Lys therapeutics

« Gluno(zu)mab : une stratégie unique au monde pour traiter les maladies neurovasculaires »

SFNV – aviesan presentation

November 18, 2022

Manuel BLANC, President & co-founder
mblanc@lystherapeutics.com

WHO is Lys Therapeutics?

Our goal is to develop **first-in-class innovative drugs for patients** suffering from **neurological disorders** with **unmet medical needs**

Neurovascular diseases
Neurodegenerative disorders

Our ambition:
Create major societal impact

WHO is Lys Therapeutics? **Pipeline**

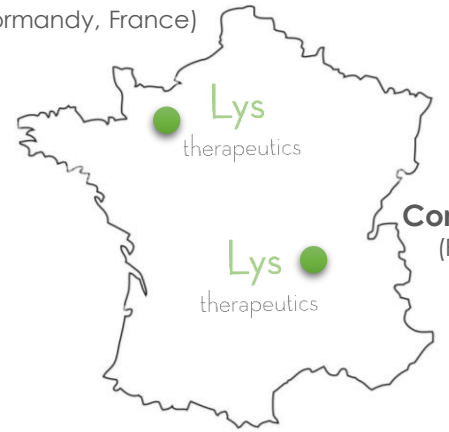
As of October 2022

	Research	Preclinical development	Clinical development
Gluno(zu)mab			
Neurovascular B.U.			
Ischemic stroke	Clinical trial in preparation Proof of Concept (POC) studies completed		
Neurodegeneration B.U.			
Multiple Sclerosis	Clinical trial in preparation POC studies completed		
Parkinson's Disease	POC studies ongoing		
Rare CNS diseases	Mechanism of action studies		
Others			
Confidential	Mechanism of action studies		

WHO is Lys Therapeutics? **In a nutshell**

Corporate:

HQ & labs: Caen
(Normandy, France)

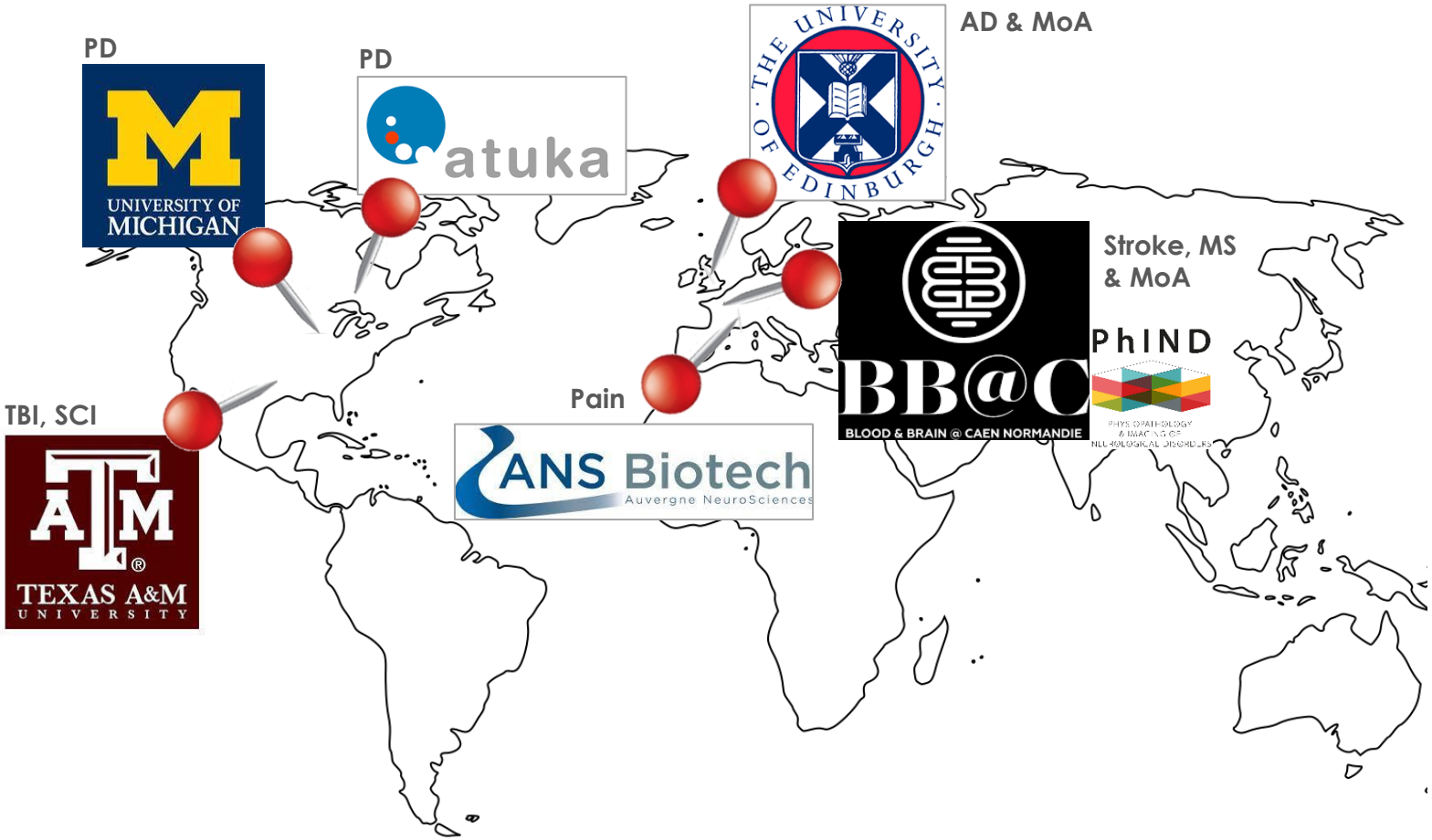


Corporate offices: Lyon
(Rhone-Alpes, France)

Incorporation: March 2021
Seed round in 2021: €5.5M

Laureate & Grand Prix Lys Therapeutics i-Lab 2021

Our main collaborations:



WHAT is Lys Therapeutics?

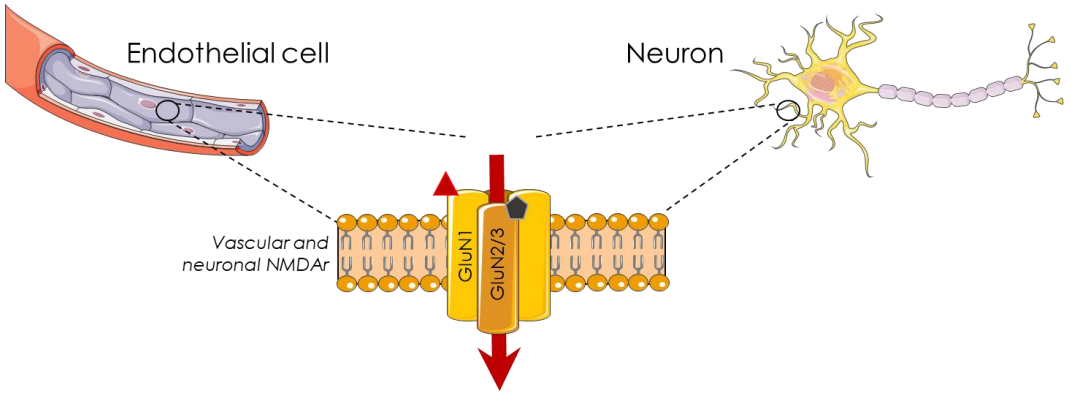
A fully-characterized mechanism of action

Glunomab/Glunozumab® immunotherapy: a groundbreaking mechanism of action

In the **pathophysiology** of neurological diseases such as **stroke**, **multiple sclerosis, Parkinson's disease and other neurodegenerative disorders**, one protease called **tissue plasminogen activator (tPA)** is triggering **off-target toxicity** via the binding to NMDA receptors (NMDAr) present on vascular endothelial cells and neurons, leading to its consequent hyperactivation and causing **deleterious increase of the permeability of the blood brain barrier, as well as strong neuroinflammation and excitotoxicity**.

