



Blood Brain Barrier and BDNF Delivered To the Brain Using PLGA Nanoparticles

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Concept of the blood-brain barrier

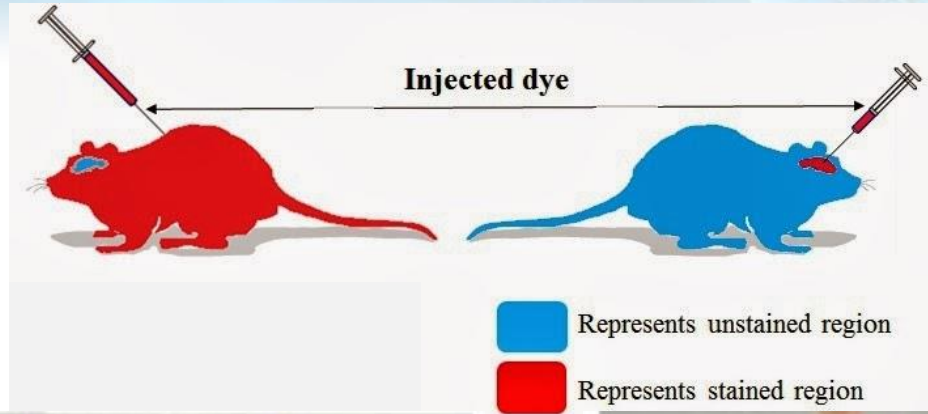
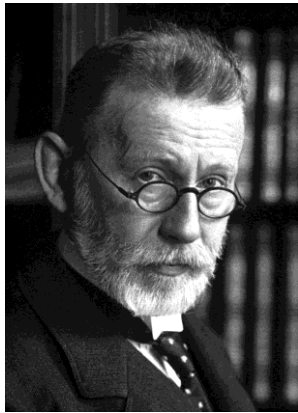


Paul Ehrlich



Edwin Goldman

Concept of the blood-brain barrier



Concept of the blood-brain barrier



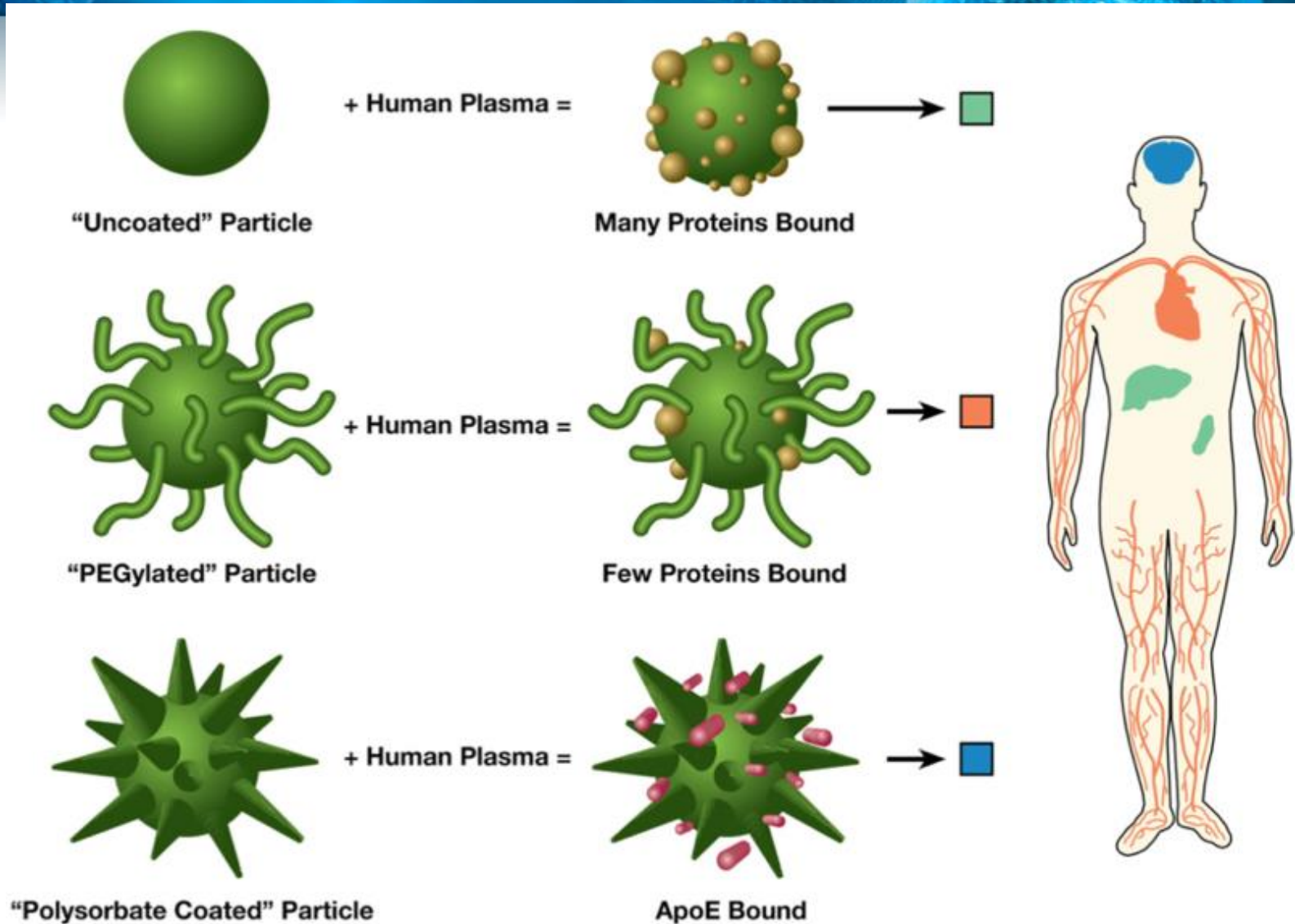
Lina Solomonovna Stern

How to overcome the blood brain barrier?

