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AAV MEDIATED BRAIN DELIVERY OF AN ADCC-ENHANCED ANTIBODY OBVIATES XENOGRAFT GROWTH IN MOUSE MODELS OF HER2+ BREAST CANCER BRAIN METASTASIS

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Disclosures

Dan Laks is a full-time employee of Voyager Therapeutics

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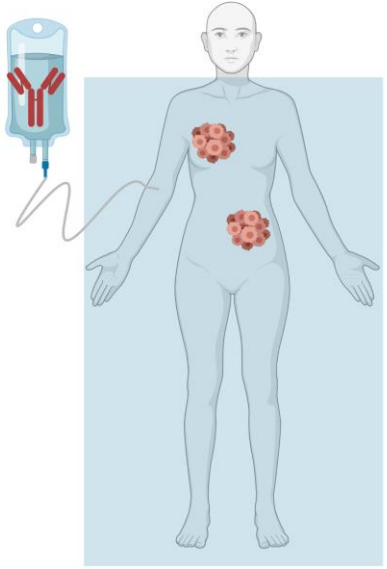
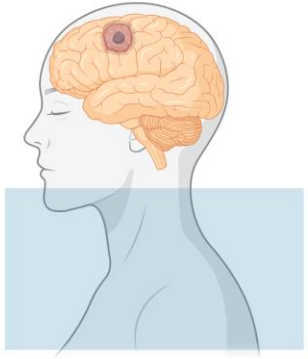
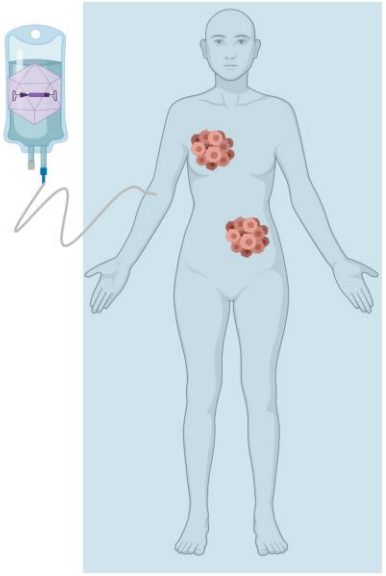
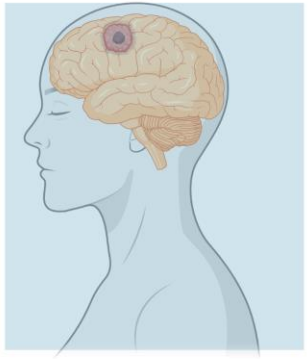
Hypothesis: AAV mediated production of anti-HER2 antibodies in the CNS will mitigate prognosis of metastatic HER2+ breast cancer





Systemic αHER2 antibody therapies are limited in their CNS distribution by the blood-brain barrier and CNS efflux





AAV gene therapy can enter the brain and generate stable expression of therapeutic antibodies

Addressing an unmet medical need

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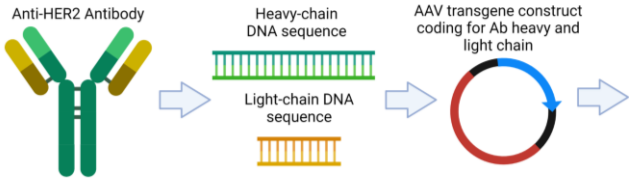
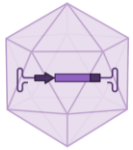
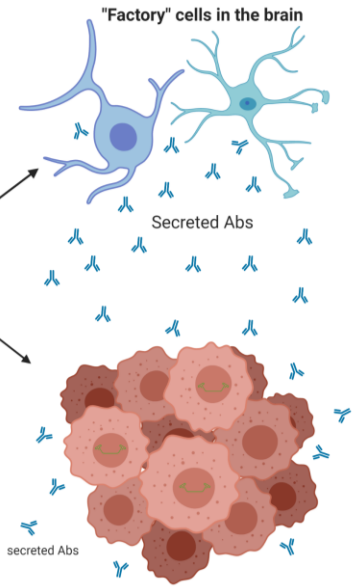
Strategy: Employ brain cells as antibody factories through AAV mediated gene therapy

