23 de octubre de 2024

TAT-Cx43, a Src inhibitor peptide for glioblastoma therapy

VNiVERSiDAD D SALAMANCA

Arantxa Tabernero

MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
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Content

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1218 ~ 2018

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CAMPUS DE EXCELENCIA INTERNACIONAL

Salamanca, Spain

INSTITUTO DE NEUROCIENCIAS CASTILLA Y LEÓN
INCyL

Center of **Research Excellence**
Junta de Castilla y León 2024

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GIR, UIC, IBSAL

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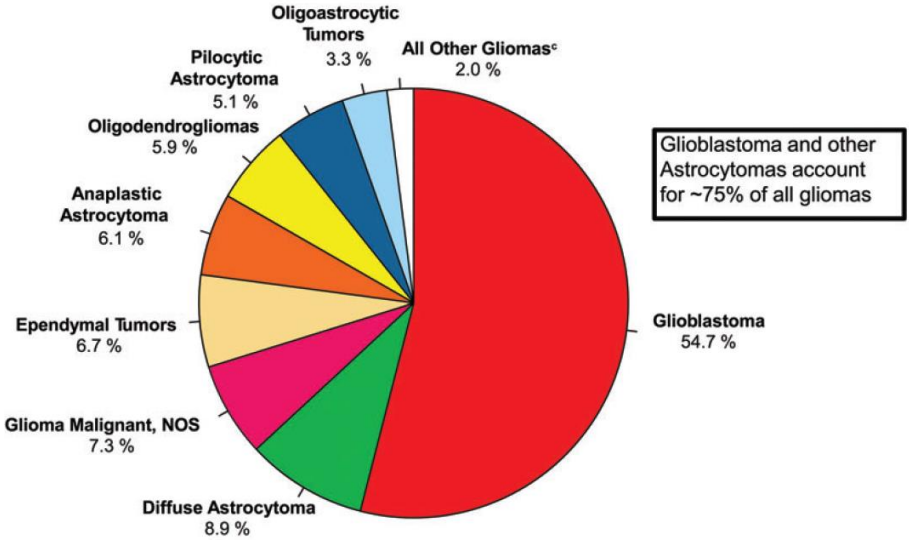
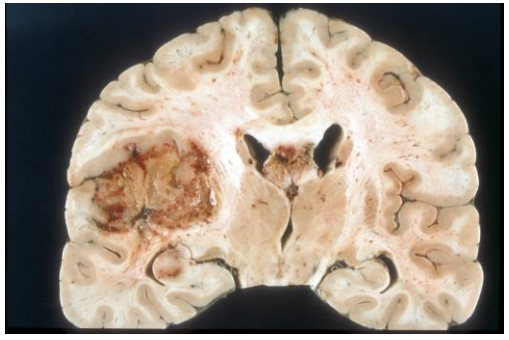
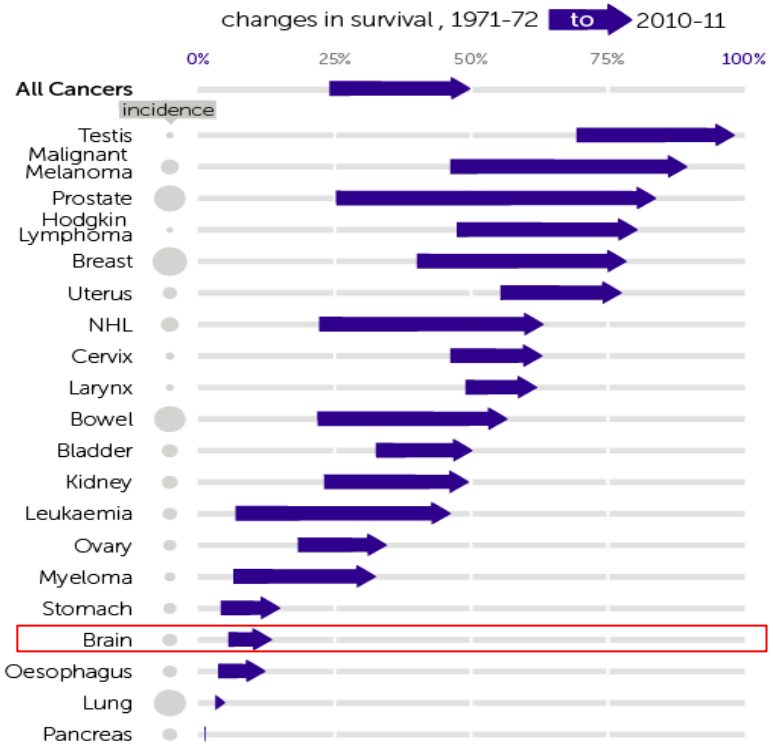
The Product

a) Target Indication

Glioblastoma, unmet clinical need







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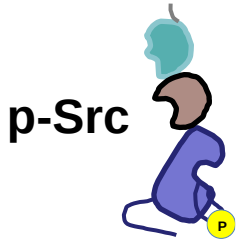
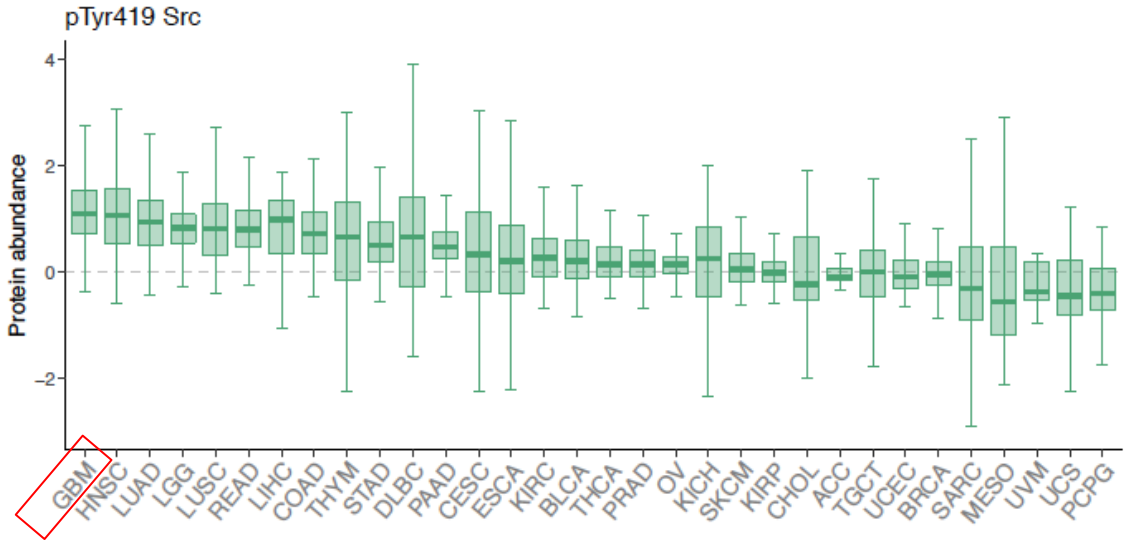
Adult Glioblastoma IDHwt EGFRamp or EGFRvIII

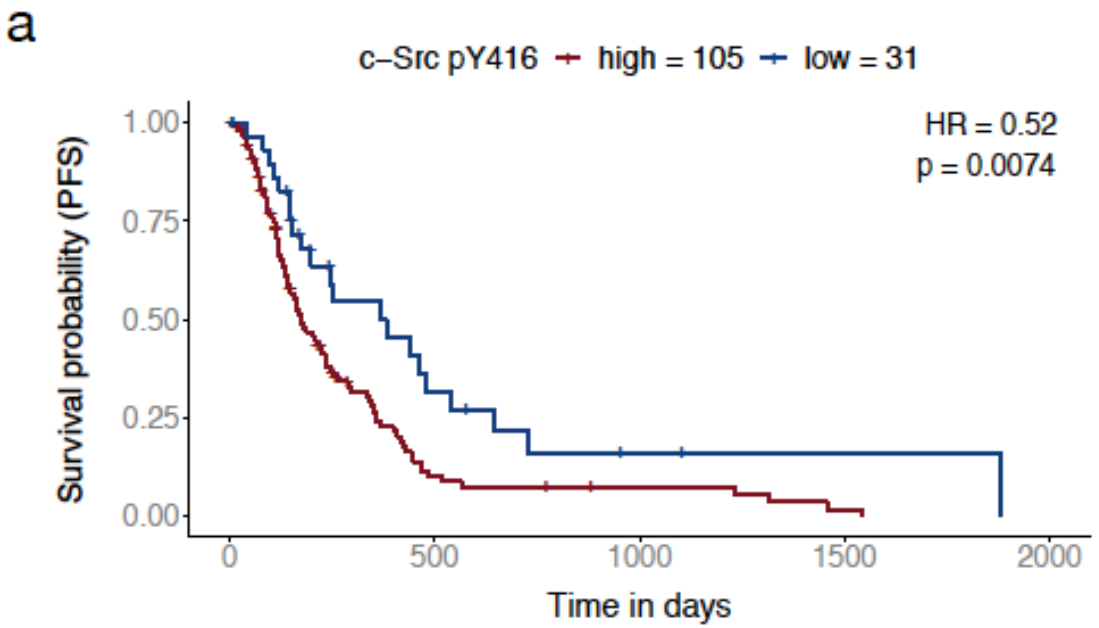


active

Src activity is a prominent **target** in **glioblastoma**



Pelaz and Tabernero
Oncogene. 2022 Nov;41(45):4917-4928.



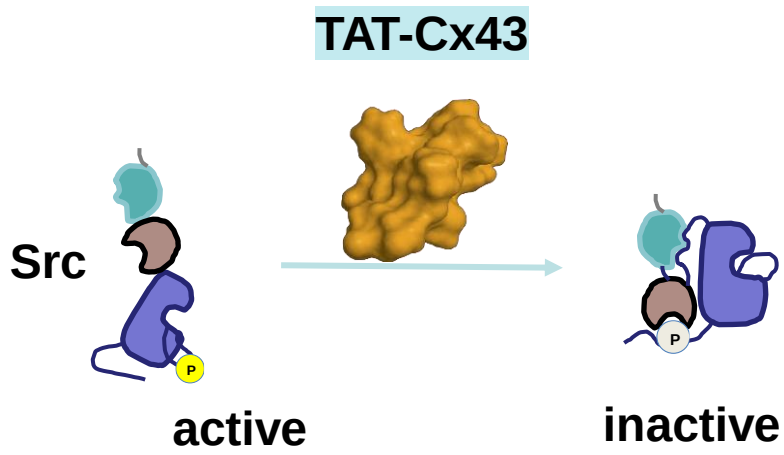
Pelaz et al.
Cancers. 2021 13:4262.

