Exploration of the Renal Autonomous Cholinergic System via Single-Cell RNA Sequencing

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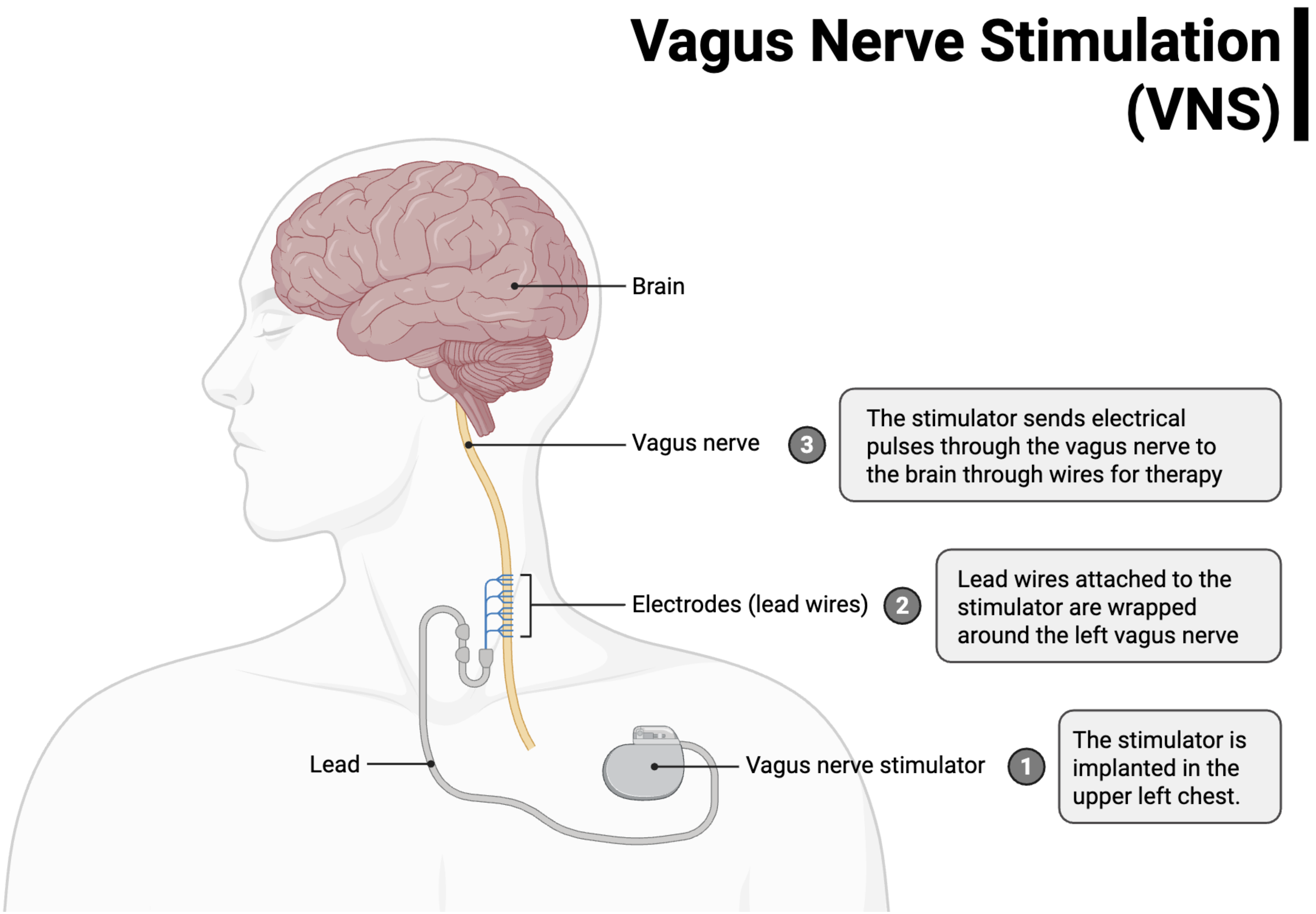
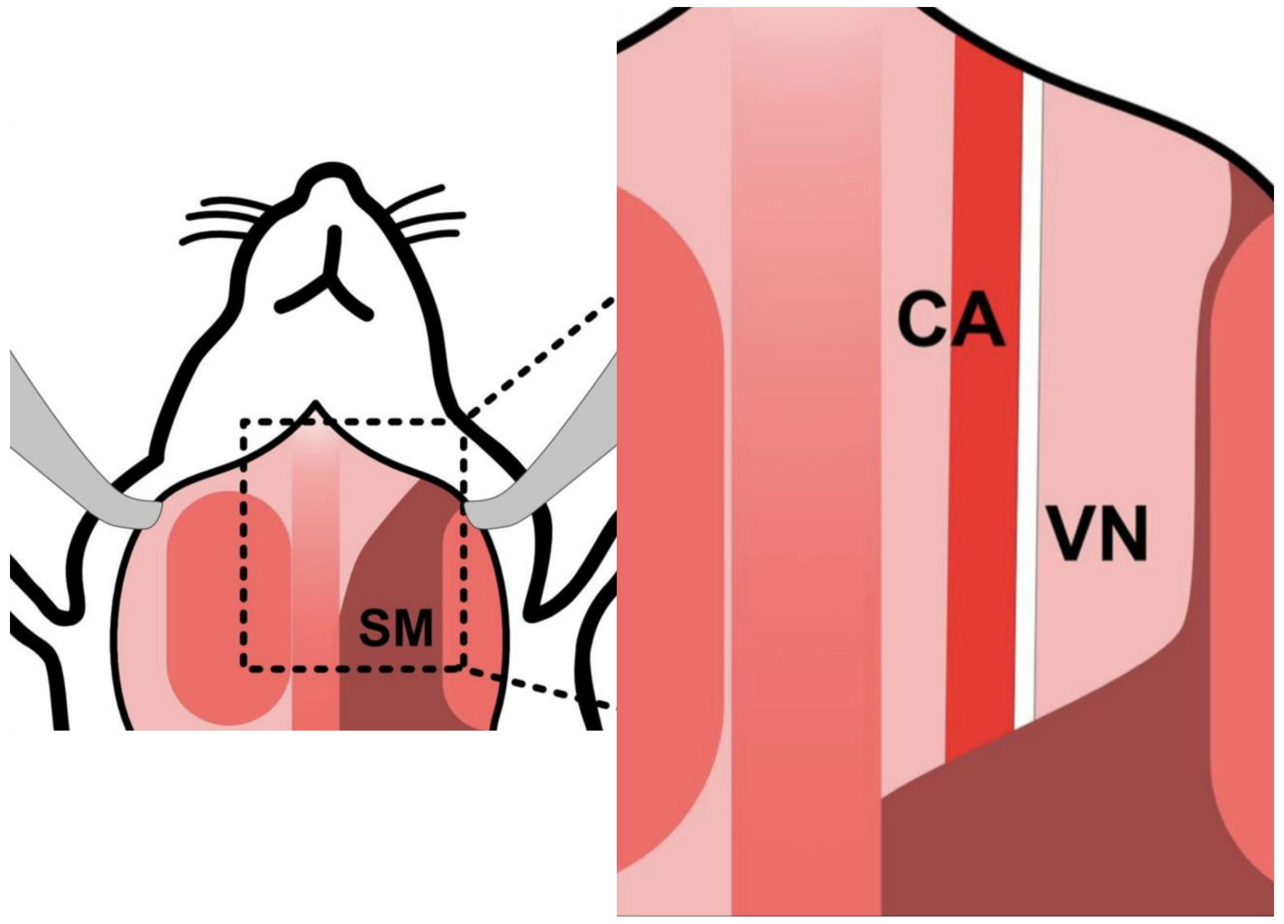
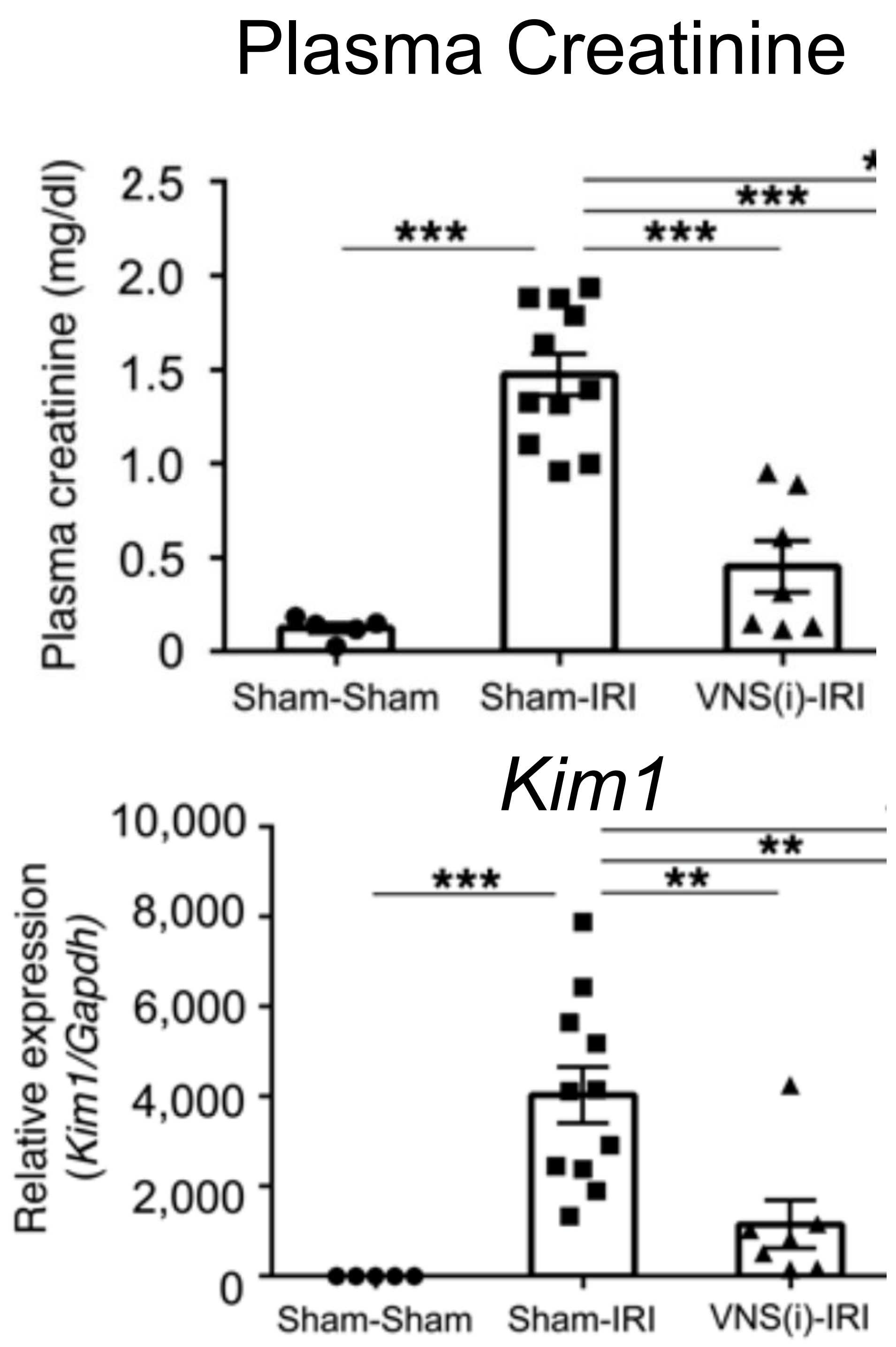
Therapeutic approaches of vagus nerve stimulation (VNS)







Clinical application

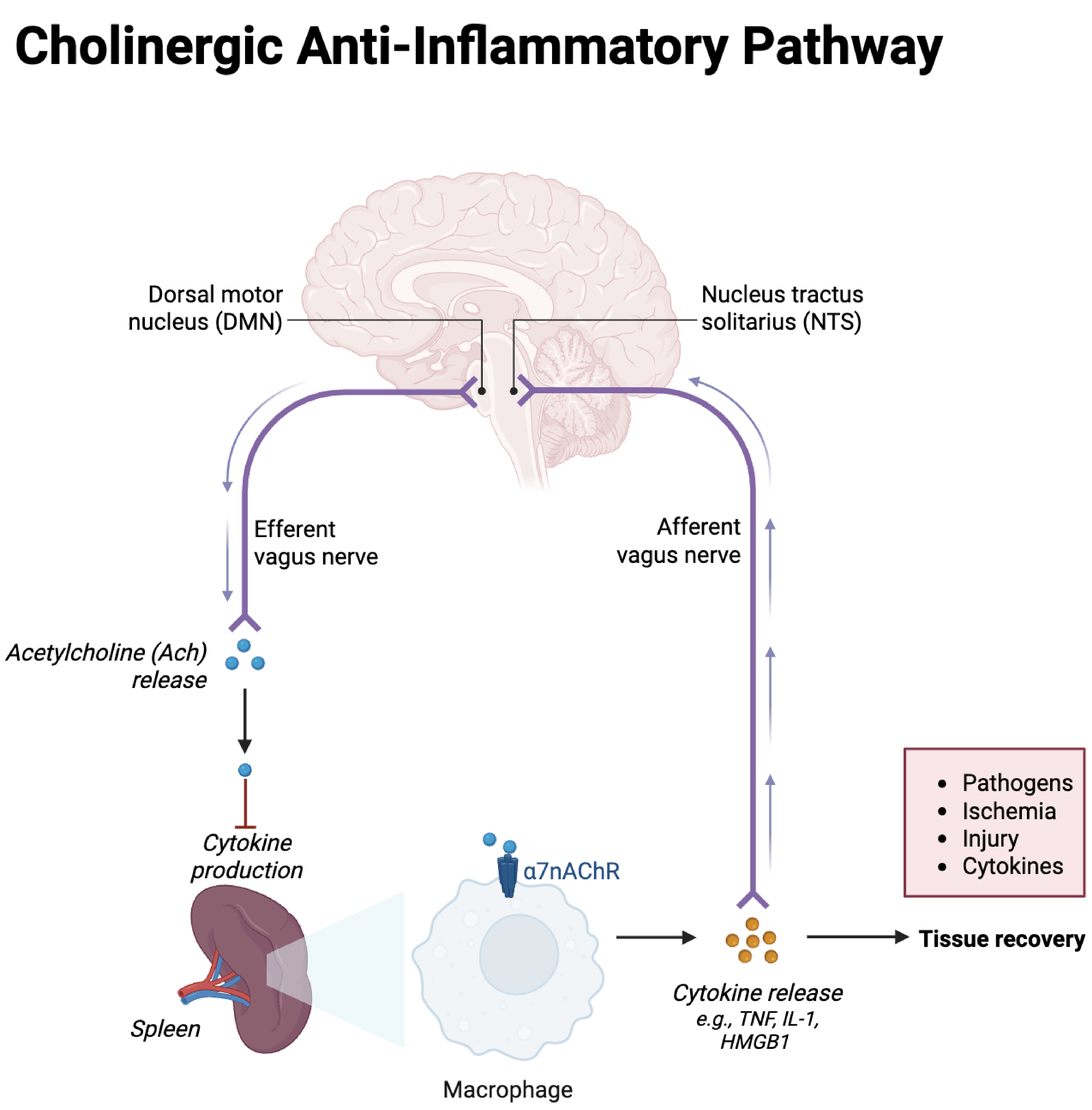
- Treatment-resistant epilepsy and depression (FDA)
- Clinical trials: headache, inflammatory bowel disease (IBD)… and others

