The mechanisms and translation of ischemic stroke

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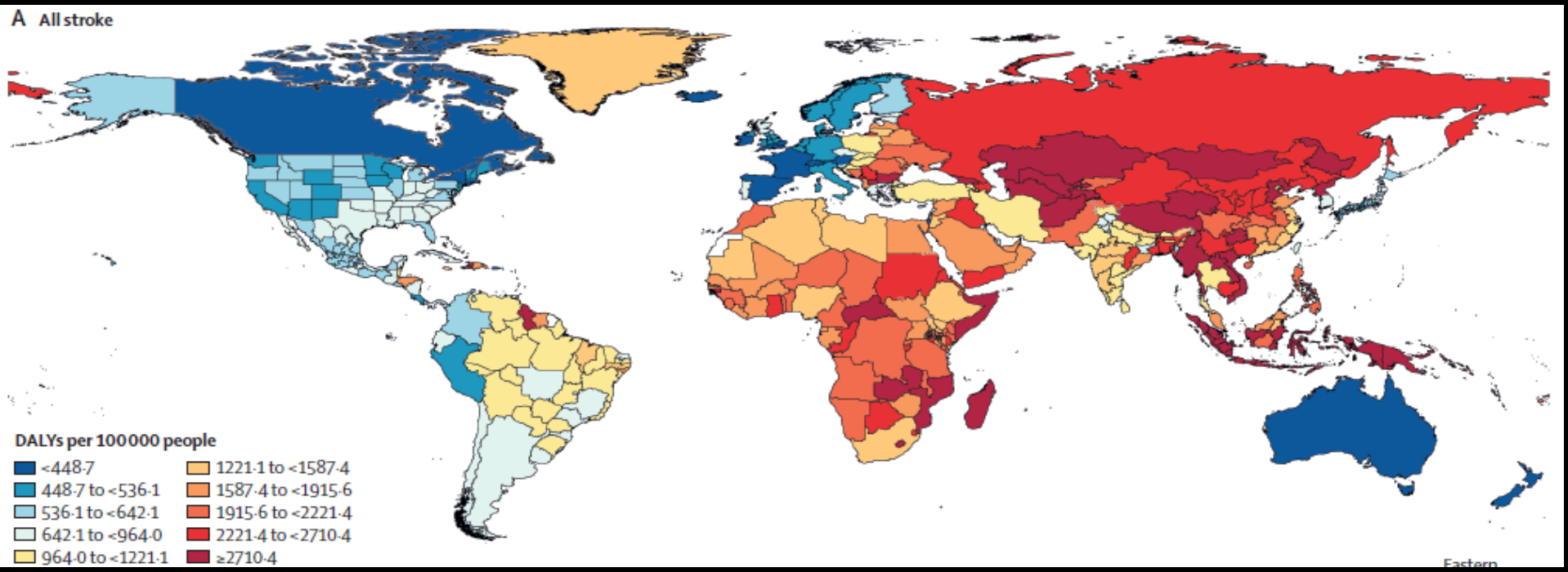
Outline

1. 神经可塑性(Neuroplasticity)
2. 神经保护(Neuroprotection)
3. 纳米酶(Neuroprotection)

Global disease stroke

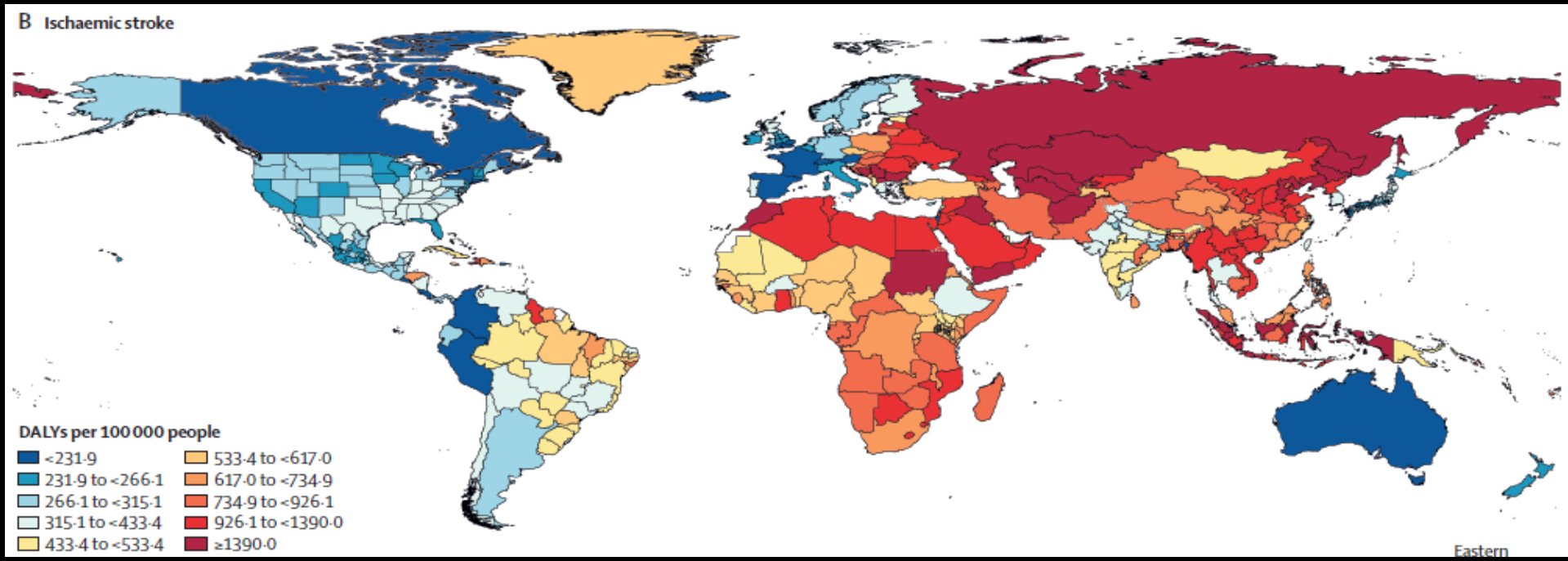


62.4% Ischemic stroke 27.9% Haemorrhage 9.7%Subarachnoid haemorrhage

12.20 million incident cases，**6.55 million** death in stroke

GBD 2019 Stroke collaborators. Lancet Neurol. 2021 Oct;20(10):795-820.

Ischemic stroke



Top five risk factors：

High systolic blood pressure

High body mass index

High fasting plasma glucose

Ambient particulate matter pollution

Smoke

GBD 2019 Stroke collaborators. Lancet Neurol. 2021 Oct;20(10):795-820.

Stoke: prevention and control

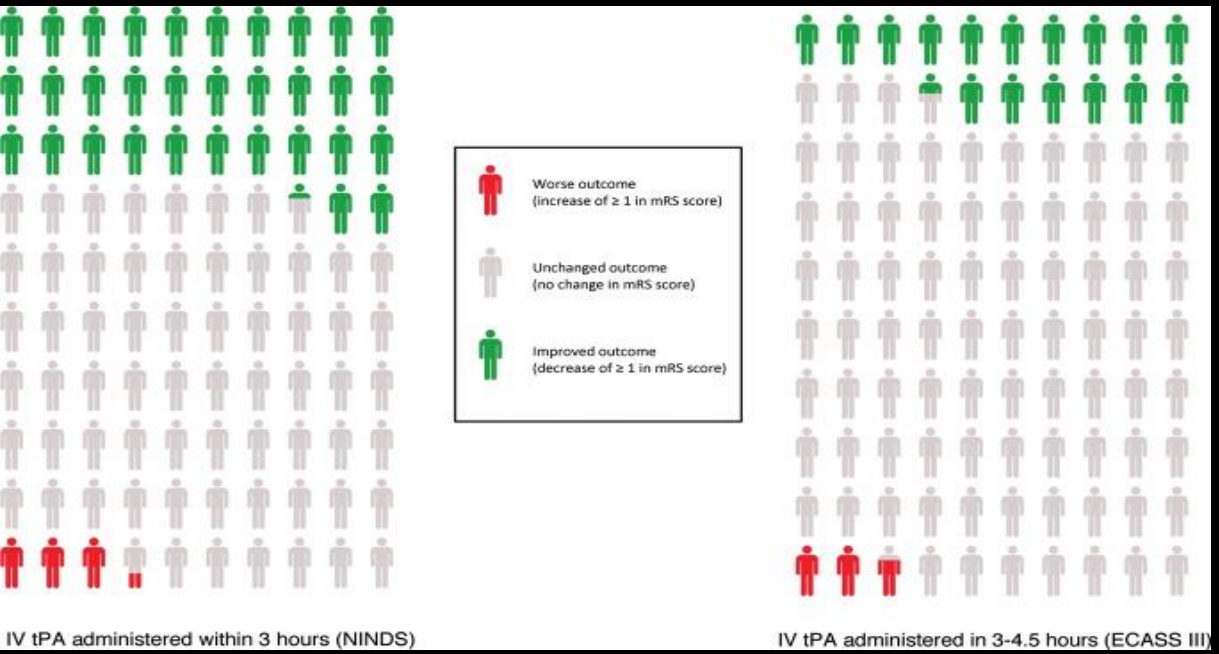
1、High risk factors
  (1) High blood pressure
  (2) Hypercholesterolemia
  (3) High fasting plasma glucose
2、General risk factors
  (1) atrial fibrillation or other heart disease
  (2) Sleep apnea
  (3) Smoking
  (4) Alcohol use
  (5) Less exercise
  (6) High Body mass index
3、New risk factors
  (1) Carotid stenosis
  (2) Homocysteine

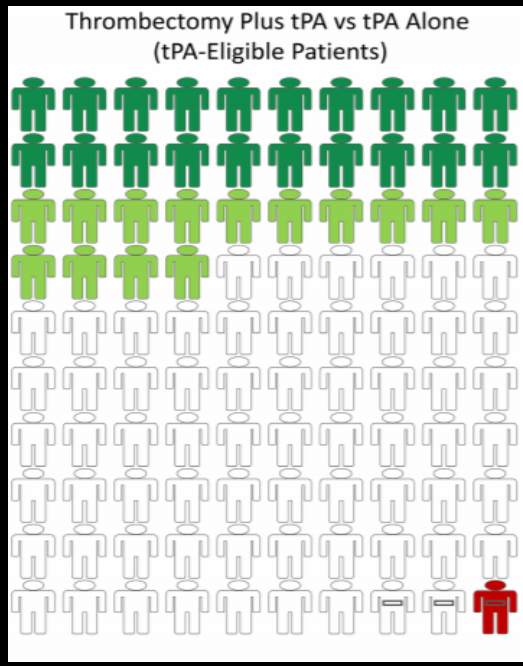
USA：1950 stroke intervention，1972-1985.death rate decreases 35%

