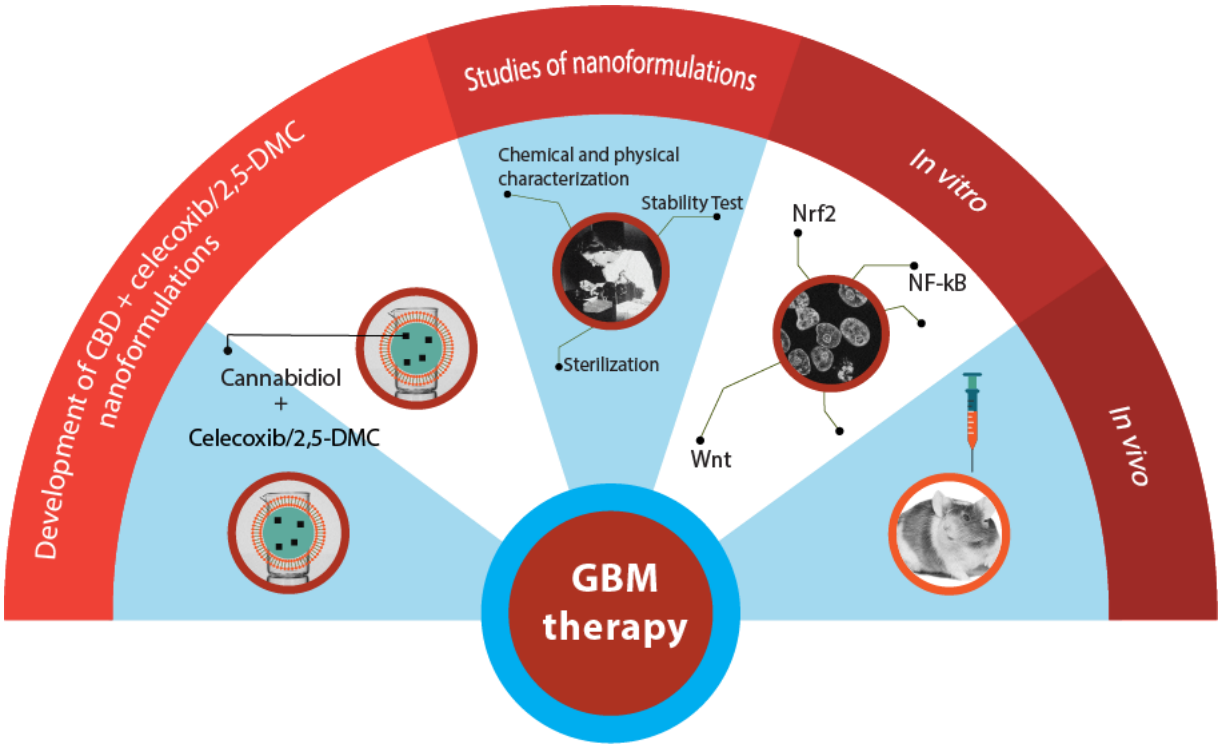
For the general audience

Recently, an increasing incidence of brain tumors has been reported from multiple studies. Glioblastoma (GBM) is the most common and the most deadly brain tumor in adults. The current gold standard for GBM treatment includes surgery, adjuvant radiotherapy, and temozolomide chemotherapy. Unfortunately, the GBM stem cells that remain after surgery and survive these aggressive treatments lead to almost inevitable tumor recurrence. GBM is thus refractory to all currently available therapies. Thus, novel treatment options for GBM that enhance or work in conjunction with conventional treatments are urgently needed.

The aim of this project is to find a novel therapeutic strategy based on the application of the **liposomal nanoformulations of CBD with celecoxib and CBD with 2,5-dimethylcelecoxib (2,5-DMC), which due to their anticancer properties could enhance the standard GBM treatment with temozolomide**. Studies show that CBD, the cannabinoid from *Cannabis sp.* has strong anticancer properties, reducing the growth of many tumor types, including GBM. Our previous studies proved that also the anti-inflammatory drug, celecoxib, and its dimethyl analog, 2,5-DMC, halt the growth of GBM cells, interfering with its crucial signaling pathways and inducing apoptotic death of tumor cells.

In this project, we hypothesize that simultaneous administration of CBD and celecoxib, or CBD and 2,5-DMC may exert an even stronger anticancer effect than the administration of these compounds as single agents. Additionally, in this project, we plan to load the substances into modern, nano-sized drug carriers, namely liposomes, which due to their lipophilicity and small size, cross the blood-brain barrier and reach the tumor cells more efficiently. In this project, we want to verify if such nanoformulations augment the effects of temozolomide and could potentially become a new adjuvant therapy, supporting a standard GBM treatment.

Thus, the planned research goals include 1) preparation and the physico-chemical analysis of the liposomal nanoformulations of CBD with celecoxib/2,5-DMC; 2) the analysis of their impact on GBM cells viability, proliferation, cell cycle, apoptosis, the ability to generate oxidative stress, as well as the ability to modulate Wnt/β-catenin, NF-κB, and Nrf2 pathways. This part of analysis will be performed *in vitro*, using three GBM cell lines. Besides the cancer cells, also normal, non-cancerous astrocytes will be used in order to verify if the analyzed nanoformulations are not toxic to healthy brain cells; 3) the third research goal will include the analysis, if the chosen (based on the results of the previous analysis) nanoformulation will be effective *in vivo*, in a mouse GBM xenograft model. In this stage of research we will compare the impact of the nanoformulation *per se*, and administered together with temozolomide. Eventually, we will verify if the proposed nanoformulation may become a candidate for the adjuvant therapy of GBM.



Schematic representation of the planned research of liposomal nanoformulations of CBD and celecoxib/2,5-DMC in the treatment of GBM