Animal model

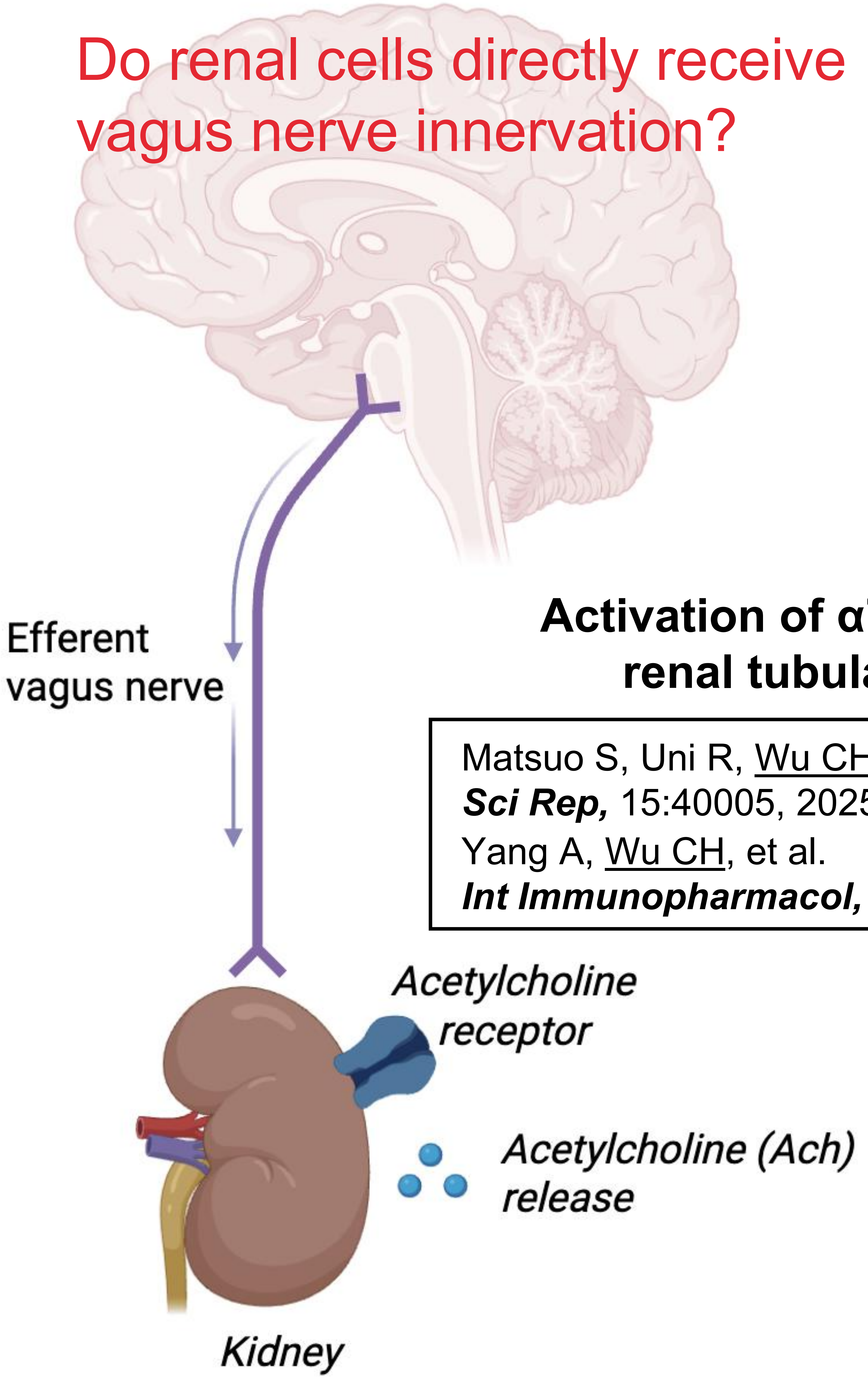
- **Attenuates systemic inflammation (Nature, 2000)**
- **Reduces tissue damage in acute kidney injury (T. Inoue. J Clin Invest. 2016)**

VN: vagus nerve   CA: carotid artery SM: Sternocleidomastoid muscle

The canonical Cholinergic anti-inflammatory pathway



Do renal cells directly receive vagus nerve innervation?



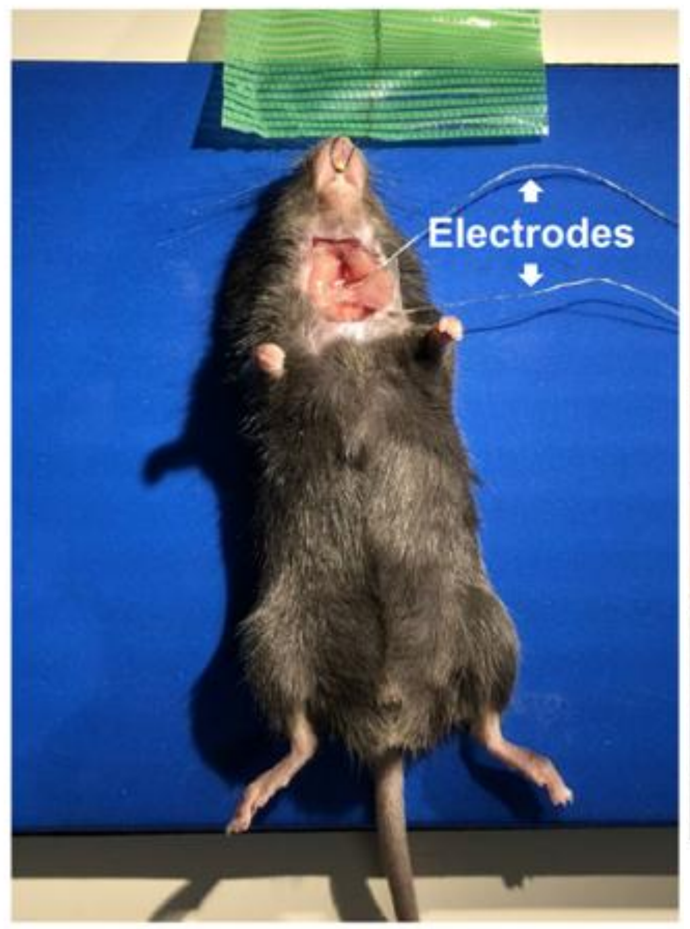
Activation of α7nAChR in renal tubular cells

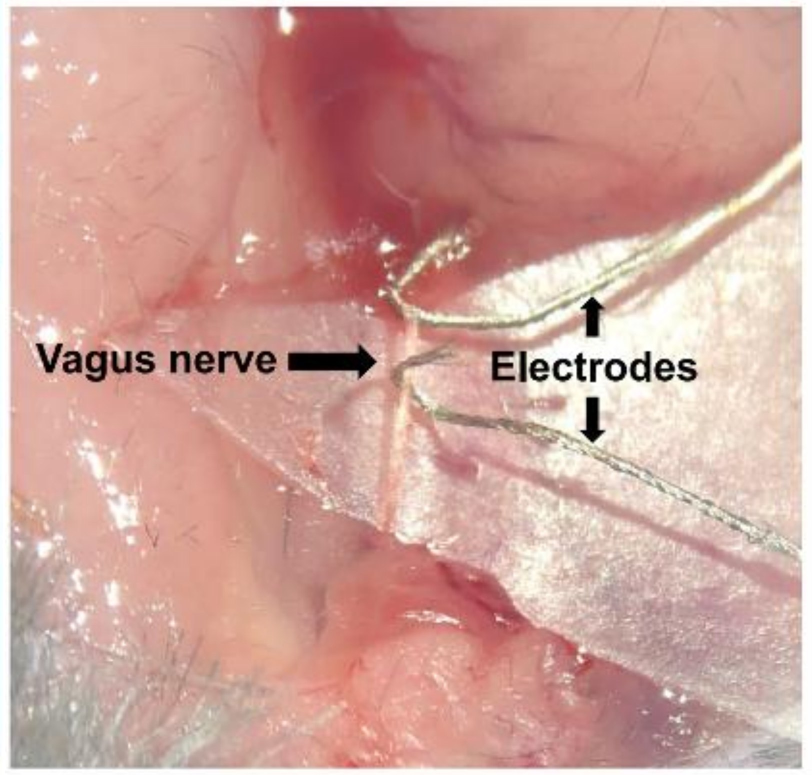
Matsuo S, Uni R, Wu CH, et al.
Sci Rep, 15:40005, 2025
Yang A, Wu CH, et al.
Int Immunopharmacol, *138:112555, 2024*

α7nAChR: α7 nicotinic acetylcholine receptor

Increase in Renal Acetylcholine (ACh) After VNS

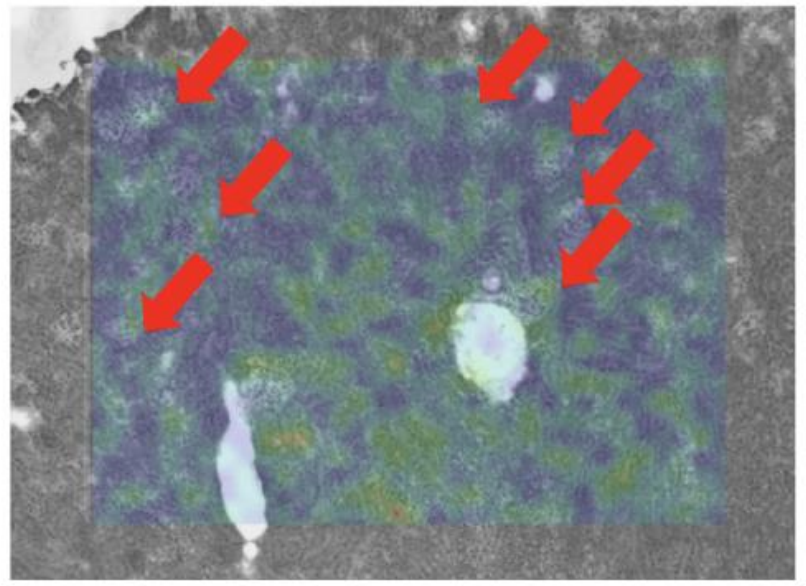
5 Hz, 1 ms pulse, 50 μA, 10 minutes





Unpublished data

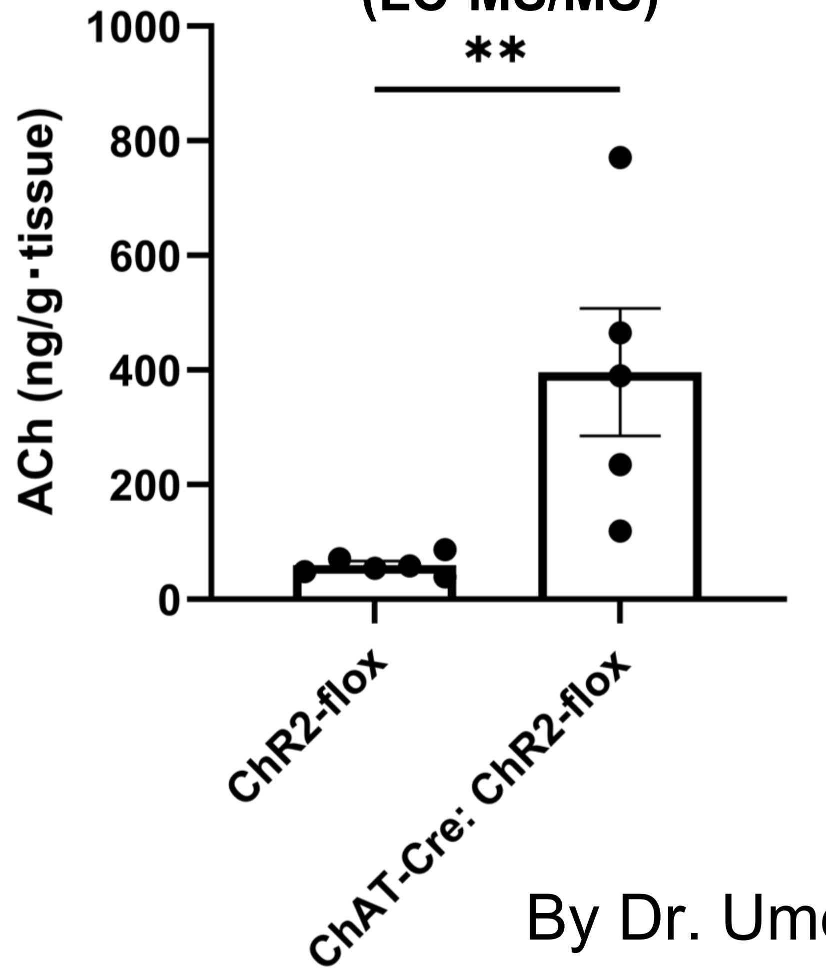
Imaging MS



Imaging MS showed the presence of acetylcholine in kidney section

ACh increase after VNS

Acetylcholine concentration (LC-MS/MS)



