CNS PENETRANT AAV VECTORS ENCODING HER2 ANTIBODIES REDUCE TUMOR BURDEN IN MODELS OF BREAST CANCER BRAIN METASTASIS

ASGCT 25TH ANNUAL MEETING

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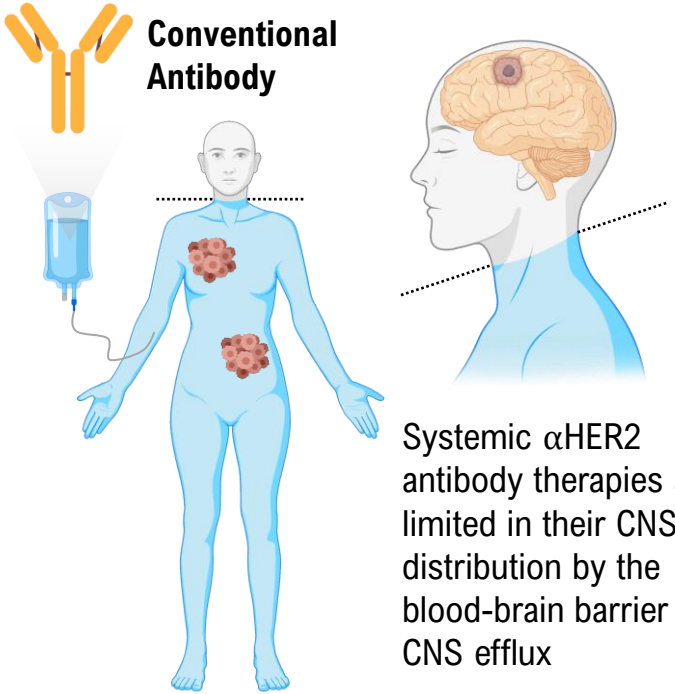
Rm 204, Abstract #63
May 16, 2022, 5:15 pm

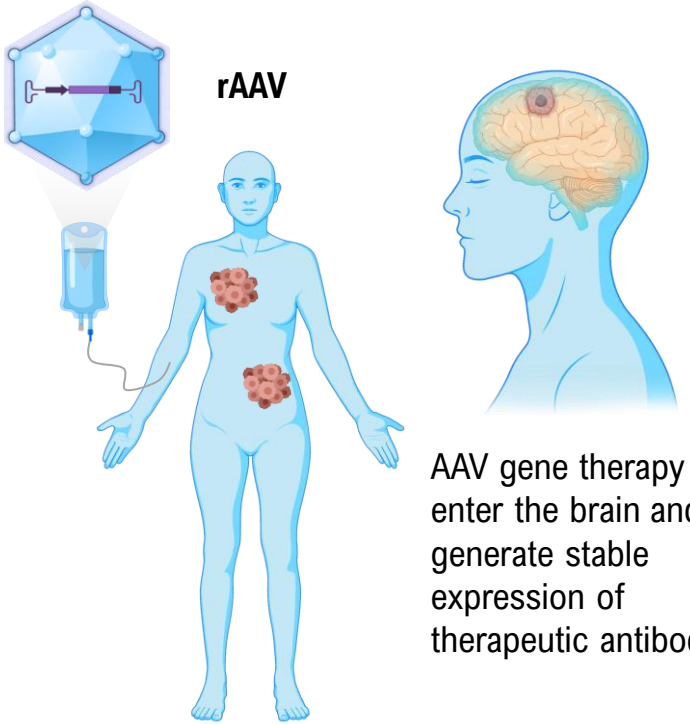
Disclosures

Dan Laks is a full-time employee of Voyager Therapeutics

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



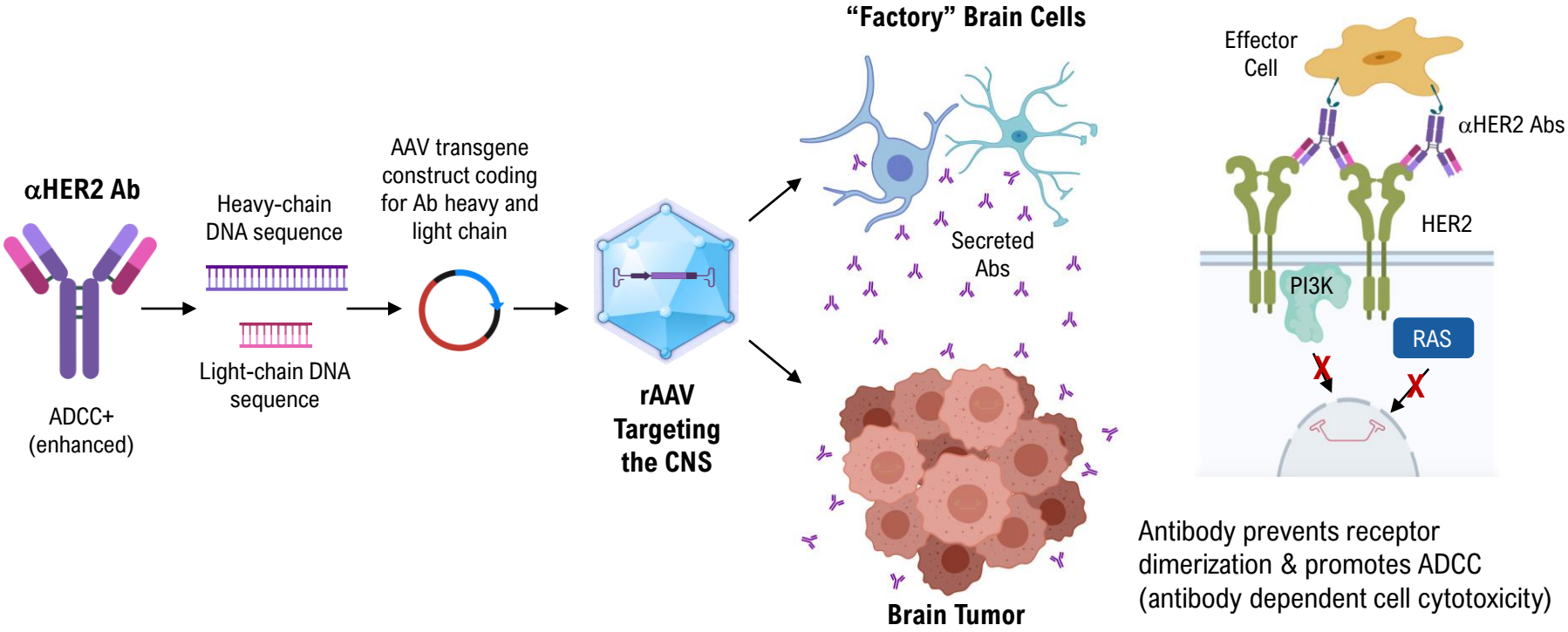
Systemic αHER2 antibody therapies are limited in their CNS distribution by the blood-brain barrier and CNS efflux



