WashU Medicine

THE BRAIN TUMOR CENTER
At Washington University School of Medicine In St. Louis

Intradermal administration of immune modulating Spherical Nucleic Acids as anti-glioma therapy

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CRS, Philadelphia

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
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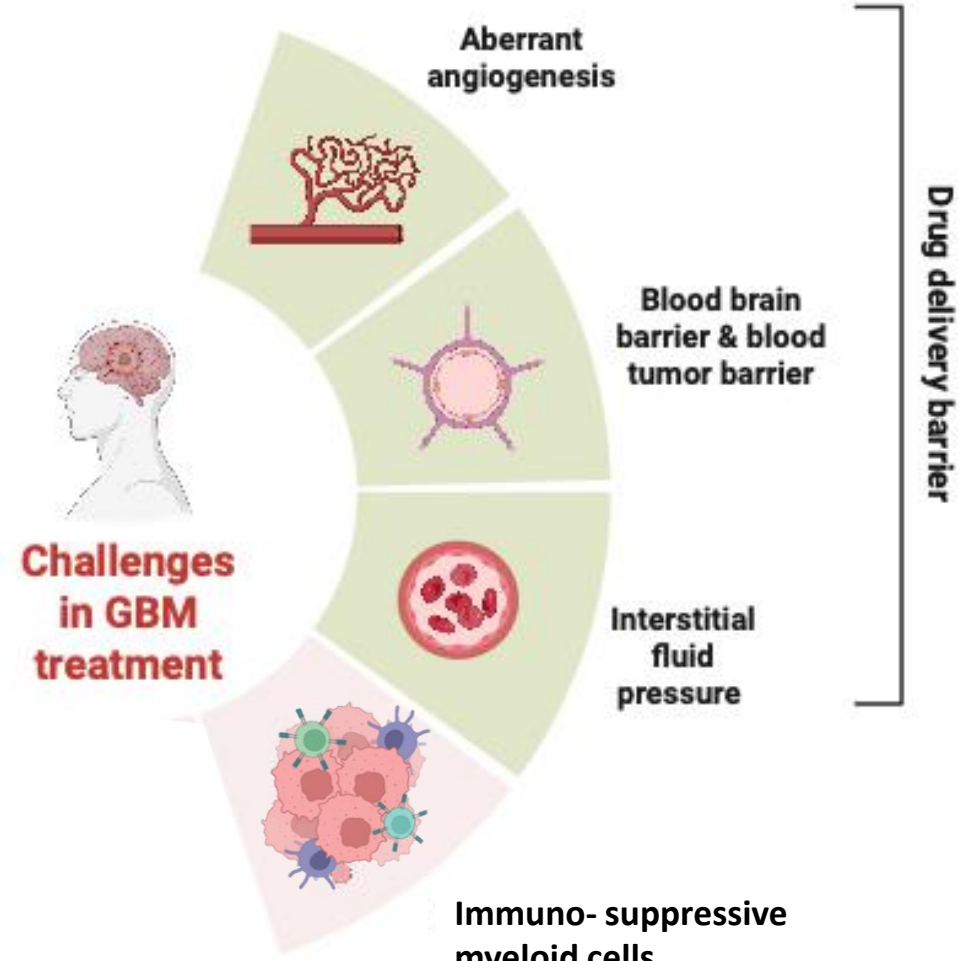
Challenges in brain tumor (Glioblastoma) drug delivery

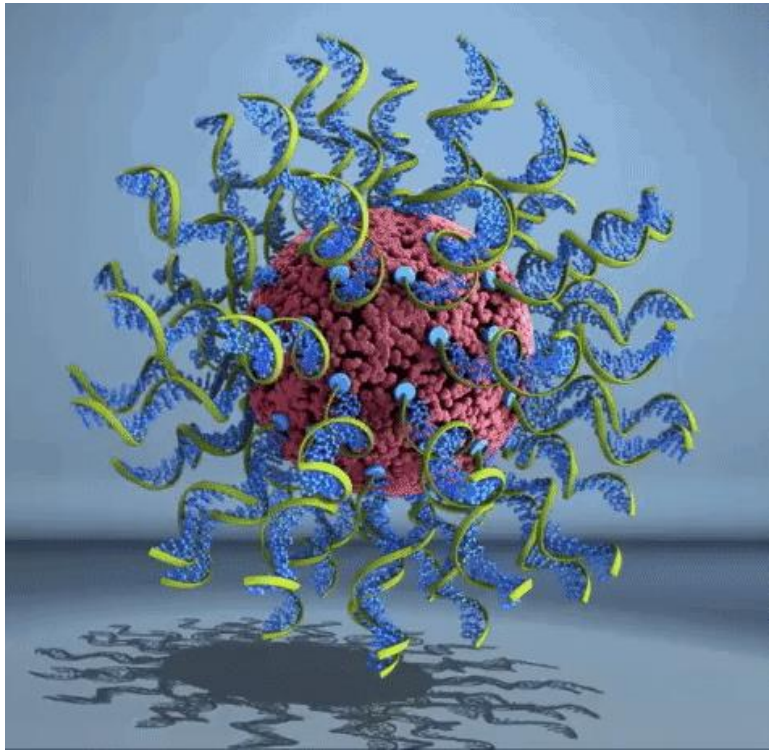


GOALS

Drug delivery to local tumor and peripheral immune rich sites

Re-programming immune cells for anti-tumor effect

The Tool : The Spherical Nucleic Acids (SNAs)

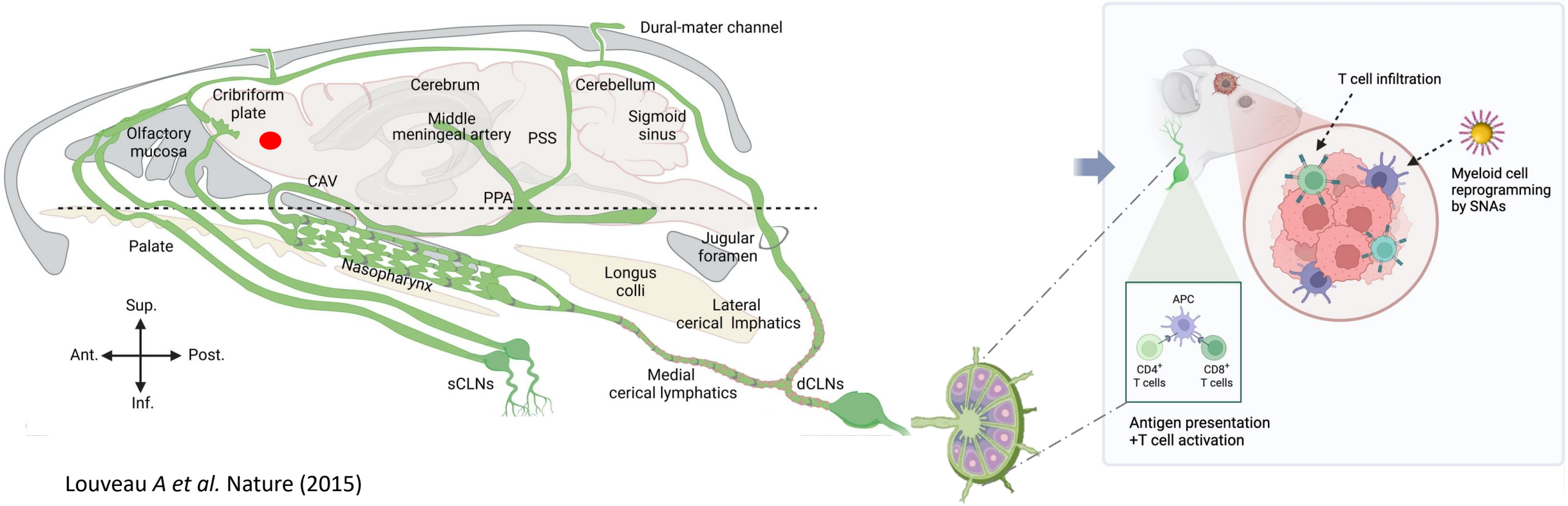


Chad A. Mirkin

1. Design concept = Core + Oligos
2. High stability of oligonucleotides
3. Highly tunable structures
4. Cross BBB, penetrate cells and tissue effectively w/o transfection reagents