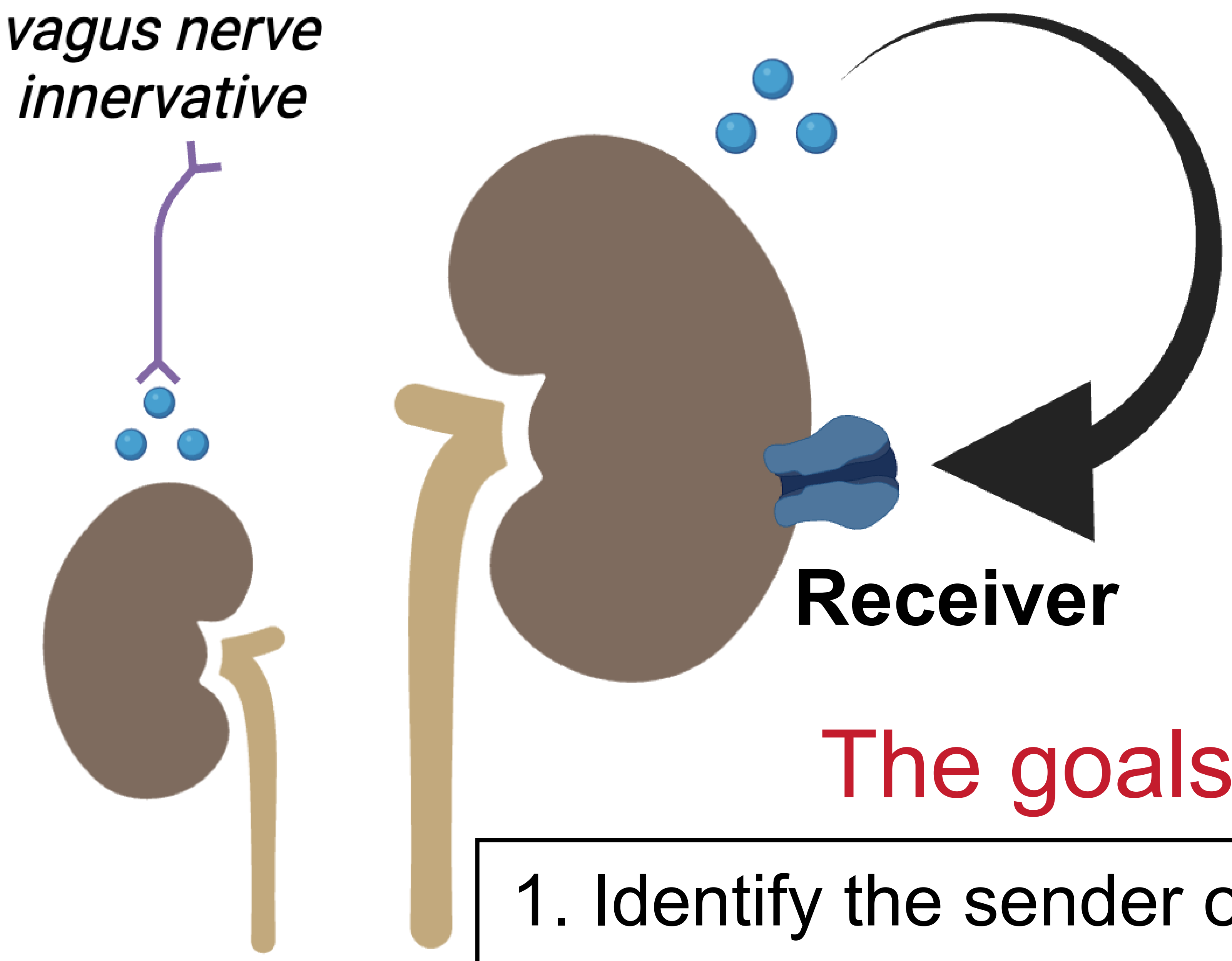
By Dr. Umene

Hypothesis

Renal Autonomous Cholinergic System (RACS)

Sender

Non-neuronal acetylcholine producing cells



The goals of this study

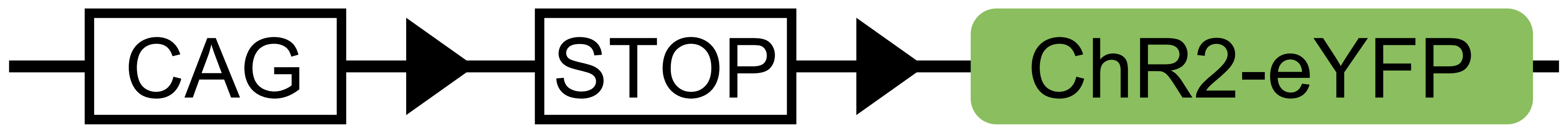
1. Identify the sender of ACh (ChAT positive cells)
2. Identify the receiver of ACh (receptor, cell type)
3. What is the physiological role of this system

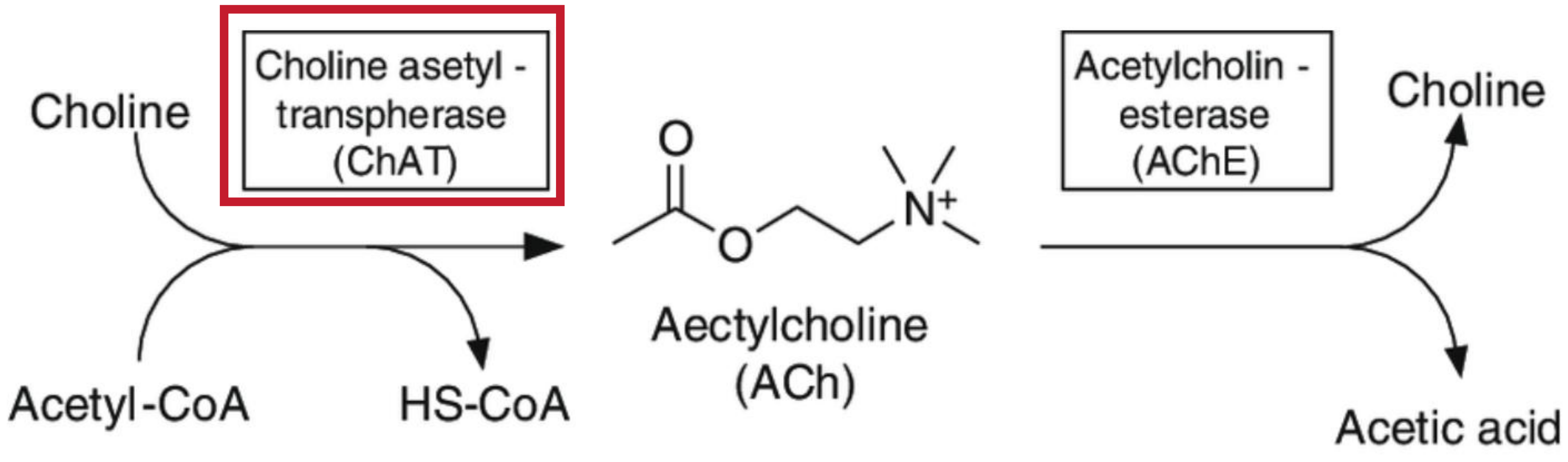
The sender:
Choline O-Acetyltransferase (ChAT)-reporter mice

