Epigenetic editing activates SORLA (Sortilin-related receptor with A-type repeats) to reduce soluble Beta amyloid (Aβ) and Tau in sporadic Alzheimer's Disease patient neurons

Melanie Silvis[1], Tengyu Ko[1], Zaki Jawaid[1], Tyler Borrman[1], Jackson Powell[1], Sophia Li[1], Surabhi Godbole[1], James Y.S. Kim[1], Daniel Hart[1]
1 Epicrispr Biotechnologies, South San Francisco, United States

1. Abstract

Introduction
Reduced neuronal expression of SORL1, encoding the endosomal trafficking receptor SORLA, is a causal contributor to Alzheimer's disease (AD) pathogenesis through dysregulated amyloid precursor protein (APP) processing and increased β-amyloid (Aβ) generation. Restoring endogenous SORL1 expression represents a compelling disease-modifying strategy, and SORL1 up-regulation may provide protection against common sporadic AD risk variants by favorably modulating APP processing; however, traditional gene replacement approaches face challenges related to payload size (SORL1 transcripts are >6kb in length), regulation, and durability. Here, we present a programmable epigenetic activation approach to upregulate SORL1 using the Epicrispr Gene Expression Modulation System (GEMS), a non-editing CRISPR-based platform designed for therapeutic *in vivo* deployment.

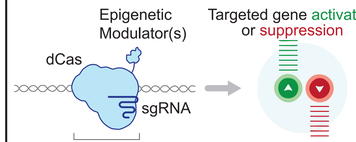
Methods
Epicrispr GEMS Cas protein and proprietary transcriptional activators were applied to two clinically relevant *in vitro* models of AD: human iPSC-derived neurons harboring PSEN1 or Swedish APP mutations associated with familial AD, and sporadic AD patient iPSC-derived neurons with common AD risk variants.

Results
Targeted activation achieved up to 450-fold induction of endogenous *SORL1* mRNA. This transcriptional upregulation translated into functional protein output, with up to 4.5-fold increases in SORLA protein. Importantly, *SORL1* activation resulted in a robust downstream disease-relevant effect, producing greater than 65% suppression of both soluble Aβ40 and Aβ42 peptides relative to controls.

Conclusion
These results demonstrate that epigenetic activation of SORL1 is sufficient to restore APP trafficking and significantly attenuate amyloidogenic processing in human AD neurons. The Epicrispr GEMS platform is compatible with clinically validated delivery modalities and enables precise, durable regulation of endogenous gene expression without permanent genomic modification.

This work establishes epigenetic activation of SORL1 as a scalable, in vivo–ready therapeutic strategy with the potential to modify Alzheimer's disease biology upstream of amyloid pathology.

GEMS:
Gene Expression Modulation System

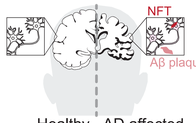


Industry leading compactness means that GEMS can be delivered therapeutically by any single delivery vector.

Epigenetic editing by GEMS is:
- **Durable** - causes long-lasting changes in gene expression
- **Safe** - no permanent DNA edits or double-strand breaks; dCas molecule is clinically de-risked and proven to be non-immunotoxic

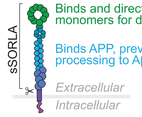
2. Background and rationale

Alzheimer's Disease (AD) is a progressive and irreversible brain disorder



- AD affects **1 in 9** people in the US ages 65+, with a total US prevalence of **7.2M** and 55M estimated globally.
- The vast majority of AD cases are Late Onset (LOAD), arising in individuals ages 65+, while a minority are Early Onset (EOAD) with a strong genetic component.
- Clinical symptoms include loss of memory and cognitive skills.
- Primary hallmarks of AD are the accumulation of Aβ plaque and neurofibrillary tangles (NFT) in the brain.
- Few disease-targeting therapies are approved, with concerns of limited efficacy and side effects.

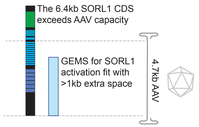
SORLA is a neural protein naturally protective against AD



Clinical associations between SORLA and AD support its protective role:
- SORL1 haploinsufficiency is causally linked to EOAD [4]
- SORLA levels are reduced in the majority of LOAD patient brains [3]
- SORL1 variants associated with reduced LOAD risk are associated with increased SORLA expression [5, 8]

Evidence supports SORLA protection in AD by multiple independent mechanisms:
- Protection against amyloidogenic APP processing [1]
- sSORLA as a positive signal for neural regeneration [6]
- SORLA role in maintaining synapse integrity and function [7]

SORLA is not a candidate for gene replacement therapy due to its large size



- Epigenetic activation of SORLA is the most potent way to harness the neuroprotective potential of SORLA therapeutically.
- Activation of SORLA has clear therapeutic benefit in SORL1 haploinsufficiency associated EOAD. Further, evidence suggests it **may have therapeutic value for a much wider population of AD patients** regardless of SORL1 mutation status, due to SORLA's protective mechanisms upstream of amyloid pathology.
- As a clinical-stage company, Epicrispr is positioned to bring its industry-leading GEMS platform to bear in the development of much-needed therapies for AD.

