Optimal drug/radiation administration schedules to delay resistance

Franziska Michor, PhD and Eric Holland, MD, PhD

Dana-Farber Cancer Institute
Physical Sciences Oncology Center

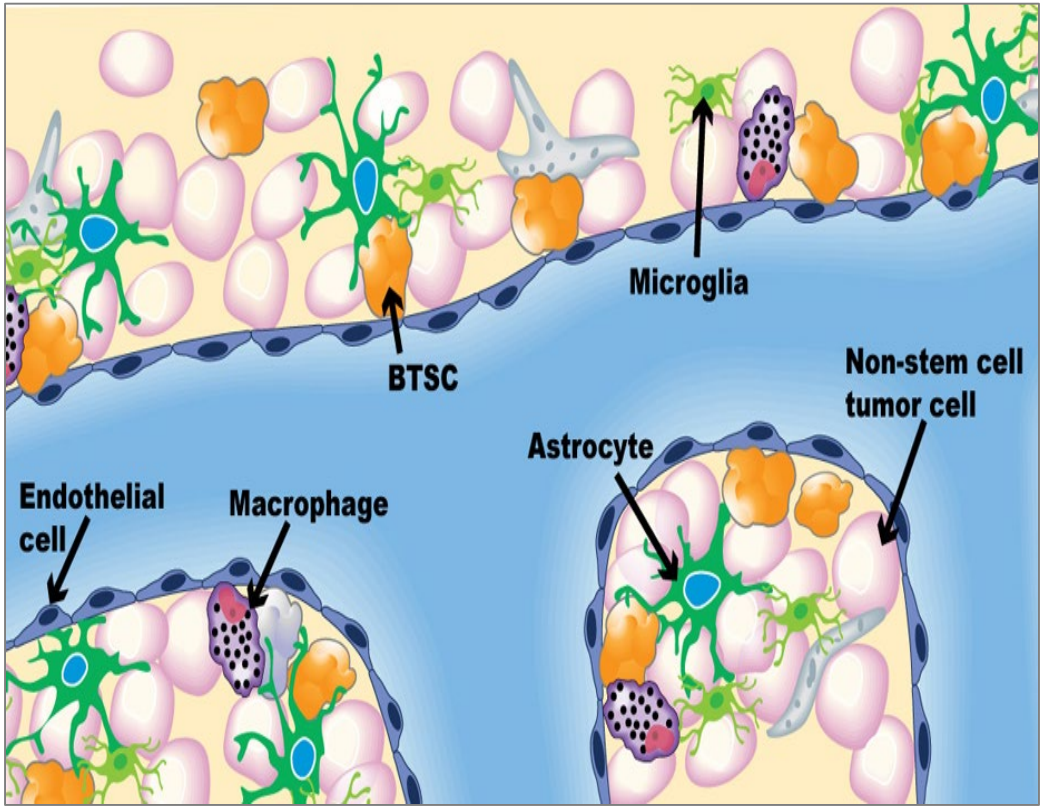
How can we use predictive mathematical modeling of patient outcomes to identify optimum treatment strategies that prevent or delay resistance?

Optimization of Treatment Strategies

Currently FDA approved administration strategies for most therapies were not chosen by a systematic investigation of the entire possible search space.

Radiotherapy for brain cancer (glioblastoma) is given in 2 Gray fractions 5 days a week for 6 weeks

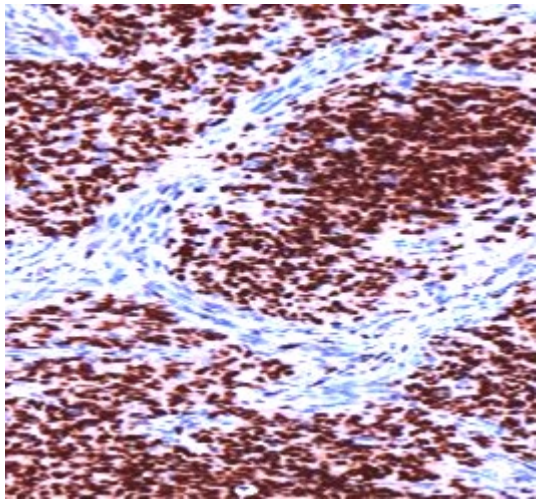
Optimizing radiation response in glioblastoma



