

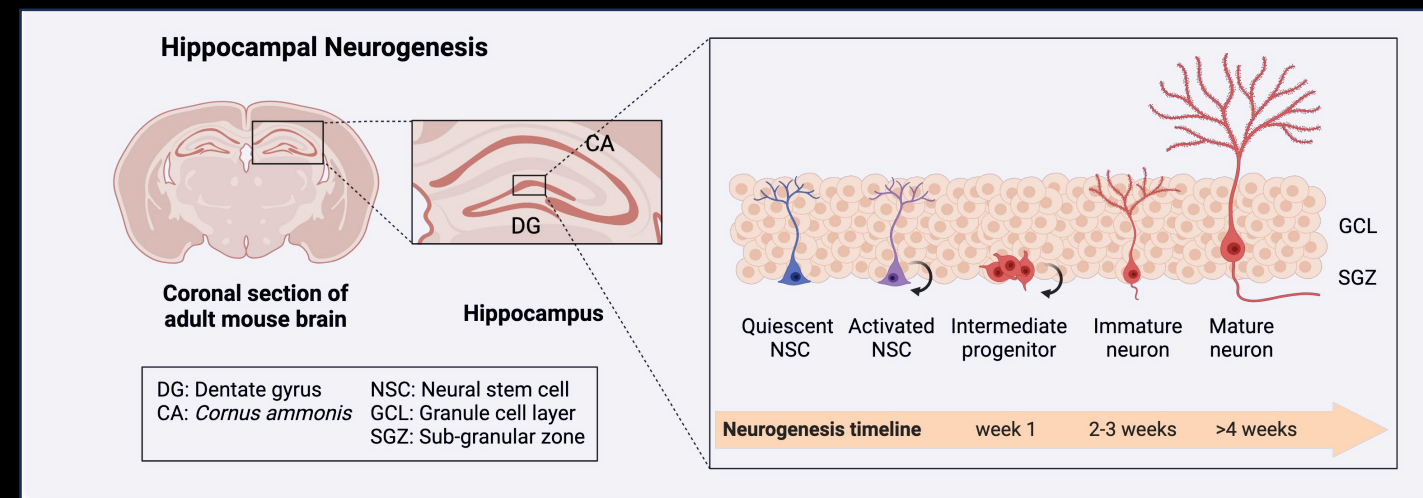


Alzheimer's Disease-Related Modulation of Adult Neurogenesis and LRP1

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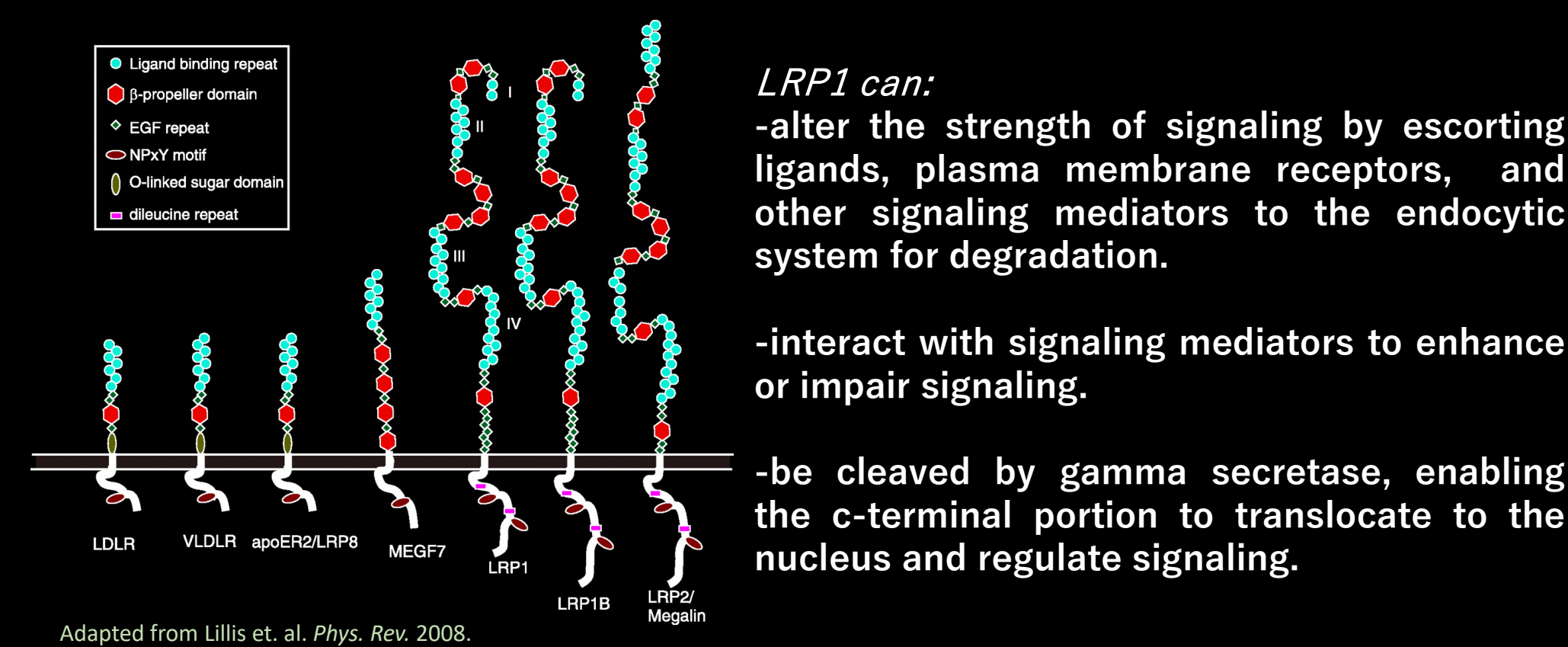
Adult hippocampal neurogenesis is essential for memory function



1. The **subgranular zone (SGZ)** is a site of adult neurogenesis in humans, generating new neurons which integrate into hippocampal trisynaptic circuitry.
Deng, Alimonte, Gage *Nature Reviews Neuroscience* 2010
2. Ablating adult neural stem cells impairs spatial memory in adult mice.
Imayoshi et al. *Nature Neuroscience* 2008
3. Adult hippocampal neurogenesis is impaired in multiple animal models of Alzheimer's disease.
Rodriguez et al. *PLoS One* 2008; Verret et al. *Neurobiol Aging* 2011; Zafetel et al. *J Alzheimers Dis* 2018; Scopa et al. *Cell Death Differ* 2019
4. Enhancing adult hippocampal neurogenesis improves cognition in Alzheimer's disease models.
Choi et al. *Science* 2018; Morello et al. *Mol. Neurobiol.* 2018; Souza et al. *Neurotox Res.* 2013; Rodriguez et al. *Curr Alzheimer Res.* 2011
5. Patients with higher Braak stages of Alzheimer's disease have reduced markers of hippocampal neurogenesis.
Moreno-Jimenez et al. *Nature* 2019

LRP1-a link between Alzheimer's disease and neurogenesis?

LOW DENSITY LIPOPROTEIN RECEPTOR RELATED PROTEIN 1 (LRP1) is a multifunctional member of the LDL receptor family, interacting with hundreds of various targets.

