Quantitative Systems Pharmacology Modeling Evaluates CNS Enzyme Delivery for Different Treatment Modalities for Hunter Syndrome

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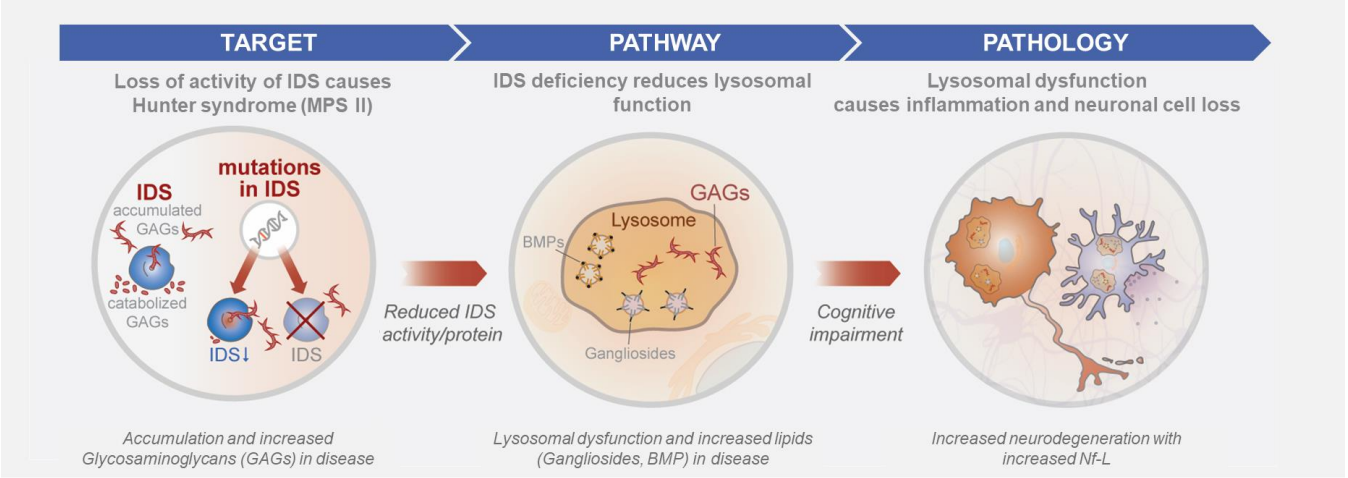
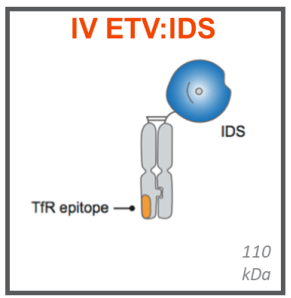
HUNTER SYNDROME: CHALLENGES TO ENZYME DELIVERY AND DISTRIBUTION

- Mucopolysaccharidosis II (MPS II, Hunter syndrome) is a rare inherited lysosomal storage disorder caused by iduronate-2-sulfatase (IDS) deficiency
- Disease hallmark is accumulation of the glycosaminoglycans (GAGs): Heparan and Dermatan Sulfate (HS and DS)
- Multiple tissues and organs are affected, and two thirds have severe neuronopathic form
- Current standard of care is a weekly IV infusion of a recombinant form of IDS, which is unable to cross the blood-brain barrier (BBB) and has no discernible effect on neurodevelopment
- Brain delivery is a critical unmet need in Hunter Syndrome
- Molecules with different delivery routes and different MoAs of biodistribution approved or being evaluated in the clinic

Adapted from Munzer SSEIM 2022

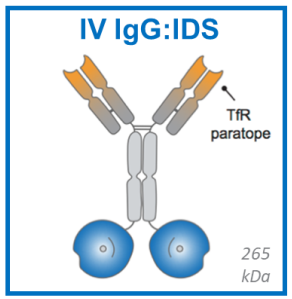




IDS enzyme fused to engineered Fc with TfR binding domain

monovalent TfR binding (Kd = 200 nM)

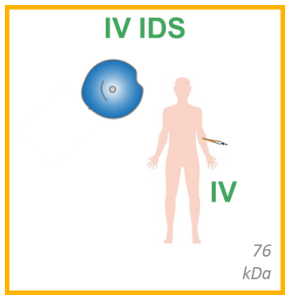
Ullman 2020; Arguello 2022



Two IDS molecules fused to IgG with TfR binding Fabs

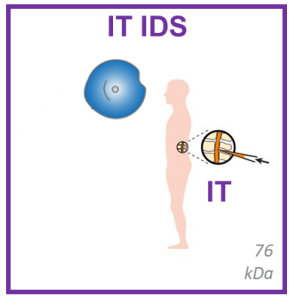
bivalent Fab binding to TfR (Kd = 2.6 nM)

Sonoda 2018; Arguello 2022



Elaprase – naked IDS molecule dosed intravenously

commercially approved recombinant form of IDS



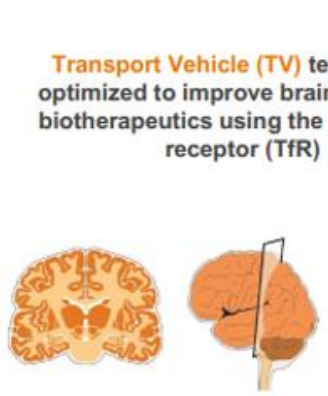
Elaprase – naked IDS molecule dosed lumbar intrathecally

Jafarnejad 2022, GRC

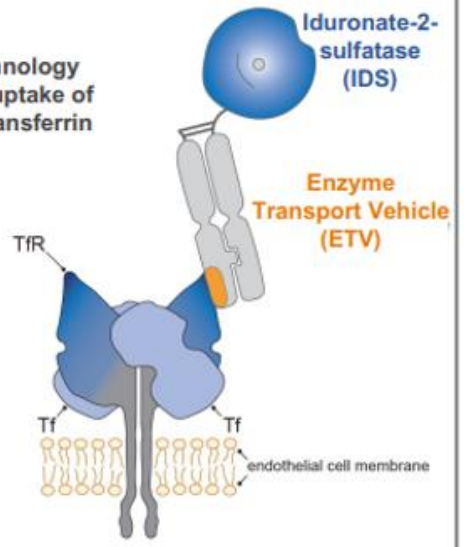
DNL310 (ETV:IDS) ENGINEERED TO CROSS THE BLOOD BRAIN BARRIER

Enzyme Transport Vehicle (ETV)

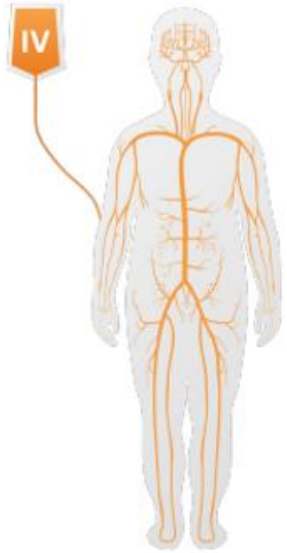
Transport Vehicle (TV) technology optimized to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)



Capillary TfR expression in the brain facilitates widespread biodistribution of TV and cargo



Administration by weekly IV infusion



Extensive tissue penetration

TfR is highly expressed at the blood-brain barrier. Design of the transport vehicle is optimized to enable DNL310 to cross the blood-brain barrier[1-6]

TfR may also facilitate IDS delivery into tissues such as bone, cartilage, and the heart.[2,7-9]

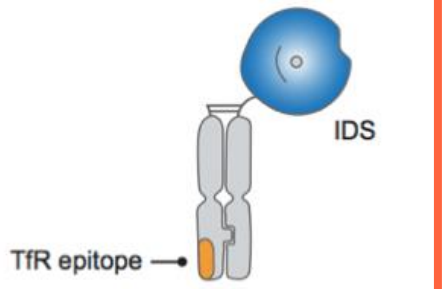
DNL310 has the potential to treat neuronopathic and physical manifestations of MPS II

1. Jefferies WA, et al., 1984. 2. Qian ZM, et al., 2002. 3. Bakardjiev AI, 2021. 4. Arguello A et al., 2021. 5. Arguello A, Mahon CS et al., 2022. 6. Ullman JC, et al., 2020. 7. Wang S, et al., 2020.8. Gammella E, et al., 2017. 9. Carlevaro MF, et al., 1997.