Japan： Stroke intervention，Stroke diseases first to third

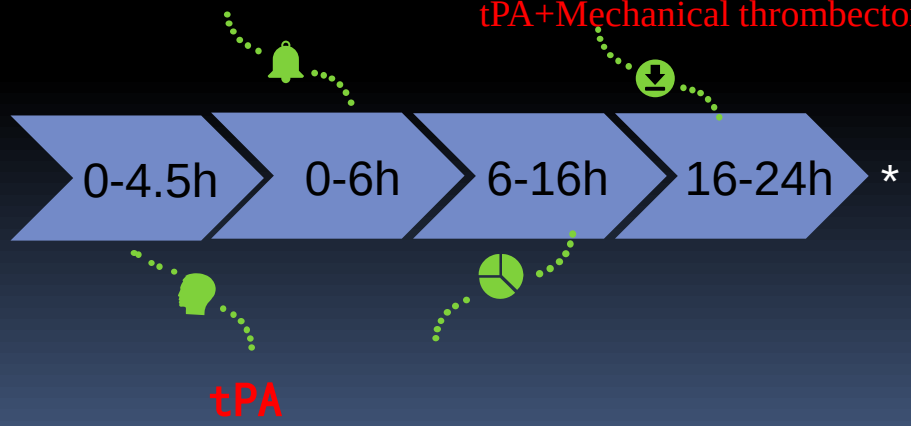
陈竺部长：我们抓脑卒中的筛查和防控，就等于牵住了我国慢病防控的牛鼻子！

Stroke therapy

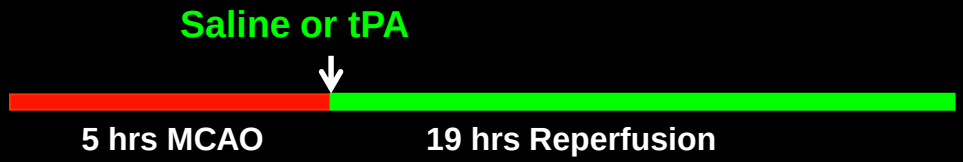




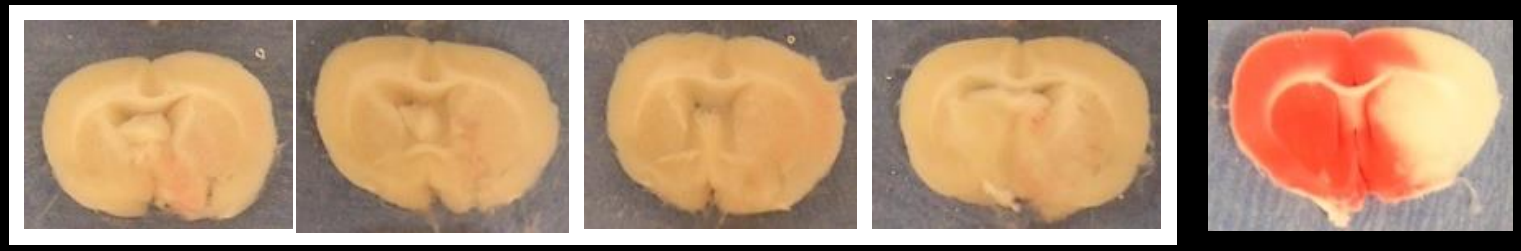
IV tPA (tissue plasminogen activator）



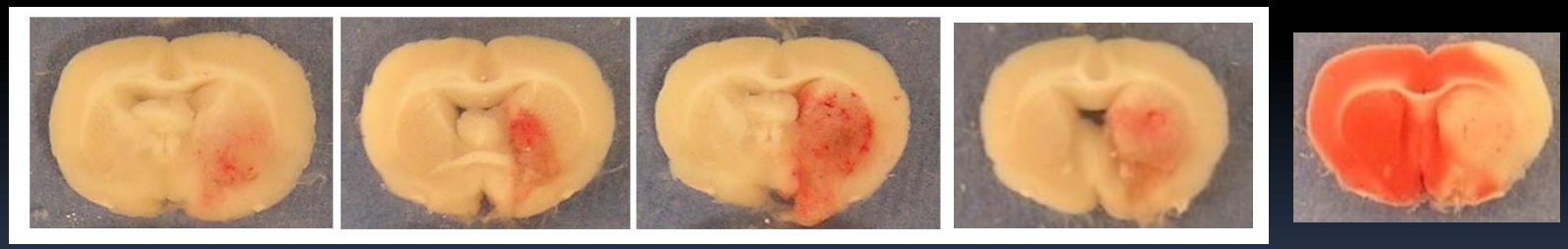
tPA induces intracerebral hemorrhage（ICH）



Saline-treated rats

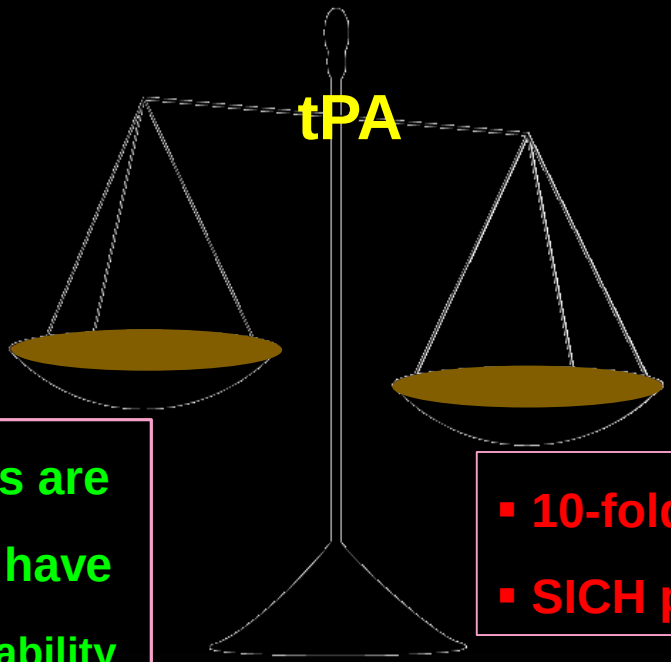


tPA-treated rats



(Liu W et al, Stroke. 2009)

