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A Mathematical model for BMP4 induced differentiation therapy in combination with radiotherapy in glioblastoma

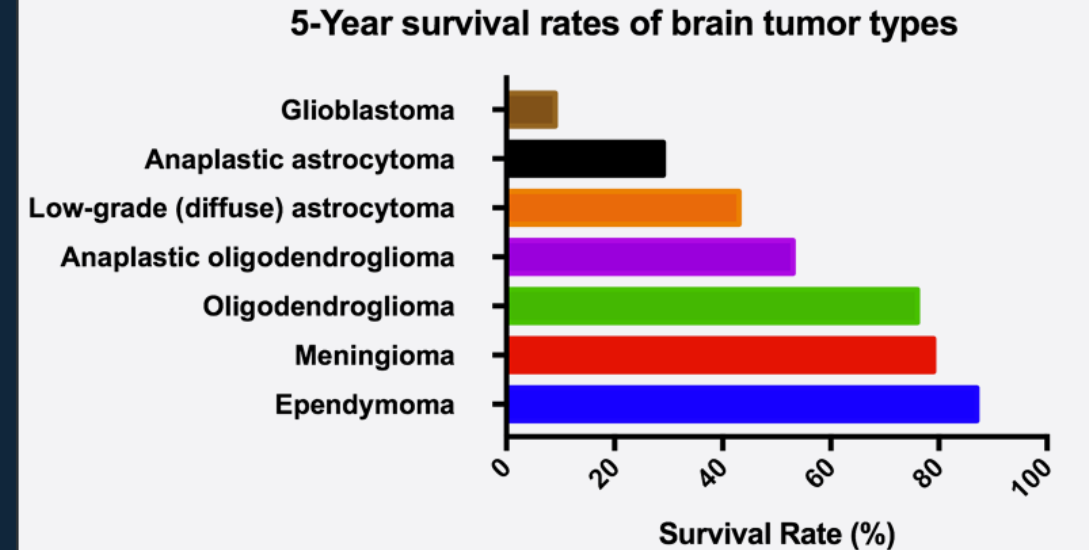
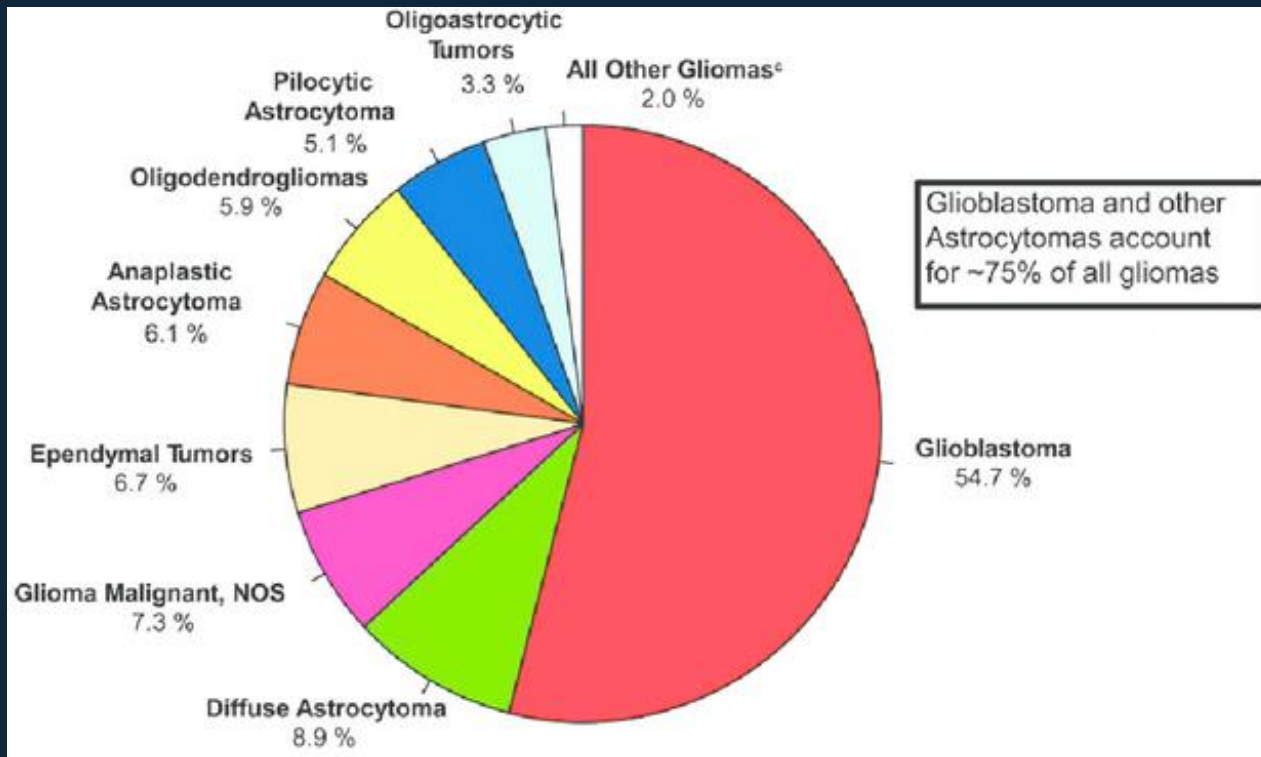
Data-driven mechanistic models of complex
biomedical systems

Nicholas Harbour, Markus Owen, Matthew Hubbard, Lee Curtin, Kristin Swanson

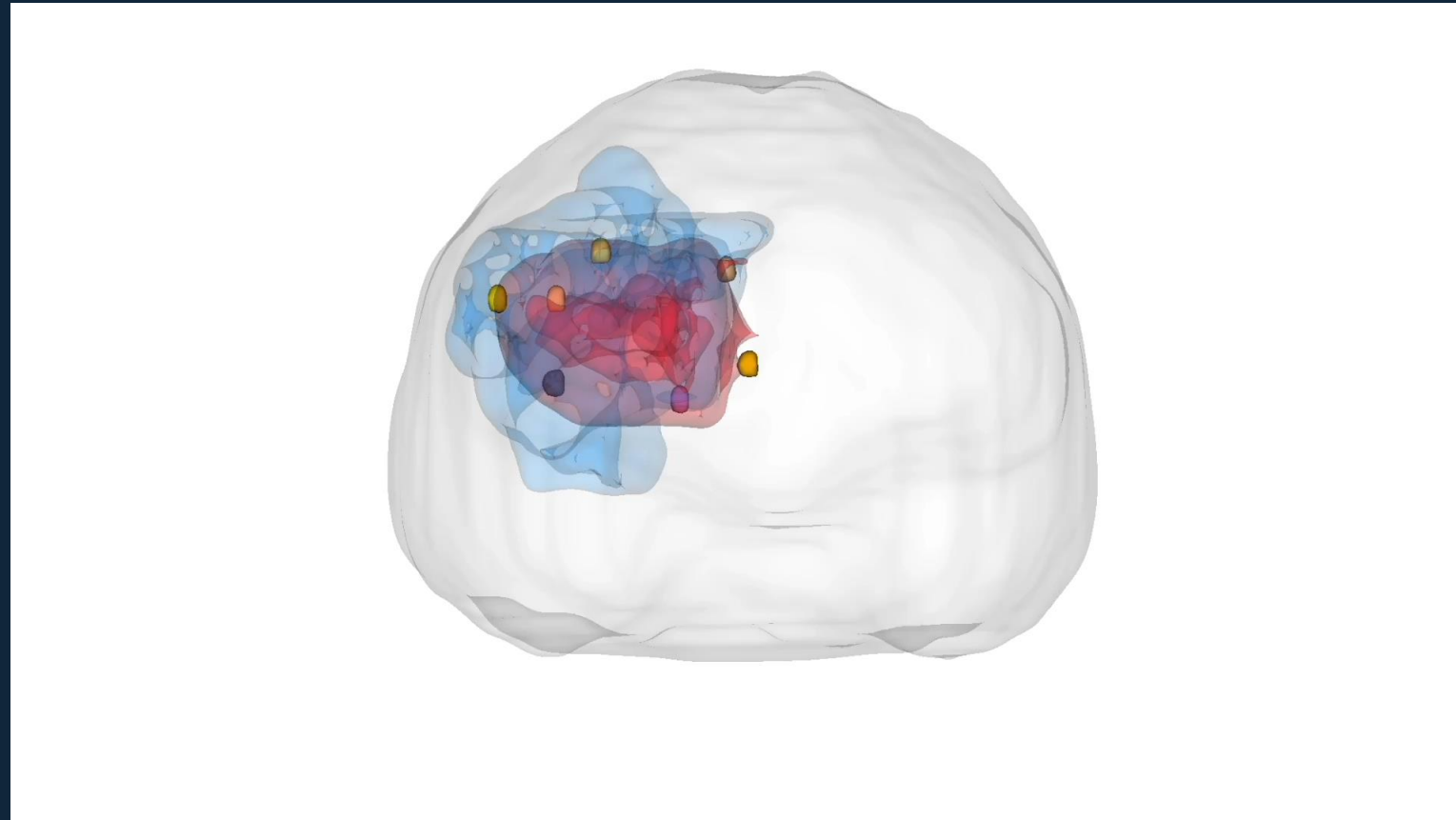
Glioblastoma (GBM)