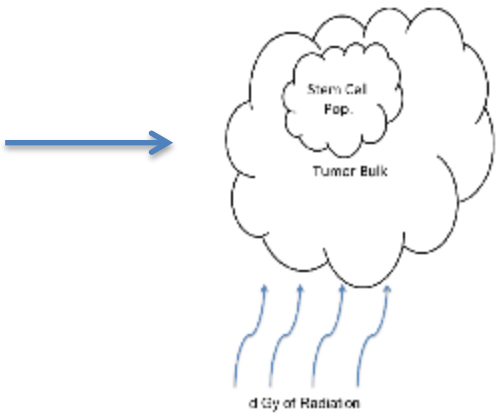
Charles et al, Cell Stem Cell 2010

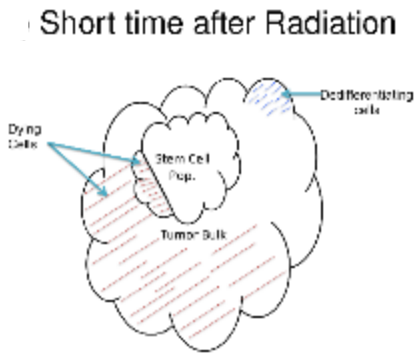
Optimizing radiation response in glioblastoma

1. Understanding of intratumor heterogeneity based on mouse modeling of PN GBM



2. Mathematical modeling of treatment response





Leder et al, Cell 2014

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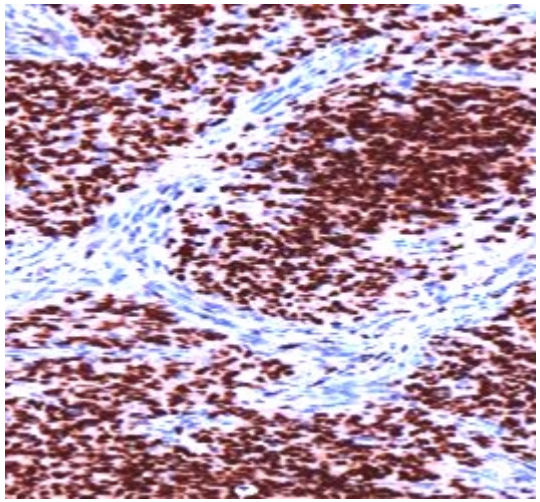

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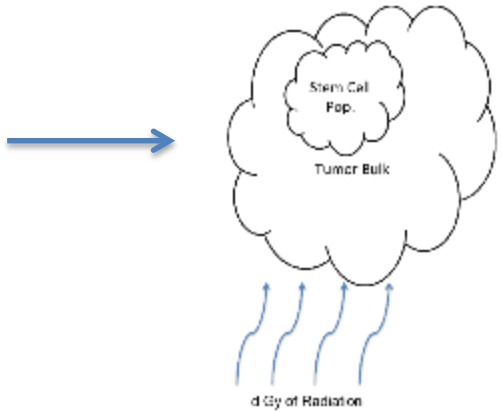

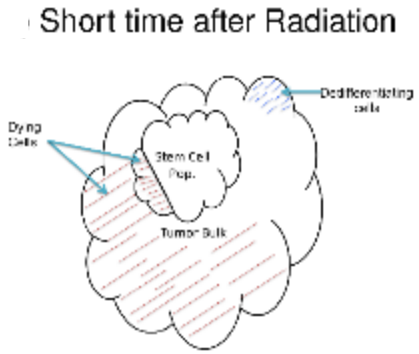

$$N_1^d = N_0^d e^{-\alpha_d d_i - \beta_d d_i^2} \left[(1-\gamma) e^{r_d (t - L_d)^+} + \gamma e^{-\nu t} + \alpha_s \gamma \nu \int_0^t e^{r_d (t - s - M_d)^+} \right.$$

$$\left. \times \int_0^{(s-L_S)^+} e^{-\nu y} e^{r_s (s - y - L_s)^+} dy ds \right] + \alpha_s N_0^s e^{-\alpha_s d - \beta_s d^2}$$

$$\times \int_{L_s}^{\max(t_i, L_s)} e^{r_s (s - L_s)} e^{r_d (t - s - M_d)^+} ds,$$

$$N_1^s = N_0^s e^{-\alpha_s d_i - \beta_s d_i^2} e^{r_s (t - L_s)^+} + \gamma \nu N_0^d e^{-\alpha_d d_i - \beta_d d_i^2} \int_0^t e^{-\nu s} e^{r_s (t - s - L_s)^+} ds$$

