Development of a brain-penetrant EGFR inhibitor and non-invasive predictive biomarker of response for glioblastoma

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David Geffen
School of Medicine

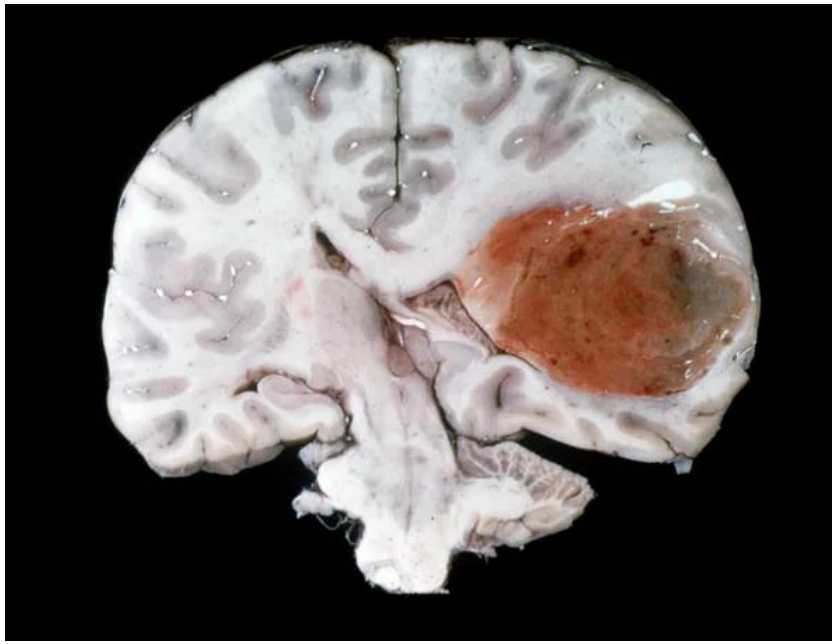
Disclosures

- Co-Founder and Shareholder
  - *Katmai Pharmaceuticals, Trethera Corporation*

- Shareholder
  - *Sofie Biosciences*

- Contracted Research/MTA/Consulting Agreements
  - *Abbvie*
  - *Roche*
  - *Sanofi*
  - *Astra Zeneca*
  - *Erasca*

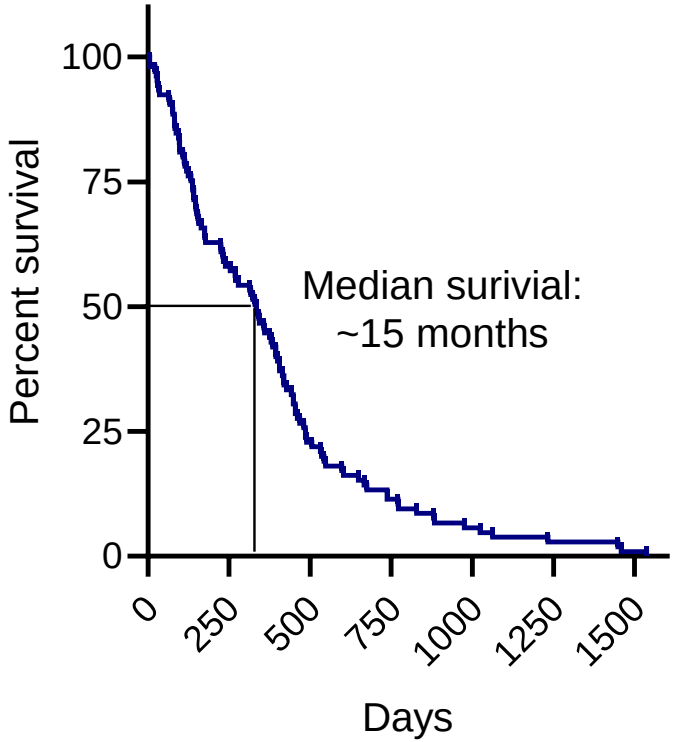
Glioblastoma (GBM): A universally fatal malignancy



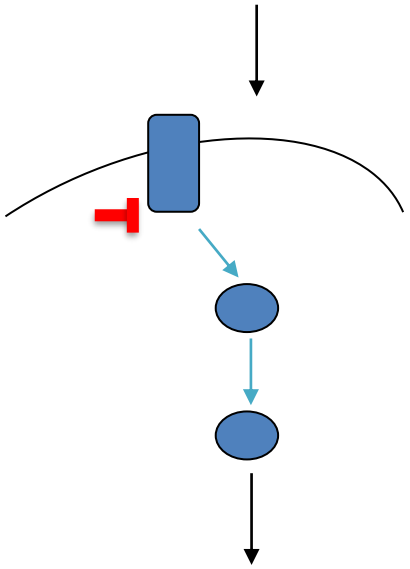
Steka B, *Scientific American,* March 2019

Standard of Care

Surgery/Chemo/Radiation

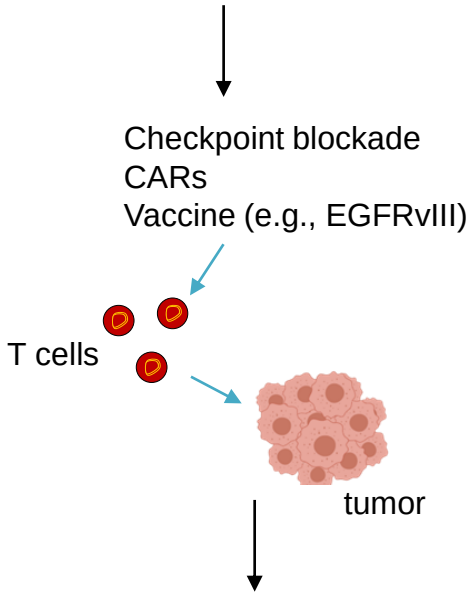


Targeted Therapy



No improvement over SoC

Immunotherapy



Too early, yet 'signal' only in minority of patients

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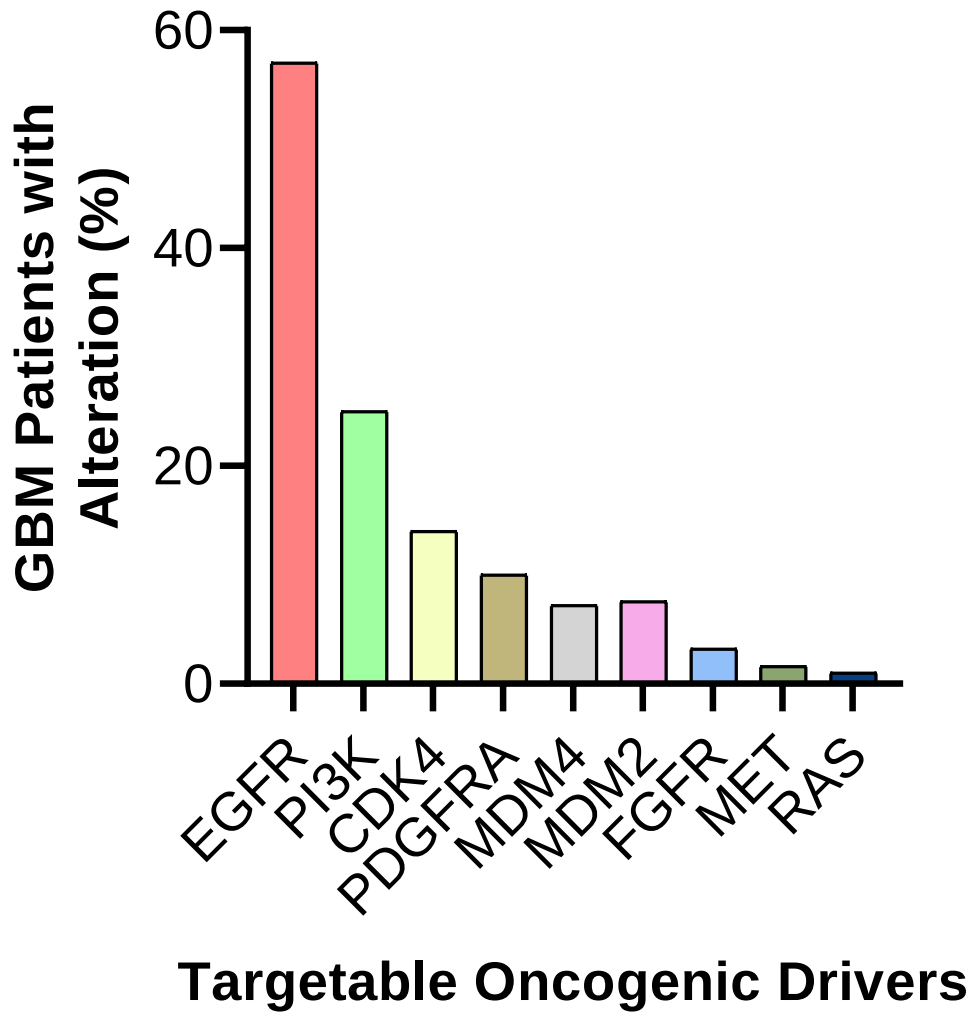
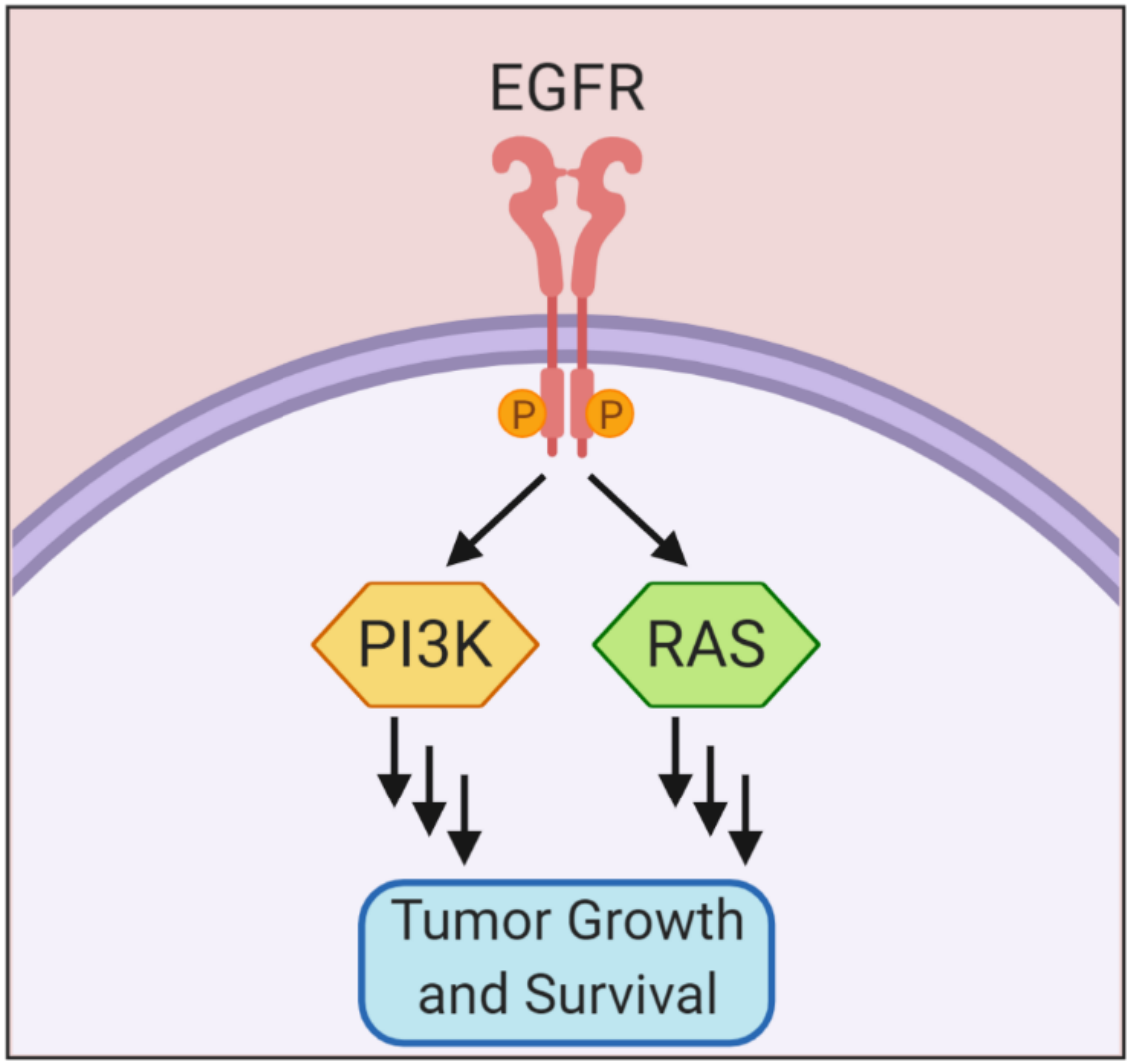
The epidermal growth factor receptor (EGFR) is frequently altered in GBM





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TCGA *Cell*, 2013

EGFR tyrosine kinase inhibitors (TKIs) have failed for GBM patietns

NSCLC or Breast Cancer

Therapy	Clinical Trial	Result
Erlotinib	NSCLC Phase III (2005)	**Recurrent disease: Improved PFS and OS vs chemo**
Lapatinib	HER2 BrCa Phase III (2006)	**Recurrent disease: Improved PFS vs chemo**
Gefitinib	NSCLC Phase III (2010)	**Front line setting: Improved PFS and OS vs chemo**
Afatinib	NSCLC Phase III (2013)	**Front line setting of metastatic disease: Improved PFS vs chemo**

Sherpherd et. al., *NEJM* (2005); Maemondo et. al., *NEJM* (2010) Sequist., et al. *Journal of Clinical Oncology* (2013); Geyer et. al., *NEJM* (2006)

Glioblastoma

Therapy	GBM Clinical Trial	Result
Erlotinib	Phase II (2004)	**Failed**
Lapatinib	Phase I/II (2009)	**Failed**
Gefitinib	Phase II (2004)	**Failed**
Afatinib	Phase I/II (2014)	**Failed**