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

Addressing an unmet medical need

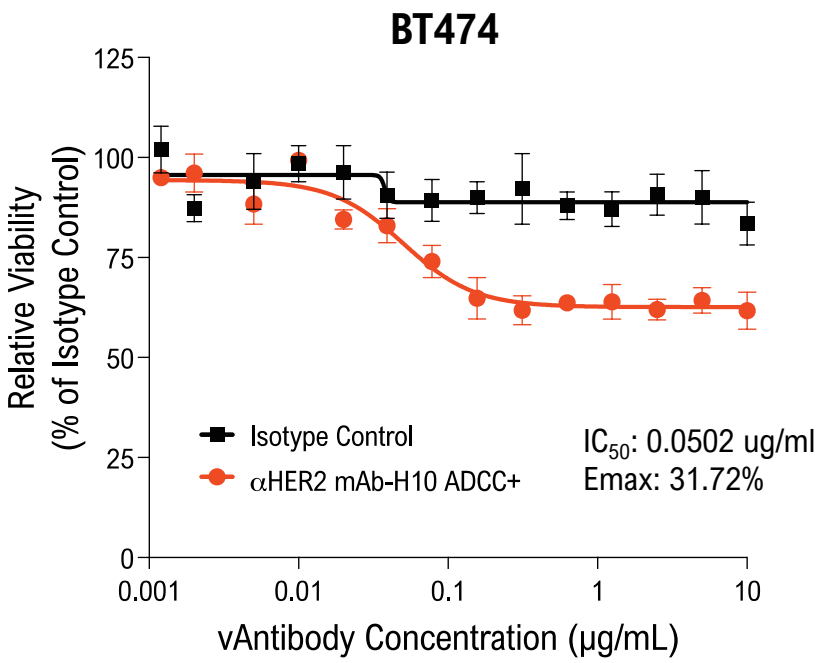
Strategy: Employ brain cells as antibody factories through AAV mediated gene therapy



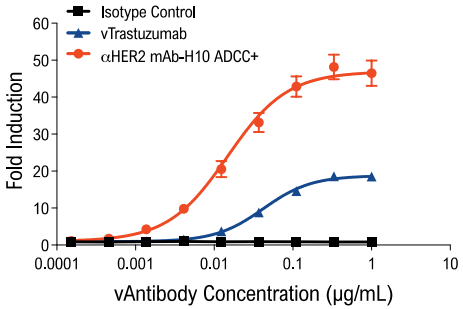
Antibody prevents receptor dimerization & promotes ADCC (antibody dependent cell cytotoxicity)

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

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



Promega ADCC Reporter Bioassay
FcγRIIIa V158 Variant (High Affinity)
BT-474 Target Cells



Promega ADCC Reporter Bioassay
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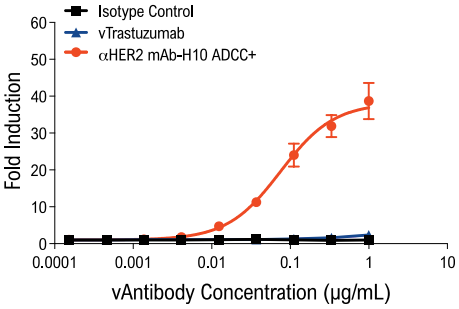

