



Dec 6, 2025. 10:30-10:45
Room 2 (701B)

Neuroimmune Communication in the kidney: The Frontier

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Disclosures

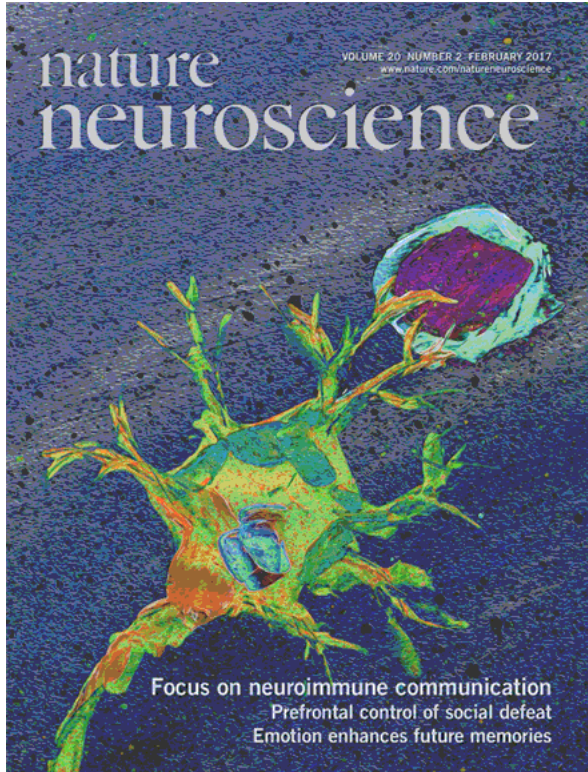


No relevant financial relationships with ineligible companies.

Agenda

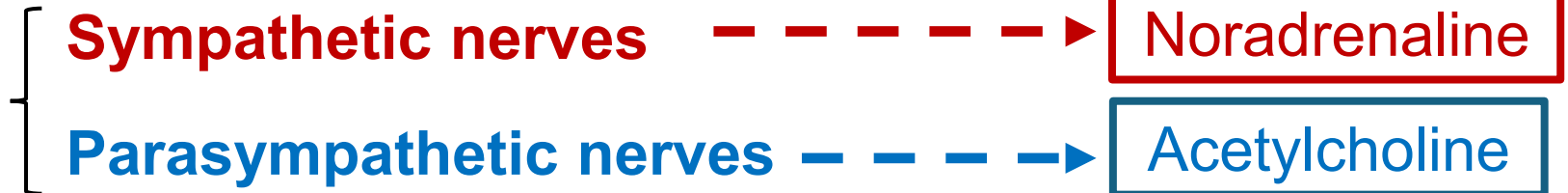
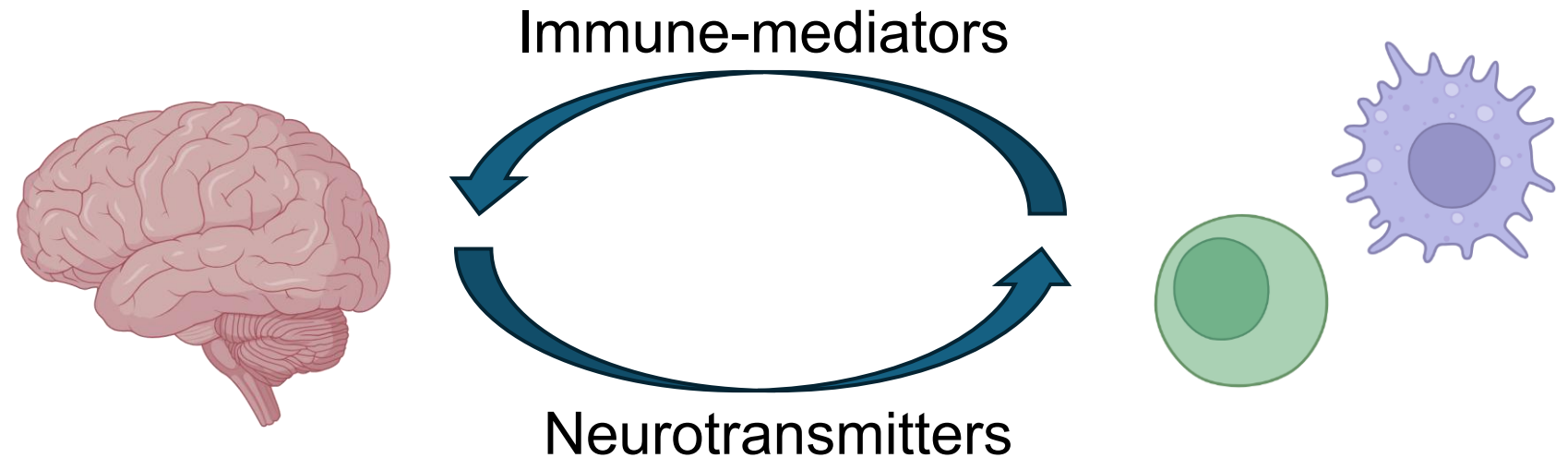
- **Neuroimmune communication**
- **Cholinergic anti-inflammatory pathway (CAP)**
- **CAP and acute kidney injury**
- **Autonomic nervous system**
- **Optogenetics: selective nerve stimulation by light**
- **Summary**

Neuroimmune communication

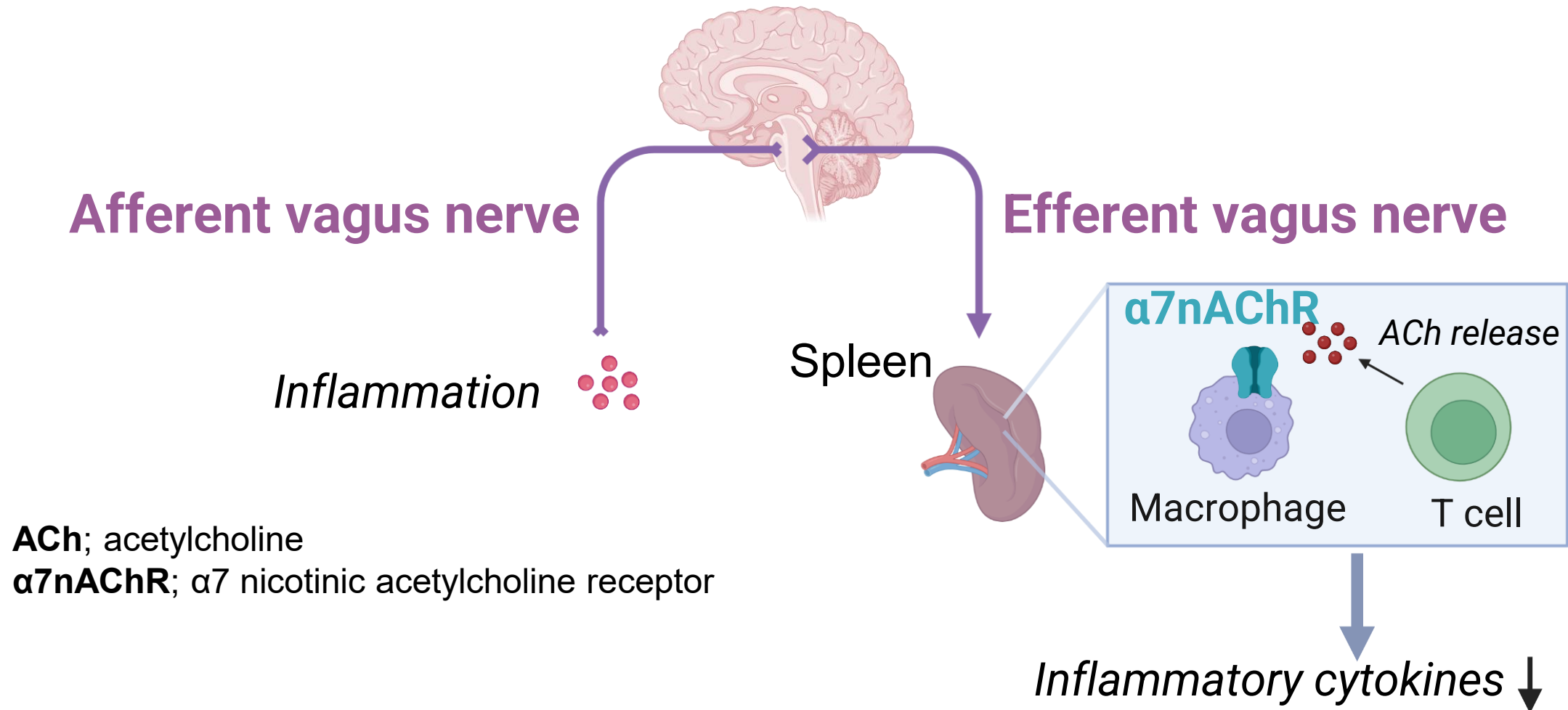


Nervous system

Immune system

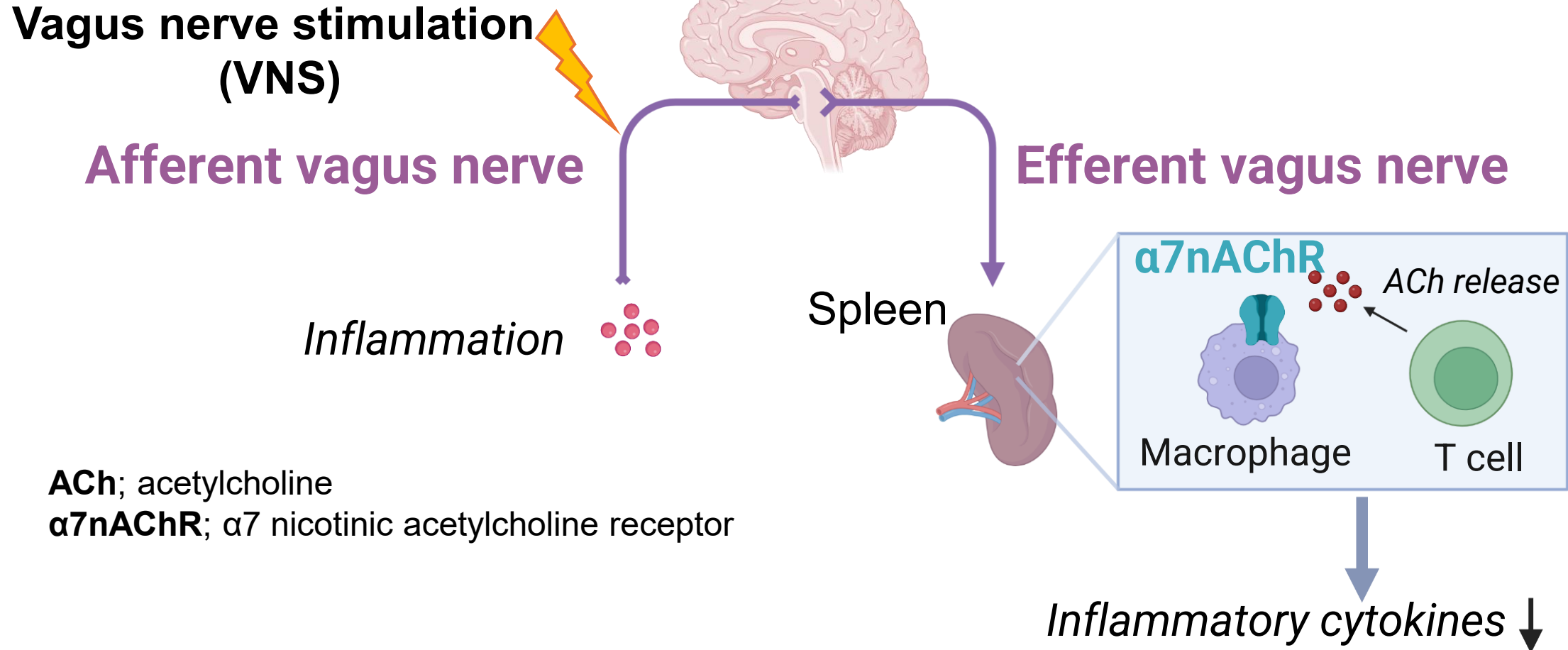


Cholinergic anti-inflammatory pathway (CAP)



ACh; acetylcholine
α7nAChR; α7 nicotinic acetylcholine receptor

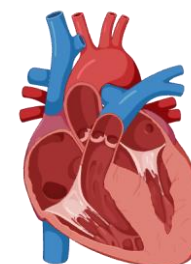
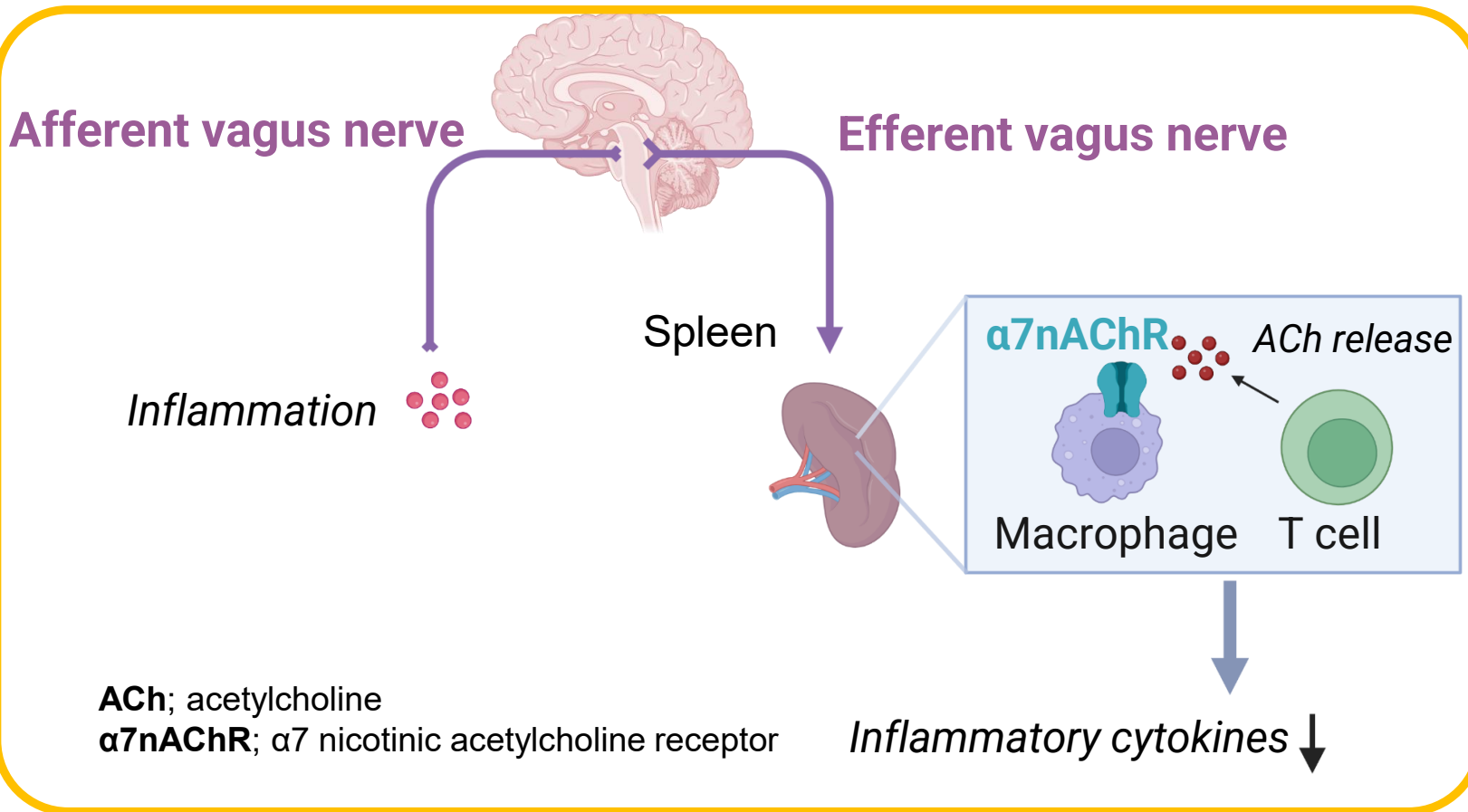
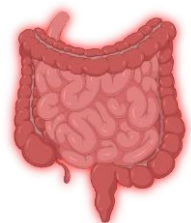
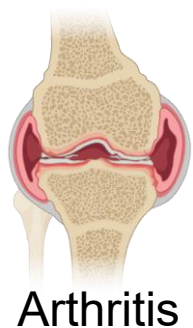
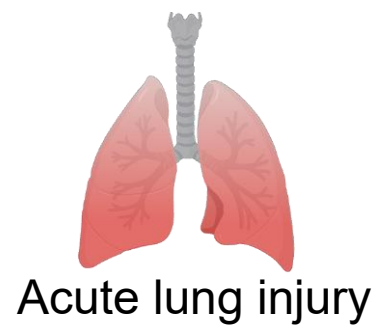
Cholinergic anti-inflammatory pathway (CAP)



