Multiscale systems pharmacology for optimizing multidrug anticancer therapies

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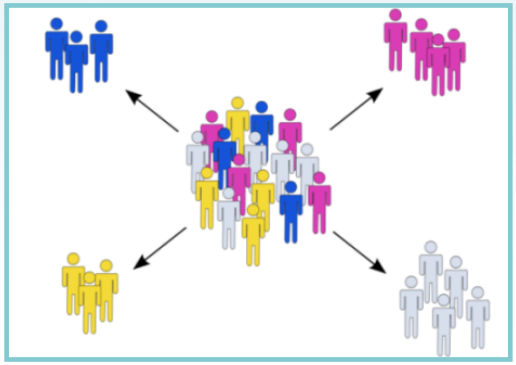
Optimizing Anticancer Therapies

- Numerous anticancer drugs, possible combinations and scheduling.
- Large inter-patients differences in cancer diseases: need for treatment personalization

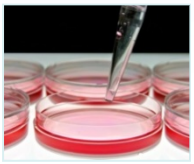


⇨ New **systems pharmacology** approaches

ODE-based physiological modeling

- Physiological meanings of variables and parameters (drug concentrations, intracellular protein amounts, reaction rates)

- Advantages:
  i) low computational cost,
  ii) allow direct model/data comparison,
  iii) allow **multi-scale model design and calibration**:



Outline

I) An *in vitro* systems pharmacology proof of concept

II) Towards personalization of temozolomide-based combination therapies:

i. TMZ pharmacokinetics (PK)

ii. TMZ pharmacodynamics (PD)

I) A systems pharmacology proof of concept

Ballesta et al. PLoS Comp Biol 2013

- 2 cell populations (NIH-3T3 mouse fibroblasts):
  - Parental = «Healthy»
  - SRC-transformed = «Cancer» [**SRC** : oncogene mutated in various cancers]
- SRC-transformed cells **resistant** to single agent therapies (staurosporine, etoposide, …) but not parental cells...
- Resistance due to alteration of apoptosis pathways

A systems pharmacology proof of concept

Ballesta et al. PLoS Comp Biol 2013

Optimal drug combinations to eradicate resistant «cancer» cells w/o harming «healthy» cells?

A systems pharmacology proof of concept

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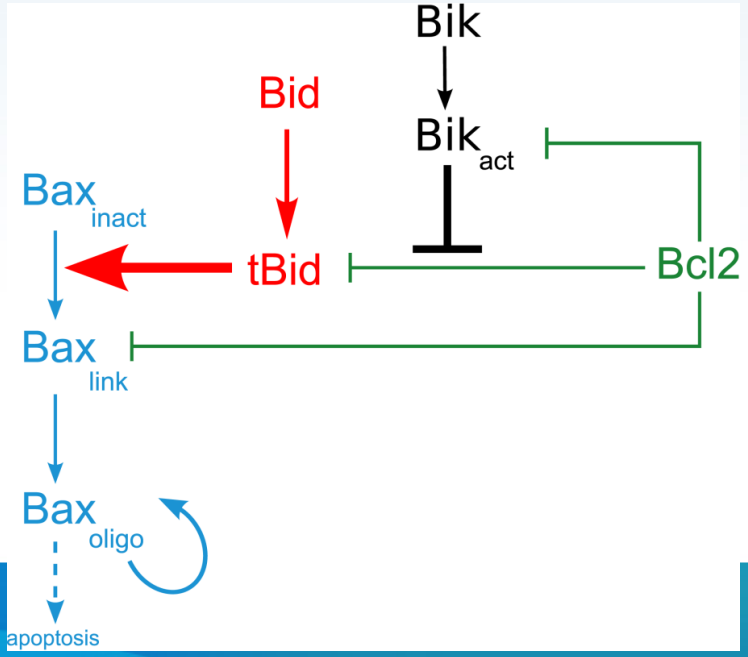
Optimal drug combinations to eradicate resistant «cancer» cells w/o harming «healthy» cells?

Mathematical model of mitochondrial pathway of apoptosis



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A systems pharmacology proof of concept

Ballesta et al. PLoS Comp Biol 2013

Optimal drug combinations to eradicate <u>resistant</u> « cancer» cells w/o harming « healthy» cells?

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Mathematical model of mitochondrial pathway of apoptosis

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Specific experiments (Protein degradation kinetics and relative levels, drug cytotoxicity)

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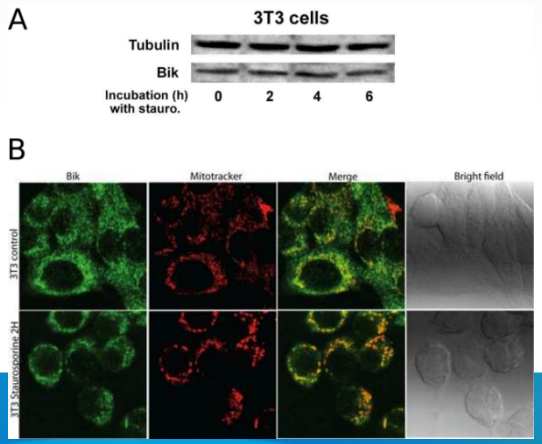

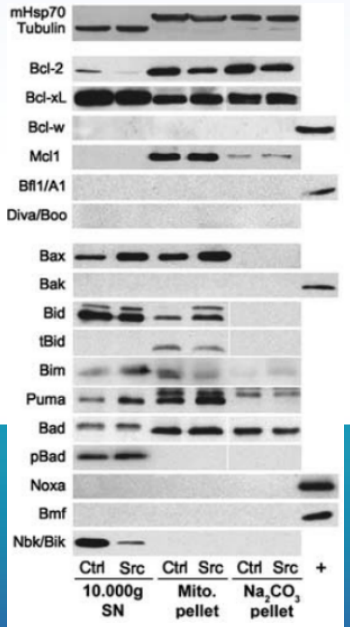

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A systems pharmacology proof of concept

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Specific experiments (Protein degradation kinetics and relative levels, drug cytotoxicity)

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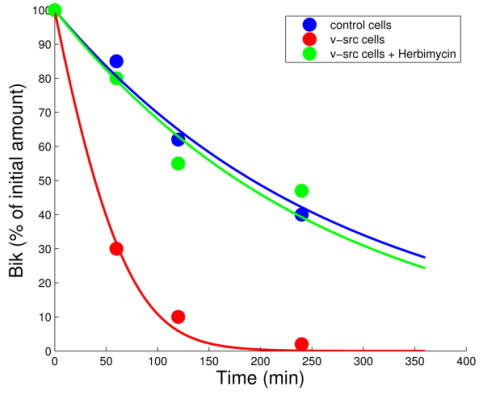
Parameter Estimation



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A systems pharmacology proof of concept

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Optimal drug combinations to eradicate resistant «cancer» cells w/o harming «healthy» cells?