Magic bullet

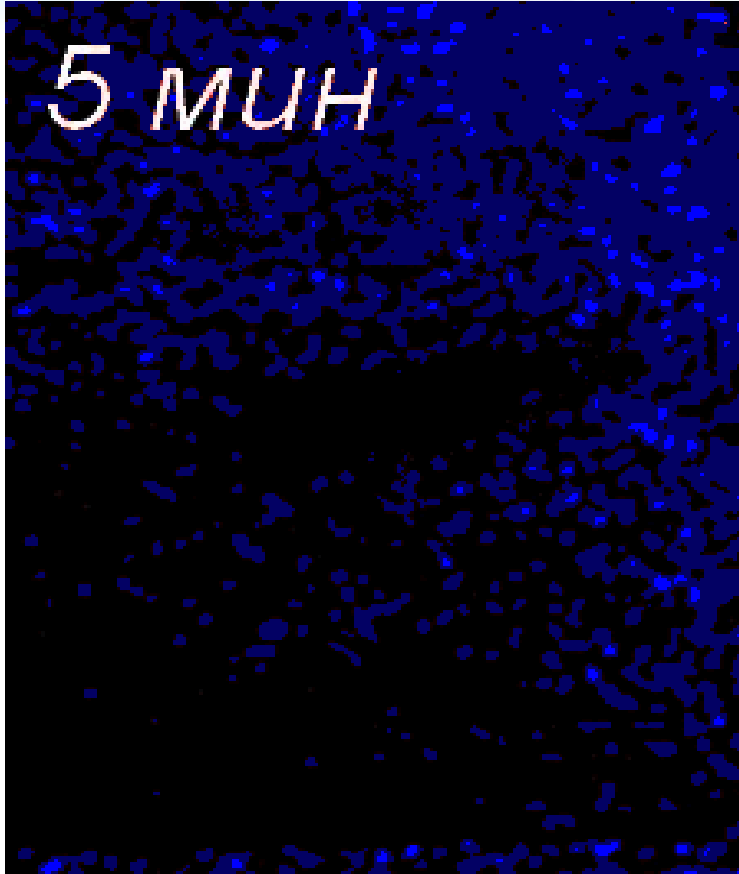


Distribution of nanoparticles depending on the modification of their surface



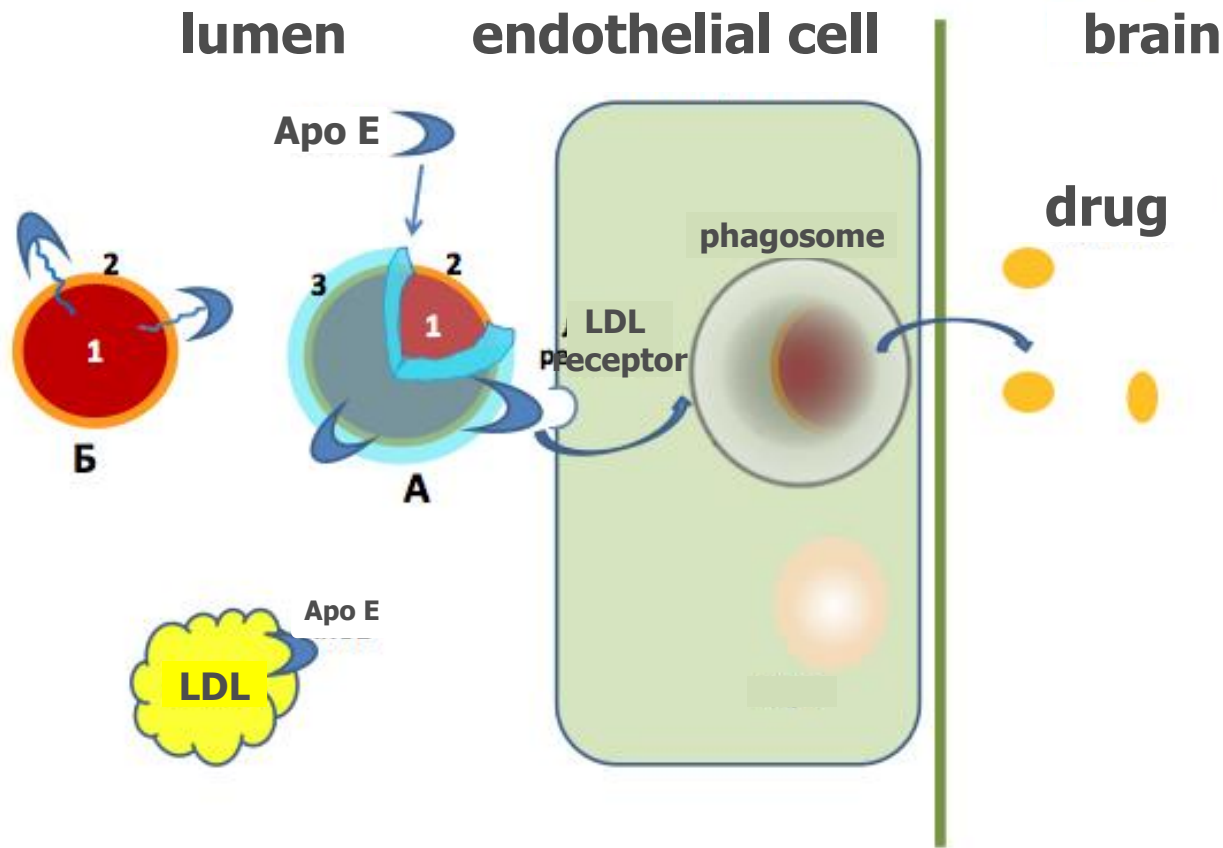
Comparison of pharmacokinetic parameters of TNF and nanoTNF

	C max мкг/мл	Vd мл	AUC мг/мл/мин	Cl мл/мин	t_{1/2}
TNF	0,32	163	20,6	2,6	26
Au-TNF	3,0	18	248	0,21	182

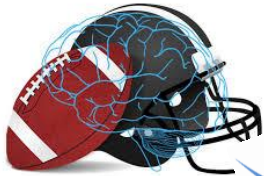
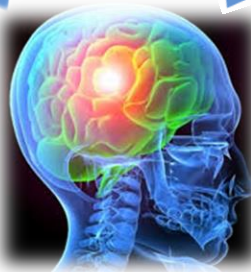


Alyautdin R. N., Reichel A., Lobenberg R., et al. Interaction of poly(butyl)cianoacrilate nanoparticles with blood-brain barrier in vivo and in vitro // J. Drug Target. - 2001. – Vol. 9. - P. 209-221