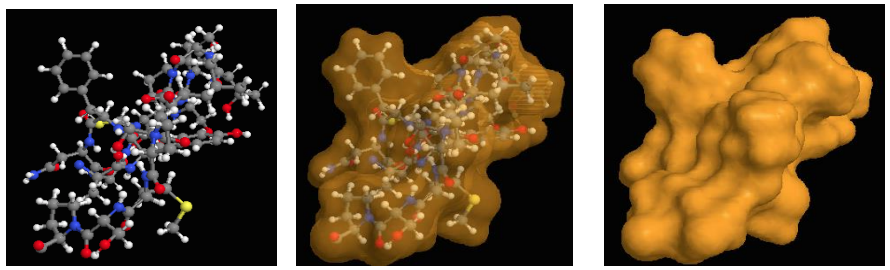
TRGAted. The Cancer Proteome Atlas

Du J et al. (2009). Bead-based profiling of tyrosine kinase phosphorylation identifies SRC as a potential target for glioblastoma therapy. ***Nat Biotechnol*** *27: 77-83.*

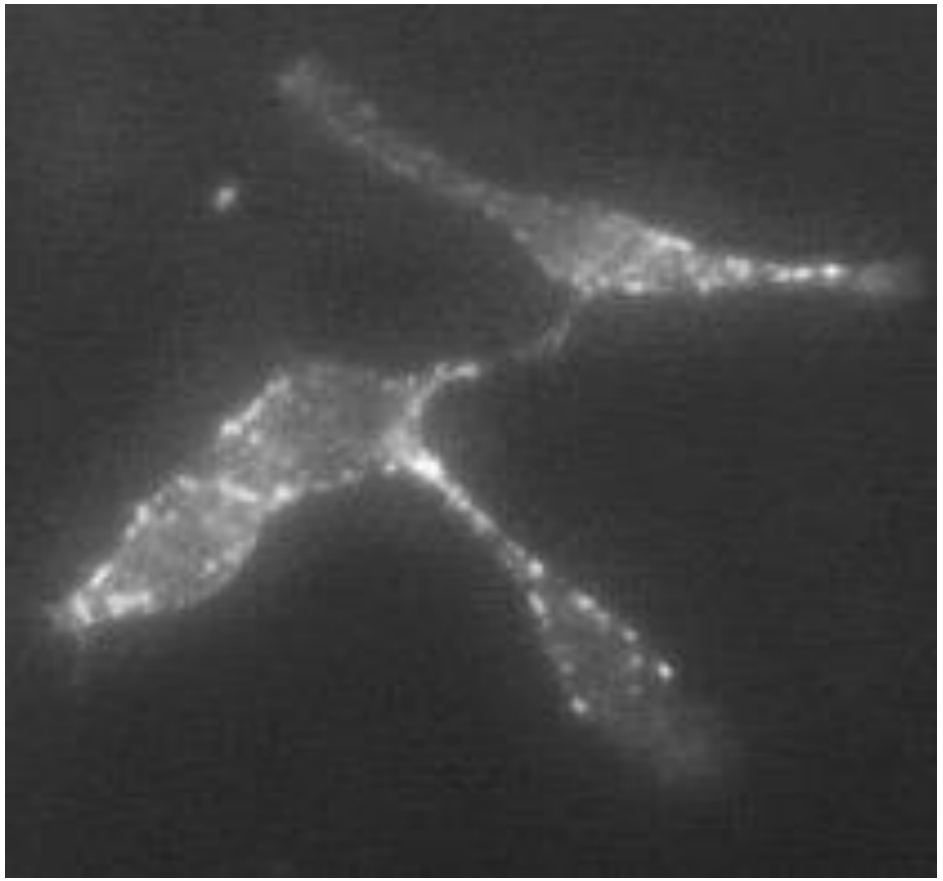
The Product

TAT-Cx43, a Src inhibitor peptide for glioblastoma therapy

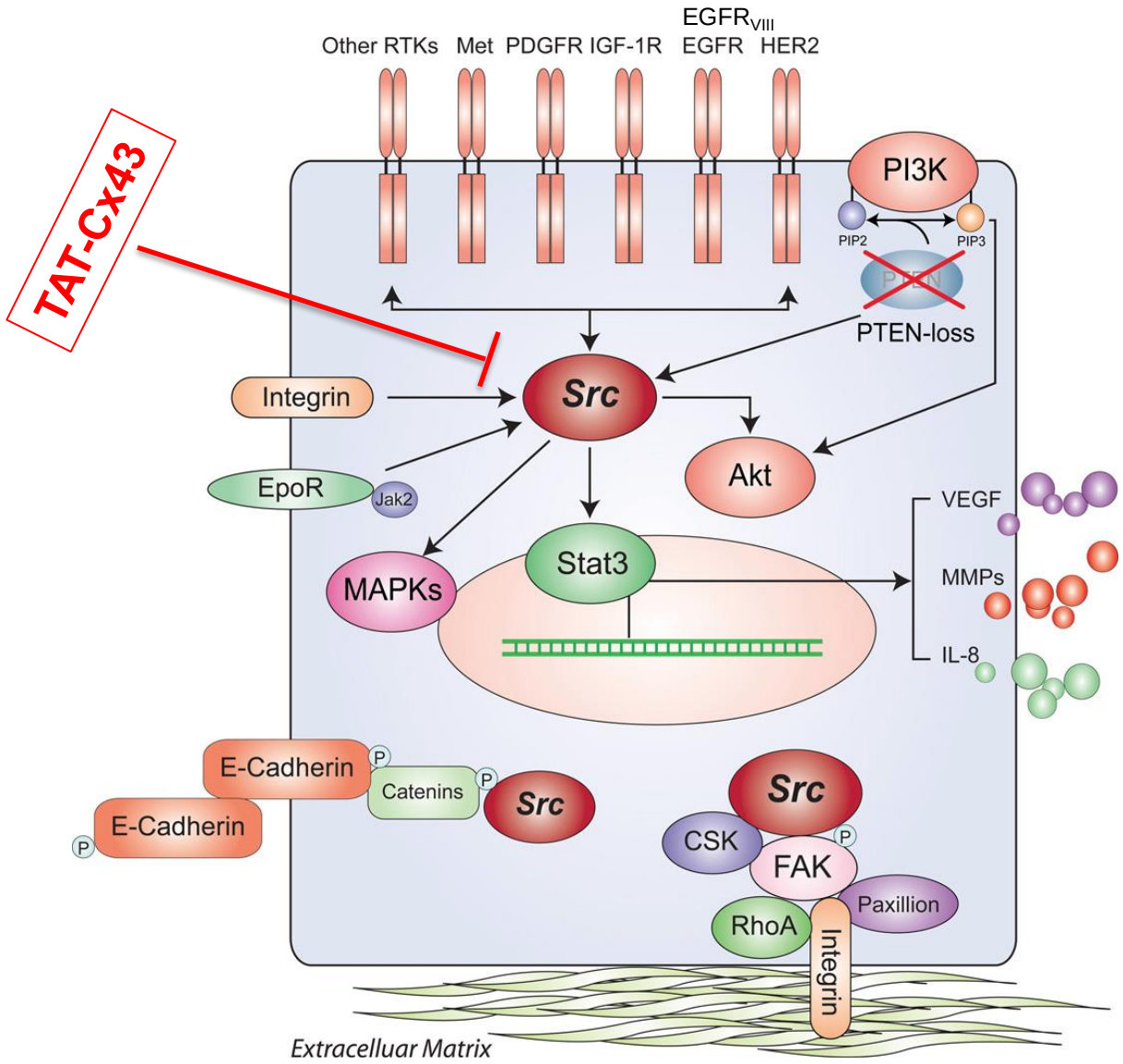




Cell-penetrating peptide



TAT-Cx43 targets key oncogenic pathways and cellular processes



Survival
Proliferation
Differentiation
Invasion
Metabolism
Autophagy
Stemness
Drug resistance
Vascularization

Gangoso et al. ***Cell Death Dis****. 2014 23;5:e1023.*

Gangoso et al. ***Front Mol Neurosci****. 2017; 10:418.*

*González-Sánchez et al****. Oncotarget*** *2016, 6, 10454.*

Jaraíz-Rodríguez et al. ***Stem Cell Reports*** *2017, 9:451.*

Jaraíz-Rodríguez et al. ***J. Vis. Exp****. 2017 e56457.*

Talaverón et al. ***Int J Mol Sci*** *2020 21:8852.*

Jaraíz-Rodríguez et al., ***Neuro-Oncology*** *2020 22:493.*

Pelaz SG et al., ***EBioMedicine.*** *2020 62:103134.*

Pelaz SG et al., ***Cancers*** *2021, 24:4262.*

Tabernero et al., ***Oncogene*** *2022, 41:4917.*

Álvarez-Vázquez et al. ***Neuro-Oncology****, 2024. 5:1230.*

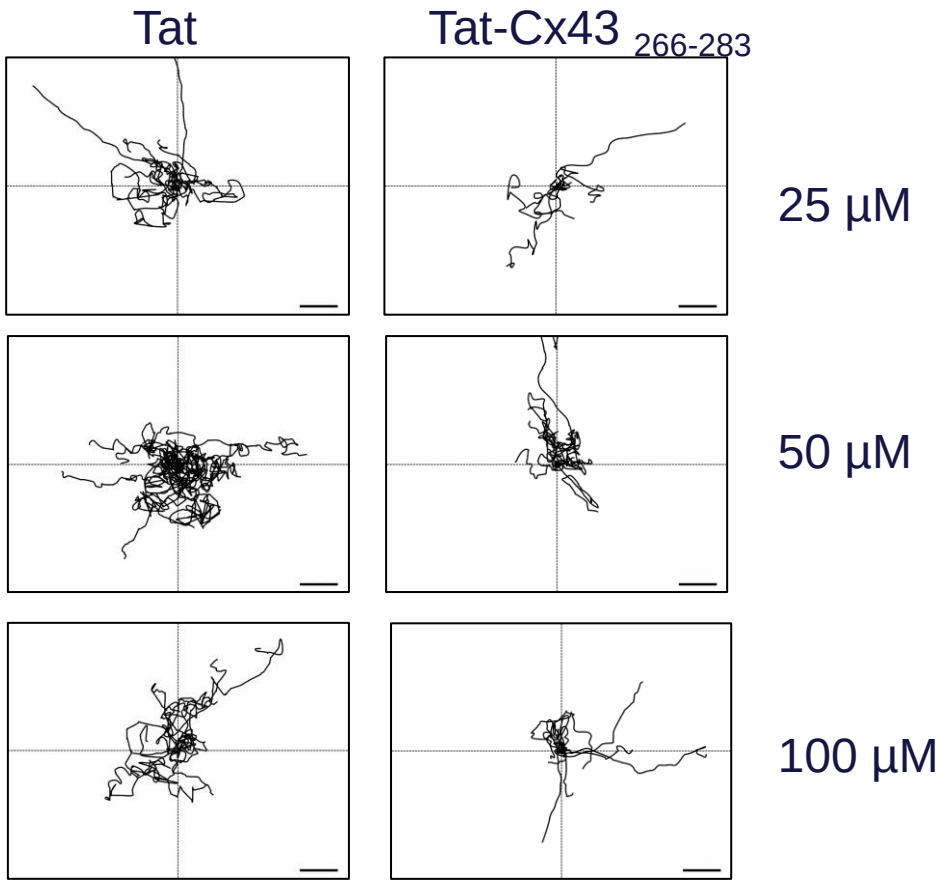
Pelaz et al. ***Translational Research****, 2024. Jun 12:95.*

Anti-tumor effect of TAT-Cx43 in preclinical GBM models **in vitro and in vivo**

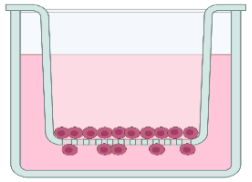
- **10 murine cell lines:** C6, Gl261, SB28, SVZ-NSCs, SVZ-EGFRwt, SVZ-EGFRvIII, NSC-EGFRvIII, NP, NPE, and NPE-IE.
- **16 Human Glioblastoma cell lines:** G166, G179, G144, GliNS2, E15, E20, E22, E26, E28, E43, E51, L0, L1, L2, T4121 and 23M.
- **5 Primary GBM cells and explants**: G9, G12, G13, G15 and G16.