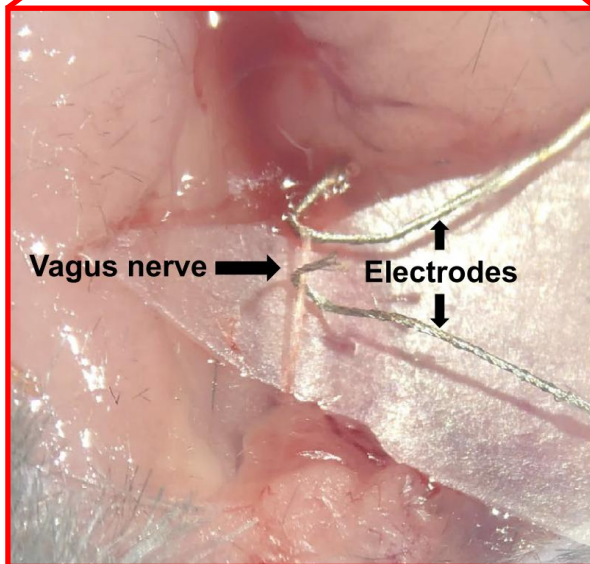
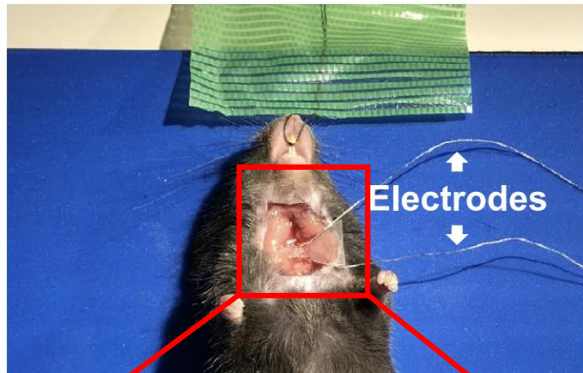
ACh; acetylcholine
 $\alpha 7nAChR$; $\alpha 7$ nicotinic acetylcholine receptor

CAP in diverse diseases

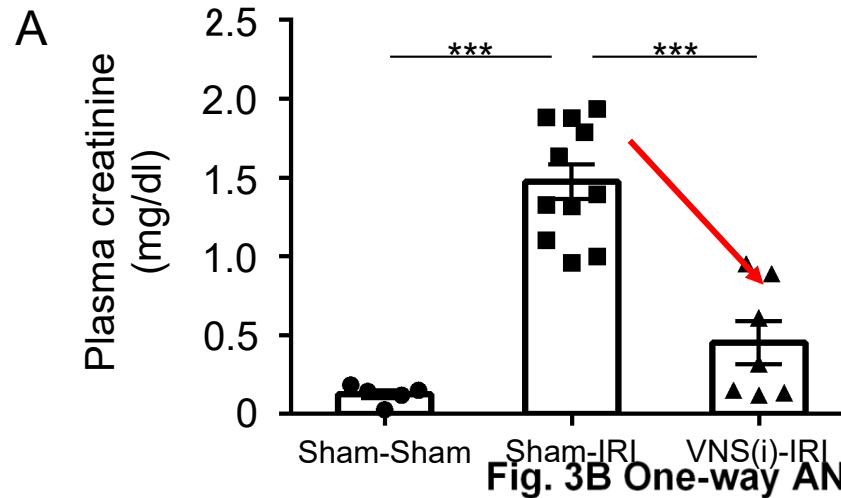
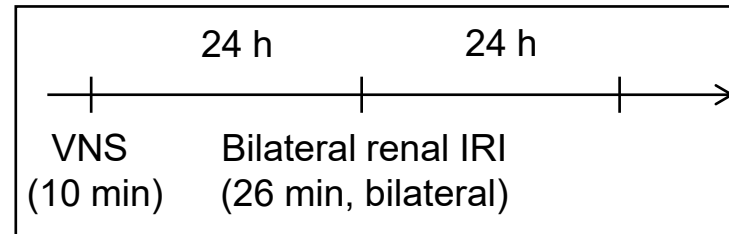
Cholinergic anti-inflammatory pathway (CAP)



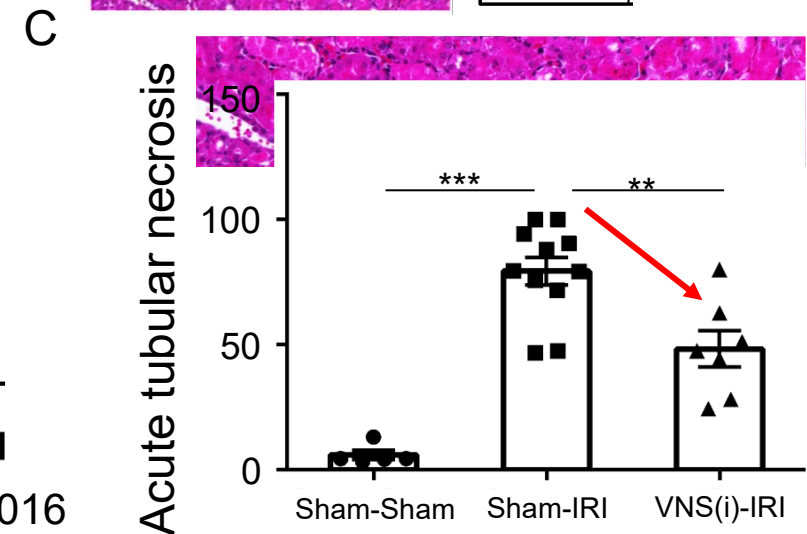
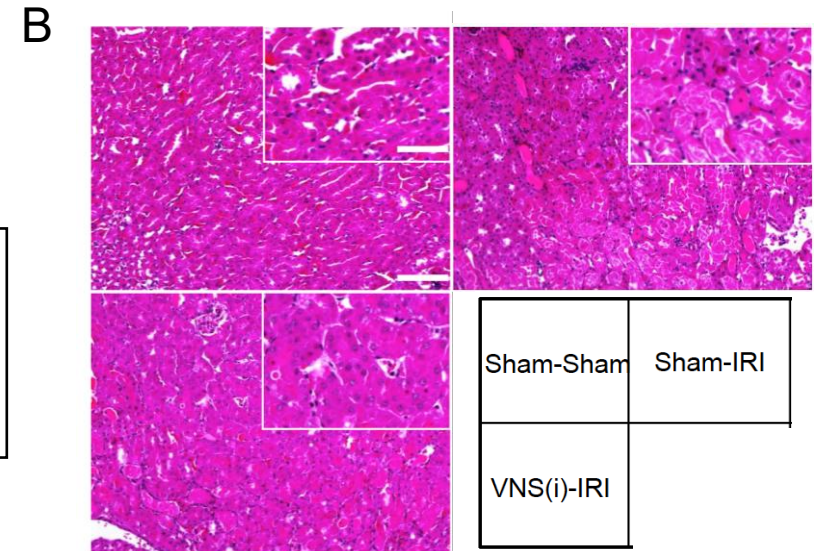
Vagus nerve stimulation (VNS) ameliorates acute kidney injury



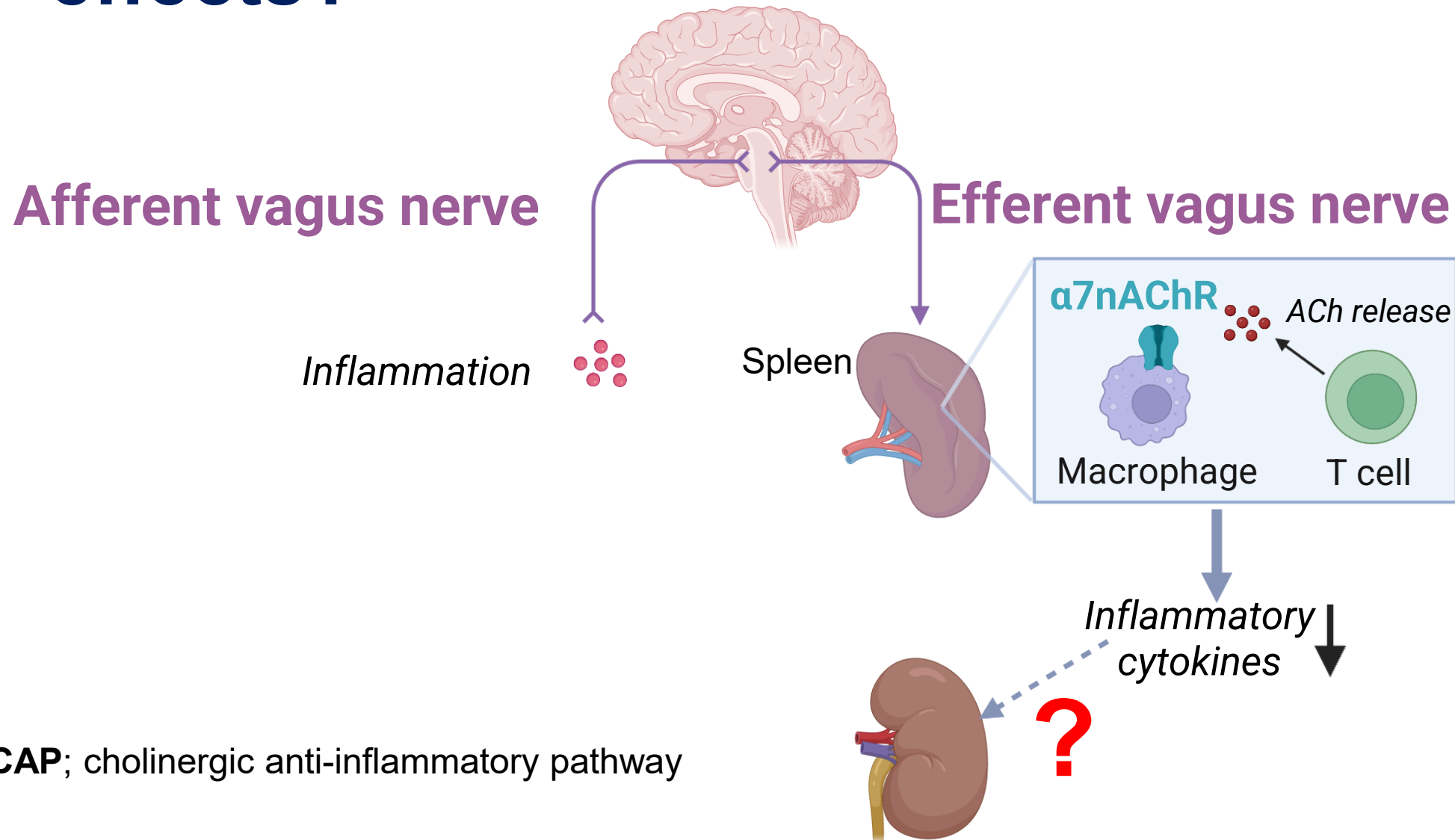
VNS; vagus nerve stimulation



Inoue et al. *J Clin Invest* 126(5):1939-52, 2016

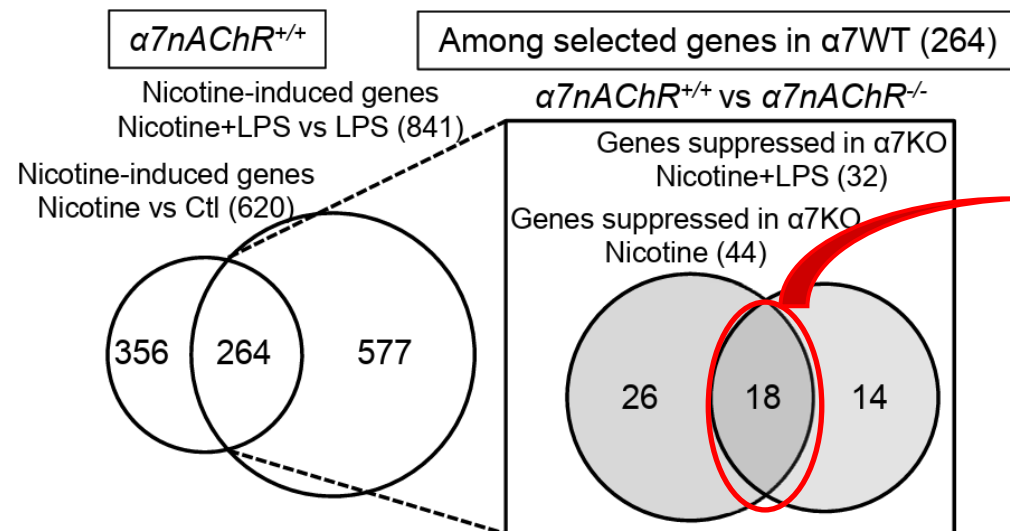
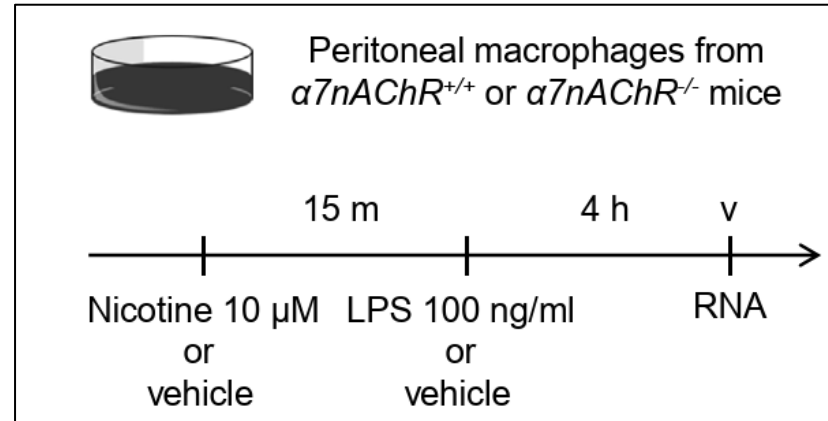


How CAP exerts its renoprotective effects?