- Kenny Chen

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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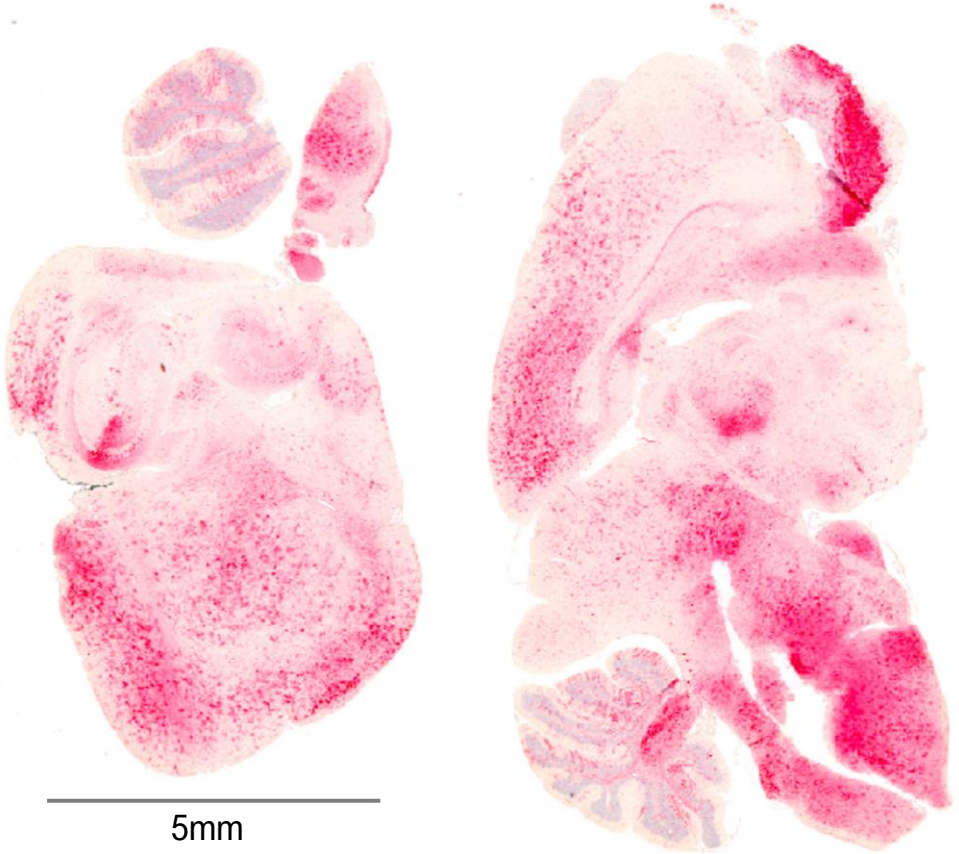
Proof of Concept Delivery:
Broad expression in the brain using the Voyager TRACER Capsid 9P39

Sagittal mouse brain slices after i.v. administered AAV with 4e11 VG TRACER capsid 9P39, expressing EGFP transgene

9P39 has mouse specific BBB penetrance- serves as proof of concept

-9P39 data outlined in Nonnenmacher, 2020



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

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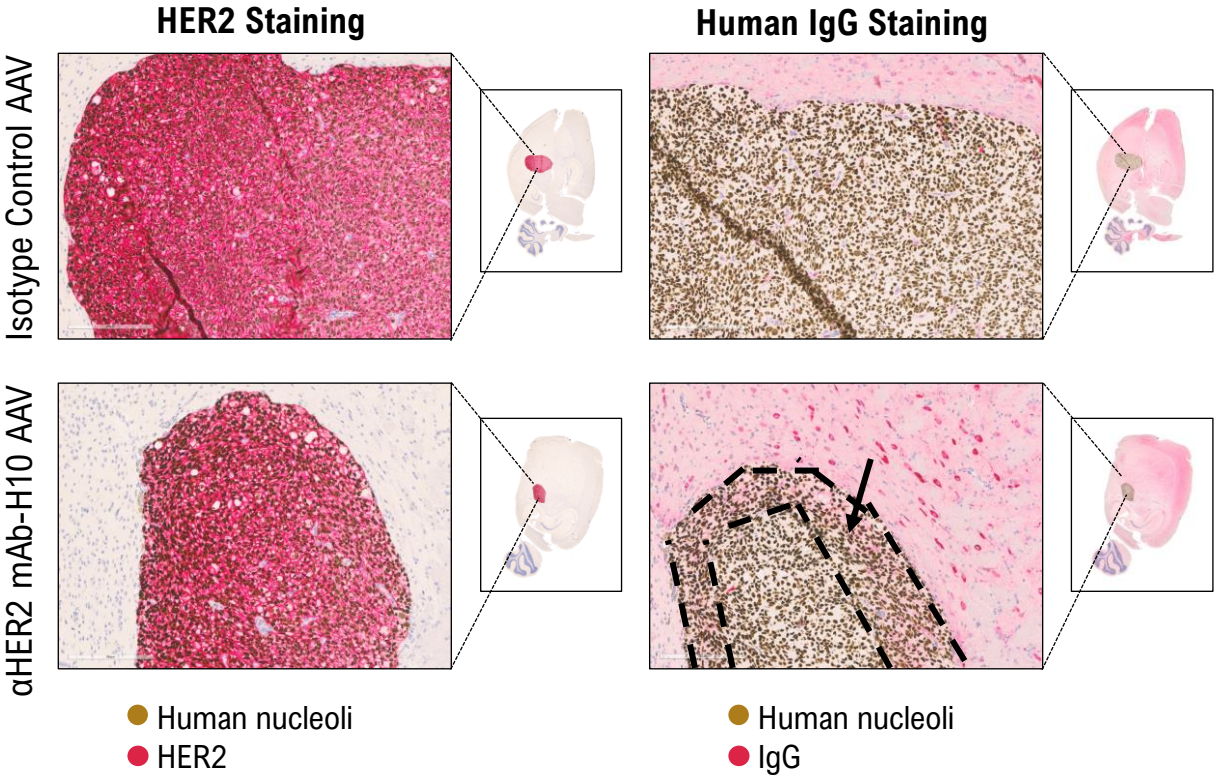
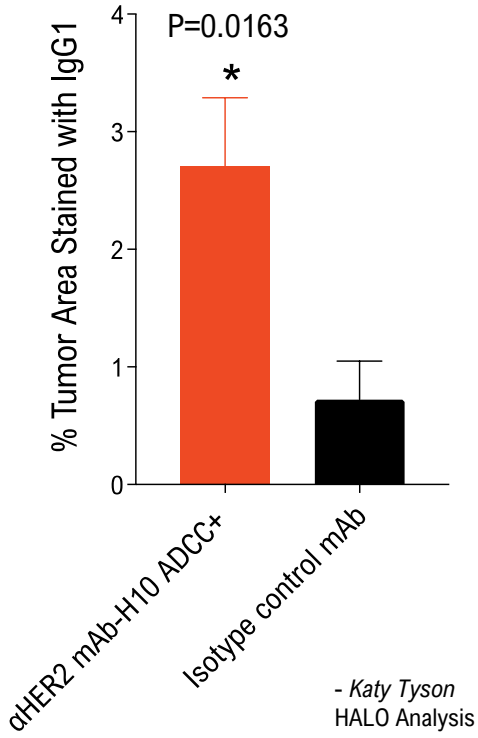
HER2+ orthotopic xenograft brain tumors in mouse co-stain with vectorized αHER2 ADCC+ mAb



