THINK TANK EXECUTIVE SUMMARY: Dystonia Models and the Search for New Drug Therapies

“We want to establish standardization and then set the framework that these are the tests to use. This will give us new tools and new pathways for drug discovery for dystonia.”
Researchers are still trying to untangle the specific triggers that lead to the involuntary muscle movements and postures that characterize dystonia. While some patients have a family history of the disease, others acquire it after an injury, trauma or side effect of medication, and still others develop it without having clear risk factors. Since dystonia is actually a collection of syndromes, developing a single treatment has been a challenge. Animal models can open a window into the biochemical, anatomical, and physiological changes that occur in dystonia, and can also be useful in preclinical drug testing.

“Dystonia is a very, very heterogenic disorder,” said Dr. H.A. Jinnah, who added that about 75% of cases are idiopathic, meaning they have no known cause. Yet he noted that it would be useful to look for shared mechanisms and common pathways that span the different forms of dystonia, in the hopes of developing treatments that work for most patients. He cited Botox (botulinum type A) and deep brain stimulation (DBS) as examples of therapies that are effective across a broad number of dystonias. Still, he and other researchers acknowledged that several different compounds might ultimately be necessary to treat the range of dystonic conditions.

Animal models provide data insight

Several researchers presented data on animal models that mimic dystonia, and explained how they’re being used to identify therapeutic targets. Dr. Angelika Richter presented data on dtsz-mutant hamsters, which developed paroxysmal (or sudden, recurring attacks of) dystonia. Like their human counterparts, the mutant hamsters developed episodes of abnormal twisting and posturing, and were initiated by factors such as stress, excitement, or caffeine. The hamsters had abnormal electromyography (or EMG) results, but unaltered consciousness, and responded to diazepam (Valium) but not to anti-seizure drugs. The severity of symptoms was also age-dependent, reaching their peak severity around 30 to 40 days of life, and then declining to almost complete remission by 10 weeks.

Dr. Richter and her team then tested different drug compounds to see which would have an effect. They found that GABA-potentiat- ing agents, D1/D2 receptor blockers, and openers of the KCNQ2-5 potassium channel produced the best results, while NA+ channel blockers, as well as drugs that increase dopaminergic activity and reduce GABAergic inhibition exacerbated the disorder. These findings were confirmed when they examined which regions of the hamsters’ brains were most affected. Since abnormal striatal activity “seems to play a critical role,” Dr. Richter said, drugs targeting structures that regulate the firing rate and pattern of striatal neurons could be logical choices for further study in humans.

Dr. Ellen Hess presented research on mice with CACNA1A mutations. In the “tottering” mouse model, these mutations produced an unstable gait and paroxysmal dystonia with episodes lasting 30 minutes. These mice also had abnormal calcium signaling, which introduced an avenue for Dr. Hess and her team to explore different drug treatments. They found, that L-type calcium channel blockers such as nimodipine, nifedipine, and particularly nifedipine were very effective in treating dystonia; conversely, L-type calcium channel agonists induced dystonia in the mutant mice model. Based on this research, nifedipine is now in clinical trials for dystonia, Dr. Hess noted. “We need to prioritize which drugs would be most effective,” she said. “We have to have some agreement on which mechanisms we want to test.”

Small markets, major needs

Dr. Karen Wilcox noted that the epilepsy community in the 1970s faced many of the same challenges as the dystonia community. About 25-40% of patients were considered unresponsive to existing treatments, and the pharmaceutical industry had little interest in developing drugs for a relatively small market. Yet patient advocates were able to successfully lobby Congress for funding, leading to an agreement between the National Institutes of Health and the University of Utah in 1974. Through the Anticonvulsant Drug Development program (ADD), industry and academic researchers contribute about 800 to 1,000 compounds each year to the University to perform in vivo and in vitro efficacy and toxicity tests. The results can help sponsors decide whether to further test a drug in humans.

Dr. Wilcox noted that about 1.8% of compounds make it through the full work-up, and the initiative has led to the successful development of 10 new antiepileptic drugs that are staples of treatment today. These newer agents are safer and more effective than past treatments, she noted.

The ADD program has been ideal for medical chemists and small biotechnology start-ups that can’t afford to run their own preclinical tests, according to Dr. Wilcox. Yet challenges remain in con-
vincing pharmaceutical companies to commercialize drugs that treat a relatively rare, heterogeneous disorder. The epilepsy community was able to convince drug makers that antiepileptics might be useful in a range of large-market conditions, including migraine, neuropathic pain, and mood disorders. Similarly, the dystonia market might be larger than it appears, sharing pathways, for example, with other movement disorders such as Parkinson’s disease.