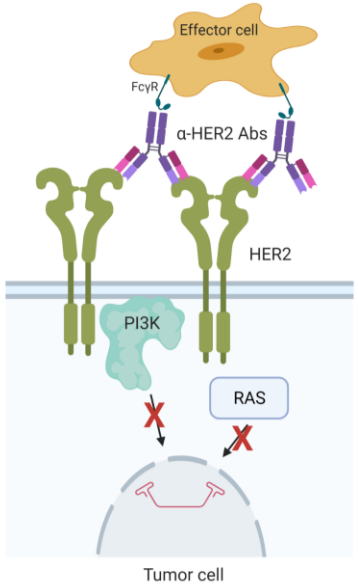


ADCC+
(enhanced)



rAAV targeting
the CNS





Antibody prevents receptor dimerization & promotes ADCC (antibody dependent cell cytotoxicity).

Vectorized antibodies are a method to generate persistent, high coverage target-engagement in the CNS

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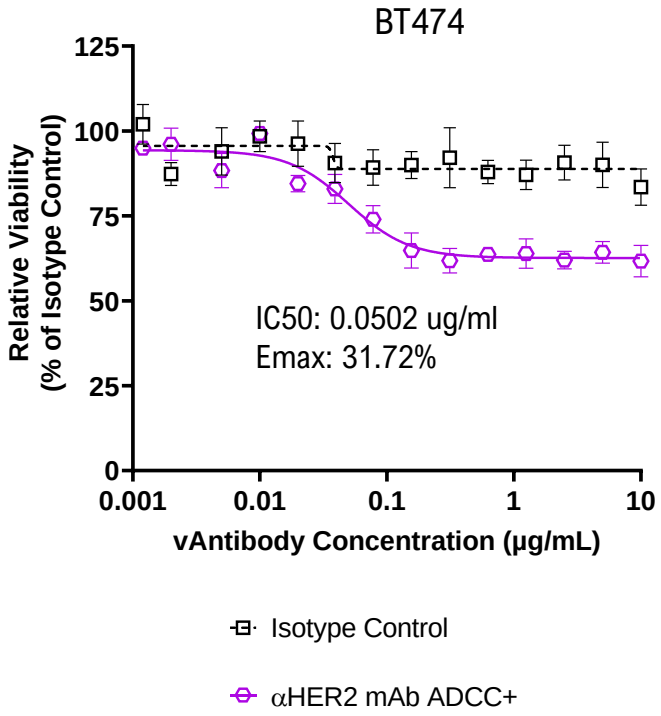
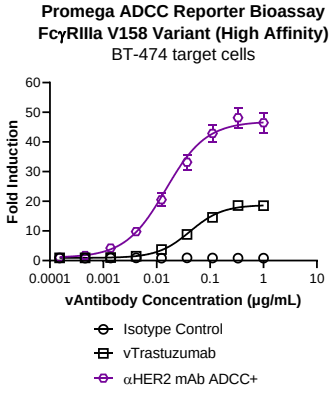
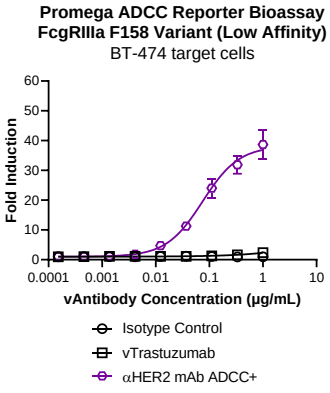
Transgene: A vectorized αHER2 mAb with enhanced ADCC (ADCC+) properties







Cell/Tumor models

BT-474-Luc: Primary HER2 ductal carcinoma, breast cancer tumor cells.

MDA-MB-361-Luc: Originated from breast cancer brain metastasis tumor cells, of HER2 adenocarcinoma (glandular), cultured as tumorspheres.

