Role and therapeutic targeting of T-type calcium channels in glioblastoma

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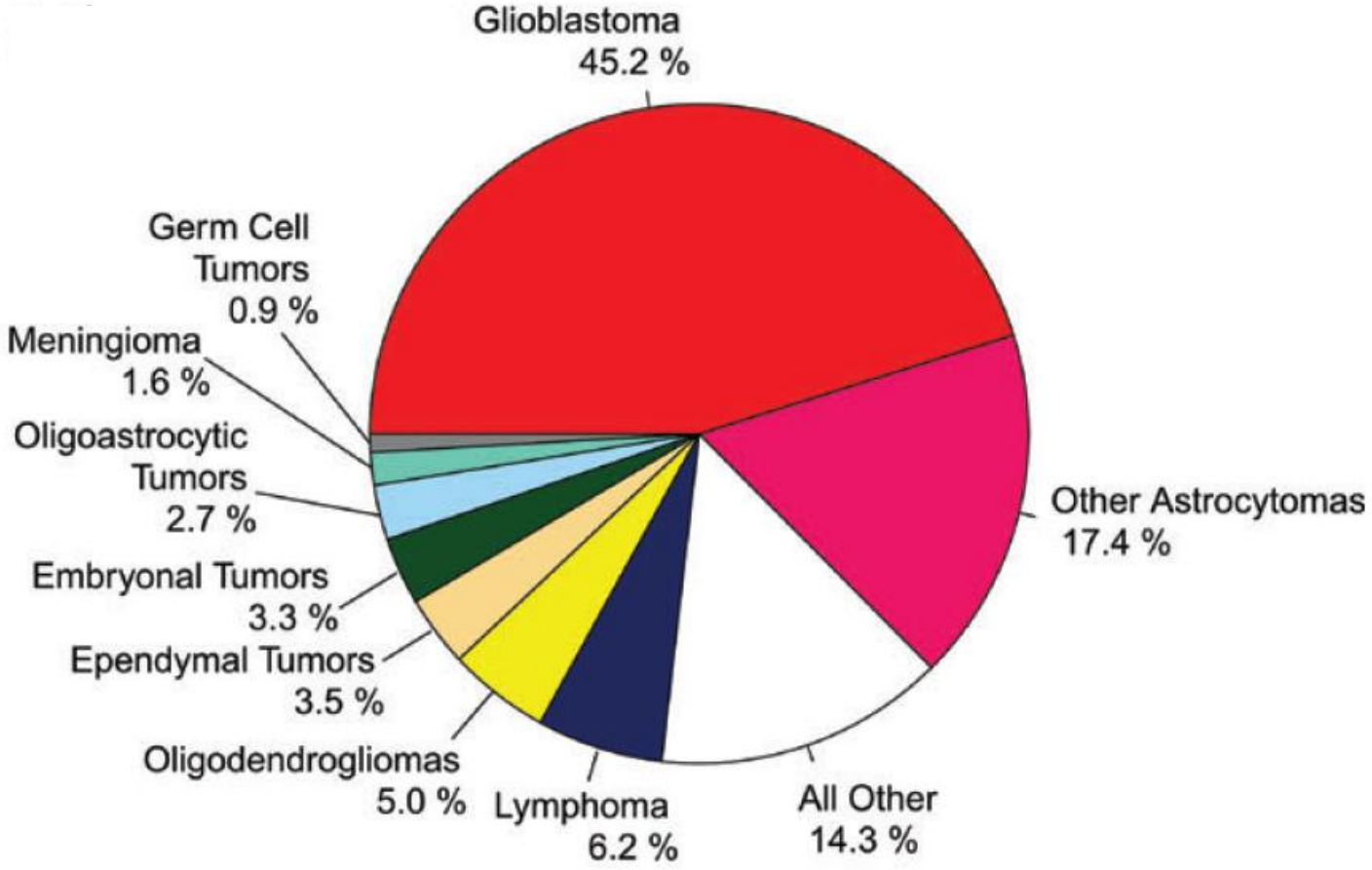
Brain Tumors in the World and in the USA

- The worldwide incidence rate of primary malignant CNS tumors is ~3.5 per 100,000. This represents an estimated ~ 250,000 individuals (~26,000 in the USA).

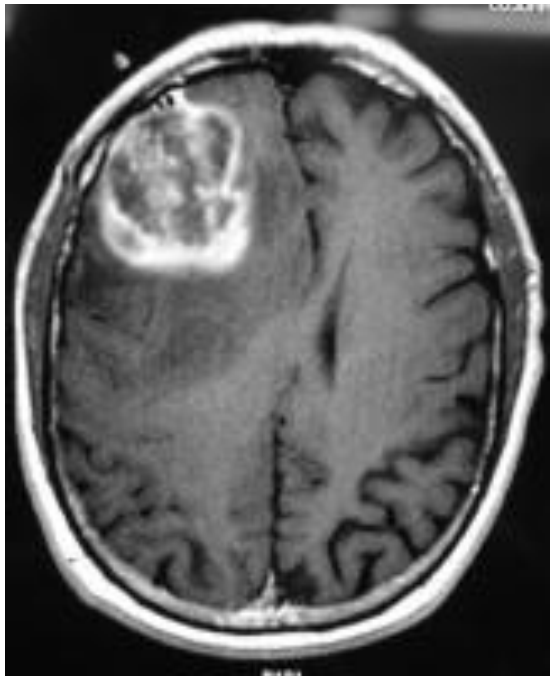
- ~ 200,000 people die from brain tumors worldwide (~18,000 in the USA).

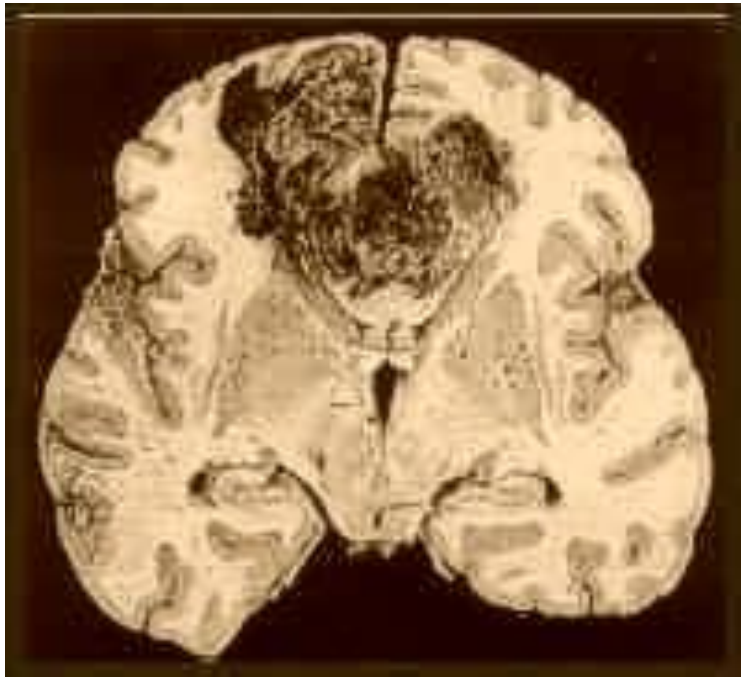
Distribution of Malignant Primary Brain and CNS Tumors by Histology



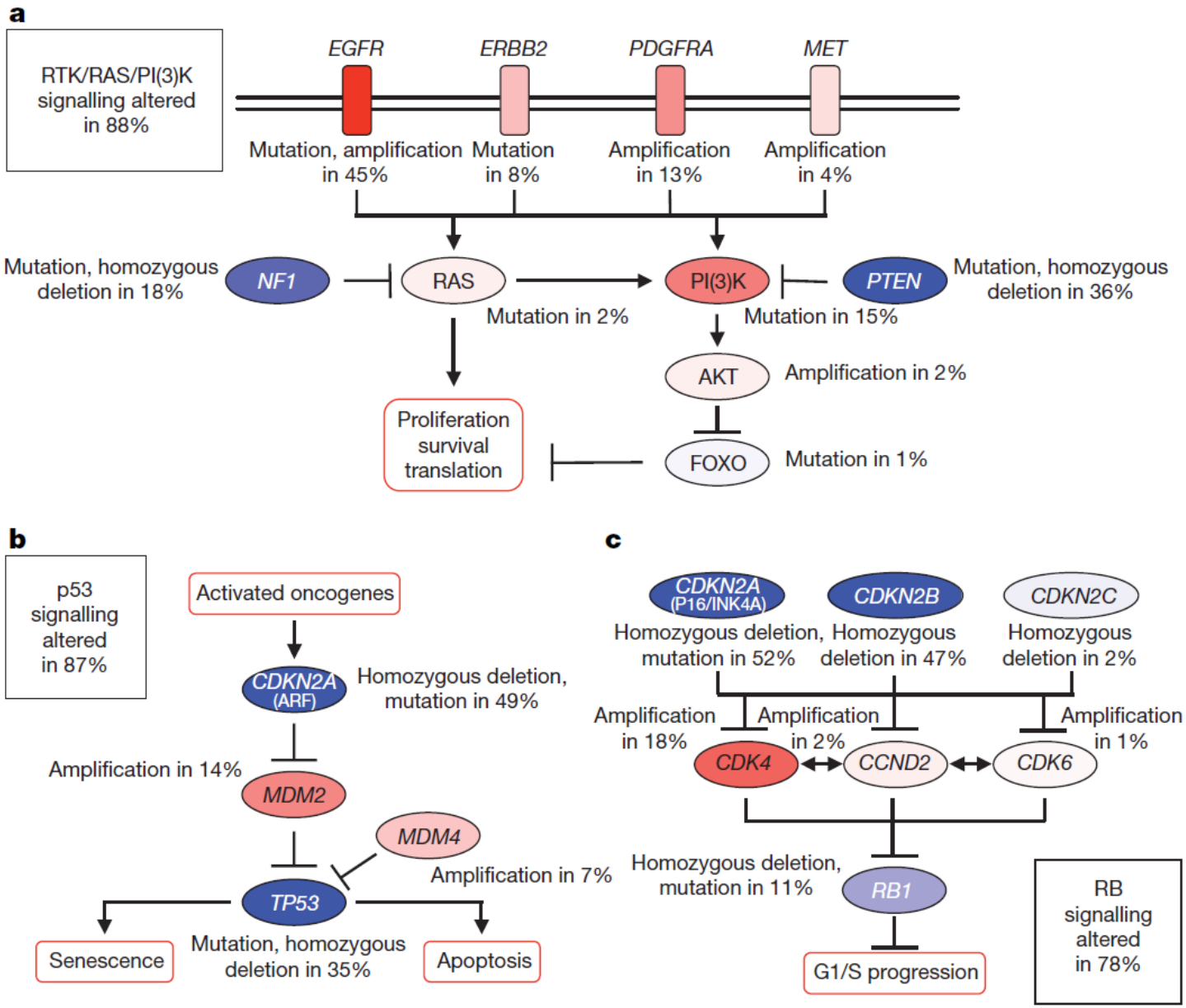
Glioblastoma (GBM)