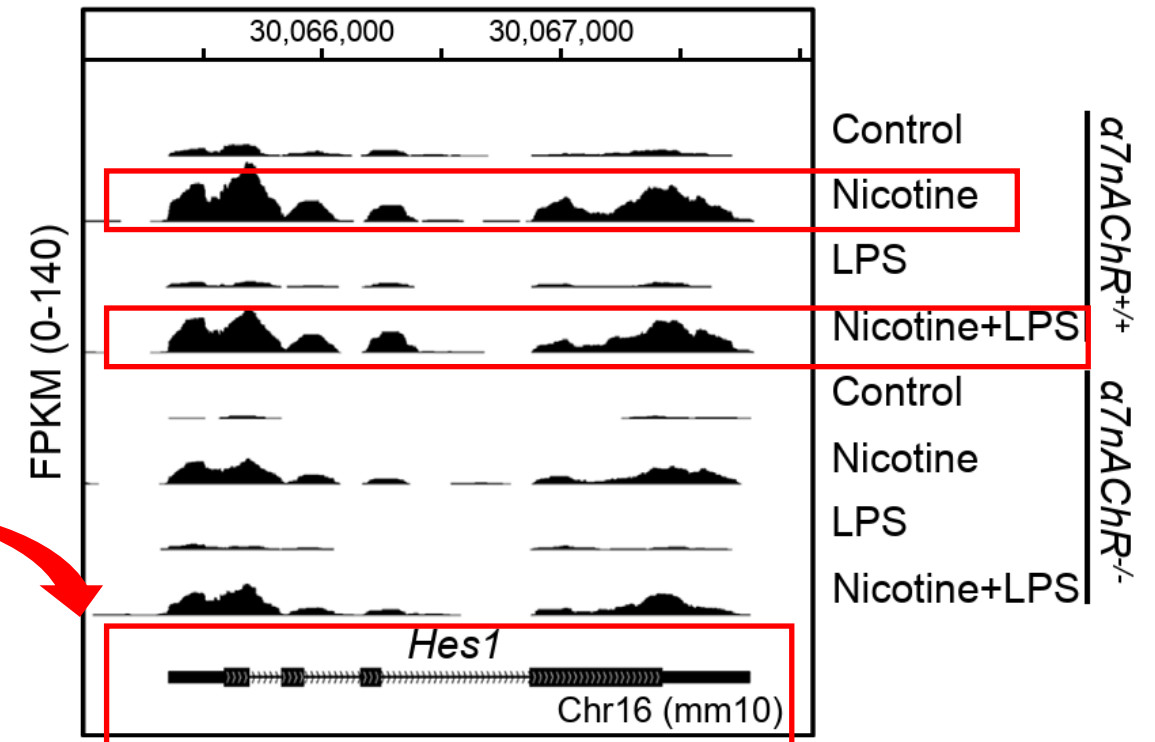


CAP; cholinergic anti-inflammatory pathway

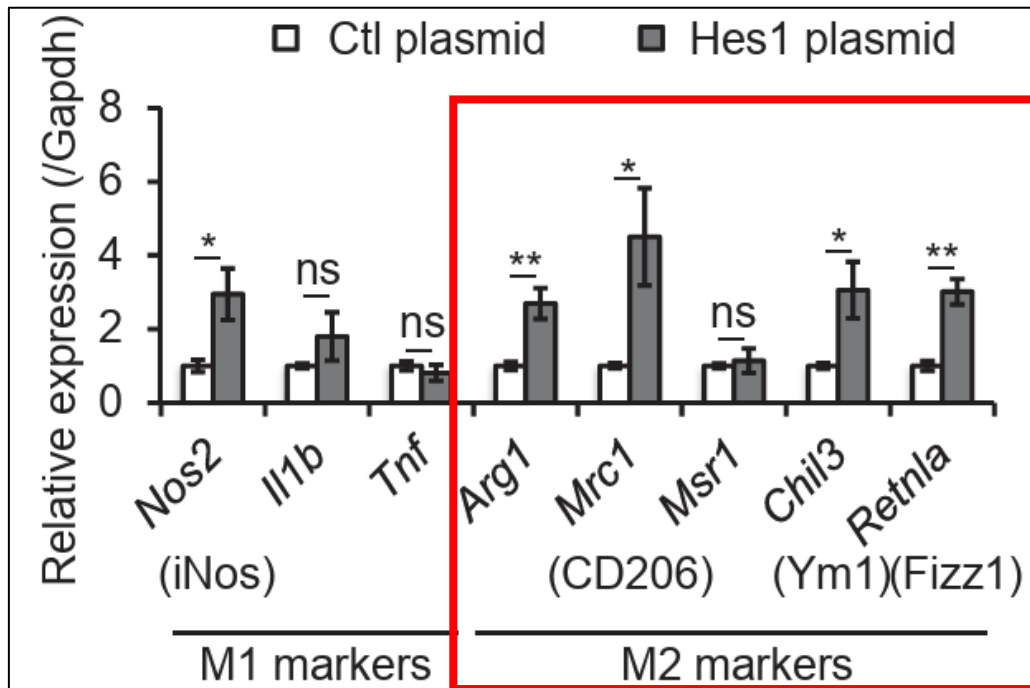
VNS induces the expression of Hes1 in peritoneal macrophages



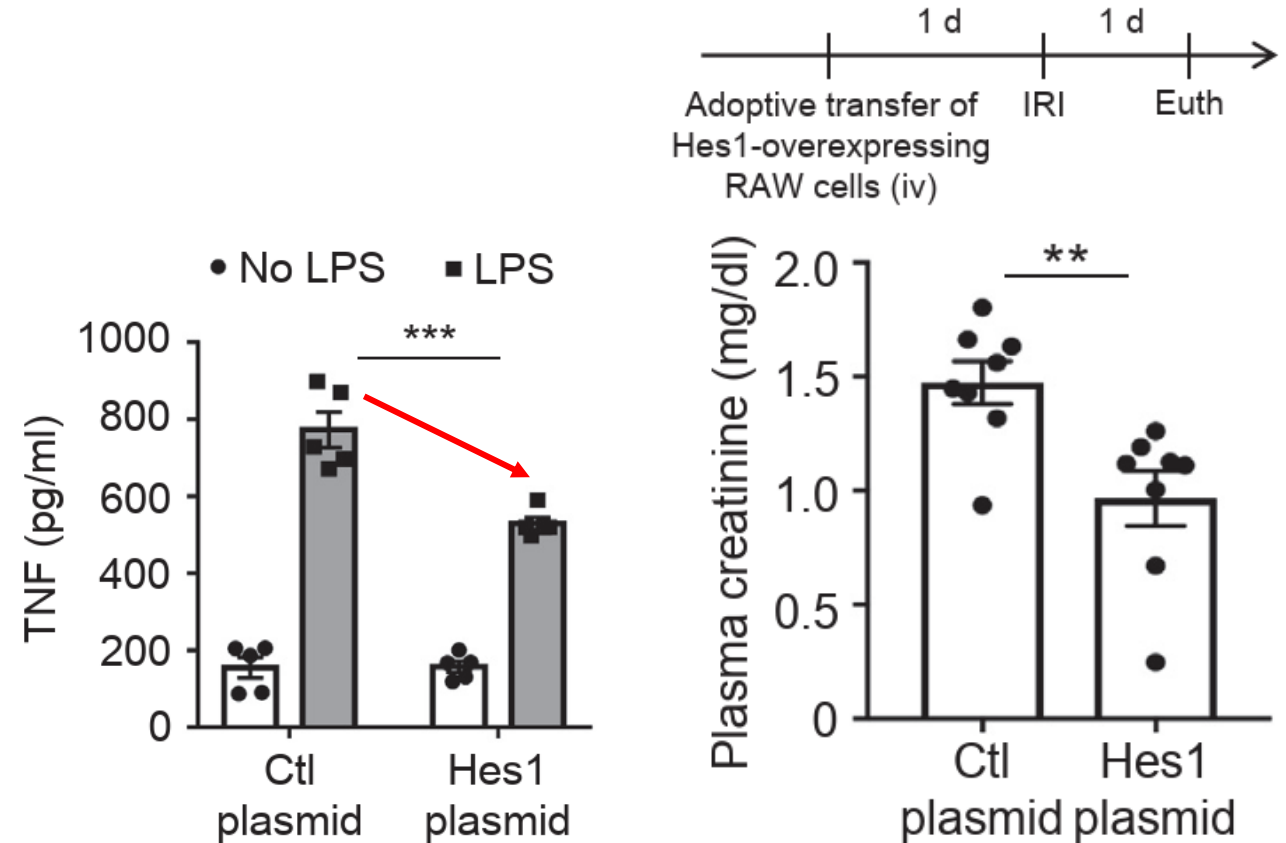
Hes1; hairy and enhancer of split-1



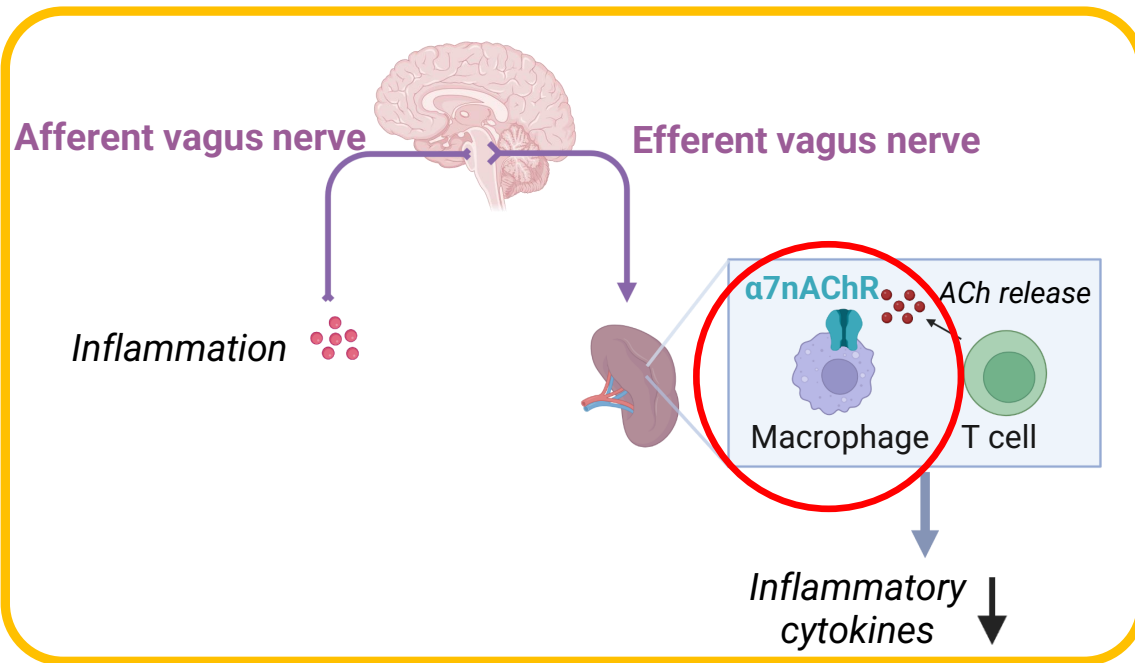
VNS modulates peritoneal macrophage phenotype towards anti-inflammation



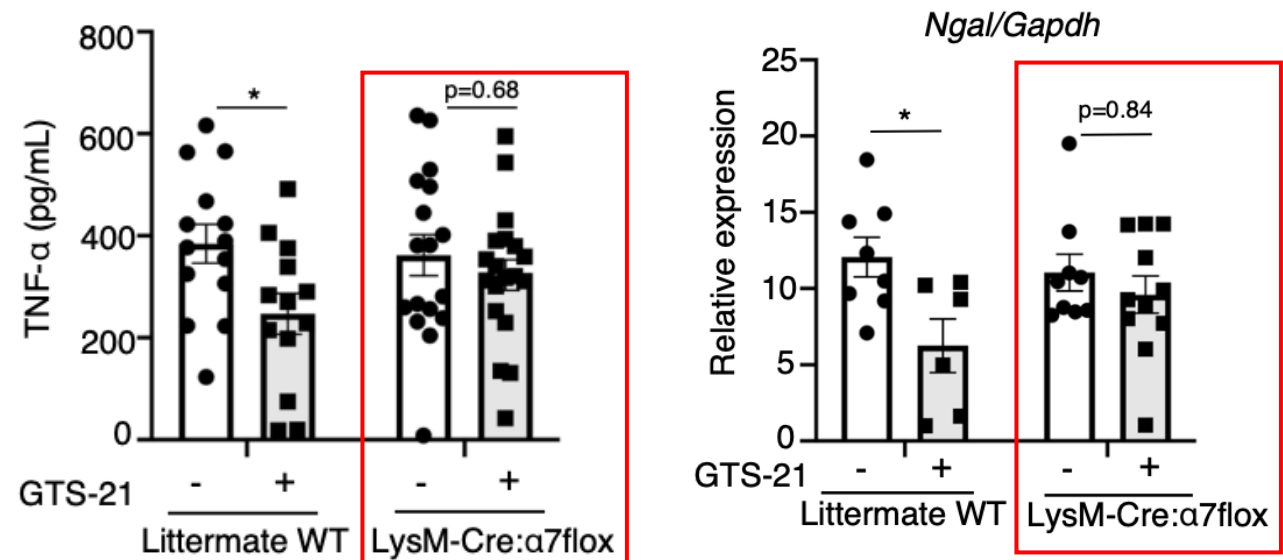
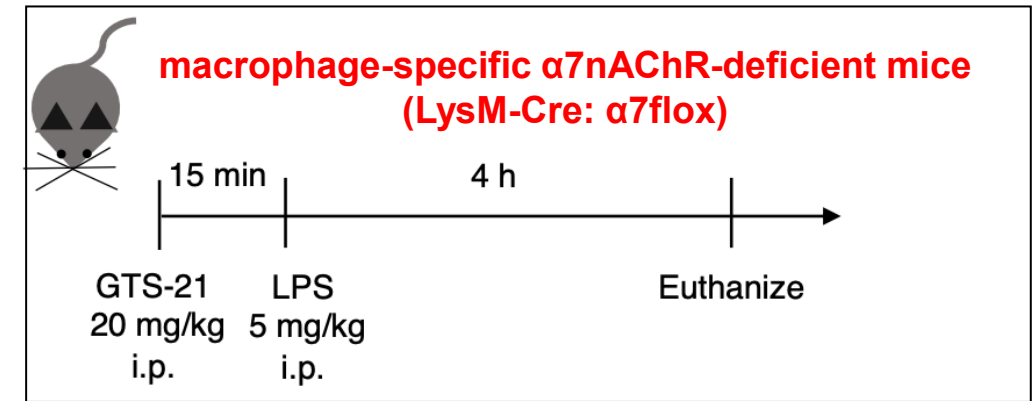
anti-inflammatory