Leder et al, Cell 2014

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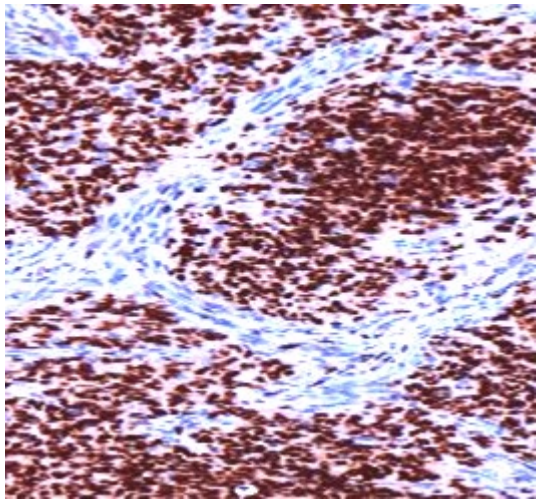

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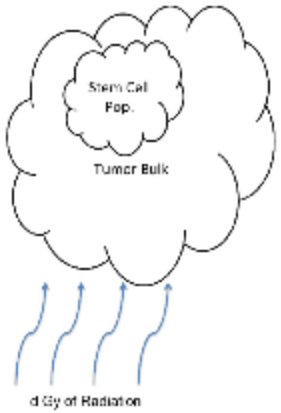
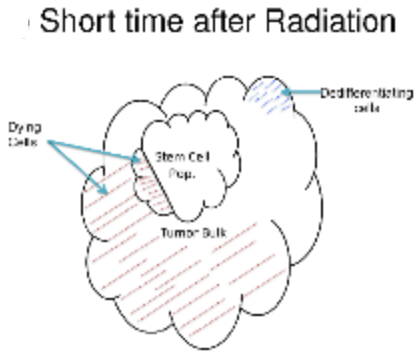
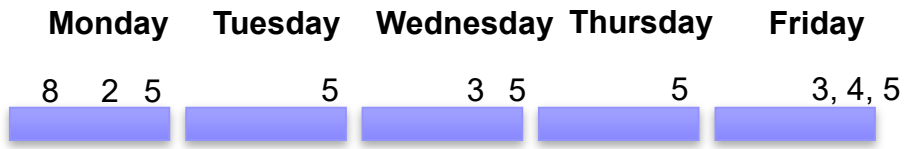