GBM is the most common primary malignant brain tumour (USA 2007-2011)

GBM has 5-year survival rate of only 5%

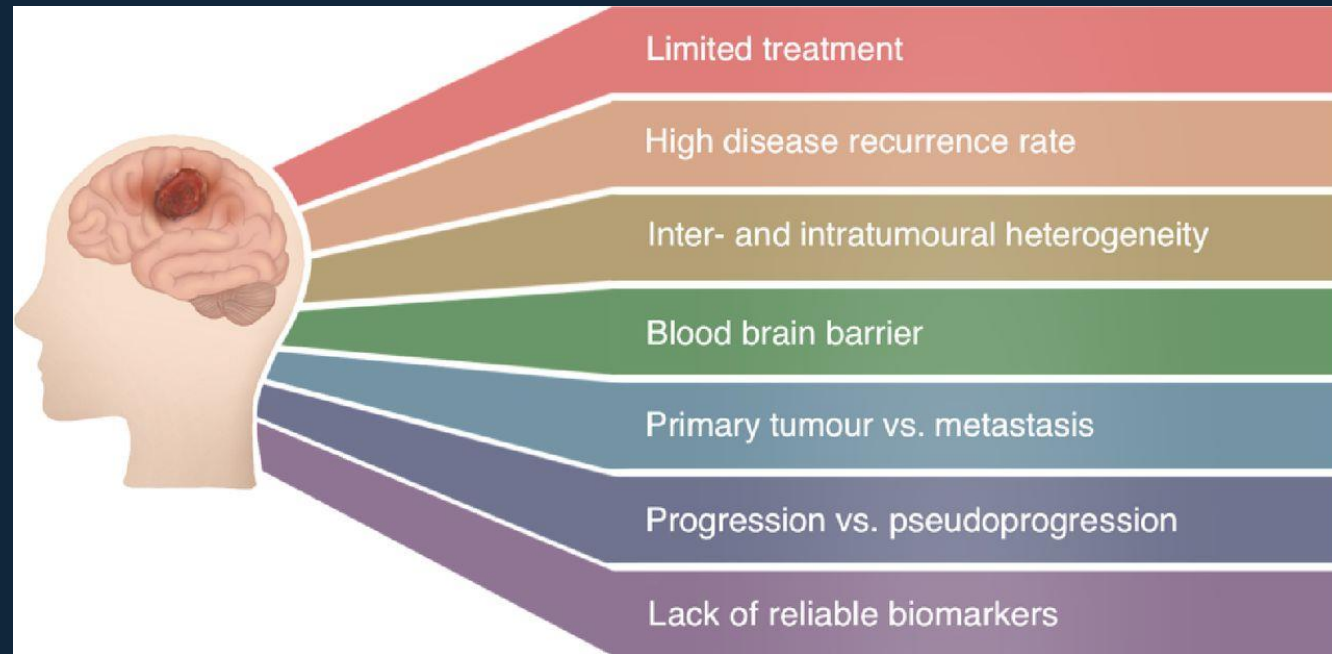
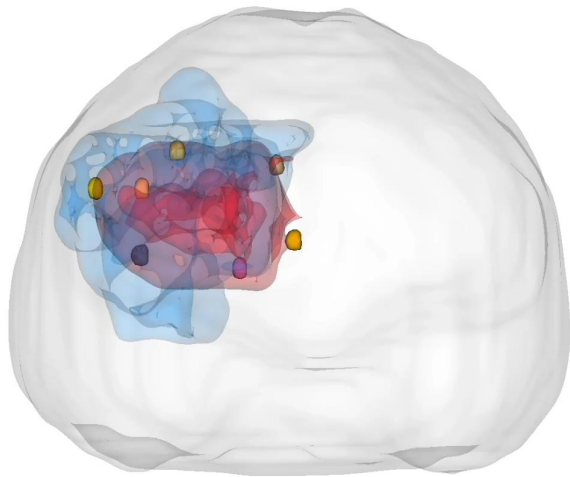


