4th Nuclear Technologies for Health Symposium
NTHS 2020
February 13-14, 2020
Nantes, France
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FINAL PROGRAM
SCIENTIFIC COMMITTEE

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ORGANIZATION

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Dear colleagues,

It is our great pleasure and honor to welcome you to the fourth edition of the Nuclear Technologies for Health Symposium (NTHS 2020) in Nantes, France, from 13 to 14 February 2020. The symposium is hosted by the Innovative Radiopharmaceuticals in Oncology and Neurology (IRON) Laboratory of Excellence (LabEx) project sponsored by the French government.

The NTHS Scientific Committee have worked together to prepare a program that includes plenary lectures given by distinguished speakers addressing the state of the art and new developments in molecular imaging, with a focus on advanced technologies such as artificial intelligence, and in targeted radionuclide therapy. The latest achievements in the specific fields of the symposium topics will be communicated during interactive oral and poster sessions.

The NTHS meeting remains a unique opportunity to bring together the various actors in these fields and is of interest to both junior and senior basic scientists, as well as clinical researchers and practitioners. The meeting promotes interactions between these different groups.

On behalf of the Organizing Committee, we welcome you to Nantes. We are delighted that you joined us for the NTHS 2020 - a stimulating meeting offering enjoyable and rewarding interactions between researchers of different backgrounds, from nuclear physics to medicine, including chemistry, biology and many other disciplines.

Nicolas Arlicot
NTHS 2020 symposium chair

Françoise Kraeber-Bodéré
IRON LabEx leader
The Organizing Committee would like to express their sincere appreciation to the following organisations for their support to the 4th Nuclear Technologies for Health Symposium - NTHS 2020.

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Prof. Férid Haddad, coordinator
GENERAL INFORMATION

VENUE
Musée d’arts de Nantes
10 rue Georges Clemenceau
44000 Nantes
Tram line 1 station « Duchesse-Anne »
Bus Lines C1, C6, 11, 12 and busway 4 station « Foch-Cathédrale »

ON SITE REGISTRATION DESK OPENING
Thursday, February 13, 08:30 - 17:00
Friday, February 14, 08:30 - 17:00

LANGUAGE
English is the official language of the Symposium. All presentations will be made in English.

INSTRUCTIONS FOR ORAL COMMUNICATION PRESENTERS
Please note that you need to bring your power point presentation on a USB key and load it on the computer of the symposium (PC, power point 2010) during a coffee or lunch break prior to your session. No private computer will be allowed.

INSTRUCTIONS FOR POSTER PRESENTERS
Posters will be on display for the entire symposium (installation: thursday, February 13 before 09:15 and removal friday, February 14 before 16:45). Poster sessions will occur during coffee breaks and lunches.

Free WIFI

SYMPOSIUM DINNER (for registered only)
Thursday, February 13, 19:00
La Passagère
Passage Pommeraye
1 Rue du Puits d’Argent
44000 Nantes
Tel : 02 40 89 50 50
SCIENTIFIC PROGRAM
08:30  Registration and welcome coffee

Welcoming words

09:15  Opening and welcome Dr Nicolas Arlicot, Pr Françoise Kraeber-Bodéré

Session 1: Radiomics and artificial intelligence in multimodality imaging
Chairs: Dr Thomas Carlier, Dr Diana Mateus
Session sponsored by SIRIC ILIAD

09:30  Pr Eric Aboagye (Imperial College London, United Kingdom)
Use of radiomics for risk stratification of cancer and beyond

10:00  Jesús J. Bosque (Mathematical Oncology Laboratory (MOLAB), Ciudad Real, Spain)
Evolutionary dynamics rules the spatio-temporal metabolic activity in human cancer: Prognostic implications

10:15  Constance Fourcade (LS2N, Centrale Nantes, Keosys, Nantes, France)
Active Organs Segmentation in Metastatic Breast Cancer Images combining Superpixels and Deep Learning Methods

10:30  Sarah Rosas González (UMR U1253 iBrain, Tours, France)
3D automatic brain tumor segmentation using a Multiscale Input U-Net network

10:45 - 11:15  Coffee break and posters

11:15  Noémie Moreau (LS2N, Centrale Nantes, Keosys, Nantes, France)
Comparison between traditional and deep learning-based semi-automatic segmentation methods for metastatic breast cancer lesions monitoring

11:30  Rita Lai (DIMA, DIBRIS, Università di Genova, Genova, Italy)
Metabolic response of normal bone marrow predicts therapeutic effectiveness standard treatment in Hodgkin Lymphoma: a PET/CT study

11:45  Ludivine Morvan (LS2N, Centrale Nantes, UMR 1232 CRCINA, Nantes, France)
Difficulties of applying ConvNets to PET images and survival data

Session 2: Poster Pitches
Chairs: Dr François Guérard, Dr Nicolas Arlicot, Pr Françoise Kraeber-Bodéré

12:00  12 Pitchers: Mylène Richard, Florian Moulin, Charles-Henri Malbert, Déborah Casas, Clarisse Brossard, Loris Roncalli, Anis Krache, Samuel Valable, Ayfer Yurt Kilcar, Jean-Charles Sébille, Hamid Marzag, Zumrut Biber Muftuler

13:00 - 14:00  Lunch break and posters
Session 3: Targeted radionuclide therapy
Chairs: Dr Emmanuel Garcion, Dr Nicolas Lepareur

14:00  Pr Uwe Haberkorn (University Hospital Heidelberg, Germany)
*Fibroblast activation protein as a target for the imaging and therapy of tumors*

14:30  Thomas Sounalet (GIP ARRONAX, Subatech, CNRS/IN2P3, Nantes, France)
*Target development for the production of Cu-67 and Tb-149 for future radiotherapy treatment at GIP ARRONAX*

14:45  Anne-Marie Frelin-Labalme (GANIL, CEA/DRF-CNRS/IN2P3, Caen, France)
*Measurement of radionuclide spatial and temporal distribution and dose calculation for in vitro assessments of 222Pb-αVCAM-1 targeted alpha therapy*

15:00 - 15:30  Coffee break and posters

15:30  Samuel Valable (ISTCT, UMR 6030 CNRS, Caen, France)
*Early brain metastases treatment using VCAM-1 targeted alpha-particle therapy*

15:45  Justine Perrin (CRCINA, UMR 1232 Inserm, Nantes, France)
*Reversing cold tumor microenvironment with targeted α-therapy*

16:00  Sébastien Gouard (CRCINA, UMR 1232 Inserm, Nantes, France)
*Impact of dose fractionation on efficacy and toxicity of targeted alpha-therapy using an astatine-211 radiolabeled anti-CD138 mAb in a syngeneic murine Multiple Myeloma model*

16:15  Christelle Bouvry (Centre Eugene Marquis, ISCR, UMR 6226 CNRS, Rennes, France)
*Pharmacokinetics study of 188Re-SSS/Lipiodol for HCC treatment: preliminary results from Phase 1 study*

16:30 Museum private guided tour

19:00 Symposium dinner
Session 4: PET imaging in neurology: current state and future expectations
Chair: Pr Pierre Payoux, Dr Nicolas Arlicot

09:00  Pr Guy Bormans (KU Leuven, Belgium)
Design and preclinical validation of PET tracers for CNS

09:30  Pr Javier Arbizu (Clinica Universidad de Navarra, Pamplona, Spain)
How can we help the clinical diagnosis?

10:00  Fabien Caillé (UMR 1023 IMIV, Orsay, France)
[18F]Crizotinib PET Imaging to Address the Impact of P-glycoprotein Transport Function at the Blood-Brain Barrier on the Brain Delivery of Crizotinib

10:15  Fabien Chauveau (Lyon Neuroscience Research Center, Lyon, France)
Preclinical evaluation of myelin radiotracers in a rat model of focal demyelination

10:30  Anne-Claire Dupont (UMR U1253 lBrain, CHU Tours, France)
18FPEB binding is not sensitive to glutamate concentration in healthy human brain

10:45  Dominique Gouilly (UMR 1214 Inserm, Toulouse Neuroimaging Center, France)
Effect of Neflamapimod on neuroinflammation using DPA-714 in PET scan in selected Alzheimer disease patients

11:00 - 11:30 Coffee break and posters
Session 5: Innovative radiopharmaceuticals: from conception to clinical validation
Chairs: Dr Cécile Perrio, Dr Anne-Sophie Salbert
Session sponsored by IRC TransForMed

11:30  Pr Antony Gee (King’s College London, United Kingdom)
*How about “Translation of radiotracers”*

12:00  Mickaël Bourgeois (Arronax, CRCINA UMR 1232 Inserm, CHU Nantes, France)
*Centralized production of 64Cu-ATSM for multicentric clinical trial*

12:15  Marie Brandt (Ludwig Boltzmann Institute Applied Diagnostics, Vienna, Austria)
*DFO⁺ and oxoDFO⁺: Optimized New Chelators for Zirconium-89 ImmunoPET*

12:30  Sylvain Pardou (Subatech, CEISAM, CRCINA UMR 1232 Inserm, Nantes, France)
*Perspective for a very fast radiolabeling pathway of new astatine compounds and comparison studies in different medias*

12:45  François Guérand (CRCINA UMR 1232 Inserm, Nantes, France)
*Simplified access to astatinated and radioiodinated antibodies by direct nucleophilic substitution of preconjugated arylboronic acids*

13:00 - 14:00 Lunch break and posters

14:00  Simon Specklin (Imagerie Moléculaire In Vivo, Orsay, France)
*Design and synthesis of an Optical-PET bimodal imaging probe based on a NIR fluorophore and fluorine-18*

14:15  Anzhellka Vorobyeva (Department of Immunology, Genetics and Pathology, Uppsala, Sweden)
*The use of a non-residualizing label provides a high-contrast radionuclide imaging of EpCAM expression using engineered scaffold protein DARPin Ec1*

14:30  Judith Delage (Radiopharmacy unit, Lausanne University Hospital and University of Lausanne, Switzerland)
*Preclinical theranostic study of 1C1m-Fc anti TEM-1 fusion proteins*

14:45  Clémence Maingueneau (ISTCT UMRT 6030 CNRS, Caen, France)
*Development and in vivo preclinical validation of [18F]FLUSONIM, a highly hydrophilic 18F-labelled 2-nitroimidazole derivative for high performance hypoxia PET imaging*

15:00  Anton Larenkov (Russian State Research Center, Lomonosov Moscow State University, Russia)
*New Folic Acid Conjugate for 68Ga-labeling with Improved Pharmacokinetic Properties*

15:15  Charles-Henri Malbert (Aniscan, INRA, Saint-Gilles, France)
*Lower binding potential of GLP-1 receptor in the pancreas as a consequence of diet-induced obesity*

15:30 - 15:45 Coffee break
**Session 5: Innovative radiopharmaceuticals: from conception to clinical validation**

**Chairs:** Dr Cécile Perrio, Dr Anne-Sophie Salabert

*Session sponsored by IRC TransForMed*

**15:45**  
Alexandre Lugat (Department of Endocrinology, CRCINA UMR 1232 Inserm, Nantes, France)  
*Development of a mouse model of liver metastases of pancreatic neuroendocrine tumor and phenotypic analysis with $^{68}$Ga-DOTATOC and $^{18}$F-FDG-micro-PET/CT*

**16:00**  
Pierre Courault (Lyon Neuroscience Research Center, Hospices Civils de Lyon, France)  
*Change in Expression Of 5-HT6 Receptor At Different Stages Of Alzheimer’s Disease: A Postmortem Study With The Pet Radiopharmaceutical [$^{18}$F]2FNQ1P*

**16:15**  
Amandine Pallardy (Nantes University Hospital, Nuclear Medicine Department, Nantes, France)  
*Assessment of osteoblastic activity with $^{18}$F-sodium fluoride PET in aortic bioprosthesis structural valve dysfunction: first results of a monocentric observational pilot study*

**16:30**  
Bruno Maucherat (ICO Cancer Center, Nuclear Medicine Department, Saint Herblain, France)  
*Prospective evaluation of FDG and FES PET imaging for selecting second line hormonotherapy in estrogen receptors positive metastatic breast cancer patients: preliminary results*

**16:45 - 17:00**  
Poster pitch and oral presentation awards ceremony

**17:00**  
End of the symposium
ABSTRACTS
Evolutionary dynamics rules the spatio-temporal metabolic activity in human cancer: Prognostic implications

Jesús J. Bosque¹, Juan Jiménez-Sánchez¹, Álvaro Martínez Rubio¹,², David Molina-García¹, Julián Pérez-Beteta³, Gabriel F. Calvo⁵, Antonio F. Honguero-Martínez³, Germán J. Londoño⁴, Ana M. García-Vicente⁶, Víctor M. Pérez-García¹

¹ Mathematics Department, Mathematical Oncology Laboratory (MOLAB), Universidad de Castilla-La Mancha, Ciudad Real, Spain.
² Mathematics Department, Universidad de Cádiz, Cádiz, Spain.
³ Thoracic Surgery Unit, Complejo Hospitalario de Albacete, Albacete, Spain.
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Hypothesis
Mathematical studies based on evolutionary tumor dynamics suggest that the peak of metabolic activity in malignant neoplasms would shift from central locations to the periphery during the tumor's natural history. ¹⁸F-FDG PET/CT provides information on the spatial distribution of metabolic activity within the tumor. We hypothesized that tumors showing a larger distance between its center and the point of maximum uptake in ¹⁸F-FDG PET/CT could be associated to a poorer prognosis.