Munzer SSEIM 2022

HEAD-TO-HEAD COMPARISON OF ETV:IDS WITH COMPETITOR MOLECULES: MODEL-BASED DIFFERENTIATION IN BIODISTRIBUTION AND BIOMARKER RESPONSE

IV ETV:IDS

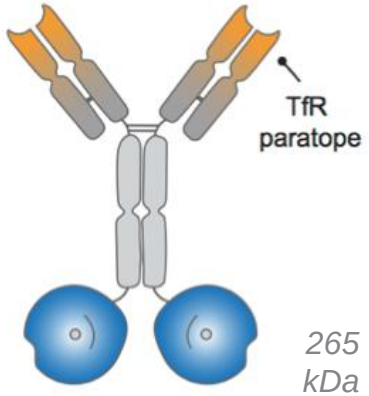


IDS enzyme fused to engineered Fc with TfR binding domain

monovalent TfR binding (Kd = 200 nM)

Ullman et al. *Science Translational Medicine*, 2020; Arguello et al. *Journal of Experimental Medicine*, 2022

IV IgG:IDS

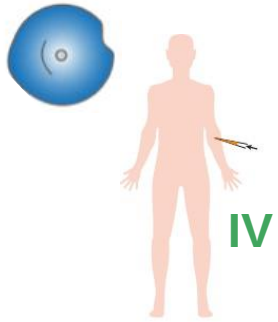


2 IDS molecules fused to IgG with TfR binding Fabs

bivalent Fab binding to TfR (Kd = 2.6 nM)

Sonoda et al. *Molecular Therapy*, 2018; Arguello et al. *Journal of Experimental Medicine*, 2022

IV IDS



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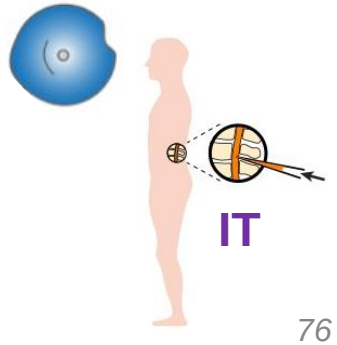
IT IDS



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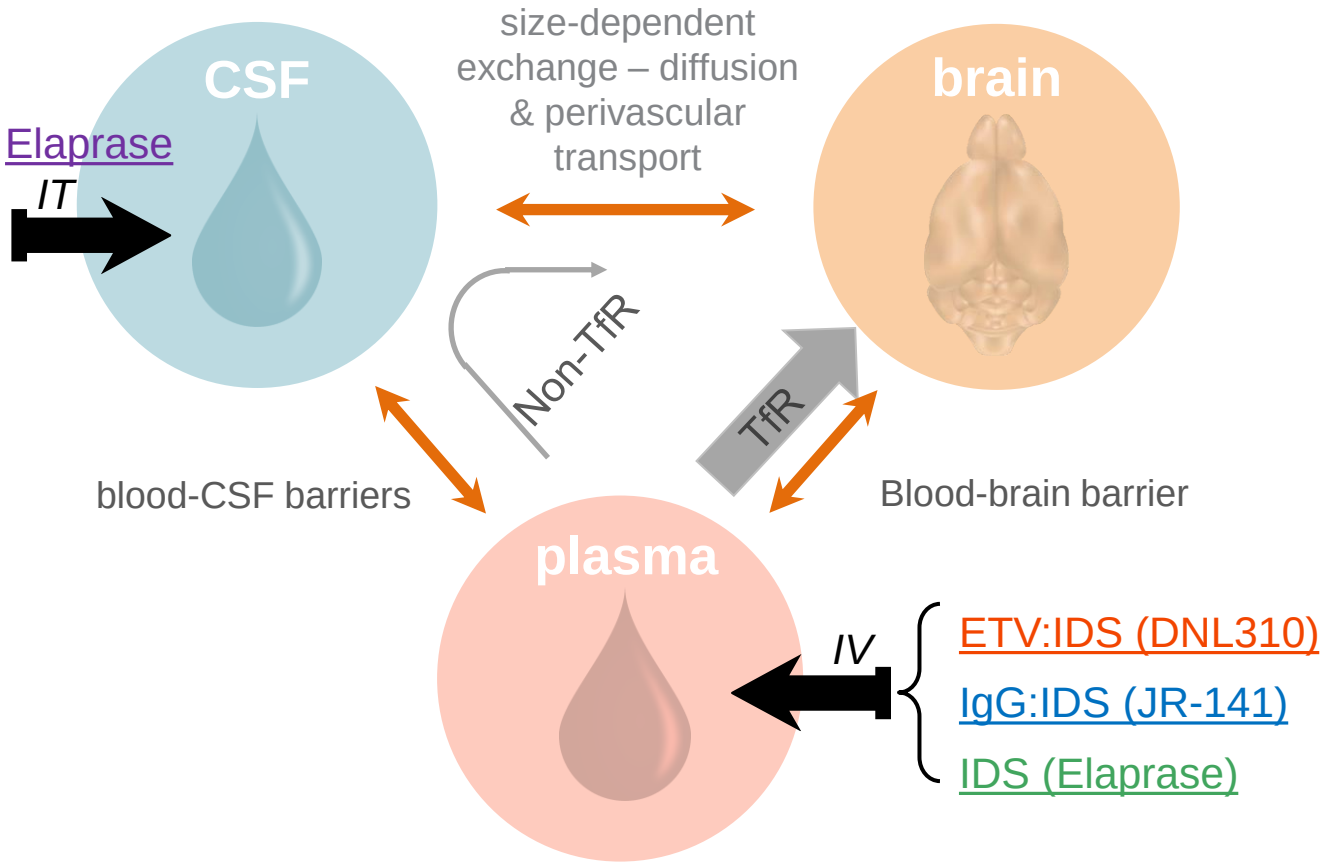
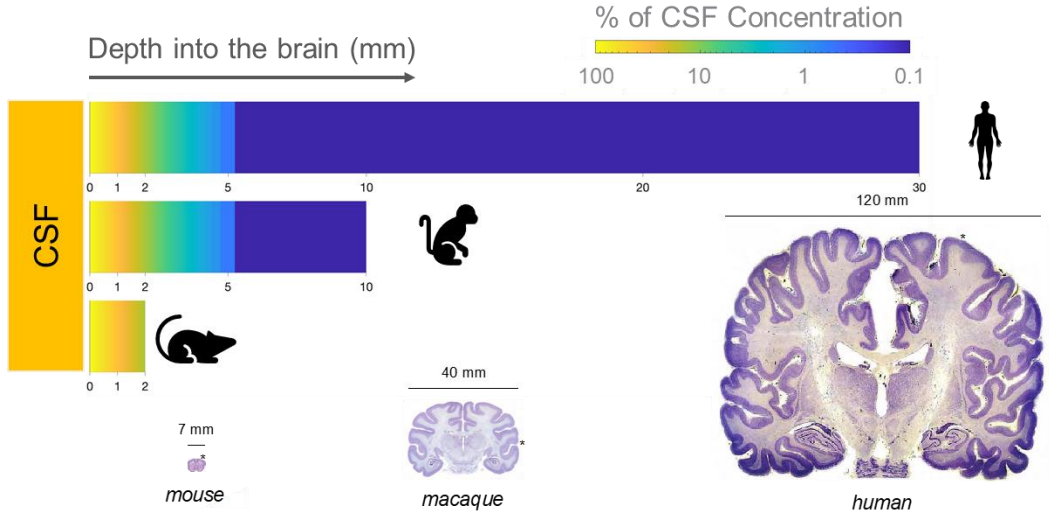
DNL310 QP MODELING INTEGRATES ANATOMY, PHYSIOLOGY & DRUG DELIVERY