tPA thrombolysis: a medical dilemma

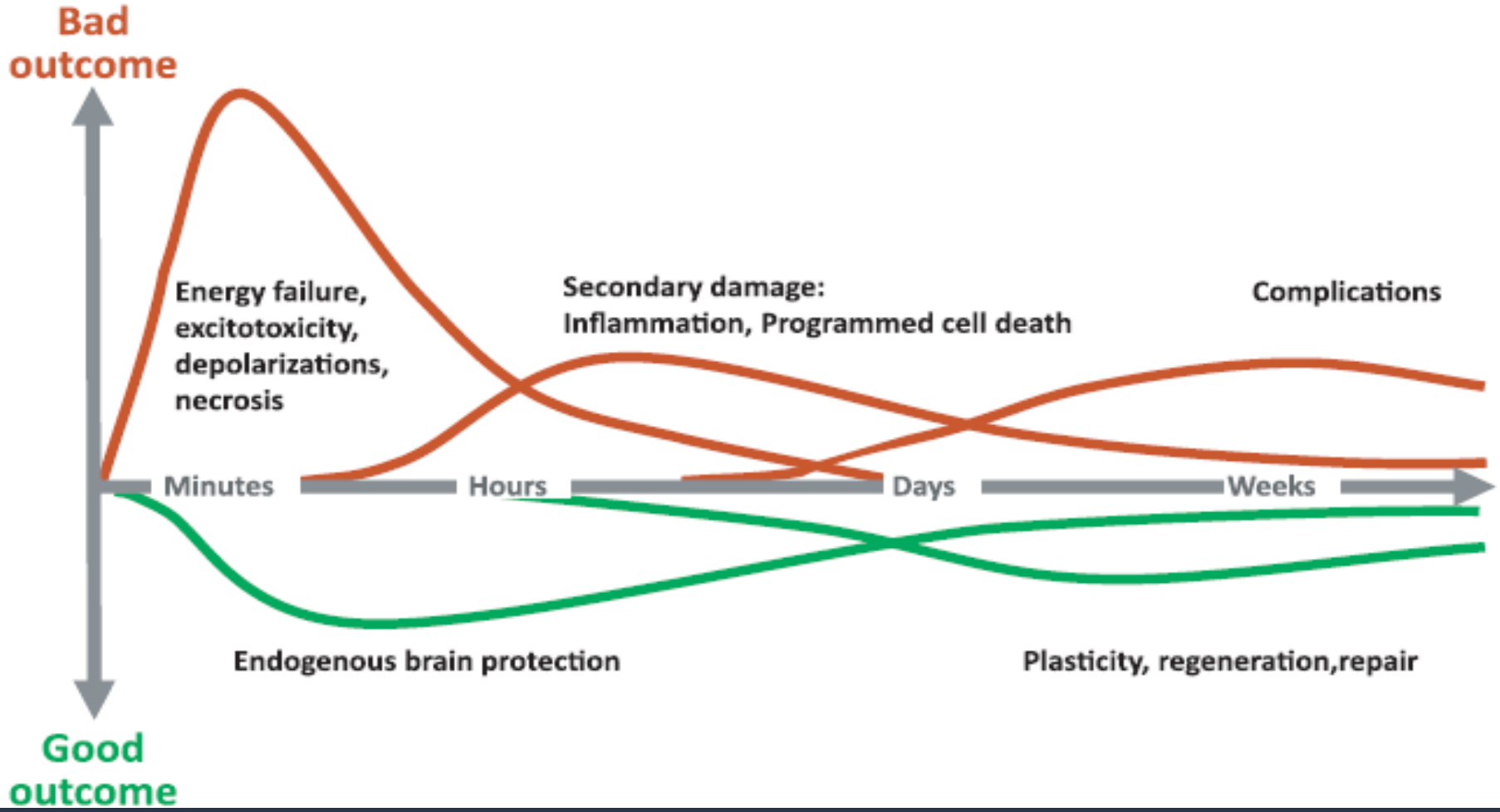


- tPA-treated patients are 30% more likely to have minimum or no disability

- 10-fold increase of SICH
- SICH patients have 61% death rate

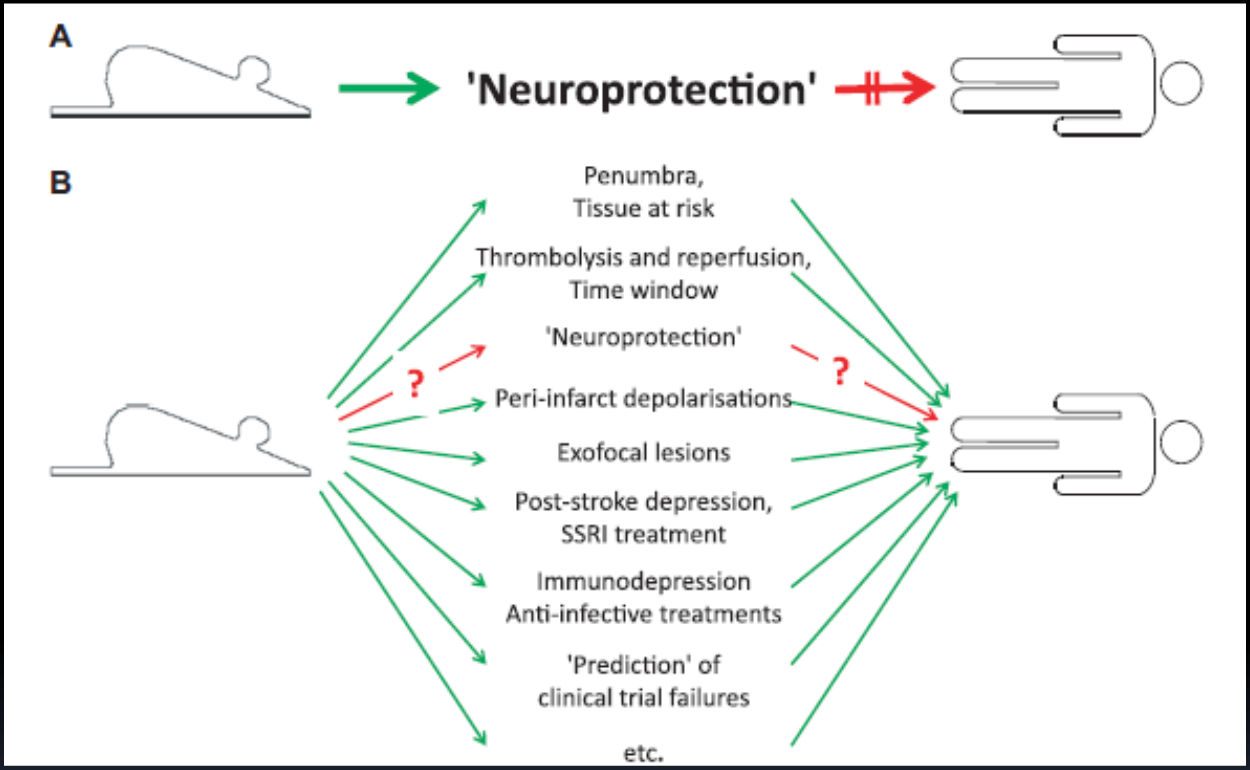
SICH: symptomatic intracerebral hemorrhage

Cellular and molecular mechanisms of ischemic stroke



Dirnagal, ANN N Y Acad Sci. 2012.

Translational roadblock for neuroprotection

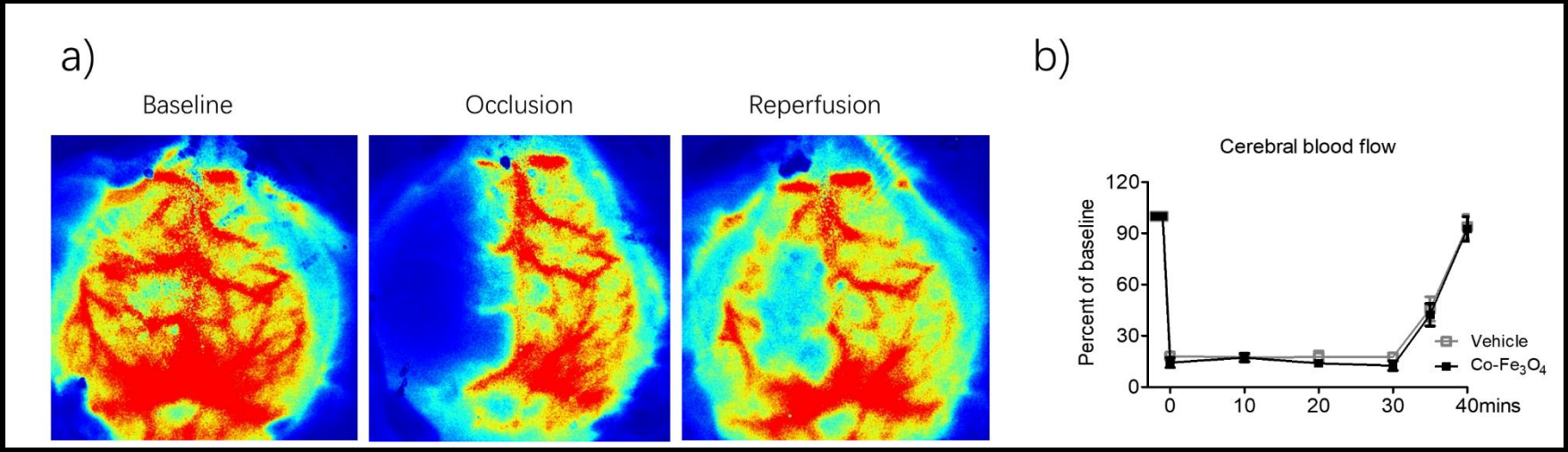


Dirnagal and Endres, Stroke. 2014.

Questions

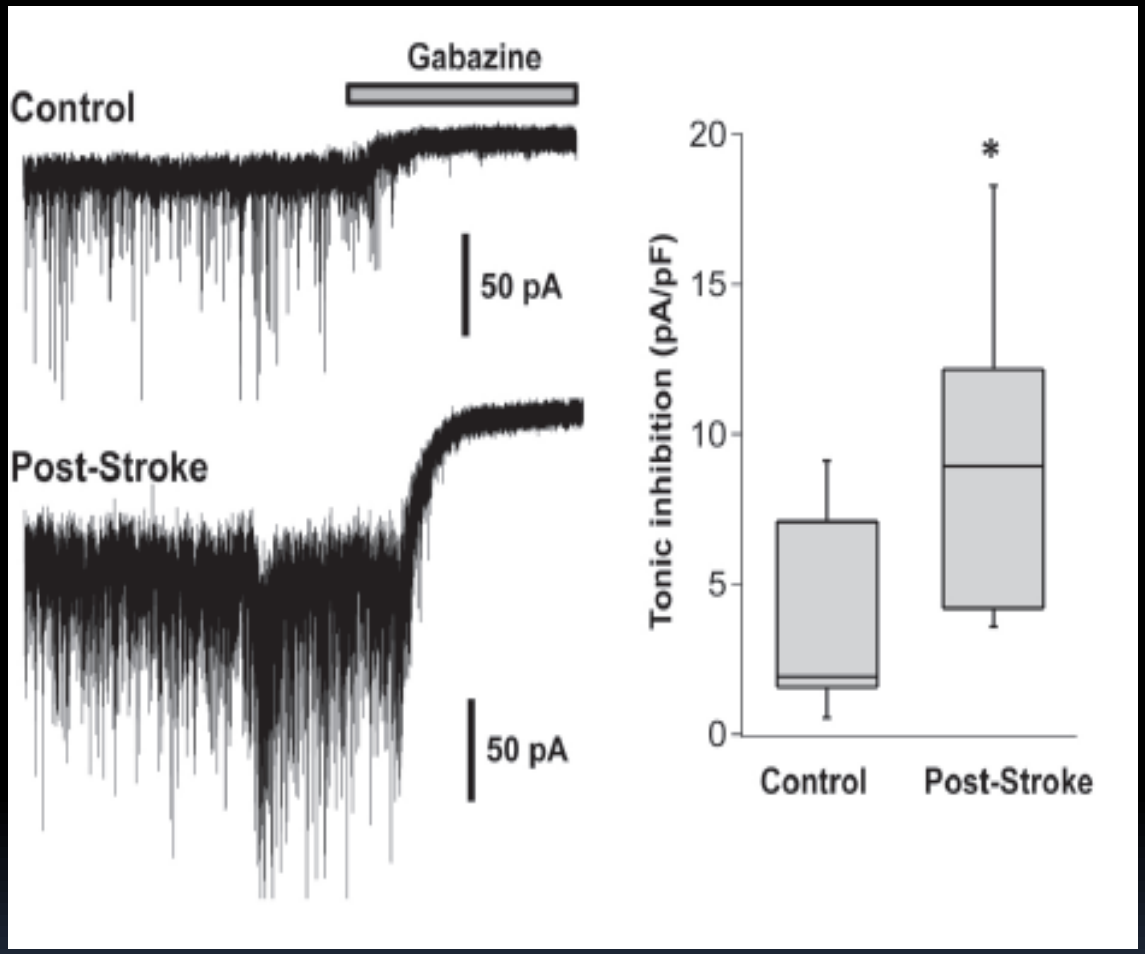
- How about the road for neuroplasticity?
- Mechanical Thrombectomy?
- Back to neuroprotection?

