April 12, 2023

The Challenge is Delivery: Showcasing Opportunity in the Peripheral / Central Nervous System

Presenter: Samantha Sarett, Genetic Medicine

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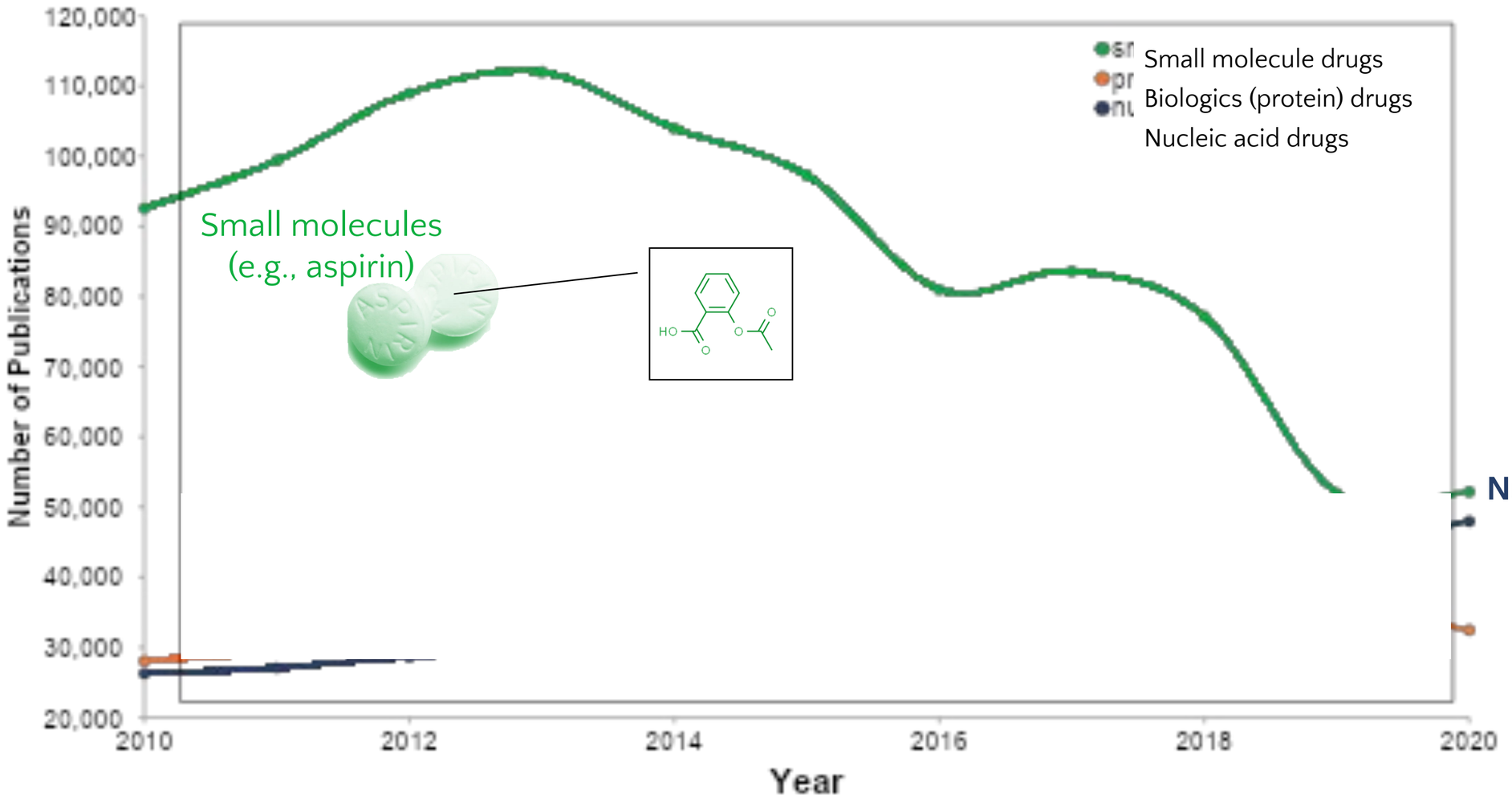
Eli Lilly and Company[1]; Mass. Eye and Ear [2]; Northeastern University[3]

Outline

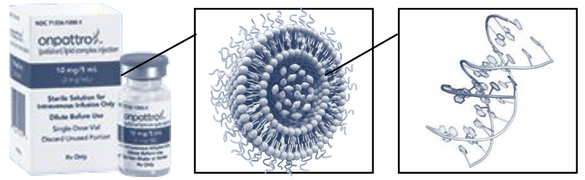
- Nucleic acid delivery background
- Peripheral / central nervous system delivery
  - Clinical status
  - Long-term vision
- An exploratory route: Nose-to-brain spotlight
- Looking ahead

Genetic Medicine Background

Increasing Interest in Nucleic Acid Drugs

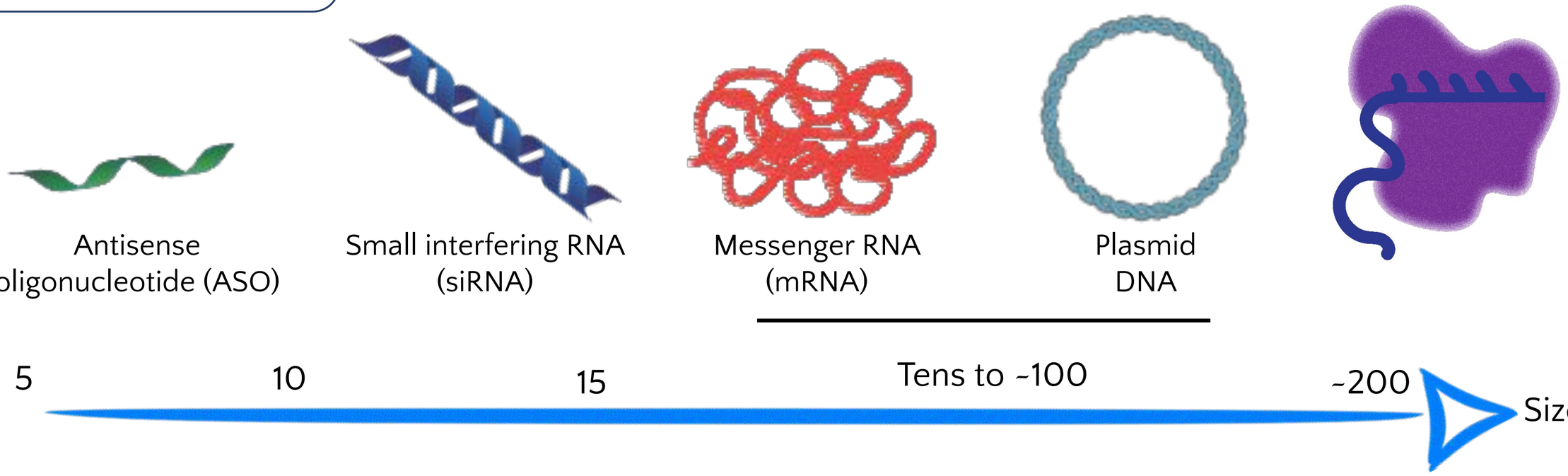


Nucleic acid drugs
(e.g., siRNA)



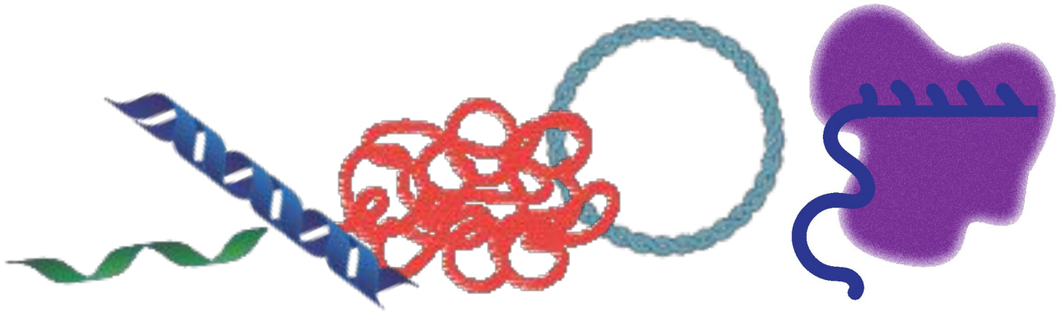
Nucleic Acids: A Diverse Class of Drugs

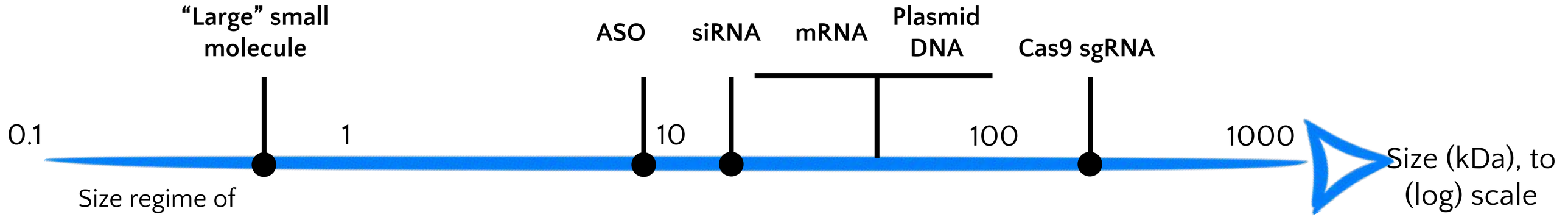
The class is diverse, but the **delivery challenge is consistent**



…With Challenging Delivery Properties

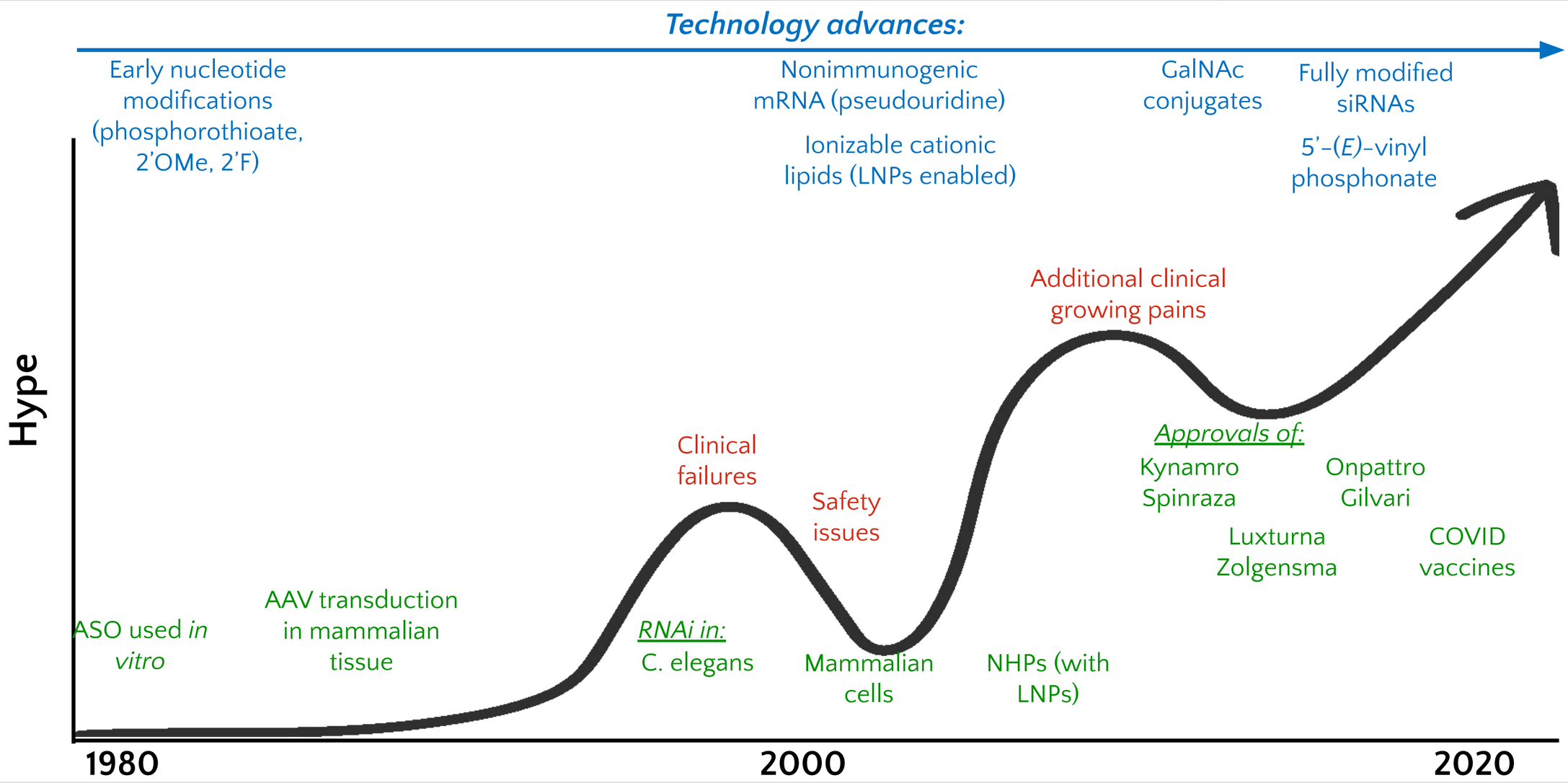
Large size, hydrophilicity, and potential for degradation *in vivo* necessitates technology advances for this class





