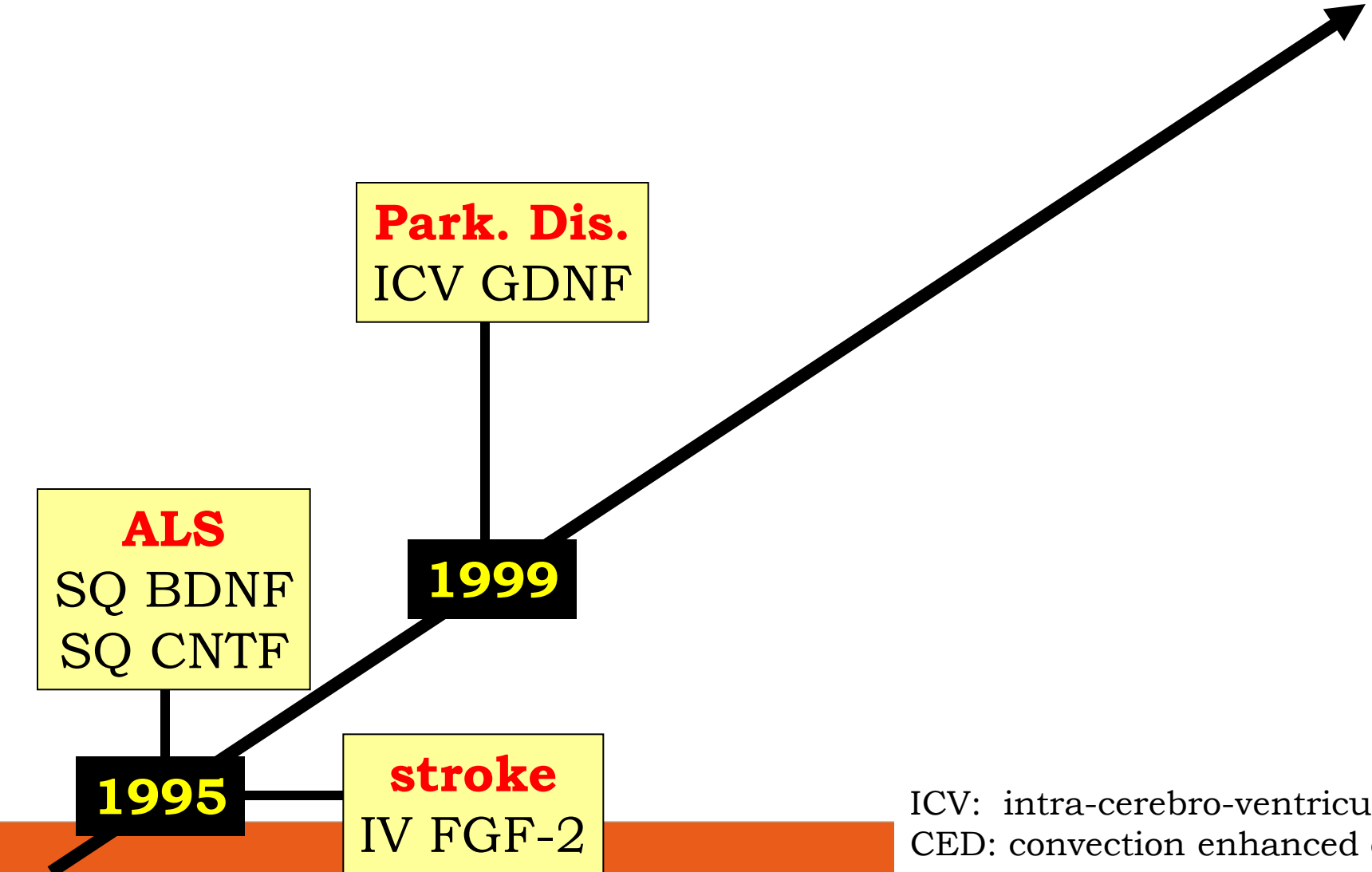
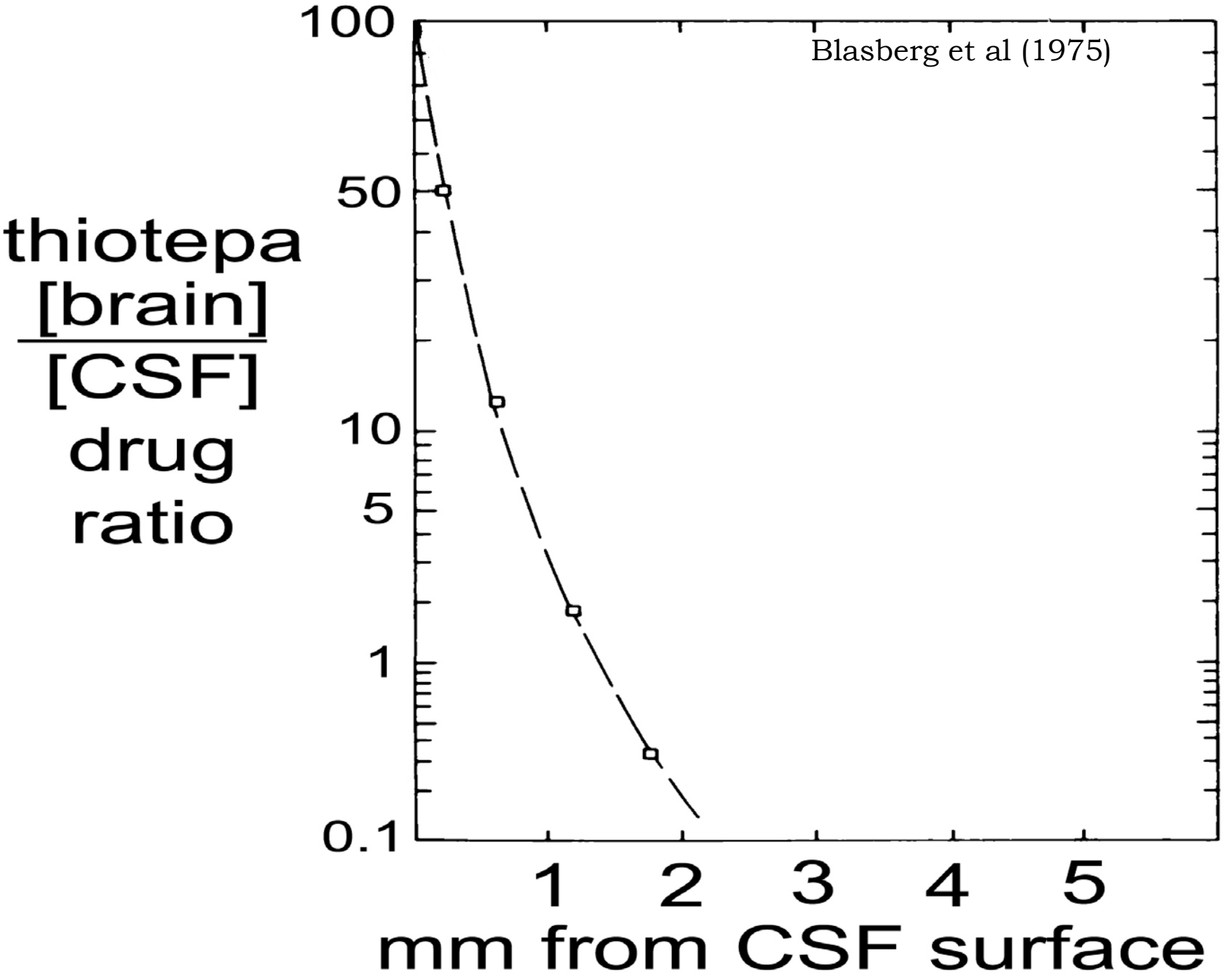
The Brain and Biotechnology

In 2017, there are no biologics that are FDA approved for CNS disease, wherein drug action requires transport into the brain across the BBB

