Broad Collaborations Bring New Energy to Autism Therapeutics

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Locked inside the brain of a child with autism spectrum disorder is a person who cannot tell his mother when he has a sore throat, or a stomachache, or why some days he needs a pile of toy train engines just to feel safe. Put those same children in a clinical trial in which the outcome measure follows changes in behavior and it's easy to see why developing a treatment for autism spectrum disorder (ASD) has proven so thorny.

For starters, scientists still do not have a clear idea of the genetic pathways that lead to ASD. The impact of autism's core symptoms—repetitive behavior, social impairment, and communication difficulties—can vary widely. Even though these symptoms all describe behavior, ASD affects the whole body. As with other developmental disorders, people with ASD can suffer from gastrointestinal problems, seizure disorders or immune deficiencies. When that heterogeneity is multiplied by 1.5 million within the United States, it is no wonder the medical community needs three words —autism spectrum disorder—just to describe the condition.

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Most of the work in autism therapeutics has been geared toward intervention. In 2009, the U.S. Food and Drug Administration approved Bristol-Meyers Squibb's ABILIFY (aripiprazole) for treatment of irritability and aggression in autism. Risperidone, originally manufactured by Janssen L.P., now available as a generic, is used for the same reason. These drugs help with outbursts and tantrums, but do not address the core symptoms of autism and ASD.

Some compounds to treat ASD's core symptoms have made it to clinical trials. A few years ago, the now-defunct Neuropharm LTD teamed up with the advocacy organization Autism Speaks for a clinical trial to test a low dose of PROZAC (fluoxetine) aimed at repetitive behaviors. Unfortunately, the trial found no differences between treatment and placebo.

The PROZAC trial may have failed, but it remains significant because it was the first autism treatment given the FDA Fast Track designation, a process designed to test potential therapeutics that address an unmet need. Clara Lajonchere, vice president of clinical programs for Autism Speaks, says the failed trial laid the groundwork for other companies to seek Fast Track approval for ASD.

Because ASD is so heterogeneous, children with ASD show a wide variety of symptoms and their response to treatment is so variable, making it hard to say definitively whether a drug "works" or not. "It's possible that one family's version of autism may be treatable in a way that no one else's is," says John Constantino, M.D., a professor of pediatric psychiatry at Washington University in St. Louis, Missouri.

Complex Disease, Difficult Issues

The difference among different autism spectrum disorders lies in the severity of symptoms. So many genetic pathways have been implicated in autism spectrum disorders that Bryan King, M.D., a professor of psychiatry at the University of Washington, Seattle, comments that many clinicians and investigators now refer to the condition as "autisms" because it is hard to pin down a single target for a single drug treatment that can address such diverse biochemical pathways. Still, says King, "there is reason to believe we may find a compound that does improve repetitive behaviors in autism or does improve some measure of social interaction. As genetic pathways are found to converge, the target list for innovative treatments will become more focused."

Interest from pharma has grown in the past few years. Two companies have begun clinical trials on drugs that aim for core symptoms, using vastly different approaches.

One is the Rye, New York, based Curemark, which has an enzyme replacement therapy ready to start a randomized double blind, placebo-controlled Phase III clinical trial. Curemark founder and CEO Joan Fallon, D.C., first came in contact with ASD in her chiropractic practice in the early 1990s, when parents brought in children with developmental problems.

Fallon says many parents remarked that their children with developmental disabilities favored carbohydrates over protein. She analyzed the children's blood and urine and found that they lacked the digestive enzyme chymotrypsin, which splits peptide amide bonds, thus digesting a protein. With private funding, she and colleagues came up with a way to orally deliver high levels of chymotrypsin. The company is nearly ready to recruit patients for its Phase III trial. Once the clinical trial ends, Fallon says she and her colleagues will analyze the data and then seek a partnership with a large, specialty pharmaceutical company. "Hopefully this might help some children and it will give new light to the physiology of autism and perhaps it will spur other research," says Fallon.

