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Breaking Barriers: Gold Nanoparticle-Based Strategies for Delivering Biologics to the Brain

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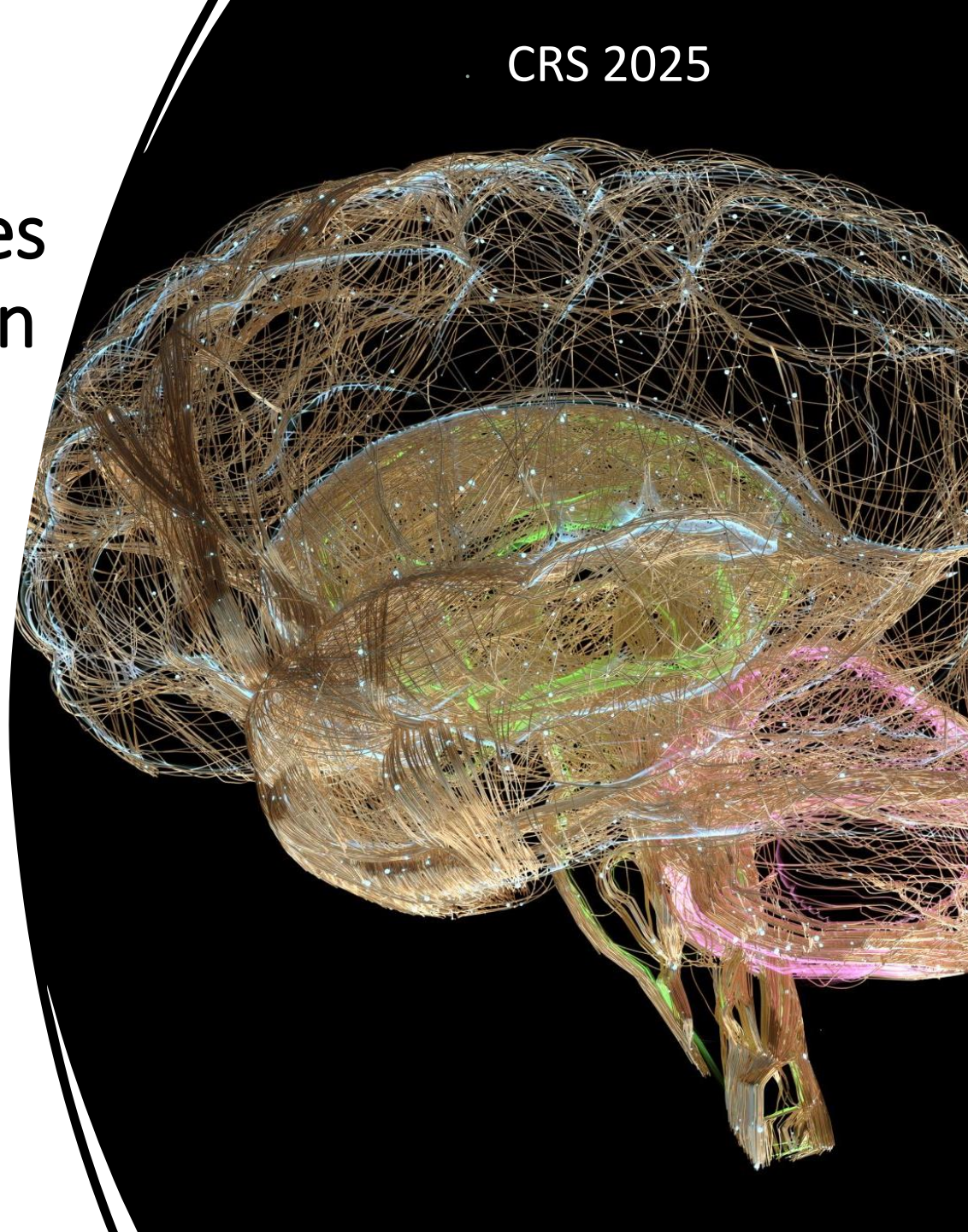
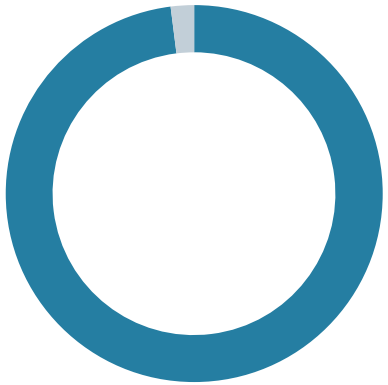
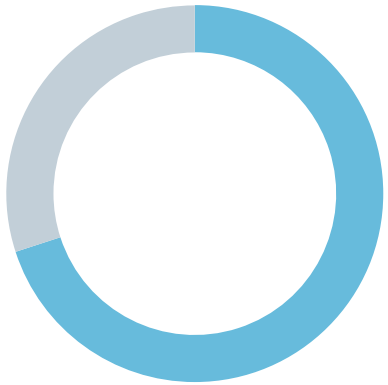


The BBB challenge



~98%

of therapeutics are brain excluded



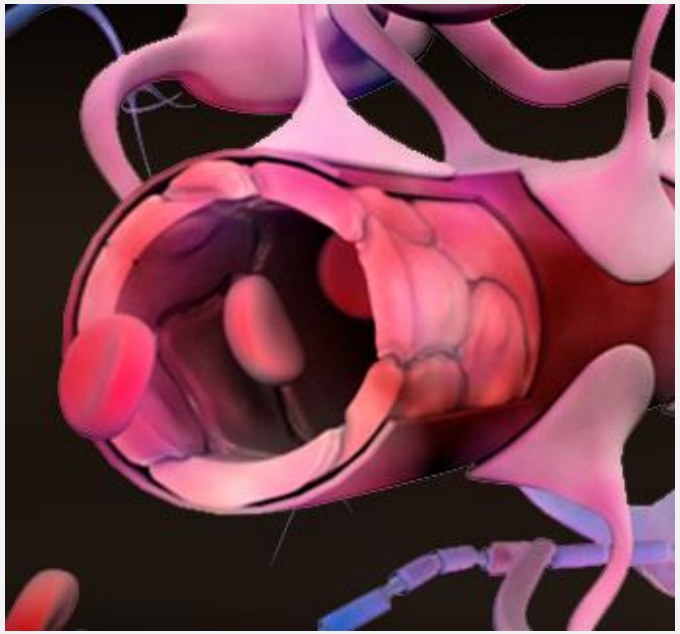
~70%

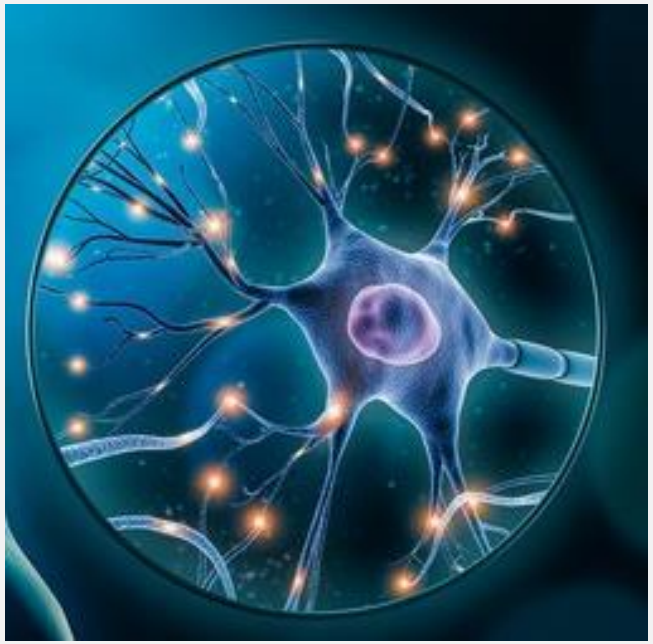
Of currently developed therapeutics for CNS indications are biologics

<0.01%

of antibodies’ injected dose is actually delivered to the brain

Multiscale Biological Barriers

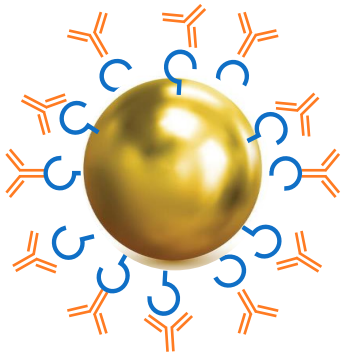




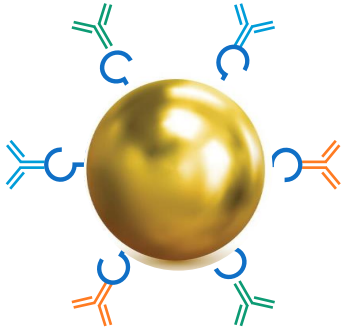
The need: overcoming all barriers in a single delivery system