Targeting CNS Immunity via Meningeal Lymphatics (MLVs)

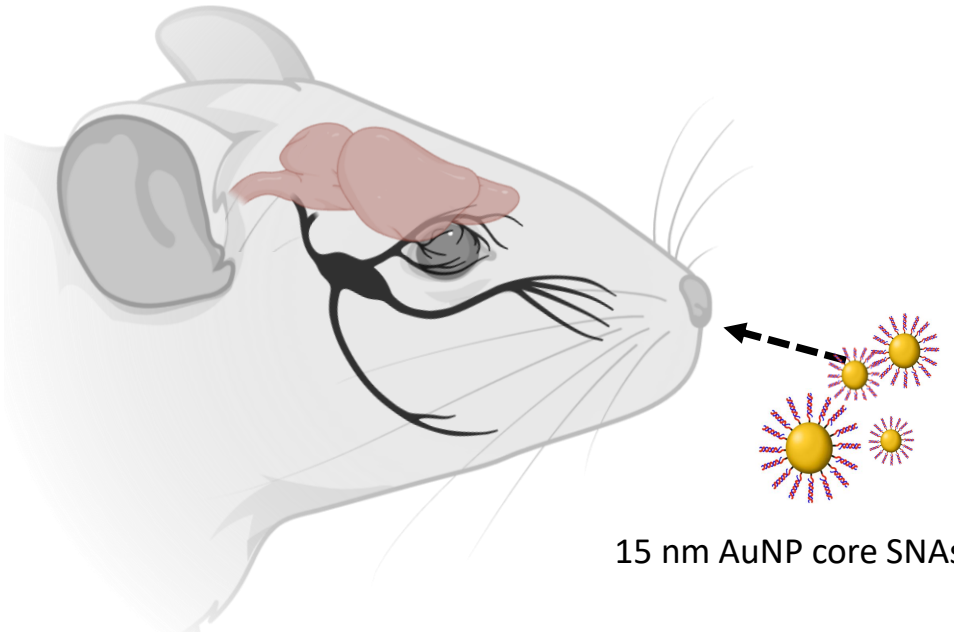
MLVs are promising target for enhancing GBM immunotherapy.



Louveau *A et al.* Nature (2015)

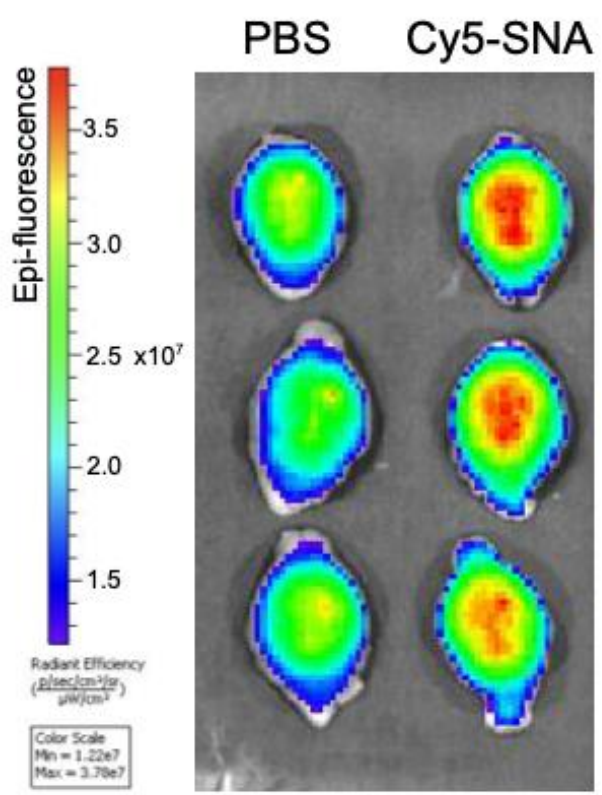
Leveraging Neural Pathways for SNA Delivery to the Brain

Intranasally delivered SNAs access the brain through the trigeminal nerve

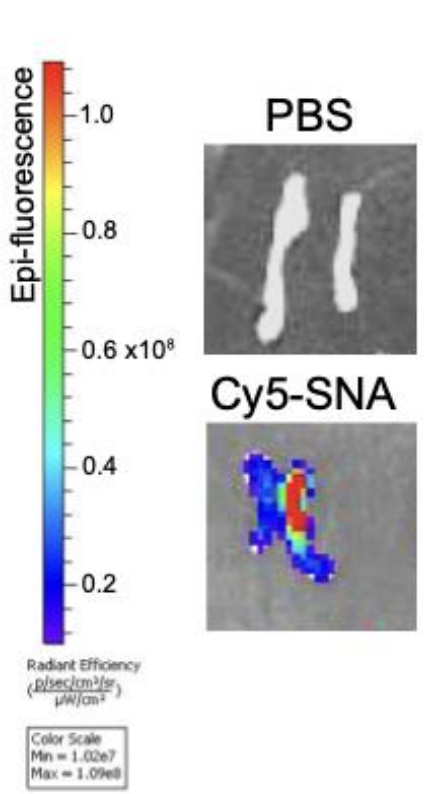


15 nm AuNP core SNAs

Brain uptake



Trigeminal nerve

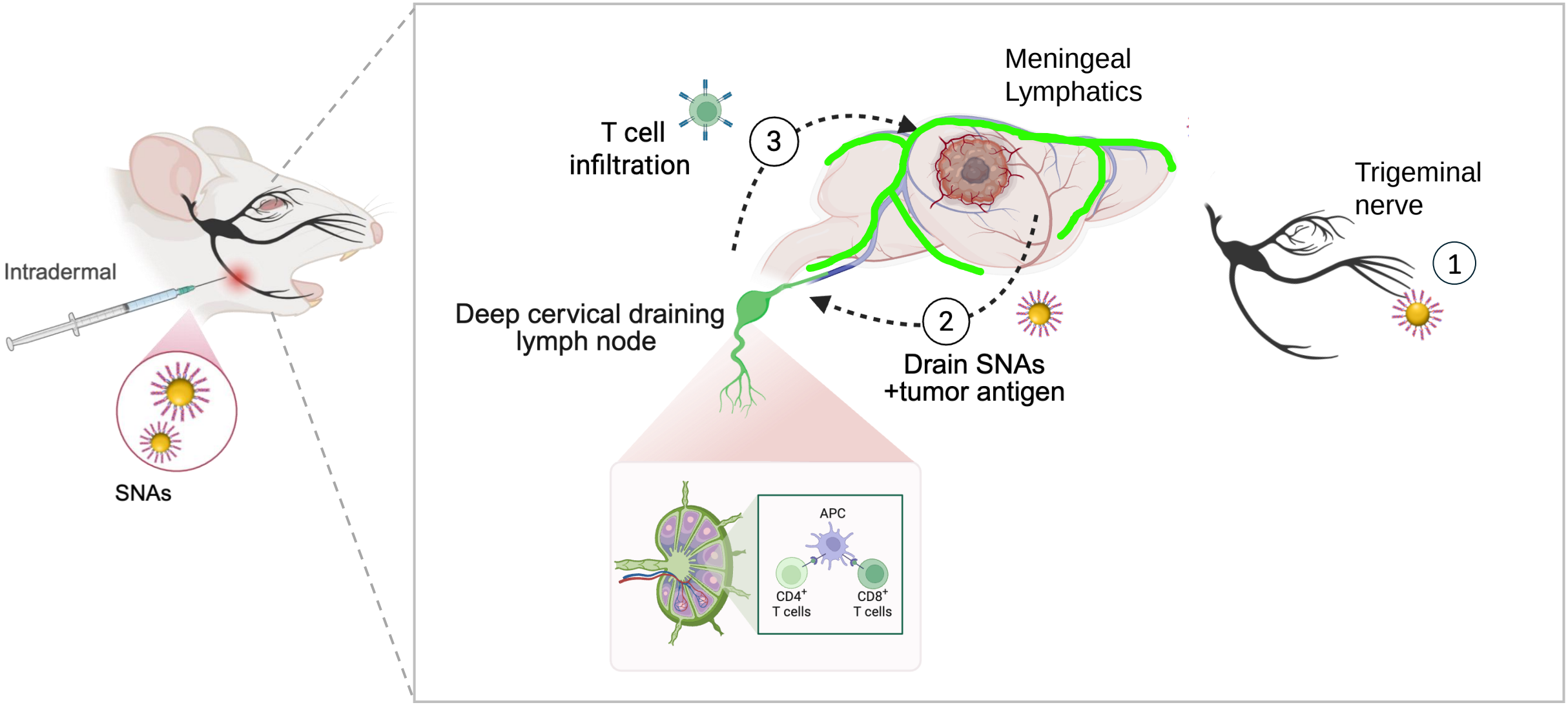


Mahajan et al. PNAS (*in Press* 2025)

