A mechanistic mathematical model predicts optimal patient selection and dosing schedules for PARP inhibitor/radiation combination therapy for glioblastoma

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Background
There is great interest in combining PARP inhibitors (PARPi) with radiation therapy for treatment of glioblastoma. This is based on promising preclinical data, particularly the ability of PARPi to radiosensitize radioresistant stem-like cells thought to be responsible for treatment failure. This strategy is currently being evaluated in early phase clinical trials. However, it is not known how to optimally schedule the combination therapy or which patients will benefit from it. We are using mathematical and mouse modelling to address these questions.

Methods
We developed and parametrized an ordinary differential equation-based mechanistic mathematical model of glioblastoma response to PARPi/radiation combination therapy using preclinical and clinical data. The model accounts for the differential treatment response of stem-like and differentiated cells and, additionally, incorporates the effects of p53 and PTEN mutations. We (retrospectively) validated the model using longitudinal MRI and survival data from genetically engineered mouse models (GEMM) and intracranial patient-derived xenografts (PDX) with different p53 and PTEN statuses. We then used the validated model to predict which patients would benefit from the combination and optimize dosing schedules to maximize survival.

Results
The model successfully predicted the response of GEMMs and PDXs with different p53 and PTEN statuses to different radiotherapy schedules. The model predicts that p53-deficient tumors will receive little benefit from the addition of PARPi to radiotherapy. This prediction was successfully validated using multiple PDX datasets. The model predicts that p53 wild-type tumors will receive a substantial survival benefit from the combination therapy. Optimized schedules initially reduce the total cell number before enriching for quiescent stem-like cells at the end of treatment.

Conclusions
Patients with p53 wild-type tumors are good candidates for PARPi/radiation combination therapy. We established novel schedules, informed by mathematical modelling, that will be prospectively evaluated in preclinical trials. If successfully validated, these will inform future clinical trials of PARPi/radiation combination therapy.

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