- Infiltrative fast growing tumor
- Average survival after diagnosis ~ 15 months





Genetic alterations in glioblastoma (TCGA)

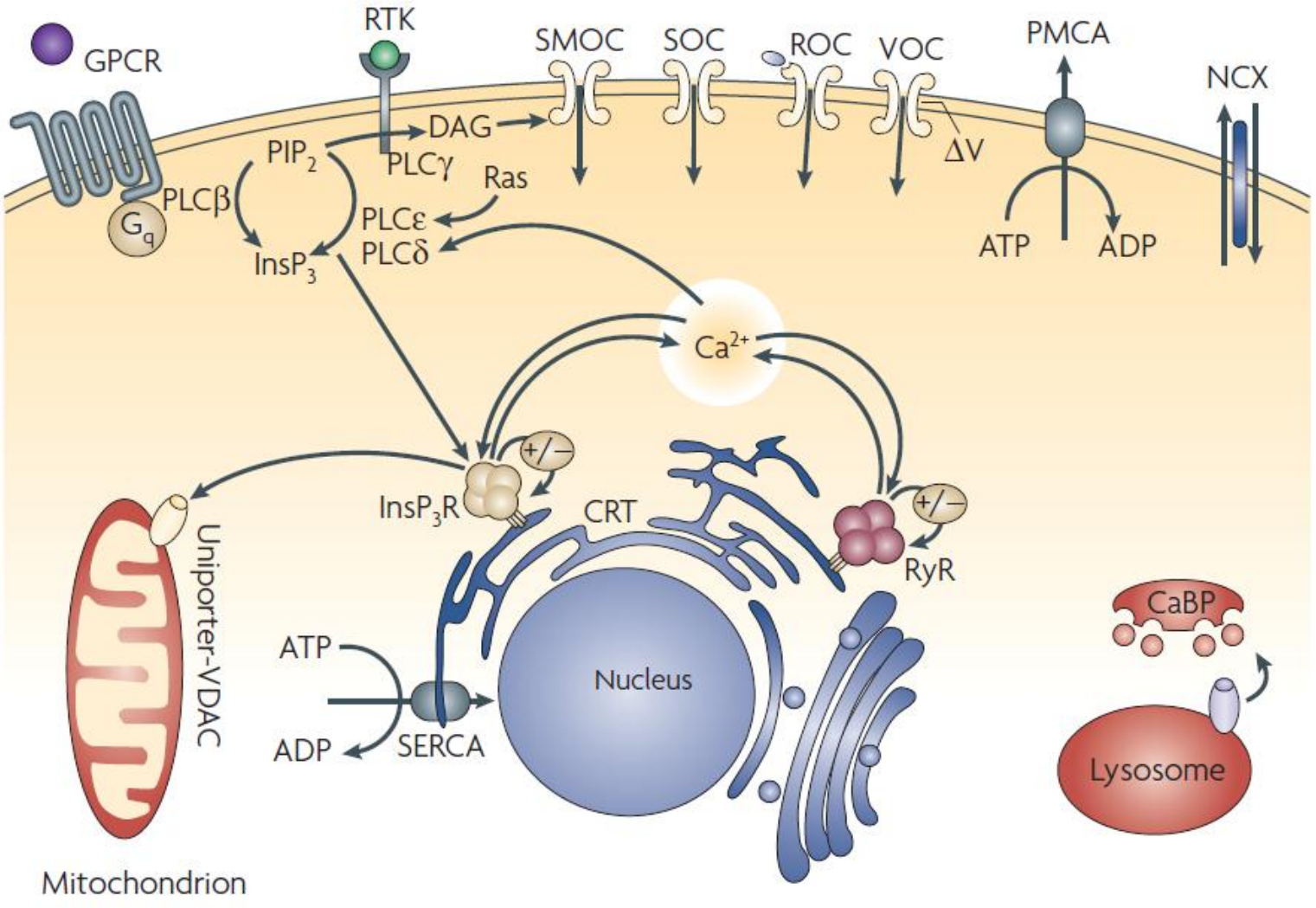


TCGA, Nature, 2008

Why is GBM so difficult to treat?

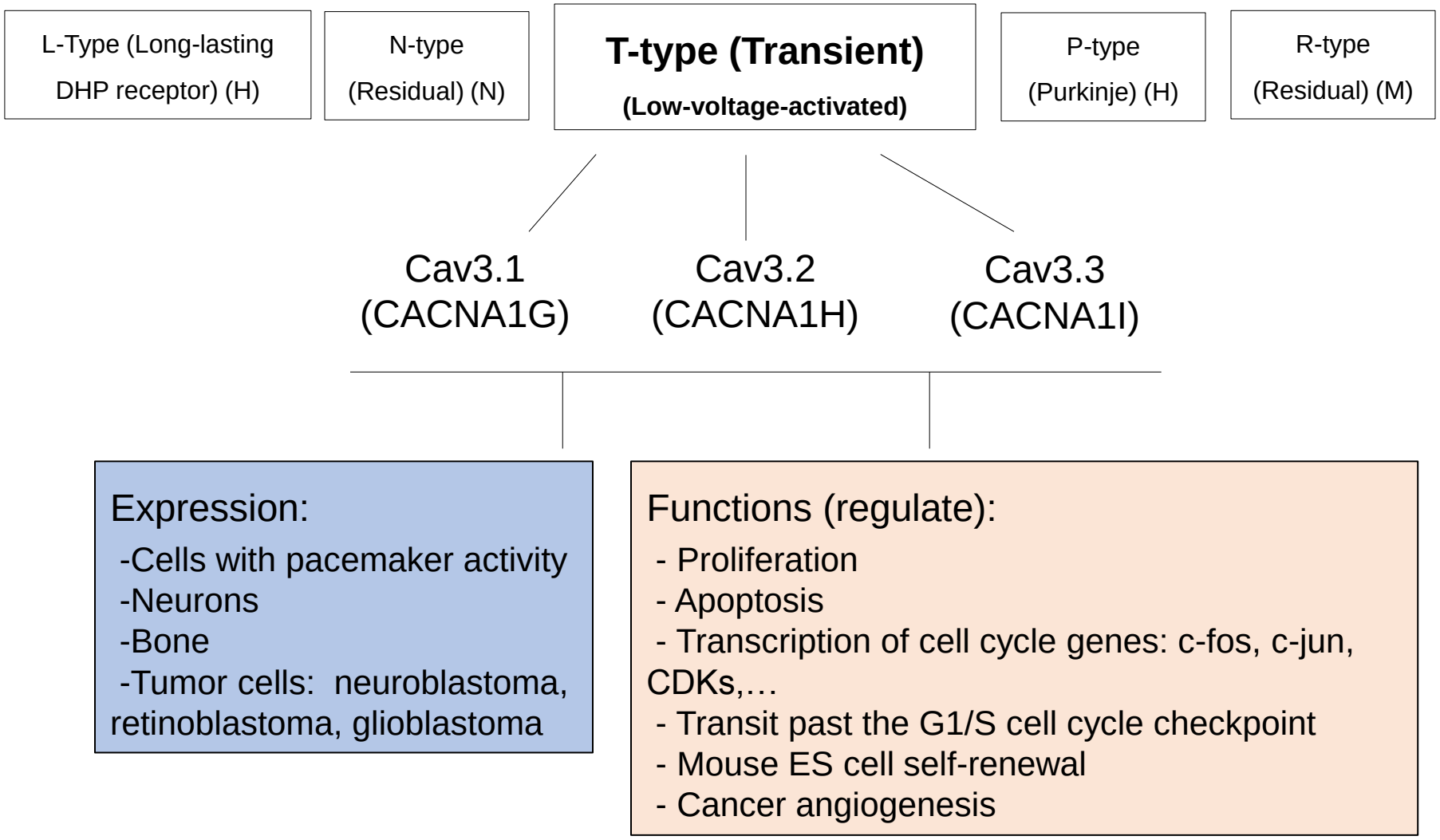
- Blood-brain barrier
- Invades critical brain structures
- Resistance to DNA-damaging agents, i.e. radiation and chemotherapy
  - GBM stem cells (GSCs)
- Genetic heterogeneity and complexity

