RAMAN Spectroscopy enhanced imaging of Glioblastoma in Cell Culture and in Vivo Model

Summary

Development of a 3D Spectroscopy enhanced imaging technology to improve Brain Tumor resection. Research will be focused in this initial study phase on glioblastoma cell cultures and mice in-vivo glioblastoma model Student shall access the MD-PhD Graduate Program of the University of Bern

Research field: Neuroscience
Supervisor: Prof. Dr. Michael Reinert
Status: The position is available.
Offered by: Neurocentro della Svizzera Italiana, EOC Ospedale Civico di Lugano

Description

Raman Spectroscopy enhanced imaging of Glioblastoma in Cell Culture and In-vivo Model

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Project Description:

Of all cancers, brain tumors represent the most intimidating and difficult to treat type of tumor. Considering the estimated incidence of 60 per 100'000 population for intracranial neoplasms including primary and metastatic lesions, the treatment of patients with brain tumors constitute a significant obligation for health care professionals and social institutions. In 2004 the annual cumulative costs for brain tumor care in Switzerland were estimated of 175 million CHF, which, considering the prevalence poses by far the highest per per patient cost of all neurological diseases. Glioblastoma (GBM) is the most common and aggressive primary brain tumor, resulting in disproportionally high rates of morbidity and mortality. With an annual incidence of up to 7 per 100'000 this malignant glioma reaches an annual age- adjusted mortality rate of approximately 4 per 100'000. The median age at the diagnosis is 56-64 years whereby 10% of patients are younger than 50 years. In contrast to other solid cancers such as breast and colon tumor, no stage dependent cure can be expected and the disease is practically always fatal regardless of early detection and maximal radiooncological therapy. Despite their aggressiveness, the vast majority of malignant gliomas do not metastasize systemically, and therefore systemic control of disease is not relevant in GBM. However, a major factor determining therapeutic failure is the highly infiltrative characteristic of glioma cells. Undetectable by current intraoperative imaging techniques they invade and migrate

over considerable distances into with conventional techniques registered normal tissue. Using intraoperative functional stimulation techniques such as continuous electrophysiological stimulation, surgical resection can be augmented to a maximum up to 1mm of functional eloquent structures. Contemporary standard treatment consists of maximal surgical resection, followed by concomitant radiotherapy and chemotherapy with temozolomid. The median survival time thus can be augmented to 14.6 months, whereby the median time to recurrence is estimated at 6.9 months. Longer recurrent free survival has been paralleled with completeness of resection. However completeness of resection is question of debate regarding the nature of extension. Although advances in intraoperative techniques such as the introduction of fluorescence with 5-delta-aminolevulinic acid and intraoperative electrophysiologic mapping has further augmented the surgical resection, the visualization of tumor in the marginal areas however has remained a surgical challenge. Chasing the last remnant of infiltrative tumor has shown to have a positive effect on progression free survival and hence outcome.

Therefore surgical techniques which help visualize in the depth the remnant part of infiltrative tumor not visible to the human eye and possibly not visible directly on the surface of the resection, represents the next generation of intraoperativ tumor recognition.

Gold nanoparticles (GNPs) are bio-inert and widely nontoxic and thus appear promising also due to their multiplex labeling properties. GNPs have been applied to enhance local radiotherapeutic effects, can deliver chemotherapeutics as well as antibodies for cancer-targeting and treatment, transmit agents for thermotherapy and can deliver small interfering RNA for gene regulation. GNPs are already used in FDA approved clinical trials. Raman spectroscopy reporter molecules can be tagged to GNPs can be delivered into the brain and spectral detection of GNPs with surface enhanced Raman scattering (SERS) can be distinguished to a ultra high sensitivity and specificity making the spectrum analogous to a fingerprint. Tuning the GNPs specificity for GBM cells is a further challenge to extend or optimize directed tumor cell detection. Cell receptor may therefore be used as a target for nanoparticle homing to tumors. GNPs loaded with monoclonal endothelial growth factor receptor (EGFR) antibody can be internalized by EGFR expressing GBM cells. In this context it must be noted that 40-60% of GBM cases exhibit EGFR amplification and EGFR overexpressions.

Aim of the current study

The aim of the current study is to develop an improved 3D visualization of glioblastoma for in vivo resection using RAMAN microscopy. Therefore tumor specific GNPs will be developed and injected into mouse harboring a xenograft induced model of GBM. In a second phase GNPs will be specifically improved for GBM subtypes.

With the envisaged findings of this study a possible new approach for surgical resection of glioma will be possible. The biomolecular structure of tumors are different in each patients and intraoperative imaging may be selectively enhanced depending its specific spectrum, meaning that in future previous to a total resection of glioma a biopsy of tumor will reveal the biomolecular spectral analysis of receptors of the tumor, thus selective intraoperative injection of targeted GNPs

will permit complete tumor visualization in 3D and permit tumor resection, possibly also in lower grade gliomas.

Research Focus

The Doktorand will be working mainly on in –vitro and in –vivo Mice GBM Models in the laboratories of the Neurocenter of Southern Switzerland and the Department of Neurosurgery of the University of Basel. Together with the FHNW and IAP UNIBE the bio-availability in gliomas will be studied in cell cultures as well as in-vivo tumor resection in the mice.

The photo-acustic signaling in the in-vivo model will be assessed in a second phase at the IAP UNIBE.

The Doktorand shall be introduced into the MD- PhD Program of the University of Bern

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