Mouse	cells	administration	ref
C57bl/6	Gl261	IP	*Jaraíz-Rodríguez et al., Neuro-Oncology 2020*
C57bl/6	Gl261-GSCs	Intracranial + IP	*Jaraíz-Rodríguez et al., Neuro-Oncology 2020* *García-Vicente et al., BioRxiv 2023.*
C57bl/6	NPE-IE NSCs	Intracranial + IP	*Álvarez-Vázquez et al., Neuro-Oncology 2024*
NOD/SCID	Human G166 GSCs	Intracranial + IP	*Jaraíz-Rodríguez et al., Neuro-Oncology 2020*

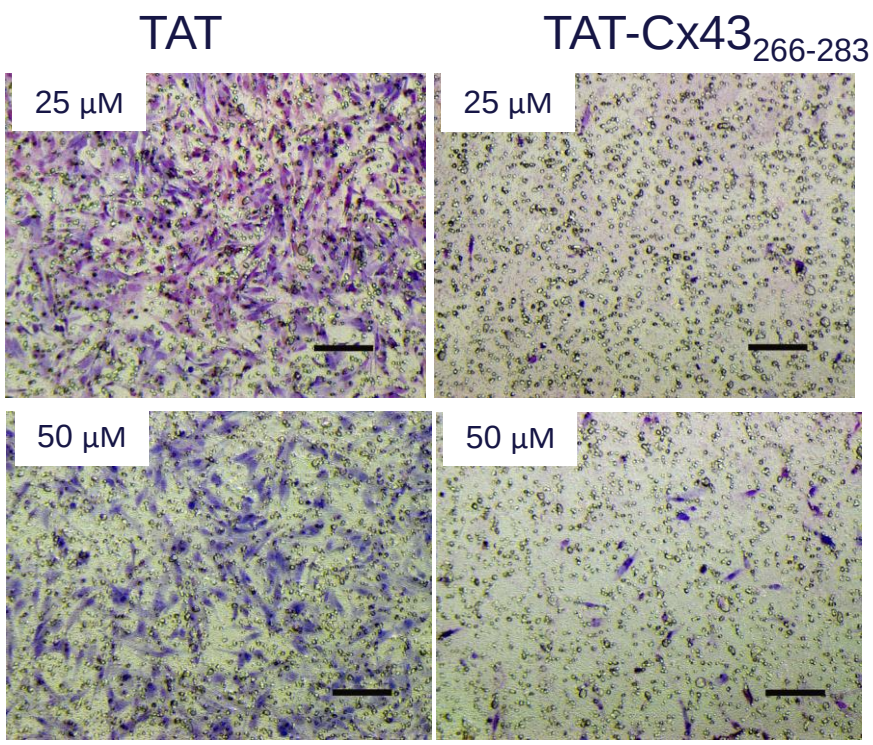
TAT-Cx43 inhibits primary GSC **migration and invasion**

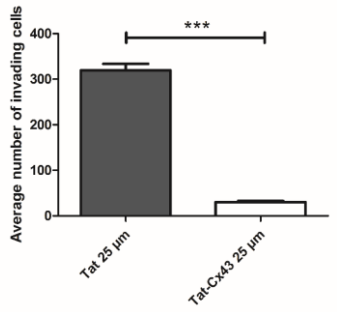


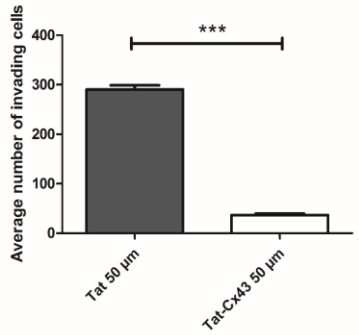
Primary GSCs invasion



Transwell cell migration assay with Matrigel

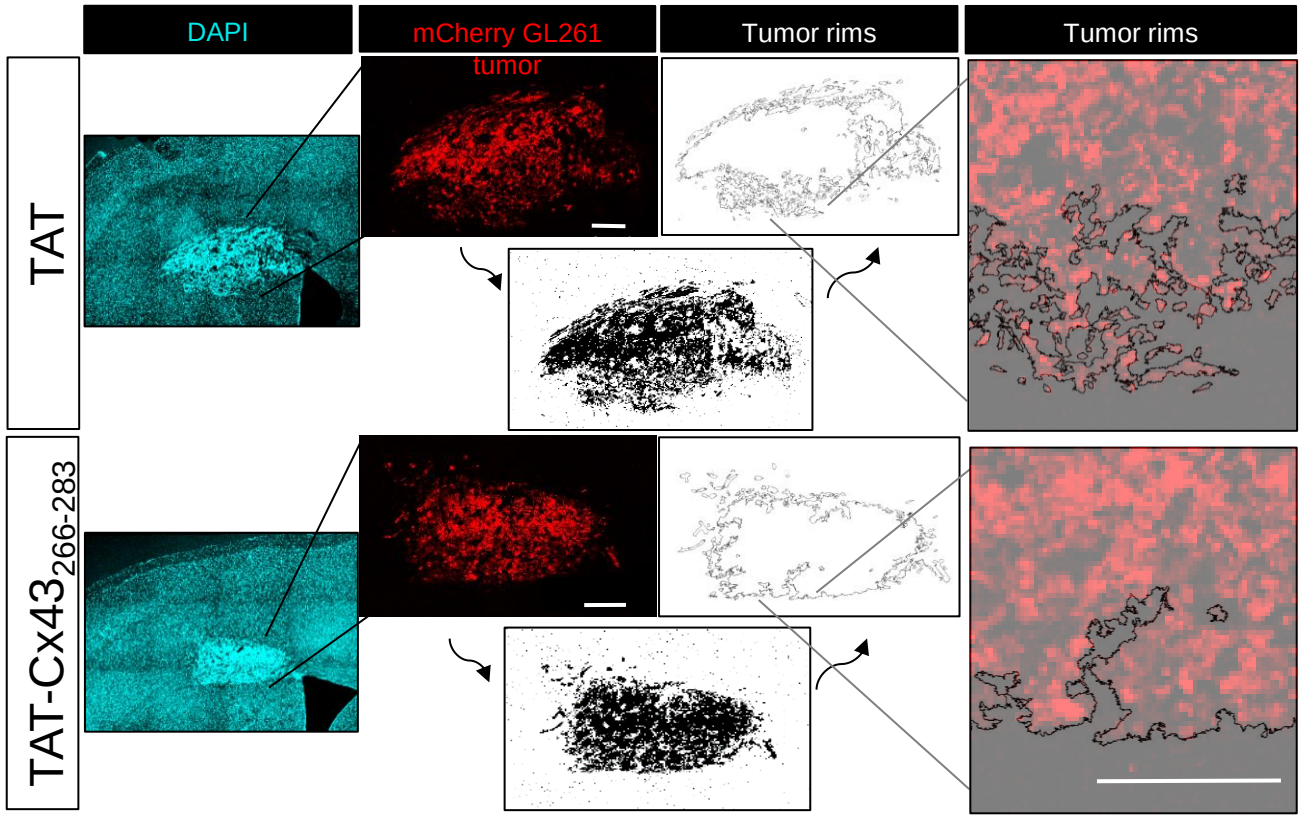


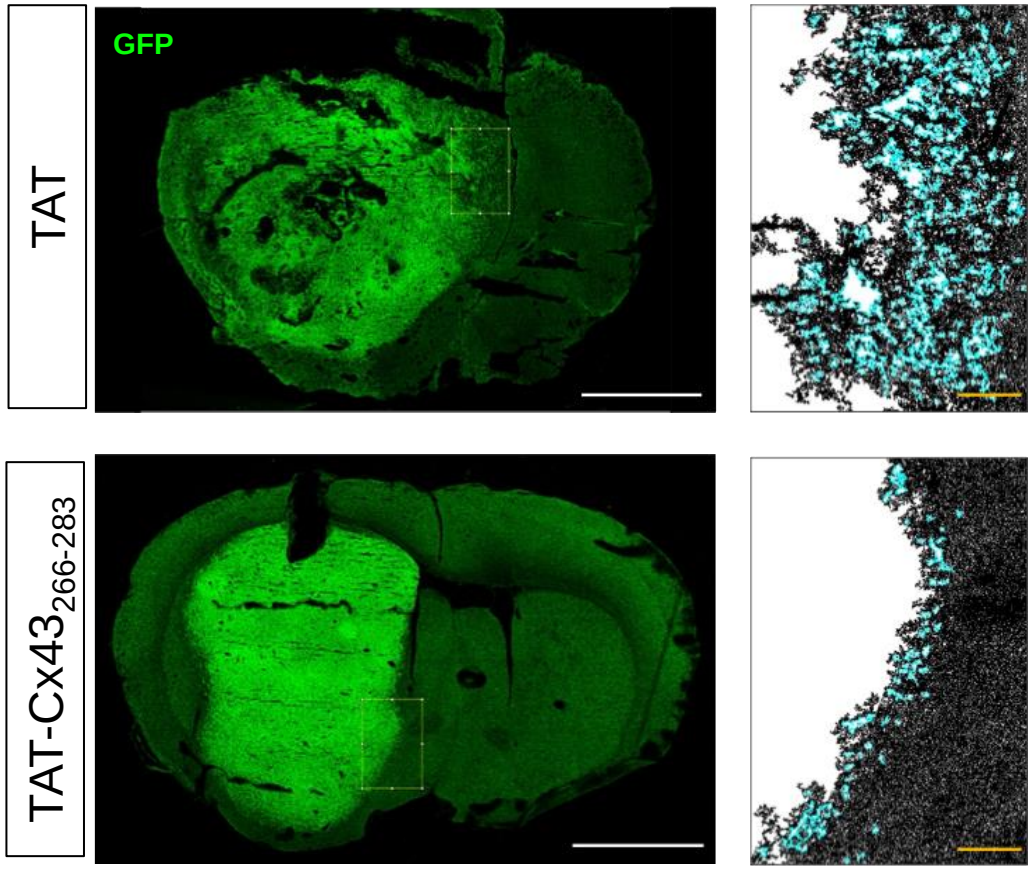




Jaraíz-Rodríguez et al. **Stem Cell Reports** 2017, 9:451-463

TAT-Cx43 reduces GSC **invasion in vivo**

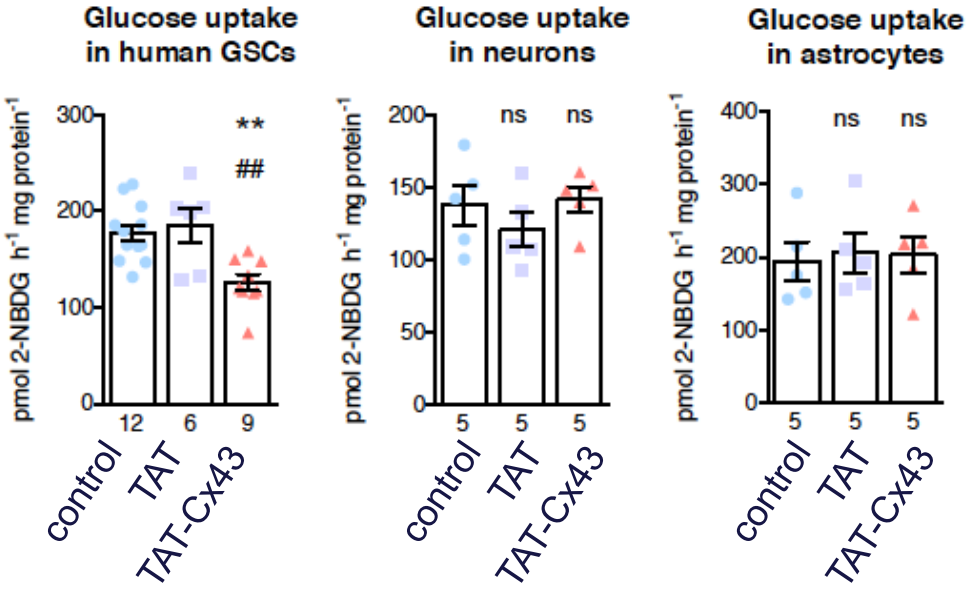


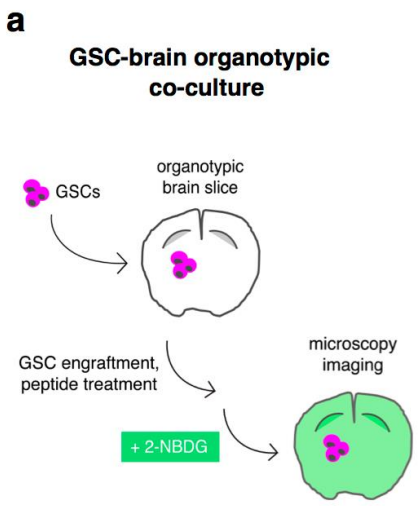


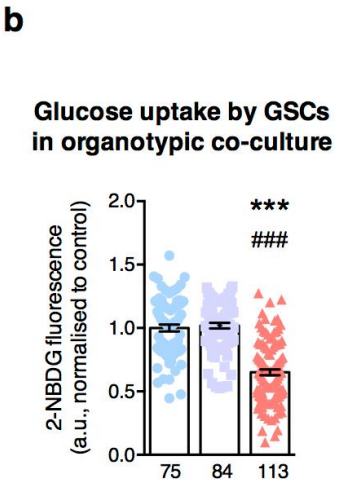
Jaraíz-Rodríguez et al. **Neuro-Oncology** 2020, 22: 493.