Current standard of care in GBM

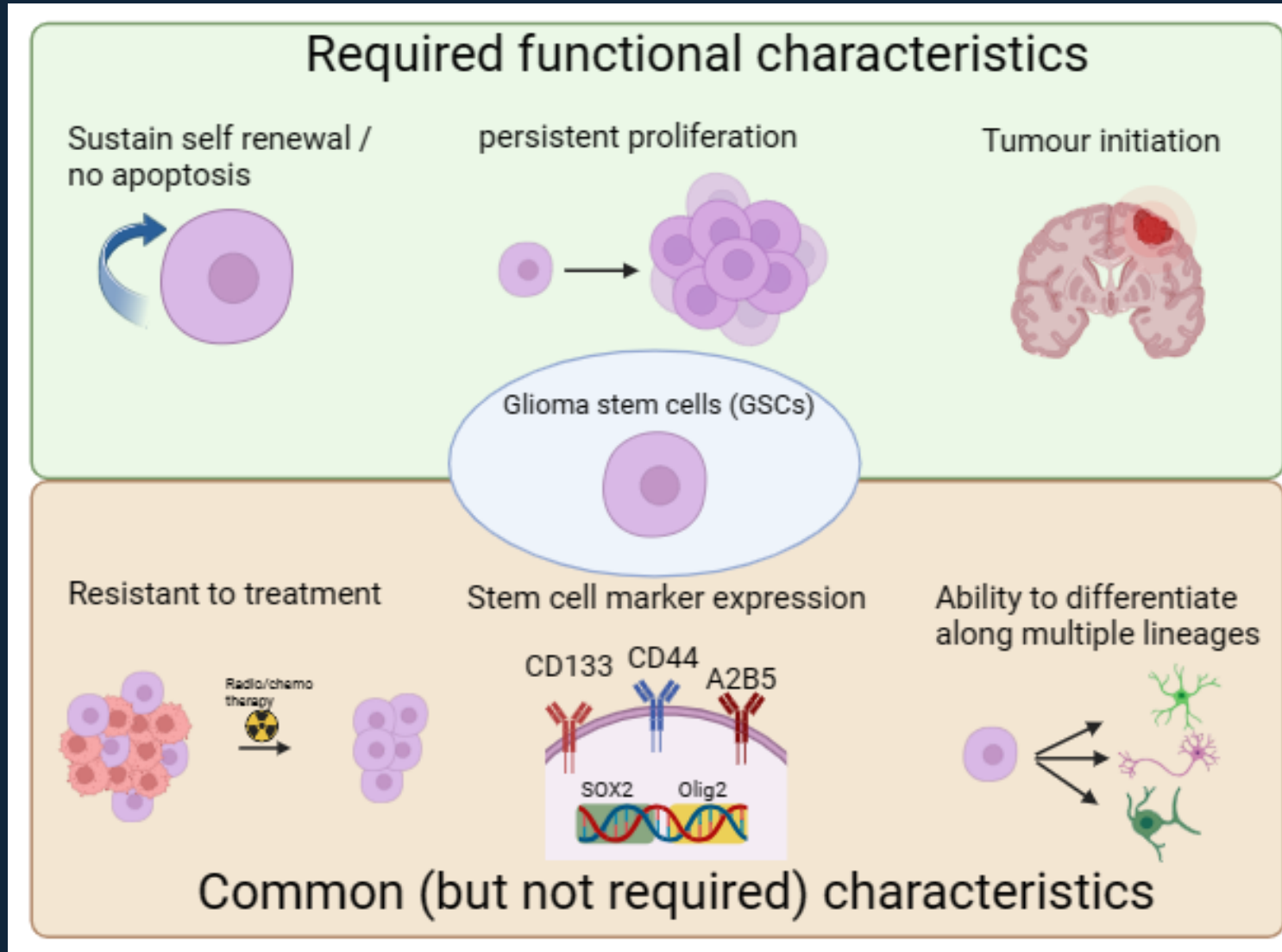


Why does standard of care fail

- 1) GBM is highly diffuse – complete surgical resection is impossible
- 2) GBM is heterogenous – In particular a critical subpopulation, the glioma stem cells (GSCs) are highly resistant to both radio and chemo therapy.

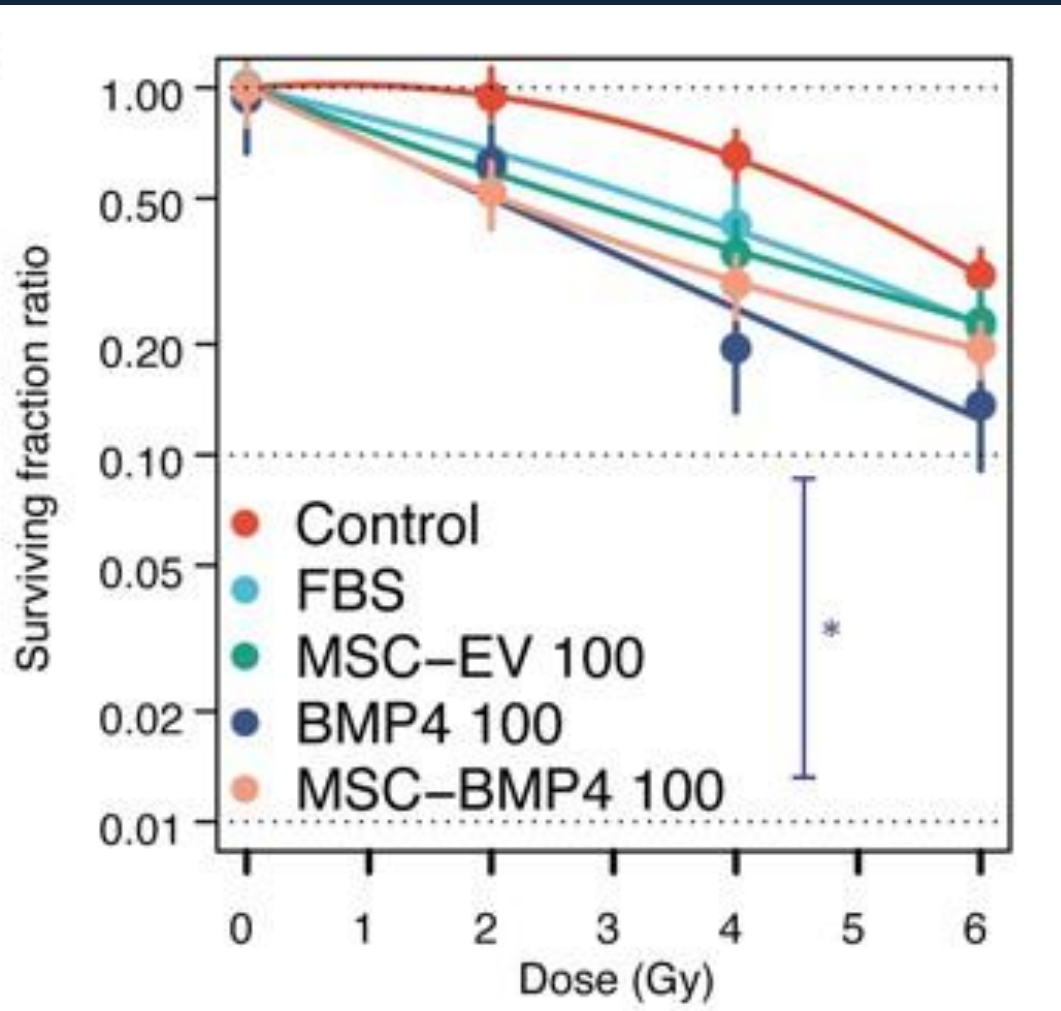


Cancer stem cells / glioma stem cells (GSCs)

