



Targeted delivery of biotherapeutics to CNS and other tissues

April 2026

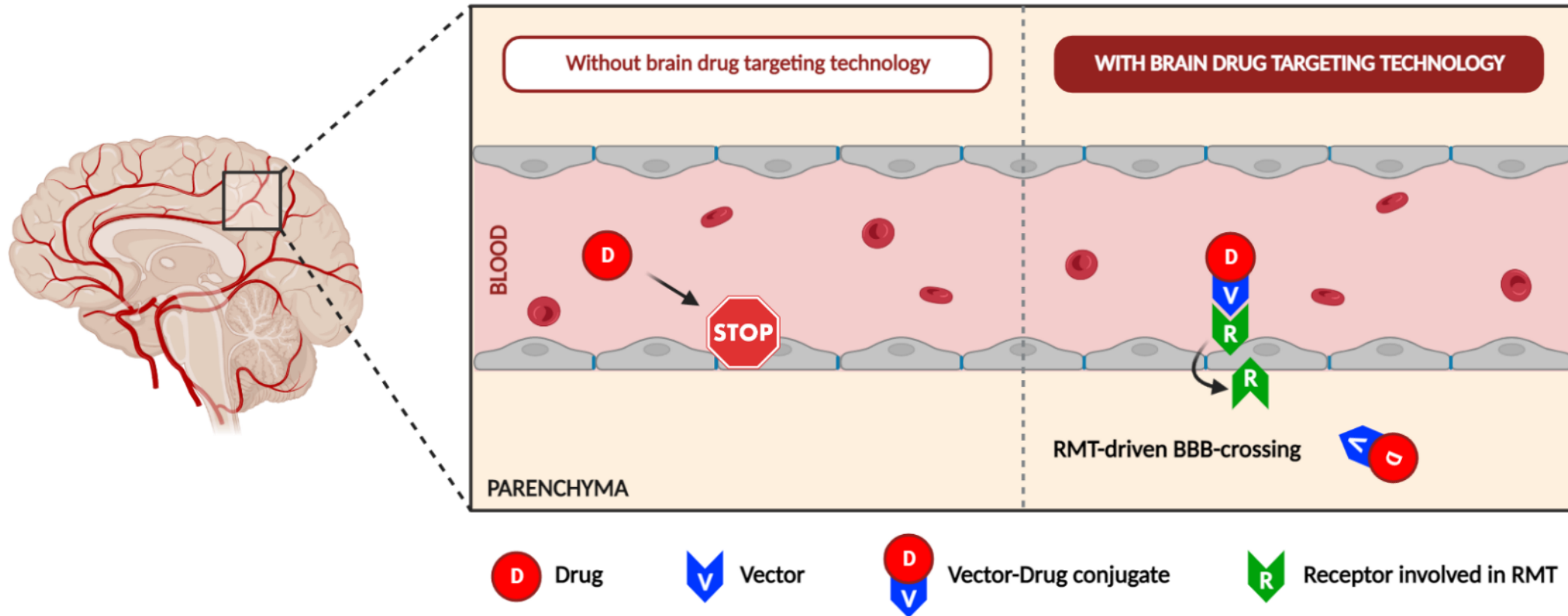
Company overview

- ❑ **VECT-HORUS:** established in Marseille in 2005, spin off from the **NeuroPhysiopathology Institute** (INP, Dir. Michel KHRESTCHATISKY), CNRS/AMU.
- ❑ **Focus:** Drug delivery to the CNS / other organs via **receptor-mediated transport (RMT)**
- ❑ **Co-founders:** Alexandre TOKAY, CEO and Michel KHRESTCHATISKY, Scientific counsel
- ❑ **CBO:** Jamal TEMSAMANI
- ❑ **CFO:** Carole IMBERT
- ❑ **CSO:** Claudia FROMONT
- ❑ **Ad. HR :** Florence FERCHAT
- ❑ **Scientific staff :** 45
- ❑ **Collaborations with Pharma Companies:** Novo Nordisk, Ionis, RadioMedix, ...
- ❑ **Embedded in a solid academic environment** (CNRS, CEA, INSERM, etc.)
- ❑ **A strong IP protection** with 8 patent families.
- ❑ **Fund raising** > 40M€



Primary focus: RMT-driven BBB-crossing for CNS Delivery

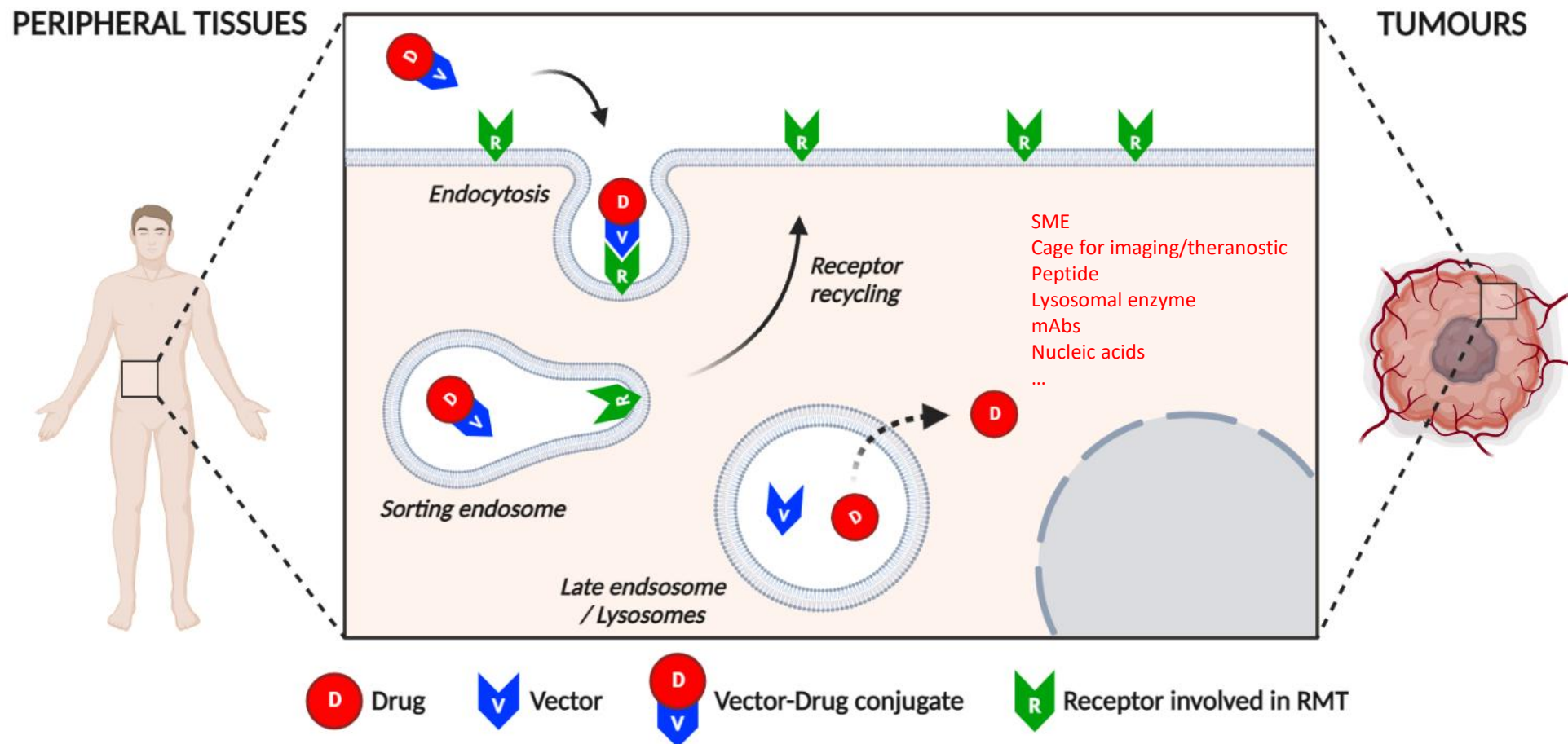
Overcome the Blood-Brain Barrier (BBB) challenge...



Receptor-mediated transport (RMT) is considered as the **method of choice** to transport into the CNS (bio)pharmaceutical agents such as small organic molecules, peptides, oligos, proteins, mAbs.

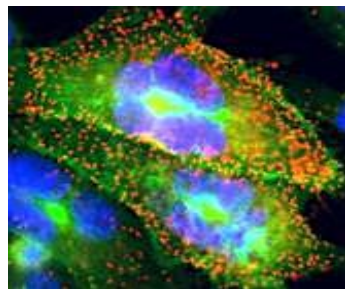
Potential for delivery to peripheral tissues/tumours

... and **unlock biological barriers of peripheral tissues or tumours** for the targeted delivery of (bio)therapeutic/imaging agents

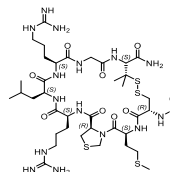


Overview of VECT-HORUS' targeting Vectors

1



Receptor targeting peptides HTS peptide libraries



Small Cyclic Peptides
~ 1 kDa



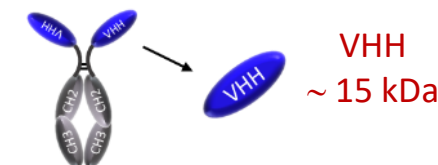
LDL-receptor:

- ✓ Portfolio of ~200 **peptide** variants using medicinal chemistry-based optimization
- ✓ LDLR-binding affinities from nM to μ M
- ✓ *In vitro* plasma half-life up to 10 hrs
- ✓ No competition / no overlap with LDL-binding site
- ✓ *In vivo* PoC in mice. including specific **targeting/PET** imaging of LDLR-expressing tumours (GBM. pancreatic...)
- ✓ **Phase 1 Development of a Theragnostic agent** (RadioMedix)