Methods
We used two cohorts of patients imaged with ¹⁸F-FDG PET/CT: one of 61 breast cancer (BC) patients and another of 161 non-small cell lung cancer (NSCLC) patients. The tumors were delineated using an automatic gradient-based algorithm. For each tumor, additionally to the standard metrics (SUVmax, metabolic tumor volume, total lesion glycolysis), we computed the tumor’s centroid, its distance to the voxel of maximum uptake and that distance normalized to the tumor size. Next, we carried out a survival analysis for each variable splitting the populations in groups. For the theoretical study we developed a mesoscopic simulation algorithm accounting for the competition of several clonal populations in a genetically heterogeneous tumor.

Results
The defined metrics showed prognostic value for progression free survival in both BC (p-value=0.006, c-index=0.899) and NSCLC (p-value=0.004, c-index=0.651) and also for overall survival (BC, p-value=0.006, c-index=1; NSCLC, p-value<0.001, c-index=0.754). Additionally, they outperformed traditional biomarkers like metabolic tumor volume and maximum standardized uptake value. The mechanism suggested by the mathematical model to explain this fact is the colonization of the tumor periphery by most aggressive genotypes, driving tumor growth.

Conclusion
Based on ideas from an evolutionary dynamics computational model, we found a simple ¹⁸F-FDG PET/CT image biomarker with prognostic value. This demonstrates that the geometrical distribution of the metabolic activity, and not only their absolute values, carry information of clinical relevance for the clinics.
Active Organs Segmentation in Metastatic Breast Cancer Images combining Superpixels and Deep Learning Methods

Constance Fourcade1,2, Gianmarco Santini2 PhD, Ludovic Ferrer3,4 PhD, Caroline Rousseau3,4 MD PhD, Mathilde Colombié4 MD, Mario Campone3,4 MD PhD, Mathieu Rubeaux2 PhD and Diana Mateus1 PhD

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2 Keosys, Saint Herblain, France
3 University of Nantes, CRCINA, INSERM UMR1232, CNRS-ERL6001, Nantes, France
4 ICO Gauducheau Cancer Center, Saint Herblain, France

Acknowledgments. This work is partially financed through “Programme opérationnel régional FEDER-FSE Pays de la Loire 2014-2020” noPL0015129 (EPICURE) and by the SIRIC LILAD Nantes-Angers-INCA-DGOS-Inserm 12558 grant.

Hypothesis
In the clinical follow-up of metastatic breast cancer patients, semi-automatic measurements are performed on 18FDG PET/CT images to monitor the evolution of the main metastatic sites. Apart from being time-consuming and prone to subjective approximations, semi-automatic tools cannot make the difference between cancerous regions and active organs, presenting a high 18FDG uptake.
In this work, we develop and compare fully automatic deep learning-based methods segmenting the main active organs (brain, heart, bladder), from full-body PET images.

Methods
We combine deep learning-based approaches with superpixels segmentation methods. In particular, we integrate a superpixel SLIC segmentation at different depths of a convolutional neural network, i.e. as input and within the optimization process. Superpixels reduce the resolution of the images, keeping sharp the boundaries of the larger target organs while the lesions, mostly smaller, are blurred. Results are compared with a deep learning segmentation network alone.
The methods are cross-validated on full-body PET images of 36 patients from the ongoing EPICUREstudy. The similarity between the manually defined ground truth masks of the organs and the results is evaluated with the Dice score. Moreover, these methods being preliminary to tumor segmentation, the precision of the networks is defined by monitoring the number of segmented voxels labelled as “active organ”, but belonging to a lesion.

Results
Although the methods present similar high Dice scores (0.96 ± 0.006), the ones using superpixels present a higher precision (on average 6, 16 and 27 selected voxels belonging to a tumor, for the CNN integrating superpixels in input, in optimization and not using them, respectively).

Conclusion
Combining deep learning with superpixels allows to segment organs presenting a high 18FDG uptake on PET images without selecting cancerous lesions. This improves the precision of the semi-automatic tools monitoring the evolution of breast cancer metastasis.
Objective
To provide an accurate, automatic and reproducible brain tumor image segmentation algorithm by improving state of the art 3D U-Net network on multimodal Magnetic Resonance Imaging (MRI) image segmentation.

Methods
Our proposed network consists of two components: a modified 3D U-Net responsible for segmentation, and a multiscale-input module which has been thought to maximize learning from independent features associated to each MRI image modality before they are merged in the encoding/decoding architecture, avoiding loss of specific information provided by each modality (Figure 1).

The preoperative MRI images used in this work were provided by BraTS 2019 Challenge. The training dataset contains four modalities T2, FLAIR, T1 and T1c for each of the 335 glioma patients. All the subjects in the training dataset are provided with ground truth labels for 3 regions: enhancing tumor, edema, and the necrotic and non-enhancing tumor core (Figure 2). The validation and test dataset includes the same MRI modalities for 125 and 166 subjects respectively which have no expert segmentation annotations.

Results
We obtained mean dice scores of 0.775 ± 0.212, 0.865 ± 0.133 and 0.789 ± 0.266 for enhancing tumor, whole tumor and tumor core, respectively with and over-all dice of 0.81 on test dataset, metrics were computed by the online evaluation platform of BraTS 2019 Challenge. We obtained similar results on validation dataset with an overall dice of 0.80. Qualitative results are shown in Figure 2.

Conclusion
We can conclude that our model generalized well since values obtained on validation and test datasets are very close. We have experimented incorporating different modifications into U-Net architecture, results are promising but is still possible to improve them. Further study is needed to demonstrate the usefulness of this module over other improvements.
Figure 1. Proposed Multiscale Input U-Net

Figure 2. Qualitative results. Example of predicted segmentation on a) axial, b) sagittal and c) coronal view
Comparison between traditional and deep learning-based semi-automatic segmentation methods for metastatic breast cancer lesions monitoring

Noémie Moreau¹,², Caroline Rousseau³,⁴ MD PhD, Ludovic Ferrer³,⁴ PhD, Mario Campone³,⁴ MD PhD, Mathilde Colombié⁴ MD, Nicolas Normand¹ PhD and Mathieu Rubeaux² PhD

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Hypothesis

In the context of metastatic breast cancer disease management, the lesion sites can be monitored on PET/CT images using manual or semi-automatic segmentation to initiate more precise characterizations, which is time consuming and error prone. In a first step towards automating segmentation, we compare the performances of semi-automatic traditional and deep learning-based segmentation methods.

Methods

308 metastatic lesions from 16 patients of the EPICURE study were manually delineated by an ICO nuclear medicine physician using the Keosys viewer. The SUV\textsubscript{max} seed point was extracted from these delineations to mimic a one-click user initialization, and was employed to automatically build a bounding box around each lesion. 5 traditional region growing-based algorithms (Nestle, 41% SUV\textsubscript{max}, Daisne, Black and a STAPLE of the 4 previous methods) were compared against a 3-fold cross validated deep learning segmentation method based on U-Net. The bounding boxes defined earlier were used i) to contain the spread of the traditional methods and ii) to define patches during the training of the deep learning algorithms. All methods were applied to the SUV-converted PET data. Segmentation performances were evaluated calculating the Dice score between the semi-automatic segmentations and ground-truth expert manual segmentations.

Results

The 5 traditional methods give very heterogeneous results depending on the location and contrast of the lesions, with a Dice score of 0.33 ± 0.24, 0.12 ± 0.07, 0.20 ± 0.15, 0.19 ± 0.13, 0.16 ± 0.14 for Nestle, Daisne, Black, 41% SUV\textsubscript{max} and STAPLE methods, respectively. On the other hand, the deep learning approach obtained a Dice score of 0.48 ± 0.19.

Conclusion

Using a deep learning approach to segment cancerous lesions semi-automatically improves the performances against traditional methods. These first results in a difficult clinical context are promising, since they could be improved, particularly by considering the anatomic site of the different lesions.
Metabolic response of normal bone marrow predicts therapeutic effectiveness standard treatment in Hodgkin Lymphoma: a PET/CT study

Hypothesis
The present study aimed to verify whether metabolic response of active bone marrow (ABM) to chemotherapy is correlated with treatment effect on neoplastic lesions in patients with Hodgkin lymphoma.

Methods
We studied 121 patients with Hodgkin Lymphoma. All patients underwent PET/CT imaging at baseline, after 2 cycles of ABVD and one month after treatment completion (EoT). Fifty-one patients showed a positive interim scan (Deauville score ≥4), and were moved to BEACOPP scheme according to HD0607 trial. All PET/CT scans, were analysed to identify the intraosseous volume (IV) of all vertebral bodies at all time points. An iterative scheme was applied to each CT slice to identify the external bone border and thus to extract the IV and its metabolic activity from co-registered PET images. According to our previously validated procedure, inactive BM was defined by IV voxels with a SUV <1.1, while voxels over this cut-off identified ABM.

Results
No differences disease extensions were observed at baseline examination. Before treatment initiation, mean SUV of intraosseous voxels (1.91±0.38 vs. 1.93±0.40, respectively, p=ns) and extension of inactive BM (22±11% and 21±16%, respectively, p=ns) were remarkably similar between the two groups. At the interim PET after the same two ABVD cycles, responders showed a significantly increase in SUV mean (2.03 ±0.71 vs. 1.76±0.40, respectively, p<0.01) and a significantly lower extension of inactive BM with respect to non-responders (22±19% vs. 26±15%, respectively, p<0.01). This difference even increased at EoT scan (25±10% vs. 30±15%, respectively, p<0.01). Average SUV at EoT showed a progressive decrease in responders with respect to non-responders (1.73 ±0.23 vs. 1.66±0.40).

Conclusion
ABVD-failure patients are associated with a peculiar metabolic response of normal BM to chemotherapy. This response is characterized by a more evident loss of active BM in favour of its inactive counterpart.
Difficulties of applying ConvNets to PET images and survival data

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Objectives
Prior work has shown the effectiveness of Convolutional neural networks (CNN) for PET images segmentation. Also, given the demonstrated prognosis value of handcrafted radiomics features, similar is expected from learned features. However, standard CNNs for classification or regression are not directly applicable for radiomics and survival analysis. In this work, we discuss the challenges of adapting deep learning approaches and propose potential methodologies to overcome them.

Methods
We designed experiments to illustrate the difficulties to process PET images and survival data with CNNs. We discuss among others, the influence of the databases size, the image resolution, the annotation and the data augmentation, the problems in predicting survival quantities, and the use of non-medical data to train the feature extraction step. We used two datasets: the DTD dataset and a database of multiple myeloma PET images (IMAJEM) to train a standard CNN. The tasks of texture recognition and survival prediction were formulated as a multi-class (7) classification problem.

Results
We show that for the DTD dataset, the model needs more than 1000 images to yield a correct result. The IMAJEM dataset has only 89 images (801 with data augmentation) with a lower resolution (less than 32*32 for lesions compared to 512*512 for DTD). For the same input size and number of output classes, this amount of data is insufficient to train the network from scratch for the survival task even with data augmentation. Also, when using one separate label for censored data, the network predicts all data as censored, highlight two issues: the class imbalance and the non-trivial handling of censored data.

Conclusion
Alternatives exist but all of them have limitations. The successful application of deep learning techniques for the radiomics and the survival analysis task needs the specific development of novel adaptions.
Hypoxia image-Guided Radiotherapy for the treatment of brain metastases from primary lung cancer, a preclinical study

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Objectives

Patients with lung cancer frequently develop brain metastases. Conventional treatment that involves radiotherapy (RT) is however often not efficient enough. There is a pressing unmet therapeutic need for a better characterization of factors at the origin of radioresistance such as hypoxia in order to develop more personalized treatments. The objectives of this preclinical study were to characterize hypoxia in brain metastases by multimodal imaging and to evaluate the therapeutic interest of a personalized RT based on tumor hypoxia.

Methods

Brain metastases models consisted of injections, in nude rats, in two brain regions (cortex and striatum) of human lung primary cancer (H1915 and H2030 cell lines) to mimic the multiple foci observed in the clinical situation. Hypoxia was characterized using -Oxygen saturation mapping-MRI, (SatO²-MRI)(7T Bruker) and ¹⁸F-FMISO-PET (Inveon-Siemens )[CYCERON-platform] . Animals were then divided into three groups: control, whole-brain-RT (WBRT, standard treatment for patients) and image-guided RT. The latter option was performed using a preclinical irradiator associated to a TPS (Smart Plan; Xrad-225Cx irradiator, CYCERON Platform). Treatment efficacy was evaluated using [¹⁸F]-FLT-PET, brain metastases volume and overall survival.

Results

Multimodal imaging revealed a pronounced hypoxia detected by [¹⁸F]-FMISO-PET and SatO²-MRI. Interestingly, heterogeneity in the hypoxic status was observed between striatal and cortical metastases. SatO²-MRI-guided RT showed a significant interest in comparison to WBRT characterized by an early decrease in tumor cell proliferation as revealed by [¹⁸F]-FLT-PET, a decrease in tumor volume and increase in survival.

Conclusion

We show, for the first time, at the preclinical level that hypoxia is a hallmark of the microenvironment of brain metastases from primary lung cancer. Personalized RT guided by hypoxia imaging (MRI/PET) may be of interest to control metastatic growth while reducing dose at the healthy brain.

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Hypothesis
The advent of immunotherapy by checkpoint inhibitor has profoundly changed the prognosis of patients with metastatic melanoma. The objective of our study was to evaluate the prognostic and predictive performance of 18F-FDG PET/CT of the initial extension assessment of stage IIIB-C-D and IV melanomas.