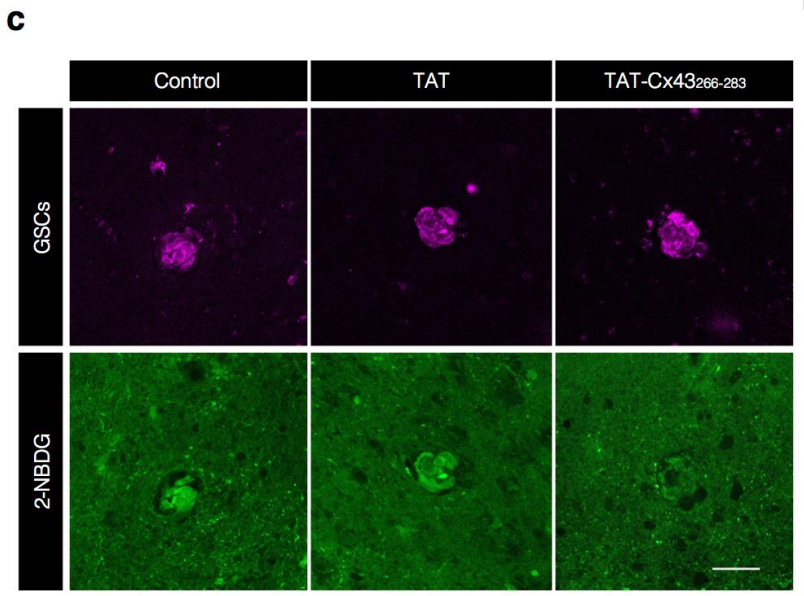
Álvarez-Vázquez et al. **Neuro-Oncology**, 2024, 26: 1230.

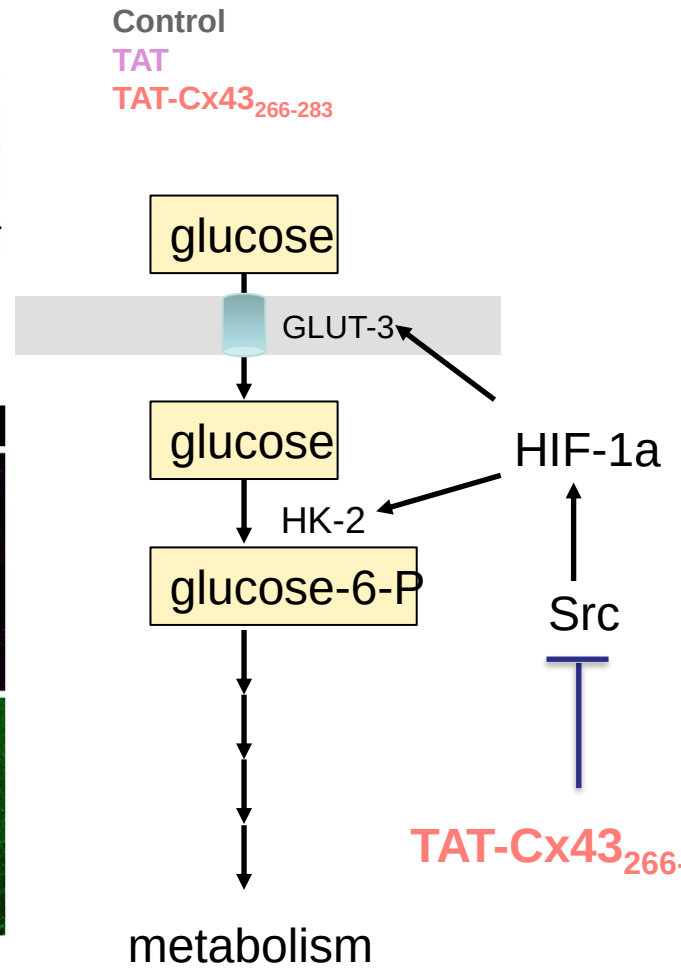
TAT-Cx43 decreases **glucose uptake** selectively in GSCs





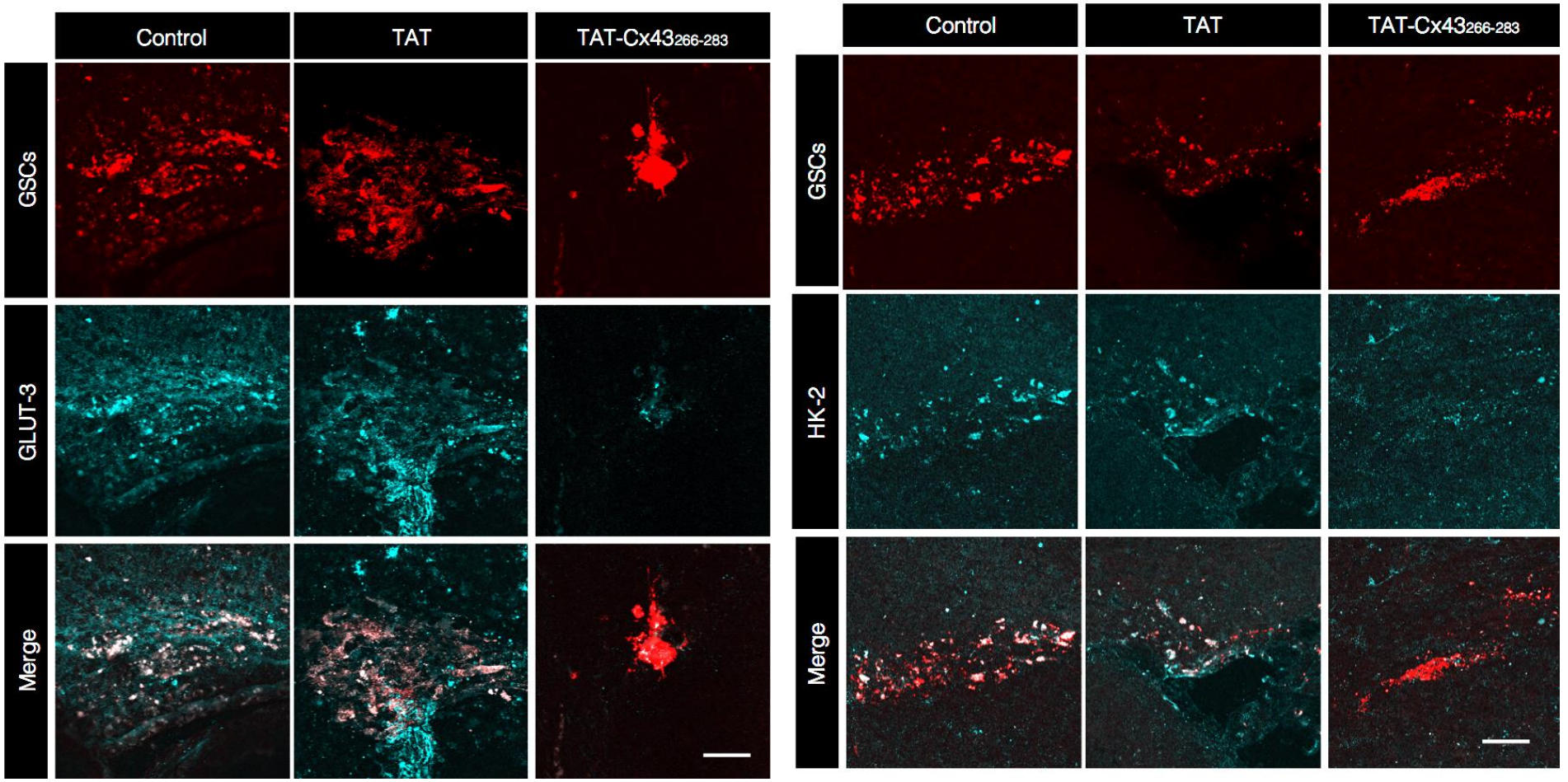






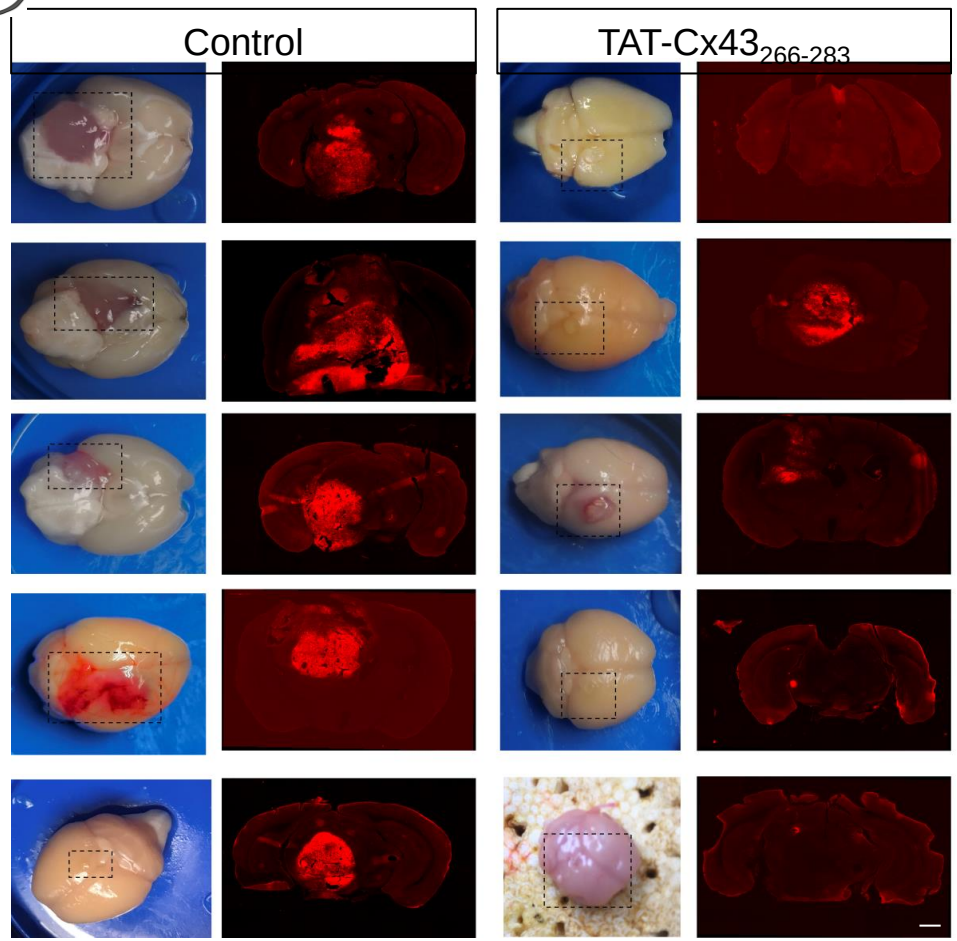
Pelaz SG et al., **EBioMedicine.** 2020 Dec;62:103134.