Gold Nanoparticles

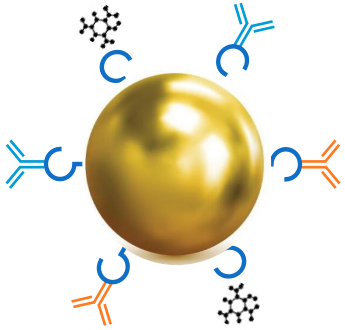
Golden-Antibody



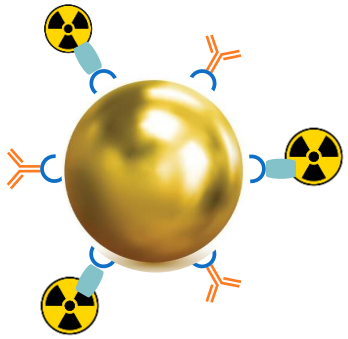
Golden-Bispecific



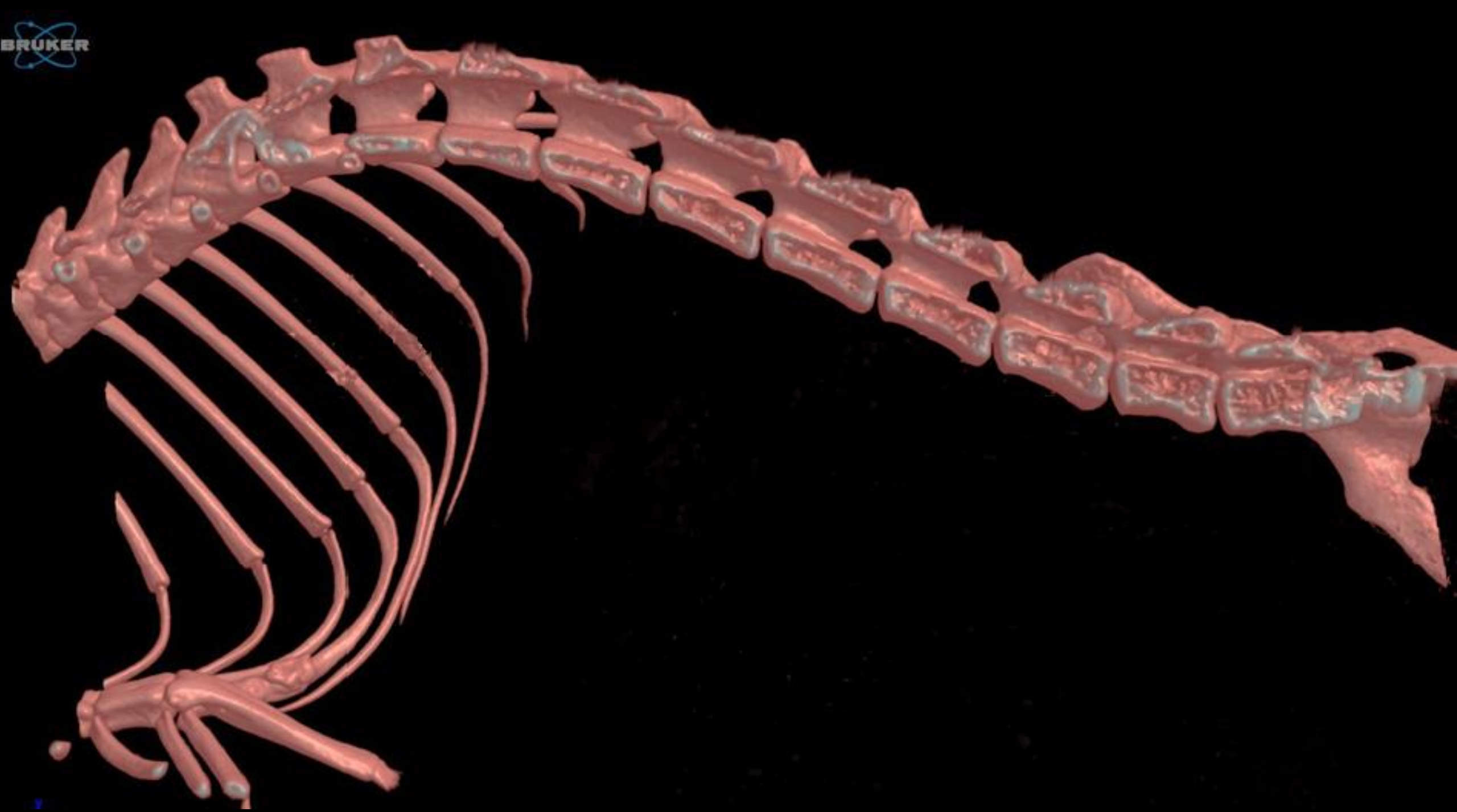
Golden-ADC



Golden-RT

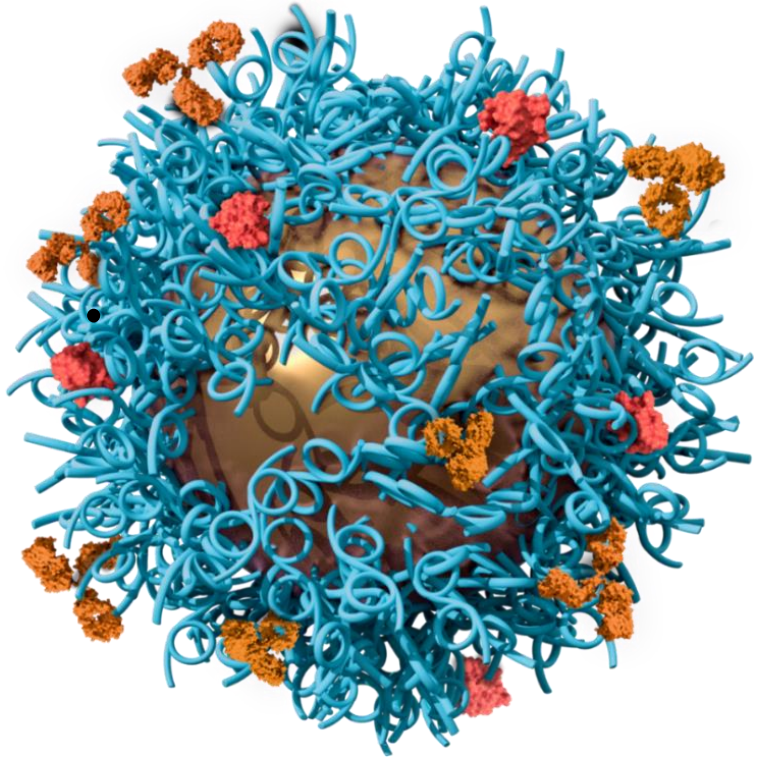


Multiple therapeutic modalities

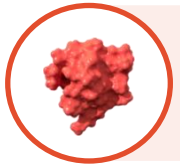

BRUKER

Brain delivery platform

- Harnessing the highly effective brain penetration of insulin
- A novel structure that enhances efficacy
- Can carry up to 30 antibodies on a single particle
- Versatile cargo combinations to address various diseases



Gold nanoparticle core
Carrier

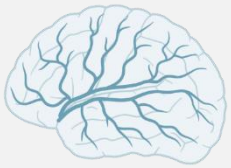


Insulin
Trojan horse

3 PEG linkers Novel structure

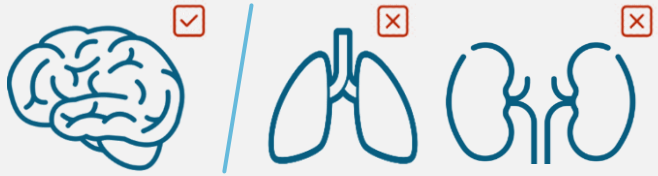
Therapeutic antibodies
Cargo

Interesting Facts on Insulin



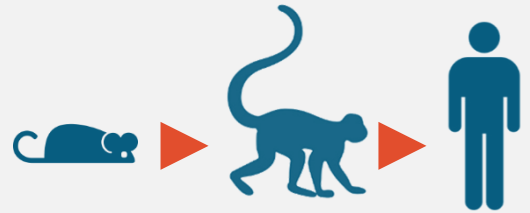
High expression on brain BMV*

+



Selectivity compared to peripheral organs

+



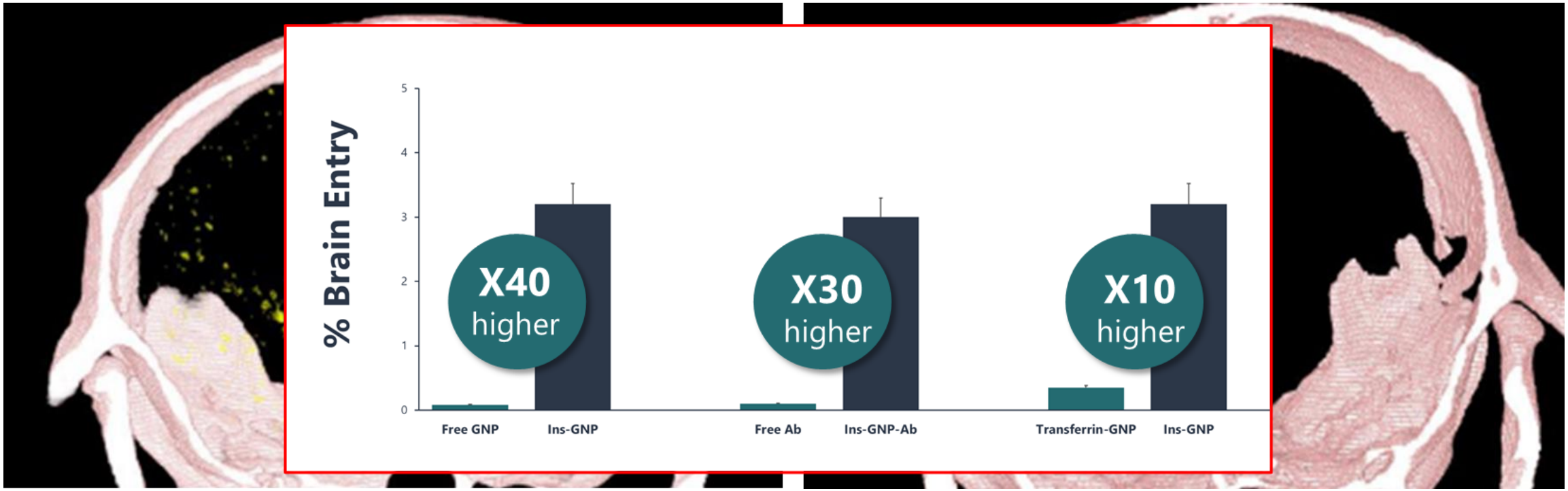
Translatability across species

* BMV – Brain Micro Vessels

Greater availability of the insulin receptor (IR) on the endothelial membrane, compared to the TfR
TfR on the BBB is >99.99% saturated (25,000 nM in plasma), while insulin plasma concentration is 0.3 nM, only 1% of the total brain endothelial IR concentration; thus ***the majority of the brain endothelial IR are unoccupied***

Insulin Receptor (IR) and IGF-1 are found to be overexpressed in various cancers including: breast, prostate, endometrial, ovarian, lung, colon and osteosarcoma.