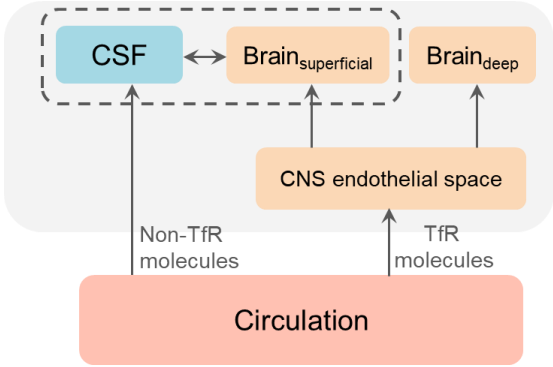
The different IDS molecules have different routes of access to the brain



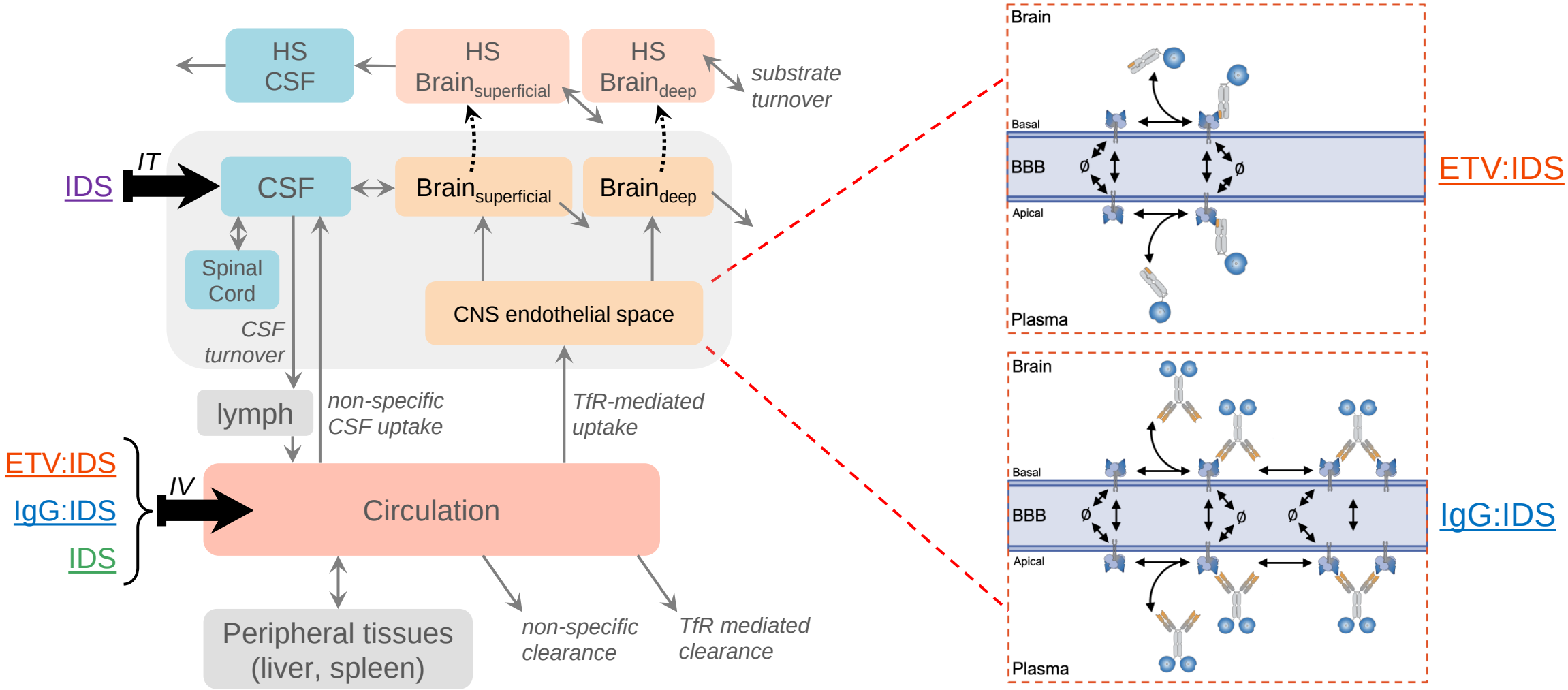
Brain size / anatomical relationships inform physiological predictions of drug distribution



Non-TfR molecules access only the 'superficial' brain



QSP MODEL STRUCTURE FOR PREDICTING BIODISTRIBUTION AND HS REDUCTION



- Different valency / affinity in TfR binding explains parenchymal:vascular ratios for ETV:IDS and IgG:IDS in mice (Arguello et al. *JEM*, 2022)
- The higher affinity and bivalent architecture partly explains differential systemic PK of ETV:IDS and IgG:IDS

HS, heparan sulfate (GAG biomarker of relevance in MPS II)

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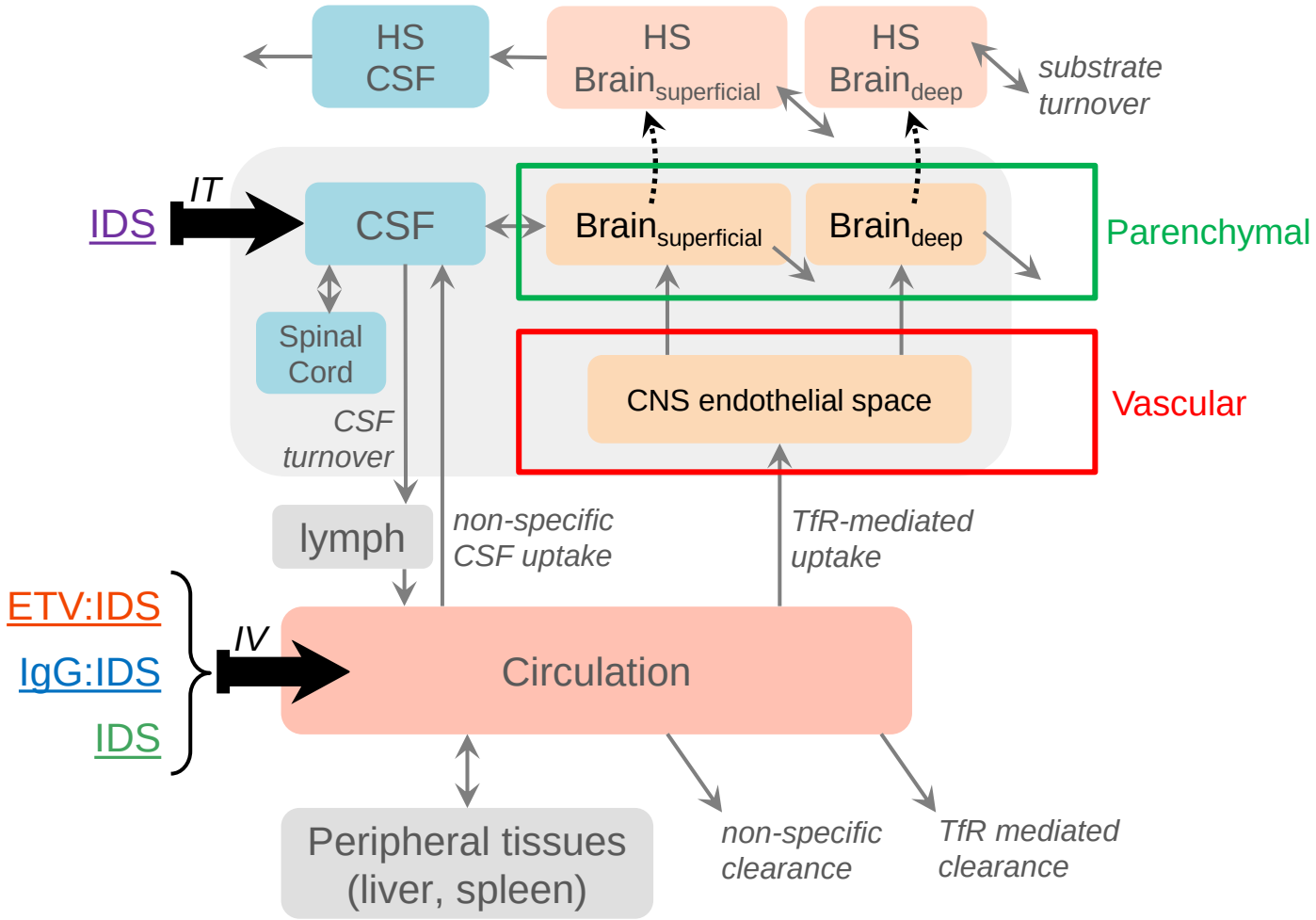