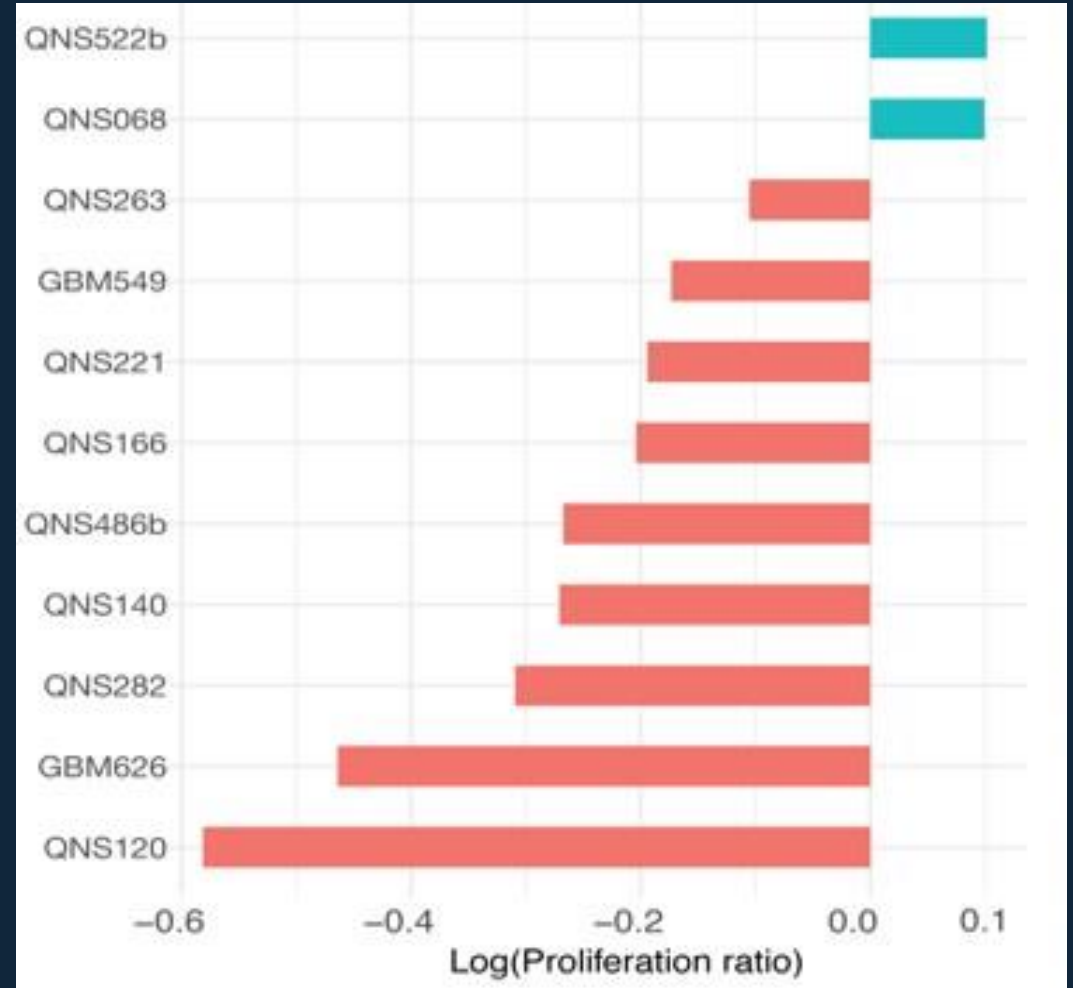


BMP4 targets GSCs

BMP4 increases radiosensitivity of GSCs

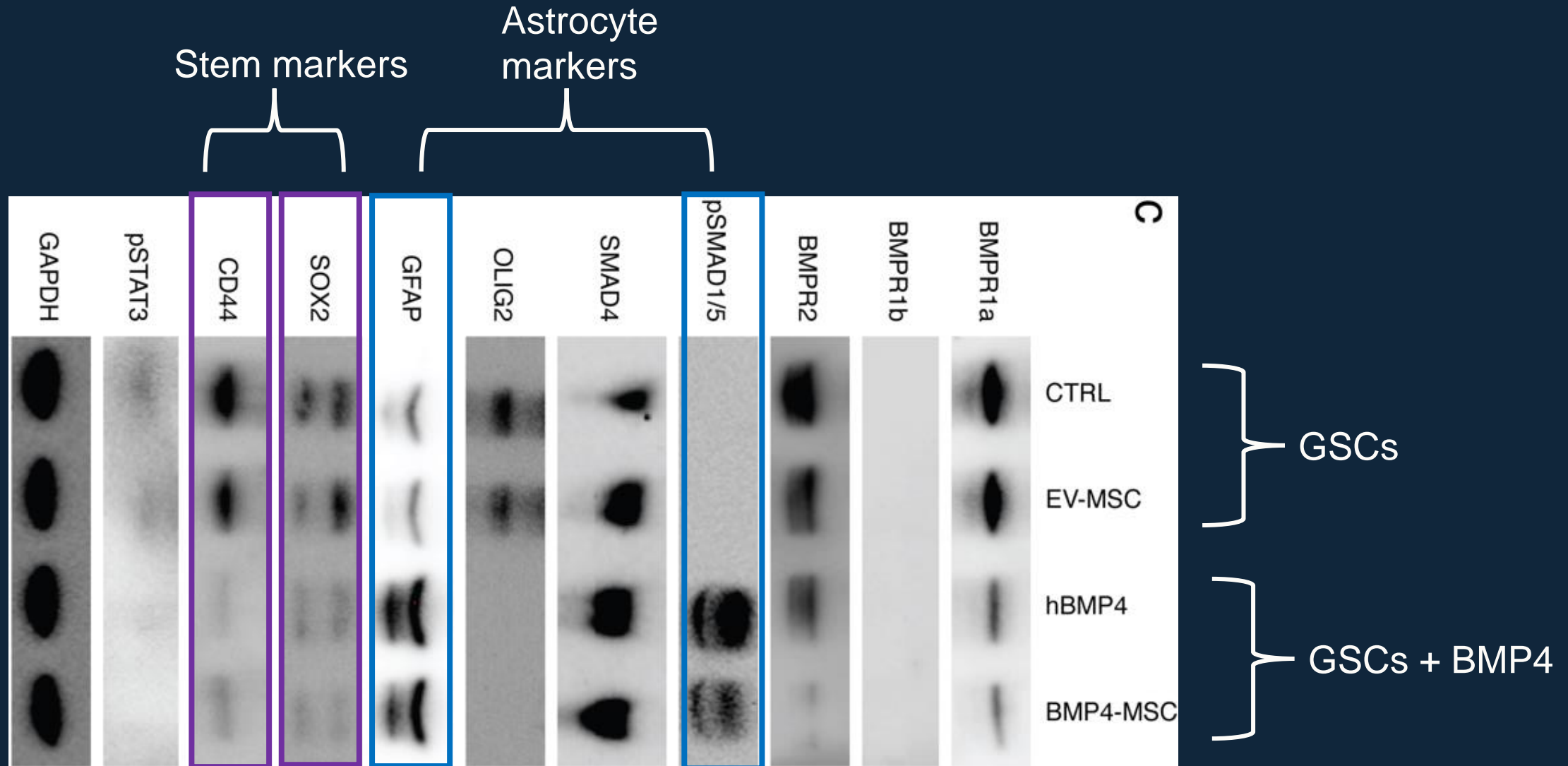


BMP4 decreases the proliferation rate of GSCs



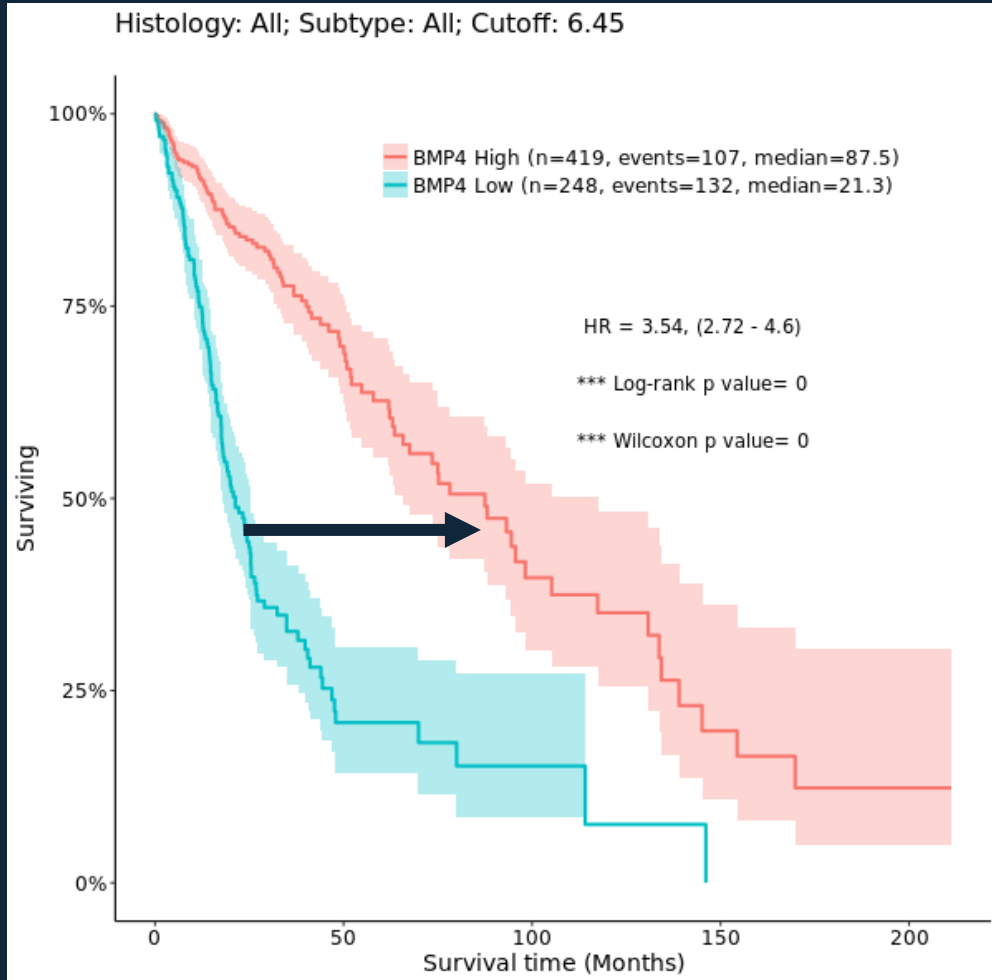
Patient derived cell lines

BMP4 causes differentiation to astrocytic-like lineage

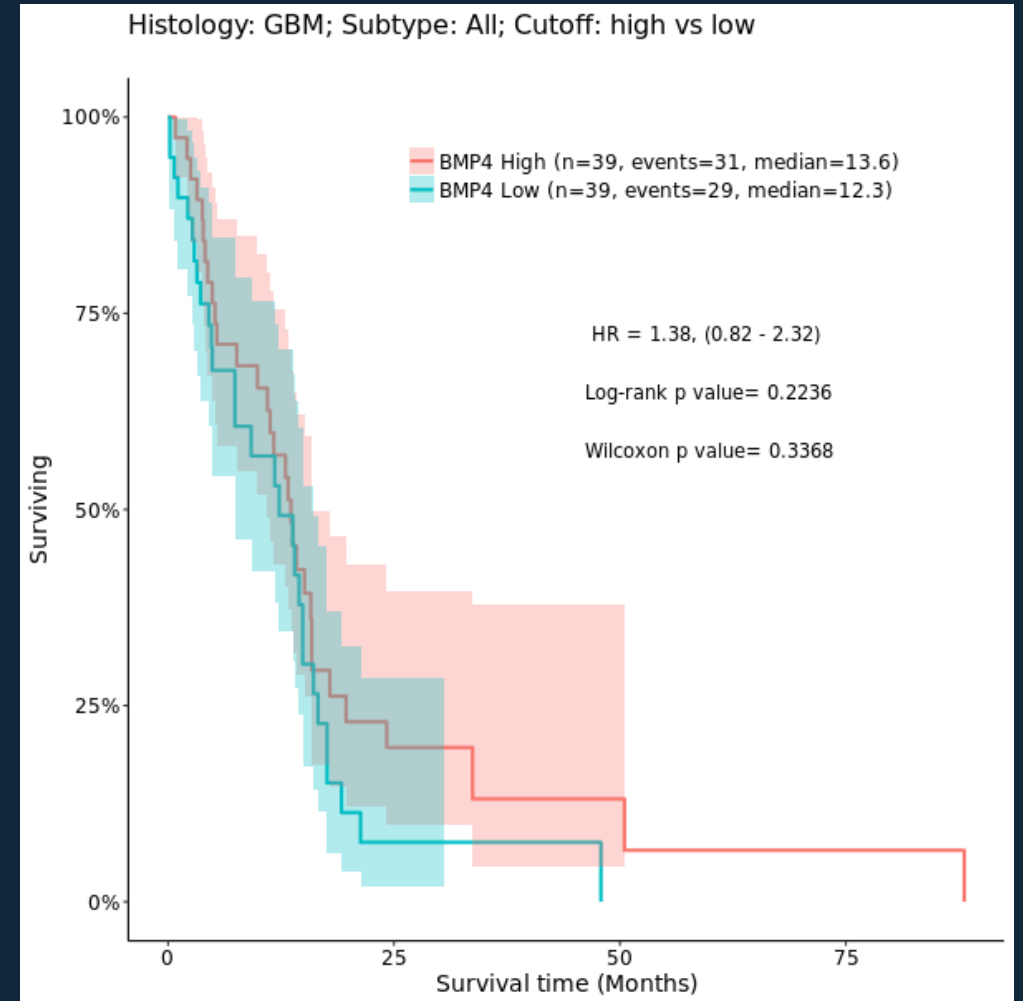


BMP4 is prognostic in Glioma

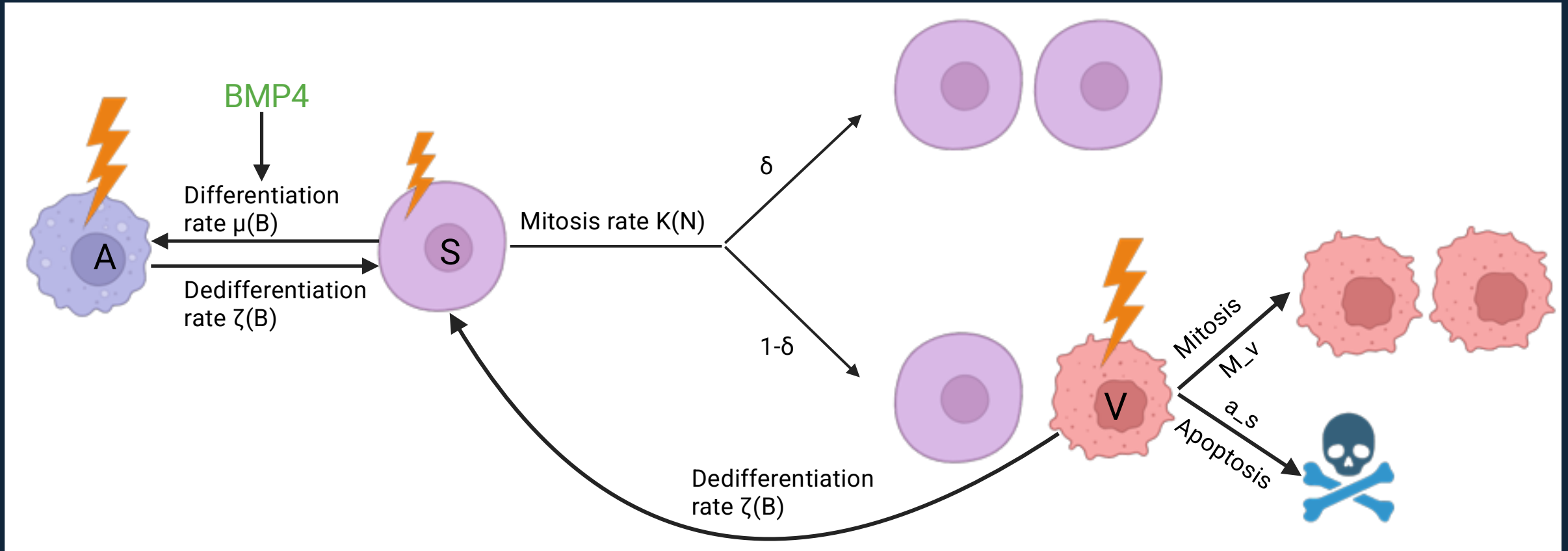
Across all glioma subtypes