Methods
We retrospectively included 57 patients who had 18F-FDG PET/CT prior to the introduction of anti-PD-1 immunotherapy. The parameters extracted were SUV max, SUV peak, MTV and TLG of the most fixed lesion (MTV LM, TLG LM), as well as MTV total and TLG total, obtained by adaptive segmentation. The 18F-FDG PET/CT were dichotomized using the optimal threshold measured according to the area under the curve in the ROC (Receiver Operation Characteristic) curves. These parameters were evaluated using a Cox model. Overall survival and progression-free survival analyses were performed using the Kaplan Meier model.

Results
The median follow-up was 25.4 months, 38 patients had progressed or recurred, and 20 patients had died. TLG LM > 132.59 (p = 0.0011), MTV total > 12 cm3 (p = 0.0139), and TLG > 94.17 (p = 0.0084) were significantly associated with a shorter progression-free survival. TLG LM > 145.92 (p = 0.0062), MTV total > 10.16 cm3 (p = 0.0051), and a metastatic spread > 2 organs (p = 0.0001) were associated with a shorter overall survival.

Conclusion
We confirm the potential prognostic interest of PET-TDM at 18FDG before immunotherapy of stage IIIB-C-D and IV melanomas on progression-free survival and overall survival. The combination of these metabolic markers reflecting tumor burden with clinical and biological prognostic factors could allow early identification of patients at high risk of anti-PD1 failure.

Keywords: Immunotherapy, melanoma, FDG PET/CT, prognostic value
Target development for the production of Cu-67 and Tb-149 for future radiotherapy treatment at GIP ARRONAX

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Objectives

Cu-67 and Tb-149 are two radioisotopes who can be interested for radiotherapy in medicine nuclear. Indeed, Cu-67 emits an emission of β\textsuperscript{-} with its mean energy of 141 keV and Tb-149 emits α particle with its short-range at 3.9 MeV with an intensity of 16.7%. These radiotoxic emissions β\textsuperscript{-} and α particle can destroyed tumour cells. These interesting radioisotopes dedicated for the radiotherapy treatment can furthermore be used to practice theranostic which combine therapy and diagnostic by including other radioisotope of Cu-64 for Cu-67 and Tb-152 or Tb-155 for Tb-149. These radioisotopes are produced by irradiating with accelerated particles delivered in cyclotron GIP ARRONAX, in Nantes, on metallic targets. These metallic targets must be made and it is the subject of my presentation.

Methods

The metallic targets are made by the electrodeposition technique. This consists to reduce the metallic cations in solution on a metallic substrate to have a metallic solid target adapted on irradiation condition. To produce Cu-67, the Zn-70 target is adapted and is irradiated with deuon. The Gd-154 target is used to produce Tb-149, it is known that to do electroplating with Lanthanide family to have a metallic solid target is difficult. To overcome this difficulty, we have used the EMMC technique, Electrodeposited Metal Matrix/Metal particle Composites. This technique consists to use the suspension particles of gadolinium salts in solution and during the electrodeposition, these particles are trapped in the Ni deposit.

Results

Due to the high prize of Zn-70 and Tb-149, the experiments have been realized with natural element. Promising first results will be presented along with data on the characterization of the deposits of through MEB-EDS and ICP-OES, this characterization allows to define the quality of deposit.
Measurement of radionuclide spatial and temporal distribution and dose calculation for in vitro assessments of $^{212}$Pb-αVCAM-1 targeted alpha therapy

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Objective

The interest of using Targeted Alpha Therapy (TAT) for the treatment of metastatic lesions is increasing due to the short range and the high linear energy transfer of α-particles. New developments require preliminary studies relying on dosimetry to assess their efficiency and toxicity, which is challenging with α-particles. During in vitro experiments, assumptions are made about the radionuclide distribution in the culture medium, which could have a significant impact on dose calculation. In this study, we measured the spatial and temporal distribution of α-emitting $^{212}$Pb coupled to an anti-VCAM-1 antibody in in vitro irradiations.

Methods

15 kBq of $^{212}$Pb-α-VCAM-1 was added to two test wells without cells. The first well had a 2.5-µm-thick mylar-base and was placed above a silicon detector. The second well was a commercially available dish and was placed below an identical detector. Experimental energy spectra of α-particles were measured in both configurations during 20 hours. Spectra were analyzed using a Monte Carlo approach to determine the radionuclide spatial and temporal distribution and to calculate the absorbed dose in cells not expressing VCAM-1.

Results

The radionuclide spatial distribution was composed of a uniform distribution and concentration gradients at the top and the bottom, all subjected to temporal variations. The absorbed dose in cells calculated from this distribution was compared with the dose expected for a uniform and static distribution and found to be 1.75 times higher. This discrepancy is significant and is and could impact the accuracy and the reliability of studies without experimental dosimetry.

Conclusion

This study presented an innovative dosimetry method applied to in vitro assessment with tumor cells not expressing VCAM-1. It could similarly be applied to radiopharmaceuticals targeting receptors on the cells surfaces or internalized into the cells, which would improve the accuracy of in vitro studies.
EARLY BRAIN METASTASES TREATMENT USING VCAM-1 TARGETED ALPHA-PARTICLE THERAPY

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Objectives
Brain metastases (BM) frequently develop from primary breast cancer. Despite external beam radiotherapy (EBRT), overall survival is low (mean, 6 months from diagnosis). The therapeutic challenge is to treat in a targeted manner at an early stage when relatively few metastatic tumor cells have invaded the brain. Vascular cell adhesion molecule-1 (VCAM-1), overexpressed by endothelial cells during the early stages of BM development, is a potential target. The aim of this study was to investigate the therapeutic value of targeted alpha-particle radiotherapy combining 212Pb with anti-VCAM-1 antibodies (212Pb-αVCAM-1).

Methods
Human breast carcinoma cells that metastasize to the brain, MDA-MD-231-Br-GFP, were injected into the left cardiac ventricle in nude mice. 21 days after injection, 212Pb-αVCAM-1 specificity towards BM was determined in a biodistribution study and systemic/brain toxicity evaluated. Therapeutic efficacy, assessed using anatomical MRI and histology, and overall survival after 212Pb-αVCAM-1 treatment were compared to that observed after EBRT.

Results
With a tumor/healthy brain dose deposition ratio of 6 (5.52e108 and 0.92e108 disintegrations per g of BM and healthy tissue, respectively), 212Pb-αVCAM-1 showed good specificity. MRI analyses showed a significant reduction in metastatic burden after 212Pb-αVCAM-1 treatment compared to EBRT (p<0.001), translating to an increase in overall survival of 28.99 ± 7.25 % (p<0.01). No major toxicity was observed.

Conclusion
The present investigation demonstrates combining anti-VCAM-1 antibodies with an alpha-emitting radionuclide, 212Pb (212Pb-αVCAM-1) provides a very specific and efficient treatment for tumor cells, whilst minimizing healthy brain tissue damage due to the short range of the alpha-particles.

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Reversing cold tumor microenvironment with targeted α-therapy


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Objectives
Actual cancer therapies are facing numerous challenges towards tumor cell destruction: tumor microenvironment involves immunoregulatory cells and cytokines, which prevent anti-tumoral immune response. Therapeutic combination could be the key to turn these « cold » tumor microenvironment into « hot » ones: more vascularised and infiltrated with immune cells. To this end, this project focus on combining targeted alpha-therapy (TAT) and adoptive T-cells transfer (ACT).

Methods
This therapeutic combination was conducted in a Multiple Myeloma (MM) murine model using a 5T33-OVA MM cell line expressing the CD138 antigen and H_{2}K^{b}/OVA_{257-264} complexes grafted subcutaneously to C57BL6/KalwRij mice. TAT was delivered through i.v. injection of a 213-bismuth radiolabelled anti-CD138 antibody. To further reinforce its efficiency, TAT was combined with an ACT of tumor specific OT-1 T-cells. This therapeutic combination resulted in a significant tumor growth delay and improved survival, compared to ACT or TAT alone (Ménager et al. 2015).

Based on these results, the aim of this project was then to understand the impact of TAT on the “cold” tumor microenvironment and on ACT efficacy. Tumor infiltrated cells were analysed by flow cytometry to identify in situ immune populations, and cytokines production were assessed by RT-qPCR on tumor fragment.

Results
Although OT-1 T cells infiltrated the tumor after ACT, only combination with TAT resulted in regulatory CD4 T cell drop and production of IL-2 and IFNγ within the tumor. Furthermore, OT-1 T cells motility was increased on TAT treated tumor slices as observed by ex vivo time lapse.

Conclusion
Combining TAT and ACT appears to turn this “cold” tumor model into a “hot” one with regulatory T cells depleted, proportion and motility of tumor-specific CD8 T cells increased and IL-2 and IFNγ produced in the tumor. Next, we aim to investigate impact of this combination on metabolism and hypoxia in tumor microenvironment.
Impact of dose fractionation on efficacy and toxicity of targeted alpha-therapy using an astatine-211 radiolabeled anti-CD138 mAb in a syngeneic murine Multiple Myeloma model

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Objectives
Multiple myeloma (MM) is a B-cell malignancy of terminally differentiated plasma cells developing in the bone marrow. In spite of a very active search for new treatments, cure is almost never achieved. Targeted alpha-therapy (TAT) is a new cancer treatment modality using tumor specific antibodies coupled to alpha particle-emitting radionuclides and is suitable to treat MM residual disease. CD138 (Syndecan-1) appears to be a good antigen candidate to TAT since it is expressed by most human and mouse myeloma cells. The aim of the study was to evaluate the benefit of dose fractionation of an astatin-211-labelled anti-mouse CD138 antibody (211At-9E7.4) in a syngeneic mouse myeloma model compared to TAT delivered in one injection.

Methods
C57BL/KaLwRij mice were grafted with 10⁶ 5T33 MM cells by i.v. injection. Ten days after tumor engraftment, TAT efficacy was assessed by a dose escalation study of 211At-9E7.4 mAb with 5 activities ranging from 370 to 1110 kBq. A dose fractionation protocol was evaluated using activities of 660 kBq delivered in two or three fractions, and 1320 kBq delivered in two fractions. Delay between dose fractions was one to two weeks. Animal survival was monitored for 110 days after tumor graft and toxicity was assessed mainly by analysis of hematologic parameters.

Results
Dose escalation of single dose demonstrated a significant survival benefit for the mice treated with 211At-9E7.4 mAb at 555 kBq, 660 kBq and 740 kBq. However, we observed transient leukocyte and red cell decreases. Treatment with 1110 kBq 211At-9E7.4 mAb was highly toxic. Concerning dose fractionation, treatments with 1320 kBq 211At-9E7.4 mAb delivered in two fractions of 660 kBq over 2 weeks, at D10 and D18, or at D18 and D24 post grafting, were both lethal. However, animals receiving the same treatment delivered with a 2 week delay between each injection (at D10 and D24 post graft) exhibited a median survival similar to those treated with a single injection of 660 kBq 211At-9E7.4 mAb. Apart from this dose fractionation, no other had a beneficial impact on survival.

Conclusion
Treatment with 1320 kBq 211At-9E7.4 mAb, delivered as 2 x 660 kBq, and a delay of 2 weeks between each injection, was associated with improved median survival when one injection of 1100 kBq 211At-9E7.4 mAb was lethal. No survival benefit has been shown with the other dose fractionation protocols. These results will constitute the base of further fractionation protocols to deliver a dose sufficient to eradicate residual disease or to control its progression with limited toxicity.

SESSION 3: Targeted radionuclide therapy
Pharmacokinetics study of $^{188}$Re-SSS/Lipiodol for HCC treatment: preliminary results from Phase 1 study

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Objectives
To evaluate biodistribution and pharmacokinetics of $^{188}$Re-SSS/Lipiodol after intra-arterial injection for palliative treatment of hepatocellular carcinoma (HCC).

Methods
A Phase 1 clinical study was initiated for the treatment of patients suffering from inoperable HCC. Inclusion criteria were measurable tumour, uni- or multinodular, occupying less than 50% of hepatic volume, BCLC stages A-C (or CLIP 0-4), without portal vein thrombosis, after escape, intolerance or contraindication to Sorafenib. 6 patients were treated at first dose-step ($1581 \pm 414$ MBq) and 6 at step 2 ($3331 \pm 472$ MBq) by intra-arterial injection of $^{188}$Re-SSS/Lipiodol via a transfemoral catheter. Pharmacokinetics data were obtained by collecting blood samples at 1, 6, 12, 24, 48 and 72h, urinary samples at 24, 48 et 72h, and faeces samples at 72h, and with 4 or 5 scintigraphies (SPECT/CT) over a period of 72h.

Results
A mean peak of $1.90 \pm 0.67$ % of injected activity is observed in serum at 12h then decreasing quickly. Elimination is mainly through urines, remaining very low with $0.97 \pm 0.59$ % of injected activity over 72h. Digestive elimination is quasi non-existent. TLC analyses of serum and urine samples indicate metabolites are essentially hydrophilic. Scintigraphies show an important, and stable in time, hepatic fixation ($79.40 \pm 8.87$ %), with a very good tumour targeting ($58.15 \pm 13.59$ %). Only notable extrahepatic fixation is in the lungs, which thus represent main organ at risk.

Conclusion
These preliminary results demonstrate exceptional properties of $^{188}$Re-SSS/Lipiodol, with good tumour targeting and excellent stability in vivo. Tolerance and treatment response are also encouraging. Completion of this dose-escalation study should enable to determine maximum tolerable dose for this new promising treatment.
Identification and targeting of novel fusion genes in glioblastomas with chromothripsis

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Hypothesis
Glioblastomas (GB) are the most frequent and most aggressive (WHO grade IV) central nervous system (CNS) tumors. GB are characterized by genomic instability and display many copy number abnormalities. Chromothripsis (CT) has been described in 9% of cancers but may occur in up to 39% of GB. CT is a cataclysmic event whereby a few chromosomes (chr) shatter into tens to hundreds of pieces. The chr fragments are then randomly reassembled. This can lead to the juxtaposition of the coding sequences of two genes, giving rise to potential oncogenic fusion genes. Targeting such genes may open new therapeutic avenues in GB.