▲ **tPA** is binding to NMDA receptor (off-target)

→ **Strong toxicity**



Inflammation & neuroinflammation | **Blood brain barrier issues** | **Synaptic stress & excitotoxicity** (incl. oxidative stress)

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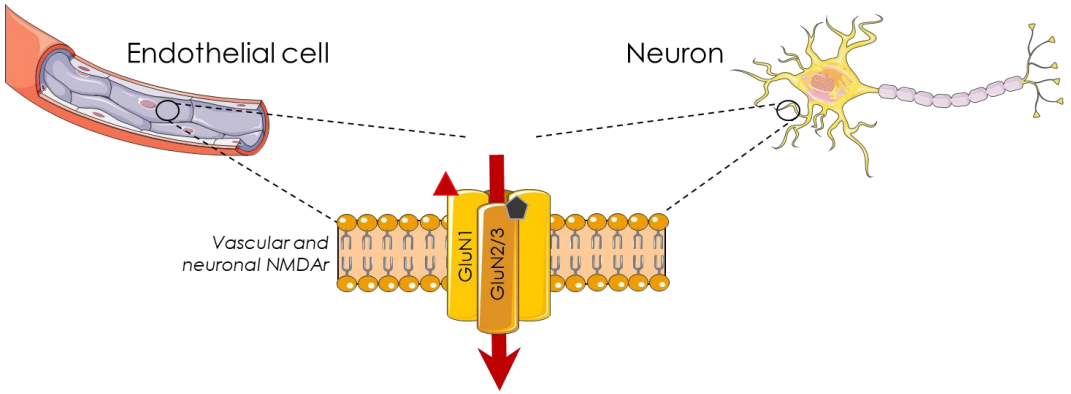
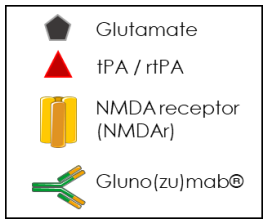


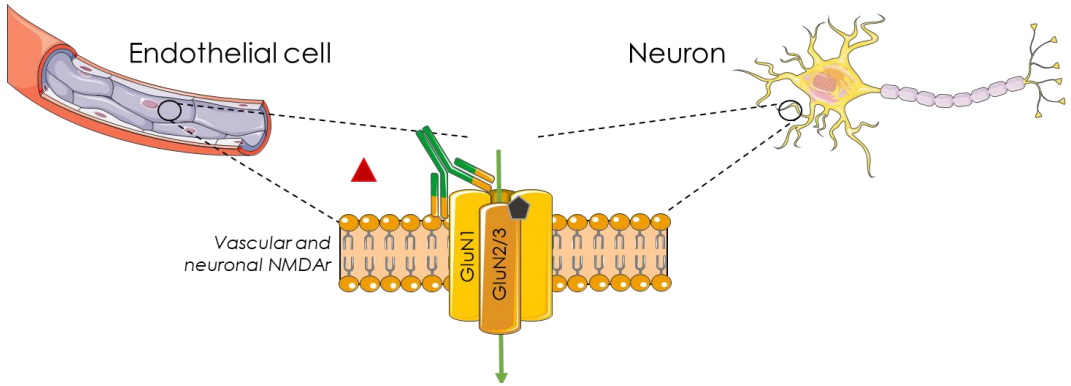
Inflammation & neuroinflammation | **Blood brain barrier issues** | **Synaptic stress & excitotoxicity** (incl. oxidative stress)

+Gluno(zu)mab i.v.



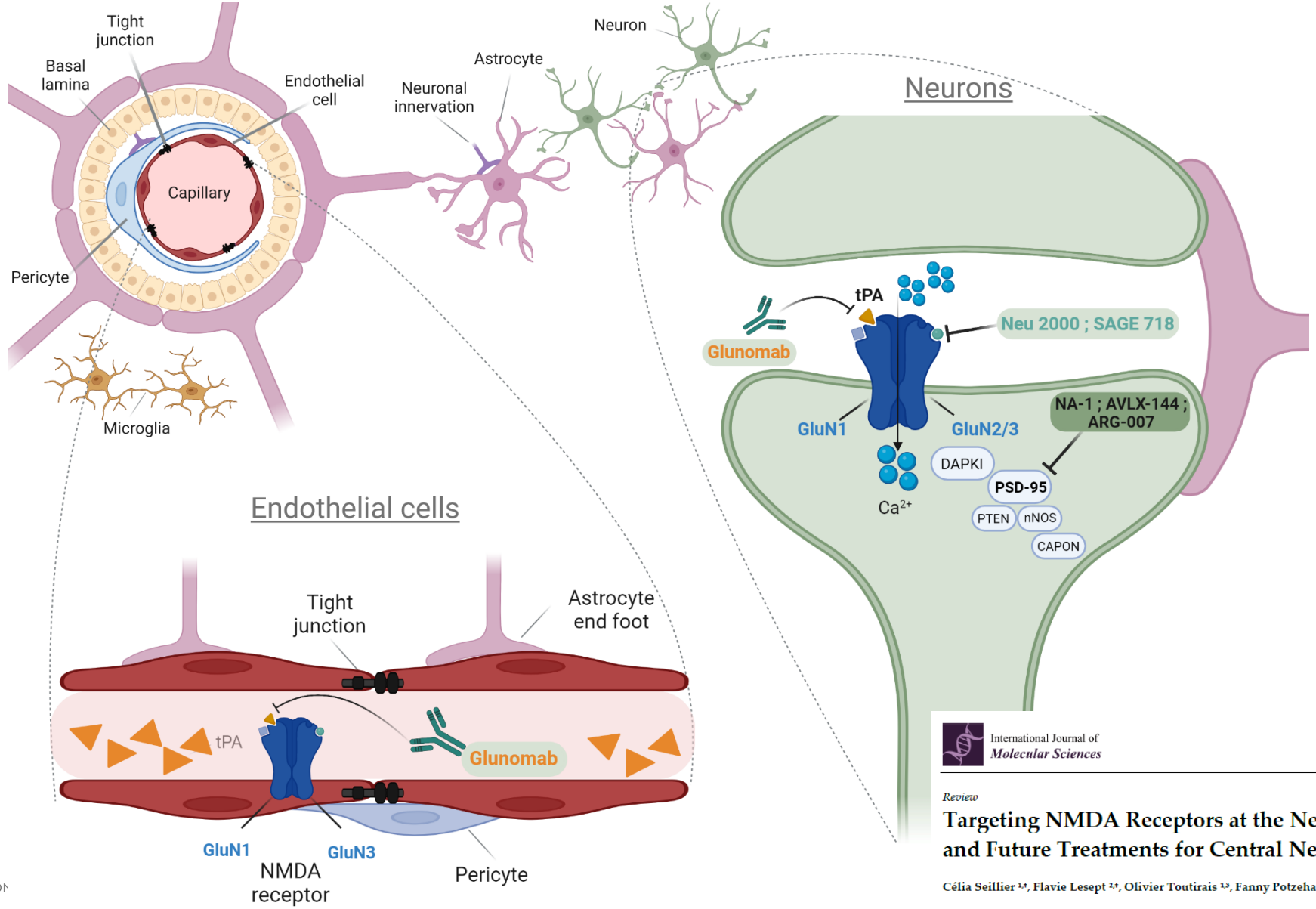
Gluno(zu)mab counteracts this off-target toxicity

→ **Cerebral and vascular protection**



~~Inflammation & neuroinflammation~~ | ~~Blood brain barrier issues~~ | ~~Synaptic stress & excitotoxicity~~ (incl. oxidative stress)

WHAT is Lys Therapeutics? **Differences vs. other NMDAR-targeting drugs**



International Journal of *Molecular Sciences*

MDPI

Review

Targeting NMDA Receptors at the Neurovascular Unit: Past and Future Treatments for Central Nervous System Diseases

Célia Seillier [1,†], Flavie Lesept [2,†], Olivier Toutirais [1,3], Fanny Potzeha [2], Manuel Blanc [2] and Denis Vivien [1,4,*]