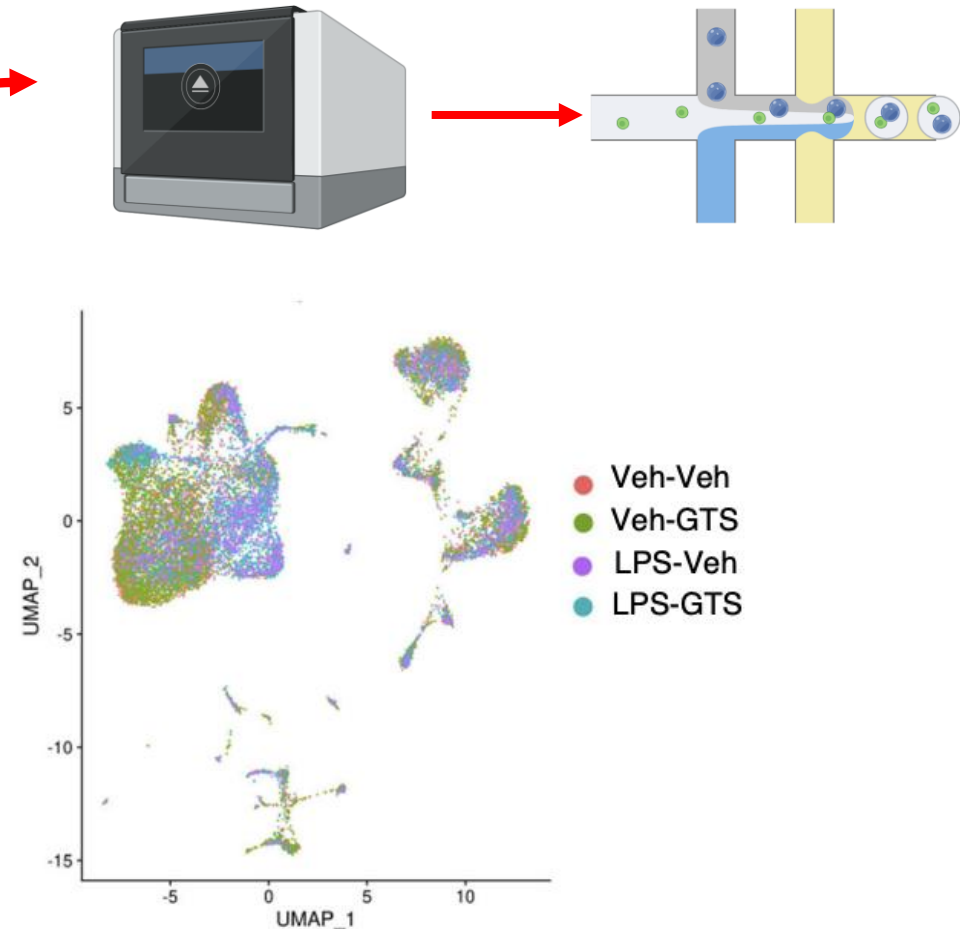
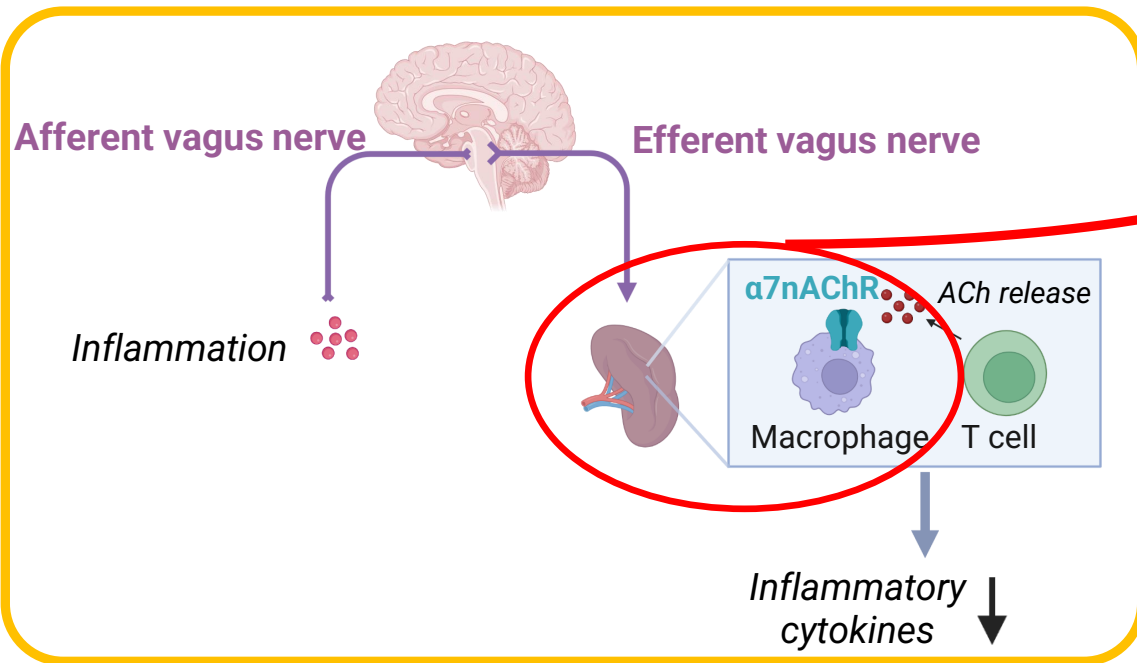
The effect of CAP was abrogated in macrophage-specific $\alpha 7$ nAChR knockout mice



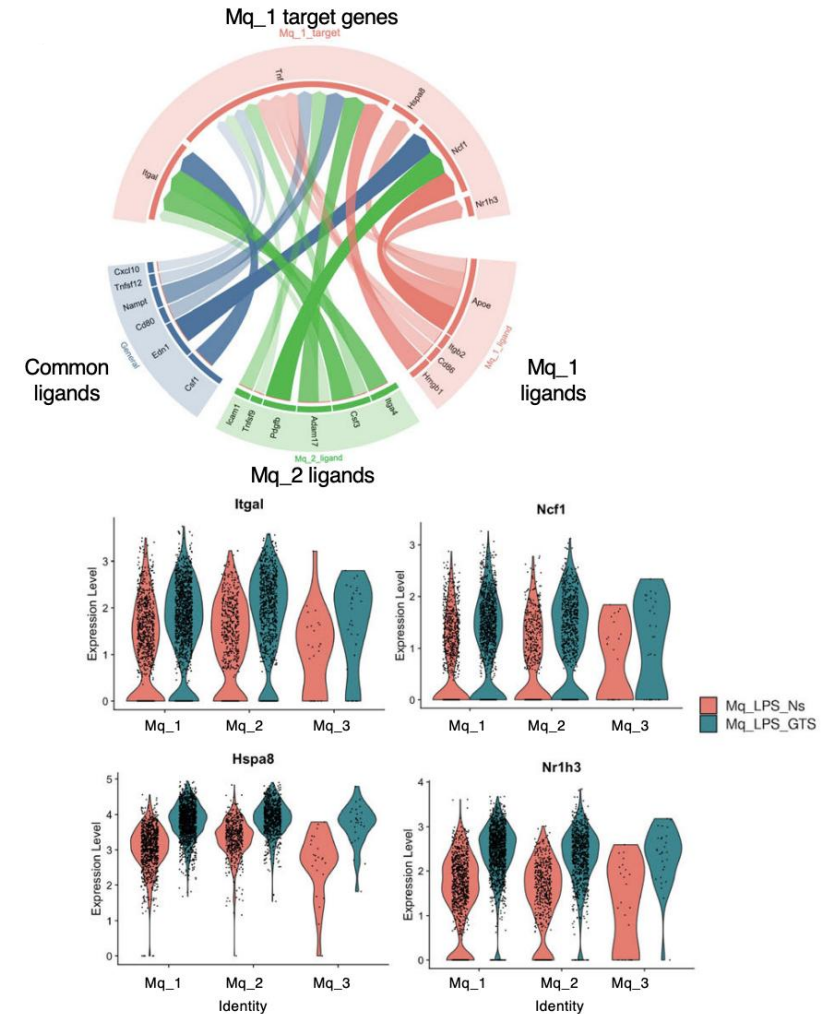
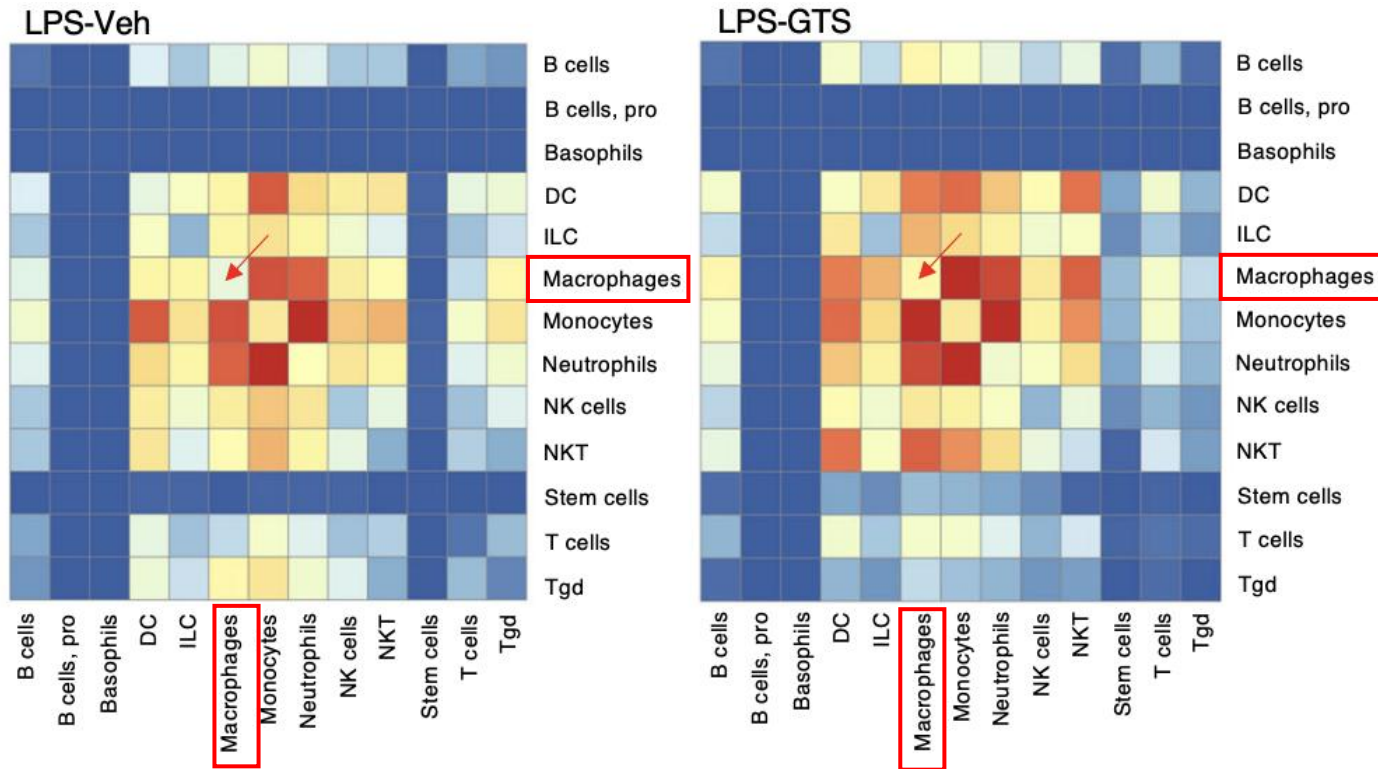
CAP; cholinergic anti-inflammatory pathway
GTS-21; $\alpha 7$ nAChR specific agonist



Mapping the $\alpha 7$ nAChR agonist response in splenic macrophages via single-cell RNA sequencing

