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Characterisation of new therapeutic targets for invasive paediatric gliomas

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Diffuse midline glioma (DMG in English) is one of the most fatal pediatric brain cancers. The only treatments available are chemotherapy and radiotherapy, but they are not very effective. Therefore, it is urgent to find targeted treatments to improve the care of these children. Genomic and epigenomic studies have identified an important mutation that affects histone H3. The result of the mutation is a substitution of Lysine 27 for Methionine (H3K27M) which is the source of 80% of DMG and deregulates the PRC2 complex (Polycomb Repressive Complex 2), including the enzymatic activity of EZH2, which is therefore being studied as a therapeutic target. Chemical inhibition of EZH2 in vitro by GSK126 induces a decrease in tumor growth of DMG lines and cell death by apoptosis. To study the response of DMG cells to GSK126 treatment, proteomic analysis shows the induction of proteins involved in cholesterol synthesis. Based on these results, a combined strategy was developed and studied in vitro, 3D cultures (spheroids) and in vivo in chorioallantoic membrane of the chick embryo and in an orthotopic mouse model. Low dose GSK126 treatment in combination with inhibitors of enzymes involved in cholesterol synthesis showed strong growth inhibition in combination treatments, but not in single treatments, both in DMG cells in vitro and in DMG spheroid cultures. This efficacy has been validated in vivo, on the preclinical chicken embryo model and the orthotopic intracranial DMG mouse model. Our results reveal an unexpected sensitivity inducible by GSK126 to inhibitors of cholesterol biosynthesis in highly aggressive pediatric glioma and warrants further evaluation as a new treatment strategy. This combination therapy is expected to have few side effects due to the low dose used to achieve significant anti-tumor activity

Biography

Currently, she carries out a research activity in the Pasteur Institute in Paris after her thesis at the University of Bordeaux, France, where she conducted research on the diffuse midline glioma or DIPG. During these studies, she was able to discover a combination of reconstituted treatment of methyltransferase inhibitor and an anti-hypercholesterolemia drug that was effective in vitro and in vivo reducing tumor growth of DIPG. This combination therapy should have few side effects due to the low dose used to achieve significant antitumor activity. She was able to launch a new therapeutic approach “epi-drugs” which is based on the use of epigenetic inhibitors in combination with other drugs to produce synergistic effects.