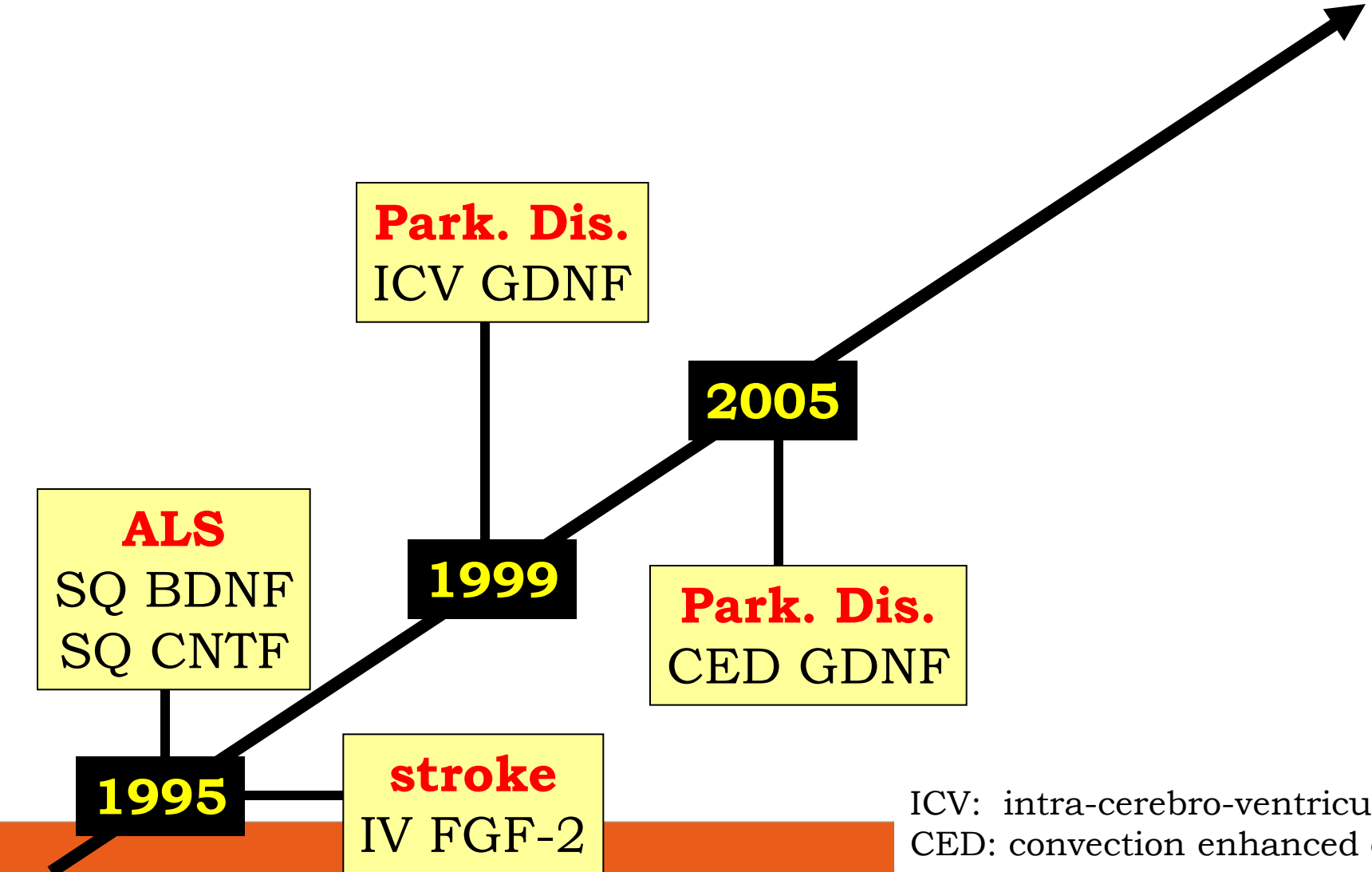
History of biologic drug development for the brain and spinal cord



ICV: intra-cerebro-ventricular
CED: convection enhanced diffusion

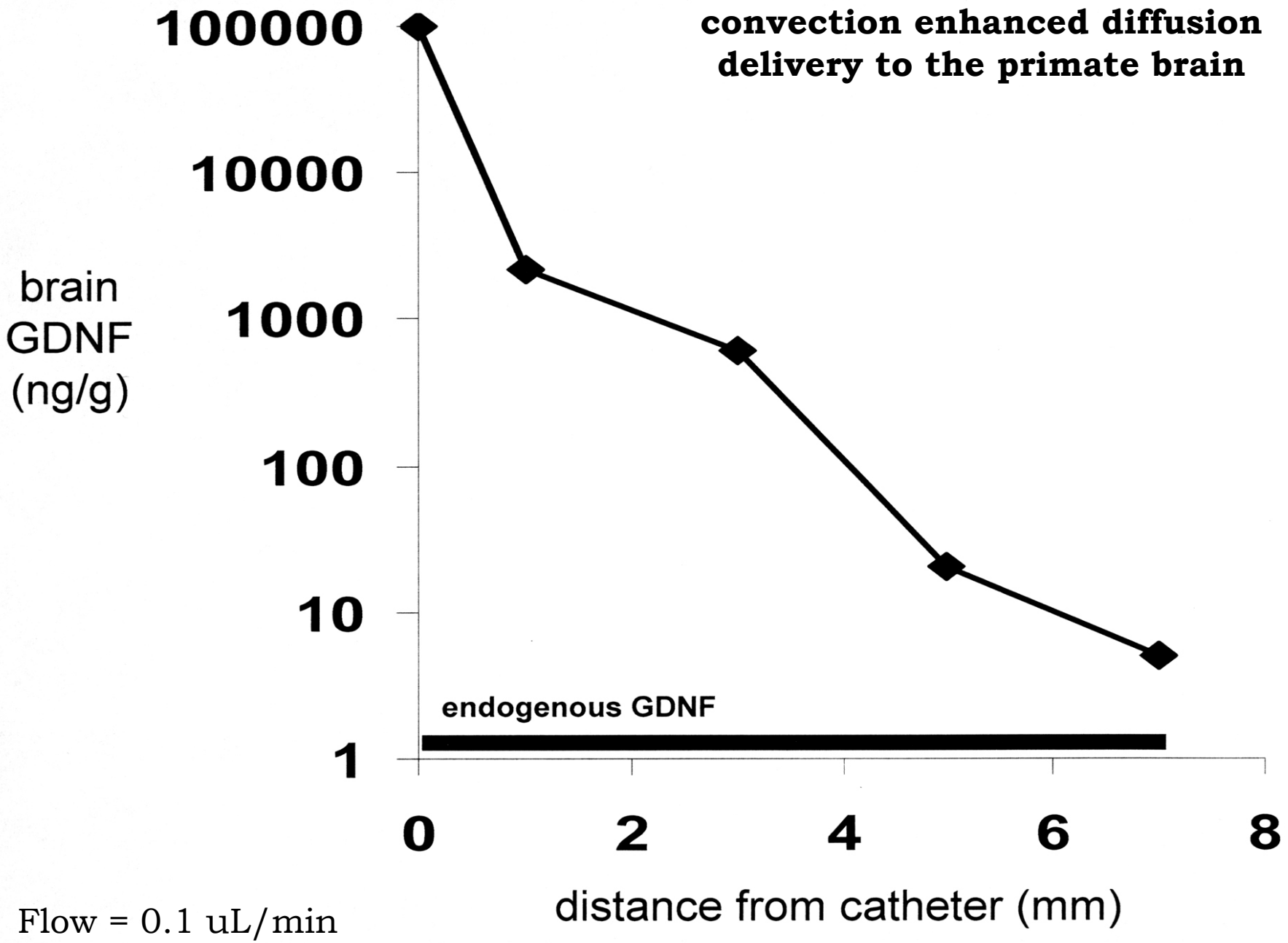

Blasberg et al (1975)
thiotepa
[brain]
[CSF]
drug
ratio
100
50
10
5
1
0.1
1
2
3
4
5
mm from CSF surface

