TOWARDS AN IN VITRO MODEL OF EARLY ALZHEIMER'S DISEASE PATHOLOGY

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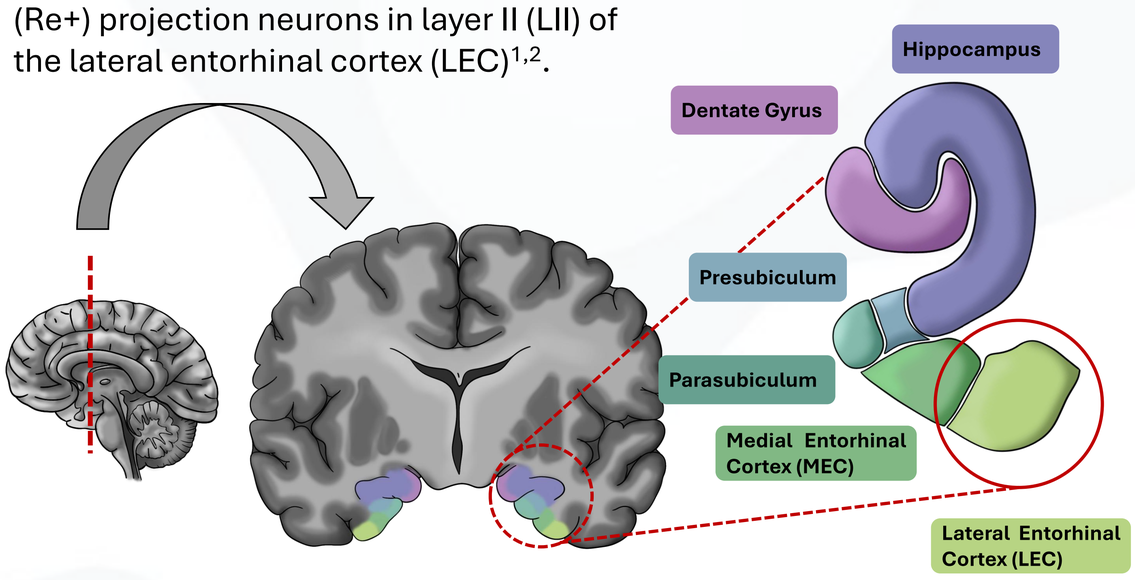
INTRODUCTION: Focusing on the Lateral Entorhinal Cortex

Cortical onset of AD → reelin expressing (Re+) projection neurons in layer II (LII) of the lateral entorhinal cortex (LEC)[1,2].



