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Drug Development in Critical Times

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At the Advocacy Forum at the Eighth Annual Meeting of the American Society for Experimental NeuroTherapeutics (ASENT), "Drug Development in Critical Times: The Role of Patient Advocates," it became clear that patients and patient advocates, in addition to federal regulatory agencies, academic scientists, and the pharmaceutical industry, all play essential roles in drug development. Moreover, a strong yet flexible network among all of these stakeholders is emerging, which has the potential to propel drug development forward at a rapid pace, even for orphan diseases. This network is, of necessity, centered on patients, who provide not only motivation and the evidence of a clinical benefit if it is achieved, but are also key participants at all stages of the drug development pathway.

PATIENTS AND PATIENT ADVOCATES WORK WITH THE FDA

From the point of view of the Food and Drug Administration (FDA), patients and patient advocates have been missing for too long in the drug development process, said Russell Katz, M.D., Director of the Division of Neuropharmacological Drug Products at the FDA's Center for Drug Evaluation and Research. In response to activism from the HIV/AIDS community in the late '80s, two specific programs were established to address this deficiency. The first, called the patient representative program, provides for patient input at public advisory committee meetings; while the second, the patient consultant program, provides patient input to sponsors from the early stages of the drug development process, usually towards the end of phase 2 trials. Both programs recognize that patients and advocates have a unique, personal, and

sometimes more practical perspective on the decision-making process involved in drug development. In planning trials, for example, patients and advocates might offer ideas about changes that could reduce the burden on study subjects, thus encouraging more participation and retention in the study. They may also have a different perspective on the risk/benefit ratio, recognizing that some patients with life-threatening diseases are willing to endure significant risks even if the potential benefit is unclear. Said Perry Cohen, a patient representative with Parkinson's disease, "The risk of doing nothing is, for someone who has a serious or life-threatening illness, a big risk." Patient consultants are asked to provide the patient perspective on such issues as appropriate outcome measures with meaningful clinical benefits, compassionate use policies for experimental treatments, and recruitment-retention strategies for clinical trials.

Patient consultants have, to this point, only been involved in oncology studies, however the program has recently been expanded to include the anti-viral and neurology divisions, with three consultants identified to advise on Parkinson's disease studies. Initiation of the program has been slowed by the lengthy process required to clear consultants with regard to conflict of interest concerns. In the interim, one option being considered is the convening of groups that would provide advice on general issues not specific to any particular drug or illness. Several audience members representing advocacy groups enthusiastically supported this idea, noting that people with different neurologic diseases share many common concerns. Cohen, who served as an FDA patient representative on the Deep Brain Stimulation Advisory Panel, suggested that a generic panel could take up issues such as the Research Participants Bill of Rights, which would create a framework for developing trust among patients, sponsors, and clinical scientists as a means of expediting clinical research. Another issue of broad concern is how to communicate with patients if a trial is stopped. Rather

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than hearing about it on television, patients should be told by their physician or the sponsor if a trial is halted for any reason, as they will need specific information about how best to manage any change in their treatment. Moreover, maintaining open lines of communication with patients demonstrates respect for patients as partners in the development process.

PATIENT ADVOCACY GROUPS AND PHARMACEUTICAL COMPANIES

The second speaker at the Advocacy Forum was William Ju, M.D., Chief Operating Officer of PTC Therapeutics, Inc. PTC Therapeutics is a biopharmaceutical company that was formed in 1998 by Stuart Peltz and Allan Jacobson, focusing on small molecule drugs that regulate gene expression by targeting post-translational control mechanisms. The company's lead compound, PTC124, targets a particular type of genetic mutation called a nonsense mutation, which causes the protein-making machinery of the cell to prematurely stop building proteins. Such mutations result in the production of short, non-functional proteins in as many as 1800 genetic diseases, including about 13% of Duchenne Muscular Dystrophy (DMD) and 10% of Cystic Fibrosis (CF) cases. PTC124 allows cells to read through the premature stop signal, allowing it to continue to build full-length functional proteins. In animal models of DMD and CF, PTC124 was shown to partially restore protein production and improve function as well. The FDA granted PTC124 fast-track designation for the treatment of CF, and most recently (subsequent to this meeting, on March 30, 2006) for the treatment of DMD. The drug has also been granted orphan drug status in the United States and by the Committee for Orphan Medicinal Products of the European Medicines Agency. Designation as an orphan drug provides incentives to pharmaceutical companies developing drugs for low-incidence conditions. These incentives may include faster reviews, tax incentives, and prolonged exclusivity of patents.

