



# Decoding the pituitary's stem cell biology across life

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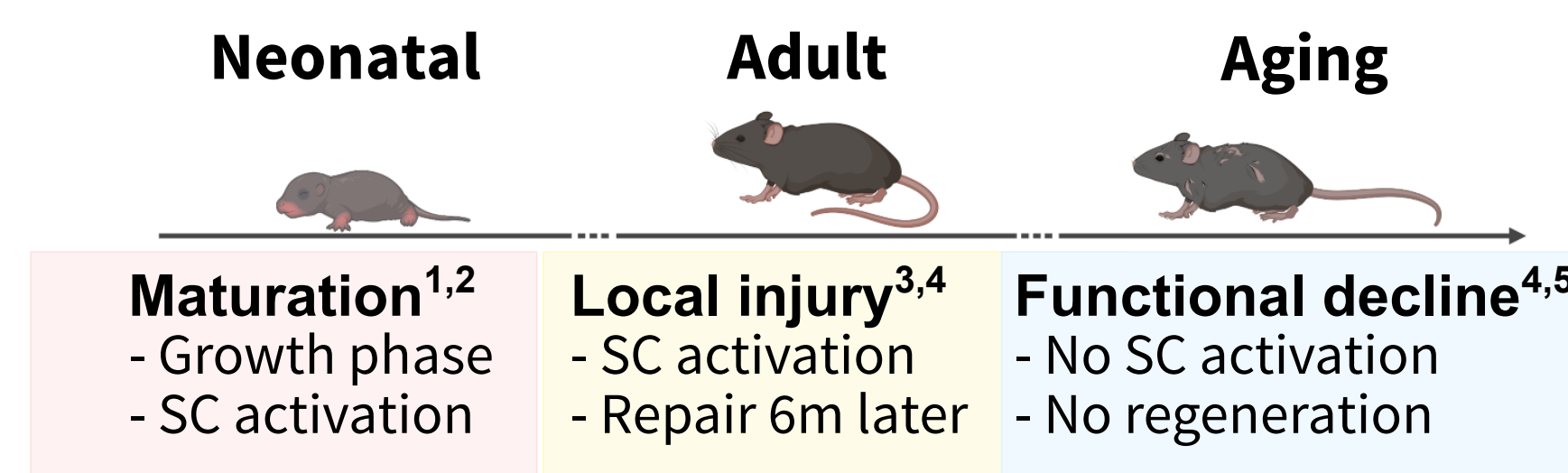
## Main research goals

Decoding pituitary stem cell (SC) biology across life

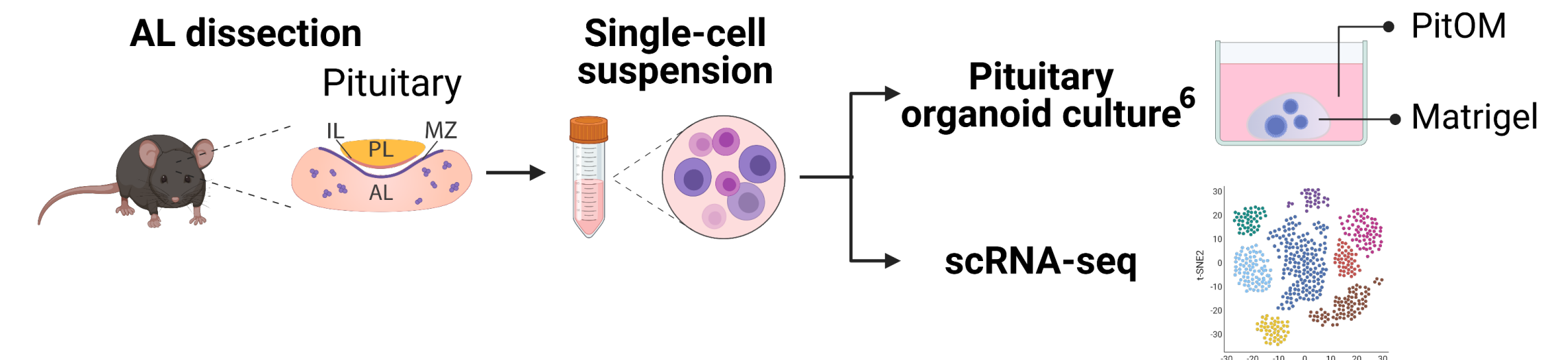
=> **Role and behaviour** during pituitary remodeling

