Significance and Mechanisms of Ischemic Postconditioning against Stroke

Heng Zhao, PhD

Department of Neurosurgery,

Stanford University

The 14th Annual International Conference on Dose-Response

Outlines

1. Protective effect of IPostC
   a) Research history
   b) Therapeutic time windows
   c) Long-term protective effect

2. Mechanisms: free radicals, BBB, metabolisms, cell signaling pathways

3. Immune cells and IPostC

The research history of postconditioning

- 1955, Sewell et al, Ventricular fibrillation
- 1996, Na et al, postconditioning
- 2003: Z.Q. Zhao et al, Myocardial ischemia
- 2006: Heng Zhao et al: Stroke

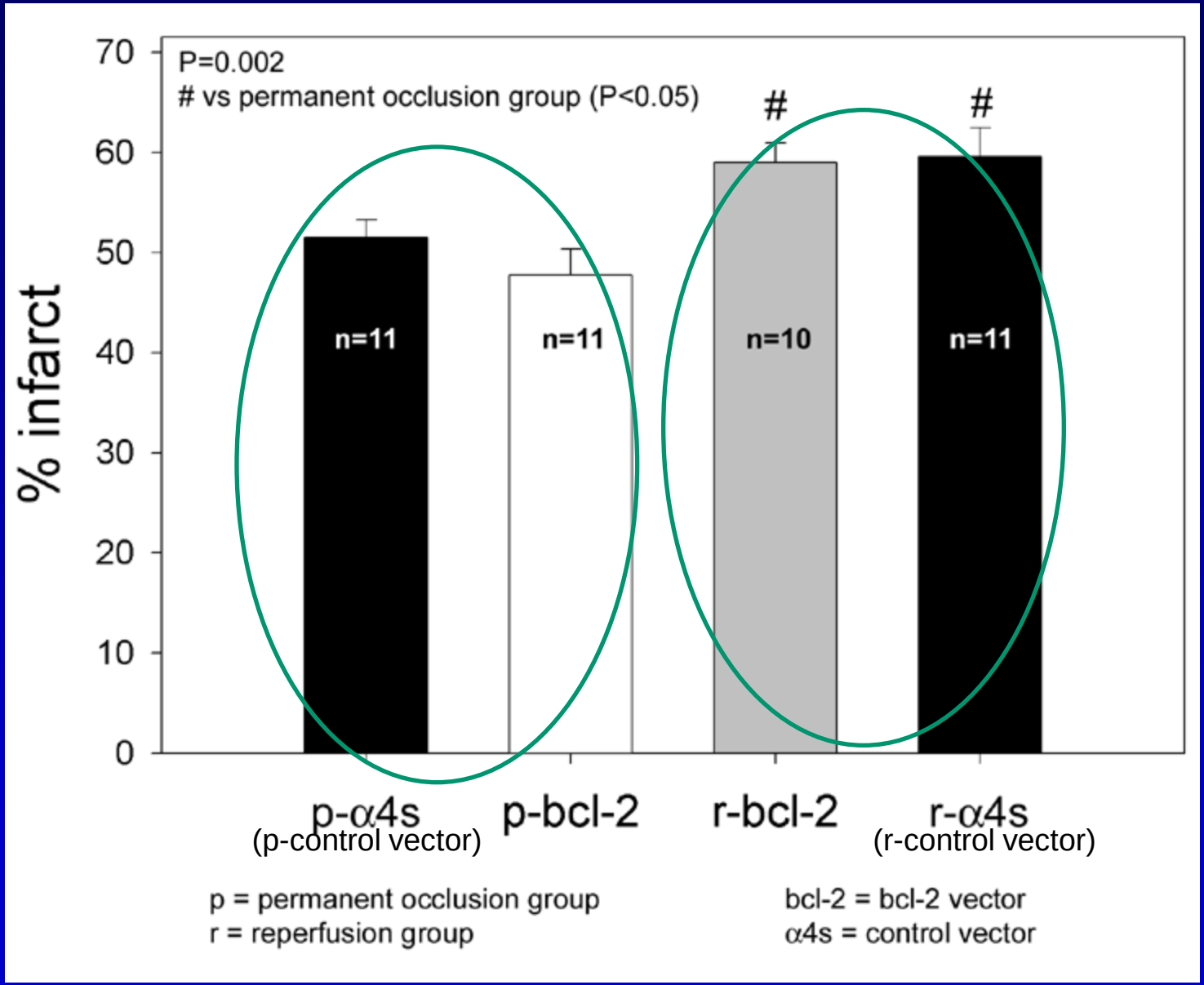
H Zhao, 2009

Stroke model: two CCA occlusion plus distal MCA occlusion

- Partial reperfusion
  - Bilateral CCA released after 2h of ischemia while the distal MCA remained occluded
- Total reperfusion
  - Three vessels released after 2h of ischemia

Zhao et al, 2003

Partial reperfusion reduced infarcts compared with complete reperfusion



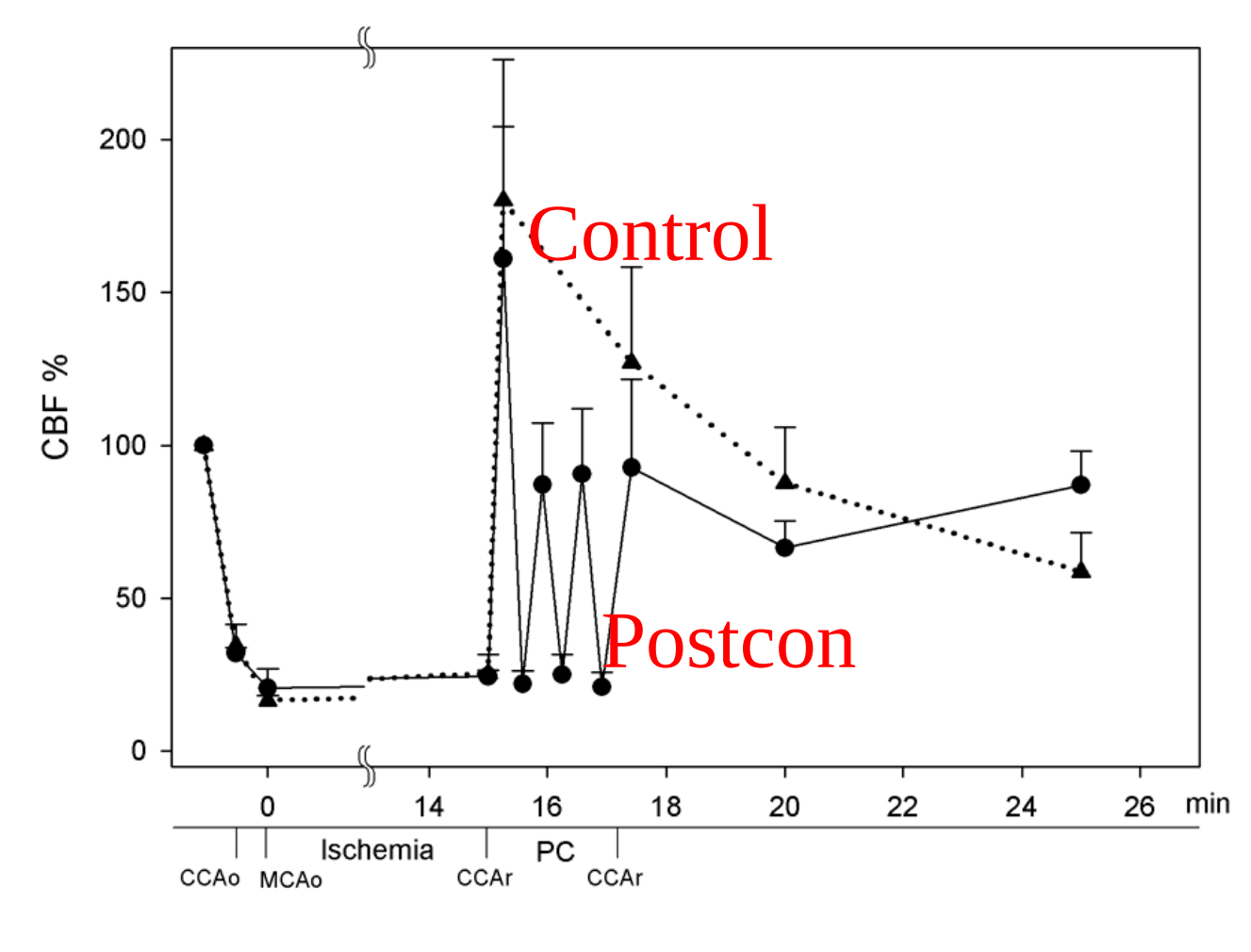
Rapid Communication

Interrupting reperfusion as a stroke therapy: ischemic postconditioning reduces infarct size after focal ischemia in rats

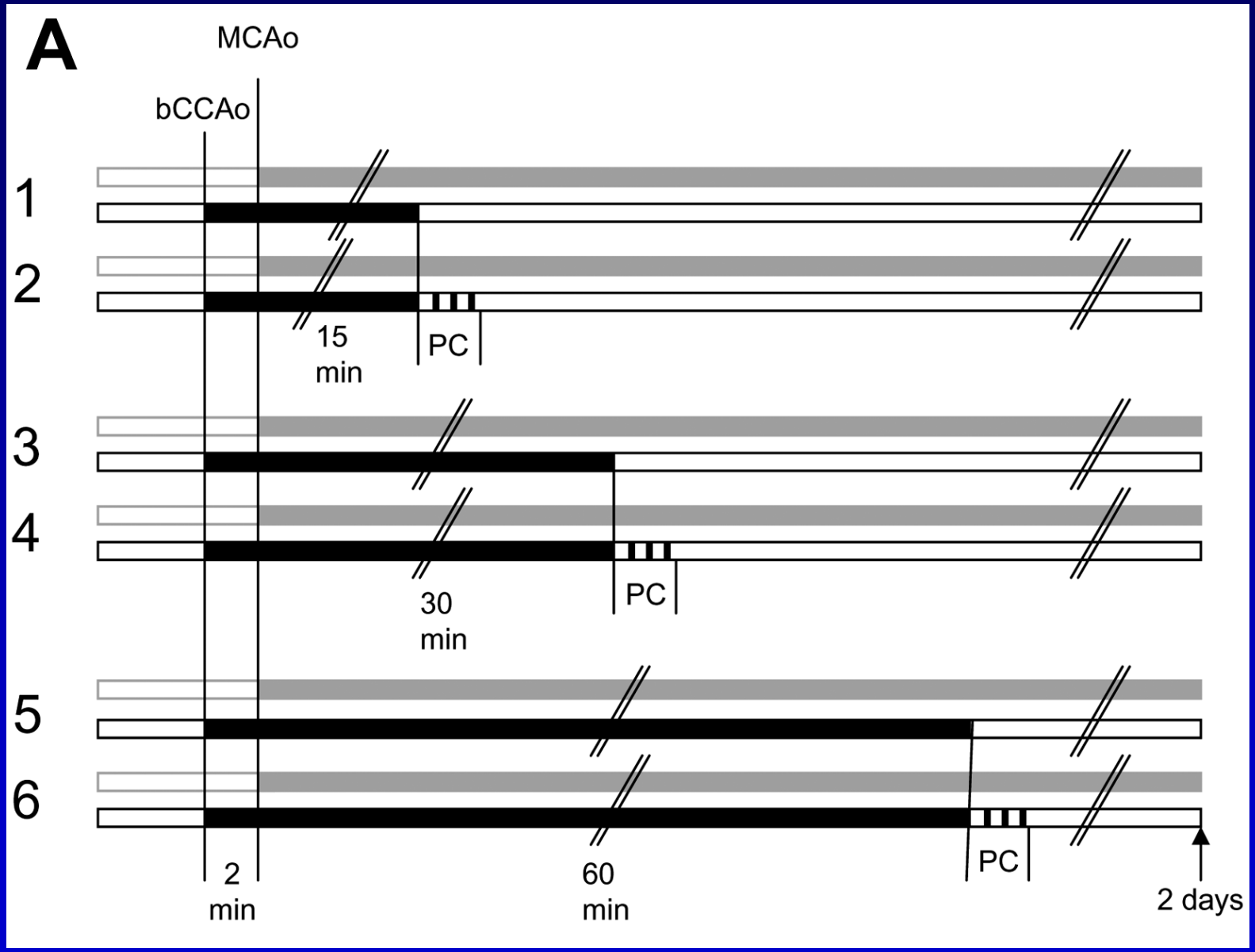
Heng Zhao[1,2], Robert M Sapolsky[1,2,3] and Gary K Steinberg[1,2]

Zhao et al, 2006

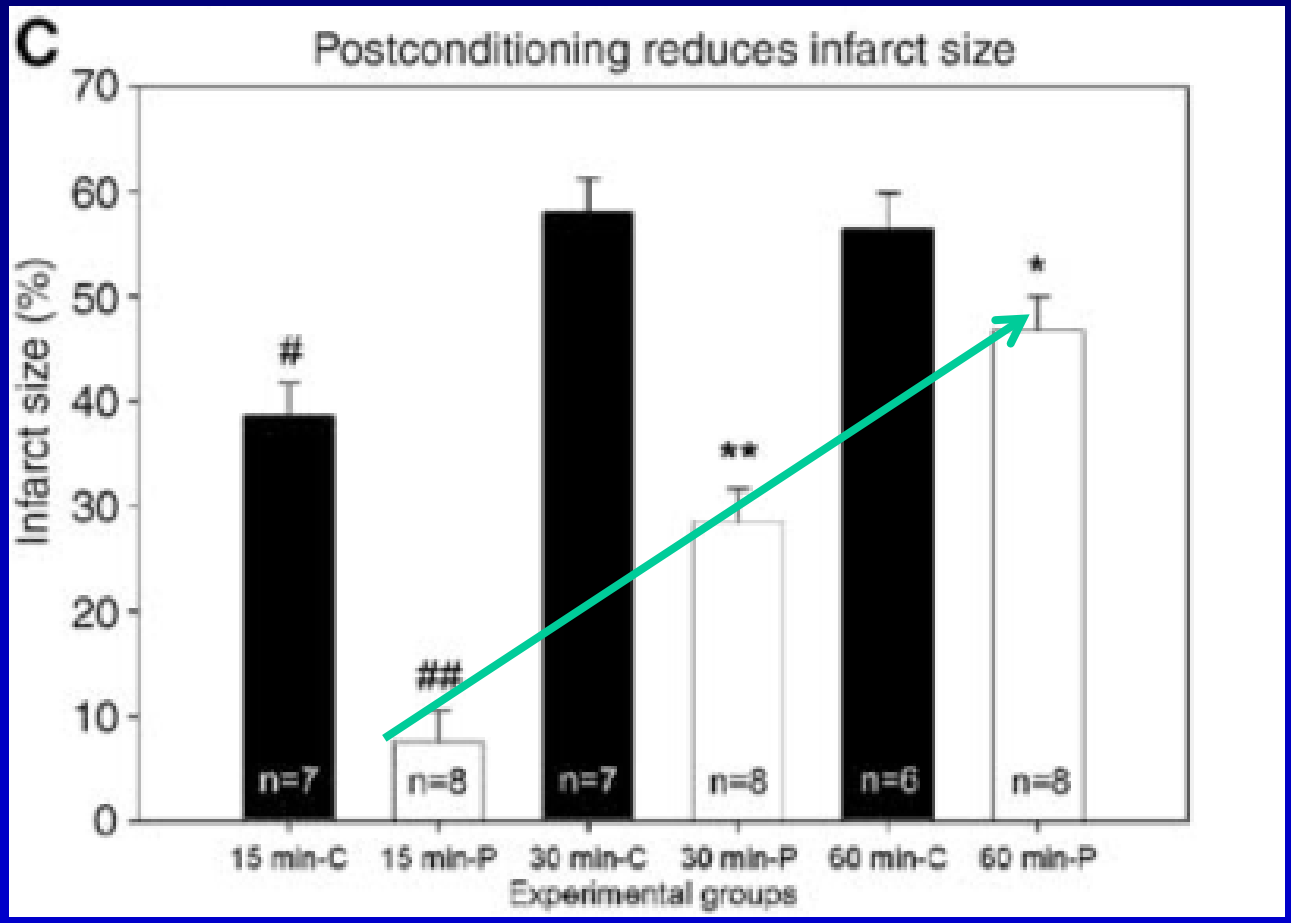
Postconditioning interrupts hyperemic response after reperfusion



