How to determine a new drug combination for Temozolomide-resistant brain tumor cells, through cellular Pharmacokinetics/ Pharmacodynamics Model

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Résumé

Temozolomide (TMZ)-based chemotherapy is the most common pharmacological treatment in patients with diagnosed Glioblastoma multiforme (GBM), the most frequent and aggressive type of primary brain tumours in adults. Even if TMZ administration has improved patient overall survival, the prognosis remains dismal and no major therapeutic advance has been accomplished within the past 10 years. This may be related to the tumour heterogeneity and plasticity ultimately leading to treatment escape, such challenge being further complicated by large inter-patient variability.

This work presents a new quantitative systems pharmacology approach combining experimental and mathematical expertise to design efficient TMZ-based combination therapies. Since multiple regulatory pathways may be deregulated initially or activated upon drug exposure in GBM cells, this study aims to identify which targeted molecules, affecting key intracellular functions (DNA repair, cell cycle, apop- tosis, etc.), can be associated with TMZ to enhance its efficacy. This concept of synthetic lethality is implemented thanks to a mechanism-based approach consisting of an ODE model of TMZ pharmacoki- netics - pharmacodynamics (PK-PD), evaluated in two cancer cell populations- TMZ sensitive and TMZ resistant LN229 GBM human cell- to account for tumor heterogeneity.

The cellular model was able to reproduce multi-type datasets of several independent studies, performed in both LN229 cells. The calibrated PK-PD model was used as a powerful tool to investigate new multi- drug strategies. Any combination of TMZ with a single targeted molecule required almost entire inhibition of the target to be effective. The optimal strategy,

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defined as the one minimizing TMZ dose and inhibition level of molecular targets in both cell lines, consisted in combining TMZ to two inhibitors of distinct repair pathways. It is currently investigated experimentally.