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MALVERN, Pa.—Clinical-stage company Ocugen Inc. shared last month that preclinical data regarding the nuclear hormone receptor gene NR2E3 as a genetic modifier and therapeutic agent to treat retinal degenerative diseases had been published in *Nature Gene Therapy*. Ocugen's genetic modifier, OCU400 (NR2E3-AAV) has been granted orphan drug designations for NR2E3 mutation-associated retinal diseases and CEP290 mutation-associated retinal diseases, both of which are inherited retinal diseases (IRDs).

Retinitis pigmentosa (RP) is a set of genetic disorders characterized by a loss of cells in the retina. Symptoms typically appear in childhood, beginning with poor nighttime vision and then loss of peripheral vision followed by total vision loss. OCU400 is a novel gene therapy product candidate that Ocugen believes could be an effective means of restoring retinal function in a variety of inherited retinal diseases. The therapy features a functional copy of the nuclear hormone receptor gene NR2E3 and is delivered via an adeno-associated viral vector. It's thought that NR2E3 expression within the retina can stabilize the retina and rescue photoreceptors.

"OCU400 is based on the nuclear hormone receptor gene, NR2E3," explains Dr. Shankar Musunuri, Ocugen's chairman, CEO and co-founder. "NR2E3 is a genetic modifier gene that regulates many gene expressions and associated gene networks, responsible for cell development, function and survival, and brings homeostasis to the retina by restoring normal cell function and health without any off-target effects. These modifier genes behave like master genes in the retina. Because of their potential effectiveness, they have the ability to treat multiple retinal inherited degenerative diseases with a single product, a broad-spectrum therapy rather than developing a gene therapy product for each IRD."

The recently published data detailed how OCU400 was tested in five unique mouse models of RP, which were administered the therapy via subretinal injection. The models included rd1 (PDE6β- associated RP), Rho-/- and RhoP23H (both Rhodopsin associated RP), rd16 (Leber congenital amaurosis) and rd7 (enhanced S-cone syndrome).

"One of the biggest advantages of our modifier gene therapy platform is that it has the potential to eliminate the need for individual gene replacement and gene editing strategies and may revolutionize gene therapy treatments for eye diseases. Inherited retinal degenerations such as RP affect over 1.5 million people

worldwide. Over 150 gene mutations have been associated with RP, and this number represents only 60 percent of the RP population. The remaining 40 percent of RP patients cannot be genetically diagnosed, making it difficult to develop individual treatments. Our modifier gene therapy has potential to eliminate the need for developing more than 150 individual products and provide one treatment option for all RP patients," said Arumugham. "We are completing preclinical studies for OCU400 and anticipate commencing a Phase 1/2a clinical trial in patients in 2021."

"Dr. Haider and her vision research team have successfully demonstrated proof of principle in their elegant study by rescuing five animal models of RP by resetting homeostasis. This is the foundation work for the development of the first broad-spectrum therapy for inherited retinal degeneration diseases, and is a game-changer for rescue even after disease onset," remarked Dr. Cheryl Mae Craft, a professor of ophthalmology at the USC Keck School of Medicine.

Dr. Neena Haider is an associate professor of ophthalmology at Harvard Medical School and an associate scientist at the Schepens Eye Research Institute of Massachusetts Eye and Ear, and developed the modifier gene therapy platform.

Musunuri tells *DDNews* that Ocugen believes NR2E3-AAV could address a number of ophthalmic conditions, including "enhanced S-cone syndrome, Leber congenital amaurosis, rhodopsin-associated RP, Goldman-Favre syndrome and clumped pigmentary retinal degeneration, to name a few." The company is also advancing OCU410 (AAV-RORA), he notes, which is based on the genetic modifier RORA and is being developed against dry age-related macular degeneration.

He adds that Ocugen has seen increased interest in gene therapies in recent years, and expects that trend to continue.

"With the approval of gene therapy products in the U.S. and EU, there is a significant increase industry interest. Absolutely, gene therapies offer potential one time treatment for life. These are transformative therapies that have potential to offer a cure for many patients struggling with debilitating diseases across the globe. The future is here, and it will continue to be fascinating to watch significant number of patients across the globe getting better with these transformative therapies in the coming years," Musunuri states.

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