2



Receptor targeting VHH HTS llama **VHH** libraries



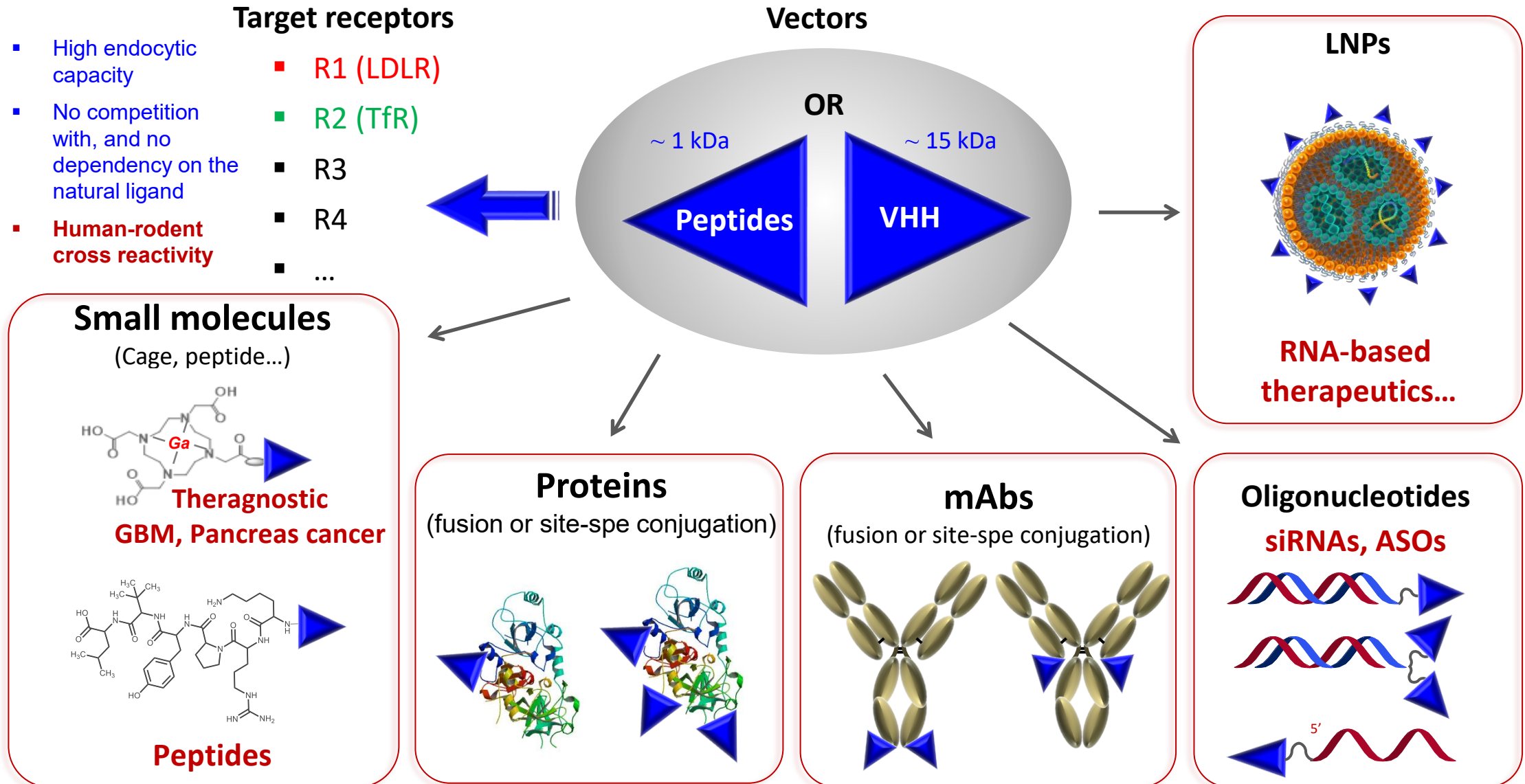
TfR:

- ✓ Portfolio of ~150 **VHH-TfR** variants by site-directed mutagenesis. >30 humanized
- ✓ TfR-binding affinities from nM to μ M
- ✓ No competition / no overlap with Tf-binding site
- ✓ No apparent immunogenicity
- ✓ *In vivo* PK and PD PoC in mice. including **brain** delivery of peptides and mAbs. modulation of **gene** expression...

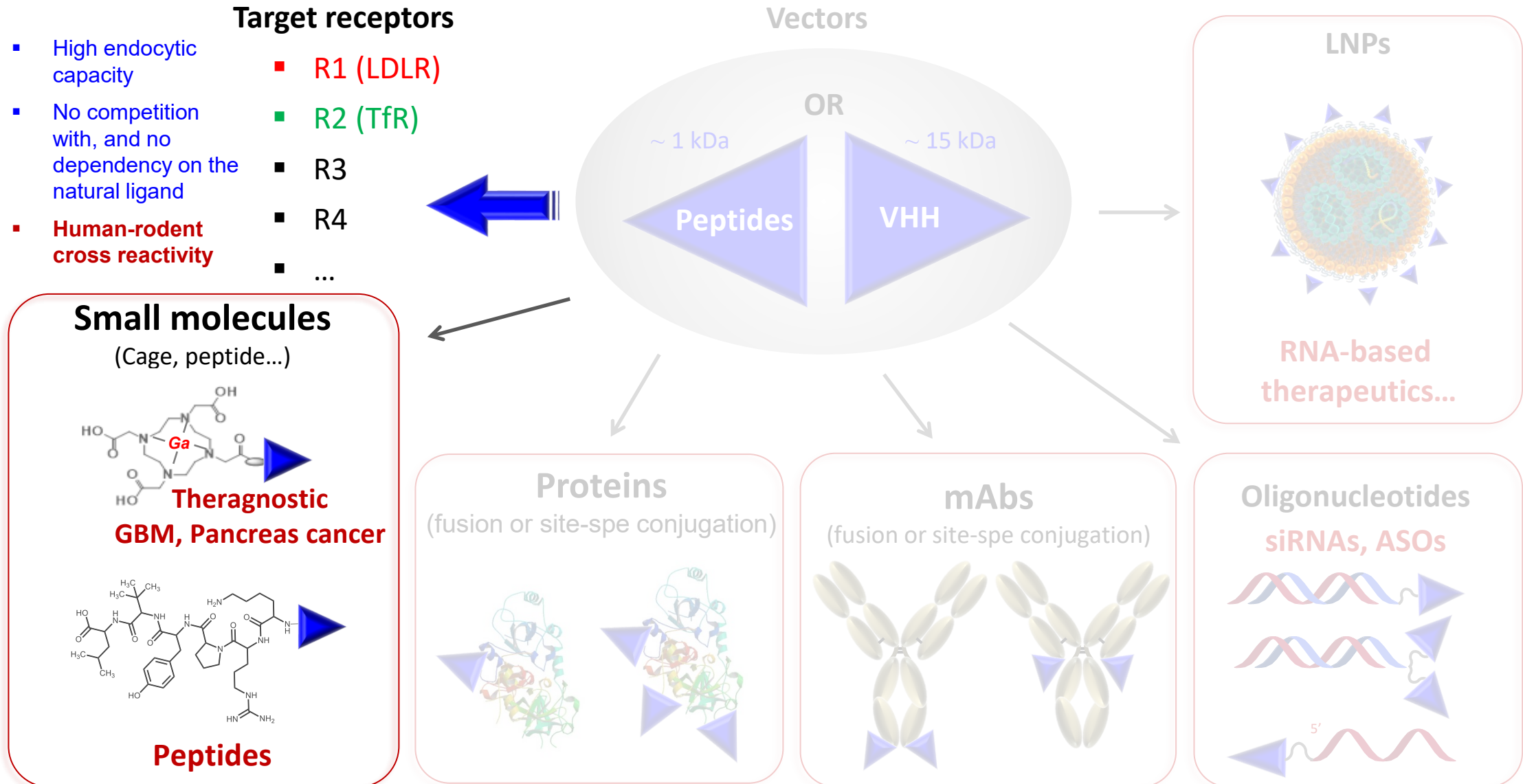
RAGE:

- ✓ Portfolio of 5 VHHR3
- ✓ *In vivo* PK PoC in mice. **lung** delivery of Fc fragment

Conjugation versatility of peptide- and VHH-based vectors



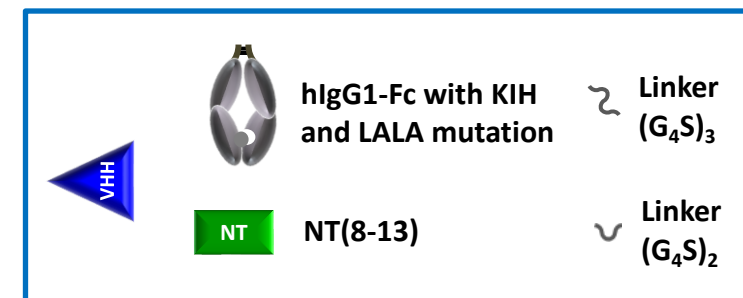
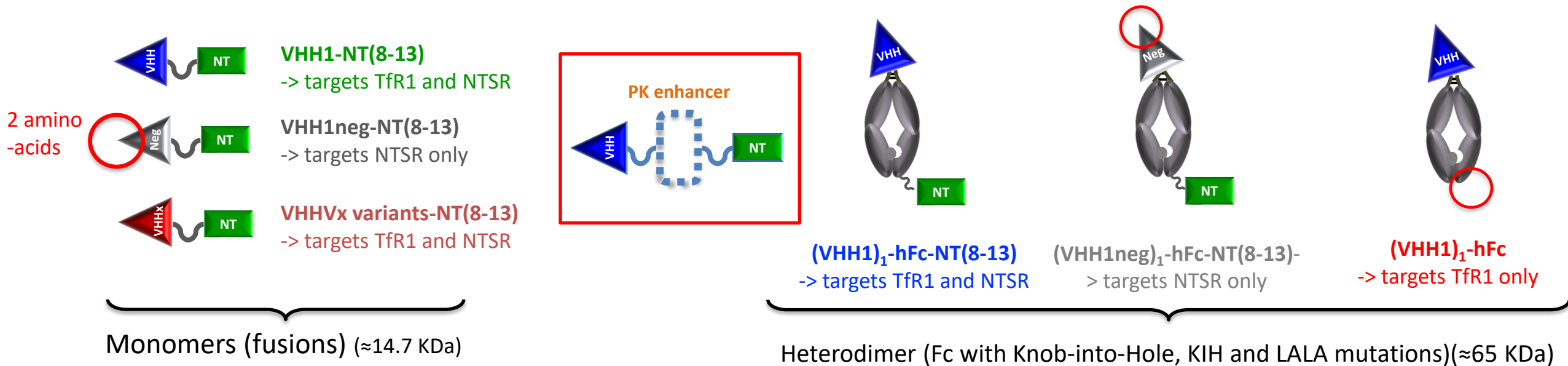
Conjugation versatility of peptide- and VHH-based vectors