The Calcium Signalsome

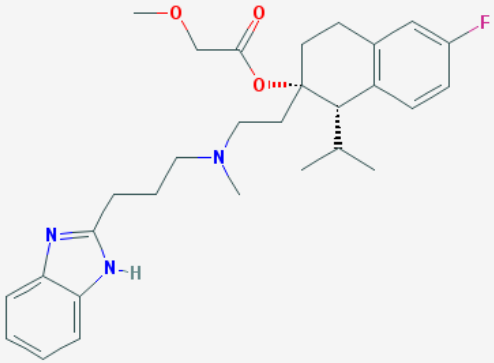


From Roderick and Cook, Nature Reviews Cancer

Voltage Gated Calcium Channels



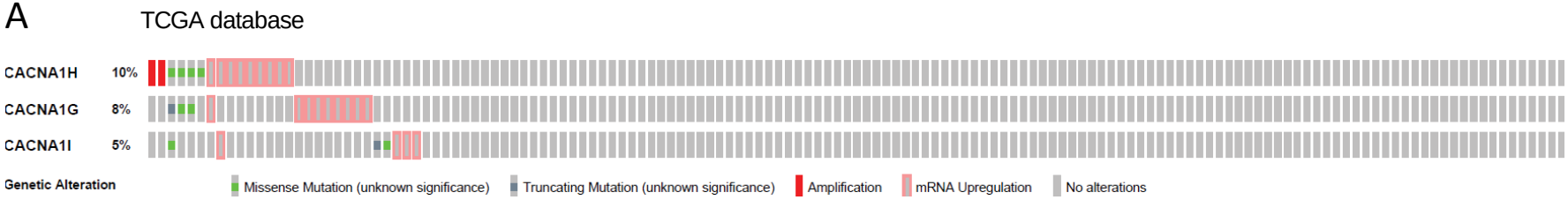
Mibefradil: a T-type (and L-type) calcium channel blocker



Chemical Names:	Mibefradil; 116644-53-2; Posicor; Mibefradil [INN:BAN]; Mibefradil (INN); CHEMBL45816;
Molecular Formula:	$C_{29}H_{38}FN_3O_3$
Molecular Weight:	495.628723 g/mol
FDA proved drug:	by Roche
Treatment :	Hypertension, chronic angina pectoris
Concentration:	T-type block: 1-10 µM, L-type block: 100-300 µM fold as of T-type
Side effects:	Drug-drug interactions leading to irregular heart rhythms

T-Type Calcium Channels (TTCC) are highly expressed in GBM tumors and expression correlates with poor patient survival.

A



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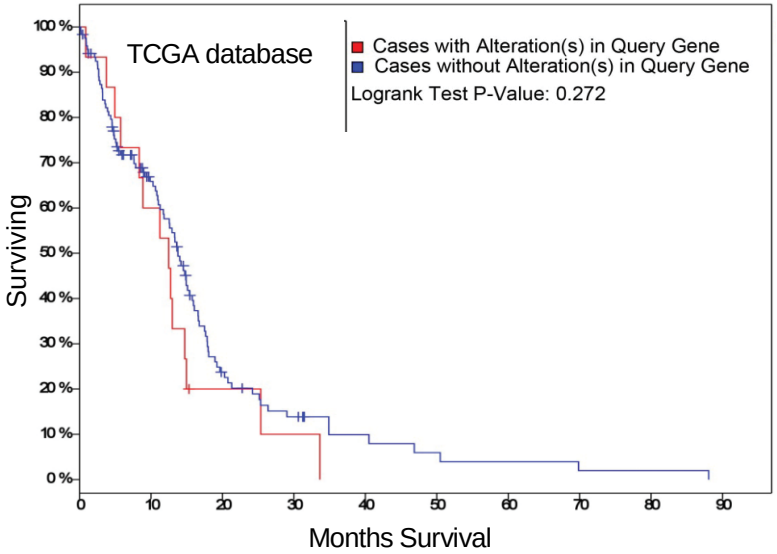

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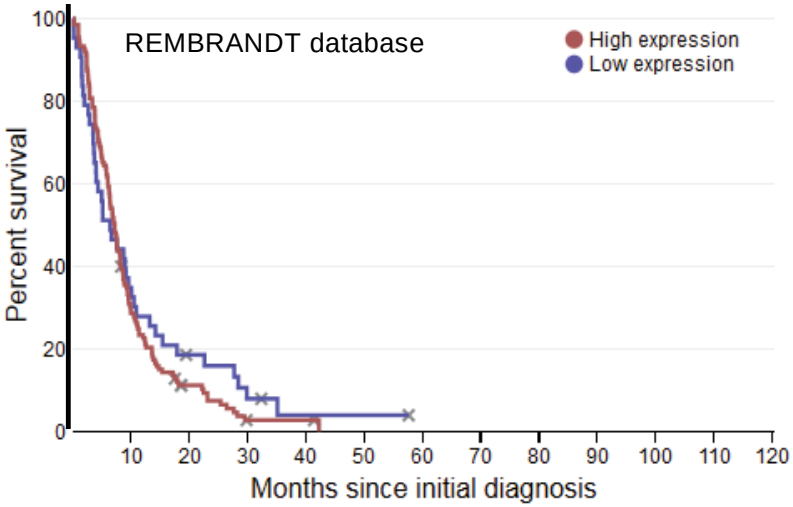
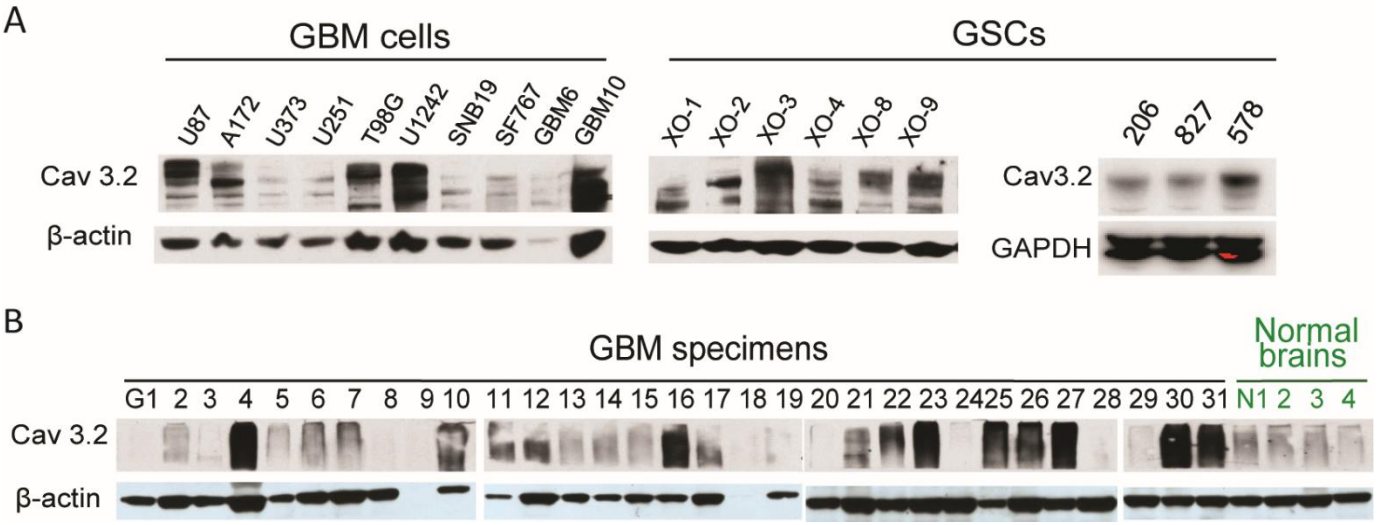
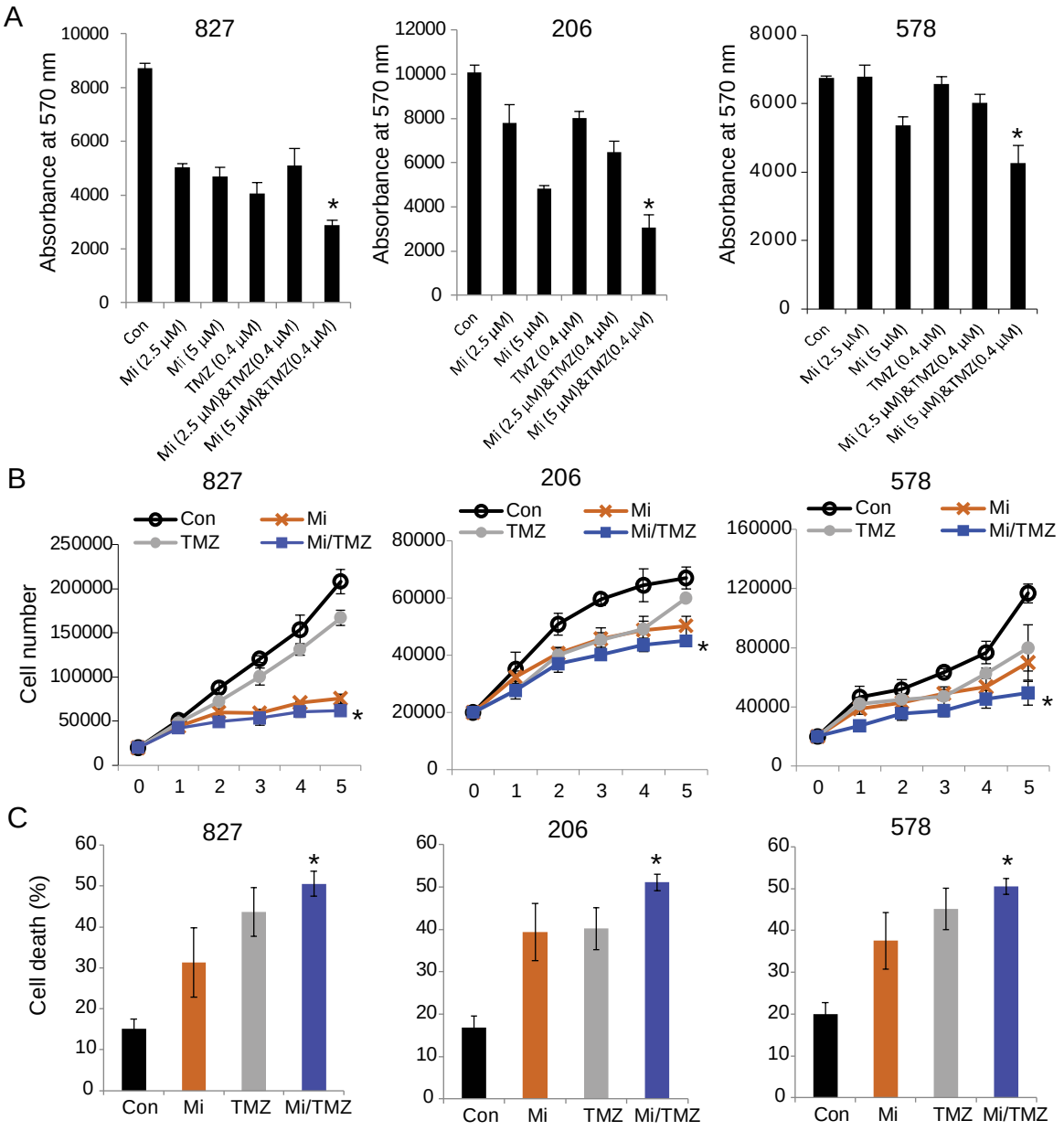