Transport of drugs through blood brain barrier

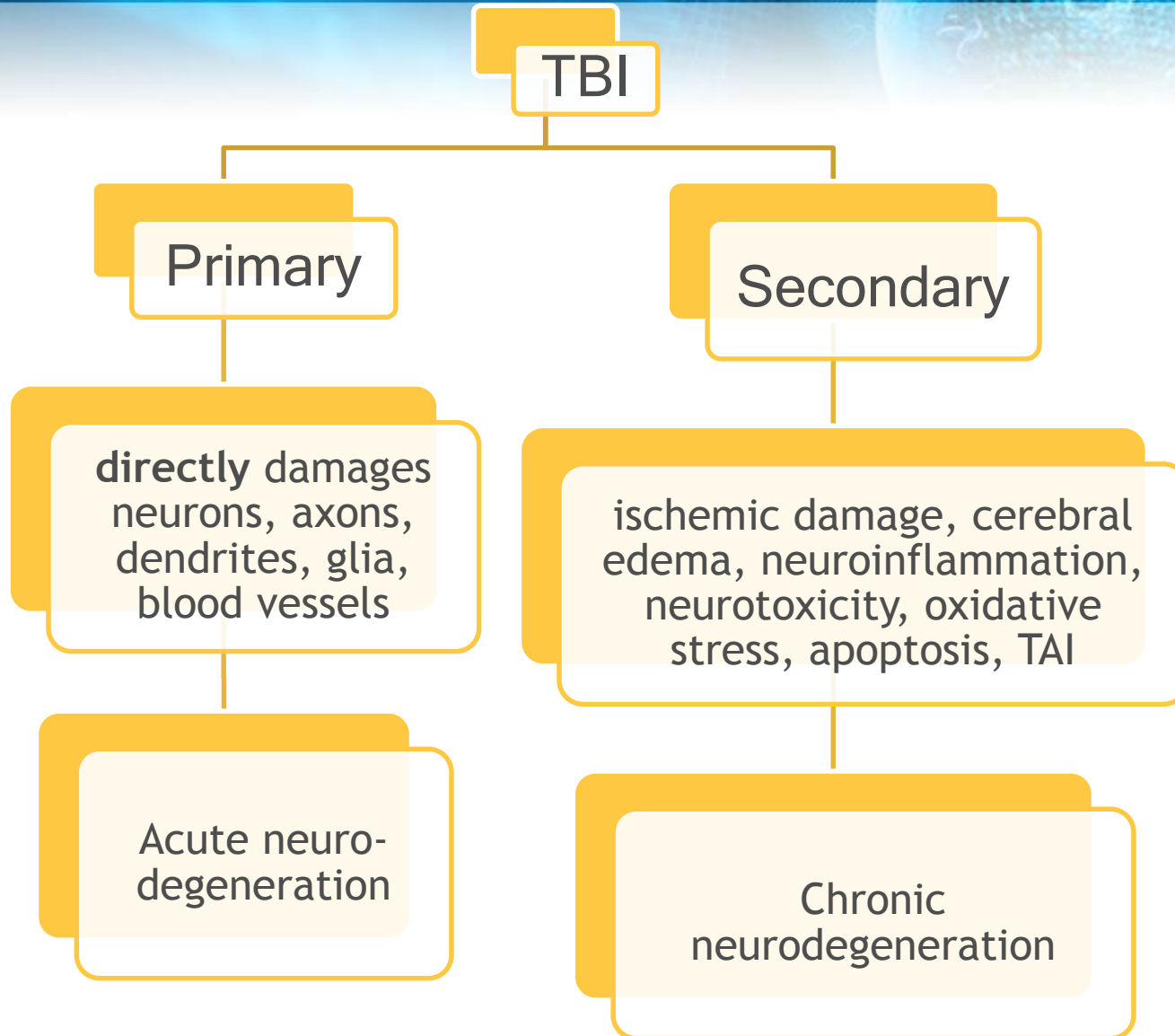


Traumatic Brain Injury

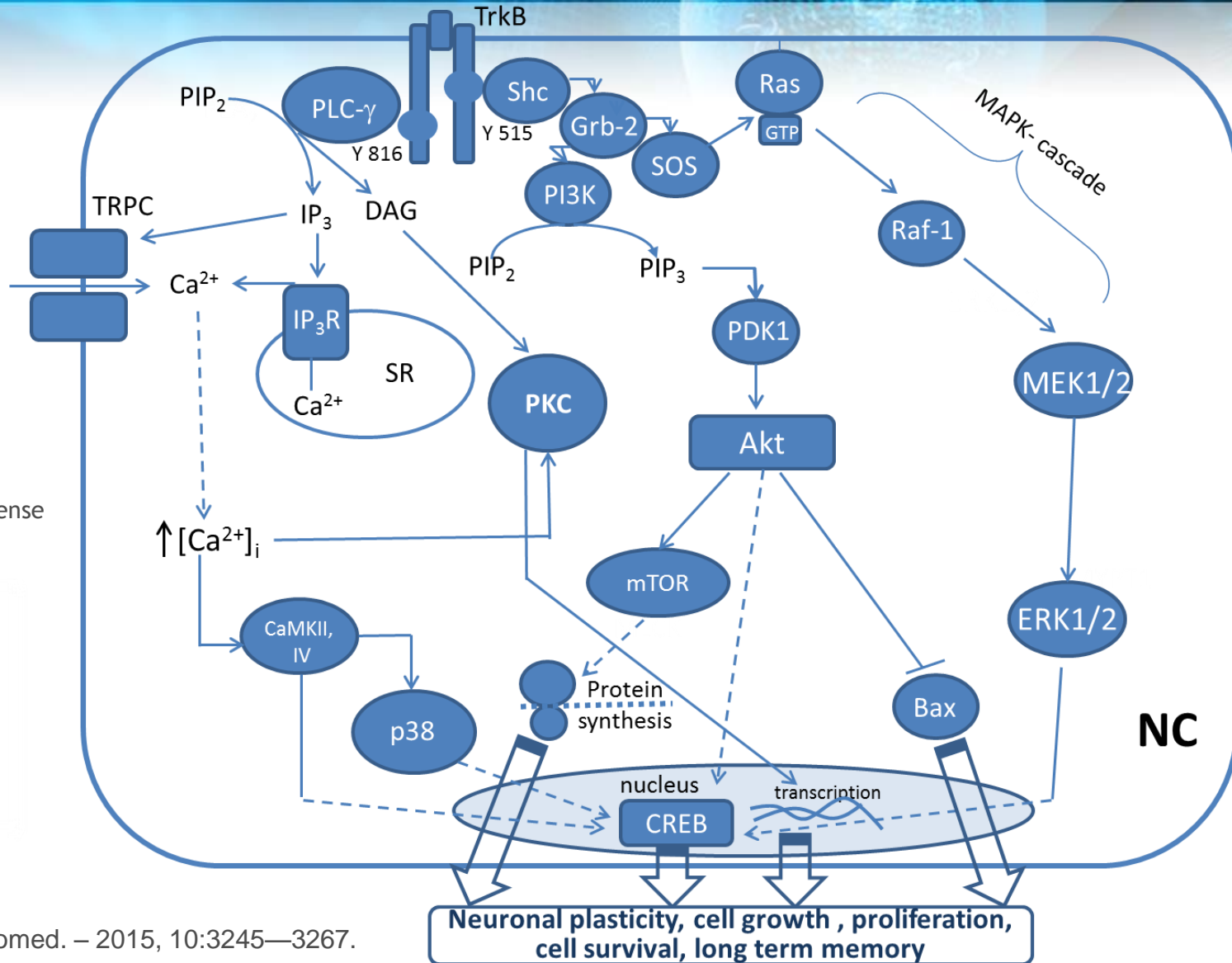
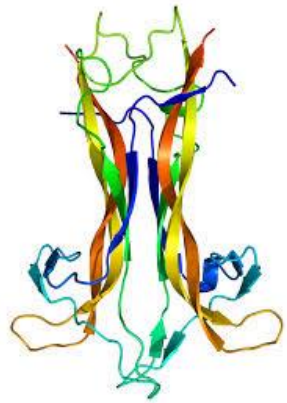


The TBI incidence is predicted to surpass many diseases as the **main cause** of death and disability by the year **2030**