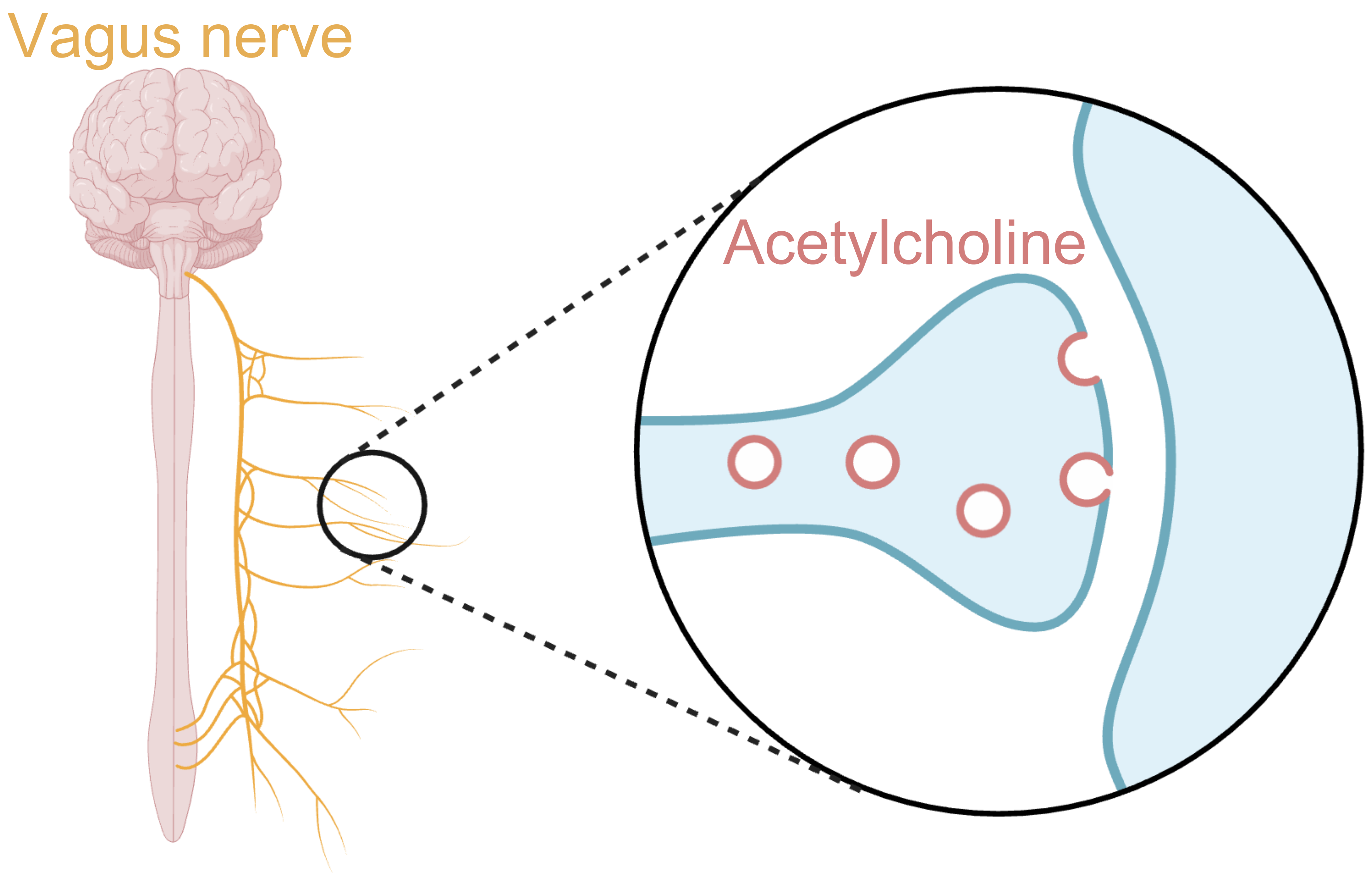
ChAT-Cre

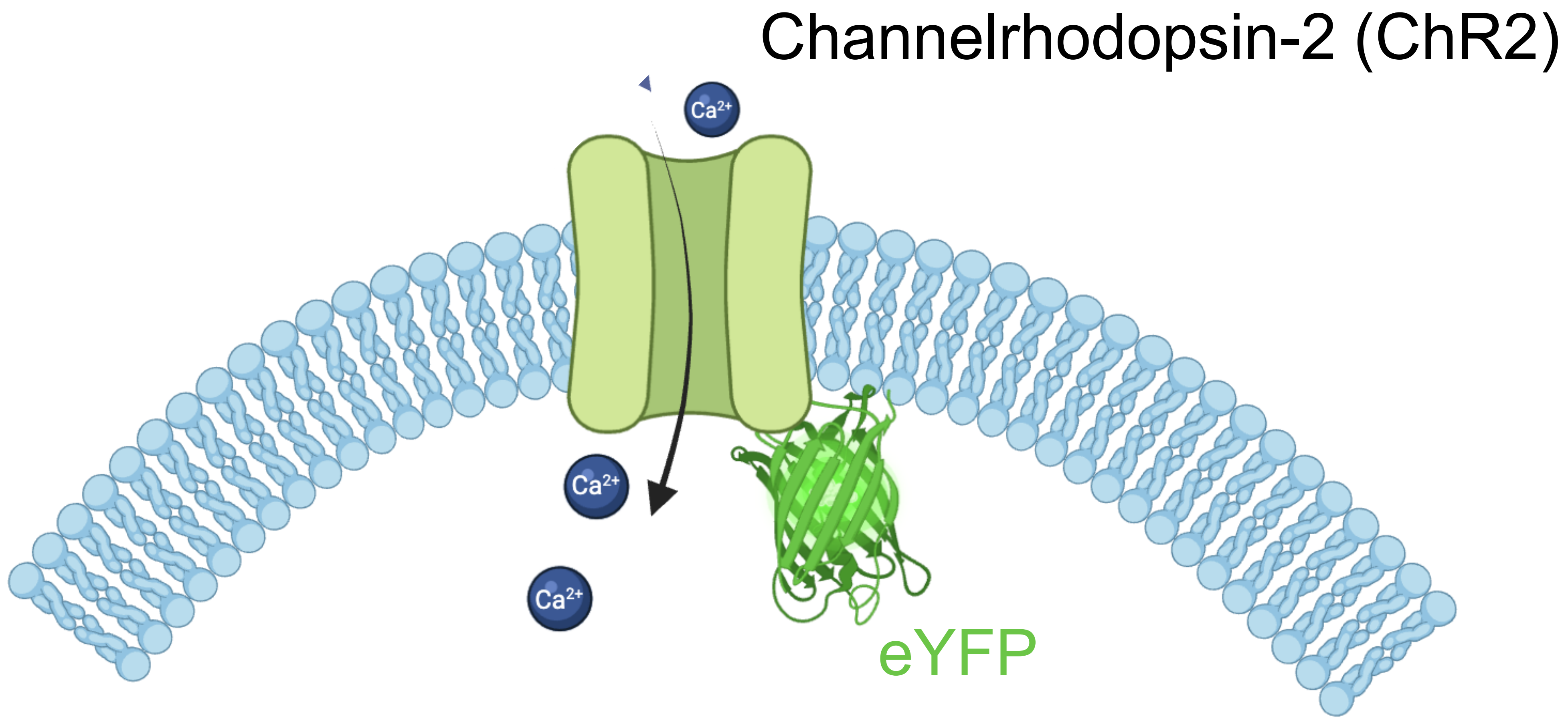
×

eYFP



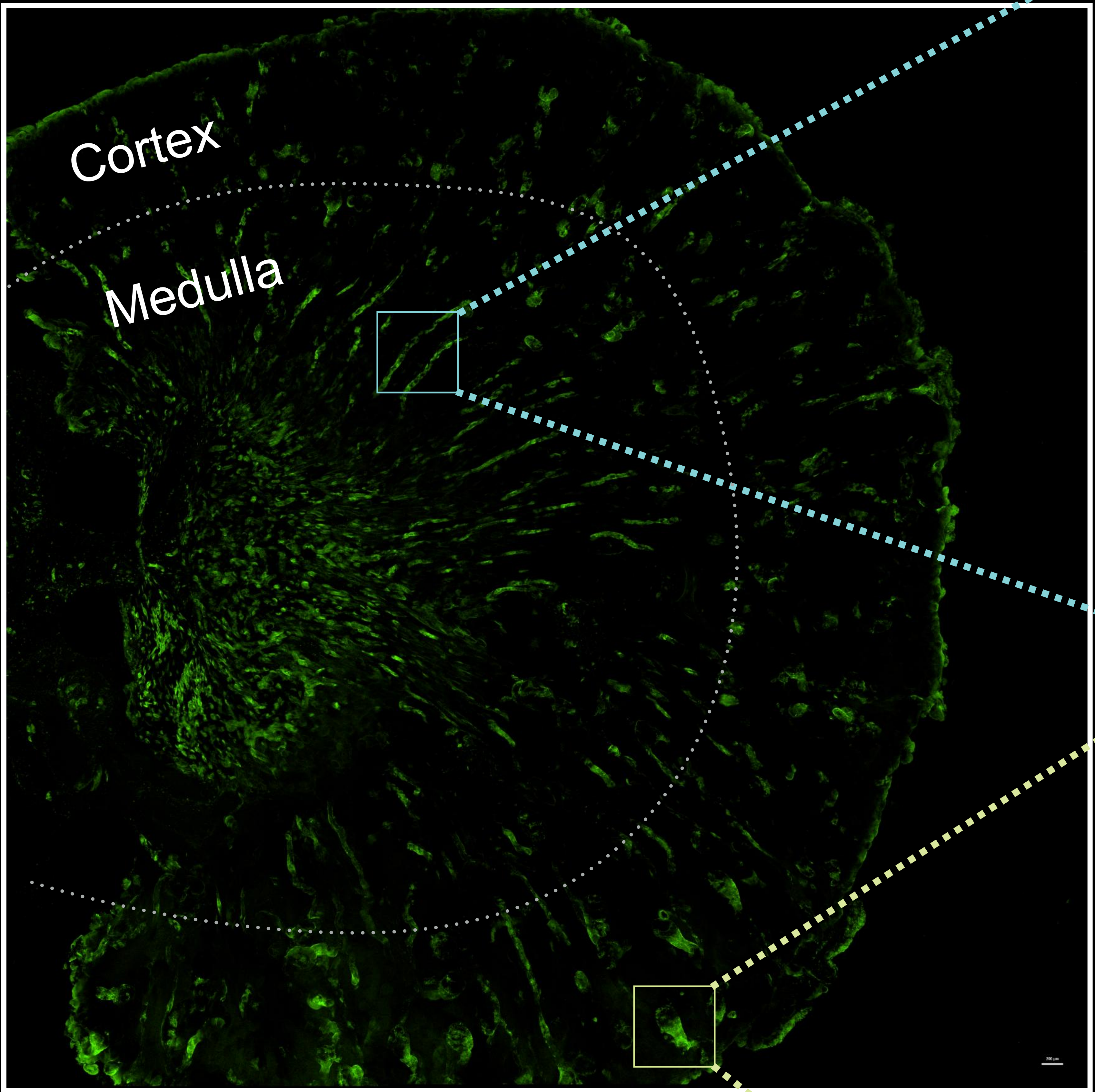


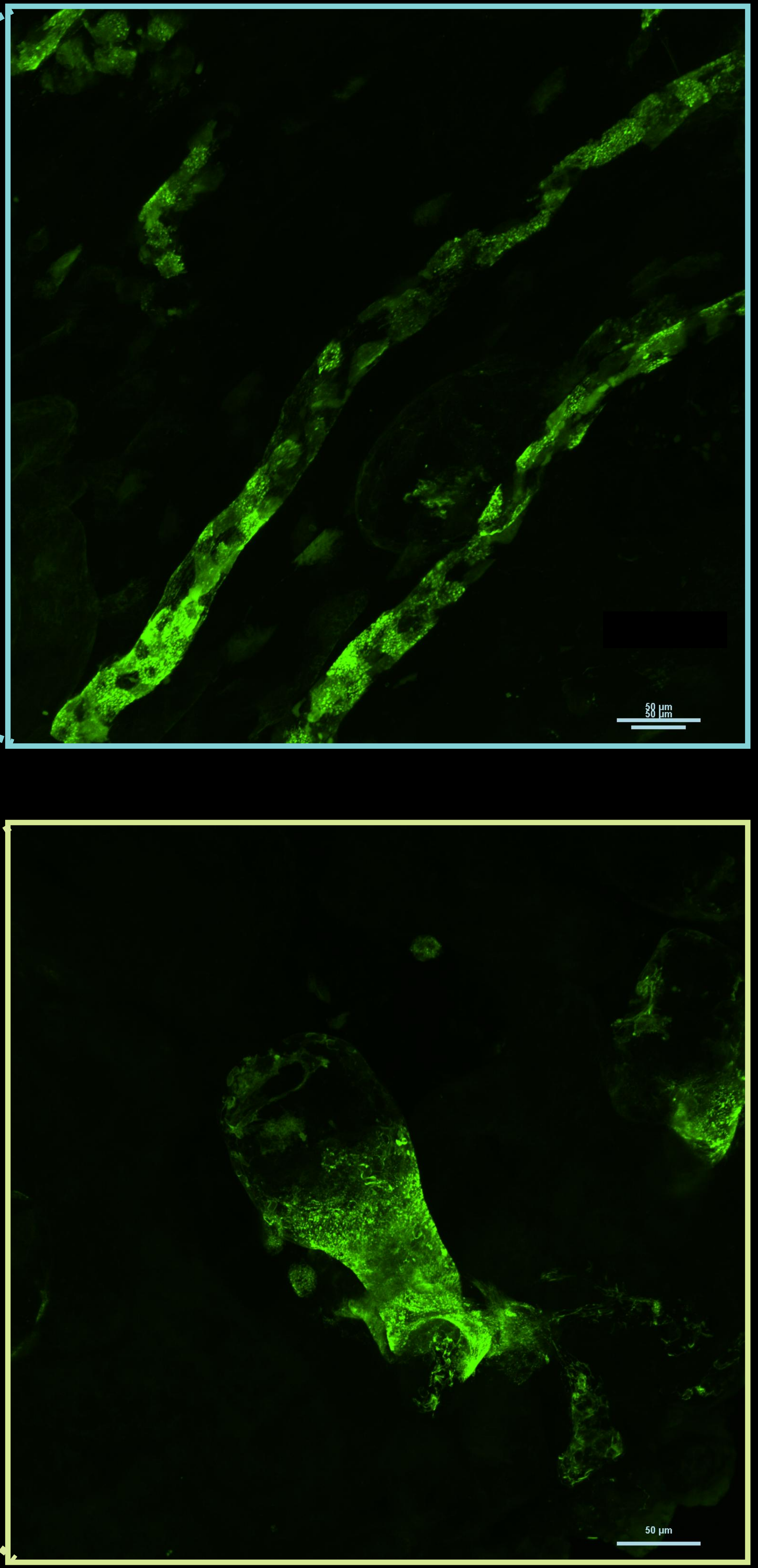




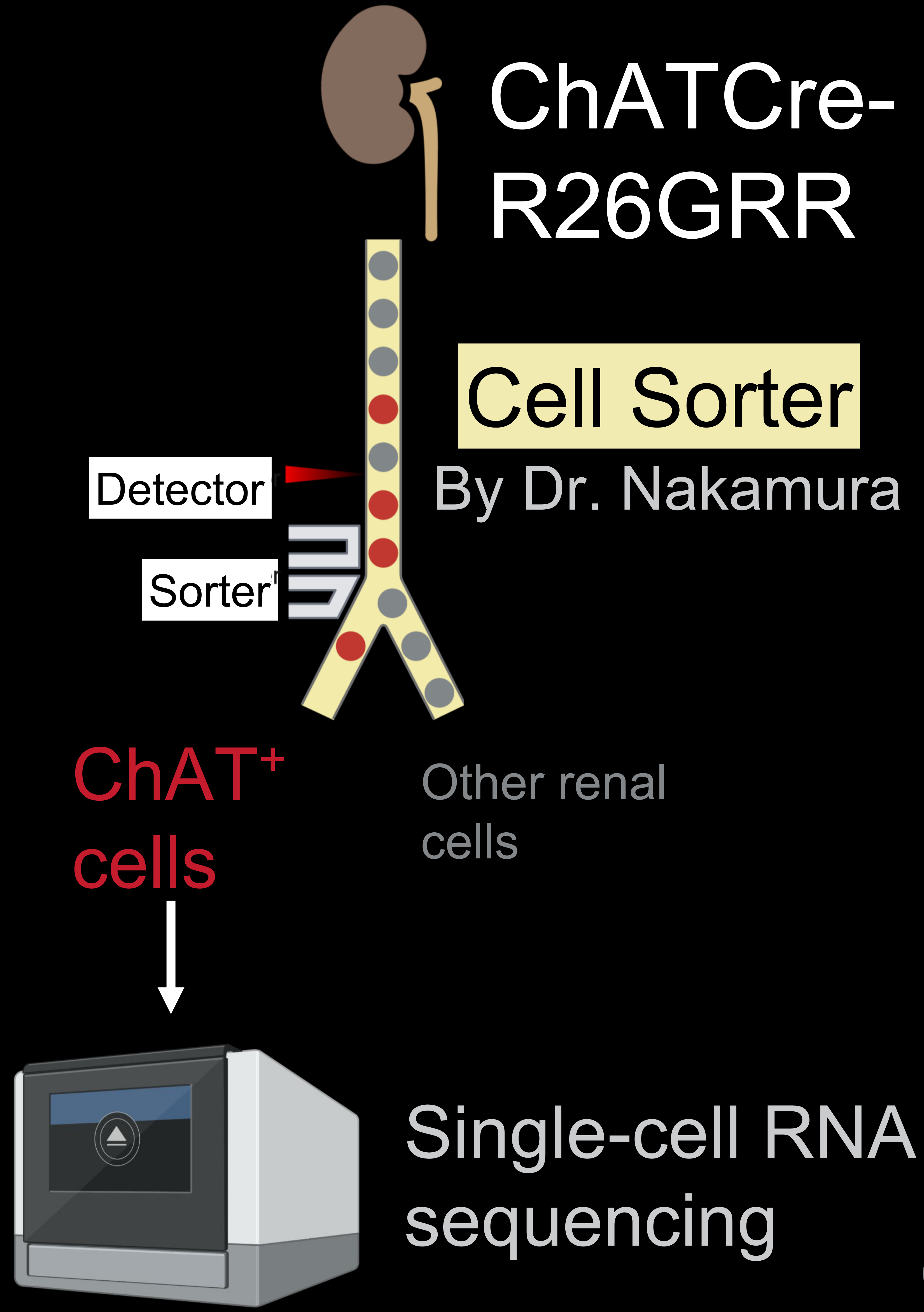
The sender:
Choline O-Acetyltransferase (ChAT)-reporter mice

