fed back to a collaborating company called Innolyst, which is performing a meta-analysis of the trends observed by various researchers and will disseminate data to the research community.

The CHDI model is being applied in various degrees to the SMA challenge: the NINDS pilot project has similar structure and function, as do the research efforts coordinated by the SMA Foundation and other advocacy groups. Each has adopted an active and involved role in the planning and implementation of discovery and development efforts, with a coordinated focus on the end goal of developing an effective treatment as quickly as possible.

IDENTIFYING NEW THERAPIES THROUGH HIGH THROUGHPUT SCREENING IN MOTOR NEURONS

In any drug discovery effort, one of the key steps is developing a method to rapidly screen compounds *in vitro* in order to identify molecules that might be useful treatments for the disease in question. One of the most useful approaches used in screening for a disease such as SMA, in which a particular population of cells is susceptible to cell death (i.e., motor neurons), is to develop cell-based methods that use these particular cells. The problem is that motor neurons have been difficult to isolate and culture, said Lee L. Rubin, Ph.D., senior vice president for research and development and chief scientific officer at Curis, Inc. With support from the SMA Foundation, Curis has adapted, for large scale or high through-put use, a method for growing large numbers of motor neurons from mouse embryonic stem cells by treating the stem cells with a small molecule agonist of the hedgehog pathway and another compound called retinoic acid. The Hedgehog signaling pathway is responsible for motor neuron differentiation during normal development. Motor neuron cultures created using this technique can be used to screen compounds for their abil-

ity to increase levels of SMN. By using mouse embryonic stem cells from transgenic SMA mouse models that have low levels of SMN, the company can test for molecules that increase the amount of SMN protein in SMN-deficient motor neurons.

Interestingly, before the SMA mouse model was available the company had begun screening compounds using human fibroblast cultures from SMA patients. Although fibroblasts express lower levels of the SMN protein than do neurons, the screen was still useful in identifying several compounds capable of increasing SMN. One compound in particular appeared much more potent than drugs currently being tested in the clinic for SMA. Yet when these same compounds were later tested in the motor neuron cultures, none were capable of elevating SMN levels, suggesting that there are regulatory pathways in motor neurons that are not present in fibroblasts. This may mean that screening in motor neurons will turn out to be essential in the identification of effective drugs for SMA, said Rubin.

EXPLORING AND EXPLOITING THE PHARMACOPOEIA THROUGH DRUG REPURPOSING

While the search for newly discovered or synthesized compounds that are effective against SMA and other diseases continues at companies such as Curis, other organizations are looking at the existing pharmacopoeia, reasoning that drugs approved for other indications may also be effective against other diseases. The CHDI, in fact, encompasses both approaches. Another company, CombinatoRx, Inc., takes this approach of repurposing drugs one step further, searching for combinations of approved drugs that may have synergistic therapeutic effects arising from the targeting of multiple pathways. Curtis Keith, Ph.D., senior vice president of research and cofounder of CombinatoRx, said this approach allows novel therapeutic strategies to move more rapidly to human proof-of-concept trials, because safety, toxicity, and pharmacology profiles have already been established, and because manufacture of the drug has already been achieved.

CombinatoRx has developed a cell-based screening platform that tests millions of combinations of drugs in varying dose ratios to rapidly identify “hits.” The assays incorporate different disease models and biological disease networks in order to assess activity against a variety of targets. Using complex computational biology techniques, the system is able to identify novel synergistic and antagonistic effects of certain drug combinations, which may suggest not only which combinations should be further tested in animal models but also may identify new mechanistic pathways that are involved in the particular disease.

For example, Keith described a project from the company’s inflammation program. They wanted to find a steroid that retained anti-inflammatory properties but with reduced toxicity. Rather than tackling this problem by altering the chemistry, they used a systems biology approach and found that a low-dose steroid plus a non-steroid amplifier provided the properties they desired. Comparing this new formulation with prednisolone, they were able to demonstrate a similar anti-inflammatory effect without the safety and toxicity problems of prednisolone.

Strong relationships with disease foundations have been the key to the success of CombinatoRx, said Keith, and the company is currently building a neurodegenerative franchise, with the support of the SMA Foundation, CHDI, and the National Institutes of Health. The SMA program includes developing a primary high-throughput cell-based assay for total cellular SMN protein. This assay is agnostic to molecular targets, thus allowing identification of multitarget mechanisms. This primary screen has identified multiple novel single agents, which will be further tested in secondary assays and in primary combination screening. After consultation with SMA thought leaders, including those from the SMA Foundation, combinations identified through this process will be tested in *in vivo* models and pharmacokinetic profiles will be developed. In the meantime, the company is “planning for success” by developing plans for clinical trials and evaluating regulatory considerations in anticipation of filing a new drug application.

CONCLUSIONS AND FUTURE DIRECTIONS

The representation of industry, nonprofit, and academic partners at this satellite symposium reflected the vibrant and dynamic nature of the drug discovery process currently focused on SMA.

- Dr. De Vivo described how the genetics and neuropathology of the disease suggest potential therapeutic strategies that are already being pursued.
- Dr. Klinger described the challenges that small populations present for drug developers and the need to establish mechanisms for conducting trials in advance of drugs becoming available.
- Dr. Pacifici described how advocacy organizations are changing the face of drug discovery by creating new models with an explicit focus on a particular disease.
- Dr. Rubin presented information on progress in developing motor neuron cultures that are providing important clues about SMA and that may be useful in searching for treatments.

- Dr. Keith described a novel approach that screens combinations of existing drugs in search of synergistic activities that will be useful in treating diseases such as SMA.

Following on the heels of the American Society for Experimental NeuroTherapeutics Advocacy Forum, the speakers at this symposium highlighted the need for a broad and diverse approach to advance drug discovery, as well as the necessity of continued support from the

advocacy community, patients, and family members of people affected by SMA or other neurodegenerative diseases. With all stakeholders working together and sharing their discoveries and observations with the entire SMA community, the prospects for finding a treatment for SMA by 2010, as was suggested by Dr. De Vivo, appear promising. Moreover, the SMA model should provide inspiration, guidance, and relevant useful information to those working to find cures for other neurodegenerative diseases.