Size regime of drugs with classically “good” pharmacokinetic properties

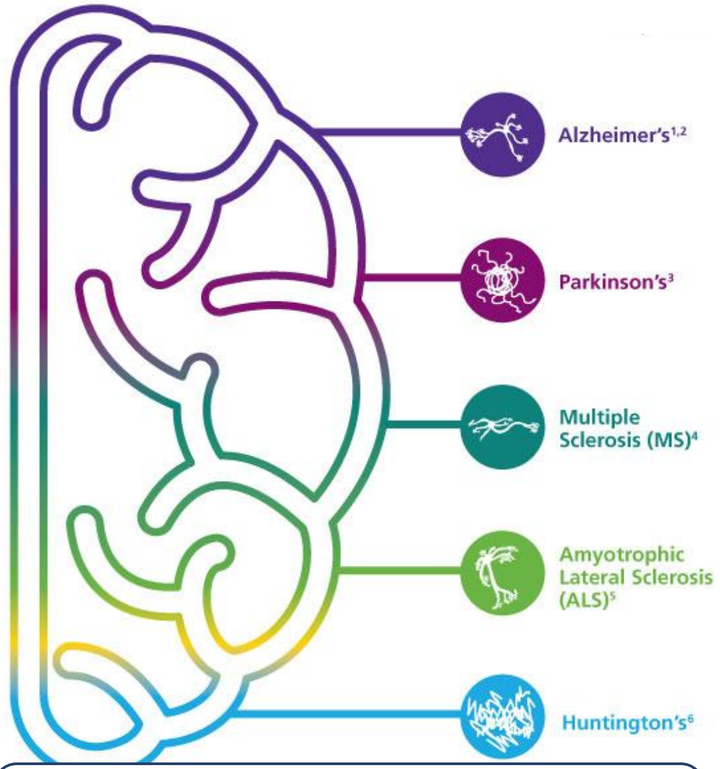
Progress as Technology Advances



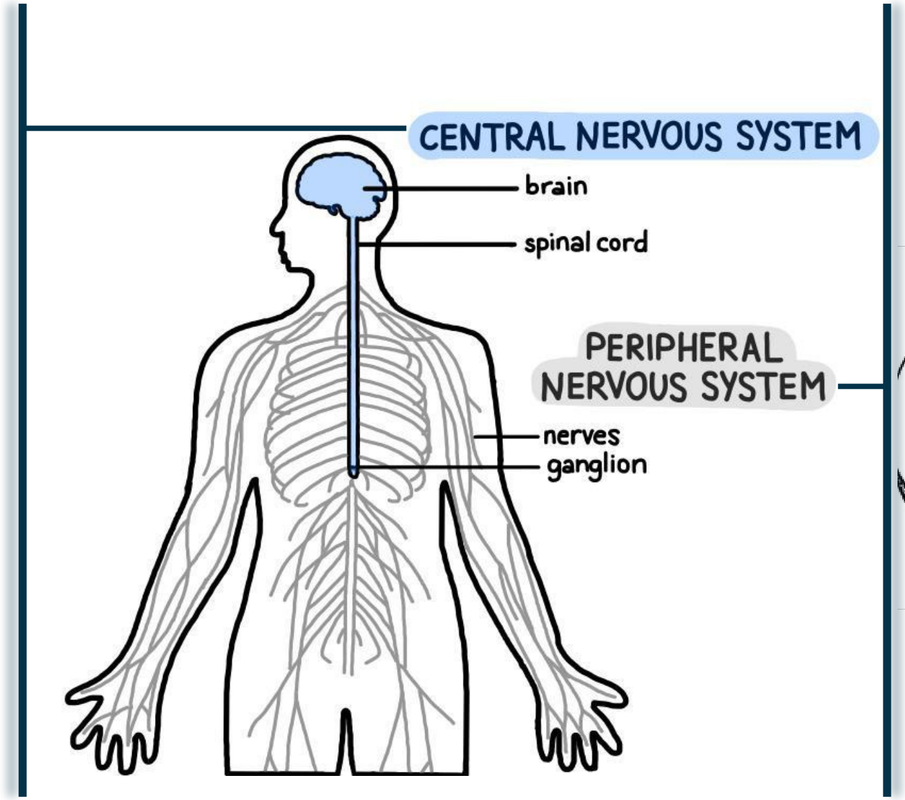
Adapted from Setten RL et al. 2019, Nat Rev Drug Discovery.

Peripheral / Central Nervous System Delivery

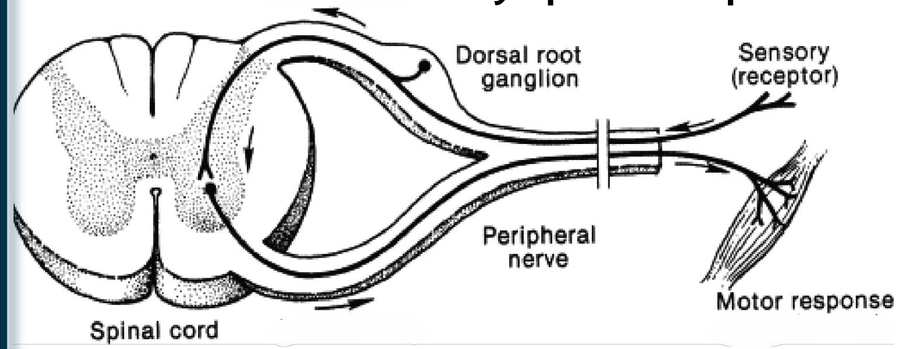
The Opportunity is the Clinical Impact



Devastating indications lack disease-modifying treatments



PNS mediates sensory (pain) response



1/5 of adults in the U.S. experience chronic pain

https://www.simplypsychology.org/peripheral-nervous-system.html

So How Do We Deliver?

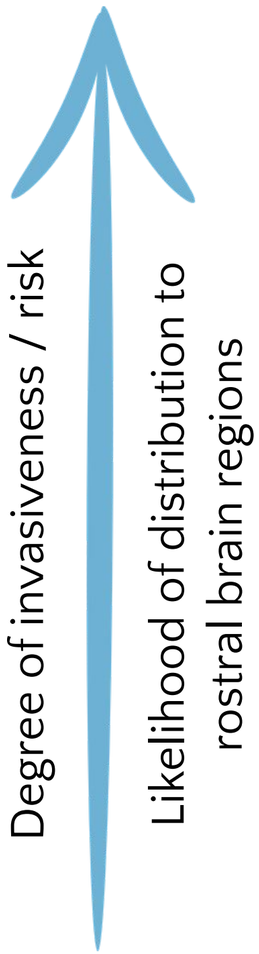
Achieving effective delivery to P/CNS targets is particularly challenging

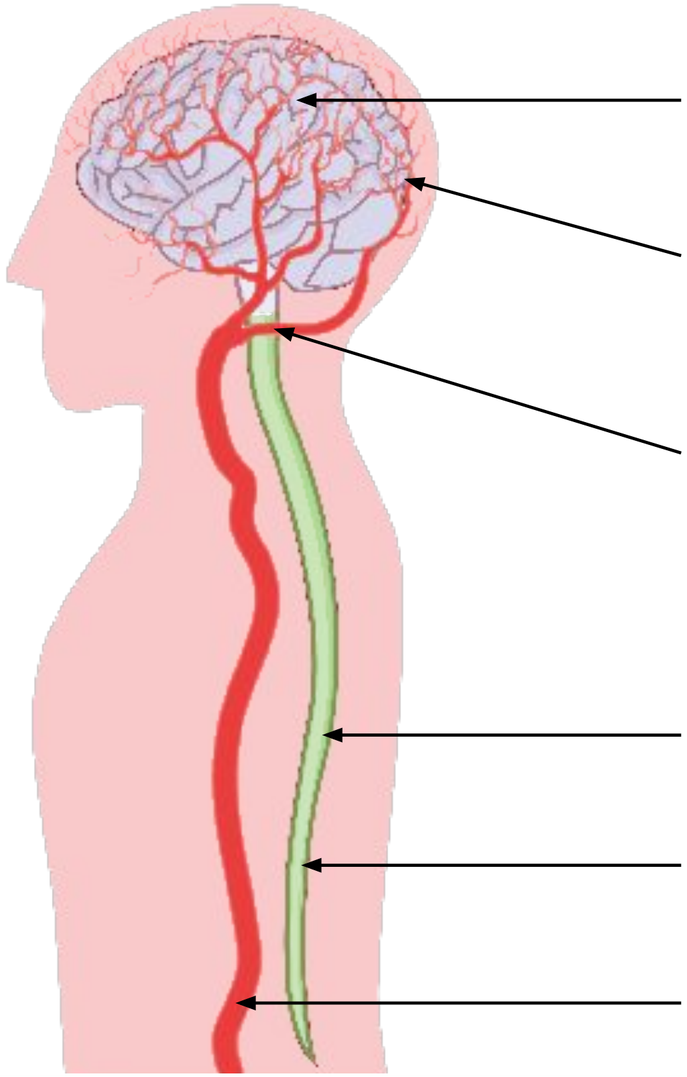
https://mbi.ufl.edu/research/research-areas/chronic-neurological-diseases/
cdc.gov. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229282/pdf/main.pdf

How Do We Deliver: Route Overview

Achieving effective delivery to P/CNS targets is particularly challenging

Invasive routes of administration are the norm





Intracortical (IC) injection into brain tissue itself

Intracerebroventricular (ICV) injection into cerebral lateral ventricles

C4 / C5; site of intracisterna magna (ICM) injection

L1; common site of catheter termination / drug exit

L4 / L5; site of intrathecal (IT) injection

Systemic administration (delivery across blood-brain-barrier)