eYFP





50 µm kidney sections



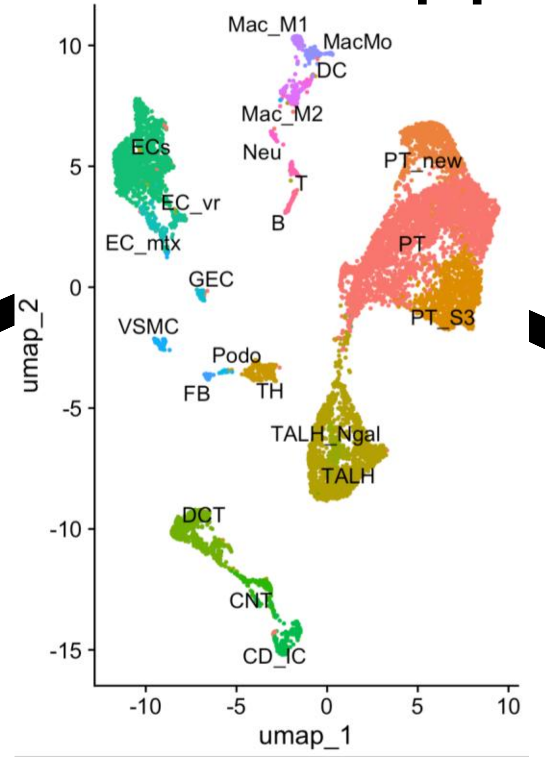
Unpublished data

The sender:
Choline O-Acetyltransferase (ChAT)-reporter mice

Renal

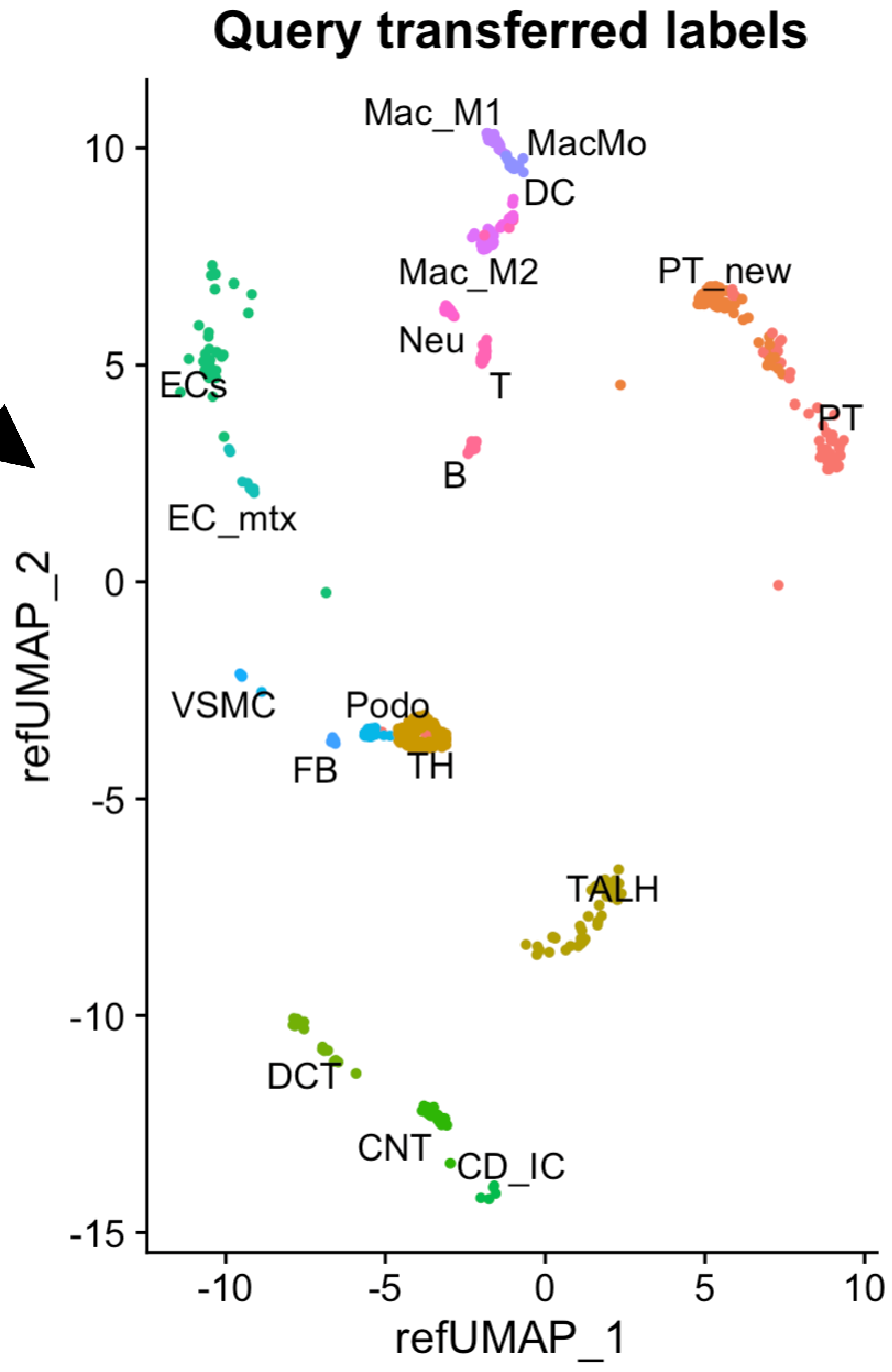
ChAT^{+} cells

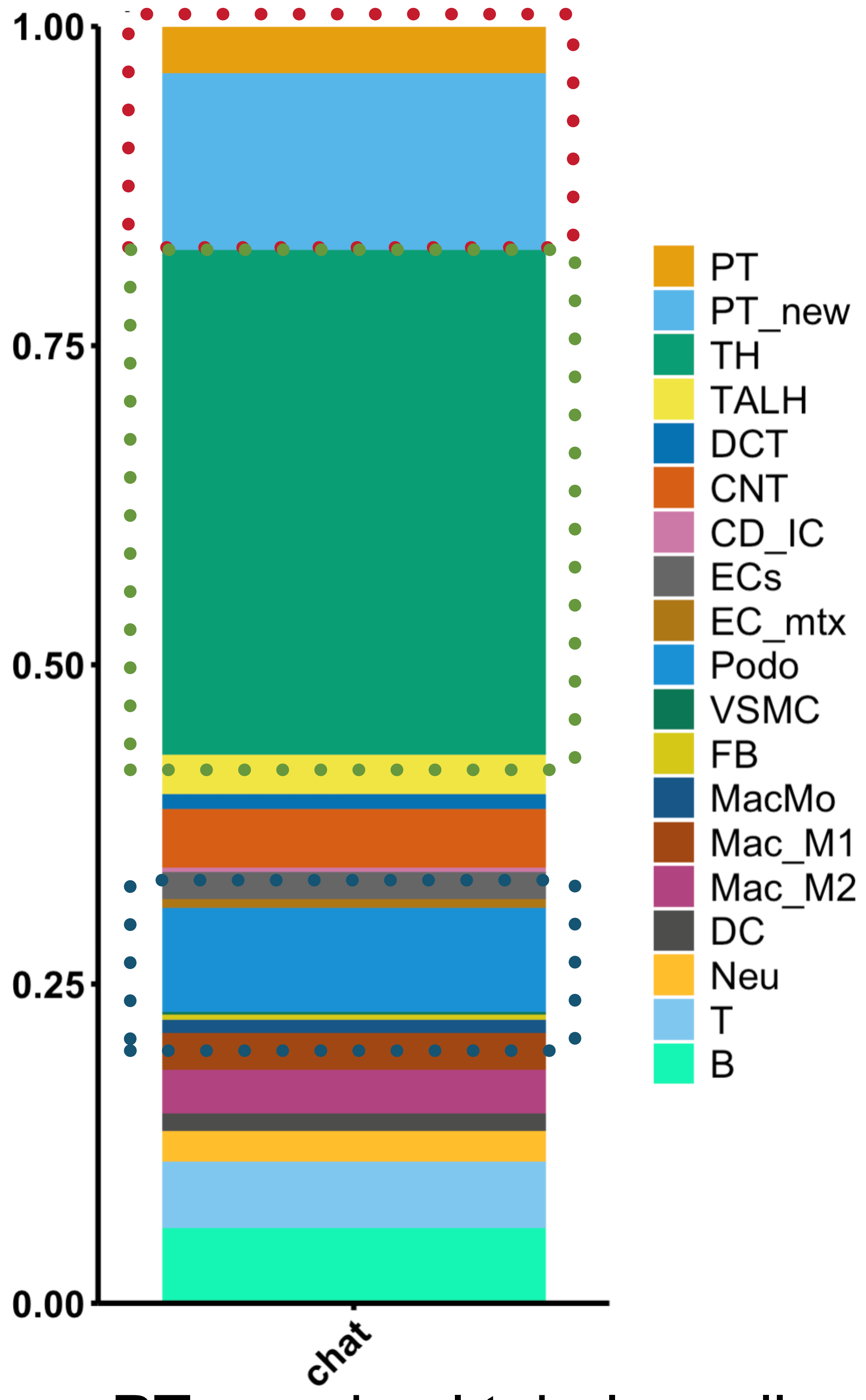
Cell type annotation via transfer mapping



Reference annotation (VNS-IRI)