Methods
205 GB (180 GB IDH1 / 2 wild, 9 GB IDH1 / 2 mutated, 16 GB with H3 histone mutation) were studied by whole genome SNP arrays (CytoSNP850K®, Illumina). GB with CT patterns were RNA sequenced (RNaseq) to detect fusion genes (Integragen).

Results
In 37.6% of GB (77/205 GB), GB displayed CT patterns. The most frequently involved chrs were chromosomes 7, 9 and 12. RNaseq could be performed in 64 cases (out of 77). 138 fusion genes were detected. 20% of the fusions were identified in CT regions. Eighteen fusions (9 in frame and 9 out of frame) were validated by RT-PCR followed by Sanger sequencing. Recurrent fusion partners were EGFR gene, a major driver in GB, and other genes such as VOPP1, CPM and PPM1H. Those genes have been involved in oncogenesis and tumor progression.

Conclusion
The presence of CT points to underlying gene fusions in GB. Gene fusions most often involve EGFR but also novel potential oncogenes that may be involved in gliomagenesis and/or tumor progression. Such gene fusions may represent therapeutic targets in GB. The development of RNA interference may represent a new therapeutic approach to target the fusion gene products.
DRUG COMBINATION: Analysis of miRNA networks in GBM reveals an essential contribution of hsa-miR-22-3p in response to radiation treatments and subsequent growth

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Hypothesis
MicroRNAs (miRNAs) represent a major set of cell regulatory elements coded by the genome. Although their signature in cancer is not fully known and they are not yet a basic element of diagnosis, the role of oncomirs and tumour suppressor miRNAs are becoming increasingly documented. Alongside to intrinsic signals in which they exert essential roles in cancer such as cell proliferation or apoptosis, miRNAs are also responding to environmental conditions. Hence, developing novel approaches to target miRNA-pathways represents a pivotal issue in research and may result in a major breakthrough for human health.

Methods
To better understand how miRNAs participate in the radio-resistance of GB cells we have studied how exposure of GB cells derived from patient to radiation regulates their miRNOME. For this purpose 12 patient derived cell lines were grown as floating neurospheres at different level of O2 and exposed in vitro to radiations (RX or 188Re nanocapsules).

Results
Less than ten miRNA on more than 2000 analyzed appeared as up- or down-regulated by radiations. These miRNAs were included in a complete in vitro and in vivo functional study through U87MG-Lenti-miR cell constructs overexpressing pre-miRs of interest. These tools made possible to generate major results in demonstrating that the expression of a single miRNA impacts the entire GB development. We notably defined a major role in radioresistance for oncogenic miR22 associated with TET1 DNA demethylase tumor suppressor repression in the GB.

Conclusion
In this context of radioresistance we were committed to the development of new nanovectors capable of releasing miRNAs that were validated for functional activity in vitro and in vivo through an original miRNA-ON integrative sensor system. Overall these date support the interest of drug combinations based on mi/siRNA delivery and loco-regional radiation therapy for further development and testing toward clinical transfer.
Investigation of tumor and micro-environmental responses following the application of an innovative targeted radiotherapy in glioblastoma

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Glioblastoma (GB) is the most common and aggressive tumor in the central nervous system. The standard first-line treatment is based on surgery followed by radiotherapy and chemotherapy (temozolomide). Despite this conventional combined approach, patients have a median survival time of 15 months and GB remains an unmet medical need. Hence, loco-regional vectorized radiotherapy represents a promising option. Indeed, results from our team have already shown the efficiency of lipid nanocarriers loaded with Rhenium 188 (a beta- and gamma emitter) on the survival of rodent cancer models¹-²-³. This kind of strategy has led to further developments toward possible clinical trials (Dosisphere, submitted Nanorad.01).

The next step here is to develop alpha radiopharmaceuticals based on Astatine 211 and to study the added value of such a strategy⁴-⁵. New radiopharmaceuticals will be developed by use of antibodies directed against syndecan-1 (SDC1 or CD138) and the receptor CXCR4 (CD184) which are in the GB markers facing the tumor micro-environment, associated with malignant phenotypes, tumor progression and treatment resistance⁶-⁷. Through in vitro and in vivo orthotopic models, investigations will include study of targeting, clearance, bio-distribution and efficiency of these new radiopharmaceuticals. While focusing on tumor cell intrinsic responses, this work will imply an analysis of microenvironmental immune and inflammatory responses. For instance, tumor-associated macrophages (TAM) populations represent up to 50% of tumor mass⁸ and their recruitment can be increased following internal radiation treatment⁹. As an initial focus, we produced some pivotal data on the polarization of TAMs in response to GB cells issued from patients (already exposed to radiations or not). Not only GB cells condition medium affects their anti-tumoral (M1) or pro-tumoral phenotype (M2) but those phenotypes affect responses to radiation⁹. This work will allow better understanding of Astatine 211 alpha therapy which is prior to the development of a First In Human study.
References

[18F]Crizotinib PET Imaging to Address the Impact of P-glycoprotein Transport Function at the Blood-Brain Barrier on the Brain Delivery of Crizotinib

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Objectives
Crizotinib is a tyrosine kinase inhibitor approved for non-small cells lung carcinoma. The brain accumulation of crizotinib is mainly restricted by the P-glycoprotein (P-gp, ABCB1), a major efflux transporter at the blood-brain barrier, which limits its efficacy against CNS lesions. We hypothesized that the brain delivery of crizotinib can be improved using a clinically feasible protocol of P-gp inhibition. We report the preparation of an original precursor for isotopic radiolabelling of [18F](R,S)-crizotinib and the first brain PET images in rats with and without ABCB1 inhibition.

Methods
A racemic spirocyclic hypervalent iodine(III) complex was synthesized for radiosynthesis with [18F]fluoride. Radiofluorination was realized using a TRACERlab FXFN module and conditions were optimized monitoring the conversion rate by radio-TLC. The crude radiotracer was purified by semi-preparative HPLC. Radiochemical yield (RCY) and molar activity (Am) were assessed by radio-HPLC. Dynamic PET acquisitions were performed in anesthetized rats during 60 min after [18F](R,S)-crizotinib injection (37 ± 5 MBq) with or without ABCB1 inhibition using tariquidar (8 mg/kg, 15 min i.v. prior to radiotracer injection).

Results
The racemic precursor was synthesized from 2,4-dichloro-1-iodobenzene in 5 steps and 2% yield. Up to 52% conversion rate was obtained using tetraethylammonium bicarbonate as a base in DMF at 160 °C for 10 minutes. Deprotection with 3 M HCl(aq) at the same temperature for 10 minutes gave full conversion. Ready-to-inject [18F](R,S)-crizotinib was obtained in 5 % RCY and 60 ± 10 GBq/µmol (n = 7) Am. PET baseline experiments showed no penetration in the rat brain whereas [18F](R,S)-crizotinib enters the brain under ABCB1 inhibition.

Conclusion
An original precursor for crizotinib radiofluorination was synthesized and [18F](R,S)-crizotinib was successfully radiolabelled. The first PET images of [18F](R,S)-crizotinib in the rat brain demonstrated the relevance of P-gp inhibition to improve its brain delivery. Investigation with the enantiomerically pure [18F]crizotinib are ongoing.
Preclinical evaluation of myelin radiotracers in a rat model of focal demyelination

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Objectives
Focal demyelinated lesions and progressive failure of remyelination are the main characteristics of multiple sclerosis (MS). While several remyelination strategies are under clinical investigation, there is no consensus on which imaging technique can offer the best reliable measure of remyelination. PET may provide a direct and quantitative detection of myelin content. Building on pioneer [\textsuperscript{11}C]PiB studies, the main objective of this work is to progress towards a second generation of fluorine-18 labelled myelin radiotracers.

Methods
[\textsuperscript{18}F]BF227 (n=10), [\textsuperscript{18}F]AV-45 (n=5) and [\textsuperscript{11}C]PiB (n=5) were evaluated in a rat model of focal demyelination induced by a stereotactic injection of lyso-phosphatidyl-choline (LPC) in the right corpus callosum, vs saline in the contralateral site. MRI was used to confirm demyelination, and exclude animals with necrosis or hydrocephalus. In vivo PET was immediately followed by ex vivo autoradiography. Brain sections were subsequently stained with Sudan Black B (SBB).

Results
In vivo, [\textsuperscript{18}F]BF227 and [\textsuperscript{11}C]PiB showed a similar ratio of WM to GM uptake in the whole brain (1.2 at 30min) while [\textsuperscript{18}F]AV-45 showed an early, increased ratio (1.3 at 10min). Despite extended areas of demyelination observed on MRI, focal demyelination was hardly detected on PET images, whatever the radiotracer: corpus callosum ipsi-to-contralateral uptake ratios were comprised between 0.95 and 1. [\textsuperscript{18}F]BF227 and [\textsuperscript{18}F]AV-45 autoradiograms showed similar WM to GM uptake ratios, and similar corpus callosum ipsi-to-contralateral uptake ratios (Fig. 1A). Only [\textsuperscript{18}F]AV-45 showed a significant correlation with the optical density of SBB-stained myelin measured in the same sections (Fig. 1B).

Conclusion
In contrast to previous reports, LPC-induced demyelination was not detected in vivo. MRI highlighted pitfalls of the animal model that might lead to false-negative PET detection. Nevertheless, high-resolution ex vivo autoradiography after MRI-confirmed demyelination suggests that [\textsuperscript{18}F]AV-45 provides a better myelin biomarker than [\textsuperscript{18}F]BF227.
Figure 1. (A) Autoradiography yielded similar results for $[^{18}\text{F}]\text{BF227}$ and $[^{18}\text{F}]\text{AV-45}$, in terms of i) white matter (WM, green ROI) to gray matter (GM, violet ROI) uptake ratio, and ii) ipsilateral (red ROI) to contralateral (green ROI) uptake ratio. (B) Only $[^{18}\text{F}]\text{AV-45}$ correlated significantly with optical density ratio after Sudan Black B staining of myelin (*p<0.05).
**18FPEB binding is not sensitive to glutamate concentration in healthy human brain**

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**Objectives**

Impairment of the metabotropic glutamate receptor 5 (mGluR5) is involved in various neurologic disorders. PET imaging with 18FPEB allows to evaluate dynamic changes in receptor availability underlying neuropathological conditions, but the influence of fluctuations in endogenous glutamatergic levels into receptor binding has not been well established yet. Our study aimed to analyse in healthy volunteers the correlation between endogenous Glutamate (Glu), Glutamine (Gln) and Glutamate + Glutamine (Glx) levels measured by MRS and mGluR5 binding of 18FPEB.

**Materials and Methods**

13 healthy subjects (33.8 years old ±8.0) were explored by both MR and PET modalities. MR spectra were acquired using PRESS sequence with an echo time of 35 ms, a repetition time of 2 s, 100 and 10 averages for suppressed and unsuppressed water acquisitions respectively. Glu, Gln and Glx levels were quantified both as water-scaled concentrations and as ratios to creatine from MRS data collected from the anterior-cingulate cortex (ACC right and left) with LCModel. PET emission data were collected in list-mode for 60 minutes after 18FPEB injection (280MBq±37) and were analyzed using PMod to calculate the BPND using the simplified reference tissue model 2. To test for an interaction, we correlated the 18FPEB (ACC BPND/Cerebellum BPND) with Glu/Cr, Gln/Cr, Glx/Cr ratios in the ACC. Spearman rank coefficient was used for univariate correlation analysis and significance was accepted at p<0.05.

**Results**

No statistically significant correlation was evidenced between Glu and Gln concentrations and 18FPEB binding. ACC BPND/Cerebellum BPND vs Glu/Cr : r=0.303, p=0.315 ; Gln/Cr : r=0.299, p=0.320 ; Glx/Cr : r=0.083, p=0.789.

**Conclusion**

18FPEB binding did not show sensitivity to glutamate concentrations in physiological conditions as an independent outcome. Therefore, 18FPEB appears not to be able to detect acute fluctuations in glutamate. This is tangible proof that 18FPEB is a reliable tracer to figure out the mGluR5 availability despite heterogeneity of glutamate concentrations.
Effect of Neflamapimod on neuroinflammation using DPA-714 in PET scan in selected Alzheimer disease patients

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Background and objectives
In Alzheimer disease pathophysiology, there are a large amount of evidence showing a deleterious impact of neuroinflammation on disease progression (Henstridge et al., 2019). Microglial activation seems to be one of the main actors responsible for the chronic immune response (Heppner et al., 2015). Furthermore, the p38 alpha MAPK has been recognized as a leading therapeutic target for a broad range of central nervous system disorders (Correa and Eales, 2012). A novel compound VX-745 or Neflamapimod seems to be the most selective inhibitor of the p38 alpha MAPK (Alam 2015). We have therefore started a proof of concept study to assess the effect of Neflamapimod on neuroinflammation in a population of Alzheimer disease patients at an early stage.

Hypothesis
We expect to observe a decrease of neuroinflammation among treated patients in comparison to the placebo groups, after 12 weeks of treatment. We also expect to see an improvement in their cognitive abilities.