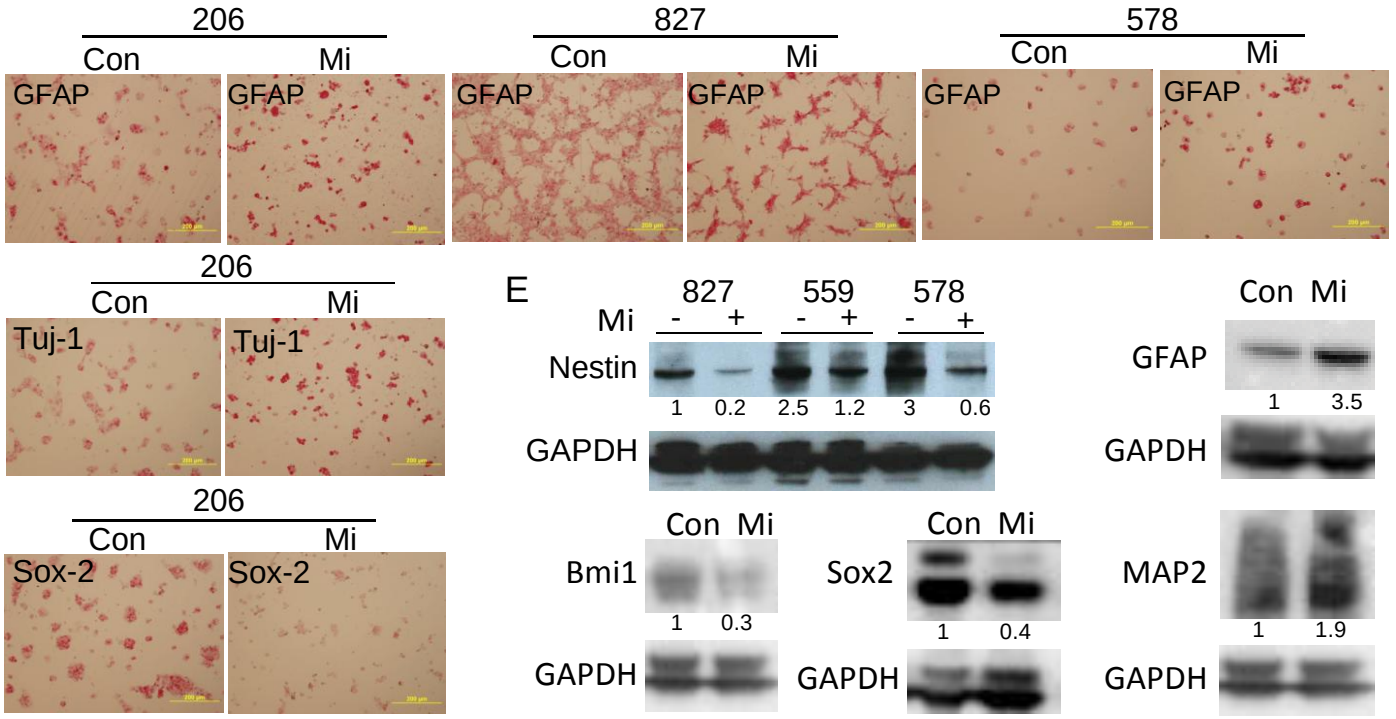
TTCC Cav3.2 are expressed in GBM cells, stem cells and tumors



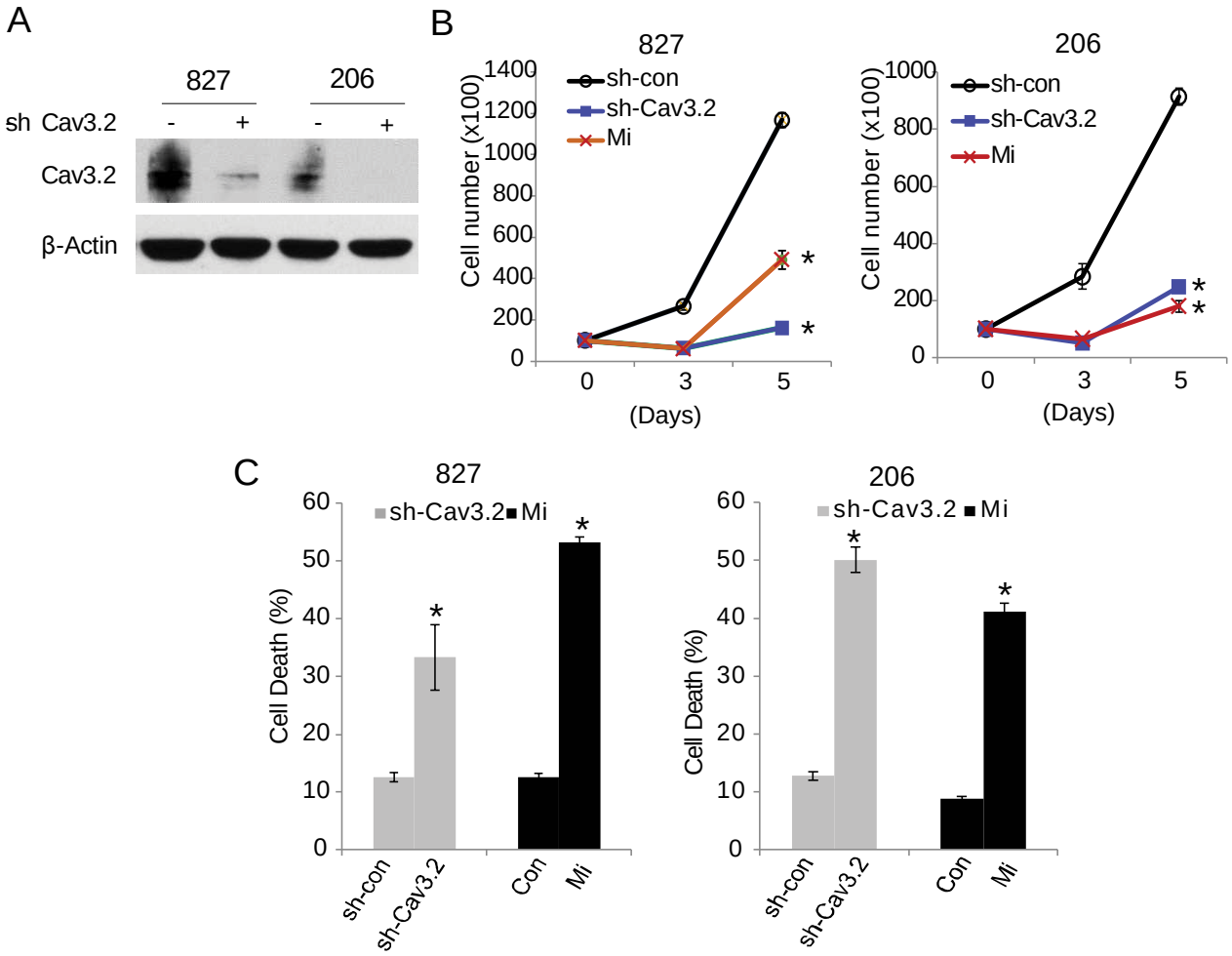
TTCC blockage with mibefradil inhibits GBM cell proliferation and survival