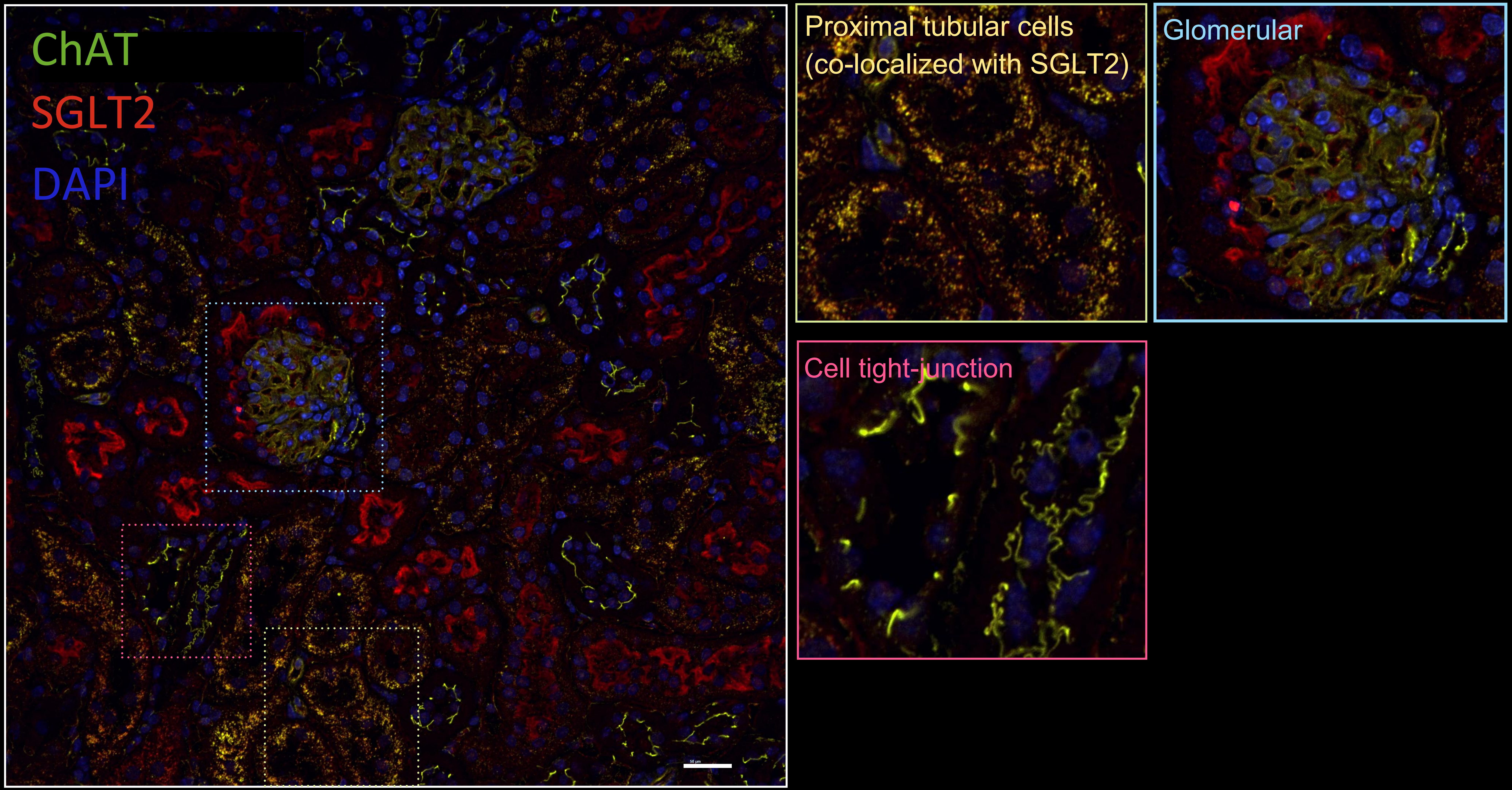
Unpublished data





PT: proximal tubular cells
TH: thin loop of Henle
Podo: podocytes

The sender:
Choline O-Acetyltransferase (ChAT)-reporter mice



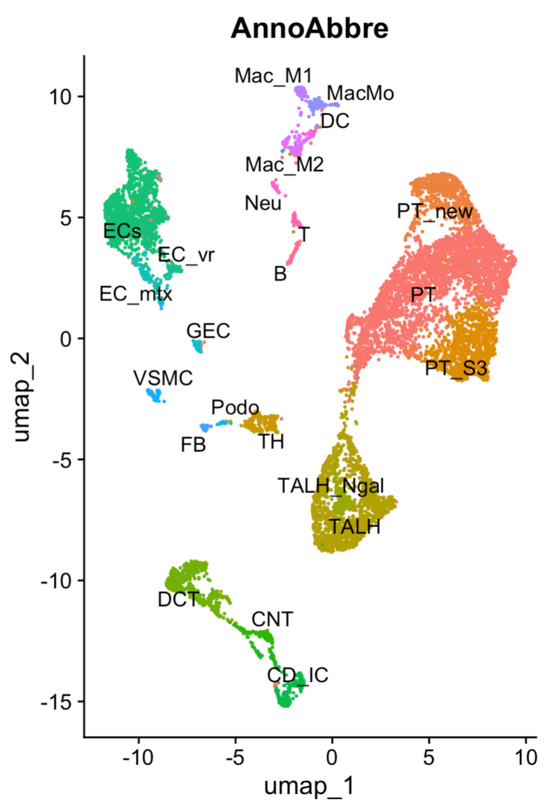
Scale bar: 50μm

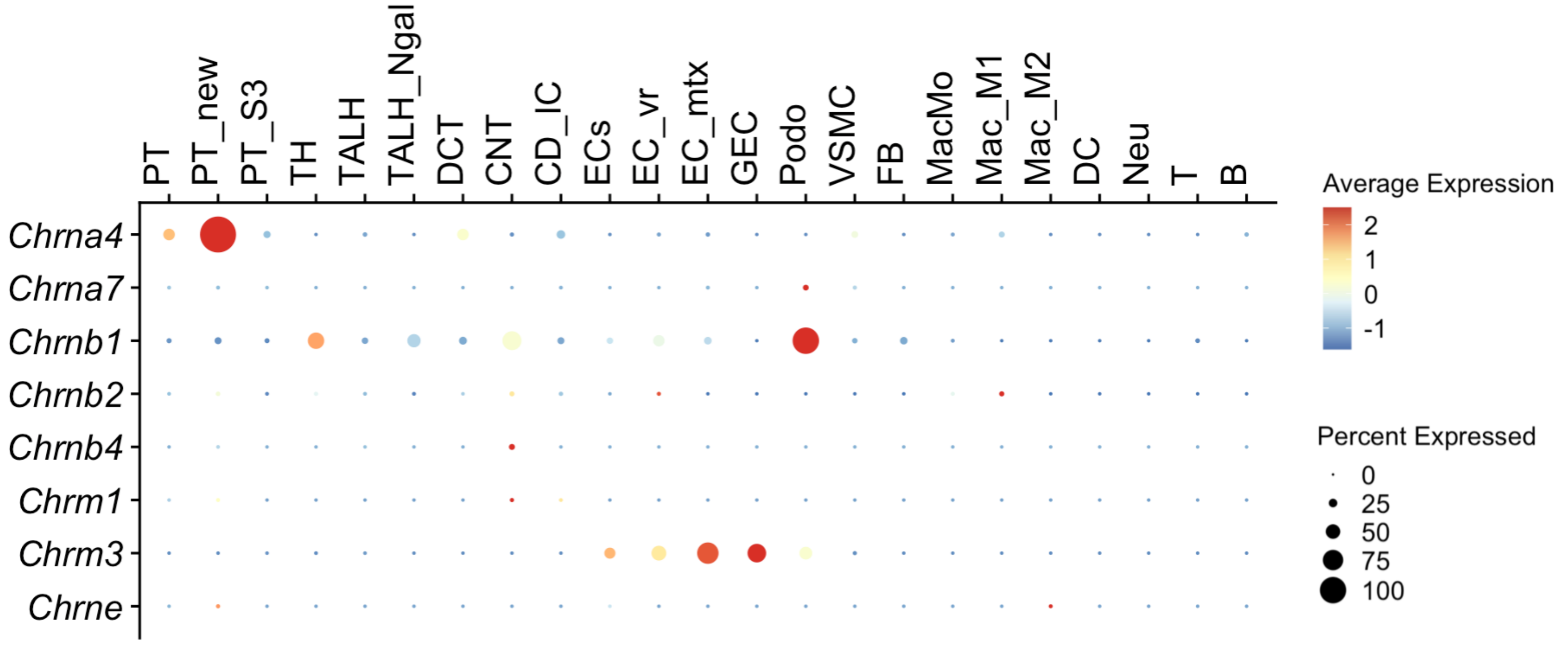
Unpublished data

The receiver cell: Acetylcholine receptor

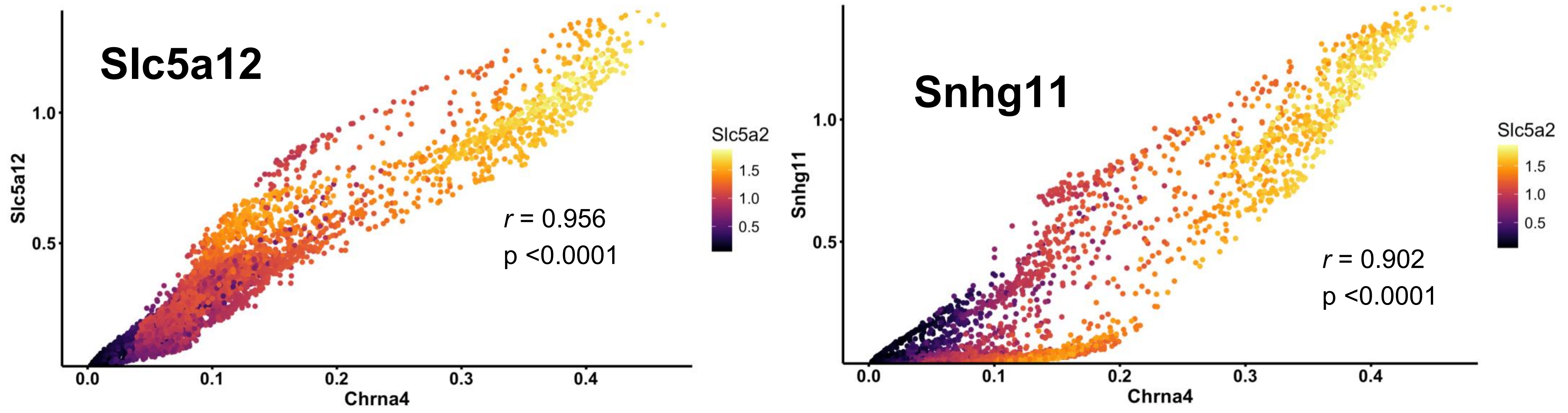
Unpublished data

α4nAChR (encoded by Chrna4)

