Today, cancer treatments mainly rely on surgery or external beam radiation to remove or destroy bulky tumors. Chemotherapy is given when tumors cannot be removed or when dissemination is suspected. However, these approaches cannot permanently treat all cancers and relapse occurs in up to 50% of the patients’ population. Radioimmunotherapy (RIT) and peptide receptor radionuclide therapy (PRRT) are effective against some disseminated and metastatic diseases, although they are rarely curative. Most preclinical and clinical developments in this field have involved electron-emitting radionuclides, particularly iodine-131, yttrium-90 and lutetium-177. The large range of the electrons emitted by these radionuclides reduces their efficacy against very small tumour cell clusters or isolated tumour cells present in residual disease and in many haematological tumours (leukaemia, myeloma). The range of alpha particles in biological tissues is very short, less than 0.1 mm, which makes alpha emitters theoretically ideal for treatment of such isolated tumour cells or micro-clusters of malignant cells. Thus, over the last decade, a growing interest for the use of alpha-emitting radionuclides has emerged. Research on targeted alpha therapy (TAT) began years ago in Nantes through cooperation between Subatech, a nuclear physics laboratory, CRCNA, a cancer research centre with a nuclear oncology team and ITU (Karlsruhe, Germany). CD138 was demonstrated as a potential target antigen for Multiple Myeloma, which is a target of huge clinical interest particularly suited for TAT because of the disseminated nature of the disease consisting primarily of isolated cells and small clusters of tumour cells mainly localized in the bone marrow [1]. Thus anti-CD138 antibodies were labelled with bismuth-213 from actinium-225/bismuth-213 generators provided by ITU and used to target multiple myeloma cells [2]. In vitro studies showed cell cycle arrest, synergism with chemotherapy and very little induction of apoptosis [3].

The European Community 7th Framework Program TARCC (Targeting Alpha Radionuclides to Combat Cancer) project was a great opportunity to set up collaborative studies within a group a ten partners (Centre de Recherche en Cancérologie de Nantes-Angers, Division of Radiological Chemistry, Department of Radiology, University Hospital, Basel, Switzerland, Department of Nuclear Medicine, Klinikum Rechts der Isar + Institut für Radiochemie, Technische Universität Munchen, Munich, Klinik für Nuklearmedizin, Medizinische Hochschule, Hannover, Germany, Department of Radiation Physics, University of Gothenburg, Göteborg, Sweden, Department for Nuclear Medicine, University Medical Centre, Ljubljana, Slovenia, Subatech, Nantes, France, Institute for Transuranium Elements, Karlsruhe, Germany, Ion Beam Applications, Louvain-la-Neuve, Belgium and Inserm-Transfert, Paris). The TARCC project addressed several issues standing in the way of the development of TAT. Indeed, the use of alpha-emitting radionuclides in medicine has been hindered by a few devastating experiences with very long half-life radionuclides such as polonium-210. Such effects should not occur with short half-life alpha-emitting radionuclides, however the very high cytotoxic potential of high linear energy transfer (LET) radiation makes them potentially very effective but also potentially very toxic if their biodistribution and targeting is not carefully controlled [4]. It was the primary objective of the TARCC project to develop and test means to achieve this targeting in preclinical studies.

In summary, production of astatine-211 and labelling of phenylalanine and phenylalanine-analogues, peptides (substance P) [6] and antibodies [7,8] by electrophilic and nucleophilic substitution reactions were improved. New methods for astatine labelling (hypervalent astatine, aminooxy functionalized peptide resulting in stable oxime formation) were developed. The Pourbaix diagram of astatine in non-complexing medium was defined [9]. Peptide and protein labelling with bismuth-213 was optimized. A variety of peptides were synthesized: somatostatin analogues and somatostatin-based antagonists with high hydrophilicity and high affinity [10], metabolically stabilized gastrin derivatives [11], hybrid somatostatine/gastrin peptides, chelated and bismuth-213 and actinium-225-labelled tumour homing F3 peptide dimer [12,13] and bivalent haptons for pretargeting [14]. Labelling protocols were defined for all these molecules.

