Background: Glioblastomas (GBMs) are highly aggressive brain tumors. Despite recent improvements in surgical treatment, radiotherapy and chemotherapy, the 5-year survival rate for patients with GBM remains low and novel and tailored therapies are needed. Various pathways are involved in gliomagenesis, among which the Wingless (Wnt) signaling. Dickkopf protein-related protein 3 (Dkk-3) interacts with proteins of Wnt pathway as inhibitor. The Wnt signaling contributes to activity of the claudins, that are critical components of tight junctions (TJ), whose expression was altered selectively in cerebral microvessels of GBM. The mutations of this pathway show clinical implication, because they lead to the onset of several cancers, including brain tumors, being also involved in tumor angiogenesis. The aim of this study was to determine the role of Wnt pathways to directly regulate tumor grown, apoptosis process by targeting Dkk-3, TJ alteration involving claudin-5 and to suggest possible therapeutic interactions involving Wnt/Toll-like receptors (TLRs) pathways.

Methods: In the present study we investigated the expression of Dkk-3, claudin-5, apoptosis markers and TLR-4 receptor protein levels in in vitro studies on U-138MG and A-172 human glioblastoma cell lines and in GBM human patient's tissues.

Results: We showed a significant Dkk-3 and Claudin-5 downregulation, with the apoptosis process involvement and with an interesting TLR-4/Wnt modulation.

Conclusions: We concluded that combined modulation of Wnt/Dkk-3/claudin-5 and TLR-4 pathways, simultaneously targeting apoptosis and survival signaling defects, might shift the balance from tumor growth stasis to cytotoxic therapeutic responses, flowing in greater therapeutic benefits.