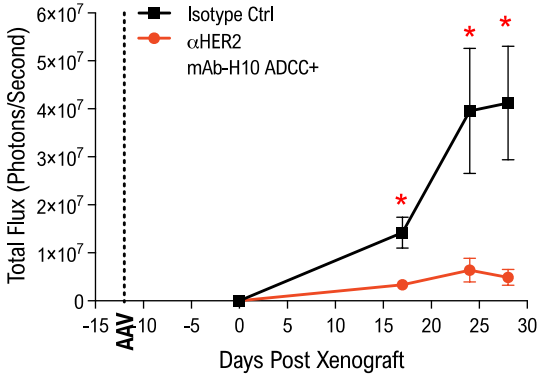


- *Katy Tyson*
HALO Analysis

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

Model 1

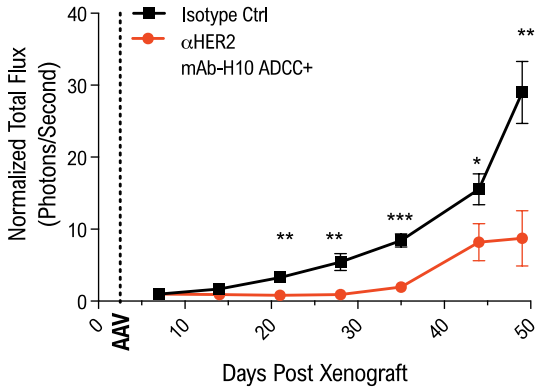
Systemic Prevention of Metastasis



- i.v. administration of 5e11 Vg AAV-9P39 in a tumor prophylaxis study design
- CNS-targeted AAV vector
- Deliver AAV 12 days prior to engrafting MDA-MB-361-Luc tumorspheres (orthotopic)
- N=10 per group

Model 2

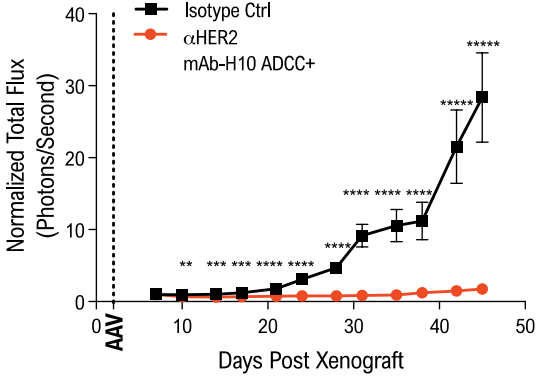
Systemic Treatment of Metastasis



- i.v. administration of 2.5e11 VG AAV-9P39 in a tumor treatment study design
- CNS-targeted AAV vector
- Deliver AAV 2 days post engrafting MDA-MB-361-Luc tumorspheres (orthotopic)
- N=5 per group

Model 3

Local Treatment of Metastasis



- Intra-tumoral administration of 6e10 VG AAV PHP.eB in a tumor treatment study design.
- Deliver AAV 2 days post engrafting BT-474-Luc cells.
- N=15 per group