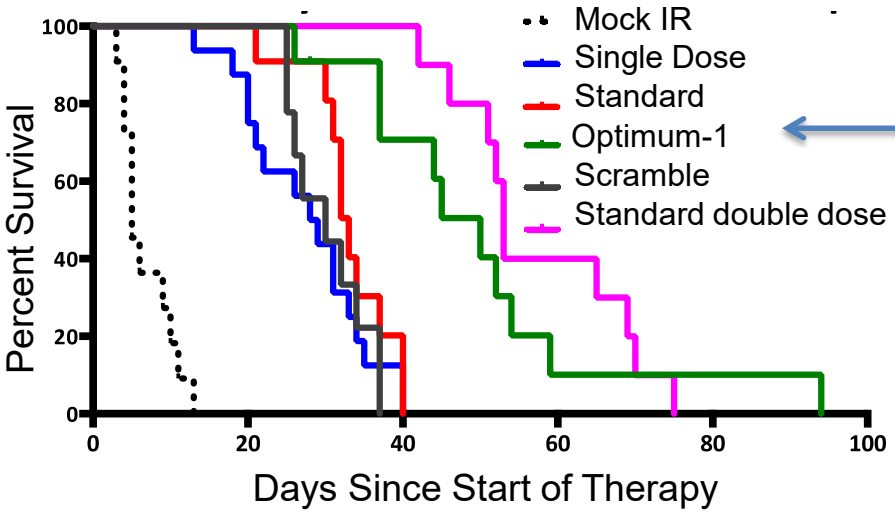


3. Identification of optimum schedule to maximize survival



One week of tx, total of 10 Gy, each dose is 1 Gy

4. Validation in mouse trials



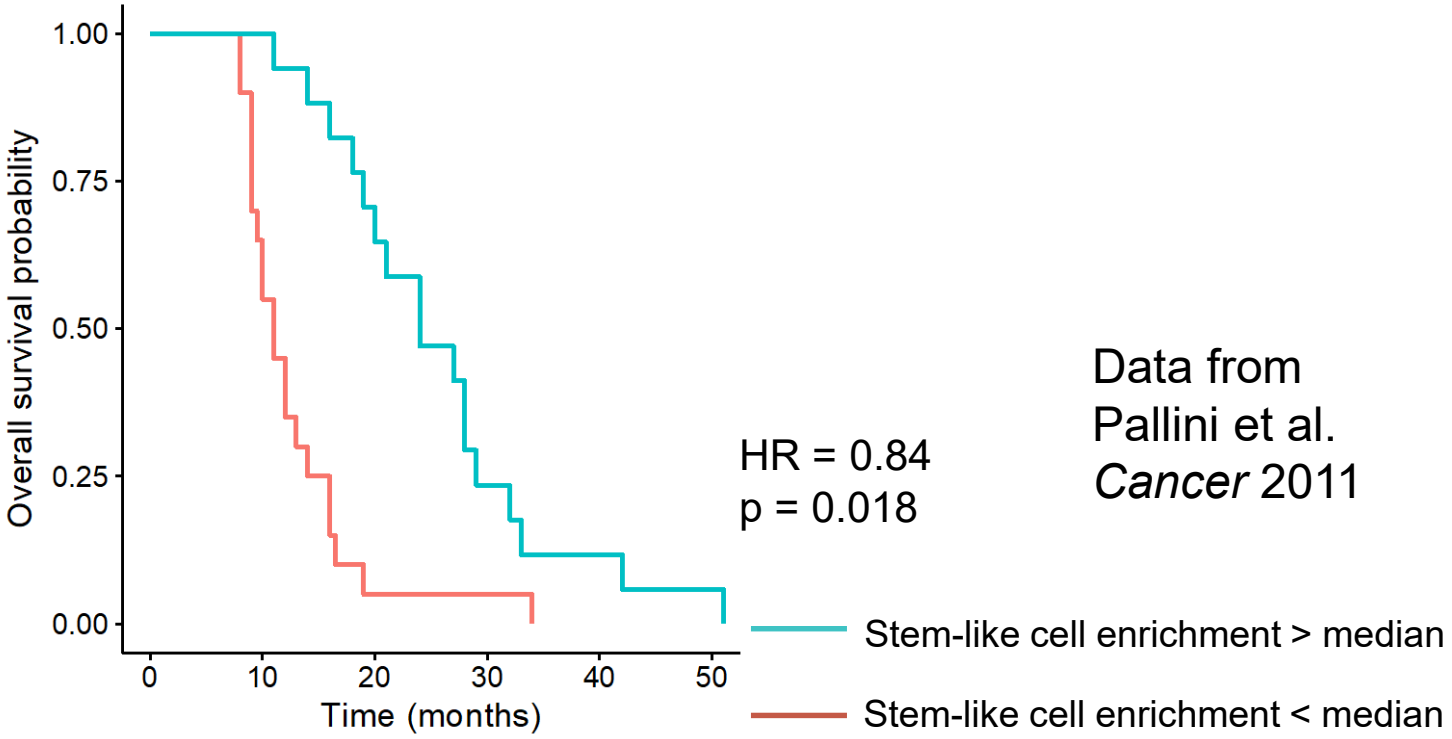
Leder et al, Cell 2014

Enriching for stem cells in mice and men

Optimal schedule enriches for slower proliferating, radioresistant stem-like cells in the mouse model

- Achieved by timing radiation fractions to maximize dedifferentiation process

Enrichment of stem-like cells is associated with prolonged survival in patients (n = 37): All patients received 60 Gy radiation + adjuvant temozolomide