GBM only



Stem cell model with BMP4

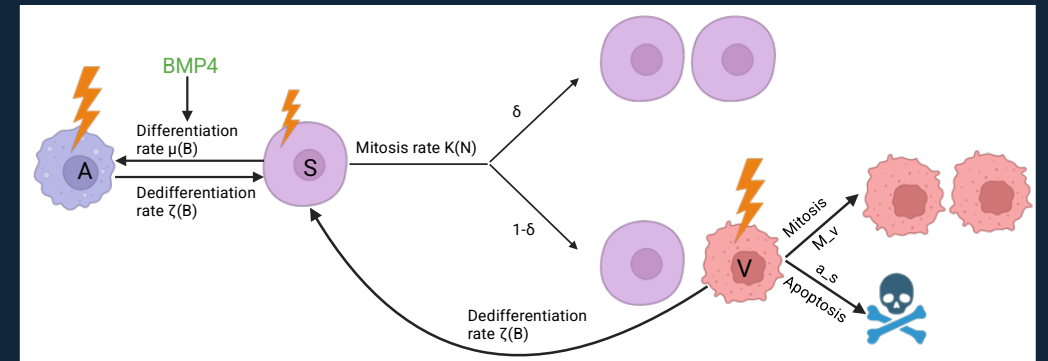


Stem cell model with BMP4

$$\frac{ds}{dt} = \underbrace{\delta m_s K(N)s}_{\text{Symetric division of GSCs}} + \underbrace{\zeta(B)(a+v)}_{\text{Dedifferentiation of TCs and ALCs}} - \underbrace{\mu(B)s}_{\text{Differentiation}}$$

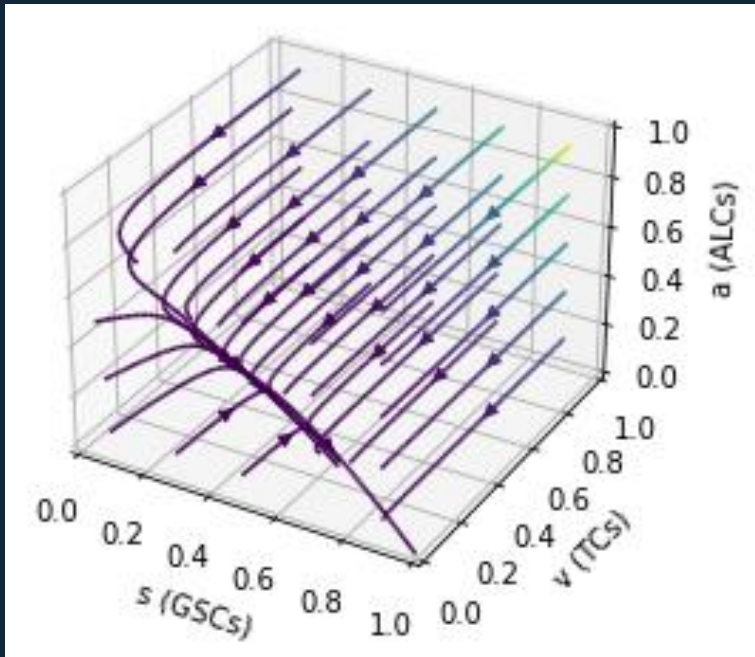
$$\frac{dv}{dt} = \underbrace{(1-\delta)m_s K(N)s}_{\text{Asymetric division of