**Testing hypotheses**

Dr. Warren Stern of QRxPharma noted that new chemical entities have a higher failure rate and take longer to bring to market than drugs that have already been approved by the Food and Drug Administration. Yet even if researchers focus their efforts solely on the latter, there are still thousands of potential candidates to test for dystonia. “It’s really essential that there be some sort of animal model that shows that a new or repurposed drug works in that way,” Dr. Stern said. In dystonia, for instance, researchers believe that the misfolding of protein torsinA is a possible cause of the disorder. Confirmatory tests can then be conducted on animal models that exhibit torsinA misfolding to see if blocking or reversing it has therapeutic potential. Compounds that exhibit the most potential will then undergo further testing in humans to determine which patients might benefit, the optimal dosing regimens and duration, and whether there are any toxicity concerns.

While animal models can help define the underlying disease pathology, “window” of treatment opportunity, and potential drug targets, researchers note that they’re only as effective as their ability to parallel the human condition. Dr. Olaf Riess stressed that animal models can only achieve an approximation of the disease state. “All of the models are poorly described; there’s a lot of work to do,” he said. “It’s difficult to overlay the different phenotypes and say, that’s the one we should go with. None of them have dystonia that we are looking for in the human.” Dr. Riess noted that there is currently no standard governing which behavioral studies should be used to test these “dystonic” animals, and added that these models are susceptible to environmental and stress factors that can impact results. He and his research team are now using “intellicages” in an attempt to standardize environmental conditions across labs, so that study results can be replicated.

**Moving forward**

Progress has been made on a number of fronts. Dr. Henry Paulson noted, for instance, that there has been significant interest from pharmaceutical companies in siRNA (or short interfering RNA), a technology used to block the expression of a mutant gene. Dystonia is a prime target for this approach because the disease has a clear genetic link, with a defined window of susceptibility (meaning that it can be prevented) and without neuronal loss (meaning that its effects can be reversed). When dystonia is linked to a mutation in the DYT-1 gene, siRNA can be used to block the production of the “toxic” protein that causes the disease. While the technology seems to be effective, the biggest question is how to deliver it to the brain, Dr. Paulson noted. Long-term safety questions about the current approach remain, including the possibility of triggering an inflammatory immune response, disrupting endogenous microRNA pathways, or causing other off-target effects. Researchers are unsure why mice injected with the shRNA-expressing virus had a higher death rate than a control group. Still, drug and medical device companies are also exploring other delivery mechanisms – such as transporting siRNA through venous stents.

A drug’s success in animal models can sometimes predict its success in clinical trials – but not always. Dr. Stern cautioned that there have been a number of examples, particularly in neurology, where drugs that appeared to be neuroprotective in animal models failed “uniformly” in late-stage clinical trials.

**Ideas into action**

Each day Think Tank attendees shared ideas on how to speed drug development in an area that has been traditionally overlooked by large pharmaceutical companies. Suggestions ranged from testing drugs that are already FDA-approved for other indications, tapping into government funding sources, and using the clout of patient advocacy groups to lobby for more federal support. Small biotechnology companies can also play a role in the early drug discovery process – and then license promising compounds to a larger company, most likely one already in the neurology space. These efforts and others will pave the way toward bringing compounds to market with novel mechanisms of action that can treat the spectrum of dystonia-related conditions.

The Foundation’s Think Tank has consistently been fertile ground for spirited discussion and debate and for generating new ideas. The challenge is to take the best concerns, the best ideas emanating from this knowledgeable group and turn them into action. Accordingly, in November 2007, the Bachmann-Strauss Board of Directors reviewed and approved a new initiative that grew out of the scientists’ discussion on animal models and drug development.

With a goal of accelerating the pace of drug therapies for dystonia, the Foundation has allocated funding for an Antidystonia Drug Development Program. This will establish a model system to study genetic and non-genetic models of dystonia and identify drugs that can either move directly into clinical trial or be put forward for product development by a bio-technology or pharmaceutical company. The Foundation will have oversight of the direction of the Program, which will have tight criteria and call for achievement of benchmarks within a relatively short timeframe.

Dr. Ted Dawson, chairman of the Bachmann-Strauss Scientific Advisory Board said, “Right now, there are no agreed upon behavioral assessments for dystonia. We want to establish standardization and then set the framework that these are the tests to use. This will give us new tools and new pathways for drug discovery for dystonia.”
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