Challenge: Mucociliary clearance

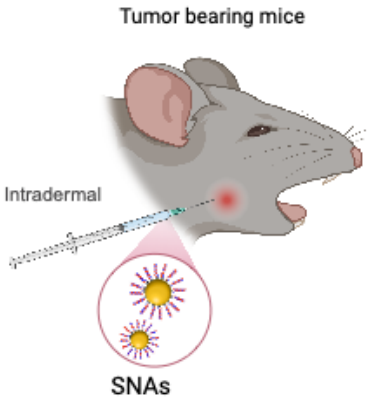
Need for innovative delivery strategies to improve SNA retention and targeting in the CNS.

Hypothesis: Facial Intradermal (i.d.) delivery of SNAs engages the neuro-lymphatic interface, enabling access to both CNS and peripheral immune structures to provide a robust anti-glioma immunity



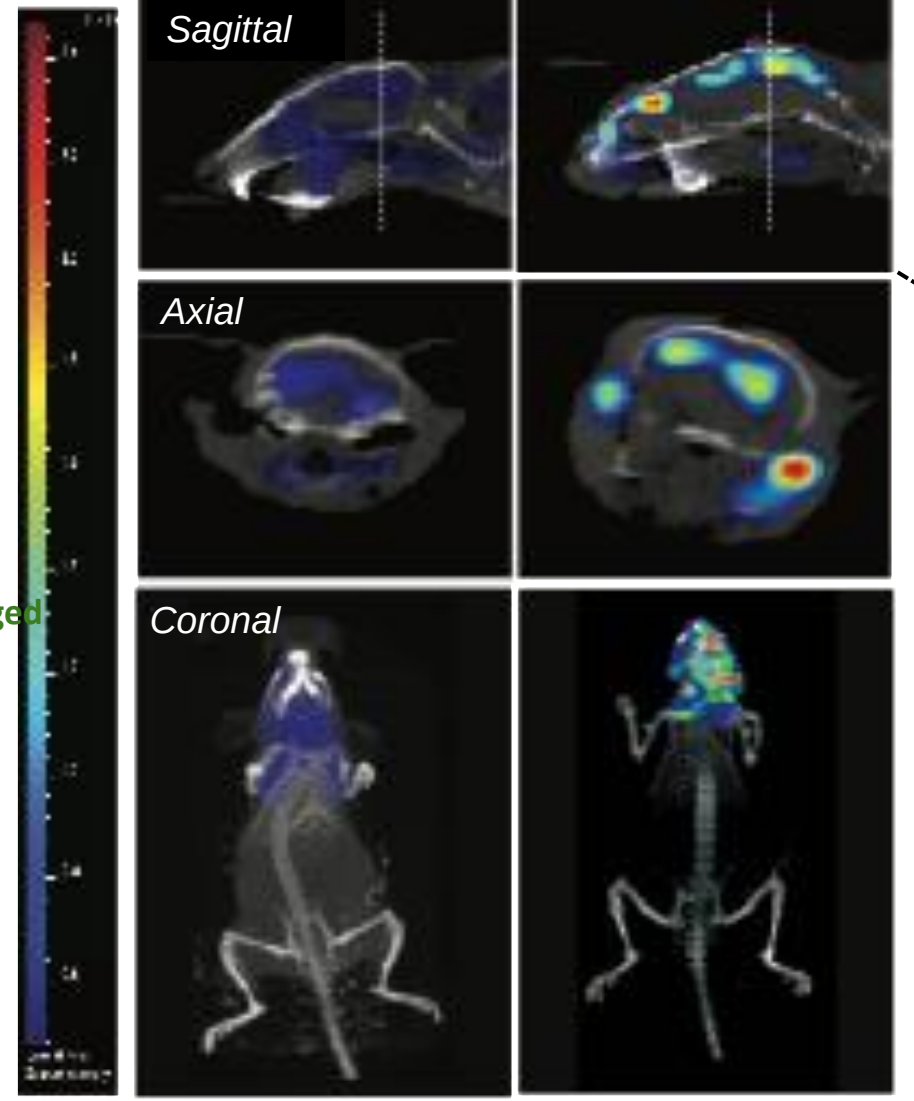
Created in https://BioRender.com

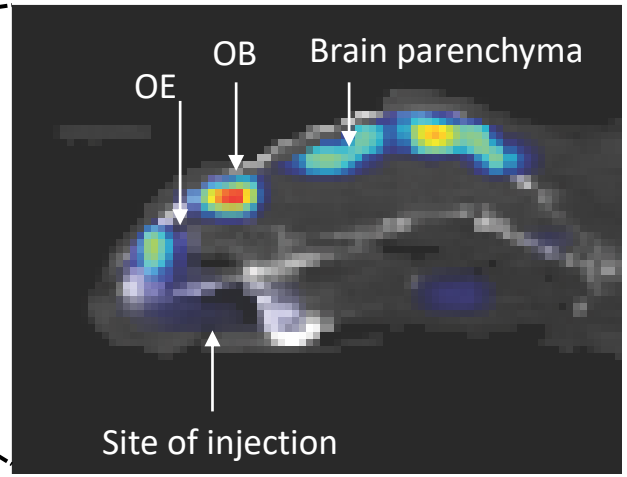
3D IVIS/CT of mice post i.d. injection with ICG-tagged SNAs indicate accumulation of SNAs in the brain parenchyma