Protocols for postconditioning

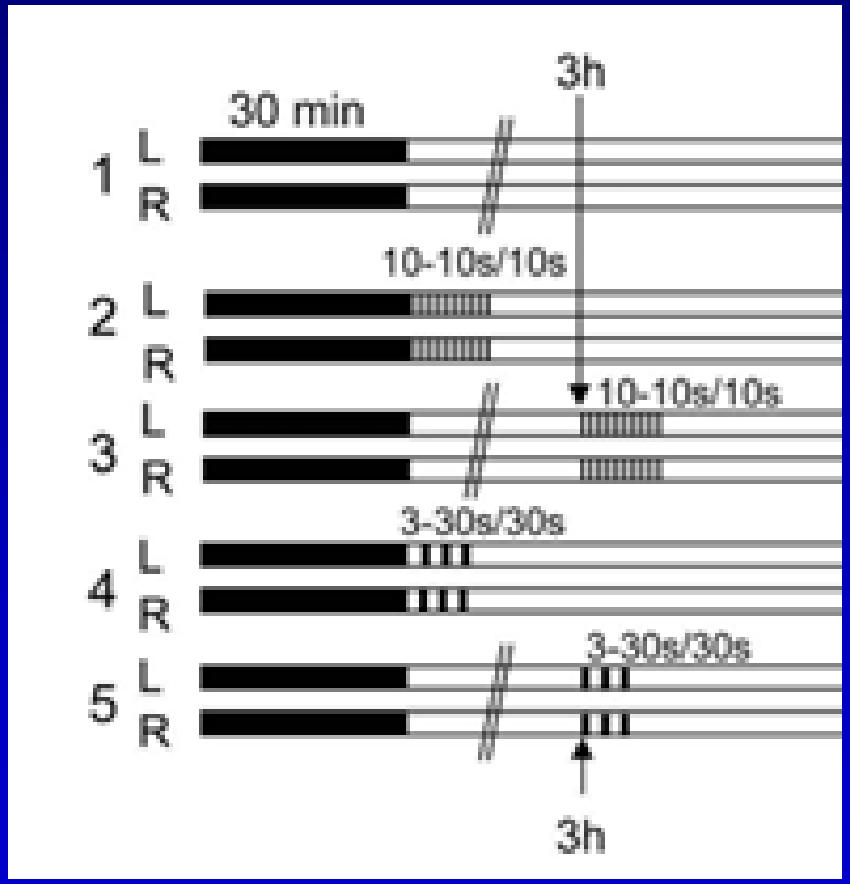


Postconditioning reduces infarction as a function of ischemic severity



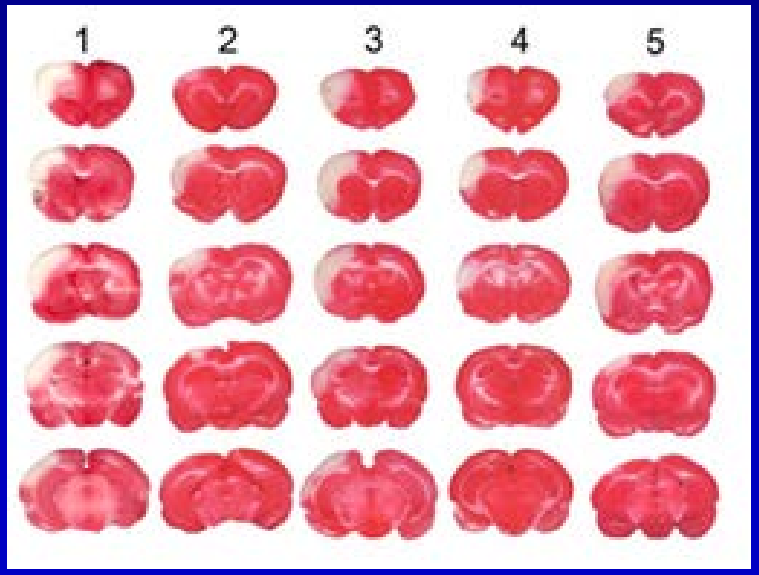
Zhao et al, J. CBF & Metab., 2006

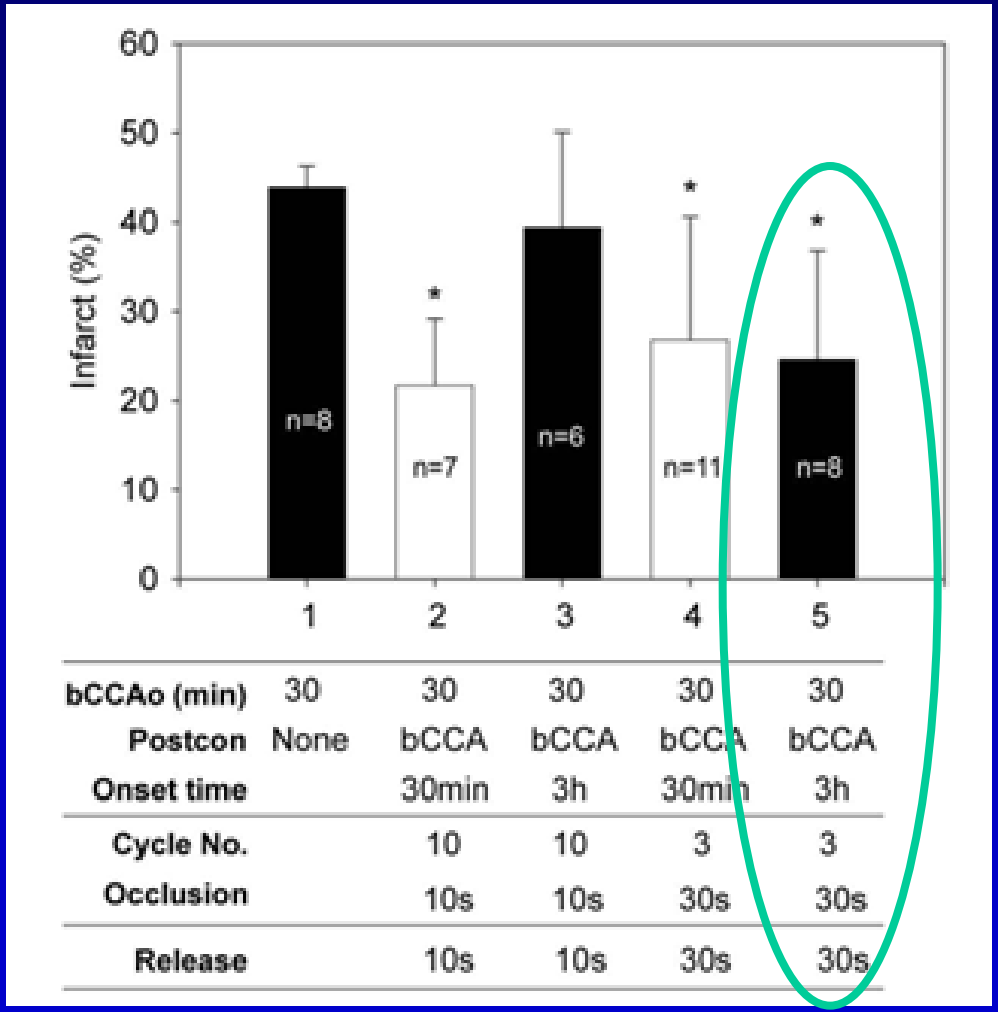
Delayed postconditioning was conducted 3h post stroke onset