TAT-Cx43 decreases **glucose uptake in vivo**

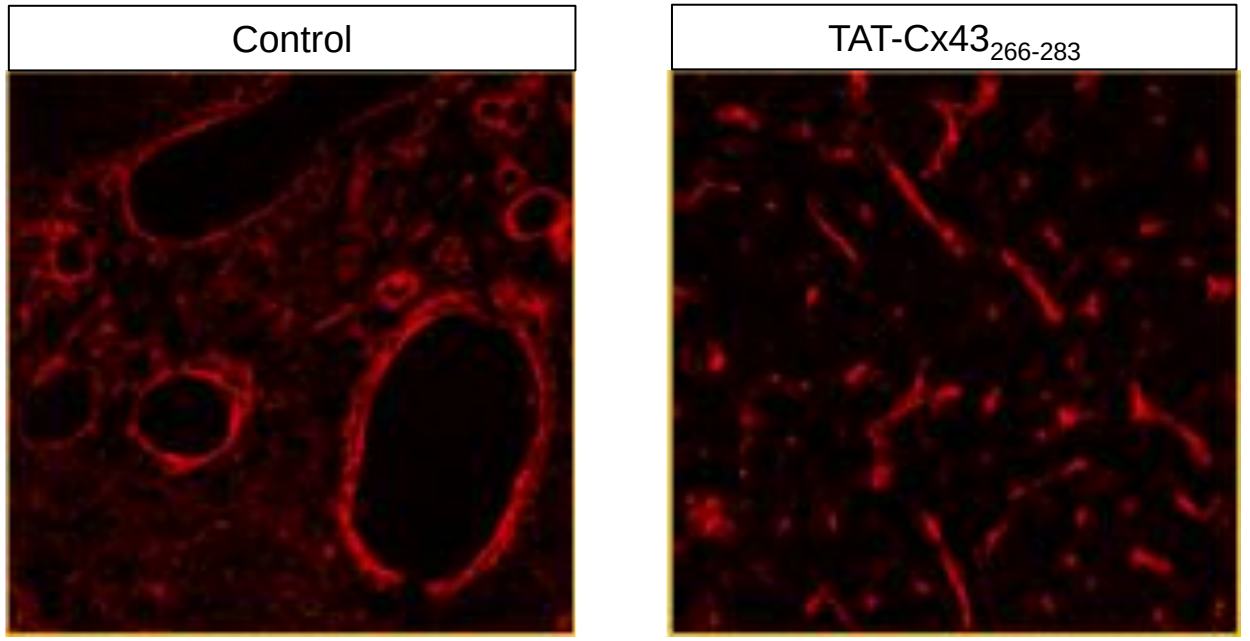


Pelaz SG et al., **EBioMedicine.** 2020 Dec;62:103134.

TAT-Cx43 normalizes aberrant **tumor vascularization**



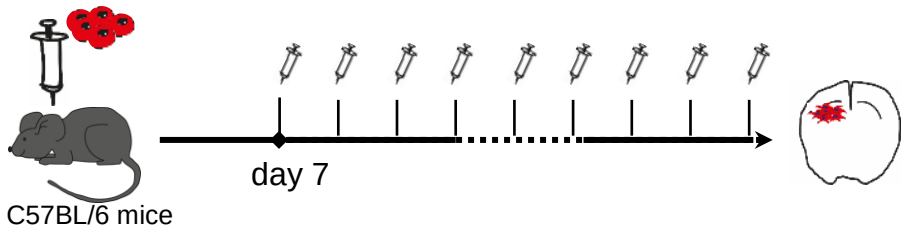
Jaraíz-Rodríguez et al. **Neuro-Oncology** 2020, 22: 493.



Álvarez-Vázquez et al. **Neuro-Oncology**, 2024, 26: 1230.

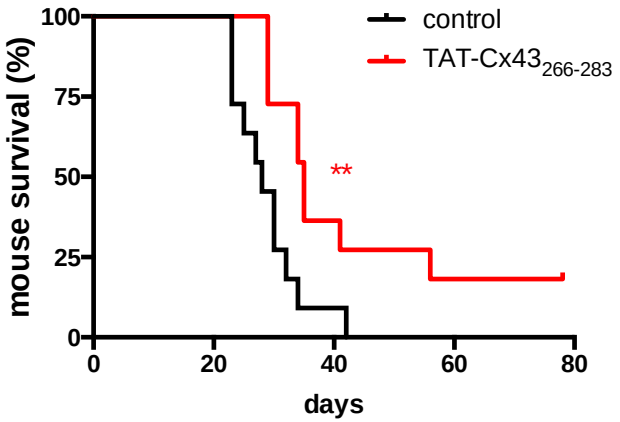
Effect of TAT-Cx43 on **survival** of glioma-bearing mice

GSCs
NSCs GBM-driver mutations



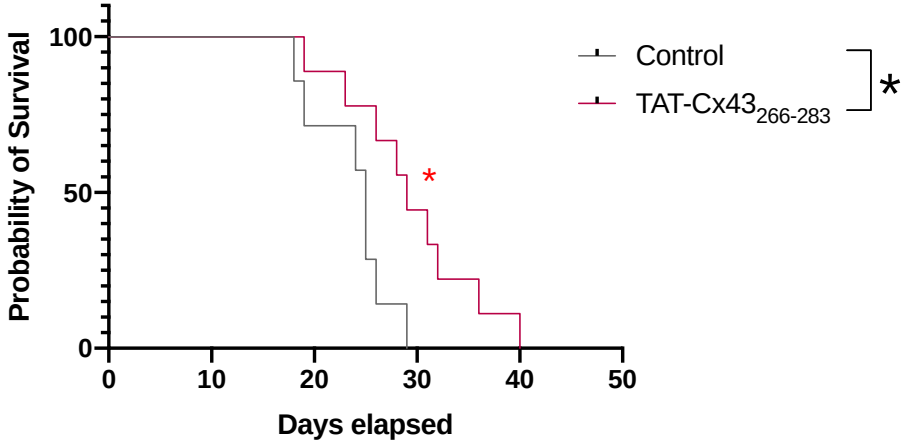
Intracranial: 100μM; 1 dose
Intraperitoneal: 13mg/kg; twice per week

GL261-GSCs in C57BL/6 mice



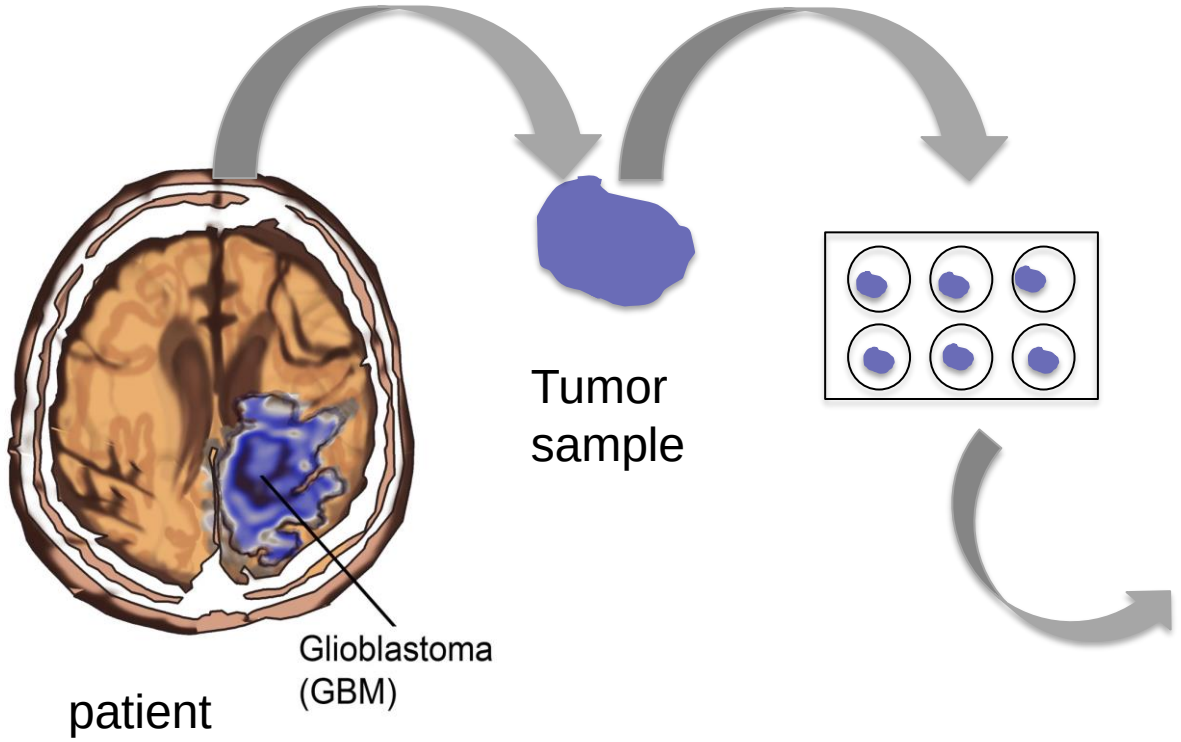
Jaraíz-Rodríguez et al. **Neuro-Oncology** 2020, 22: 493.

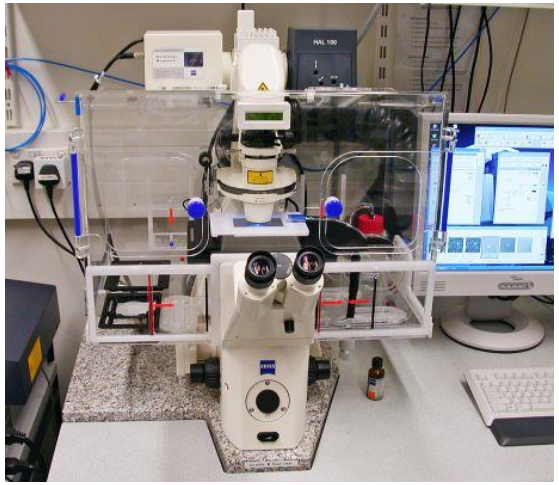
NPE-IE in C57BL/6 mice



Álvarez-Vázquez et al. **Neuro-Oncology**, 2024, 26: 1230.