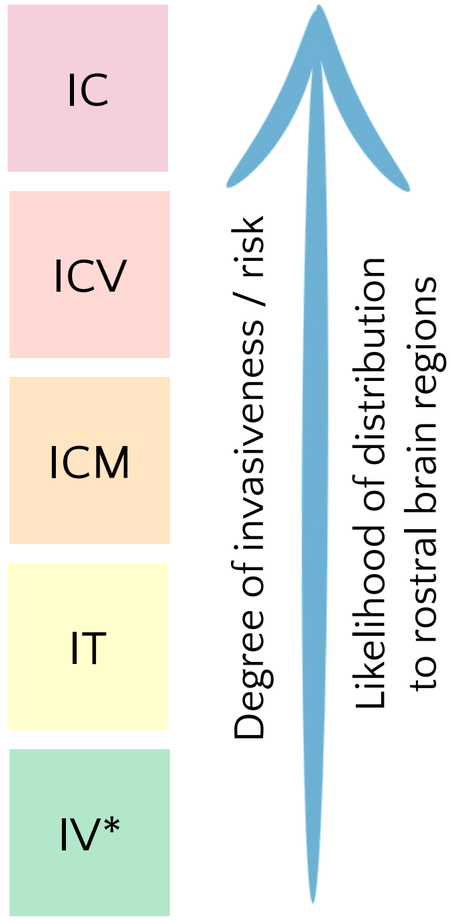
https://mbi.ufl.edu/research/research-areas/chronic-neurological-diseases/
cdc.gov. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229282/pdf/main.pdf

Clinical Status

Clinical Routes Reflect the Challenge

Drug	Indication	Company	Status	RoA
Antisense oligonucleotides (ASOs) and small interfering RNA (siRNA)				
Nusinersen (Spinraza)	**SMA**	**Ionis/Biogen**	**Approved**	**IT**
Tofersen (Qalsody)	**ALS**	**Ionis/Biogen**	**Approved**	**IT**
Ulefnersen (FUS ASO)	ALS	Ionis	P3	IT
Tominersen (HTT ASO)	HD	Ionis / Roche	P2	IT
(IONIS-MAPTRx (Tau ASO)	AD	Ionis/Biogen	P2	IT
Zilganersen (GFAP ASO)	Alexander disease	Ionis	P2	IT
WVE-003 (HTT ASO)	HD	Wave Life Sciences	P1/2	IT
ION859 (LRRK2 ASO)	PD	Ionis	P1	IT
ION464 (SNCA ASO)	MSA	Ionis	P1	IT
ION541 (ATXN2 ASO)	ALS	Ionis	P1	IT
ION260 (ATXN3 ASO)	SCA3	Ionis	P1	IT
ALN-APP (APP siRNA)	Early-onset AD	Alnylam	P1	IT
NI0752 (Tau ASO)	AD	Novartis	P1	IT
GTX-102 (UBE3A ASO)	Angelman syndrome	Ultragenyx	P1	IT

Every small nucleic acid in the clinic for CNS diseases is delivered locally

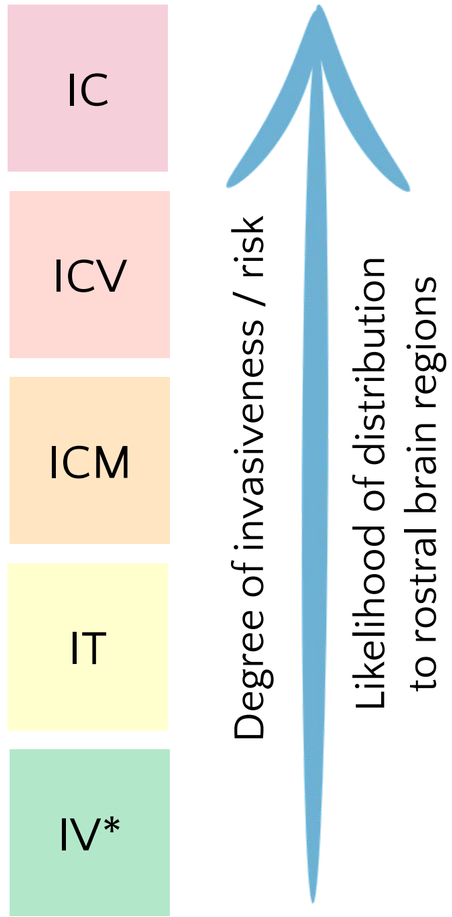


*AAV9 crosses the infant BBB

https://doi.org/10.1016/j.molmed.2021.03.010. Therapeutic AAV Gene Transfer to the Nervous System: A Clinical Reality (cell.com)
Antisense technology: an overview and prospectus (nature.com)

Clinical Routes Reflect the Challenge

Drug	Indication	Company	Status	RoA
Adeno associated viral vectors (AAVs)				
Zolgensma (AAAV9-SMN)	SMA (<6 months)	Avexis/Novartis	Approved	IV
AAVrh10-SGSH	MPSIIIA	Lysogene	P2/3	ICV
AAV2-AADC	PD	Voyager Tx	P2	IC (striatum)
AAV2-NTN	PD	Sangamo Tx	P1/2	IC (putamen and SN)
rAAV9-ZFN for hIDUA	MPSI	Regenxbio	P1/2	ICM
AAV5-NAGLU	MPSIIIB	UniQure Biopharma	P1/2	ICV
AAV9-CLN3/6	Batten disease	Nationwide Children's Hosp.	P1/2	IT
AT-GTX-502 (CLN3)	Batten disease	Amicus	P1/2	IT
SBT101	Adrenomyeloneuropathy	Swan Bio	P1/2	IT
AXO-AAV-GM2	Sandhoff / GM2 disease	Sio Gene Therapies	P1/2	IT
TSHA-120 (GRT)	Giant axonal neuropathy	Taysha Gene Therapies	P1/2	IT
AAV2-AADC	PD	Neurocrine Biosciences	P1	IC
AAV2-GDNF	PD	NINDS	P1	IC (putamen)
AAV2-hNGF	AD	Ceregene	P1	IC (basal forebrain)
AAVrh10-hAPOE2	AD	Weill Medical College	P1	ICM



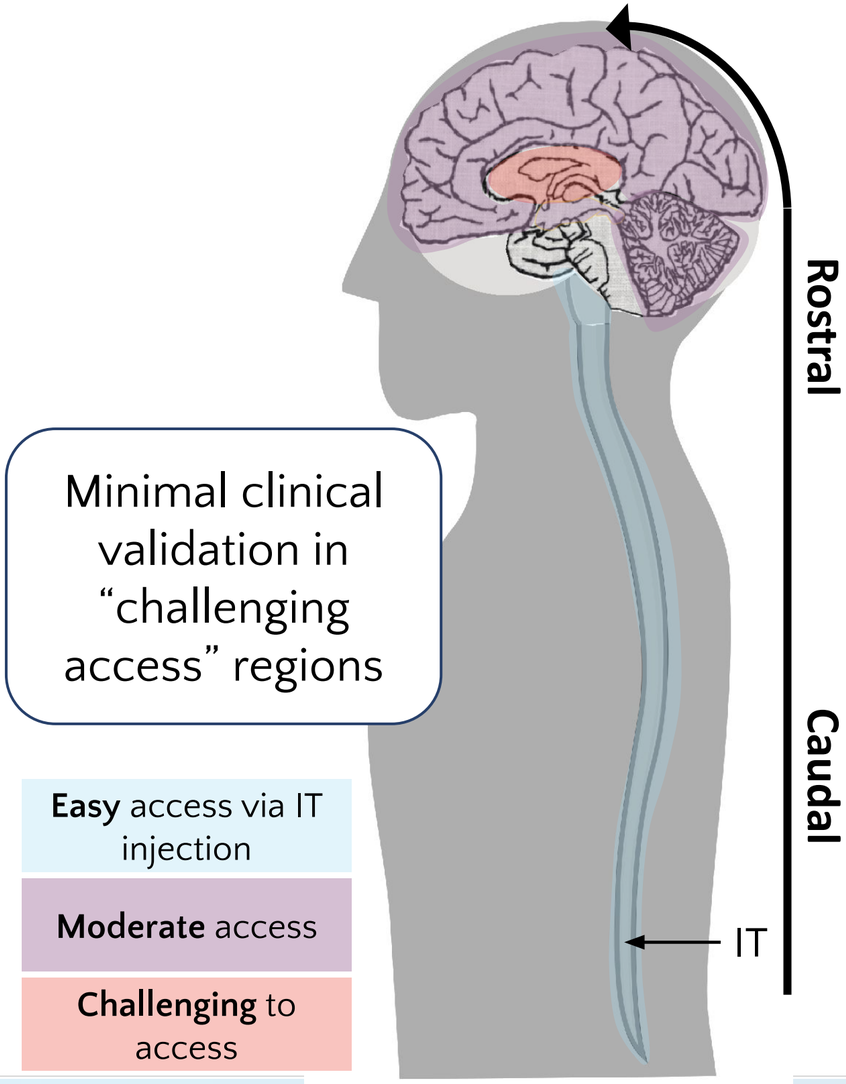
*AAV9 crosses the infant BBB

One-time therapies offer potential to increase invasiveness for greater effect

https://doi.org/10.1016/j.molmed.2021.03.010. Therapeutic AAV Gene Transfer to the Nervous System: A Clinical Reality (cell.com)
Antisense technology: an overview and prospectus (nature.com)

Challenge Differs by Tissue Target

Drug	Indication	Company	Status	Region Target
Antisense oligonucleotides (ASOs) and small interfering RNA (siRNA)				
Nusinersen (Spinraza)	**SMA**	**Ionis/Biogen**	**Approved**	**Spinal cord, brain stem**
Tofersen (Qalsody)	**ALS**	**Ionis/Biogen**	**Approved**	**Spinal cord, cortex**
Ulefnersen (FUS ASO)	ALS	Ionis	P3	Spinal cord, cortex
Tominersen (HTT ASO)	HD	Ionis / Roche	P2	Basal ganglia, cortex
(IONIS-MAPTRx (Tau ASO)	AD	Ionis/Biogen	P2	Cortex, hippocampus
Zilganersen (GFAP ASO)	Alexander disease	Ionis	P2	Brain stem, cerebellum
WVE-003 (HTT ASO)	HD	Wave Life Sciences	P1/2	Basal ganglia, cortex
ION859 (LRRK2 ASO)	PD	Ionis	P1	Basal ganglia
ION464 (SNCA ASO)	MSA	Ionis	P1	Basal ganglia, cerebellum, brain stem
ION541 (ATXN2 ASO)	ALS	Ionis	P1	Spinal cord, cortex
ION260 (ATXN3 ASO)	SCA3	Ionis	P1	ION260 (ATXN3 ASO)
ALN-APP (APP siRNA)	Early-onset AD	Alnylam	P1	Cortex, hippocampus
NI0752 (Tau ASO)	AD	Novartis	P1	Cortex, hippocampus
GTX-102 (UBE3A ASO)	Angelman syndrome	Ultragenyx	P1	Cortex, hippocampus, cerebellum
STK-101 (SCN1A ASO)	Dravet syndrome	Stoke Tx	P1	Hippocampus
Recent ASO failures				
WVE-003 (HTT ASO)	HD	Wave Life Science	P1/2	Basal ganglia, cortex
Tominersen (HTT ASO)	HD	Ionis/Roche	P3	Basal ganglia, cortex
WVE-004 (G4C2 ASO)	ALS / FTD	Wave Life Sciences	P1/2	Cortex, spinal cord