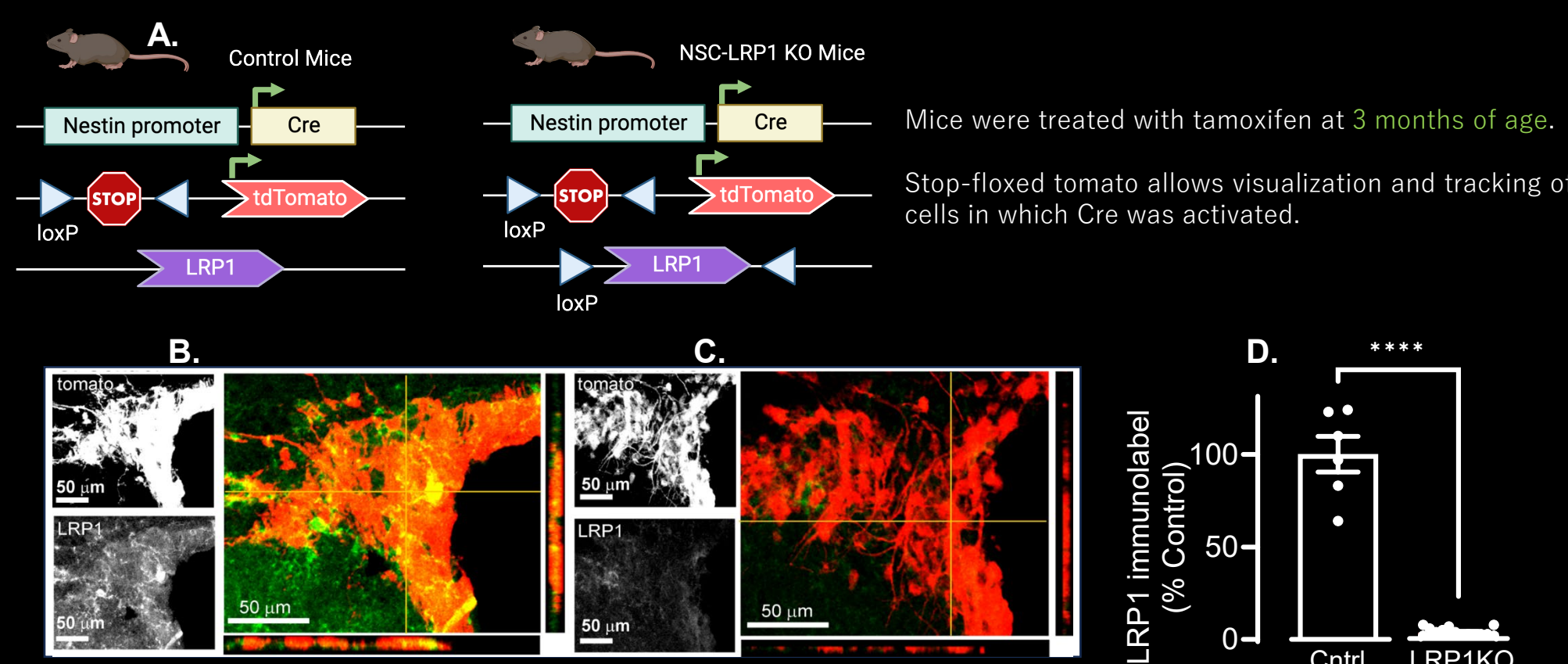


LRP1 is a major receptor for:

ApoE4
Amyloid beta
Tau

What is the effect of LRP1 KO on hippocampal neurogenesis?