- Neonatal maturation
- Local injury
- Functional decline at aging

## Introduction



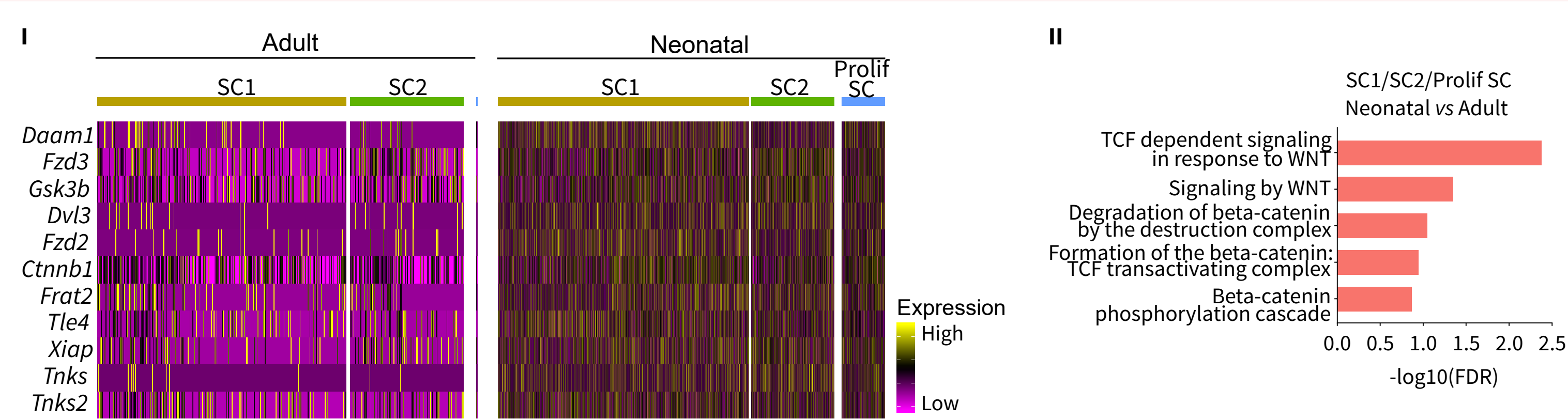
## Methods



## 1. The neonatal maturation phase<sup>1</sup>

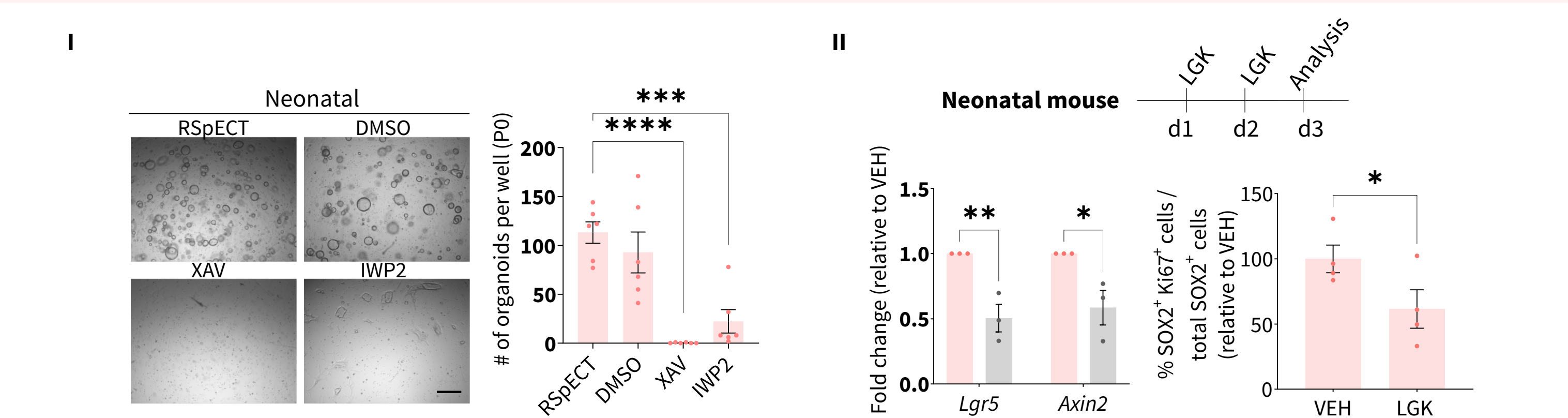
**PANEL 1A | scRNA-sequencing exposed a pronounced WNT landscape in the neonatal gland.**

- DEG analysis revealed increased expression of WNT signaling-associated genes in the neonatal SC clusters.
- GO analysis exposed enrichment of WNT pathway terms in the neonatal SC compartment.