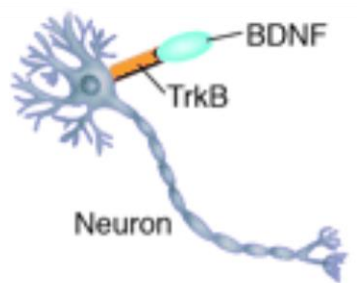
Traumatic Brain Injury



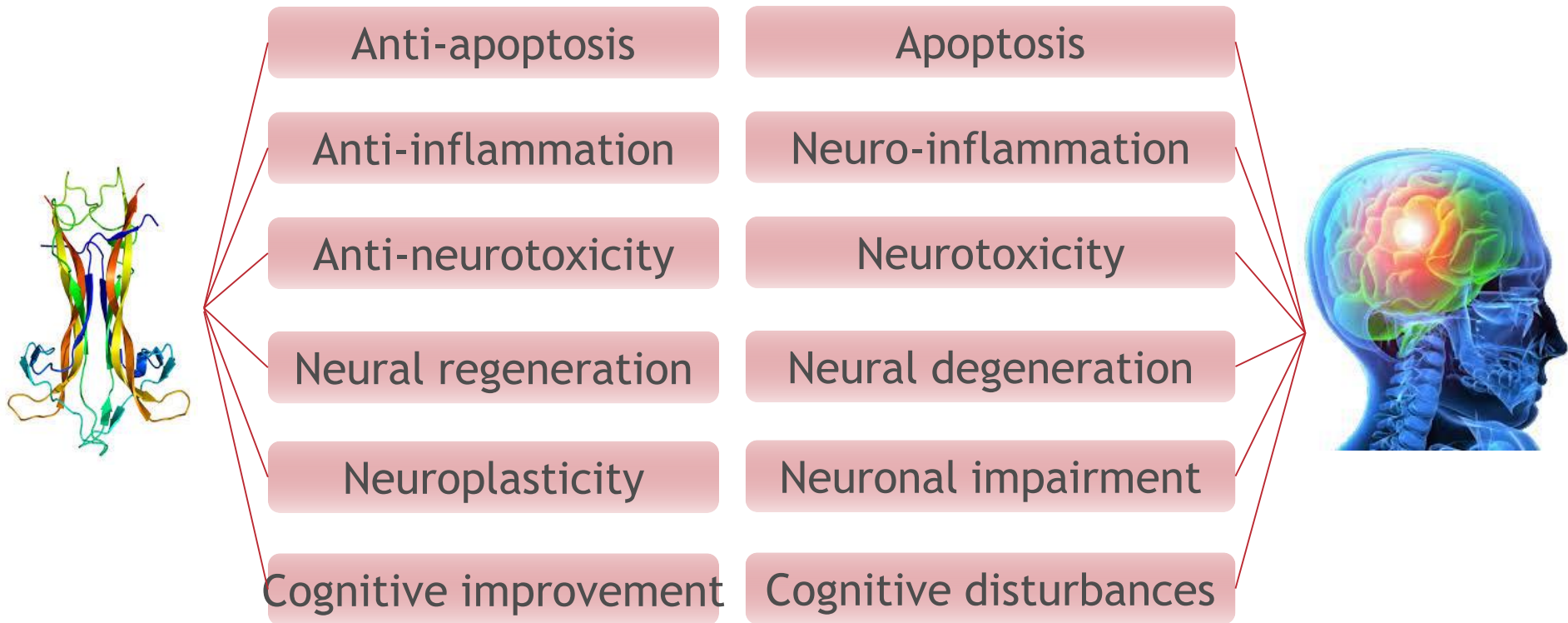
Brain-derived neurotrophic factor



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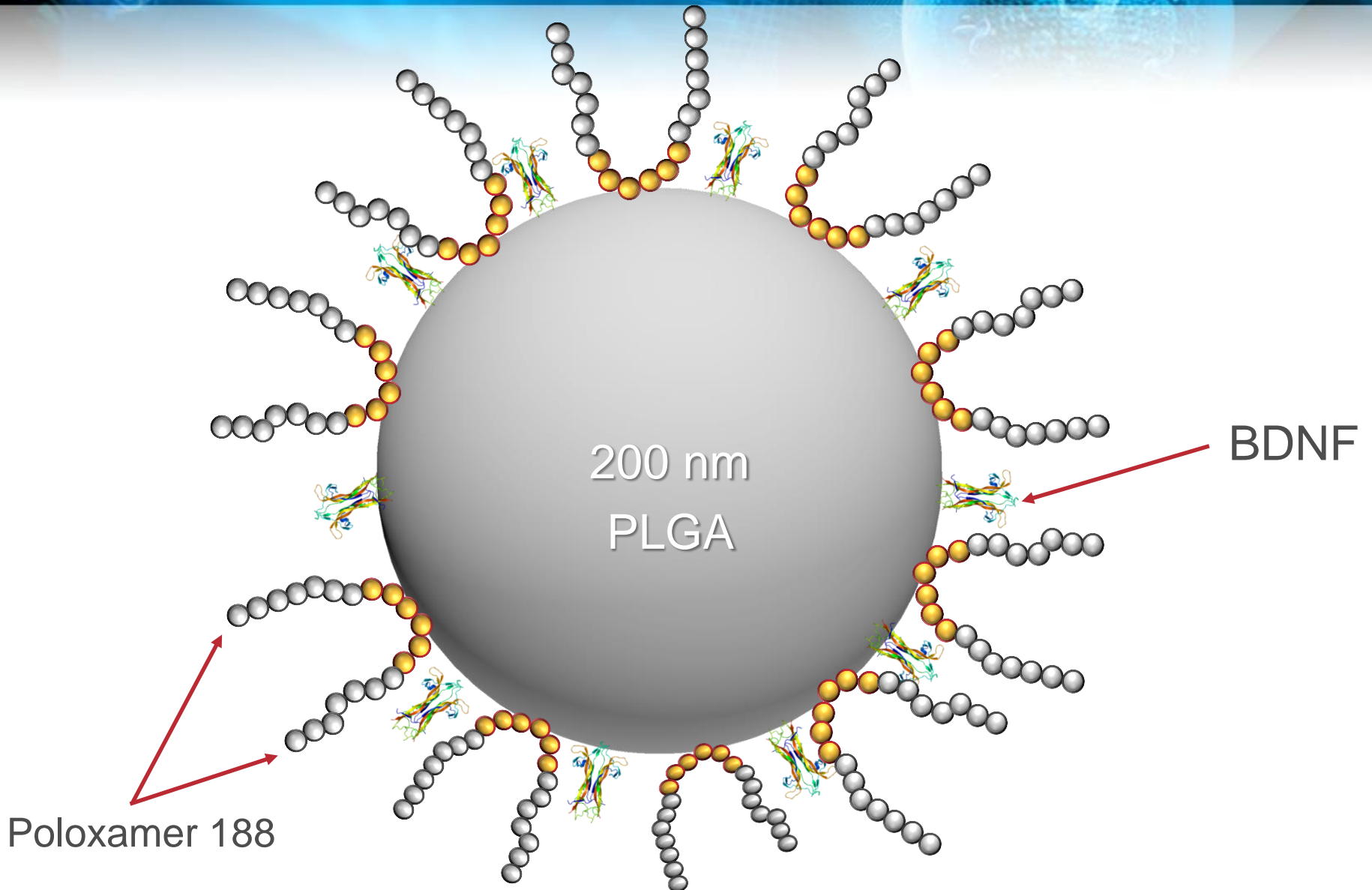