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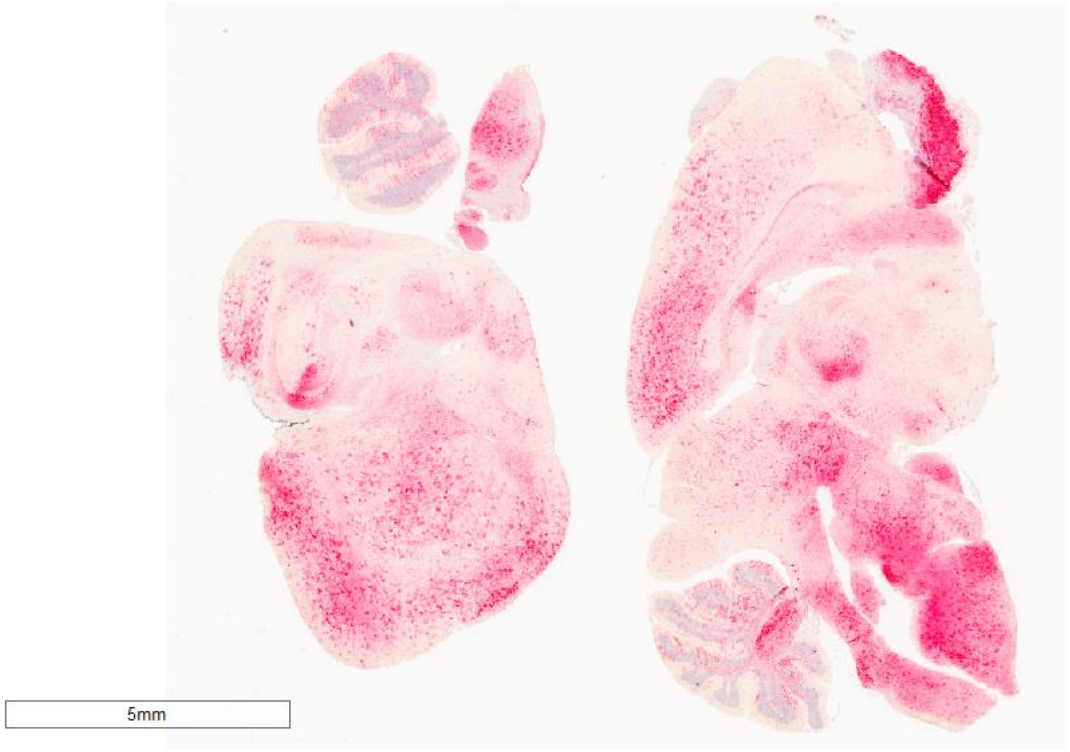
Delivery: Broad expression in the brain using a Voyager TRACER Capsid

Sagittal mouse brain slices after i.v. administered AAV with TRACER capsid, expressing EGFP transgene



IHC performed with anti-GFP antibody- **red** chromogenic dye

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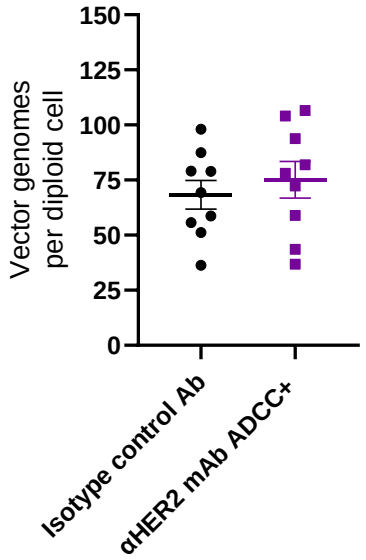
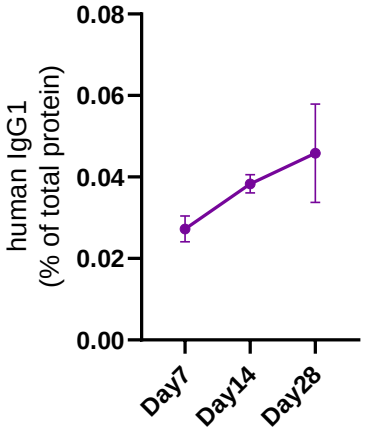
Durable brain expression upon i.v. administration of AAV mediating αHER2 ADCC+ mAb

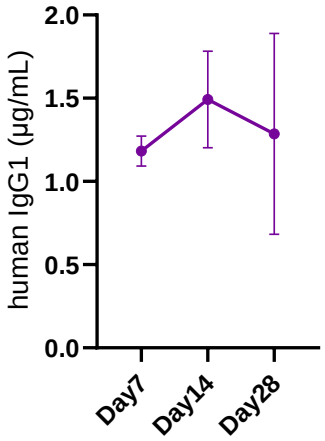
- 28 Day AAV Transduction: **Brain** vector genomes