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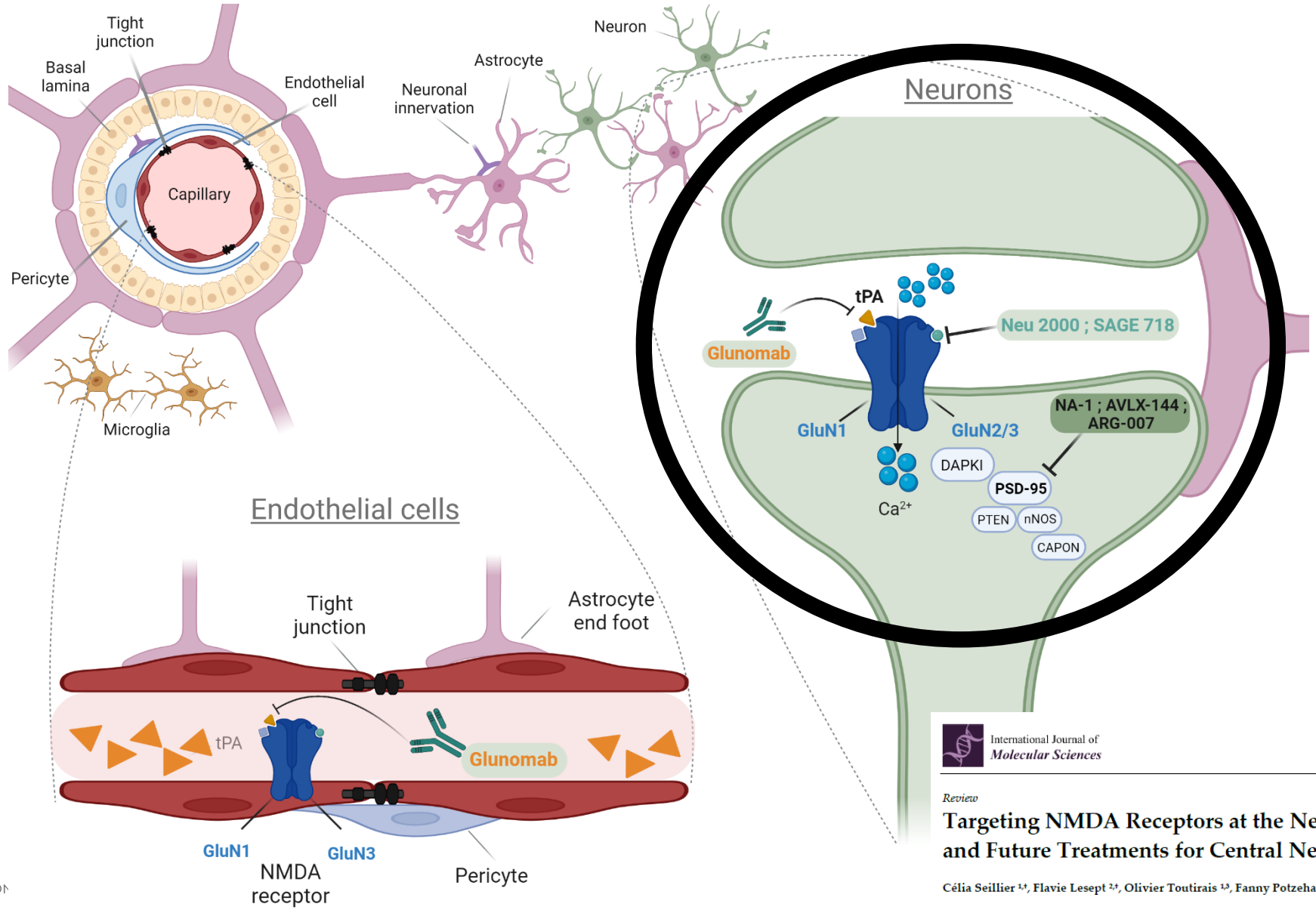

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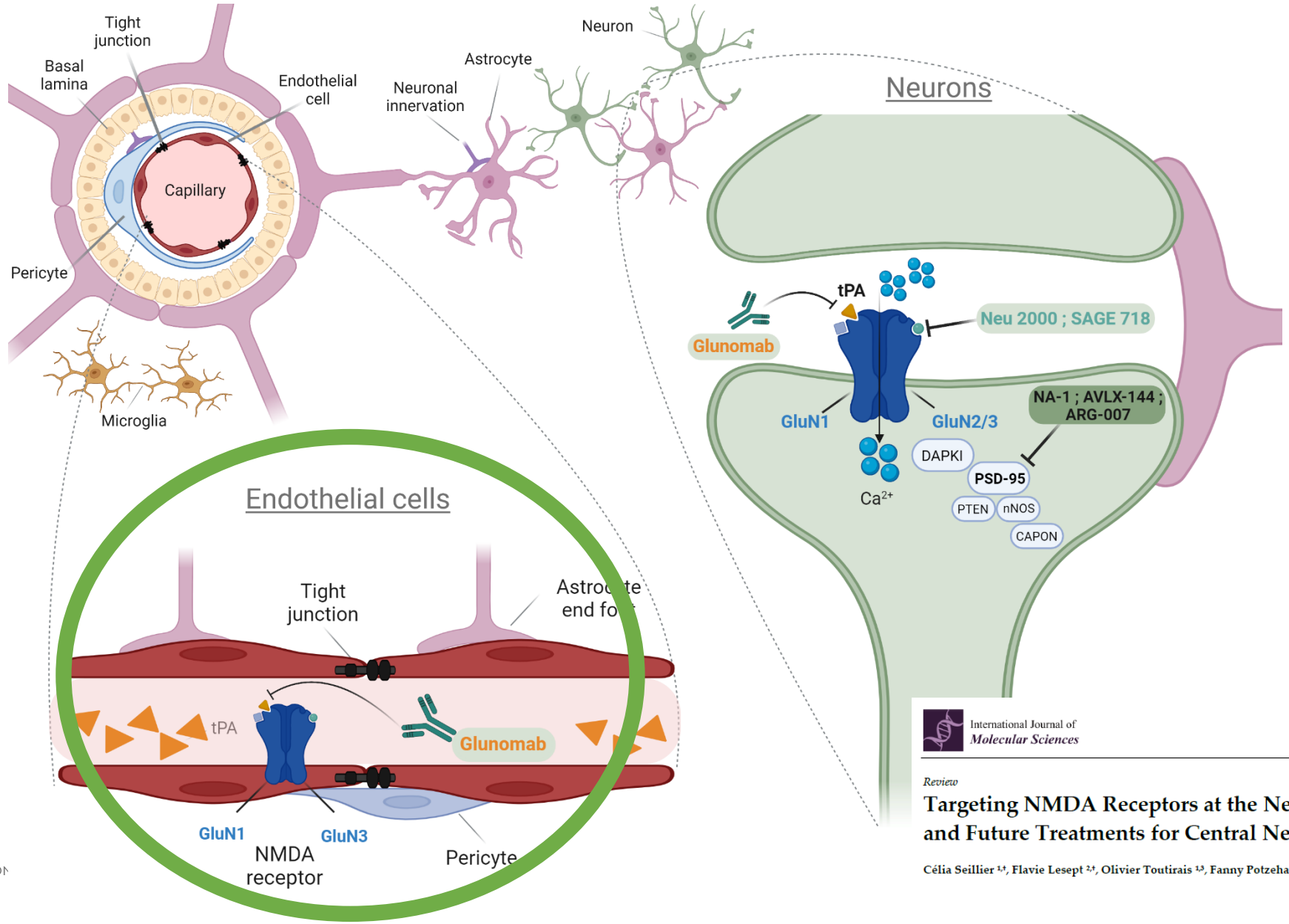

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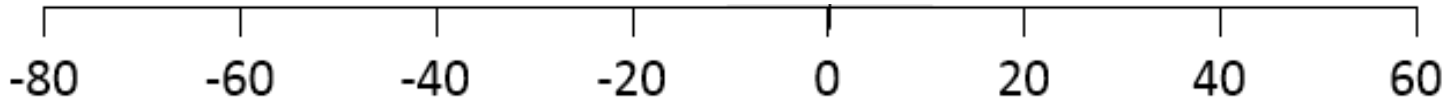
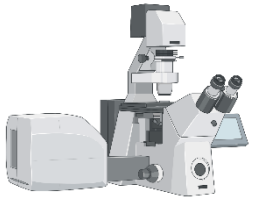


Calcium imaging
(trafficking of Ca^{2+} through NMDAr)

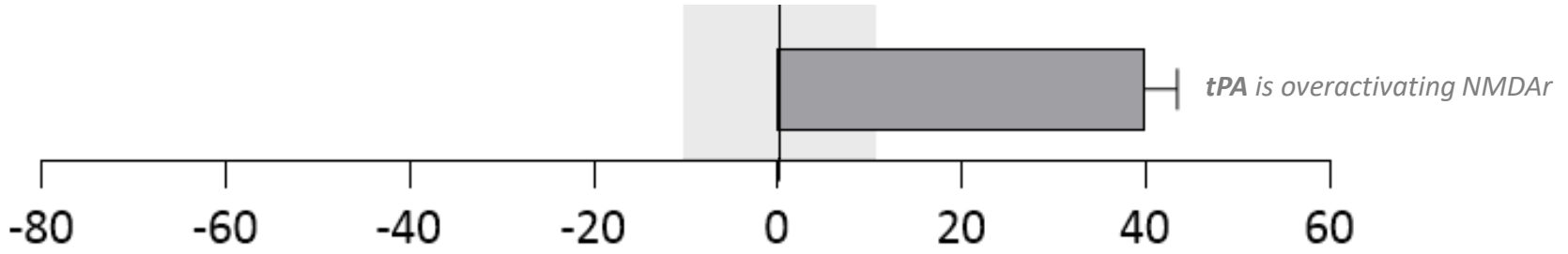


Source: Lesept et al. & unpublished data (F. Potzeha)

WHAT is Lys Therapeutics? **Differences vs. other NMDAR-targeting drugs**

rtPA

NMDAr physiological functioning



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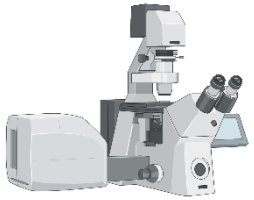