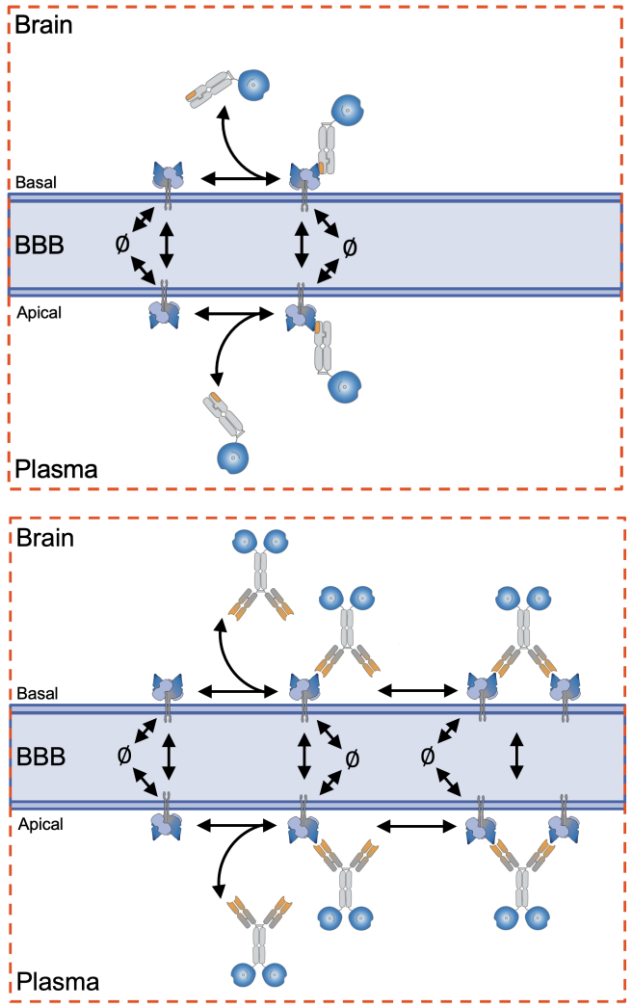

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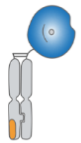
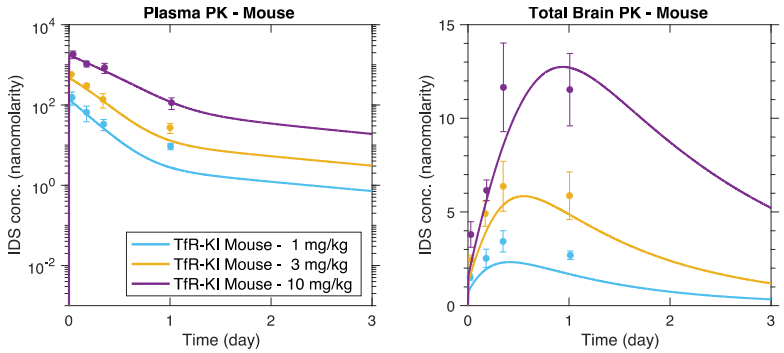
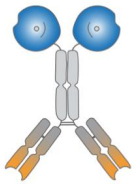
PRECLINICAL MOUSE DATA UTILIZED TO QUANTITATE DIFFERENTIAL EFFICIENCY OF BRAIN UPTAKE BETWEEN ETV:IDS AND IgG:IDS

Plasma and brain PK in TfR$^{mu/hu}$ KI mice
(model calibrated to data from Arguello et al. JEM, 2022)

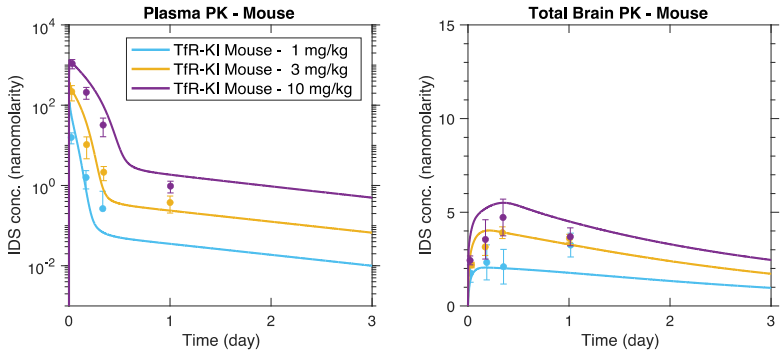


ETV:IDS

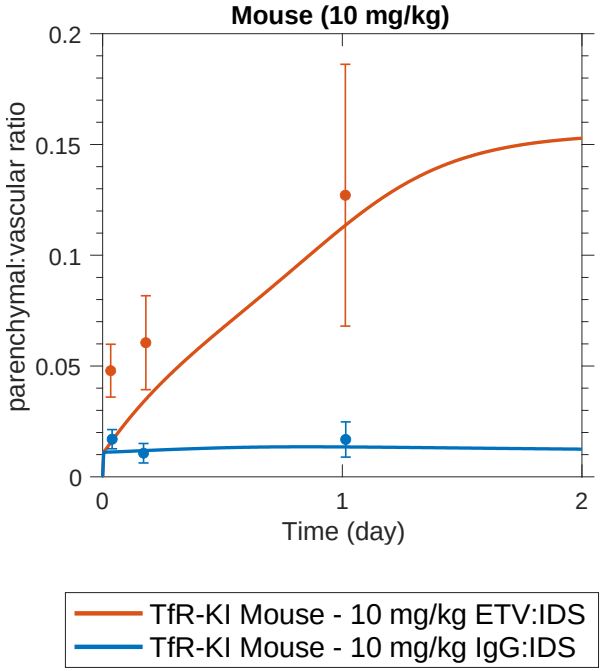




IgG:IDS



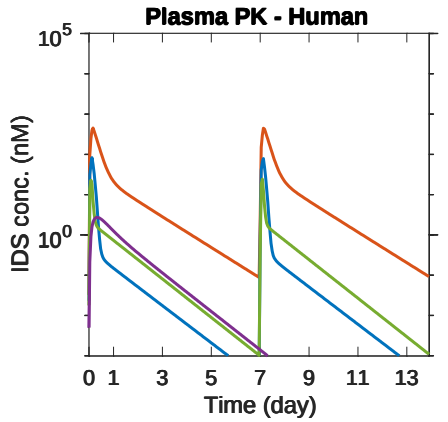
Ratio of parenchymal and vascular PK in TfR$^{mu/hu}$ KI mice
(model calibrated to data from Arguello et al. JEM, 2022)