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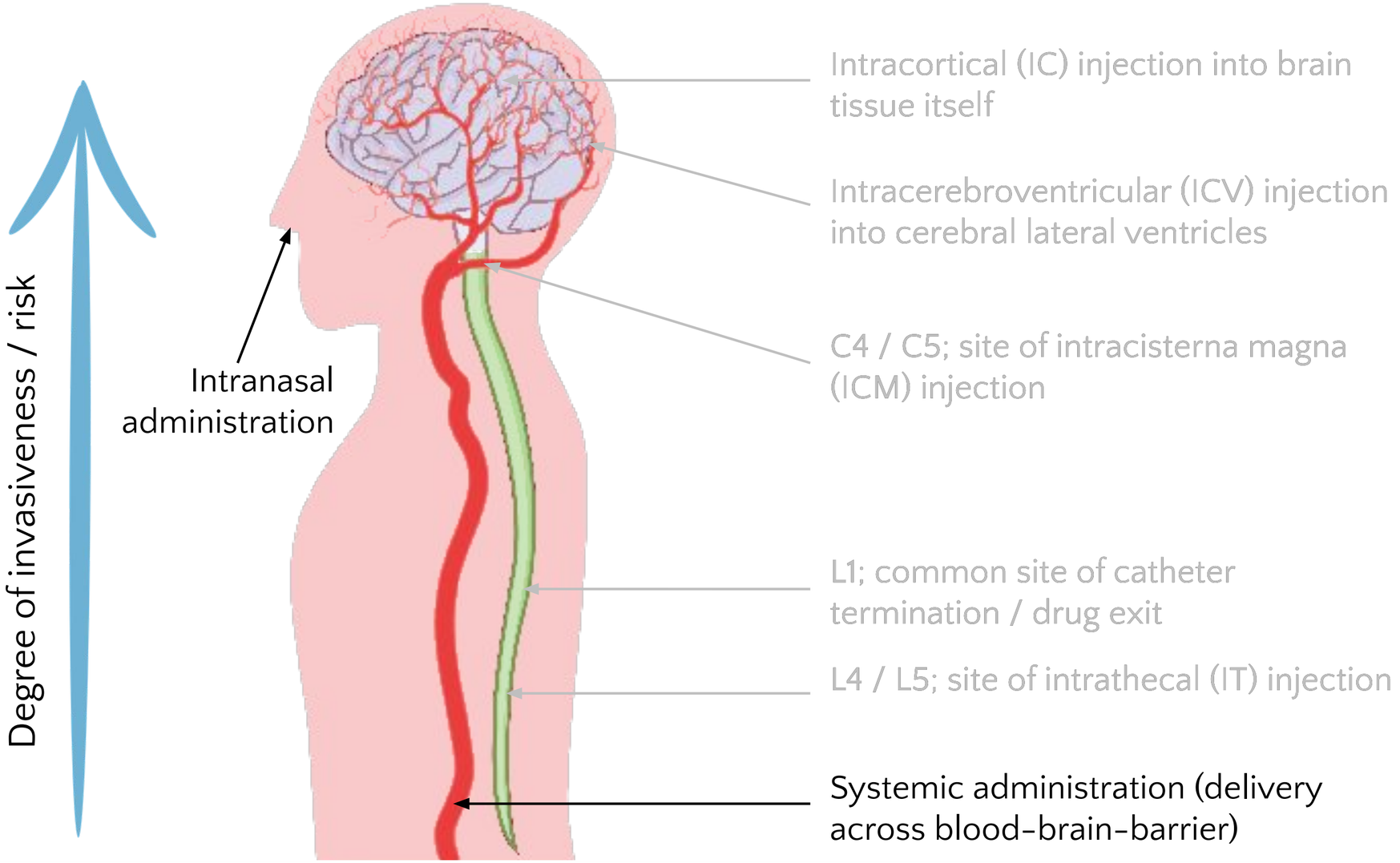
Antisense technology: an overview and prospectus (nature.com)

Long-Term Vision

How Do We Deliver: Ideal World

Achieving effective delivery to P/CNS targets is particularly challenging

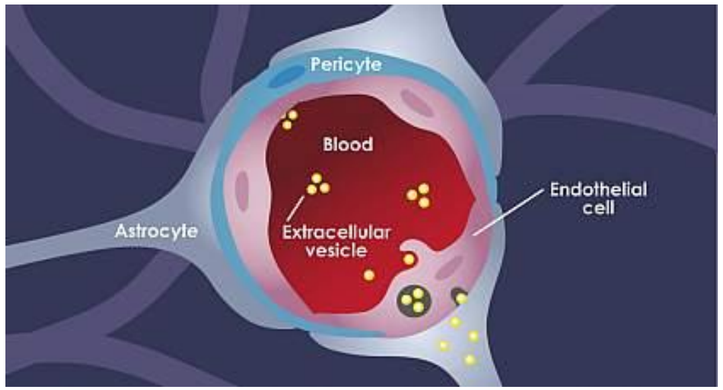
Moving beyond invasive routes of administration is the dream



https://mbi.ufl.edu/research/research-areas/chronic-neurological-diseases/
cdc.gov. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229282/pdf/main.pdf

Looking Beyond Local Administration

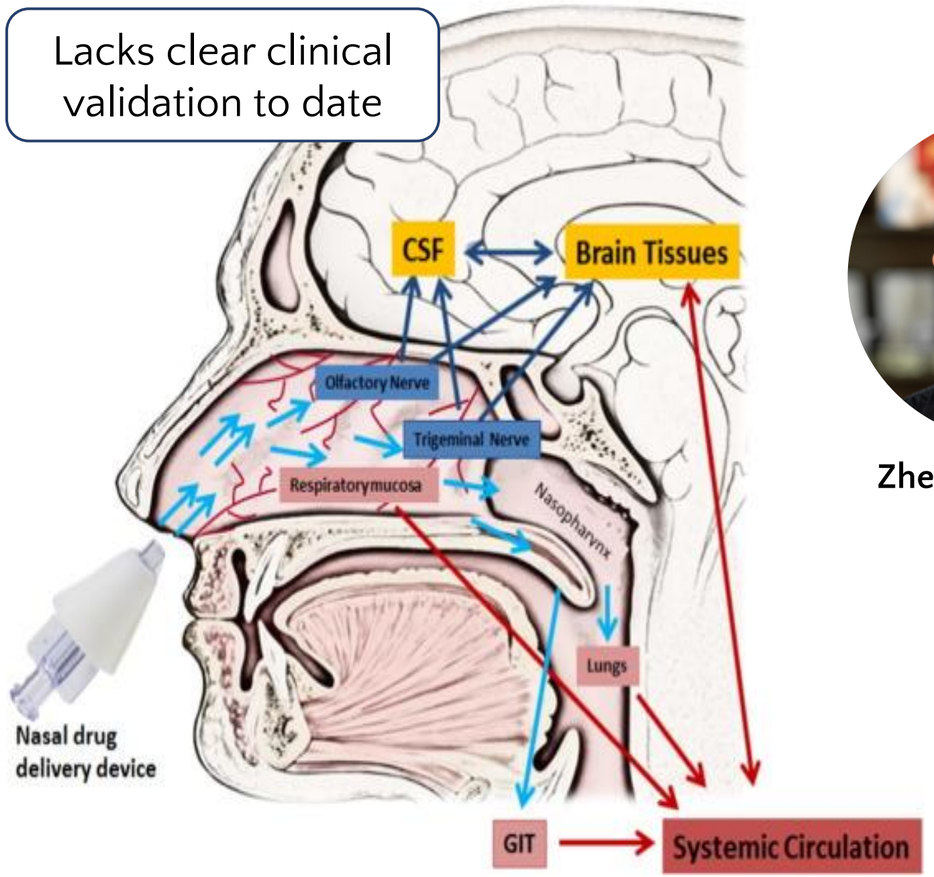
Intravenous administration:
Must cross BBB



Typically poor delivery efficiency (~0.1%) requires prohibitively high doses or delivery advances

Nose-to-brain administration:
Bypasses BBB

Lacks clear clinical validation to date



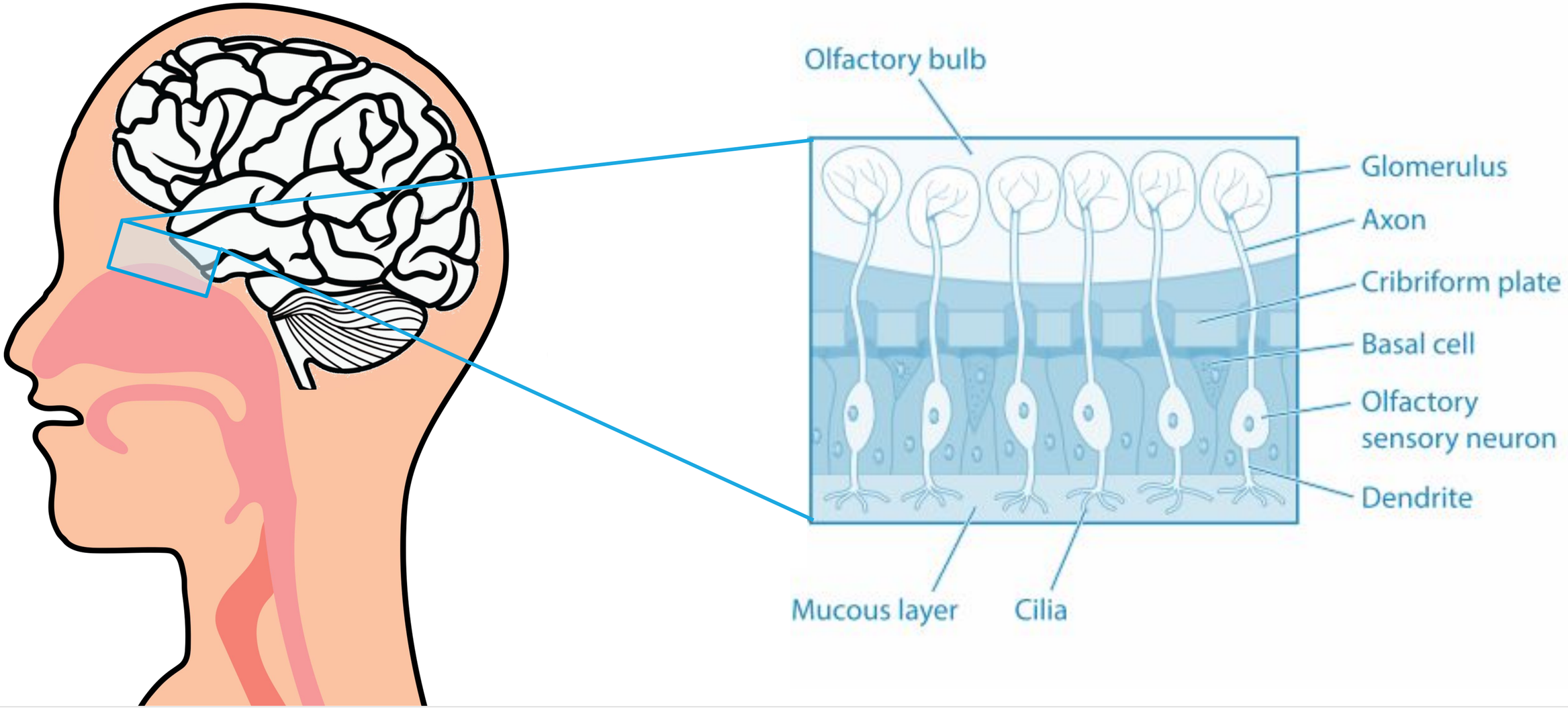
Zhefeng (Eddie) Li

Saeideh Nozohouri

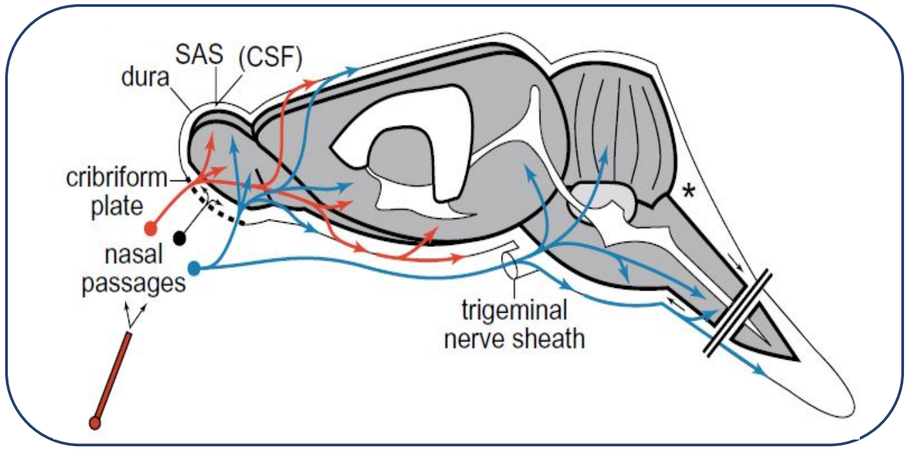
Adapted from Wikipedia. Adatped from NIH. Kapoor et.al. 2016, JCR.