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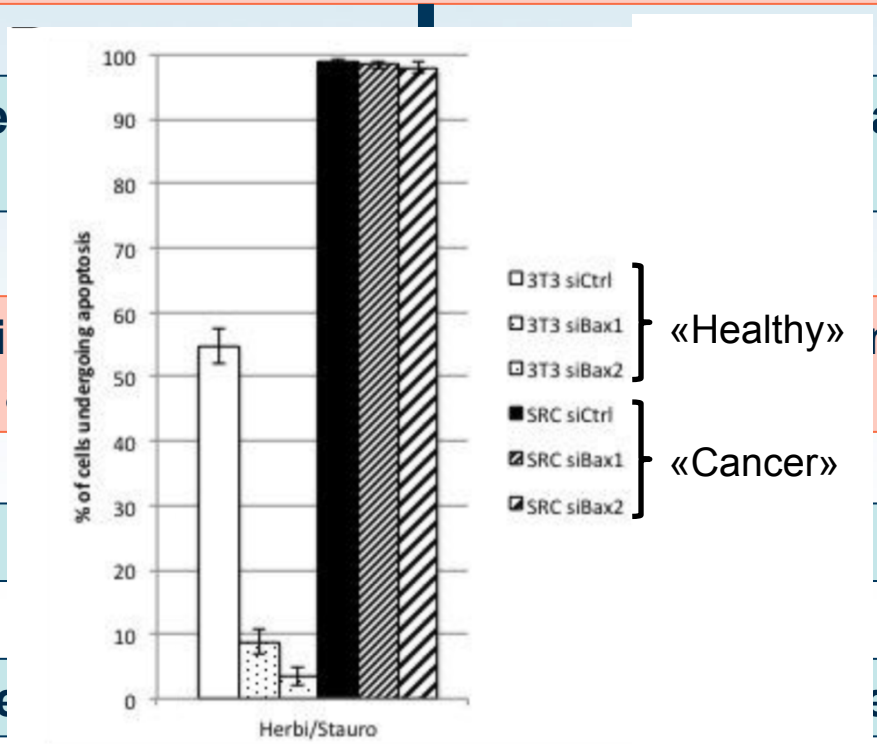

EXPERIMENTAL VALIDATION of non-intuitive optimal therapies circumventing resistance w/o toxicities

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Outline

I) An *in vitro* systems pharmacology proof of concept

II) Towards personalizing temozolomide-based combination therapies:

i. TMZ pharmacokinetics (PK)

ii. TMZ pharmacodynamics (PD)

II) Personalizing Temozolomide Combination Therapies

- Anticancer drug **Temozolomide (TMZ)** approved since 1999 for treatment of glioblastoma (GBM).
- Dismal survival of 12-14 months of GBM patients, despite chemotherapy

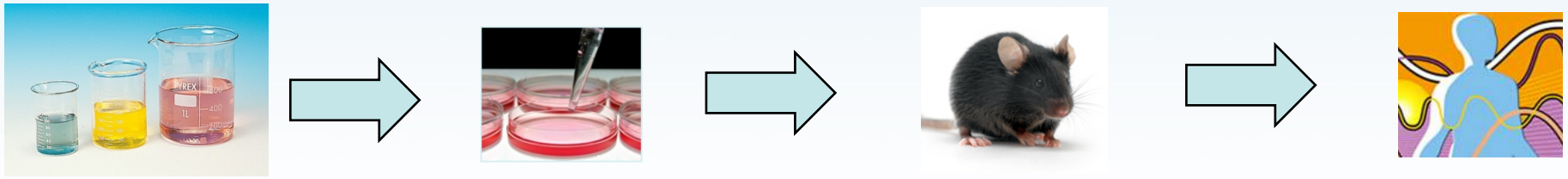
Aim: improve GBM management through personalized TMZ-based combination therapies.

II) Personalizing Temozolomide Combination Therapies

How: Multi-scale systems pharmacology approach

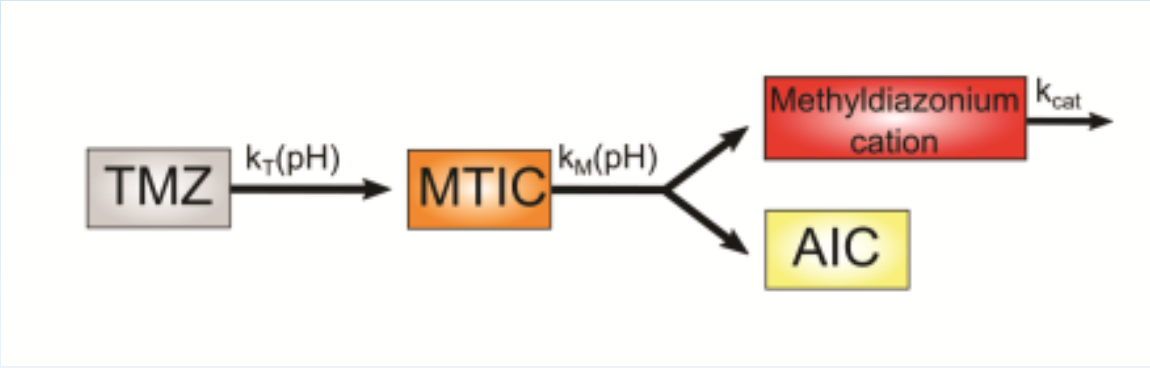
i. TMZ pharmacokinetics:

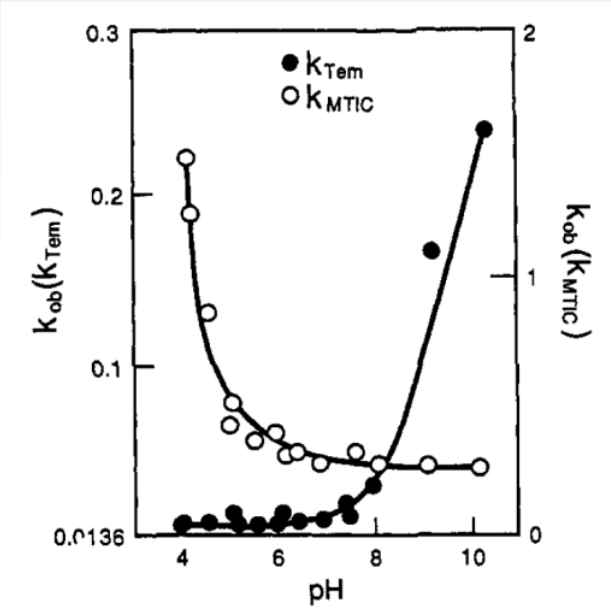
Ballesta et al., CPT: pharmacometrics & systems pharmacology, 2014



ii. TMZ pharmacodynamics

1.TMZ PK in buffer solutions





Denny et al., Biochemistry, 1994

Reactions are pH-dependent:

- TMZ metabolism faster at high pH
- MTIC degradation faster at low pH

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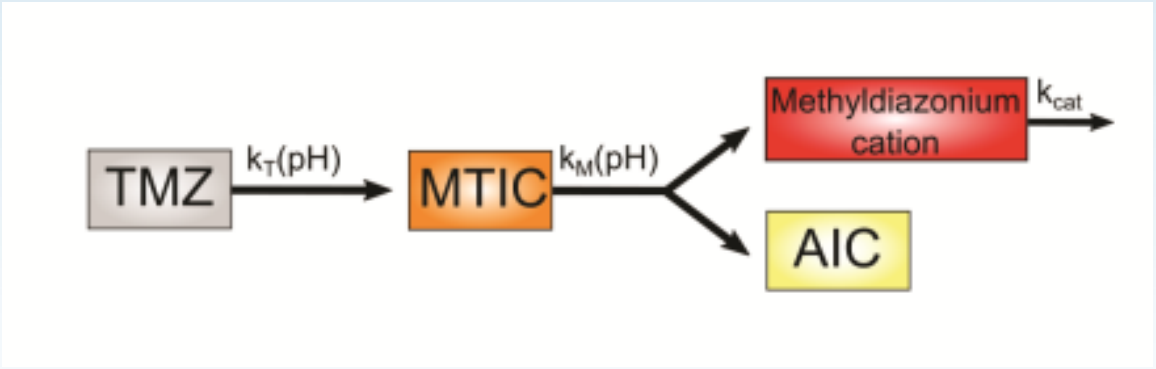
1.TMZ PK in buffer solutions

- Equations based on the law of mass action:



$$\frac{dT}{dt} = -k_T T$$

$$\frac{dM}{dt} = k_T T - k_M M$$

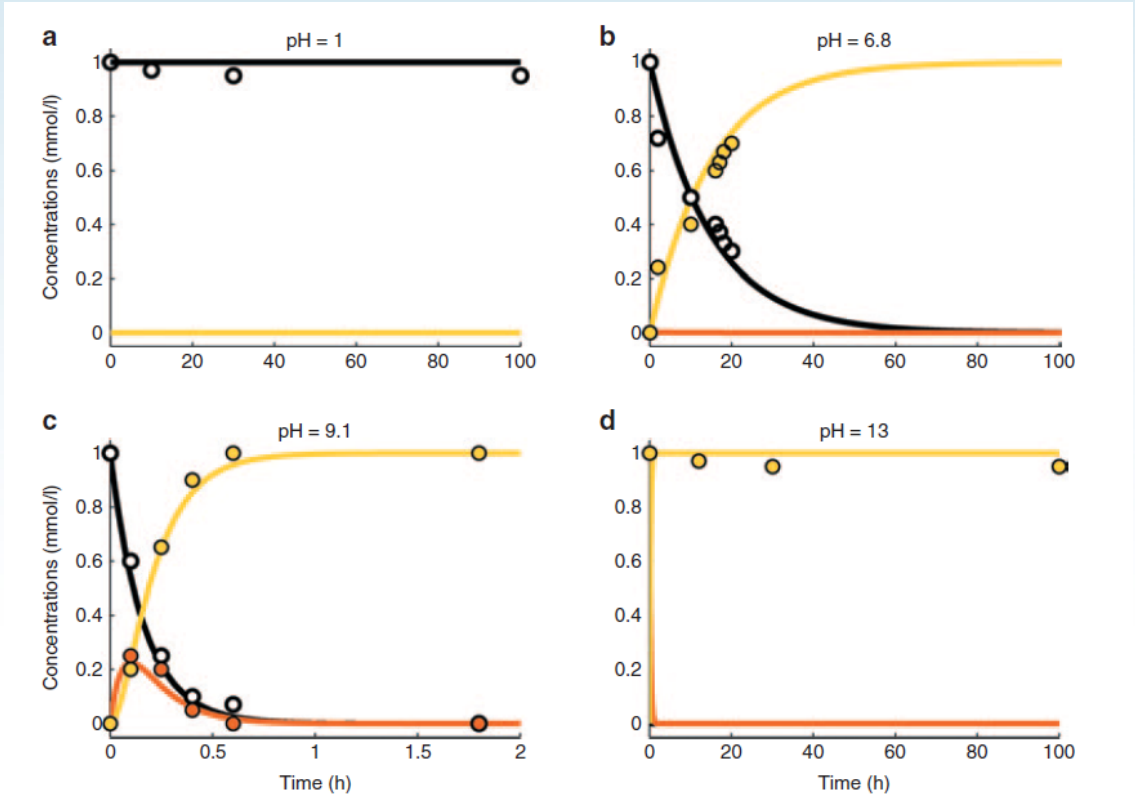
$$\frac{dA}{dt} = k_M M$$

pH-dependent parameters: $k_T(pH) = k_{T0} e^{\lambda_T pH}$

$$k_M(pH) = k_{M0} e^{-\lambda_M pH}$$

1.TMZ PK in buffer solutions

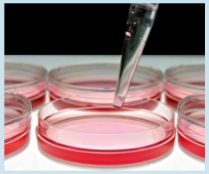
- Parameter estimation from data in Andrasi et al., 2010:



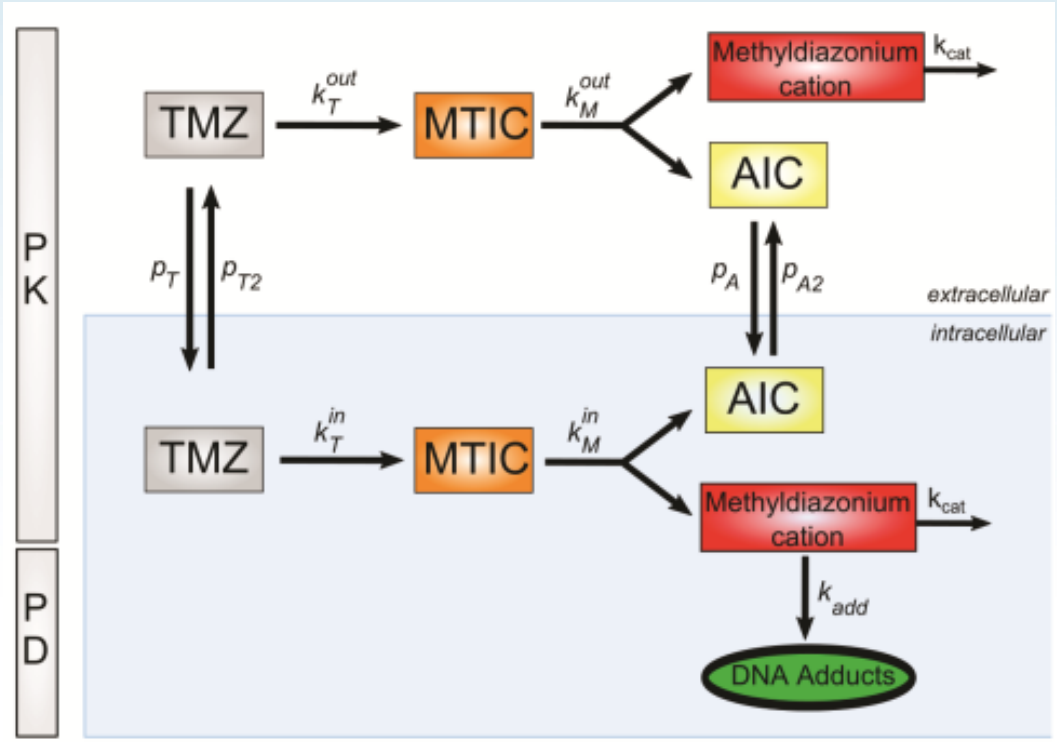
Optimal parameter values:

$$\begin{cases} k_{T0} = 1.1\,10^{-7}\ h^{-1} \\ \lambda_T = 1.96 \\ k_{M0} = 292\ h^{-1} \\ \lambda_M = 0.33 \end{cases}$$