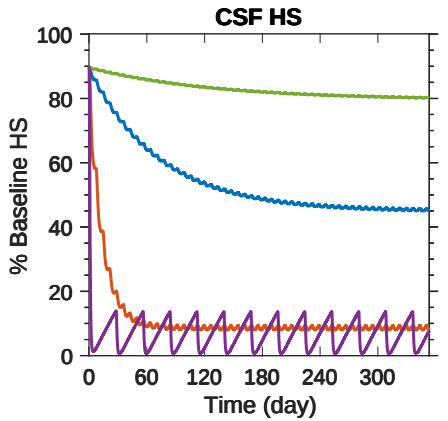


Monovalent TfR binding of ETV:IDS with optimized affinity for brain delivery, resulting in increased parenchymal distribution compared to IgG:IDS

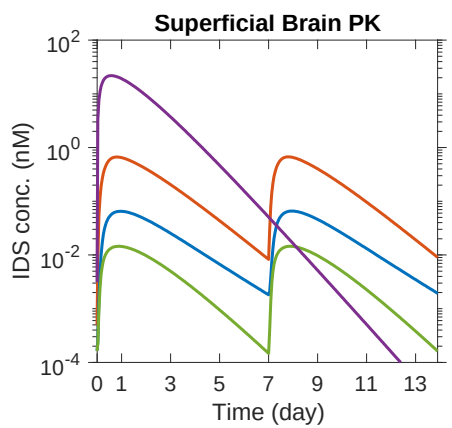
QSP SIMULATIONS FOR THE 4 DIFFERENT IDS ERT MODALITIES IN HUMANS

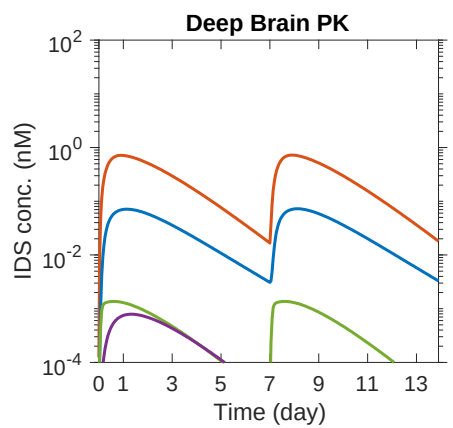
Clinically measured

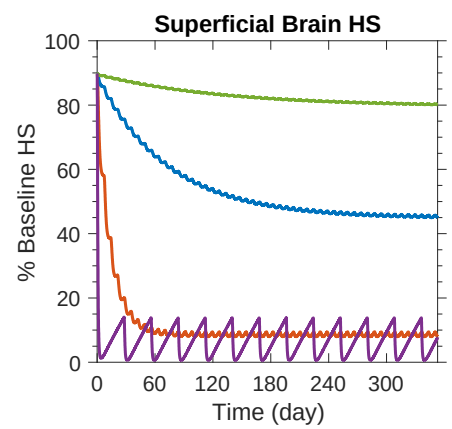


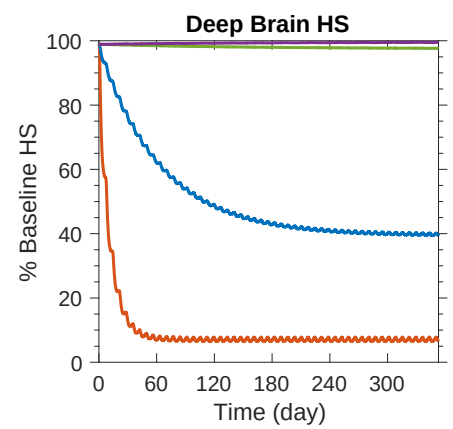


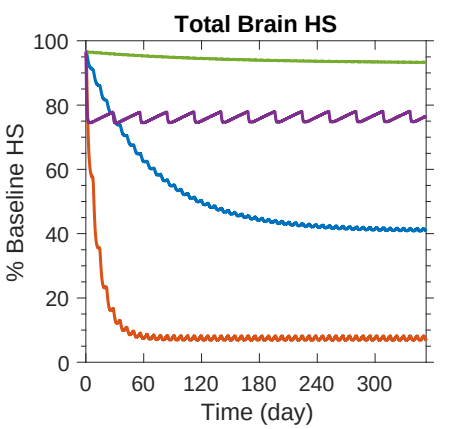
Unmeasurable in clinic

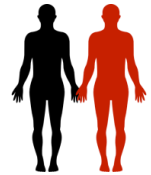












Clinically relevant doses for the IDS ERT modalities:

3 mg/kg QW **ETV:IDS**

2 mg/kg QW **IgG:IDS**

0.5 mg/kg QW **IV IDS**

10 mg Q4W **IT IDS**

simulations include 12 week pretreatment with IV Elaprase to mimic clinical scenario

- Molecules binding TfR are taken up by brain microvascular endothelial cells, accessing deep and superficial brain to varying degrees
- Modeling predicts total brain HS reduction in the following order: ETV:IDS (QW) > IgG:IDS (QW) > IT Elaprase (Q4W) > IV Elaprase (QW)

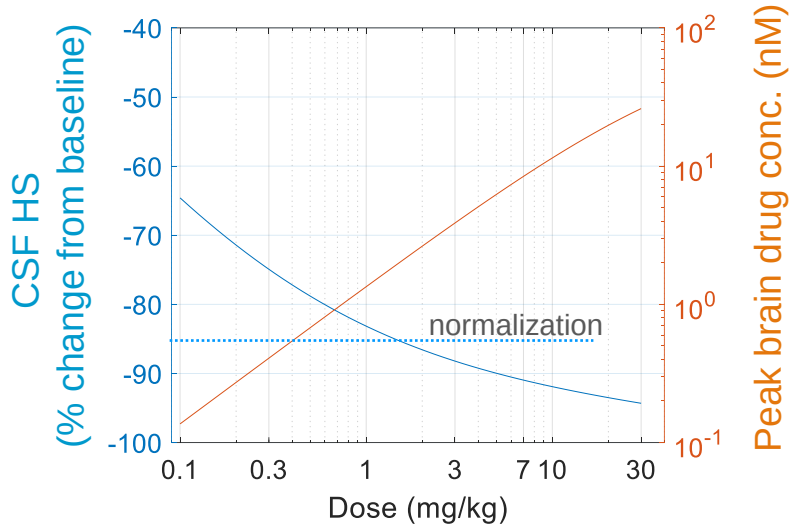
ETV:IDS CLINICAL DOSE SELECTED TO ACHIEVE HEPARAN SULFATE NORMALIZATION IN PATIENTS

- ETV:IDS shows robust reductions in CSF heparan sulfate (HS)
- Modeling suggests normalization is achieved at doses of approximately 1.5 mg/kg and greater

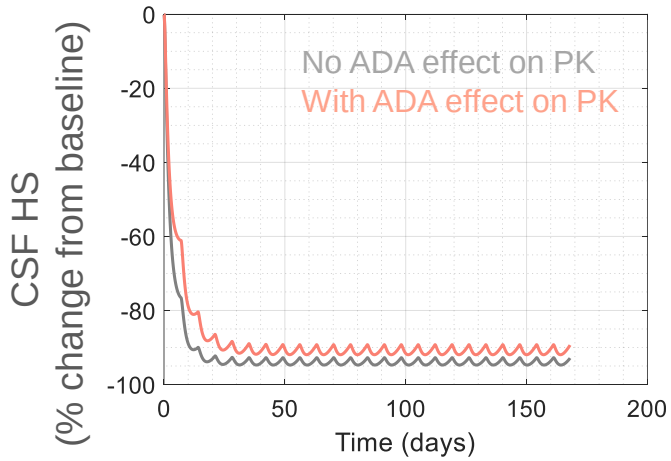
- Clinical doses selected to account for high anti-drug antibodies (ADAs) in a small subset of patients (~10% of patients)