Targeted delivery in the CNS of the **Neurotensin peptide (NT 8-13)**

❑ Rationale for neurotensin NT(8-13) vectorization

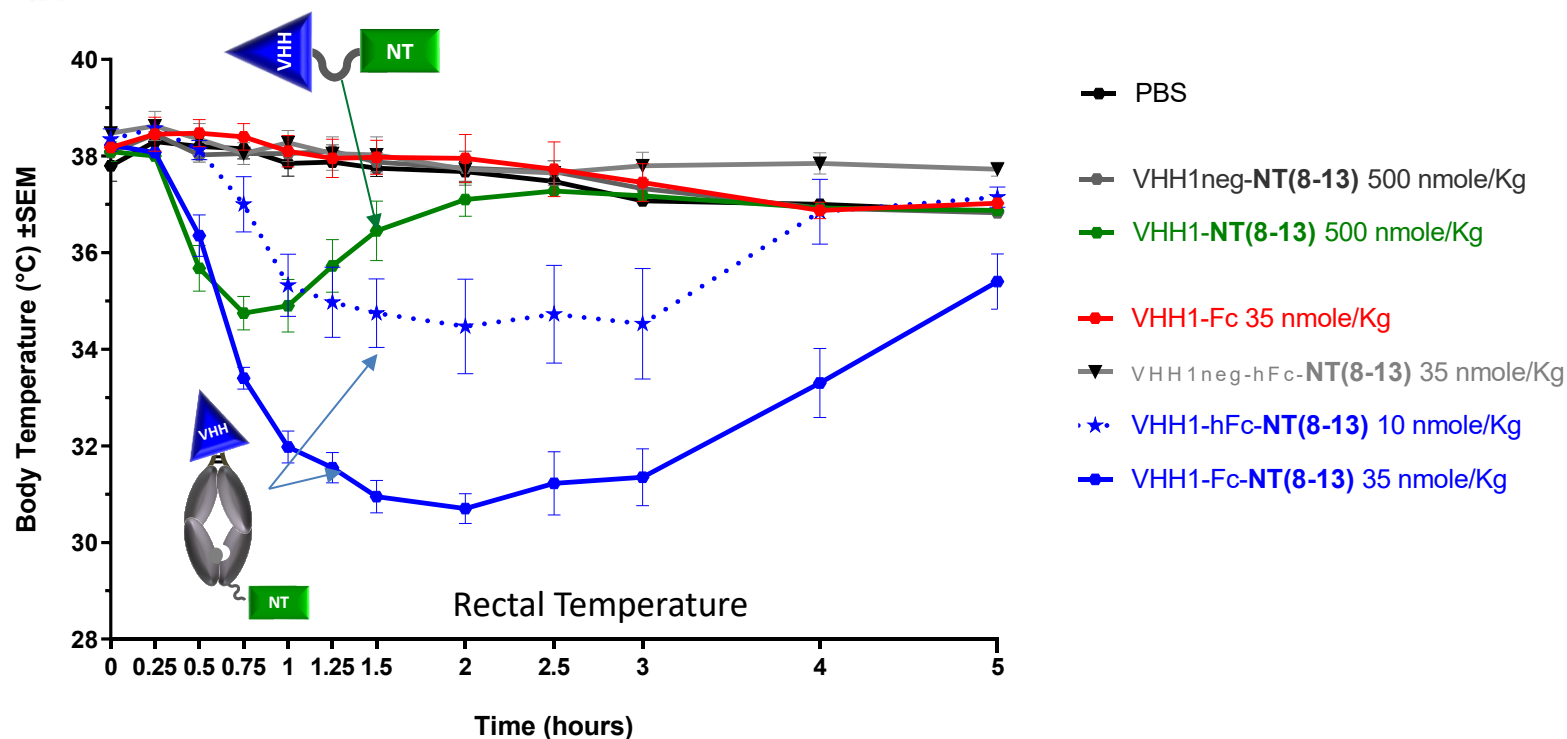
- **Neurotensin** is a neuropeptide that can induce a variety of **central effects, including hypothermia (HT)**.
- **No BBB-crossing** -> no central effect upon systemic administration as neurotensin peptide alone.



Targeted delivery in the CNS of the **Neurotensin peptide (NT 8-13)**

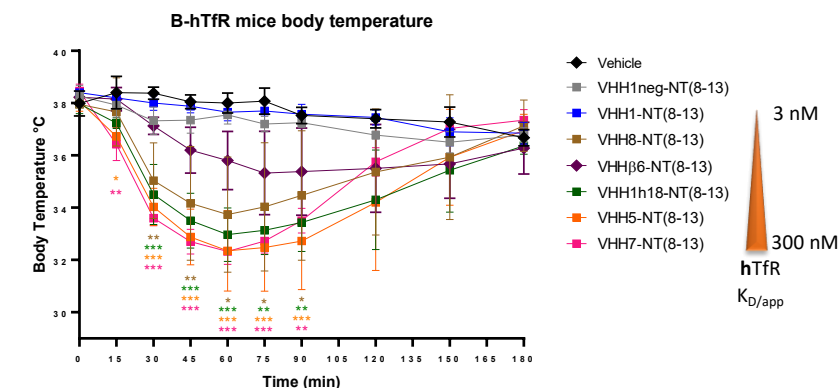
IV administration to C57Bl/6 mice (n=4) of:

- **VHH1-hFc**, **C5-hFc-NT(8-13)**, VHH1neg-hFc-NT(8-13) at **35 nmol/kg**
- **VHH1-hFc-NT(8-13)** at **10 nmol/kg**
- **VHH1-NT(8-13)** and VHH1neg-NT(8-13) at **500 nmol/kg**



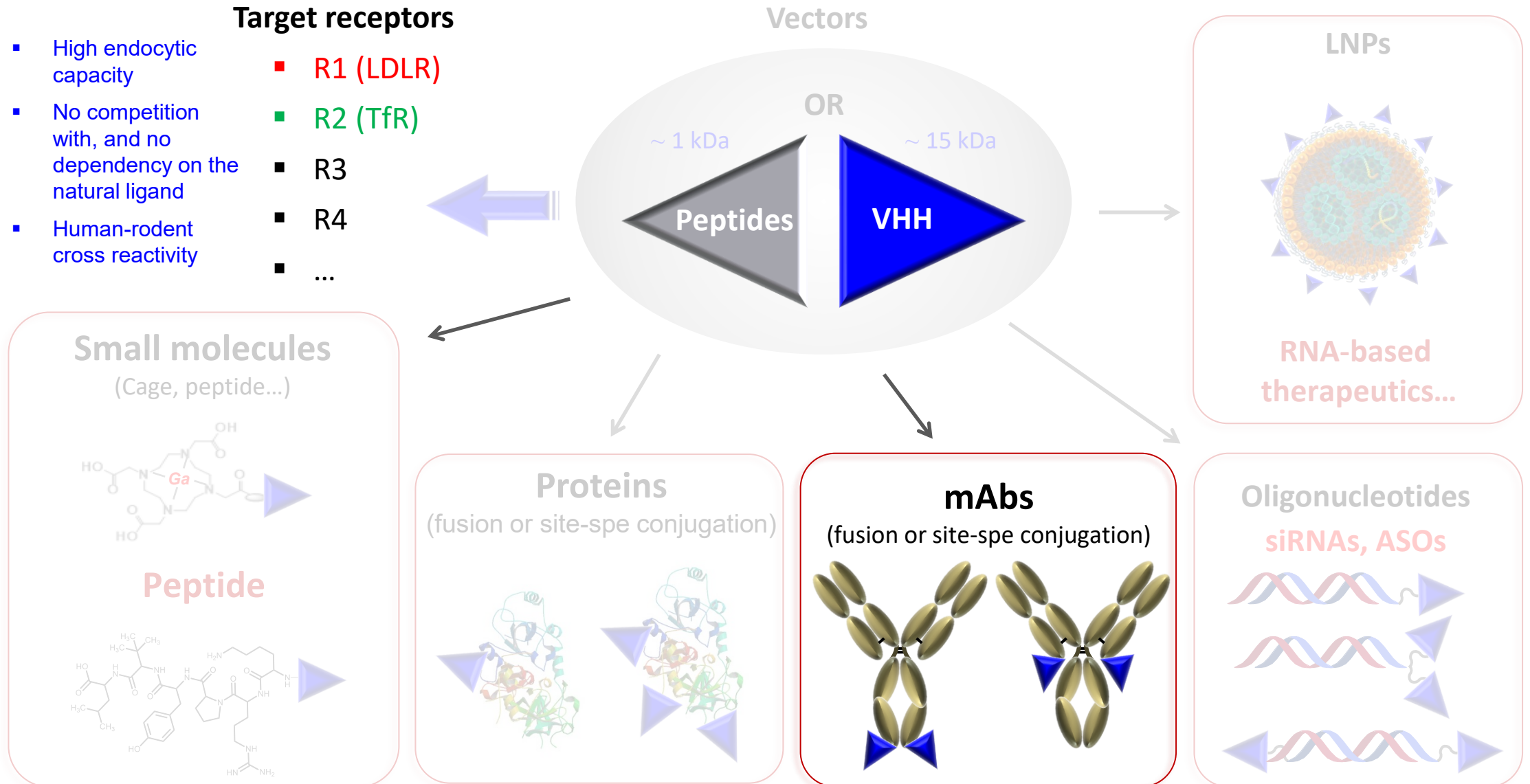
IV administration to B-hTfR mice (n=3-4) of vehicle, VHH1neg-NT8-13, **VHH1-NT8-13**, VHH1h18-NT8-13, VHHβ6-NT8-13, **C5V5-NT8-13** and **C5V7-NT8-13** at **550 nmol/kg**; Rectal Temperature was measured over 3 hr.

B-hTfR mice



- ⇒ No effect of the negative controls on mice body temperature
- ⇒ The monovalent Fc conjugate **(VHH1)_{1k}-Fc-NT(8-13)_{1h}** induces a dose-dependent central hypothermia
- ⇒ Demonstration that vectorization with VHH1 allows NT(8-13) to reach its brain target in **pharmacological amounts**

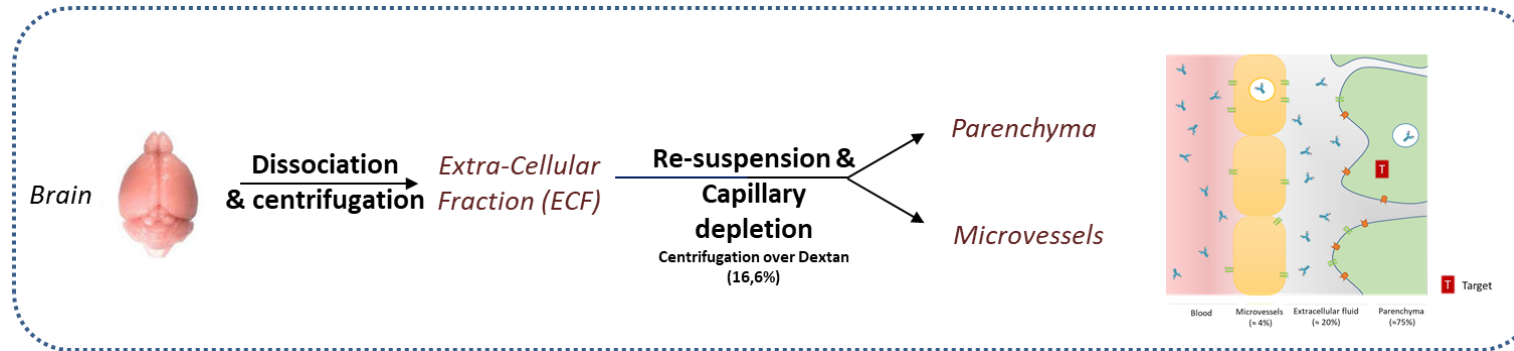
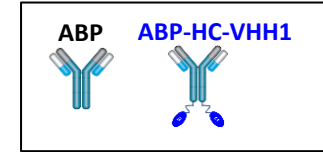
Conjugation versatility of VHH-based vectors: **mAbs** POC for efficacy