Insulin shuttles gold nanoparticles across the BBB



Insulin +

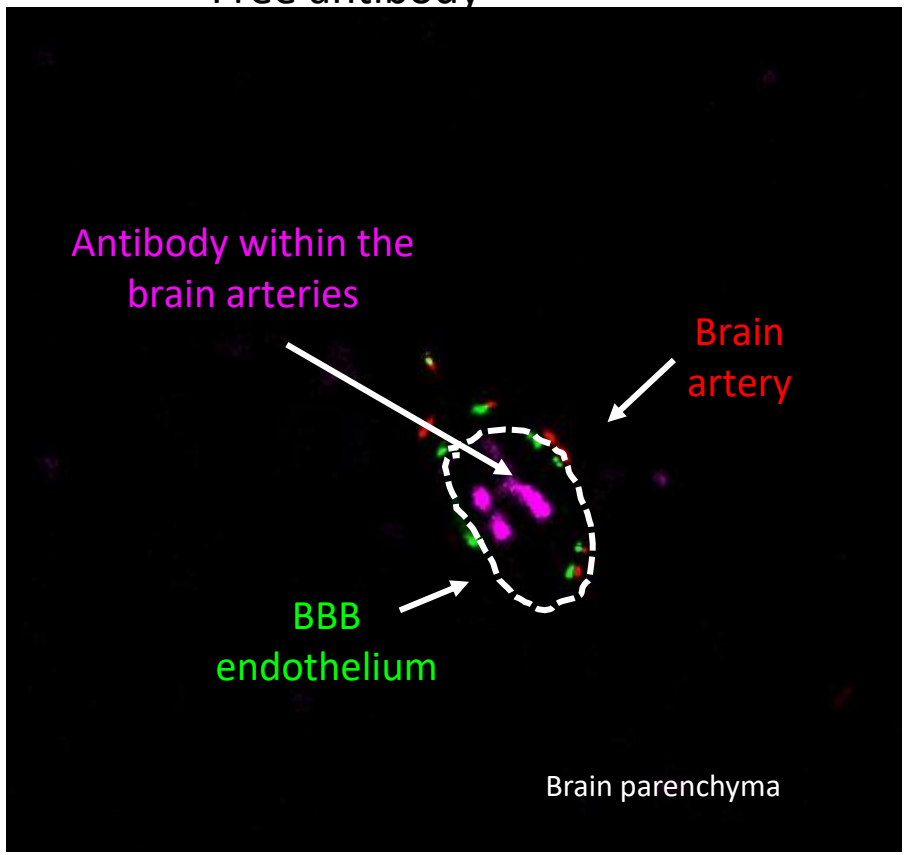
No Insulin -

R. Popovtzer PCT/IL2021/050279
Betzer & … Popovtzer, *Nanomedicine* 2017
Sadan & …..Popovtzer, *under review*, 2024

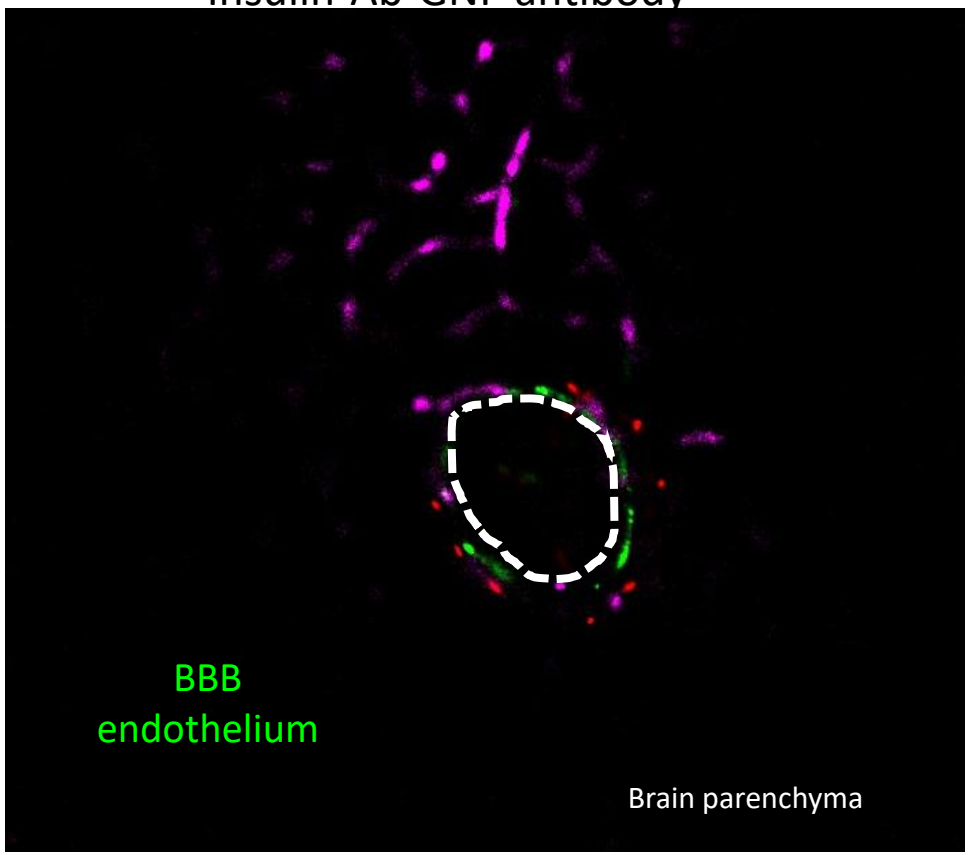
Insulin-Ab-GNP brain penetration

Super-resolution microscopy show the migration of Ins-Ab-GNP within the brain (right) while free antibody is blocked within the brain blood vessel (left)