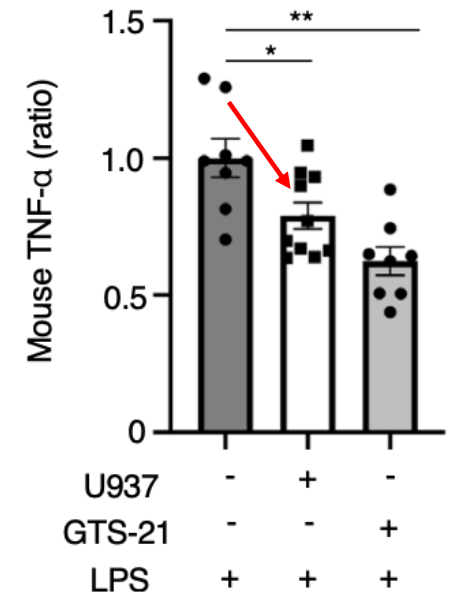
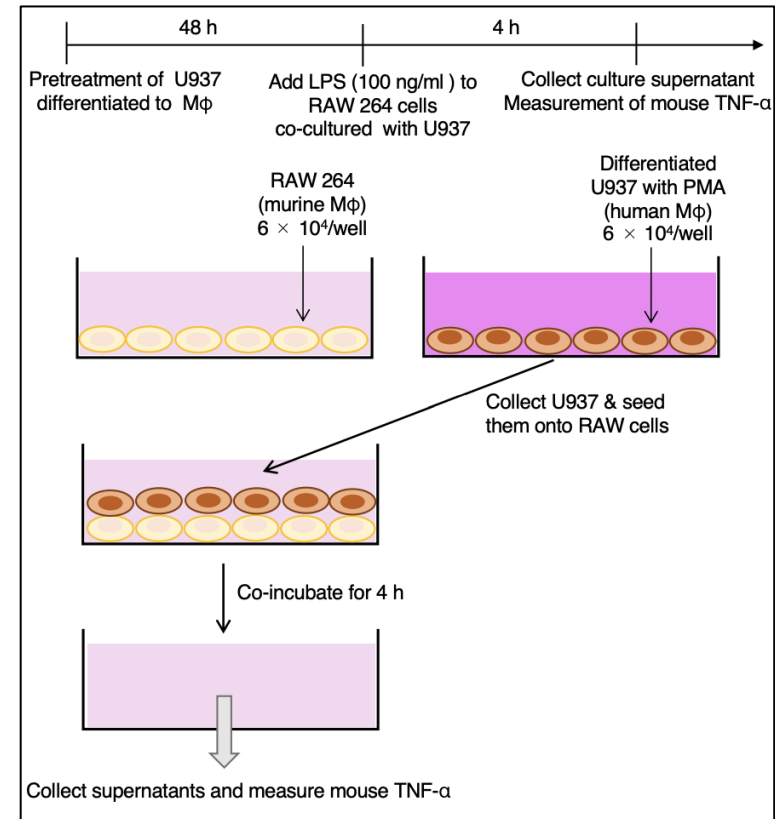
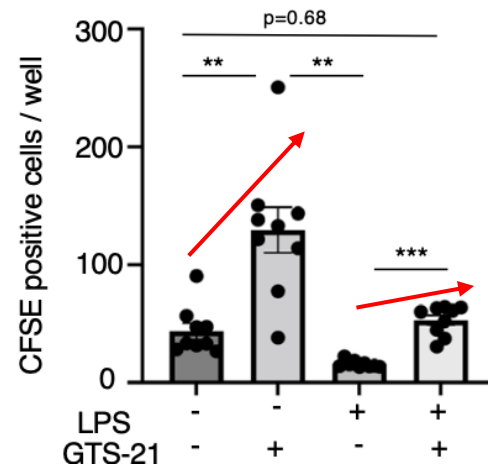
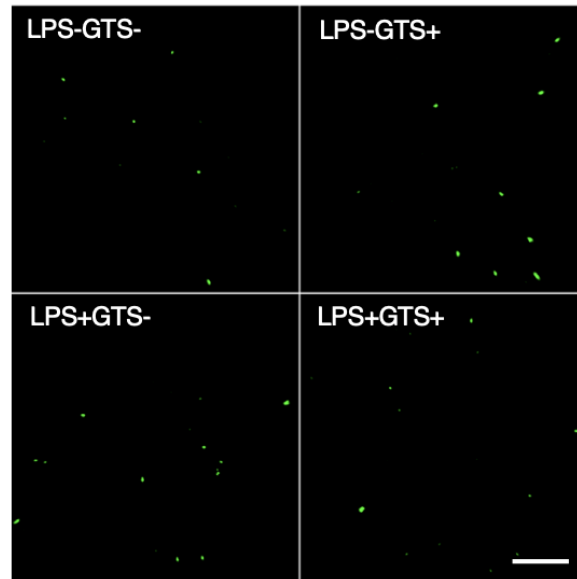
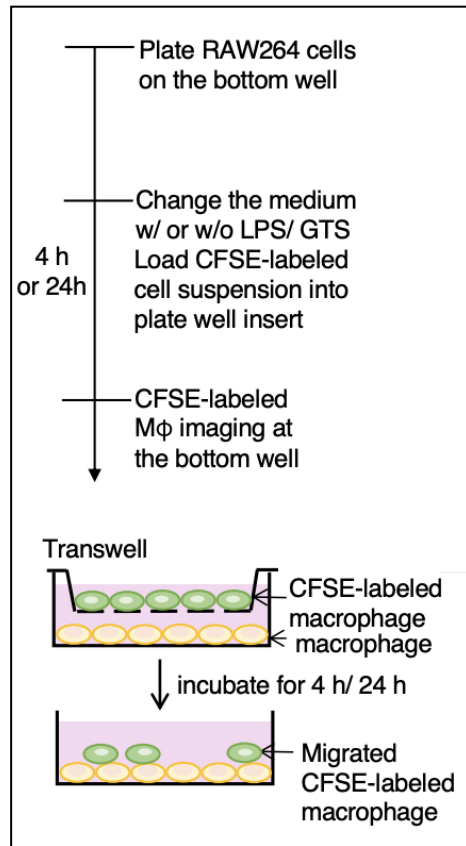


α7nAChR agonist enhances macrophage–macrophage interactions in the spleen

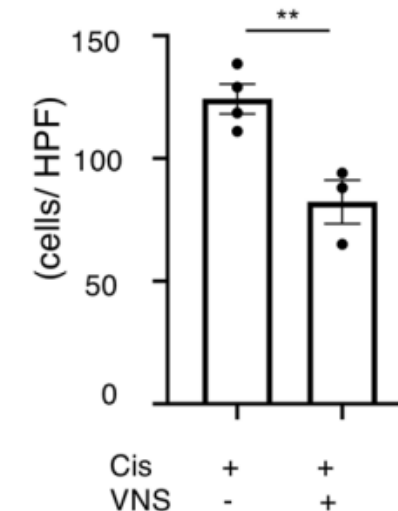
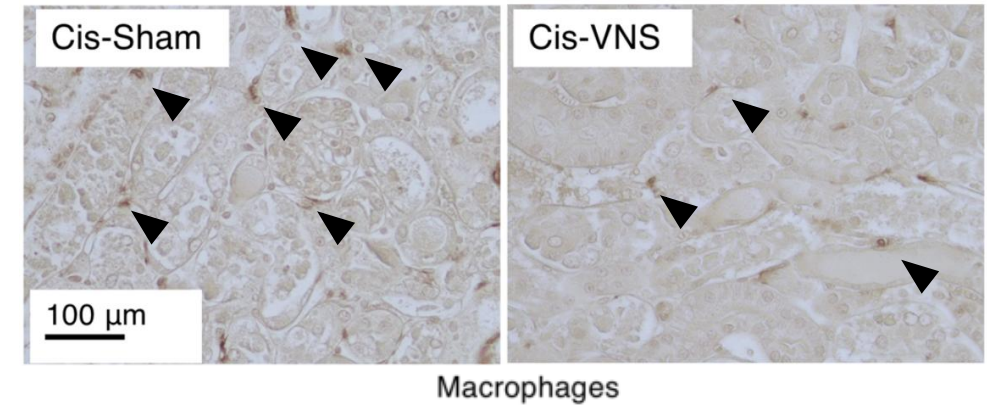
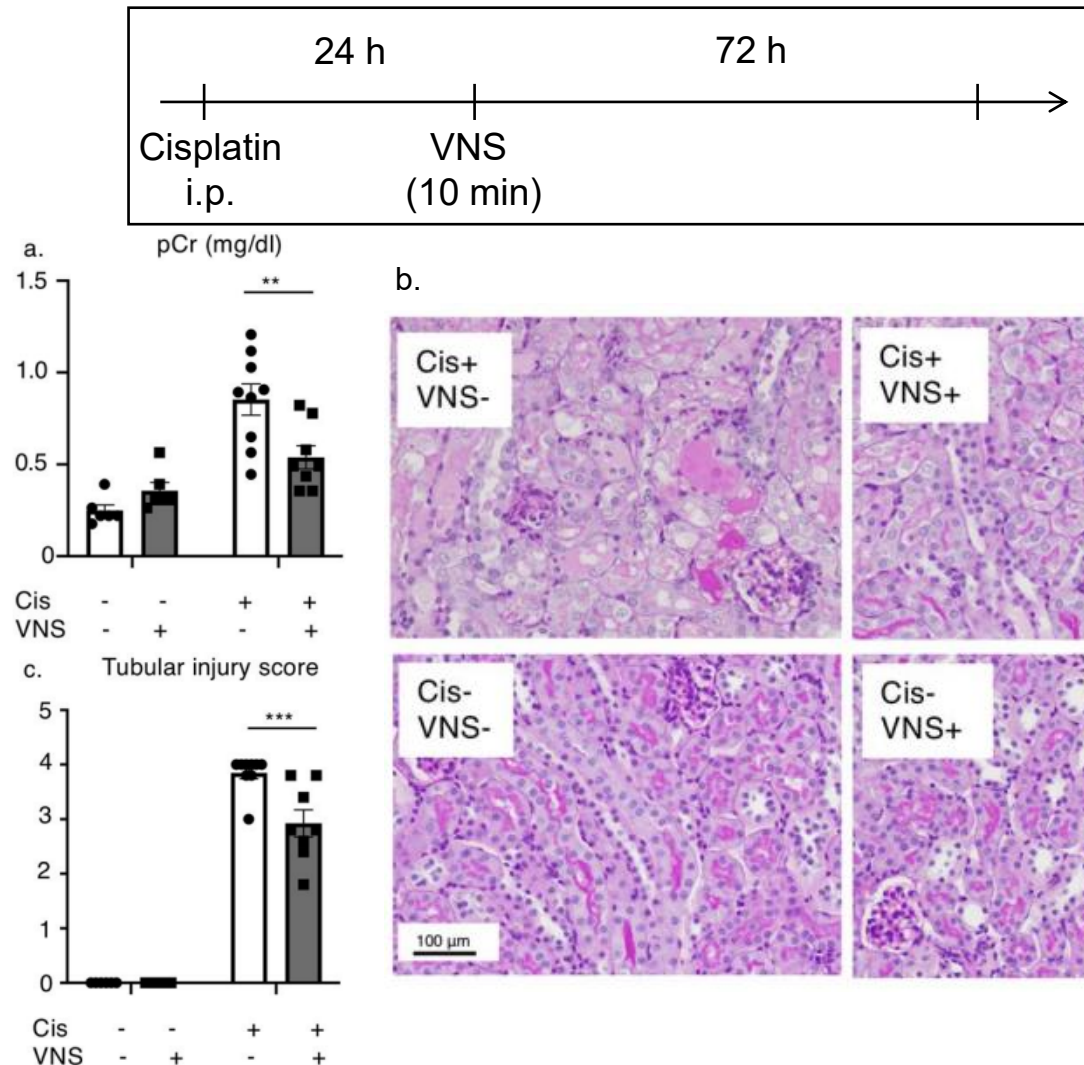


GTS-21; α7nAChR specific agonist

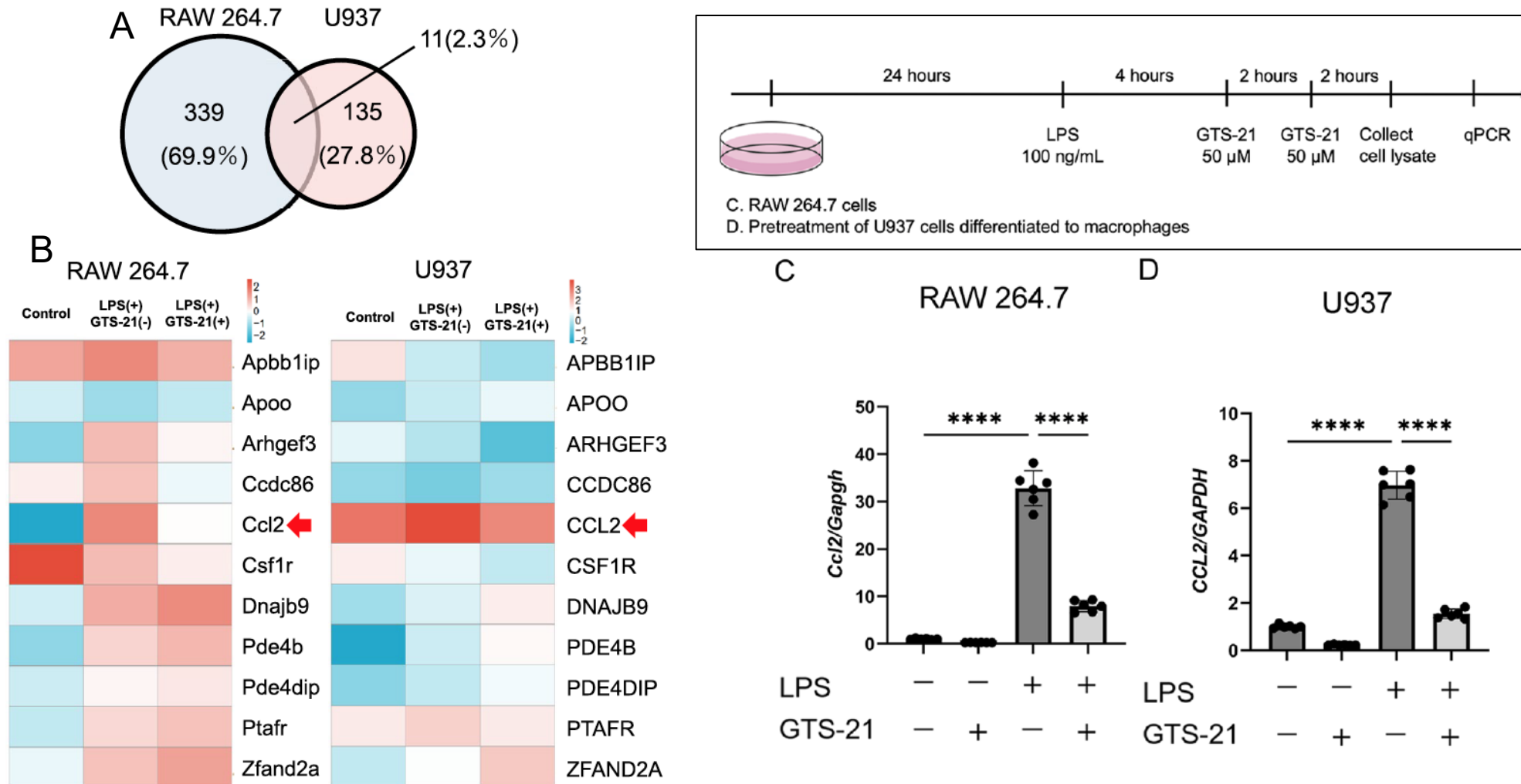
Macrophage–macrophage interactions exert anti-inflammatory effects