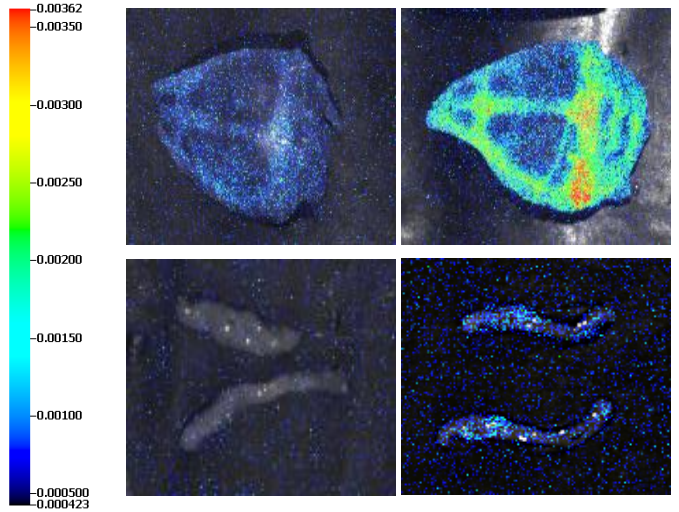
Indocyanine green (ICG) tagged AuNP SNA

Control mouse i.d. SNA injected mouse





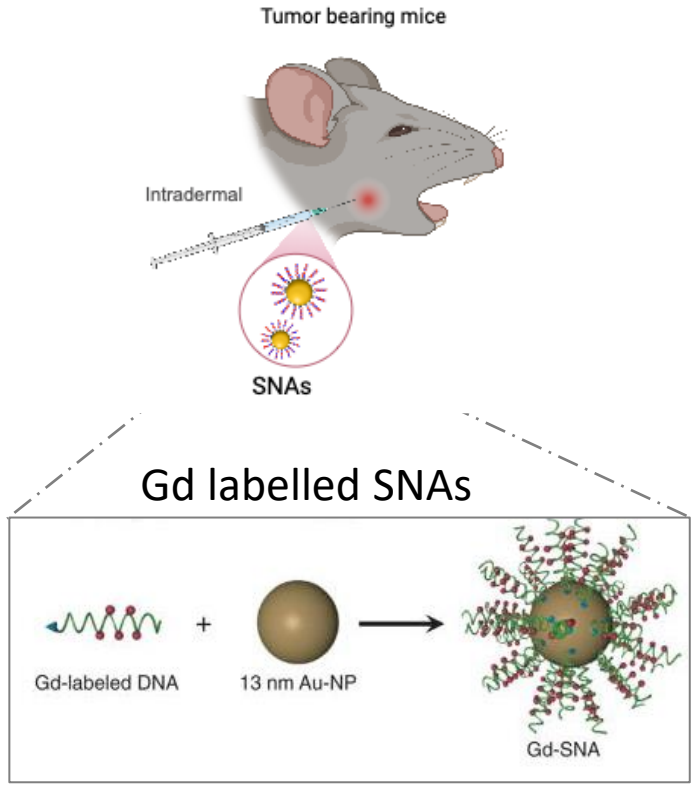
Control mouse i.d. SNA injected



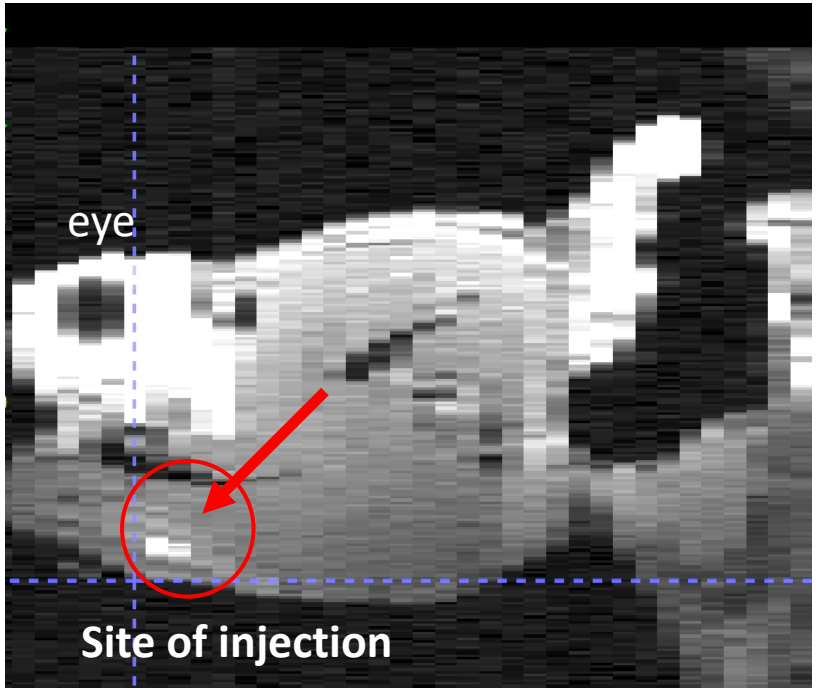
Skull + Dura

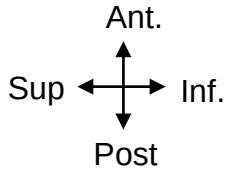
Trigeminal Nerve

I.d. administration of Gadolinium(III)-SNAs using MRI shows route of entry to the brain



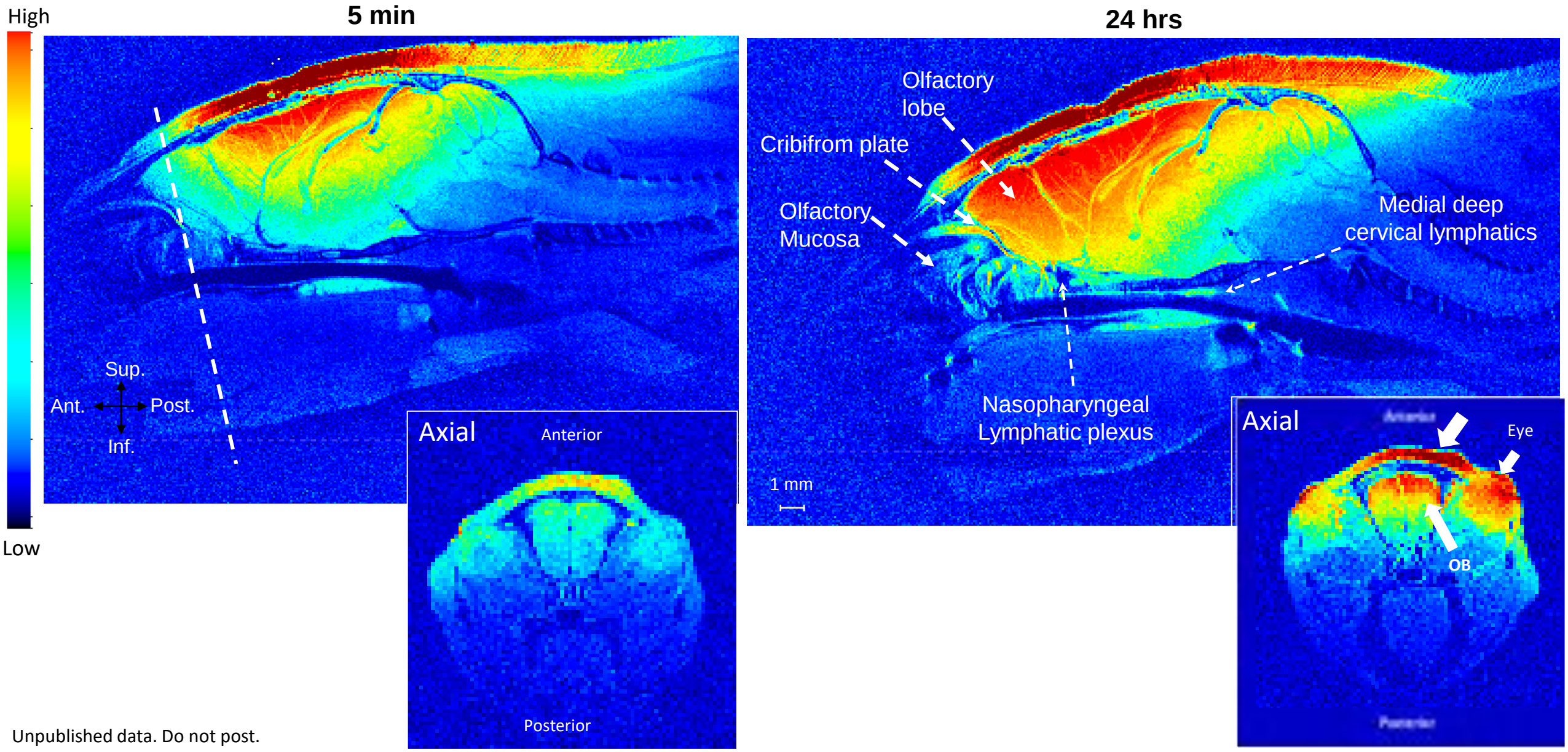
T1 weighted MRI images of mouse head (grayscale) showing Gd(III)-SNA accumulation 5 min post administration