History of biologic drug development for the brain and spinal cord



ICV: intra-cerebro-ventricular
CED: convection enhanced diffusion

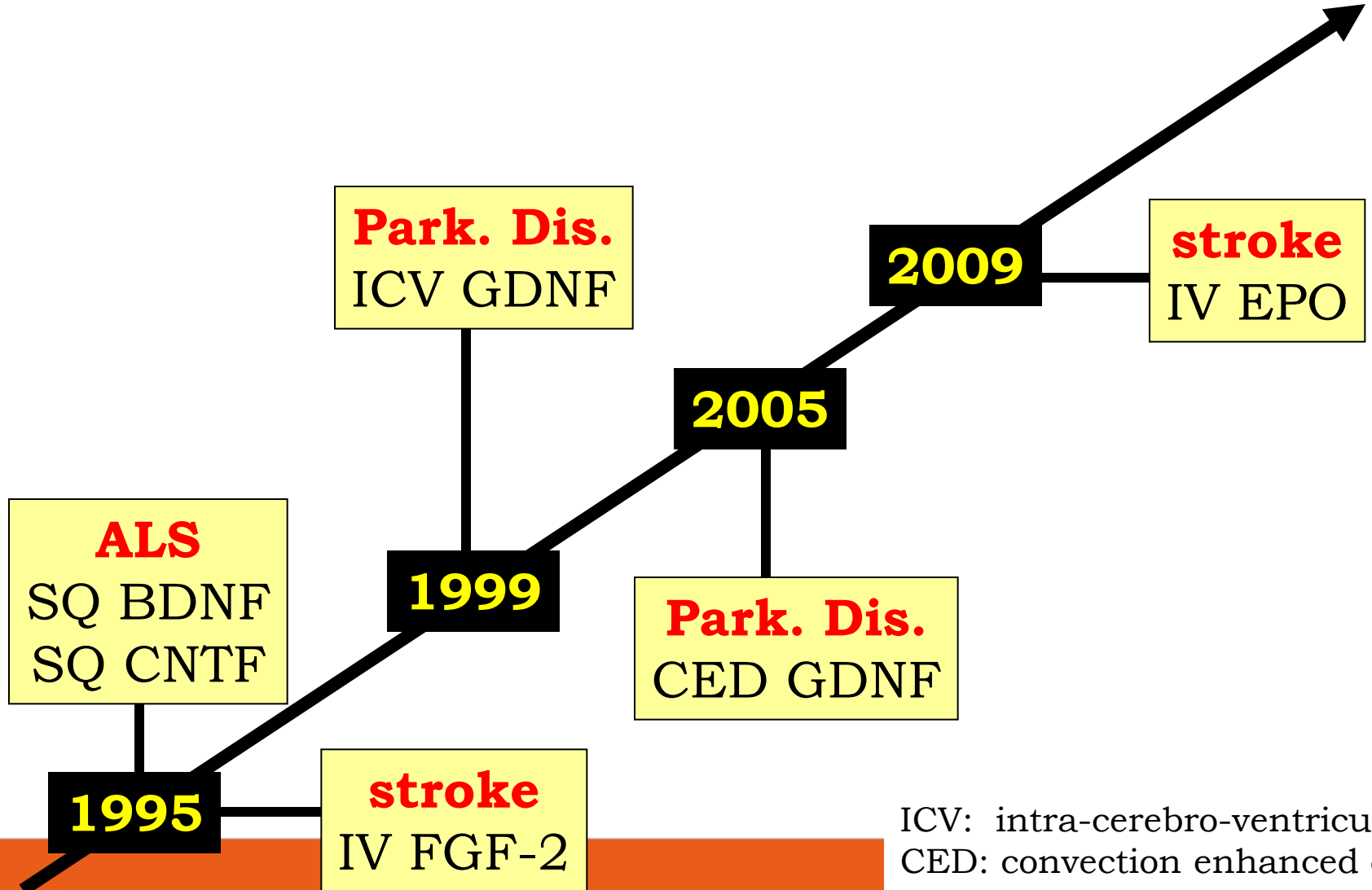
Brain [GDNF] after 7 days of convection enhanced diffusion delivery to the primate brain



Flow = 0.1 uL/min

Salvatore et al (2006)

History of biologic drug development for the brain and spinal cord



ICV: intra-cerebro-ventricular
CED: convection enhanced diffusion

Brain uptake of biologic drugs:
CSF as surrogate measure of brain penetration

2017 Press Release

"Robust CNS Penetration" of therapeutic antibody for Parkinson's disease based on finding of CSF/plasma ratio of 0.3%

Antibody distribution into CSF reflects transport across the choroid plexus, which forms the blood-CSF barrier

The blood-CSF barrier at the choroid plexus is anatomically distinct from the blood-brain barrier (BBB) at the capillary endothelium of brain tissue

The choroid plexus, at the blood-CSF barrier, is >100-fold leaky compared to the BBB at the brain capillary endothelium

All proteins in plasma leak across the choroid plexus at a rate inversely related to molecular weight

The CSF/plasma ratio for all plasma IgGs, none of which cross the BBB, ranges from 0.2 to 0.3%

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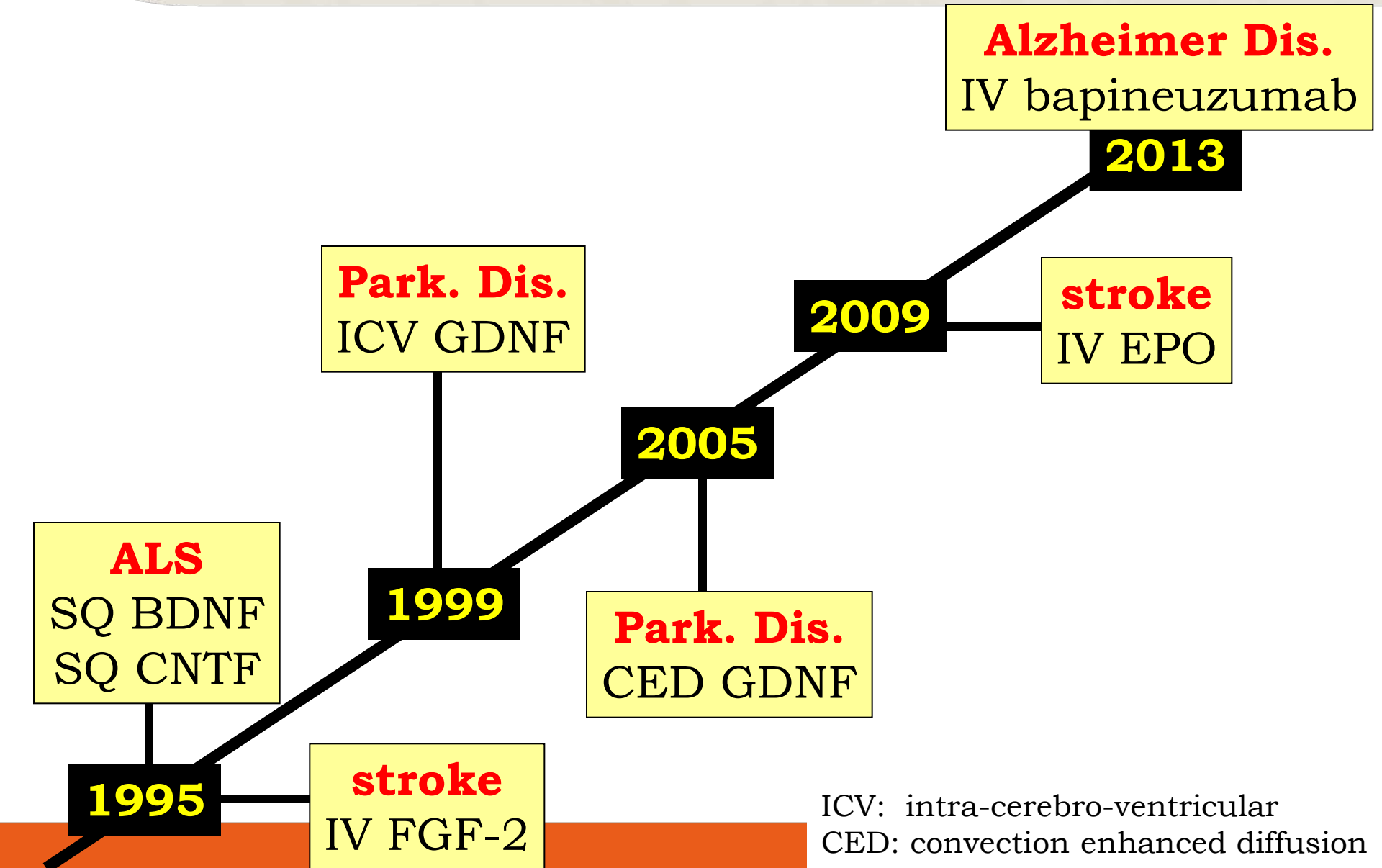
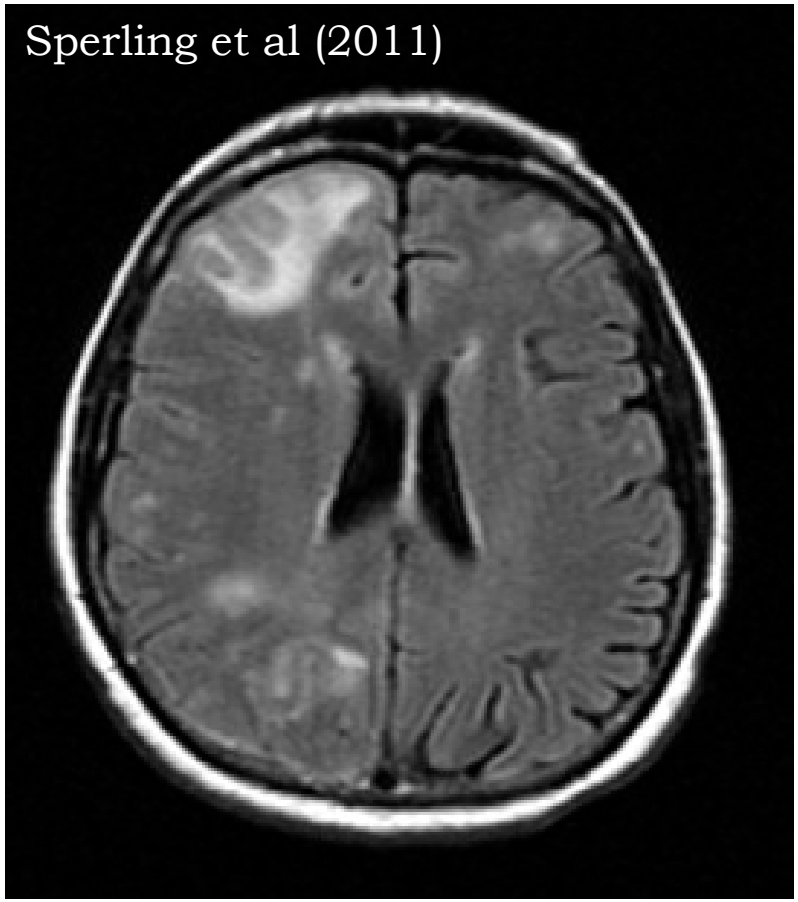
History of biologic drug development for the brain and spinal cord



