Malignant brain tumors are amongst the most lethal solid tumors. The gold standard in therapy is concurrent radiochemotherapy, using the alkylating compound temozolomide (TMZ). It has been proposed that stem-like tumor cells mediate therapy resistance and regrowth.

We identified stem-like cells in human glioblastoma, gliosarcoma, oligodendroma and oligoastrocytoma. These cells exhibited a substantial heterogeneity with respect to proliferation rate and growth as spheres, adherent or semi-adherent cultures. Based on the expression of the intermediary filaments Nestin and GFAP, the transcription factors Sox2, Oct4, Nanog, as well as regulators and signalling molecules, such as p53, EGFR, PDGFRα, and PTEN we defined subtypes of stem-like brain tumor cells (SCIC). CD133 expression varied largely between different SCIC lines. We determined the responsiveness of SCIC subtypes to TMZ and chloroquine and related it to the expression of the repair enzyme MGMT and key players in apoptotic and autophagic processes.

Dose curves showed that responsiveness to TMZ was significantly different. Strong responsiveness to TMZ did not only depend on the methylation status of the MGMT promoter but on additional features, some of which appeared to be related to the SCIC stemness state. Co-application of chloroquine, a drug used in malaria prevention, which presumably affects autophagy, enhanced responsiveness of SCIC to TMZ in a dose-dependent manner. Both, TMZ and chloroquine induced cleavage of PARP, a key player in apoptosis and a measure for caspase 3 activity. The levels of cleaved PARP, however, differed largely between the various SCIC lines. Expression of Beclin and LC3B, proteins which are associated with different autophagy-associated processes were up-regulated in some but not all SCIC-lines. This indicates, that different SCIC subtypes respond differently to cell death inducing reagents and parallels our findings concerning the different proliferation and differentiation capacity of SCIC subtypes.