An Exploratory Route: Nose-to-Brain Spotlight

The Site of N2B Delivery

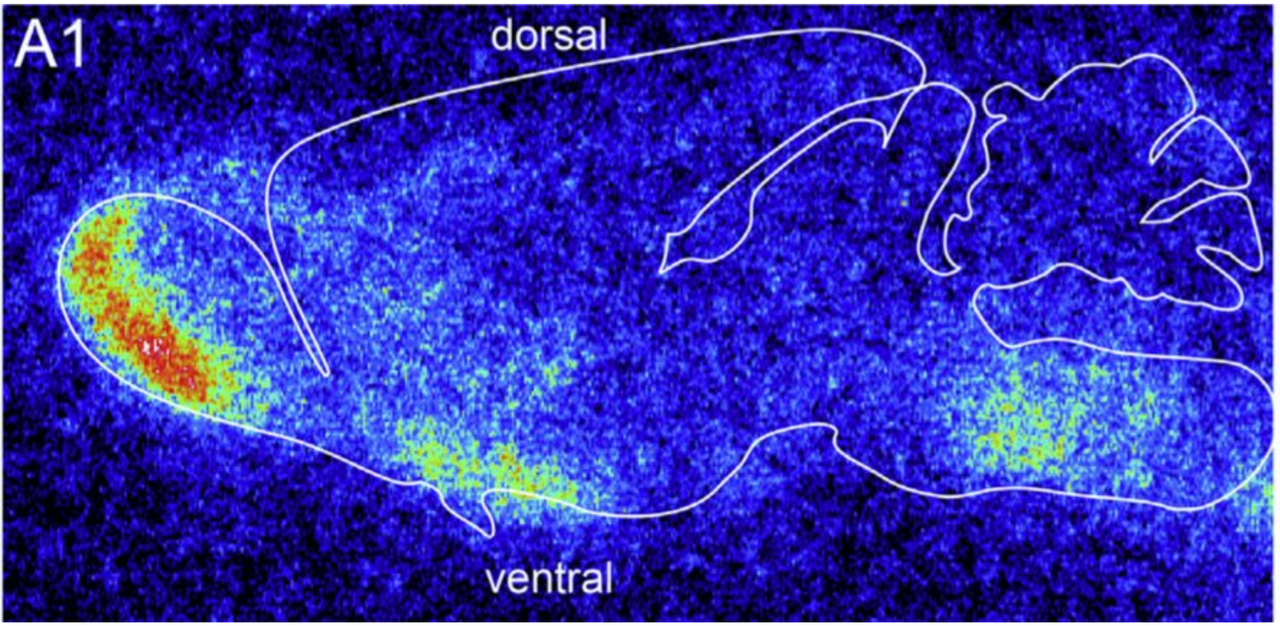


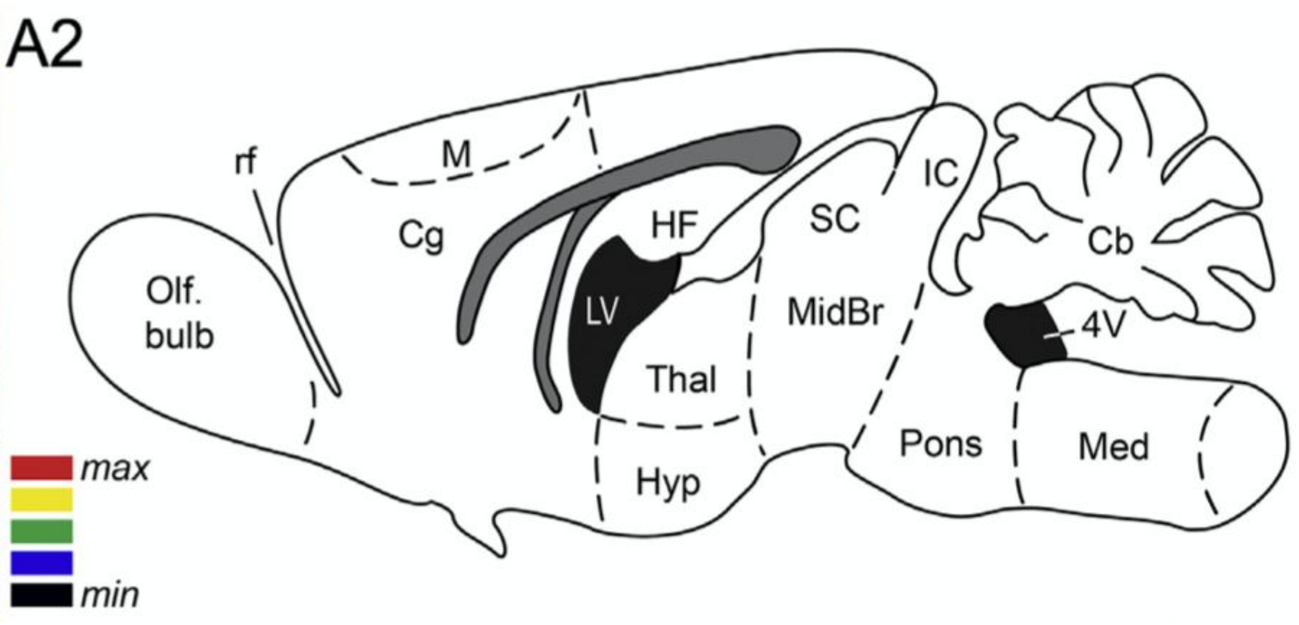
The N2B Transit Route



Proteins (here, IgG) shown to distribute along olfactory and trigeminal nerves in rats within 30 minutes

Extracellular transit pathway (perineural or direct)

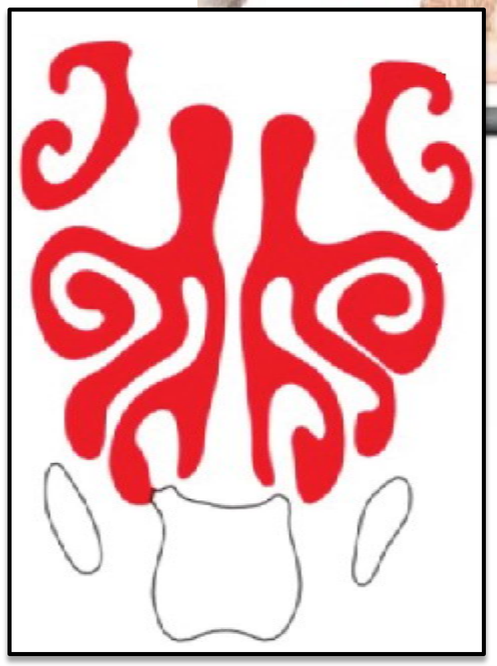




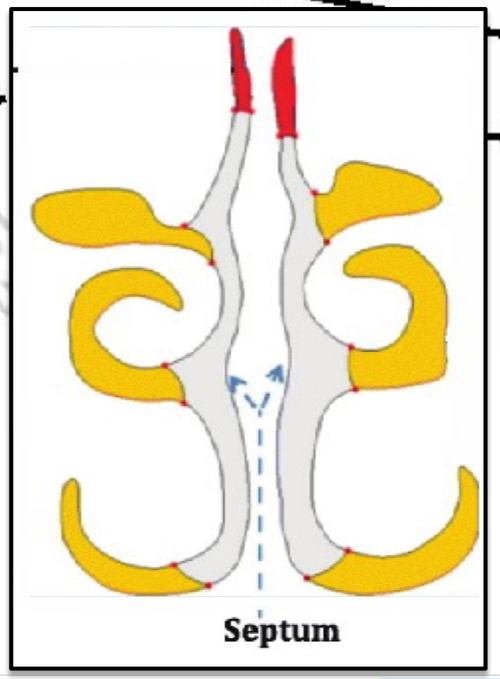
NN Kumar et al. JCR

Problem: Anatomy and Translation

Roden



Olfactory epithelium is ~**50%** of nasal epithelium



NHPs /

Olfactory epithelium is ~**10%** of nasal epithelium

Slide credit: Zhefeng (Eddie) Li

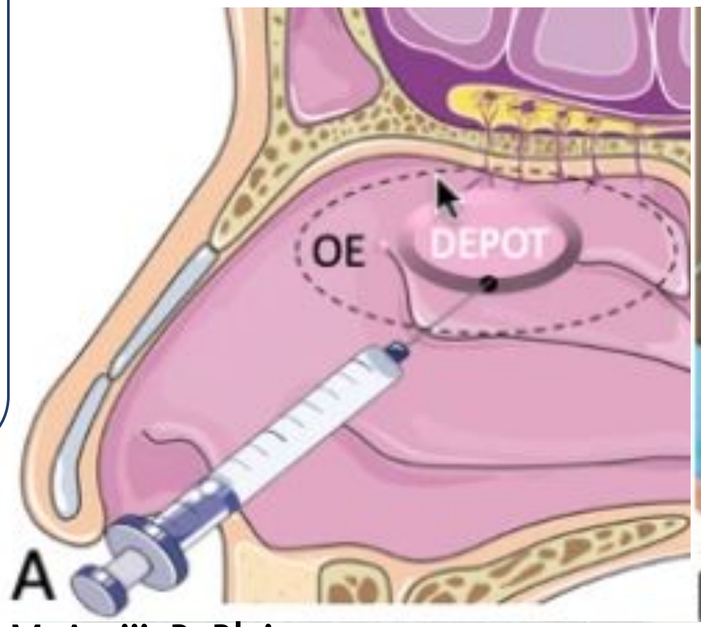
10.1186/s12989-019-0290-8

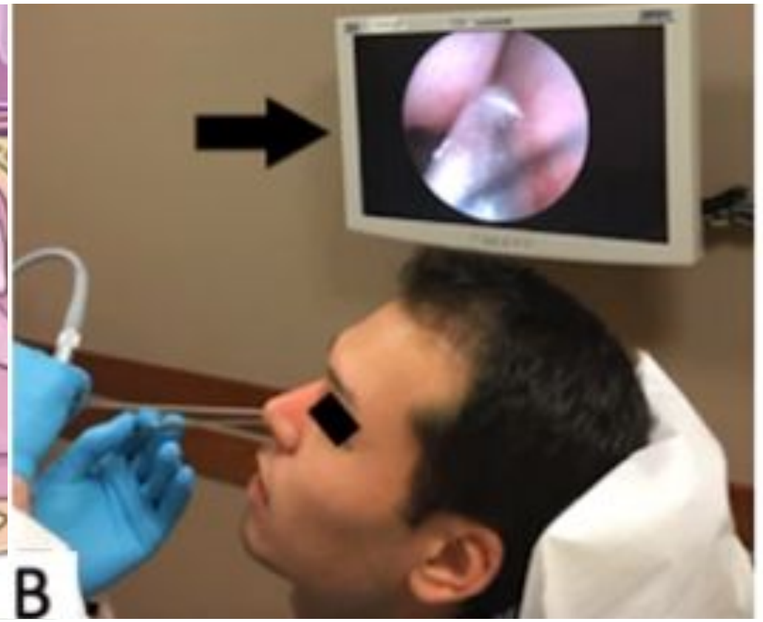
Addressing the Translation Gap

With traditional nasal administration, brain distribution is likely **overestimated** in rodents

We identified a **translatable approach that also localizes** drug

Minimally invasive nasal depot (MIND)





M. Amiji, B. Bleier

Favors N2B delivery by **localizing and retaining dose beneath olfactory epithelium**