To be used in the cell culture study



2.TMZ PK in U87 glioma cultured cells



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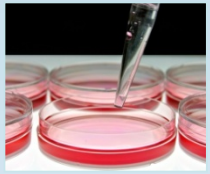
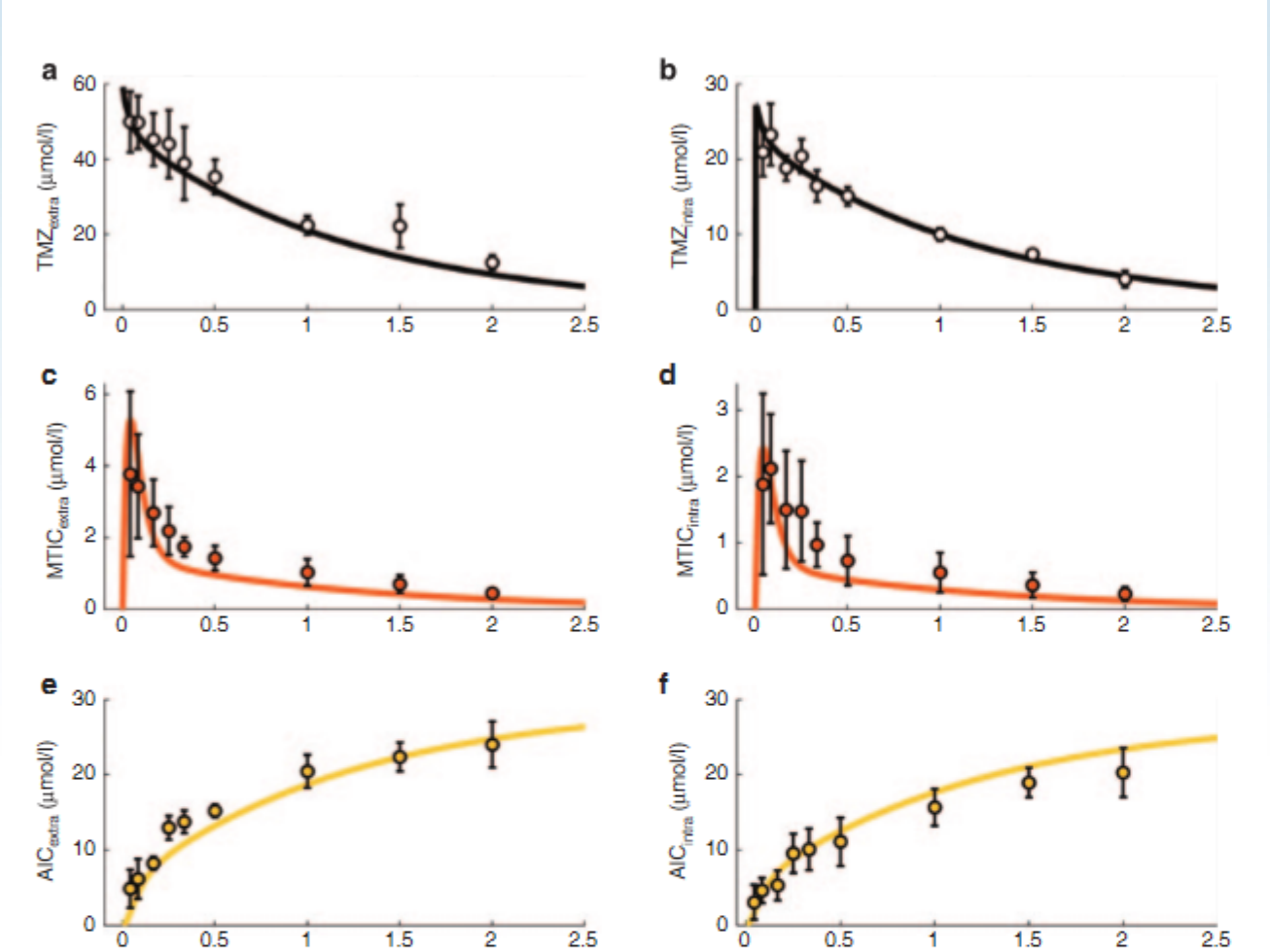


2.TMZ PK in U87 cells: Data fit



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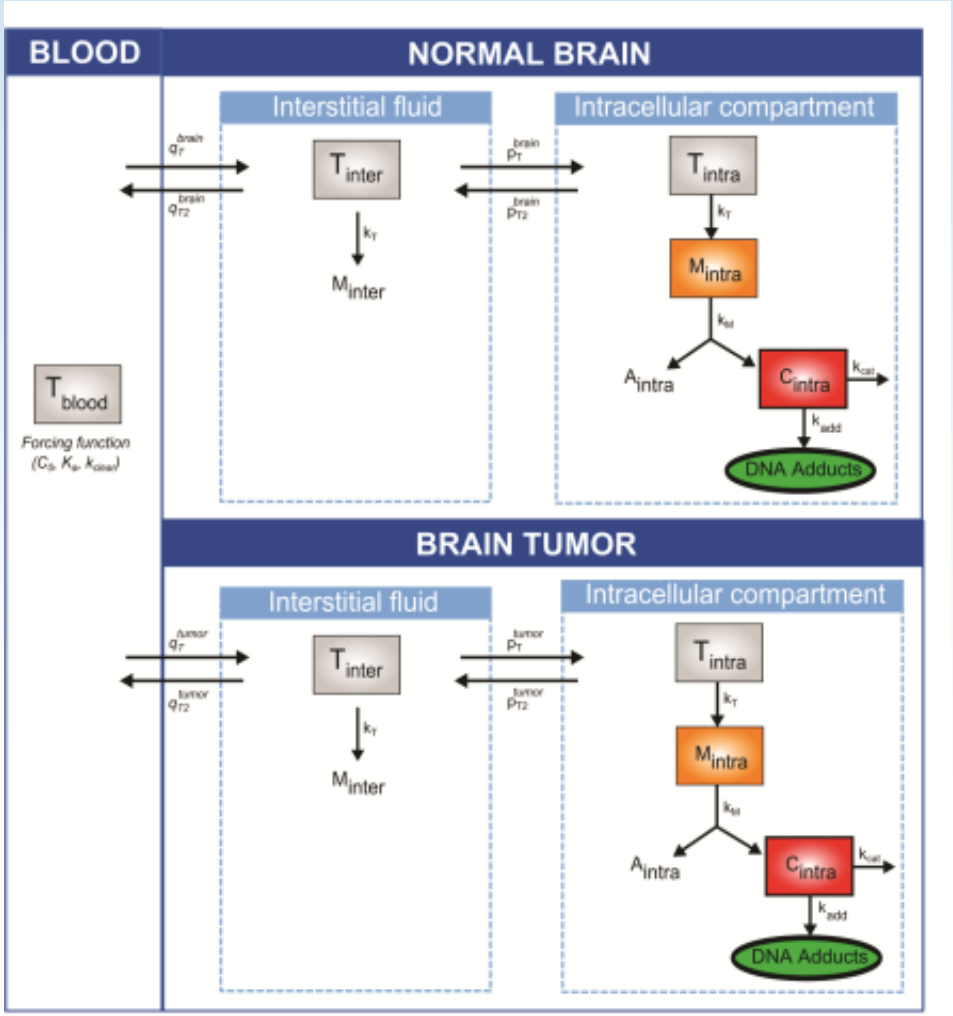
3. TMZ brain disposition in mice



