Maria Sklodowska-Curie
National Research
Institute of Oncology
Gliwice Branch

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title	**Image-guided delivery of molecularly targeted radioimmunotherapy to FAP-positive glioblastoma (GBM) tumours**
Short Project Title	Targeted radioimmunotherapy to FAP-positive glioblastoma

SUPERVISORY TEAM	
Primary Supervisor	**Prof. dr hab.n.med. Gabriela Kramer-Marek**
Associate Supervisor(s)	To be selected

DIVISIONAL AFFILIATION	
Primary Division	**Radiopharmacy and Preclinical PET Imaging**
Site	**Gliwice, Poland**

PROJECT PROPOSAL

Research background:

Despite intensive therapeutic regimens, almost all patients with GBM eventually relapse, mainly due to diffuse microscopic infiltration of tumour cells into the surrounding brain parenchyma and relatively immune-depleted ("cold") GBM microenvironment. **Therefore, identifying and targeting cooperative pathways within a particular GBM subtype is likely to lead to new treatment paradigms that will ultimately allow more efficient tumour suppression and durable responses.**

Cancer-associated fibroblasts (CAFs) are prominent stromal components with diverse functions (e.g., mutual signalling interactions with cancer cells; cross-talk with infiltrating leukocytes). CAFs are also a substantial source of growth factors (e.g. PDGF, EGF), cytokines and chemokines (e.g. IL-8, TNFα, CCL) that promote tumour growth and can modulate immunotherapy responses. Several studies have recently demonstrated a link between down-regulation of fibroblast activation protein (FAP), one of the most prominent CAF markers, and the inhibition of tumour growth and progression. Of note, it has been recently revealed that **subpopulation of GBM cells with mesenchymal signatures overexpress FAP**. **Importantly, GBMs with mesenchymal features have also elevated levels of PD-L1,** and therefore, may be more amenable to immunotherapy.

Therefore, we **hypothesise that locoregional administration of molecular radionuclide therapy** using cytotoxic radioisotope such as lutetium-177 (β^- emitter), conjugated to FAP-targeting vector, will selectively deliver high doses of this therapeutic to residual GBM cells left within the tumour bed and **will enhance response rates to anti-PD-L1 immunotherapy**. Furthermore, we postulate that **PET imaging** using FAP-specific **^{68}Ga-radiopharmaceutical** will non-invasively **measure FAP expression level** at the baseline and its changes post-delivery of the radioimmunoconjugate.

PROJECT AIMS

Aim 1: **To radiolabel** with **gallium-68 FAP-specific peptide** and **to optimise** the radiochemical yield, metabolic stability, and pharmacokinetics of this novel radiopharmaceutical.

Rationale: Although ^{18}F-FDG remains the most widely used PET imaging agent, the high uptake by surrounding normal brain tissue limits its use for the imaging of GBM tumours. Similarly, most of the amino acid-based PET tracers, including ^{18}F-FET, suffer from various levels of physiological background uptake in the grey

matter of the brain and acute inflammatory lesions. Recently, the diagnostic utility of FAP-specific small-molecule quinoline-based radiotracers (FAPI-74 and FAPI-46) has been established and the high FAP expression level confirmed in GBM patient using the gallium-68 labelled DOTA-bearing analogue (^{68}Ga-FAPI-46). However, FAPI radiotracers exhibit very rapid clearance from the tumours which limit their potential therapeutic effectiveness. **Boulding on these results, we plan to prepare a peptide-based radioconjugate** in order to: **i) better understand the relationship between FAP protein expression level and immune suppression in GBM** tumours with mesenchymal features and, **ii) facilitate the design of combinatorial immune therapeutic paradigms** that can restore and/or induce robust tumour immunity.

Aim 2: **To investigate** whether **FAP specific PET radiotracer** will non-invasively **capture dynamic changes in FAP** expression in the brain setting.
This aim will provide us with insights on the *in vivo* behaviour of the ^{68}Ga-DOTA-Pep in different animal models and allow optimisation of the protocol for image-guided delivery of the therapeutic regimen using ^{177}Lu-DOTA-Pep (***Aim 3***).

Aim 3: **To determine** whether **targeting FAP** in combination with PD-L1 inhibitor **enhances the overall anti-tumour immune response** augmenting tumour T cell infiltration. The key question is:

1) Will ablation of FAP+ stromal and tumour cells by targeted radioimmunotherapy (^{177}Lu-DOTA-Pep) decrease the immunosuppressive GBM tumour microenvironment (TME) and enhance the sensitivity to anti-PD-L1 inhibitors?

CANDIDATE PROFILE	
Pre-requisite qualifications of applicants	MSc (Master's degree)
Intended learning outcomes:	The student will learn: - The background to *in vitro* and *in vivo* assessment of novel PET radioligands - PET/MRI/BLI image acquisition and analysis - The role of immuno-oncology agents in glioblastoma models - Assessment of immune cell infiltrates by immunohistochemistry, flow cytometry, ELISA - Assessment of TME using molecular techniques
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☒ **Biological Sciences** ☐ Physics or Engineering ☒ **Radiochemistry** ☐ Maths, Statistics or Epidemiology ☐ Computer Science ☒ **Medicine**
Deadline for applications:	**20.08.2023** (23:59, CET+1)
Form of application:	https://rekrutacja.polsl.pl/tematy/#1684836553467-007e9b39-cc0a email: Gabriela.Kramer-Marek@gliwice.nio.gov.pl Gabriela.Kramer-Marek @icr.ac.uk
Doctoral stipend:	**PLN 4425/month (take-home pay)**