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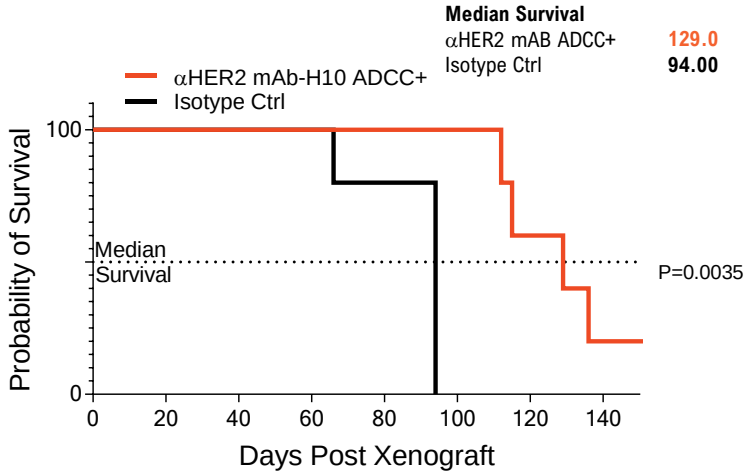
vHER2 gene therapy confers survival benefit

Model 2

i.v. Administration in a Tumor Treatment Study Design (Mouse Orthotopic Xenograft)

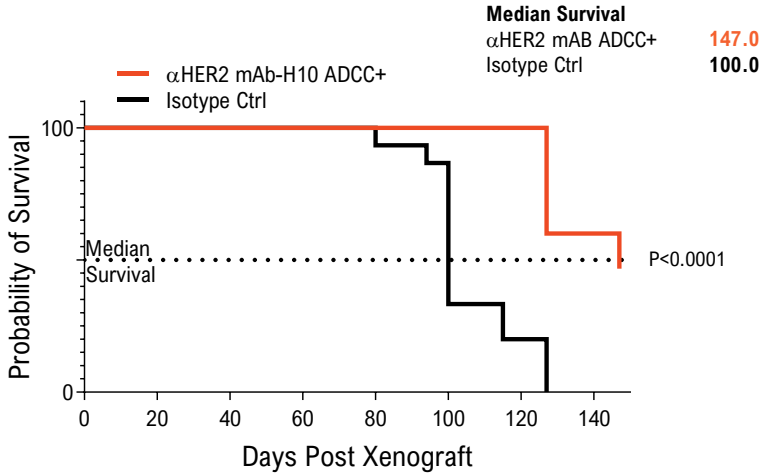
- AAV-9P39 delivery 2 Days post xenograft of MDA-MB-361-Luc tumorsphere cells
- N=5 per group



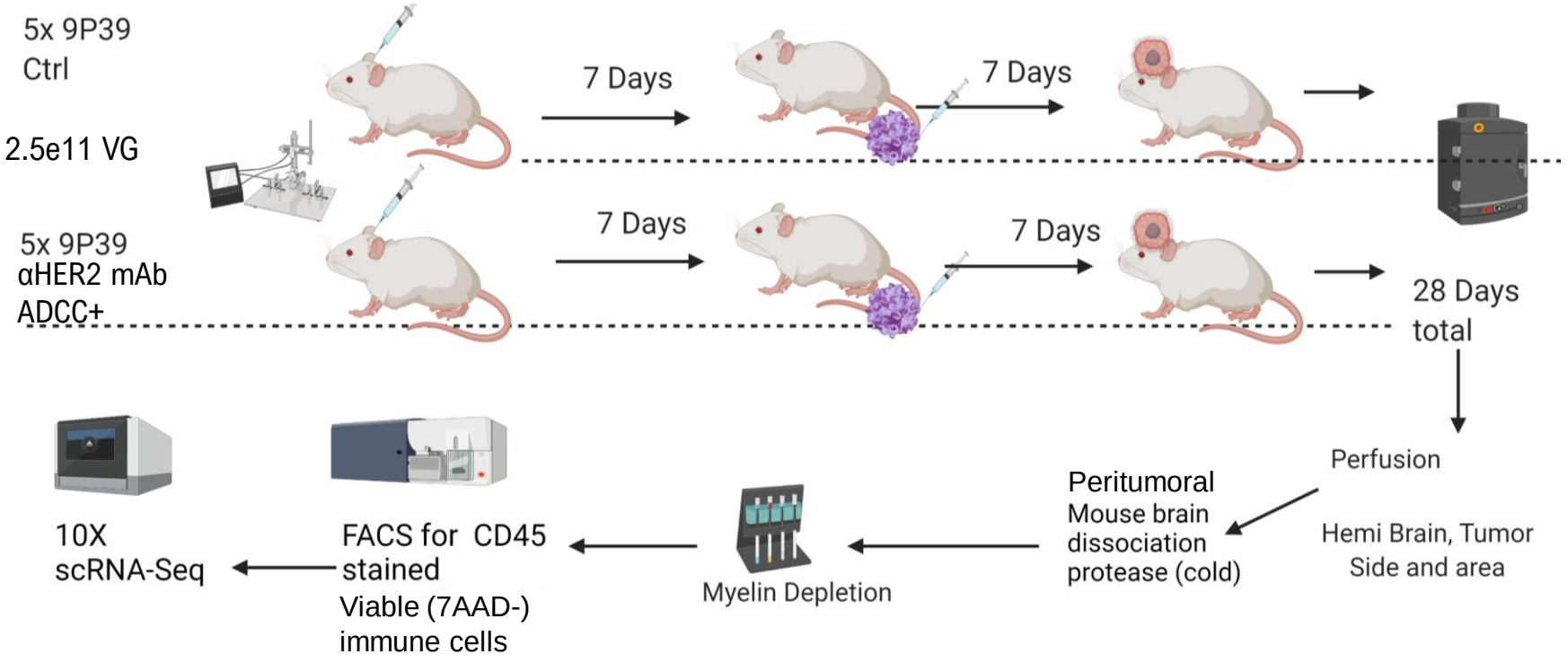
Model 3

Direct Intracranial Injection Administration in a Tumor Treatment Study Design (Mouse Xenograft)

