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Collaborating to explore new gene regulation therapies [1]

Discovery [2]

Novartis has entered into a research and development collaboration with Sangamo Therapeutics to explore potential gene regulation therapies for neurodevelopmental diseases. Proprietary technology platforms from both companies will be harnessed to facilitate progress toward potentially transformative treatments for life-long, debilitating conditions.

Sangamo is renowned for work on zinc finger proteins, which may be engineered to target select DNA sequences and switch specific genes on or off through the modulation of transcription. Novartis has deep experience with adeno-associated viruses (AAVs), which can be engineered to transport genes to specific cells within the body. The three to five year collaboration [3] leverages zinc finger protein transcription-factors (ZFP-TFs) and AAVs. The Novartis-Sangamo team will pursue three targets in neurology.

“New medicines for those with neurodevelopmental diseases are desperately needed, and gene therapy offers great promise for helping these patients,” says Jay Bradner, President of the Novartis Institutes for BioMedical Research. “Working with the team from Sangamo, we intend to reach previously undruggable gene targets by coupling their novel ZFP-TF platform with our AAV platform in order to innovate a next-generation gene therapy payload.”

Novartis continues to expand its capabilities in several distinct gene therapy platforms – AAVs, chimeric antigen receptor T-cells (CAR-Ts) and clustered regularly interspaced short palindromic repeats (CRISPR). The collaboration with Sangamo will introduce an additional genomic technology platform and is expected to enhance the utility of Novartis AAVs.

AAVs are naturally occurring viruses that are not known to cause human illness. They have varying affinities for different tissues and can be engineered to carry and deliver genes to precise cellular locations throughout the body. Novartis has focused on the use of AAVs to replace the function of faulty genes in patients with single gene mutations. AveXis, a Novartis company, has optimized a particular type of AAV, called AAV9, to carry genes to target cells within the central nervous system. This AAV gene delivery vehicle is the backbone of an approved gene therapy for patients with a progressive neuromuscular disease called spinal muscular atrophy.

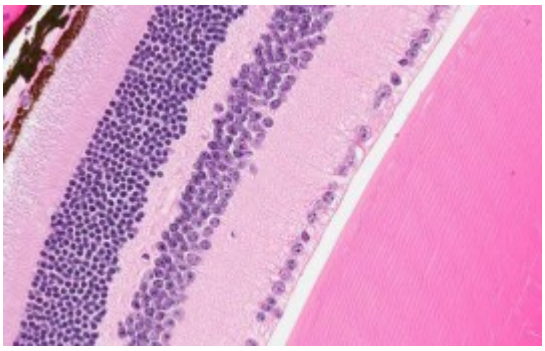
While AAVs have many advantages that make them well-suited for gene therapy, one disadvantage is that they can’t carry large genes. The collaboration between Novartis and Sangamo will enable the team to expand their focus by targeting diseases caused by mutations in one copy of a large gene.

“The gene for a ZFP-TF is small enough to fit inside an AAV,” explains Ricardo Dolmetsch, Head of Neuroscience at the Novartis Institutes for BioMedical Research. “We can use it to increase the production of a large gene in someone who still has one intact copy of the gene. This dramatically expands the range of diseases that we can potentially target with gene

therapy because many diseases are caused by the loss of a single copy of a gene.”

Researchers have used ZFP-TFs – which are mammalian – to regulate genes in the lab for many years. A number of zinc-finger based therapies, including zinc finger nucleases, are currently undergoing clinical testing. Each ZFP-TF from Sangamo is engineered to bind a target region of genomic DNA in a manner that is highly specific and selective. Further, ZFP-TFs are highly tunable, meaning that they can be designed to precisely modulate the expression of targeted genes to varying extents. After identifying its target, the ZFP-TF recruits a host of other proteins that help switch genes on or off.

The Novartis-Sangamo team will work to identify potential new therapies for several diseases, including an autism spectrum disorder.



Discovery [2]

Experimental gene therapy discovered in-house enters clinical testing [4]

Tags:
Cell and Gene Therapy [5]
Drug Discovery [6]
Neuroscience [7]
Genetic Disease [8]

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Links
[1] https://www.novartis.com/stories/discovery/collaborating-explore-new-gene-regulation-therapies
[2] https://www.novartis.com/stories/discovery
[3] https://investor.sangamo.com/news-releases/news-release-details/sangamo-announces-global-collaboration-novartis-develop-genomic
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