BDNF vs TBI

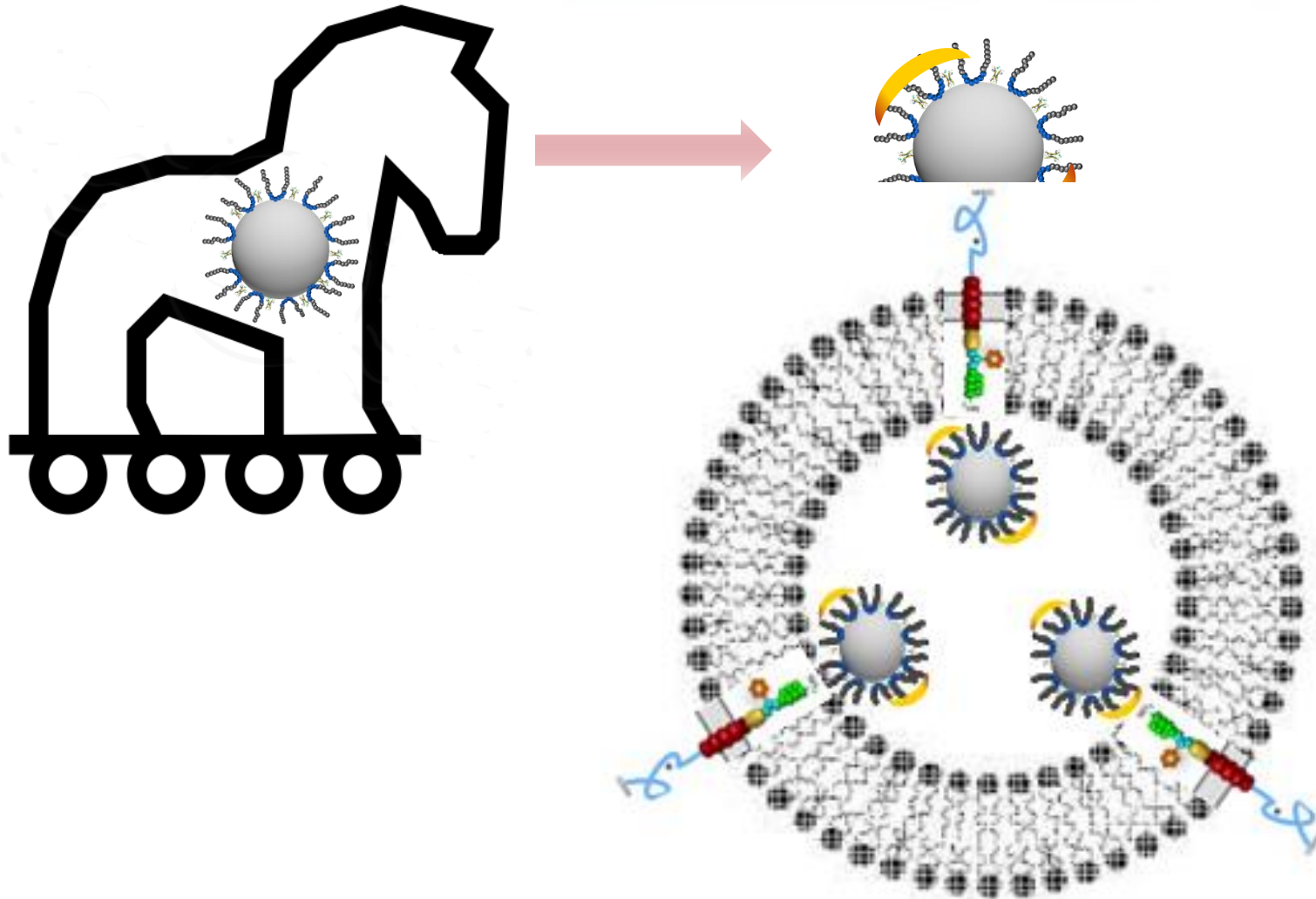


BDNF is an excellent candidate for developing new therapies for treatment of TBI?

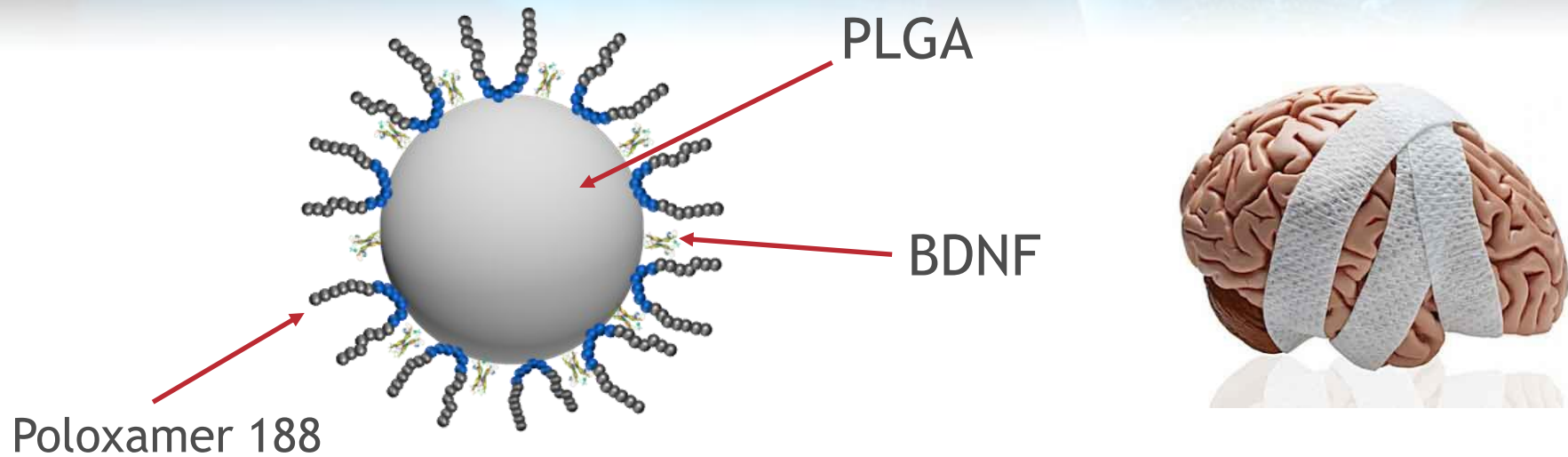
Delivery to the brain



Poloxamer 188



Objectives



- ✓ To design NPs, capable to transport BDNF through BBB.
- ✓ To evaluate efficacy of BDNF brain targeting.
- ✓ To evaluate efficacy of the neuroprotective action of the compound using the model of TBI.

Experiment design



- 1. BDNF adsorption**
- 2. BDNF delivery**
- 3. BDNF effect**

Experimental TBI

PROTOCOL

Mouse closed head injury model induced by a weight-drop device

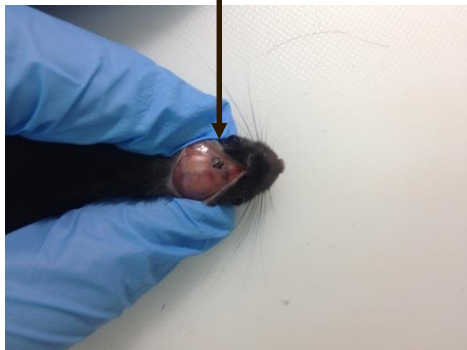
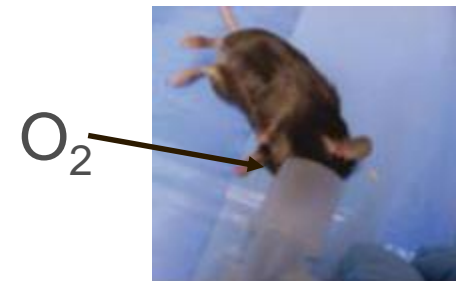
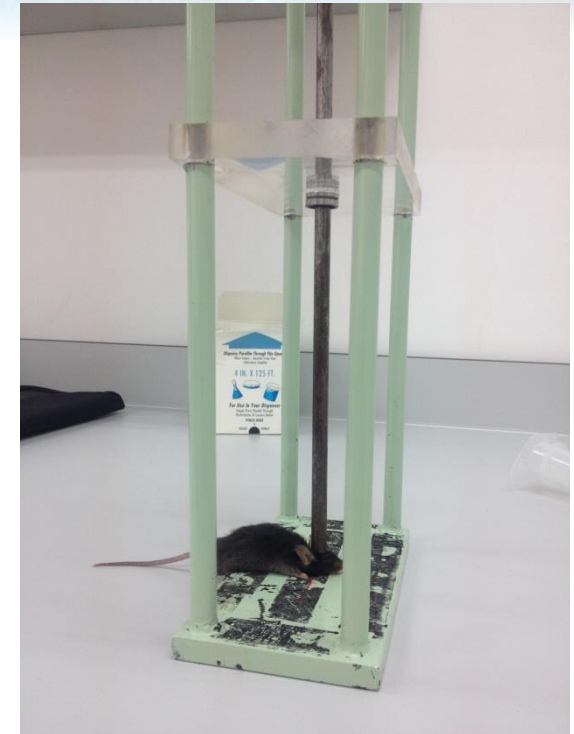
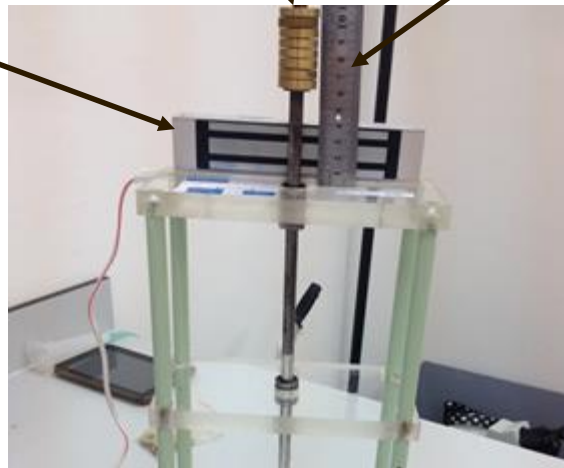
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Flierl, et al. *Nature protocols* 4.9 (2009): 1328-1337