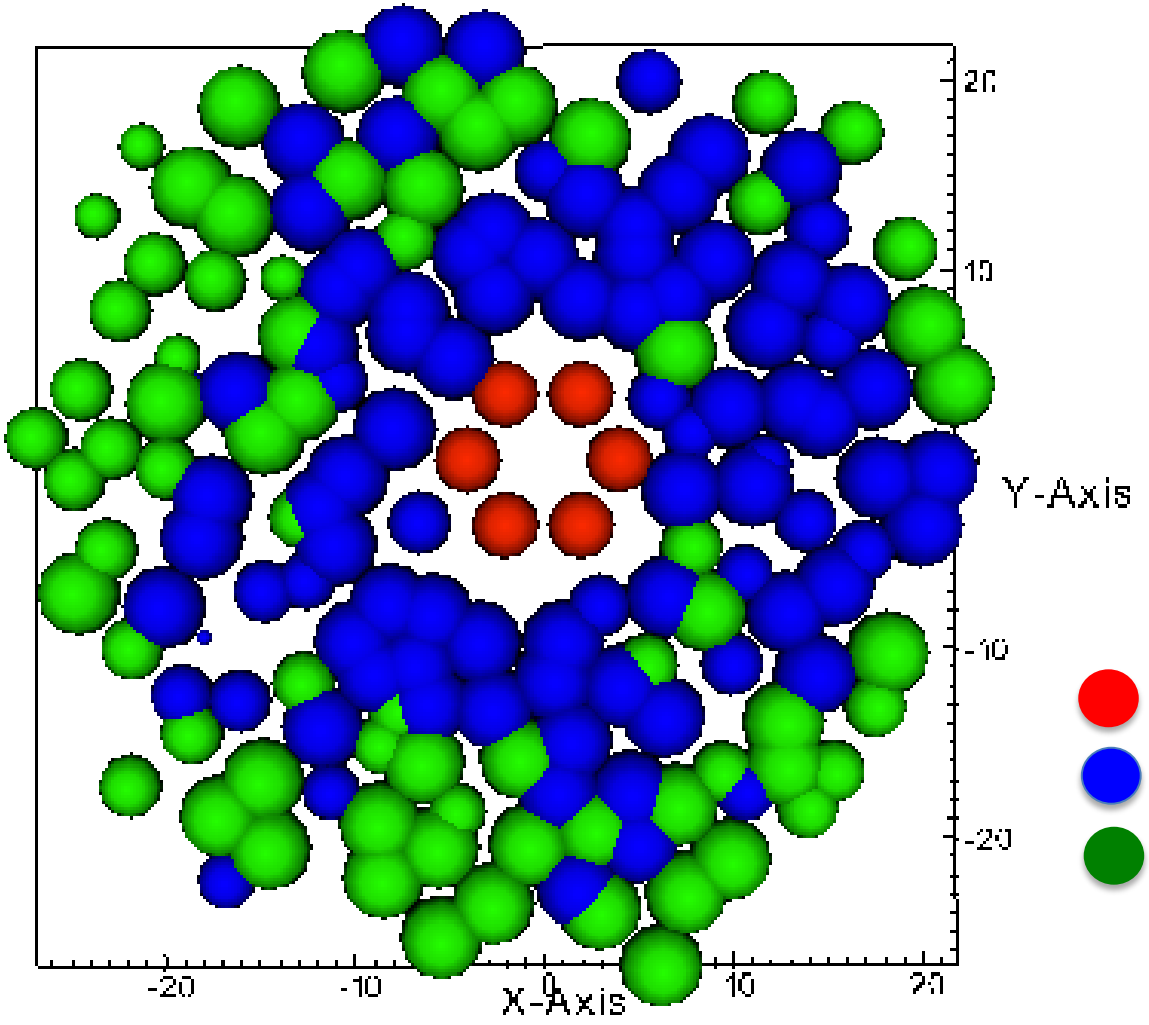
Data from Pallini et al. *Cancer* 2011

A pilot trial for refractory GBM at BWH/DFCI

- Comparison to control arm: 35 Gy in 10 fractions; 1 fraction/day; 5 days/week
- Identified schedule: 28 Gy in 7 fractions (1 fraction/day) then 9 Gy in 9 fractions (3 fractions/day)
  - Maximizes differentiated cell killing per fraction using hypofractionation at the start of treatment
  - Enriches for stem-like cells using ultrafractionation at the end of treatment
  - Hopefully easier to implement than Optimum-1 and infinitesimally worse
- IRB approved, starting to enroll now

