Autism Speaks and SAGE Labs develop rat models for translational autism research

August 2 2012

Autism Speaks, the world's leading autism science and advocacy organization, today announced its expanded collaboration with Sigma Advanced Genetic Engineering (SAGE) Labs, an initiative of Sigma Life, to develop the first rat models with modified autism associated genes, intended to accelerate discovery and translational autism research.

Expansion of the collaboration follows initial behavioral studies demonstrating that the first two publicly available gene knockout rats, part of the seven rats generated through the collaboration to date, exhibit hallmark characteristics of autism, such as social deficits and repetitive behaviors. Many behavioral characteristics of autism observed in these rats are not seen in other animal models currently used for autism research. SAGE Labs and Autism Speaks now plan to generate additional genetically modified rat models of key autism-associated genes, including CNTNAP2 and MET.

"Autism spectrum disorders are a complex condition with significant unmet medical needs. Although uniquely human, fundamental aspects of the biology underlying autism can be effectively modeled in animals to advance our understanding of cause and enable translation of basic scientific discovery into medical breakthroughs that improve the quality of life for individuals on the spectrum," says Robert Ring, Ph.D., Vice President of Translational Research at Autism Speaks. "These new autism-relevant rat models have already demonstrated great potential for the field. Our new agreement ensures that additional models will continue to be developed and made available to accelerate progress along

the entire translational research continuum, from academia to the pharmaceutical industry."

"Modeling human conditions in rats, rather than the mice that have come to predominate preclinical studies, enables more predictive studies of complex neurobehavioral conditions. Rats are unique in that they exhibit richer, more human-like social behaviors than mice, juvenile play being one example. The more complex neural circuitry and greater cognitive capacity in rats also enables researchers to complete many of the demanding—and crucially informative—cognitive tests that mice cannot perform. In addition, on a practical level, performing initial studies in rats also provides a direct path for drug development," says Edward Weinstein, Ph.D., Director of SAGE Labs.

Initial behavioral studies of the gene knockout rats generated by SAGE Labs are being conducted by Richard E. Paylor, Ph.D., Professor at the Baylor College of Medicine. In some cases, behaviors observed in the rat models have differed from existing mouse models. For example, whereas FMR1 knockout mice exhibit elevated social interactions, rats lacking the same gene participate much less in social play and emit fewer ultrasonic squeaks during play sessions than control rats. These types of social impairments, such as reduced verbal and interactive play, more closely parallel social behavior symptoms seen in humans with FMR1 mutations. Rat models lacking functional NLGN3 and FMR1 genes also display other unexpected characteristics, including compulsive chewing on water bottles and wood blocks. Compulsive and repetitive behaviors are core symptoms in individuals with autism spectrum disorders.

"At SAGE Labs we use CompoZr Zinc Finger Nuclease technology to perform targeted genetic modifications in species previously not amenable to such modifications — be it gene knockout, transgene insertion, point mutations, or conditional gene knockout. We can help

researchers and pharmaceutical companies access rats, rabbits and other species that best model a medical condition of interest and provide a direct path for preclinical efficacy and toxicology testing," says Weinstein.

Currently SAGE Labs publicly provides two rat lines with knockouts of autism-associated FMR1 and NLGN3 genes. The remaining five gene knockout rat lines developed in the original collaboration—for the genes MECP2, NRXN1, CACNA1C, PTEN, and MGLUR5—are expected to be released soon. The CNTNAP2 and MET knockout rat lines to be generated in the expanded collaboration are expected to be available in 2013.

Provided by Autism Speaks