- Anti-HER2 vAb (ADCC+): **Brain**



- Anti-HER2 vAb (ADCC+): **CSF**



Ongoing studies demonstrate durable vAb expression for over 90+ days in mouse brain

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HER2+ orthotopic xenograft brain tumors in mouse co-stain with vectorized αHER2 ADCC+ mAb

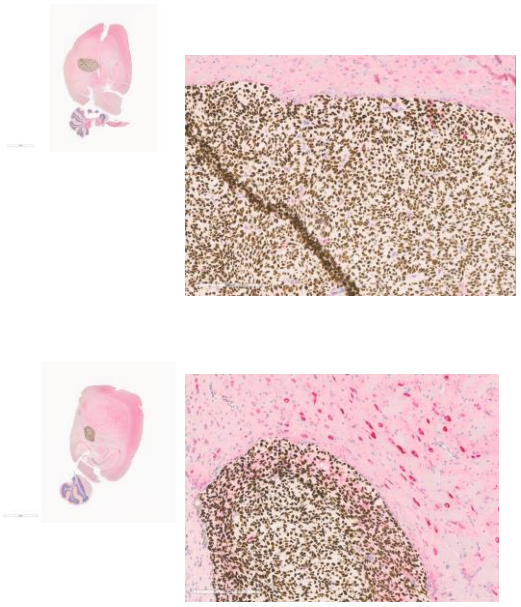
Isotype control AAV

αHER2 mAb AAV

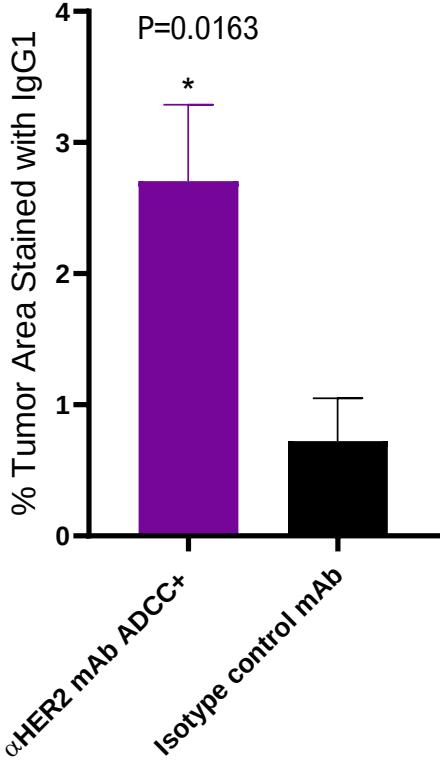
HER2 staining

human nucleoli (brown)
HER2(red)

Human IgG staining



human nucleoli (brown),
IgG(red)



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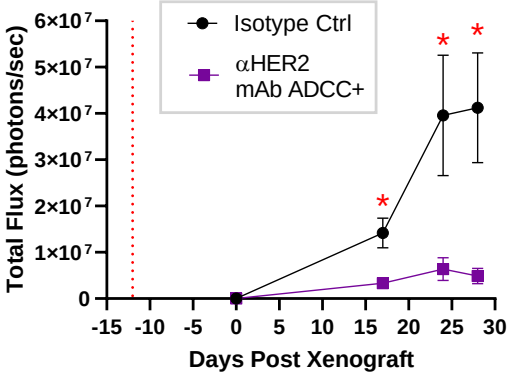
Proof-of-principle: Demonstration of pre-clinical efficacy in 3 models

Model 1

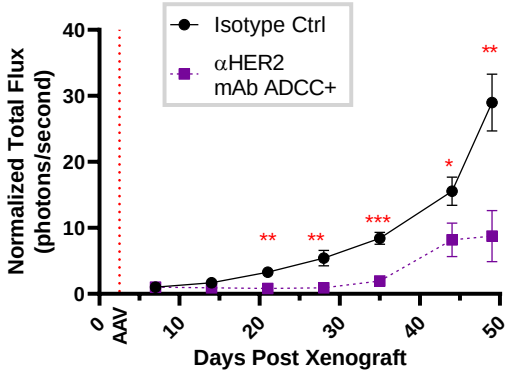
Systemic Prevention of Metastasis



- i.v. administration of AAV in a tumor prophylaxis study design
- CNS-targeted AAV vector
- Deliver AAV 12 days prior to engrafting MDA-MB-361-Luc tumorspheres
- N=10 per group