Free antibody

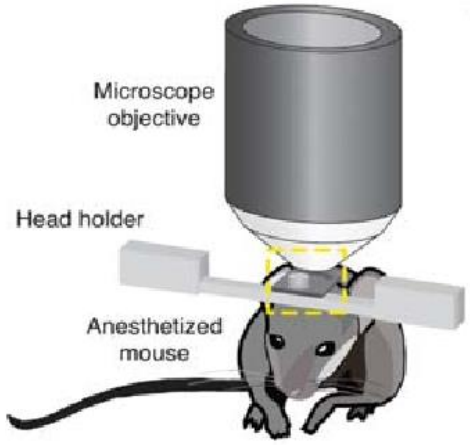


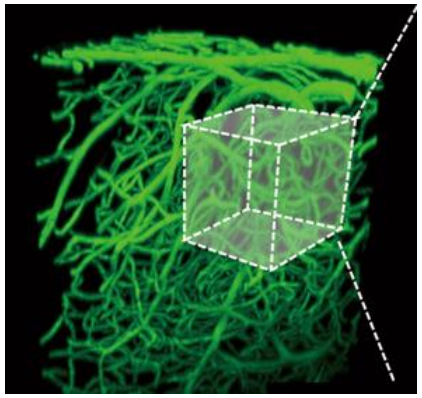
Insulin-Ab-GNP antibody

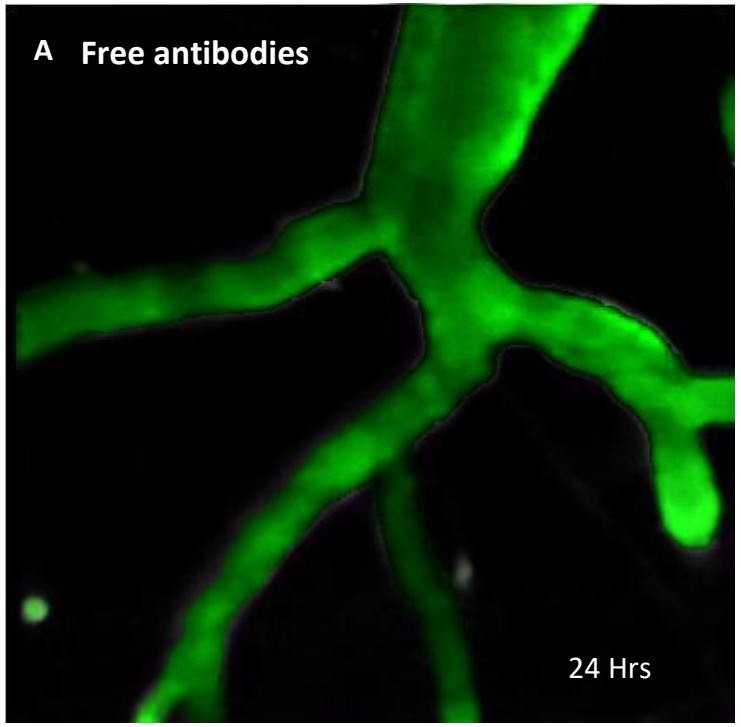


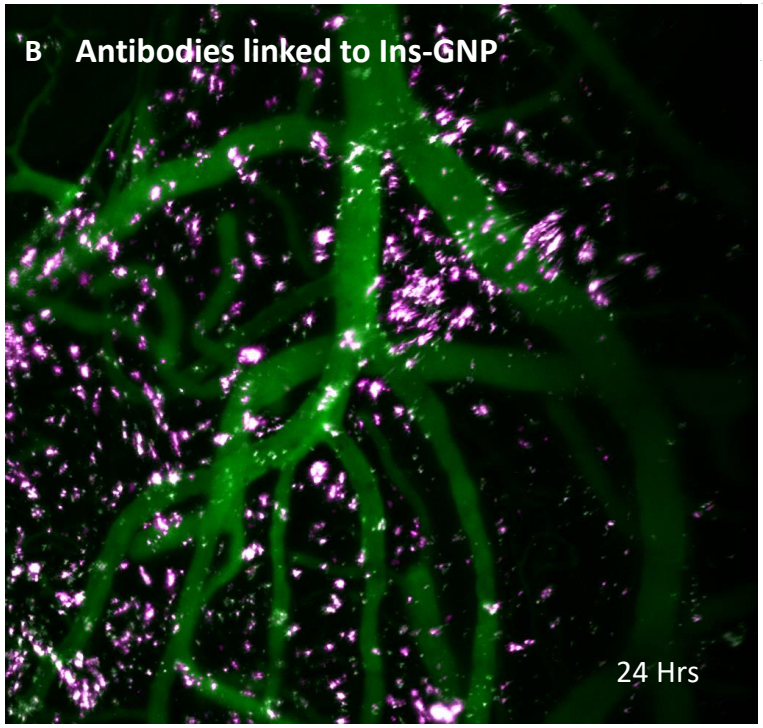
Super resolution microscopy of brain sections stained with - CD31 (endothelial marker) – Green (488), SM22 (arterial marker) – red (568), Ab (microglial marker) – magenta (647)

Efficient brain delivery







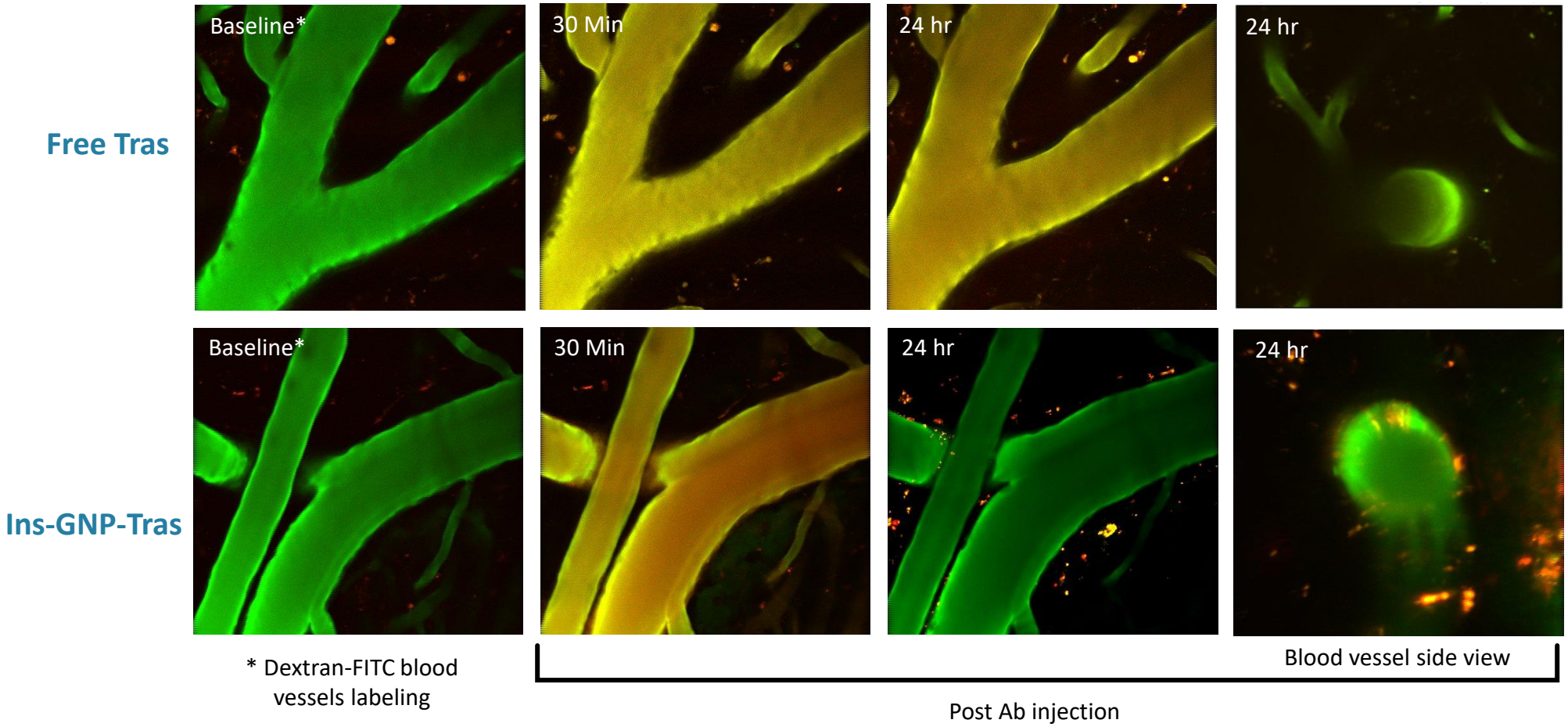


Real-time *in vivo* two-photon imaging of healthy brain (GNP-Cetuximab, 24h post IV injection)

Insulin-GNP-Ab real-time brain penetration

Insulin-GNP-Abs penetrate the brain while free Abs are restricted to the blood vessels

Real-time *in vivo* two-photon time-course imaging of healthy brain (insulin-GNP-Trastuzumab vs free Trastuzumab , 30m and 24h post IV injection)