King is cautious about Curemark's prospects. One of the basic principles guiding medical research is that association does not mean causation. So the observation that children with autism or ASD lack chymotrypsin may be unrelated to what causes the disease. "It's not always the case that what we think we're doing for intervention is actually

responsible for the final outcome,'' says King, whose institution is not part of Curemark's clinical trials. On the flip side, King says, ''Curemark's approach is certainly different from many others, but they are doing studies; others have simply asserted that their treatment works.''

The "X" Files

The second therapy starting Phase II clinical trials for ASD came from studies done on Fragile X Syndrome, a developmental disorder caused by a mutation in a single gene, which can also cause autism. People with this condition cannot make fragile X mental retardation protein (FMRP), a protein that is critical for brain development and for establishing synaptic connections. FMRP exerts some of the function by regulating a metabotropic glutamate receptor (mGluR) and, indirectly, mGluR-dependent protein synthesis. Mark Bear, Ph.D., an HHMI researcher at MIT, mapped Fragile X pathways in a genetically engineered Fragile X mouse. In 2005, Bear and Randall Carpenter, M.D., initially founded Seaside Therapeutics through private funding, and then later, through NIH grants and patient advocacy organizations, including Autism Speaks.

Seaside Therapeutics licensed a compound from Merck that normalizes activity in this critical signaling pathway and began clinical trials to treat Fragile X. Today the company is testing two candidates for Fragile X, autism, and ASD.

Carpenter says the company is working to understand the molecular pathophysiology behind these developmental disorders and then trying to normalize those pathways through targeted treatments. These pathways link areas of the brain that control synaptic plasticity for learning. As the brain develops, connections between synapses strengthen when responding to important information and weaken in response to noise. This delicate balance in the signal-to-noise ratio appears to be dysregulated in Fragile X and autism spectrum disorders.

The theory is that we all learn from experience, but people with developmental disorders do not learn from experience at the same rate or level. Consequently, children with Fragile X or those along the autism spectrum may have delays in reaching developmental milestones such as sitting up, walking, or talking, or may never reach certain milestones such as social awareness, or master such skills as higher math or reading. Carpenter says targeted therapeutics can potentially restore the balance between signal and noise, thereby retuning the brain and improving learning. The compounds that Seaside Therapeutics has in clinical trials have so far shown improvement in behavior. With more long-term treatment (at least longer than the two or three months for a clinical trial), Carpenter hopes function will improve.

"You're not going to raise IQ in a four-week trial," says Carpenter. "Our goal is not to turn everyone into Einstein, but to allow people to be functional contributing members of society who can live independently."

It Takes a Really Big Village

Such efforts do not happen in isolation. Until relatively recently, academic researchers studied autism through the confines of their respective specialties. Ultimately, universities began organizing autism researchers into communities of scientists from wide ranging disciplines. The NIH funds collaborative research through their Autism Centers of Excellence program. Early on, according to Carpenter, Seaside Therapeutics carefully laid the groundwork for a diverse group of collaborators.

Marguerite Colston, spokesperson for the Autism Society, a U.S. grassroots autism organization, and the parent of a son with autism, sees value in collecting anecdotes from parents. Colston keeps a daily log of what her son eats, his toileting schedule, and what he did in school. Many parents, she says, can offer an untapped resource of useful observations. "We want to build a database of anecdotal data, which can be de-identified,'' says Colston. The Autsim Society would then use that database to get more funding for research into treatment.

Recently, Autism Speaks launched two collaborative efforts, says Lajonchere. In late 2010, the organization teamed with Sigma Life Sciences to create a number of knockout rat models that simulate various symptoms and pathologies of autism. In January 2011, Autism Speaks launched their Translational Medicine Initiative, bringing together a wide representation of experts from academia, pharma, industry partners, and the federal government.

Lajonchere says that one goal of this initiative is to develop strategies for novel clinical trial design that includes the identification and development of additional outcome measures that are more sensitive to change. The initiative also hopes to develop long-term close collaboration with researchers in the preclinical area and encourage dialog with the clinicians and researchers on the other end of the pipeline. Several pharmaceutical companies have demonstrated a willingness to share compounds for potential new therapies once researchers are able to identify viable targets.

"Collaboration and open dialogue are keys in translational medicine. Bringing together the entire research community will provide the best way forward,'' says Lajonchere.

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