Ren et al, 2008

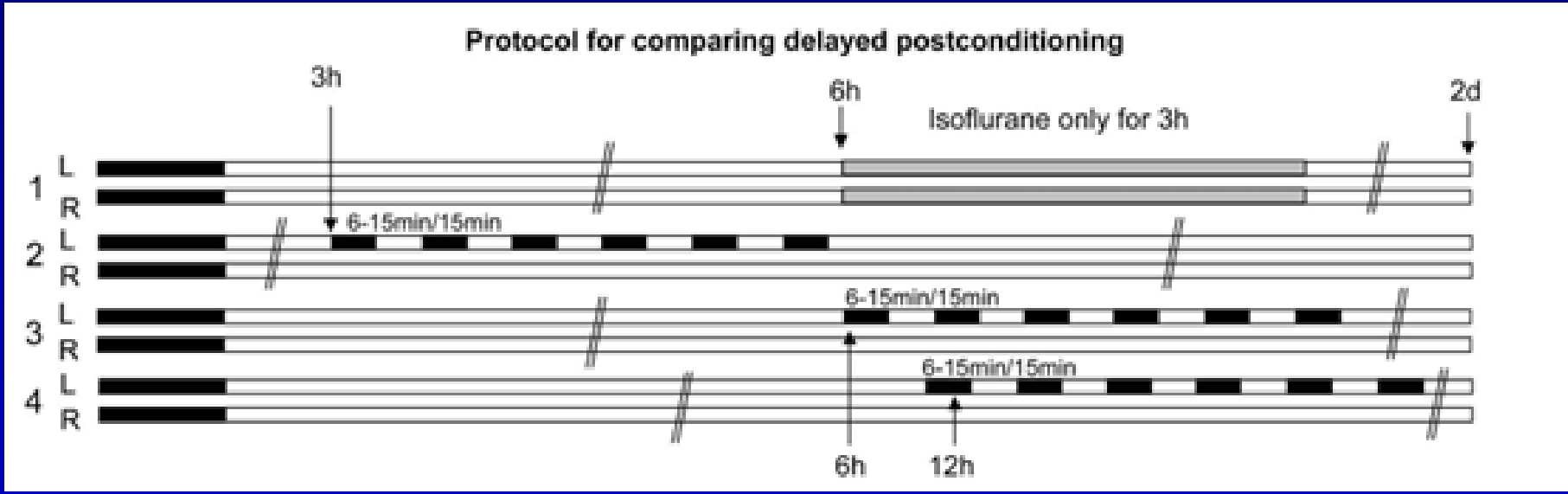
Delayed postcon reduced infarction



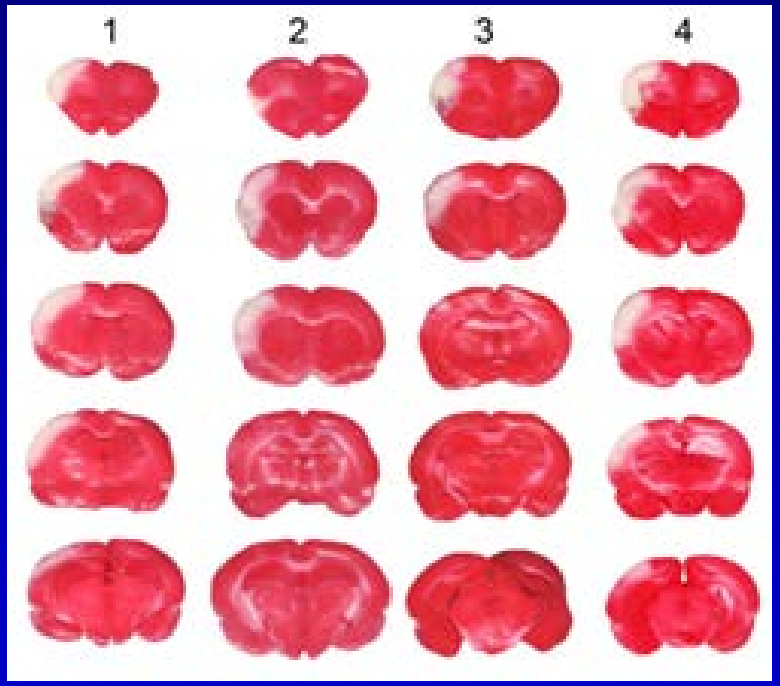


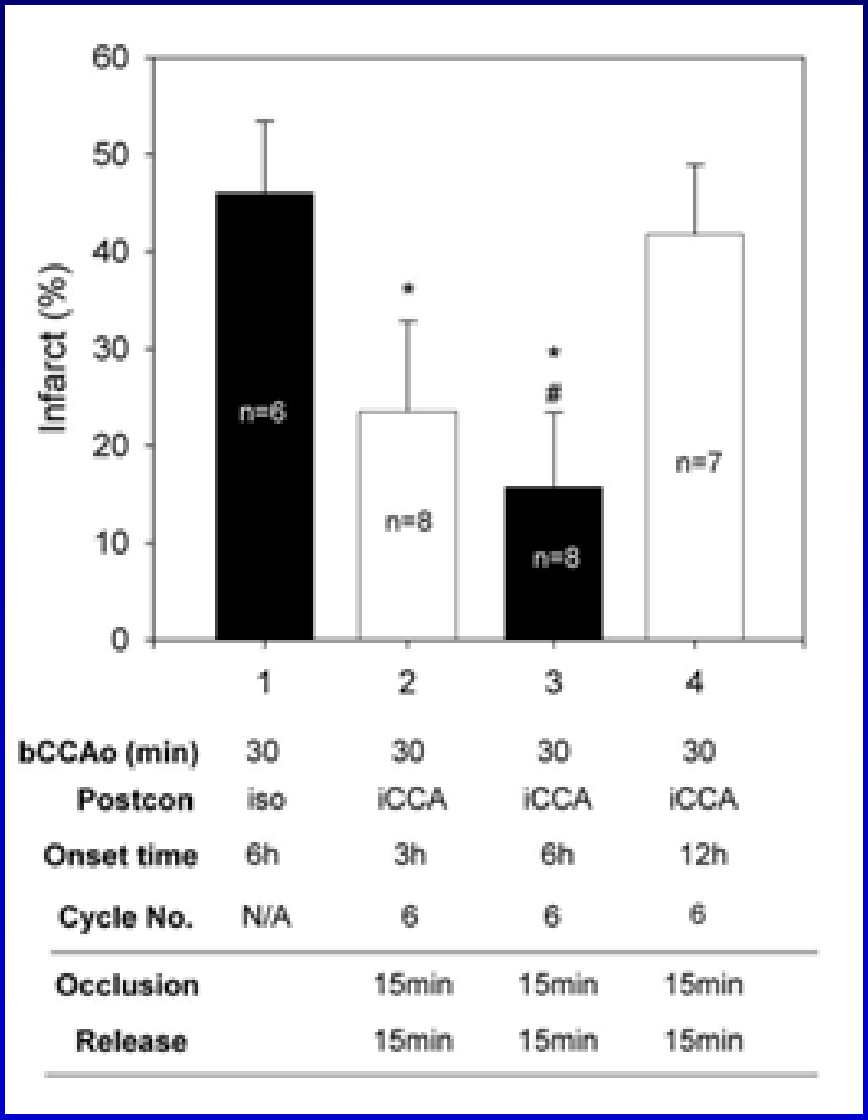
Ren et al, 2008

Delayed postcon was performed as late as 6h after stroke onset

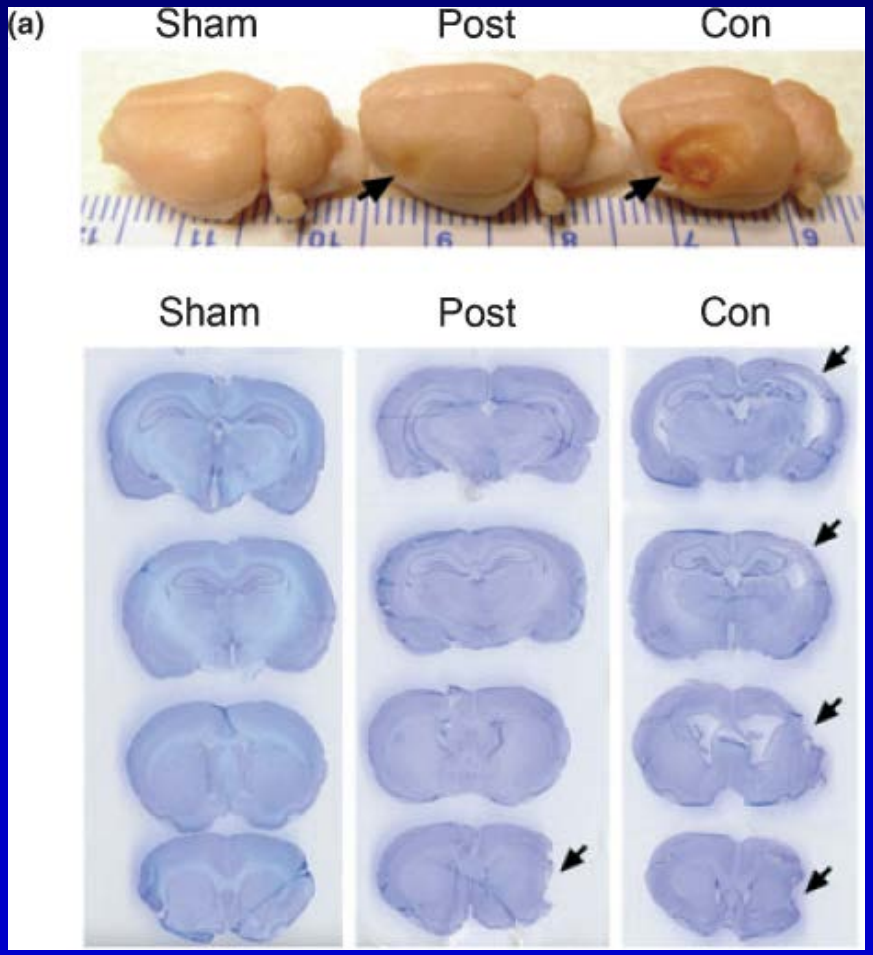


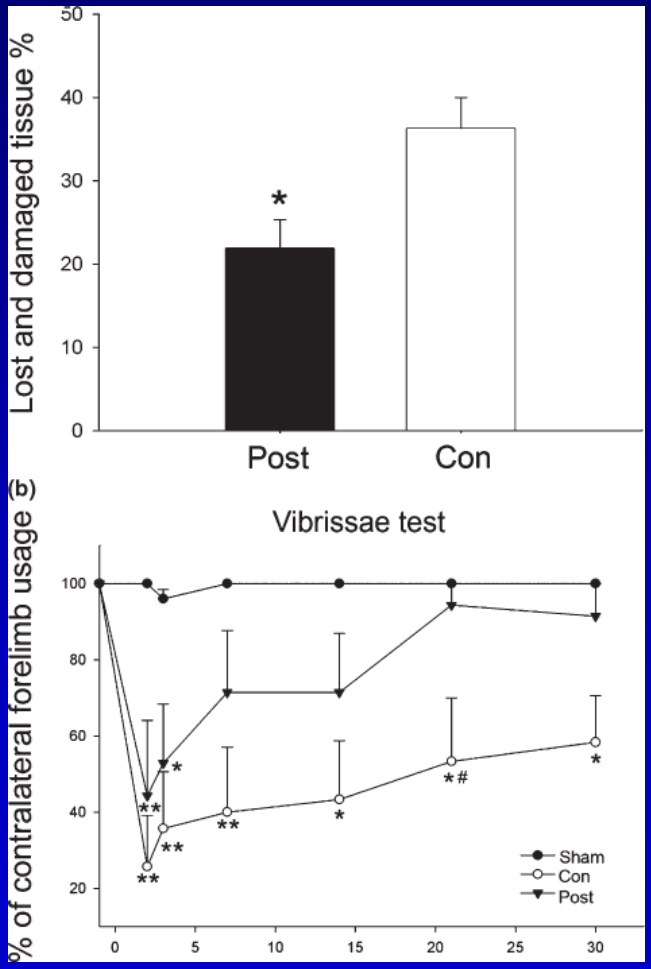
The therapeutic time window can be extended to 6 hours after stroke onset





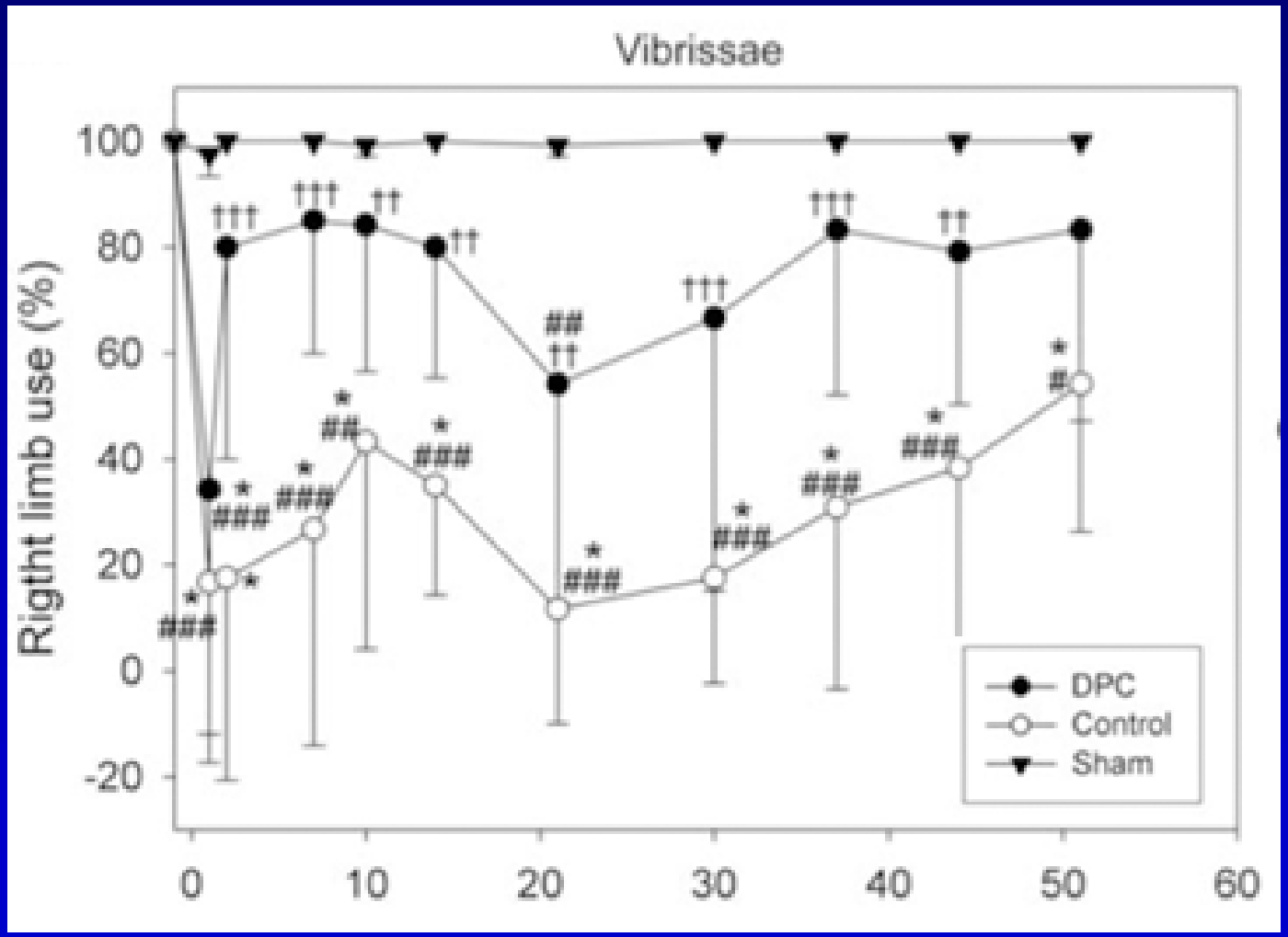
Rapid ischemic postconditioning offers long-term protection up to 1 month





Gao et al, 2008, J. Neurochemistry

Delayed postconditioning attenuates neurological deficits up to 2 months



Summary (I)

1. Research history
2. Therapeutic time windows
   - Rapid IPostC
   - Delayed IPostC
3. Long-term protective effect of IPostC

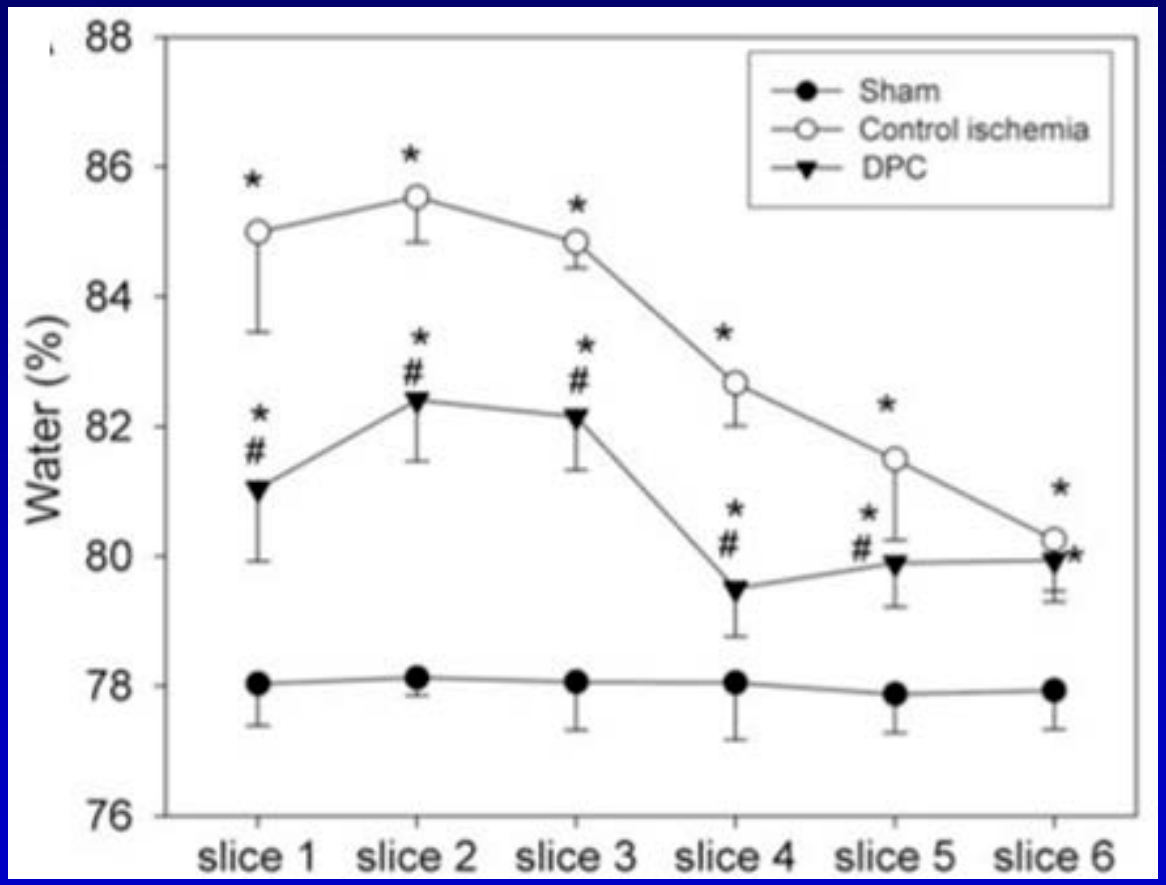
Outlines

1. Protective effect of IPostC
   a) Research history
   b) Therapeutic time windows
   c) Long-term protective effect

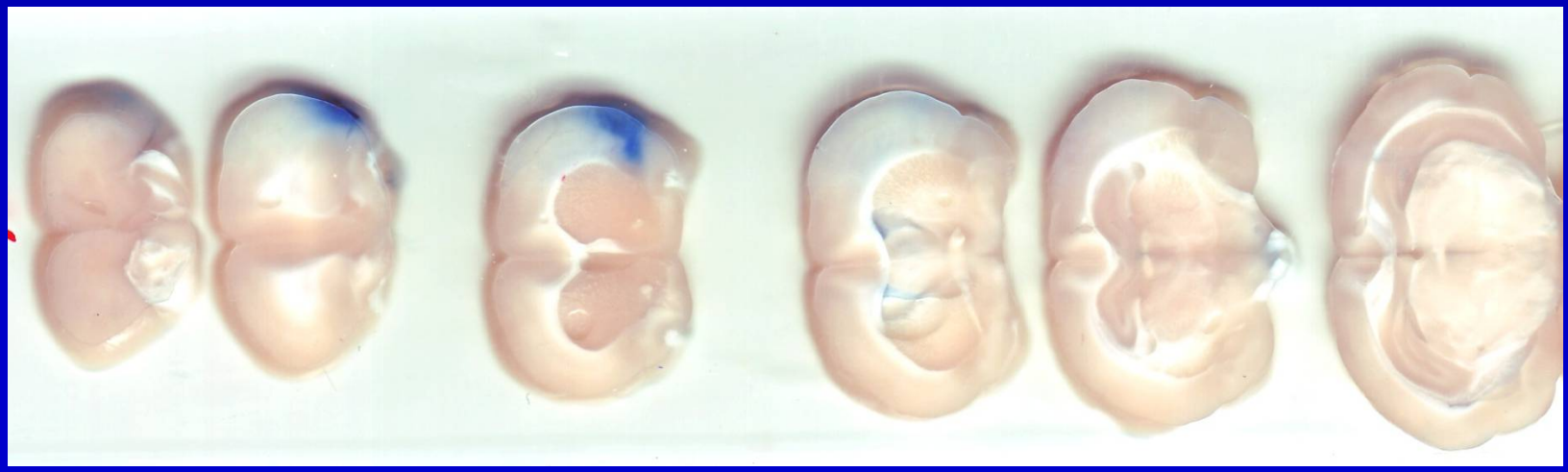
2. Mechanisms: free radicals, BBB, metabolisms, cell signaling pathways

3. Immune cells and IPostC

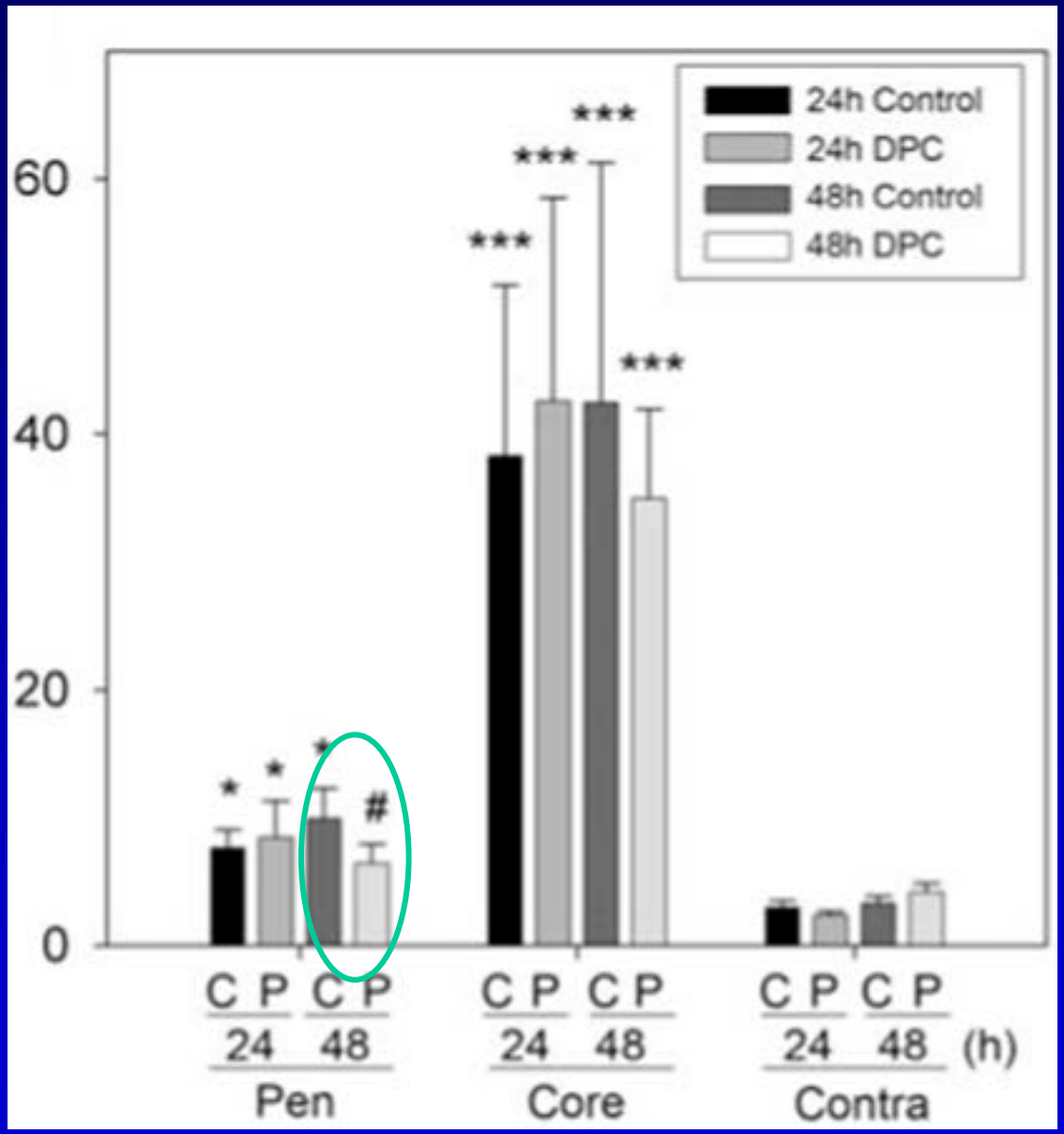
Delayed postconditioning reduces edema caused by stroke