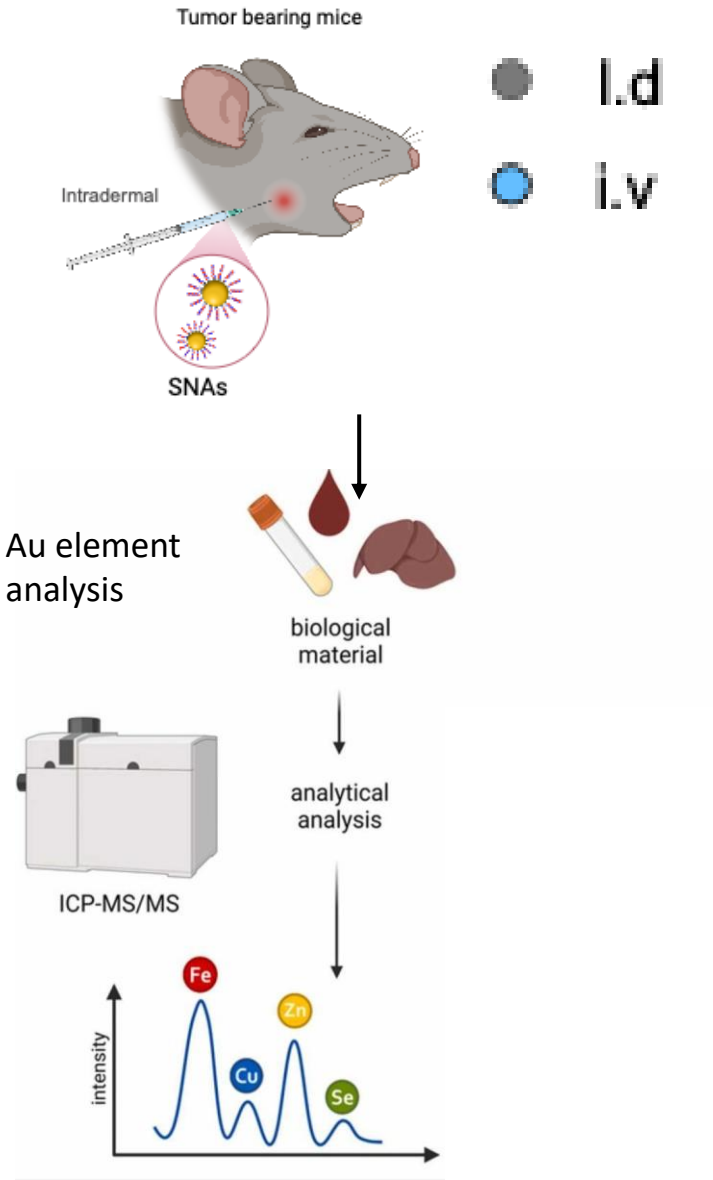


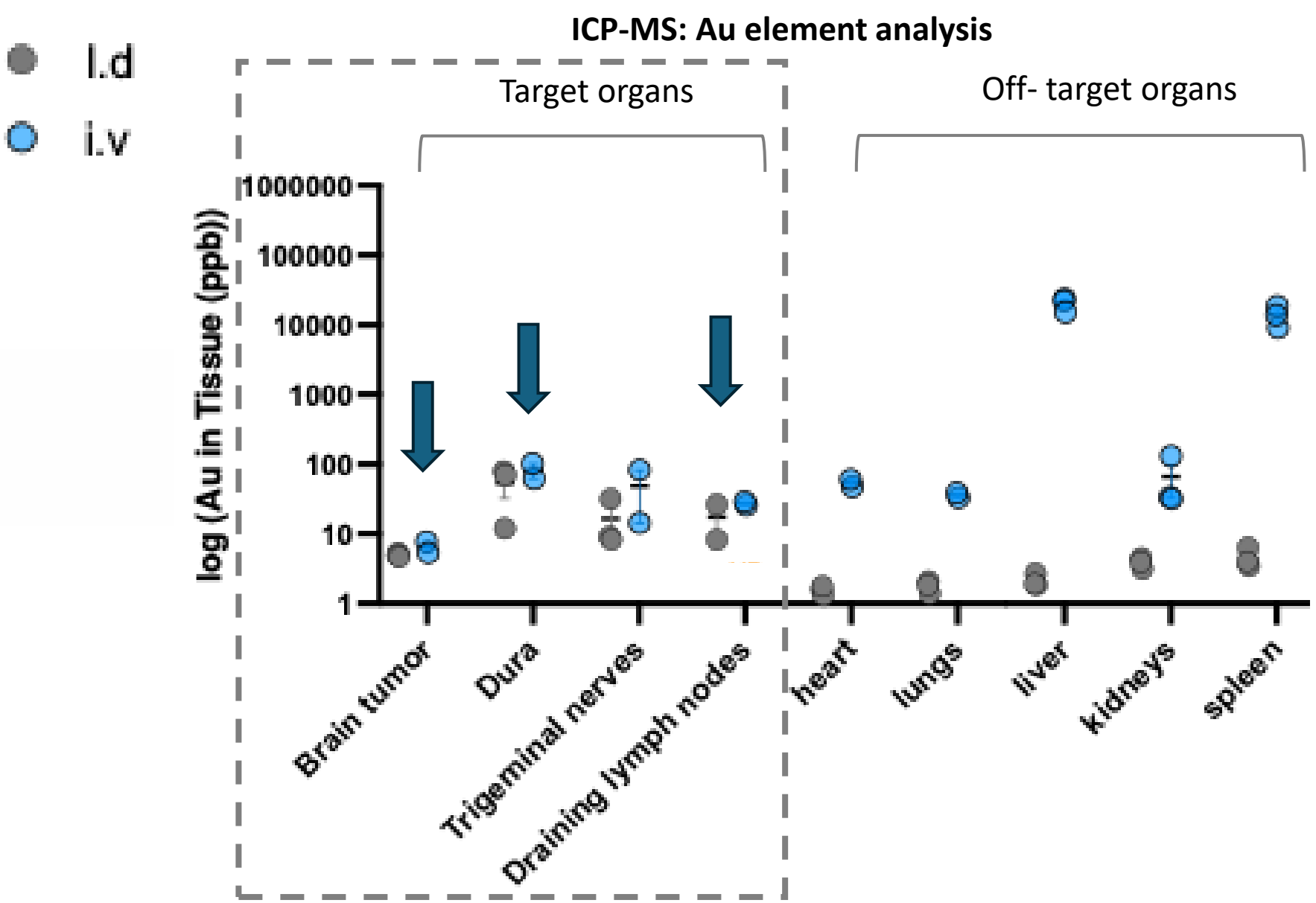
Cao-Dai Phung

I.d. administered Gd(III)-SNA accumulates in olfactory mucosa, olfactory bulb, nasopharyngeal, and medial deep cervical lymphatics



Facial i.d. SNA administration reduces off-target organ biodistribution as compared to intravenous administration

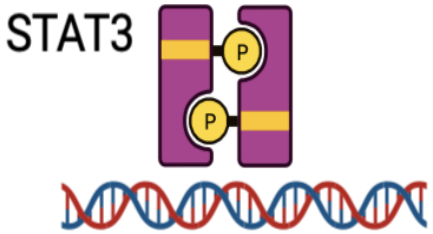


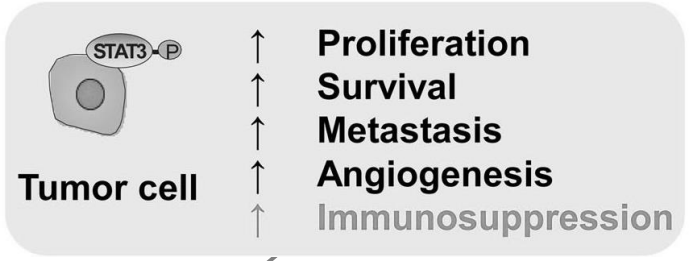


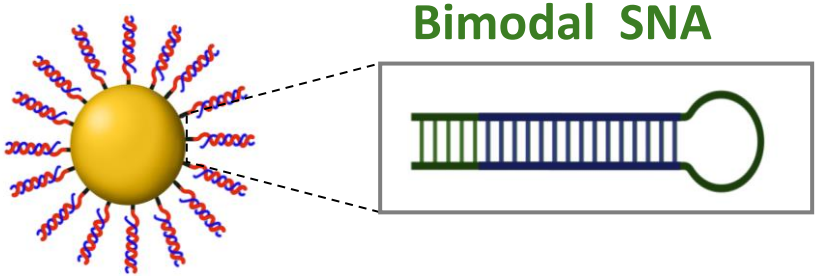
Single entity immune modulating SNA targeting: cGAS and STAT3