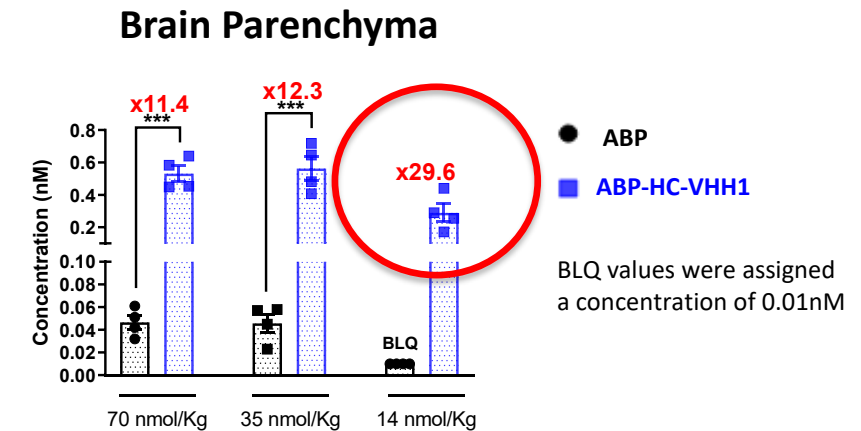
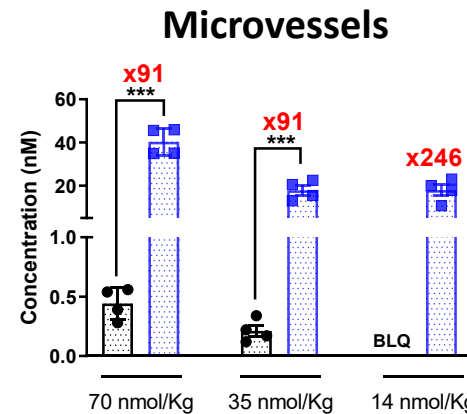
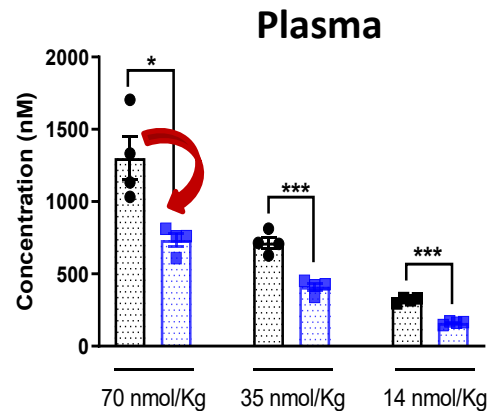
Targeted delivery in brain of mAbs



□ **In vivo** evaluation of ABP-HC-VHH1 vs ABP brain delivery after intravenous injection at 14, 35 and 70 nmol/kg to VHH17/BL6 mice at 2h post i.v



Brain microcapillary depletion is used to separate the BBB from the post-vascular brain compartments (ECF and parenchyma)

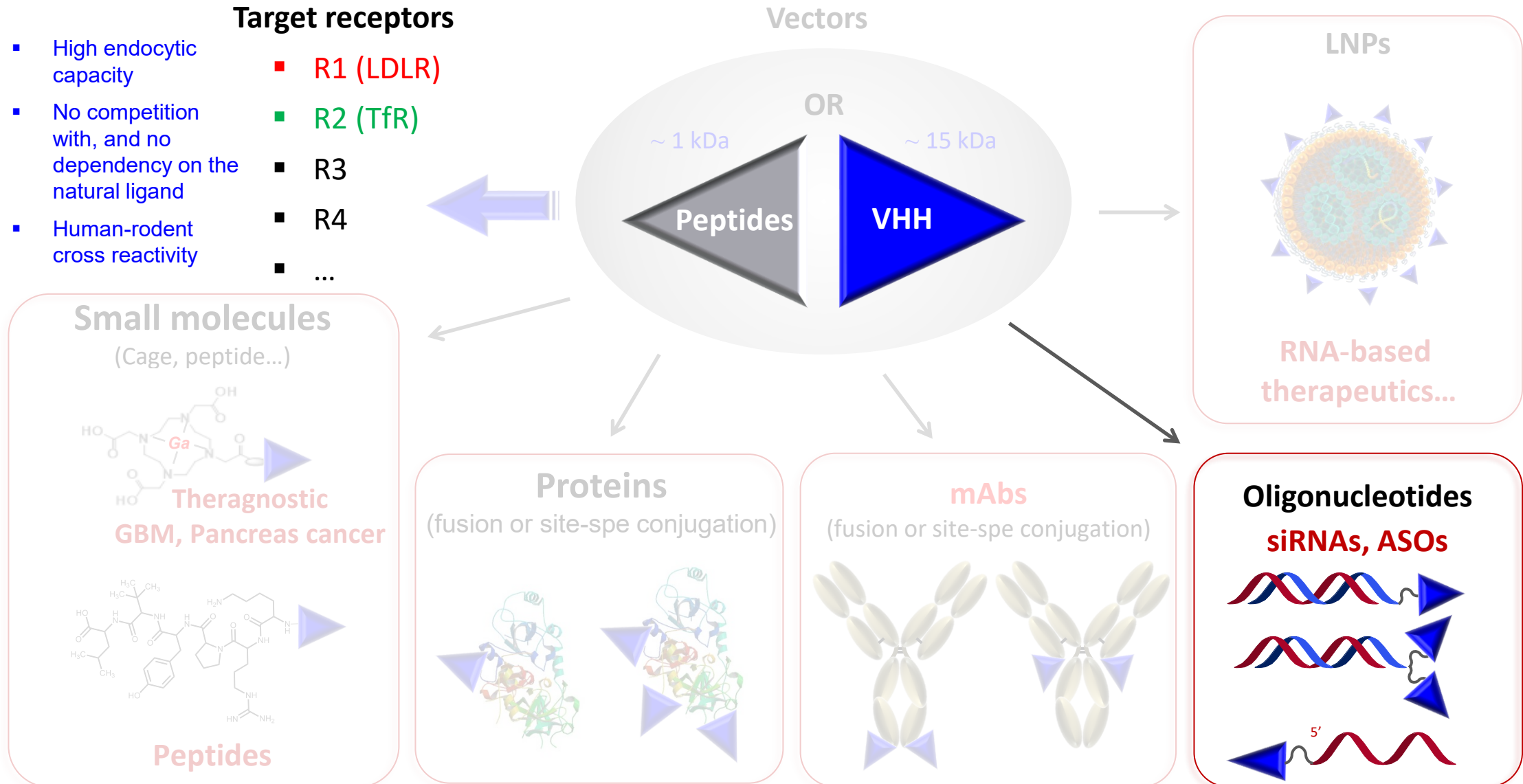


⇒ Lower plasma exposure with vectorized ABP antibody compared to non-vectorized ABP, consistent with **TfR-mediated distributional clearance**

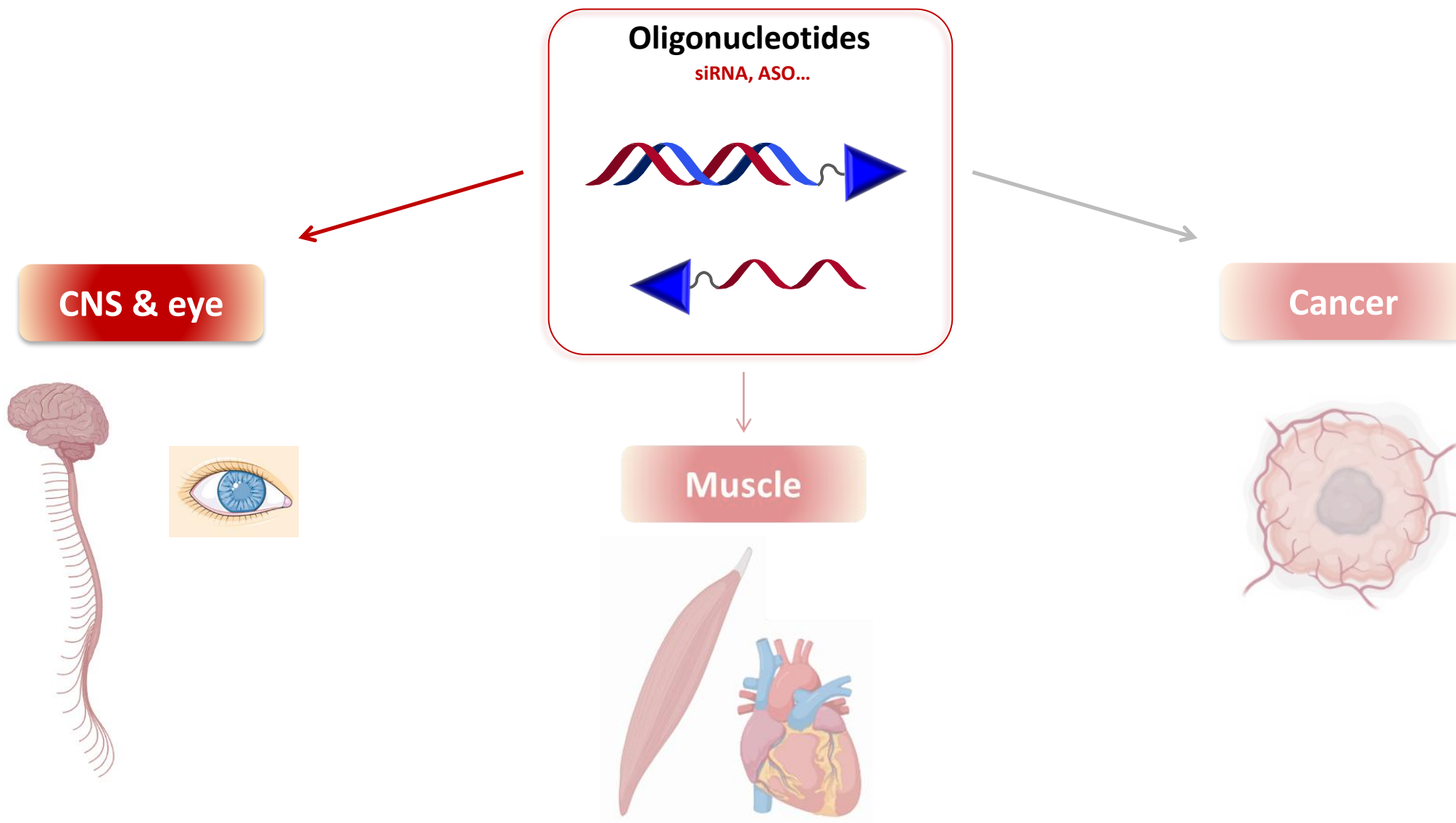
⇒ Accumulation in brain microvessels, indicating **BBB targeting**

⇒ Accumulation in brain parenchyma, indicating **BBB crossing**

Conjugation versatility of VHH-based vectors: **oligonucleotides**



Exploring VHH_{TfR}-Oligo conjugates for a wide range of disease areas



Potent KD potential of VHH_{TfR}-hFc-siRNA across all brain regions after systemic RoA at low dose

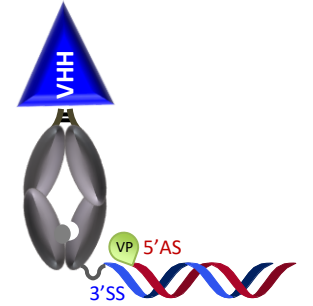


Systemic **multi IV vs. single SC** of **VHH-hFc-siSOD1-5'VP** in C57Bl/6 mice
14 days after last administration
(ISH on left hemisphere)

Multi-dose IV
3x 1.5 mpk (Q2Dx3)