15 mg/kg QW dose is predicted to yield robust heparan sulfate reduction in patients, even those with ADAs

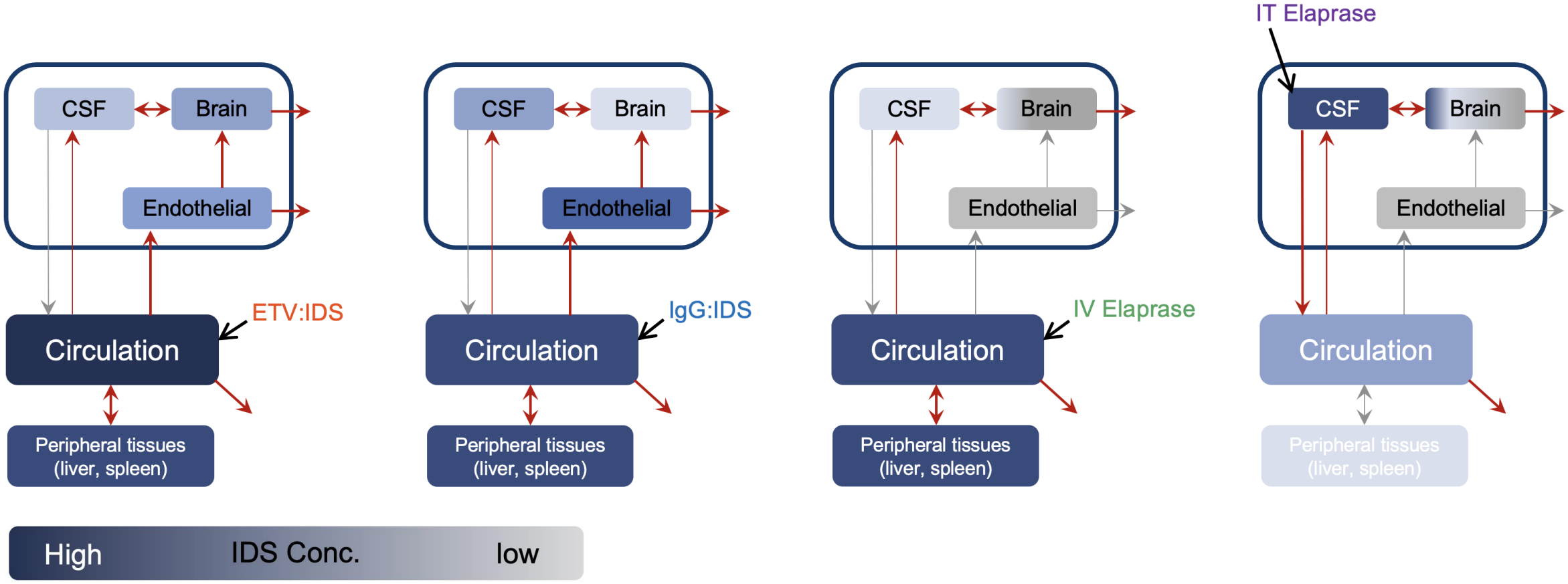
Dose response of CSF HS reduction using PK/PD model



CSF HS reduction with 15 mg/kg weekly dosing



CONCLUSIONS



- IDS platform QP model can predict biodistribution of IDS ERT modalities
- Simulation results support the superiority of brain biodistribution and predicts robust HS reduction for ETV:IDS (optimized TfR affinity / valency) in comparison to other IDS ERT modalities

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THANK YOU TO THE PATIENTS, THEIR FAMILIES, AND OUR CLINICAL COLLABORATORS

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Mihalis Kariolis
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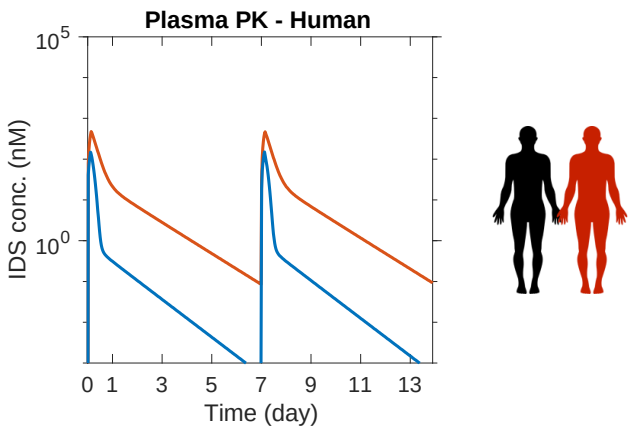
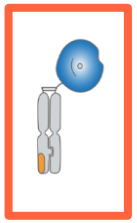
QSP SIMULATION COMPARISON OF EQUAL DOSE ETV:IDS & IgG:IDS IN HUMANS





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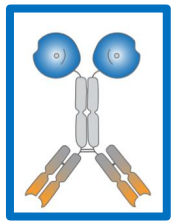

IgG:IDS
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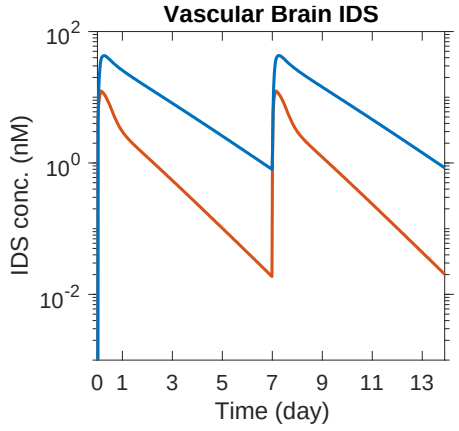
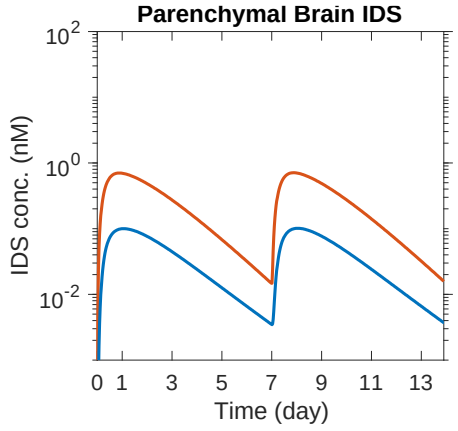
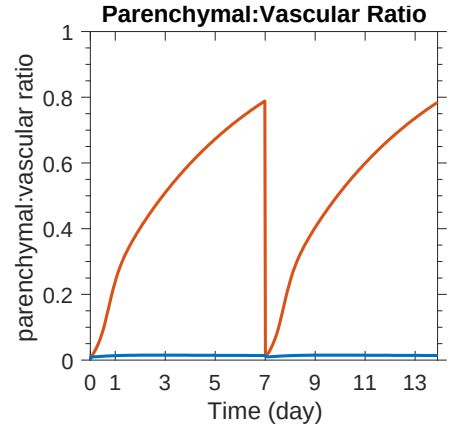
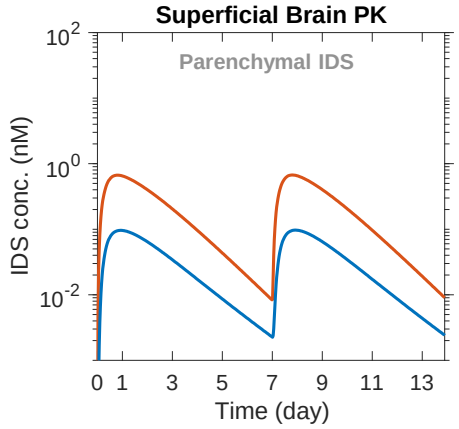
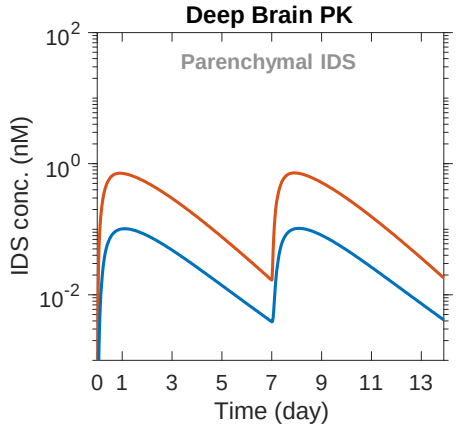
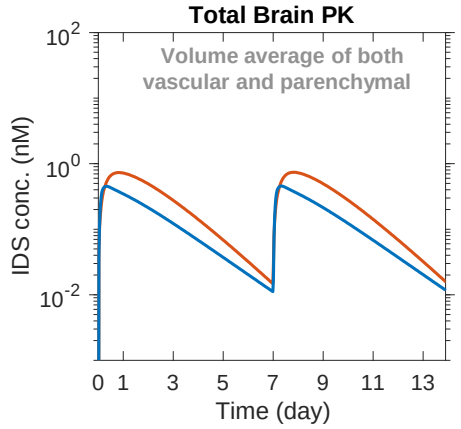