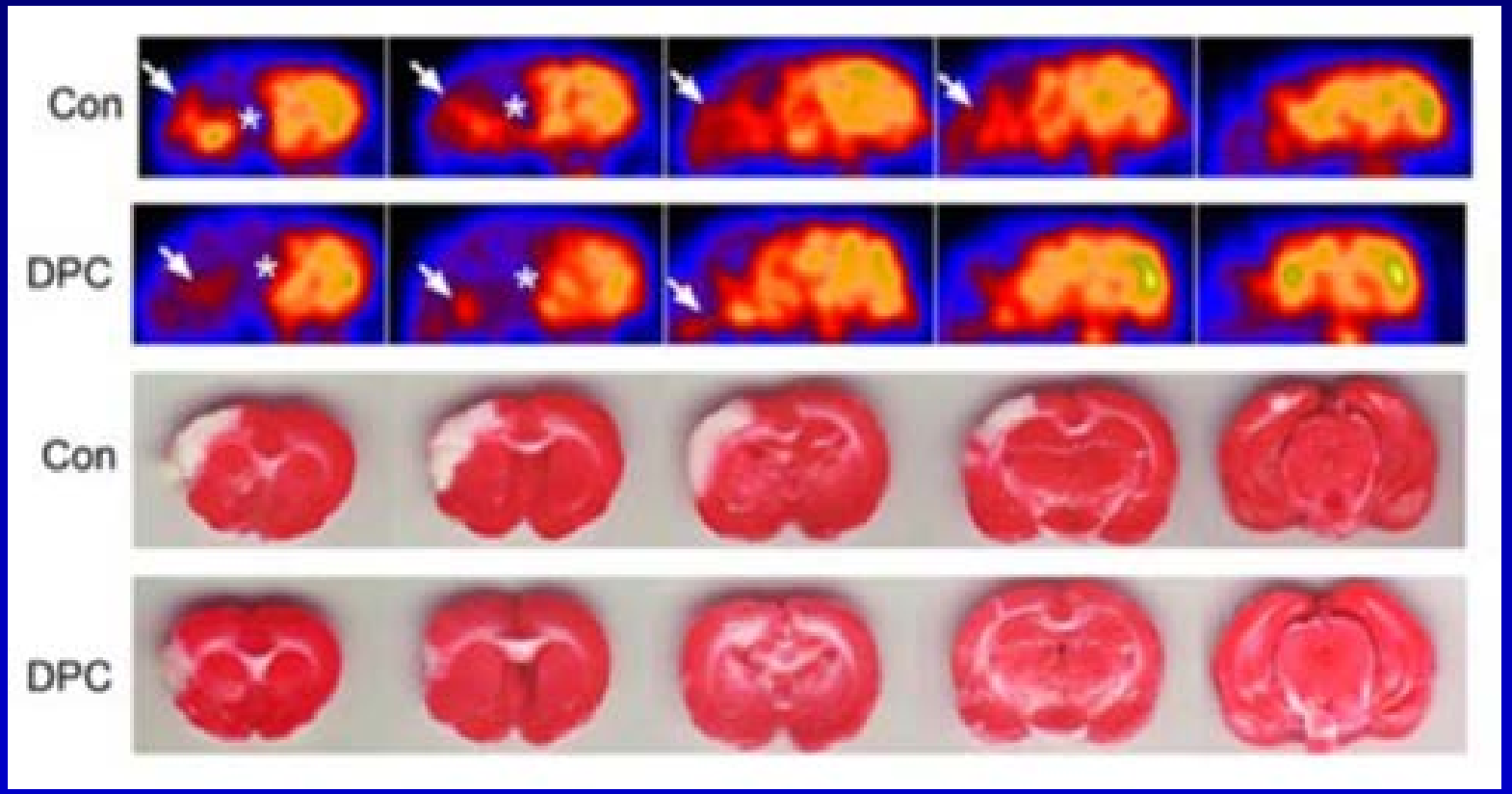
Evans blue is used to detect BBB leakage



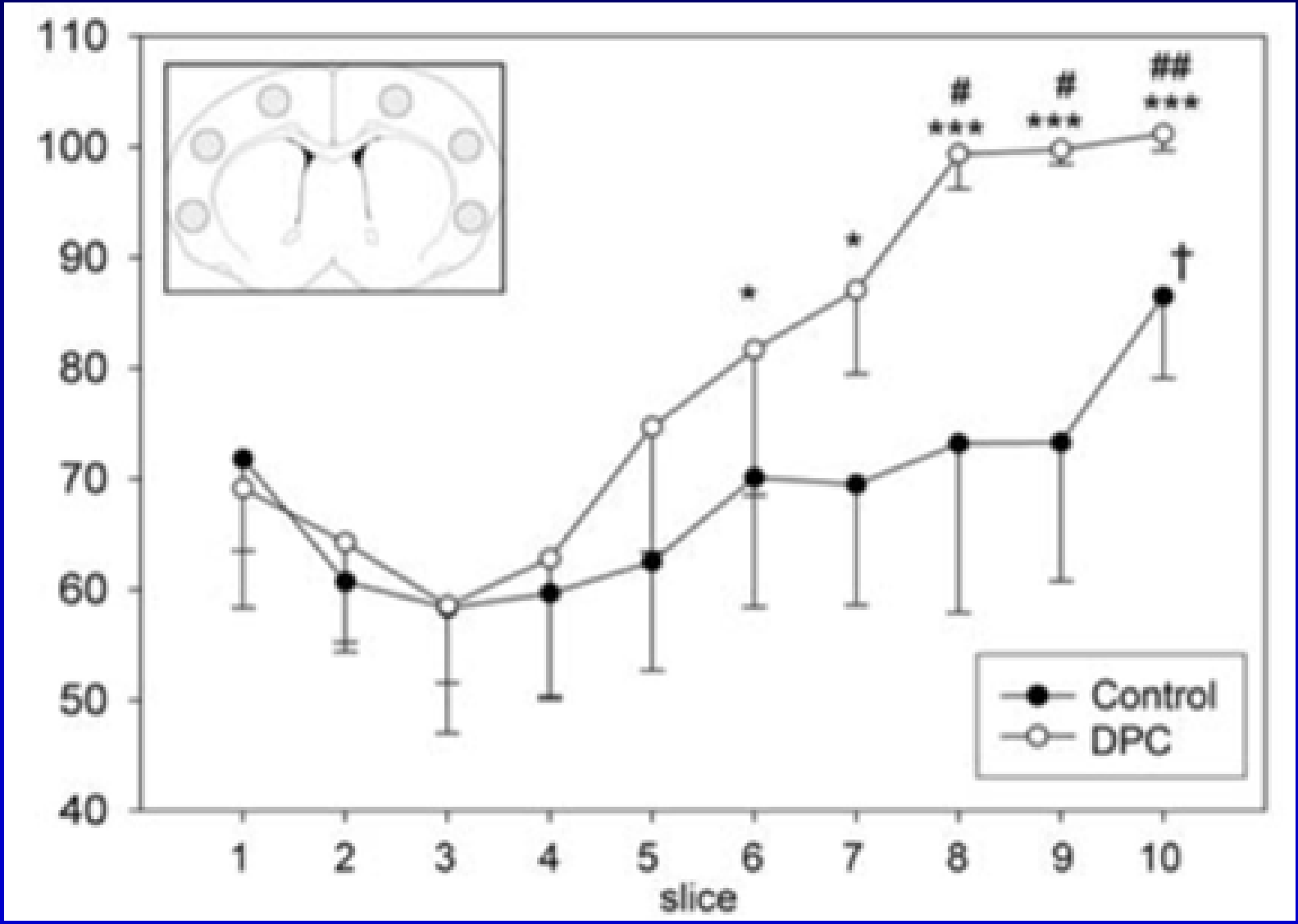
Delayed postconditioning reduced BBB leakage at 48h post-stroke



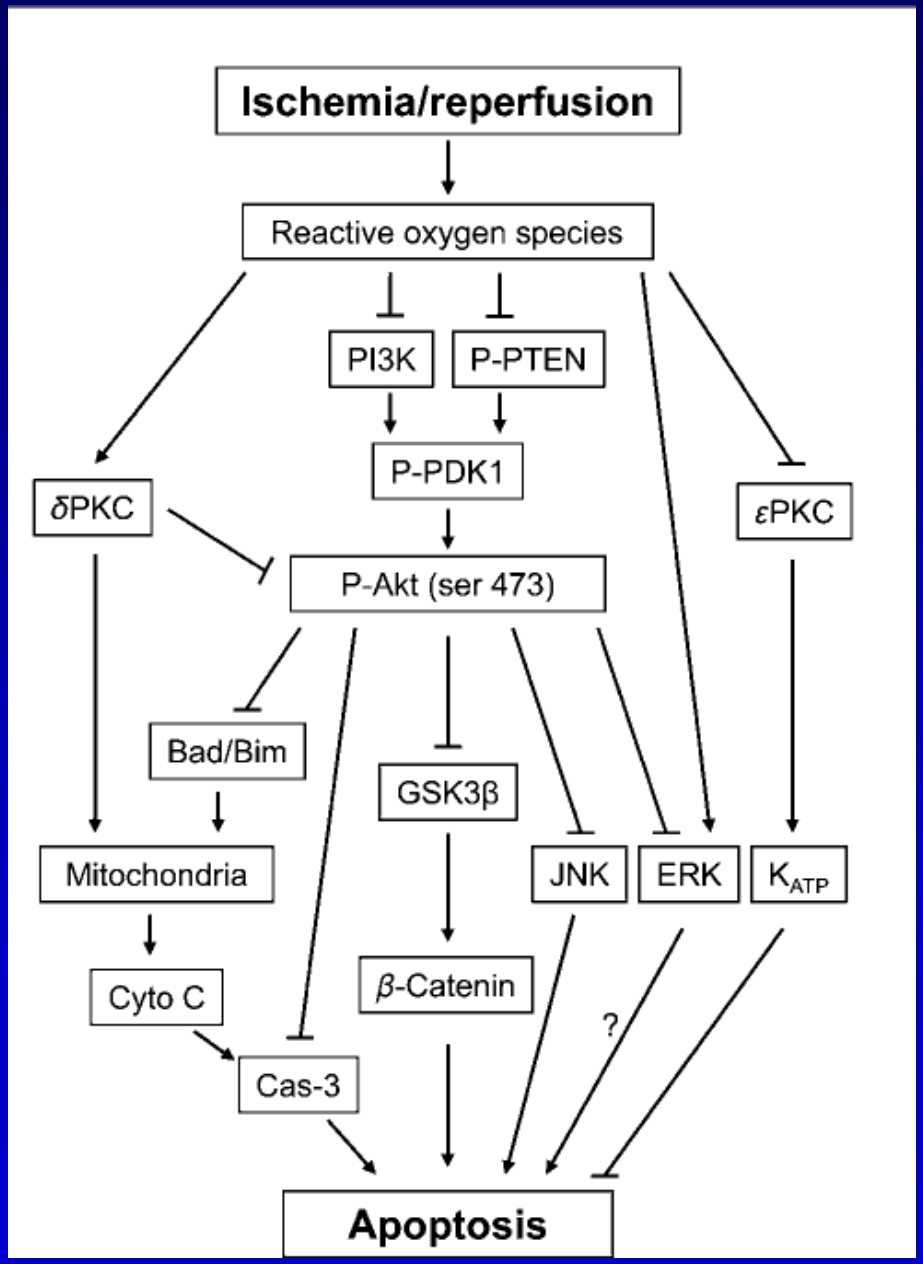
FDG uptake measured by PET imaging



Delayed postconditioning improves metabolism after stroke

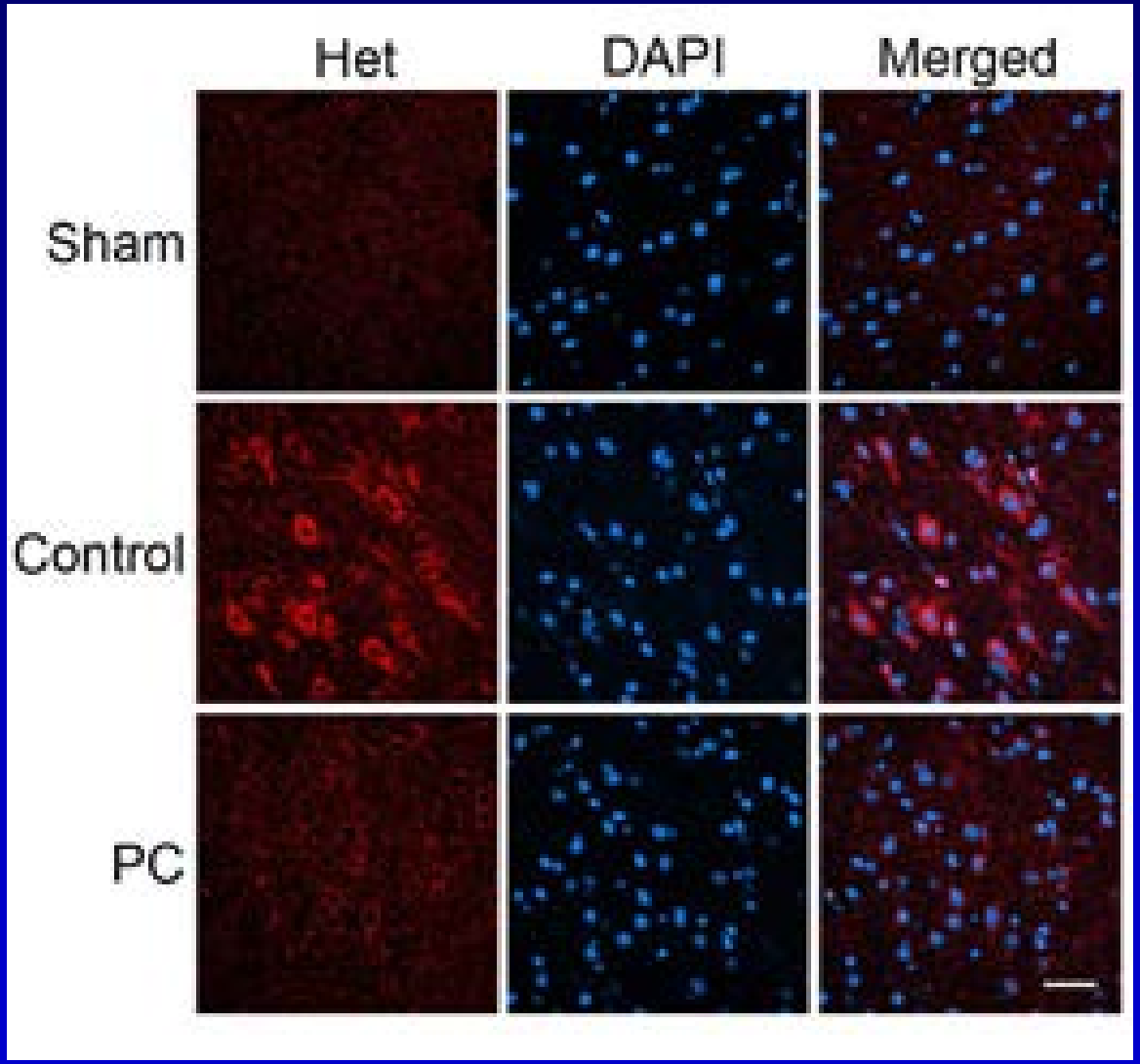


Postcon regulates various cell signaling pathways

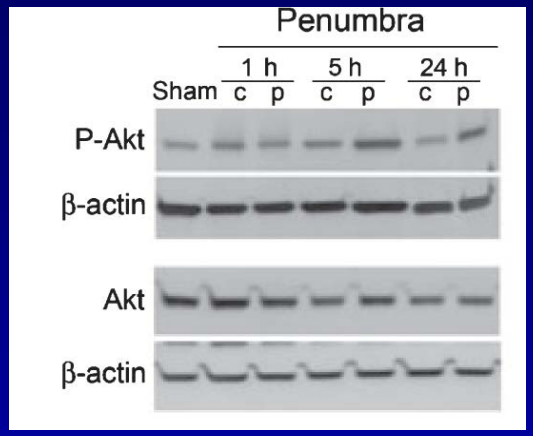


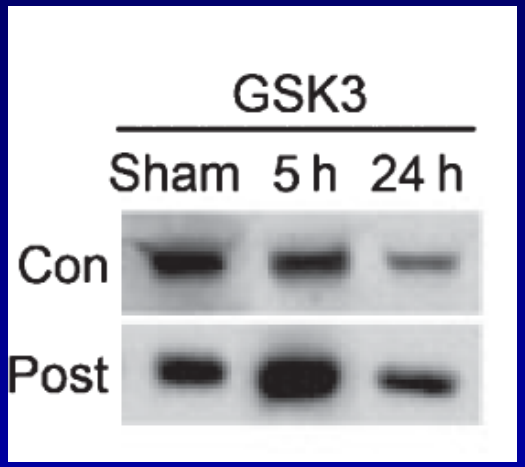
Postconditioning inhibits ROS generation:

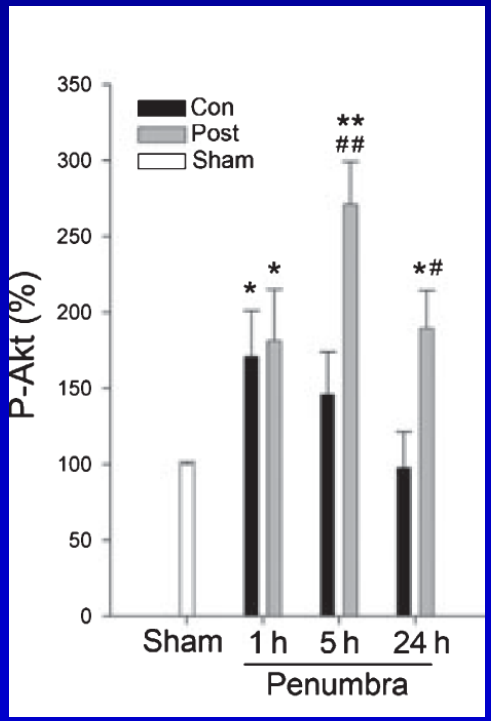
In situ detection of superoxide radicals by injection of hydroethidine

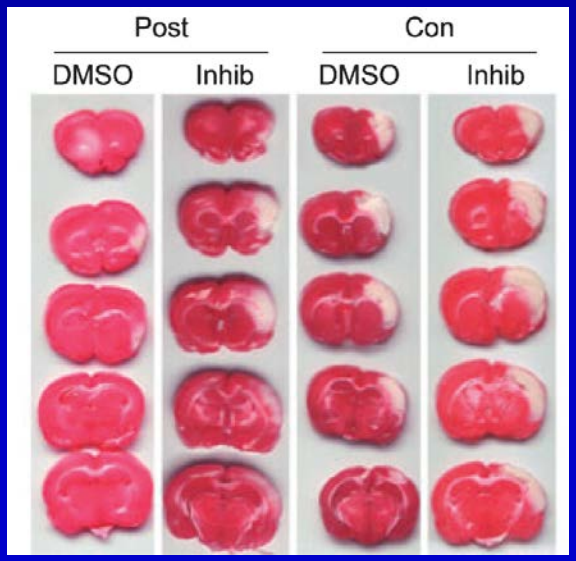


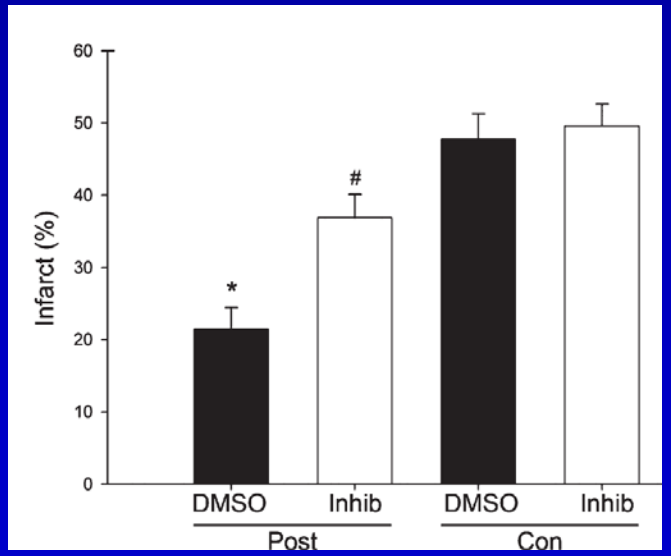
Akt activity contributes to the protective effects of ischemic postconditoning