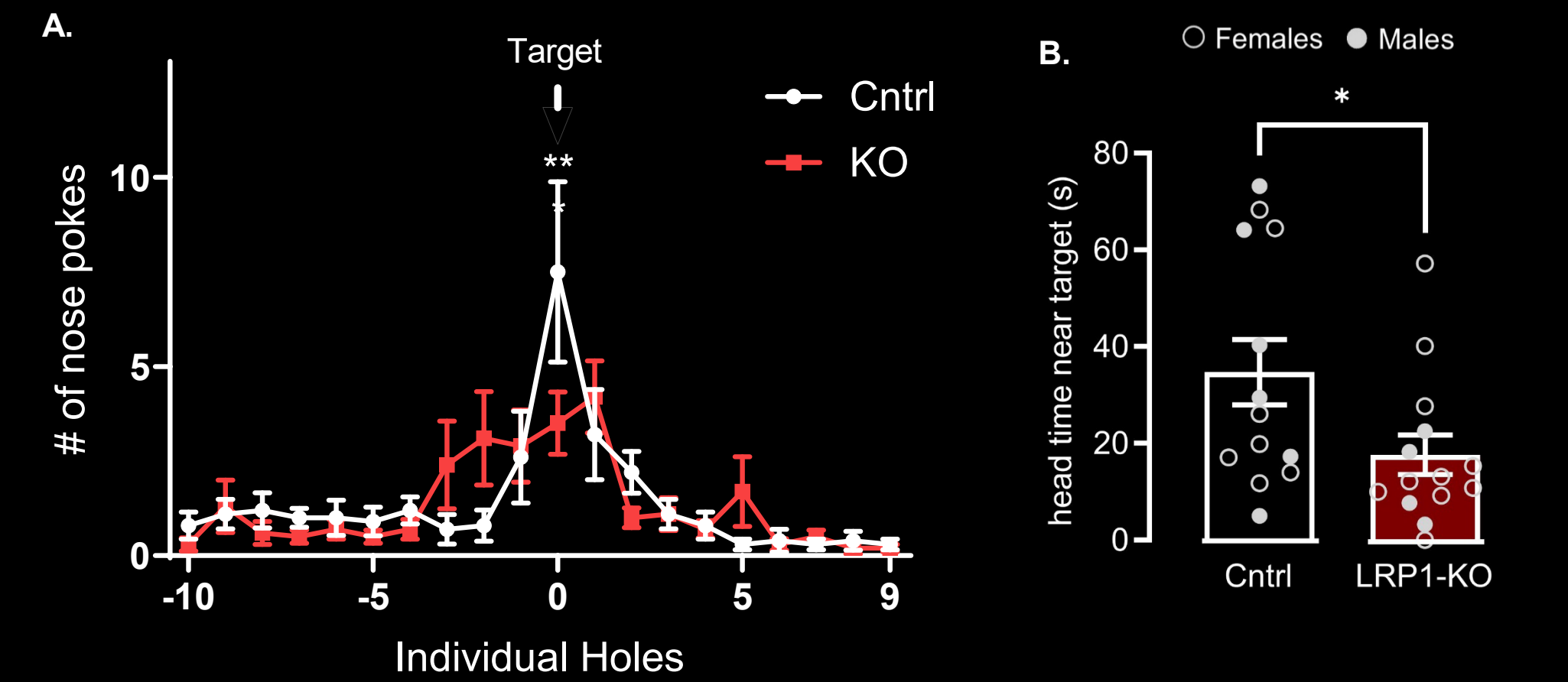
F1: Nestin-Cre^{ER} mediated knockout of LRP1 in adult mice



(A) Nestin:Cre^{ER};tdTomato mice were crossed with LRP1^{fl/fl} mice to create Nestin-Cre^{ER};tdTomato:LRP1^{fl/fl} mice (LRP1-KO) or Nestin-Cre^{ER};tdTomato:LRP1^{+/+} (Control). IHC was performed in (B) Control and (C) LRP1 KO mice, showing signal of tdTomato (red) colocalizing with LRP1 signal (green), together with orthogonal views. (D) LRP1 immunolabeling was quantified in tdTomato positive NSCs 1-month after tamoxifen (n=4-5 mice). ****p<0.0001 via student's t-test.
Dietert et al. *Stem Cells* 2023

How does LRP1 KO in neural stem cells (NSCs) affect behavior?