Methods
Our main objective will be to compare the level of microglial activation in PET scan. Inflammation will be assessed using DPA-714 as one of the most specific radioligand of the translocator protein (Chauveau et al., 2009). TSPO polymorphisms will be considered in our analyses. In addition, we plan to investigate the effect on Neflamapimod on the neuropsychological status of our patients, on brain structure, and on biomarkers of inflammation.

Results
Preliminary results of the study will be stated. Our methods of analysis for DPA-714 images will be highlighted for further discussion.
Centralized production of $^{64}\text{Cu}$-ATSM for multicentric clinical trial

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Objectives

[$^{64}\text{Cu}$]-diacetyl-bis($N^4$-methylthiosemicarbazone) (=[$^{64}\text{Cu}$]-ATSM) appears to be a promising radiopharmaceutical compound for positron emission tomography phenotypic imaging of the tumor microenvironment redox deregulation observed during hypoxia. The objective of this study is to describe the hospital radiopharmacy production of $^{64}\text{Cu}$-ATSM which encounters the GMP and radiosafety regulation.

Methods

The ARRONAX in-house radiopharmacy is governed by the Nantes University Hospital. The radiopharmacy production operates both radionuclide production and pharmaceutical manufacturing aspects. For $^{64}\text{Cu}$-ATSM, ARRONAX cyclotron produces copper-$^{64}$ through the $^{64}\text{Ni}(d,2n)^{64}\text{Cu}$ nuclear reaction with overnight bombardment of deuteron on enriched nickel-$^{64}$ target. Copper-$^{64}$ is extracted and purified by ARRONAX radiopharmacy to $^{64}\text{CuCl}_2$ solution for the radiolabeling of $^{64}\text{Cu}$-ATSM by automatized process. After the radiolabeling $^{64}\text{Cu}$-ATSM is conditioned under aseptic conditions for a clinical ready-to-use solution.

Results

Copper-$^{64}$ production ($^{64}\text{CuCl}_2$ solution) process exhibits reproductive results for any specification parameters in hydrochloric acid 0.1 M. The radiolabeling process of $^{64}\text{Cu}$-ATSM appears to be repeatable and in conformity for each specification parameters of the ANSM authorized IMPD. Validation steps (bioburden, aseptic vials filling) confirm the capacity to produce sterile and pyrogen-free $^{64}\text{Cu}$-ATSM for clinical trial. The stability tests have showed a sufficient stability during the 24 hours after the end of synthesis.

Conclusion

The developed method to produce clinical dose of [$^{64}\text{Cu}$]Cu-ATSM was GMP/GRPP-compliant, reliable, reproducible and in compliance with radiation safety requirements. The process was fully validated and in accordance with the acceptance criteria (radiochemical purity, radionuclieic purity, stability, sterility, endotoxin content, residual solvent content). This automated process has been optimized and our results demonstrate that this reliable automated manufacture allows the production of doses for multicentric clinical studies. This clinical trial is the first one approved for a copper-$^{64}$ radiopharmaceutical in France. The inclusions are opened and the first patient with rectal cancer has been injected.
DFO* and oxoDFO*: Optimized New Chelators for Zirconium-89 ImmunoPET

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Objectives
The only chelator clinically applied thus far for the imaging of 89Zr-labelled antibodies by PET is the siderophore DFO[1]. However, DFO does not fulfill the octadentate coordination preferred by zirconium, which results in complexes that are unstable in vivo. This consequently leads to release and unspecific uptake of the radiometal in, e.g., the bones, which impacts the detection of bone metastases and results in unnecessary radiation doses to non-targeted tissue. The previously reported octadentate version of DFO, termed DFO*, provides 89Zr4+ complexes with increased stability[2]. However, its solubility in H2O needs to be improved to facilitate bioconjugation chemistry. Thus, an analogue containing a polyether scaffold (oxoDFO*) with higher water solubility was developed[3]. The modular synthesis of oxoDFO* and the possibility to increase its denticity also provides an opportunity to use the chelator for other radiometals. Radiolabelling experiments of oxoDFO* are presented here for the first time.

Methods
Radiolabelling of DFO*, oxoDFO* and DFO as reference compound was performed at RT at pH 7.4 in HEPES buffer with [89Zr]Zr-oxalate with different precursor concentrations. The stabilities of the complexes were tested by challenging experiments with excess DTPA. The radioactive compounds were analyzed by radio-ITLC and radio-HPLC.

Results
DFO* and oxoDFO* could be radiolabelled with 89Zr with a RCY > 95% within 120 min at RT with an ideal concentration of 10 µM. DTPA challenging experiments showed negligible transchelation of the octadentate complexes within 48 h and significantly higher stability in comparison to 89Zr-DFO.

Conclusion
oxoDFO* is the first octadentate, water soluble chelator for 89Zr and expected to provide complexes with the radiometal of high in vivo stability; radiolabelling experiments and preclinical evaluation are ongoing. Through bioconjugation to antibodies, oxoDFO* represents a valuable future tool for immunoPET imaging in cancer diagnosis.

PERSPECTIVE FOR A VERY FAST RADIOLABELING PATHWAY OF NEW ASTATINE COMPOUNDS AND COMPARAISON STUDIES IN DIFFERENT MEDIAS

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Objectives
Astatine-211 is a very promising radioisotope for nuclear medicine. Being a halogen and a 100% alpha emitter makes him one of the best candidate for targeted radiotherapy. However, 211At is only available in trace concentrations. In addition, the current astatined compounds in use, based on aryl-astatine bond, undergo deastatination during the internalization in cells, leading to a loss of effective activity [1]. To overcome this issue, we investigated a strategy based on astatoalkyne.

Methods
We synthetized an arylalkyne iodonium salt as precursor of astatoalkyne [2]. The radiolabelling was done in a mixture of acetonitrile/water 9:1 with sodium sulfite as reducing agent of At. The purification was done with C18 cartridge. After purification, the isolated astatoalkyne was placed in different media for stability study (PBS, Fenton-like and human serum). We compared the astatoalkyne stability by chromatography with ethyl 3-astatobenzoate, an analogue of the reference compound SAB (N-succinimidyl 3-astatobenzoate) prepared from an iodonium salt as precursor [3].

Results
The new compound is, to our knowledge, the first reported that contains a carbon(sp)-astatine bond. With this compound, we obtained > 85% radiochemical yield within less than 30 min at room temperature. The purification process led to > 95% radiochemical purity. Nevertheless, the in vitro stability assays highlighted an instability in either oxidizing [4] (several hours) or in human blood serum (few minutes), with release of free astatine. The SAB analogue remained stable in those conditions.

Conclusion
We are currently investigating the mechanisms responsible for the compound instability. The analogous radioiodinated compound is thus investigated to understand the stability difference between astatoalkyne and iodoalkyne.

References
Simplified access to astatinated and radioiodinated antibodies by direct nucleophilic substitution of preconjugated arylboronic acids

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Hypothesis
Astatine-211 and radioiodine are used in radioimmunotherapy and nuclear imaging. However, current approaches for labelling monoclonal antibodies (mAbs) exhibit limitations. Electrophilic radiohalogenation in two [1] or one [2] steps requires the use of the halogen radionuclides in an unstable oxidation state (especially astatine) in addition to toxic precursors. Furthermore, two-step methods result in suboptimal radiochemical yields (RCYs), while the one-step method is not applicable to radioiodine. A nucleophilic approach we recently developed demonstrated a higher robustness, but it remains a two-step approach [3]. There may thus be room for improvement by the development of a one-step nucleophilic strategy.

Methods
Our strategy is based on mAbs pre-conjugated with arylboronic acids that have previously been reported for radiohalogenation of small molecules [4]. Since the reported conditions (organic solvent) are not compatible with mAbs, the challenge was to adapt this chemistry to aqueous medium via a model compound (4-chlorophenylboronic acid) before transferring it to mAbs by optimizing the nature of the catalyst, ligand, buffer and pH of reaction.

Results
Model compound gave quantitative RCYs with both radionuclides using Cu(OTf)$_2$pyr$_4$ and 1,10-phenanthroline in TRIS buffer (pH 6). Transposition to mAbs gave RCYs ≥85% with immunoreactivities >85%. Biodistribution study with iodine-125 has shown an excellent conservation of the pharmacokinetic properties (biodistribution study with astatine-211 analogue in progress).

Conclusion
We have developed the first direct method of antibody radiolabeling applicable to both astatine and radioiodine. Compared to previous methods, the global RCYs were nearly doubled and the procedure duration largely decreased. These results should facilitate the transfer of astatine-211 to the clinic and accelerate development of theranostic tools based on the radioiodine/astatine pair.

References:
Design and synthesis of an Optical-PET bimodal imaging probe based on a NIR fluorophore and fluorine-18

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Objectives
Among the ever-growing development of imaging probes, an increasing attention has been focused in the past few years on the synthesis of scaffolds exhibiting more than one imaging modality. The combination of two or more imaging agent on the same structure allows to fully exploiting each imaging asset with a unique affinity of the probe for its target. In this context, our group is investigating the development of a generic probe combining PET and Near InfraRed (NIR) optical imaging modalities, leading to new bimodal theranostic tools. As a proof of concept, the designed probe will be conjugated to a PSMA ligand for an in-vivo evaluation in a xenograft murine cancer model.

Methods
The designed bimodal tool relies on a scaffold functionalized with fluorine-18 radionuclide as positon emitter for PET imaging, a cyanine as the NIRF optical dye and an azide moiety which serves as an attachment point to the targeting vector. After radiolabeling of the probe, conjugation with an alkyne-derived PSMA ligand by CuAAC affords the bimodal PET/NIRF tracer in a fully automated radiosynthesis. In vivo evaluation will be performed by PET imaging followed by in vivo fluorescence imaging and ex vivo analysis of tumoral tissue.

Results
The non-radioactive reference and a tosylate precursor were synthesized from a bifunctionnal scaffold and IR780 cyanine in a short synthesis of 6 and 7 steps respectively. Radiolabeling by tosylate substitution was performed in DMSO at 100 °C affording the labeled cyanine in 19% RCY, which was quantitatively conjugated to the PSMA ligand.

Conclusion
A versatile bimodal PET/NIRF probe was developed in this work, which can be easily conjugated to a targeting vector by click chemistry. The in vivo evaluation is on-going to further demonstrate the potential of our multimodal tool for both diagnostic and optical guided surgery applications.
The use of a non-residualizing label provides a high-contrast radionuclide imaging of EpCAM expression using engineered scaffold protein DARPin Ec1

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Hypothesis
Radionuclide-based imaging of the expression of molecular therapeutic targets might facilitate stratifying patients for specific therapeutics. New type of imaging probes, based on designed ankyrin repeat proteins (DARPins), have demonstrated excellent contrast of imaging of human epidermal growth factor type 2 (HER2) expression in preclinical models. We hypothesized that non-residualizing labels would provide the best imaging contrast for DARPins that internalize slowly after binding to cancer cells. The hypothesis was tested using DARPin Ec1 that bound to epithelial cell adhesion molecule (EpCAM). EpCAM is overexpressed in many cancers and is a promising therapeutic target.

Methods
Ec1 was labeled with 125I using direct and indirect (PIB) methods to obtain non-residualizing labels, while residualizing labels were obtained by labeling it with 99mTc. EpCAM-expressing BxPC3 pancreatic cancer cell line was used for in vitro and in vivo characterisation. Biodistribution was measured in BALB/C nu/nu mice bearing BxPC3 xenografts at 3 and 6 h after injection. EpCAM-negative Ramos xenografts were used as a negative control. MicroSPECT/CT imaging was used to confirm the biodistribution data.

Results
All labeled Ec1 variants preserved target specificity and picomolar binding affinity to BxPC-3 cells. In murine model, all the variants provided similar tumor uptake at 3 h pi. However, 125I-PIB-Ec1 had lowest retention in normal tissues, which provided appreciably higher tumor-to-organ ratios. The uptake of 125I-PIB-Ec1 in BxPC3 xenografts was significantly higher (p < 0.0005) than in Ramos xenografts, which demonstrated specificity of targeting. MicroSPECT/CT imaging confirmed high-contrast visualization of BxPC3 xenografts. Furthermore, 125I-PIB-Ec1 demonstrated the highest imaging contrast in preclinical models than any other EpCAM-imaging agent reported to date.

Conclusion
DARPin Ec1 in combination with a non-residualizing label is a promising probe for imaging EpCAM expression several hours after injection. This can be utilized for imaging of EpCAM expression using SPECT with 123I and PET with 124I.
Preclinical theranostic study of 1C1m-Fc anti TEM-1 fusion proteins

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Hypothesis
TEM-1 (tumor endothelial marker-1), a single pass transmembrane cell surface glycoprotein has been described as a suitable candidate for cancer therapy. 1C1m-Fc, an anti TEM-1 scFv-Fc fusion antibody has been developed in Lausanne. We decided to study it in vitro in a novel theranostic approach.

Methods
1C1m-Fc was first tested for purity (electrophoresis) and affinity to TEM-1 (flow cytometry) and conjugated to p-SCN-Bn-DOTA using different excess molar ratio in buffer pH 9. After 1 hour at 37°C, the non-coupled ligand was eliminated by ultrafiltration on 50kD filters. The number of chelates grafted by antibody was evaluated with a mass spectrometry analysis. The immune fraction of the modified antibody was measured by flow cytometry, using TEM-1 positive and negative cell lines. The purity and the stability of the native and of the conjugated antibody were evaluated up to one year by HPLC. The fusion protein antibody (500pmol) was labeled with 177Lu (non-carrier added, 20MBq) in ammonium acetate buffer (0,4M; pH 5,6). To determine radiolabeled antibody immunoreactivity, Lindmo assays were performed. In vivo characterization in xenograft models was done with biodistribution and spect imaging studies.