ICV: intra-cerebro-ventricular
CED: convection enhanced diffusion

BBB dysfunction in antibody trials in Alzheimer's disease:

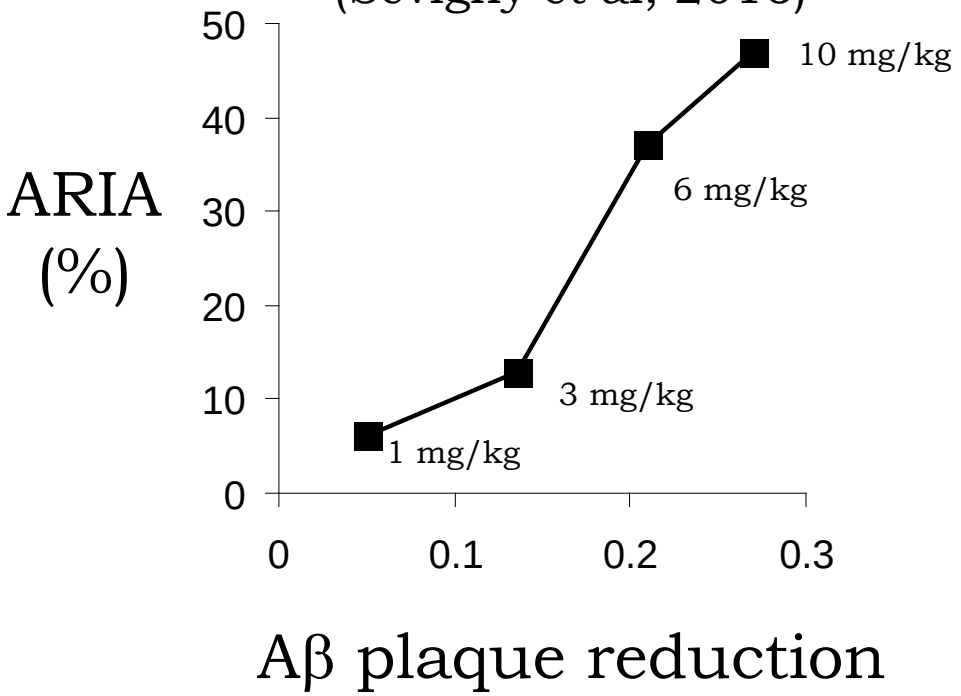
Amyloid-Related Imaging Abnormality (ARIA)



FLAIR MRI shows multiple areas of vasogenic brain edema in AD subject on bapineuzumab

Aducanumab in humans

(Sevigny et al, 2016)