Middle cerebral artery occlusion (MCAO)moddel



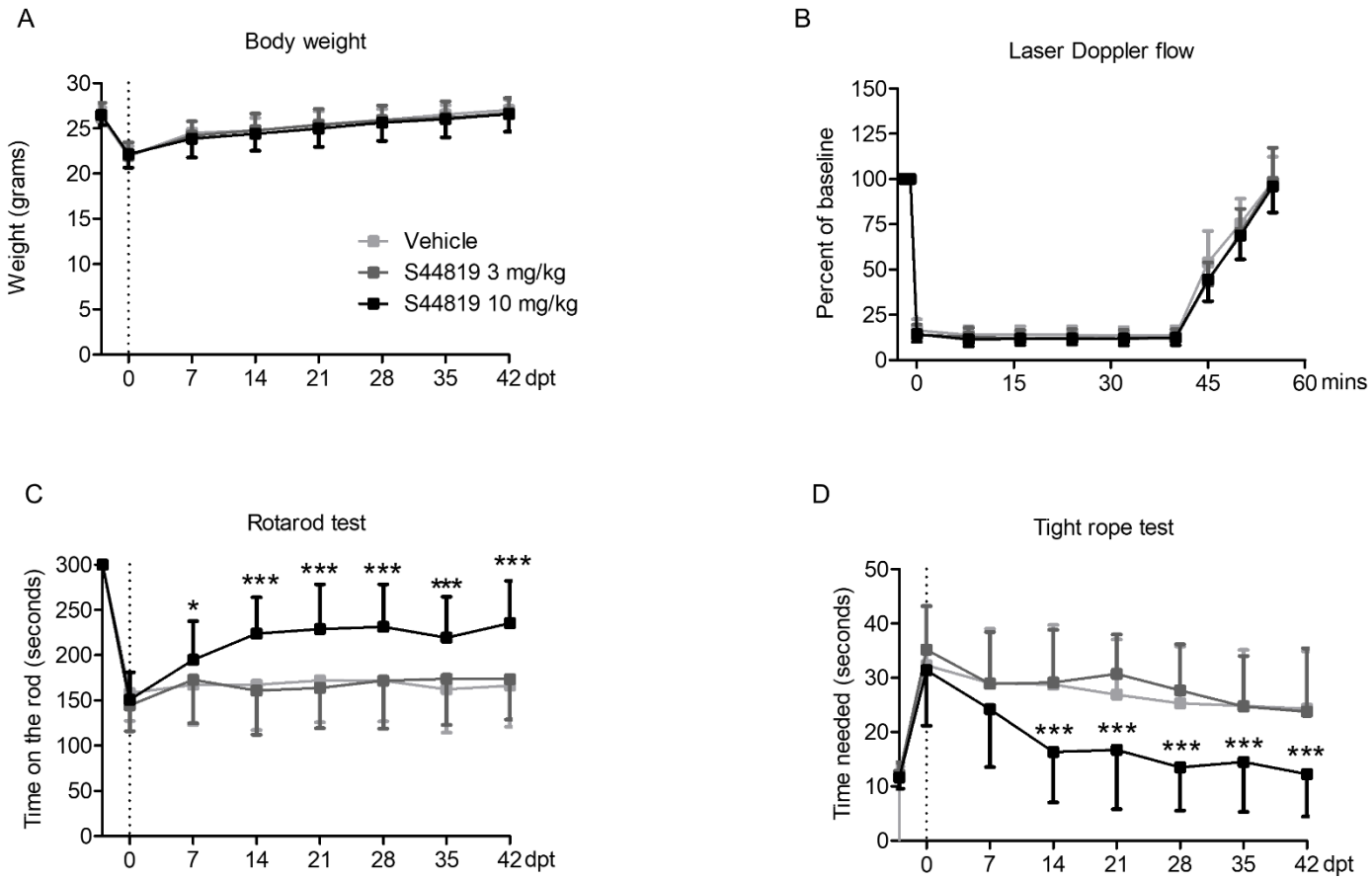
Liu et al. ACS Appl Mater Interfaces. 2021

Elevated tonic inhibition in peri-infarct cortex



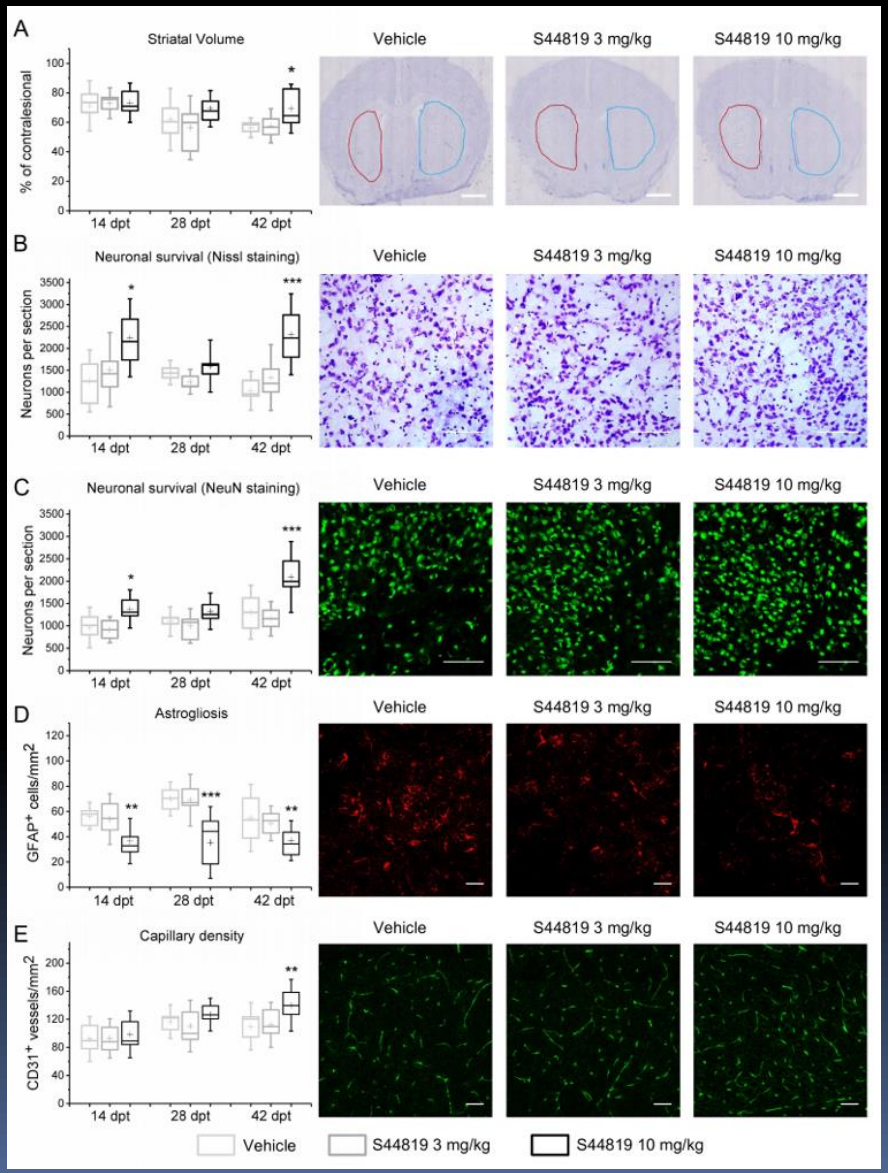
Clarkson et al, Nature. 2010.

Postacute delivery of S44819 improves poststroke motor-coordination



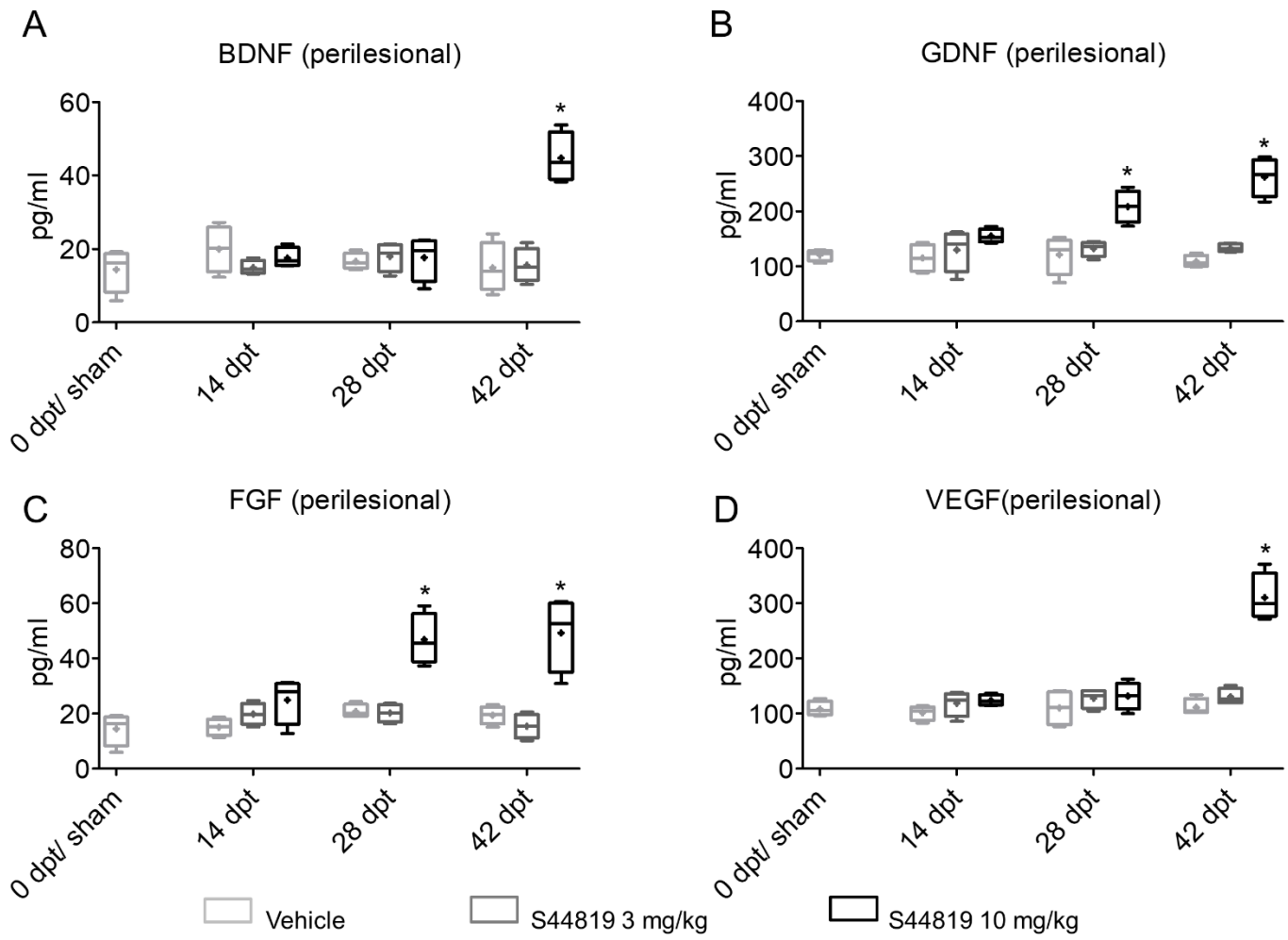
Wang et al. Stroke. 2018.