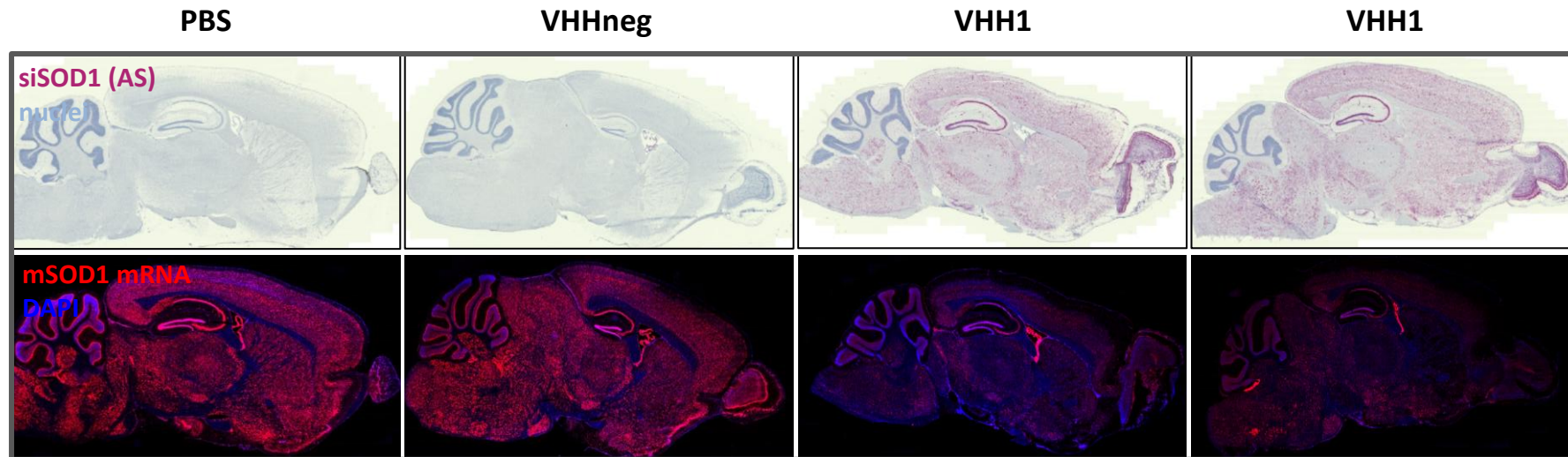


Single dose SC
4.5 mpk



siSOD1 AS
biodistribution
(miRNAScope®)

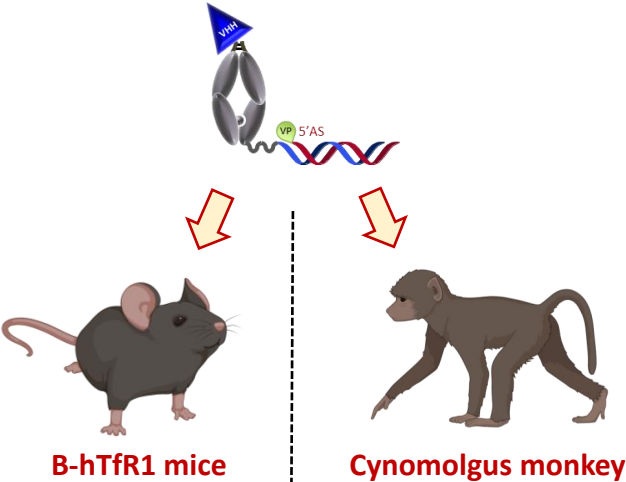
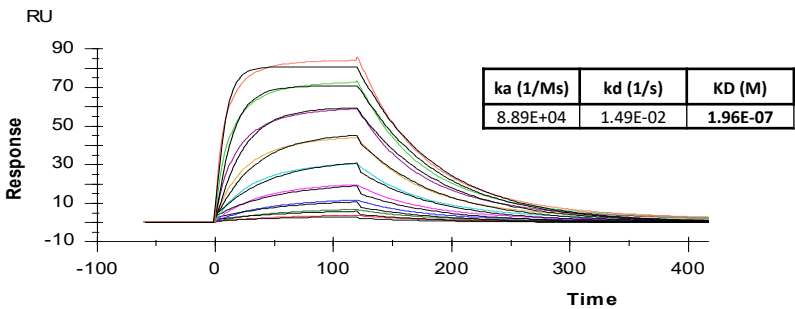
SOD1 mRNA
Knock-Down
(RNAScope®)



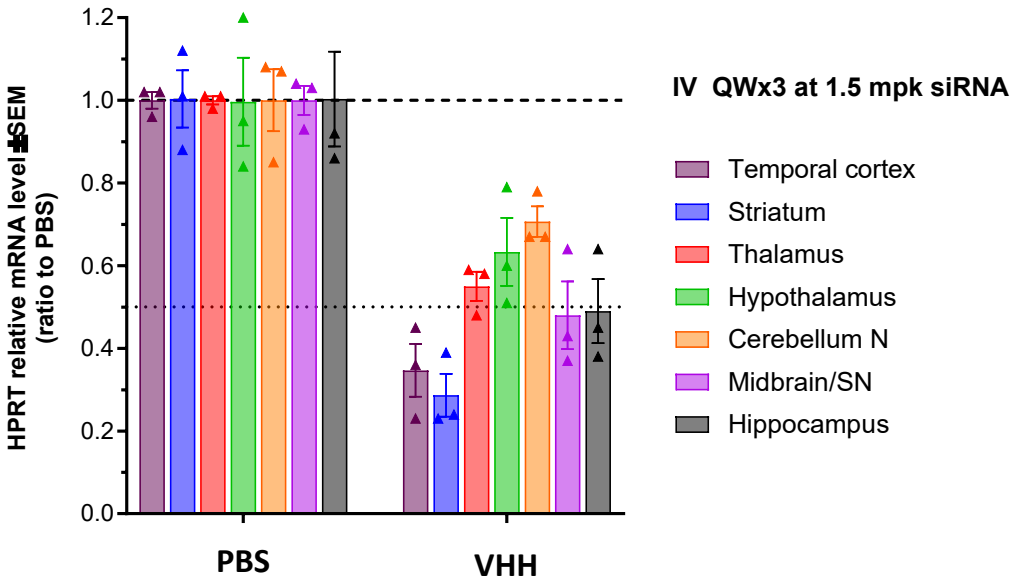
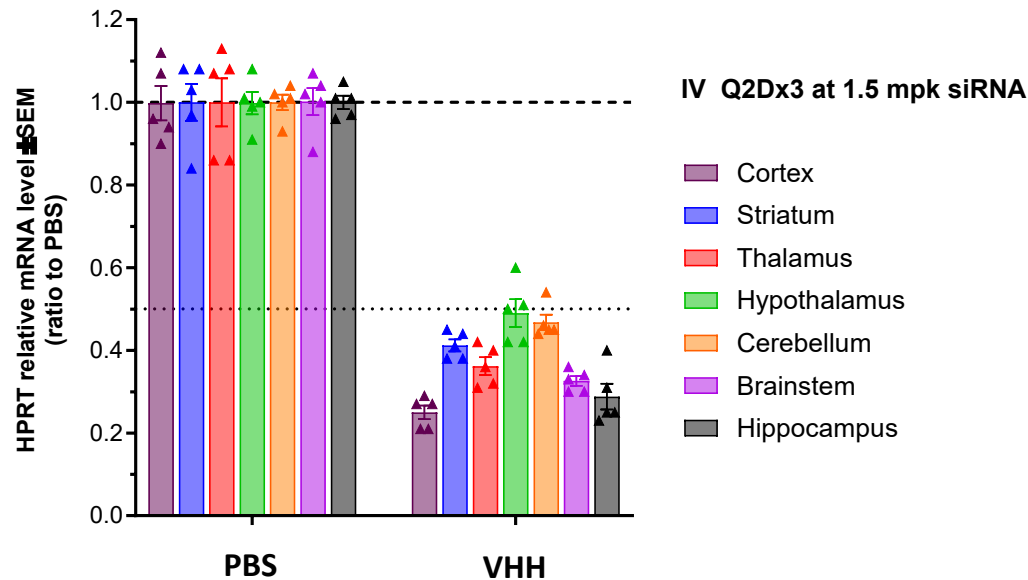
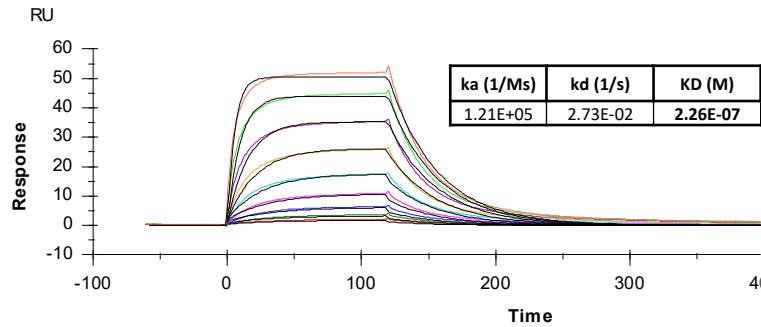
⇒ TfR-dependent distribution in the brain correlates with broad target mRNA KD

Same VHH variant with h/NHPTfR cross-reactivity leads to similar target engagement in B-hTfR mice and NHP

VHH-hFc-siHPRT in hTfR-mice



VHH-hFc-siHPRT in NHP



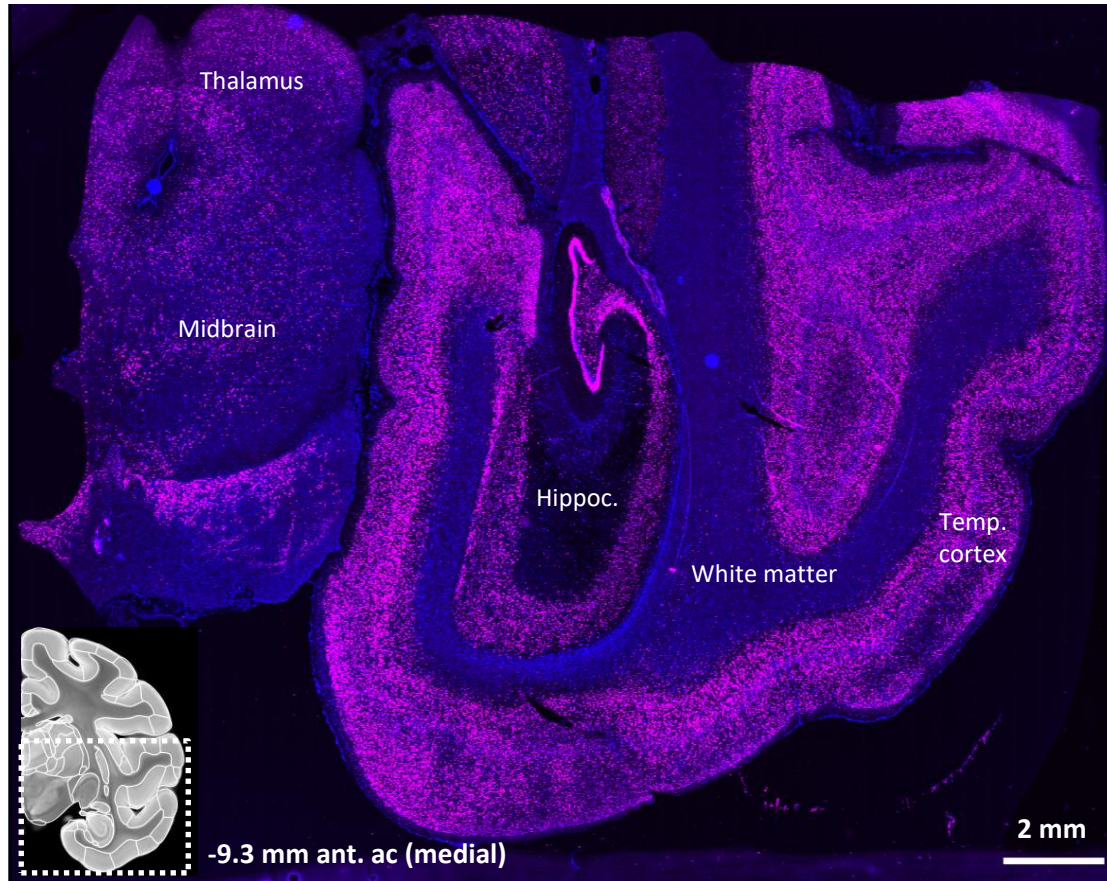
VECTrans[®] achieves robust target engagement in the deep brain in monkeys