Ju said that PTC Therapeutics began working with patient advocacy groups, including the National Organization for Rare Disorders (NORD), the Muscular Dystrophy Association (MDA), the Cystic Fibrosis Foundation (CFF), and Parent Project Muscular Dystrophy (PPMD) even as PTC124 was undergoing pre-clinical studies; and has continued to work with these groups as the drug has progressed through Phase 2 clinical studies. The company has also worked closely with governmental agencies such as the FDA Office of Orphan Products Development and the NIH Office of Rare Diseases, and with international patient groups and governmental agencies.

Since the early days of drug development, these organizations have provided validation and encouragement to

the company, access to experts in the field and investigator networks, financial support, and a means to gather input from and communicate with patients on a variety of issues. Communication with patients and advocacy groups is particularly important with regard to obtaining advice about drug development issues, such as formulations that would be acceptable to patients; developing patient awareness about upcoming clinical trials; learning how best to communicate with patients and families, including understanding their expectations; and communicating with patients and advocates about the constraints and pressures the company faces with respect to release of data and meeting the demands of shareholders. Contact with patients and families also provides tremendous inspiration to company employees, added Ju.

In response to a question from the audience, Ju said that advocacy organizations representing other rare diseases are welcome to contact PTC Therapeutics at any time. The company believes that PTC124 could work in a broad range of genetic disorders in which a nonsense mutation is the cause of the disease, and would be interested in validating this hypothesis in cells that might be provided through advocacy organizations.

THE LARGE PHARMA PERSPECTIVE

Lest anyone think that only small pharmaceutical companies are motivated to develop drugs for rare diseases, Reijo Salonen, M.D., Ph.D., Worldwide Therapeutic Head in Neurosciences at Pfizer provided the large pharma perspective. Large pharmaceutical companies have played a key role in the development of orphan drugs, said Salonen, particularly in the areas of cancer therapeutics, monoclonal antibodies, enzyme and enzyme inhibitors, and receptor and ion channel modulators. Their attention to therapies for rare diseases often arises as a result of the identification of disease targets relevant to both common and rare diseases. For example, the search for treatments for Alzheimer's disease, a relatively common disorder, is proceeding primarily along three different paths: mitochondrial dysregulation and oxidative stress, protein misfolding, and immune system dysfunction. All of these pathways are likely to be important for less common neurologic diseases as well, and each suggests numerous strategies for intervention.

"I'm not saying that if you target one disease, you'll immediately find a target and a compound that works across all diseases that have that characteristic, but you gain so much information about the overall process that, in the worst case, you gain a lot more knowledge of different pathways that can help develop drugs for orphan indications," said Salonen. Research on common diseases sheds light on orphan diseases and vice versa, he added.

The process of developing a molecule into a drug is

similar for orphan diseases as for common diseases, including the need to demonstrate a clinical effect and establish dosing and safety parameters. But there are additional difficulties with orphan drugs related to the smaller number of potential subjects for clinical trials and the lack of clearly established endpoints. For large pharmaceutical companies, treatments for rare diseases may not fit strategically into the company's product profile and the commercial potential may be low. As a result, large pharmaceutical companies are using a variety of creative approaches to facilitate orphan drug development, including line extension, out-licensing of compounds, and global filing of regulatory documents. As an example of line extension, Salonen pointed to Revatio (sildenafil), a drug used to treat the rare condition pulmonary arterial hypertension (PAH). Originally marketed as the multi-billion dollar erectile-dysfunction drug Viagra, this phosphodiesterase 5 inhibitor was subsequently shown to improve exercise capacity and hemodynamics in people with PAH, and has been approved in both the United States and Europe for this indication. A different strategy was used by Novartis in the development of Gleevec, a new generation anti-cancer agent used to treat chronic myeloid leukemia (CML). Designation as an orphan drug and worldwide filing of new drug applications provided Novartis with the incentives they needed to develop the drug, which has since been approved for the treatment of several other rare forms of cancer.

Large pharmaceutical companies have also spurred the development of orphan drugs by forming collaborations with smaller companies as well as with non-profit foundations and other organizations. Robert Pacifici, chief scientific officer for Cure HD Initiative (CHDI), Inc., a non-profit biotech company dedicated to finding treatments for Huntington's disease, said he was encouraged to see a company as large as Pfizer thinking about developing compounds for orphan indications, and asked how organizations such as CHDI can access the resources of large pharmaceutical companies in order to enable development of some of large pharma's discoveries. "We're going to do absolutely everything we can from our end to lower your barrier of entry into these different fields," said Pacifici. This might include, for example, providing accessibility to animal models that could provide validating data. Another way that some of the non-profit organizations can speed drug development is by relinquishing intellectual property rights, said Pacifici. "There's really no risk from our standpoint of doing that."

Salonen said that Pfizer is currently developing mechanisms to accomplish some of the goals that Pacifici mentioned. "The best I can do right now is to say it's under very vigorous discussion currently," he said.