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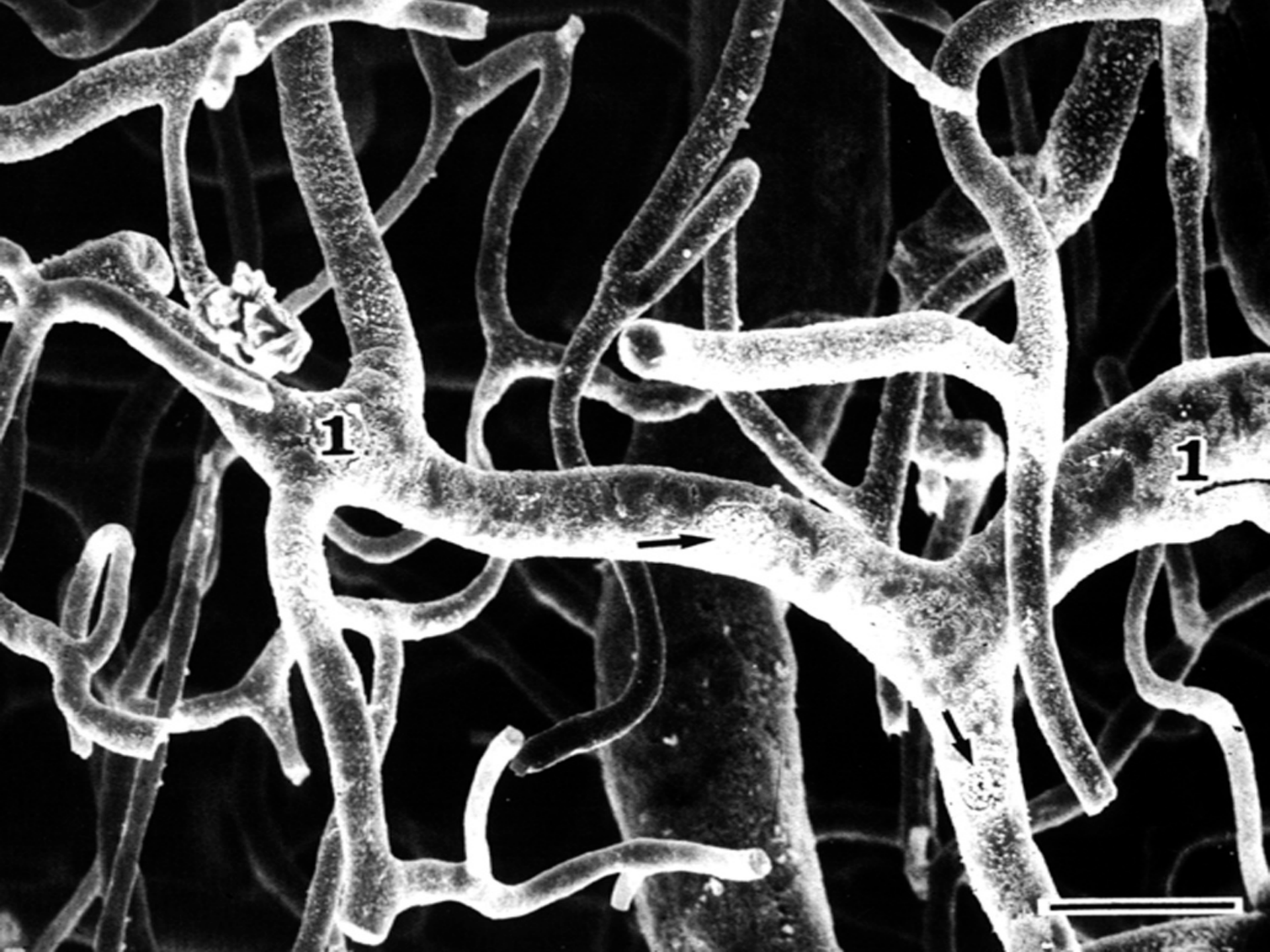
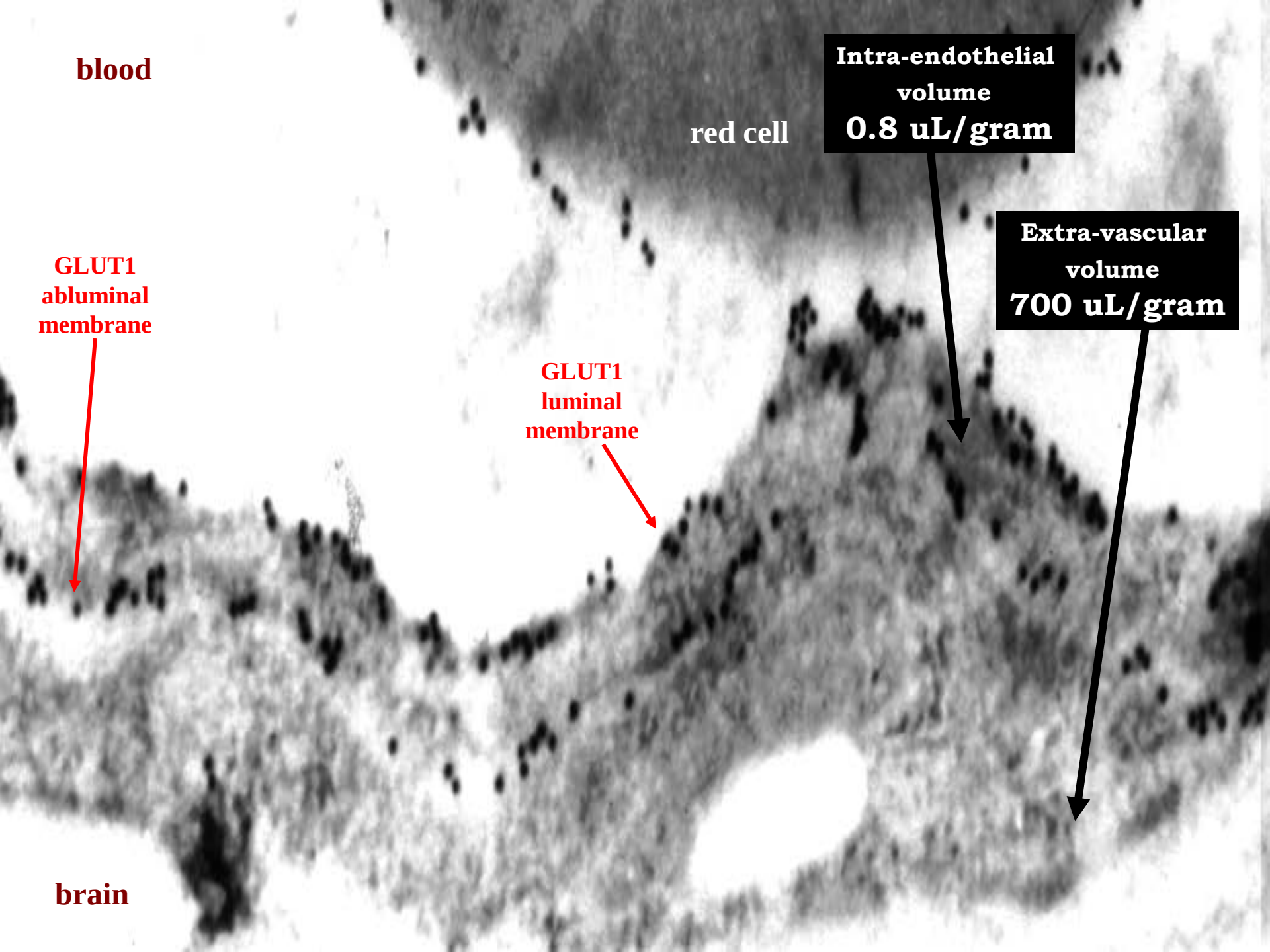
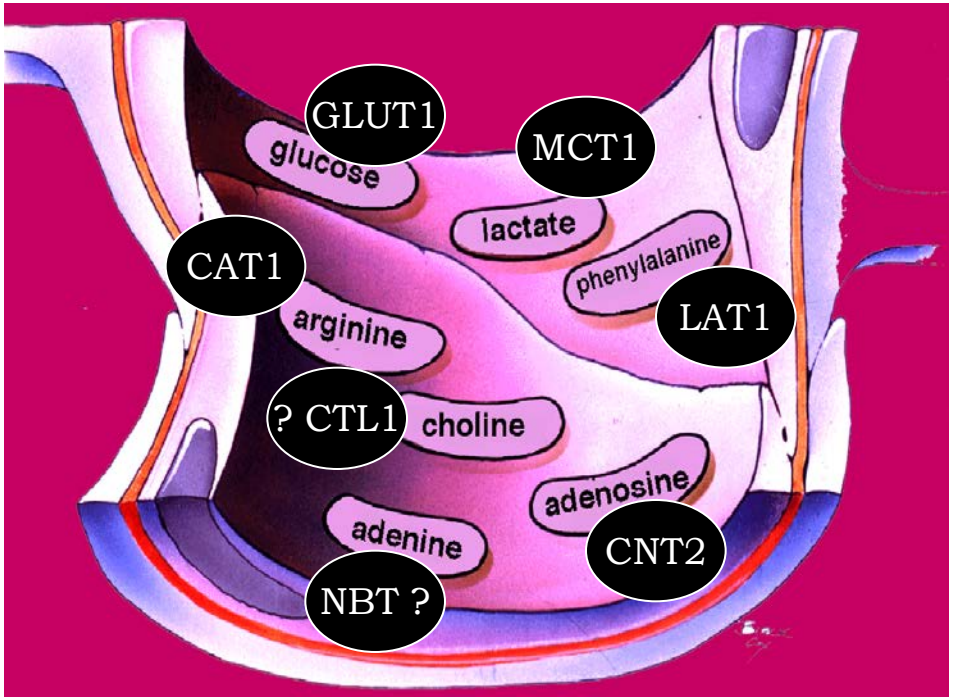
Past CNS Clinical Trials with Biologics and no BBB Delivery Technology

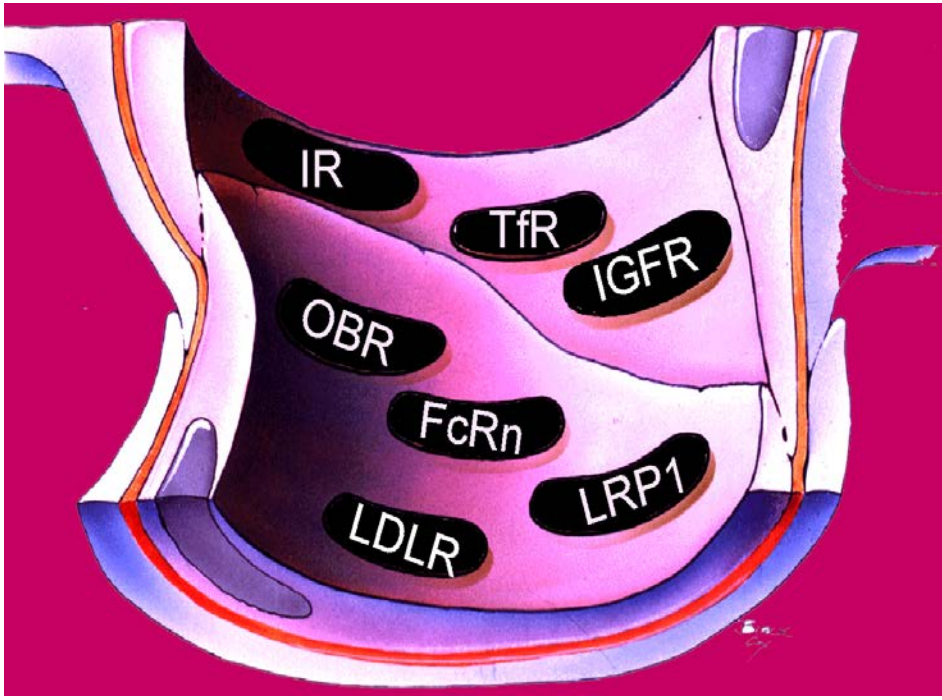
	disease	drug	BBB	Result
1	ALS	BDNF	Not considered	Fail
2	stroke	FGF-2	BBB said to be disrupted	Fail
3	PD	GDNF	Bypass BBB with CSF	Fail
4	PD	GDNF	Bypass BBB with CED	Fail
5	stroke	EPO	Use CSF as index of BBB	Fail
6	AD	Bapineu-zumab	Drug induces BBB disruption	Fail


1
1


blood
red cell
Intra-endothelial volume
0.8 uL/gram
Extra-vascular volume
700 uL/gram
GLUT1 abluminal membrane
GLUT1 luminal membrane
brain