Can be a quick, simple, and out-patient procedure in patients

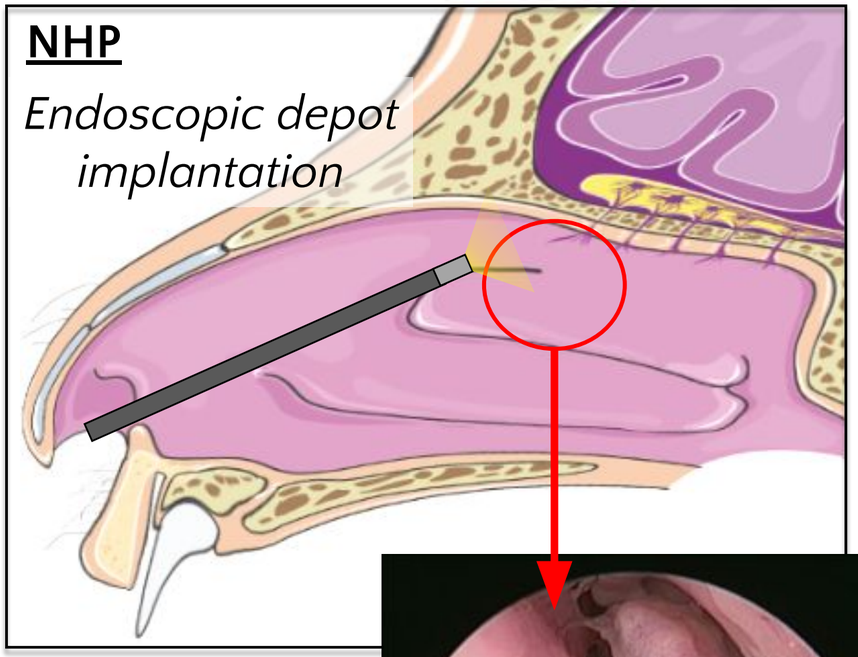
Mansoor Amiji

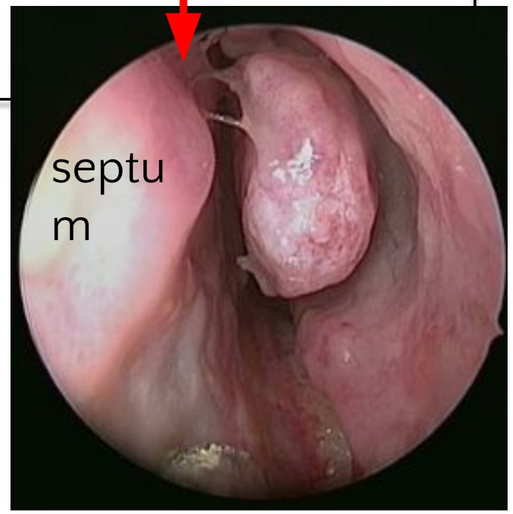
University Distinguished Prof., Prof. of Pharmaceutical Sciences & Prof. of Chemical Engineering, Northeastern University

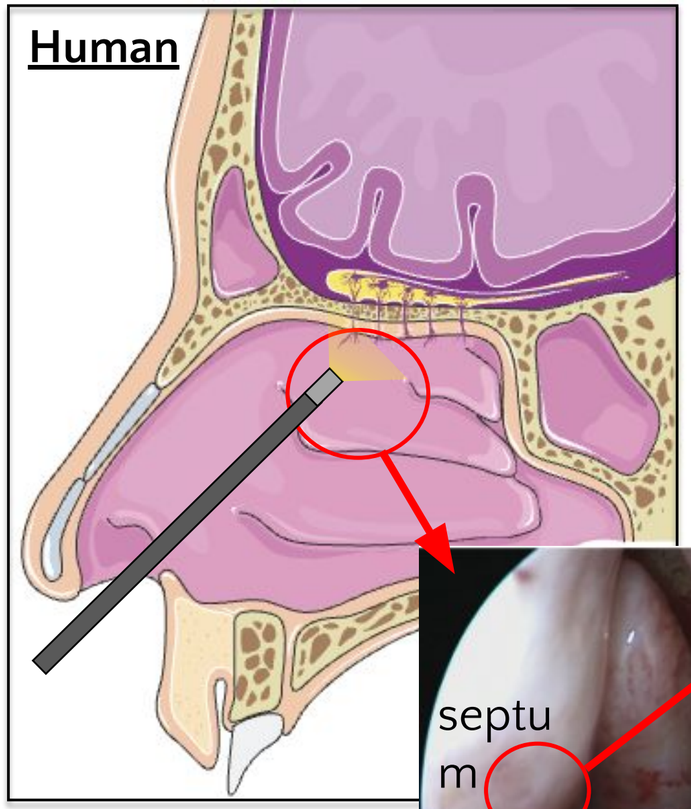
Benjamin Bleier

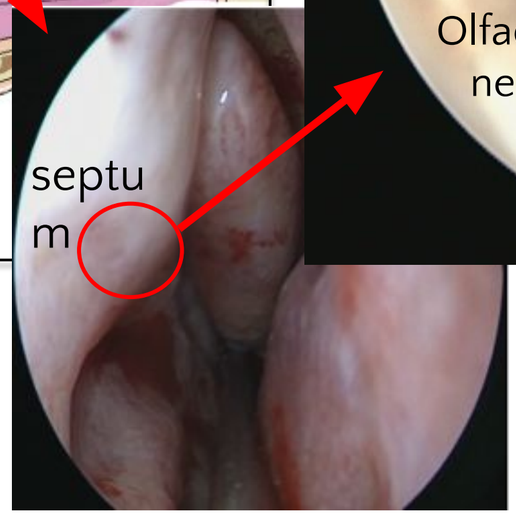
Director, Endoscopic Skull Base Surgery, Mass. Eye and Ear; Associate Prof. of Otolaryngology–Head and Neck Surgery, Harvard Medical School