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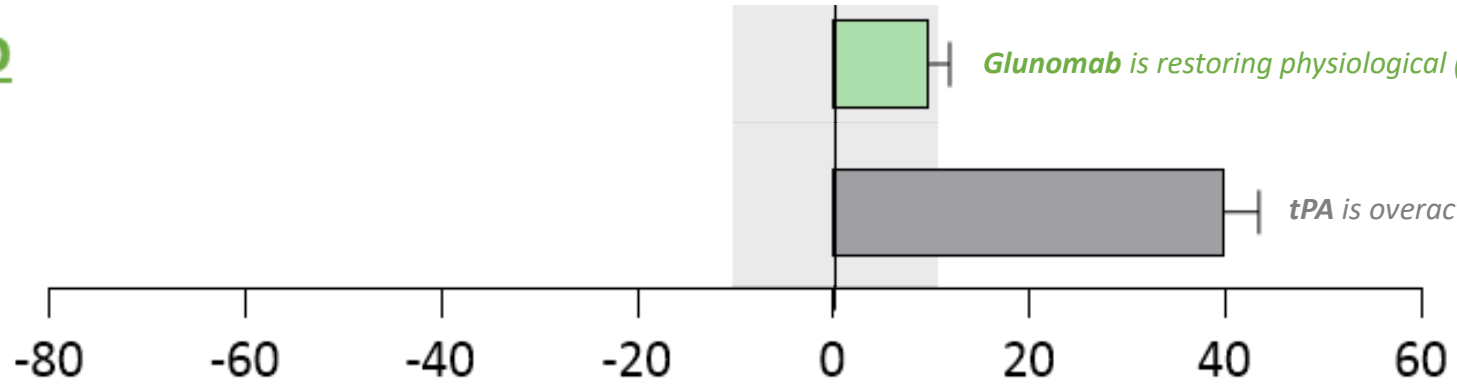
WHAT is Lys Therapeutics? **Differences vs. other NMDAR-targeting drugs**

rtPA + Glunomab

rtPA

NMDAr physiological functioning



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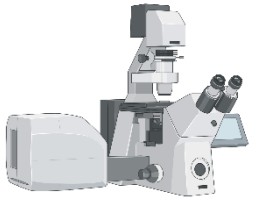

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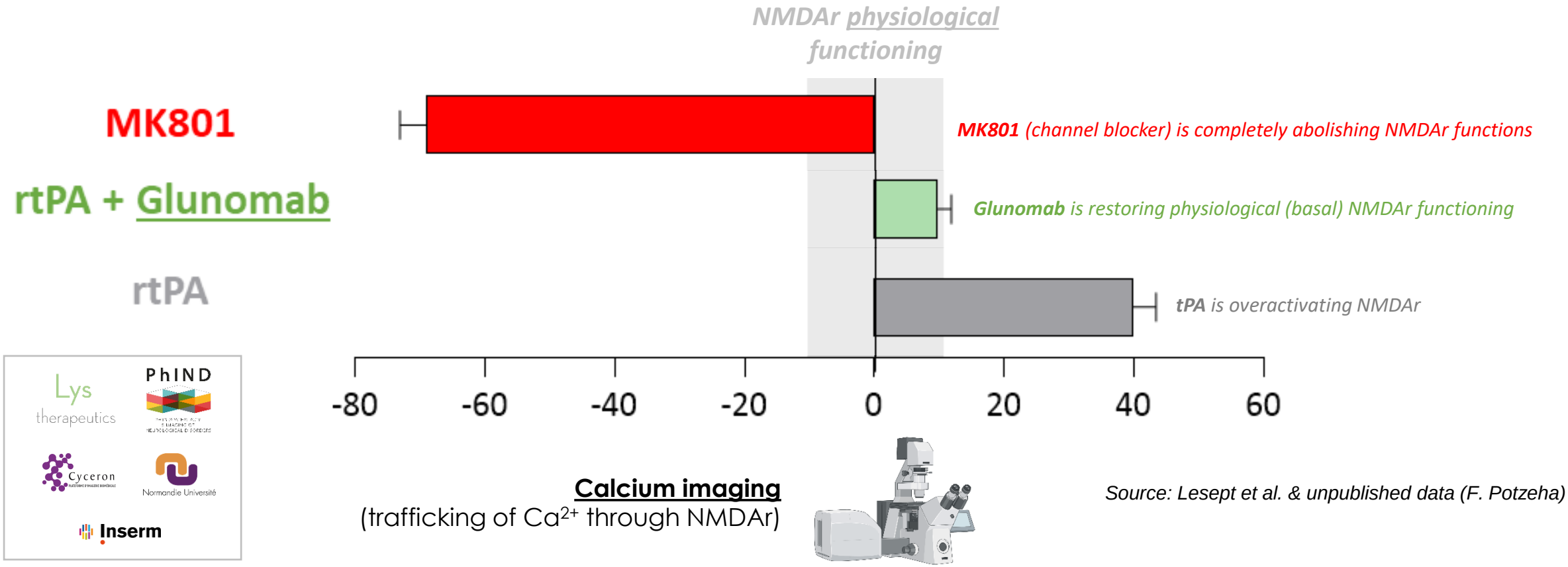

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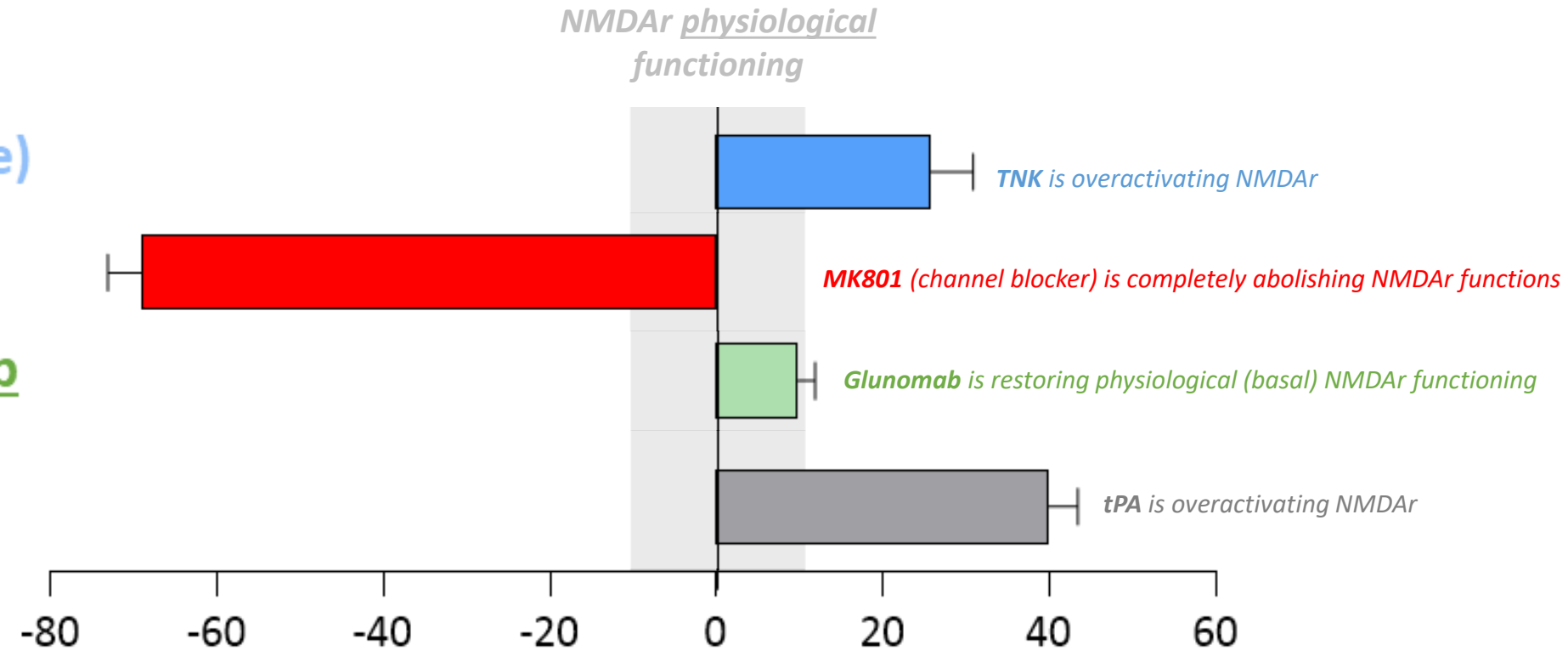
WHAT is Lys Therapeutics? **Differences vs. other NMDAR-targeting drugs**

TNK (tenecteplase)

MK801

rtPA + Glunomab

rtPA



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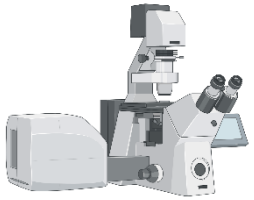