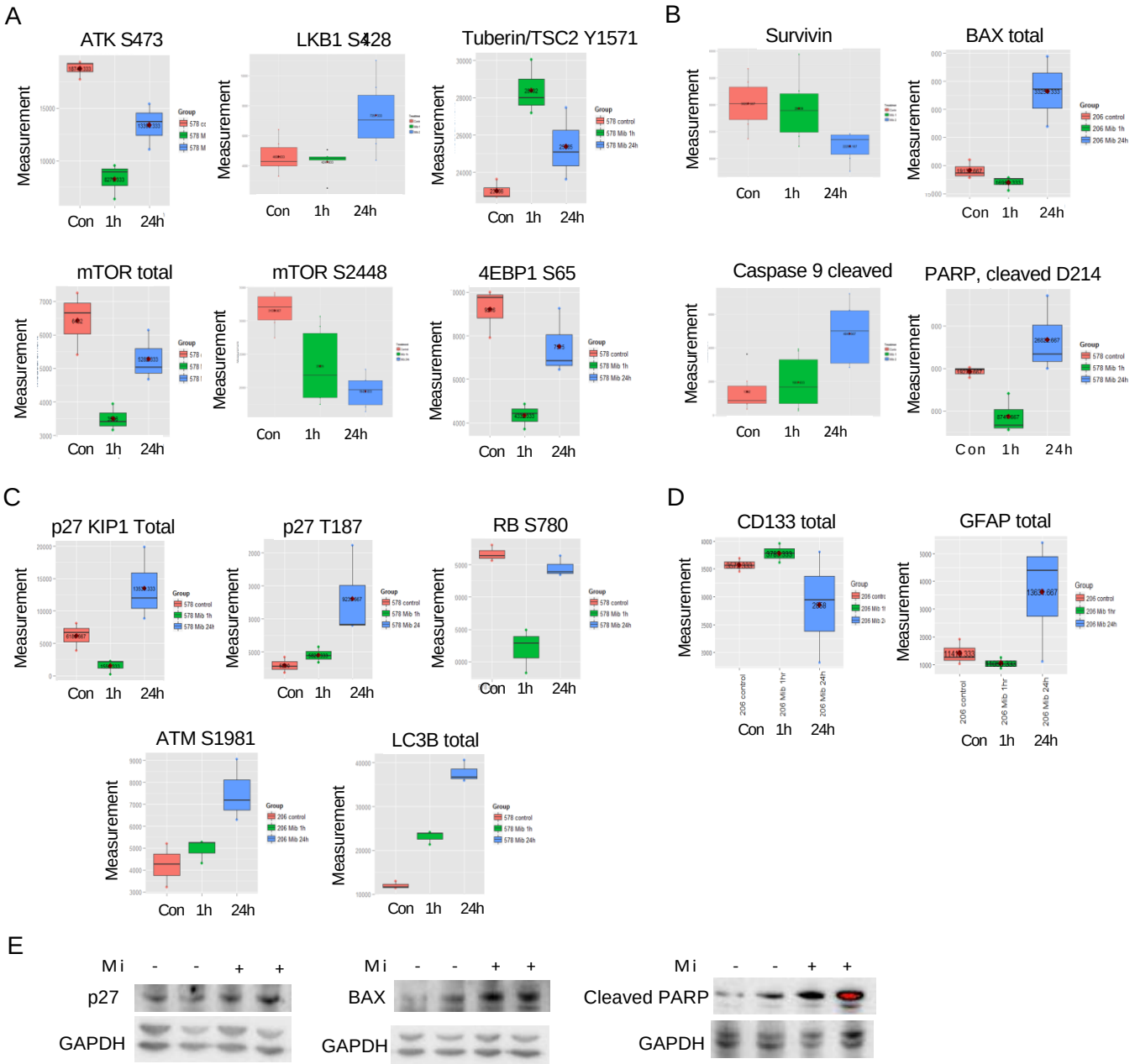
TTCC blockage induces GBM stem cell differentiation



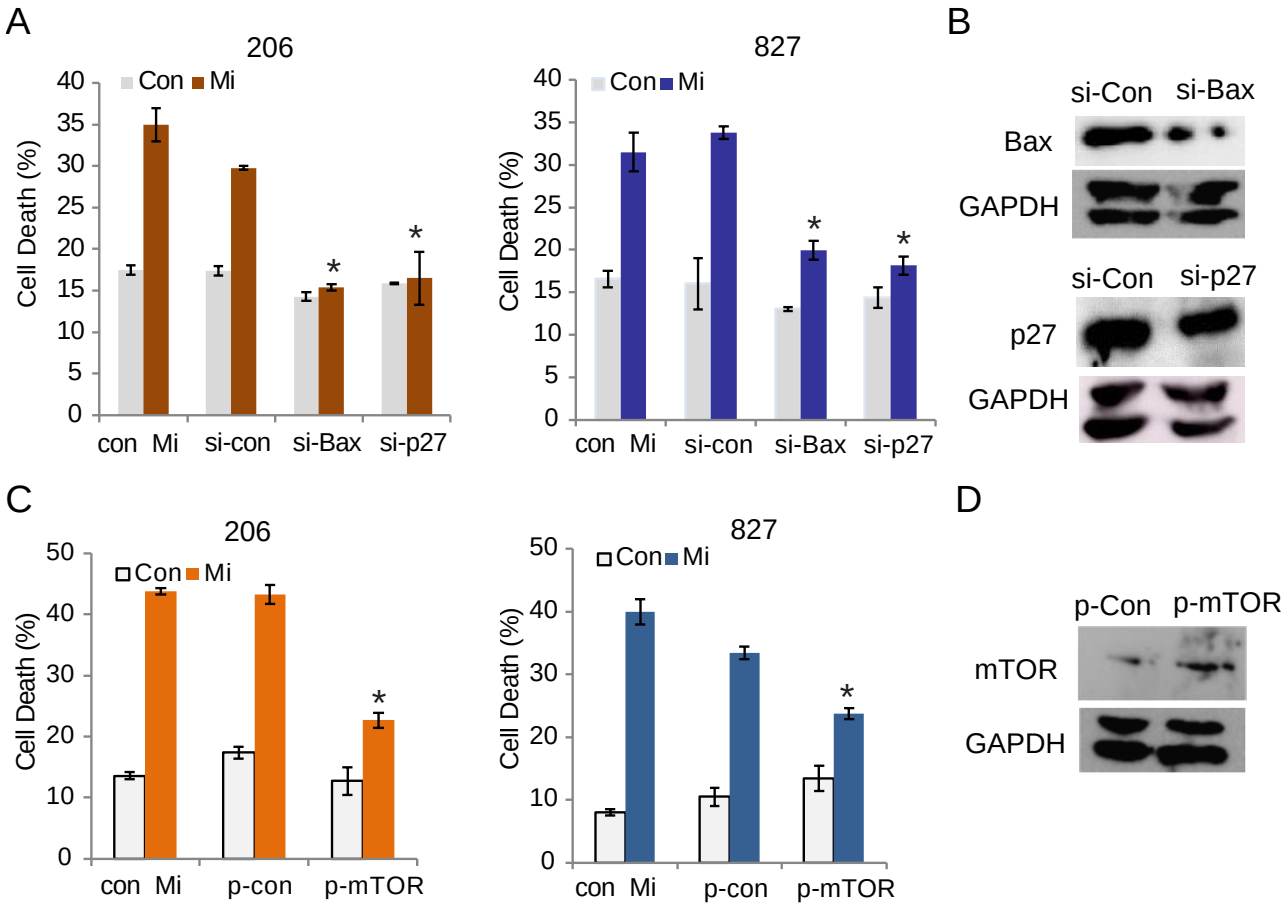
TTCC expression silencing inhibits GBM cell proliferation and survival



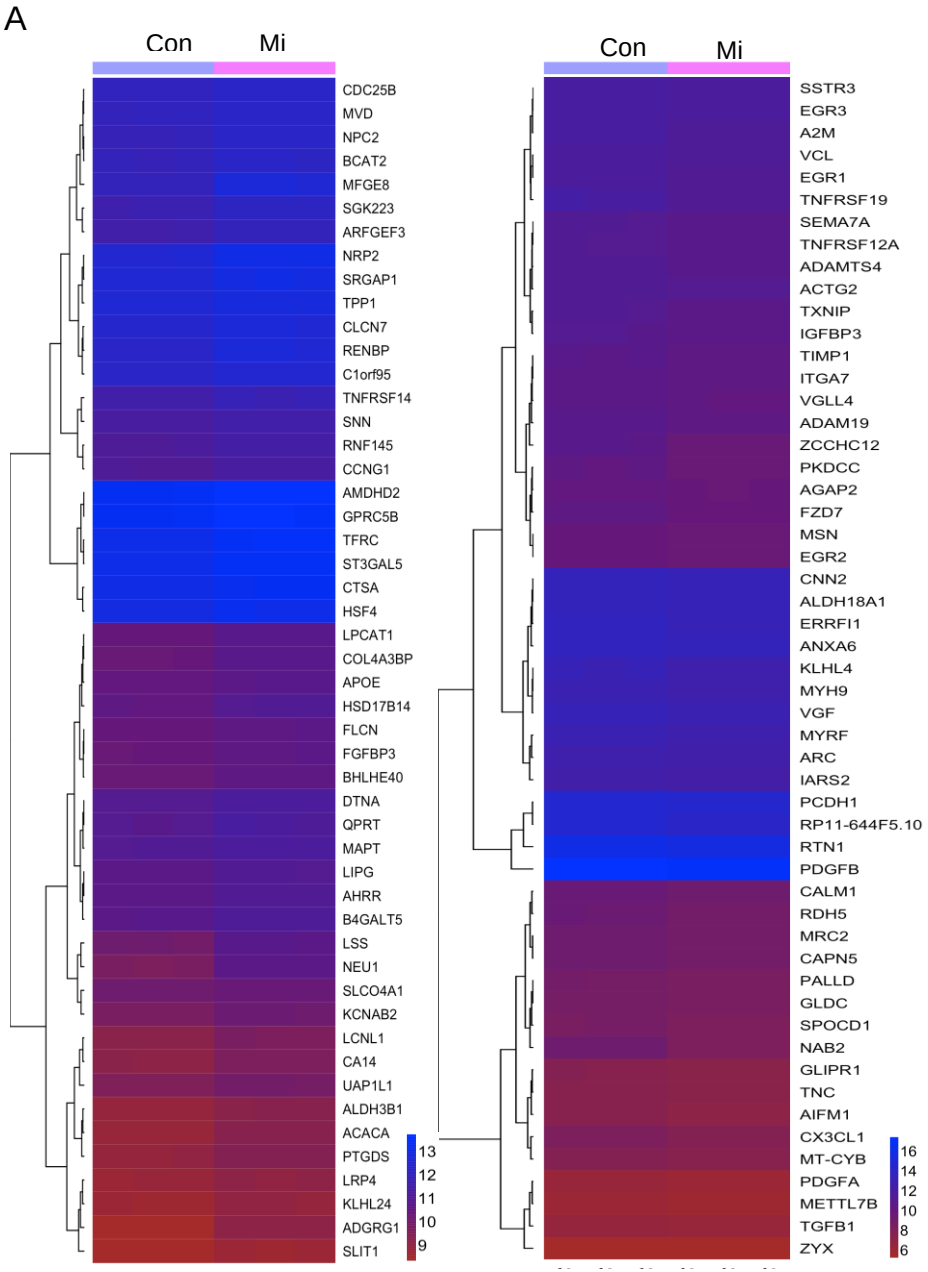
TTCC blockage alters multiple cancer signaling molecules and pathways