Reardon et. al., *Neuro-Oncology* (2014); Vogelbaum, M. A., et al. *Journal of Clinical Oncology* (2004); Rich, Jeremy N., et al. *Journal of Clinical Oncology* (2004)

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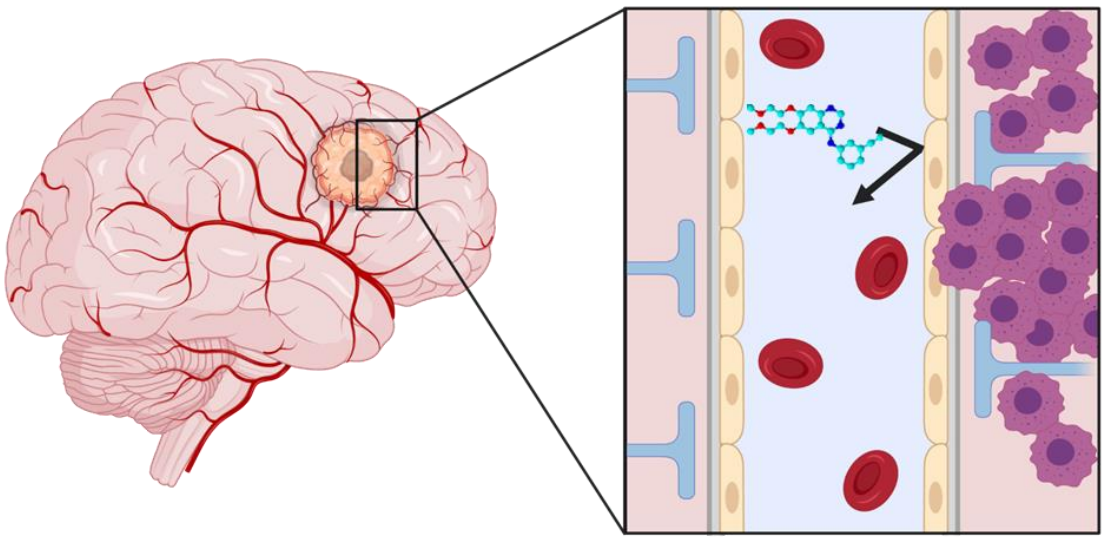
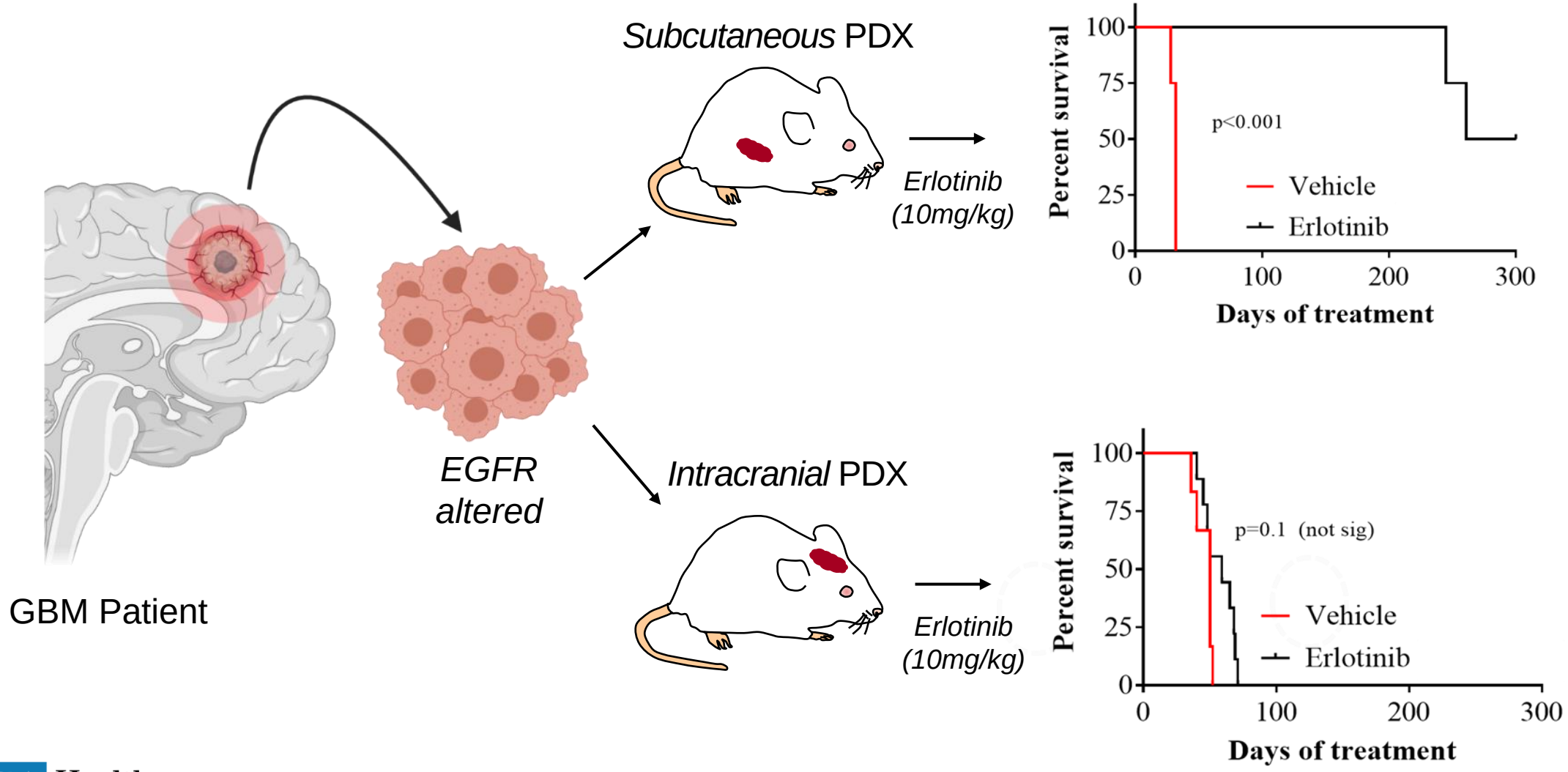
EGFR TKIs – designed for non-CNS cancer - have low brain penetration



Compound (Brand Name)	Company	Penetration Rate (%)
Afatinib (Gilotrif)	Boehringer Ingelheim	0.7
Erlotinib (Tarceva)	Genentech	8
Gefitinib (Iressa)	AstraZeneca	1.1
Lapatinib (Tykerb/Tyberb)	GlaxoSmithKline	0.1

Bohn et. al., Targ. Oncol, 2016.
Vivanco et. al., Can Discov, 2012.

Intracranial GBM fail to recapitulate responses to EGFR TKIs in subcutaneous models



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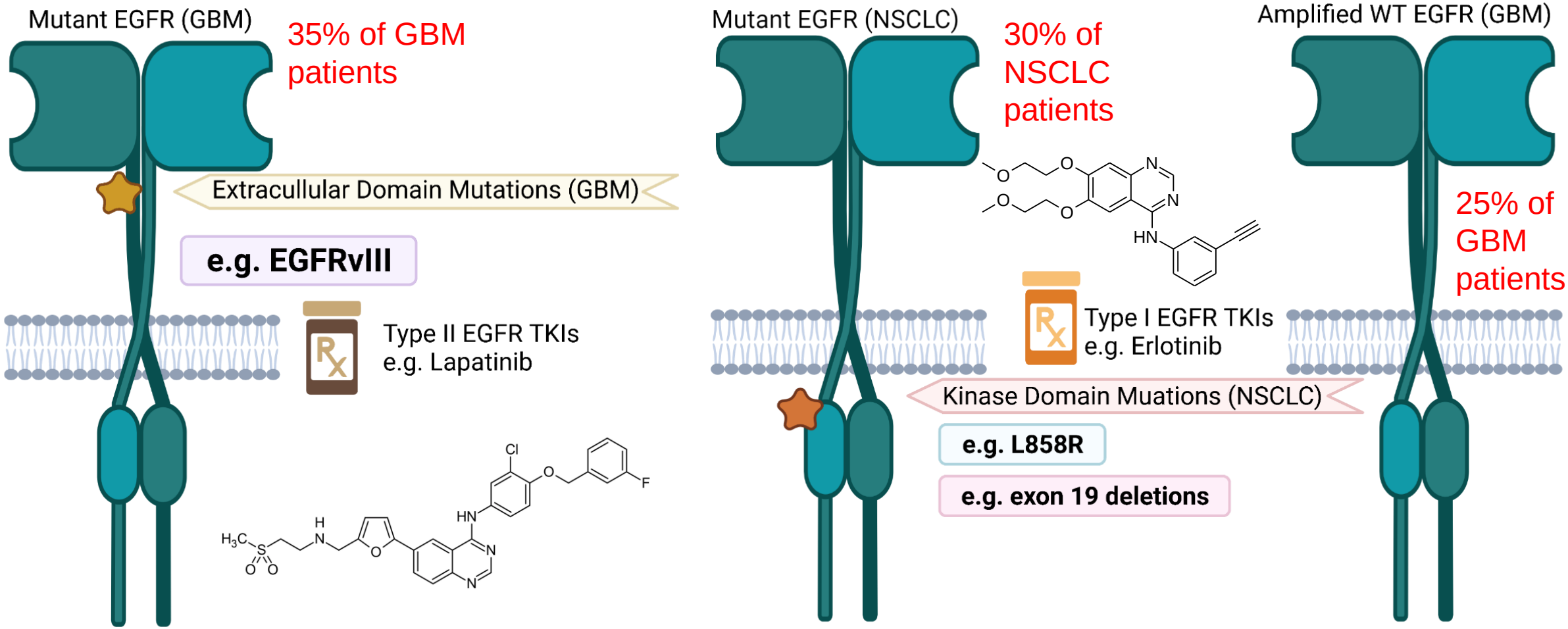
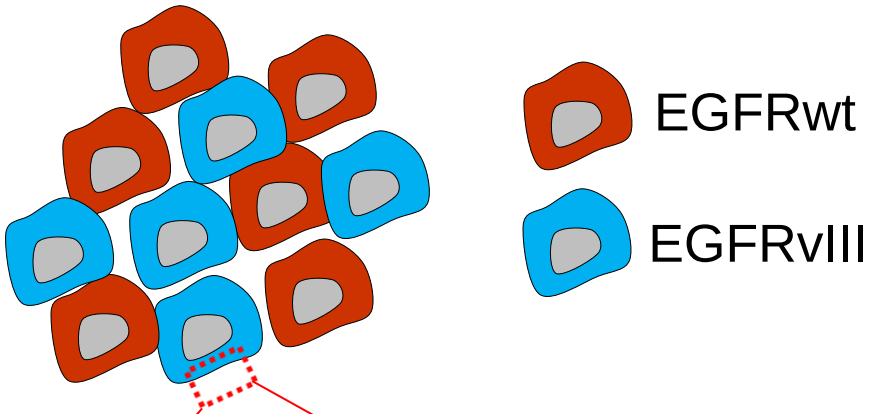
The type of EGFR alteration impacts EGFR TKI affinity



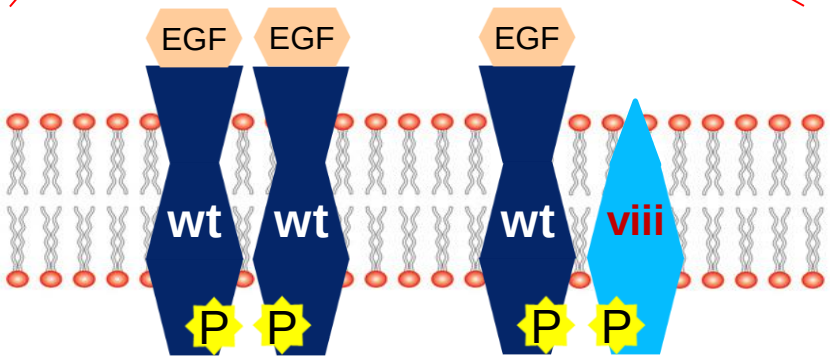
Vivanco et. al, *Cancer Discovery* 2012

Graphic adapted from Gomez et. al., *Cancer Biology & Medicine* 2013

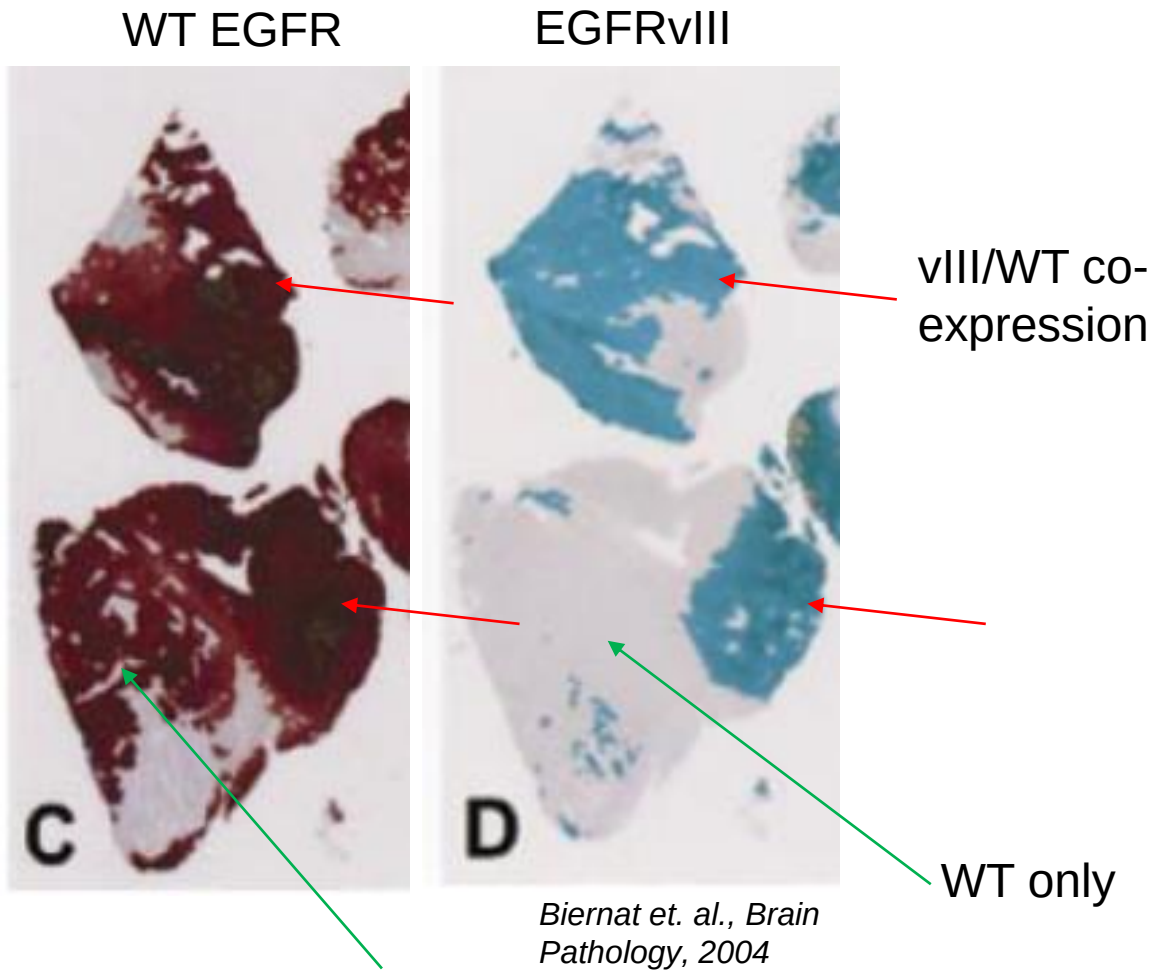
In patients with ECD mutations (e.g., EGFRvIII), both amplified Wild-Type EGFR and EGFRvIII are highly expressed