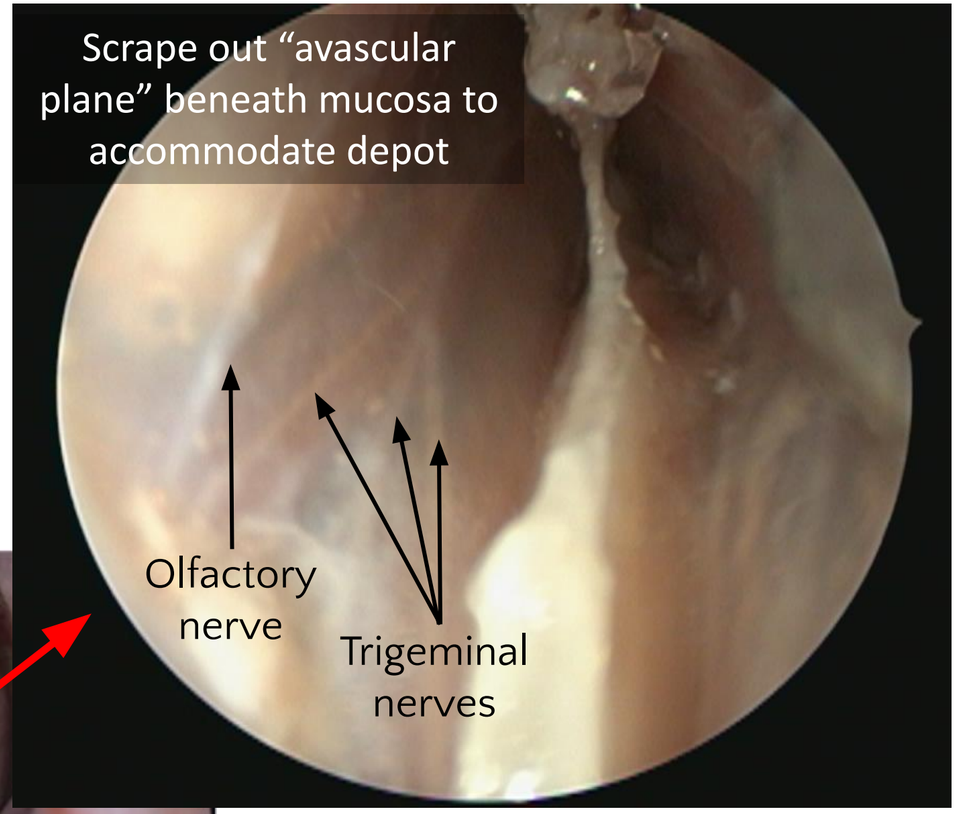
MIND in Higher Order Animals











This entire space will be filled with MIND depot

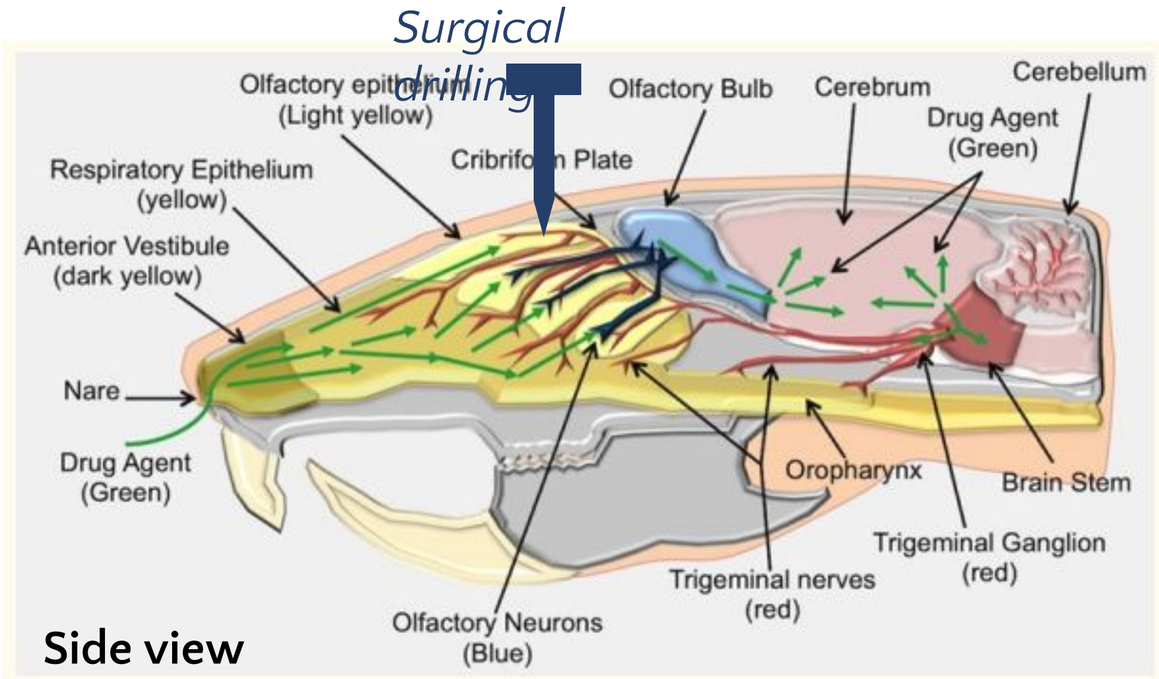
Figures: B. Bleier

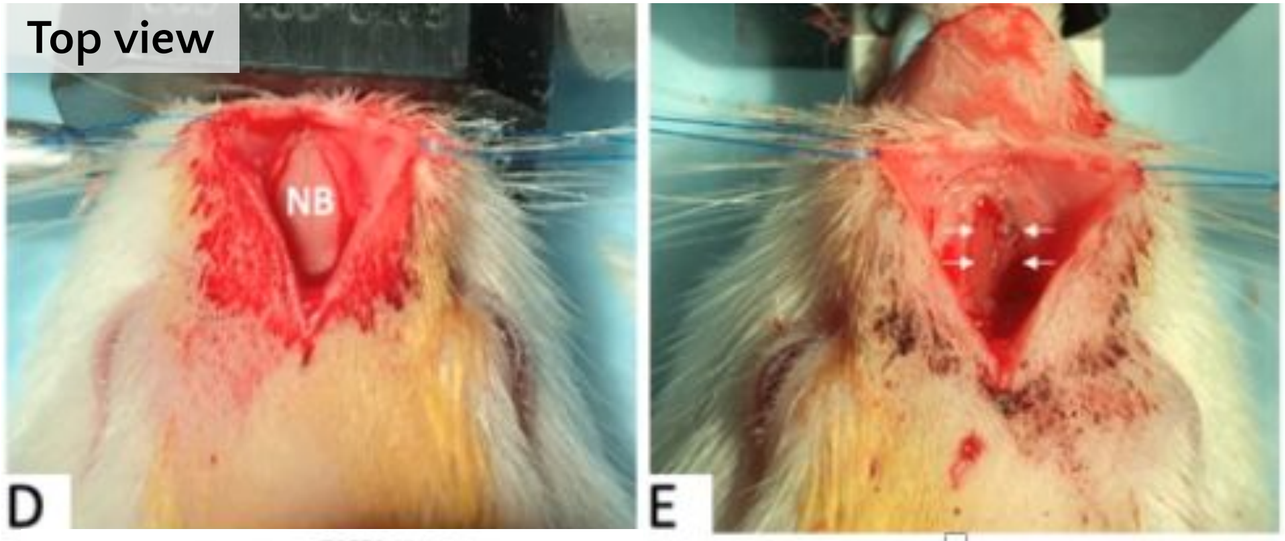
Slide credit: Zhefeng (Eddie) Li

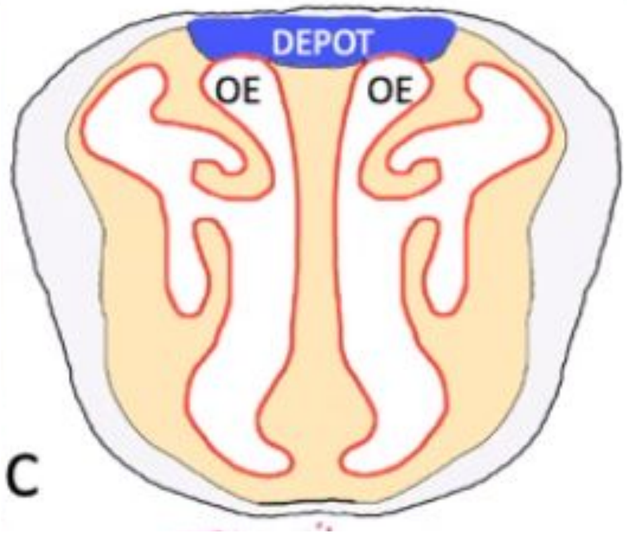
Validating: MIND in Rodents

MIND rodent model preferred for early-stage evaluations

Identical anatomic location – a bit more invasive in rats

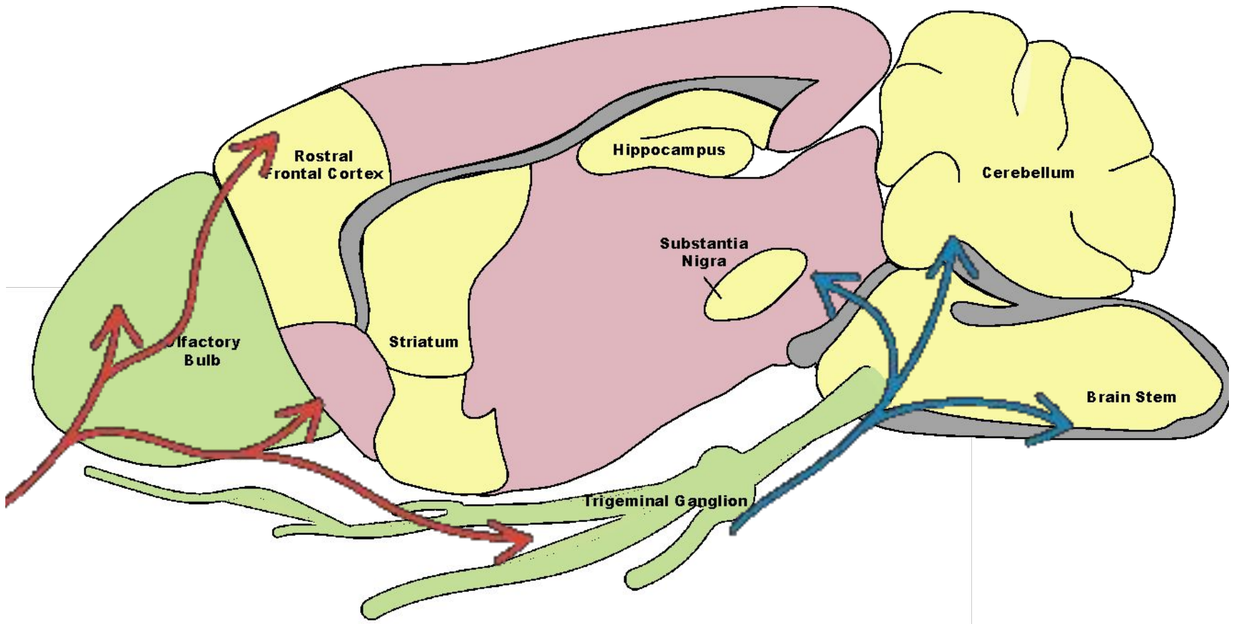






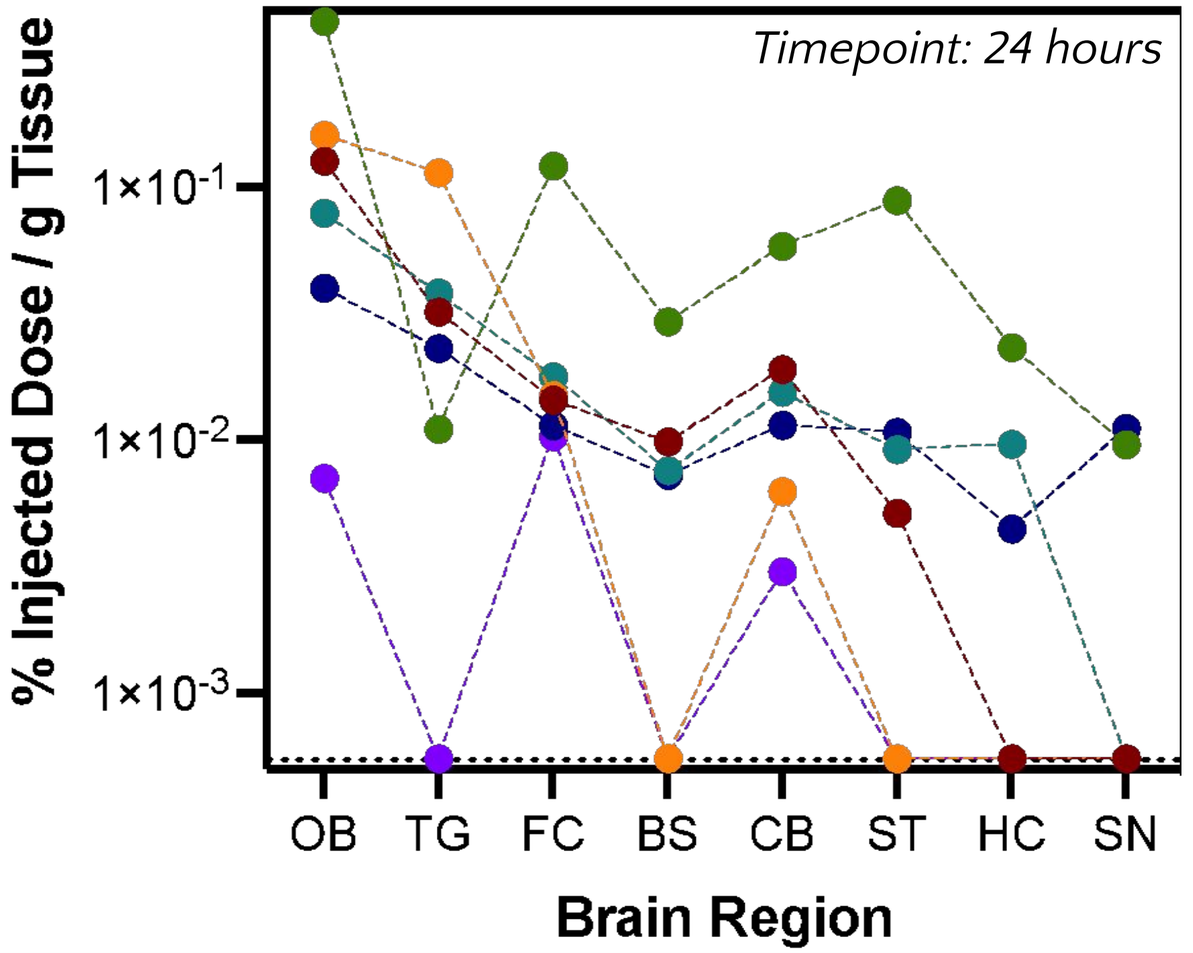
Nasal bone (NB) shaved away to allow access to olfactory epithelium (OE) from top of head

MIND Improves N2B Delivery

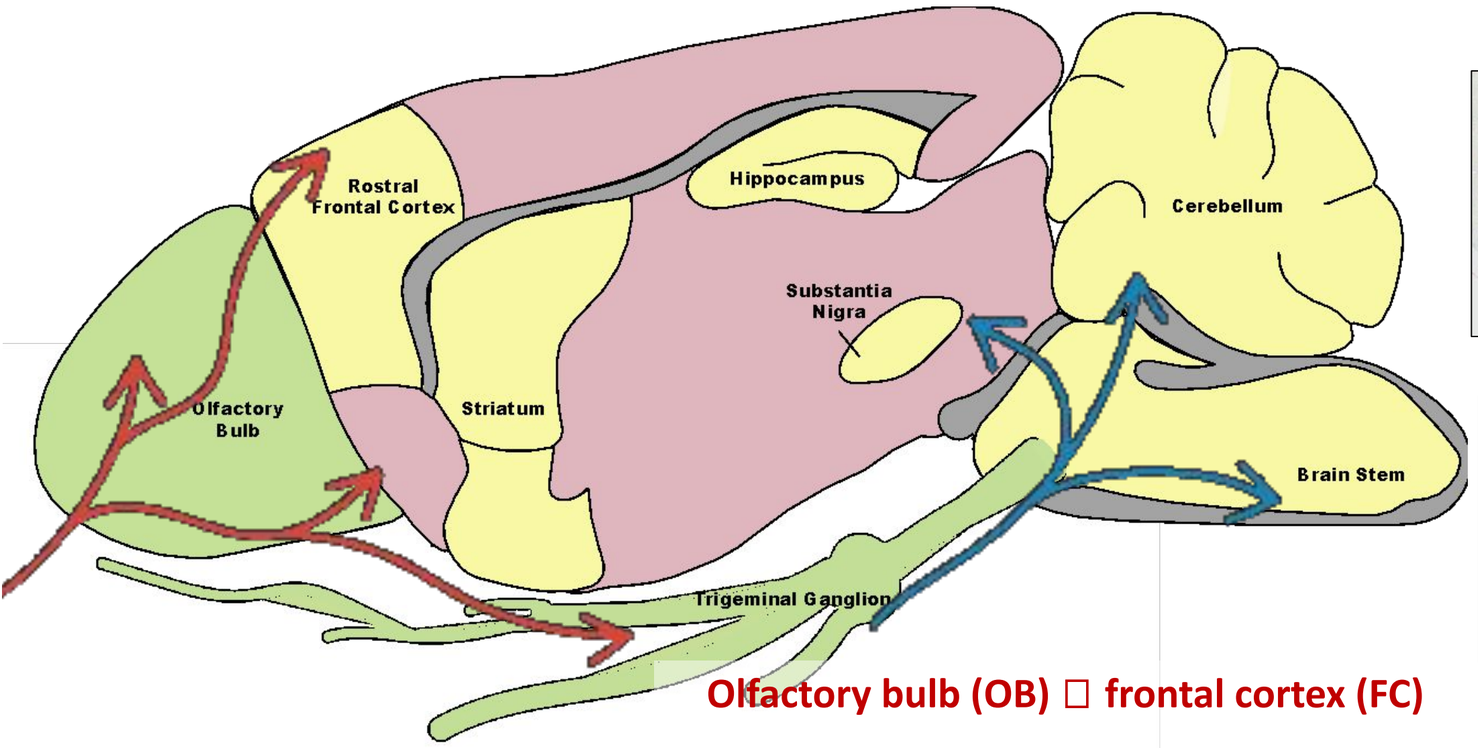


This and other data suggests **~2 orders of magnitude improved delivery vs. catheter instillation** and deeper brain distribution feasible with MIND