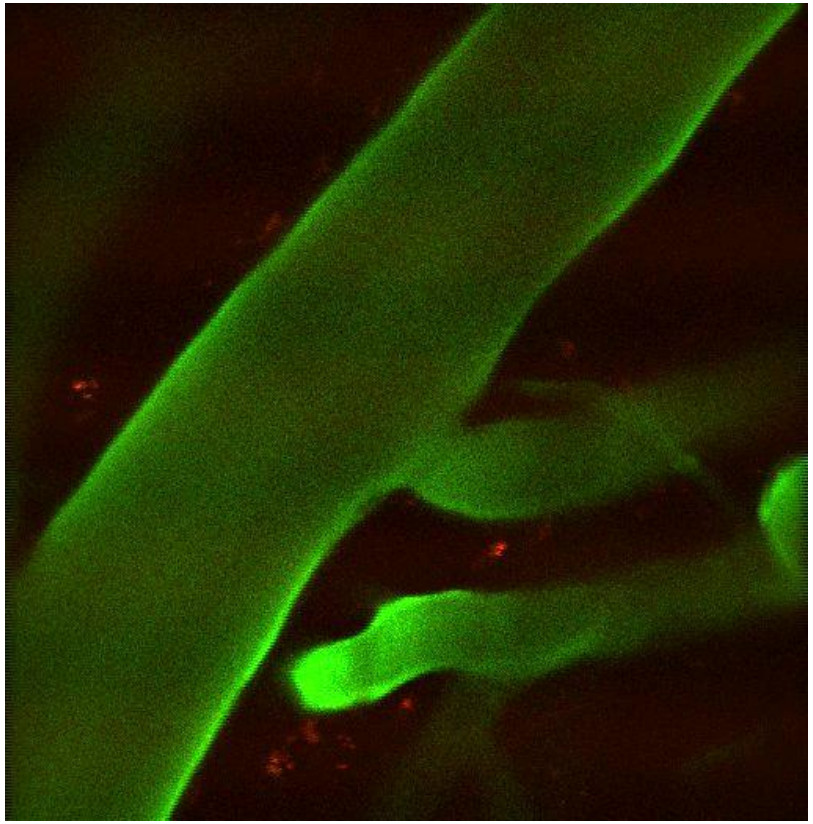


Insulin-GNP-Ab real-time brain penetration - MoA

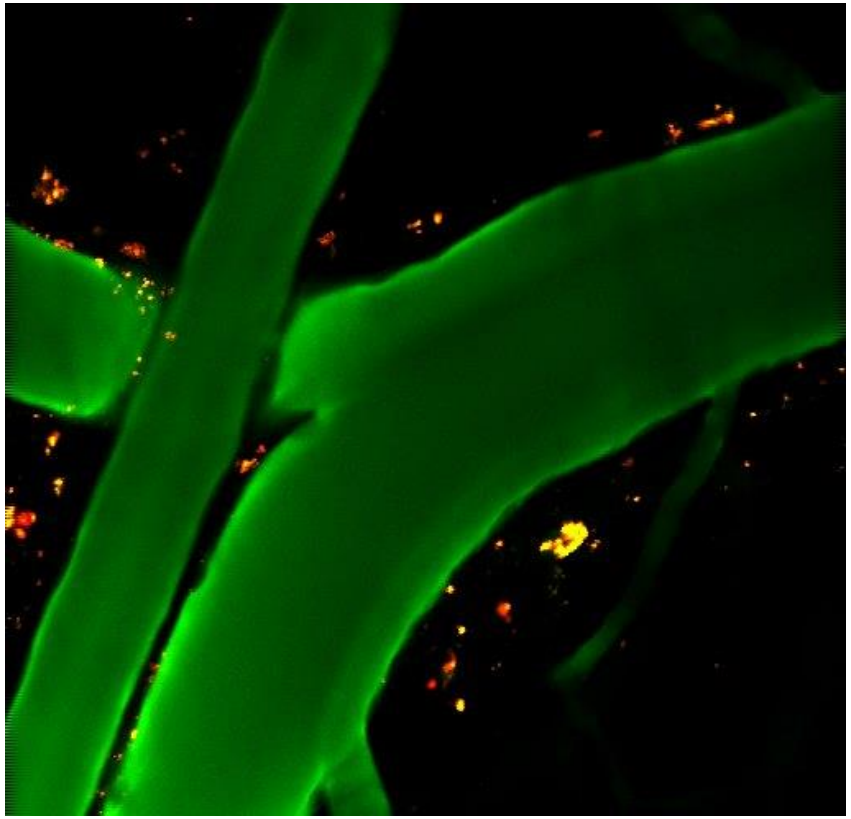
Insulin triggers brain penetration

Ins-GNP-Ab were detected near intact blood vessels within the brain after IV administration while the same particles, without insulin, were not detected in the brain.

Two-photon live imaging of healthy WT mouse brain imaged through transparent sealed glass "windows". Vasculature is fluorescently labelled with green dextran at time 0 (baseline) and 24 hours post single IV injection of ATTO595 fluorescently labelled antibodies on (A) Ab-GNPs with insulin and (B) Ab-GNPs without insulin.



Ab-GNPs
without Insulin

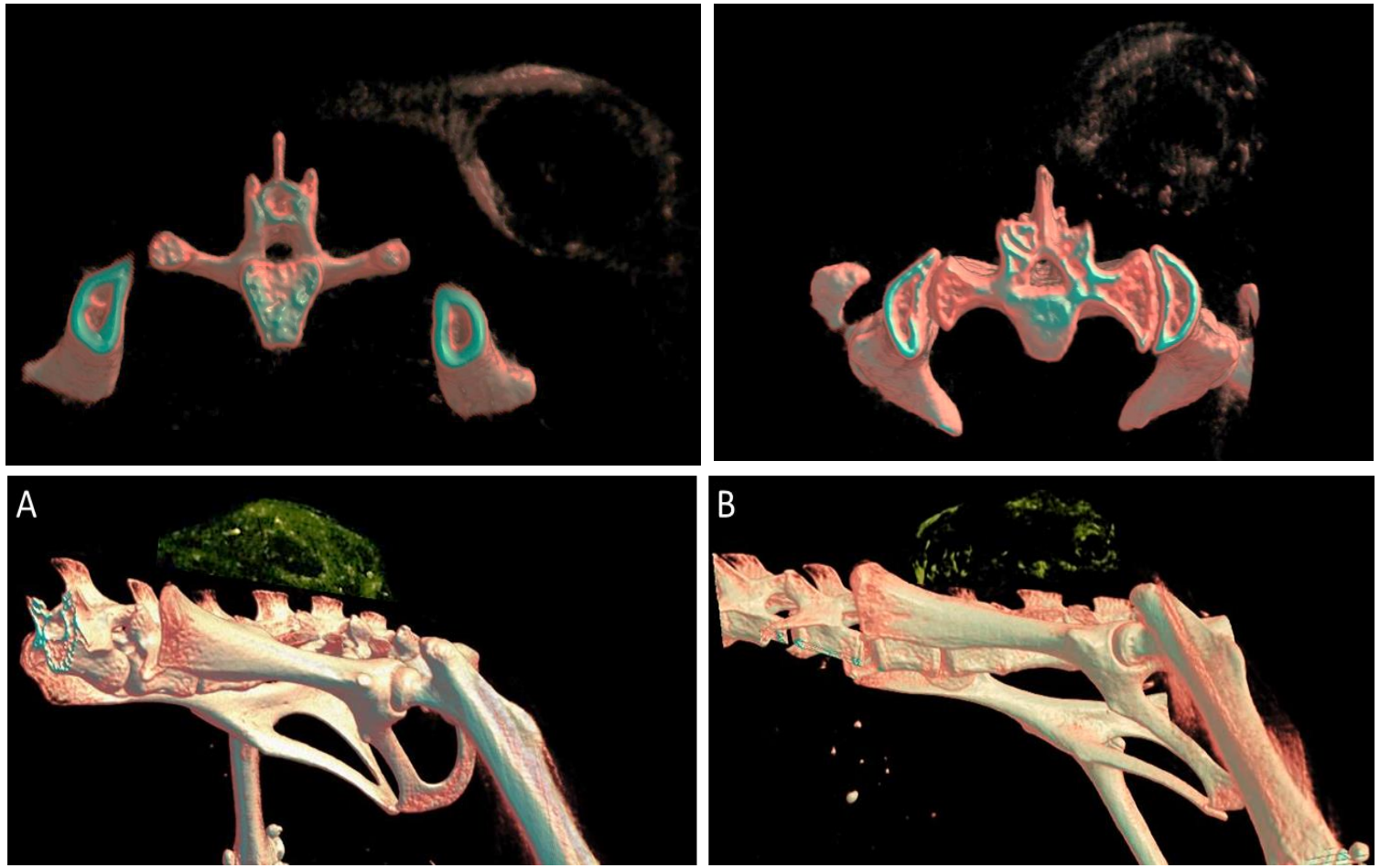


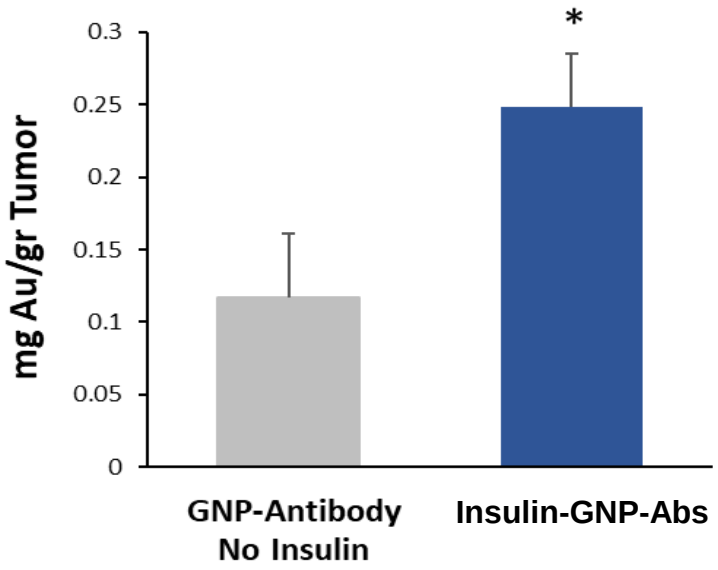
Ab-GNPs
with Insulin

Insulin effect – better targeting and intratumoral penetration

w/o insulin

with insulin

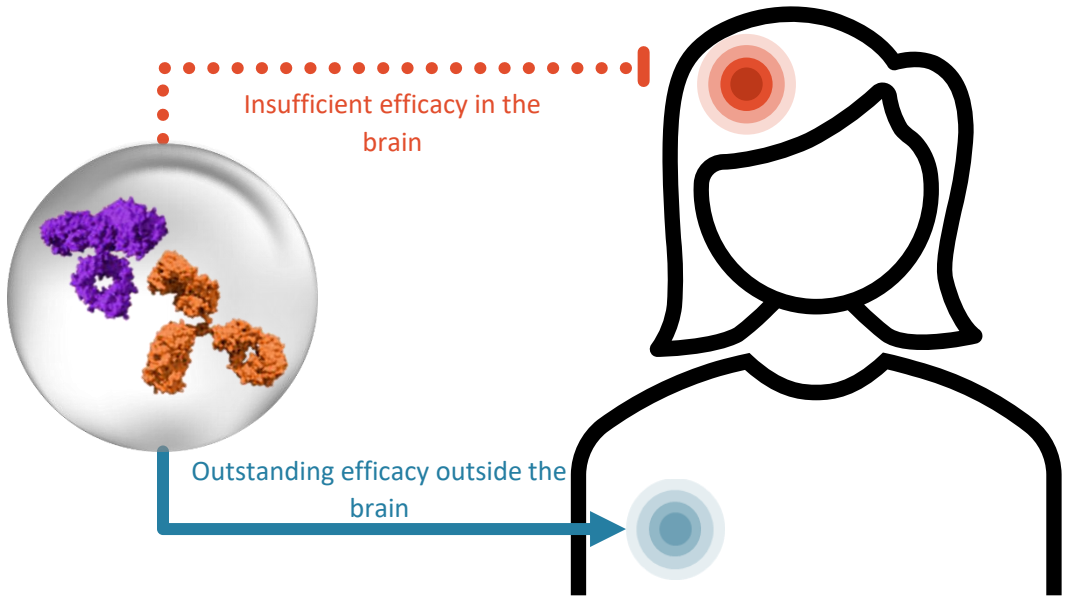




HER2-Positive breast cancer brain metastases (BCBM)