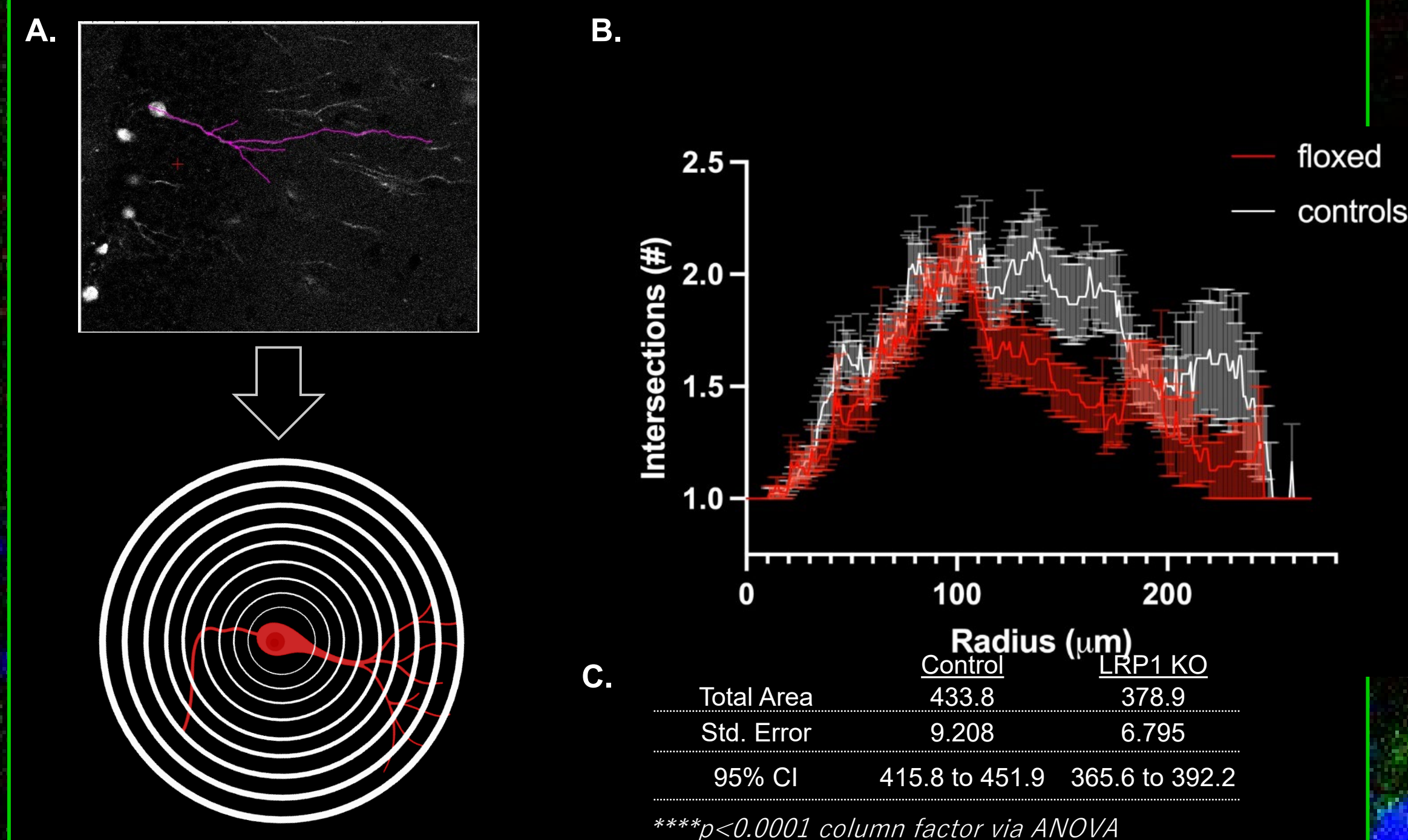
F2: LRP1 KO in NSCs impairs hippocampal-dependent memory



Mice were then trained for 5 days to identify an escape hole in the Barnes maze with spatial cues on the walls of the room. Probe trials were conducted 7 days after acquisition. (A) shows the number of investigations per each hole in its relation to the target hole located at x=0 while (B) shows the time spent investigating the target hole. n=13-15 mice/group; *p<0.05 via unpaired t-test; ***p=0.0006 via ANOVA with Bonferroni's correction.
Dietert and Marion et. al. *Cells* 2026

What is the effect on the dentate gyrus?

F3: NSC LRP1 KO decreases neuronal complexity



Sholl analysis (A) was performed using SNT ImageJ plugin. Only mature recombined neurons (DCX-NeuN+ tdTom+) were traced for (B) analysis showing # of intersections plotted against distance from the soma. (C) Area under the curve analysis was performed, and comparisons were made for n=36-42 cells/group.
Dietert and Marion et. al. *Cells* 2026

MAJOR QUESTION

Does altering LRP1 activity cause amyloid- or tau-dependent impairment of neurogenesis and memory?