OBJECTIVES: develop a versatile neuronal culture platform

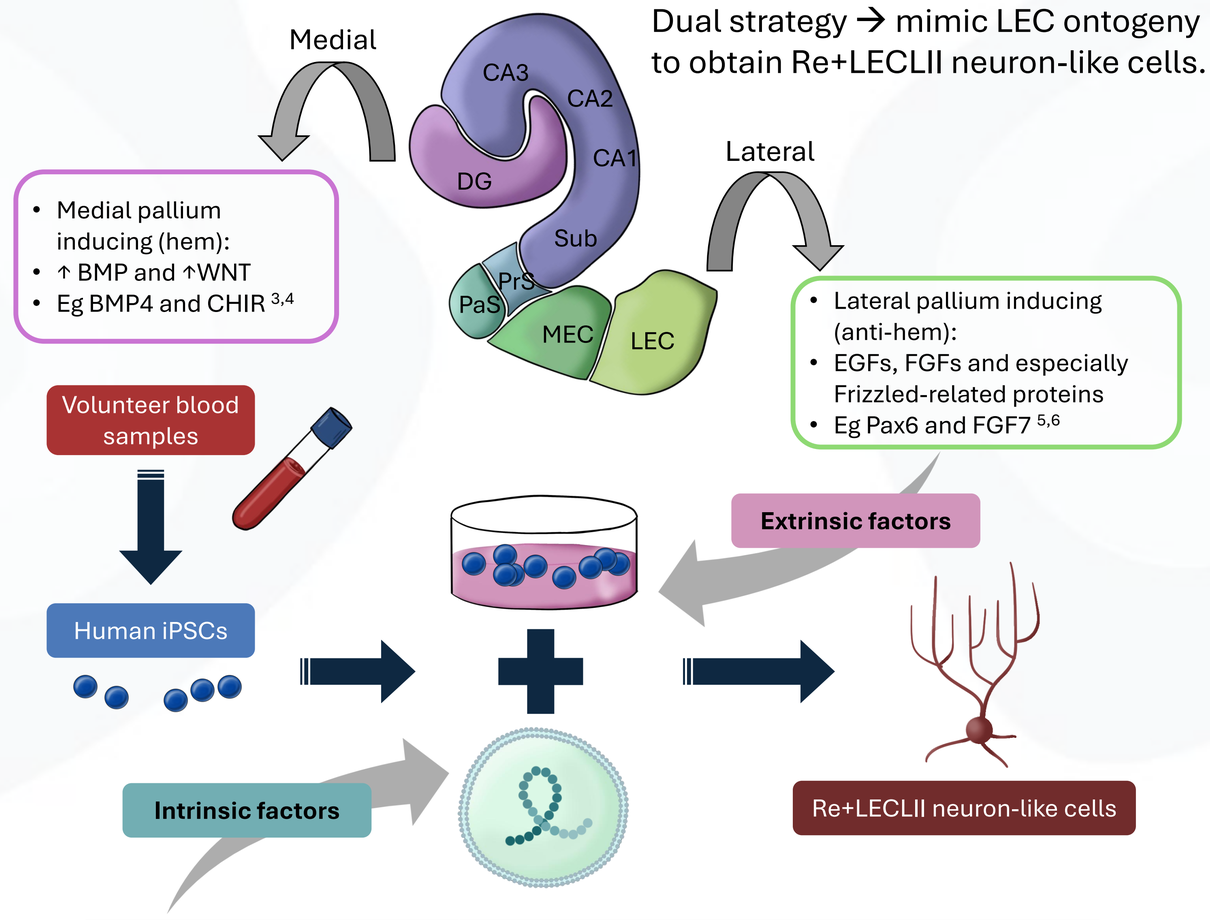
Convert induced pluripotent stem cells (derived from human blood cells) into cells that display a phenotype similar to human Re+LECLII neurons.

→ Apply this protocol to cells from both healthy volunteers and AD patients with different genetic risk profiles.

→ Use transcriptomic techniques to explore the molecular processes occurring in these Re+LECLII neuron-like cells.

METHODS: In vitro model of early AD

Dual strategy → mimic LEC ontogeny to obtain Re+LECLII neuron-like cells.



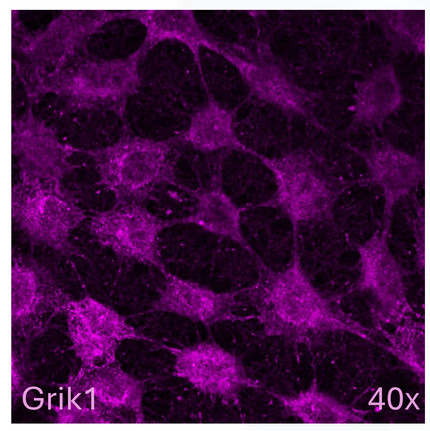
Transcription Factors	Relevant Function
FOXP1	Neuronal development[7]
SOX5	Neuronal development[7]
MEF2C	Neuronal development[7]
TCF4	Neuronal development[7]
HDAC9	Regulation of dendritic growth[8]
LMO7	Cytoskeletal development & dynamics[9,10]
TBR1	Neuronal differentiation, dendritic growth[11]

RESULTS: Inducing differentiation

Marker	Relevant Function
RELN	Neuronal development[7]
CTIP2	Neuronal development[7]
PENK	Neuronal development[7]
GRIK1	Glutamate receptor, ionotropic, kainate 1[12]

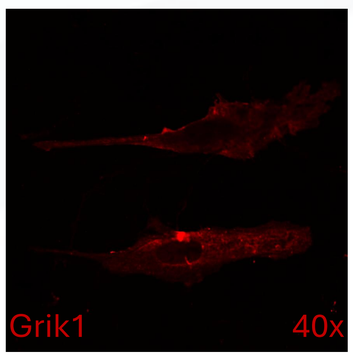
→ Co-expression → thought to form a specific Re+LECLII molecular signature

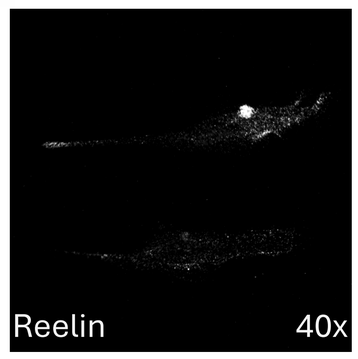
20-day old cells derived from healthy volunteers + extrinsic factors → express CTIP2 and GRIK1 (known to be expressed in LECLII neurons).