References

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3. Dodson, Sara E. et al. "LR11/SorLA expression is reduced [...]." (2006)
4. Holstege, Henne et al. "Characterization of pathogenic SORL1 [...]." (2017)
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7. Williams, C Andrew et al. "The Alzheimer's disease risk gene SORL1[...]." (2025) Preprint.
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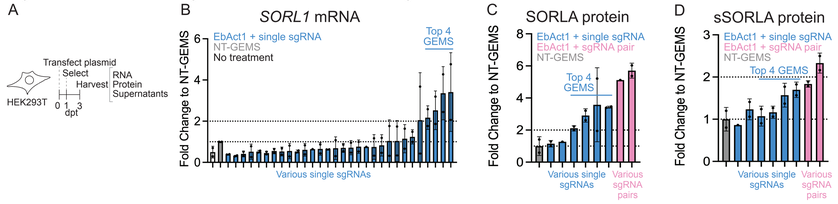
3. Robust and rapid GEMS screening platform in human cells identifies activators of SORLA

- From a small screen in human cells, we identified 4 GEMS with EbAct1 small activator that activate both *SORL1* mRNA and SORLA protein by at least 2-fold (Figure 1B,C).
- 2 GEMS increase the soluble form of SORLA (sSORLA), confirming correct trafficking and processing of SORLA at the cell surface (Figure 1D).
- GEMS using sgRNA pairs that are combinations of the top 4 performing single sgRNAs further potentiate activation of SORLA at the protein level (Figure 1C,D), highlighting a future strategy for efficacy optimization.

Figure 1. Robust screening platform identifies GEMS epigentic activators of SORLA in human cells



4. GEMS strongly and durably activate SORLA in healthy iPSC-neurons, with transient and AAV delivery

- 3 out of 4 hit GEMS identified in the initial screen translate successfully to a differentiated cell type relevant to AD pathophysiology: cortical neurons.
- Transient mRNA delivery to healthy iPSC-neurons drives strong activation of SORLA at the protein level (>6-fold, Figure 2C) with our top GEMS using the EbAct1 small activator. Further, these GEMS increase soluble sSORLA levels, confirming correct processing (Figure 2D).
- Durable activation of SORLA coupled with transient delivery would meaningfully expand therapeutic delivery options. We coupled transient delivery of our top sgRNAs with our long-lasting small activation EbAct2 [2] and observed long-lasting SORL1 activation out to 10 days post mRNA transfection (Figure 2E).

Figure 2. Transient GEMS delivery to healthy iPSC-neurons strongly and durably activates SORLA

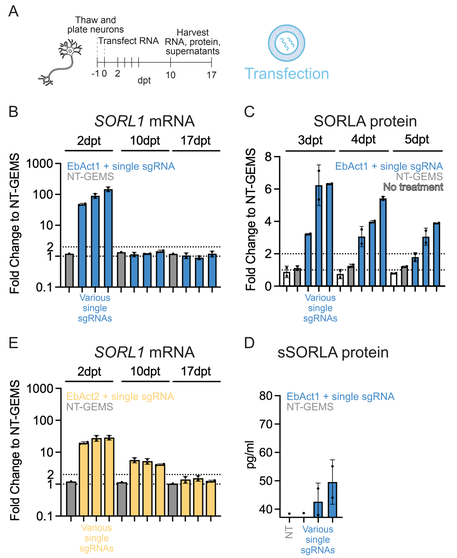
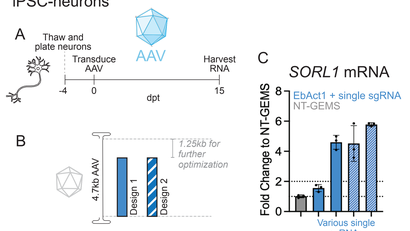
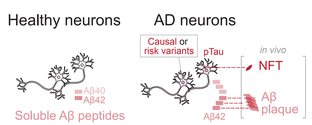


Figure 3. AAV-delivered GEMS activate SORL1 in iPSC-neurons



- We designed two prototypes of GEMS EbAct1 AAV cargo and delivered them to healthy iPSC-neurons using the AAV9 capsid (Figure 3A), observing significant activation of *SORL1* mRNA with both designs, up to 5.8-fold (Figure 3C).
- These early AAV prototypes have free 1.25kb space for additional engineering to enhance efficacy (Figure 3B).



