Development of antibody radiolabeled drug conjugates (ARDC) using 195mPt-Carboplatin for theranostic approach in ovarian cancer

Context

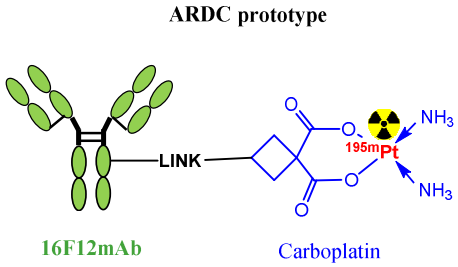
Due to the ovary anatomical location and the absence of early symptoms, many of ovarian cancers are diagnosed at an advanced stage (i.e., stage III and IV) when it has already spread over the peritoneum as peritoneal carcinomatosis (PC). Treatment has consisted for long in cytoreductive surgery followed by intravenous chemotherapy based on platinum (cisplatin or carboplatin) and taxanes (paclitaxel, docetaxel). However, the relapse rate remains high (50%) with a 5 year-survival rate between 25% and 50% and new treatments are required.

Over the last years, targeted radionuclide therapy (TRT) or more specifically radioimmunotherapy (RIT) has appeared as a new tool in cancer therapy. In TRT, radionuclides are administered to patients with cancer to selectively irradiate tumour cells with alpha, Auger or beta particles. RIT is a TRT form in which monoclonal antibodies (mAbs) are used as carriers. It is successfully employed for the treatment of radiosensitive non-Hodgkin lymphoma B (Zevalin® approved in Europe and USA in 2002, and Bexxar® approved in USA in 2003). RIT also represents an attractive tool for treating solid tumours and many radiopharmaceuticals are currently tested in clinical phase I/II or III trials (e.g., ^{177}Lu-octreotate in neuroendocrine tumours and ^{90}Y-clivatuzumab in pancreatic cancer). However, it is still challenging because solid tumours are more radio-resistant than haematological malignancies. High linear energy transfer (LET) particles including Auger electrons as emitted by ^{195m}Pt have a high LET of 4 - 26 keV/µm and are expected to produce locally multiply damage sites in cells and particularly when DNA-targeted leading to high cytotoxicity. ^{195m}Pt is a particularly attractive Auger electron emitter since it can be incorporated in chemotherapeutic drugs, namely cisplatin or carboplatin (Azure *et al.* Biophys Res Com 1992). ^{195m}Pt emits a mean number of 33 electrons per decay. For this reason, it is the most interesting Auger emitter available for clinic today. Moreover, it has a physical half-life of 96.5h which is suitable for clinical applications. Auger electrons emitted by ^{195m}Pt range from few nm to about 80 µm leading to a very weak side irradiation. In addition to Auger electrons, ^{195m}Pt emits gamma rays (129.8 keV (2.8%), 98.9 keV (11.9%)) that could be used for diagnostic applications. Therefore, the ^{195m}Pt-based radiopharmaceutical could be used in a theranostic approach (Zeevart *et al.* J Label Comp Radiopharm 2013).

Project Summary (with expected results)

The project aims at developing an antibody radiolabeled drug conjugate (ARDC) for the diagnosis and treatment of ovarian peritoneal carcinomatosis using the 16F12 mAb patented by us in 2014, and directed against Mullerian Inhibiting Substance type II Receptor (MISRII) expressed by ovarian cancer cells. 16F12 mAb will be bound to radioactive carboplatin (^{195m}Pt/^{193m}Pt-carboplatin) using a proteolytically cleavable peptide linker (LINK) allowing release of ^{195m}Pt/^{193m}Pt -Carboplatin within cell cytoplasm after mAb internalization. The platinum ^{195m}Pt emits cytotoxic high LET (LET) Auger electrons. The project will consist of synthesizing ^{195m}Pt-carboplatin-LINK-16F12 mAb (ARDC) and assessing its biological properties *in vitro* and *in vivo* in mice. The new ARDC will combine targeting properties of 16F12 mAb with alkylating and high LET radiation properties of

carboplatin and ^{195m}Pt, respectively. We expect it to overcome solid tumor resistance to treatments while being accompanied of few toxicities.



Candidate profile

The purpose of this post-doctoral project will be to actively contribute to the validation of such ARDC with a first proof of concept. The candidate will be sequentially involved in the chemical development of the carboplatin-linker part, the ligation process to the mAb and finally the radiolabeling with platinum. In this context, we are inviting applications from **highly motivated organic chemists**. The candidate needs to have a *strong background in organic chemistry and structural analyses (NMR, MS). Skills and experience in the development of antibody drug conjugates and/or radiopharmaceuticals would be an advantage but is not a pre-requisite*.

This post-doctoral fellowship proposal is dedicated to worldwide **PhD students** who comply with the Marie Curie program mobility rules. (**Not to have stayed or worked in France for more than 12 months**, **during the 3 last years** and **not have stayed more than three years in a non-EU country)**.

The post-doc will start in fall 2016, for a period of 24 months. The contract will be signed with ENSCM (Ecole Nationale Supérieure de Chimie de Montpellier), institution involved in the **PRESTIGE program**.
The net salary will be around 2 400€/month.

Application / Submission

Please send a CV, a motivation letter and two recommendation letters to vincent.lisowski@umontpellier.fr and jean-pierre.pouget@inserm.fr

Deadline for submission of applications: 2016, September 30th
The successful candidate will be mainly hosted for chemistry in the Institute of Biomolecules Max-Mousseron (Team F9) in Montpellier (France).
Lab Website : http://www.ibmm.univ-montp1.fr/