Bax, p27, and mTOR partially mediate the anti-tumor effects of TTCC blockage

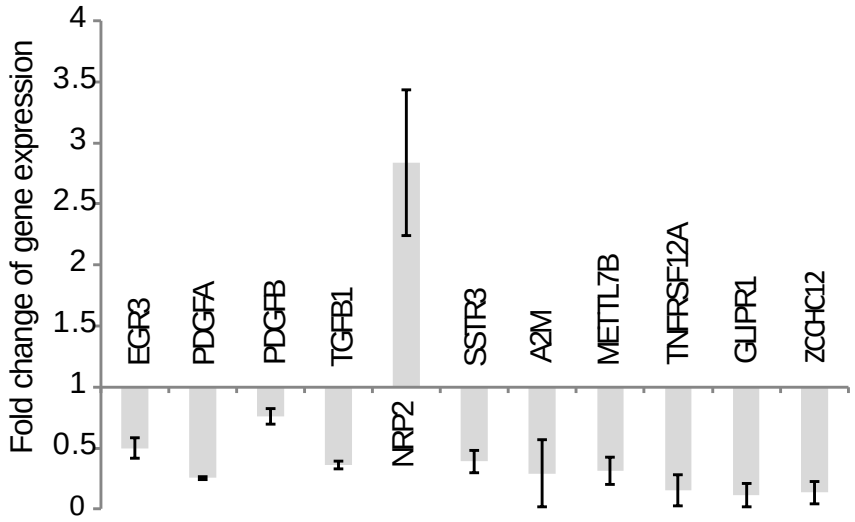


TTCC blockage alters the transcription of oncogenes and tumor suppressors in GBM

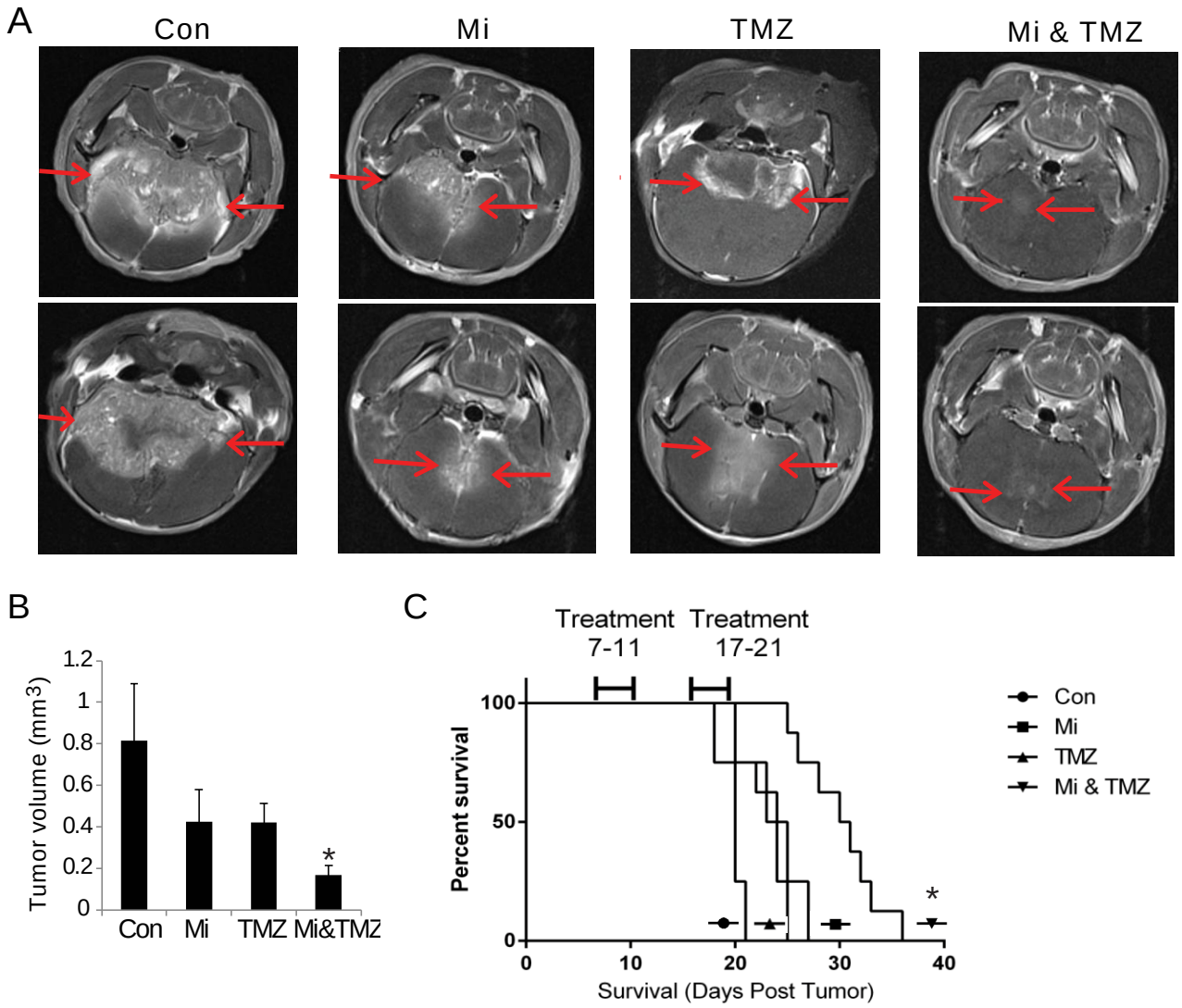


TTCC blockage alters the transcription of oncogenes and tumor suppressors in GBM

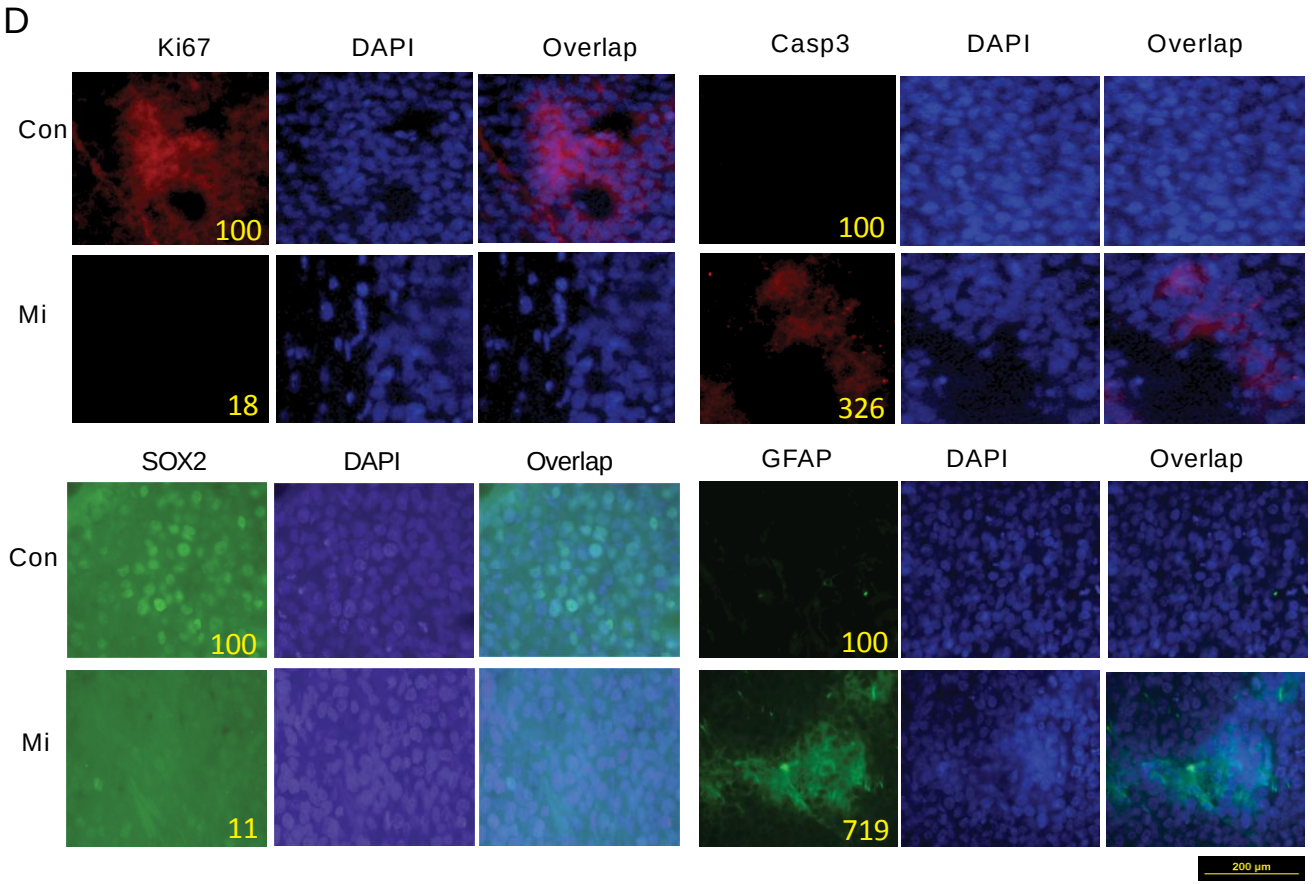
B



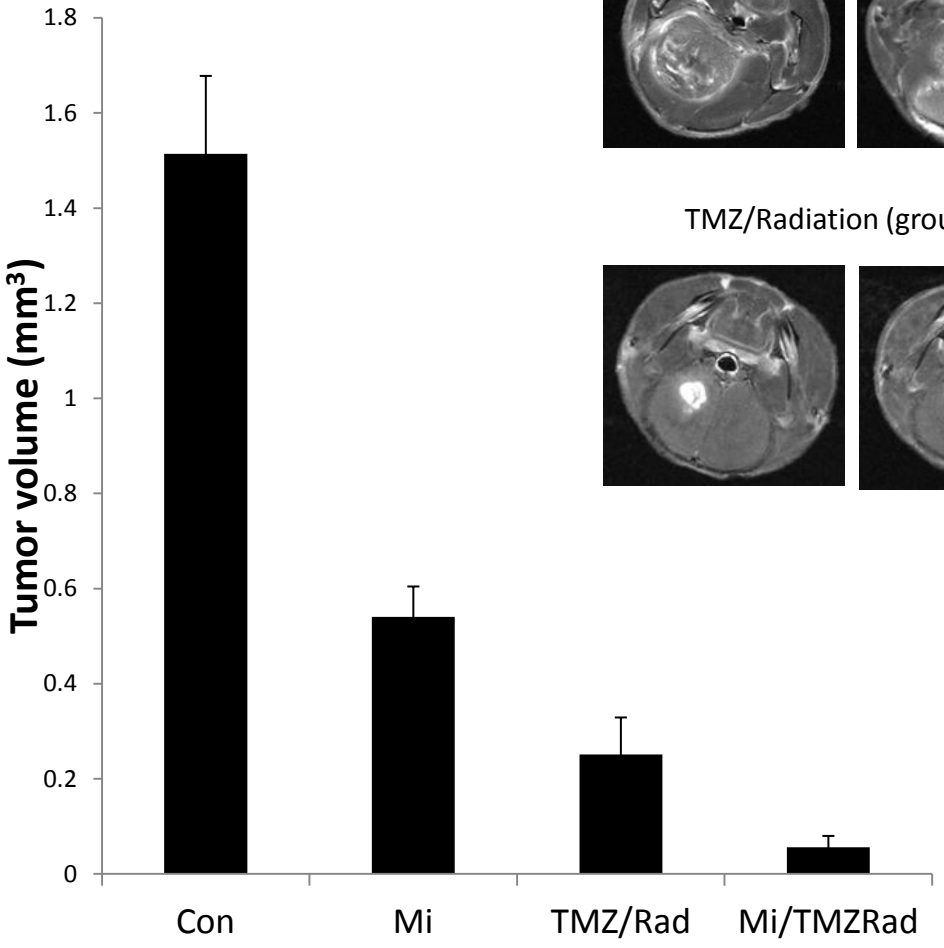