Target cGAS-STING to activate immune system

To inhibit STAT3 overexpression in cancer and immune cells



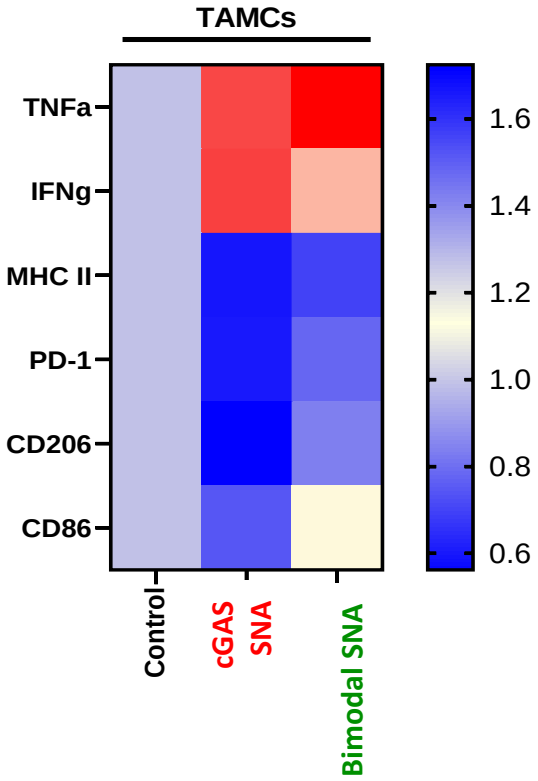




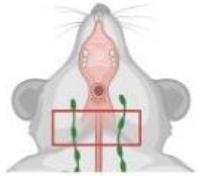
Size (diameter): 50 nm
Zeta potential: -80 mV
AuNP core: 15 nm (d.m)
Oligonucleotide: Thiol conjugated dsDNA
dsDNA/NP density: 120-180

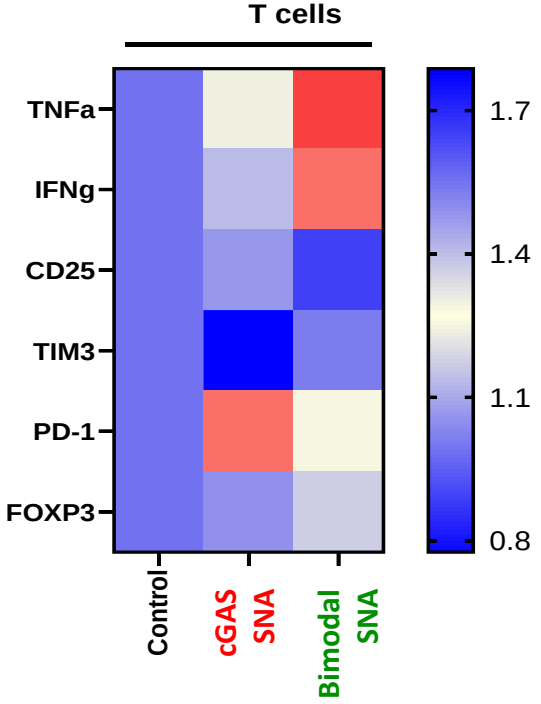
Intradermal SNA delivery impacts local and peripheral immunity in glioma model

Tumor immune cells

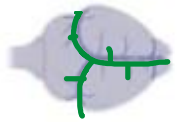


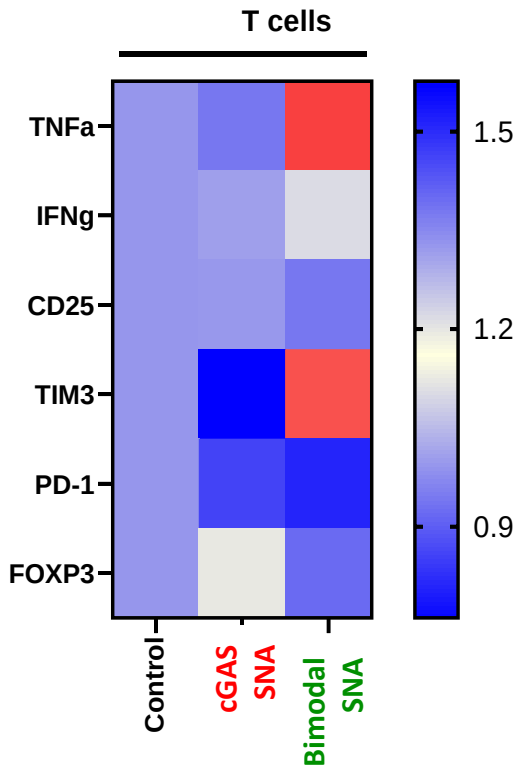
Cervical draining lymph nodes



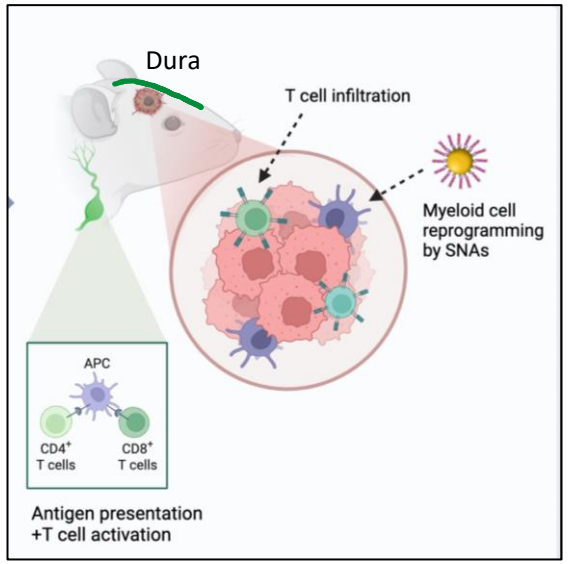


Dura/Meninges





Syngeneic glioma model: SB28

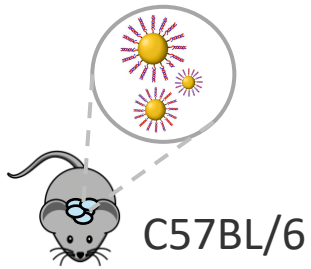


Unpublished data. Do not post.