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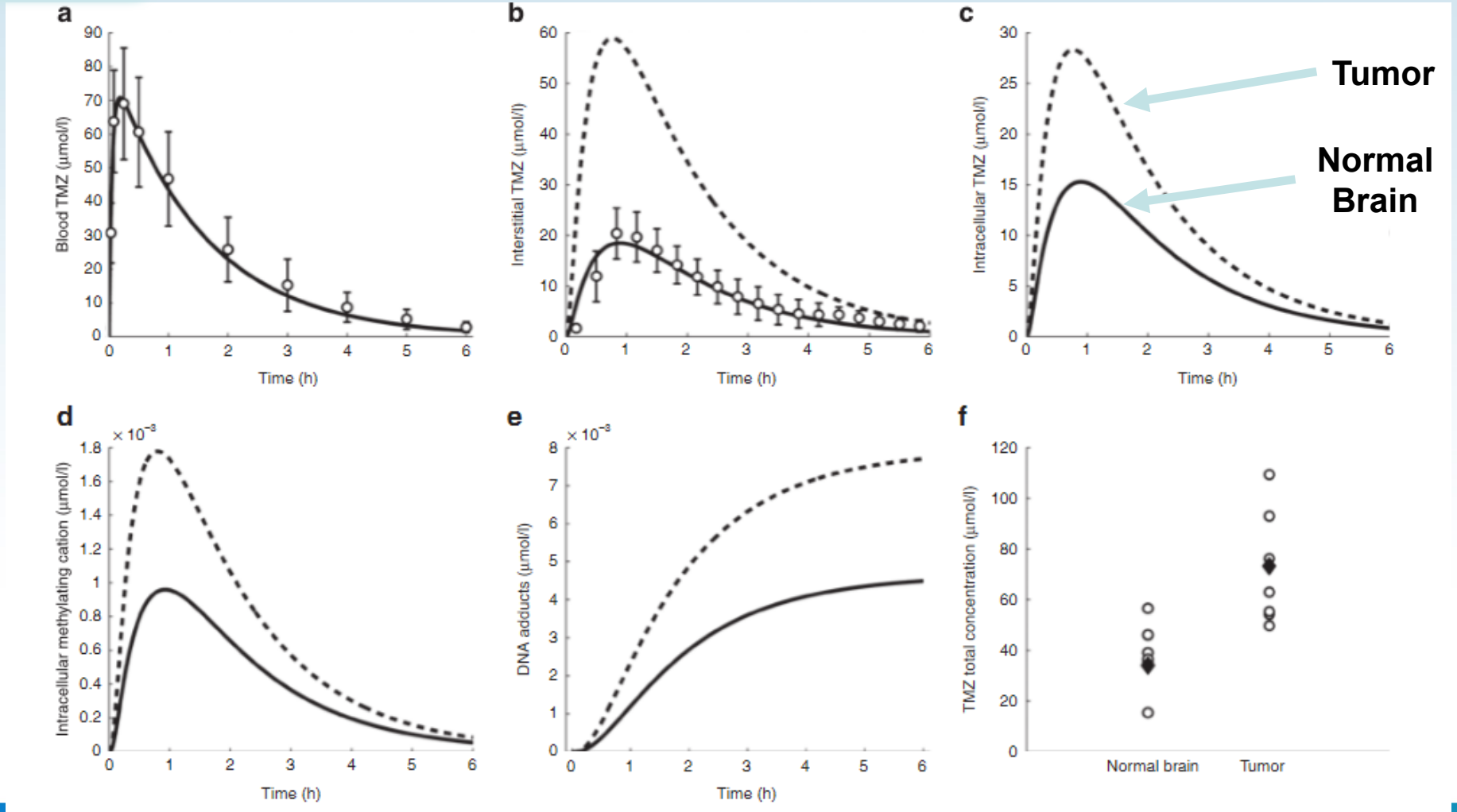

Orthotopic nude mouse model of U87 human glioma cells, blood and normal brain microdialysis

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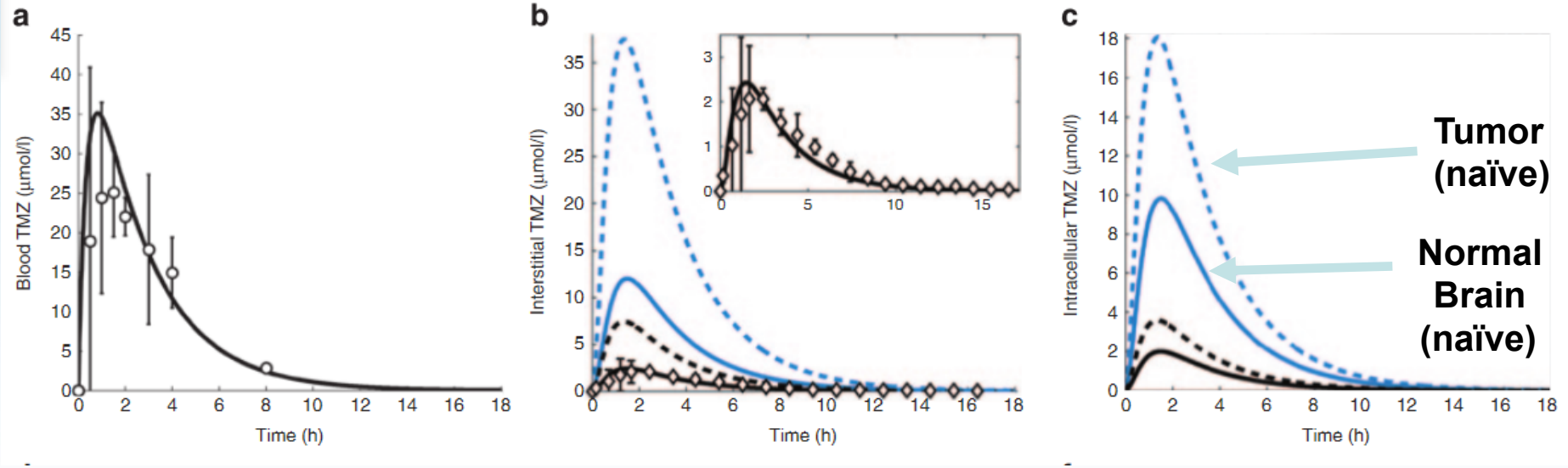
4. TMZ brain disposition in patients



Dots= clinical data from literature, Black=clinical data fit, Blue=Naïve scaling from mice.