GSCs}} + \underbrace{m_v K(N)v}_{\text{Mitosis of TCs}} - \underbrace{a_v v}_{\text{Apoptosis of TCs}} - \underbrace{\zeta(B)v}_{\text{Dedifferentiation}}$$

$$\frac{da}{dt} = \underbrace{\mu(B)s}_{\text{Differentiation}} - \underbrace{\zeta(B)a}_{\text{Dedifferentiation}}$$



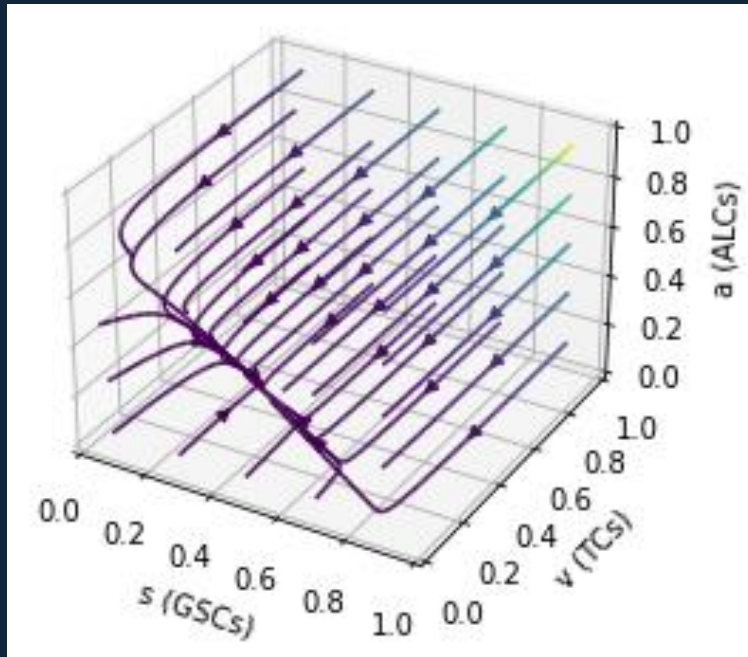
Phase plane

No BMP4



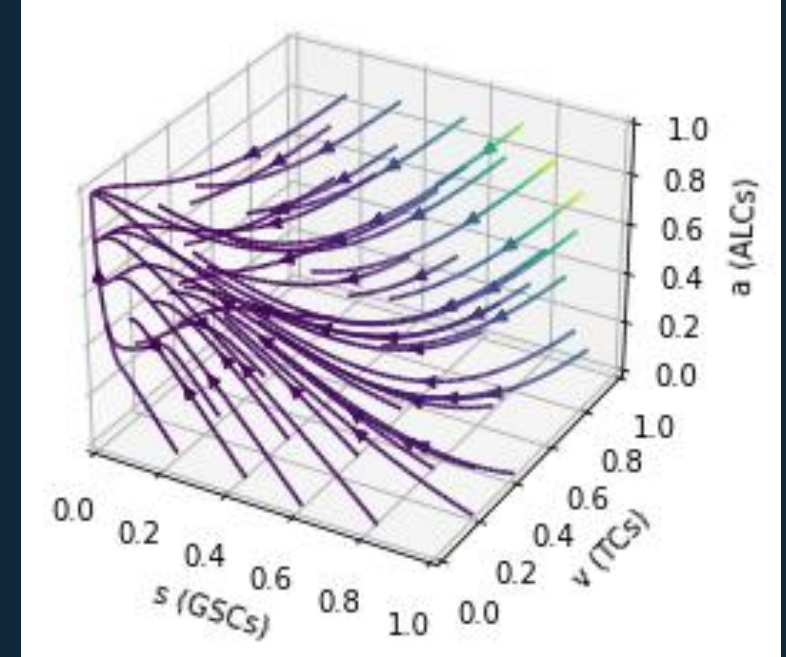
Steady state $(1,0,0)$

Low BMP4 (representing endogenous expression)