Intradermal SNA delivery promotes survival of aggressive glioma mouse model

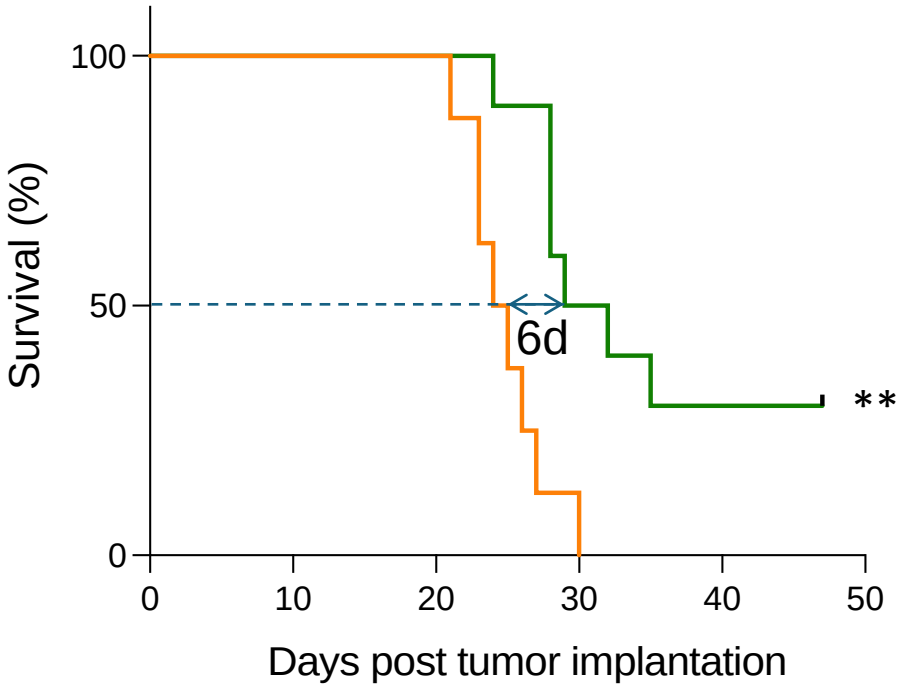
SB28 model

Syngeneic glioma model

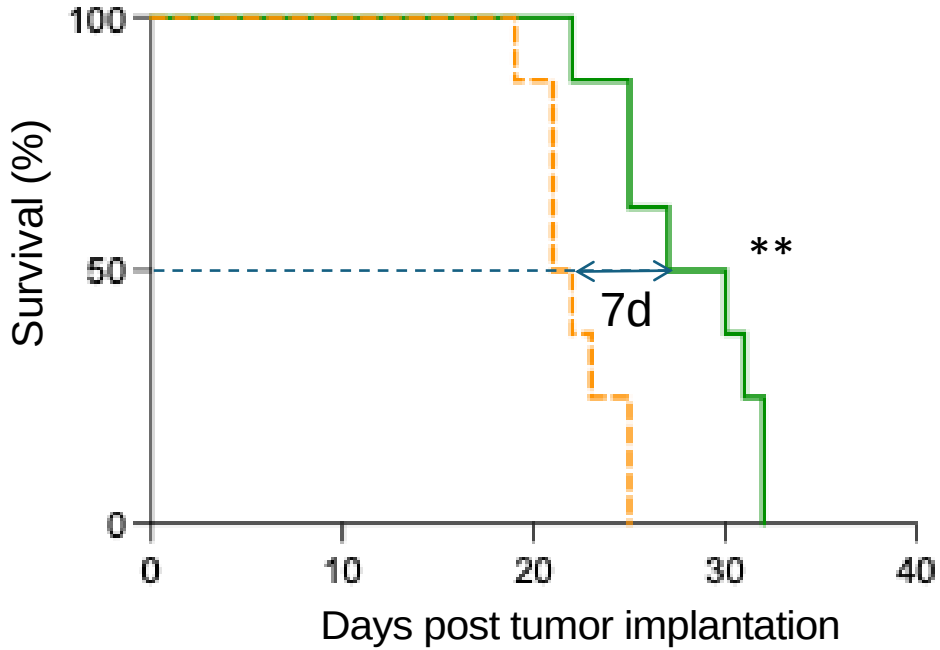


Checkpoint-resistant high-grade glioma (HGG)

Intratumor route



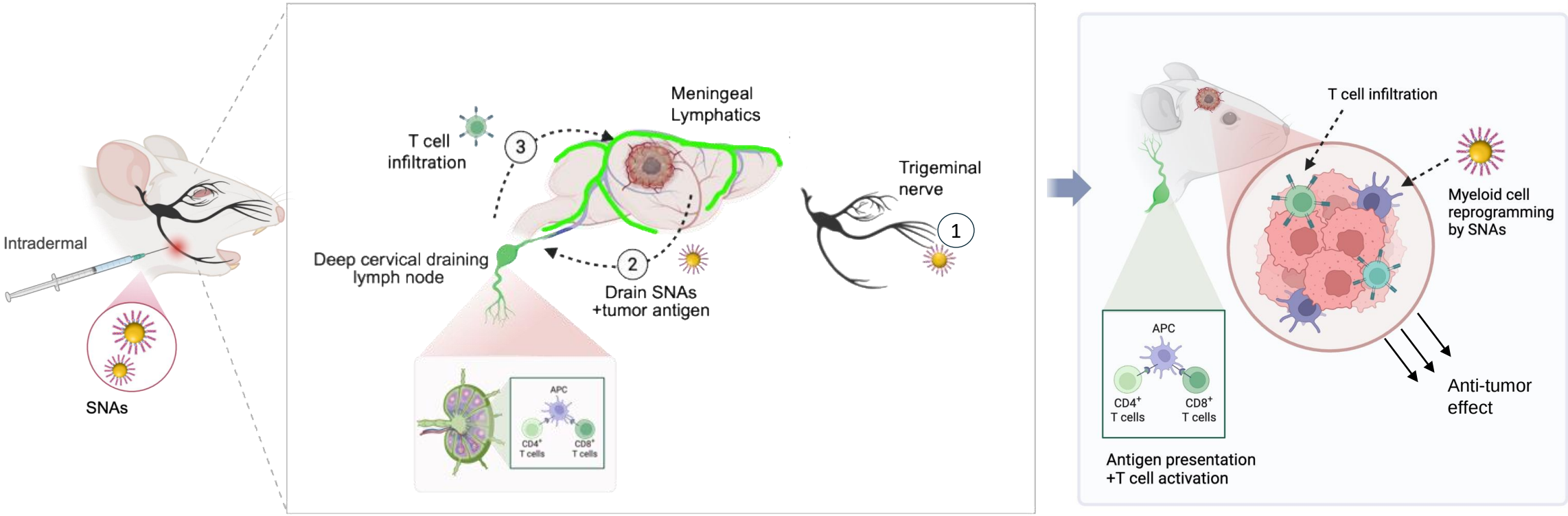
Facial intradermal



Harnessing the Neuro-Lymphatic Interface for Glioma Immunotherapy via Intradermal Delivery of cGAS–STAT3 Spherical Nucleic Acids

SNA transport via trigeminal nerve elements and meningeal lymphatics

Local and peripheral immune modulation



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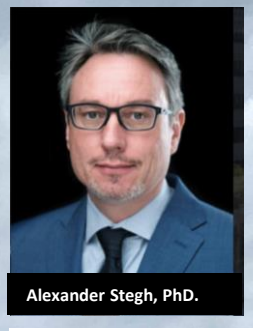
Acknowledgements


Alexander Stegh, PhD.


Rachel Jarvis


Brian Kim


Dai Phung

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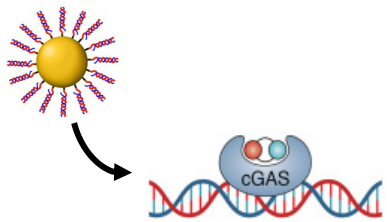
Chad Mirkin, PhD.

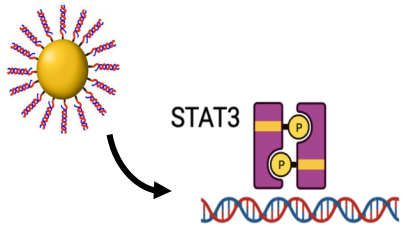
Northwestern
IIN INTERNATIONAL INSTITUTE FOR NANOTECHNOLOGY

NIH National Institutes of Health

American Cancer Society®

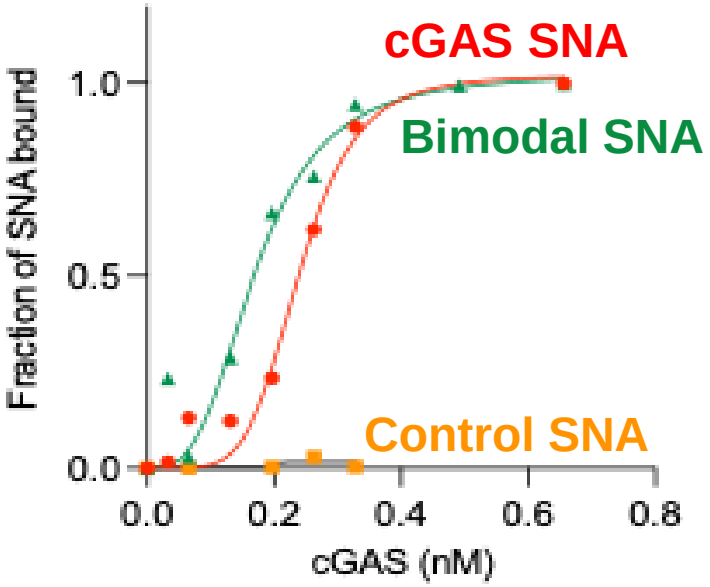
Bimodal SNAs **bind effectively** to both cGAS and STAT3