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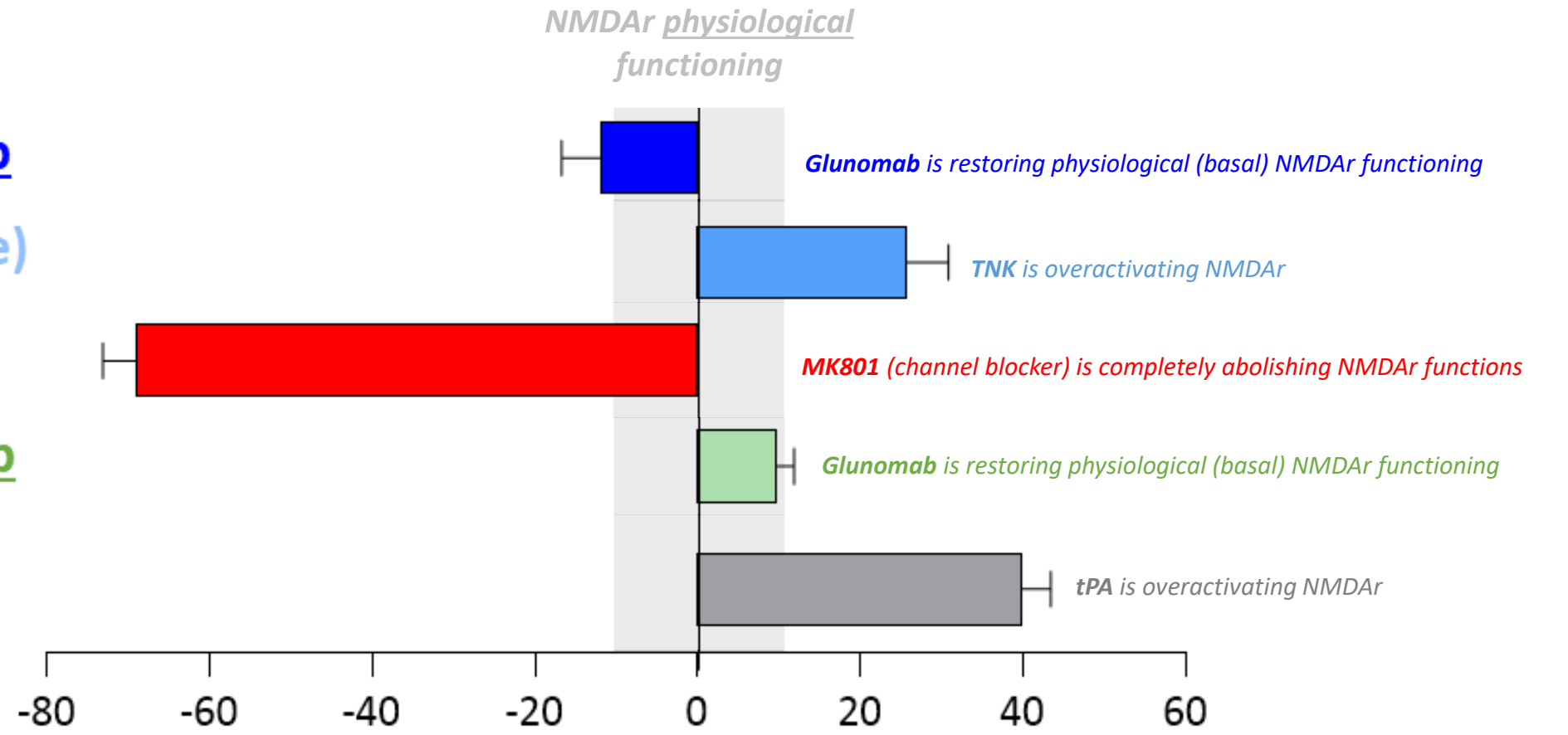

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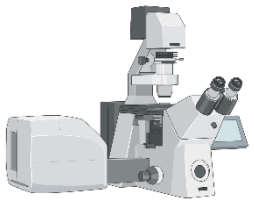

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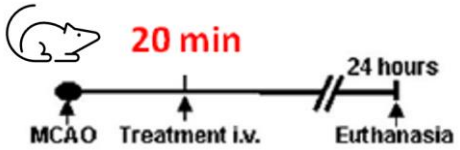
WHY Lys Therapeutics? POC data ischemic stroke

→ Glunomab: lesion volume decreased by 60% vs. control after ischemic stroke.

Therapeutic efficacy both as a standalone therapy or in synergy with the standard of care (rtPA)



MRI measures

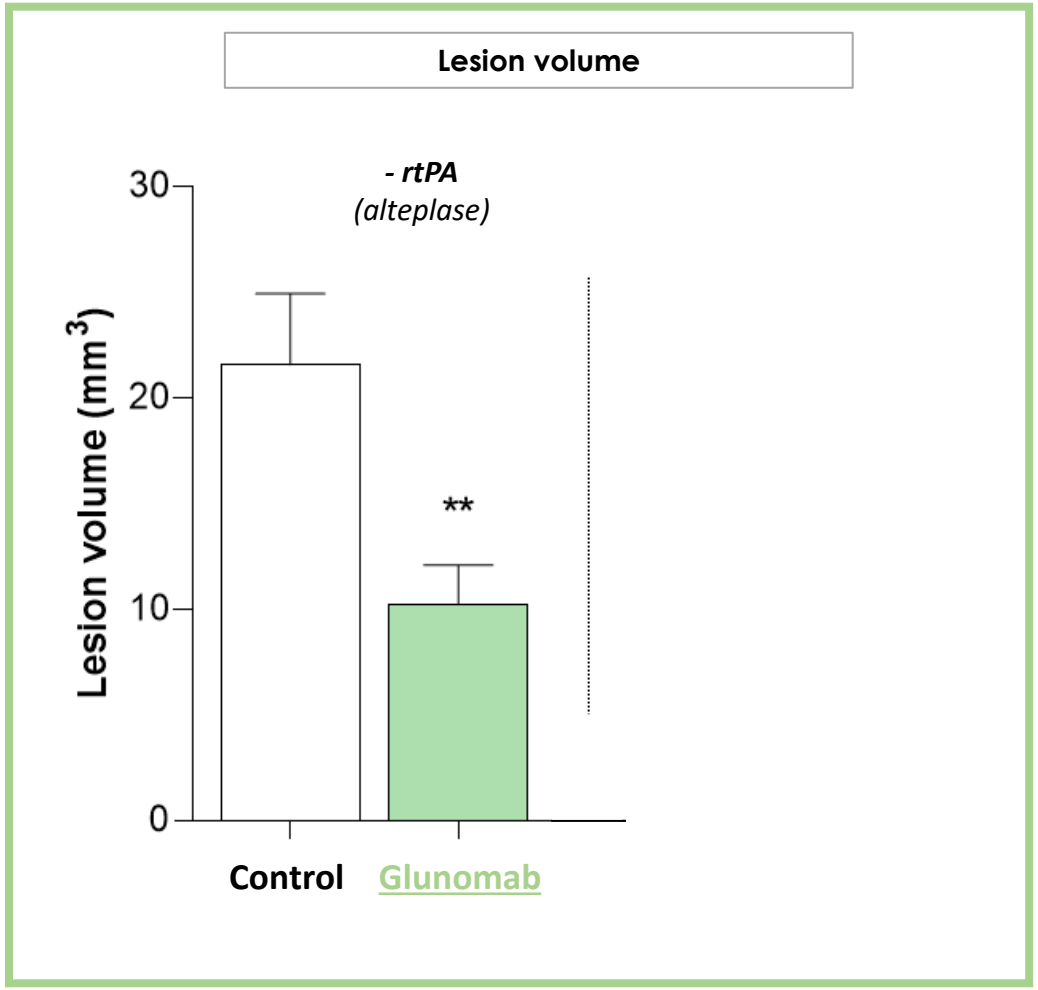


Figure: Glunomab protects the brain against MCAo-induced ischemic stroke. Therapeutic effect of an i.v. injection of 300ug of Glunomab (+/- rtPA) on brain lesion volume after MCAO-induced ischemic stroke in mice (n=12 per group, thrombin model).