Results
In flow cytometry, the TEM-1 recognizing of conjugated fragments was similar to the native antibodies for all excess molar ratio used to modify antibody. HPLC profile of the native and of conjugated antibodies was stable at one year. The labeling with 177Lu was successful with a radiochemical purity up to 95%. Immunoreactivity after radiolabelling was 90%. Biodistribution and imaging studies showed a specific uptake in TEM-1 positive tumor (15,8±1 IA/g) with liver as critical non specific healthy organ.

Conclusion
TEM-1 is an interesting target that allows theranostic approach. 1C1m seems to be a suitable candidate. The next step will be to optimized the biodistribution and to performed therapeutic tests in murine xenograft models towards a future translation in patients.
Development and in vivo preclinical validation of $^{18}$F-FLUSONIM, a highly hydrophilic $^{18}$F-labelled 2-nitroimidazole derivative for high performance hypoxia PET imaging

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Hypothesis
Hypoxia, a common hallmark of solid tumors, is associated to tumor propagation, malignant progression, and resistance to therapy. Hypoxia detection by PET imaging has been demonstrated to be useful for diagnosis, therapeutic orientation and follow-up.[1] Several $^{18}$F-nitroimidazole derivatives such as $^{18}$F-FMISO, $^{18}$F-FAZA, $^{18}$F-HX4 or very recently $^{18}$F-DIFA have reached the clinical stage but limitations were encountered due to slow clearance and low specificity.[2] We hypothesised that hydrophilicity of the radiotracers was a key parameter for hypoxia imaging and we designed a new class of $^{18}$F-nitroimidazole analogues bearing a sulfo group known to highly increase hydrophilic properties. We undertook to develop their radiosynthesis and to perform physicochemical characterization and in vivo evaluation in animal glioblastoma models already well characterized in terms of hypoxia.

Methods
The sulfo-$^{18}$F-nitroimidazole analogues were readily obtained in one step from sultone precursors by ring opening reaction with $^{18}$F-fluoride in acetonitrile for 5 to 15 min at 20-110 °C.[3] The logP and logD values were measured using a standard shake flask method. Stability, biodistribution and pharmacokinetics were studied in healthy rats and in vivo specificity for hypoxia was evaluated in glioblastoma using small-animal PET imaging and in comparison to $^{18}$F-FMISO. Additional histological experiments including ex vivo autoradiography and pimonidazole staining were also performed.

Result
The radiosyntheses were carried out in 35-70% radiochemical yields and 97-99% radiochemical purity. The logP and logD values of the radiofluorinated products were in the −(1.5-3.6) range. No radiodefluorination and no radiometabolization were observed at 2.5 h post-injection. According to the structures, hepatobiliary or renal elimination were observed. $^{18}$F-FLUSONIM that displayed the highest hydrophilicity, was selected for evaluation in tumor models. Accumulation in hypoxic tumor was rapid (30-60 min versus 2.5 h for $^{18}$F-FMISO), and muscle to tumor ratios were 3 to 10 fold higher than those obtained with $^{18}$F-FMISO. Ex vivo autoradiography and immunohistostaining demonstrated a correlation between the uptake of the radiotracer and hypoxic regions.

Conclusion
The radiofluorination of sultone-containing 2-nitroimidazoles afforded highly hydrophilic radiotracers. Among them, $^{18}$F-FLUSONIM selectively and quickly accumulated in tumor hypoxic regions and provided a better contrast image of tumor hypoxia with shorter acquisition time compared to $^{18}$F-FMISO. The overall findings led us to consider clinical transfer as promising.
References


New Folic Acid Conjugate for $^{68}$Ga-labeling with Improved Pharmacokinetic Properties

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Hypothesis

Folate receptors (FR) are cell membrane-associated target for nuclear medicine. FR are overexpressed by cells of various epithelial tumors, including tumors of the ovary, cervix, endometrium, lungs, kidneys, etc. Therefore, in nuclear medicine FR are very promising target for molecular imaging. The only healthy tissues with high FR expression are the kidneys [1].

(HE)$_n$ purification tag effectiveness for improvement of the biodistribution of $^{68}$Ga-radiopharmaceuticals was showed earlier using PSMA-based labeled compounds and affibodies [2]. In this study the influence of (HE)$_n$ tag introduction into folate-based molecule on the pharmacokinetics was evaluated. For this purpose two folic acid based compounds were synthesized and evaluated: NODAGA-1,4-buthanediamine-folic acid (FA-I) and NODAGA-[Lys-(HE)$_2$]-folic acid (FA-II). FA-II contains (His-Glu)$_2$ fragment in order to reduce kidneys accumulation.

Methods

FA-I was synthesized according to the procedures described in the literature [1]. For synthesis of FA-II Fmoc protocols were used. All chemicals and solvents were of high-purity or pharmaceutical grade and were purchased from Sigma-Aldrich or Panreac. $^{68}$Ge/$^{68}$Ga generator (Cyclotron Ltd, Russia) was used for the labeling of FA-I and FA-II with $^{68}$Ga. Radiochemical purity of labeled compounds was determined using radio-TLC and radio-HPLC. In vivo studies were carried out in normal laboratory animals, as well as in animals with xenografts of KB and HaLa cell lines.

Results

The procedure for $^{68}$Ga-labeling was developed (yield ≥ 95%). In in vivo experiments the accumulation of [${}^{68}$Ga]Ga-FA-II in healthy tissues reduced in comparison to [${}^{68}$Ga]Ga-FA-I, e.g. for kidneys the accumulation was 2-4 times lower. Tumor (KB) accumulation of [${}^{68}$Ga]Ga-FA-II remained the same as for [${}^{68}$Ga]Ga-FA-I.

Conclusion

(HE)$_n$ tag introduction into folate-based radiopharmaceuticals is the promising approach to improve their pharmacokinetic properties.


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Lower binding potential of GLP-1 receptor in the pancreas as a consequence of diet-induced obesity

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Objectives
GLP-1 receptor agonists are capable of effective weight reduction in obese subjects. However, the weight loss in response to treatment depends on BMI as a possible consequence of a lower GLP-1 receptor density. This study aimed to evaluate this hypothesis using a preclinical model of diet-induced obesity.

Methods
GLP-1 receptor density was quantified in the pancreas of 16 adult miniature pigs, eight being obese (80 ± 5 kg) while the remaining lean (42 ± 3 kg). PET-CT dynamic imaging was performed after the IV administration of [68Ga]Ga-DO3A-VS_Cys40-Exendin-4 (7 ± 4.2 MBq; 0.1 µg/kg). The radiolabelled compound was produced using an automated GRP synthesizer and quality control was performed with UV-radioHPLC. Input arterial function was continuously recorded using an extemporaneous external arterial-venous loop. Pancreas PET data were fitted to a two tissues compartment model using Pmod software, and binding potential was calculated as the ratio between K1*k3 and k2*k4.

Results
[68Ga]Ga-DO3A-VS_Cys40-Exendin-4 showed a clear pancreatic uptake in lean animals but the difference in uptake between the pancreas and the other abdominal organs was less in obese. Binding potential in obese was one-tenth (0.024395 ± 0.000523) of that observed in lean subjects (0.2056 ± 0.00328) primarily as a consequence of reduction in K1 (0.0406 ± 0.00072 vs 0.0092 ± 0.000149 ml/ccm/min in lean vs obese).

Conclusion
The use of 68Ga labeled GLP-1 receptor agonist allows to demonstrate a massive down-regulation of GLP-1 receptor within the pancreas of obese versus lean adult pigs. While this lower binding potential might explain the clinically reduced efficacy of GLP-1 receptor agonist, it also opens a new pharmacological avenue aimed towards weight reduction.
Development of a mouse model of liver metastases of pancreatic neuroendocrine tumor and phenotypic analysis with $^{68}$Ga-DOTATOC and $^{18}$F-FDG-micro-PET/CT

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Hypothesis
Prognosis of pancreatic neuroendocrine tumors (pNET) is heterogeneous and the discovery of liver metastases is a turning point of the disease. Few animal models exist to study these tumors with an indolent evolution. The aim of this work was to develop and validate a mouse model of liver metastases and to explore it by micro-PET/CT.

Methods
Immunodeficient mice received 1 million of amphicrine, overexpressing SST2 AR42J cells in subcutaneous (SC) and intraportal graft. We performed PET/CT with $^{68}$Ga-DOTATOC and $^{18}$F-FDG and biodistribution at D20 and D32 after engraftment on the same mice. A histological analysis of liver was performed to confirm the development of hepatic tumors.

Results
At D20, all of the SC tumors were detectable on $^{68}$Ga-DOTATOC-PET/CT (3/3) whereas only one was detectable on $^{18}$F-FDG-PET/CT (1/6). There was no liver abnormal focus for either radiopharmaceutical. At D32, with the same mice, there was a liver focus in all mice on $^{68}$Ga-DOTATOC-PET/CT (3/3) while no abnormalities were detected on $^{18}$F-FDG-PET/CT (0/5). After sacrifice, liver tumors were confirmed in all of the mice.

Conclusion
This study is the first one to develop a mouse model of liver metastases of pNET with a phenotype consistent with the well differentiated low-grade pNET observed in human. This model could be used to evaluate innovative radiopharmaceuticals for imaging as well as for therapy of overexpressing SST2 pNET.
Change In Expression Of 5-HT₆ Receptor At Different Stages Of Alzheimer’s Disease: A Postmortem Study With The Pet Radiopharmaceutical [¹⁸F]2FNQ1P

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Objectives
The aim of this study was to investigate the binding of [¹⁸F]2FNQ1P, a new specific radiotracer of 5-HT₆ receptors, and to quantify 5-HT₆ receptor density in caudate nucleus in a population of patients with different Alzheimer’s disease (AD) stages.

Methods
Patients were classified according to the “ABC” NIA-AA classification. In vitro binding assays were performed in postmortem brain tissue from the control (“Not”; n=8) and severe AD (“High”; n=8) groups. In vitro quantitative autoradiography was performed in human brain tissue (caudate nucleus) from patients with different stages of AD: “Not” (n=15), “Low” (n=18), “Int” (n=20) and “High” (n=15).

Results
In vitro binding assays did not show significant differences for the K_D and B_max parameters between “High” and “Not” groups. In vitro quantitative autoradiography showed a significant difference between the “High” and “Not” groups (p-value = 0.0025). We also showed a progressive diminution in [¹⁸F]2FNQ1P specific binding, which parallels 5-HT₆ receptors expression, according to increasing AD stage. Significant differences were observed between the “Not” group and all AD stages combined (“Low”, “Intermediate” and “High”) (p-value = 0.011).

Conclusion
This study confirms the interest of investigating the role of 5-HT6 receptors in AD and related disorders. [¹⁸F]2FNQ1P demonstrated specific binding to 5-HT6 receptors.
Assessment of osteoblastic activity with 18F-sodium fluoride PET in aortic bioprosthesis structural valve dysfunction: first results of a monocentric observational pilot study

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Hypothesis
Structural valve degeneration of bioprostheses (SVD) is the most common and life threatening complication in patients undergoing aortic valve replacement. A calcification process is frequently involved but its pathophysiology remains unclear. To explore the mechanism of calcification in SVD, inflammation was determined by 18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) and ongoing mineral deposition was evaluated by 18F-sodium fluoride (18F-NaF) PET.

Methods
Between January 2017 and March 2018, patients with echocardiography-confirmed SVD (mean gradient ≥ 20 mmHg, maximum velocity ≥ 3 m/s, area ≤ 1.2 cm², and/or aortic insufficiency ≥2 / 4) were proposed to participate to the study. Patients underwent 18F-NaF and 18F-FDG PET/CT and thoracic CT. Radiotracer uptake on bioprostheses was analyzed qualitatively and quantitatively by measuring the blood-pool-corrected standardized uptake value (target-to-background ratio (TBR)). Echocardiographic parameters, bioprosthesis calcium scoring (AU), and pattern of 18F-NaF and 18F-FDG activity were described. Median 18F-NaF TBR was chosen as a cutoff to establish two groups of patients.

Results
The first 21 included patients were analyzed; 4 patients (19.0%) had intraprosthetic regurgitation, 4 (19.0%) had intraprosthesis regurgitation, 4 (19.0%) had subvalvular regurgitation, and 13 (61.9%) had mixed type. Calcium score was higher in patients with significant 18F-NaF visual uptake (n=12, 57.1%) versus patients with no 18F-NaF uptake (mean 1065 ± 505 vs 462 ± 320, p 0.015). The median 18F-NaF TBR (3.49, [2.33 - 5.04]) was significantly higher than those of 18F-FDG (1.34, [1.20 - 1.47]). The patients with 18F-NaF TBR greater than the median value had a higher calcium score (mean 1059 ± 550 vs 566 ± 363, p 0.05), and showed a tendency to have more severe stenosis (indexed area 0.394 cm²/m² ± 0.123 vs 0.6 cm²/m² ± 0.132, p 0.067).

Conclusion
These preliminary results pave the way to new perspectives on the assessment of physiopathology and severity of aortic SVD pathology.
Prospective evaluation of FDG and FES PET imaging for selecting second line hormonotherapy in estrogen receptors positive metastatic breast cancer patients: preliminary results


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Objectives
About 70% of primitive breast cancers have positive estrogen receptors (ER) and benefit from hormonotherapy. However, ER expression in breast cancer metastases is heterogeneous and about 15% of metastases lost expression over time. Biopsies are not possible systematically.