Jamie Dean, Shyam Tanguturi, Brian Alexander

Upfront treatment: radiation plus temozolomide



Endothelial cell

Stem-like tumor cell

Differentiated tumor cell

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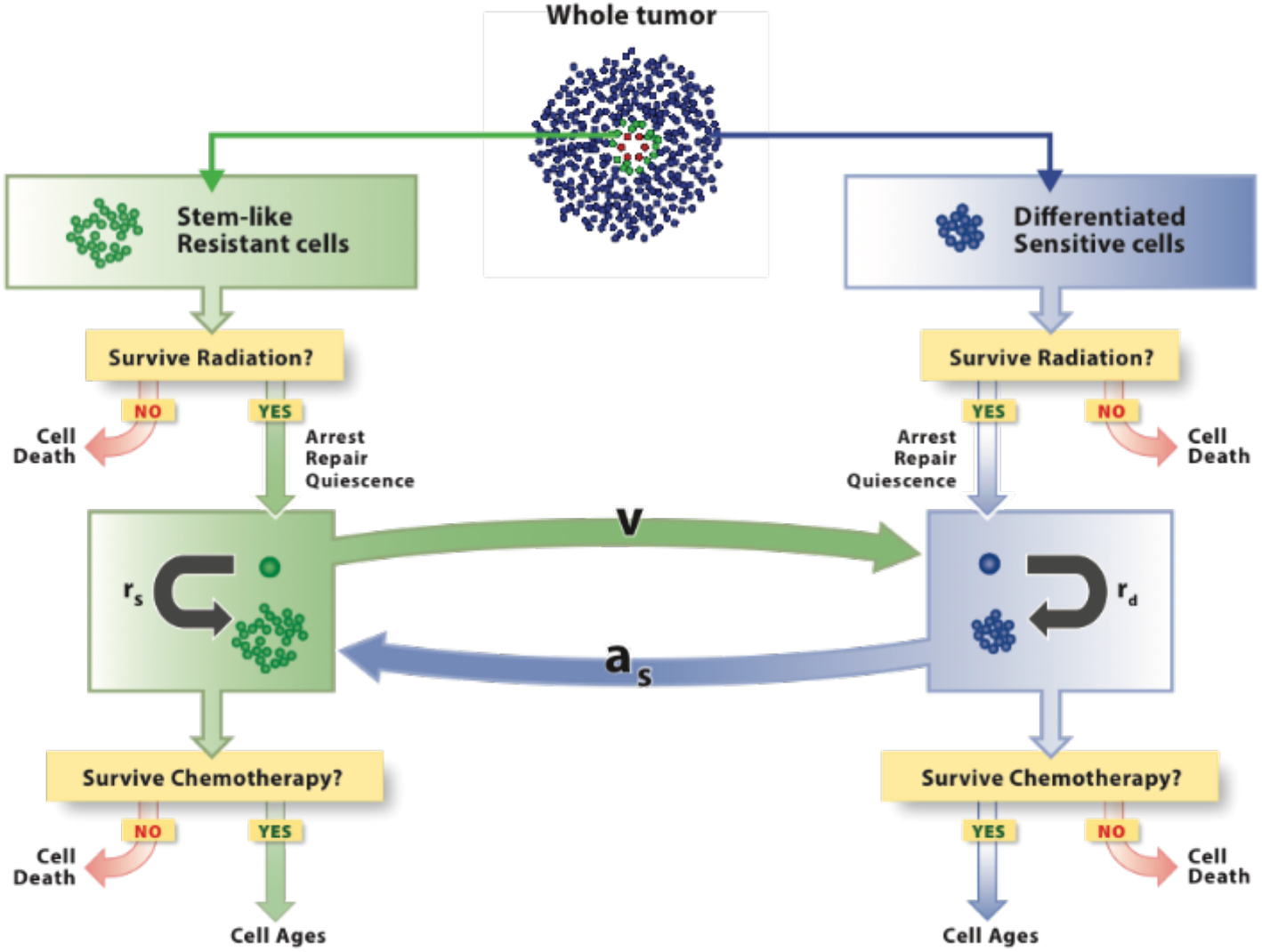
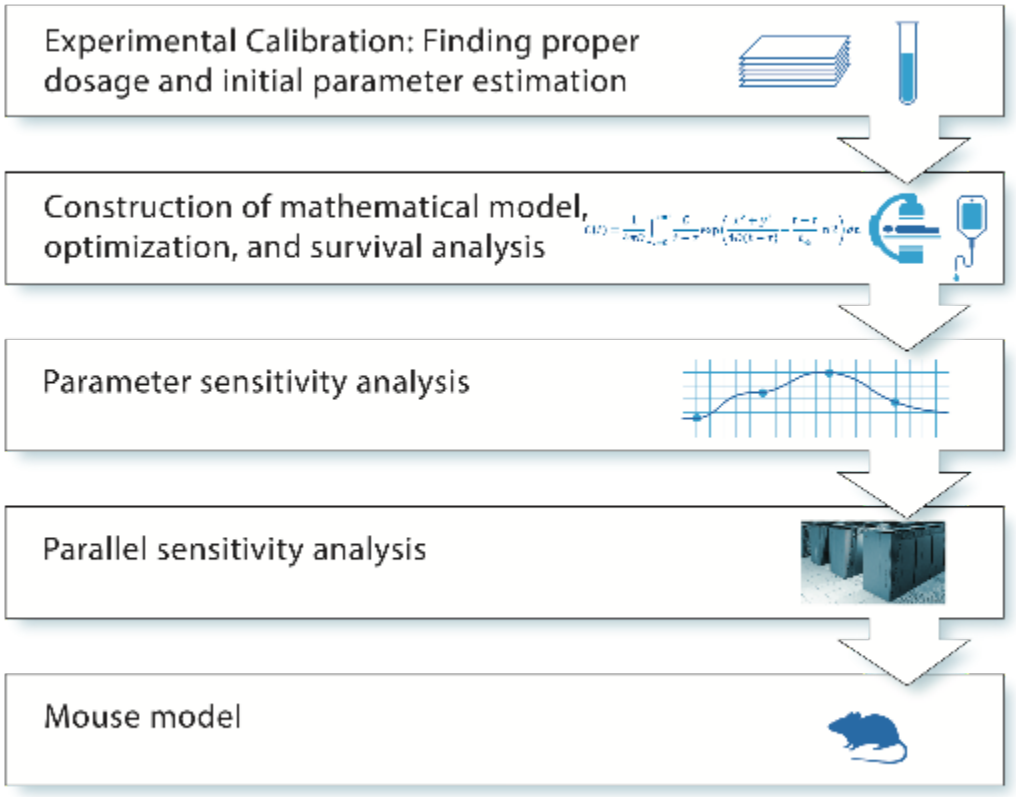
Determining optimum administration schedules for radiation and temozolomide using a spatial model