Gold Standard Treatment for HER2 mBC

stuzumab (Herceptin) + Pertuzumab (Perjeta)



With brain metastases

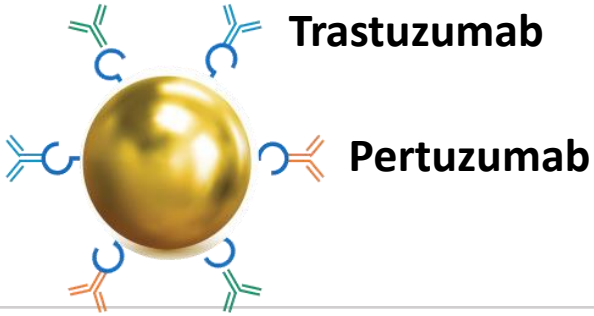
5-yr survival: 0%

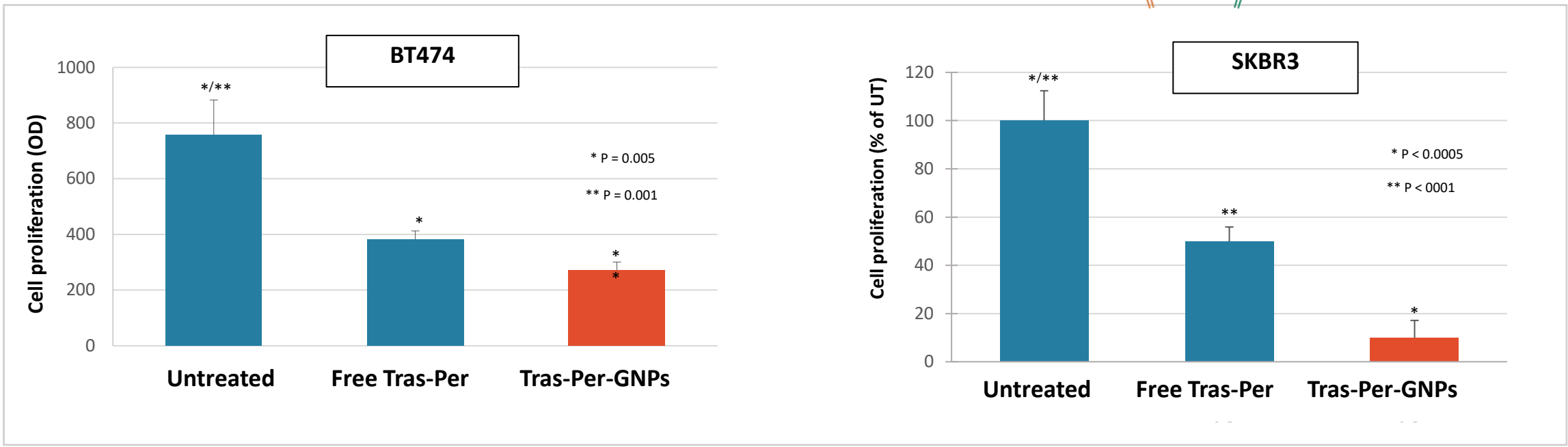
Metastatic breast cancer (mBC)

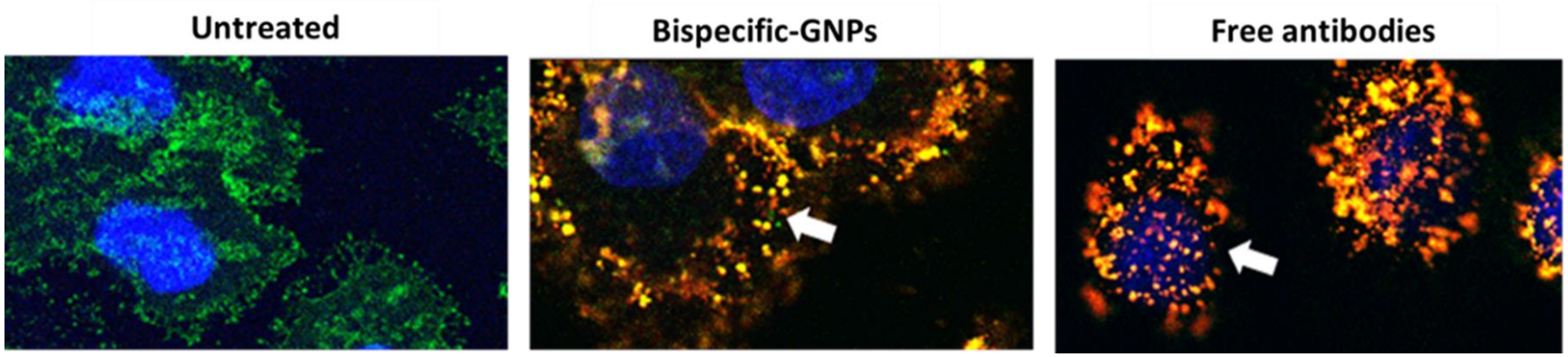
5-yr survival: >50%

nanocarry Disclosure - I'm a co-founder and CSO

Bispecific GNPs: *in vitro* efficacy

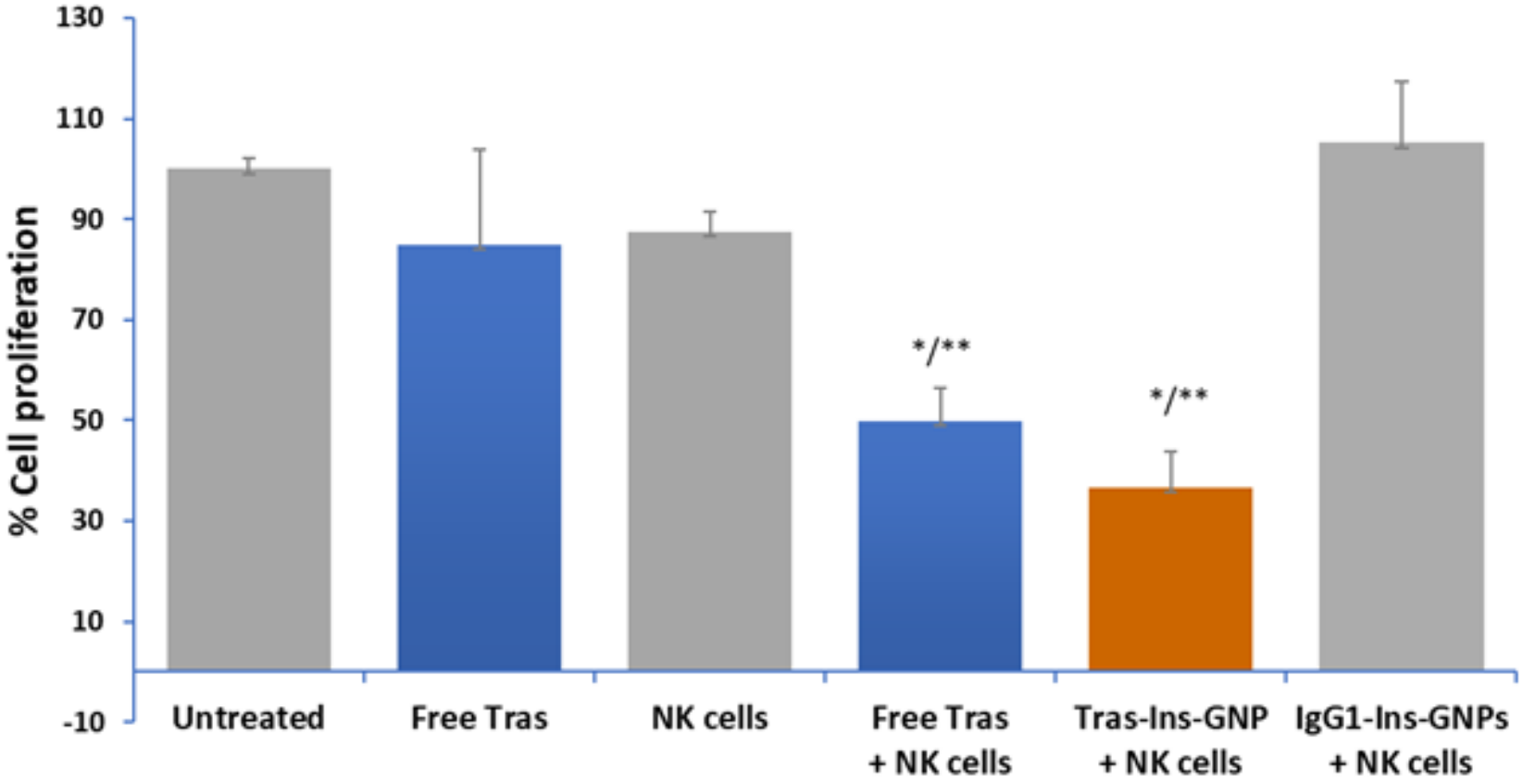


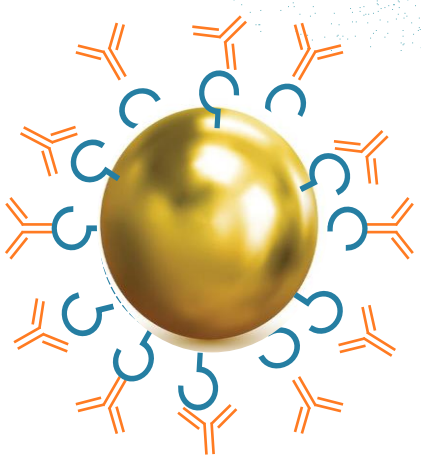




Bispecific GNP nanoplatform is internalized into BT474 breast cancer cells following binding to its membrane target HER2, in a pattern similar to free antibodies.