Source: article in preparation, Denis Vivien's lab, France

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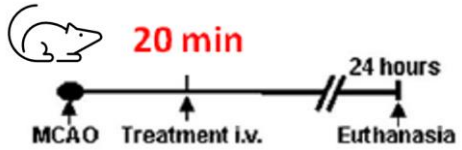

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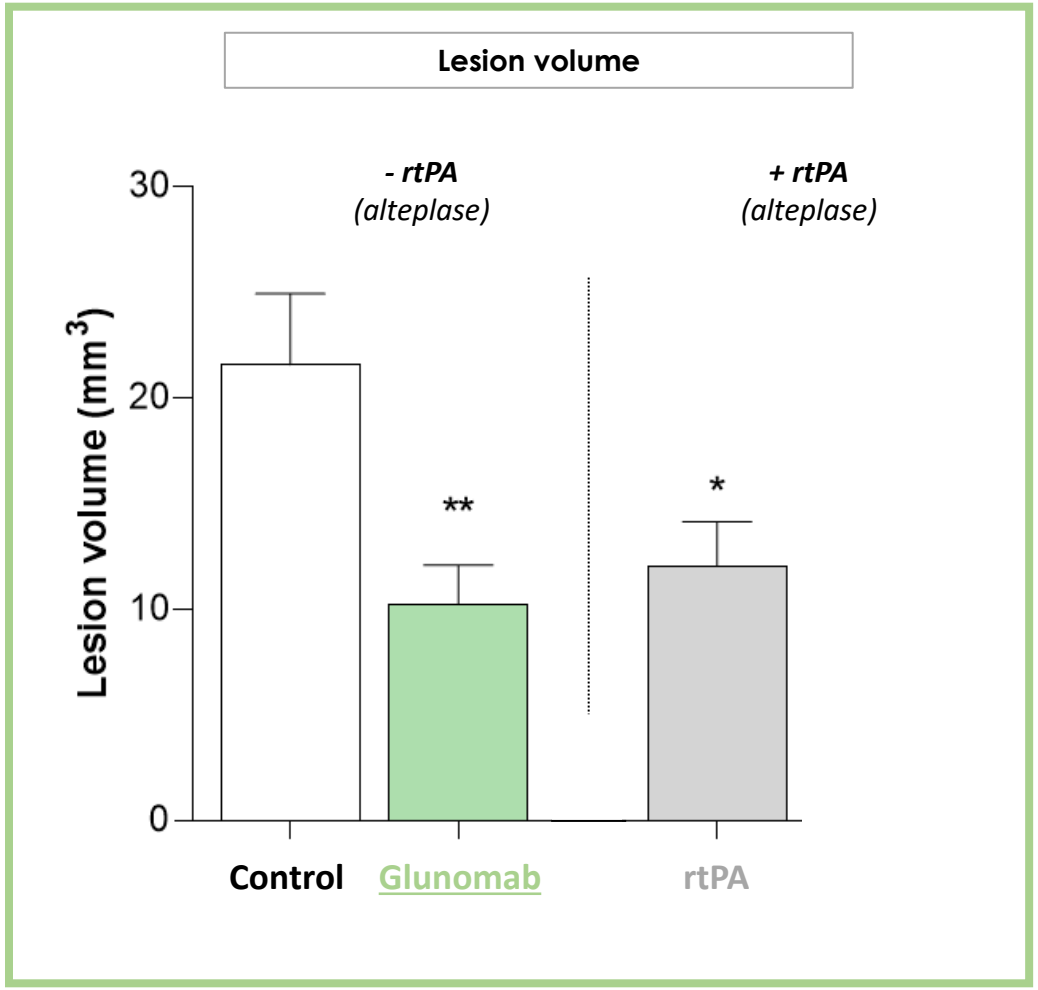

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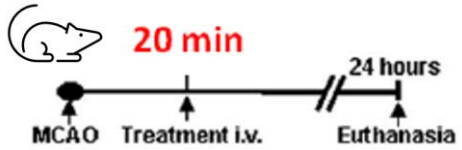

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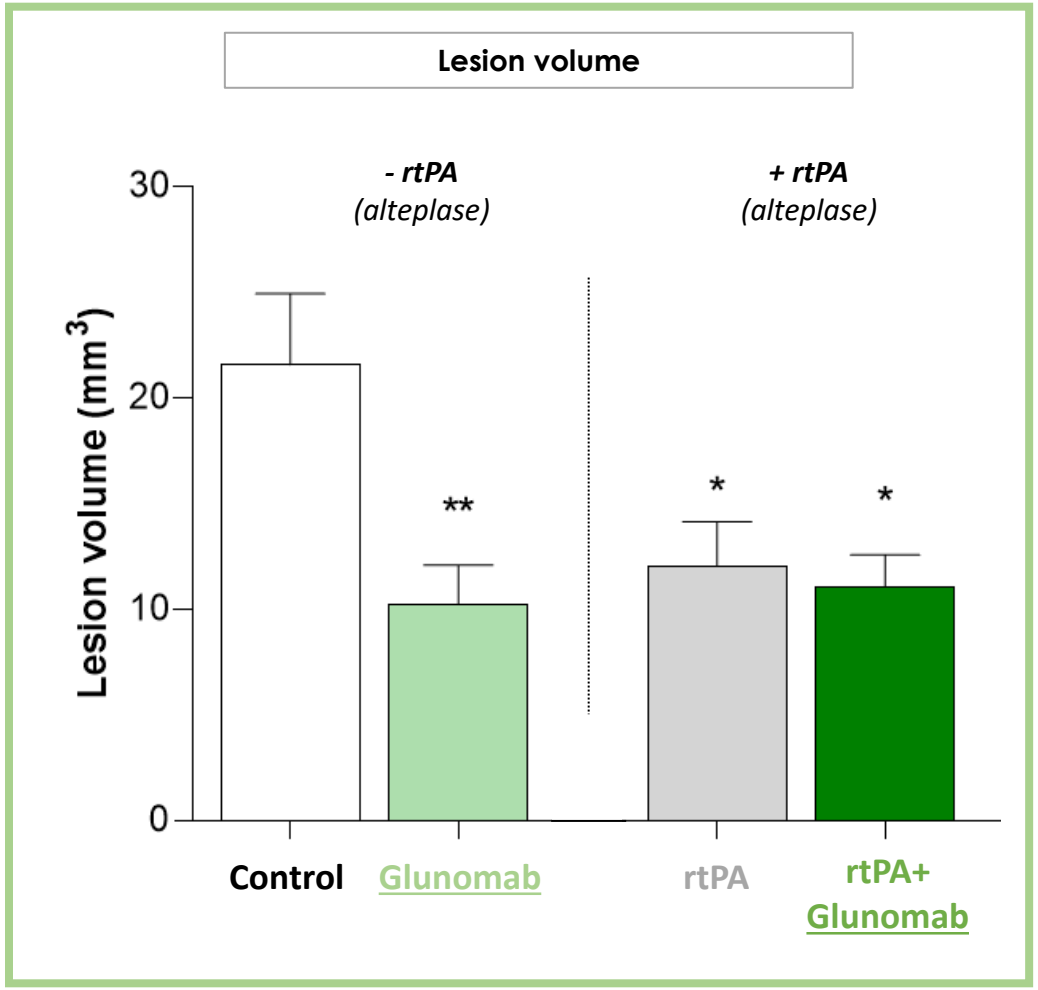

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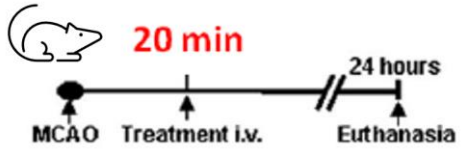
WHY Lys Therapeutics? POC data ischemic stroke

Ischemic stroke of diabetic animals: rtPA looses its therapeutic efficacy

→ Synergy of Glunomab with rtPA leading to strong lesion volume reduction

Diabetic mice



Ischemic stroke model with diabetes comorbidity *(STAIR guidelines - Stroke Treatment Academic Industry Roundtable)*

MRI measures

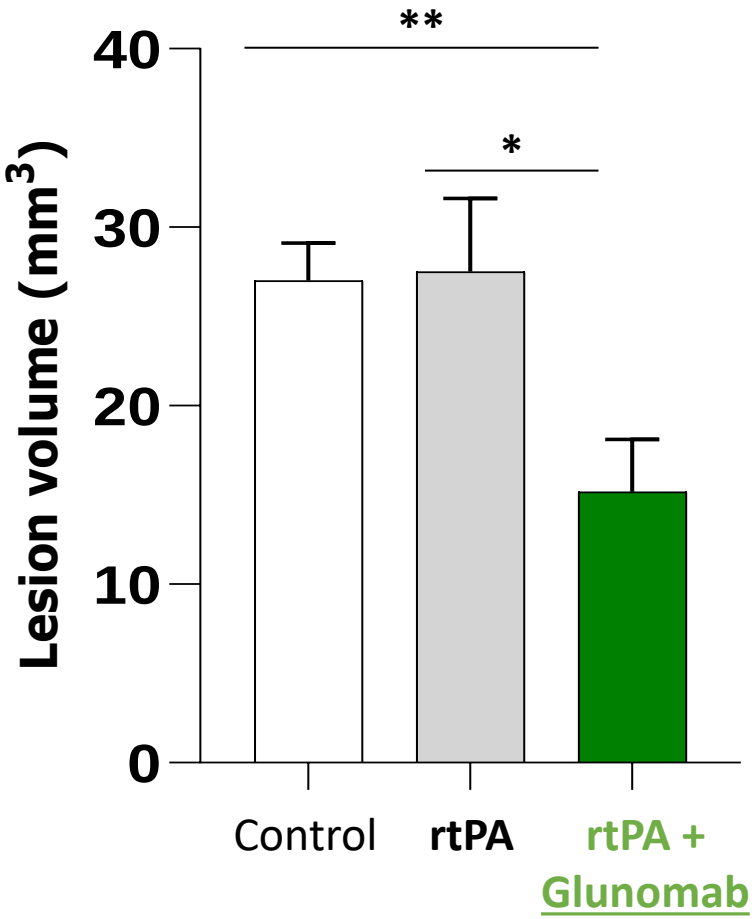


Figure: Glunomab protects the brain against MCAo-induced ischemic stroke in diabetic animals (thrombin ischemic stroke model in streptozotocin-induced diabetic animals).
Lesion volume monitored by T2-weighted MRI imaging, 24 hours after MCAo in a distal stroke mouse model following administration of vehicle (n=11), tPA 10 mg/kg (n=10) or tPA+ Glunomab 300 ug (n= 11). Kruskal-Wallis followed by Mann-Whitney tests: * p< 0,05; ** p<0,01