EGFRvIII + cells co-express EGFRwt



Fan et al, Cancer Cell 2013



Biernat et. al., Brain Pathology, 2004

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Need for BBB penetrant EGFR TKI to target both EGFRvIII and amplified wild-type EGFR

An ideal EGFR TKI for GBM:

Property	Available EGFR TKI
Target EGFRvIII	*Lapatinib, Neratinib*
Target Amplified EGFR	*Erlotinib, Gefitinib*
Brain Penetrant	*Tagrisso (30%)*

Tim Cloughesy, MD
Professor
(Neurology/Pharm)

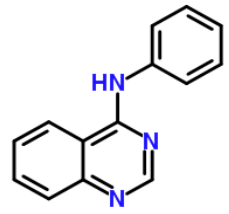
- Led ~100 clinical trials in brain tumors, 10 EGFR-directed
- Involved in development of multiple drugs of various classes (e.g., small molecules, antibody

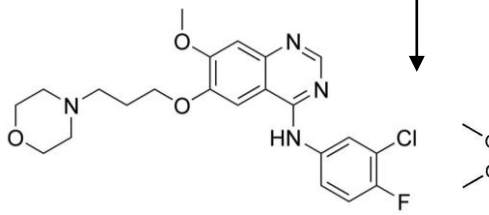
Michael Jung, PhD
Distinguished Professor
(Chemistry, Pharm)

- Co-Inventor of 2 FDA approved cancer therapies (Xtandi, Erleada)
- Founder, Trethera

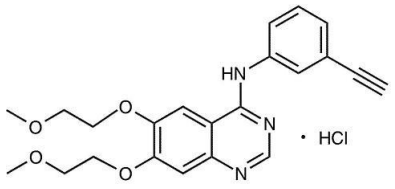
Improved BBB penetrating properties of ERAS-801

4-anilinoquinazoline
Core Scaffold





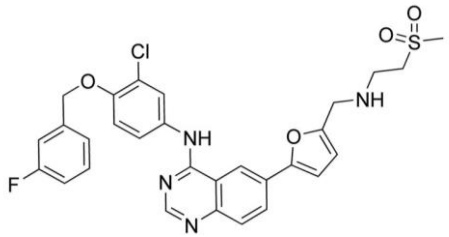
Gefitinib



Erlotinib

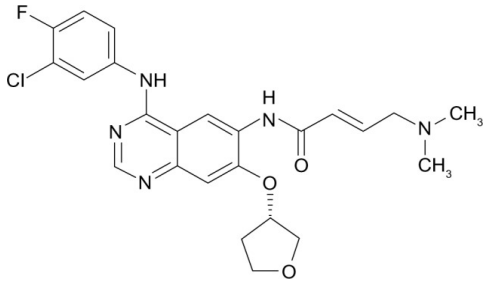
AstraZeneca

Genentech



Lapatinib

gsk GlaxoSmithKline



Afatinib

Boehringer Ingelheim

Property	*Optimal for BBB penetrance*	*FDA Approved EGFR TKI*	*ERAS-801*
Rotatable Bonds	**≤5**	✗	✓
Lipophilicity (clogP)	**≤4**	✗	✓
H-Bond Donors	**≤4**	✗	✓
H-Bond Acceptors	**≤5**	✗	✓
Polar Surface Area (Å^2)	**≤80**	✗	✓
Molecular Weight	**≤400**	✗	***≤500***

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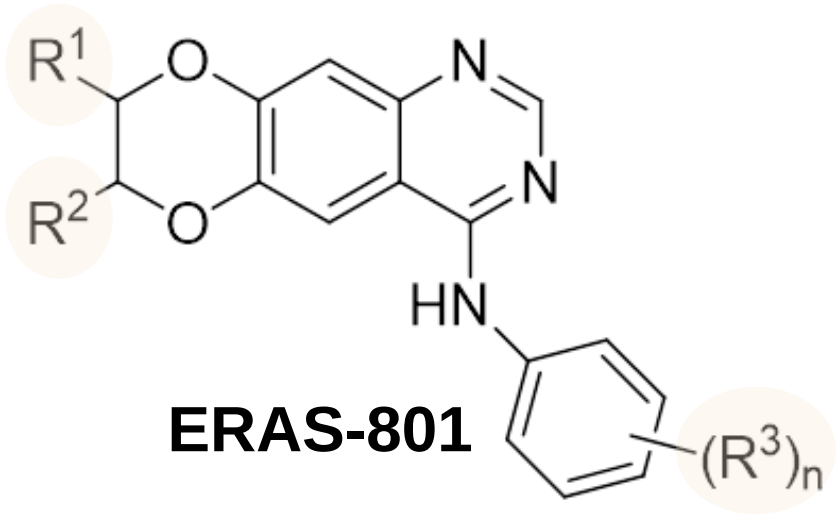
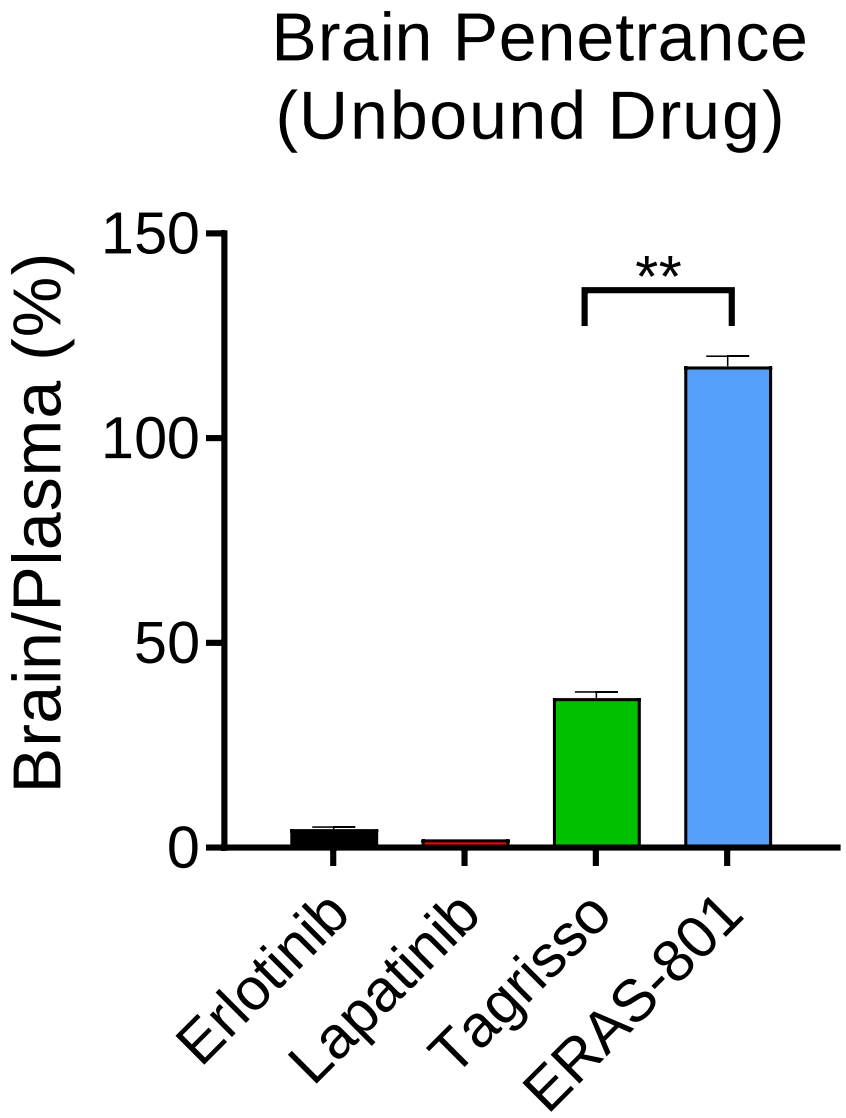
ERAS-801 shows high unbound brain exposures



ERAS-801



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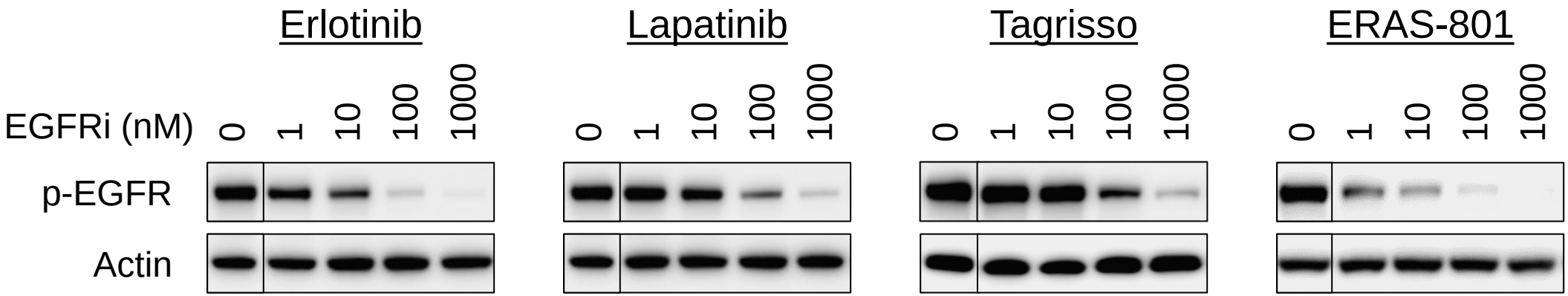
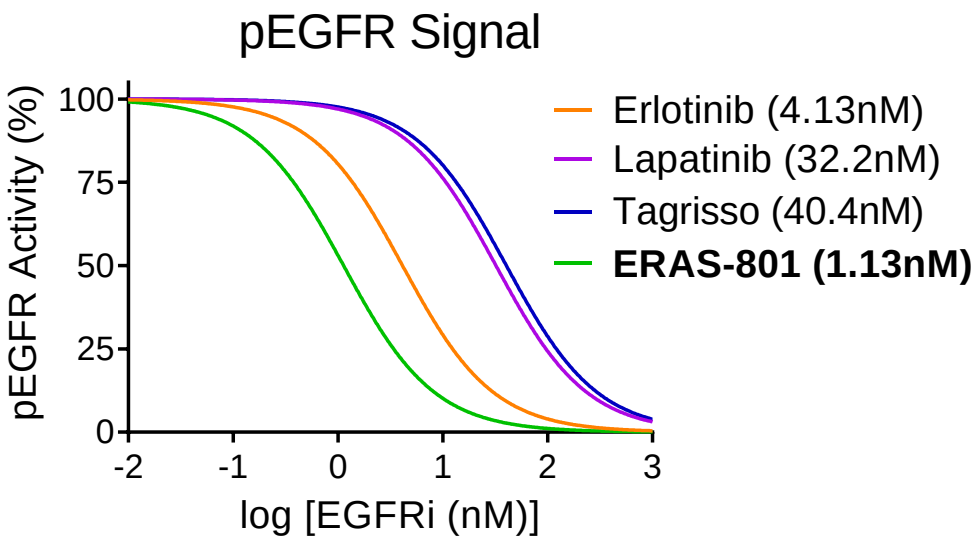
ERAS-801 has potent activity against activated WTEGFR





