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# New clinical study evaluates first drug to show improvement in subtype of autism

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In an important test of one of the first drugs to target core symptoms of autism, researchers at Mount Sinai School of Medicine are undertaking a pilot clinical trial to evaluate insulin-like growth factor (IGF-1) in children who have SHANK3 deficiency (also known as 22q13 Deletion Syndrome or Phelan-McDermid Syndrome), a known cause of autism spectrum disorder (ASD).

This study builds on findings announced by the researchers in 2010, which showed that after two weeks of treatment with IGF-1 in a mouse model, deficits in nerve cell communication were reversed and deficiencies in adaptation of nerve cells to stimulation, a key part of learning and memory, were restored.

"This clinical trial is part of a paradigm shift to develop medications specifically to treat the core symptoms of autism, as opposed to medications that were developed for other purposes but were found to be beneficial for autism patients as well," said Joseph Buxbaum, PhD, Director of the Seaver Autism Center at Mount Sinai. "Our study will evaluate the impact of IGF-1 vs. placebo on autism-specific impairments in socialization and associated symptoms of language and motor disability."

The seven-month study, which begins this month, will be conducted under the leadership of the Seaver Autism Center Clinical Director Alex Kolevzon, MD, and will utilize a double-blind, placebo-controlled crossover design in children ages 5 to 17 years old with SHANK3

deletions or mutations. Patients will receive three months of treatment with active medication or placebo, separated by a four-week washout period. Future trials are planned to explore the utility of IGF-1 in ASD without SHANK3 deficiency.

The primary aim of the study is to target core features of ASD, including social withdrawal and language impairment, which will be measured using both behavioral and objective assessments. If preliminary results are promising, the goal is to expand the studies into larger, multi-centered efforts to include as many children as possible affected by this disorder.

IGF-1 is a US Food and Drug Administration-approved, commercially available compound that is known to promote neuronal cell survival as well as synaptic maturation and plasticity. Side effects of IGF-1 administration include low blood sugar, liver function abnormalities, and increased cholesterol and triglyceride levels. Study subjects will undergo rigorous safety screening before they are enrolled in the trial, and will be carefully monitored every two to four weeks with safety and efficacy assessments.

"We are excited that the researchers at the Seaver Autism Center are undertaking this pilot study to evaluate a possible treatment for SHANK3 deficiency, which may also help everyone with ASD," said Geraldine Bliss, Research Support Chair of the Phelan-McDermid Foundation. "This will be the first clinical trial in Phelan-McDermid Syndrome to emerge from convincing preclinical evidence in a model system."

The cause of autism has been debated for many years. Currently the best scientific evidence indicates that genetic mutations are the most likely culprits, acting either directly or indirectly, in upwards of 80 to 90 percent of individuals with ASDs. In the past few years, gene mutations

and gene copy number variations have been identified that cause approximately 15 percent of cases of ASD. However, it is thought that hundreds of genes may be involved in causing autism.

One copy of the q13 portion of chromosome 22 is either missing or otherwise mutated in SHANK3 deficiency, also known as Phelan-McDermid Syndrome or 22q13 Deletion Syndrome (22q13DS). The area in question contains the gene SHANK3, and there is overwhelming evidence that it is the loss of one copy of SHANK3 that produces the neurological and behavioral aspects of the syndrome. The SHANK3 gene is key to the development of the human nervous system, and loss of SHANK3 can impair the ability of neurons to communicate with one another.

Provided by The Mount Sinai Hospital