Enhancing AAV Gene Therapy Targeting Retinal Diseases with AI-Guided Rational Design

Alessandro Barberis [1], Bryan Dafniet [1]*, Timothée Van Meter [2], Ulisse Ferrari [2], Perla El Darazi [1], Dylan Serillon [1], Deniz Dalkara [2], Julien Cottineau [1]

[1]WhiteLab Genomics, Future4Care, 8 rue Jean Antoine de Baïf, 75013 Paris, France

[2] Institut de la Vision, INSERM, CNRS, Sorbonne Université, 75005, Paris, France, [*] presenting author

WHITELAB GENOMICS

Unleash the Potential of Genomic Medicine using AI

Genomic Medicine's Principal Challenges

Specificity

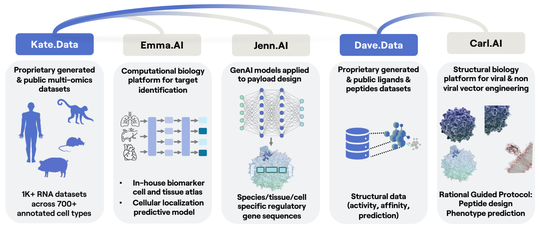
Immunogenicity

Manufacturing complexity

The Opportunity to Accelerate Drug R&D

- Enhanced efficiency
- Cost reduction
- Improved product quality
- Accelerated time to market

ALFRED, Proprietary & Modular AI Platform



About WhiteLab Genomics

WhiteLab Genomics stands at the convergence of AI and biology. Founded in 2019, backed by Y-Combinator, WhiteLab is pioneering the accelerated development of life-saving genomic medicines. By leveraging their proprietary technology, WhiteLab analyzes complex biological data powered by AI to significantly reduce development timelines and mitigate associated risks. Based on exhaustive datasets, the platform provides in-silico simulations to discover and design optimized payloads and vectors.

45+ specialists in AI and biology, including 20+ PhDs and PharmDs, in Paris and Boston.

Introduction: the GEAR Consortium

Photoreceptors are crucial retinal cells responsible for detecting light and converting it into signals that the brain can interpret. The human eye contains two main types of photoreceptors: rods, which are sensitive to low light levels, and cones, which detect colour. Various diseases can impact these photoreceptors, leading to vision problems and potentially severe visual impairment. Genomic medicine holds significant promise for treating retinal diseases of genetic or degenerative origin. However, targeting photoreceptor cells which carry most of the mutations causing retinal dystrophies remains particularly challenging. To address these challenges, the **GEAR Consortium** (Gene therapy Evaluation for the retina using AAV and AI-based Rational design) was created by **Whitelab Genomics, Institut de la Vision and ADLIN Science** with the aim of developing engineered AAVs to optimize the delivery of therapeutic genes directly to diseased retinal cells.

Vision Institute: Founded in 2009 in Paris, it is an internationally recognized center of excellence for fundamental, translational, and clinical research on vision diseases. The institute brings a combination of experimental data, techniques and know-how to the consortium: viral vector design and production in the area of ophthalmology, as well as in vitro and in vivo platforms for validation of viral vectors.

ADLIN Science: Founded in 2020, the company developed Adlin Workspace that caters to all stakeholders in biomedical research—biologists, bioinformaticians, data scientists, technicians, and team leaders—by facilitating the implementation, monitoring, and valorization of scientific projects.

Methods

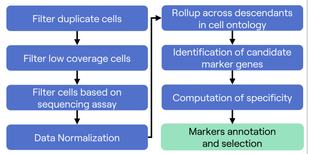
Photoreceptor-specific markers identification in humans

We utilized our proprietary single-cell Atlas (Kate.Data) to identify photoreceptor-specific markers in humans. Raw sequencing data underwent a standardized pipeline, which included the removal of duplicate and low-coverage cells, followed by data normalization and cell re-annotation to account for varying levels of granularity.

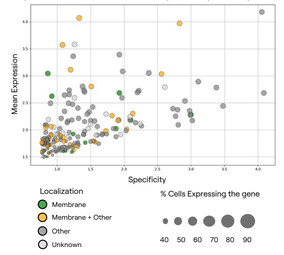
Subsequently, for each gene we computed Cohen's distances between the average expression levels in photoreceptors and other cell types, deriving specificity scores from these values.

Cell markers were ranked according to these scores, and the top 50 candidates with the highest photoreceptor specificity were selected for downstream analysis.

WLG pipeline for cell markers identification



Top 200 Genes for Cone Cell: Specificity and Expression



Markers validation in *Sus scrofa* and functional annotation

The identified markers were further validated through transcriptomics analysis in *Sus scrofa*, an animal model with anatomical and physiological similarities to the human retina.

We retrieved single-cell sequencing data from four samples in a recently published paper (Hahn et al., 2023).

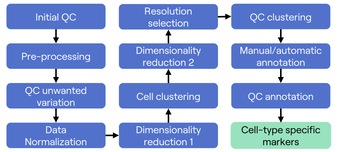
Orthologues of canonical markers characterized in mice were used to annotate the data through our in-house scRNA-seq analysis pipeline.

The samples were enriched for specific cell types (namely, photoreceptors and bipolar cells), as expected from the original experimental settings.

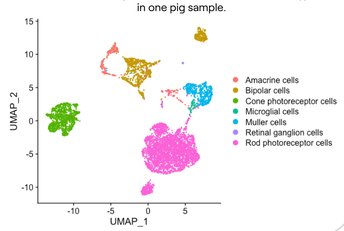
The 50 candidate markers' expressions were assessed in pigs. Additionally, we explored KEGG pathways and excluded genes involved in immune response.

45 markers were selected for further analysis.

WhiteLab's single-cell RNA-seq pipeline overview

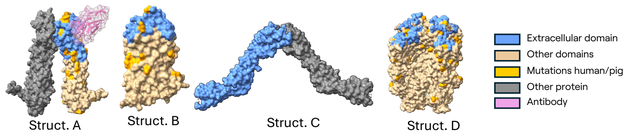


Bidimensional representation of the annotated cell types in one pig sample.



Cellular localization and structural protein analysis to select receptor

The protein's presence at the cell membrane was assessed through WhiteLab's proprietary AI algorithms and we evaluated the 45 potential targets based on multiple criteria. Four candidates receptors were identified and analyzed at a molecular level.



*	Struct.A	Struct. B	Struct. C	Struct. D
Interactors	●	●	●	○
Cross-species conservation	●	○	●	○
Resolved structure(s)	●	○	●	●
Binding site	●	○	●	○

● Relevant and usable data
○ Available data needs work
● No data/Not usable

*Non exhaustive criteria list

The final decision concerning receptor selection was discussed within the consortium, where the Vision Institute's retinal expertise reached a consensus with WhiteLab's structural analysis to select structure C as our final target.

Conclusion

Using in-house AI-driven analysis of transcriptomics and structural data of photoreceptors (Emma.AI), four receptors have been identified for an optimized delivery of therapeutic genes directly to diseased retina cells. After applying a list of in-house criteria on existing data – notably, binding information and conservation across species – a final receptor was selected.

This result paves the way for WhiteLab will apply the next steps of its ALFRED platform, using a rational guided approach to propose engineered AAV vectors specific to the selected receptor. Institut de la Vision will then perform experiments for vivo validation of the optimized AAV vectors in the coming months.

abarberis@whitelabgx.com – bdafniet@whitelabgx.com