ISH - RNAScope[™]

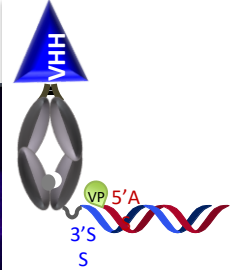
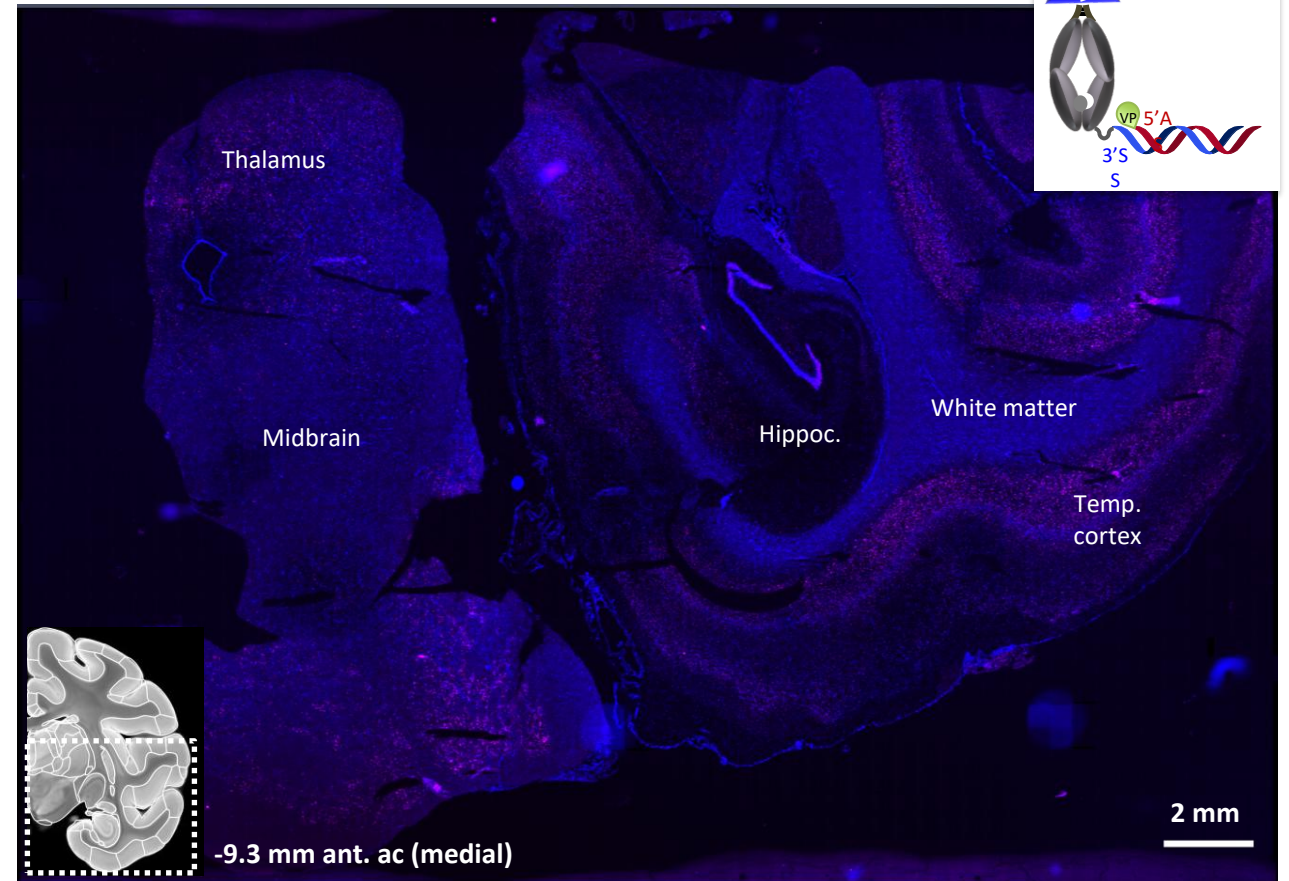
Vehicle