Mibefradil synergizes with TMZ to inhibit GBM xenograft growth and prolong survival



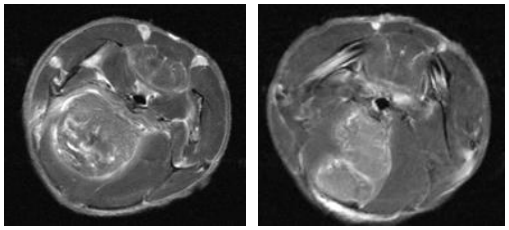
Mibefradil inhibits in vivo GBM cell proliferation and survival



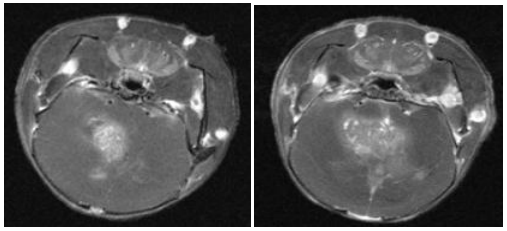
Mibefradil synergizes with TMZ and radiation to inhibit GBM xenograft growth



Control (group1)

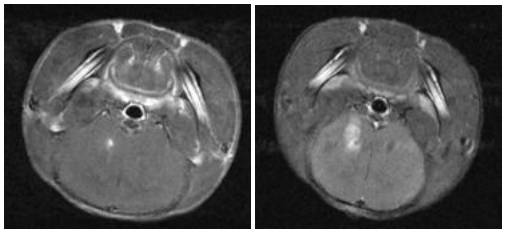


Mi (group 2)