Postacute S44819 administration prevents secondary striatal atrophy and promotes delayed neuronal survival，reduces periinfarct astrogliosis and increases brain capillary density



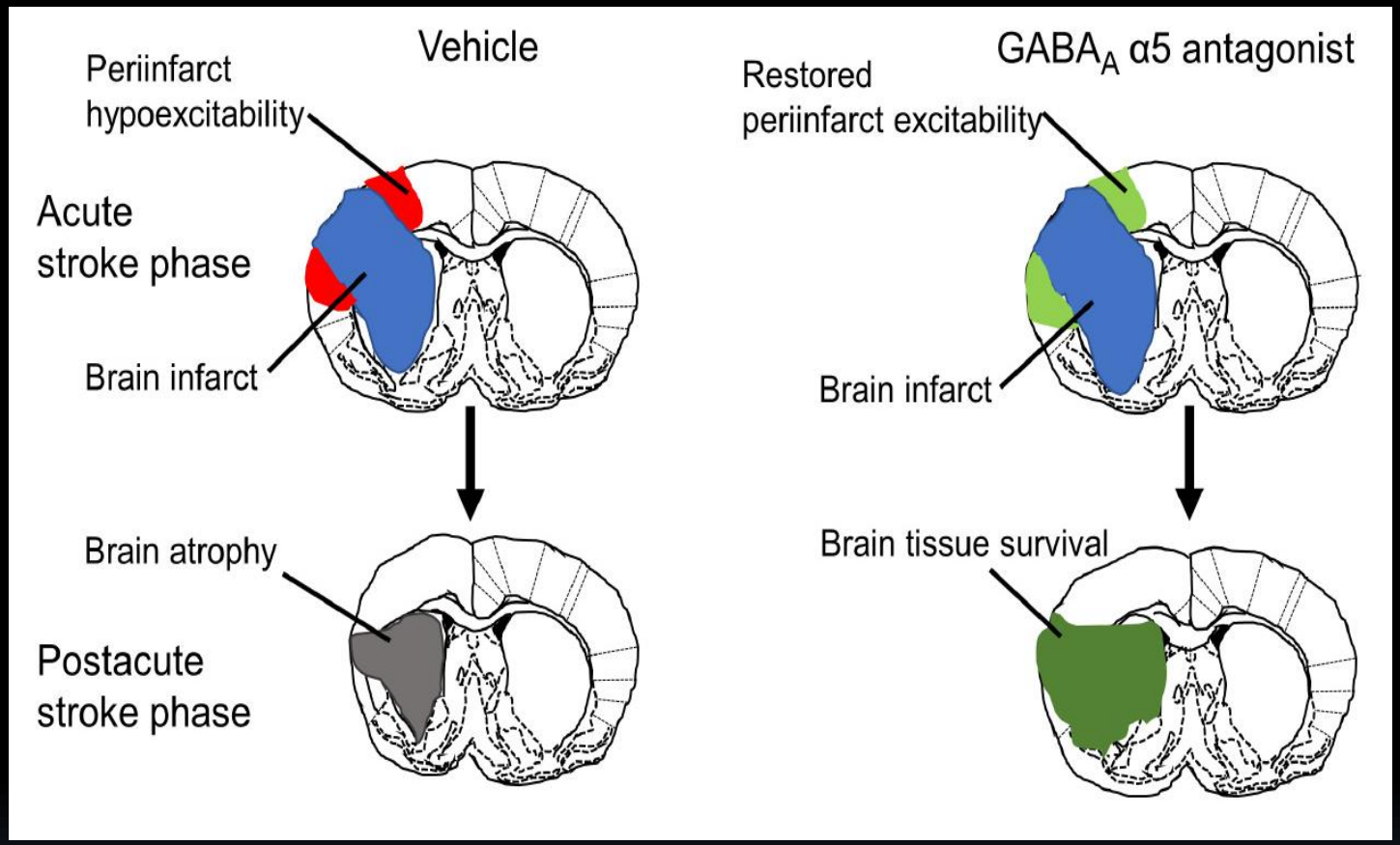
Wang et al. Stroke. 2018.

S44819 increases growth factor levels in the periinfarct, but not contralesional brain tissue



Wang et al. Stroke. 2018.

Post-acute delivery of S44819 enhances stroke outcome



Preclinical concepts and results with the GABA $_A$ antagonist S44819 in a mouse model of middle cerebral artery occlusion. Bassetal CL., et al. Neural Regen Res. 2019;14(9):1517-1518.

Post-acute delivery of α5-GABAA antagonist, S 44819, improves functional recovery in juvenile rats following stroke. Vivien Denis, er al. 2021, Experimental Neurology 347:113881.

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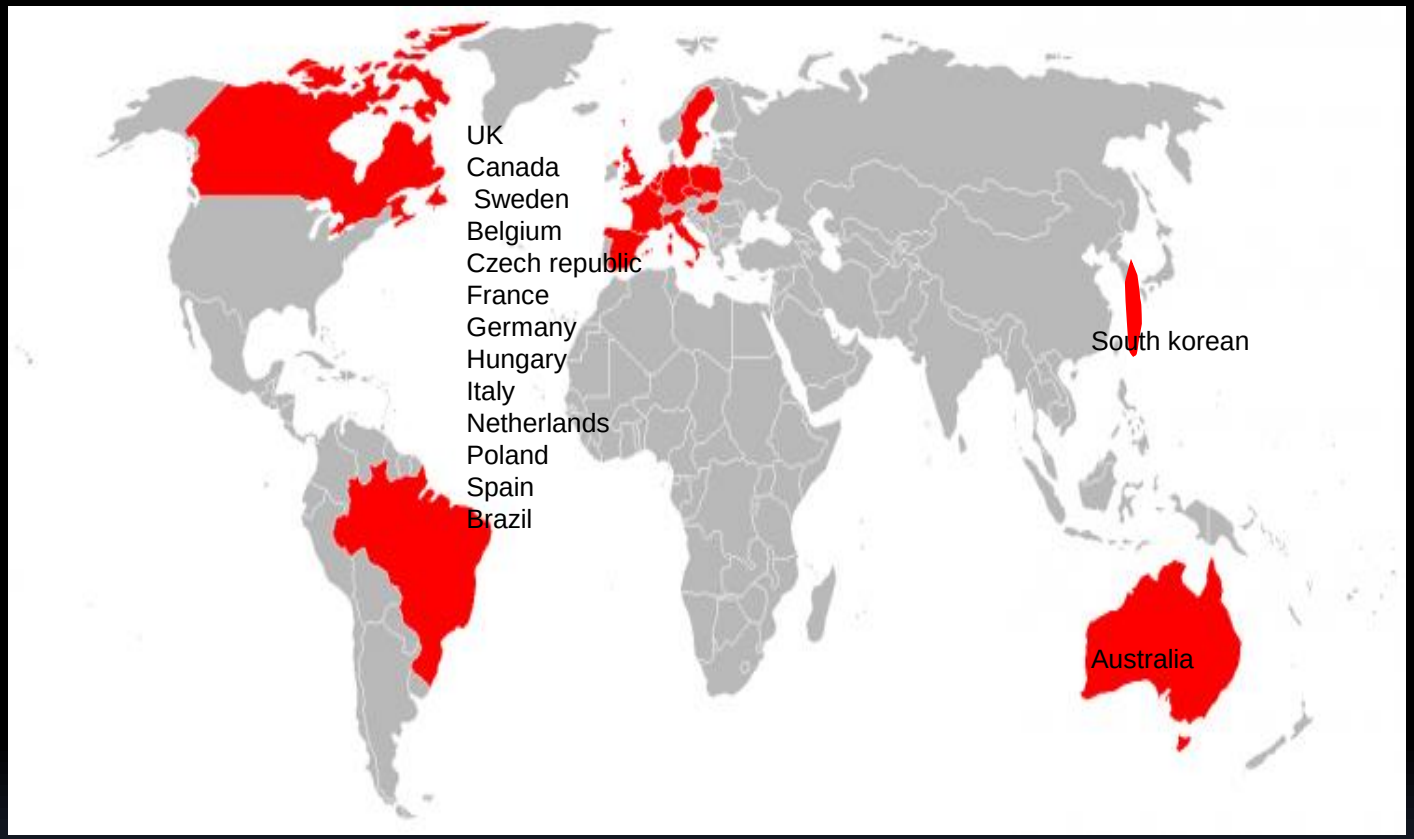
Wang et al. Stroke. 2018.

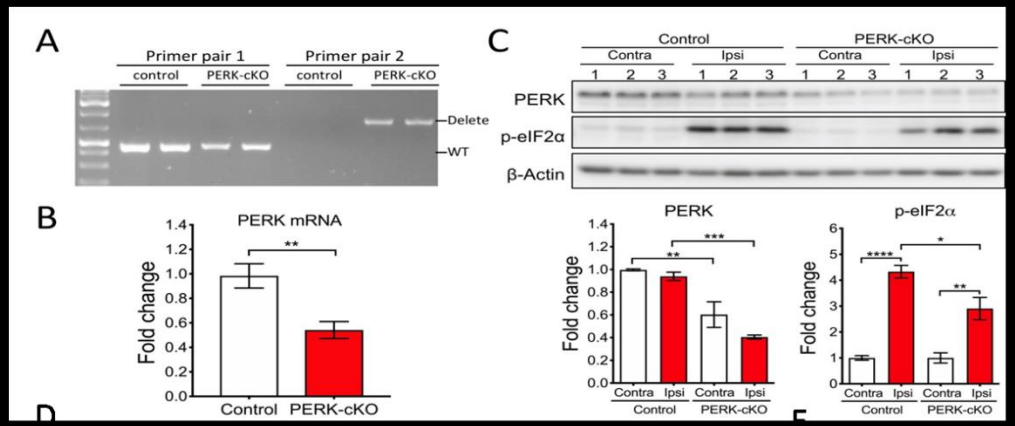
Translational of S44819 into clinical

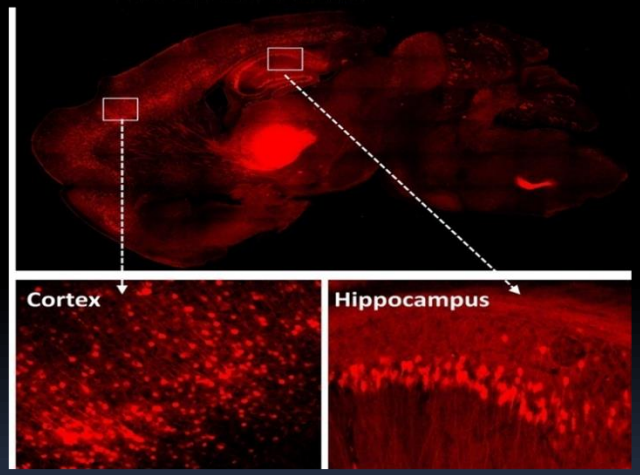


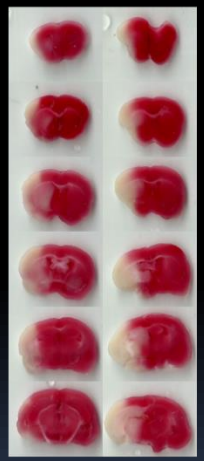
ClinicalTrials.gov Identifier: NCT02877615