- Naïve scaling from mouse overestimate human brain concentrations by approx. 5 fold
- Human mechanistic model of TMZ PK

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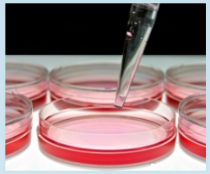
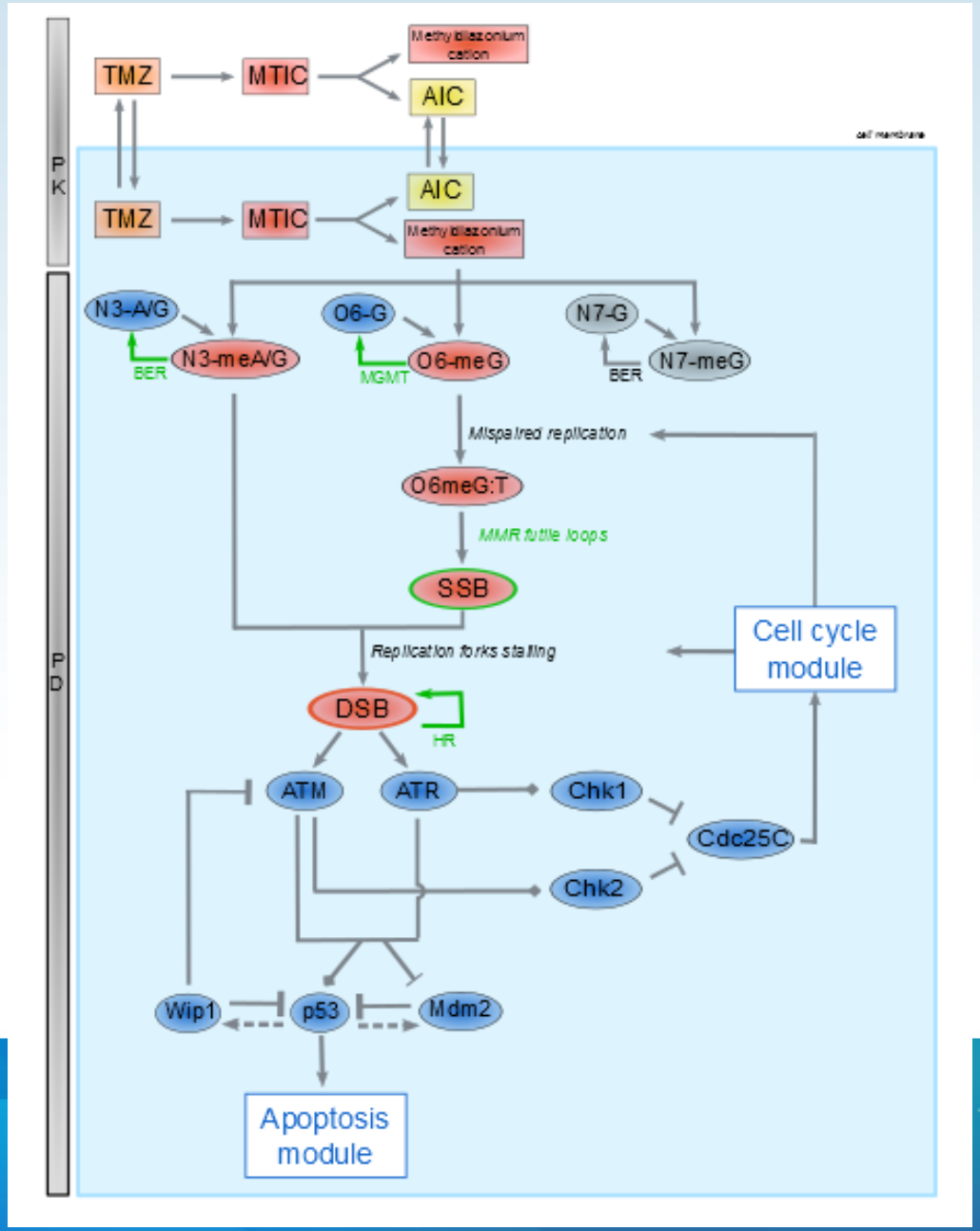