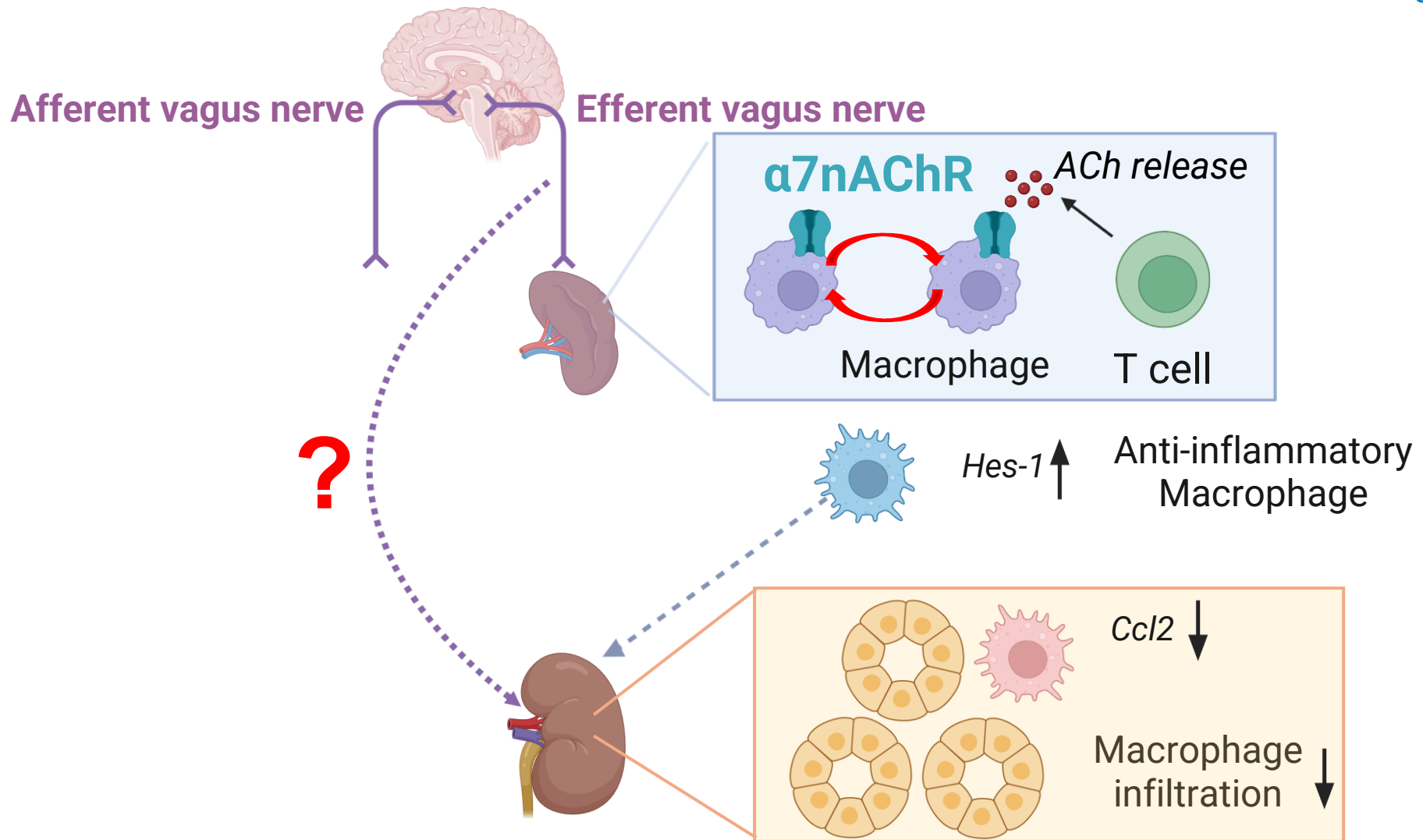
VNS is effective in protecting the kidney even after injury



$\alpha 7$ nAChR agonists attenuate Ccl2 expression in macrophages



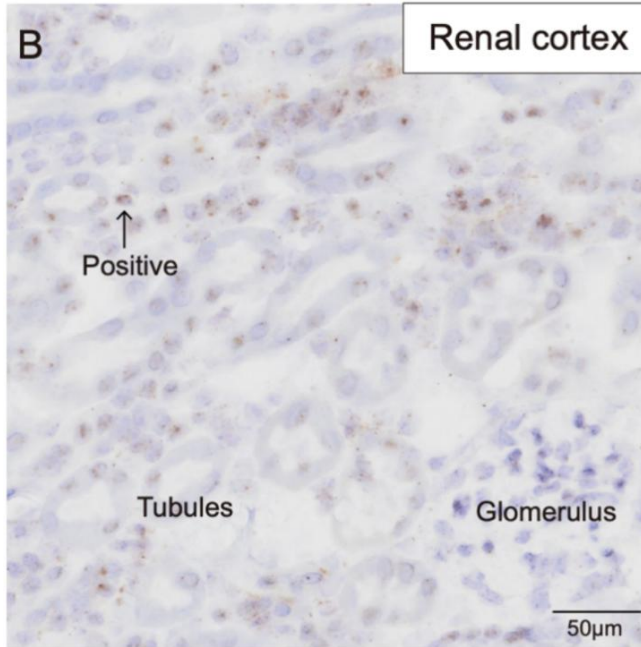
Can acetylcholine directly affect the kidney?



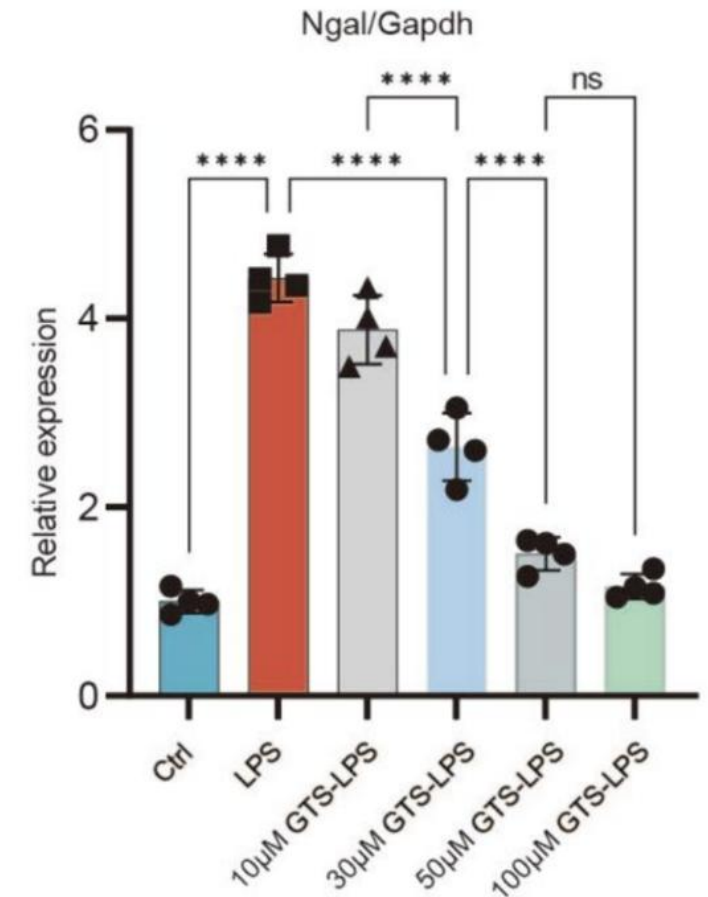
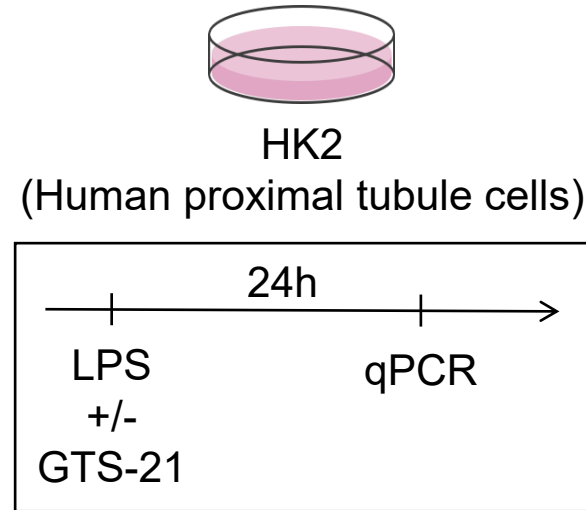
$\alpha 7$ nAChR agonists directly target renal tubular cells and mitigate tubular injury



Aobing Yang



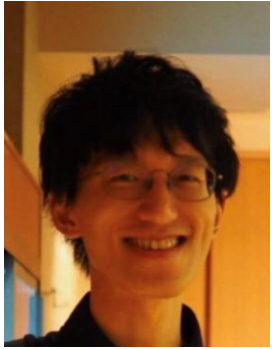
Chrna7 ($\alpha 7$ nAChR)
mouse kidney in situ hybridization



Exploration of the renal autonomous cholinergic system via single-cell RNA sequencing

Dec.5 (Fri.) 17:22-17:31

Room 7 (703)

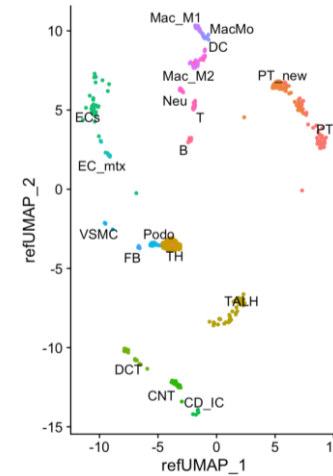


Chia-Hsien Wu

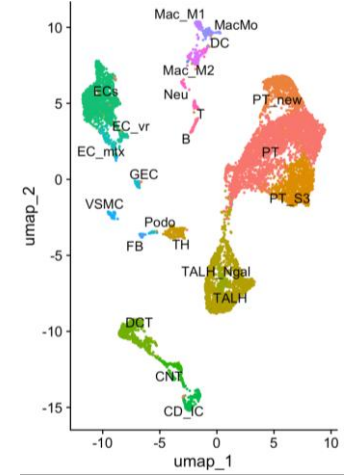
Non-neuronal acetylcholine
producing cells

Vagus nerve stimulation
+ renal ischemia/reperfusion

ChAT⁺ renal cells



Renal cells



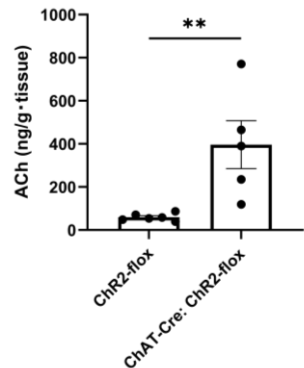
Sender

Renal Autonomous
Cholinergic System

Receiver

vagus nerve
innervative

Acetylcholine



ChAT; choline acetyltransferase (Acetylcholine producing enzyme)

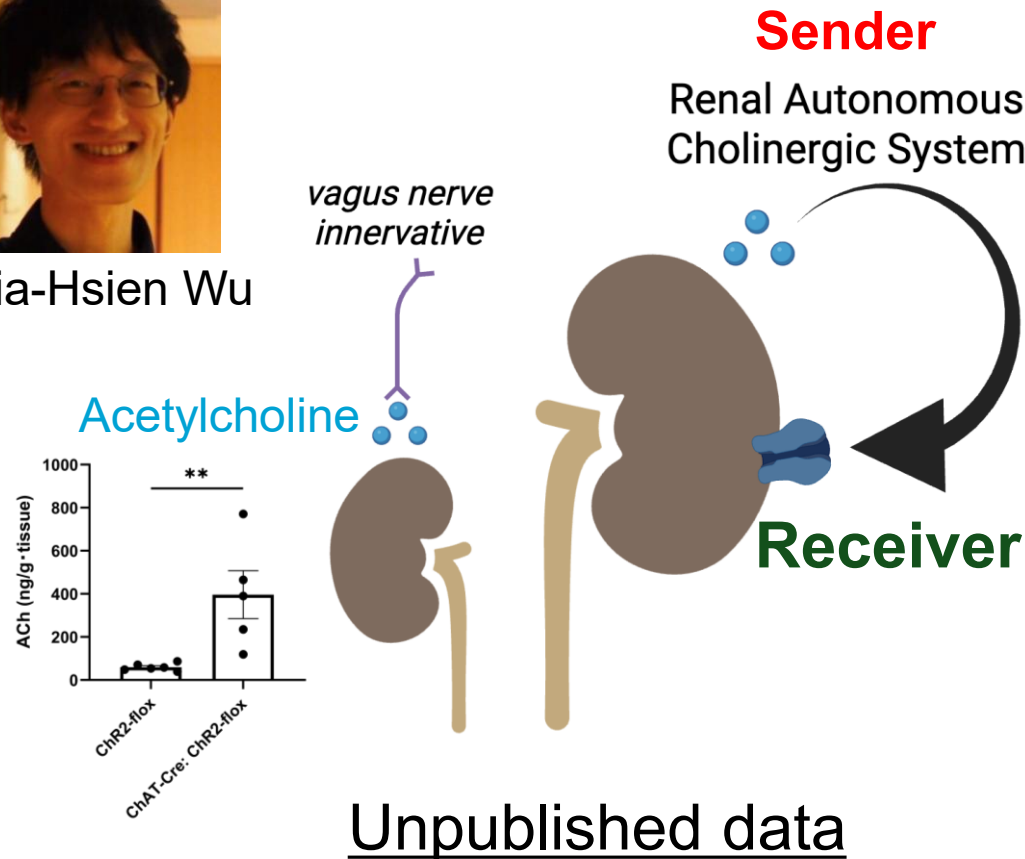
Exploration of the renal autonomous cholinergic system via single-cell RNA sequencing

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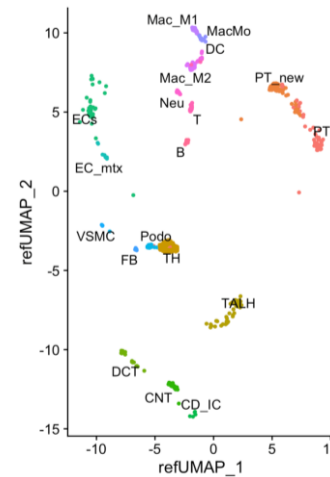


Chia-Hsien Wu



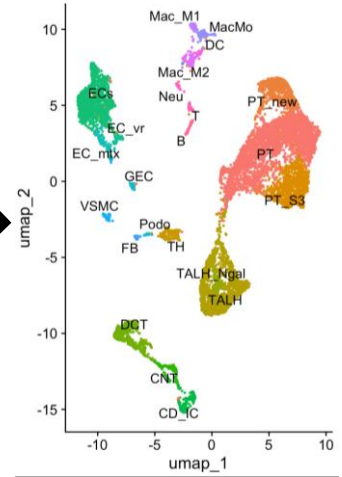
Non-neuronal acetylcholine producing cells