16α-18Fluoro-17β-Oestradiol (FES) predicts the response to the first line hormonotherapy. The aim of this prospective study (NCT03442504) was to determine the predictive value of FES PET at lesion and patient levels before a second line hormonotherapy (2nd-HT) based on the FDG response obtained 6 weeks after treatment induction.

Methods
We included 20 ER+ metastatic breast cancer patients, HER2 negative, in progression during first line hormonotherapy. For the complete study, 60 patients will be included. The patients underwent a baseline FES PET (FES-BL) and FDG PET (FDG-BL) before the 2nd-HT beginning. Follow-up with FDG PET were performed to assess treatment response, particularly with the first FDG PET at 6 weeks (FDG-6W). Semi-quantitative data were extracted from FES-BL, FDG-BL and FDG-6W, and compared to the progression free survival (PFS): SUVmax, SUVpeak and Metabolic Total Volume (MTV) with two thresholds (a fixed one to generate forty percent of SUV_{max} MTV called 40%MTV and an adaptative other called Adapt MTV).

Results
For “lesion level” analysis, results showed on FES-BL that SUV_{max} and SUV_{peak} predict the metabolic response at six weeks (p<0.05), as well as SUV_{peak} ratio between FES-BL and FDG-BL (p<0.05). At “patient level”, we did not predict the PFS despite the different MTV ratios used.

Conclusion
FES PET seemed to be interesting for the 2nd-HT response prediction. These results must be confirmed with the complete cohort of patients.
Purification of Zirconium-89 for the Radiolabeling of Monoclonal Antibodies for Positron Emission Tomography

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Hypothesis
Zirconium-89 has gained growing attention in recent in medical imaging by its half-life time (78.4h) which is adapted with the pharmacokinetics of monoclonal antibodies (mAbs). Its high positron yield (22.7%) and positrons with low energy ($E_{\text{moy}} = 395.5$ keV) provide a high resolution in PET imaging. The best chelating agent is deferoxamine (DFO) but this ligand release progressively the metal that will bind on the bones. This release is more important in little living being like rats or mouse than human being. That is why for pre-clinical study the synthesis of a new ligand stills relevant.

Methods
We aim to develop an automated system for routine production of Zirconium-89 in order to provide this isotope with high radionuclide purity and specific activity. We also investigate a new chelating agent that confront in a stability test with EDTA or DFO. Briefly, I investigated the irradiation of yttrium sputtered on niobium coins. The sputtered coins were irradiated with an incident beam energy of $<13$ MeV with various currents to determine optimal cyclotron conditions for $^{89}$Zr production. This system will automated a separation process from the literature that uses a hydroxamate resin column to purify $^{89}$Zr from an $^{89}$Y target. We have designed a system allowing control over every step in the process.

Results
This system is currently working well; more than five productions were made with good purification yield (86-96%), radiochemical purity of $>99.9\%$ and competitive specific activity (32-44 MBq/nmol). The particularity between us and all the latest work on sputtered yttrium is that we can provide both $^{89}$ZrCl$_4$ and $^{89}$Zr-[Ox]$_2$ complex. Briefly, the oxalate form gives the majority of commercially available Zirconium where the oxalic acid is highly harmful for the kidneys.

Conclusion
The use of sputtered yttrium on niobium coins have shown to be an effective and alternative way of 89-Zr production in its both forms (complex). We confirmed that the proton beam with an energy $<13$ MeV eliminated the production of 88-Zr. For the next year, we aim to develop a new chelating agent, which will be compared to the standard one. The new chelating agent is based on apple and we want to optimize the coordination sphere of Zr(+IV) by adding two Lewis bases including a carboxylic acid.
Automated two-steps manufacturing of $[^{11}\text{C}]$glyburide for PET imaging in Humans

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**Objectives**

Glyburide is an approved anti-diabetes drug binding to the sulfonylurea receptors-1 (SUR-1) which can be isotopically radiolabelled with carbon-11 for PET imaging. Glyburide is an avid probe substrate to study solute carrier O (SLCO, aka OATP) transporters of importance for pharmacokinetics. The aim of this work is to present an original and reproducible automated radiosynthesis of $[^{11}\text{C}]$glyburide and a full, European Pharmacopeia compliant, quality control to use $[^{11}\text{C}]$glyburide in PET imaging clinical trials.

**Methods**

Different non-radioactive reaction conditions (temperature, solvent, bases) were explored to realize the methylation of glyburide in one or two steps from a commercial or in-house synthesized precursor respectively. Reactions were monitored by UPLC-MS. Exploiting the two-steps approach, radiomethylation was carried out from $[^{11}\text{C}]$MeOTf using a TRACERlab FX C Pro module followed by reaction with cyclohexyl isocyanate. $[^{11}\text{C}]$Glyburide was purified by semi-preparative HPLC followed by solid-phase extraction formulation and sterilization over a 0.22 µm filter. A quality control was realized including organoleptic test, pH measurement, chemical identification with chemical and radiochemical purity assessment by analytical HPLC, residual solvents determination by headspace gas chromatography with FID detection, radionuclide purity and half-life measurement by gammaspectrometry, bubbling point filter integrity test, sterility check by incubation in growth media and bacterial endotoxins measurement using the limulus amebocyte lysate test.

**Results**

One-step non-radioactive methylation of O-desmethyl glyburide revealed regioselectivity issues, reaction occurring preferentially at the sulfonylurea moiety. The two-steps approach from an original sulfonamide precursor, synthesized in one-step and 79% yield, afforded only glyburide without side products. Ready-to-inject $[^{11}\text{C}]$glyburide was obtained in 5% non-decay corrected radiochemical yield and $110 \pm 20$ GBq/µmol molar activity within 40 minutes ($n = 5$). $[^{11}\text{C}]$Glyburide was compliant with all requirements of the European Pharmacopeia.

**Conclusion**

$[^{11}\text{C}]$Glyburide manufacturing proved to be reliable and compliant with all requirements to be used as a radiopharmaceutical for Human injection.
Elaboration of nanocarriers based on biocompatible polymers to encapsulate radionuclides for diagnosis and/or therapy of hepatocellular carcinoma

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Objectives
Hepatocellular carcinoma (HCC) represents the major primary liver cancer. Currently, diagnosis and treatment of HCC are still imperfect because distribution of diagnostic agents and anticancer drugs are often insufficient at the tumor site. Moreover, treatment agents can accumulate in healthy tissues. Therefore, the aims of the design of multifunctional nanocarriers for HCC theranostics are to diagnose and treat HCC earlier.

Methods
We have selected poly(β-malic acid) (PMLA) and its derivatives as biocompatible and (bio)degradable polymeric materials for the elaboration of biocompatible nanocarriers[1]. We have therefore synthesized and characterized random copolymers derived from PMLA in order to graft chelator molecules on the carboxylic acid functional groups of the lateral chains[2]. DOTA, NOTA and innovative chelators: cyclam TE1PA, tripod N₂O and dipicolylamine (DPA), have been chosen for this study because of their ability to chelate the following radionuclides: ⁶⁴Cu, ⁶⁸Ga & ⁹⁹mTc for diagnosis, and ⁶⁷Cu, ⁹⁰Y & ¹⁸⁸Re for therapy. For the grafting, copolymers PMLA-stat-PMLAHexyl with ratios 10/90 and 30/70 has been activated with N-Hydroxysuccinimide (NHS). Grafting has been done between NHS function and carboxylic function of chelators. Nanoparticles have been formulated using nanoprecipitation method. Moreover, the chelation of selected radionuclides has been tested according two methods: radionuclide is mixed with preformed nanoparticles or radiolabeling is done during the nanoprecipitation step.

Results
Analysis of the obtained results shows that nanoparticles are formed with satisfying, but improvable, grafting and radiochemical yields.

Conclusion
After synthesis optimization with chelators, GBVA10-9 and CPB peptides, showing a high tropism towards hepatoma cells, will be grafted onto the polymers and the chelators. Grafting will be realized either by thiol-ene addition or by NH₃/NCS coupling reaction. It will be necessary to find the appropriate levels of grafting (peptide and chelator) allowing a reproducible preparation of nanovectors efficiently internalized by the hepatoma cells.

Site-selective labeling of biomolecules via disulfide rebridging

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Objectives
Fluorine-18 labelled biomolecules are increasingly employed in clinical applications. Given their fragility and complexity, it necessitates the development of site-selective labelling techniques in mild conditions. Besides, it is essential to develop labelling procedures with minimal modification of the tertiary structure, as it can be fundamental for biological activity. Disulfide rebridging is a promising possibility as it allows protein modification as well as conservation of the tertiary structure.\textsuperscript{1} In this context, we have developed an original method for the radiofluorination of disulfide containing biomolecules via disulfide rebridging and we applied it to the labelling of octreotide, a somatostatine analogue employed for the imaging of neuroendocrine tumors.

Methods
We have evaluated two approaches in this work. The first one (Figure 1, Method A) relies on the direct one-step labeling of the peptide pre-modified with a labeling tag. To this end, via rebridging of the disulfide bond with a diphenylthiomaleimide moiety, octreotide was conjugated to an activated pyridine precursor able to undergo radiofluorination at low temperatures. The second strategy (Figure 1, Method B) relies on the preparation of a radiofluorinated prosthetic group presenting the same diphenylthiomaleimide moiety followed by rebridging of the reduced octreotide.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Peptide radiofluorination via disulfide rebridging}
\end{figure}
Results
Radiofluorination of octreotide via method A was first assessed, but labeling was inefficient in these conditions. Regarding method B, the radiofluorinated diphenylthiomaleimide was prepared in a 25 % radiochemical yield (d.c.) and was then employed for rebridging of octreotide. Complete conversion was achieved after 10 minutes at room temperature.

Conclusion
The preparation of a highly reactive radiofluorinated maleimide was carried out and enabled the selective rebridging of the native disulfide bond of octreotide in 10 minutes. To test the scope of this original radiolabeling strategy, the method will be applied on complex biomolecules (Fab, ScFv) in the near future.
Antibody anti PDL1 radiolabelling with $^{89}$Zr: feasibility and in vitro characterization

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Hypothesis
During their immunotherapy treatment, some patients with bronchopulmonary cancers develop forms of resistance and tumoral growth resumes. These resistance phenomena can occur following the expression of co-inhibitory molecules by tumor cells or tumor microenvironment (TME) such as PDL1 (for tumor) and TIM3 (for TME). Our aim is to visualize PDL1 and TIM3 expression progression during treatment with PET/CT to study evolution of TME by using anti-PDL1 & anti-TIM3 antibodies labelled with zirconium 89 ($^{89}$Zr).

Methods
We used size exclusion chromatography coupled with UV and gamma detection to define retention time of anti-PDL1 (clone 10F.9G2) and free $^{89}$Zr. The radiolabelling of the anti-PDL1 was divided into two steps: 1) Fixation of the p-NCS-Bz-DFO chelator based on nucleophilic substitution, 2) Radiosynthesis with ($^{89}$Zr). The radiolabelling step was followed by purification on a PD-10 exclusion column. In vitro immunoreactivity (IR) assays were performed on CMT167, mice bronchopulmonary cancer cells expressing PDL1. The cells (0,125 to 2.10$^6$) were incubated for 1 hour with 2 nM Anti-PDL1-DFO-Zr89 for total IR and with the addition of 2 µM for non-specific IR.

Results
The analytical method developed allowed us to characterize and quantify the different substances found at the end of radiolabelling. Analytical control revealed a pure solution, with only Zr89-Anti-PDL1. We obtain a radiolabelling yield of 67% +/-22 (n=3) and we were able to obtain samples with 100% of radiochemical purity (RCP). The specific activity was 18,1 MBq/mg +/-4,9 (n=3) and volumetric activity of 11,7 MBq/mL +/-4,5 (n=3). The in vitro assay revealed an immunoreactivity of 85,4%.

Conclusion
The volumetric activity of 11,7 MBq/mL +/-4,5 and RCP of 100% are very encouraging for in vivo injection. In vitro tests revealed an IR of 85% compared to 70% found in the literature, indicating that the antibodies were not damaged by radiolabelling.
Transport into the central nervous system of \(^{18}\text{F}\)FLT and \(^{18}\text{F}\)Fludarabine for brain tumors

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Objectives
The development of delivery systems to transport some specific radiotracers across the blood-brain barrier (BBB) needs to be investigated for brain imaging. For this purpose two \(^{18}\text{F}\)-nucleosides have been included in the present study. \(^{18}\text{F}\)FLT is widely used as a proliferation radiotracer for oncological PET studies for the diagnosis of high-grade gliomas and the follow-up of treatments. In contrast, low-grade brain gliomas are poorly visualised and the vectorisation of \(^{18}\text{F}\)FLT through the BBB could provide the opportunity to detect these tumours at an early stage. \(^{18}\text{F}\)Fludarabine is a novel specific radiotracer for non-Hodgkin’s lymphoma and recent studies have demonstrated the potential of \(^{18}\text{F}\)Fludarabine to target CNS lymphoma (CNSL). The vectorisation process was extended to \(^{18}\text{F}\)Fludarabine for early primary cerebral lymphoma imaging.

Methods
The transport into the central nervous system of both \(^{18}\text{F}\)radiotracers (\(^{18}\text{F}\)FLT and \(^{18}\text{F}\)Fludarabine) has been studied thanks to a chemical delivery system (CDS) based on a redox system 1,4 dihydroquinoline/ quinolinium salt (Figure 1). A lipophilic carrier based on 1,4-dihydroquinoline structure was linked to the radiotracer and after BBB passage, an oxidation followed by an enzymatic cleavage will lead to the release of the PET probe. To determine the best carrier, various sets of \(^{11}\text{C}\)CDS-FLT and \(^{11}\text{C}\)CDS-Fludarabine were prepared and evaluated \textit{in vivo} into rats. Further studies were to develop the radiolabelling of the entities CDS-\(^{18}\text{F}\)radiotracer in order to evaluate them in appropriate animal models.