Steady state $(s^*, 0, a^*)$

High BMP4 (treatment)



Steady state $(0,0,1)$

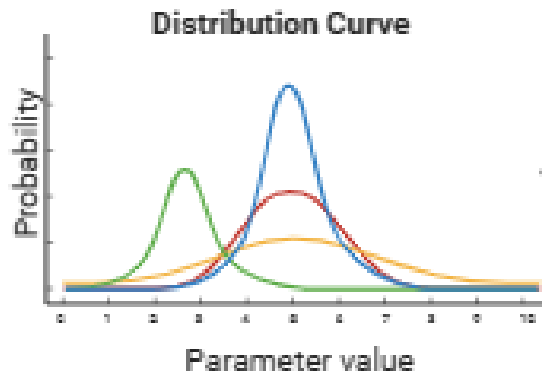
Motivations for mathematical modelling

- Which patients will respond to BMP4?
 - How will BMP4 impact survival time?
 - Optimising combination of BMP4 and radiotherapy?
-
- 1) Can the model reproduce clinically observed data?
 - 2) What predictions can the model make about BMP4 therapy?

Virtual clinical trial

Virtual clinical trial pipeline

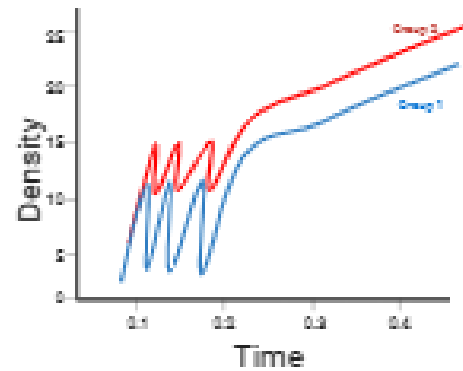
Determine patient specific parameters



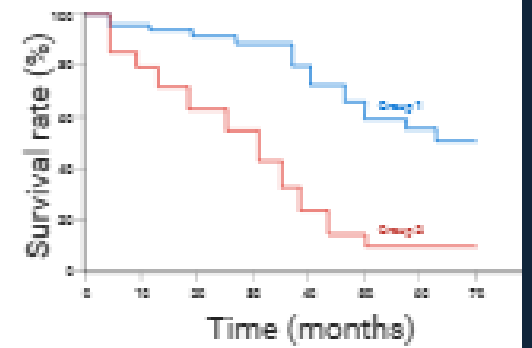
Generate a patient cohort / digital twins