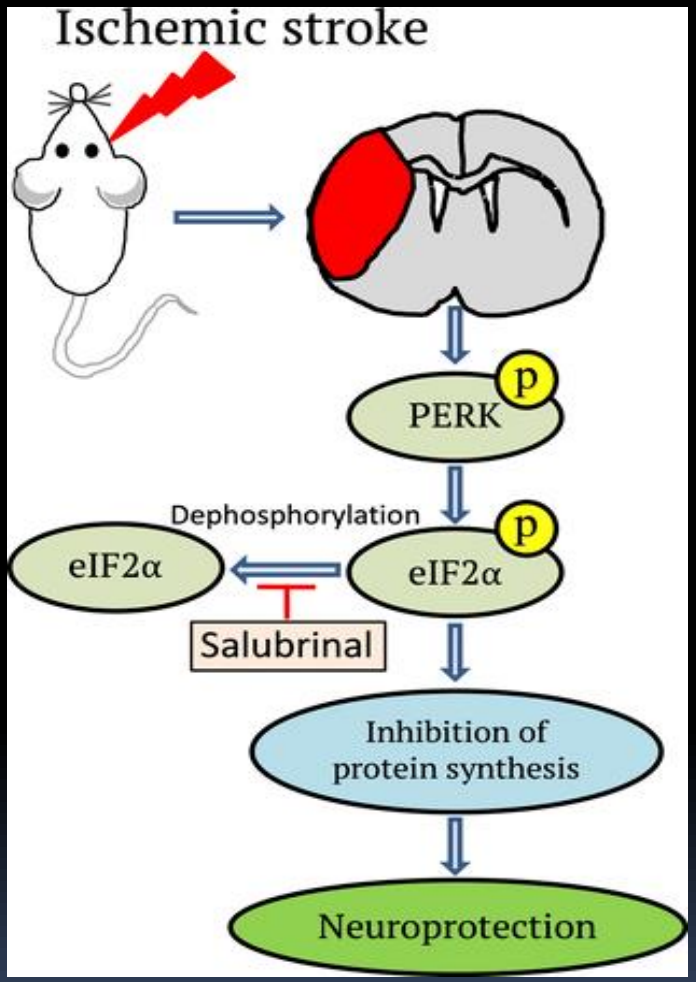
Hermann DM. Lancet Neurol. 2020.

PERK (Protein Kinase RNA-Like ER Kinase) Branch of the Unfolded Protein Response Confers Neuroprotection in Ischemic Stroke by Suppressing Protein Synthesis



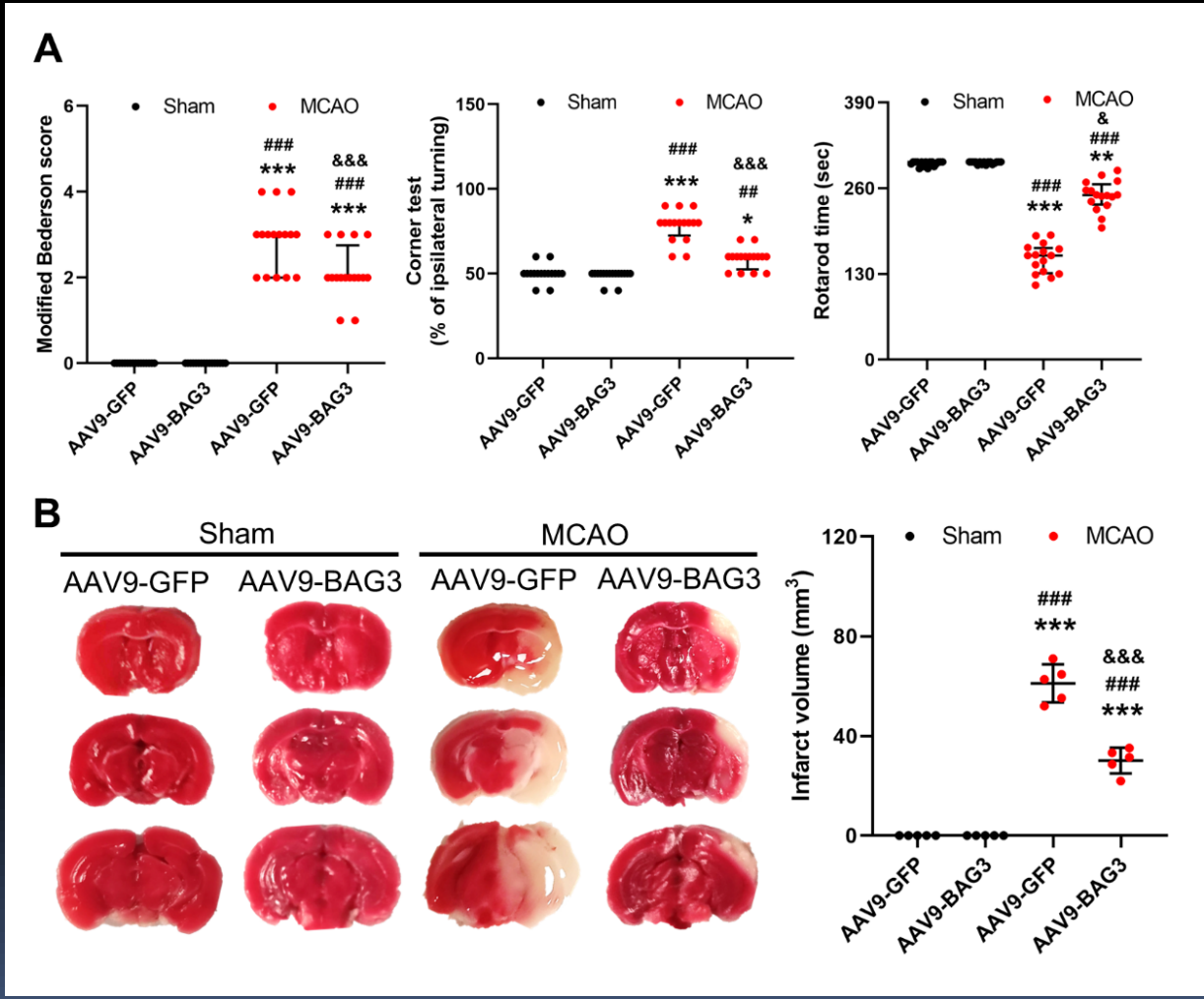






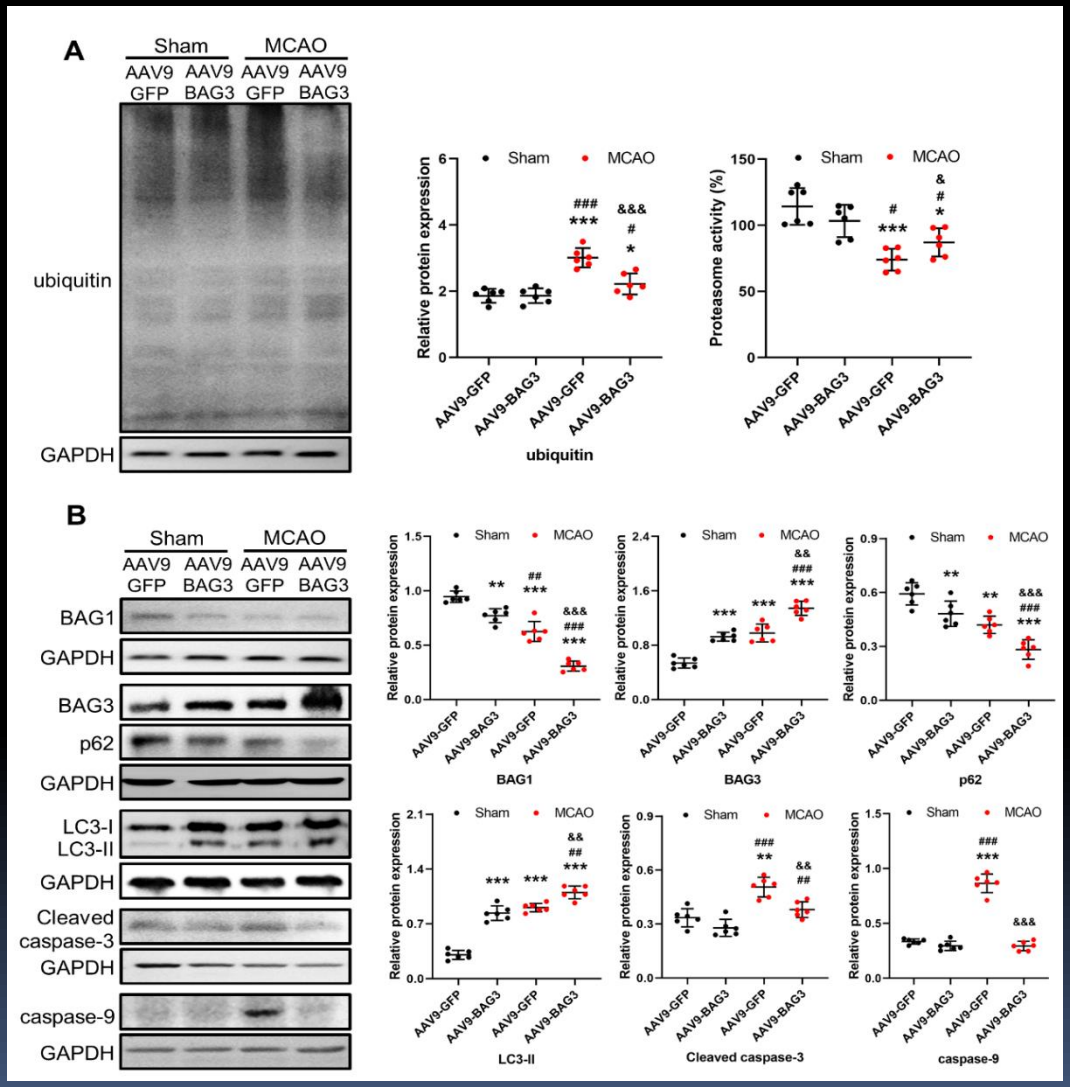
Wang et al. Stroke. 2020.