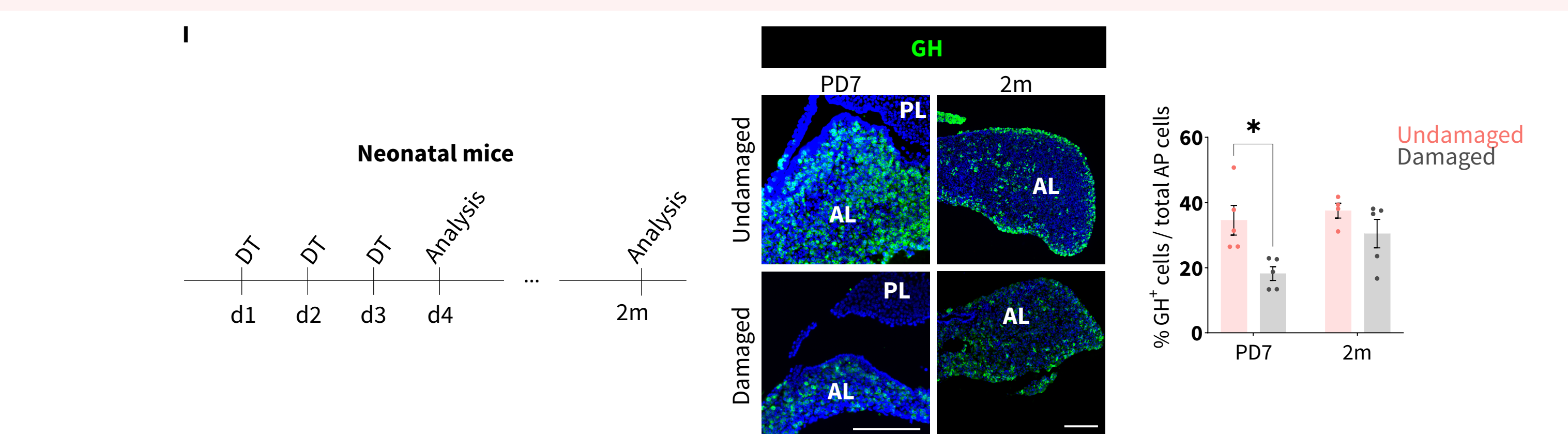
**PANEL 1B | WNT signaling is associated with the high activation modus of neonatal pituitary SCs.**

- Blocking WNT signaling (XAV, IWP2) *in vitro* reduces organoid formation.
- Blocking WNT (LGK; decreasing target gene expression) *in vivo* decreases the number of proliferating SOX2<sup>+</sup> cells.