Simulate treatment arms



Calculate survival statistics

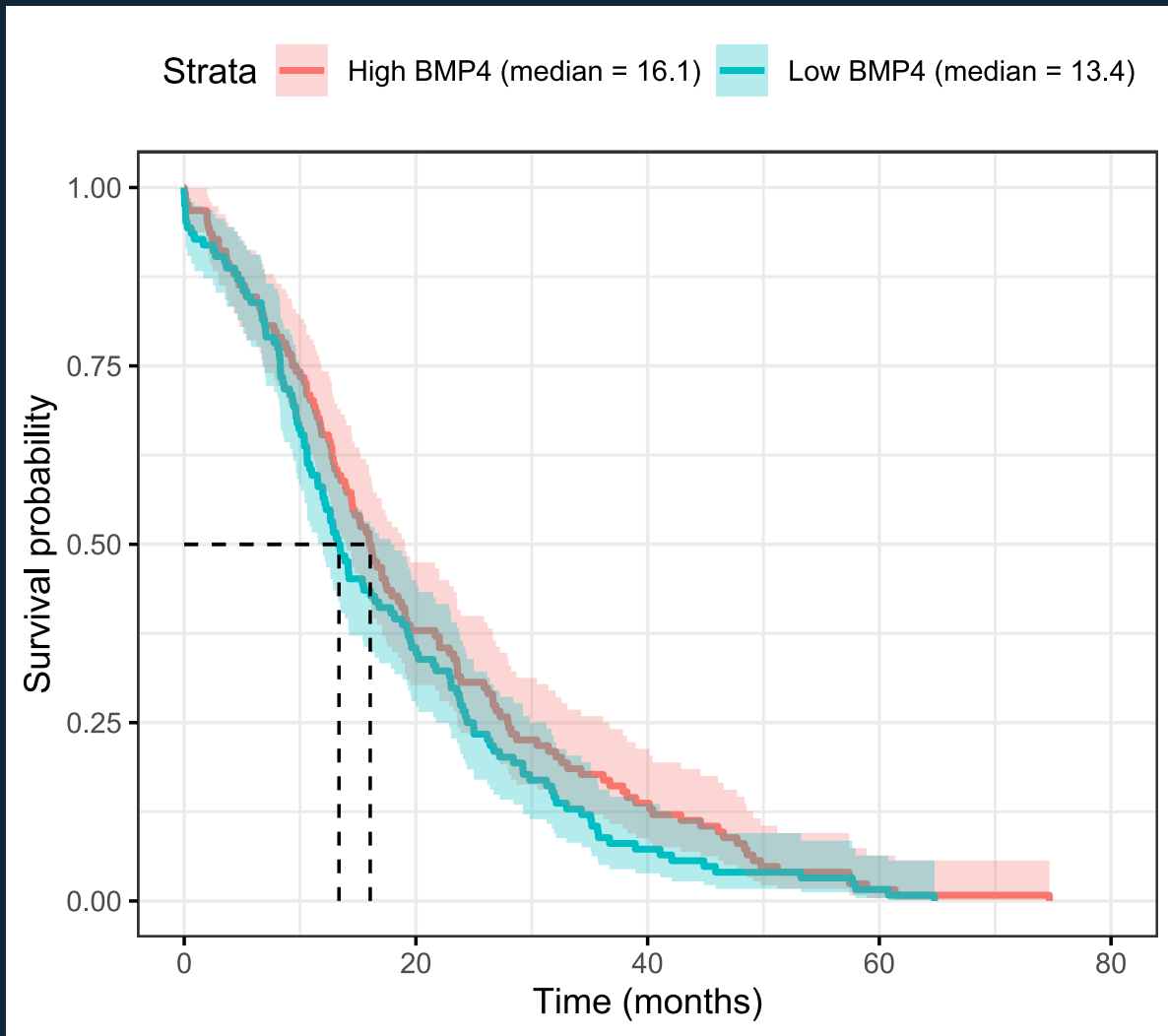


Patient specific parameters:
 $m_s, m_v, \gamma_s, \gamma_v, \mu, ICs, B_{endo}$

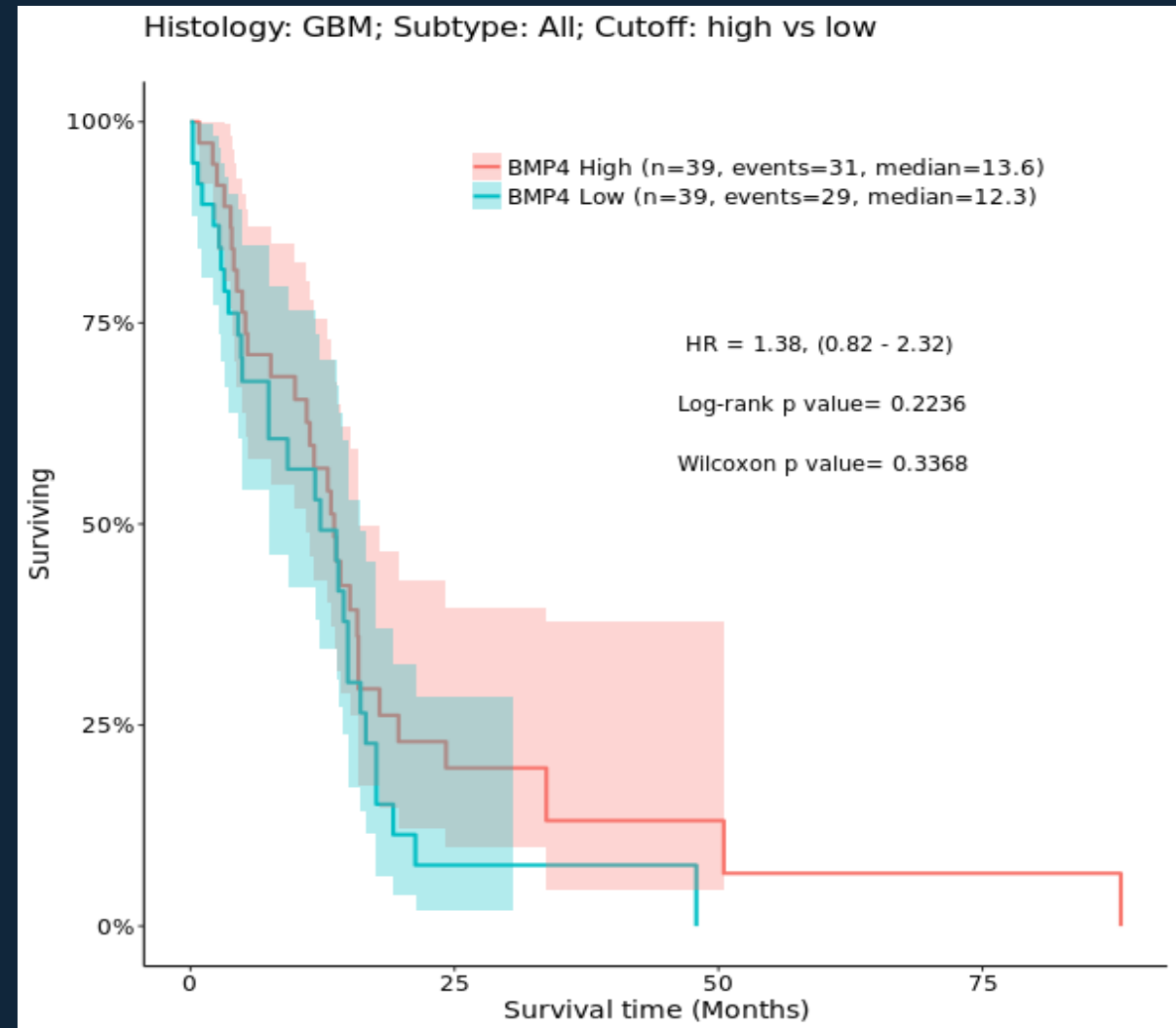
Group 1 = RT only
Group 2 = BMP4 + RT

Virtual clinical trial

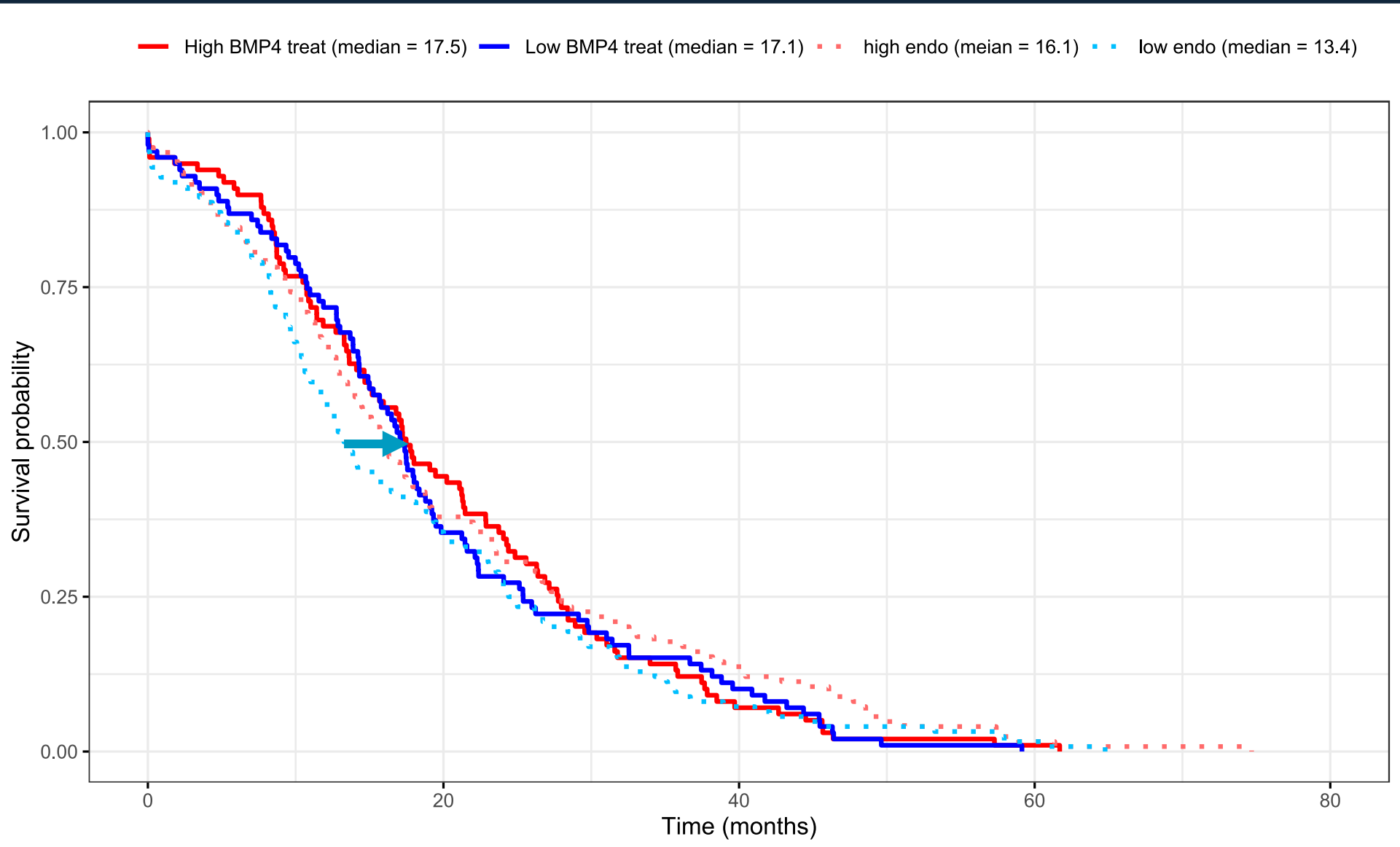
Simulated data



TCGA data



Virtual clinical trial



Limitations and outstanding challenges

- Parameter distribution is essentially unknown (lognormal was arbitrarily chosen).
- BMP4 MSC delivery is still being developed (Mayo Florida hope to trial in canines).
- Large heterogeneity in response to BMP4 between patients.
- There is no biomarker for BMP4 responsiveness.

Mathematical Neuro-oncology lab



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