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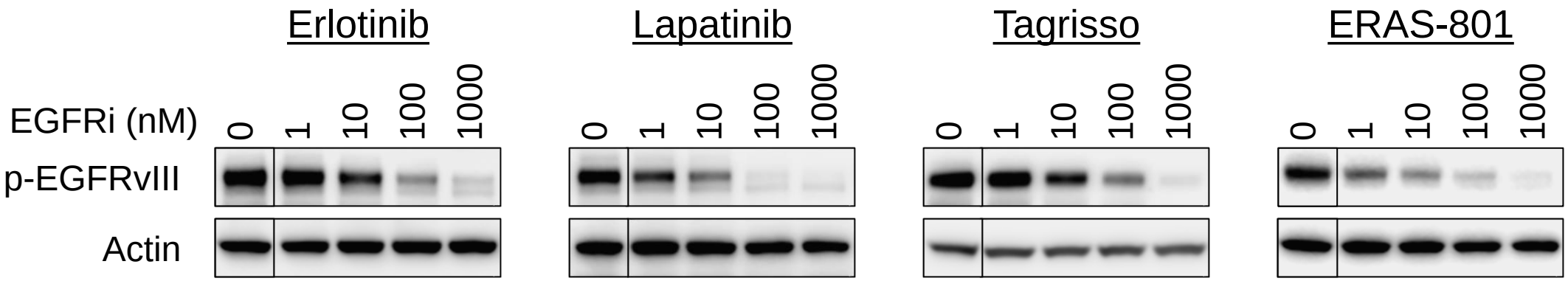
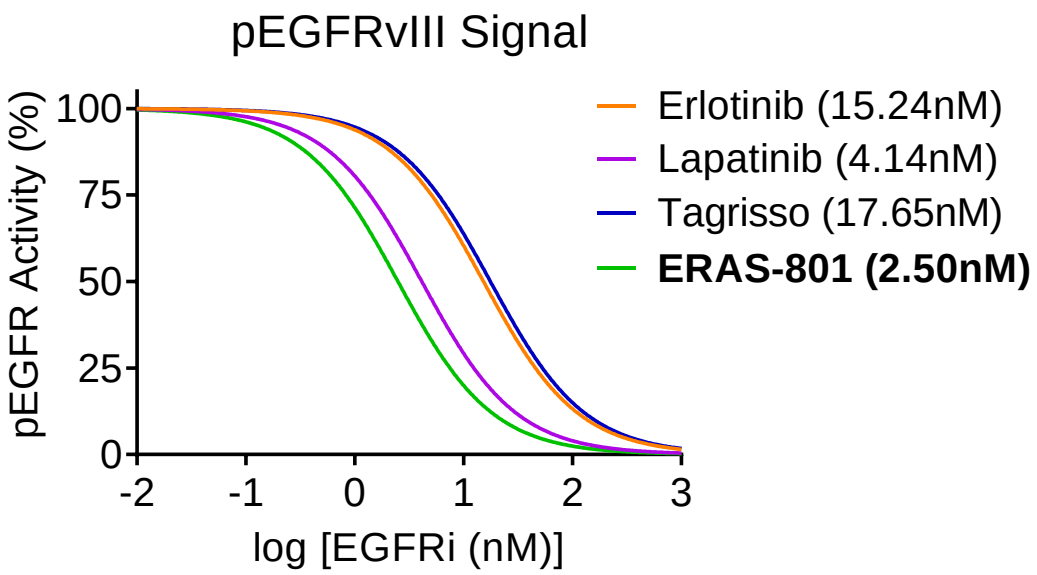
ERAS-801 is potent against EGFRvIII





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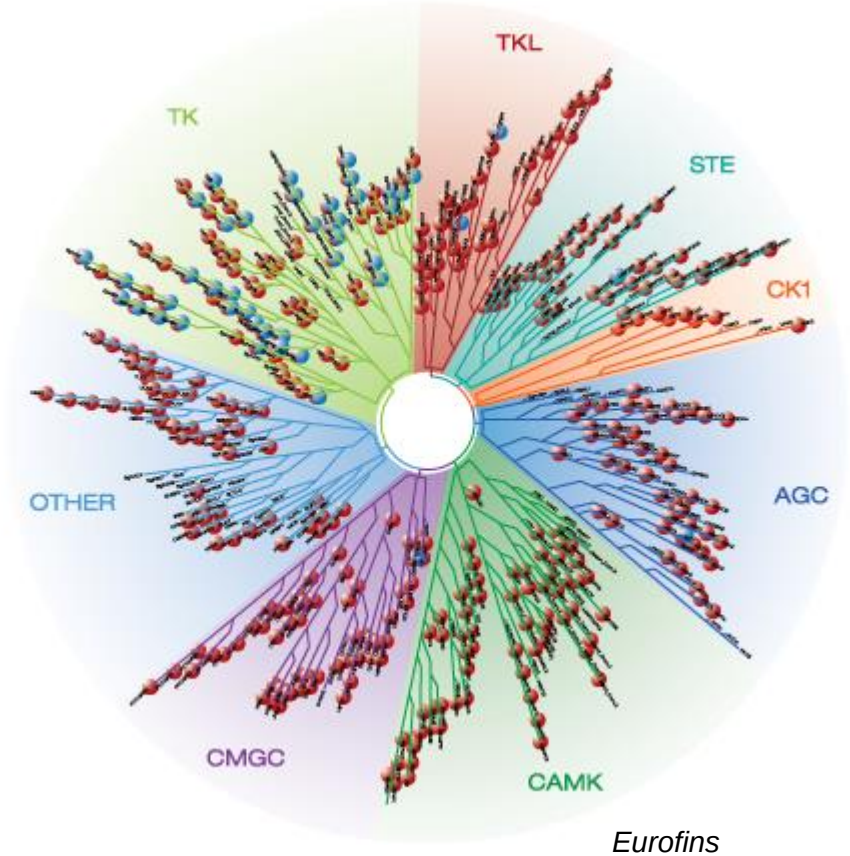
ERAS-801 is specific for EGFR

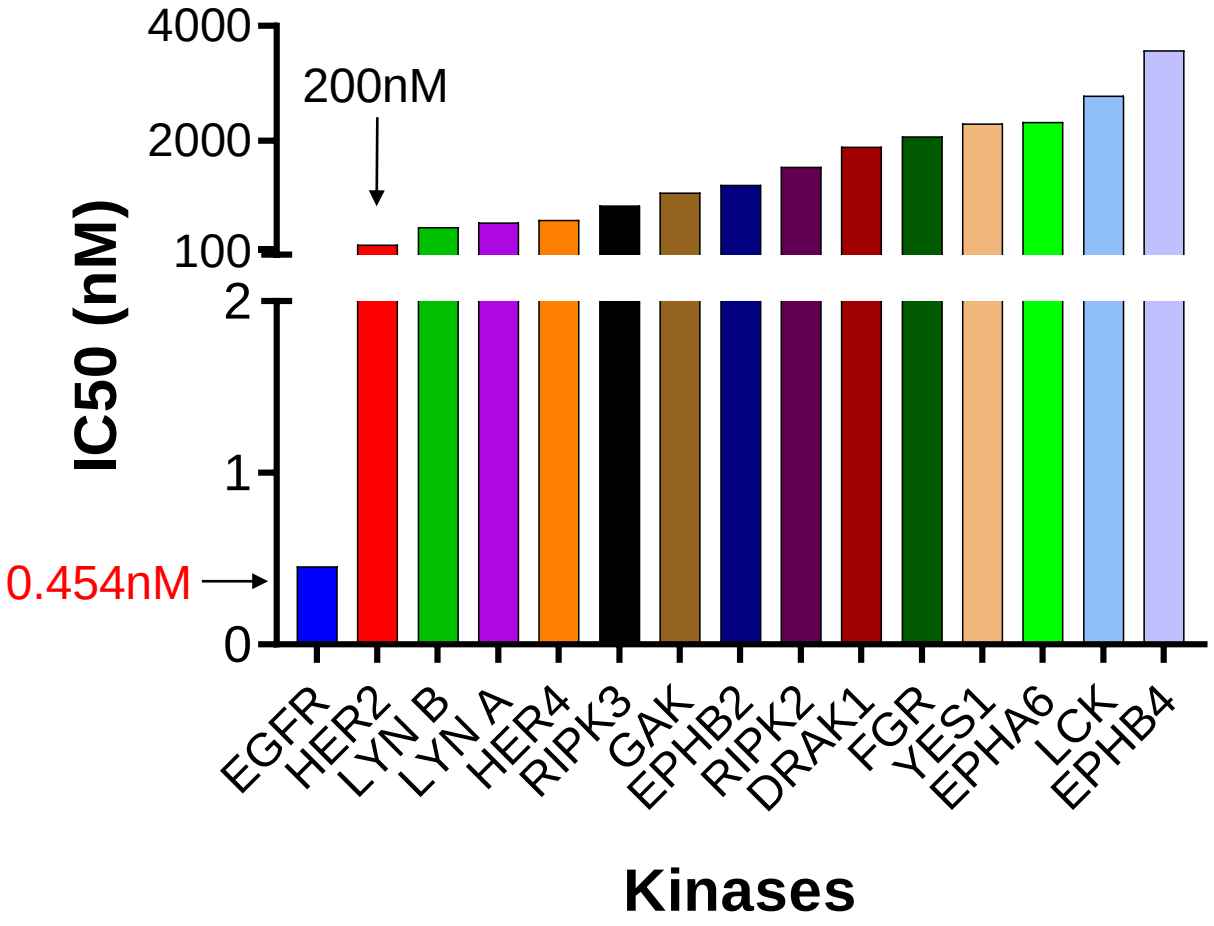
Primary Screen of ~490 WT and mutant kinases @ 10μM ERAS-801



Eurofins

15 “hits” (>50% inhibition at 10μM)

Full IC50 of “hits”



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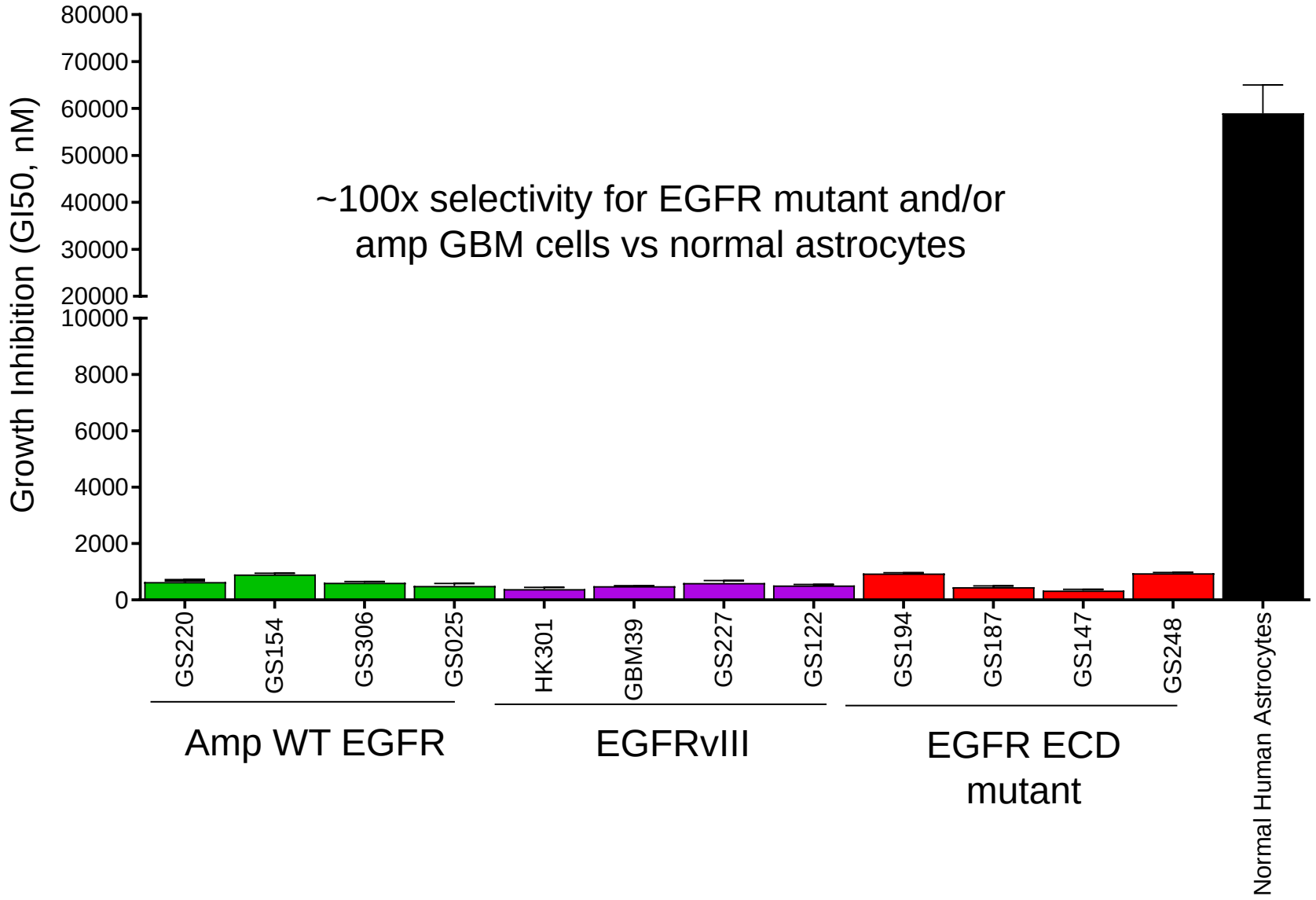
ERAS-801 is potent against EGFR altered patient derived GBM cells with negligible activity against normal brain cells