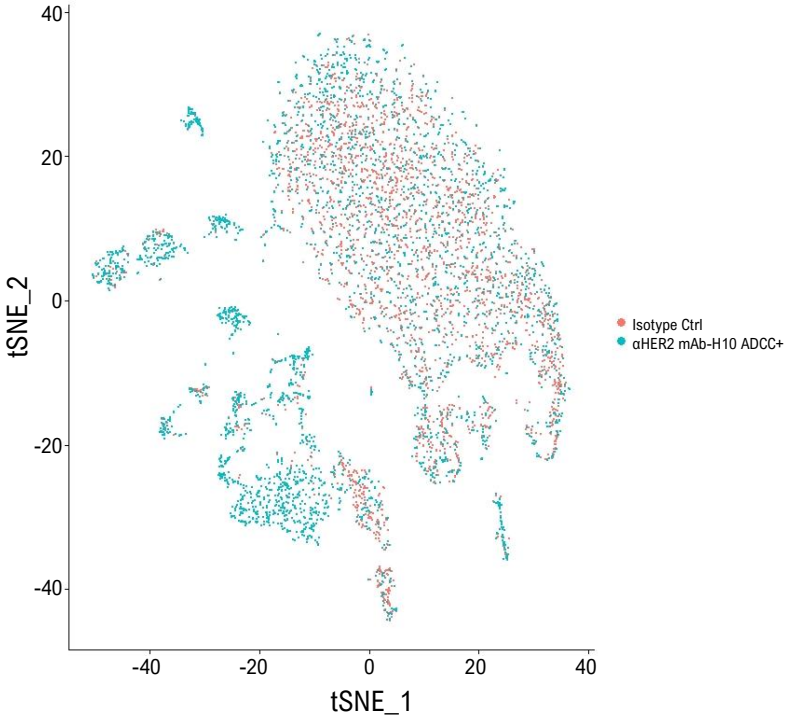
- AAV PHP.eB delivery 2 Days post xenograft of BT474-Luc cells
- N=15 per group

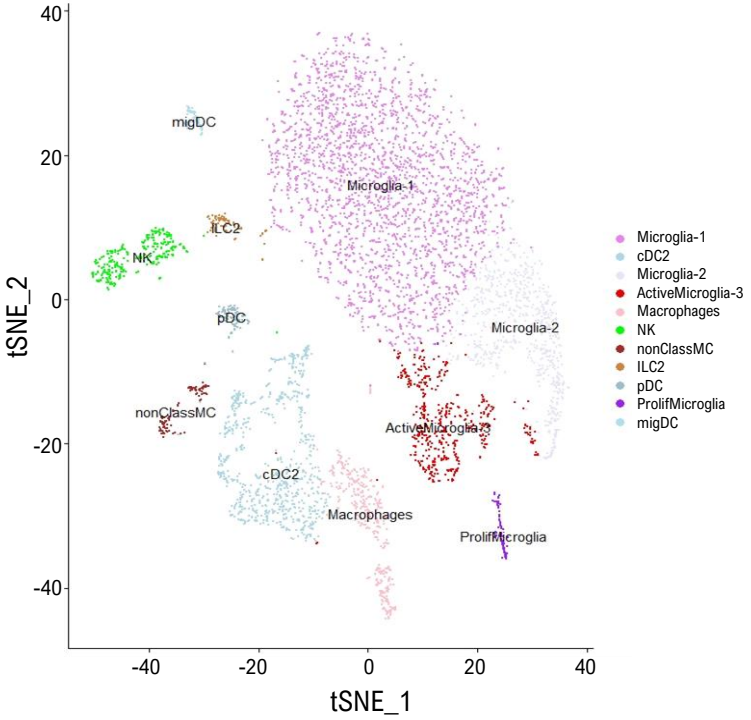


Mechanism of Action scRNA-Seq Study Design



Mechanism of Action: Peritumoral CD45+ Immune Cells Demonstrate Differential scRNA-Seq Cluster Distribution from 9P39 mediated αHER2 mAb ADCC+ as compared to isotype control