Model 2

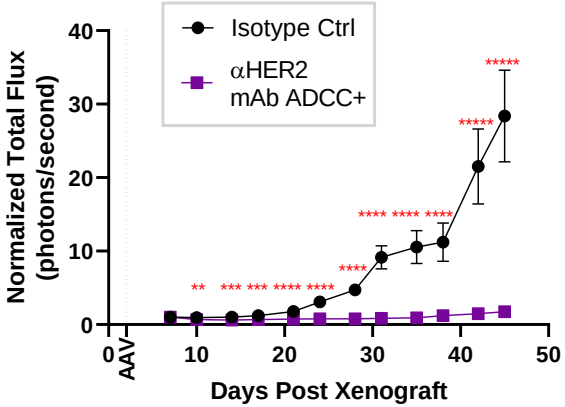
Systemic Treatment of Metastasis



- i.v. administration of AAV in a tumor treatment study design
- CNS-targeted AAV vector
- Deliver AAV 2 days post engrafting MDA-MB-361-Luc tumorspheres
- N=5 per group

Model 3

Local Treatment of Metastasis



- Intra-tumoral administration of AAV in a tumor treatment study design.
- Deliver AAV 2 days post engrafting BT-474-Luc cells.
- N=15 per group

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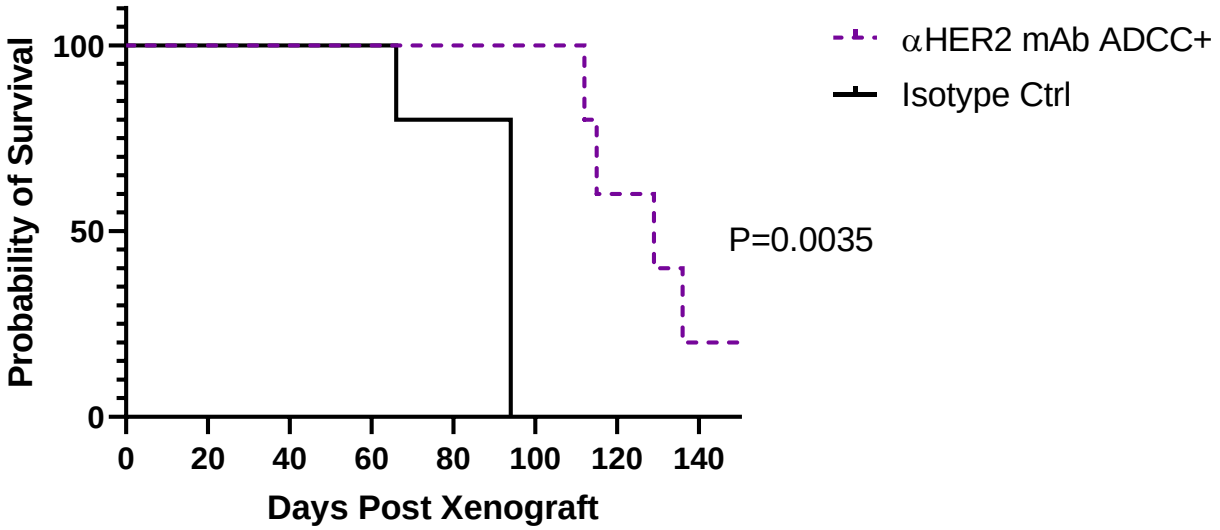
Gene therapy with blood brain barrier penetrant AAV confers a survival benefit

Model 2: i.v. administration in a tumor treatment study design (mouse orthotopic xenograft)

- AAV delivery 2 Days post xenograft of MDA-MB-361-LuC tumorsphere cells
- N=5 per group



Median survival	
αHER2 mAb ADCC+	129.0
Isotype Ctrl	94.00

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Summary and next steps

1. Addressing unmet medical need of HER2+ Brain Metastasis
2. Encoded ADCC enhanced antibody for delivery via AAV
3. Achieved broad distribution in brain with TRACER CNS targeting capsid
4. Successful intervention: attenuated tumor burden and extended survival
5. Plan to advance into NHP studies

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If you would like more information, please contact:

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