BAG3 overexpression improves neurological deficits and attenuates cerebral infarct volume in MCAO



Liu et al. Stroke. 2023;54:2114–2125

BAG3 overexpression regulates the changes in UPS, autophagy, and apoptosis in MCAO mice

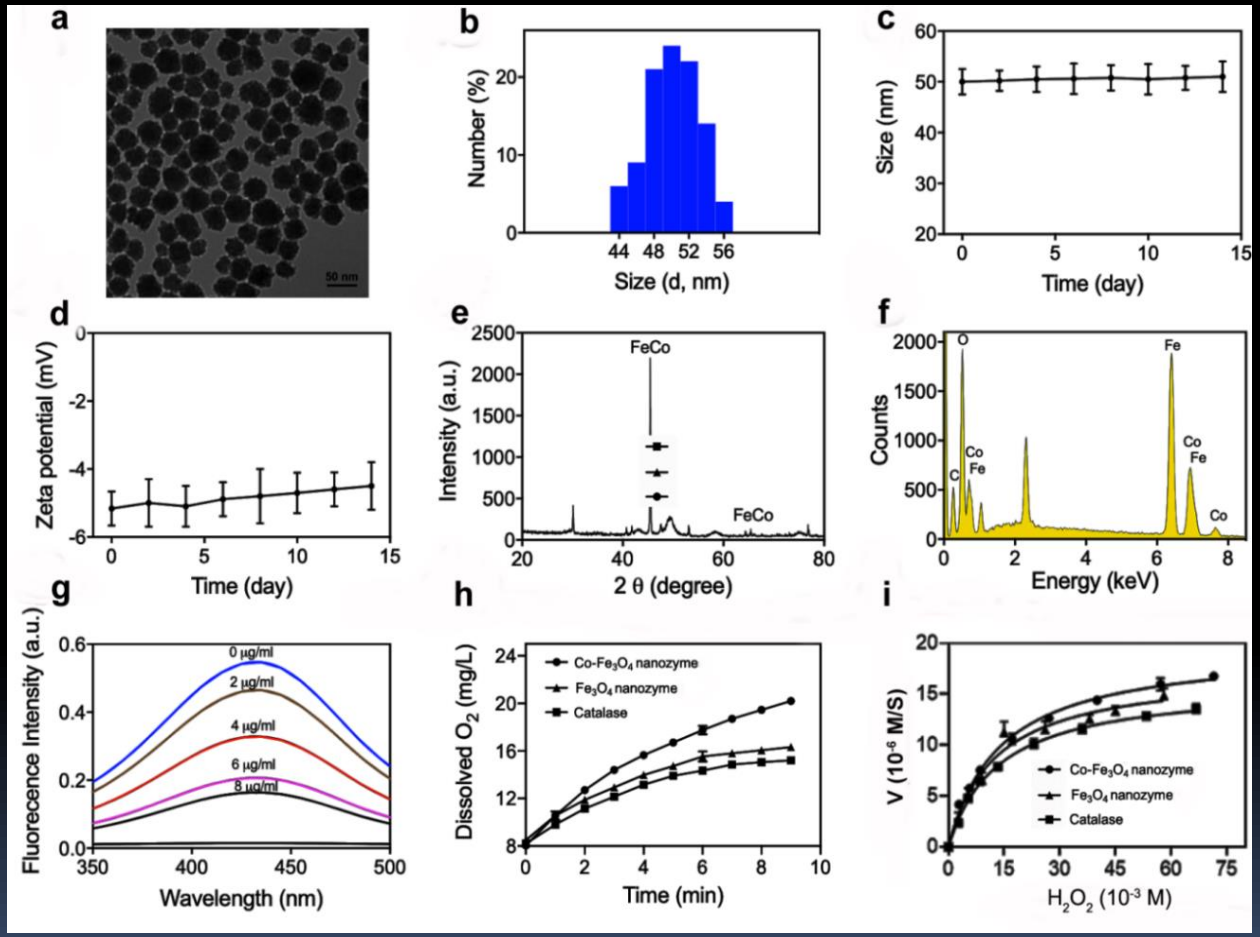


Liu et al. Stroke. 2023;54:2114–2125

Part II

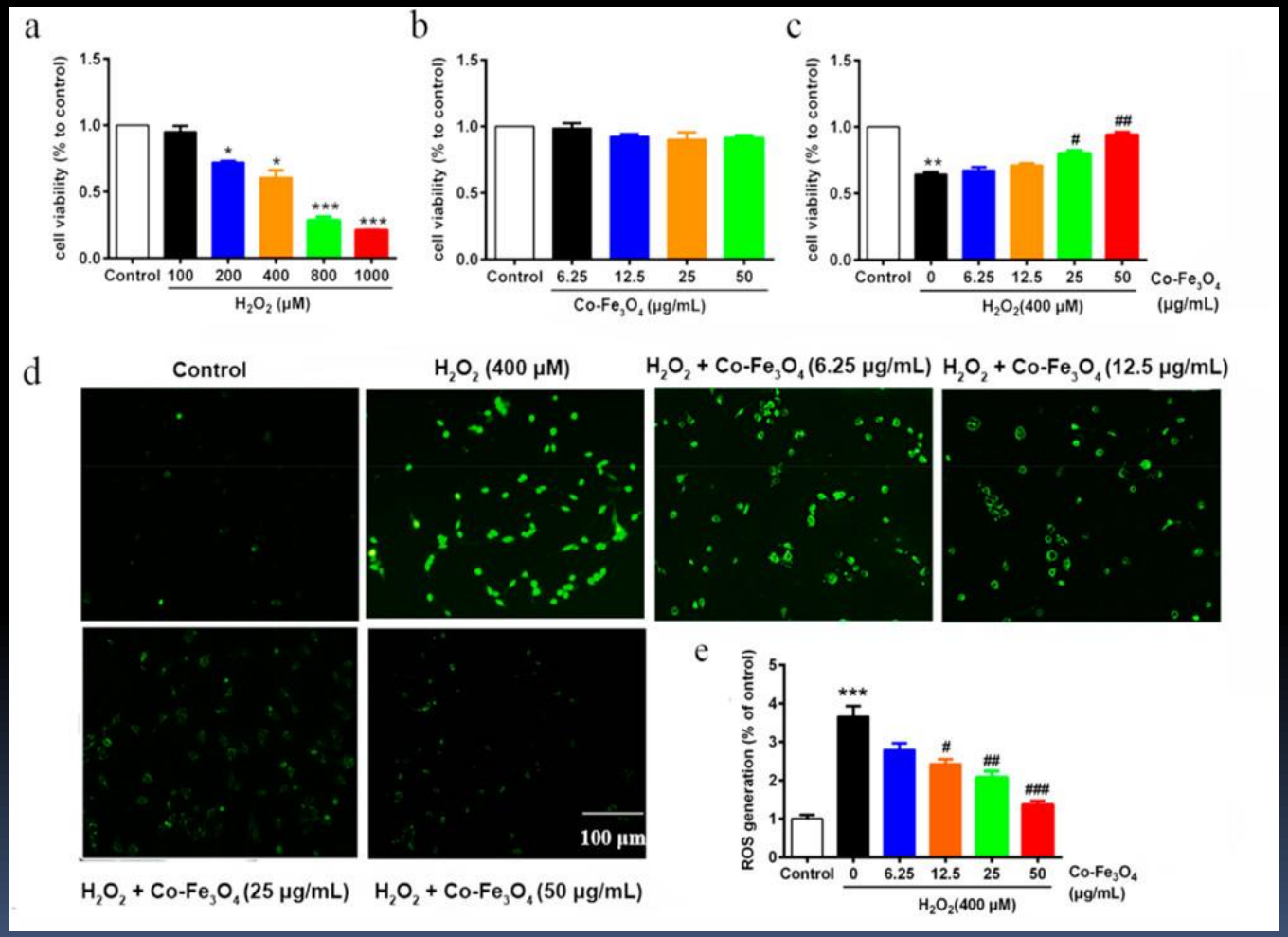
Nano material and ischemic stroke

Characterization and catalase-like activity of the Co-Fe_3O_4 nanozyme



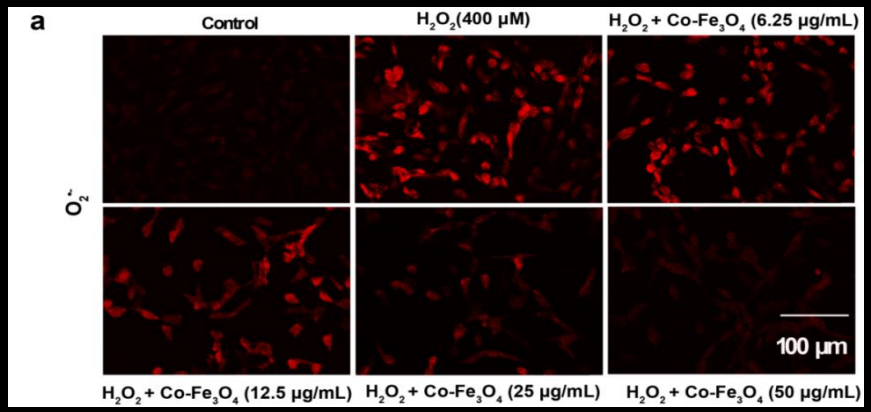
Liu et al. ACS Appl Mater Interfaces. 2021 6;13(39):46213-46224

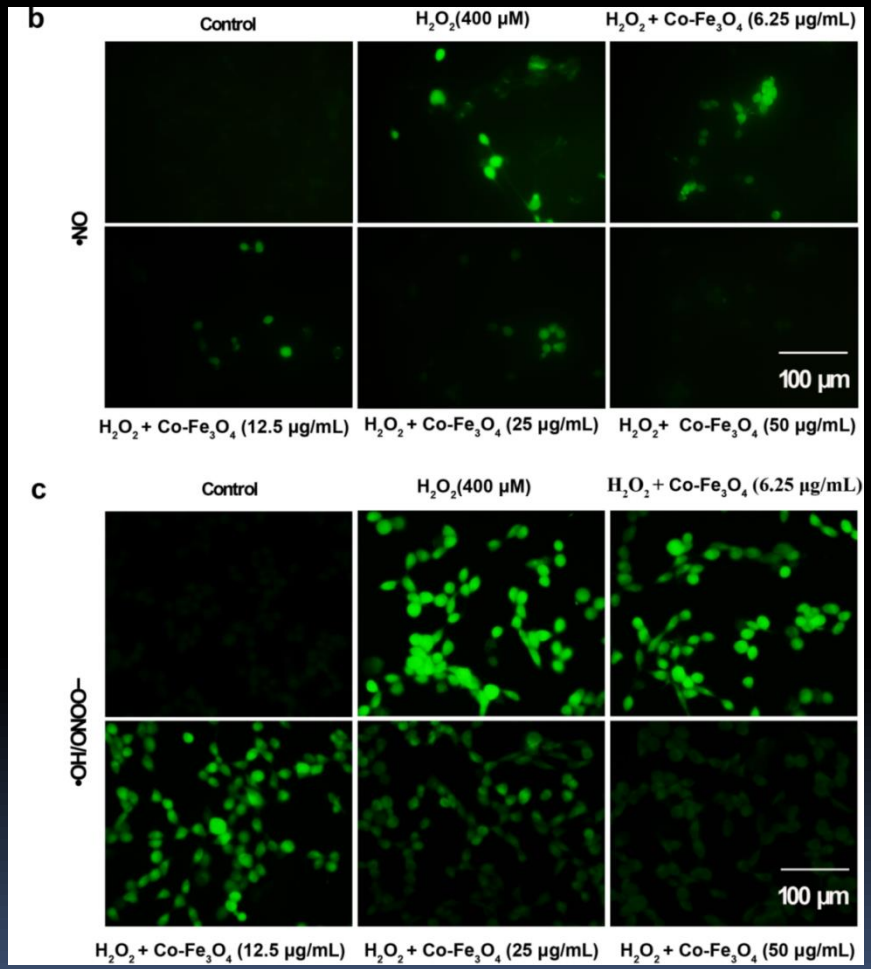
Protective effects of Co-Fe_3O_4 against H_2O_2-induced cytotoxicity and ROS generation in HT22 cells