Shown is 1 representative animal from each group

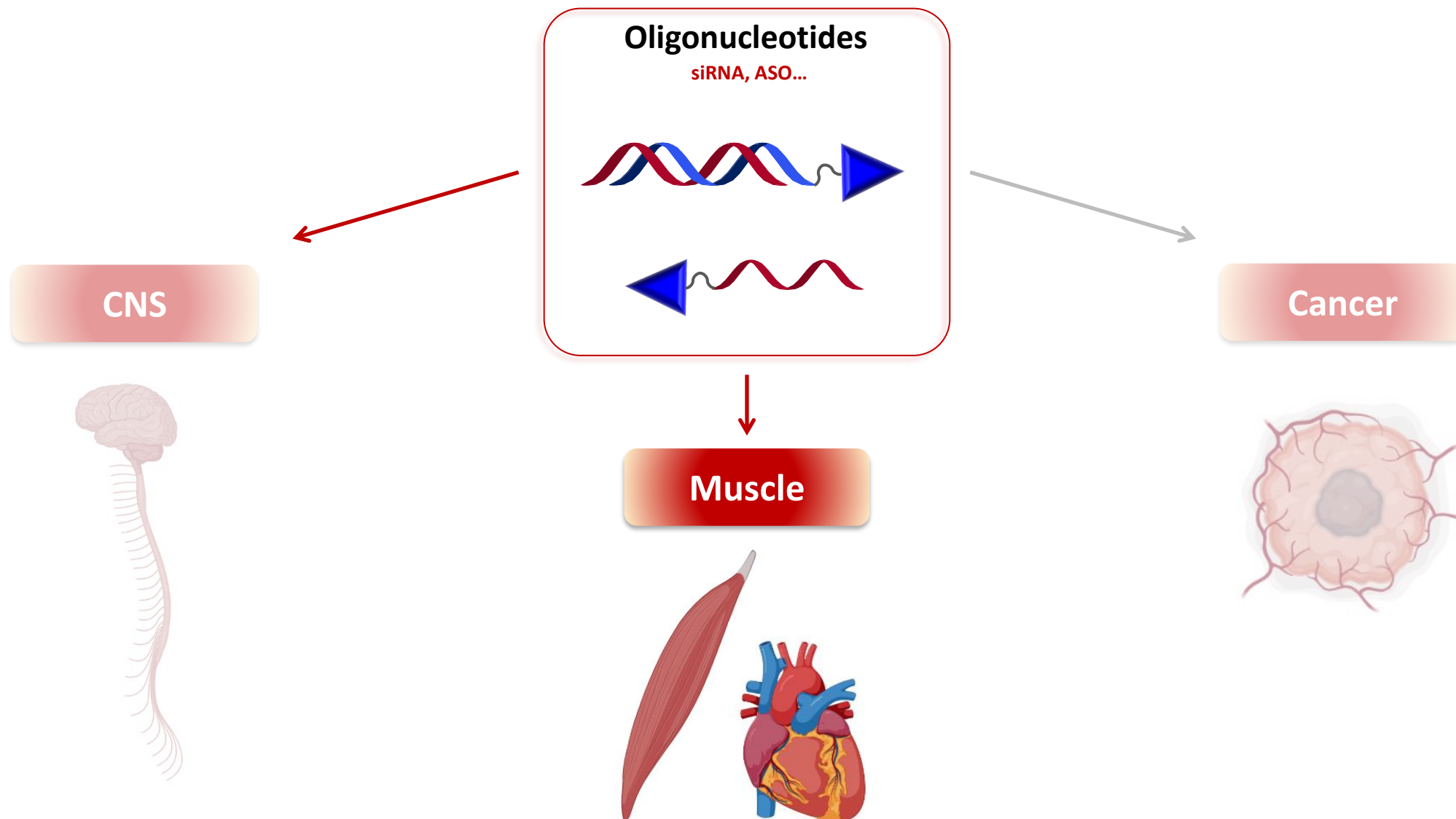
DAPI / *HPRT* mRNA



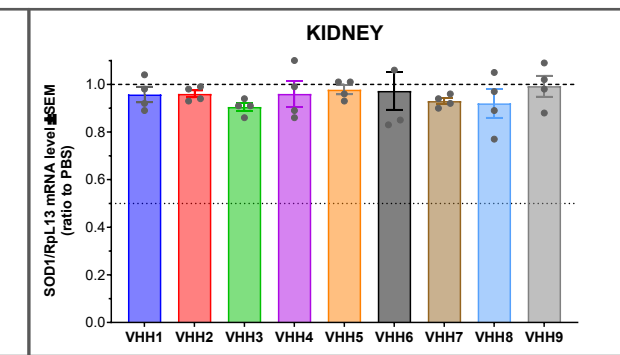
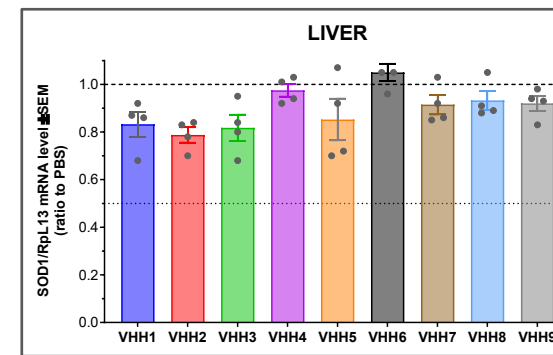
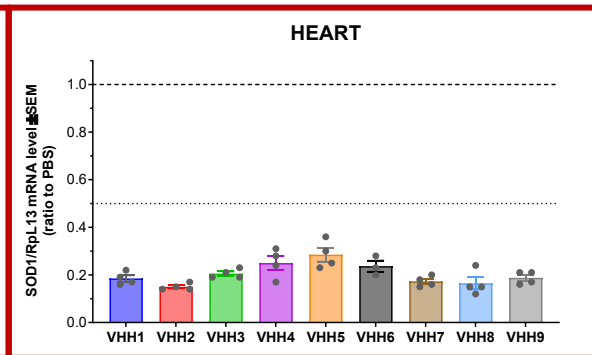
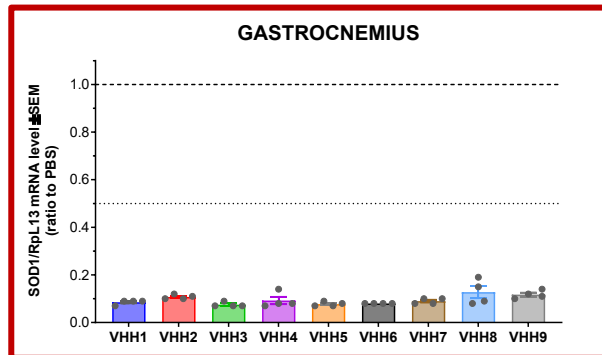
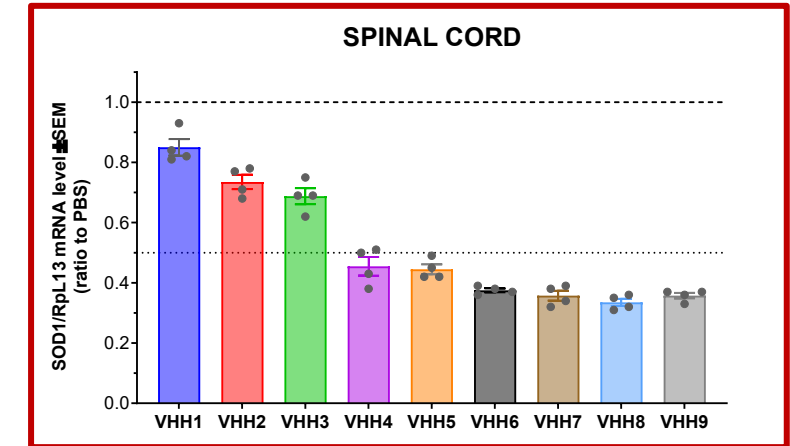
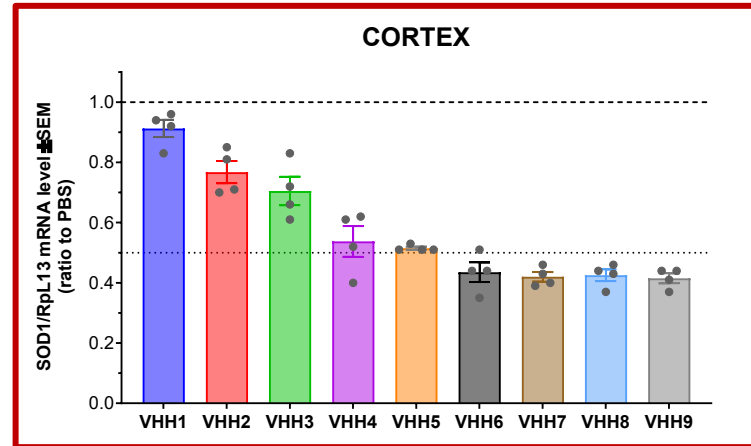
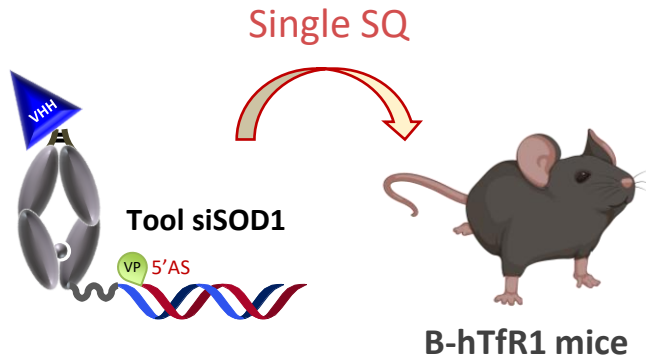
VHH-hFc-siHPRT



Exploring VHH_{TfR}-Oligo conjugates for a wide range of disease areas

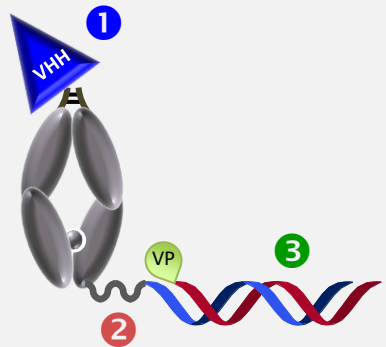


Different VHH_{TfR} allow muscle-specific vs. muscle/CNS functional delivery

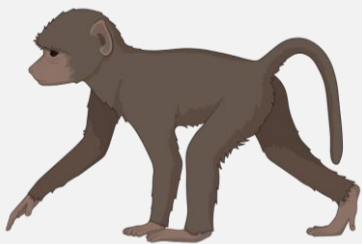


VHH-hFc-siSOD1 single SC 4.5 mpk siRNA, B-hTfR mice (ECD-hTfR^{+/+}), 14 days.

VHH_{TfR}-Oligo conjugate



- 1 VHH_{TfR} variant, TfR-binding, NHP/Human cross-reactivity
- 2 DAR=1, site, linker
- 3 Oligo = siRNA (low intrinsic uptake), optimized chemistry



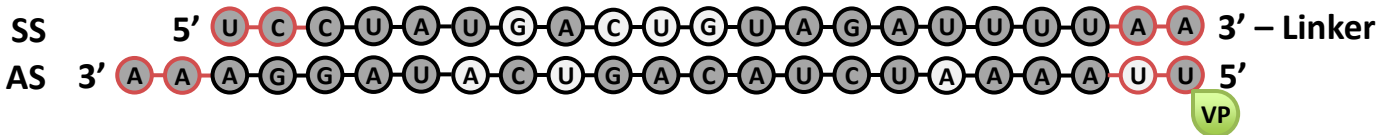
Cynomolgus monkey

IV, low dose

1.5 mpk siRNA, QWx3

Sac 28d

HPRT tool siRNA



2'-sugar modifications

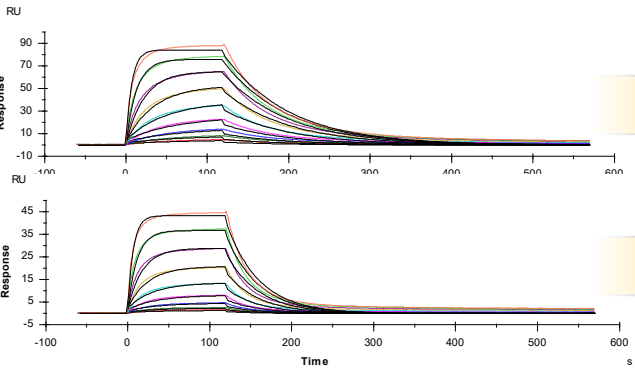
- 2'-OMe
- 2'-F

Backbone modifications

- Phosphorothioate
- Phosphodiester

VP 5'-vinylphosphonate

TfR-binding of VHH-hFc-siHPRT (SPR)

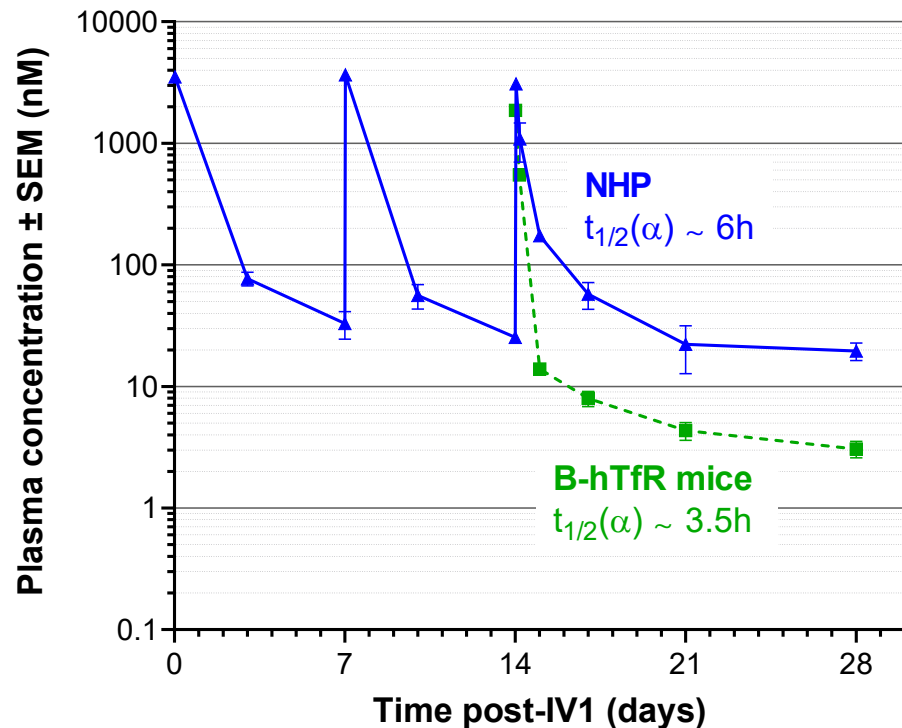


	k_{on} ($M^{-1}.s^{-1}$)	k_{off} (s^{-1})	K_D (M)
hTfR	1.12E+05	1.43E-02	1.29E-07
cynoTfR	1.04E+05	2.82E-02	2.75E-07

VECTrans[®] achieves robust target engagement in the deep brain in monkeys

Plasma PK

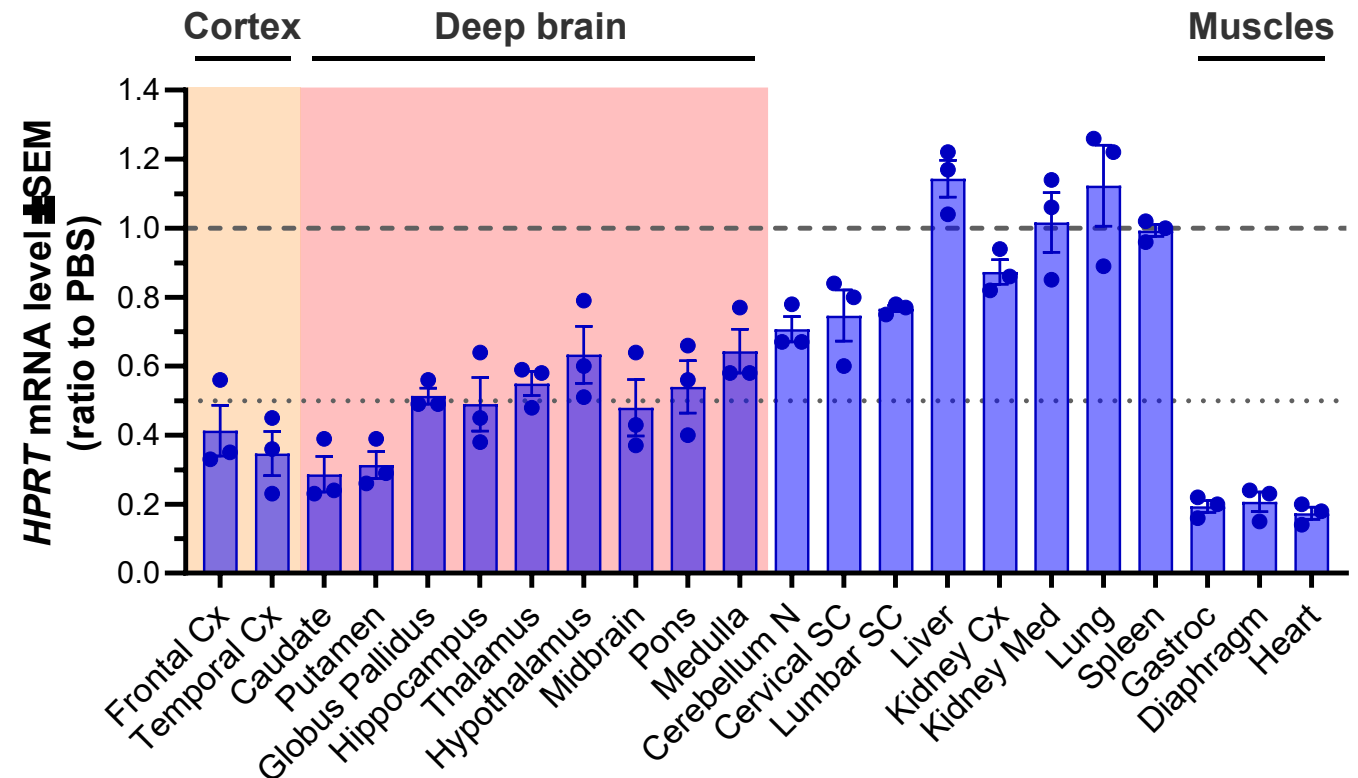
(BA method: ELISA VHH-hFc)