Effect of TAT-Cx43 on freshly removed surgical specimen of glioblastoma



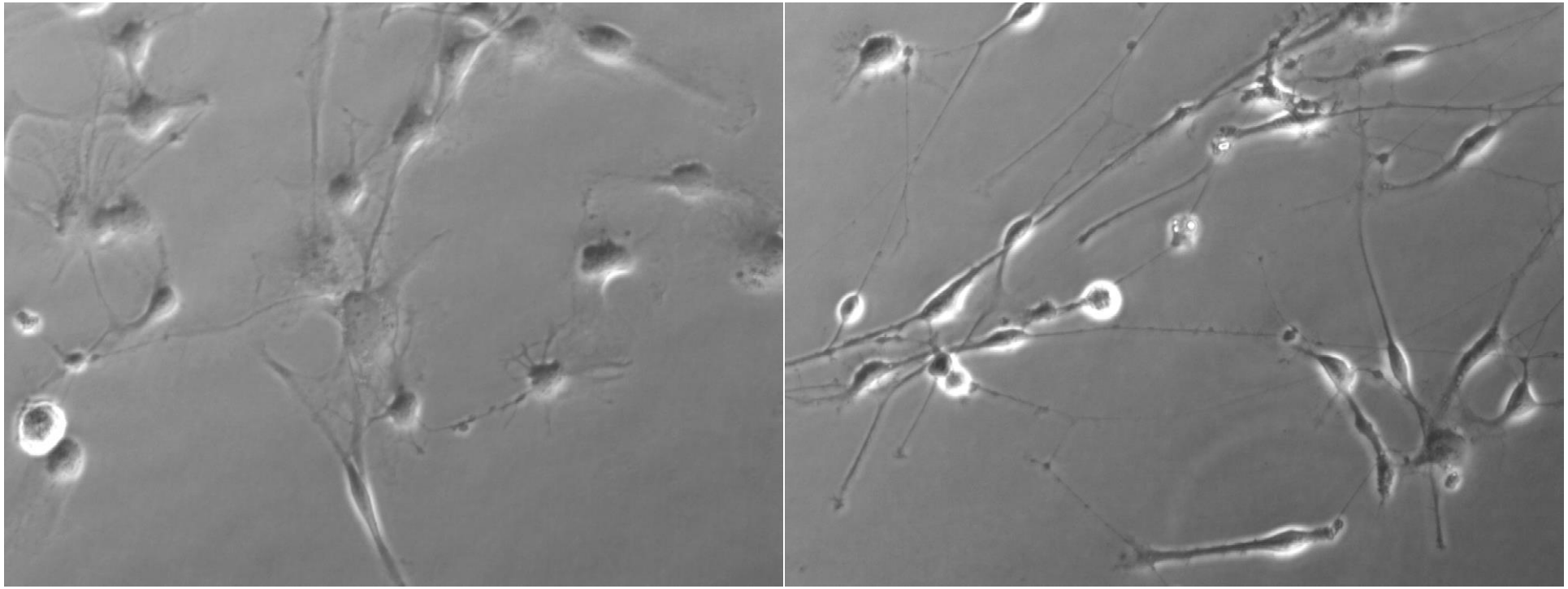


Jaraíz-Rodríguez et al. **Stem Cell Reports** 2017, 9:451-463

Effect of TAT-Cx43 on freshly removed surgical specimen of glioblastoma

TAT

TAT-Cx43



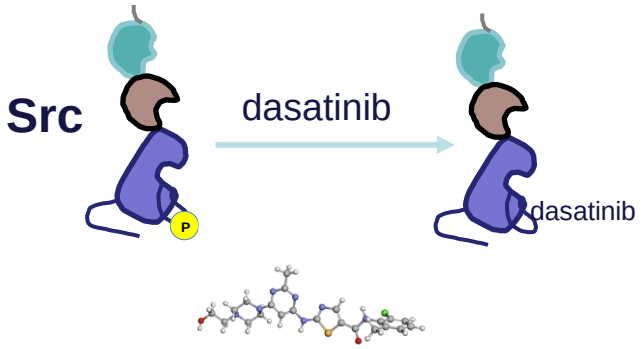
100µM 48h

Jaraíz-Rodríguez et al. **Stem Cell Reports** 2017, 9:451-463

The Product

b) Innovative mechanism of action

ATP competitive inhibitor



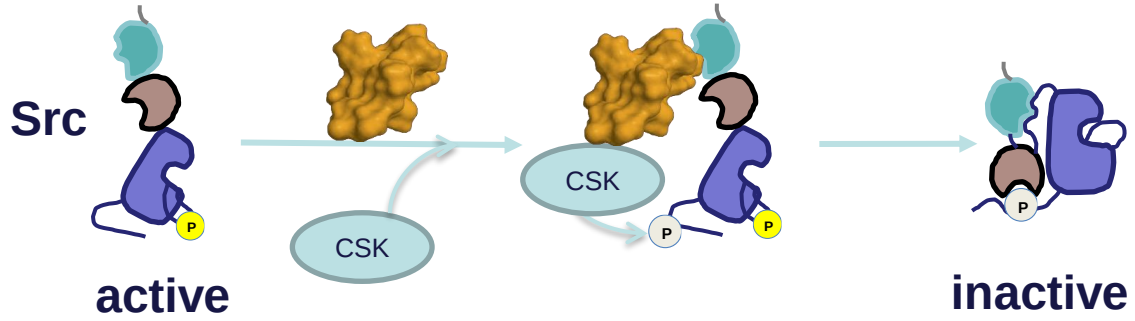
ATP pocket highly conserved

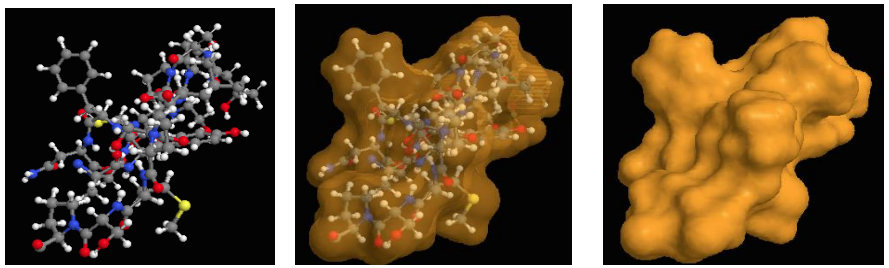
Broad target spectrum of dasatinib:
- receptor tyrosine kinases
- non-receptor tyrosine kinases
- serine/threonine kinases

Drug resistance

Shi et al, **J. Am. Chem. Soc**. 2012, 134, 6, 3001

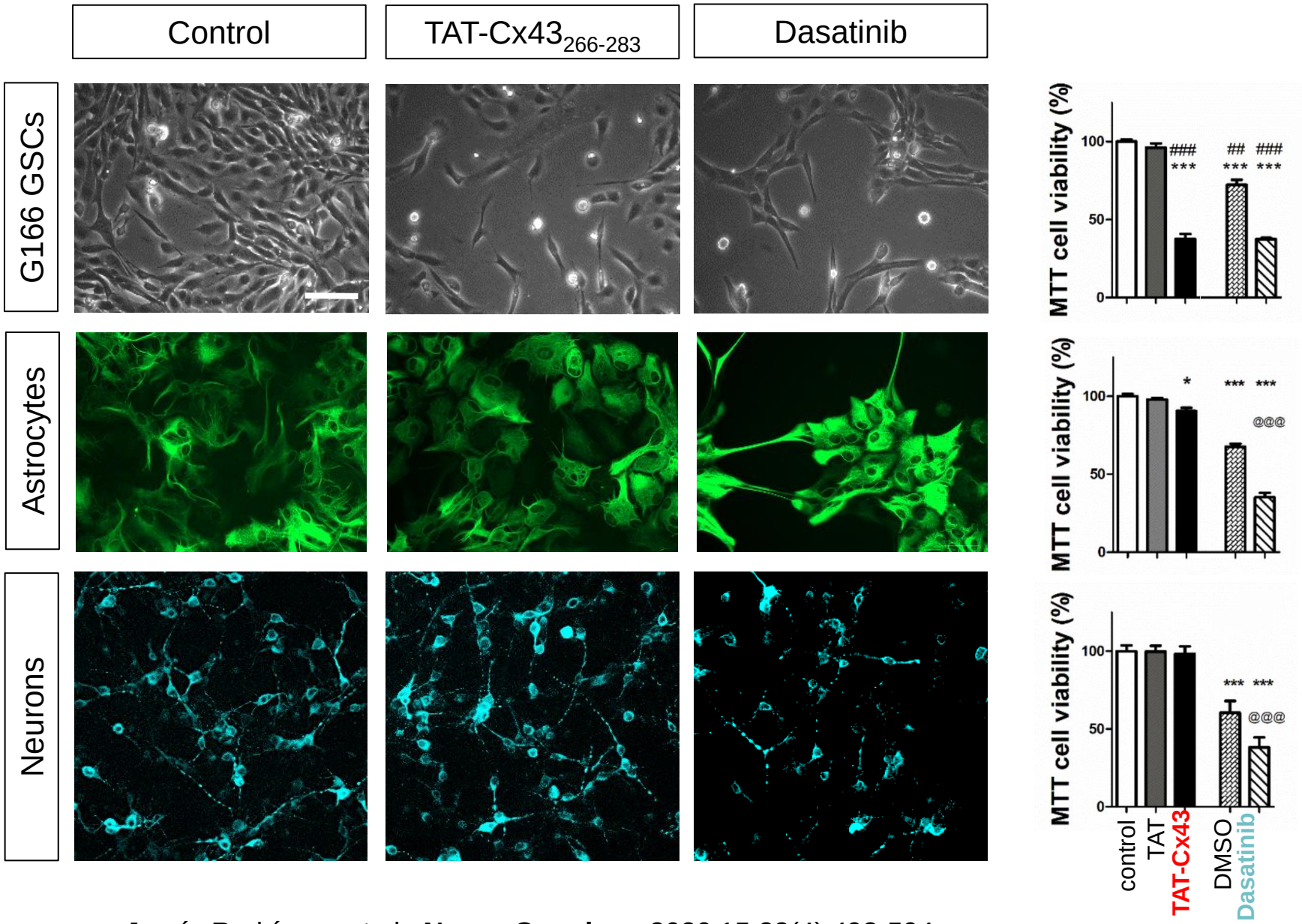
TAT-Cx43 is a peptide that recruits Src and its inhibitor, CSK





González-Sánchez et al. **Oncotarget** 2016, 6, 10454.

TAT-Cx43, higher cell selectivity and reduced toxicity vs dasatinib



Jaraíz-Rodríguez et al., **Neuro-Oncology** 2020 15;22(4):493-504

The Product

c)) Differential features facing the market

Standard of care

Surgery + temozolomide (TMZ) + radiotherapy (OS 16 months)

New approved therapeutic strategies

Tumor-treating fields (TTFs)

- Improves survival in combination with standard of care (20.9 months)
- No biomarker of response
- Device complexity

Clinical trials

- Immunotherapy
- Targeted therapies
- Anti-angiogenic

The Product

c)) Differential features facing the market

TAT-Cx43

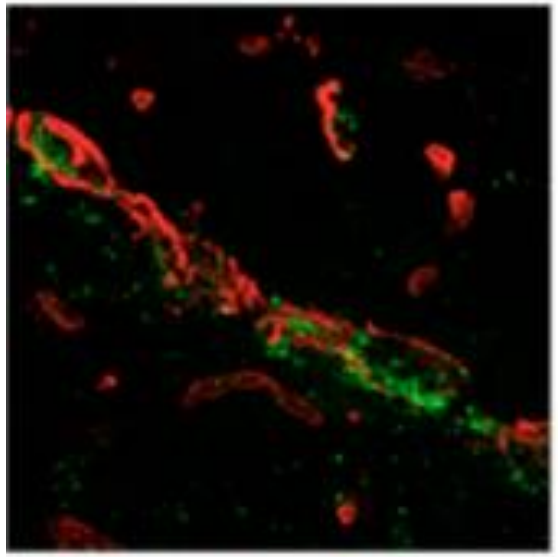
Peptide
- Low toxicity
- Low production cost compared to other biological treatments (immunotherapy)

TAT
- Good blood brain barrier penetrance after IP administration due to TAT sequence
- Good tumor cell internalization
- High solubility in water- Improved administration

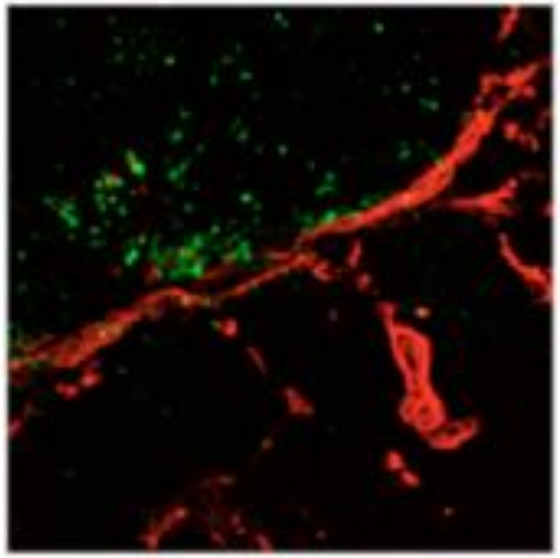
Cx43 sequence
- High specificity and cell selectivity
- Biomarker of response: The frequent EGFR alterations
- High plasma stability due to albumin binding, which also increases tumor tropism
- TAT-Cx43 targets glioblastoma cells resistant to conventional treatments