Liu et al. ACS Appl Mater Interfaces. 2021 6;13(39):46213-46224

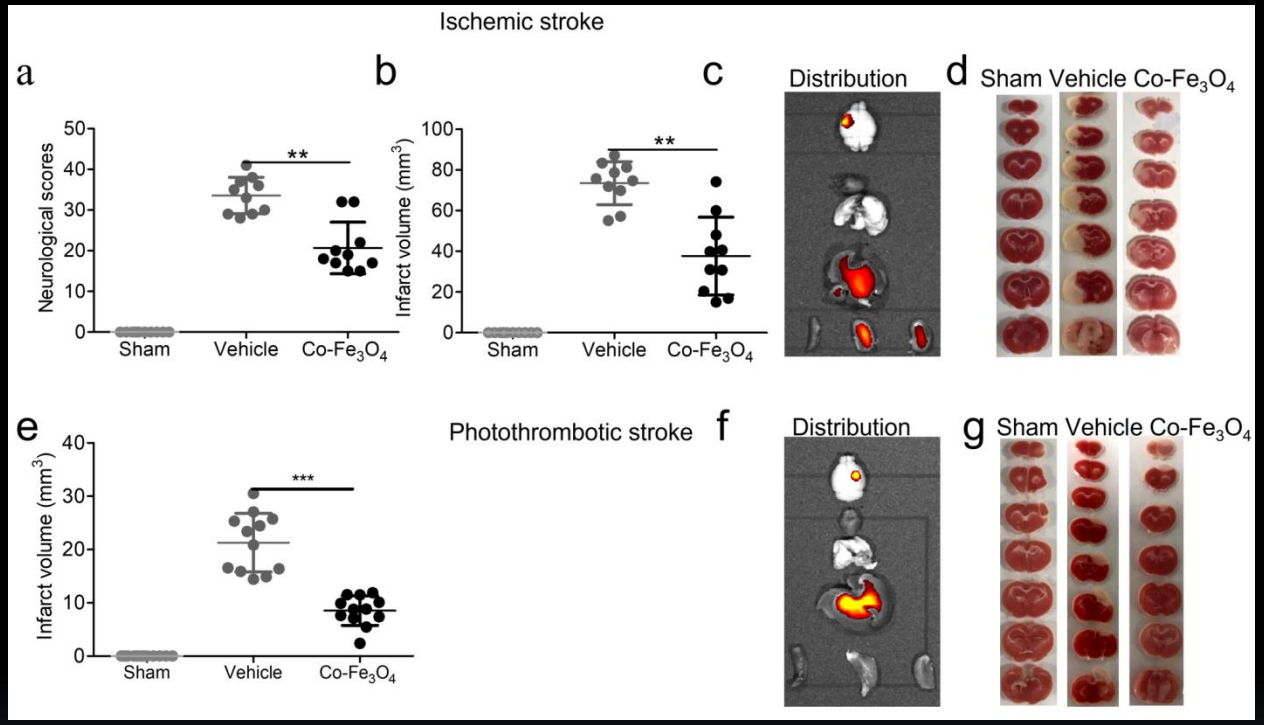
Co-Fe_3O_4 nanozyme decreased RONS activity induced by H_2O_2-treated HT22 cells in vitro





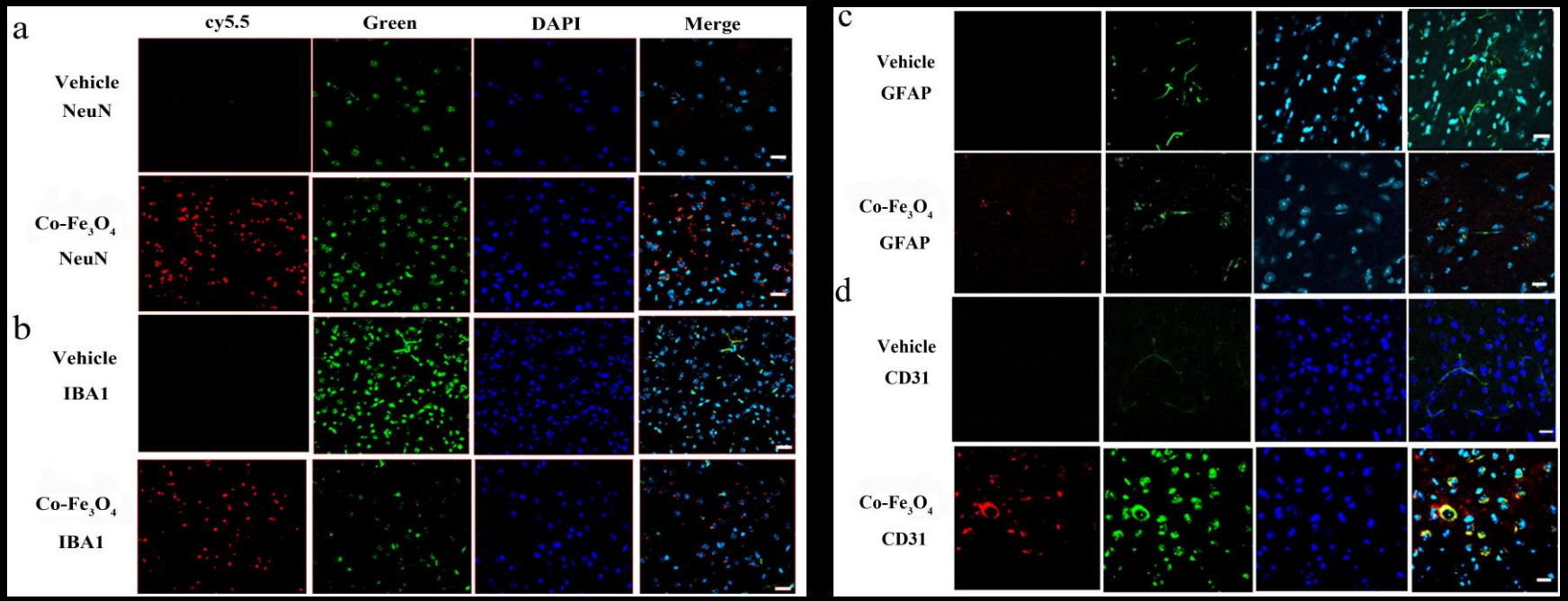
Liu et al. ACS Appl Mater Interfaces. 2021 6;13(39):46213-46224

$Co\text{-}Fe_3O_4$ nanozyme provided neuroprotection in both MCAO and photothrombotic stroke models

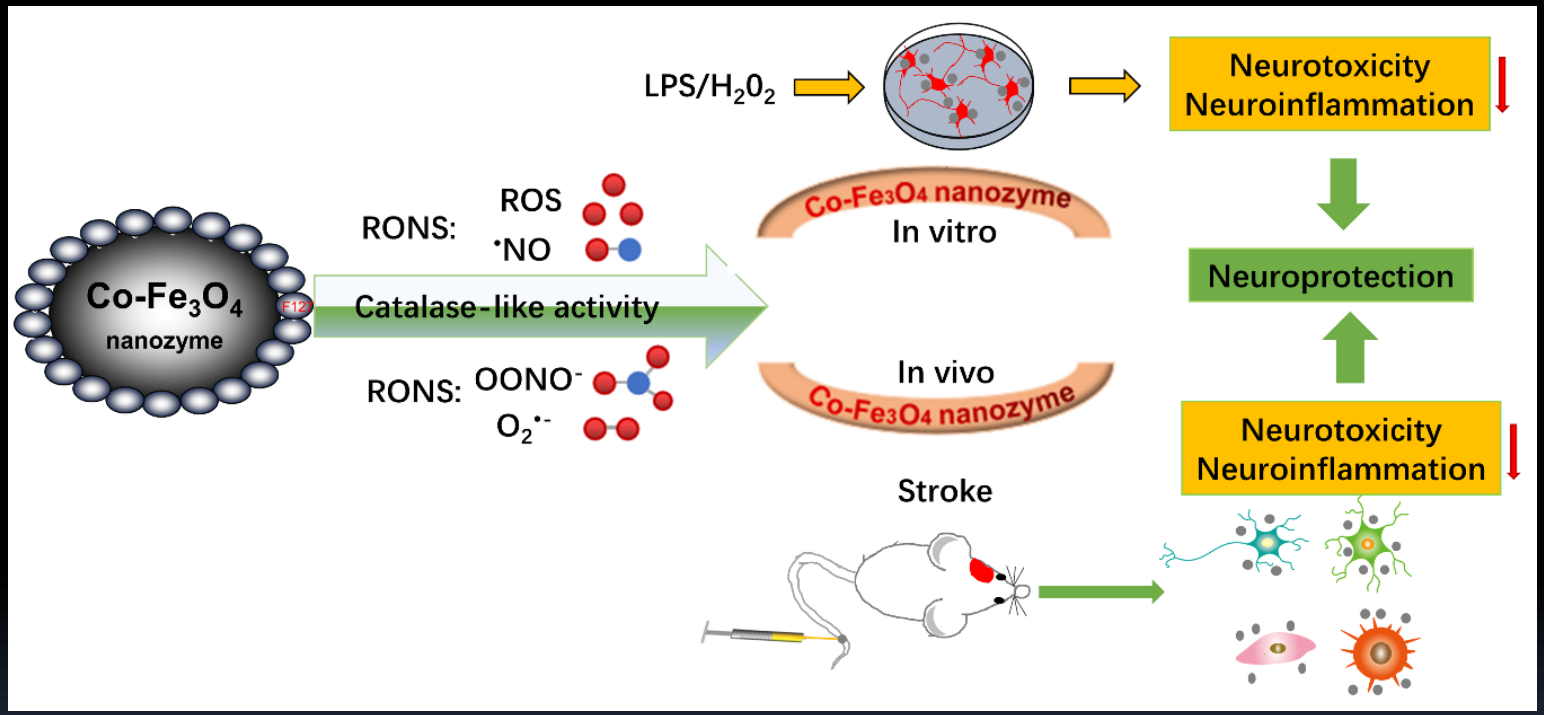


Liu et al. ACS Appl Mater Interfaces. 2021 6;13(39):46213-46224

$Co\text{-}Fe_3O_4$ nanozyme decreased the neurotoxicity and neuroinflammation induced by ischemic stroke



Graph abstract



Take home messages

1. Neuroplasticity vs neuroprotection.

2. Discover the novel target and therapy.

3. Nano materials for stroke diagnose and therapy

4. It is just a start.

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