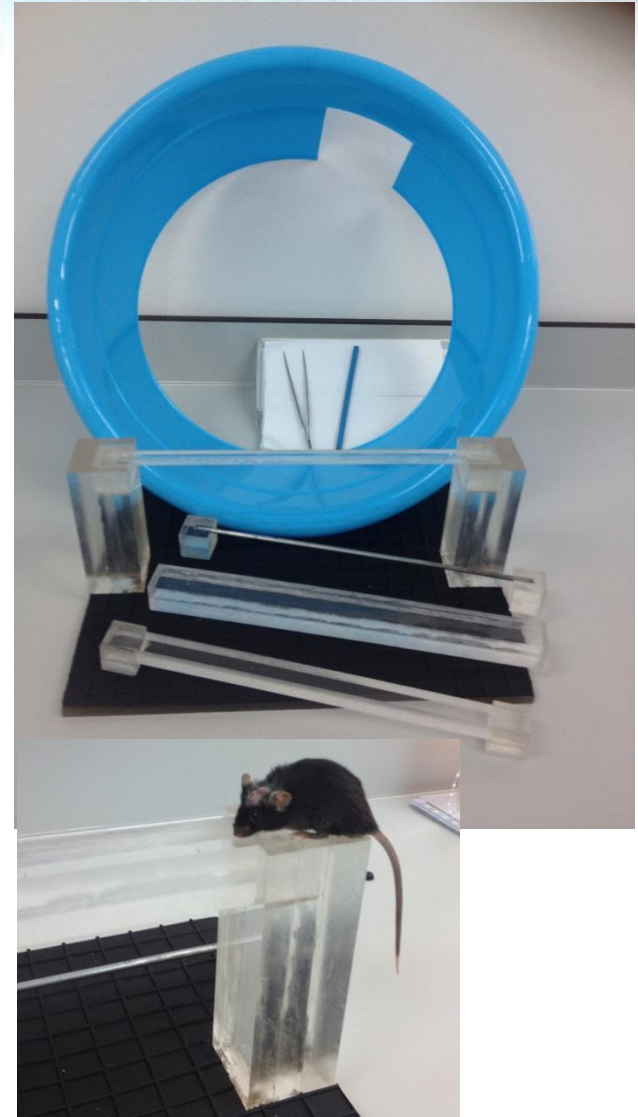
weight
height
magnet
Target area



TBI evaluation

Neurological severity score (NSS)

No	Task	Score
1	Exit circle within 3 min	1
2	Seeking behavior	1
3	Startle reflex	1
4	Straight walk	1
5	Mono- or hemiparesis	1
6	Balance on 0.7-cm-wide beam during 10 seconds	1
7	3-cm-wide beam walk within 3 min	1
8	2-cm-wide beam walk within 3 min	1
9	1-cm-wide beam walk within 3 min	1
10	Balance on 0.5-cm-diameter round stick during 10 seconds	1

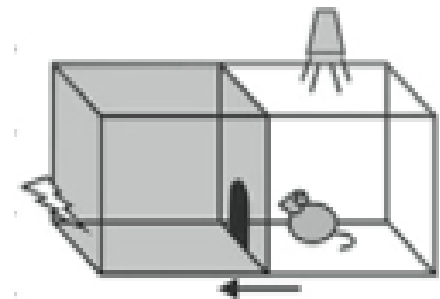


TBI evaluation

Passive avoidance (PA)



- Quick procedure for studying short- and long-term memory
- Ideal test for first screening
- Sensitive for both rats and mice



