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TEMPLATE RICHIESTA ATTIVAZIONE TOPIC AGGIUNTIVI SU FONDI PNRR

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Project title/Titolo del Progetto	Safety and dosimetry of labelled OncoFAP derivatives in patients with gastro-intestinal tumors
Principal Investigator	Arturo Chiti
Main field of interest/Ambito principale di ricerca	Diagnostica e terapie innovative nella medicina di precisione / Innovative diagnostic tools and therapies in precision medicine
Abstract	The objective of the project is to evaluate safety OncoFAP derivatives, radiolabeled with diagnostic and therapeutic aims. Data on the uptake, biodistribution, pharmacokinetics and excretion of OncoFAP derivatives is collected in pre-clinical models and translated in human studies. The value of small organic ligands for imaging of solid malignancies has been demonstrated in neuroendocrine tumors using a ligand for the somatostatin receptor 2 (SSTR2), in metastatic prostate cancer using a ligand for prostate-specific membrane antigen (PSMA) and in clear cell renal cell carcinoma using a ligand for carbonic anhydrase IX (CAIX). A high affinity moiety can be used to deliver not only diagnostic radionuclides such as 68Ga, but also therapeutic radionuclides such as 177Lu to the tumor. In the case of SSTR2 and PSMA, a similar molecular entity is used to deliver the diagnostic radionuclide for patient selection and the therapeutic radionuclide for radioligand therapy. However, these antigens are restricted to specific cancer indications only, which limits the broad applicability of these ligands. An ideal pan-tumoral target is Fibroblast Activation Protein (FAP). FAP is a membrane-bound endopeptidase that is overexpressed in the stroma of >90% of epithelial cancers including breast, gastrointestinal and lung cancer. OncoFAP was found to bind with very high affinity to both human (KD = 0.68 nM) and murine FAP (KD = 11.6 nM). The cross-reactivity between human and murine FAP facilitates the preclinical evaluation of OncoFAP. The selectivity of OncoFAP for FAP was confirmed by binding measurements against a panel of proteins including highly abundant plasma proteins such as serum albumin, none of which was observed to be bound by OncoFAP. Radiolabeled OncoFAP-DOTAGA showed a very rapid, selective, and high tumor accumulation in mice bearing subcutaneous FAP-expressing tumors, while it was rapidly cleared from the blood and healthy tissues. Notably, no accumulation was observed in tumors lacking FAP. The results from the in vivo biodistribution study thus confirmed the selective binding of OncoFAP to FAP and highlighted the promising pharmacokinetic and pharmacodynamic properties of the molecule as a radiotracer and as a therapeutic agent. Single-arm, phase I, multicenter study in patients with a suspected or confirmed diagnosis of solid tumour among breast cancer, colorectal cancer, oesophageal cancer, and pancreatic adenocarcinoma, requiring clinical staging for nodal and/or metastatic disease (based on institutional practice and risk stratification). All patients will undergo PET/CT imaging with [68Ga]Ga-OncoFAP.

	The clinical part of the PhD project will run under a clinical trial, that will be submitted for approval to the local ethics committee and to AIFA. Patients affected by colorectal cancer, gastro-oesophageal cancer and pancreatic adenocarcinoma will be enrolled. Uptake of the diagnostic radiopharmaceutical will be assessed and quantified with advanced image analyses techniques, in order to predict the feasibility of the therapeutical application of the companion radiopharmaceutical. Correlation of OncoFAP uptake with immunopathology staining for FAP will be evaluated in patients undergoing surgery or tumour biopsy collection.
Type of Co-funding	○ D.M. 352/2022 - Borse di dottorato cofinanziate dalle imprese[1]
Lab name and address	Advanced Image Analyses, Humanitas University and Nuclear Medicine Unit, IRCCS Humanitas
Brief description of the coherence of the Project in relation to the PNRR objectives[3]	The project will focus on the application in oncology of the theragnostic concept: using a molecule to detect a tumor's target and a compound molecule to hit the target with a local, super selective, radiation therapy. The theragnostic concept fits with the broader concept of precision medicine. The PhD program will run in collaboration with a dynamic and innovative pharmaceutical company, Philochem, that has an advanced laboratory for molecules development and pre-clinical studies. The clinical applications will be developed in the Nuclear Medicine Unit of the Humanitas Cancer Center, that has the capabilities of producing radiopharmaceuticals and run clinical trials. The PhD candidate will be motivated to generated data that will be available according to the principles of Open Science. Humanitas University has an international reputation and several connections with well known Universities. Philochem has close connection with the ETH Zurich and other European Universities. This will be an excellent environment for a PhD candidate aiming at building her/his education at a European level. Results of the PhD project will contribute to sustain Italian and European research in the field of radiopharmaceuticals.
N. of months abroad (min. 6, max. 18) [**compulsory**]	18
Name of the research institution/company abroad	Philochem
N. of months of internship (min. 6, max. 18) [compulsory only for D.M. 352/2022]	18
Name of the company[3]	Philochem
Scientific references	• Kelly, T., et al., Fibroblast activation protein-alpha: a key modulator of the microenvironment in multiple pathologies. Int Rev Cell Mol Biol, 2012. 297: p. 83-116. • Sollini, M., et al., State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging, 2021. 48(13): p. 4396-4414. • Millul, J., et al., An ultra-high-affinity small organic ligand of

	fibroblast activation protein for tumor-targeting applications. Proc Natl Acad Sci U S A, 2021. 118(16). • Backhaus, P., et al., Translational imaging of the fibroblast activation protein (FAP) using the new ligand [(68)Ga]Ga-OncoFAP-DOTAGA. Eur J Nucl Med Mol Imaging, 2021. 21. Meyer, C., et al., Radiation Dosimetry and Biodistribution of (68)Ga-FAPI-46 PET Imaging in Cancer Patients. J Nucl Med, 2020. 61(8): p. 1171-1177.
Type of contract	PhD scholarship of € 18.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.