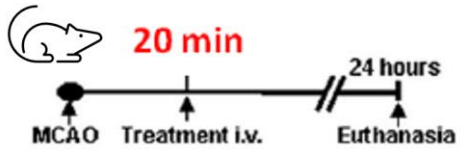
Source: article in preparation, Denis Vivien's lab, France

WHY Lys Therapeutics? POC data ischemic stroke

Ischemic stroke of diabetic animals: rtPA looses its therapeutic efficacy

→ Synergy of Glunomab with rtPA with decrease of hemorrhagic transformations and increase of blood recanalization

Diabetic mice



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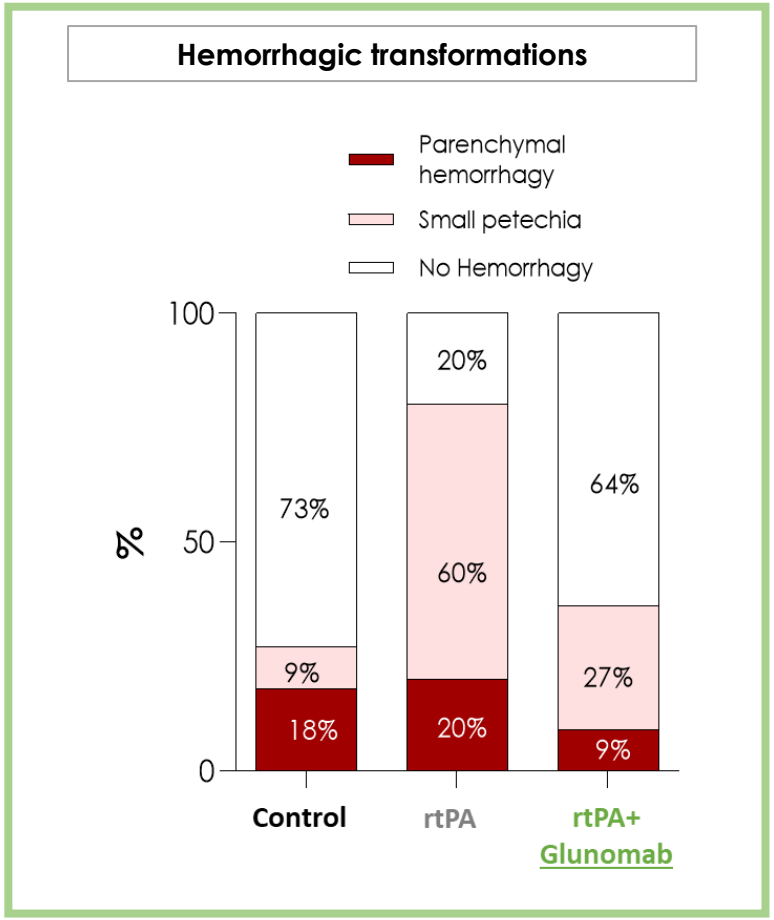
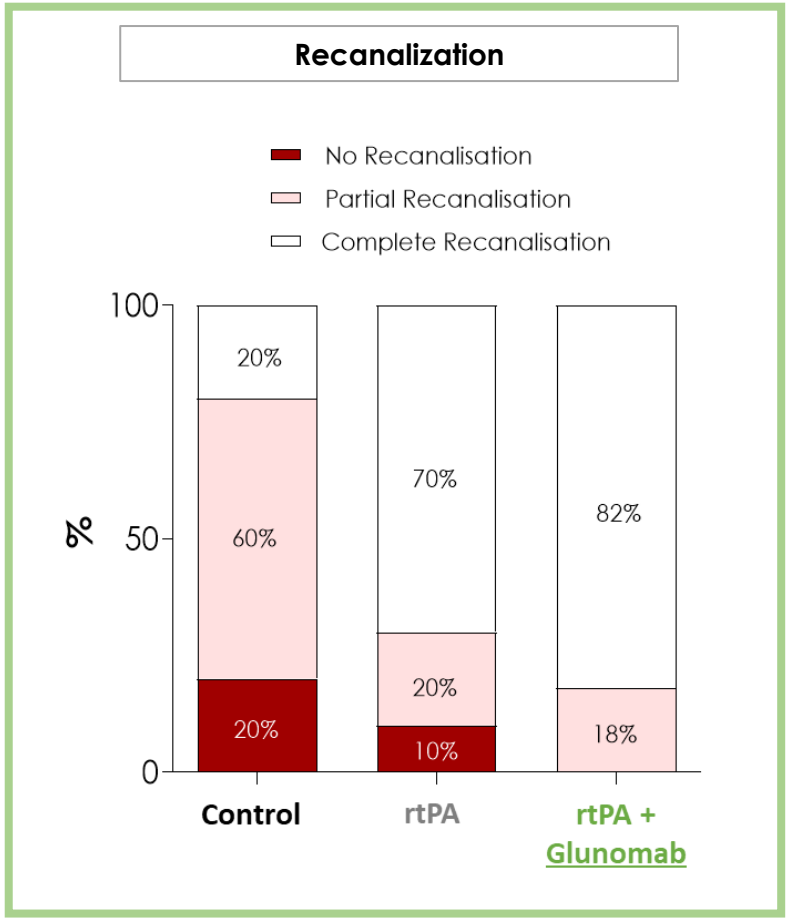


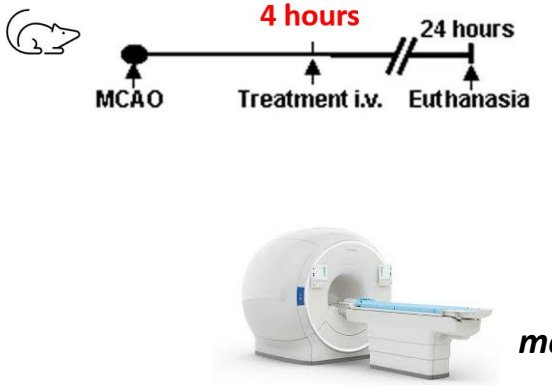


Source: article in preparation, Denis Vivien's lab, France

WHY Lys Therapeutics? POC data ischemic stroke

→ Glunomab: decrease of lesion volume and neurological long-term deficits in late-treatment.

Glunomab in combination with standard of care: therapeutic-window extension of rtPA use (synergy)