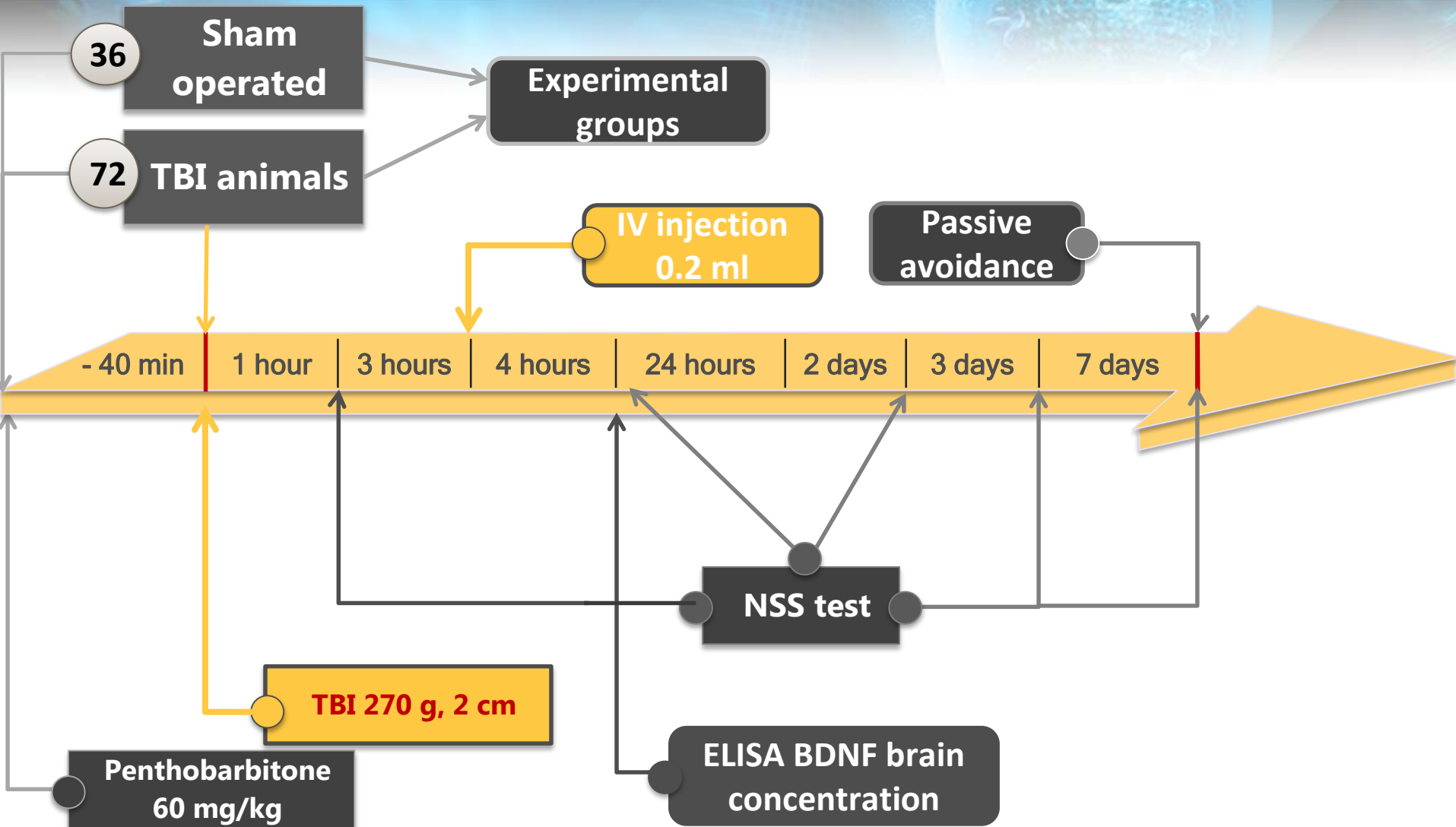
0.3 mA, 2 s, cut-off: 180 s

Experiment design

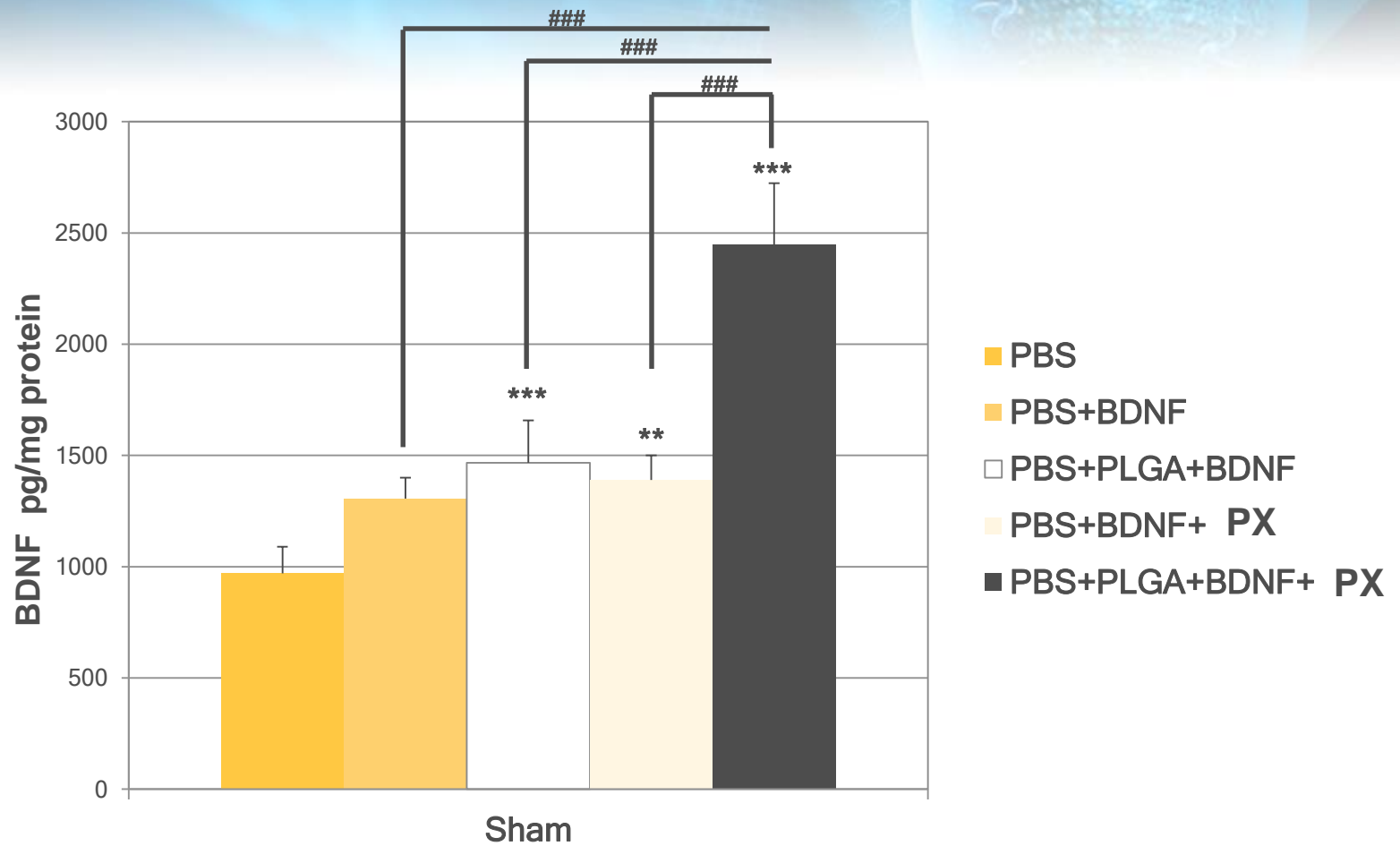
Animals (male c57Bl/6)

- 1st group - **PBS**
 - 2nd group - **PBS** + **BDNF 5 μ g**
 - 3rd group* - **PBS** + **PLGA**
 - 4th group - **PBS** + **BDNF 5 μ g** + **Pol 188**
 - 5th group - **PBS** + **PLGA** + **BDNF 5 μ g**
 - 6th group - **PBS** + **PLGA** + **BDNF 5 μ g** + **Pol 188**
- controls
-