MIND Administration of siRNA in Rats

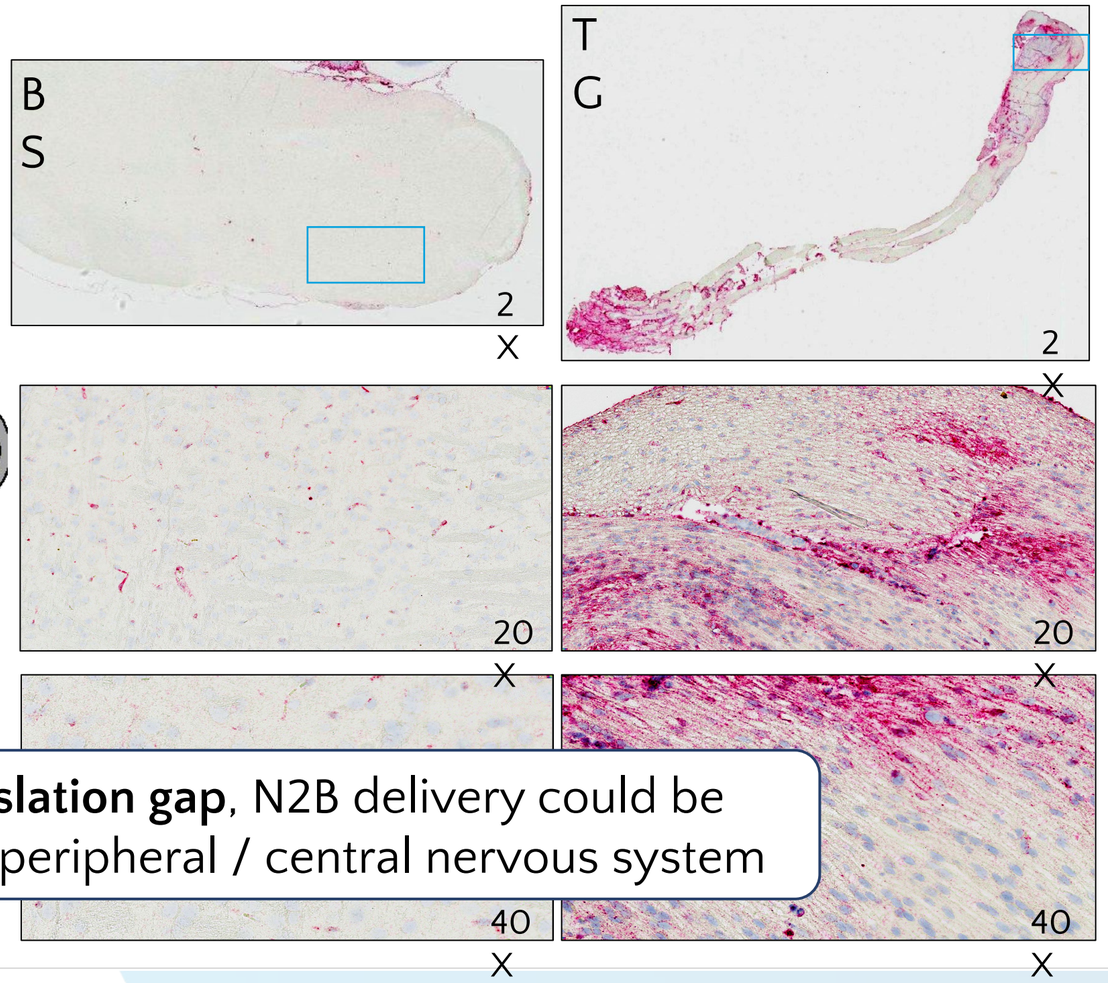


MIND Improves N2B Delivery



Olfactory bulb (OB) □ frontal cortex (FC)

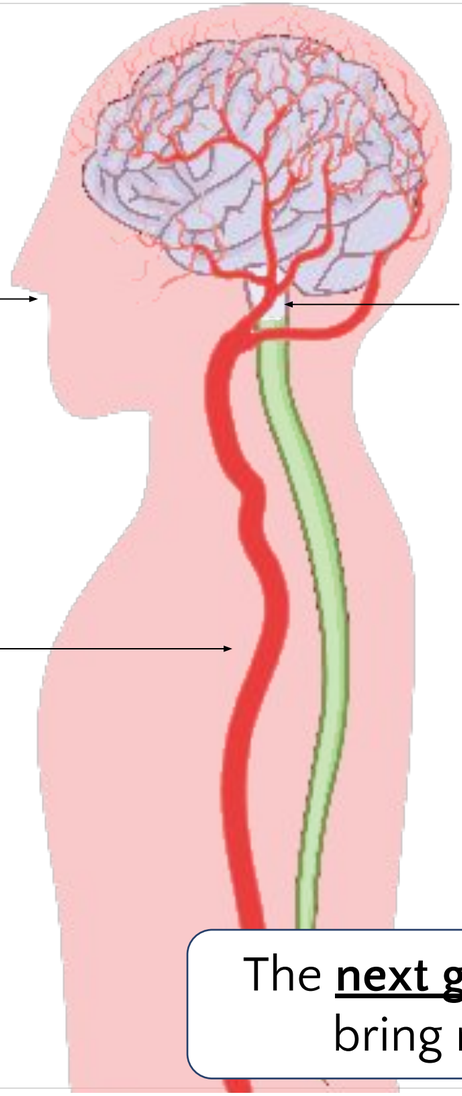
siRNA Delivery to Cells in BS, TG



Leveraging MIND to address **localization and translation gap**, N2B delivery could be impactful in meeting strategic delivery needs in the peripheral / central nervous system

Looking Ahead

Many Pathways to Meaningful Delivery

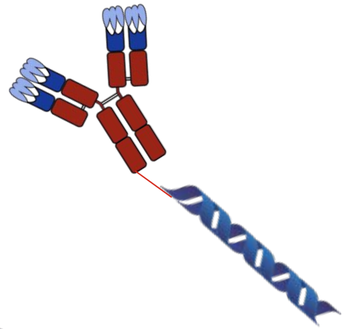


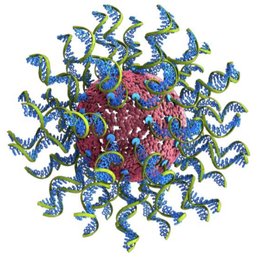
Intranasal administration

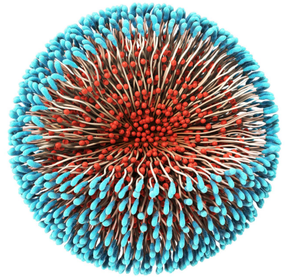
Intracisterna magna injection

Intravenous injection

Diverse pathways and **creative approaches** for nucleic acid delivery to the CNS







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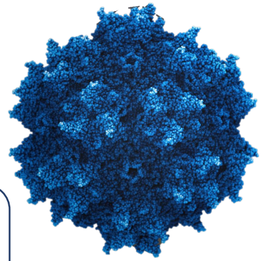

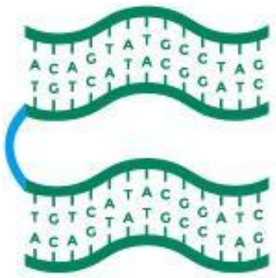

The **next generation of therapies and delivery solutions** will bring meaningful advances for many more patients

Alcyonels.com; https://www.atalantatx.com/our-science-focus/; Exicuretx.com; Precisionnanosystems.com; These photos by Unknown Author licensed under CC BY-SA

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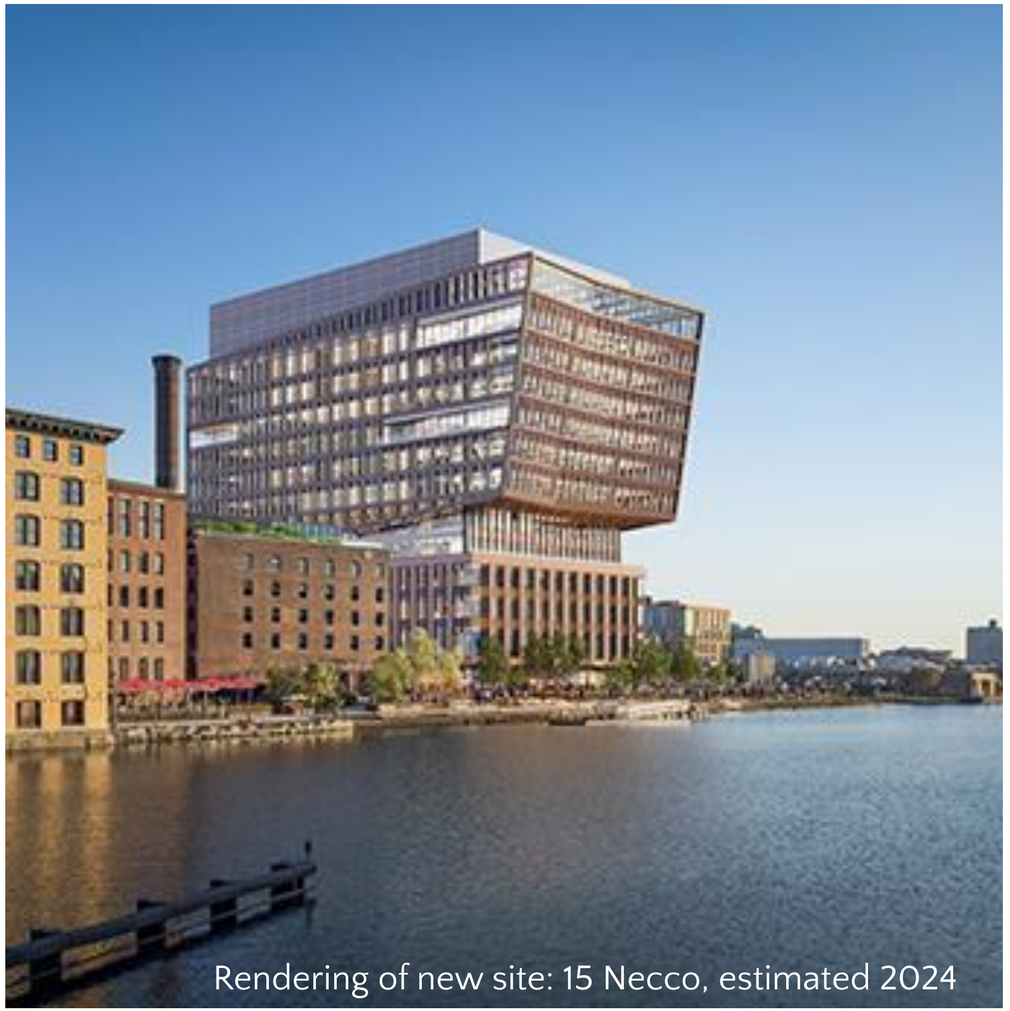
Rendering of new site: 15 Necco, estimated 2024