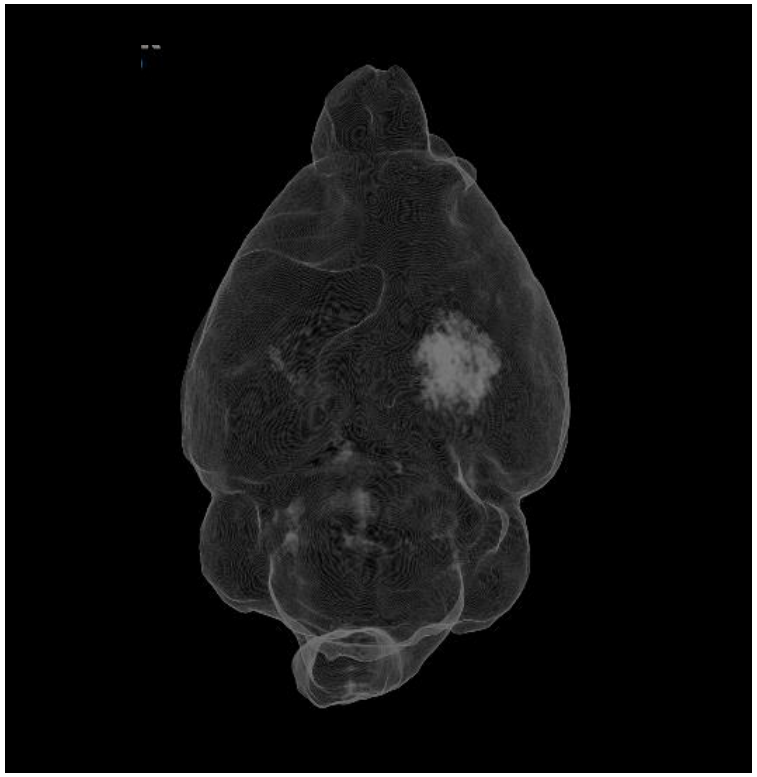
Induces antibody-dependent cell-mediated cytotoxicity (ADCC)



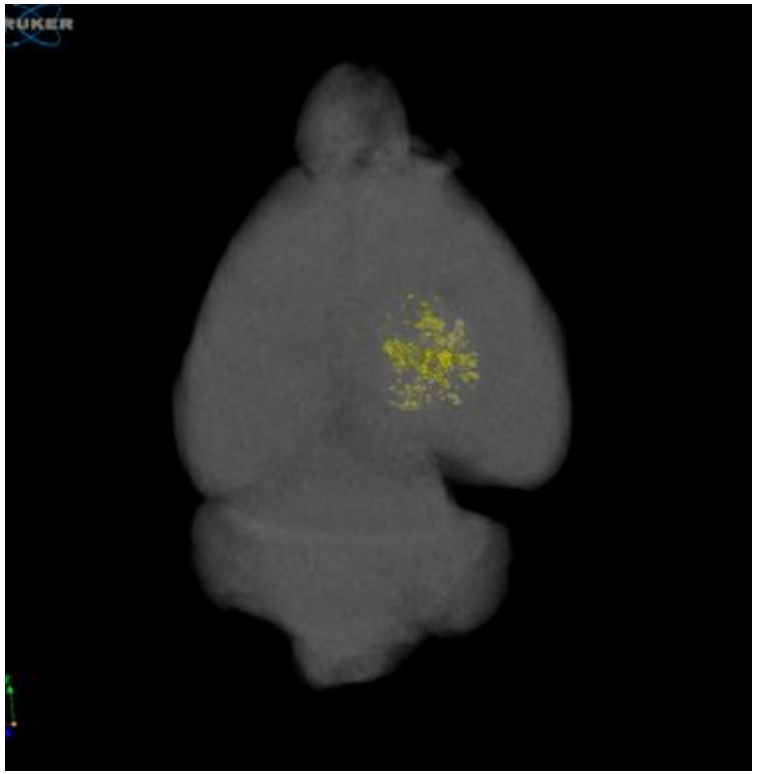


Targeted delivery: AxS007 massively reached the specific tumor site in the brain

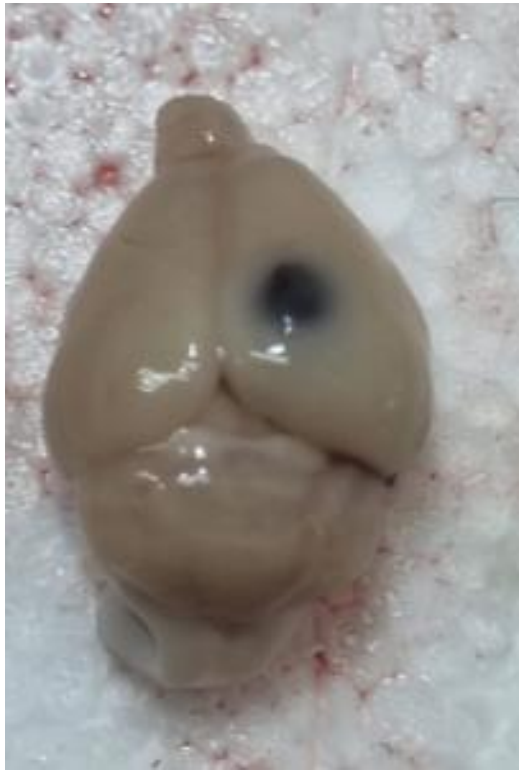
A Brain CT – before treatment (using tumor Iodine labeling)



B Brain CT – following treatment (Gold)



C AxS007 within brain tumor (visible)



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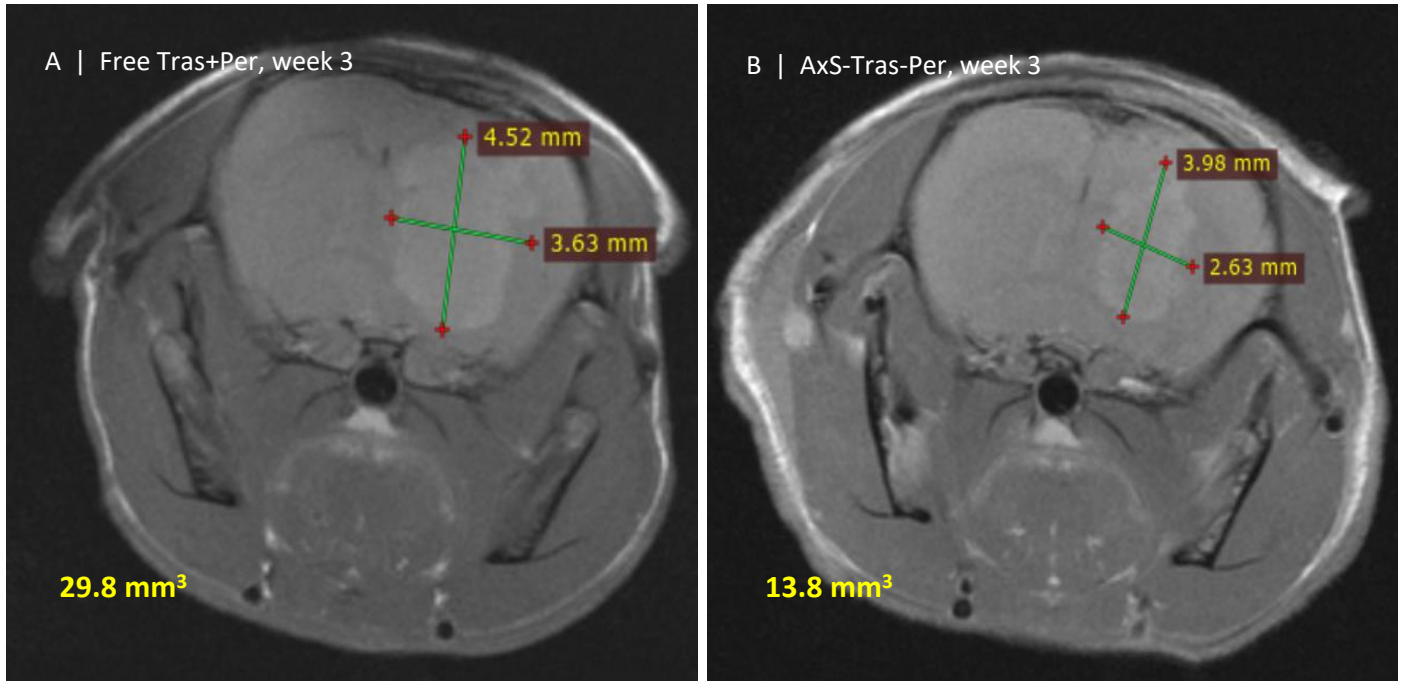
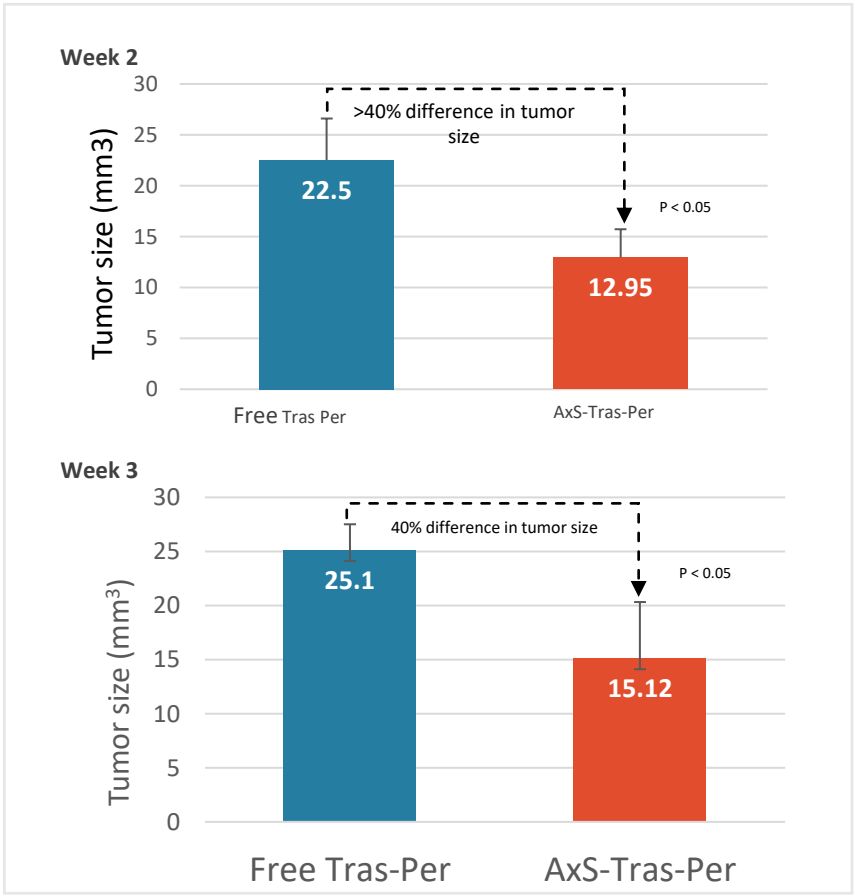
MRI imaging following 3 weeks of treatment