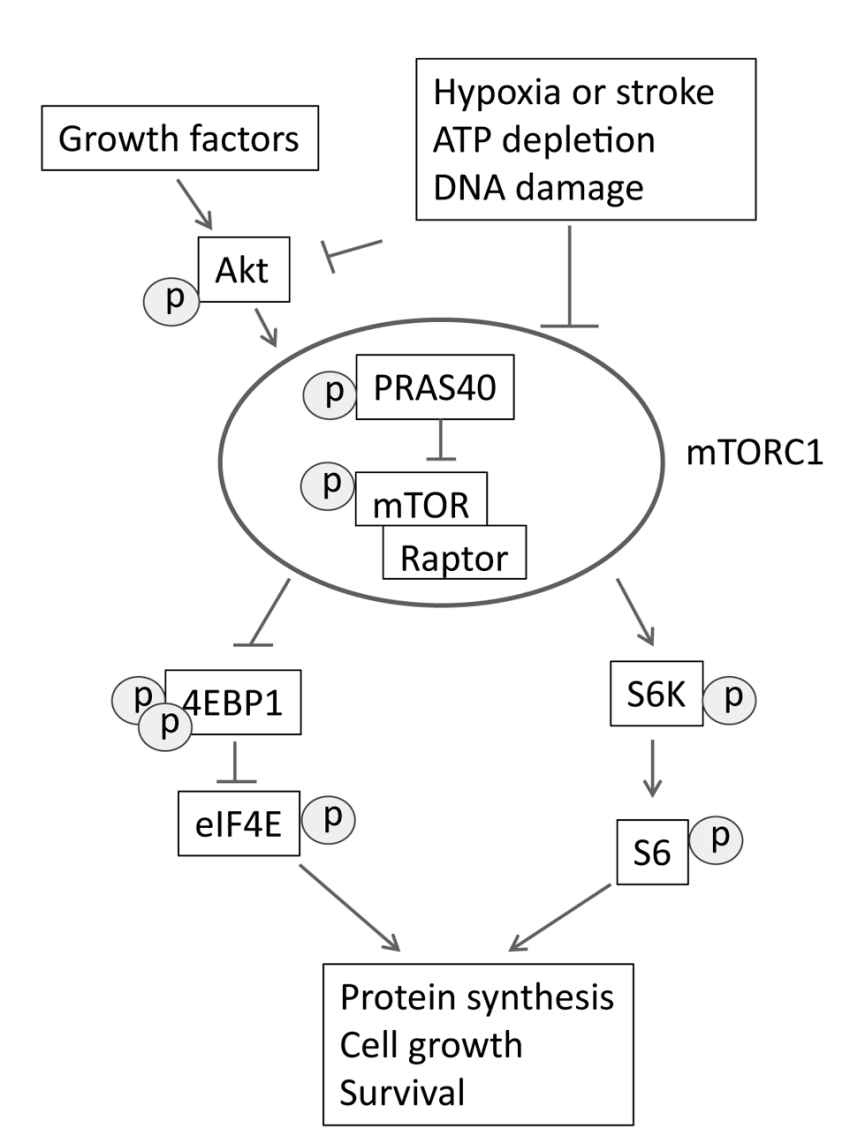






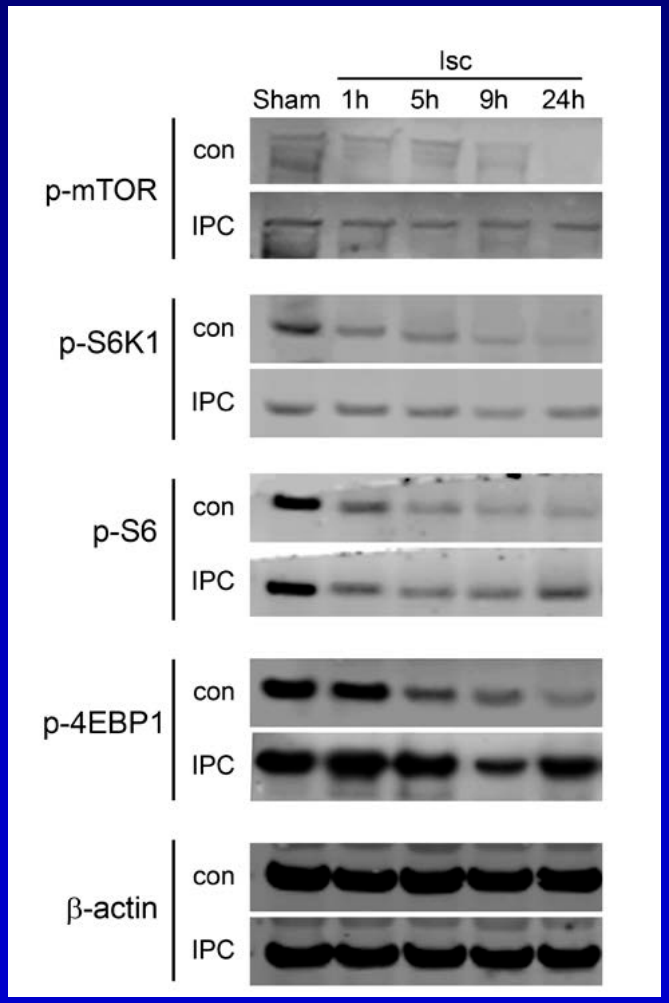
Gao et al, 2008

The mTOR cell signaling pathway



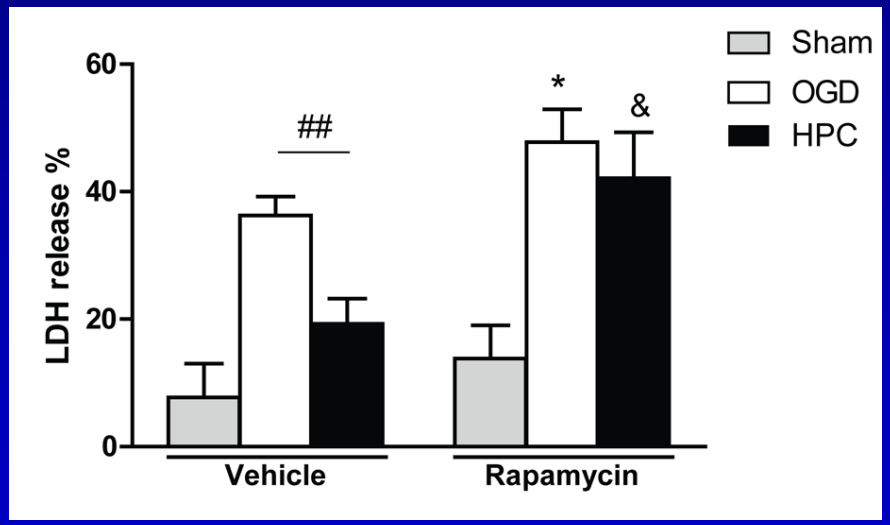
Xie et al, Stroke 2014

IPC attenuates reductions in protein phosphorylation in the mTOR pathway

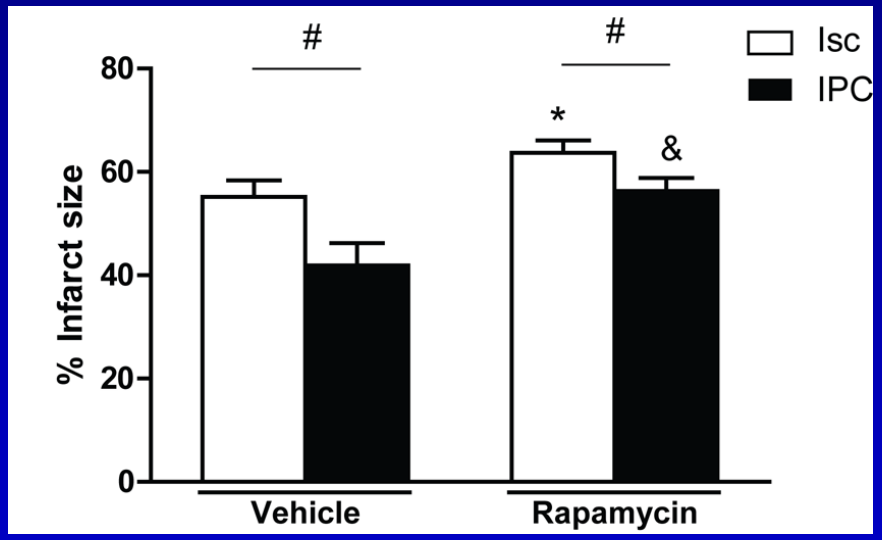


Inhibition of mTOR attenuates the protective effect of HPC/IPC

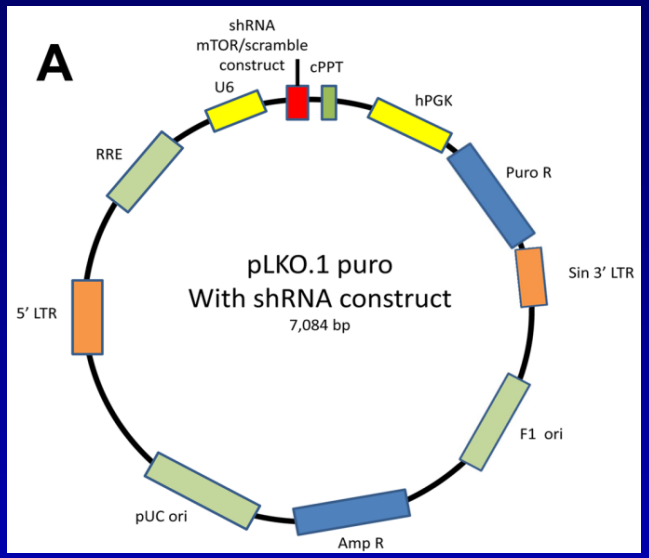
In vitro OGD model

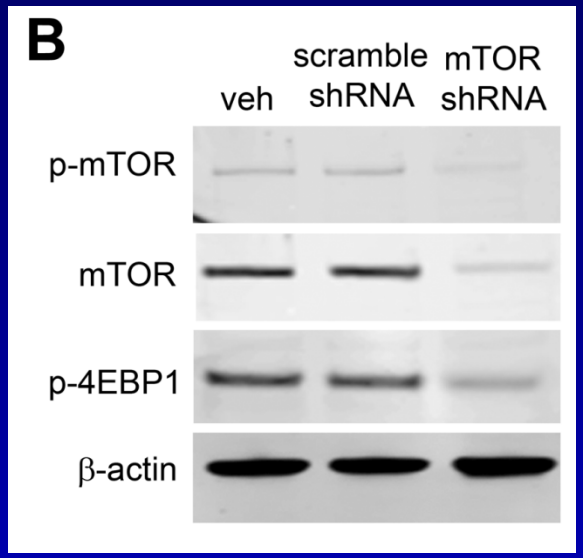


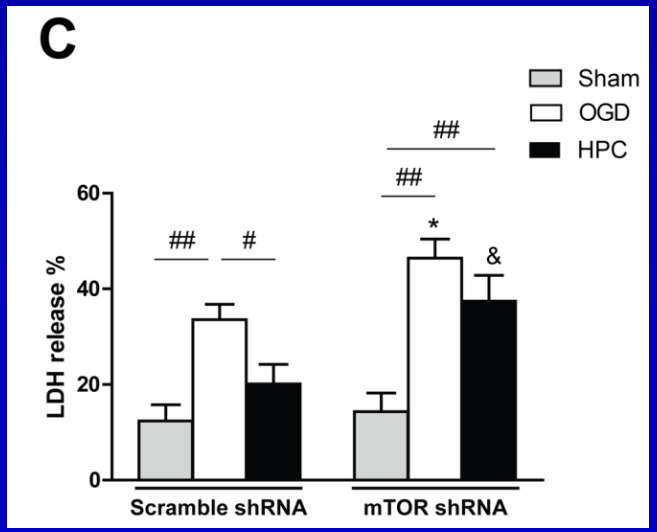
In vivo stroke model

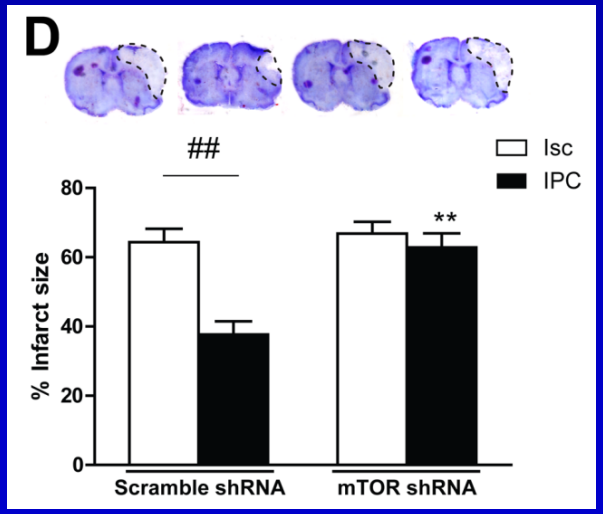


mTOR shRNA Abolished the Protective Effects of HPC (IPC) In Vitro and In Vivo



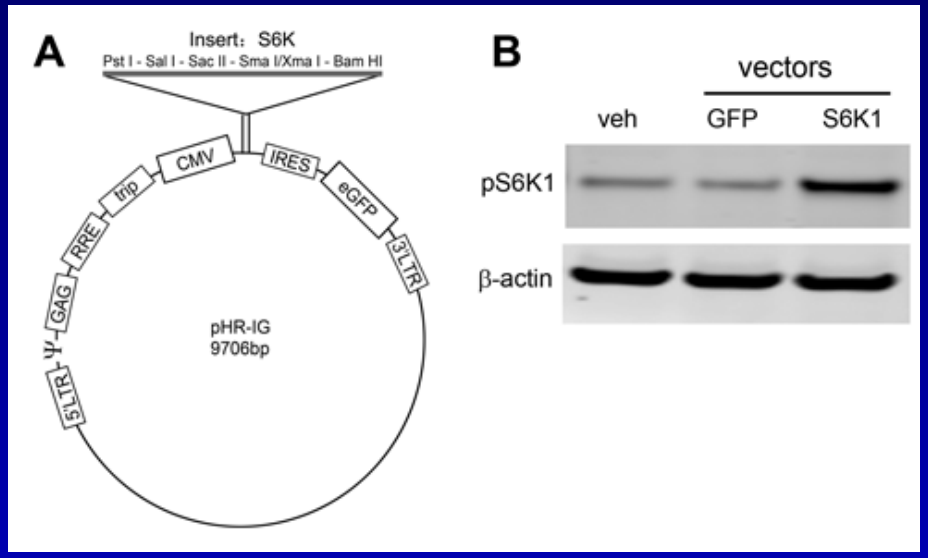


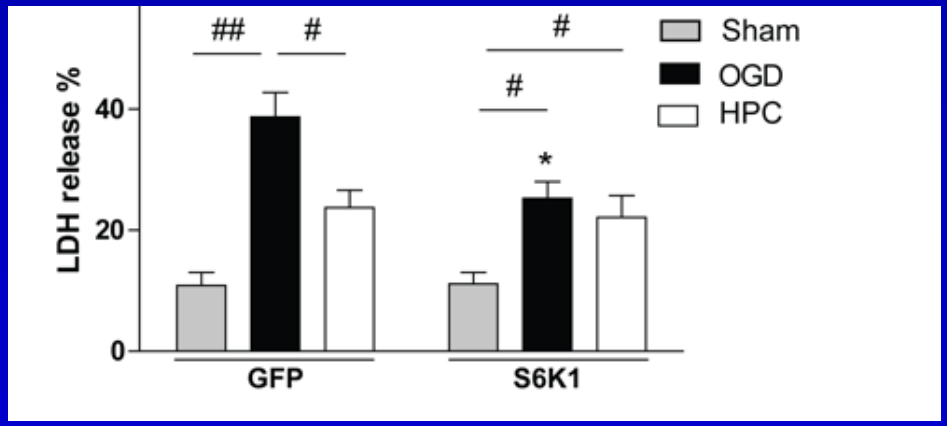




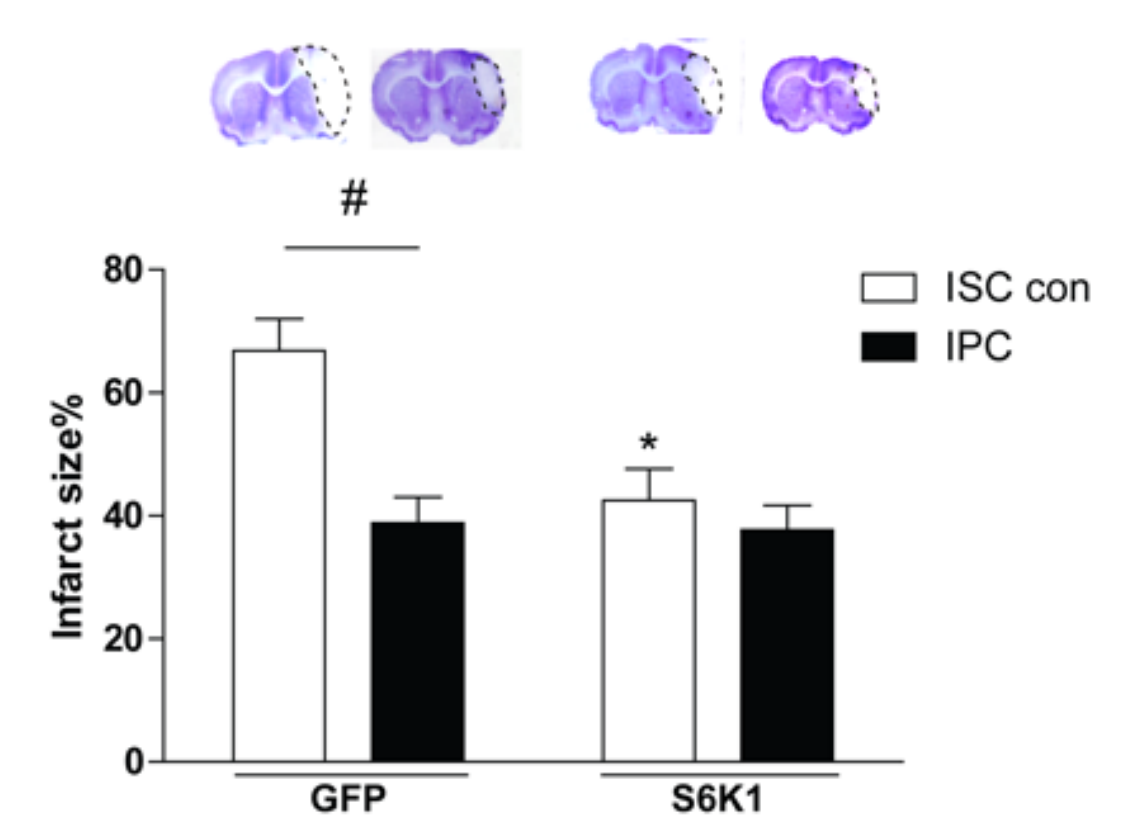
Xie et al, 2014

HPC does not provide synergistic effect with S6K1 overexpression





IPC does not provide synergistic effect with S6K1 overexpression



Summary (II)

1. Edema, BBB, and metabolism
2. Free radicals
3. The Akt and mTOR pathways

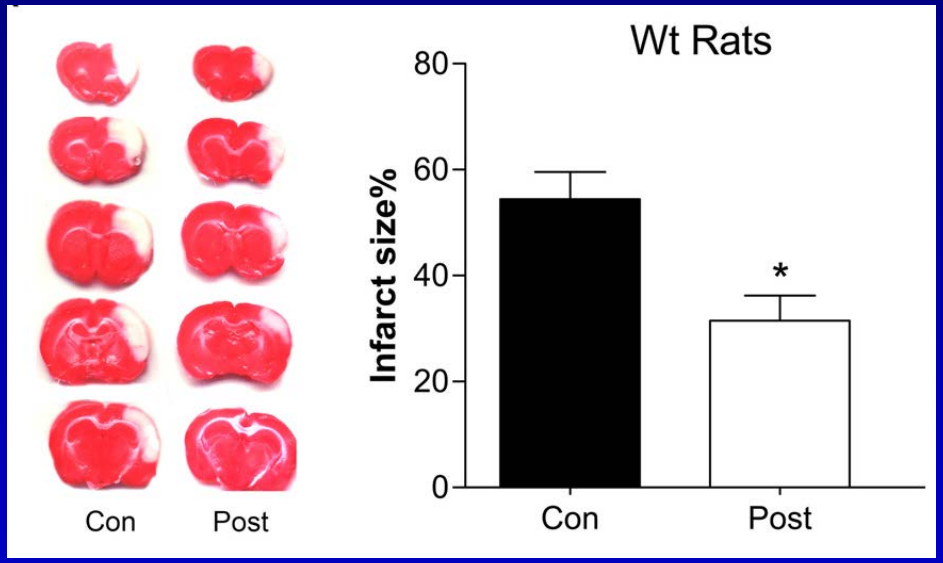
Outlines

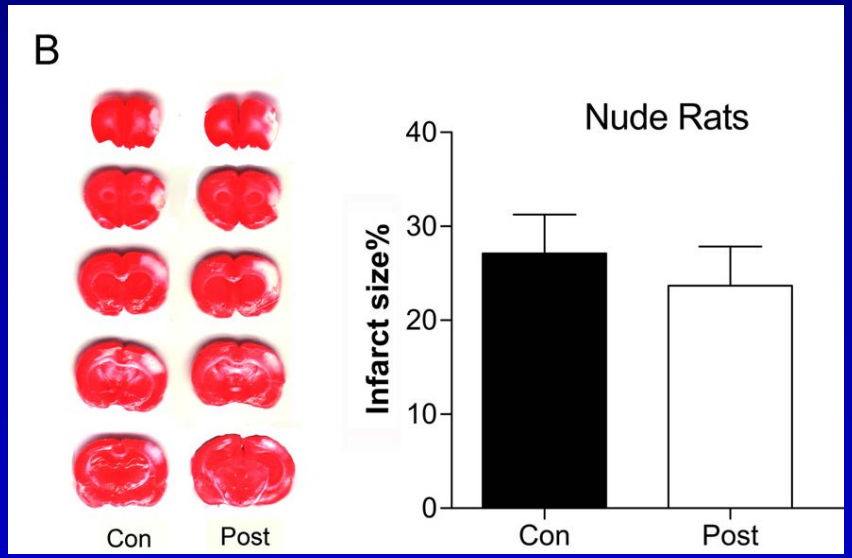
1. Protective effect of IPostC
   a) Research history
   b) Therapeutic time windows
   c) Long-term protective effect

2. Mechanisms: free radicals, BBB, metabolisms, cell signaling pathways

3. Immune cells and IPostC

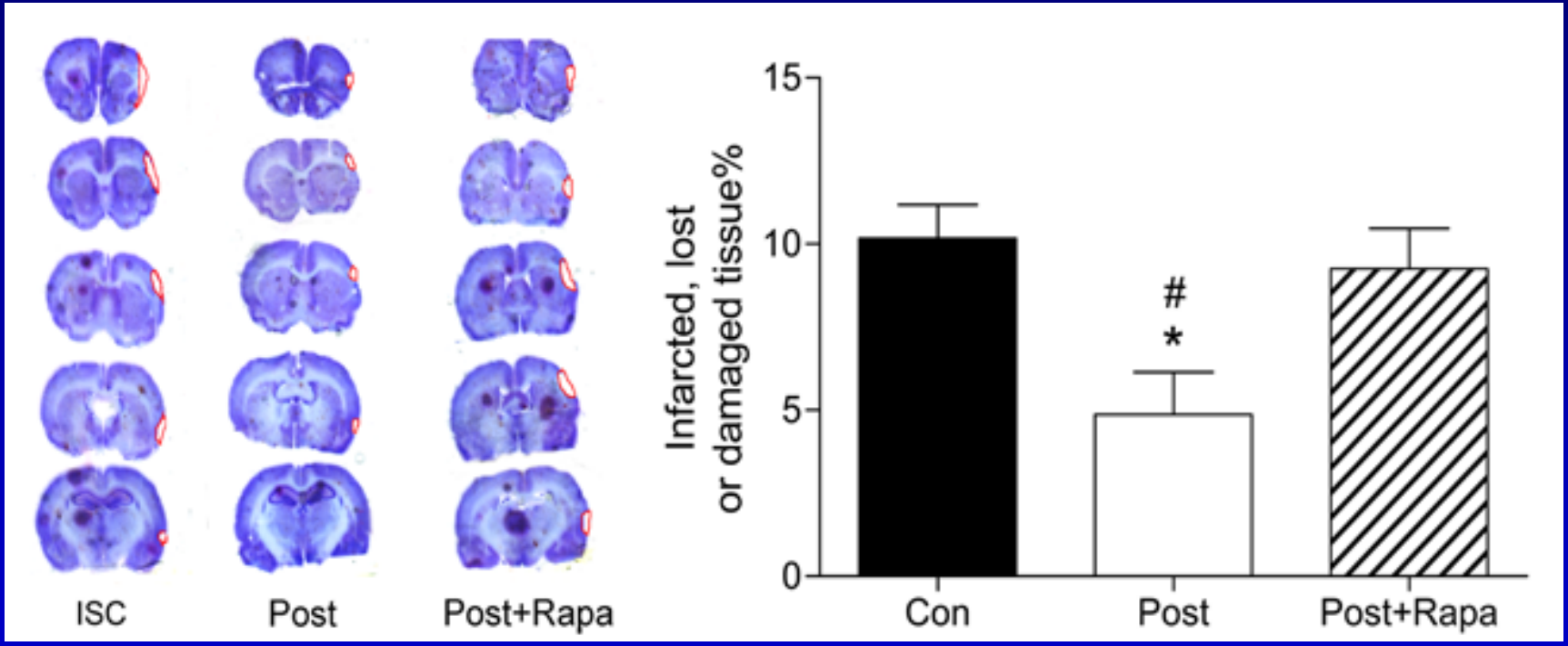
Postcon did not reduce acute infarction in nude rats