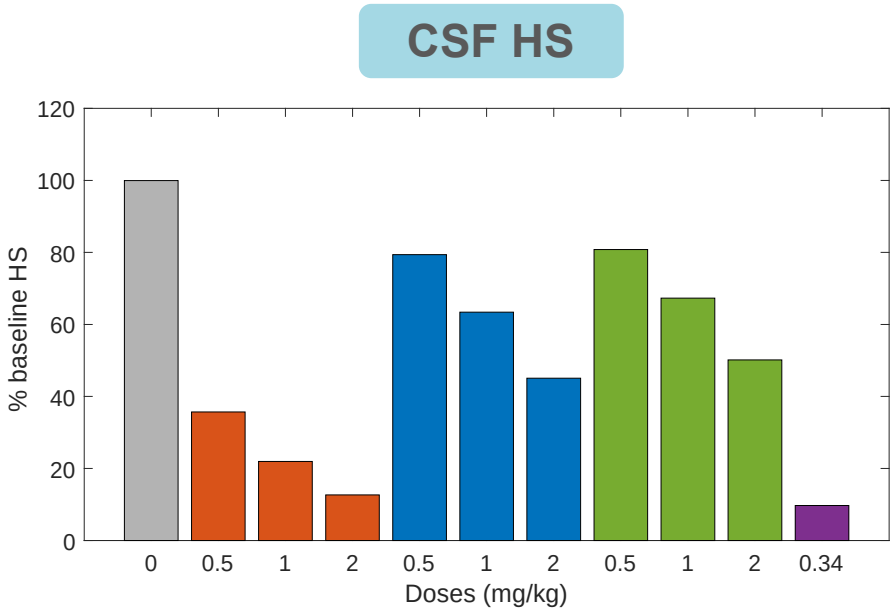
Clinical simulation comparison for an arbitrary dose of 3 mg/kg QW IV

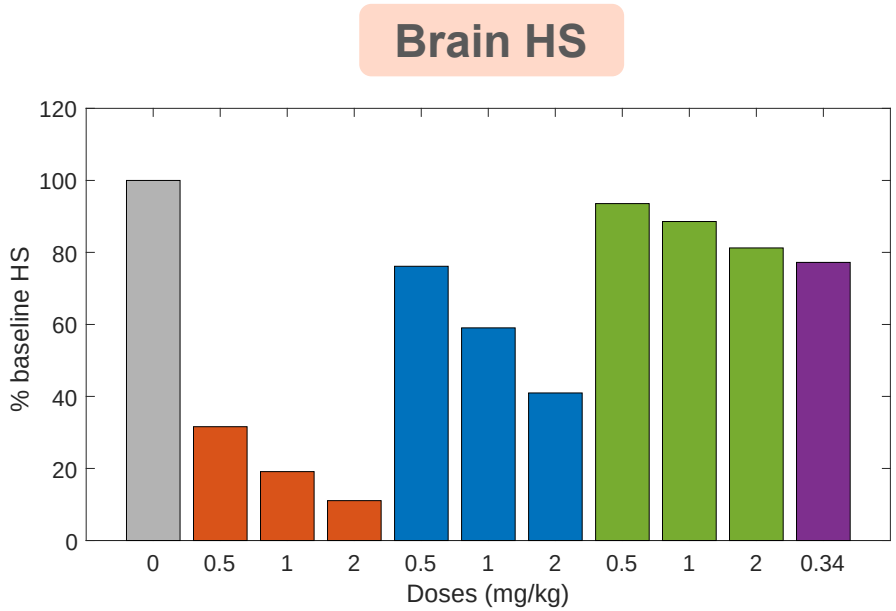
- Simulations predict improved systemic exposure for ETV:IDS relative to IgG:IDS
- Simulations predict biodistribution to brain parenchyma for ETV:IDS with significantly better efficiency relative to IgG:IDS