Workflow


Experimental Calibration: Finding proper dosage and initial parameter estimation
Construction of mathematical model, optimization, and survival analysis
Parameter sensitivity analysis
Parallel sensitivity analysis
Mouse model

Optimum radiation plus temozolomide schedule

- This model was used to predict optimum administration schedules of 10 Gy over one week **using over 4000 compute years on the world's #2 supercomputer (Livermore National Labs)**

	Monday	Tuesday	Wednesday	Thursday	Friday
Optimized	--	1 Gy 9 a.m. 1 Gy 4 p.m.	1 Gy 8 a.m. 2 Gy 9 p.m.	1 Gy 9 a.m. 2 Gy 4 p.m.	1 Gy 9 a.m. 1 Gy 5 p.m.
Suboptimal	2 Gy 2 p.m.	1 Gy 1 p.m. 1 Gy 5 p.m.	1 Gy 2 p.m. 1 Gy 3 p.m.	2 Gy 8 a.m. 1 Gy 11 a.m.	1 Gy 5 p.m.
All	TMZ 50 mg/kg 3 p.m.	TMZ 50 mg/kg 3 p.m.	TMZ 50 mg/kg 3 p.m.	TMZ 50 mg/kg 3 p.m.	TMZ 50 mg/kg 3 p.m.