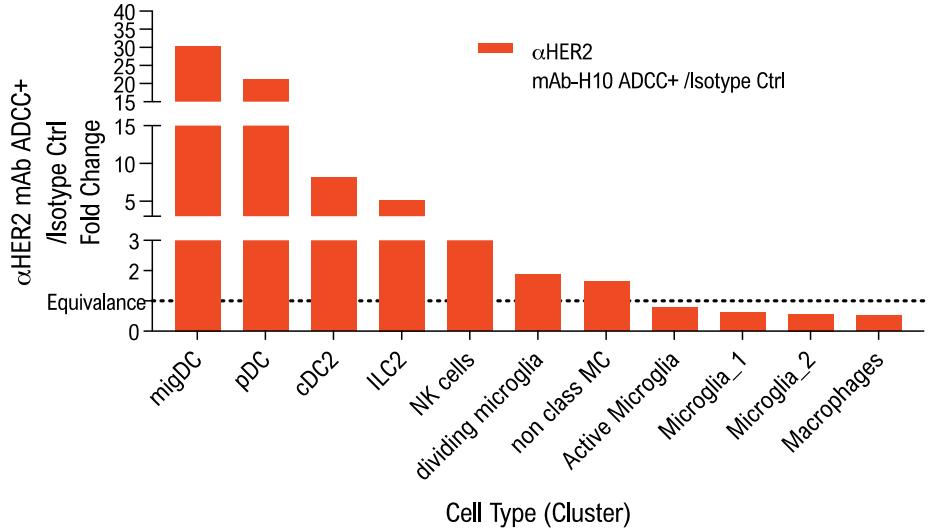


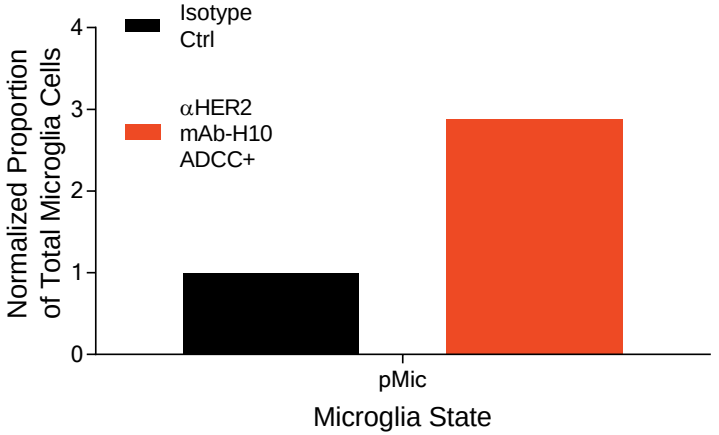
Microglia	cDC2	Macrophages	NK	ncMC	ILC2	pDC	migDC
	conventional dendrittic cells		Natural Killer	non classical monocytes	innate lymphoid cell	plasmacytoid dendritic cells	migratory dendritic cells

- Xiaoqin Ren (NGS)

Innate immune response is evident in αHER2 mAb ADCC+ treated cohort

CD45 Sorted Mouse Peritumoral Cells





pMic= proliferation microglia (Cluster 9)

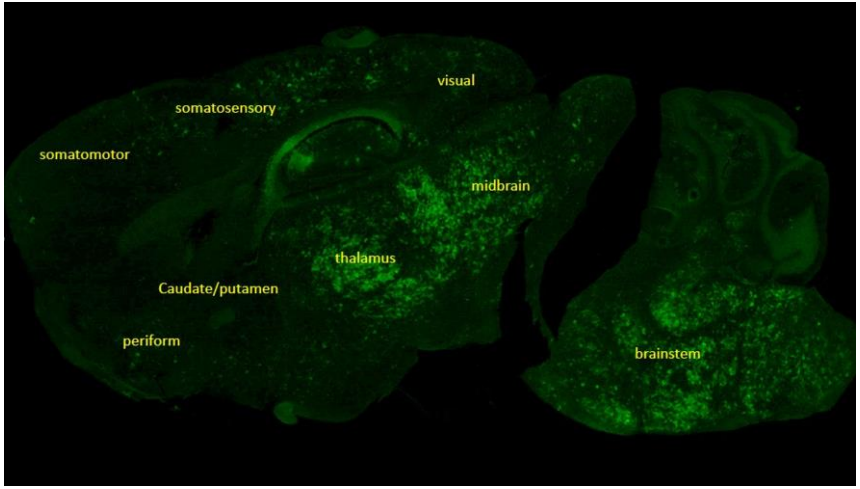
Normalized to Isotype control

Microglia | cDC2 conventional dendrittic cells | Macrophages | NK Natural Killer | ncMC non classical monocytes | ILC2 innate lymphoid cell | pDC plasmacytoid dendritic cells | migDC migratory dendritic cells

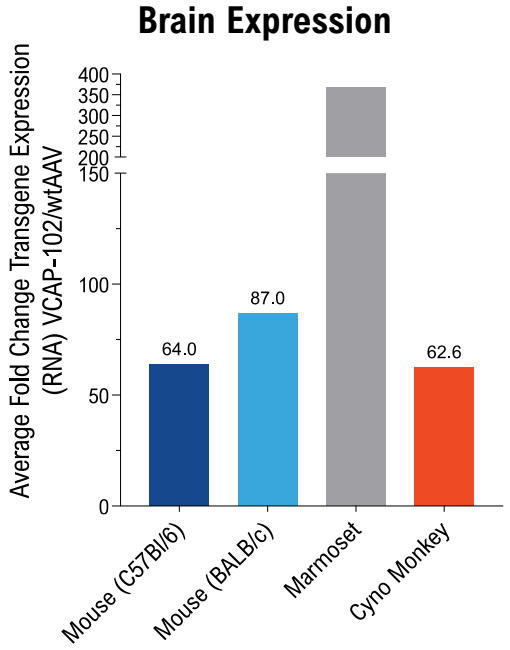
VCAP-102, a translational capsid that targets the CNS, identified by TRACER

VCAP-102 yielded a translatable enrichment over AAV9 in brain that was consistent between NHP and mouse

Session Date/Time: Thursday May 19, 2022 10:15 AM - 12:00 PM
Session title: Novel AAV Capsids for the Brain, Eye and Kidney
Room: Ballroom A
Your Presentation Time: 11:00am - 11:15am
Final abstract number: 1198 *-Tyler Moyer*