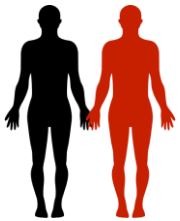
QSP MODEL PREDICTIONS OF HS REDUCTIONS IN CSF AND BRAIN

Clinically measurable

Unmeasurable in the clinic







QW **ETV:IDS**

QW **IgG:IDS**

QW **IV IDS**

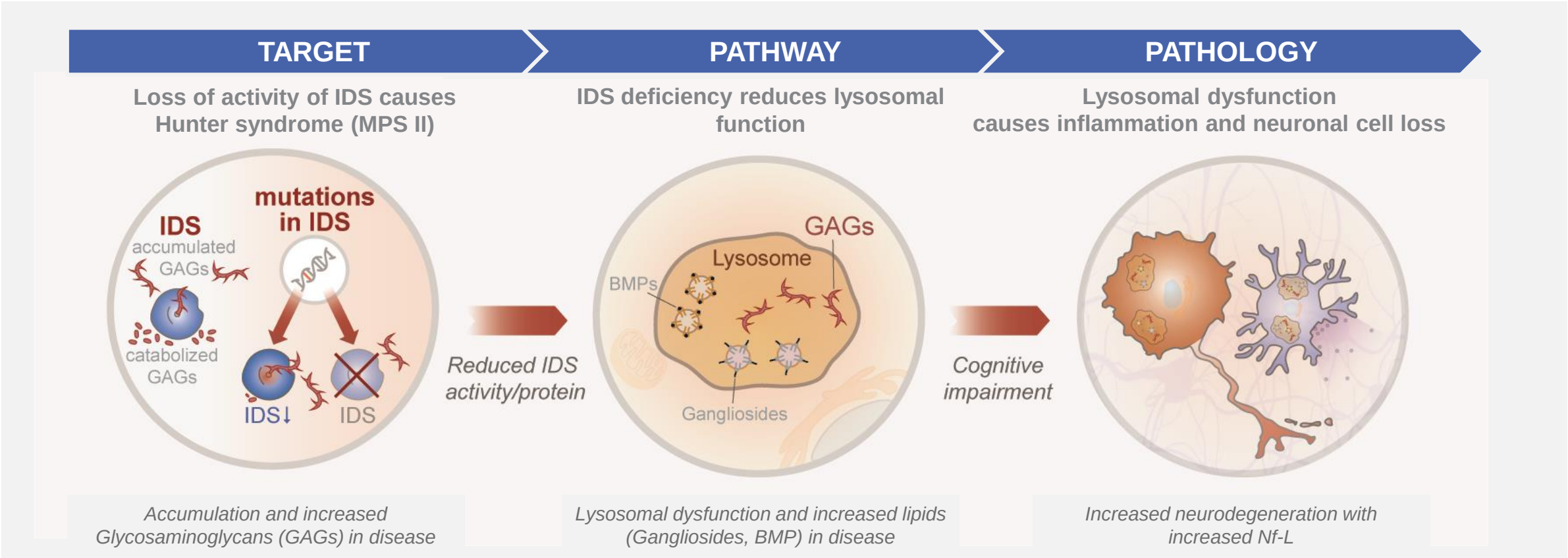
Q4W **IT IDS**

QSP model simulations for weekly IV dosing of ETV:IDS, IgG:IDS, and Elaprase at 0.5 mg/kg, 1 mg/kg and 2 mg/kg and intrathecal dosing of Elaprase at a flat dose of 10 mg (equivalent to 0.34 mg/kg for a 30 kg subject)

Model prediction:

- Elaprase accesses brain tissue primarily via the CSF and therefore penetrates only the superficial brain region; CSF biomarker changes do not reflect the activity of the entire brain tissue due to the lack of penetration into the deep brain region
- ETV:IDS and IgG:IDS access the superficial and deep brain regions via TfR-mediated transcytosis, but to varying degrees (ETV:IDS > IgG:IDS)

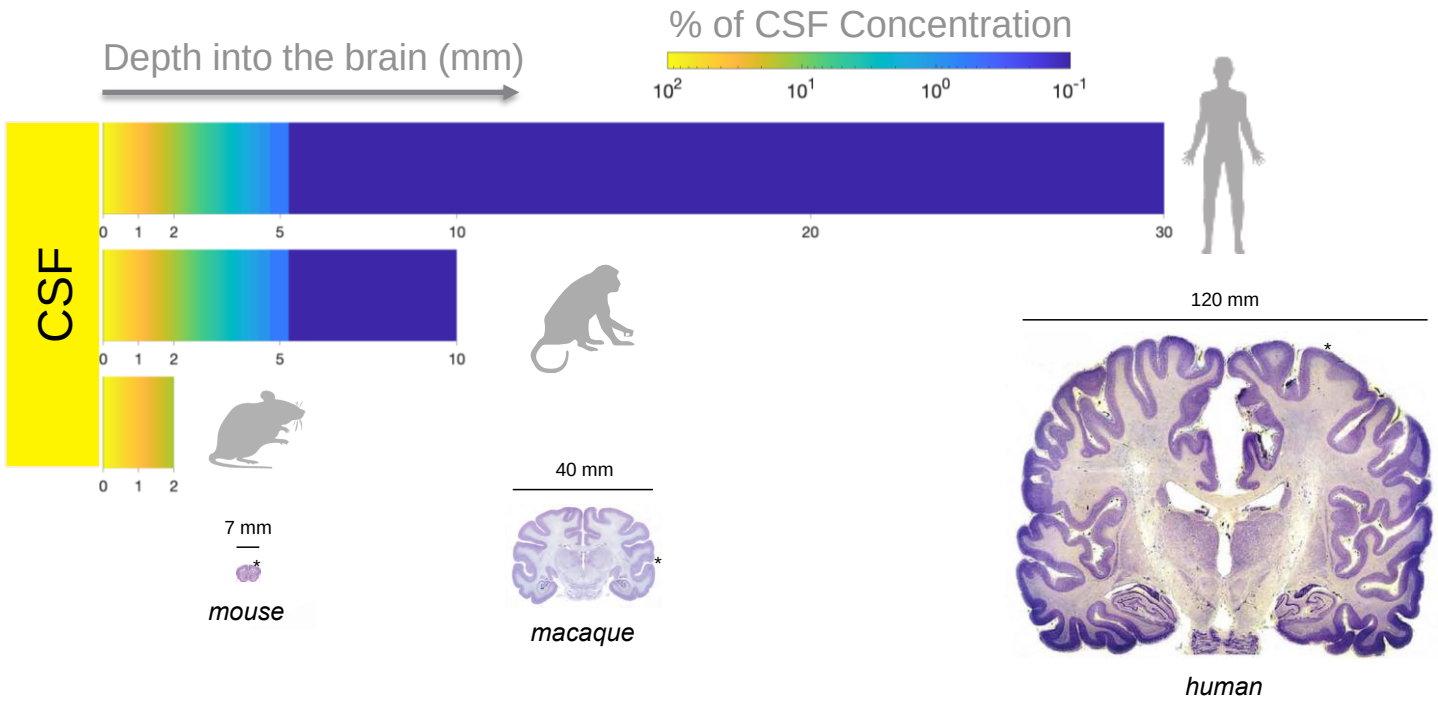
HUNTER SYNDROME: CHALLENGES TO ENZYME DELIVERY AND DISTRIBUTION



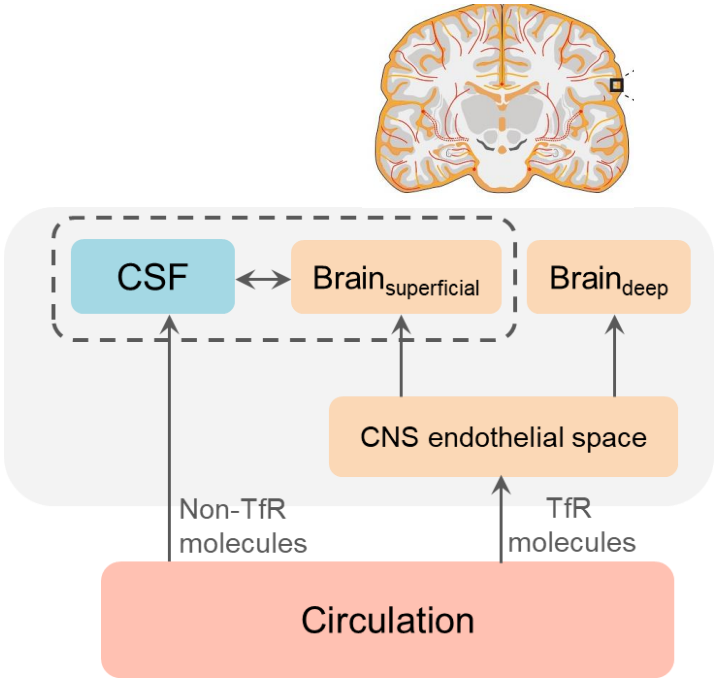
- Hunter Syndrome (Mucopolysaccharidosis type II, MPS II): an X-linked recessive disorder affecting 1 in ~100,000 males
- Mutations in the iduronate-2-sulfatase (IDS) gene → IDS deficiency & resulting toxic accumulation of glycosaminoglycans *-Disease Hallmark-*
- Lysosomal dysfunction occurs throughout the body including the CNS
- Existing widely approved ERTs do not effectively cross the BBB & do not address the neurodegeneration process

PREDICTED PENETRATION DEPTH FROM CSF INTO ADJACENT BRAIN

Brain size / anatomical relationships inform physiological predictions of drug distribution



Non-TfR binding molecules (i.e. naked enzyme) access mainly the 'superficial' brain



Predicted gradient based on a one-dimension diffusion model, assuming negligible contribution from perivascular transport for simplicity; Sources for brain sections: DeFelipe. *Frontiers in Neuroanatomy*, 2011; brainmuseum.org; Franklin & Paxinos, 2007

$\frac{Brain_{superficial}}{Brain_{total}}$ (%)	100%	50%	25%