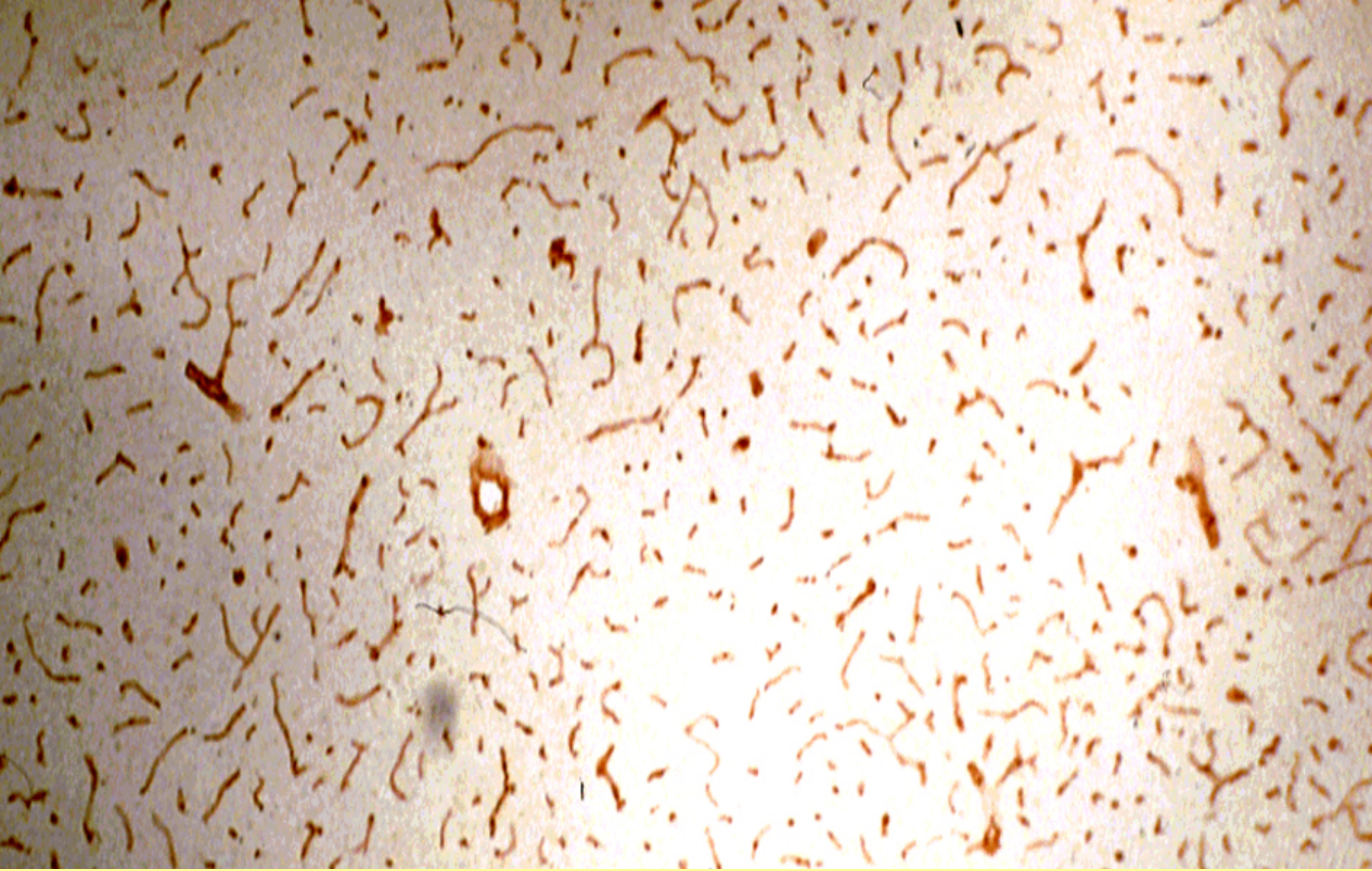
Endogenous BBB Transporters





Nutrient Transport:
Carrier-Mediated Transport

Peptide Transport:
Receptor-Mediated Transport

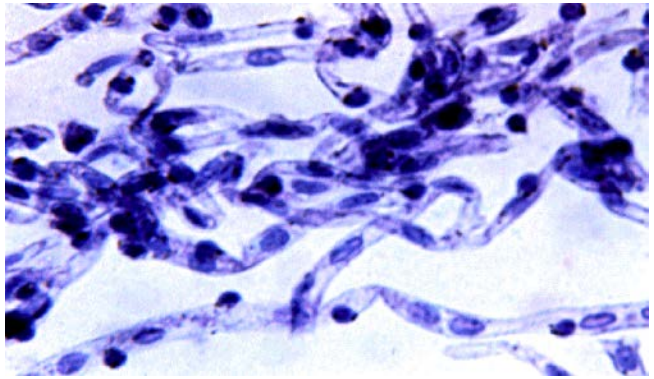


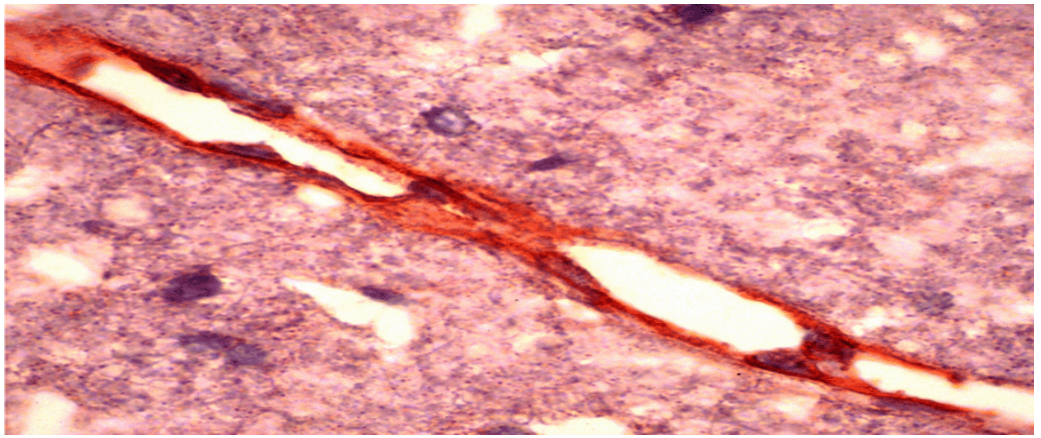
Immune-staining of capillaries in brain with an antibody to a BBB peptide receptor

Human and primate BBB insulin receptor:

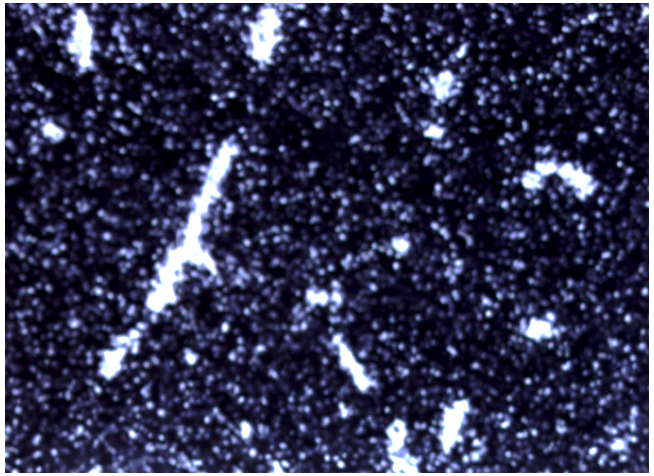
Mediates transport of insulin and an insulin receptor antibody

Human brain capillaries



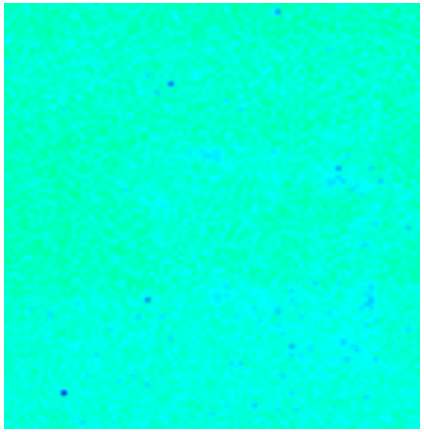


Immunocytochemistry of Rhesus monkey brain with MAb against human insulin receptor (HIR)