Experiment design



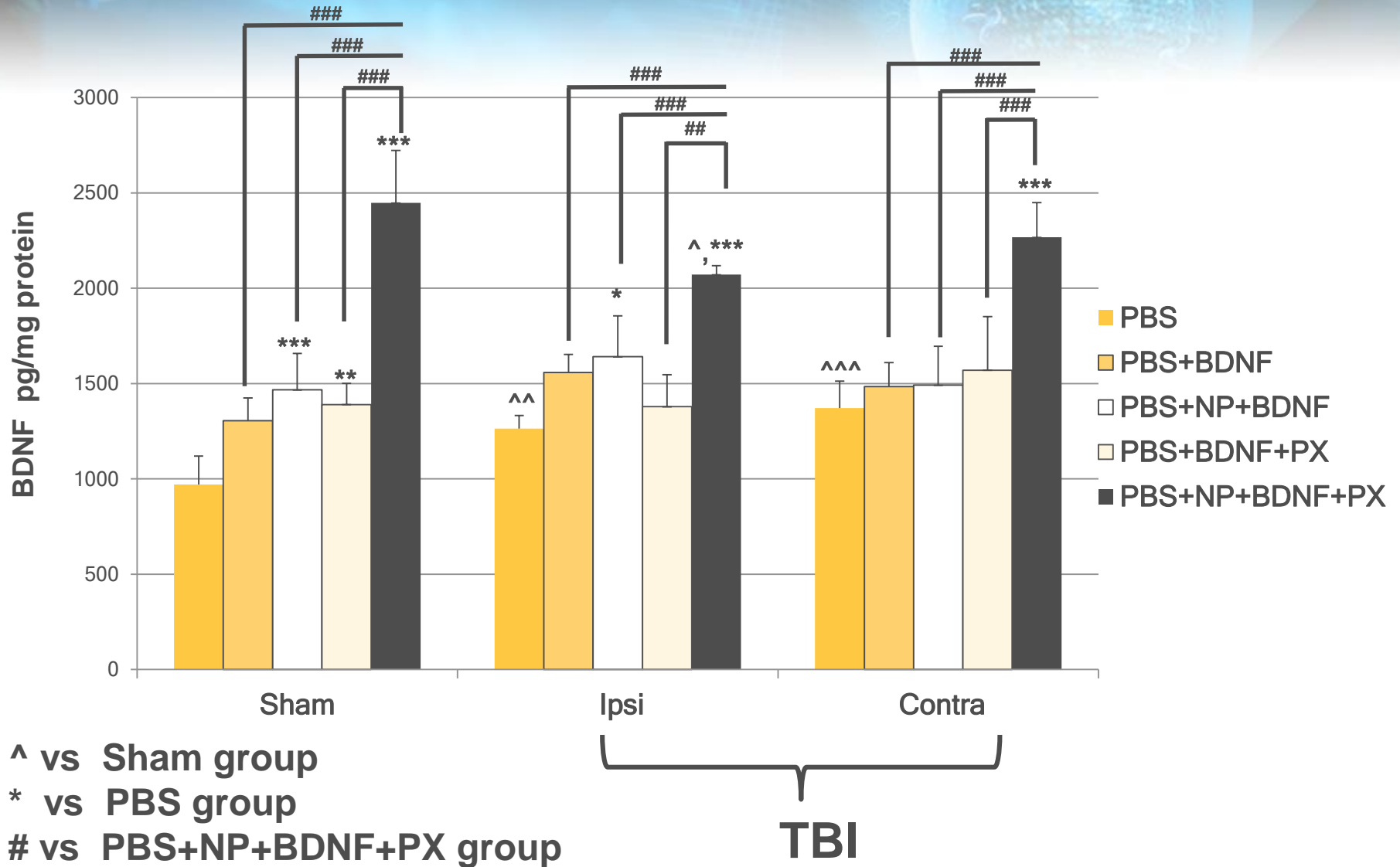
Results



* vs PBS group

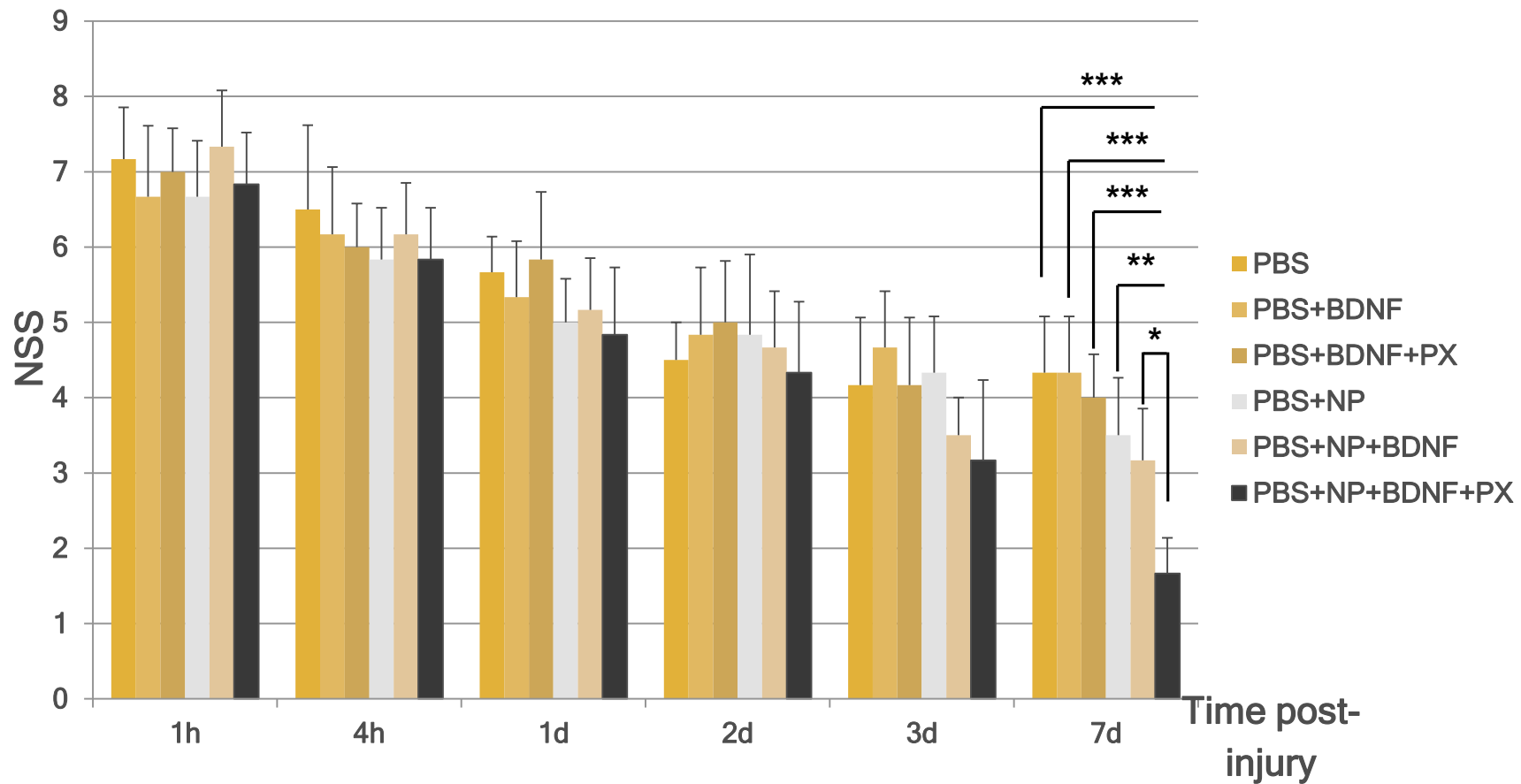
vs PBS+NP+BDNF+PX group

Results



Results

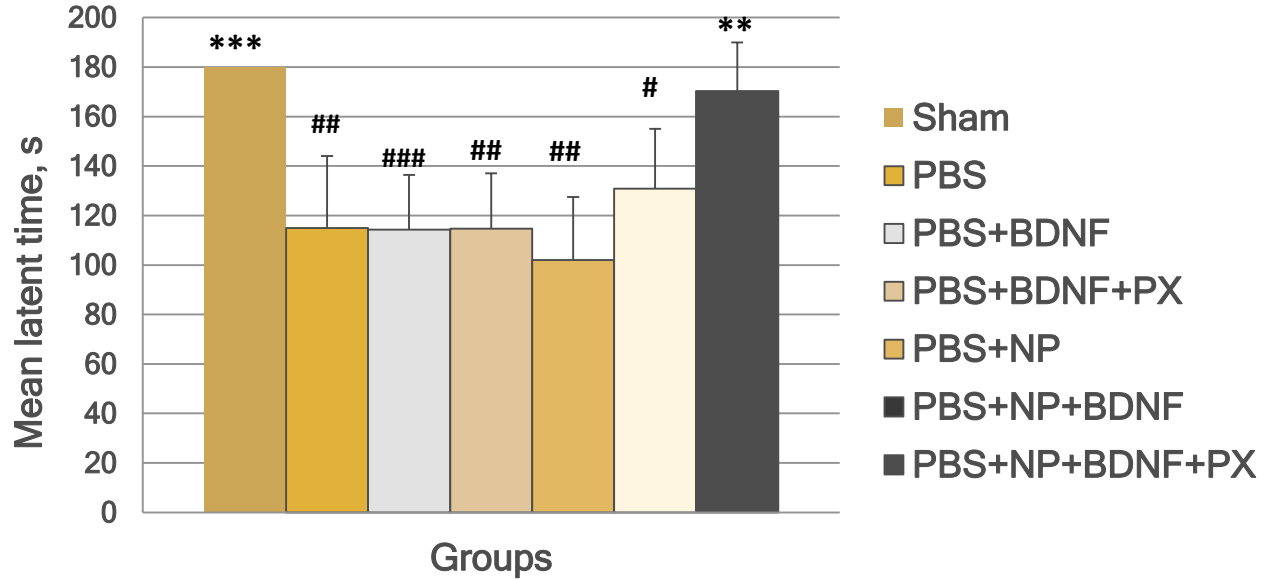
NSS 7 days after TBI



*vs PBS+NP+BDNF+PX group

Results

Passive Avoidance



* vs PBS

vs PBS+NP+BDNF+PX group

Conclusions:

- ✓ We have **designed** PLGA NPs coated by Poloxamer 188, capable of **transporting** BDNF through the BBB and providing **neuroprotective** effect in mice with TBI.
- ✓ Our study demonstrates the **potential** of using nanoparticulate delivery of BDNF into CNS in the treatment of TBI.
- ✓ We employed clinically relevant modeling of TBI, optimal time point and clinically feasible method of drug administration





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