Abstract

Charles University, Faculty of Pharmacy in Hradec Králové

Department of Biophysics and Physical Chemistry

Supervisor: Dr. Pavel Bárta

Student: Nikta Mehdizadeh

Title of thesis: In vitro study of ^{161}Tb-labelled human monoclonal antibody ramucirumab

Glioblastoma, characterized by its invasive growth and resistance to conventional treatments, presents a significant therapeutic challenge. Anti-angiogenic therapies, which aim at the inhibition of the formation of new blood vessels that nourish tumours, offer a promising avenue for combating glioblastoma. Ramucirumab, specifically targeting vascular endothelial growth factor receptor 2 (VEGFR-2), disrupts tumour vascularization and impedes tumour growth. The presented thesis delves into the development of a potential radiotherapeutic agent for the treatment of glioblastoma, an aggressive and often fatal form of brain cancer. The study focused on the enhancing ramucirumab's therapeutic efficacy by its labelling with the therapeutic radionuclide terbium-161, creating a potential novel radiopharmaceutical for targeted radionuclide therapy.

The research involved the conjugation of ramucirumab with a bifunctional chelator, DOTA, to enable stable attachment of terbium-161 radionuclide. Subsequently, radiolabelling was performed, and the resulting radiopharmaceutical underwent rigorous quality control and saline/serum assessments to ensure its high radiochemical purity and stability. The *in vitro* binding affinity and internalization of the radiolabelled ramucirumab were evaluated in human glioblastoma astrocytoma cells (U-87 MG) expressing VEGFR-2.

The results demonstrated successful radiolabelling of ramucirumab with terbium-161, achieving high radiochemical purity and stability. *In vitro* studies revealed significant binding

affinity and internalization of [^{161}Tb]Tb-DOTA-ramucirumab in U-87 MG cells, indicating its potential to selectively target and deliver therapeutic radiation to tumour cells. The stability of the radiopharmaceutical in biological media further supports its potential for *in vivo* applications.

These findings highlight the potential of ^{161}Tb-labelled ramucirumab for the targeted radionuclide therapy in glioblastoma, warranting further investigation in preclinical and clinical settings. The ability to selectively deliver therapeutic radiation to VEGFR-2-expressing tumour cells offers a promising approach for enhancing the efficacy of glioblastoma treatment while minimizing damage to healthy tissues. This targeted approach holds the potential to improve patient outcomes and quality of life by providing a more precise and effective treatment option for this devastating disease.