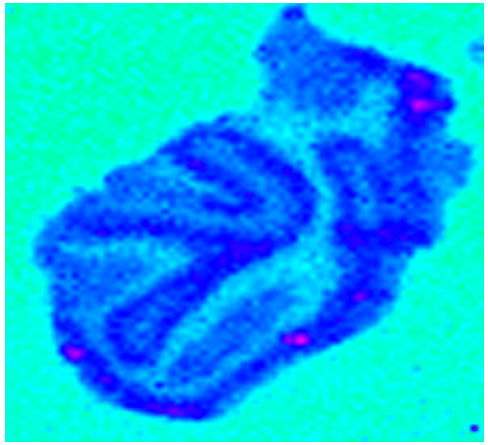


Emulsion auto-radiography of rabbit brain after carotid artery infusion of [^{125}I]-insulin

Brain scanning in Rhesus monkeys

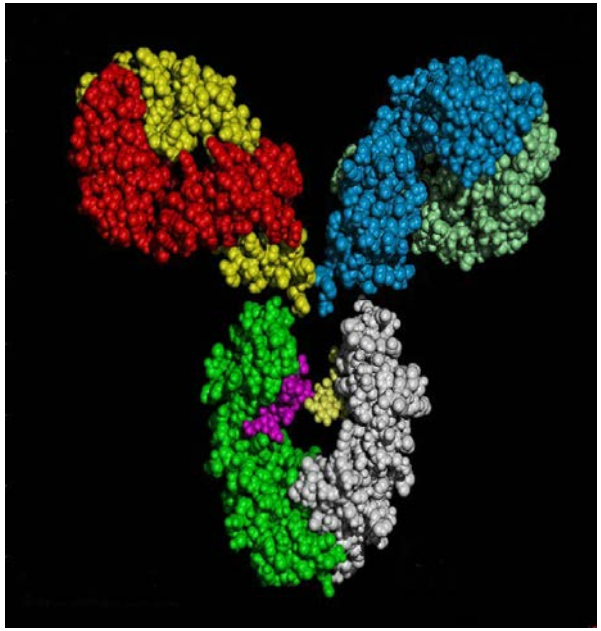


Peptide alone



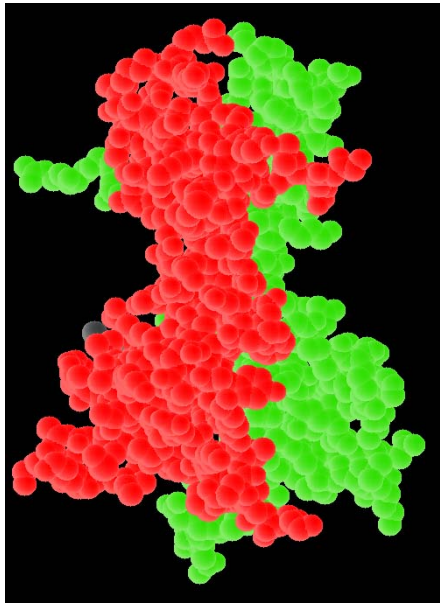
Peptide-HIRMAb

IgG Fusion Proteins for Delivery of Protein Therapeutics to the Human Brain



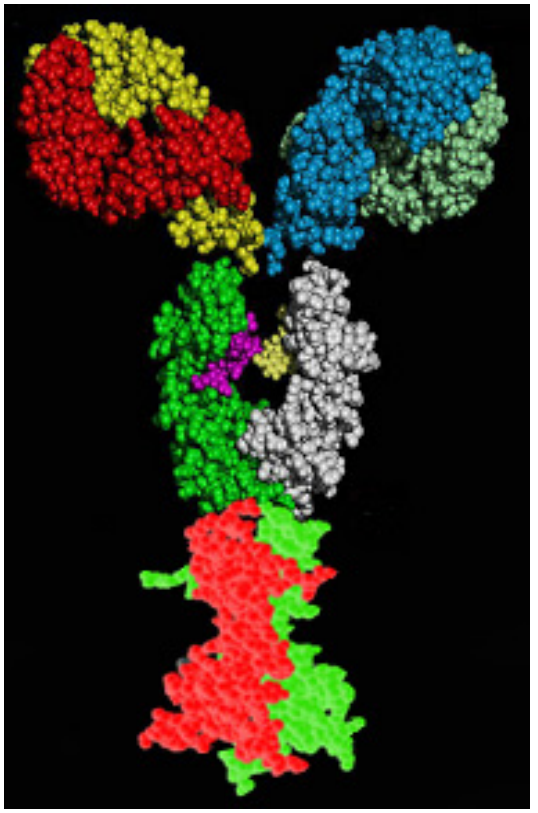
Chimeric or humanized HIRMAb

+



Recombinant protein

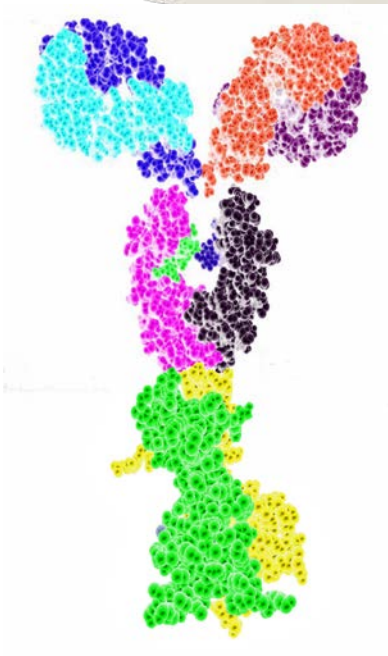
=



IgG fusion protein:
a New Biological Entity

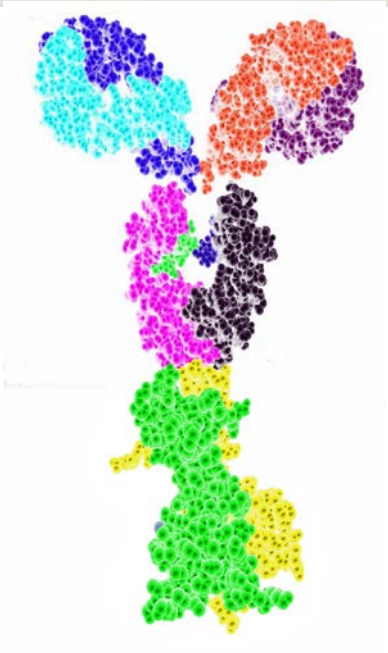
Human BBB Trojan horse fusion proteins:

Re-engineering protein therapeutics for delivery to human brain



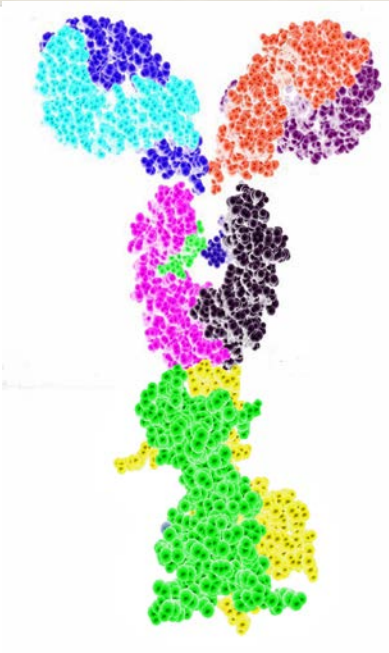
Lysosomal enzymes:

IDUA
IDS
ASA
SGSH



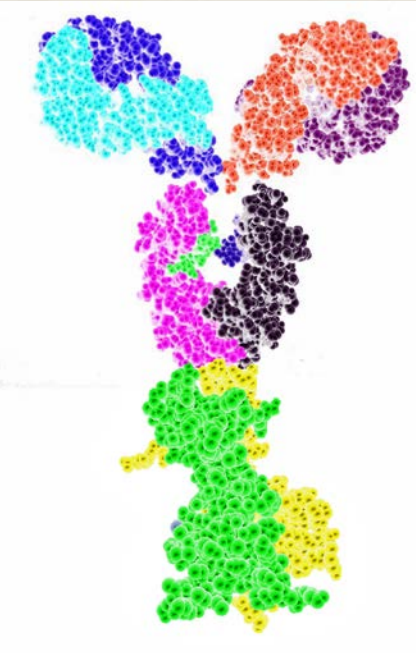
Decoy Receptors:

TNFR-II



Neuro-trophins:

EPO
GDNF



Therapeutic antibodies:

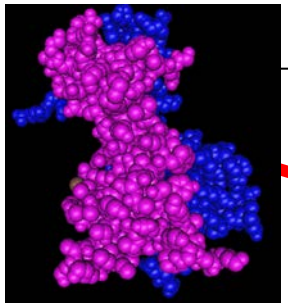
Anti-Aβ MAb

Brain scans in the Rhesus monkey:

With and Without Trojan Horse Technology

IDUA = α-L-iduronidase; lysosomal enzyme mutated in MPS-I

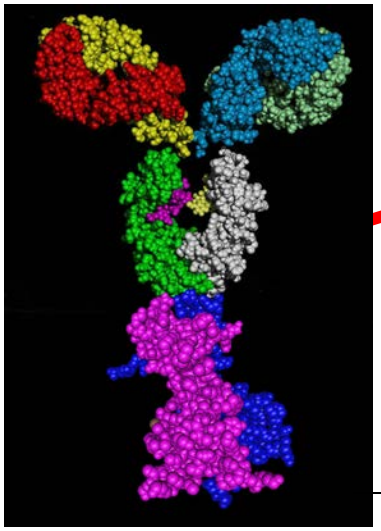
IDUA, a lysosomal enzyme



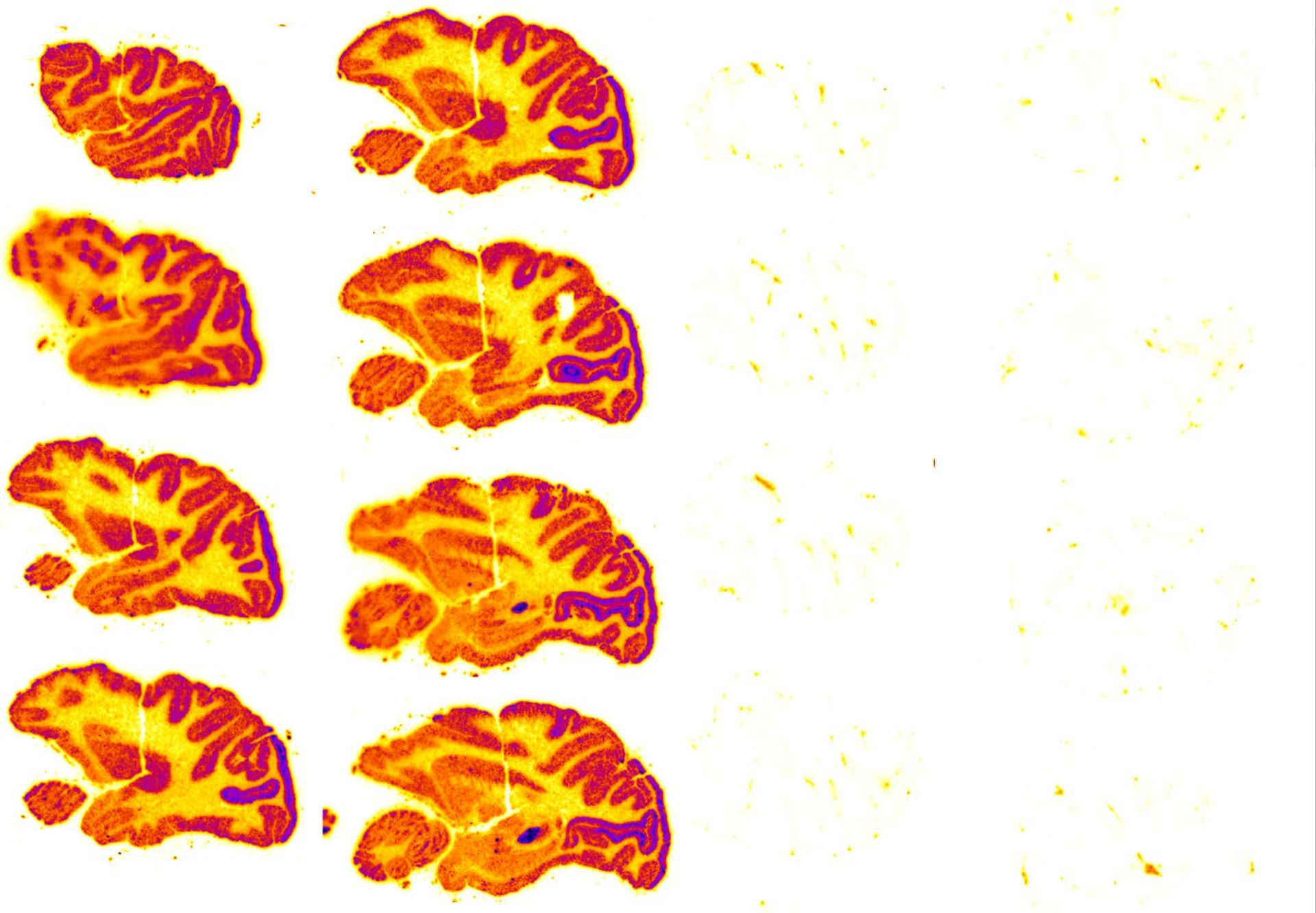
[^{125}I]-Bolton-Hunter reagent

Brain scan 2 hrs after intravenous injection

HIRMAb -IDUA Fusion protein

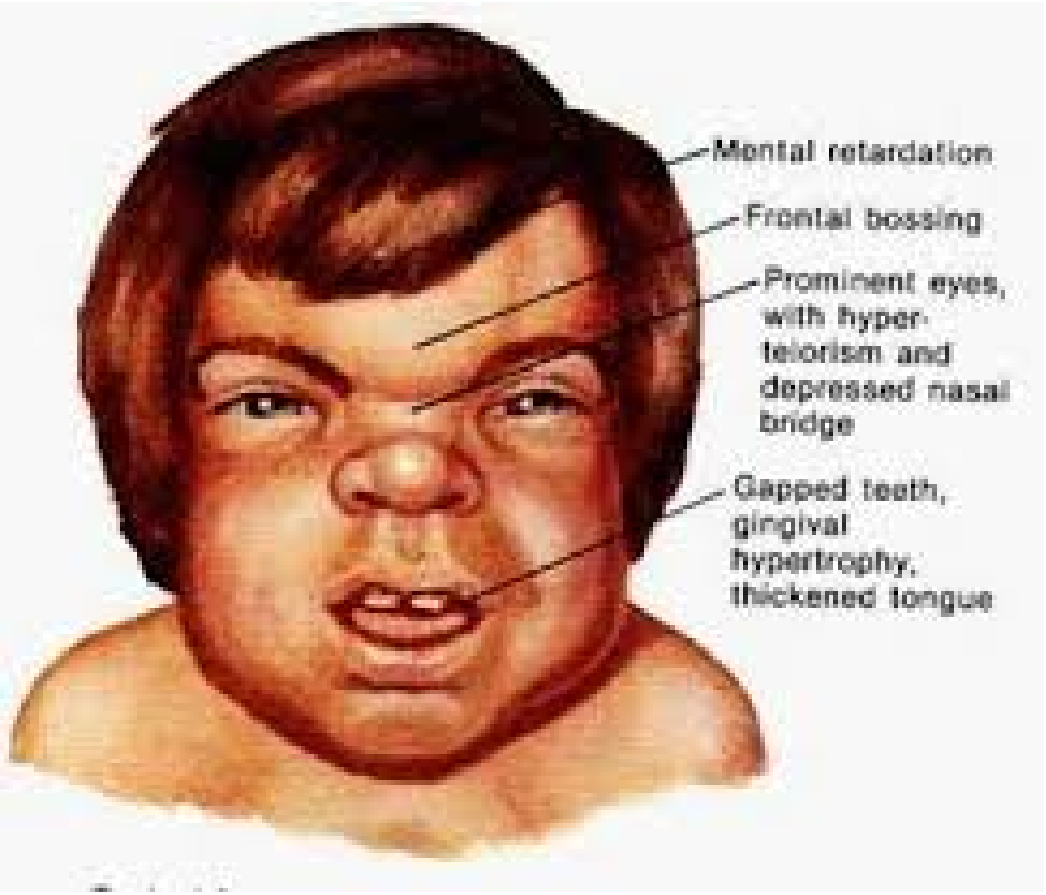


[^{125}I]-Bolton-Hunter reagent



HIRMAb-IDUA fusion protein **IDUA enzyme alone**

First BBB Trojan Horse Clinical Trials
(INDs approved 2015)



The Mucopolysaccharidoses (MPS), Lysosomal storage disorders

Mucopolysaccharidosis Type I
Hurler Syndrome
HIRMAb-IDUA fusion protein
(AGT-181)

IDUA = iduronidase

Mucopolysaccharidosis Type II
Hunter Syndrome
HIRMAb-IDS fusion protein
(AGT-182)

IDS = iduronate 2-sulfatase

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