ChAT⁺ renal cells



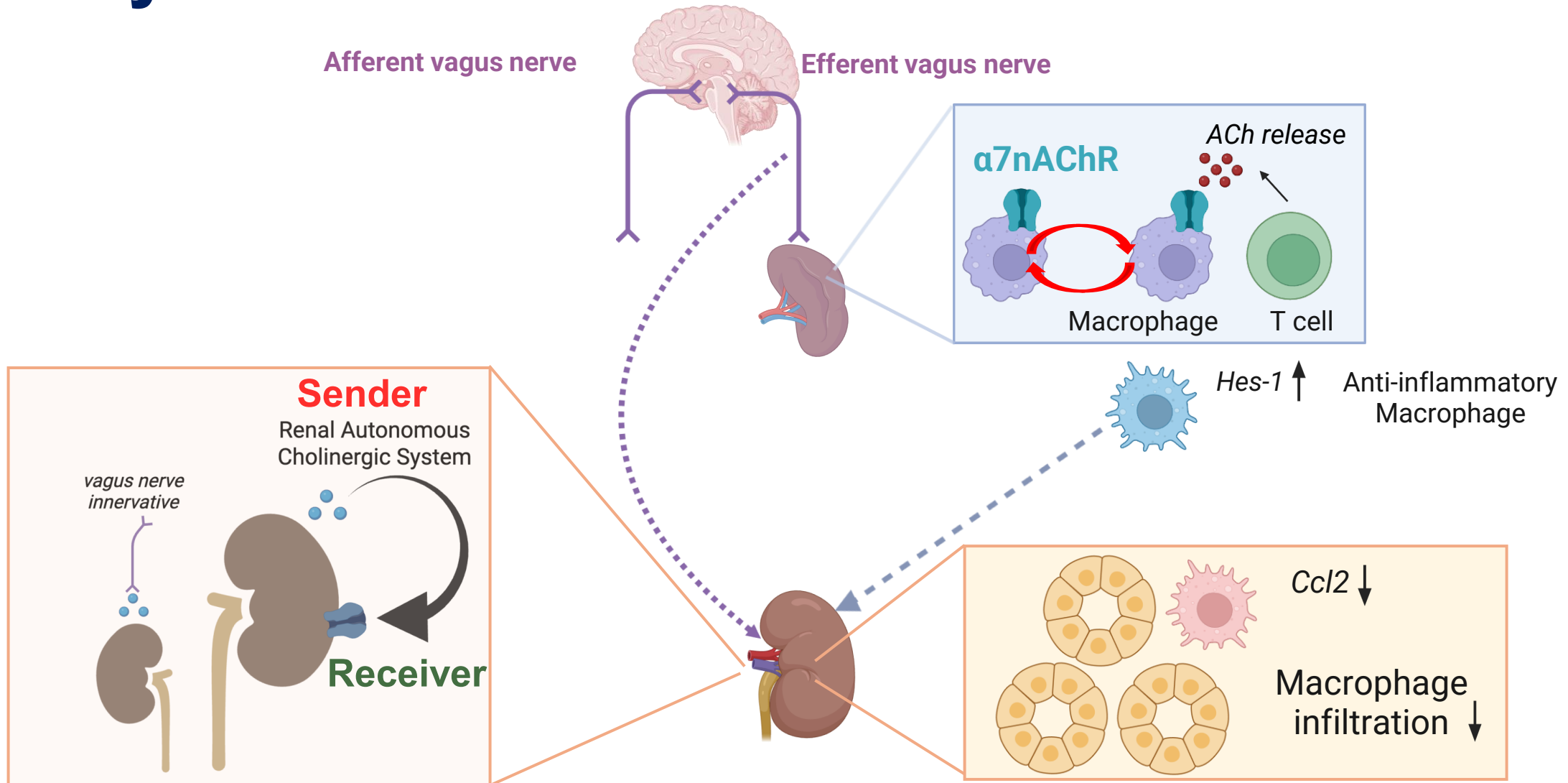
Vagus nerve stimulation + renal ischemia/reperfusion

Renal cells



- **Sender cells:** proximal tubule, loop of Henle, podocytes
- **Receiver cells:** proximal tubular cells expressing the $\alpha 4$ nicotinic acetylcholine receptor
- **VNS regulates the expression of metabolism-related genes in tubular cells**

Renal protection via the cholinergic system



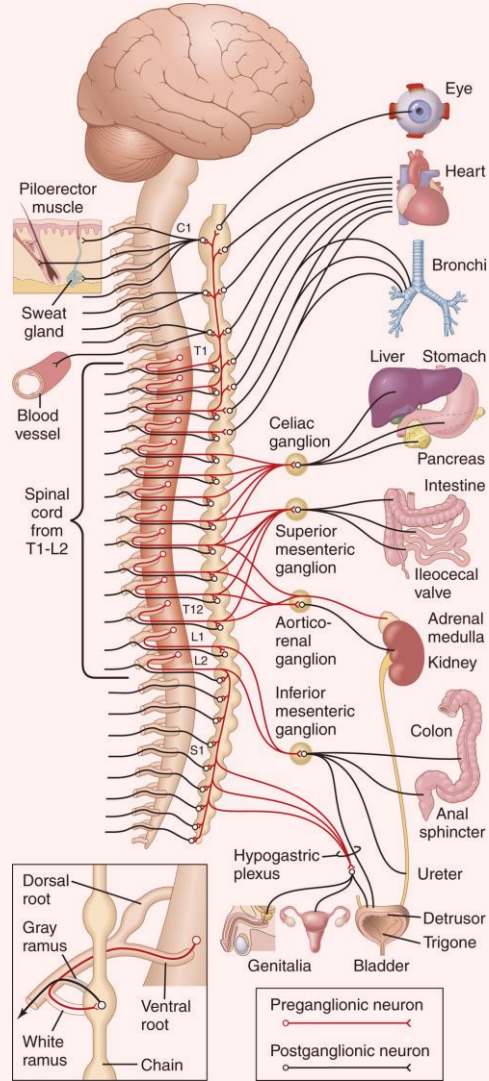
Autonomic nervous system work in concert



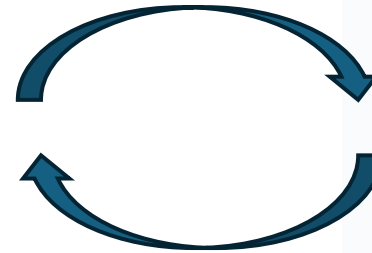
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Sympathetic nerves

Fight or Flight



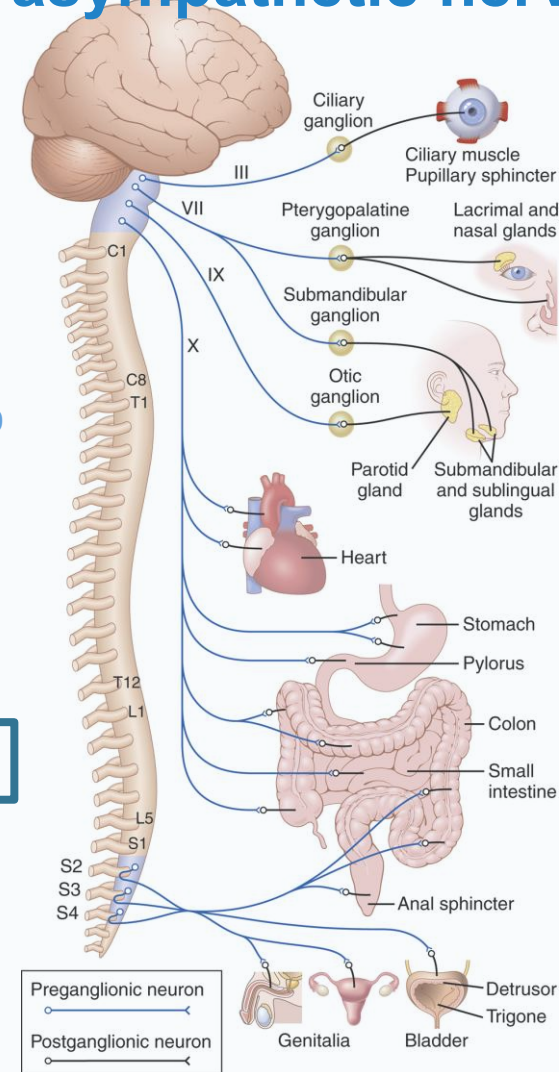
Noradrenaline



Acetylcholine

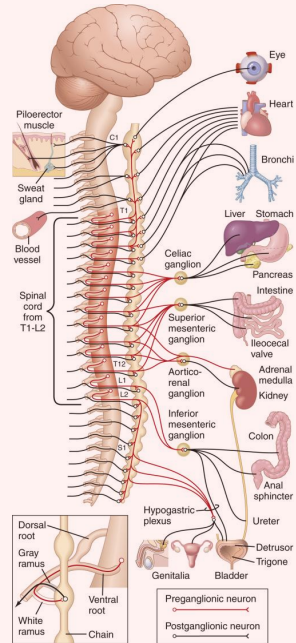
Parasympathetic nerves

Rest and Digest

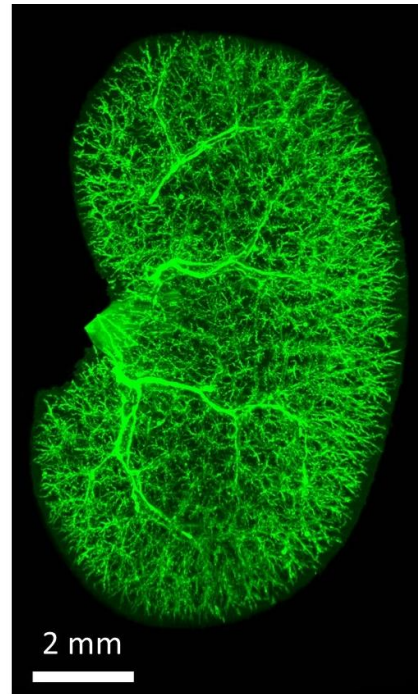


β2-Adrenergic receptor signaling provides direct protection to renal tubular cells

Sympathetic nerves

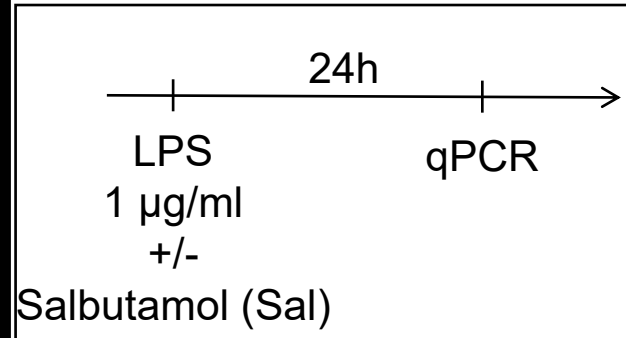


Noradrenaline

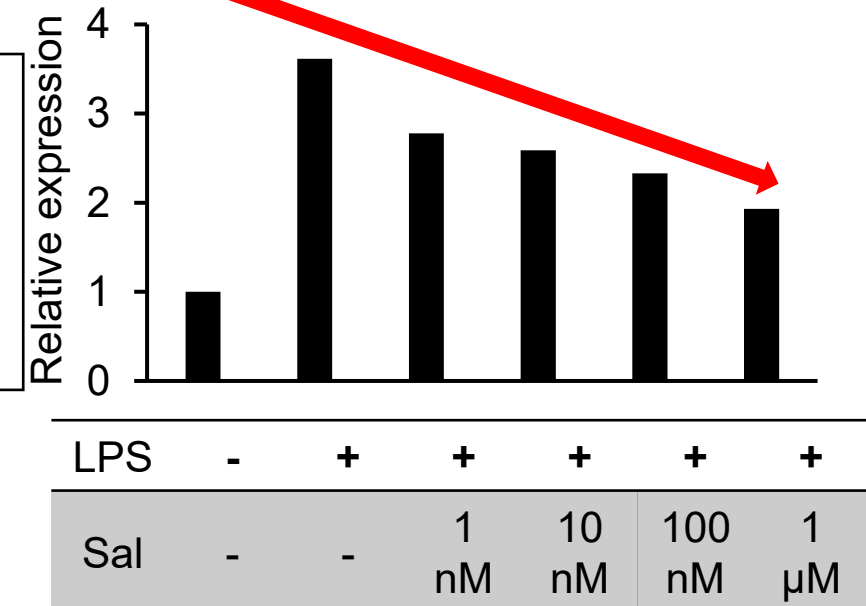


Hasegawa, et al.
Kidney Int 96(1):129-138, 2019

HK2
(Human proximal tubule cells)



Ngal (tubular injury marker)



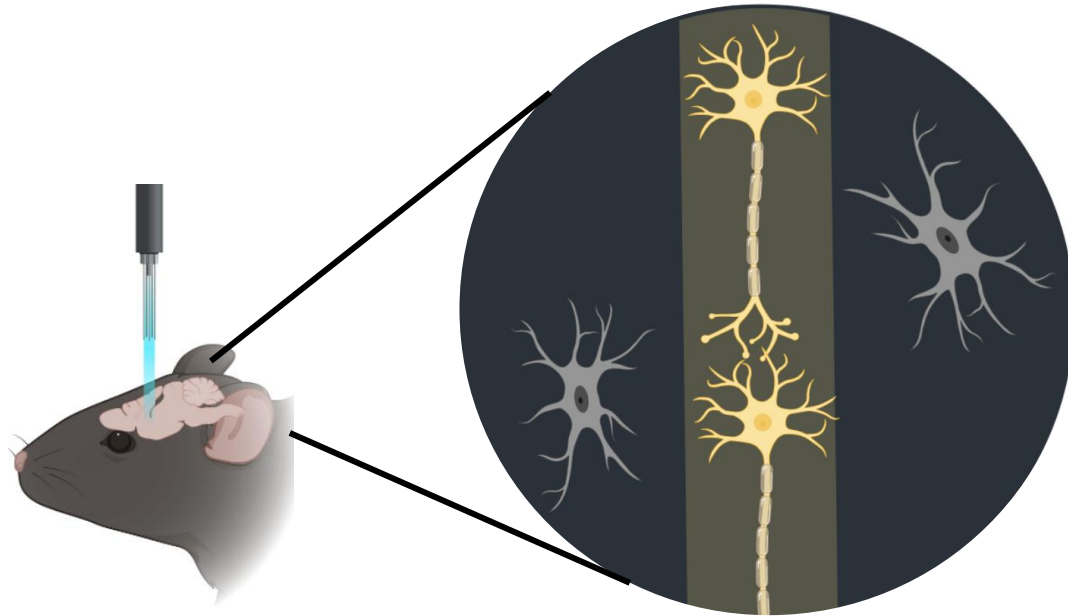
Unpublished data

Salbutamol (Sal) :
β2 adrenergic receptor agonists

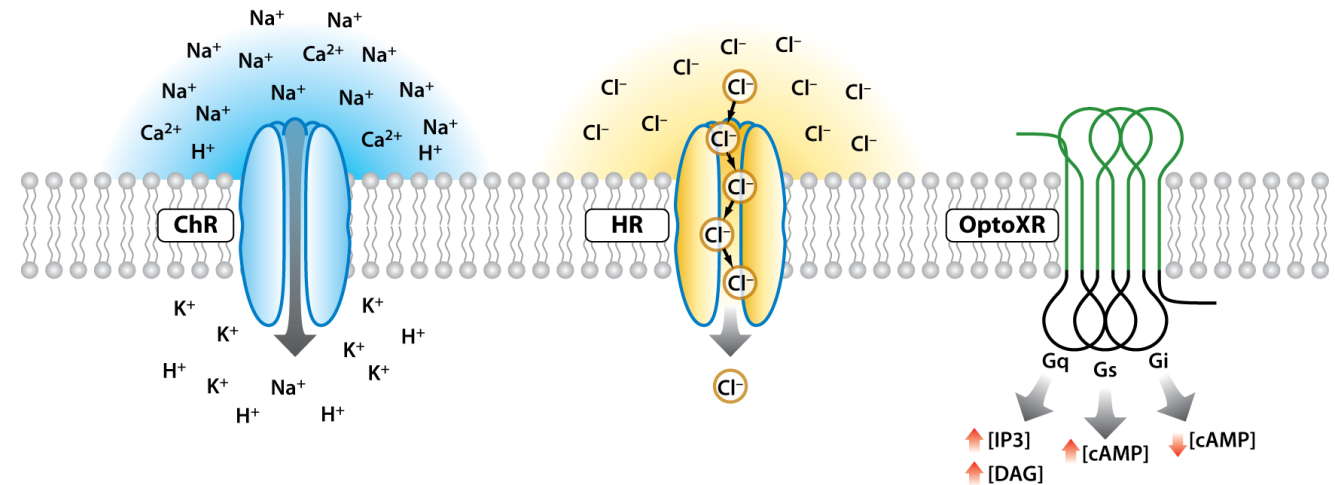
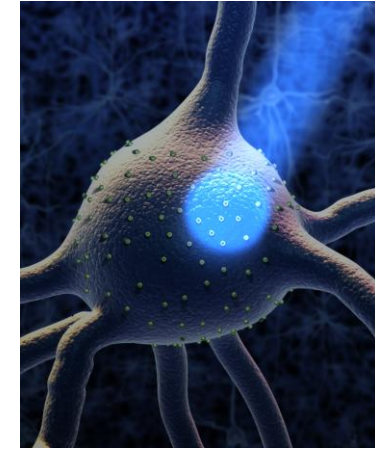
Optogenetics: precise control of neural activity