**PANEL 1C | Transgenically inflicted pituitary damage was found to be efficiently and fully restored.**

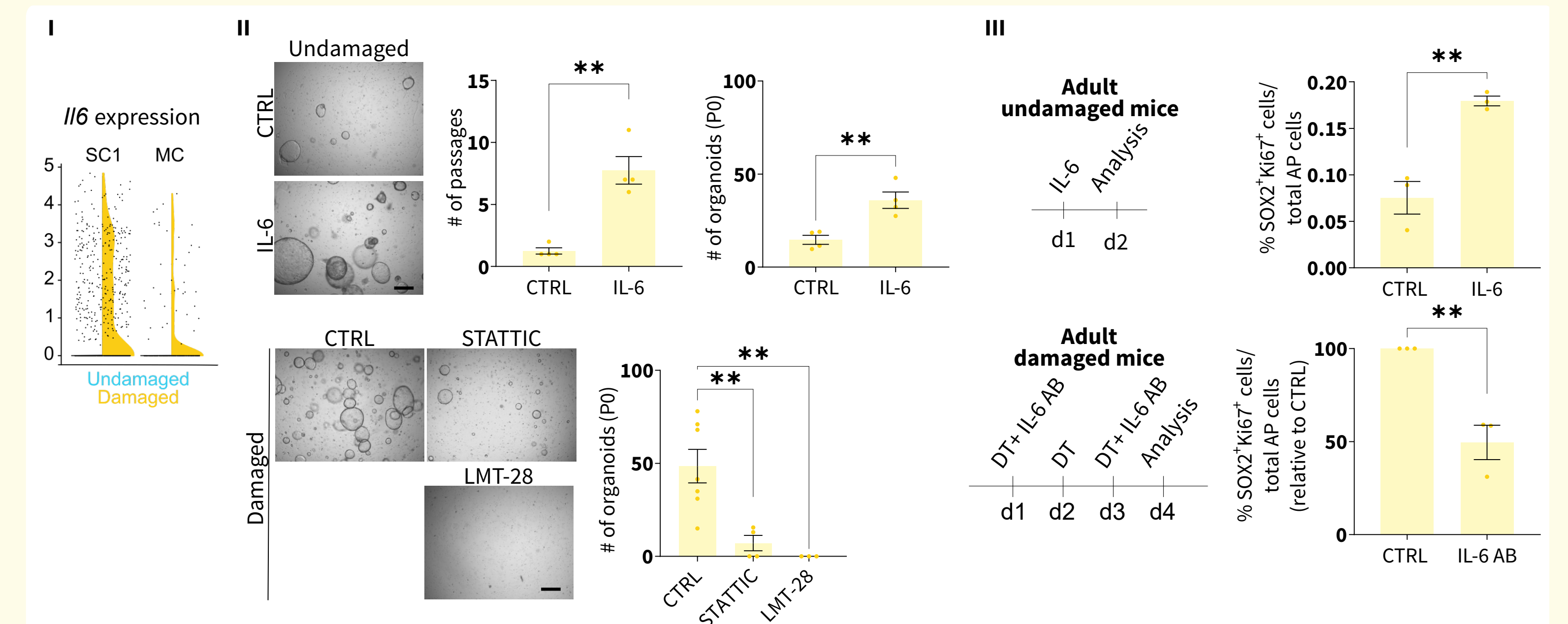
- Three-day diphtheria toxin (DT) injection of neonatal GHCre/iDTR pups resulted in 50-60% ablation of GH<sup>+</sup> cells. The population was fully restored to normal numbers, already achieved after 2 months (2m).



## 2. Adult pituitary injury and regeneration<sup>4</sup>

**PANEL 2 | Identification of interleukin-6 (IL-6) as pituitary SC activator in the adult gland.**

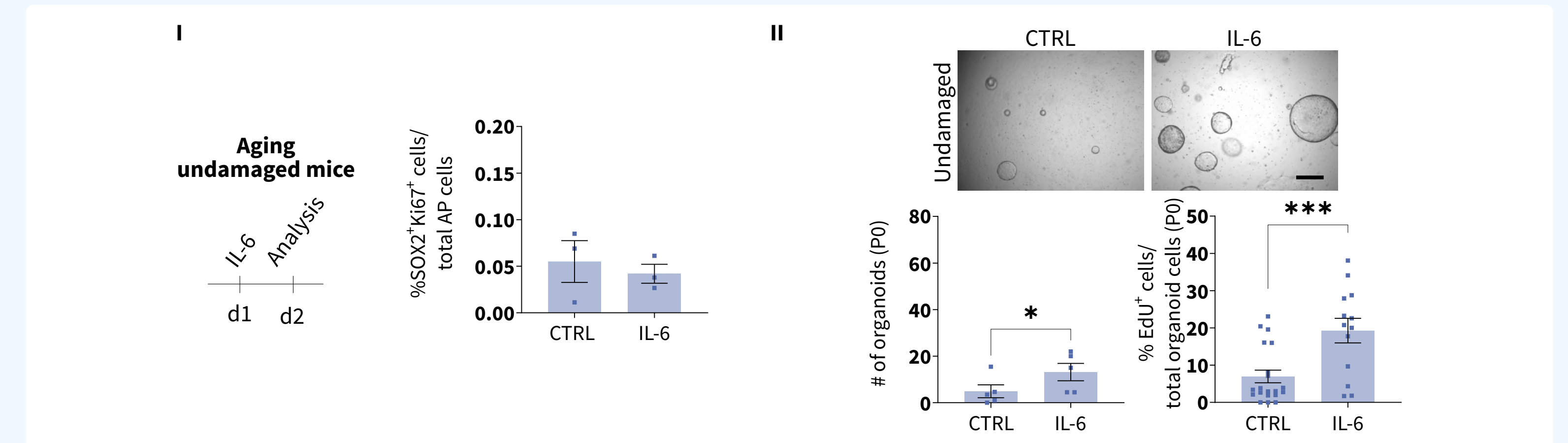
- Il6* was found highly upregulated, particularly in SC1 and mesenchymal cell (MC) clusters, after damage.
- Adding IL-6 to organoid culture augments organoid formation efficiency from undamaged (adult) AL. Adding the IL-6 inhibitors (STATIC and LMT-28) to AL cells from damaged gland largely blocks organoid formation, indicating the importance of JAK/STAT signaling.
- The proportion of proliferating SOX2<sup>+</sup> SCs is significantly elevated following IL-6 treatment in adult WT mice. Anti-IL-6 antibody treatments during the damage infliction reduced the SC proliferative reaction.



