OPTIMIZE-NB

Title Optimizing first-line therapy for aggressive neuroblastoma by systems medicine strategies overcoming secondary drug resistance.

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Project partners

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Abstract While most tumors respond to the initial therapy, the recurrence of tumors and the evolution of therapy resistance remains a major medical problem. Current therapy schedules are shaped by the contingencies of their historical development and have not undergone rational optimization to effectively induce tumor cell apoptosis and cellular senescence, and thus prevent recurrence. The applicants of OPTIMIZE-NB have previously collaborated in systems biology consortia on neuroblastoma (NB) - a genetically well characterized and often fatal malignancy of early childhood. The low genetic complexity of this and other pediatric cancers offers a unique chance to delineate and tackle core disease mechanisms with minimal noise from passenger mutations. Through combining single-cell-resolved in-vitro approaches with mathematical modeling, we have previously established that clonal regrowth of

neuroblastoma after therapy is initiated from a small subpopulation of "resister" cells that form a subset of the tumor mass with recognizable molecular and functional properties. We have also shown in initial experiments that these properties could be exploited for the rational improvement of therapy. In this project, we aim to systematically optimize treatment schedules for the first-line therapy of aggressive NB by combining computational research, in vitro experiments on patient-derived NB cell lines and NB mouse models. To this end, we will develop data-based mathematical models and perform bioinformatic work to mechanistically understand vulnerabilities created by recurrent oncogenic lesions in aggressive NBs and devise optimized schedules for co-treating with conventional chemotherapy as well as molecularly targeted therapies. We will then systematically and quantitatively evaluate in vitro how resister cells arise during chemotherapy, how combinations of targeted drugs and chemotherapy can specifically target these resister cells, and how to schedule the different therapy components for optimal therapy outcome. To verify and understand the complex process of drug response in vivo, we will evaluate the optimized schedules for the co-application of conventional chemotherapy and molecularly targeted therapies in established NB 3D cultures/organoids as well as mice and zebrafish models. To make a direct impact on the clinic, we will focus on treatment options that – when proven successful in these preclinical settings – can immediately enter clinical trials: (1) the temporal treatment regimen and dosage of conventional combination chemotherapy of aggressive neuroblastoma with 6 different drugs, and (2) the combination of chemotherapy with already approved targeted drugs with an ALK inhibitor as first proof-of-principle. Promising results of OPTIMIZE-NB will be translated into an improved design for the upcoming clinical phase III NB trial, NB-HR 2017.

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