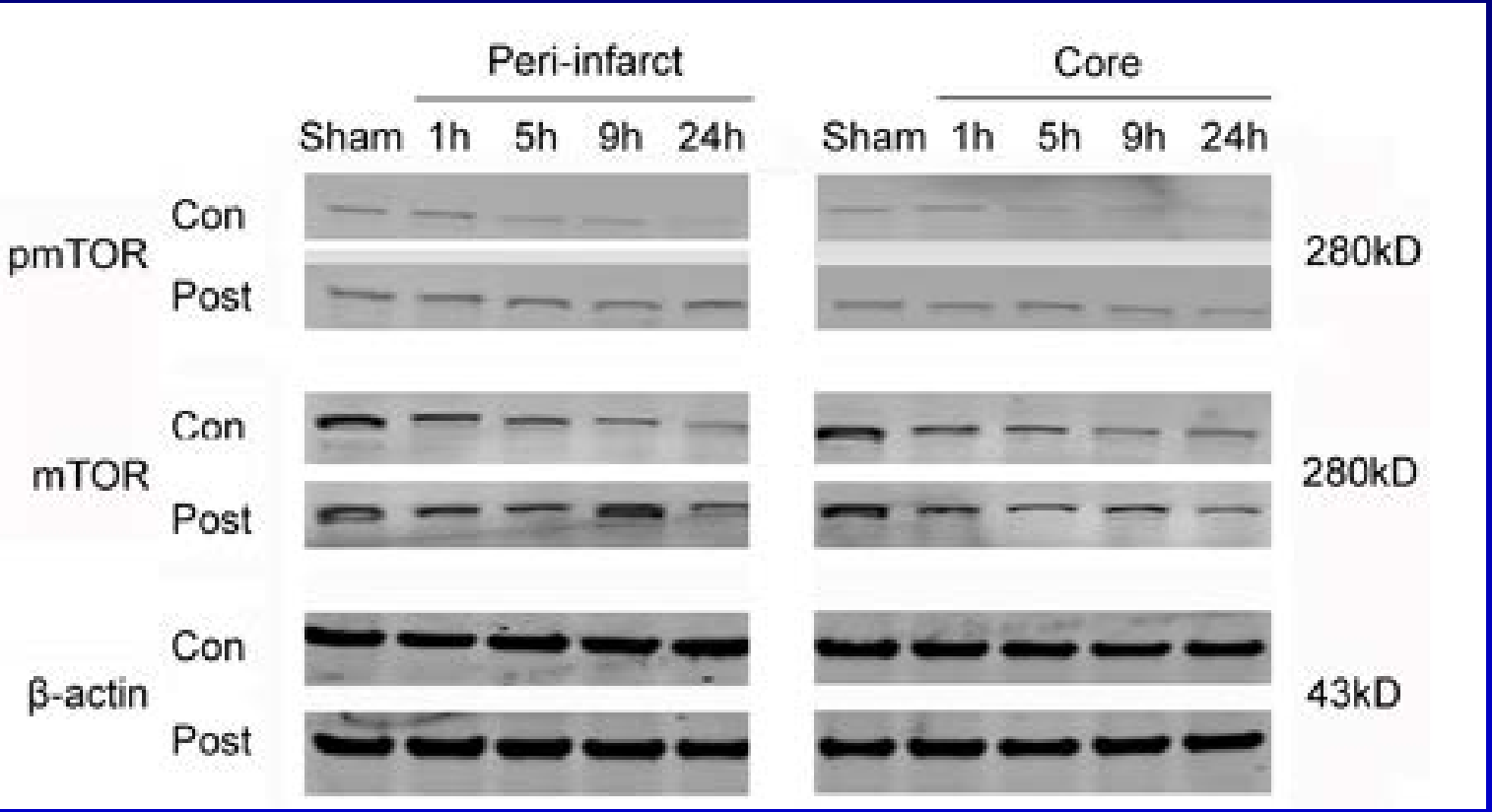


Are T cells involved in Postcon?

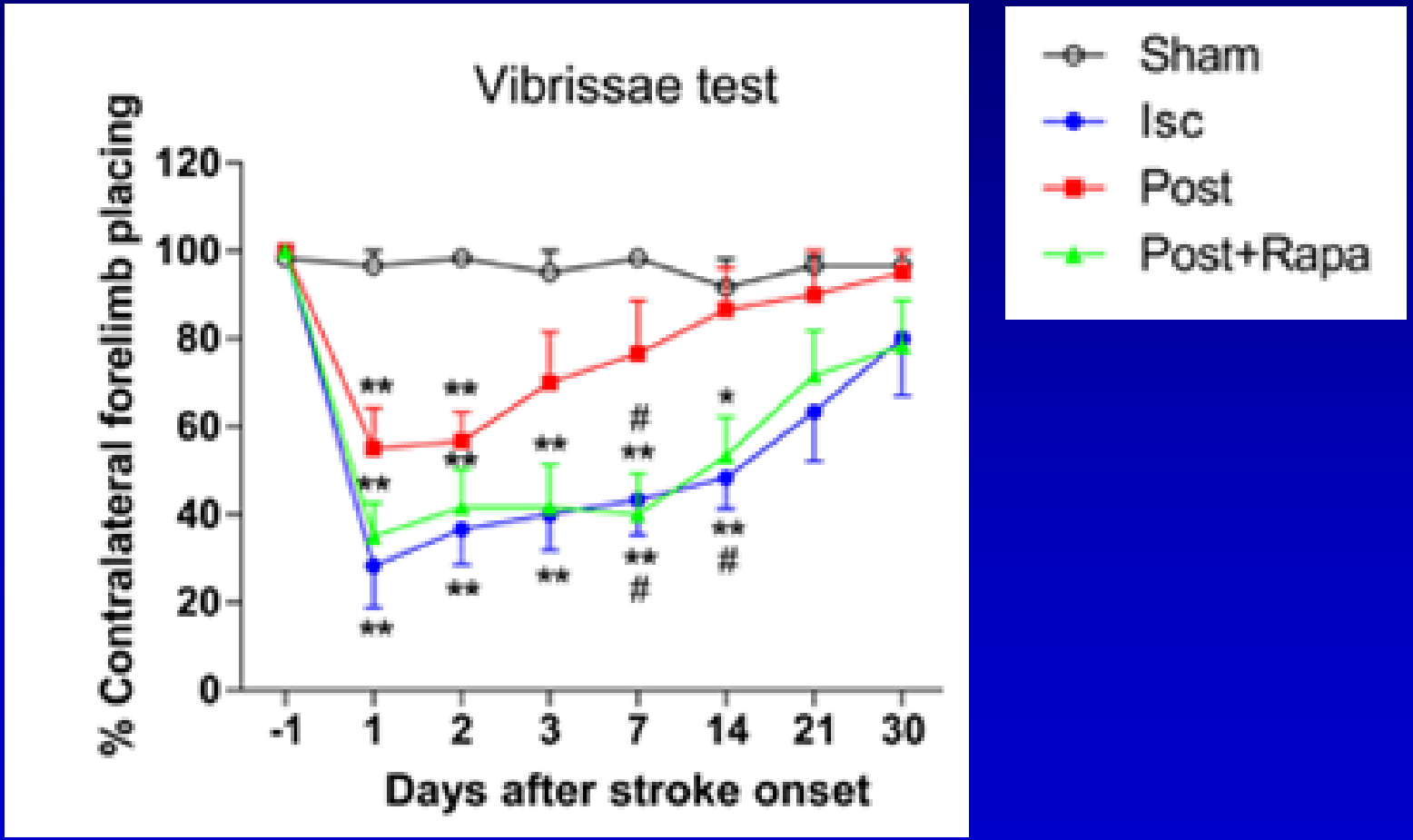
But, postcon attenuated injury measured 1 month after stroke, and mTOR inhibition abolished postcon's protection in nude rats



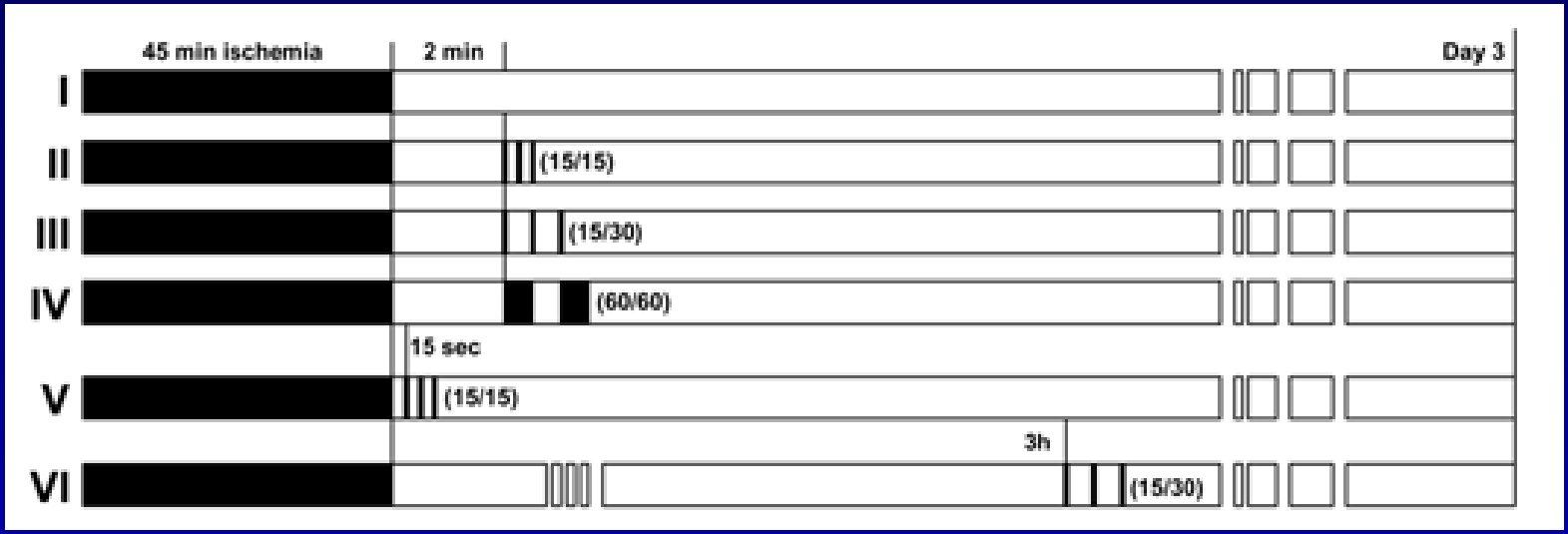
Postcon indeed improved mTOR phosphorylation in nude rats

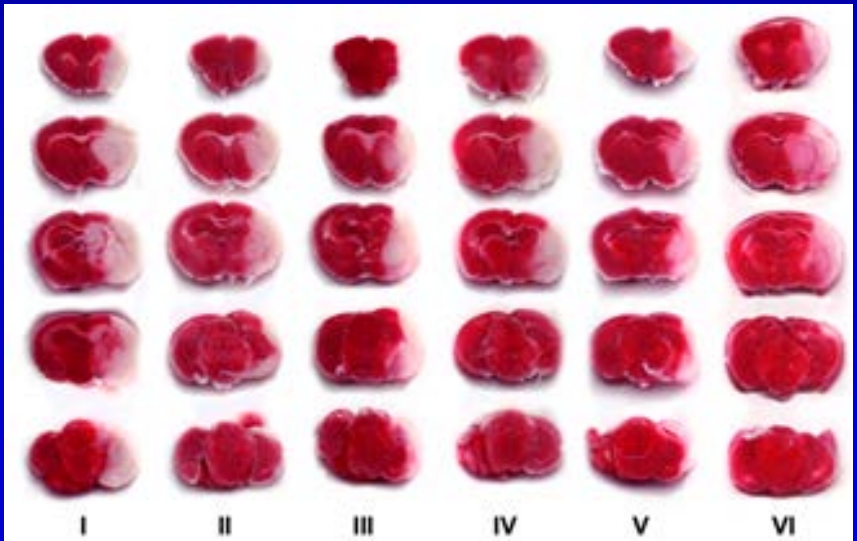


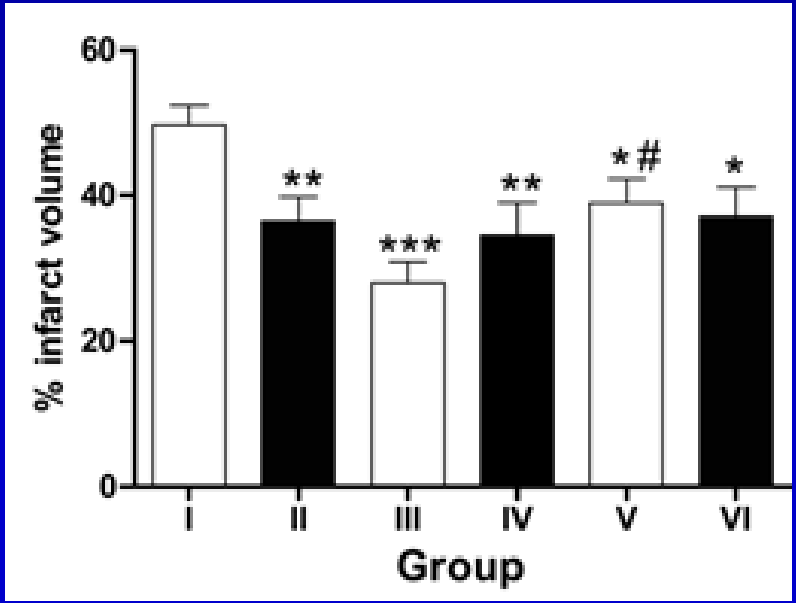
Postcon improved neurological dysfunction up to 1 month after stroke in nude rats



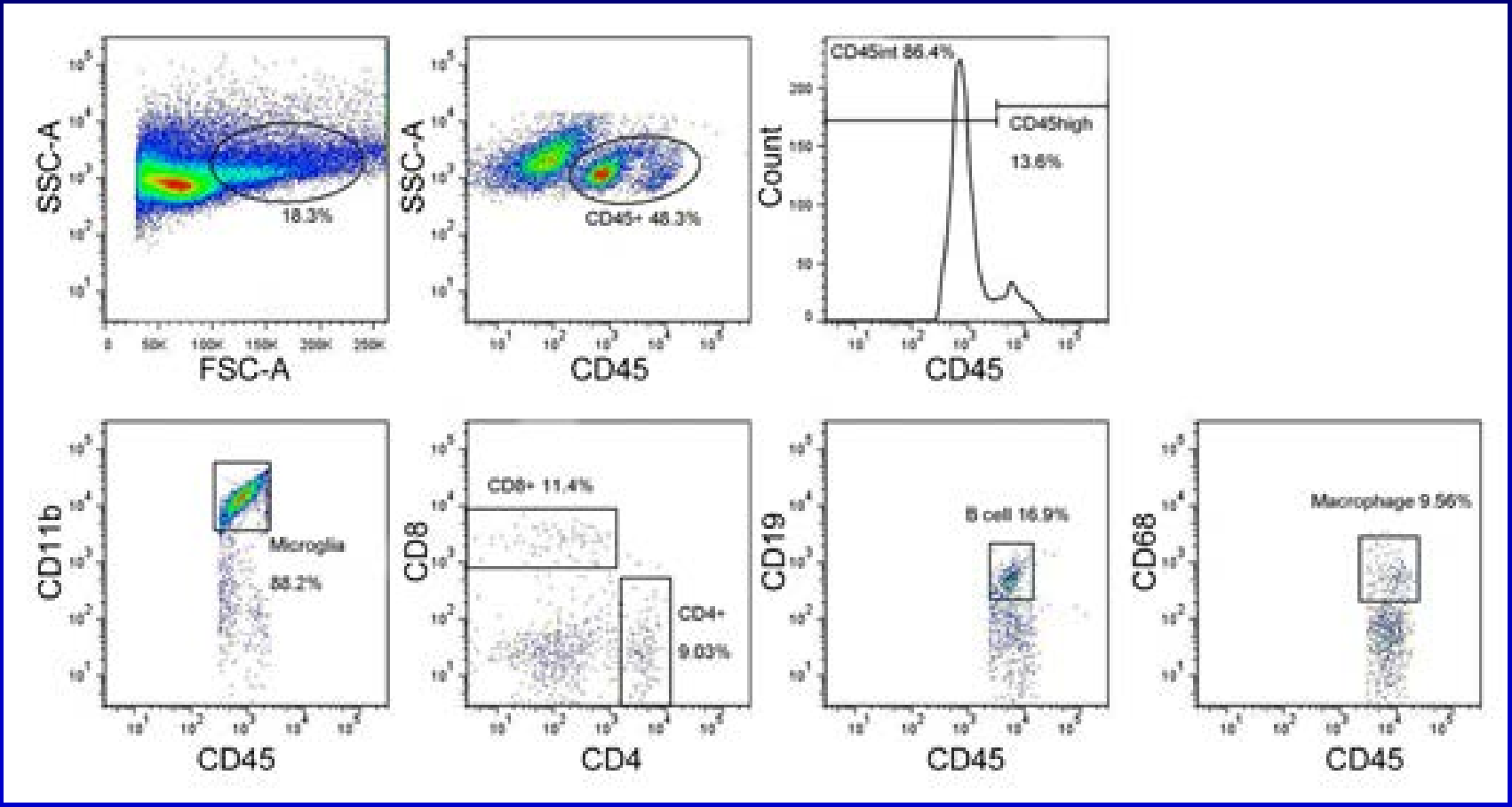
Postcon also reduced infarction in mouse MCAo model