ii. TMZ PK-PD



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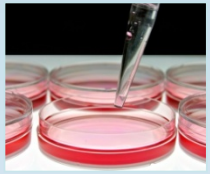
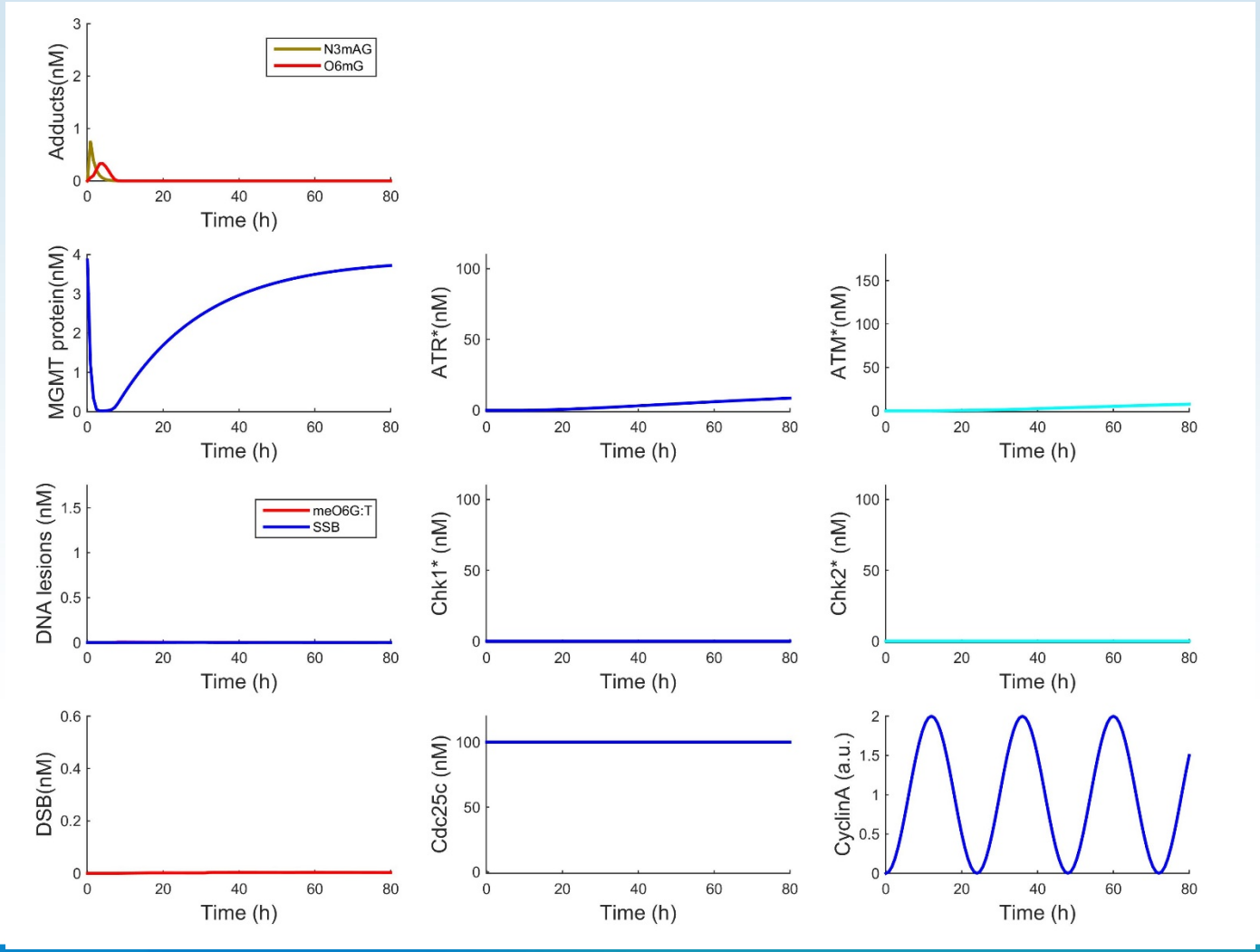
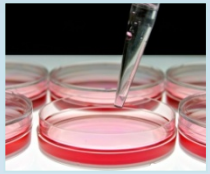
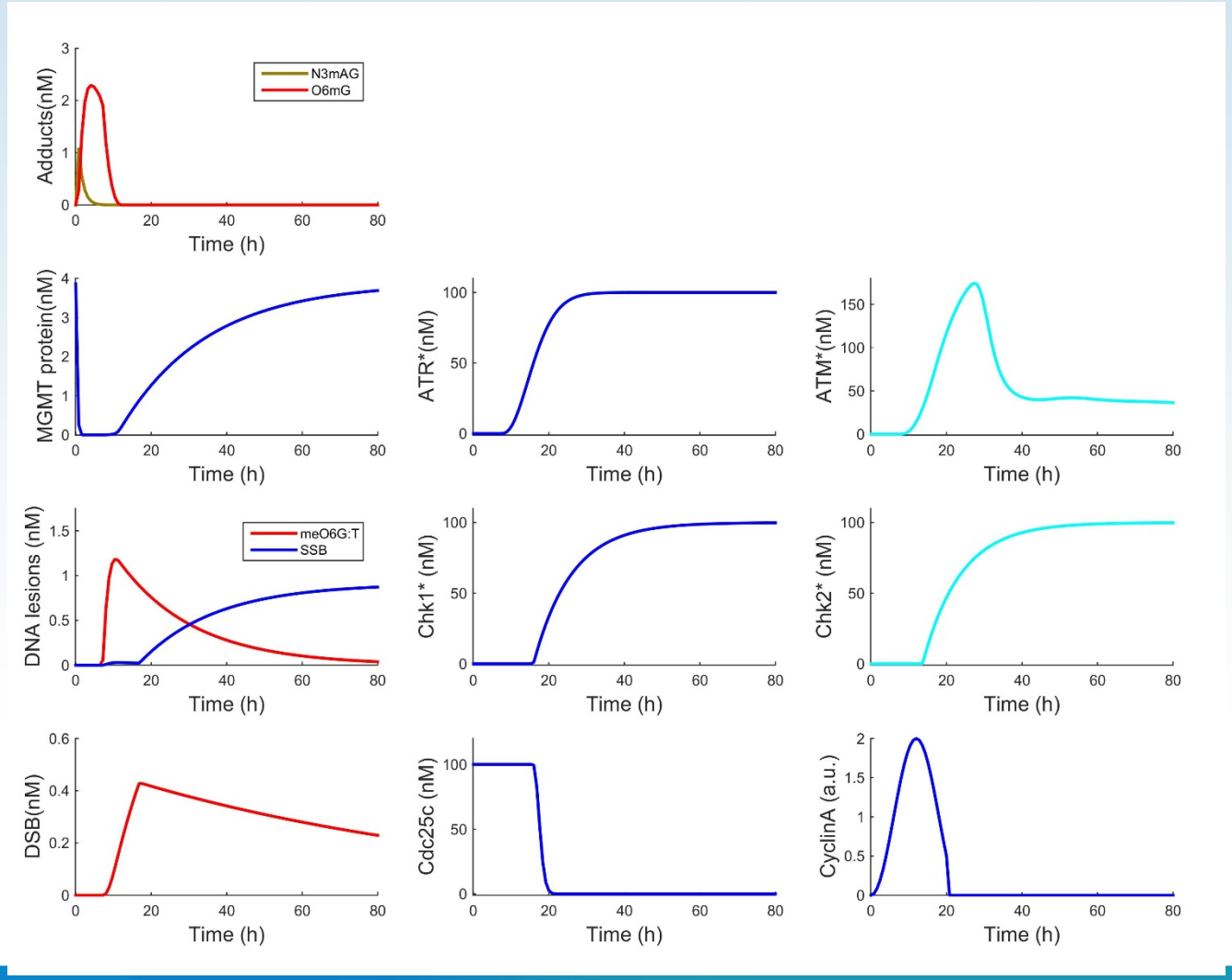