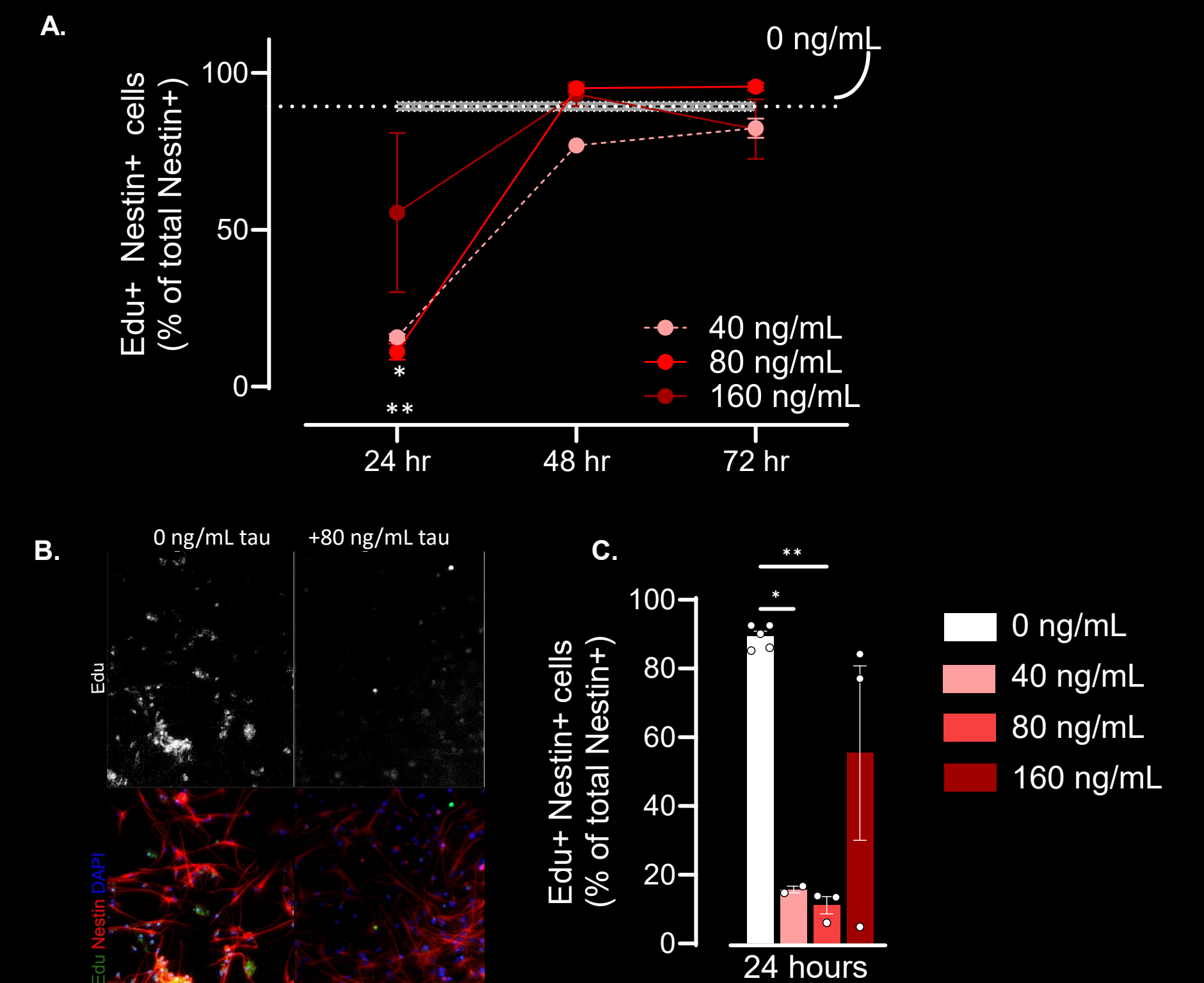
Unless otherwise stated, all results are reported as averages +/- SEM. All behavior was analyzed using Stoelting AnyMaze software and statistics were performed with GraphPad Prism

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Can exogenous tau alter neurogenesis in an LRP1-dependent manner?