BT474 xenograft in NUDE mice

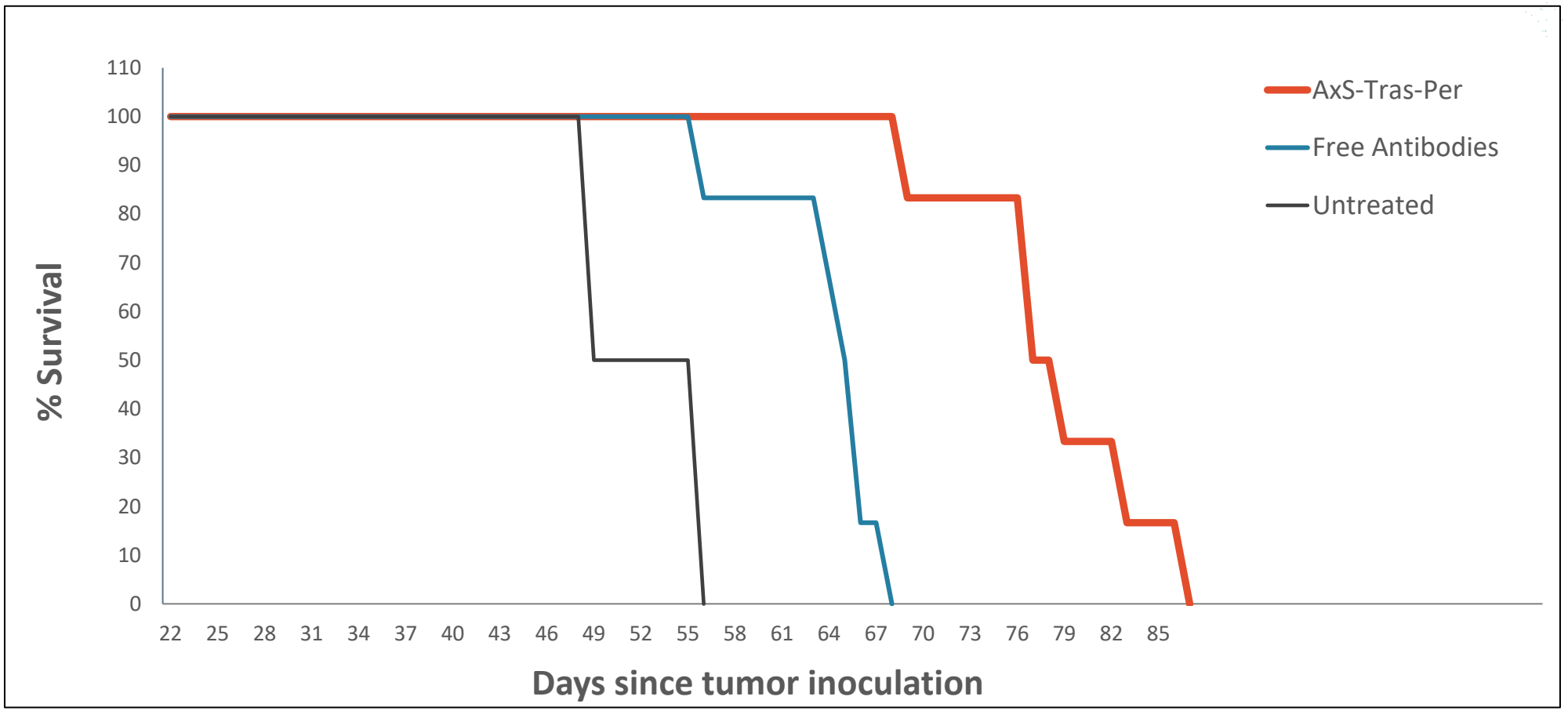




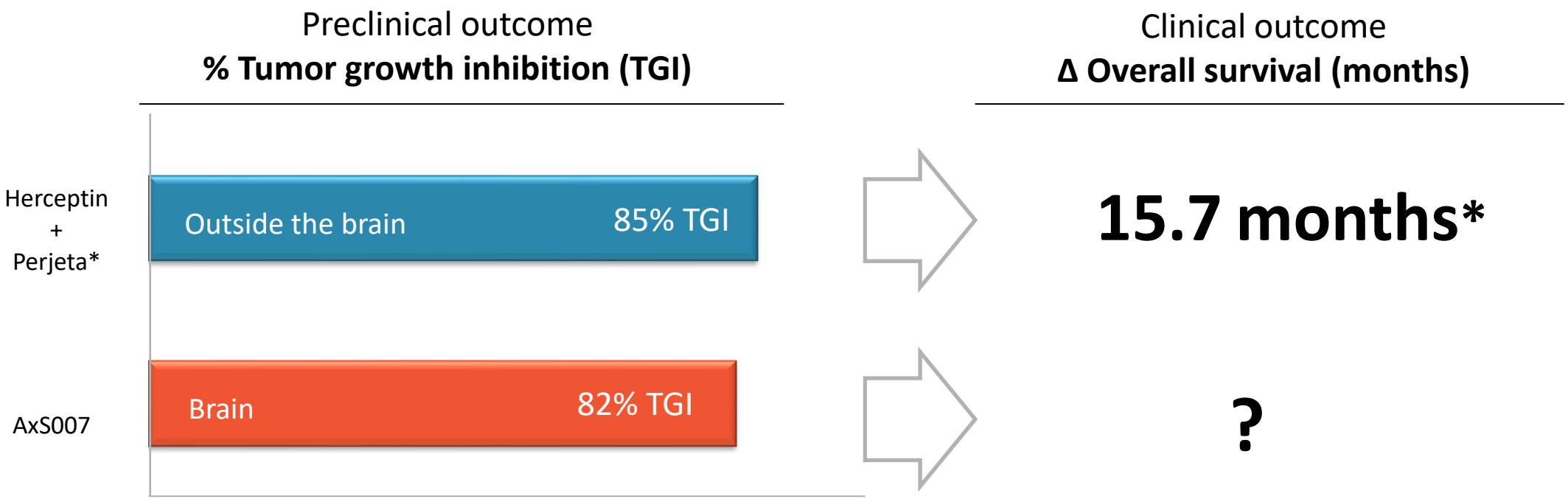
In-vivo MRI representative images of BT474-tumor baring Nude mice, 3 weeks after treatment initiation. A. Representative mouse treated with 3 weekly injections of free Trastuzumab & Pertuzumab antibodies. B. Representative mouse treated with 3 weekly injections of AxS007 (AxS particles conjugated to Trastuzumab & Pertuzumab antibodies). Tumor size (yellow) was measured with the following: 0.5*Length*(Width^2)

AxS007 extends survival by 30 days (>50%)

BT474 xenograft in NUDE mice



A gamechanger potential: AxS007 inhibits tumor growth in the brain just like the Gold Standard outside the brain



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* Fan Zhang, et al, 2015 | https://www.perjeta-hcp.com/metastatic/efficacy.html

Acknowledgments

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