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Channelrhodopsin-2 (ChR-2)

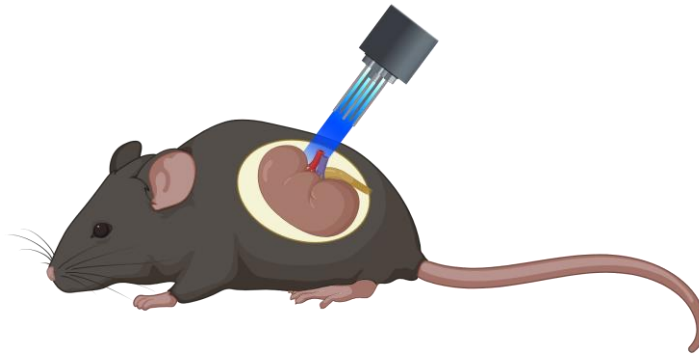
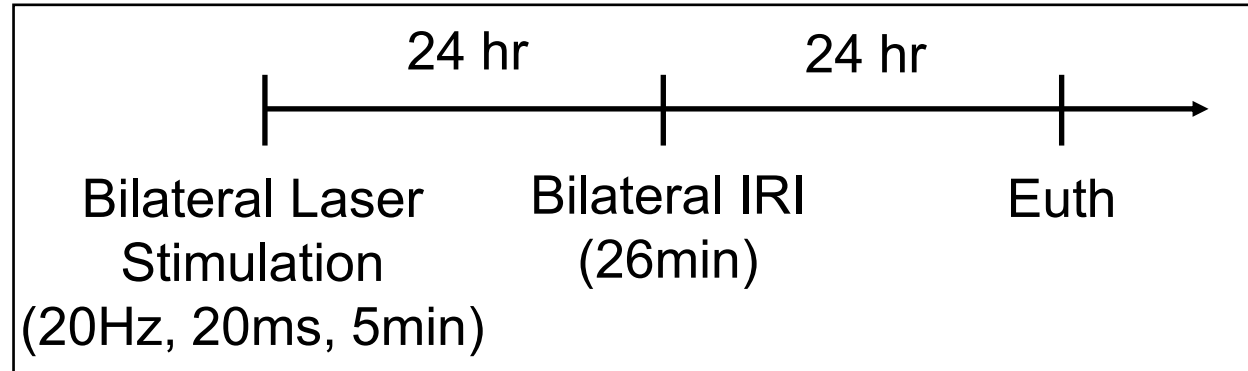


 Fenno L, et al. 2011.
Annu. Rev. Neurosci. 34:389–412

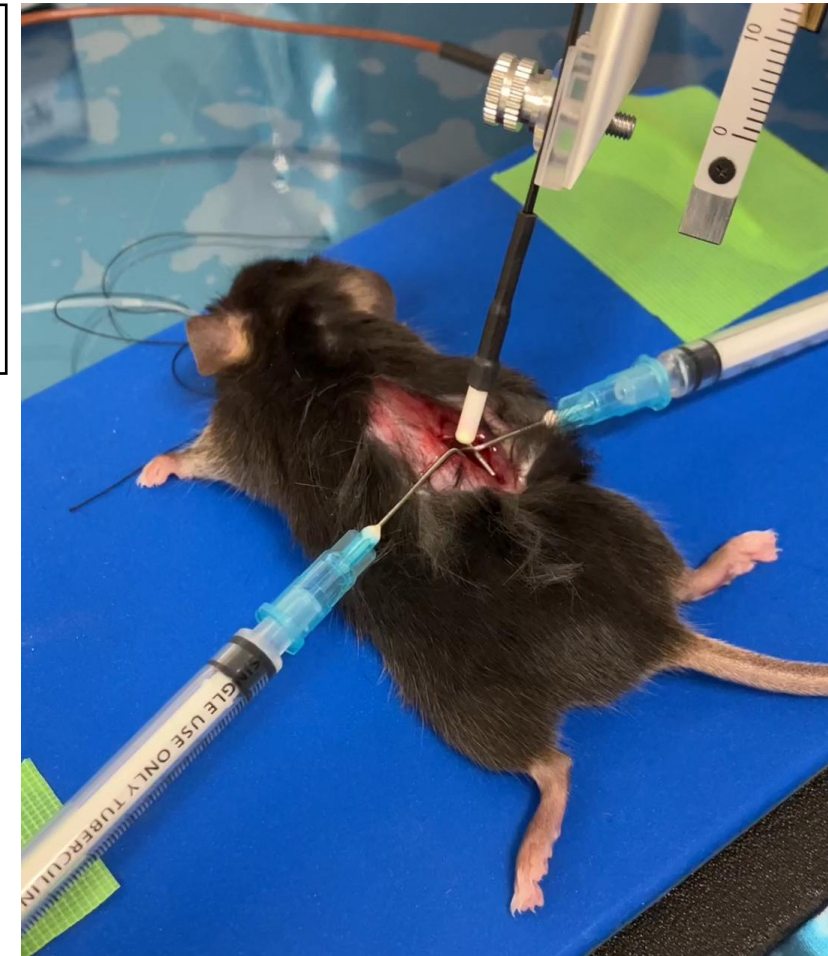
Optogenetic stimulation of renal sympathetic nerves protects the kidneys



Ryusuke Umene



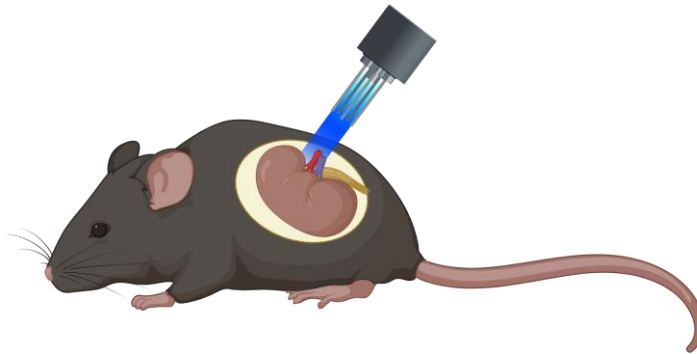
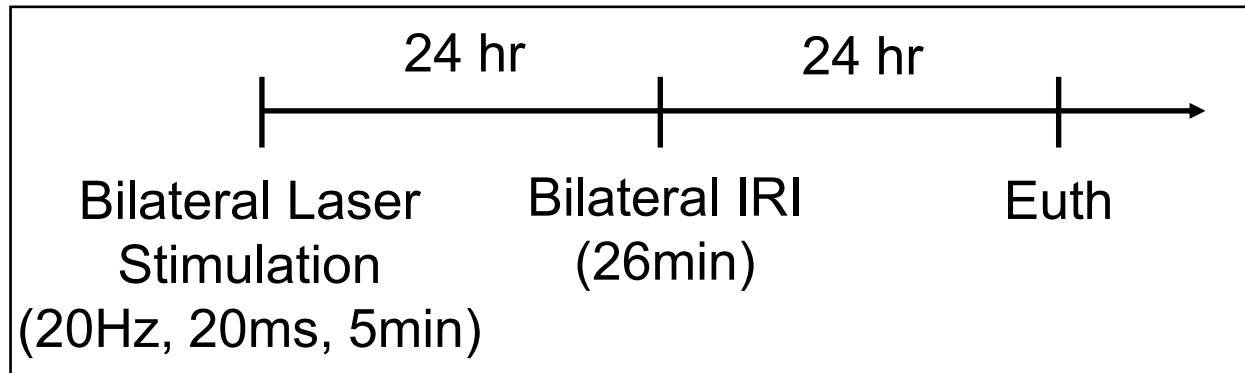
DbHCre-ChR2 mice
8w, Male



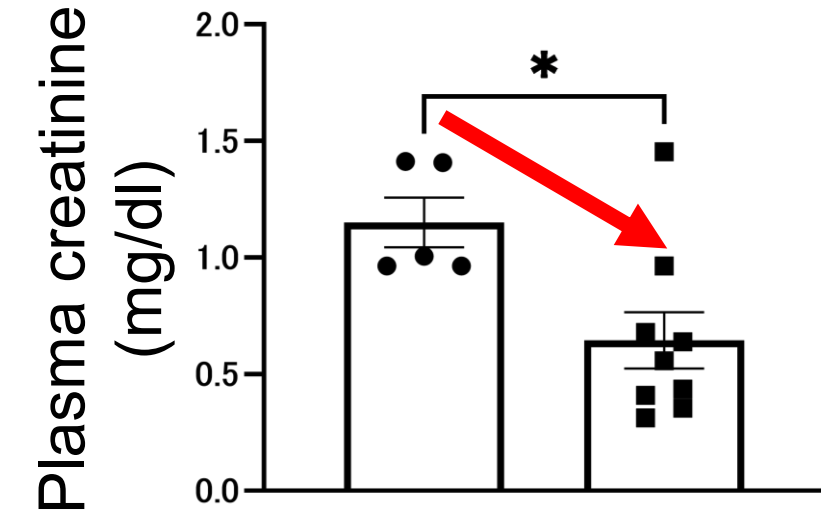
Optogenetic stimulation of renal sympathetic nerves protects the kidneys



Ryusuke Umene



DbHCre-ChR2 mice
8w, Male



Acute kidney injury

**Renal sympathetic
nerve stimulation**

+	+
-	+

Unpublished data

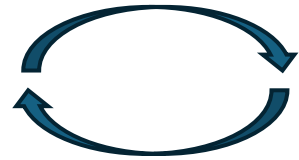
Summary



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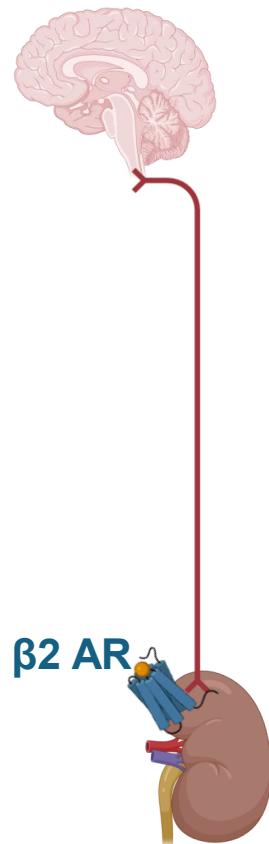
Sympathetic nerves

Noradrenaline



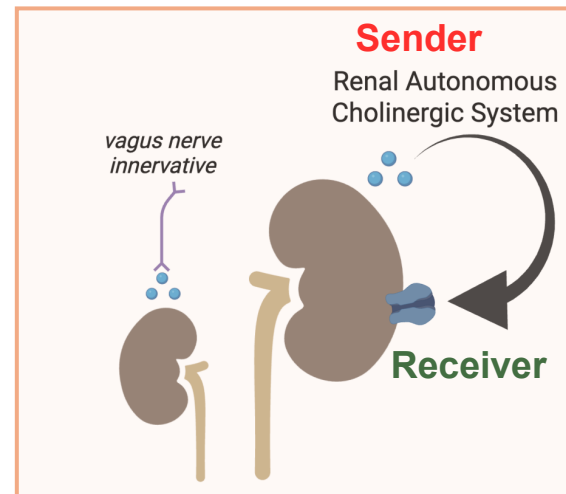
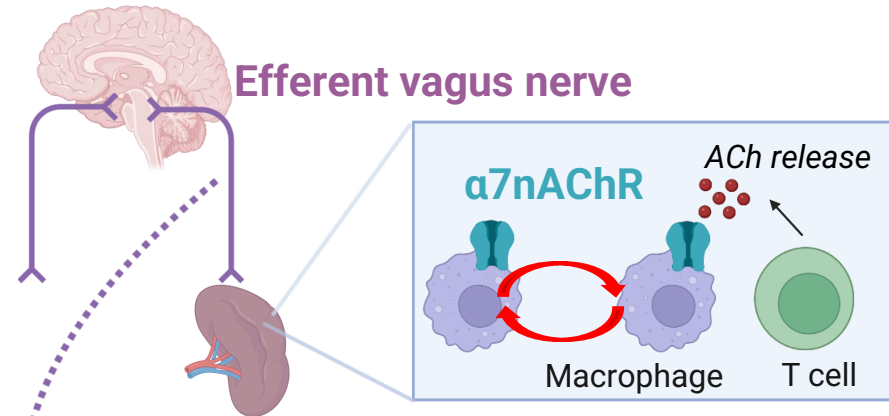
Parasympathetic nerves

Acetylcholine

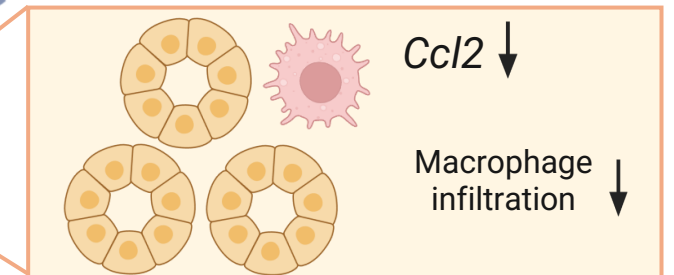


Afferent vagus nerve

Efferent vagus nerve



Hes-1 ↑ Anti-inflammatory Macrophage



Acknowledgement

Nagasaki University

Department of Physiology of Visceral Function and Body Fluid

Tsuyoshi Inoue
Yasuna Nakamura
Chia-Hsien Wu
Ryusuke Umene

Aobing Yang
Sayumi Matsuo
Shuntaro Soejima
Jun Iriki

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