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TOMATO BUSHY STUNT VIRUS NANOPARTICLES AS A PLATFORM FOR DRUG DELIVERY TO SHH-DEPENDENT MEDULLOBLASTOMA

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Plant viruses, noninfectious for animal cells, structurally stable, biocompatible and biodegradable, may be considered as self-assembling nano-containers, easy to decorate with targeting ligands by genetic or chemical modification, and rapidly produced at low costs using plants as biofactories. Thanks to these peculiar features, they have proven to be excellent candidates for a wide range of applications in nanomedicine. Their potentialities as possible drug delivery vehicles have been tested on some type of cancers, but only rarely on brain tumors that are more challenging to be reached for the presence of the highly selective blood–brain barrier (BBB). We have focused our attention on Sonic Hedgehog-dependent medulloblastoma (SHH-MB), the MB variant arising in young children (<3 years of age), with the highest risk of unfavorable outcome, exploring the possibility to use the tomato bushy stunt virus (TBSV) as novel candidate for the targeted delivery of drugs to this tumor. TBSV, type member of the genus Tombusvirus, is an icosahedral virus of 30 nm in diameter made up of 180 subunits of the coat protein (CP). TBSV nanoparticles (NPs) can both encapsulate or expose on the surface small molecules and polypeptides, are neither toxic nor teratogenic, and when intravenously injected into mice do not induce alterations of tissues/organs. Chimeric TBSV (cTBSV) NPs were designed and constructed to

display peptides specific for targeting cancer cells, and were produced on large scale in Nicotiana benthamiana plants. Purified cTBSV NPs were tested on primary cultures of Shh-MB cells and on their cerebellar precursors, both derived from Patched1 heterozygous (Ptch1+/-) knockout mice, the most widely studied model of MB, allowing to define the peptides most efficient in inducing the specific uptake of the viral NPs. In vitro experiments demonstrated also that the delivery of Doxorubicin through the cTBSV NPs allows to reduce the dose of the chemotherapeutic agent necessary to induce a significant decrease in tumor cells viability. Moreover, the systemic administration of TBSV NPs in MB symptomatic mice confirmed the ability of the virus particles to reach the tumor in a specific manner.

Overall, these results open new perspectives for the use of this TBSV-based delivery platform for the targeted delivery of drugs to MB, reducing early and late toxicity.