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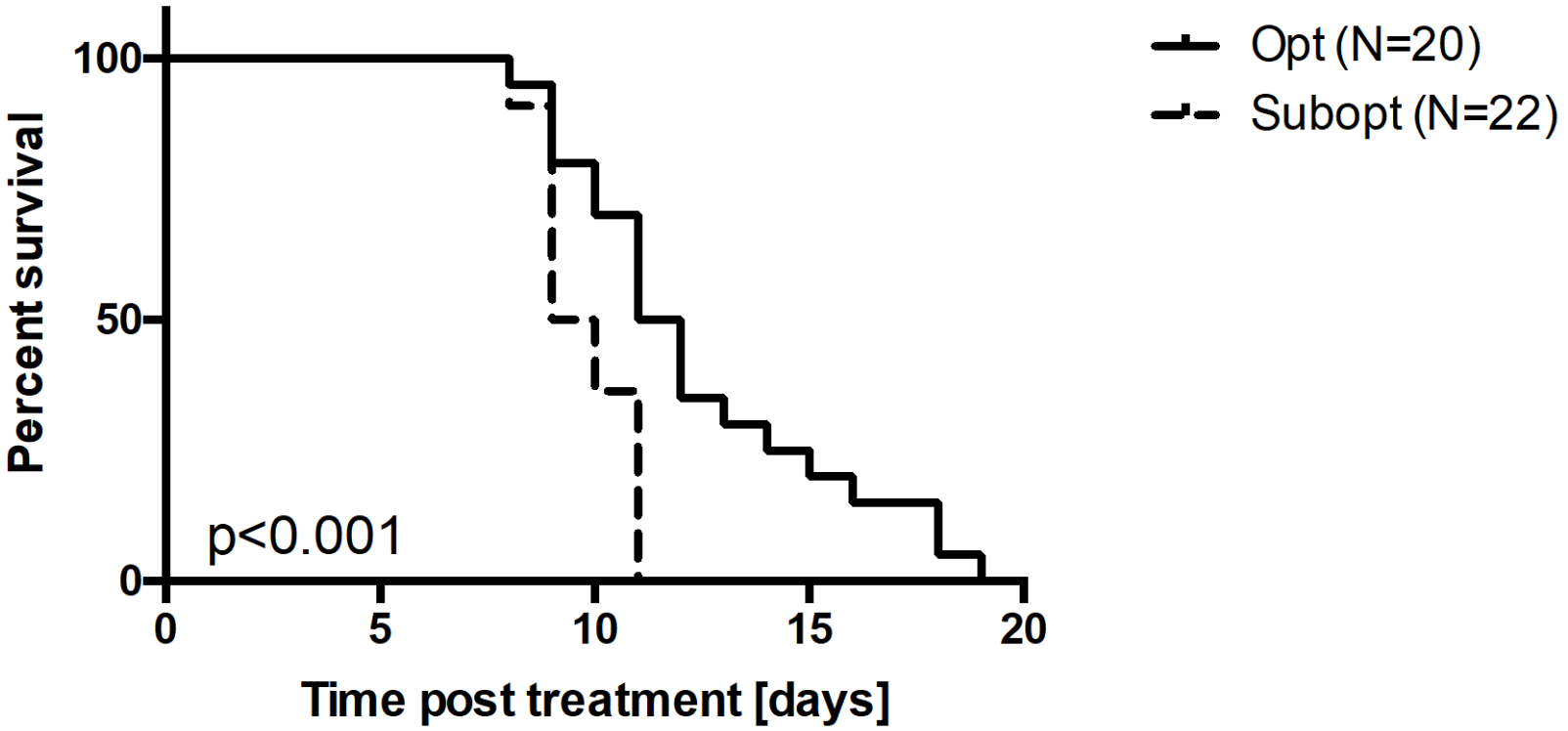
Validation in the mouse

- This prediction was validated in the RCAS/tv-a model (PDGFB+Cre in N/t-va;Ink4a/Arf-/-;PTENfl/fl;LucLSL/LSL)



Hans-Georg Wirsching and Eric Holland

Where do we go from here?

- Implementing this work as three clinical trials: pilot for feasibility, multi-institutional for efficacy or radiation alone, and trial for chemoradiation combination
- Modeling studies for combination treatment with radiation sensitizers, immunotherapy, and anti-angiogenic drugs
- Application of these methods to other cancer (lung, breast, AML, pancreatic, etc) and treatment (radiation, chemotherapy, targeted agents, immunotherapy, radiosensitizers etc) types
- Other physical sciences-based investigations into intra-tumor heterogeneity, metastasis, and treatment response

Acknowledgements

Michorlab

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Qiong Xu

michorlab.dfci.harvard.edu

The Dana-Farber Cancer Institute
Physical Sciences-Oncology Center (PSOC)

Eric Holland, Nelly Polyak, David Scadden

psoc.dfci.harvard.edu

Duke University: Amanda Randles

The Dana-Farber Cancer Institute
Center for Cancer Evolution (CCE)

Thomas McDonald, David Pellman, Nelly Polyak

cce.dfci.harvard.edu