TAT peptides cross the blood-brain barrier

10 min



80 min



brain blood vessels
TAT-Gap19

i.p. 7.5 µmol/kg

Freitas-Andrade et al. **J Exp Med**. 2019, 216

TAT: YGRKKRRQRRR

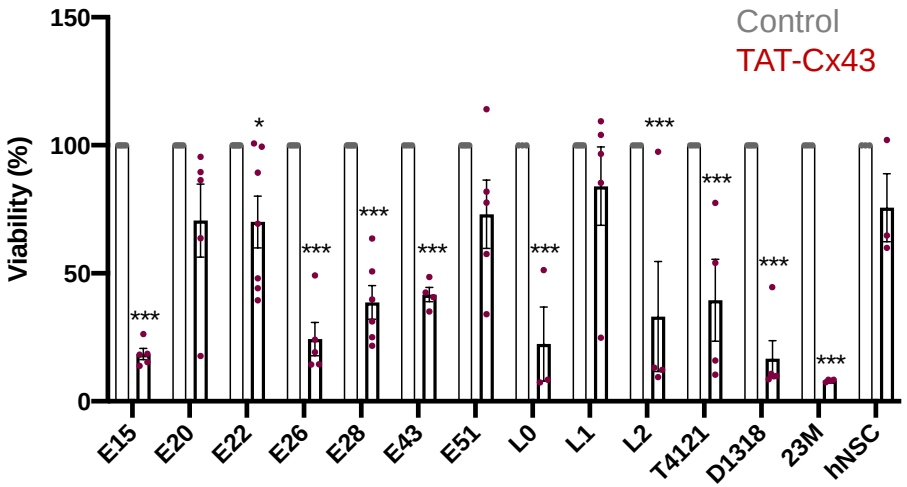
Safety and efficacy in patients with stroke

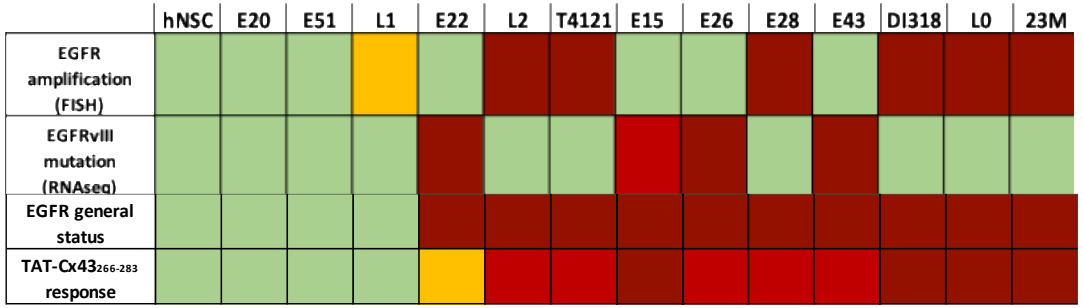
Phase 3 clinical trial NoNo Nerinetide (https://clinicaltrials.gov/ct2/show/NCT02930018),

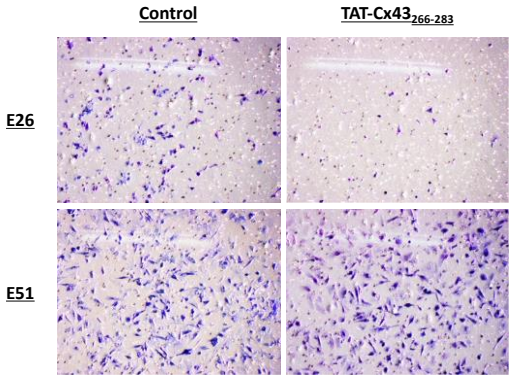
2.6 mg/kg **Single intravenous infusion**

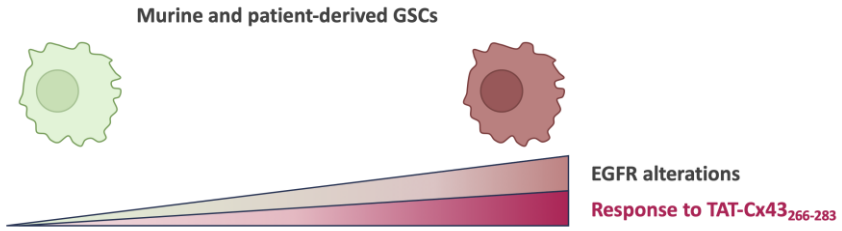
Hill *et al.* 2020, **The Lancet**, 395: 878-887; **Lancet Neurol** 11, 942-950 (2012).

Biomarker of TAT-Cx43 response: EGFR alterations









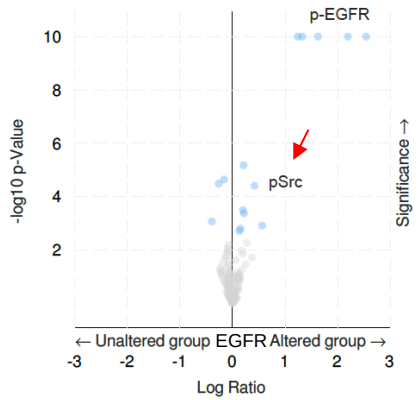
EGFRamp and EGFRvIII

- Highly frequent in GBM >50%
- Available in clinical diagnosis
- Patient stratification

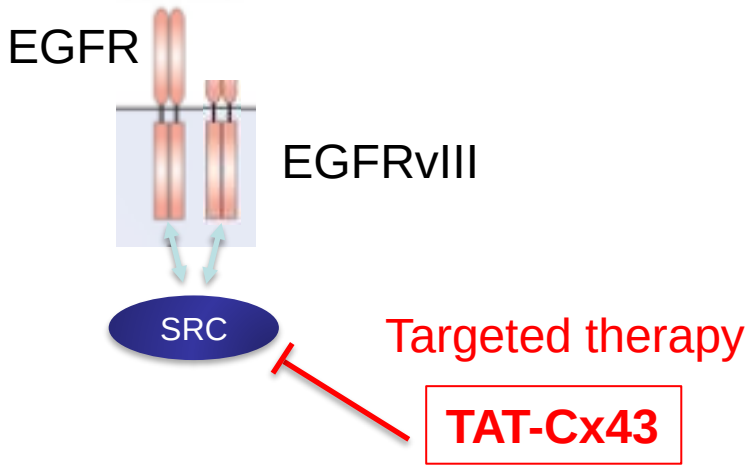
P. Sánchez-Gómez ISCIII
J. Lathia-Cleveland Clinic
S. M. Pollard- U. Edinburgh

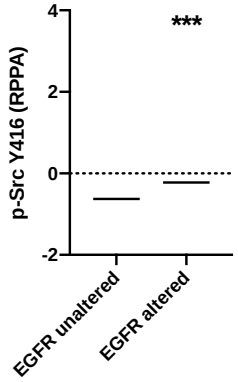
Álvarez-Vázquez et al. **Neuro-Oncology**, 2024, 26: 1230.

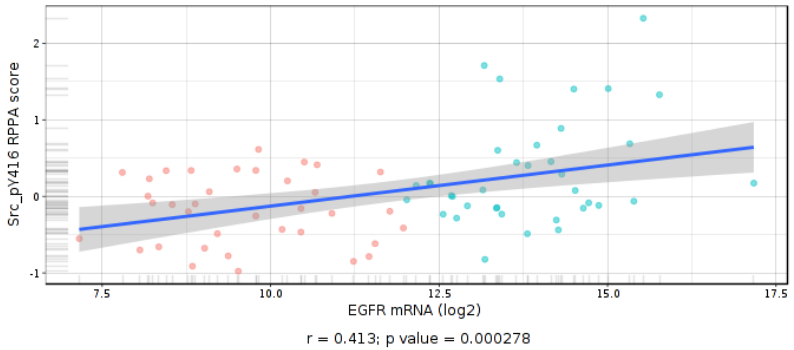
Clinical relevance of **EGFR-Src** in GBM patients

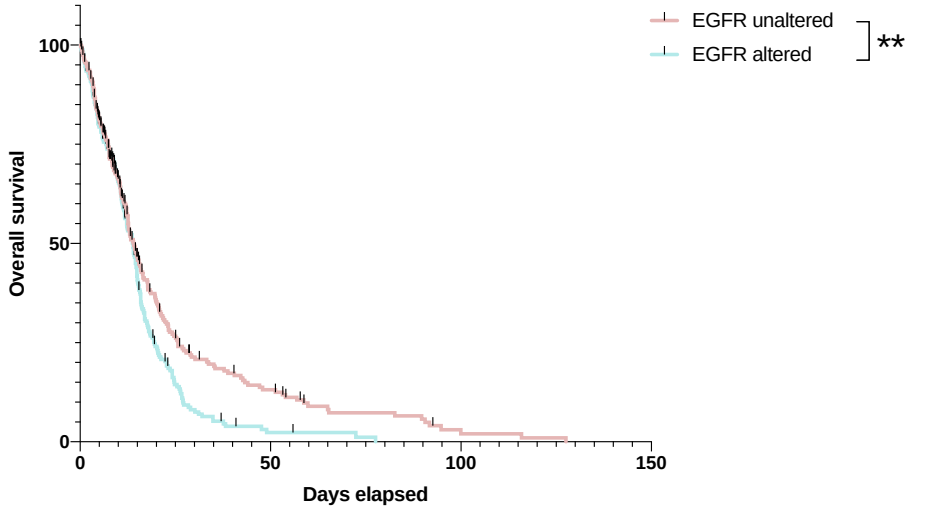


Gene	Cytoband	Log2 Ratio	p-Value	q-Value	Higher expression in
EGFR	7p11.2	2.21	1.77E-22	2.88E-20	Altered group
EGFR_PY1068		2.55	2.17E-21	1.77E-19	Altered group
EGFR_PY1173		1.62	7.54E-17	4.10E-15	Altered group
EGFR_PY992		1.33	4.50E-16	1.83E-14	Altered group
ERBB2_PY1248		1.24	5.69E-15	1.85E-13	Altered group
CTNNA1	5q31.2	0.21	5.10E-06	1.39E-04	Altered group
SRC_PY416		0.41	4.88E-05	8.83E-04	Altered group
BAX	19q13.33	0.2	1.84E-04	3.00E-03	Altered group
NOTCH3	19p13.12	0.21	5.07E-04	6.89E-03	Altered group
CDH2	18q12.1	0.16	7.97E-04	9.99E-03	Altered group
ANXA1	9q21.13	0.55	1.24E-03	0.0145	Altered group
CDK1	10q21.2	0.13	2.44E-03	0.0265	Altered group
YAP1_PS127		0.28	2.85E-03	0.029	Altered group









The Cancer Genome Atlas (TCGA)