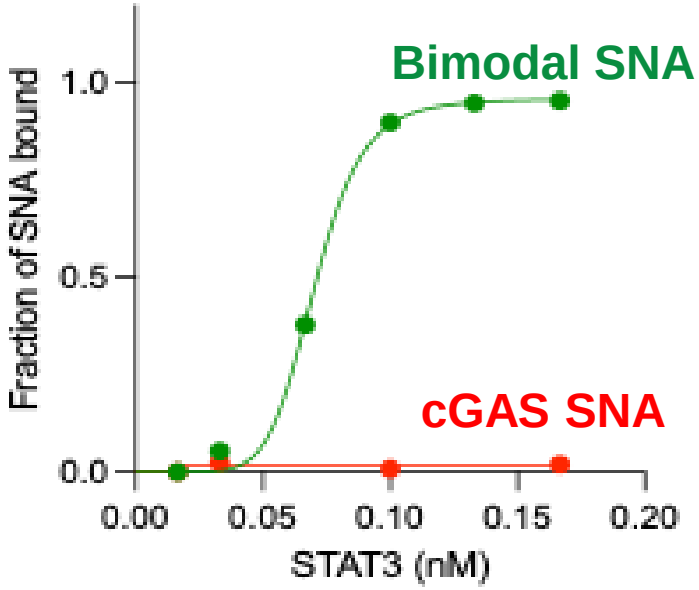


Method: (EMSA) Electrophoretic Mobility Shift Assay

A cGAS binding capacity



B STAT3 binding capacity



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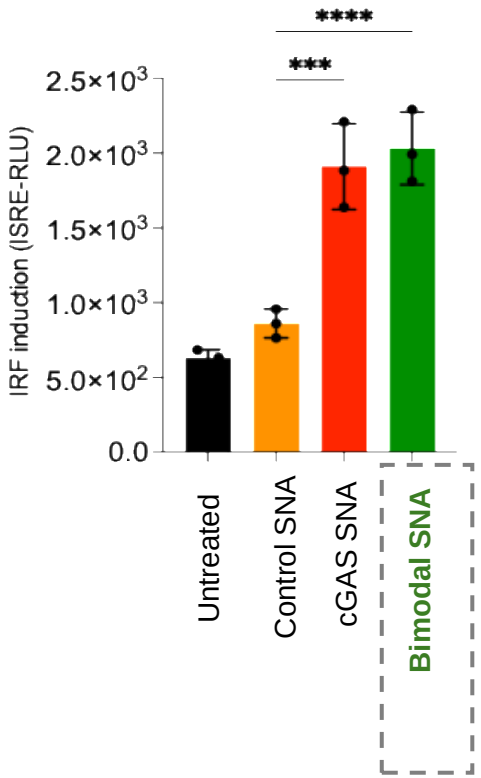
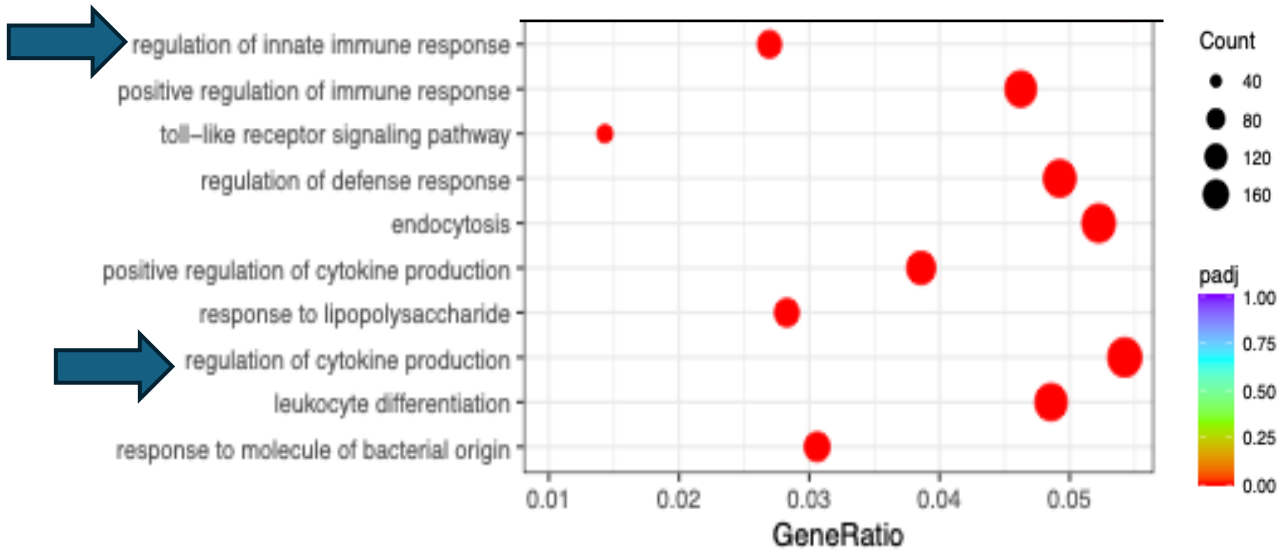
Bimodal SNAs promote cGAS-STING activation and ….

Cell-based
IRF response

RAW-Lucia™ cells

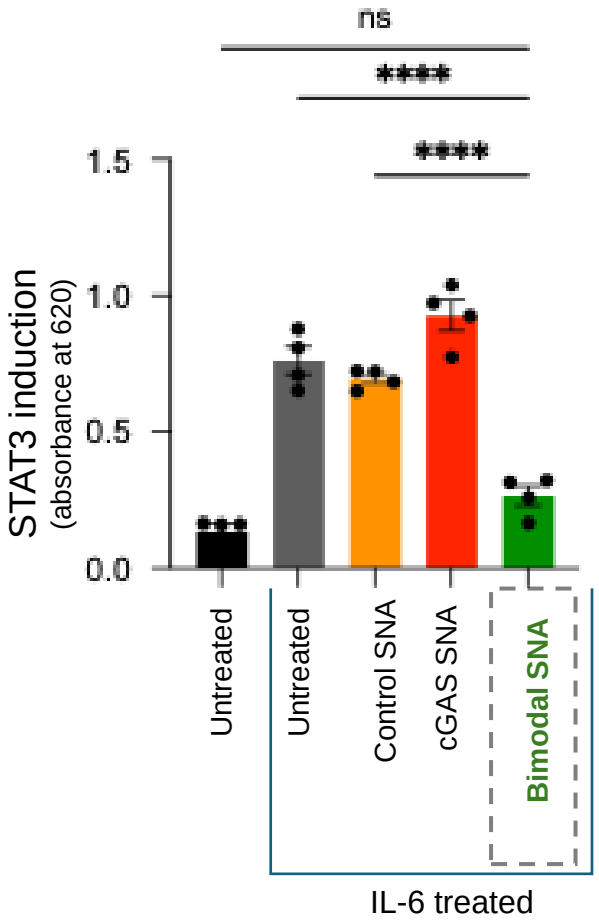


Innate and adaptive immune pathway
activation measured by RNA-seq



Bimodal SNAs also inhibit IL-6/STAT3 pathway in the presence of IL-6

STAT3 inhibition measured by IL-6/STAT3 reporter cells



RNA-seq analysis of IL-6/JAK/STAT3 pathway inhibition