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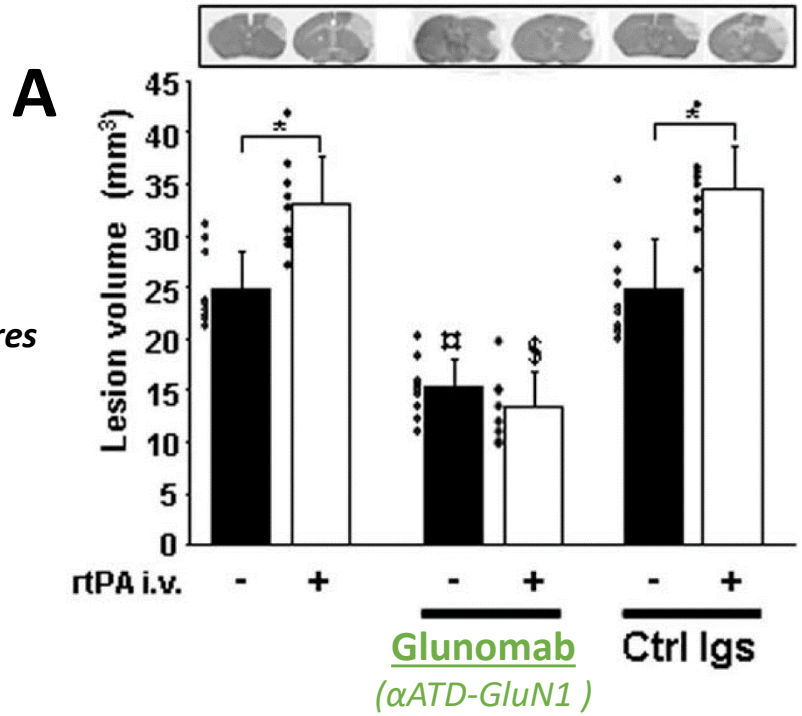
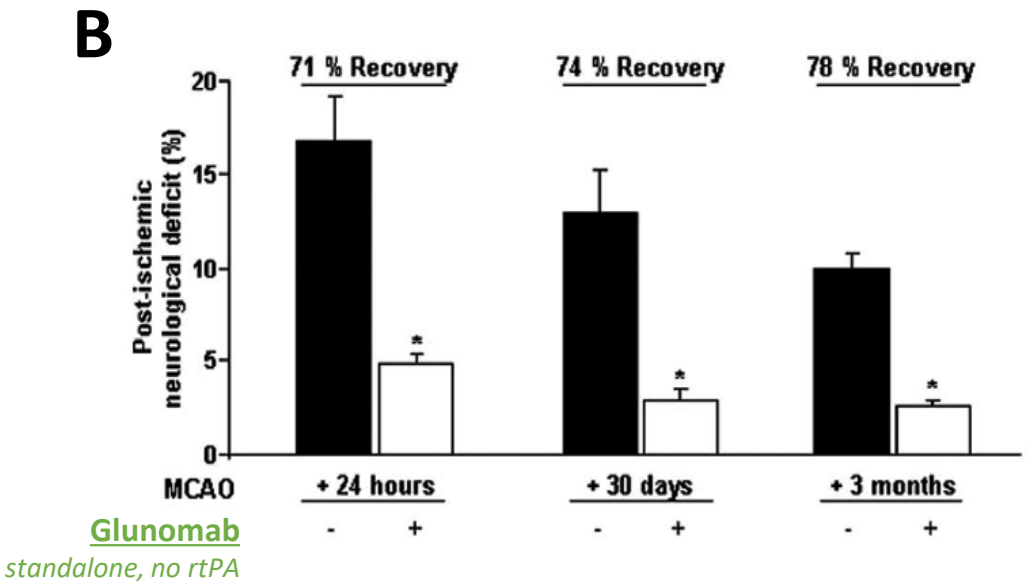




Glunomab used 4 hours after stroke: 4h in mouse would represent a therapeutic-window extension up to 12-16h in human

Figure: αATD-GluN1 (polyclonal antibody) protects the brain against MCAo-induced ischemic stroke and increases the therapeutic window of rtPA-induced thrombolysis.
A: Neuroprotective effect of a late (4h) i.v. injection of ATD-NR1 (+/- rtPA) on brain lesion volume after MCAO-induced ischemic stroke in mice.
B: Glunomab attenuates post-ischemic neurological deficits in MCAO mouse model.

Source: Macrez et al

WHY Lys Therapeutics? **Value proposition** stroke

Gluno(zu)mab prevents both endogenous and therapeutic **tPA off-target toxicity** without perturbing tPA-induced thrombolysis nor basal NMDA receptor functioning

Stand-alone therapy
(+/- thrombectomy)

Neutralization of toxicity caused by endogenous tPA:

- ✓ Decreased lesion size (neuronal death)
- ✓ Decreased neurological long-term deficits
- ✓ Restoration of blood-brain barrier integrity (anti-neuroinflammation, reperfusion injury & hemorrhagic transformation)

In combination with rtPA/TNK
(+/- thrombectomy)

Neutralization of toxicity caused by endogenous tPA
+
Improved efficacy-safety profile of recombinant tPA/TNK:

- ✓ Decreased lesion size (neuronal death)
- ✓ Decreased neurological long-term deficits
- ✓ Restoration of blood-brain barrier integrity (anti-neuroinflammation, reperfusion injury & hemorrhagic transformation)
- ✓ **Therapeutic-window extension of rtPA/TNK use (target 12-16h)**

WHAT is Lys Therapeutics? **Publications**

A groundbreaking science

Scientific background of Lys Therapeutics – Vivien *et al. (Glunomab/Glunozumab®)*:

tPA-NMDAr interaction

nature medicine (IF: 36)

The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling

Tissue-plasminogen activator (t-PA) is now available for the treatment of thrombo-embolic stroke but adverse effects have been reported in some patients, particularly hemorrhaging. In contrast, the results of animal studies have indicated that t-PA could increase neuronal damage after focal cerebral ischemia. Here we report for the first time that t-PA potentiation signaling of excitotoxic neuronal damage is mediated through the N-methyl-D-aspartate receptor (NMDAR) receptor. When deprotonated, cortical neurons release tis-active t-PA that interacts with and cleaves the NR1 subunit of the NMDA receptor. Moreover, the treatment with recombinant t-PA leads to a 37% increase in NMDA-stimulated Ca2+ fluxneurons, which may reflect an increased NMDA-receptor function. These results were confirmed in vivo by the intracranial injection of recombinant t-PA, which potentiated the excitotoxic lesions induced by NMDA. These data provide insight into the regulation of NMDA-receptor-mediated signaling and could indicate therapeutic strategies to improve the efficacy of t-PA treatment in man.

POC studies in Stroke *(ischem. & hemorr.)*

Trans. Stroke Research (IF: 7)

tPA-NMDAR Signaling Blockade Reduces the Incidence of Intracerebral Aneurysms

Cell Death & Disease (IF: 8.5)

Tissue-type plasminogen activator controls neuronal death by raising surface dynamics of extrasynaptic NMDA receptors

Neuropharmacol. (IF: 5.5)

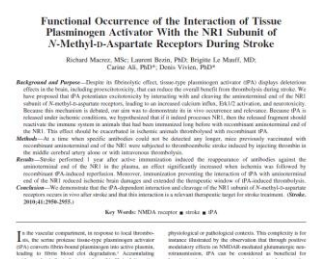
Neuropharmacology

Immunotherapy blocking the tissue plasminogen activator-dependent activation of N-methyl-D-aspartate glutamate receptors improves hemorrhagic stroke outcome

Stroke journal (IF: 8)

Antibodies Preventing the Interaction of Tissue-Type Plasminogen Activator With N-Methyl-D-Aspartate Receptors Reduce Stroke Damages and Extend the Therapeutic Window of Thrombolysis

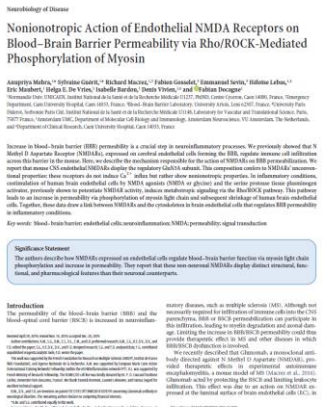
Stroke journal (IF: 8)



Functional Occurrence of the Interaction of Tissue Plasminogen Activator With the NR1 Subunit of N-Methyl-D-Aspartate Receptors During Stroke

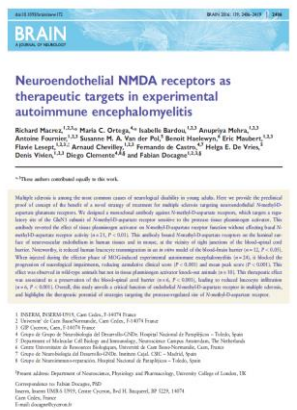
POC studies in Multiple Sclerosis

JNeurosci (IF: 6.2)



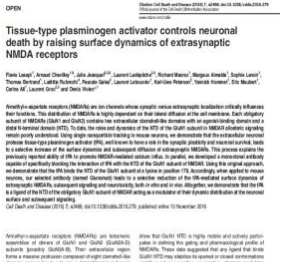
Nonionotropic Action of Endothelial NMDA Receptors on Blood–Brain Barrier Permeability via Rho/ROCK-Mediated Phosphorylation of Myosin

Brain journal (IF: 13.5)



Neuroendothelial NMDA receptors as therapeutic targets in experimental autoimmune encephalomyelitis

Cell Death & Disease (IF: 8.5)

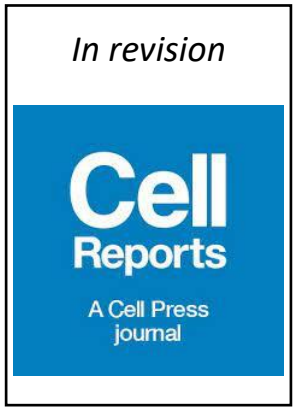


Tissue-type plasminogen activator controls neuronal death by raising surface dynamics of extrasynaptic NMDA receptors

POC studies in Parkinson's

Cell Reports (IF: 10)

In revision



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Thank you
for your attention!

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