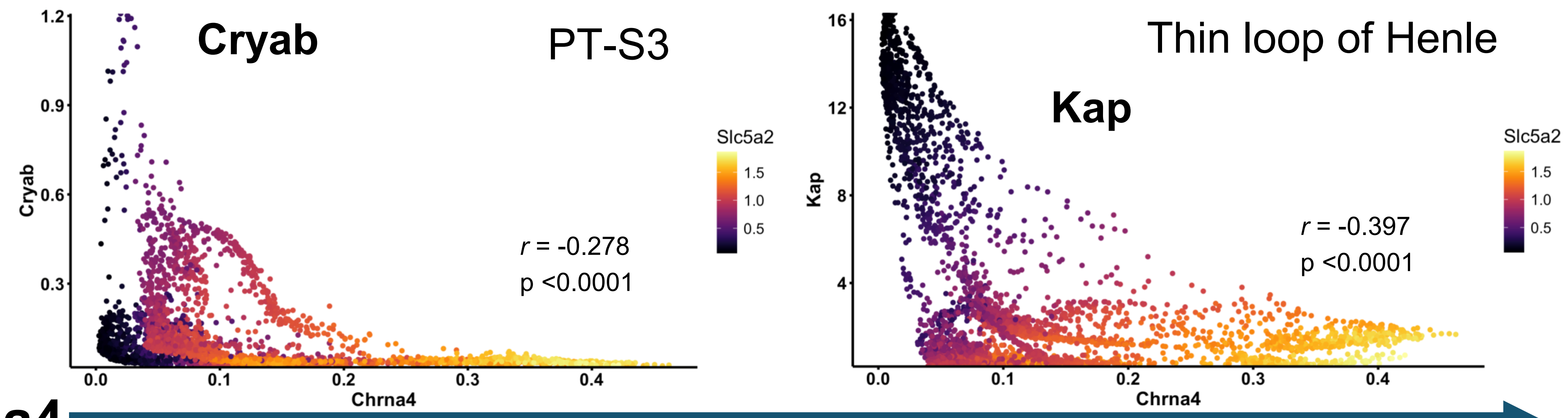




Positive correlation

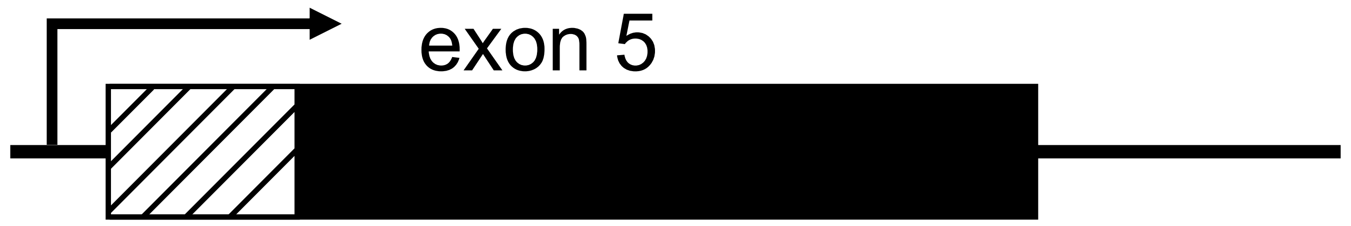


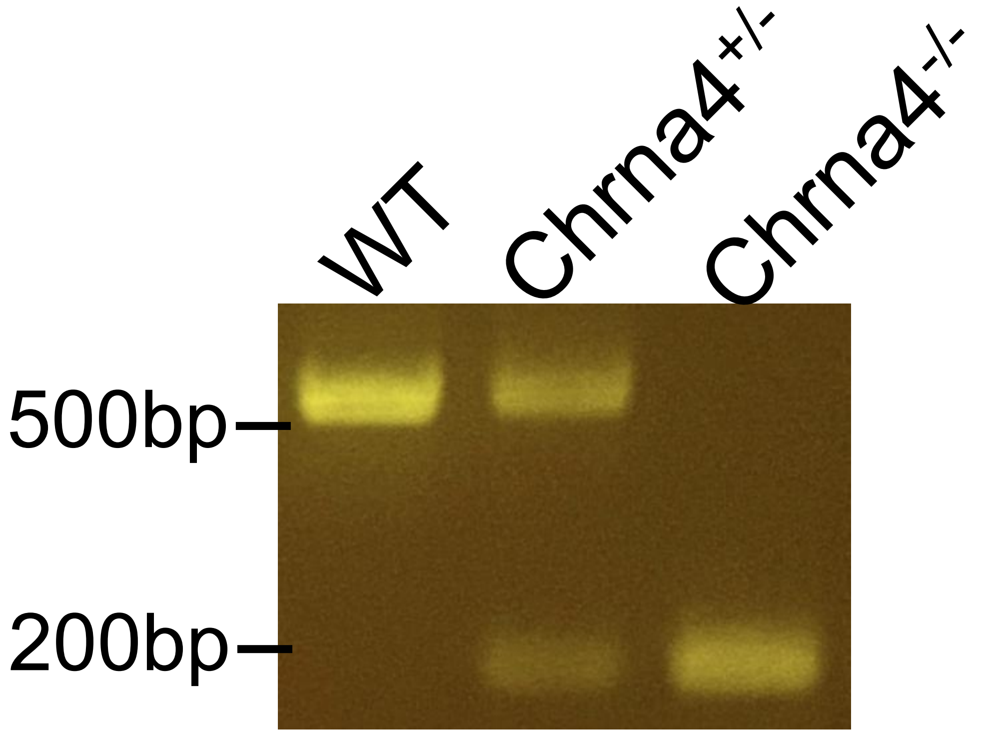
Negative correlation

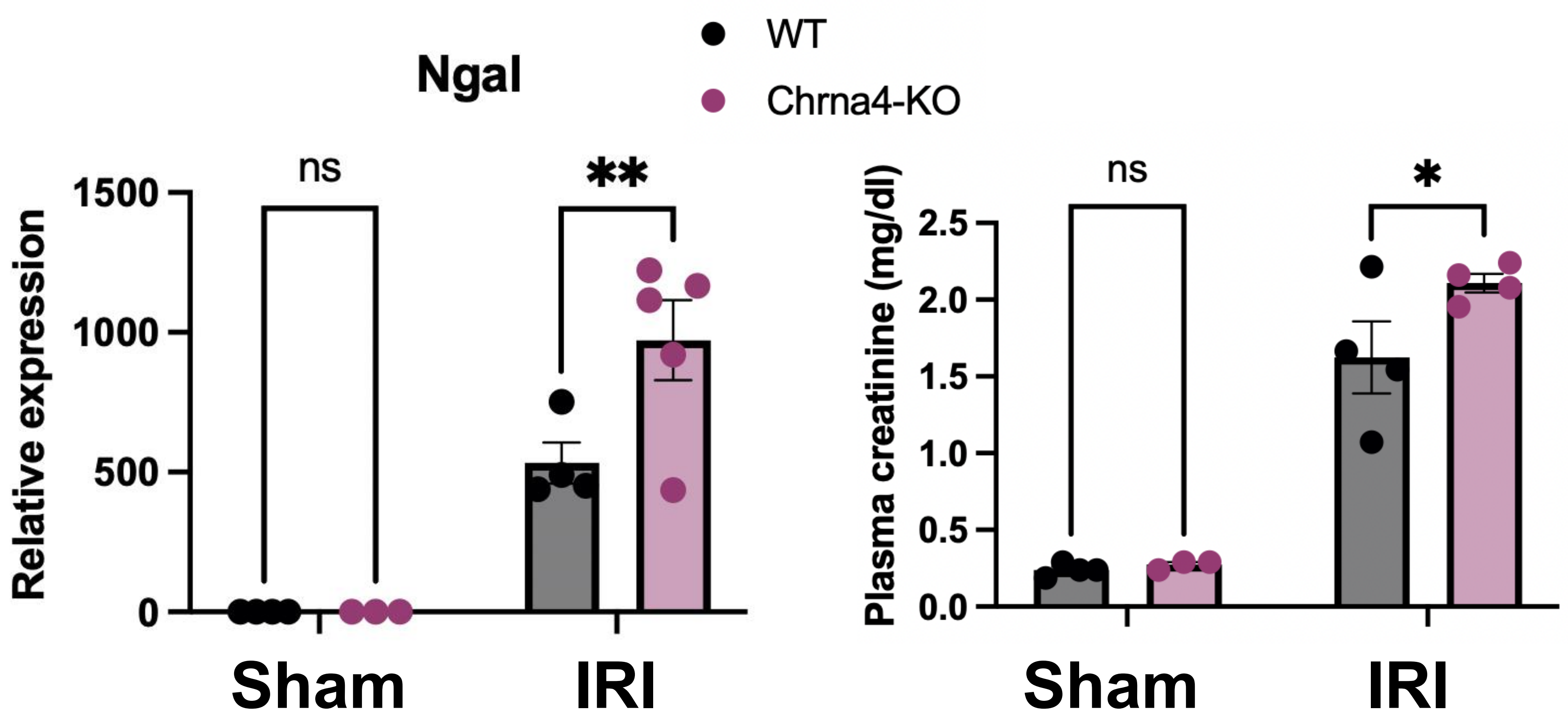


Chrna4

Chrna4 Knockout (KO) Mice

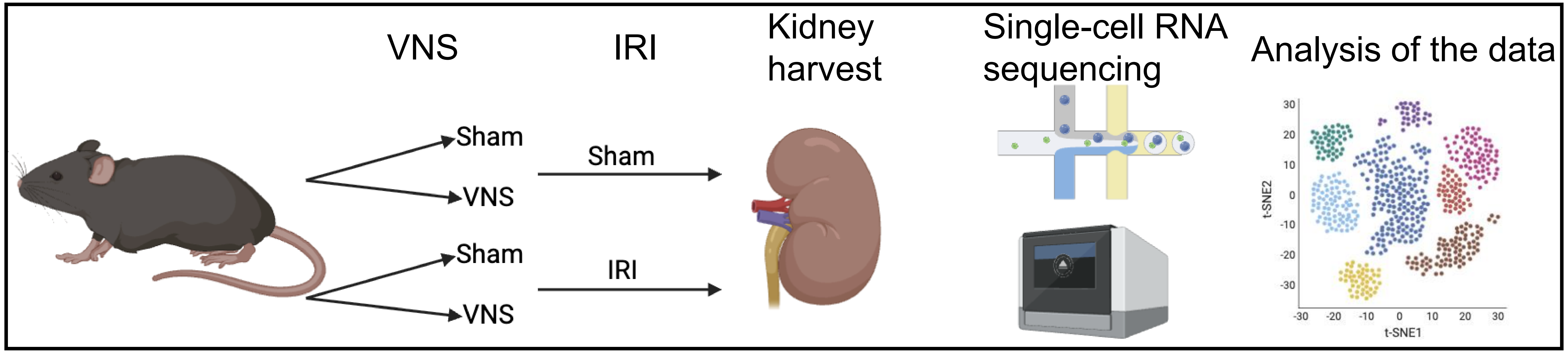


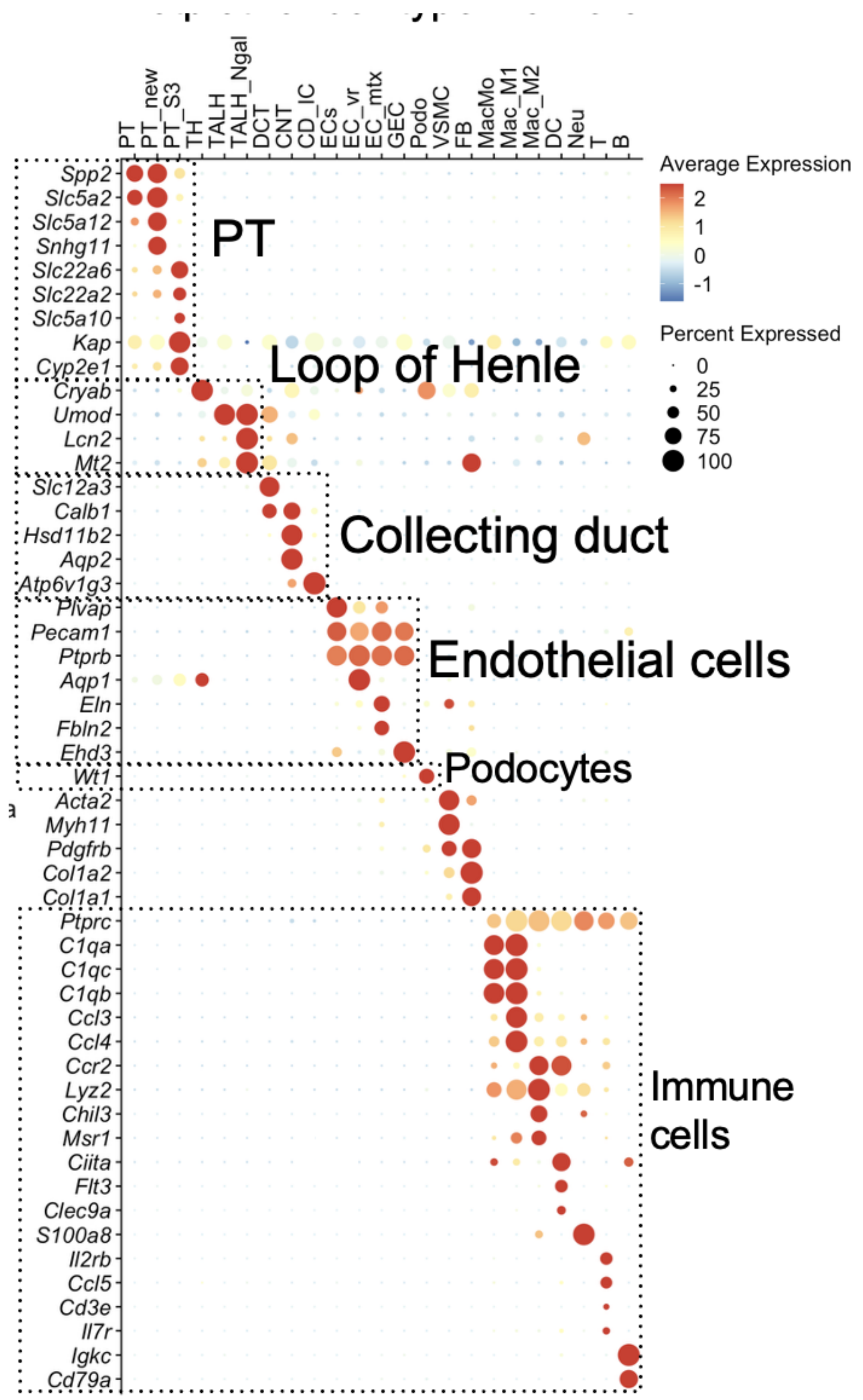


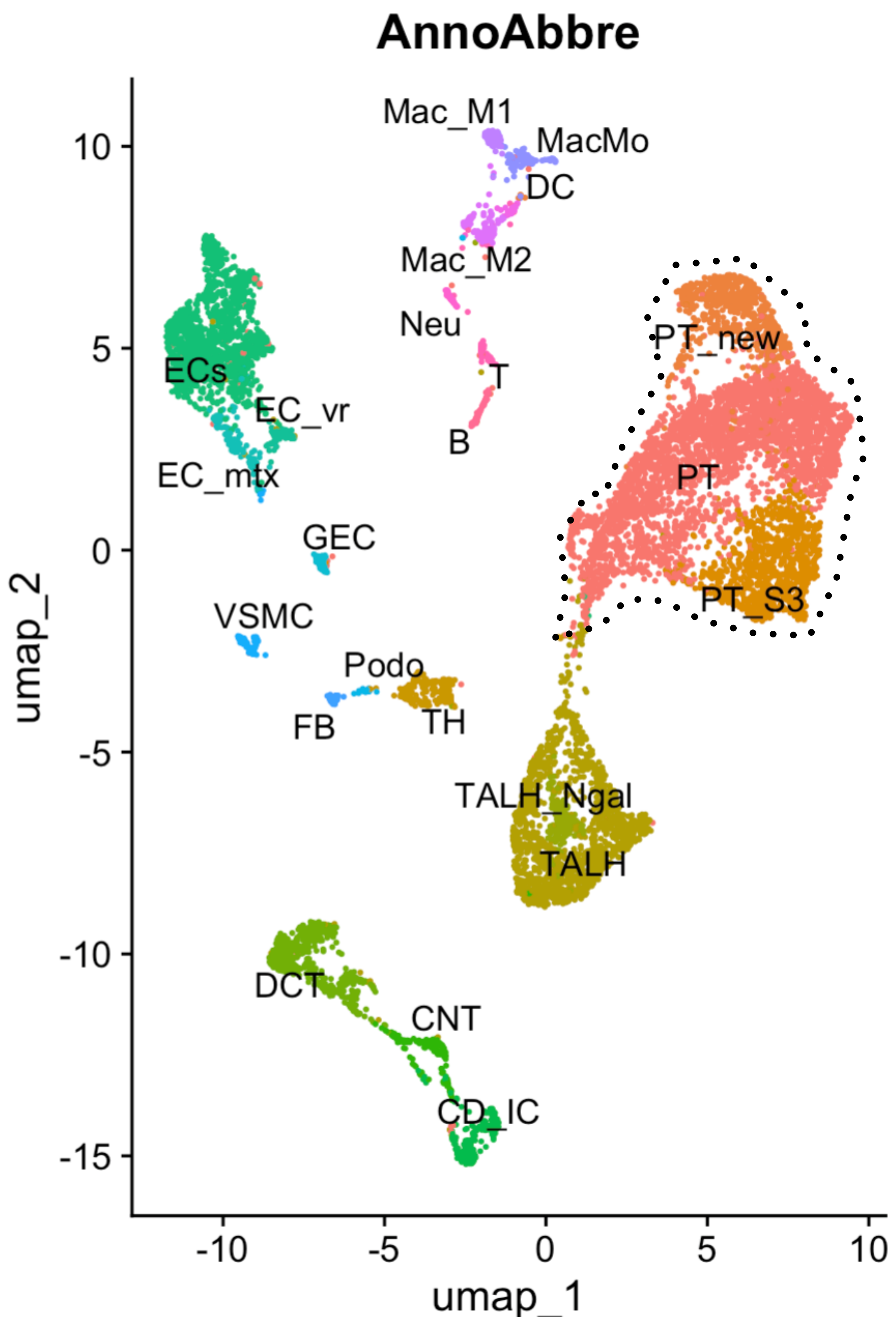


Chrna4 is important for the renal function

Investigating the physiological role of VNS in kidney

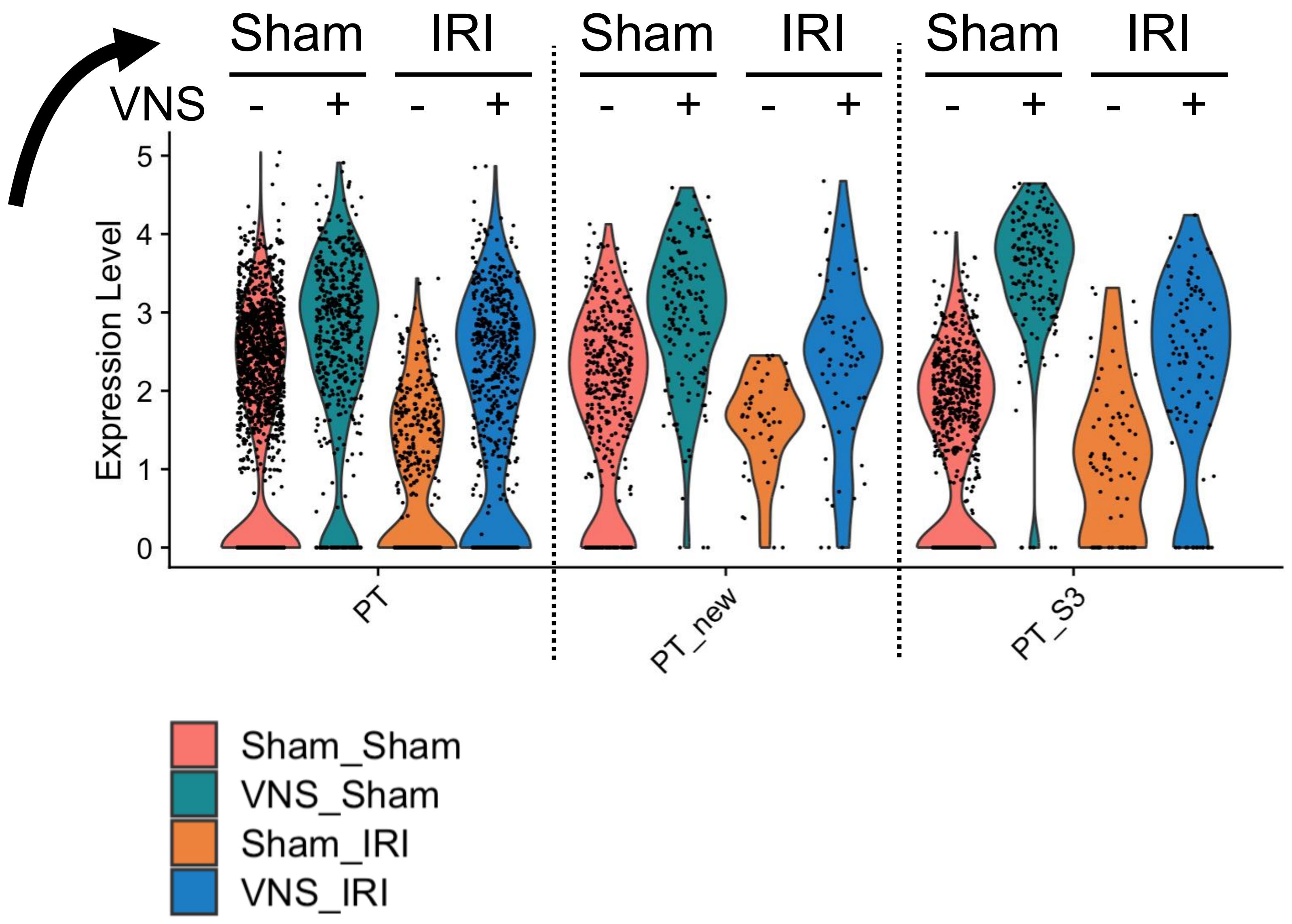


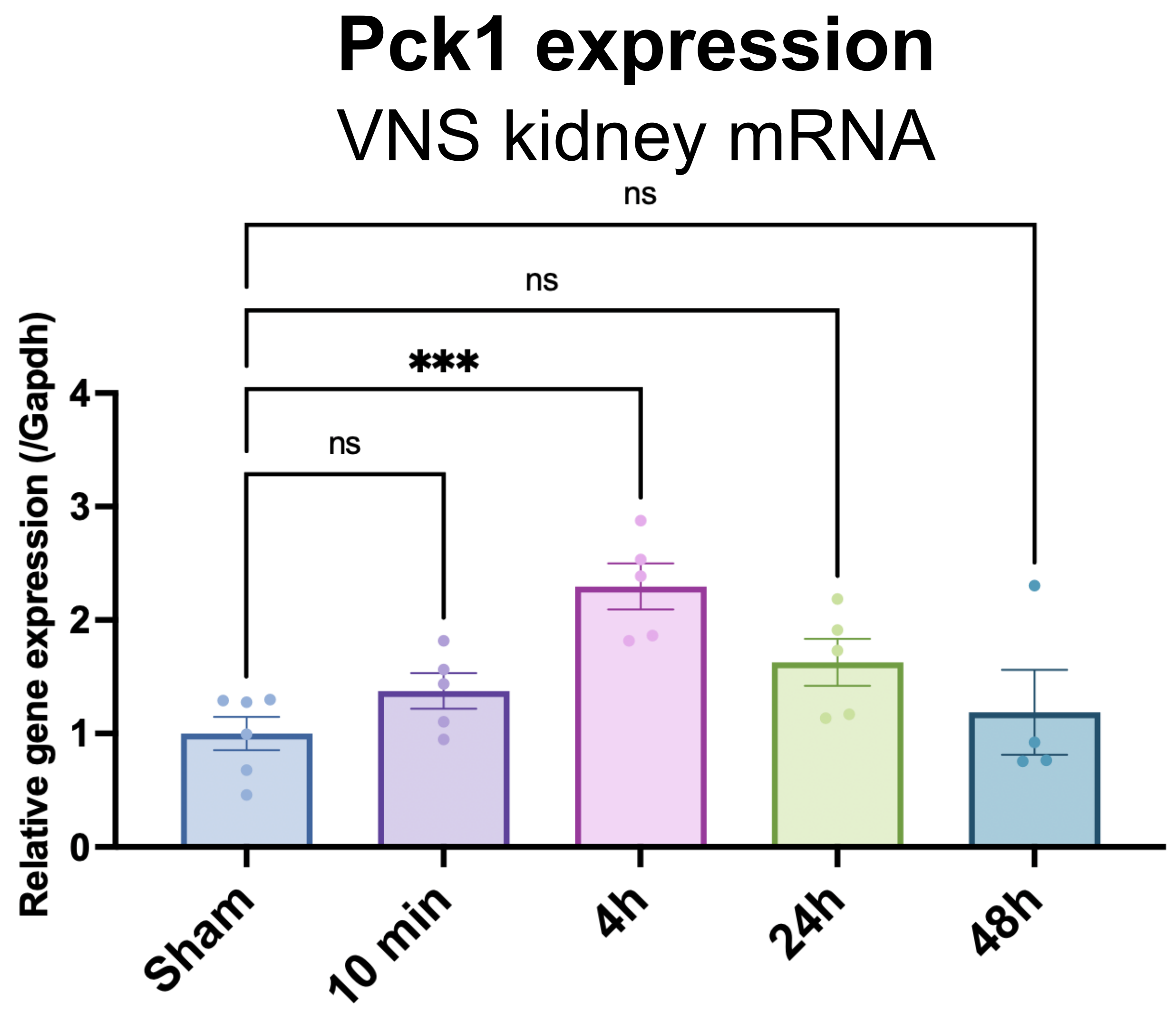


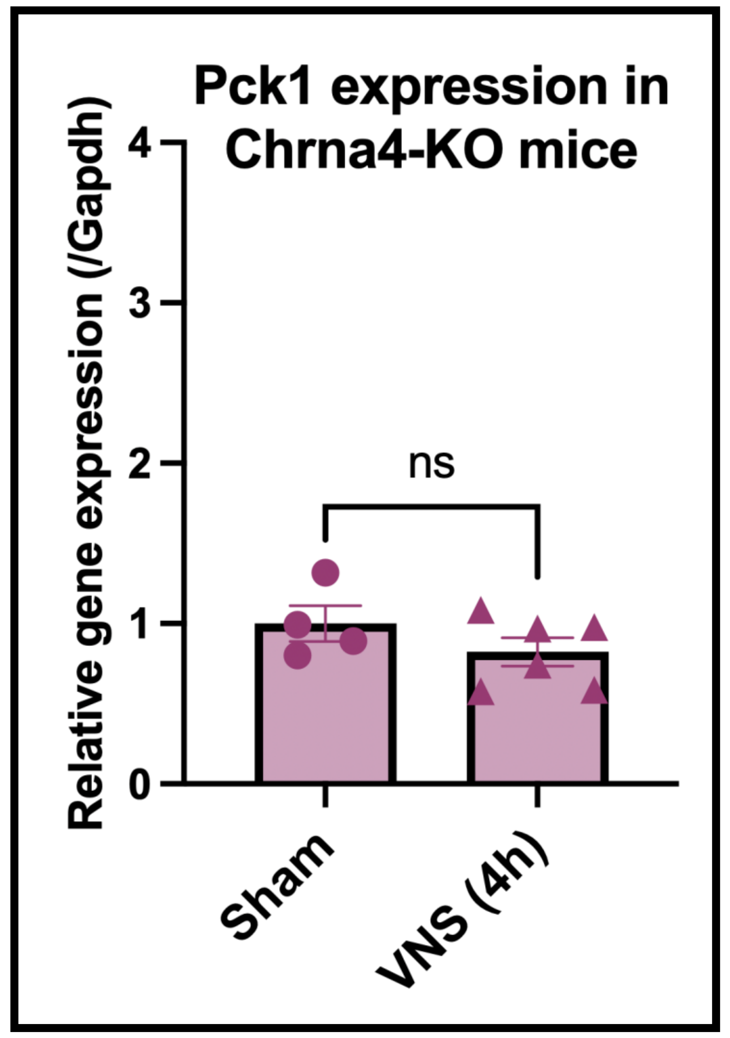


Pck1

Phosphoenolpyruvate carboxykinase 1





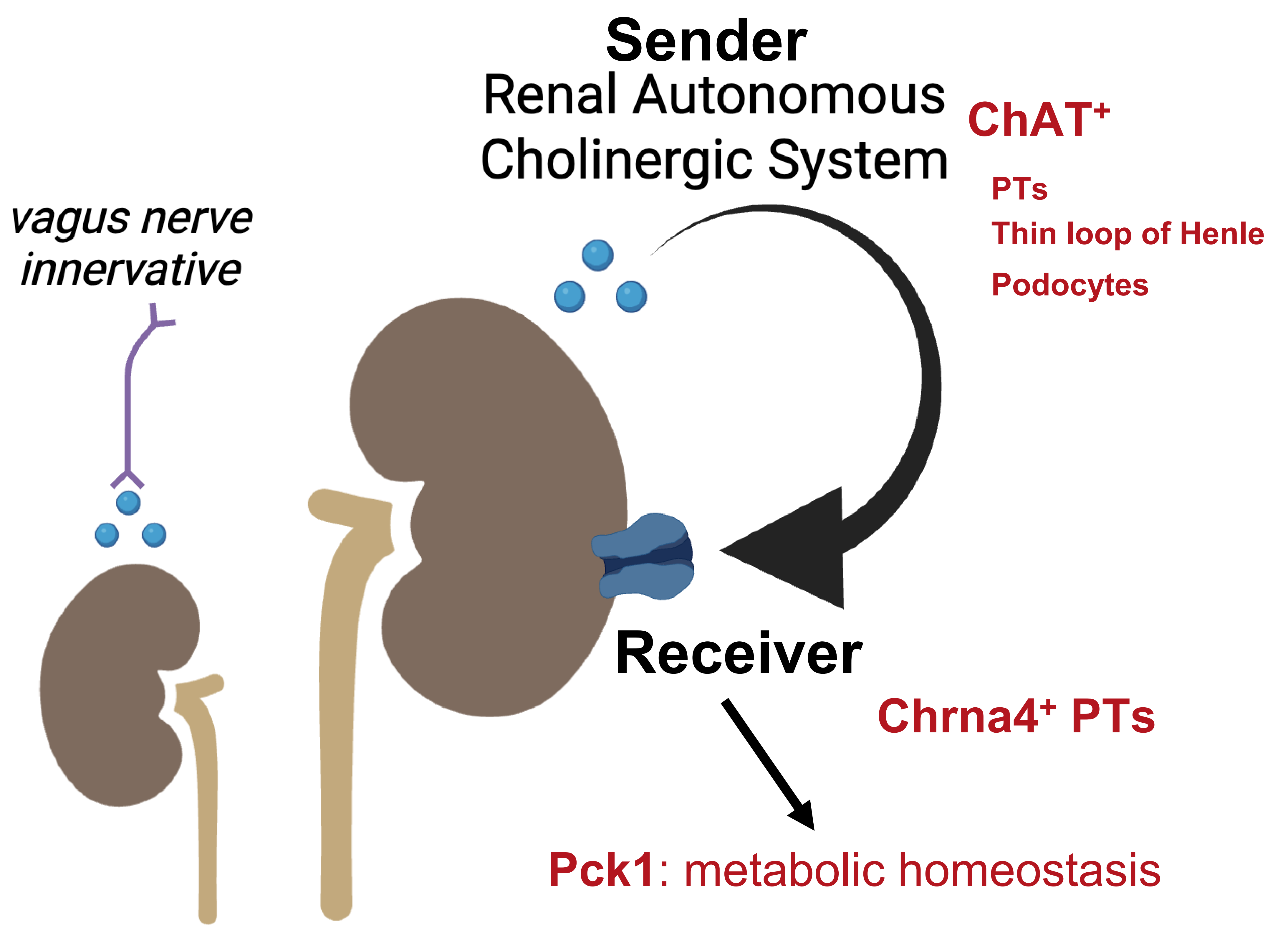