## 3. Pituitary functional decline at aging<sup>4</sup>

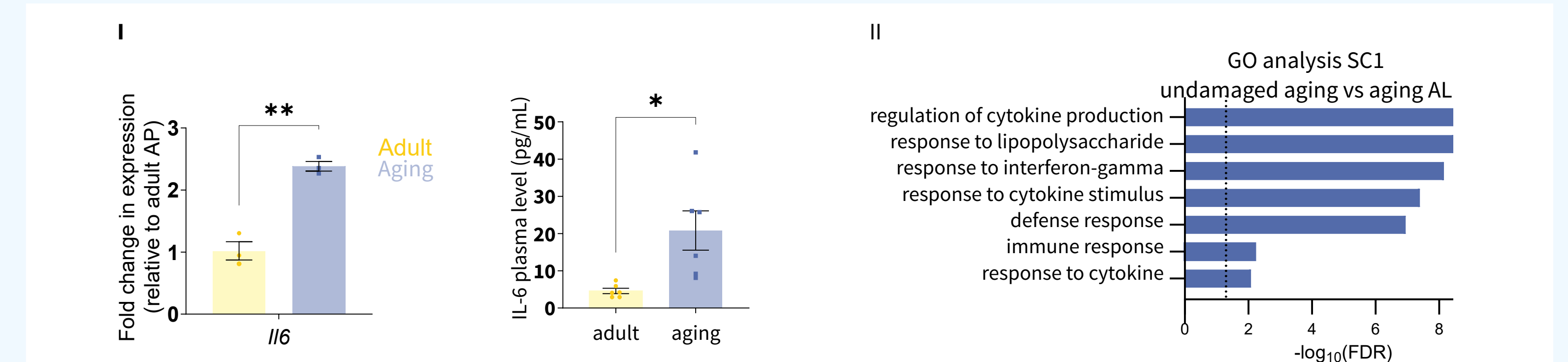
**PANEL 3A | IL-6 does not activate SCs in the aging pituitary.**

- Injection of IL-6 in aging animals does not trigger a SC proliferative response.
- Adding IL-6 to organoid culture augments formation efficiency from undamaged aging AL.



**Panel 3B | The aging pituitary is typified by an elevated IL-6/inflammatory phenotype.**

- Il6* expression is higher in aging vs adult AL, in agreement, IL-6 plasma levels are upregulated.
- GO analysis revealed upregulation of inflammatory response related terms in aging vs adult SCs.



## Highlights

**Efficient regeneration** in the neonatal pituitary after local injury  
**WNT signaling** is enriched in the neonatal vs adult SCs  
 WNT signaling is necessary for neonatal pituitary SC activation

**IL-6 is upregulated** upon local injury in the adult SCs  
 IL-6 is involved in the **acute activation** of adult pituitary SCs after local tissue damage

Aging pituitary SCs **regain activatability** when removed from their *in vivo* milieu  
 Raised **inflammatory environment** in the aging pituitary hinders full activation upon injury

## References

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