- Amyloid Precursor Protein (APP) is processed to soluble Aβ peptides Aβ40 and Aβ42 among other species. The amyloidogenic Aβ42 peptide is associated with Aβ plaques *in vivo*.
- Tau hyperphosphorylation is an early event in the formation of NFT *in vivo*.
- AD iPSC-neurons—those derived from AD patients, or engineered with AD causal mutations—have increased production of Aβ42 alone or all Aβ peptides, and increased Tau phosphorylation.
- Here we use neurons derived from AD patients (sporadic AD, ApoE4/E4 genotype) or through genome engineering (PSEN1 M146L or APP KM670/671NL Swedish) to meaningfully model the APP/Aβ processing burden and early events NFT formation in AD.

5. SORLA activation by GEMS reduces amyloidogenic Aβ processing in AD iPSC-neurons by up to 68% with both transient and lentiviral delivery

- Combining transient mRNA delivery with our durable small activator EbAct2, GEMS significantly limited both Aβ40 and Aβ42 peptide production in both healthy and AD iPSC-neurons by up to 68% (Figure 4B).
- We tested active GEMS with either EbAct1 potent activator and EbAct2 durable activator in the context of transient delivery (Figure 4C). EbAct1 achieved 81% reduction in Aβ42 peptide in healthy iPSC-neurons, while EbAct2 provided the strongest, near complete reduction (98%), emphasizing the unique advantage of durable activators when coupled with transient delivery modalities for the treatment of AD.
- We delivered GEMS with EbAct1 to PSEN1 engineered and ApoE4/E4 patient AD neurons by lentivirus (Figure 5A), and in both genetic contexts observed significant reduction of both Aβ peptide forms (Figure 5B), in some cases approaching the levels of healthy neurons.

Figure 4. GEMS potently reduce amyloidogenic Aβ peptides when delivered transiently to AD neurons

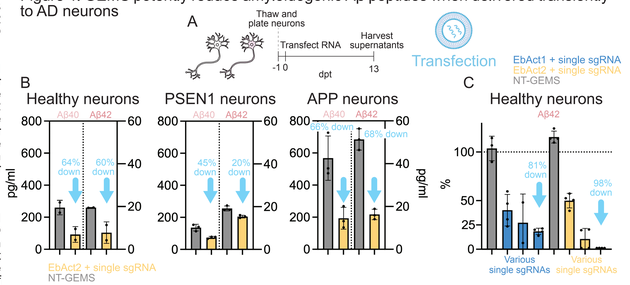
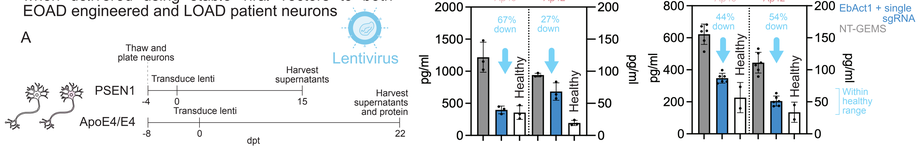


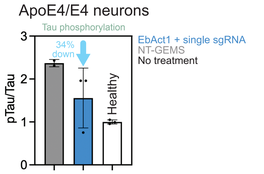
Figure 5. GEMS reduce amyloidogenic Aβ peptides when delivered using stable viral vectors to both EOAD engineered and LOAD patient neurons



6. SORLA activation reduces Tau phosphorylation in AD patient iPSC-neurons

- ApoE4/E4 AD patient neurons have elevated Tau phosphorylation compared to healthy controls (Figure 6) and were treated with SORLA activating GEMS as in Figure 5A.
- We observed a 34% reduction in Tau phosphorylation (pT231, Figure 6), confirming that SORLA activation by GEMS can also modulate early events in the hyperphosphorylation of Tau leading to NFT formation.

Figure 6. GEMS reduce Tau phosphorylation in ApoE4/E4 AD patient neurons



Conclusion

- SORLA is a neuroprotective protein with therapeutic value in both EOAD and LOAD contexts.
- Our *in vitro* work across genetic models of AD (both EOAD and LOAD) demonstrates that epigenetic activation of SORLA protectively modulates key early events in AD progression: suppressing both amyloidogenic Aβ processing and Tau phosphorylation.
- We show development of both transiently-delivered and AAV-delivered GEMS cargo for SORLA activation.
- Epicrispr's clinically validated GEMS platform is positioned to bring durable, effective SORLA therapies to AD patients.