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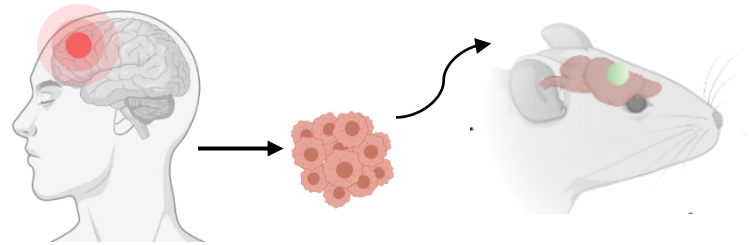
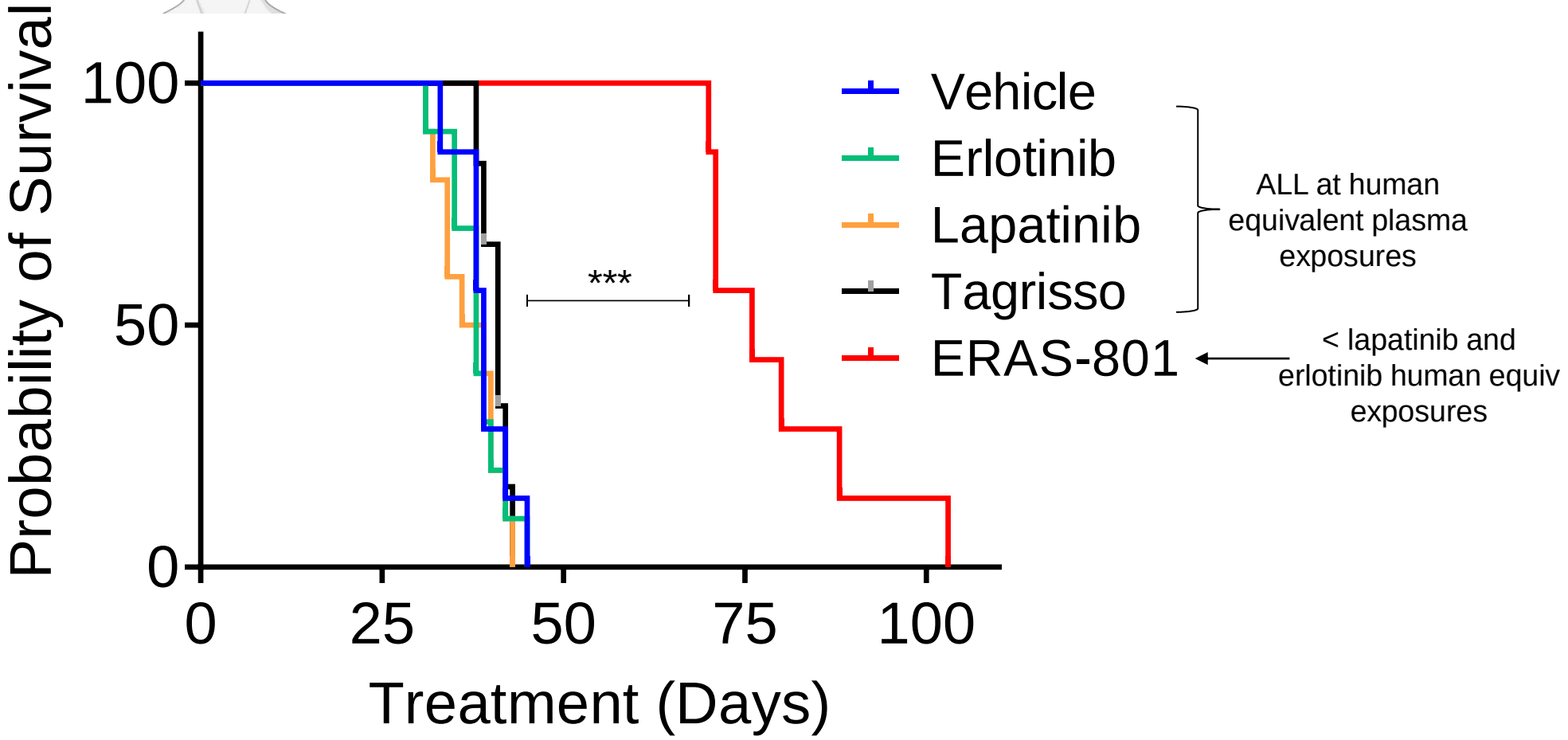
ERAS-801 significantly extends EGFRvIII PDX survival at **clinically relevant exposures**



EGFRvIII PDOX



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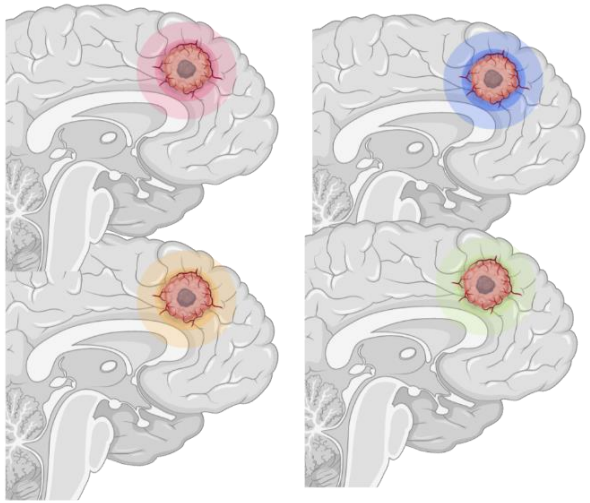
A Preclinical Trial of ERAS-801

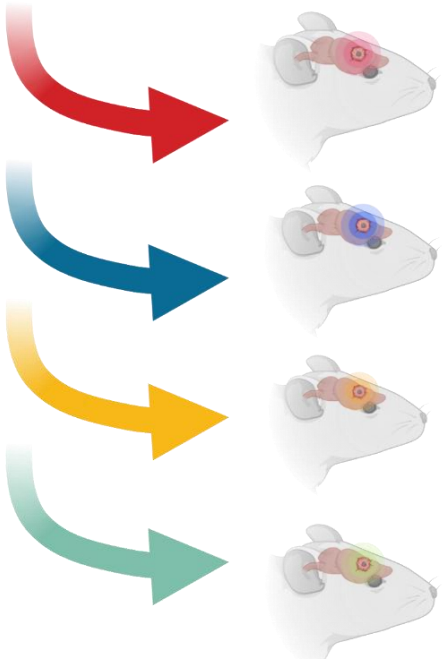


EGFR mutant

EGFR amp

EGFR Copy Number Gain (polysomy)

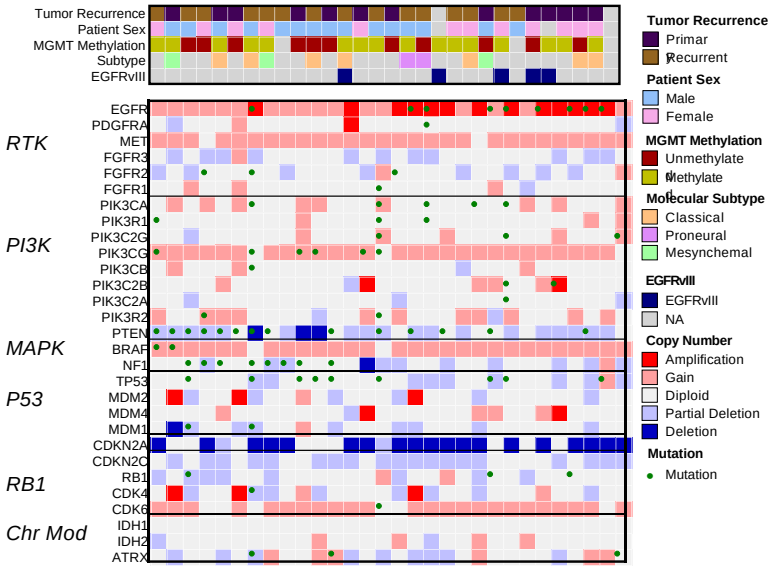
EGFR normal (wt)



Vehicle/ERAS-801

n=6-8 mice/treatment

GBM patient derived models



Short-Term Goals (n=40-50 unique models)

I) *To define the breadth of response across molecularly heterogeneous models*

II) *To define the molecular determinants of response*

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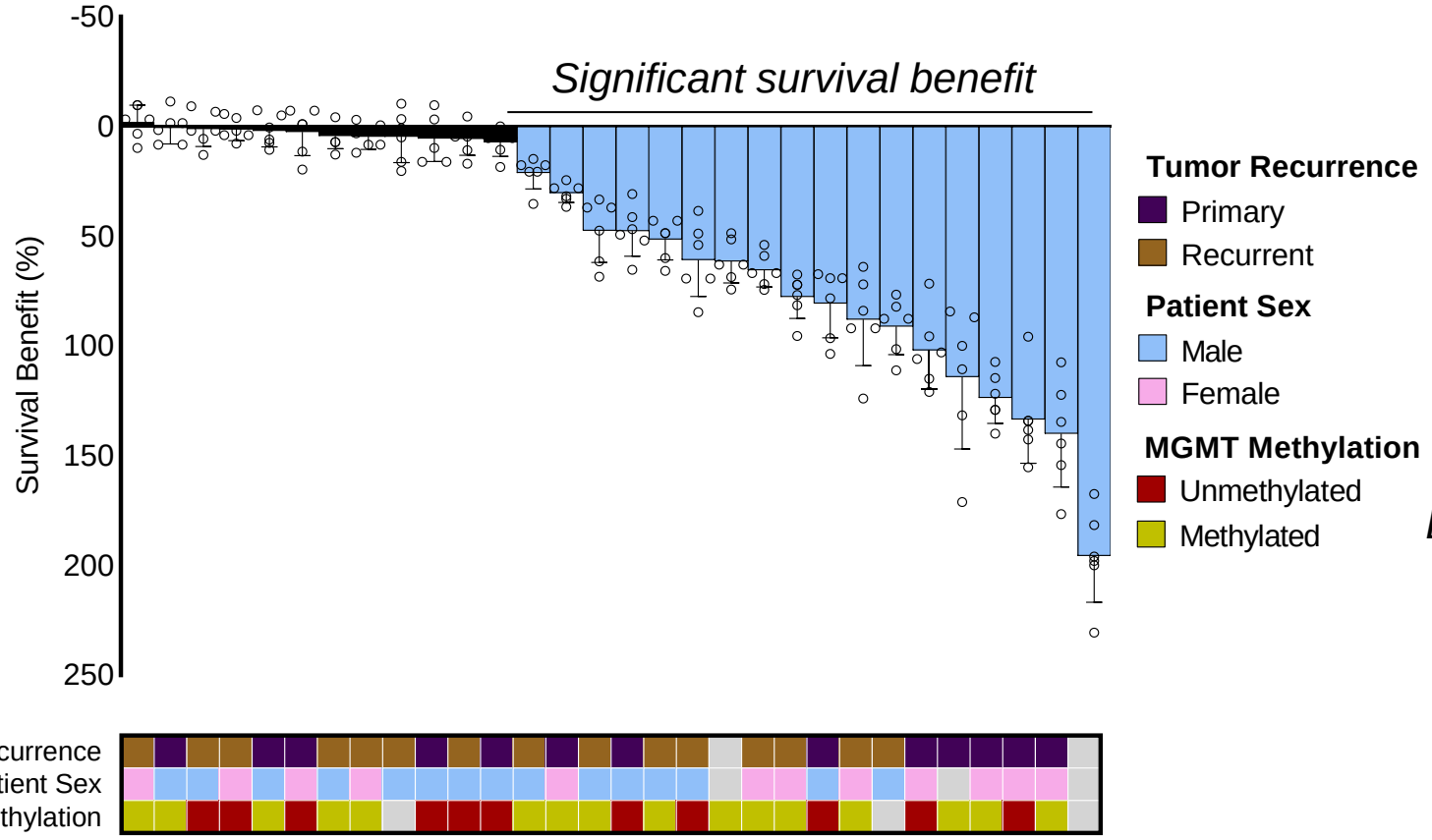
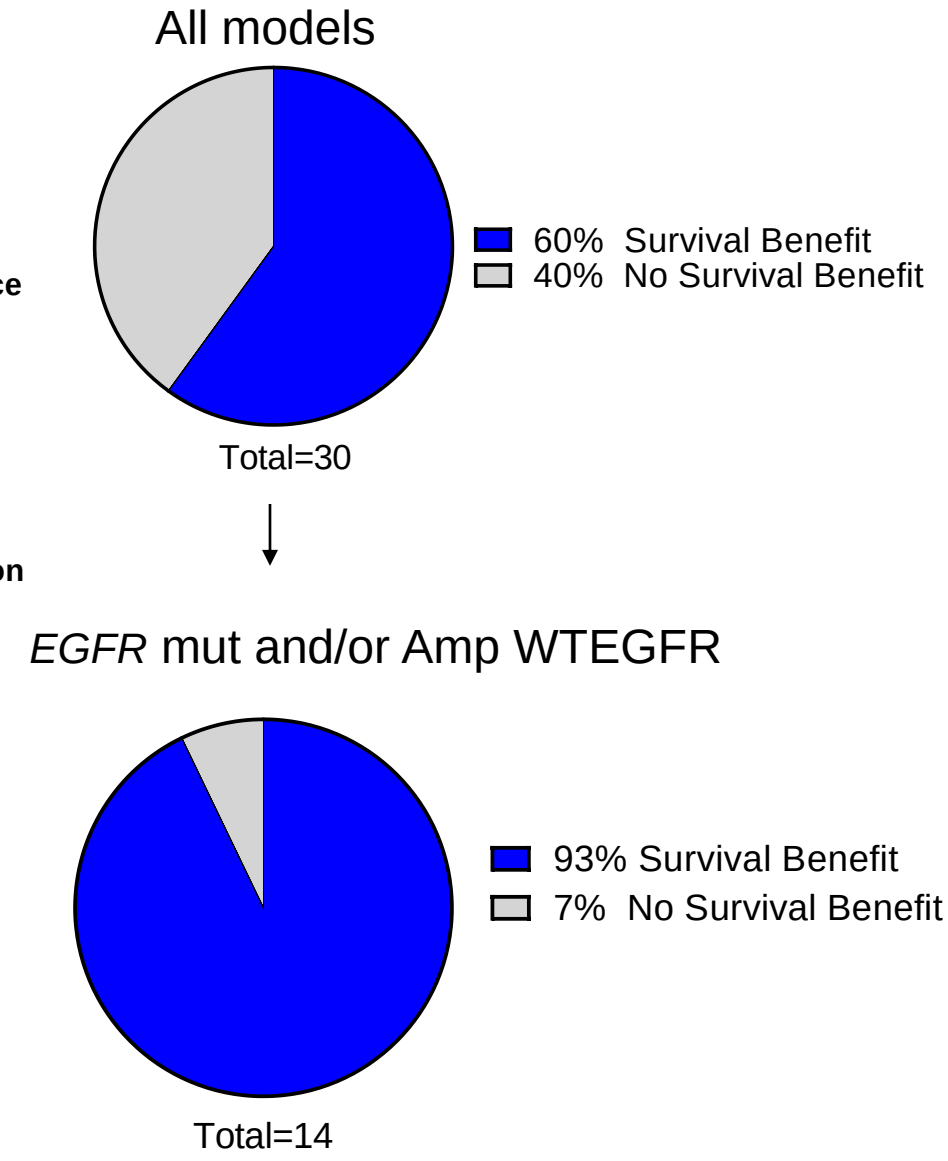
ERAS-801 improves outcome of >90% of EGFR mutant and/or amplified GBM PDXs