VENTURE PHILANTHROPY: AN OPTION FOR DRUG DEVELOPMENT

The Cystic Fibrosis (CF) Foundation has taken the concept of venture philanthropy to new heights, according to Robert Beall, Ph.D., president and CEO of the Foundation. Using an aggressive business model, the Foundation established a Therapeutics Development Program (TDP) to provide financial, intellectual, and physical resources to the quest for finding treatments for CF. Expanding on the idea of risk reduction mentioned by Robert Pacifici, Beale said that one of the goals of the program is to minimize the risk for industry partners, while providing those partners with some of the resources that advocacy groups are better positioned to develop, for example, networks of volunteers for clinical studies. "They have stockholders, we have stakeholders," he said.

For a disease such as CF that affects only about 30,000 people in the United States, access to patients is a limiting factor in clinical studies, yet the CF Therapeutics Pipeline is stocked with two dozen compounds in different stages of development. According to Beall, 98% of these drugs would not be in the pipeline without the investment of the CF Foundation. Moreover, they have a goal of doubling the number of agents in the pipeline. In order to support this aggressive drug development program, the TDP established a therapeutics development network to do early stage (Phase 1 and 2) clinical trials. The network functions as a contract research organization and supports 18 clinical sites, a data coordinating center, an external advisory committee, and a data safety monitoring board, along with some specialized centers that investigate particular aspects of CF pathology. Over the past seven years, this network has completed 36 clinical trials, said Beall.

The TDP also supports, through funding of both large and small partners, a very aggressive discovery program that conducts basic research, high throughput screening, and studies of functional and structural genomics and proteomics. Grants for these studies typically range in the \$1.5 million range, but after receiving the CF Foundation's "seal of approval," investigators often find themselves well positioned to seek additional funding. Finally, the organization funds Therapeutic Development Awards, a peer-review, milestone-driven mechanism that enables researchers to pursue evaluations of promising therapies for CF patients.

The business model that the Foundation established has been well received by both the CF community and the pharmaceutical industry, said Beall, generating funding for these programs from a variety of sources, including special events run by the CF Foundation, major gifts from donors, and royalty fees from some of the products that have been developed.

SCIENTISTS AS ADVOCACY GROUP PARTNERS

The final presentation of the Advocacy Forum was delivered by Michael Zigmond, Ph.D., professor of neurology and psychiatry at the University of Pittsburgh. Zigmond, who studies neuroprotection in cellular and animal models of Parkinson's disease (PD), said he was convinced of the importance of scientists working with patients and advocates through his experiences with Michael J. Fox, Nancy Wexler, Robin Elliott, and others. A key event in promoting such involvement by Zigmond and his colleagues occurred some 12 years ago when a patient with PD showed up in Zigmond's lab and said he wanted to do something to help. Zigmond invited the man, Jim Cordy, to participate in lab meetings, where he could add the perspective of "how will this research help me?" Cordy has been an important educational and inspirational source for the members of the lab, said Zigmond, and he also played a key role in establishing the Morris K. Udall Centers of Excellence in PD at the NIH.

Scientists have a social responsibility to participate in advocacy efforts to build public support for and promote the understanding of scientific research, said Zigmond. The biggest barrier to research in 2006 is insufficient funding, with NIH paylines falling to new lows and likely to get worse in the future. The public needs to understand the importance of research as well as the process involved in conducting basic research and advancing discoveries to the bedside. One of the barriers to promoting understanding is the lack of a common lan-

guage shared by scientists and the lay public. Scientists need to find a balance between simplicity and accuracy in their choice of words, for example by using the words "brain cells" rather than "neurons," or "visual centers" rather than "visual cortex." Scientists also need to find words that will accurately convey the level of certainty, balancing the desire to convey hope with an honest assessment of the likelihood that a scientific discovery will yield significant benefits. In communicating with the public through the mass media, Zigmond acknowledged that scientists may not be able to control the message that is conveyed. Many scientists shy away from reporters after having been misquoted or having their quotes used out of context. Nonetheless, newspapers, magazines, and other forms of mass media can be effective in reaching the public.

In the context of the difficult funding environment, scientists also need to educate and inspire young people to pursue science careers. At the 2006 World Conference on Brain Research in Steamboat Springs, Colorado, for example, scientists left the confines of the convention center to visit local elementary, middle, and high schools, giving presentations about their research and clinical work. Zigmond also says he requires trainees in his graduate programs to participate in at least one outreach program per year. Most of his students find this to be "an invigorating experience," he said. Medical students should also be getting involved with clinical studies early during their training, and, on the flip side, basic scientists need exposure to clinical studies.