

Total knockout of Parkinson's

*Michael J. Fox Foundation,
Sigma-Aldrich researchers count
on knockout rats to deliver a KO
punch to Parkinson's disease*

BY LORI LESKO

ST. LOUIS—The Michael J. Fox Foundation (MJFF) is counting on Sigma-Aldrich researchers to create genetically engineered knockout rats to gain a better understanding of the genetic causes of Parkinson's disease, discover new therapies and ultimately deliver a knockout punch to the neurodegenerative disorder of unknown cause affecting nearly 6 million people across the globe.

MJFF, dedicated to finding a cure for Parkinson's through an aggressively funded research agenda, has awarded a one-year, \$232,000 grant to the Sigma Advanced Genetic Engineering (SAGE) Labs, an initiative of Sigma-Aldrich's Research Biotech business unit. The amount of the grant was not disclosed. However, the funding is expected to enable SAGE researchers to use their novel CompoZr zinc finger nuclease (ZFN) technology in an effort to create superior preclinical research models critically needed for the development of transformative treatments for Parkinson's disease.

Dr. Edward Weinstein, director of Sigma-Aldrich's SAGE Labs, commented on MJFF's "terrific reputation among the research community for supporting activities to help advance efforts to tackle Parkinson's disease."

"As soon as we knew that we could develop knockout rat models for medical research, we realized the potential to make a significant impact on research into the treatment and prevention of Parkinson's disease models—and we began working on a partnership with the

MJFF ... and realized our goals were aligned," Weinstein says. "Both SAGE Labs and the MJFF have an interest in making the most relevant disease models widely available to the research community, in both academia and industry." SAGE researchers consulted with the MJFF scientific advisors, who make up of some of the most prominent members of the Parkinson's research community, Weinstein says.

"They helped us identify those genes that would be most important to modulate in order to create a true Parkinson's model using knockout rats," he says. "Mice have been attractive models since researchers have had the ability to precisely manipulate their genomes for the past 25 years, but the mouse models of Parkinson's disease fail to demonstrate the clinical symptoms associated with the human condition. We hope that the knockout rats will be more faithful and useful models ... to help get one step closer to the next generation of Parkinson's disease treatments."

Until recently, it has been impossible to create rat models with particular genes deactivated, or knocked out.

Though current mammalian models adequately recapitulate some outward symptoms of Parkinson's disease, no existing model has been able to accurately mimic the onset and progression of the underlying disease processes that characterize that disease in humans, Weinstein says. Research already conducted into the genetic causes of Parkinson's disease has identified a number of genes, but indicates a strong connection to mutations in five particular genes: LRRK2, alpha-synuclein, DJ-1, Parkin and PINK1.

Adopting a new approach to developing more effective and targeted research models, SAGE Labs will use the CompoZr ZFN technology in its efforts to design knockout rat models in

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which the genes known to be directly implicated in Parkinson's disease are omitted. By injecting CompoZr ZFNs into a one-cell stage rodent embryo, the NHEJ process can be harnessed to generate precisely targeted genomic deletions, resulting in founder knockout animals that pass the mutation on through their germ line.

This research is expected to facilitate the development of new models that scientists believe will provide a better understanding of Parkinson's disease at the molecular, biochemical, physiological and behavioral levels, Weinstein says.

According to Weinstein, CompoZr Zinc Finger Nucleases are engineered DNA-binding proteins that facilitate targeted editing of the genome by creating double-strand breaks in DNA at user-specified locations. Double-strand breaks lead to site-specific mutagenesis and stimulate the cell's natural DNA-repair processes, namely homologous recombination and Non-Homologous End Joining.

Katie Hood, CEO of MJFF, said in a statement that the foundation is hopeful the SAGE research "can quickly make a major impact on Parkinson's disease drug development efforts and help deliver breakthrough treatments to patients faster." **ddn**