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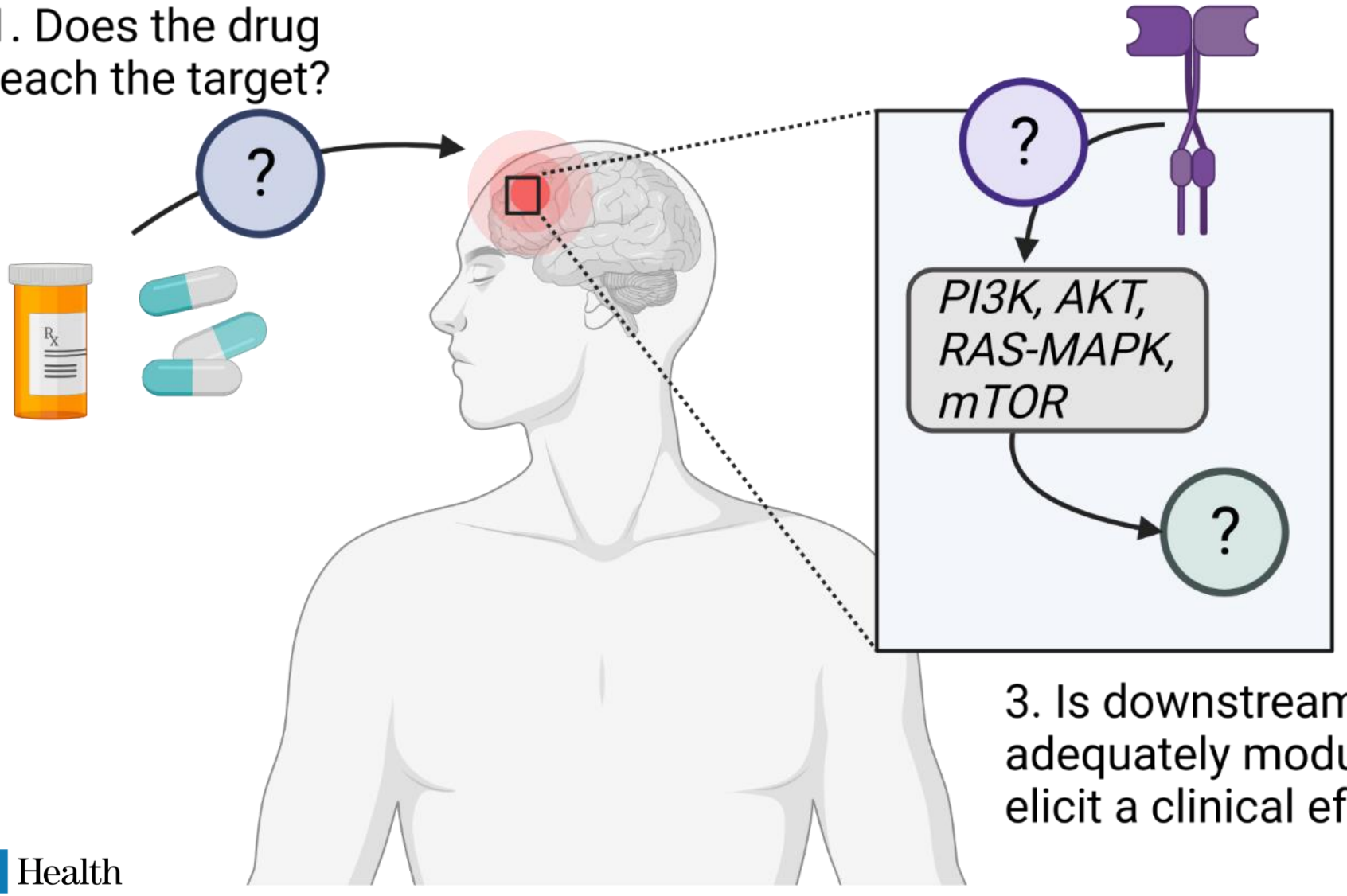
Challenge for Clinical Translation in GBM – How do we know drug is reaching the tumor and having a **meaningful** biological effect

1. Does the drug reach the target?



2. Is target sufficiently inhibited to modify downstream signaling?

3. Is downstream signaling adequately modulated to elicit a clinical effect?

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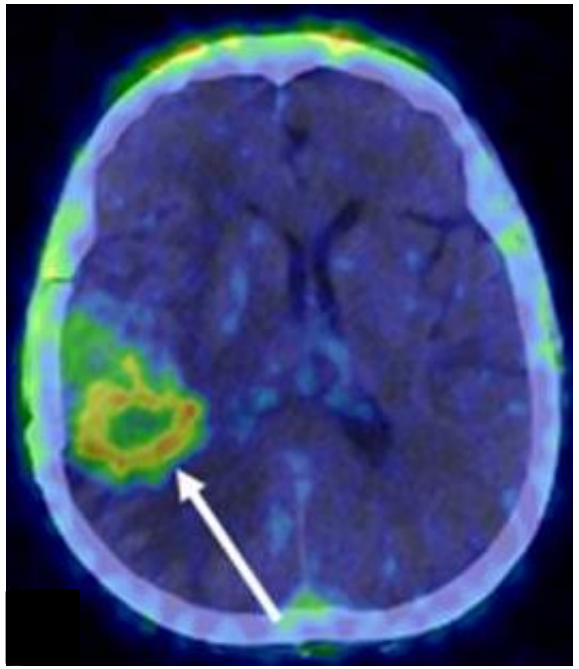
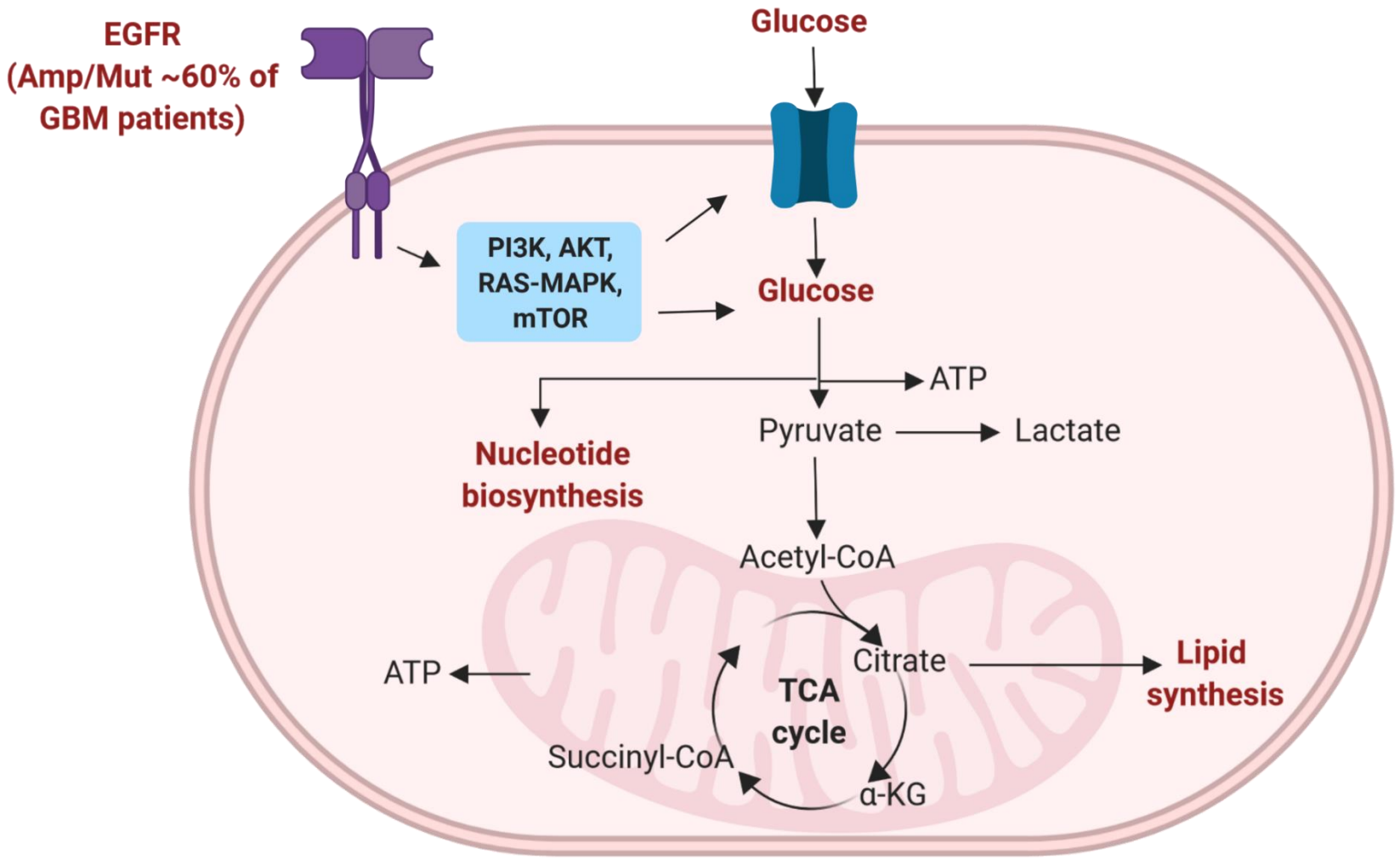
GBM tumor metabolism is regulated by aberrant EGFR signaling

^{18}F-fluorodeoxygluocse (^{18}FDG) PET



Mai et. al., *Nature Medicine* 2017

Babic et. al., *Cell Metabolism* 2013



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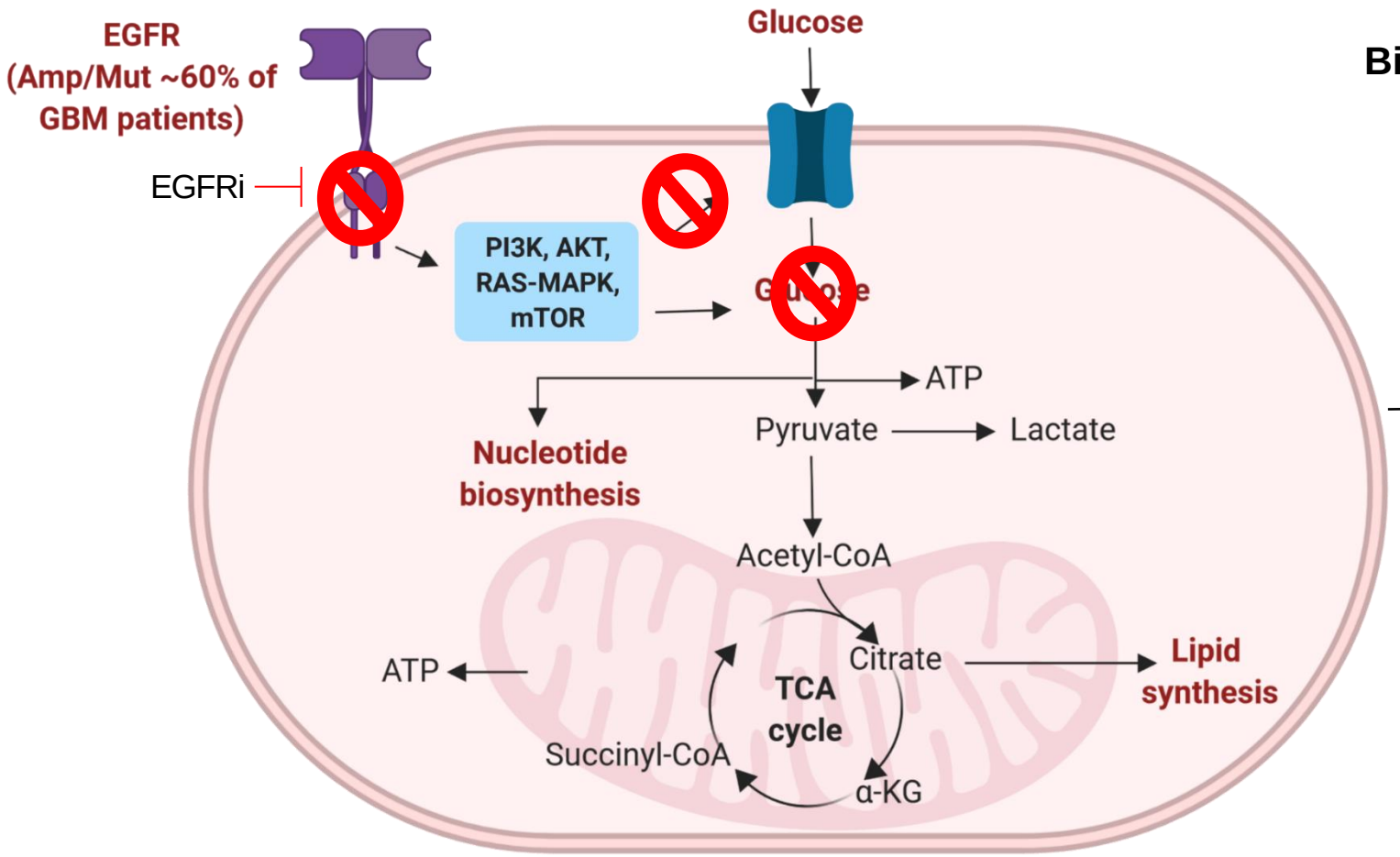
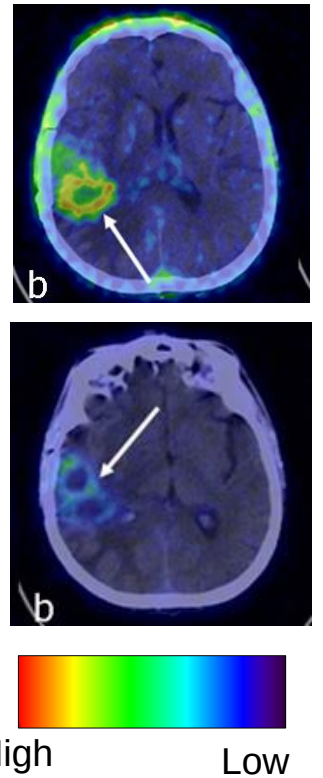
Rapid dynamics in FDG PET may serve as a non-invasive biomarker for <u>biologically meaningful</u> inhibition of EGFR signaling