**ALPHA Emitting Radionuclides and Radiopharmaceuticals for Therapy**

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Preclinical studies were performed by systemic injections in prostate cancer with bismuth-213 or lutetium-177 labelled bombesin derivatives (DOTA-PEG4-bombesin [DOTA-PESIN] and DO3A-CH2CO-8-aminooctanoyl-Q-W-A-V-G-H-L-M-NH2 [AMBA]) [15], in colorectal cancer hepatic metastases pretargeted with TF2 bispecific anti-CEA x anti histamine-succinyl-glycine (HSG) antibody and bismuth-213-labeled bivalent HSG-hapten [14], in Multiple Myeloma in a syngeneic mouse tumour model disseminated in bone marrow targeted with bismuth-213-labeled anti-CD138 antibody [16] and in rat glioblastoma treated with astatine-211-labeled phenylalanine [17].

Rat glioblastoma was also treated by local injection of astatine-211-labeled phenylalanine and locally disseminated tumors were treated by local injection in SCID mice intraperitoneal MDA-MB-435 breast cancer xenografts of a dimer of the vascular tumour homing peptide F3 labelled with bismuth-213 [12,13], in HSC45-M2 gastric cancer peritoneal carcinomatosis treated by intraperitoneal injection of bismuth-213-labeled anti-d9-E-cadherin antibody [18,19] and in orthotopic human xenografts of EGFR-overexpressing luciferase transfected bladder carcinoma cell line EJ28 treated intravesically with bismuth-213-anti-EGFR-antibody [20].

Moderate to high tumour control was achieved depending on models, with higher efficacy of alpha-therapy when compared to lutetium-177 in the prostate cancer model [15]. Efficacy was found to decrease rapidly with tumour burden in all cases. Toxicity was manageable, but long term toxicity observed in liver or kidneys depended on vectors (peptide versus antibody) and the therapeutic index was very narrow, except for local administration, with a need for microdosimetry [21].

A relative biological effectiveness (RBE) around 5 for alpha versus photons or betas was confirmed in a few models and the study of cellular response to alpha irradiation at the level of gene expression was initiated [22, 23]. Alpha-emitters were shown to be effective for the eradication of hypoxic tumour cells by a direct comparison between alpha (bismuth-213-labeled anti-EGFR-antibody) and photons in hypoxic squamous epithelium carcinoma CAL33 cells [24].

These preclinical data established good proofs of principle that allowed participating groups to proceed to clinical studies, making TARCC a real success.

In the meantime, Arronax (an acronym for "Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique") was built by IBA in Saint-Herblain near Nantes [25]. Arronax is high energy, high intensity cyclotron dedicated to research in nuclear medicine and radiochemistry. Arronax and the cyclotron facility cost was over 37 M€ and financing came from regional institutions, the French government and Europe (EDRF). Its priorities are the production of astatine-211, copper-67 and scandium-47 for therapy, copper-64 and scandium-44 for PET imaging. Strontium-82 ($^{82}$Sr/$^{82}$Rb for PET in cardiology) and germanium-68 ($^{68}$Ge/$^{68}$Ga for PET in oncology) are produced as commercial radionuclides.

Today a multidisciplinary network is set in the Nantes area with Subatech (nuclear physics, computer simulation, radiochemistry, detectors including development of a 3 photon camera), CRCNA (nuclear oncology, imaging and therapeutic from chemistry to the clinic), the Nantes University Hospital and Cancer Centre Nuclear Medicine department, Oniris (Nantes Veterinary School with its micro-PET/CT, PET/CT and SPECT/CT for dogs, cats and monkeys), which received national support for Cancéropôle Grand Ouest, the Pays de la Loire Regional Council (NucSan Project) and the French "Investissements d’Avenir" (ArronaxPlus equipment of excellence and IRON laboratory of excellence).

Our major projects are to advance the treatment of minimum residual disease of prostate cancer using astatine-211-labeled desimmunized J591 antibody to the clinic (with Atlab Pharma SAS) and to continue preclinical studies for the treatment of multiple myeloma by alpha-immunotherapy using anti-CD138 antibodies and for pretargeted alpha-immunotherapy of colorectal cancer (Immunomedics, inc.).
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