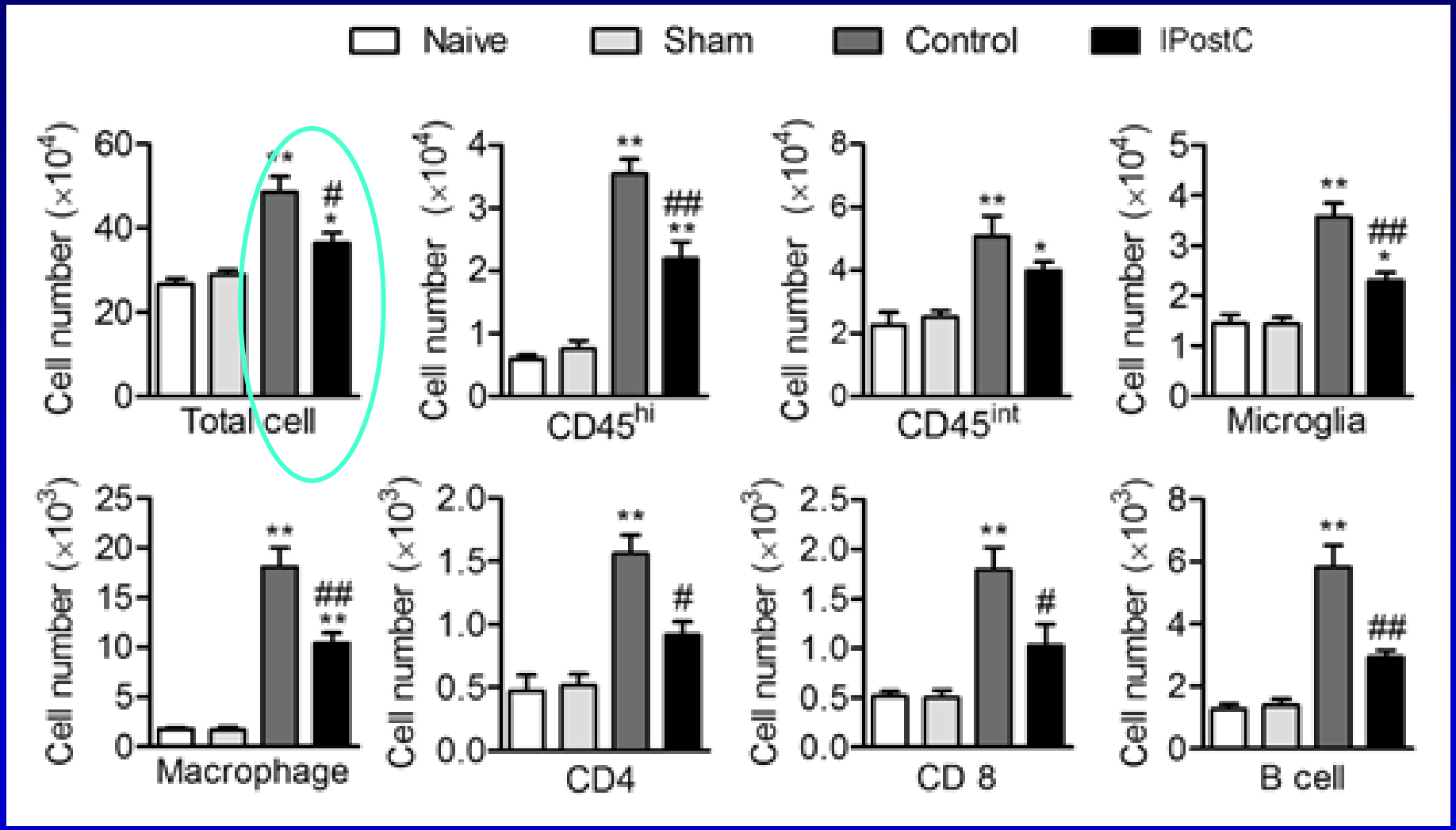




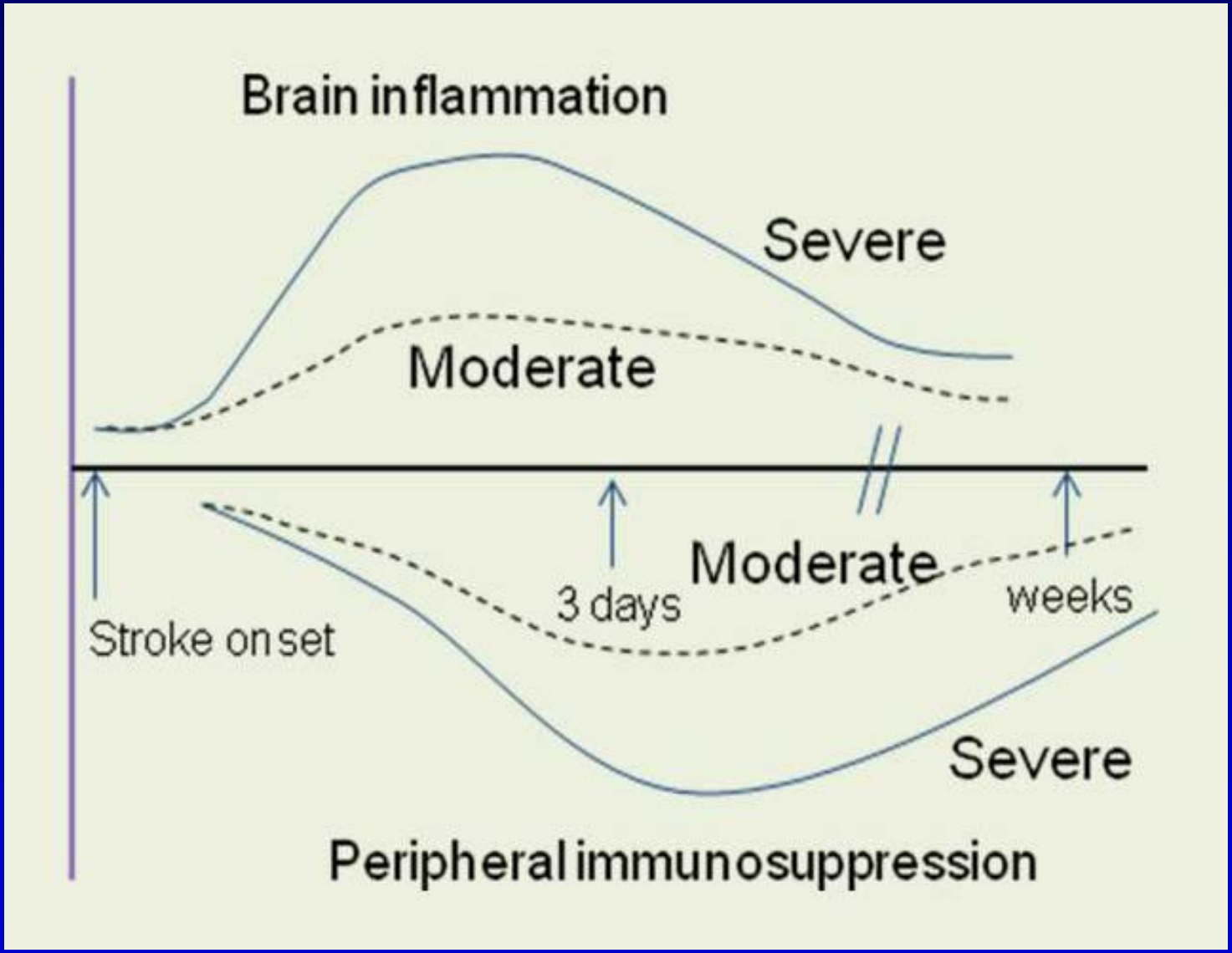
FACS to measure immune cells in the ischemic brain



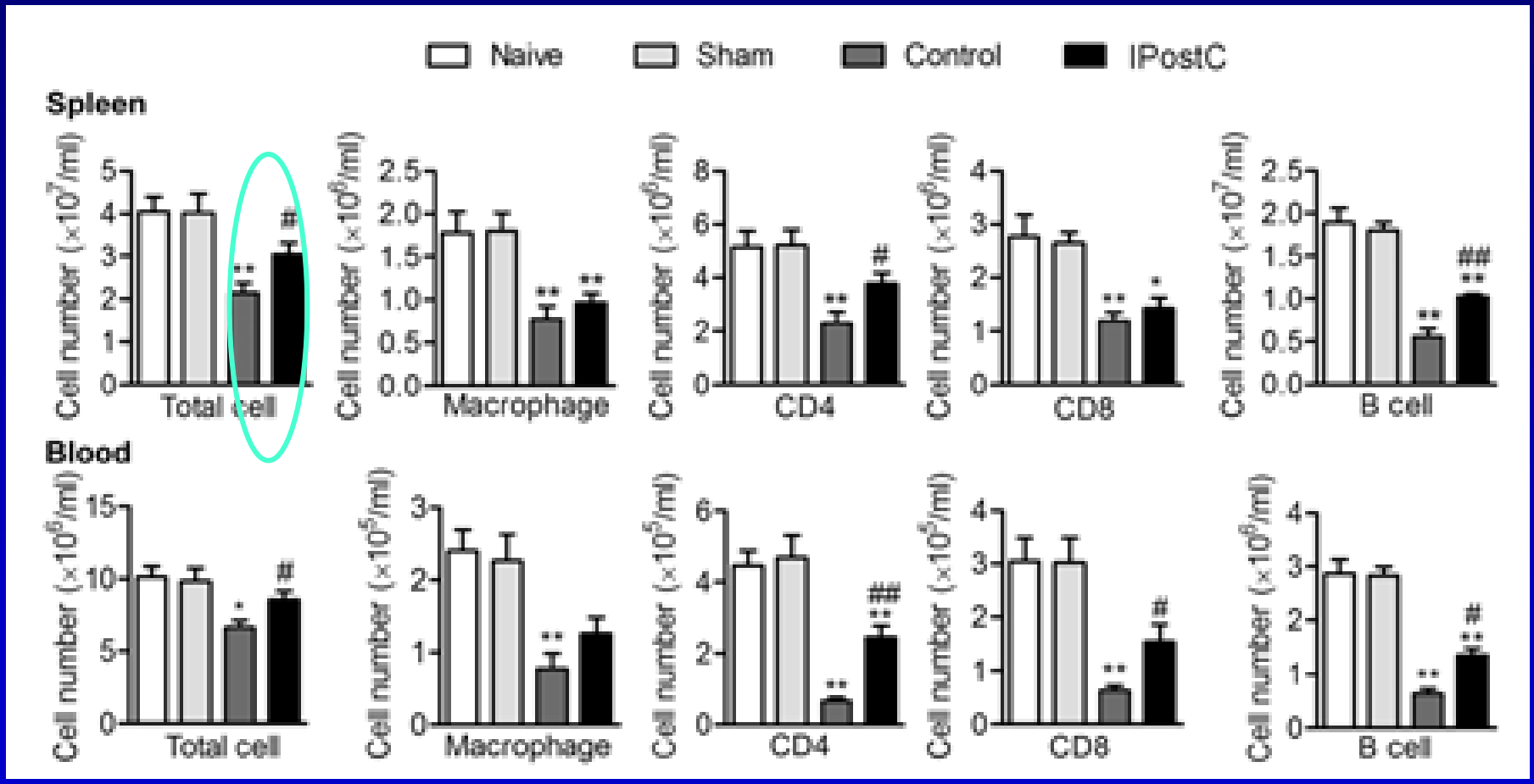
Postcon attenuated inflammation in the ischemic brain after stroke



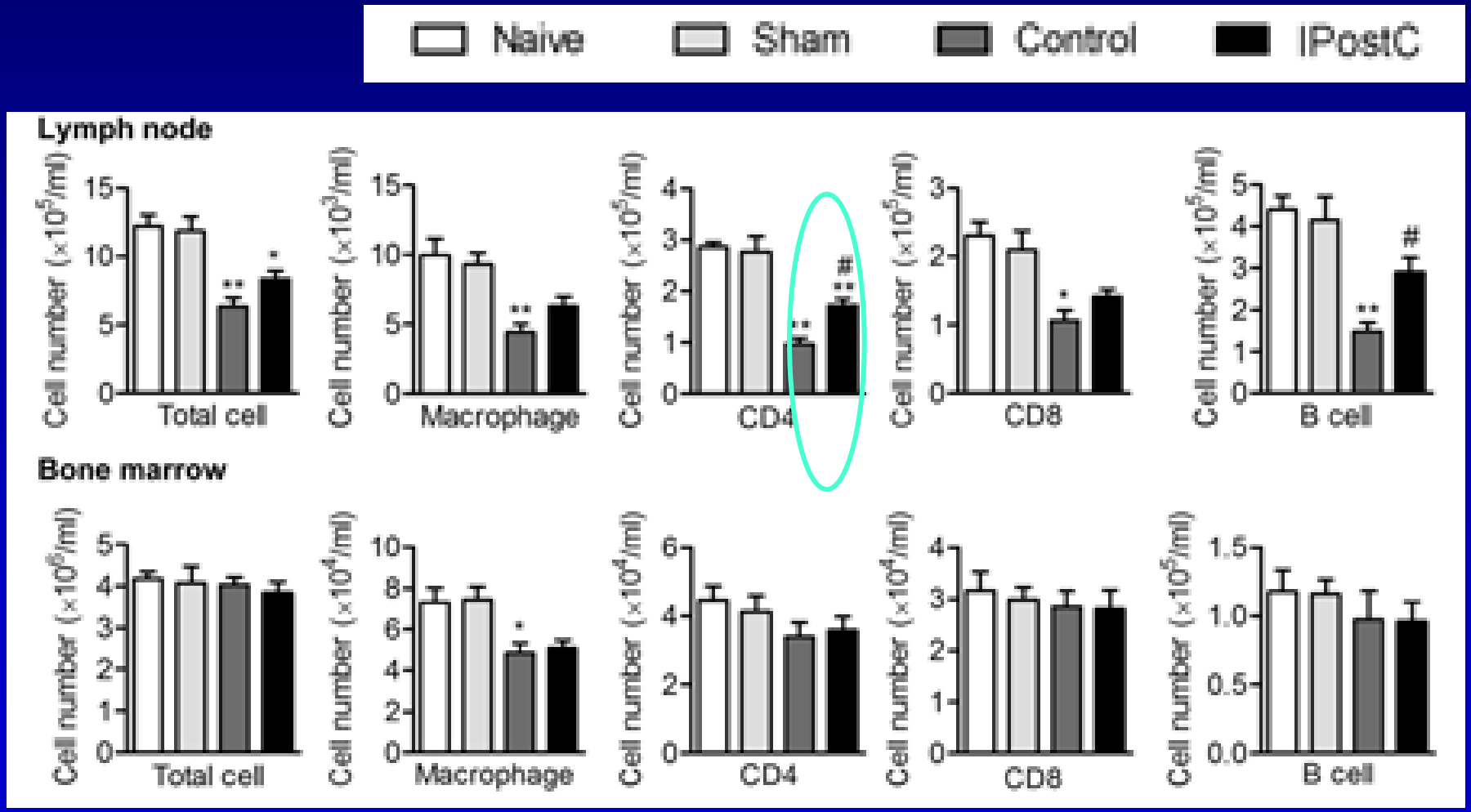
Inflammation and immunosuppression



Postconditioning attenuated immunodepression



Postconditioning attenuated immunodepression



Summary (III)

1. T cells
2. Neuroinflammation and immunodepression

Final summary

1. Protective effect of IPostC
   a) Research history
   b) Therapeutic time windows
   c) Long-term protective effect

2. Mechanisms: free radicals, BBB, metabolisms, cell signaling pathways

3. Immune cells and IPostC

Many thanks

Acknowledgment

Rong Xie
Peng Wang
Lijuan Gu
Xuwen Gao
Tetsuya Takahashi
Xiaoxing Xiong
Lijuan Gu
Chuangcheng Ren

Special thanks to

Michelle Cheng
Robert Sapolsky
Gary Steinberg
Xunming Ji

Supported by NIH and AHA grants