<u>*RAPID*</u> (hrs) Non-Invasive Biomarker of Metabolic Stress



Growth Arrest

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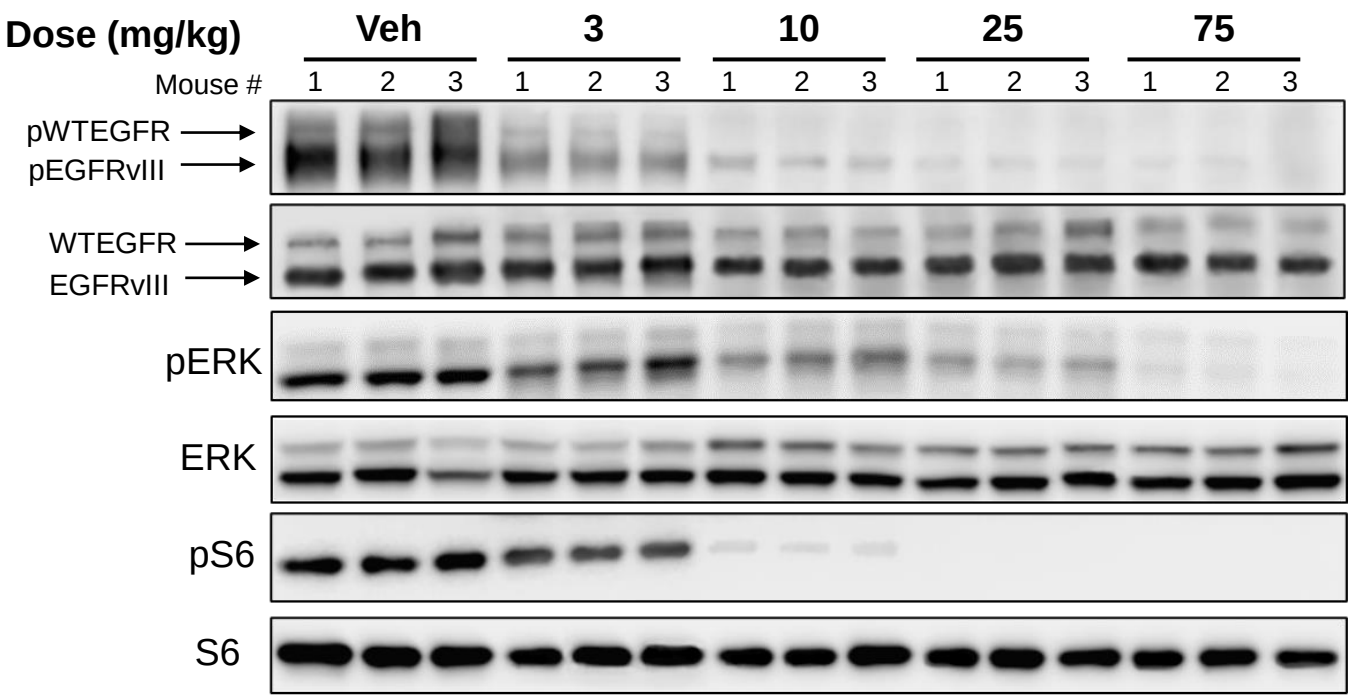
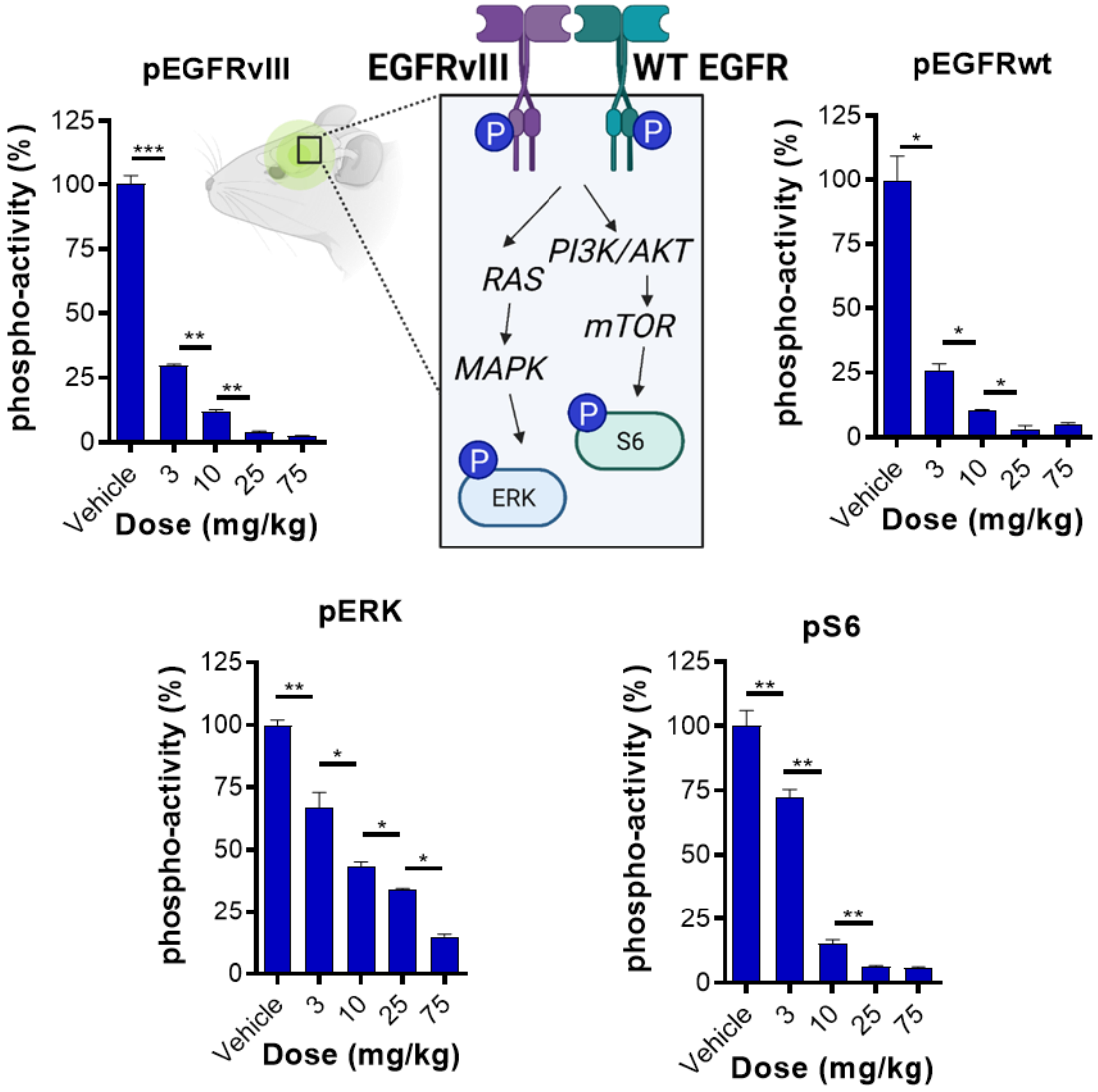
Mai et. al., *Nature Medicine* 2017

ERAS-801 can robustly inhibit intracranial EGFR signaling at predicted clinically relevant doses





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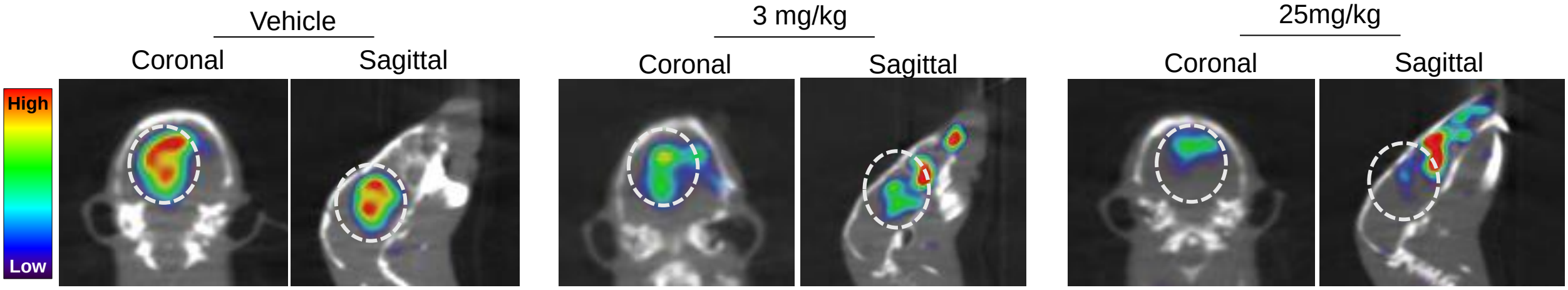
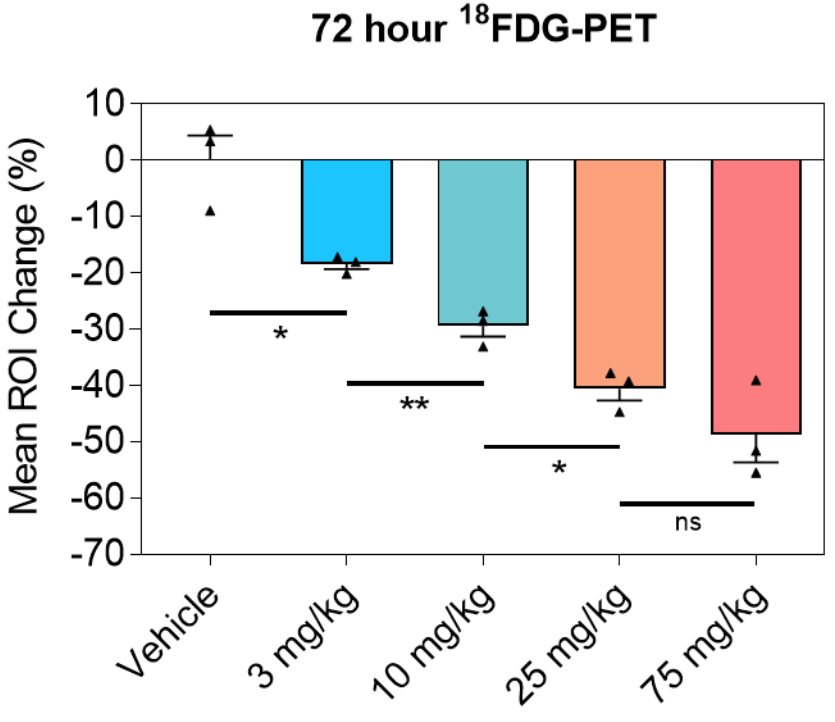
Dose dependent changes in FDG is associated with dose dependent change in EGFR signaling with ERAS-801





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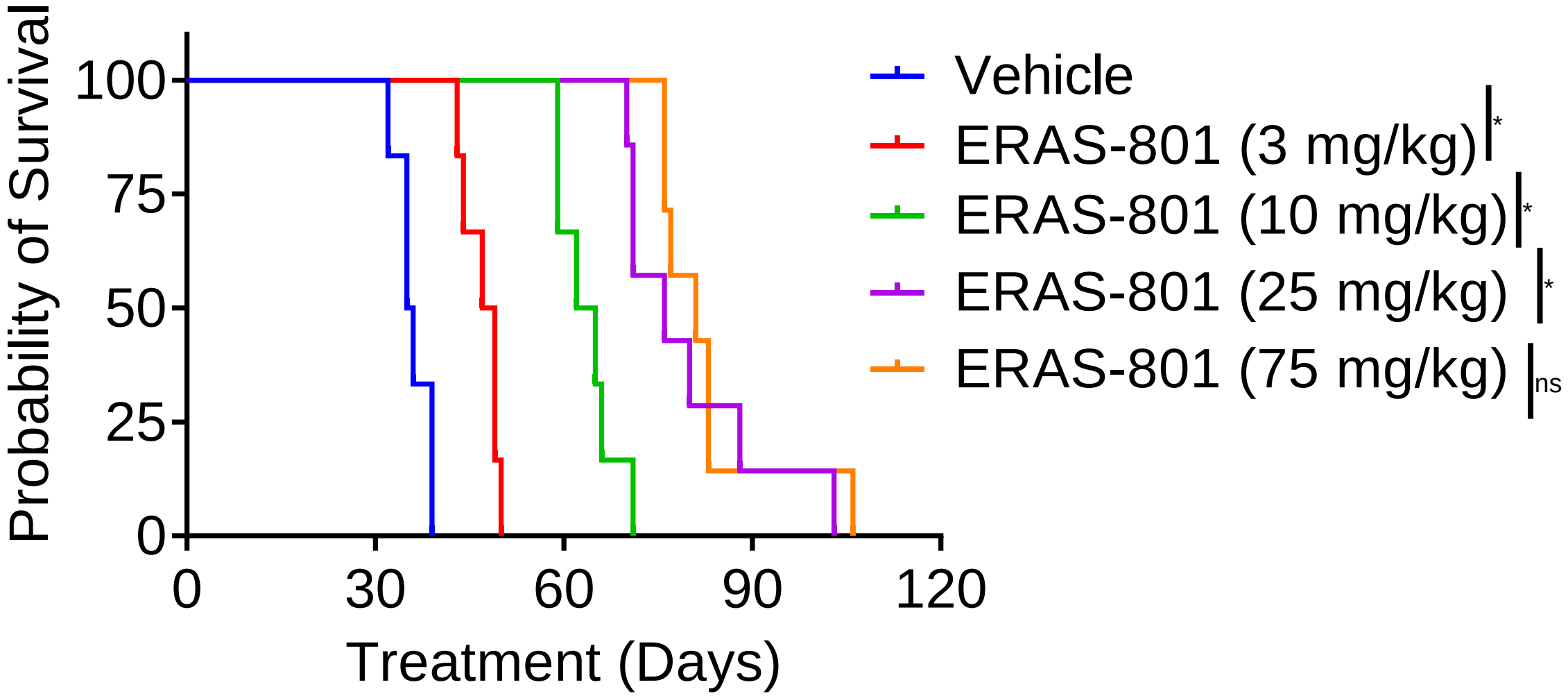
ERAS-801 induced changes in FDG uptake predict outcome in an orthotopic EGFR altered GBM PDX