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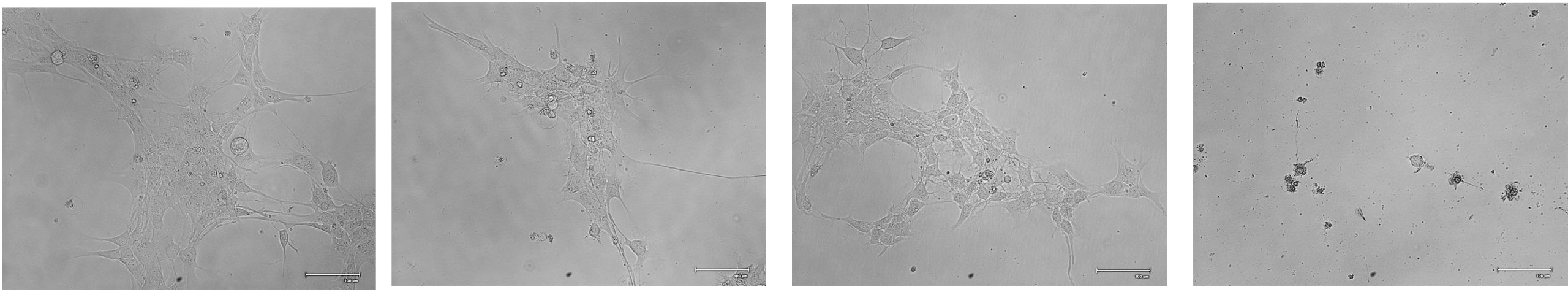
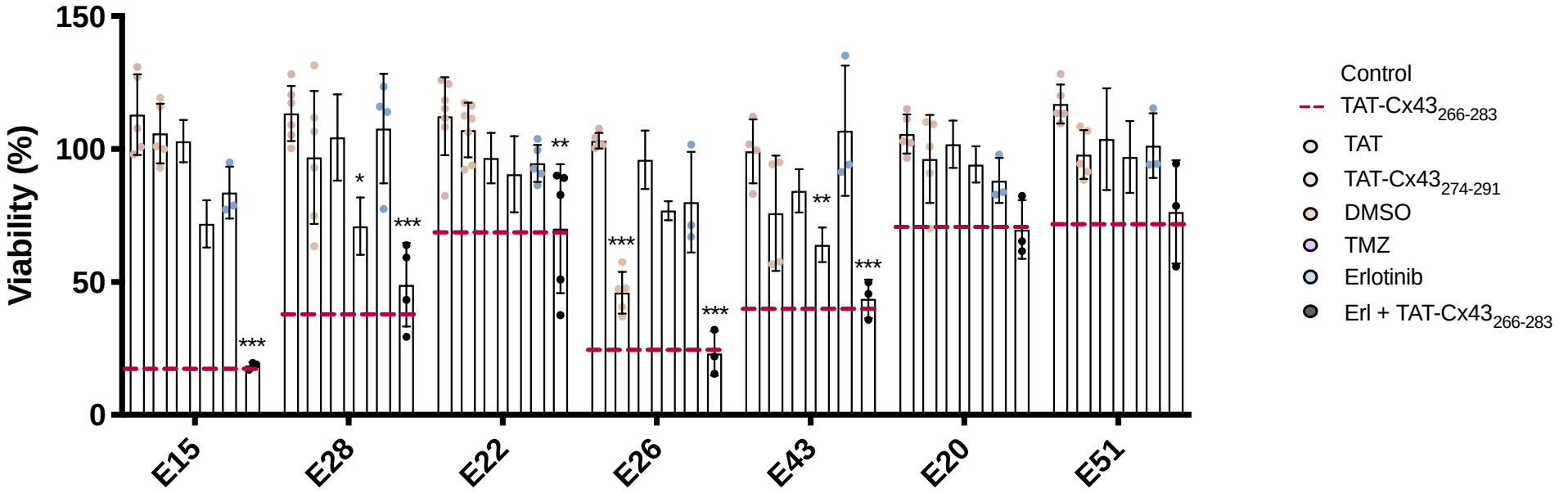
TAT-Cx43$_{266-283}$ targets human **TMZ- and erlotinib-resistant** GSCs

control TMZ Erlotinib TAT-Cx43





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The Product

d) Current status of development

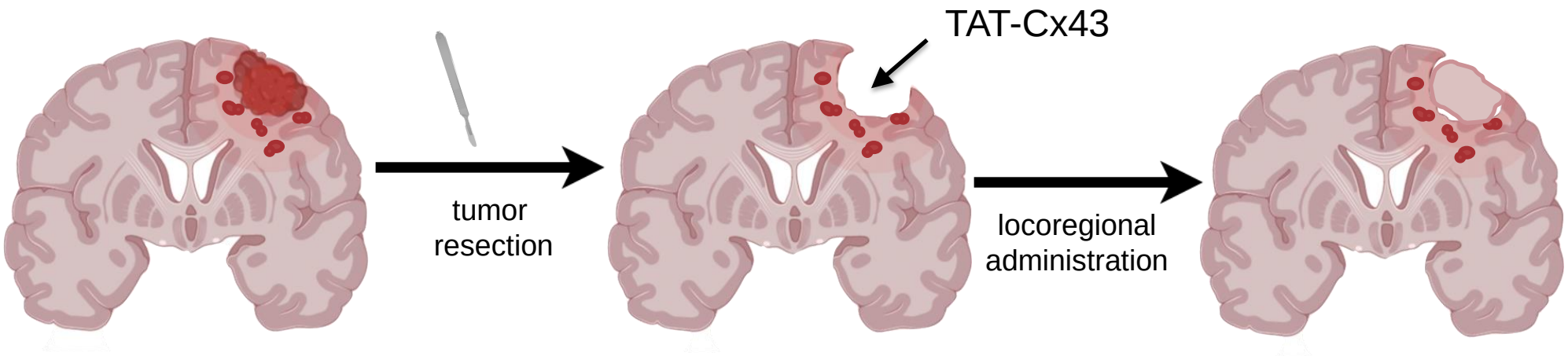
1. **No toxicity** in mouse
   Weight, behaviour, plasma analysis
   Anatomical pathology: brain, kidney, liver, heart, lung, thymus and spleen
   (Pathology Service, CIC - U. Salamanca)

2. Good **plasma stability** due to albumin binding

3. Positive results in **combination** with standard therapy (TMZ, resection and radiotherapy)

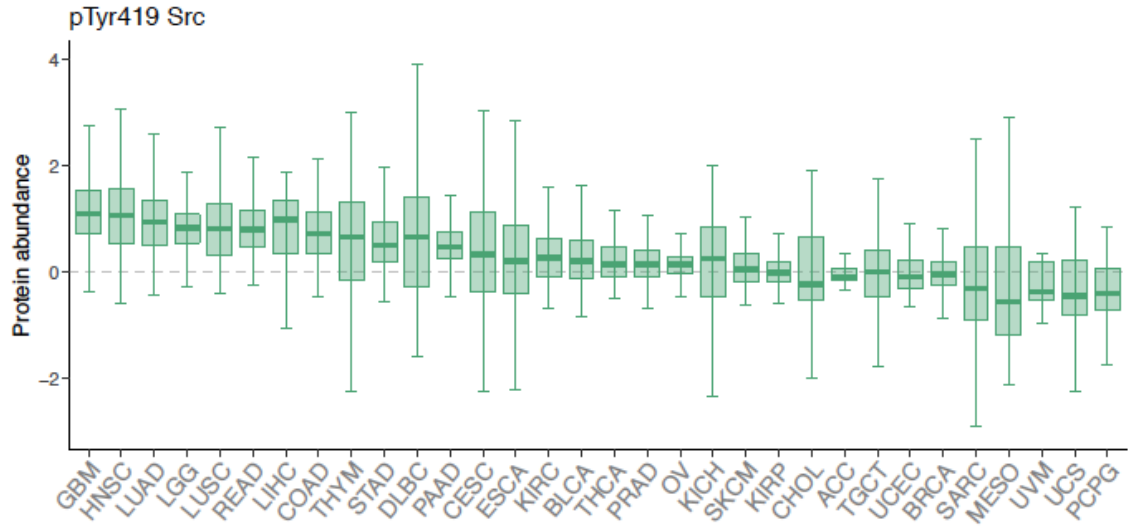
4. Exploring **other cancers** and pathologies in which Src is involved.

Combination with standard therapy (TMZ, resection and radiotherapy)



Safe and efficient
Improved survival

Exploring other cancers in which Src is involved



Increased Src activity

The Product

e) IPR protection

TAT-Cx43, a Src inhibitor peptide for glioblastoma therapy

PCTEP2023051210, WO2023139156A1

Positive International Preliminary Report on Patentability (**IPRP)**:

Novelty

Inventive step

Industrial applicability

Patent application in: USA, PCT-Europe, Canada, Australia, Japan, China and Mexico.

UNIQUE HOLDER: UNIVERSIDAD DE SALAMANCA

The Product

f) Pitfalls & Risks to be considered

1. **Funding** for good laboratory practices (**GLP**) toxicology and **FiH** studies is required
   No toxicity in mouse brain, kidney, liver, heart, lung, thymus and spleen

2. **PK/PD** studies to be completed.
   Good plasma stability due to albumin binding
   Administration: IP, IV, IC

Partnering Opportunities

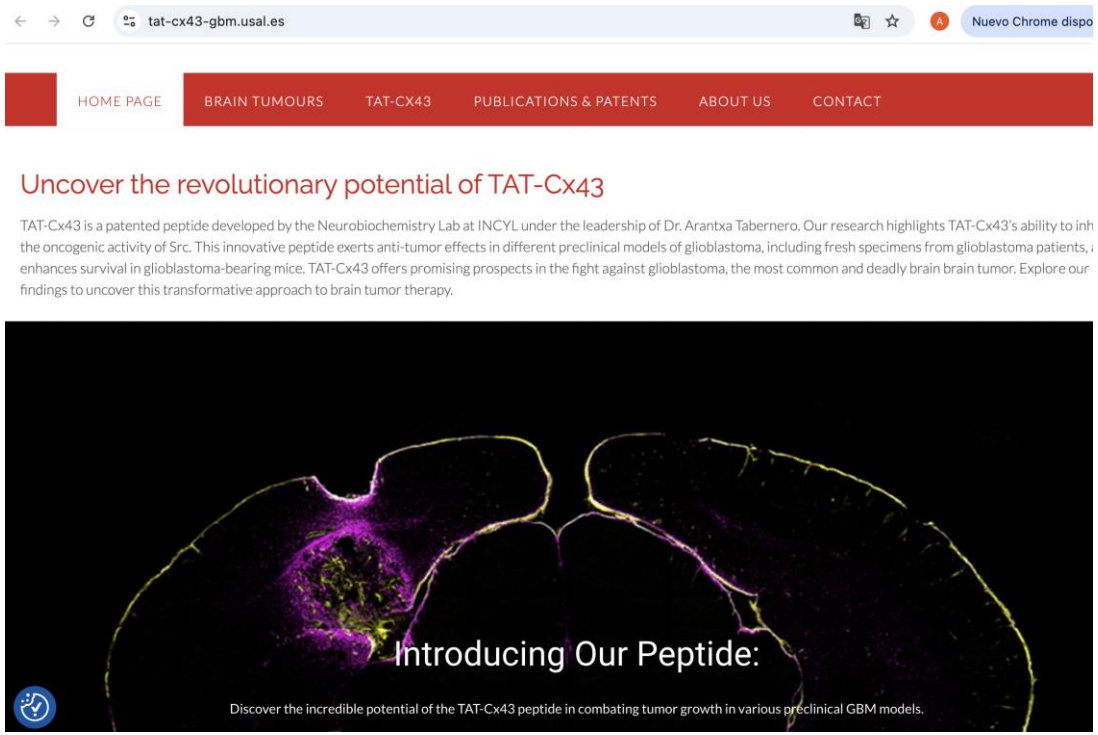
- A company willing to **license** the international patent PCTEP2023051210, WO2023139156A1

- We are open to explore **other collaborative** approaches

https://tat-cx43-gbm.usal.es/

Contact:
Arantxa Tabernero ataber@usal.es

Partnering Opportunities TAT-Cx43



https://tat-cx43-gbm.usal.es/

Contact: Arantxa Tabernero ataber@usal.es

1. **Efficacy** in preclinical models in vitro and **in vivo**
2. **No toxicity** in mouse
3. High **plasma stability**
4. **Blood-Brain Barrier** penetrance
5. **Biomarker** of TAT-Cx43 response: **EGFR** alterations
   - Highly frequent in GBMwt >50%
   - Commonly available in clinical diagnosis
   - Patient stratification for future clinical trial
6. TAT-Cx43 targets TMZ and erlotinib **resistant** cells