Study of the effect of flubendazole on the glioblastoma multiforme cells *in vitro* and *in vivo*

Glioblastoma multiforme (GBM) belongs to one of the most common and most aggressive primary brain tumours in adults. Current therapeutic strategy is insufficient, and patient's prognosis is unfavourable, therefore prompting an intensive effort to improve therapeutic options of GBM. Present research focuses mainly on the identification of the new possible targets for therapy or on the optimalization of already existing treatment strategies in GBM. Highly discussed approach to GBM therapy is microtubule targeting, which is one of the fundamental ways to tumour treatment. For this purpose, chemotherapeutics already in current common practice or drugs originally intended for a different indication, such as flubendazole (FLU), originally human and veterinary anthelmintic, could be used. In previous studies FLU has already demonstrated an inhibitory effect on cells of various solid tumours and haematological malignancies through a specific interaction with microtubules. The aim of this work was to evaluate the inhibitory effect of FLU in different *in vitro* and *in vivo* GBM models.

Study of FLU effect was performed *in vitro* using stabilized GBM cell lines (A172, T98G and U118MG) and GBM primary cultures derived from samples obtained from patients undergoing surgery at the University Hospital Hradec Králové. FLU demonstrated an inhibitory effect on the GBM cell viability and proliferation at significantly lower concentrations than the commonly used chemotherapeutic agent temozolomide. Concurrently FLU significantly affected GBM cell morphology, damaged microtubule structure and organisations, altered other components of GBM cell cytoskeleton leading to significant cell shrinkage. FLU also affected the expression and activation of the STAT3 molecule, its administration led to G2/M cell cycle arrest with subsequent apoptotic cell death.

The effect of FLU was further verified *in vivo,* in tumours generated after implantation of the GBM cell line U118MG into the model organism, the athymic mouse. After FLU administration, up to 4 times smaller tumours with lower proliferative activity were formed. In addition, the inhibitory effect of FLU on the STAT3 molecule expression was confirmed in such tumours.

FLU was demonstrated as a suitable potential antitumor drug with inhibitory effect on GBM cells. Results of this work emphasize the necessity of further research in FLU mechanism of action, focusing mainly on the interaction of FLU with the microtubules and STAT3 signalling pathway.