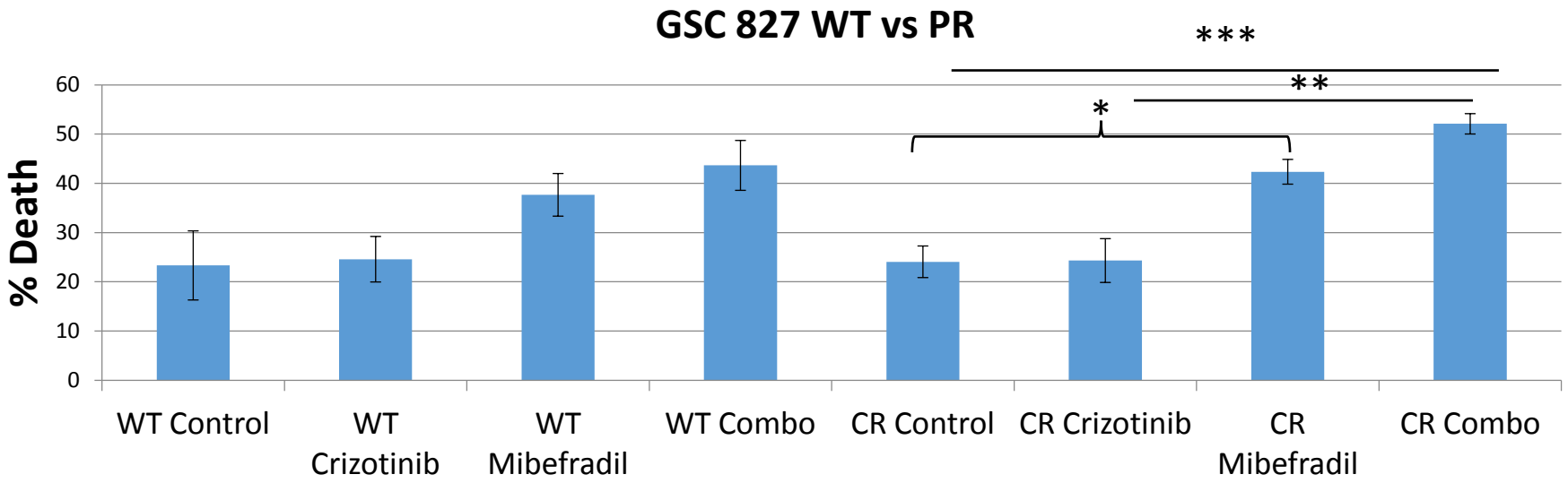


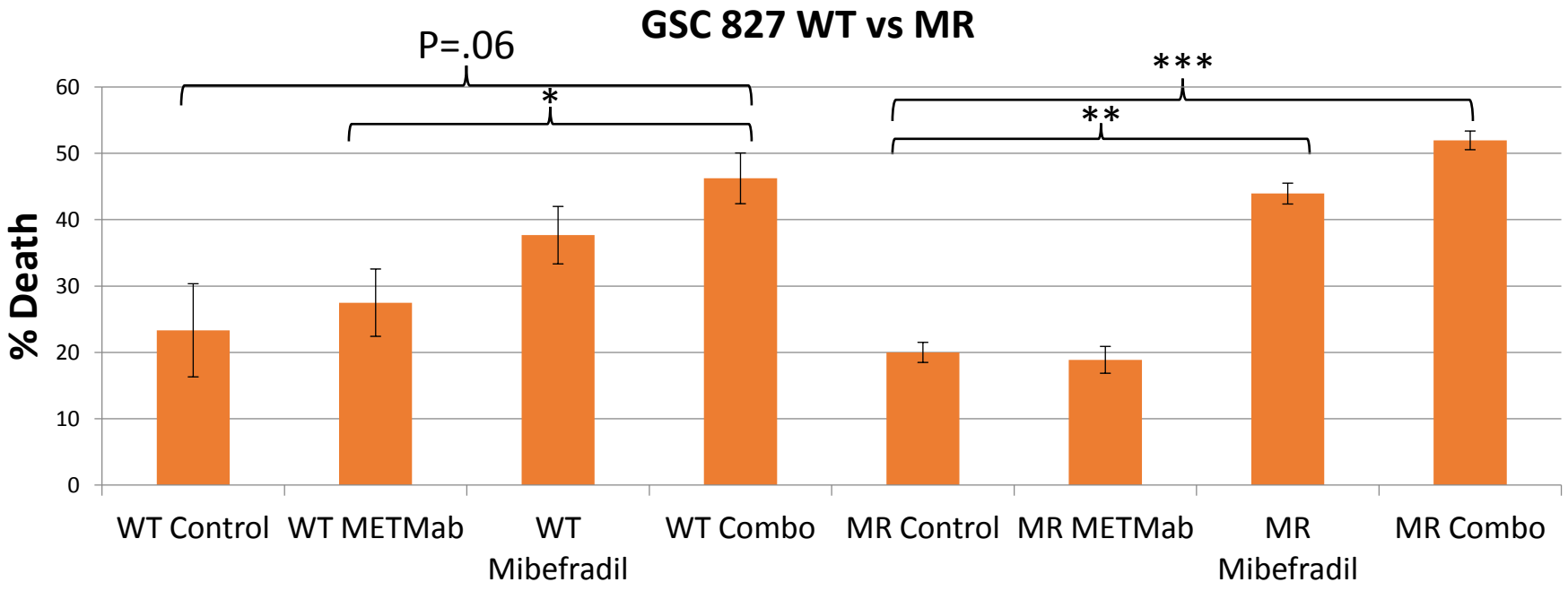
TMZ/Radiation (group 3)

Mi/TMZ/Radiation (group 4)



TTCC blockage reverses resistance to RTK-targeted therapies





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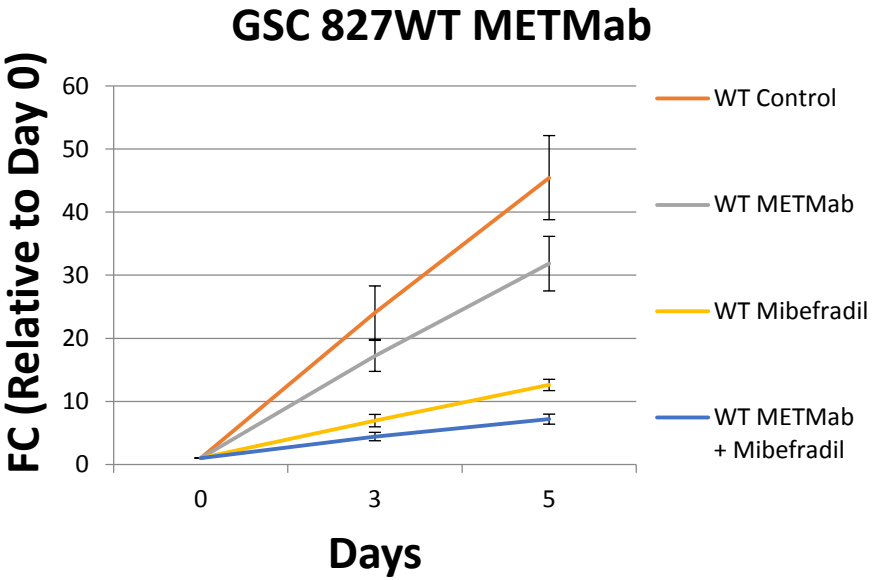

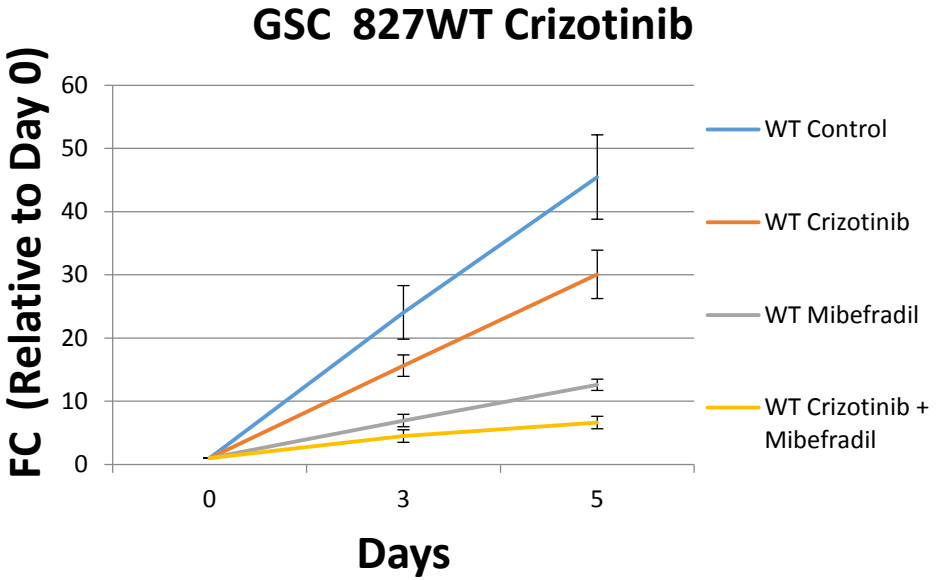

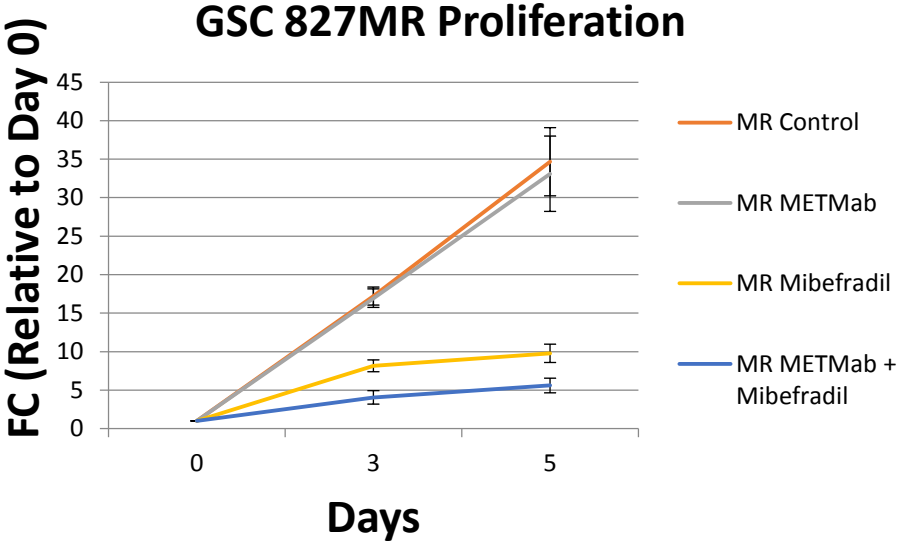

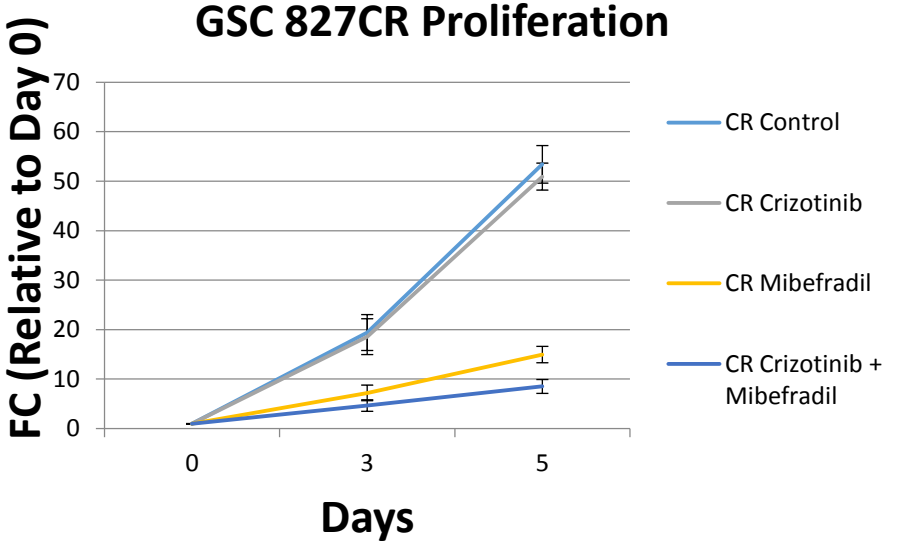

Conclusions

- T-Type Calcium Channels (TCC) are overexpressed in GBM cells, stem cells and human tumors
- TTCC blockage inhibits GBM cell growth and survival and induces GSC differentiation
- Mibefradil synergizes with TMZ and radiation to inhibit tumor growth in vivo
- TTCC blockage alters GBM cell signaling
- TTCC blockage alters the GBM transcriptome
- TTCC blockage reverses resistance to RTK targeted therapies
- TTCC blockage with mibefradil is a promising approach for GBM therapy

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