⇒ Extensive distributional clearance, yet significantly lower than in B-hTfR mice

Target mRNA knockdown across CNS & peripheral tissues

(1.5 mpk siRNA, QWx3, sac 28d)



⇒ Up to 70% target KD in the deep brain

PROPOSED COLLABORATION

1. FEASIBILITY STUDY

to select, optimize, validate :

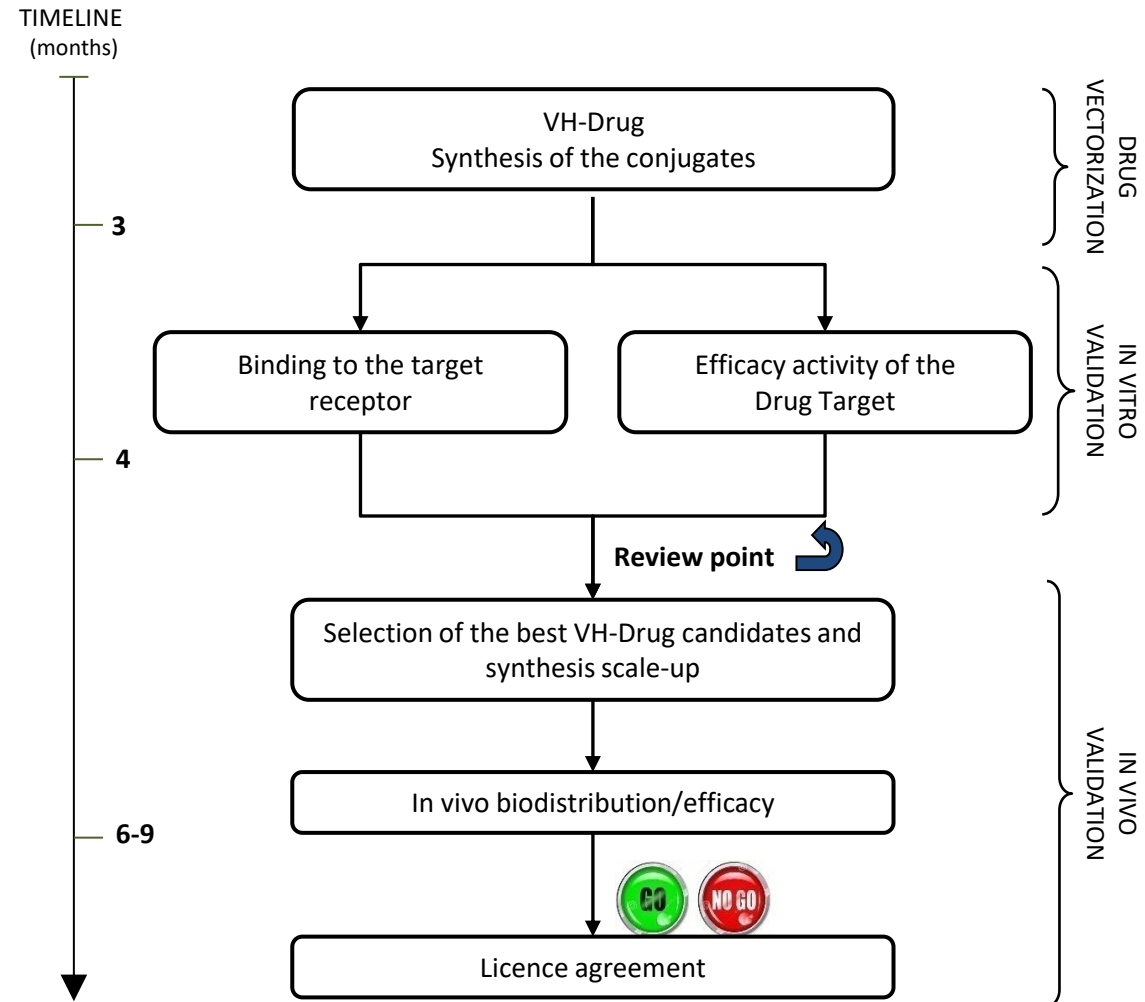
- the partner's product conjugated to VHs' vector(s),

2. LICENSE

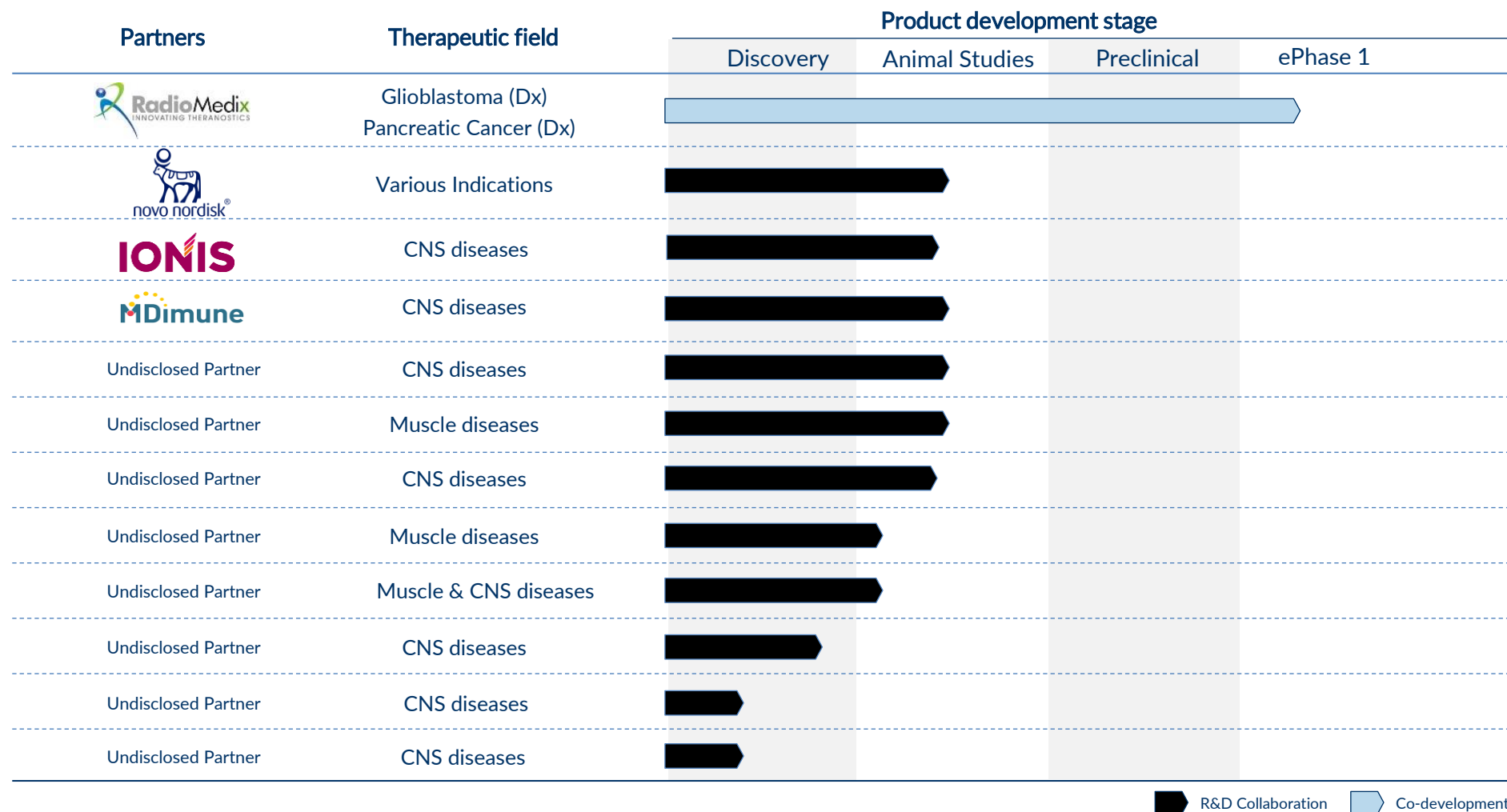
- on the conjugate coming from the feasibility study
- on VHs' patents.

FINANCIAL TERMS

- FTE for feasibility study
- Fees access, development milestones and royalties through the license.



Pipeline: Collaborations R&D



C- Propriété Intellectuelle

APPLICATION N°	TITLE	PRIORITY DATE	STATUS
WO 2010/046588	Peptide derivatives and use thereof as carriers for molecules in the form of conjugates	22/10/2008	Issued in France, Europe (22 countries), USA, Canada, South Africa, India, Eurasia, Australia, Brazil, China & Japan
WO 2011/131896	Peptide derivatives, preparation thereof and uses thereof	21/04/2010	Issued in France, Europe, USA, Canada, Eurasia, Australia, India, Brazil, China & Japan.
WO 2014/060601	Compositions and methods for drug delivery	19/10/2012	Issued in USA, China, Europe & Japan
WO 2018/138372	Compositions and methods for cancer imaging and radiotherapy	19/01/2017	Granted in Australia, Eurasia & USA. Pending in Europe, Canada, India, Brazil, China & Japan.
WO 2020/144233	Transferrin receptor-binding molecules, conjugates thereof and their uses	09/01/2019	Entered National Phases under PCT
WO2024089201	Lung Receptor-binding Molecules, Conjugates Thereof and their Uses to Detect, Prevent or Treat Lung Diseases	27/10/2022	Entered National Phases under PCT
EP 23 306000	Transferrin receptor-binding molecules, conjugates thereof and their uses to prevent or treat muscular diseases	22/06/2023	Filed in Europe. PCT June 22, 2024
EP 23 306002	Transferrin receptor-binding molecules, conjugates thereof and their uses to prevent or treat CNS diseases	22/06/2023	Filed in Europe. PCT June 22, 2024

THANK YOU FOR YOUR ATTENTION!



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