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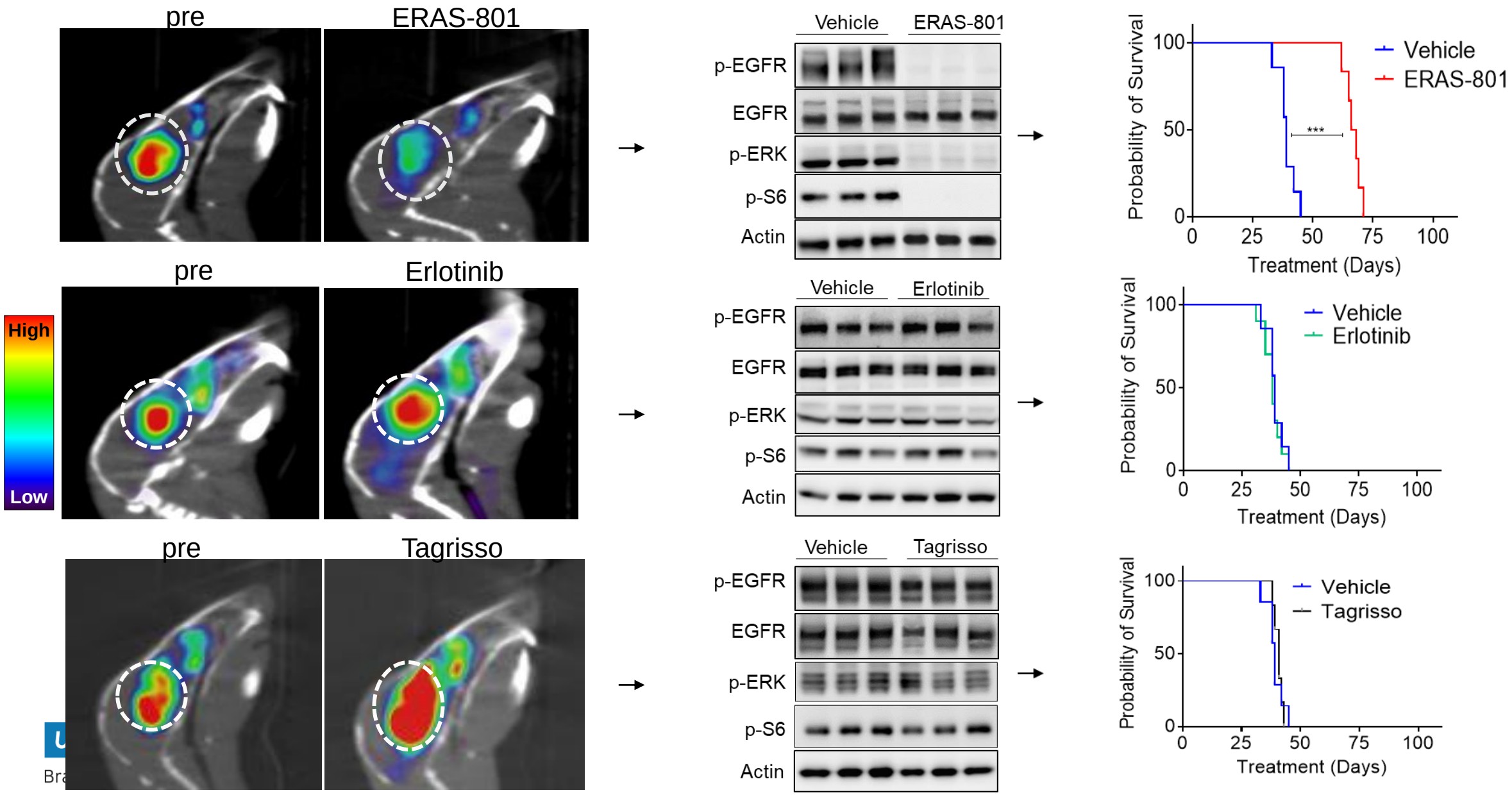
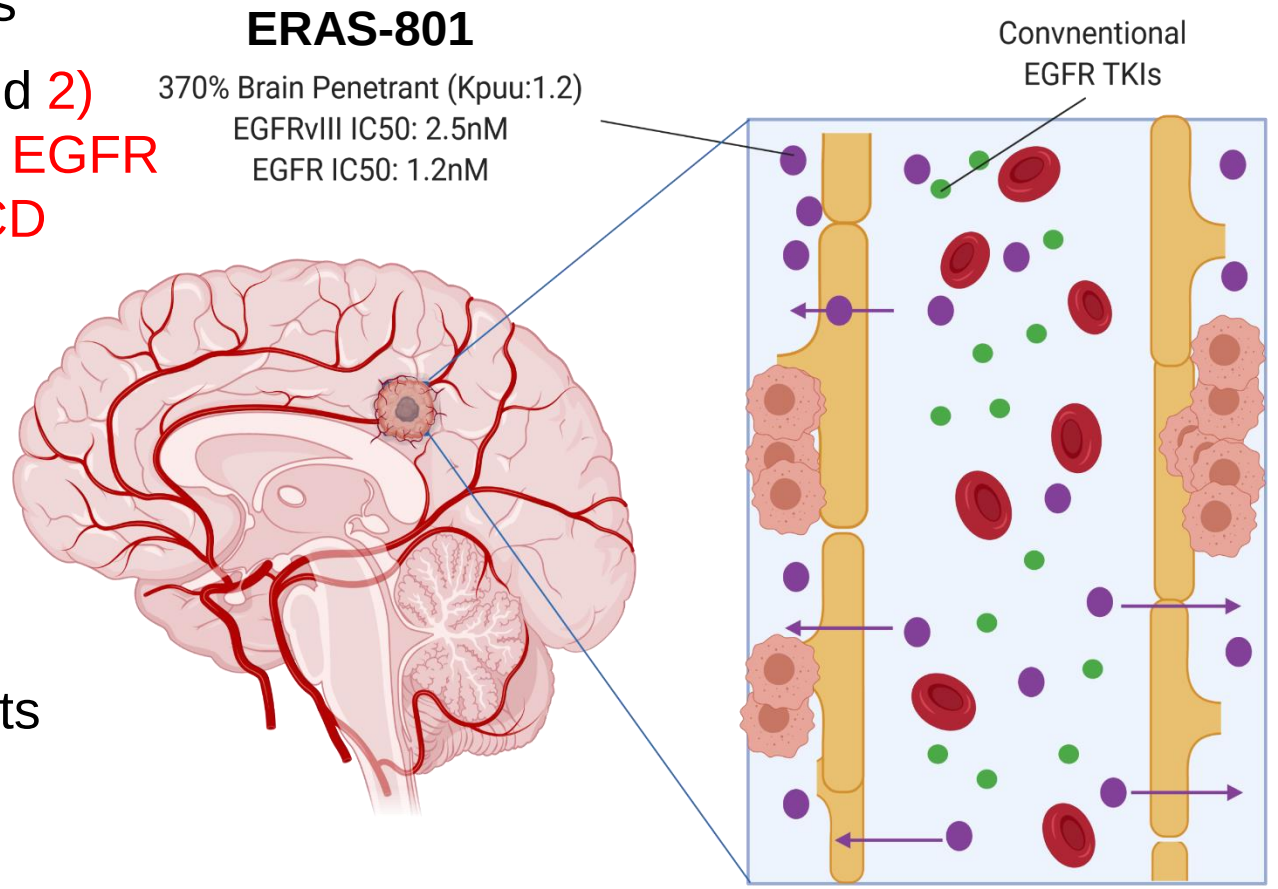
Same PDX model: FDG PET delineates ineffective EGFR TKIs compared to ERAS-801 all administered at equivalent dose



Summary

- EGFR is genetically altered in ~60% of GBM patients, yet available EGFR TKI have failed in GBM clinical trials
  - Failure due to 1) insufficient BBB penetration and 2) inability to potently inhibit all oncogenic forms of EGFR found in GBM, including amp WT EGFR and ECD mutants
- ERAS-801 has high BBB penetration (Kpuu: 1.2) and potently inhibits both ECD mutant EGFR (e.g., EGFRvIII) and amplified WT EGFR
- In GBM PDX preclinical trial, ERAS-801 extends survival of >90% of EGFR-altered patient derived orthotopic GBM xenografts with negligible side effects
- FDG PET may serve as a robust, non-invasive biomarker of meaningful target inhibition with ERAS-801



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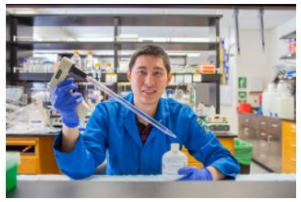
Acknowledgment



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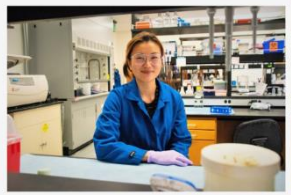

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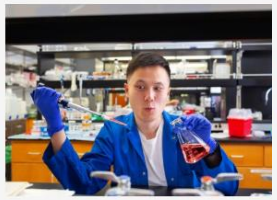

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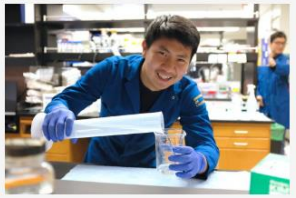

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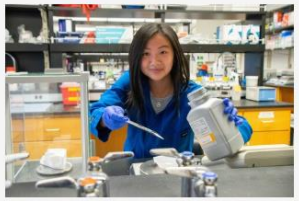

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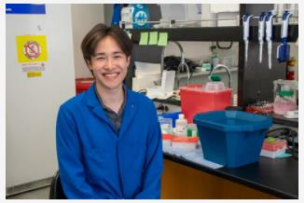

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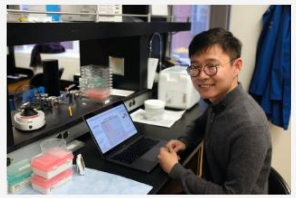

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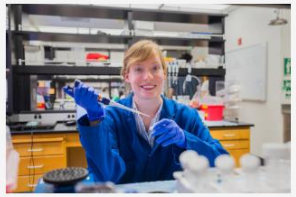

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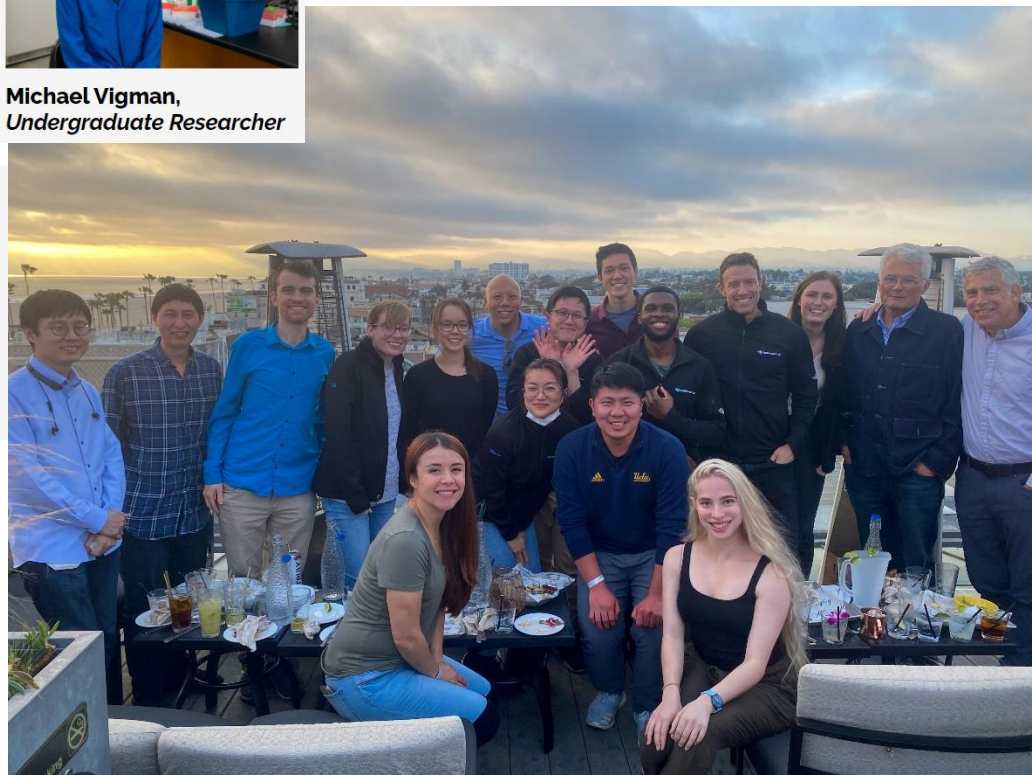

NathansonLab AT UCLA

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