Low TMZ doses: DNA damage is repaired



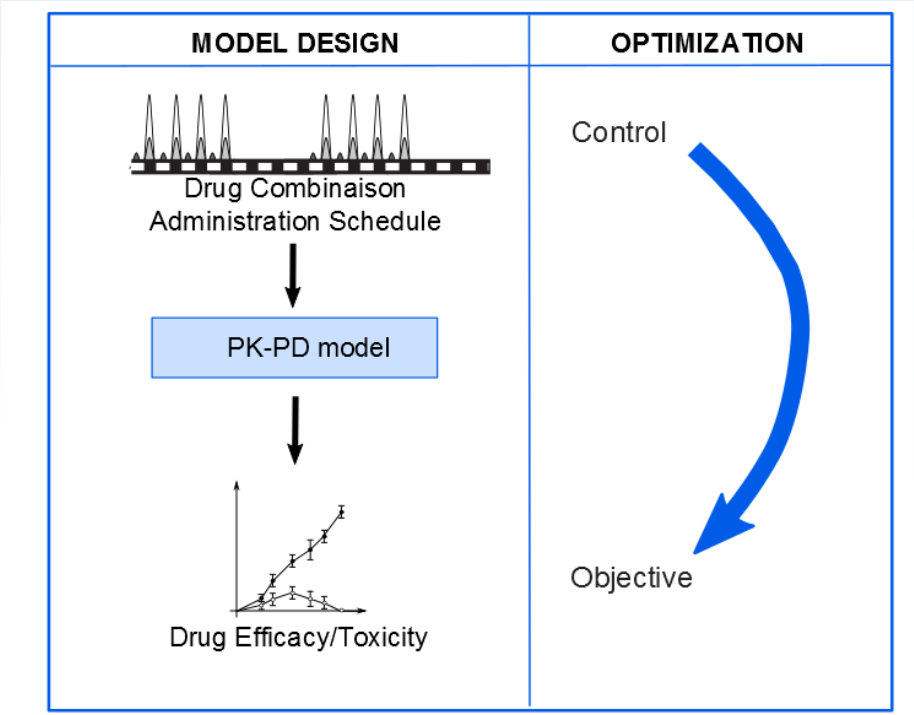


High TMZ doses: cell cycle arrest



Towards Personalized Combination Therapies

- **Calibrate protein levels to patient-derived cell lines**: (Institut du cerveau et de la moelle épinière, Paris)
- **Patient-specific combination therapies**: maximal anticancer efficacy under restricted doses

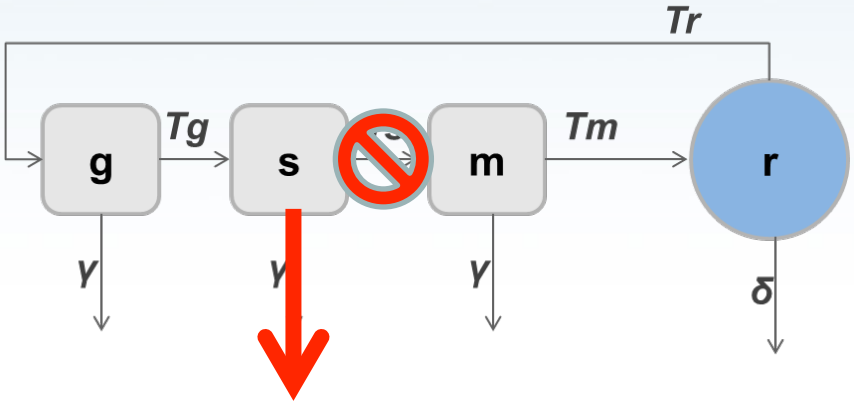


Conclusion

- Validated physiologically-based systems pharmacology approach to optimize combination anticancer therapies
- TMZ PK quantitavely characterized in cultured cells, preclinical and clinical studies; Ongoing work on TMZ PD
- Towards optimization procedures for treatment personalization
- **Future**: cancer cell population and tumor microenvironement

Perspectives

- In collaboration with Thomas Lepoutre (Inria, Lyon)
- Cancer cell population dynamics: PDE model structured in time and age of the cell in its current phase of the cell cycle.



$$\frac{\partial g}{\partial t} + \frac{\partial g}{\partial a} = -(d + T_g(a))g$$

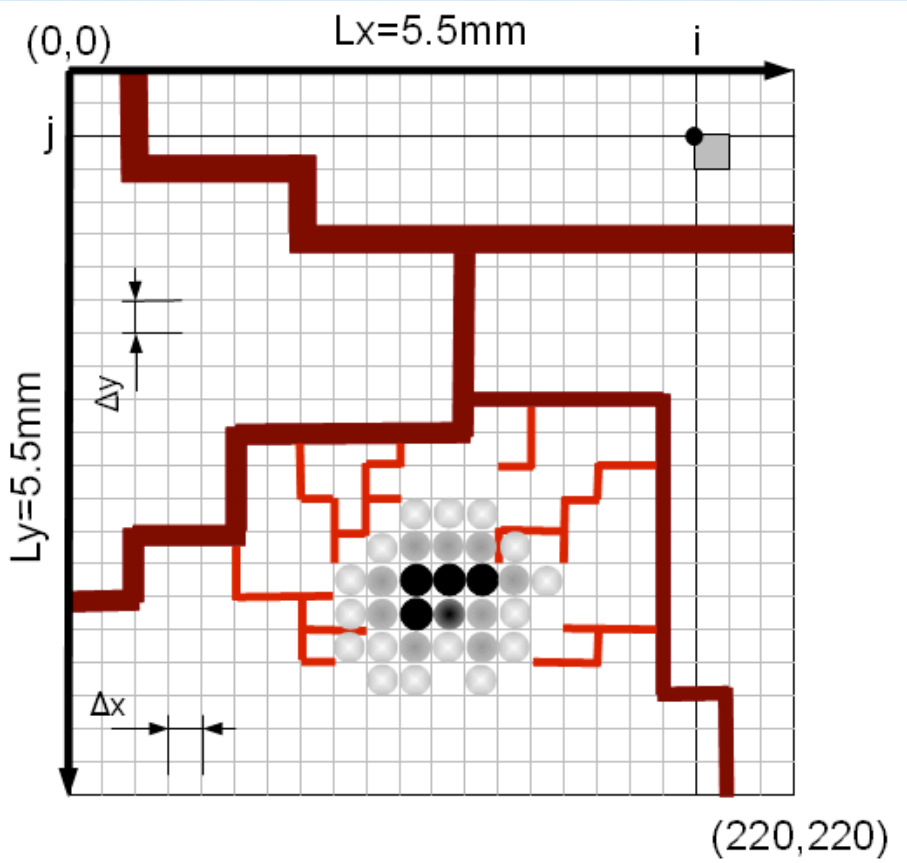
$$g(t, a = 0) = \int_0^{+\infty} T_r(a) r(t, a)\, da$$

Perspectives

- In collaboration with Angélique Stéphanou (TIMC-IMAG, Grenoble)
- Hybrid tumor model: agent-based model and space-structured PDEs

Tumour growth
Metabolism, **drug response**, cell cycle and death

Angiogenesis, vascular adaptation
Vessels permeability, diffusion of oxygen and **therapeutic molecules**



Collaborators

Mount Sinai School of Medicine, NYC

- Prof James Gallo
- Dr Hua Lv
- Dr Xiaoyan Zhang
- Dr Stéphanie Zhou

Institut du Cerveau et de la Moelle Epinière, Hopital La Pitié Salpétrière, Paris

- Dr Ahmed Idbaih
- Dr Maité Verreault
- Dr Lauriane Goldwirt