Through a modelling approach, our study presents: (1) a 2D model of a monolayer of tumor cells and a 3D model. In all model variants, we systematically investigate how the therapeutic outcome is affected by properties of the virus (e.g., the rate of viral spread), the tumor (e.g., production rate of resistant cells, cost of resistance), the healthy stromal cells (e.g., degree of resistance to virus) and the timing of treatment.

Results We find that various therapeutic outcomes are possible when resistant cancer cells arise at low frequency in the tumor. These outcomes depend on an intricate balance between the death rate of infected cells, where faster death leads to rapid virus clearance and cancer persistence. Our simulations reveal three different causes of therapy failure: rapid clearance of the virus, rapid selection of resistant cancer cells, and a low rate of viral spread due to the presence of infection-resistant healthy cells. Our models suggest that improved therapeutic efficacy can be achieved by sensitizing healthy stromal cells to infection, although this remedy has to be weighed against the toxicity induced in the healthy tissue.

Conclusions Through a modelling approach, our study provides insight into the dynamics of oncolytic virotherapy and resistance within a spatial framework. We demonstrate that the outcome of virotherapy depends not only on the parameters governing virus replication and the spatial architecture of the tumor but also on the presence of resistant-cancer and -stromal cells that act as a barrier to the spread of oncolytic virus. We hope that our computational approach aids in defining the impact of the various factors that may influence resistance and therapeutic efficacy of virotherapy. We are confident that our results, along with experimental observations, can assist the scientific community in improving the design of virotherapy.

Weblink to the preprint and the model: (https://www.biorxiv.org/content/10.1101/2022.04.06.487254v1)
SIOP therapy protocol, we immunohistochemically stained formalin fixed, paraffin-embedded slides of nephroblastoma specimens for T-cell, B-cell, NK-cell and macrophage markers (CD4, CD8, CD20, CD57, CD68). Quantification and comparison between different histologic regions (epithelial, blastemal and mesenchymal) as well as immune cell infiltration analysis was done using HALO AI by indica labs.

Results Out of the three histologic regions of nephroblastoma, the highest concentrations of T-cells and macrophages were found in mesenchymal regions (CD68+: 1884.70 cells/mm² and CD8+: 58.76 cells/mm²), the least in blastemal regions (CD68+: 662.31 cells/mm² and CD8+: 4.48 cells/mm²). Concentrations in epithelial regions were found to be in between (CD68+: 1560.16 cells/mm² and CD8+: 19.96 cells/mm²). Furthermore, overall immune infiltrates of T-cells and macrophages were lowest in patients experiencing tumor relapse (4/85 nephroblastoma patients) or metastasis (9/85 nephroblastoma patients) (p-values for overall relapse vs. no relapse were 0.0004 in CD68+ cells and 0.016 in CD8+ cells).

Conclusions Lowest immune infiltrates of T-cells and macrophages are found in the more stem cell like blastemal regions of nephroblastoma as compared to epithelial and mesenchymal regions. Overall low immune cell infiltrates of T-cells and macrophages are associated with a worse patient prognosis. Taken together this data could provide a tool for risk group stratification and improve therapy outcome.