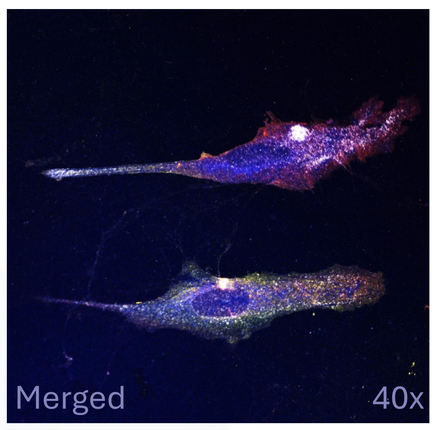


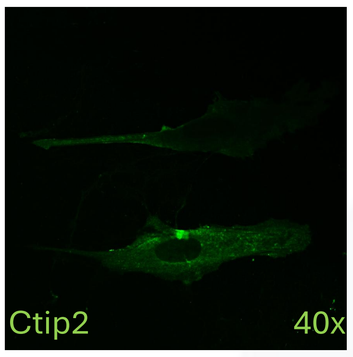
This suggests that with the extrinsic factors alone, the cells begin their differentiation but do not reach the desired phenotype.

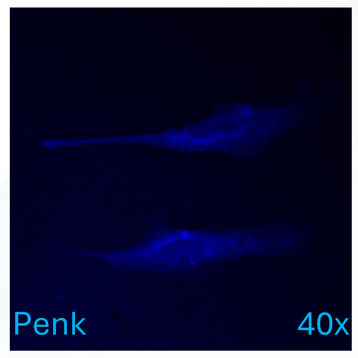
24-day old cells derived from healthy volunteers + extrinsic + intrinsic factors → cells clearly express reelin, CTIP2, GluR5, but PENK is less conclusive.







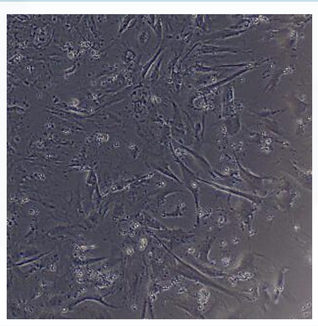




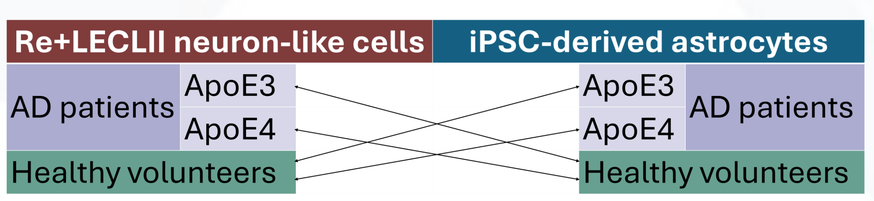
Suggesting the need for a longer time in culture or an adjustment in the factors.

FUTURE PERSPECTIVES AND NEXT STEPS

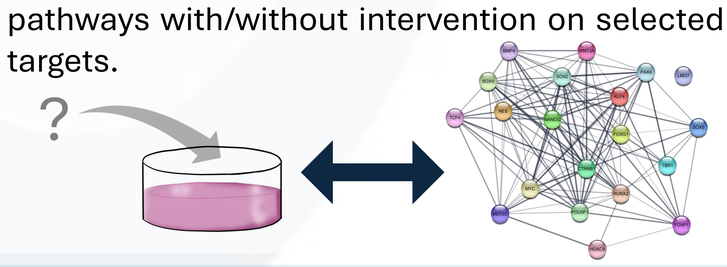
1. Survival times pose a challenge and must be further improved to allow characterization.
   → Co-culture with astrocytes.



2. Test interactions with healthy versus AD astrocytes.



3. Apply bulk transcriptomics and test associated pathways with/without intervention on selected targets.



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