VCAP-102-GFP Mouse Brain - *Charlotte Chung*



- Mathieu Nonnenmacher
- Tyler Moyer

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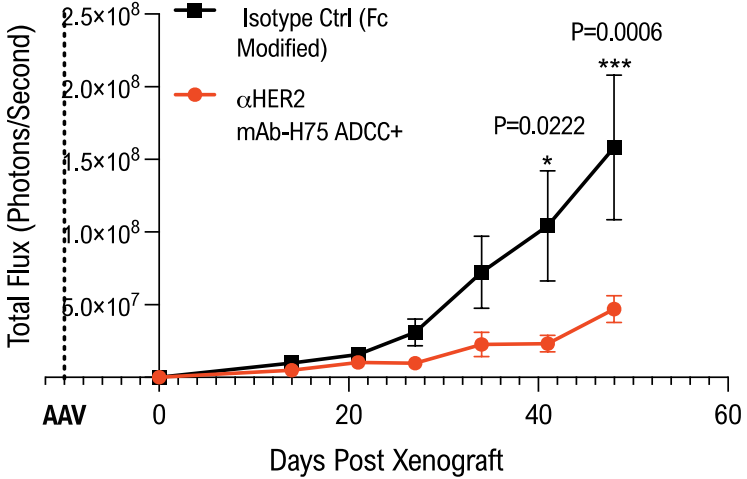
Pre-clinical efficacy of VCAP-102-αHER2 mAb ADCC+ in prophylaxis treatment model

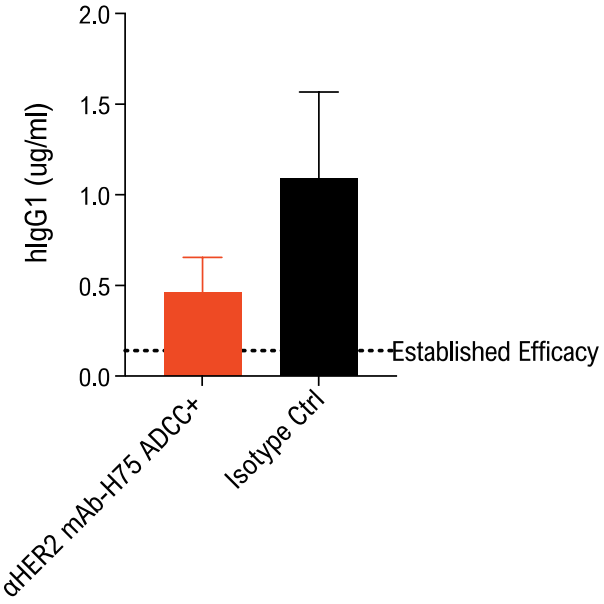
i.v. 2.5e11 VG VCAP-102 Prophylaxis Model Orthotopic Xenograft Treatment (MDA-MB-361L Cells)



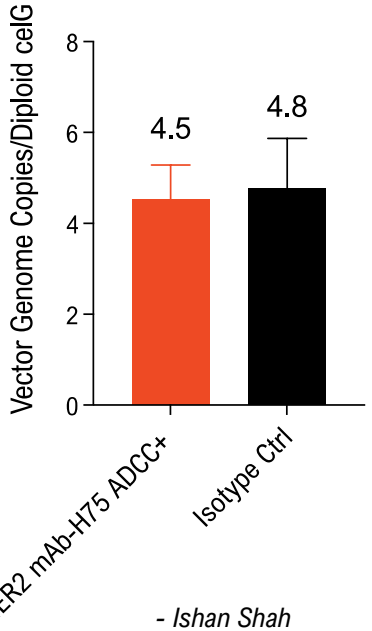
N=5; 2 Way Anova Sidak's multiple comparison test

5x Difference in Tumor Burden at Day 41 Post Xeno
3x at Day 48

Day 53: VCAP-102 CSF vAb



Day 53: VCAP-102 Vector Genome Copies: Brain



- *Ishan Shah*
- *Jeff Thompson*
- *Joe Clement*

Summary and Next Steps

A BBB penetrant capsid mediating vHER2 ADCC+ mAb brain expression represents a novel, single dose, systemic therapy for the treatment of HER2+ metastatic brain cancer

- Paired a functional ADCC+ vectorized antibody with CNS penetrant AAV including a translational capsid, VCAP-102
- This approach produced successful pre-clinical interventions that attenuated tumor burden and extended survival in mouse orthotopic xenograft models of metastatic brain cancer
- Potential mechanisms of action for our vHER2 gene therapy include inhibition of cell proliferation, ADCC and the innate immune response: Dendritic cells mediate between innate and adaptive immune responses

We plan to advance this gene therapy to tolerability and biodistribution studies in NHP

Acknowledgments

Todd Carter
Xiaoqin Ren
Ishan Shah
Sam Hasson
Mathieu Nonnenmacher
Lin-Ming Shen
Claire Sampson
Garret Heffner
Kenny Chen
Usman Hameedi
Kelly Bales
Charlotte Chung
Maneesha Paranjpe
Kyle Grant
Tim Fiore
Jeffrey Thompson
James Kaufman
Joe Clement
Katie Tyson
Nilesh Pande
Adam Gallagher
Omar Bermudez
Jiangyu Li
Ambreen Sayed-Zahid
Tyler Moyer
Michael Grannan

THANK YOU FOR YOUR TIME

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