Summary

- The sender (ChAT-positive cells):
  - Cell types — Proximal tubular, podocytes, thin loop of Henle
- The receiver (α4nAChR-expressing cells):
  - Proximal tubular cells (Slc5a12$^+$, Snhg11$^+$)
- Functional outcome:
  - VNS preconditioning induced Pck1, a gene involved in cell metabolism

Hypothesis

Renal Autonomous Cholinergic System (RACS)



Acknowledge

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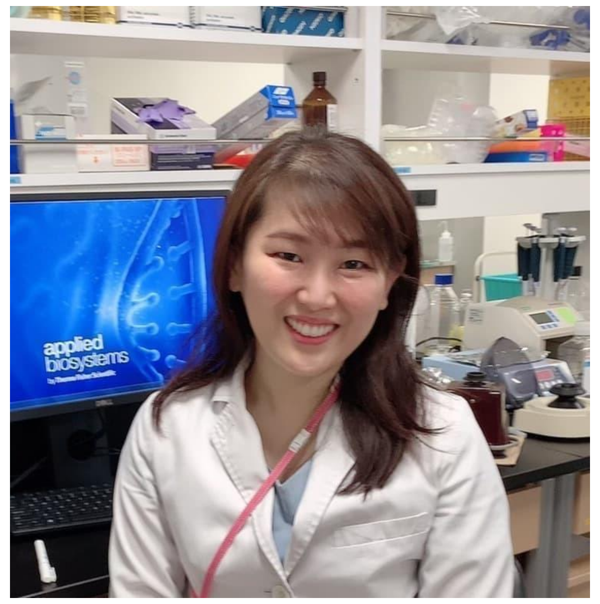

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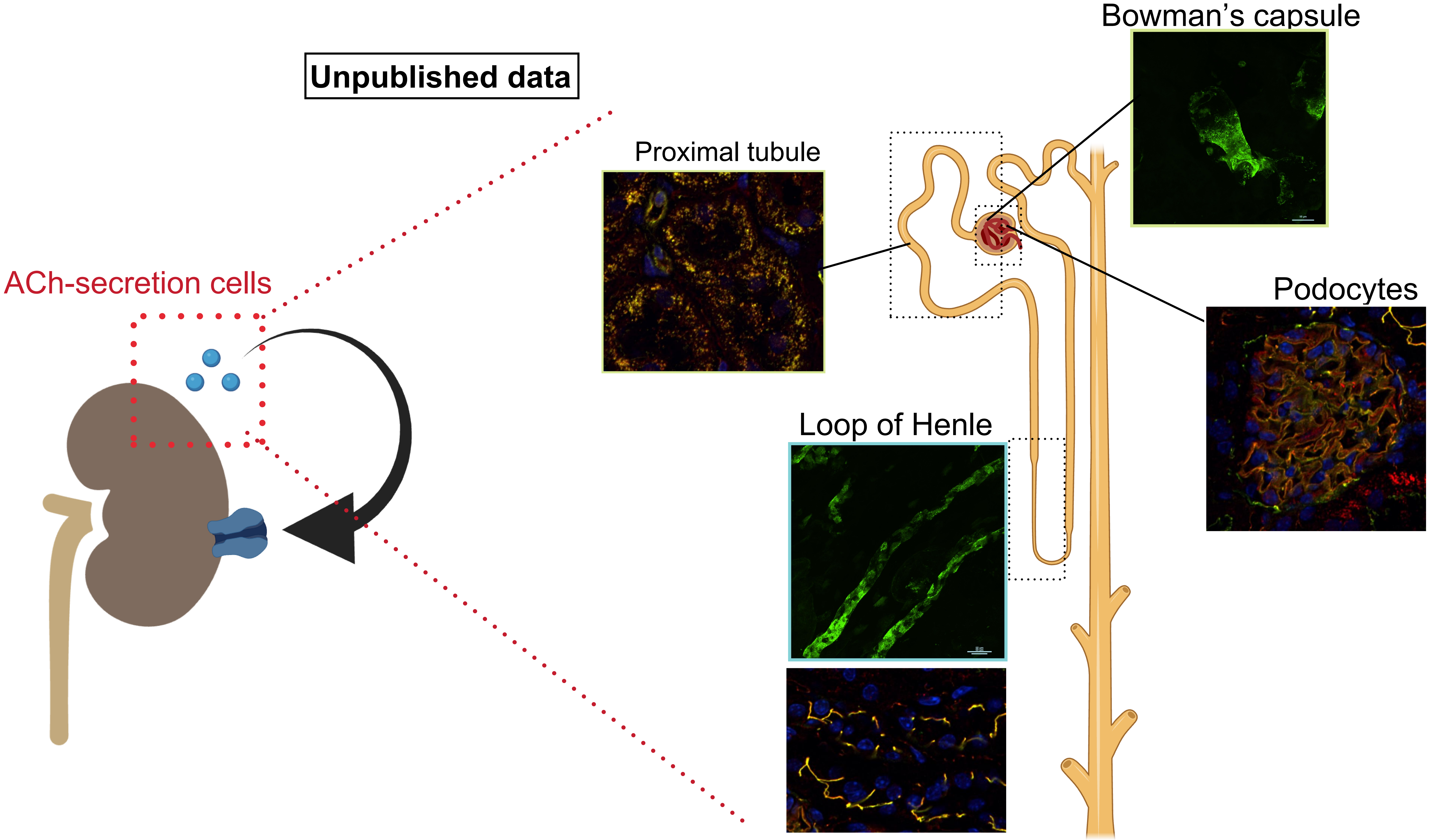
Identified ACh-Secreting Renal Cells



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過去3年間において

演題発表内容に関連し、発表者らに開示すべきCOI関係にある企業などはありません。