F4: Extracellular 2N4R tau decreases NSC proliferation after 24h of treatment (preliminary data)



NSCs were harvested from the subventricular zone for optimization experiments. Starting on day 7 in culture, cells were treated with either vehicle or the indicated amount of 2N4R tau (Stressmarq) for the indicated time. At 16 hours before harvest, cells were pulsed with EdU to enable incorporation into proliferating cells. Cells were fixed, and subject to Click-it labelling (Thermo Fisher) while co-labelling with both NSC-marker Nestin and nuclear marker DAPI. (A) Time course showing average proliferation at indicated dosages across experimental timepoints. (B) Representative images from vehicle or tau-treated cultures. 24 hours after tau exposure. (C) Replotted histogram of the 24-hour time point, showing replicates and direct comparisons of proliferation in the different tau dosages. Results are averages with SEM from n=3 wells/treatment group of a single experiment. Comparisons were made using 2-way ANOVA followed by Tukey's HSD. *p<0.05, **p<0.01.

Future directions regarding tau:

- Test the effect of exogenous tau on neurogenesis in control and LRP1KO cells *in vitro*.
- Test whether rescuing LRP1-tau interaction *in vivo* rescues dendritic complexity of newborn granule neurons.

Does stimulating LRP1 alter pathogenesis in APP/PS1 mice?

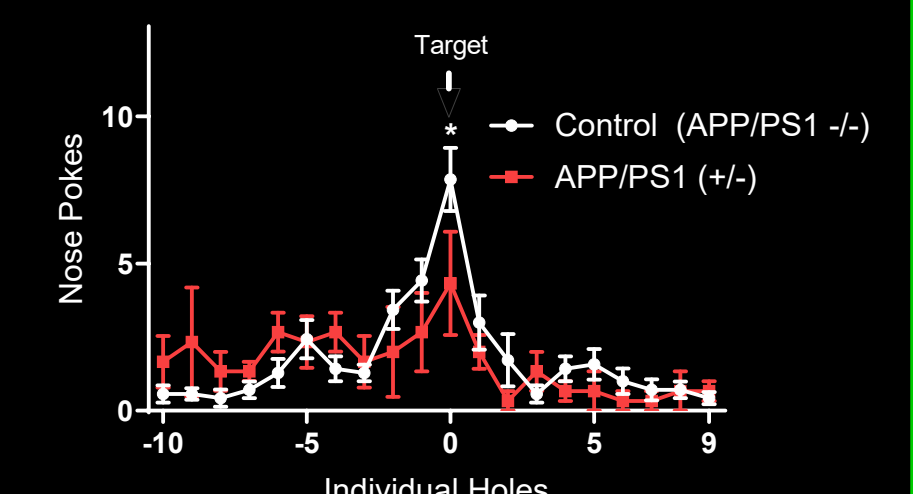
F5: Experimental schematic of LRP1 agonism in APP/PS1 mice



SP16: A gift from Serpin Pharma
SP16 is an LRP1 agonist undergoing clinical trials with no major negative effects reported.

SP16 mitigates inflammation via binding and activation of LRP1.
It is unclear whether SP16 influences amyloid processing.

Toldo et al. *JACC* 2017; <https://serpinpharma.com/the-science/>



Preliminary Barnes maze testing data APP/PS1 and control littermates (n=3-6) shows memory deficits 7d post-training in 6 month old mice.

Future directions regarding amyloid beta:

We hypothesize that prolonged treatment with SP16 will mitigate memory deficits in APP/PS1 mice, reduce accumulation of amyloid plaques, and enhance neurogenesis. These hypotheses will be tested at the conclusion of animal harvest.

Summary and Conclusions:

LRP1 impairment increases the maturation of hippocampal neurons *in vivo*, however those neurons are less complex than normal neurons. Altogether, the result is impaired hippocampal function. Ongoing experiments are testing the effects of tau and amyloid beta on LRP1-mediated effects of neurogenesis.