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"Early molecular nanoDIAGnostics of Brain tumors using Immune-PET" (DIAGBI)

The use of nanocarriers for diagnostic imaging have meant significant advantages for Positron Emission Tomography (PET) imaging. These nanocarriers can be engineered to confer to the imaging agents with a number of functionalities, which ultimately impact their biodistribution and, hence, their capacity to reach their target. This advanced PET imaging involves the combination of a functionalized nanocarrier platform with a radioisotope component. This strategy is particularly interesting for the design of antibody-based PET radiotracers, a field that is raising significant attention due to the increase in the number of monoclonal antibodies (mAbs) molecules in the context of personalized medicine in cancer.

This new generation of so-called immuno-PET imaging agents has shown the ability to target the radiotracer specifically to those cells over-expressing the targeted surface protein, thereby providing a high-level imaging of a highly specific cell population. Several clinical trials have shown the potential of immuno-PET for assessing both tumour selectivity and toxicity of mAbs before treatment administration. As such, immuno-PET is already becoming mainstream in many types of cancer such as myeloma, lung cancer, breast cancer, different types of urological cancer, hepatocellular carcinoma or gastric cancer, among others.

Nevertheless, the use of immuno-PET agents for imaging brain tumours has encountered significant challenges due to the difficulty for their transport across the BBB and subsequent diffusion across the brain tissue. In this proposal (DIAG-BI), our major goal is to confront this challenge thanks to the use of nanotechnology. We will take advantage of recent findings in the development of functionalized nanocarriers to overcome the BBB to design, develop and validate in vitro and in vivo new immuno-PET radiotracers for the molecular diagnosis of brain tumours. Our approach will be tested as a tool to provide the pharmacokinetics and biodistribution of mAbs targeting different proteins (HER3 and EGFRVIII) of Glioblastoma Multiforme (GBM), the most common and aggressive brain tumour. Non-invasive molecular diagnosis is fundamental for the correct management of GBM patients. The identification of such proteins will facilitate diagnosis, provide information about prognosis and identify therapeutic targets (HER3 and EGFRvIII) without the need to perform surgical procedures to obtain tumor specimens.

The project includes the following activities:
(1) molecular characterization of GBM through in vitro test of anti-HER3, developed and patented by a partner of the consortium, and the commercially available anti-EGFRVIII
(2) analysis of extracellular vesicles (EVs) in plasma with the aim of evaluating the presence of the selected molecular targets
(3) design and optimization of synthetic nanocarriers for the transport of novel PET immuno-radiotracers
(4) radiolabelling of anti-HER3, anti-EGFRVIII and all the nanocarriers used for their transport
(5) in vivo PET imaging using the developed nano-immuno-radiotracers in patient-derived xenograft models of GBM
(6) Finally, assess the pathway for bringing the developed PET biomarkers into future clinical trials.

Regarding the latter, the results of DIAG-BI project can be considered as a technology platform for brain tumors, as the specific mAbs, the nanocarrier and the radiotracer can be fine-tuned to a personalized level. This approach increases exponentially the value, both clinical and commercial, of the proposal and helps to enlarge the useful life of the developed technology. Definitely, the emergence of new different therapies in the management of brain tumours and poor prognosis of this disease, makes the objectives of the DIAG-BI project an unavoidable challenge for the long-awaited personalized medicine in these patients.