Results
Various parameters (base, solvent, temperature and time reaction) have been studied i) to optimize the sensitive coupling reaction of the quinolinium salt with the \(^{18}\text{F}\)radiotracer and ii) to avoid some side reactions due to our high dilution conditions. The reduction step has been conducted with BNAH and has led to the corresponding CDS-\(^{18}\text{F}\)radiotracer. The radiosynthesis was performed as a one-pot two-step procedure and after HPLC purification, the CDS-\(^{18}\text{F}\)radiotracer have been obtained with a percentage ranging from 45 to 65 % (based on HPLC profiles).

Conclusion
The radiosynthesis of CDS-\(^{18}\text{F}\)radiotracer were successfully accomplished and \textit{in vivo} evaluation will be undertaken to study the accumulation of \(^{18}\text{F}\)FLT/\(^{18}\text{F}\)Fludarabine after their release into the brain.
Investigation of $^{131}$I labelled Curcumin and Curcumin-PLGA via in vitro examination against cervical and ovarian cancer cells

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Hypothesis

Recently, use of natural products has gained more importance and it is reported that consuming them lowers cancer risk. Curcumin (CUR) is the active ingredient of turmeric and has been traditionally consumed as a dietary component for centuries. CUR has a remarkable antitumor activity against various cancers. On the other hand, treatment of advanced gynecologic cancers remains palliative in most of cases. Although systemic treatment has entered into the era of targeted drugs the antitumor properties of current therapies are still limited. Diagnosis of these cancer types accompanies to this limitation likewise treatment strategies. Cervix cancer (CC) and ovarian cancer (OC) are common gynecologic cancers in women. The polymer-based nanoparticles have been shown to be effective in delivering the chemotherapeutic agents to the targeted tumors. Poly(lactic-co-glycolic acid)(PLGA) have been extensively studied for a wide variety of drugs and biomedical applications due to their biocompatible and non-toxic properties. It is aimed to encapsulate with PLGA (CUR-PLGA) and radiolabel with iodine-131 ($^{131}$I). Furthermore, to investigate in vitro incorporation potentials of $^{131}$I labeled CUR and CUR-PLGA on CC and OC cell lines (HeLa and MDAH-2774).

Methods

CUR was encapsulated with poly lactic-co-glycolic acid (PLGA) (CUR-PLGA) and characterized by Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM) analysis. CUR and CUR-PLGA radiolabeled with $^{131}$I radionuclide utilizing iodogen method. Stability and lipophilicity studies of radiiodinated compounds were performed. Additionally, incorporation studies on HeLa and MDAH-2774 cell lines were conducted.

Results

CUR and CUR-PLGA compounds have been radiolabeled in high yield over 95% with $^{131}$I which is widely used for diagnosis and treatment in Nuclear Medicine. $^{131}$I alone has no important incorporation while $^{131}$I-CUR and $^{131}$I-CUR-PLGA have noteworthy uptake on cervical and ovarian cancer cells.

Conclusion

Radiolabeling of CUR and CUR-PLGA may be initiative discovery of novel promising imaging agents. Further studies are being planned on animal models of CC and OC.

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Conception and evaluation of new fluorinated COX-2 ligands to visualize and quantify neuroinflammation by $^{18}$F PET

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Hypothesis
CNS disorders as multiple sclerosis, stroke, neurodegenerative diseases (Alzheimer or Parkinson) lead to neuroinflammatory, which control the pathology spread and repair or regenerate the affected tissues. The visualization and quantification of neuroinflammation by PET could benefit to patients, early care, measure of treatment efficacy or disease progression. In this aim, we decided to focus our tracers development on the COX-2 target and we designed, synthesized radiolabelled and characterized new $^{18}$F COX-2 tracers.

Methods
The research of new diagnostic tools for CNS diseases based on the COX 2 binding was elaborated from the structure of drugs in the coxibs class. From these various structures we established a new pharmacophore model using indazole or benzotriazole scaffolds. To accomplish the synthesis of new original COX-2 ligands, we used an efficient pathway based on copper cyclization assisted by microwaves. In vitro evaluations was performed using the COX Fluorescent Inhibitor Screening Assay Kit from Cayman.

Radiolabelling of the lead compound, JE187, with $^{18}$F was performed by SNar using three different approaches, starting from a nitro, an iodonium and a boronic ester precursor. Potency of the tracer was evaluated by biodistribution on two animal groups, a control and the second using the cold analog to perform pre-blocking studies.

Results
The biological evaluation and the selectivity of final compounds have been performed and the first results show a high selectivity of our compounds for COX-2 (vs COX-1) but with a moderate to low affinity for the target. The most potent derivative, JE187, was selected and three different strategies were used to get the compound in a sufficient yield. The boronic ester approach afforded the best condition in terms of yields, specific activity and reproducibility. The ex vivo evaluation of the tracer demonstrated a very low brain uptake 0.05 %ID/g of tissue with a homogenous accumulation in the different brain areas.

Conclusions
We developed original COX-2 ligands which present a high selectivity over COX-1. Among the series, one derivative was labelled with $^{18}$F using three different approaches. Unfortunately and surprisingly the ex vivo evaluation revealed a very low brain uptake of the tracer making it unsuitable to image in vivo neuroinflammation.
18F labeled PET ligand for the histamine H4 receptor

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Hypothesis
Histamine (2-(1H-imidazol-4-yl)ethanamine) is an endogenous short-acting biogenic amine implicated in various physiological and pathophysiological processes. Histamine exerts its effects by binding to four specific receptor subtypes belonging to GPCR. Among them, H4Rs are expressed on microglia and in different brain regions, and seem to be involved in cancer as well as in neurodegenerative disorders such as Parkinson’s disease. To date several attempts have been conducted to develop PET tracers of this molecular target1 but no useful probe is yet available. In this context, we developed a new compound, i.e. LL039, which is the fluorinated derivative of the potent and selective H4R antagonist JNJ7777120, and evaluated it in vitro and in vivo in the rat.

Methods
The affinity of LL039 was determined on HEK-293 cells expressing the human recombinant H4R and [3H]histamine as a reference tracer according to a standard assay protocol (CEREP, France). After synthesis of the precursor and radiolabelling with [18F], the [18F]LL039 was evaluated in a rat model of focused brain inflammation well-characterized2.

Results
A Ki of 1.5 nM was obtained for LL039, indicating a high affinity for the human H4R. The [18F]LL039 was prepared from its precursor through a two-step labelling procedure, and obtained with a molar activity of 130 GBq/μmole and high purity and stability. At 1 hours post-intra-venous injection, the [18F]LL039 accumulated in the rat brain (0.1 to 0.2% injected dose/g), but its localization was homogeneous among the different regions and was not prevented by the administration of a saturating dose of the stable H4R antagonist JNJ7777120.

Conclusion
Despite a nanomolar affinity of H4R, the new compound LL039 did not bind to these receptors in a rat model of neuroinflammation. This could be related to species specificity (human vs rodent), and it would be of value to evaluated the [18F]LL039 in a rodent model receiving intra-cerebral administration of a viral vector encoding the human H4R.

Synthesis of novel alpha7-nAchR ligands: from an idea to in rodent results for Alzheimer $^{[18F]}$ TEP imaging

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Hypothesis

The neurotransmitter acetylcholine exerts its effects on the central nervous system through two distinct muscarinic mAChR and nicotinic nAChR receptor types. Due to distribution and abundance of nAChR receptors in the hippocampus and cortex enable diagnosis and therapy of some brain disorders which affect these cerebral regions. Namely, α7 nAChR agonists were identified and allowed the design of novel therapeutic agents for Alzheimer Disease (AD). In other hand, a human compatible $^{[18F]}$ labeled PET tracer for early diagnostic or validation of therapy efficiency of AD is indubitably crucial. In this aim, we envisioned to design novel α7 nAChR ligands as potential candidates for $^{[18F]}$ PET tracers design.

Methods

Synthesis, molecular modeling and in vitro evaluation of each final compound were associated to create a complete consortium able to identify the best ligands. Radio-labeling and in rodent evaluation determines the brain penetration as well as the tracer potency of drug.

Results

Based on our expertise in heterocyclic bio-mimetic development, we obtained a wide library of novel α7 nAChR ligands, containing quinuclidine, tropane or 8H-quinolizine moiety. SAR evaluation proved high range of affinity going to 0.12 nM. The most promising ligands were radio-labeled by incorporating of $^{[18F]}$ by nucleophilic substitution of appropriate precursors. Further in vivo studies in rats showed structure-dependant results concerning the passage through blood-brain barrier and the accumulation ratio to cerebellum.

Conclusion

New series of alpha 7 nAChR ligands were optimized by SAR studies. Radio-labeling and in vivo studies furnished the first results showing the potential of developed compounds as tracer candidates.
PLGA encapsulation and radioiodination of Baicalein as a potential theranostic agent for neuro-oncology and neurodegeneration

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Hypothesis
Neuro-oncological and neurodegenerative diseases create a noteworthy socio-economic burden on societies and have a substantial portion of global problems. Because of their natural properties and biological effects, the plant originated agents are under investigation for a long time and recently. In the literature search, the outstanding potential of the Baicalein (BA) compound found in the roots of Scutellaria Baicalensis Georgi has been recognized. There have been several scientific studies that reveal that BA may be a potential agent and can be used as a new therapeutic agent for the treatment of neurodegenerative diseases. It is aimed to develop a multi-functional agent in the field of neuro-oncological and neurodegenerative diseases by using Baicalein’s multi-target effects, to provide traceability and to enhance bioavailability. In this context, it is aimed to investigate PLGA encapsulation (BA-PLGA) and radioiodination of Baicalein from the viewpoint of theranostic approach.

Methods
BA was encapsulated (BA-PLGA NPs) with poly lactic-co-glycolic acid (PLGA) via the nanoprecipitation method. BA-PLGA was characterized by Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM) analysis. BA and BA-PLGA were radiolabeled with iodine-131 (¹³¹I) and quality control studies were performed utilizing chromatographic methods. Stability and lipophilicity studies of radioiodinated BA and BA-PLGA were performed. Additionally, incorporation studies on brain cancer cell lines (U87-MG and DAOY) were conducted.

Results
BA-PLGA NPs were synthesized approximately as 300 nm according to DLS measurements and SEM images. BA and BA-PLGA NPs were radioiodinated in high yields via good stability. The lipophilicity of the radioiodinated compounds give insight for blood brain barrier penetration. ¹³¹I alone has no important incorporation while ¹³¹I-BA and ¹³¹I-BA-PLGA have noteworthy uptake on breast cancer cells (U87-MG and DAOY).

Conclusion
Development of new agents originated plant compounds, such as carried within the scope of this study, for imaging and therapy contribute to the investigations in this topic.

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Quantitative assessment of 68Ga-DOTA liver uptake in obese and lean miniature pigs

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Objectives
Nonalcoholic steato-hepatitis, one of the outcomes of morbid obesity, is associated with hepatic inflammation leading to fibrosis, but the radio or cold labeled probes failed to identify its onset. We aimed to investigate the capability of 68Ga-DOTA, a compound already validated for muscle inflammation (AJNMMI, 2014) to determine the changes in liver vascularisation induced on a large animal model of diet-induced obesity.

Methods
68Ga-DOTA was used to quantify liver vascularisation in 6 lean (39 ± 3.2 kg) and 6 obese (84 ± 3.9 kg) miniature pigs. PET-CT dynamic imaging was performed after the IV administration of 68Ga-DOTA (36 ± 10 MBq). Quality control was performed with UV-radioHPLC and iTLC-SC. Input arterial function was continuously recorded using an extemporaneous external arterial-venous loop. The liver was outlined from PET and CT images using ITK-Snap. Liver kinetics data were fitted to a two tissues compartment model using Pmod software.

Results
Liver TAC differed from lean and obese animals with a peak twice as large in the lean versus obese animals. K1 and k2 were significantly less in obese compared to lean animals with the largest reduction being for K1 values. k3 and k4 were not different between groups. The flux was reduced from 0.00879 ± 0.000034 to 0.00122 ± 0.00196 ml/ccm/min) in lean vs obese.

Conclusion
Quantitative analysis of 68Ga-DOTA kinetics did not identify an increased liver uptake that could be representative of an inflammation. On the contrary, we found a marked decrease in liver flux in obese compared to the lean group. The origin for such kinetics behavior needs further investigation since it might be indicative of the early, non-inflammatory, stage of hepatic dysfunction induced by obesity.
Synthesis and in vivo comparison of $^{44}$Sc labelled DOTA-NI with $^{68}$Ga labelled DOTA-NI for hypoxia PET imaging

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Hypothesis
Positron emission tomography (PET) is an excellent tool for detection hypoxic regions in tumours. Tumour hypoxia induces malignant progression and increases the resistance of tumour cells against radiotherapy and chemotherapy. 2-Nitroimidazole-based tracers are reduced by nitroreductase enzymes and trapped in hypoxic cells, while cleared from the healthy tissues after reoxidation. The goal of this research is the radiolabelling of DOTA-nitroimidazole (DOTA-NI) with $^{44}$Sc radioisotope and in vivo investigation for tumour hypoxia imaging.

Methods
Firstly, we synthesized 2-(2-nitro-imidazol-1-yl) ethanamine by a known method. After conjugation of this compound to DOTA, the synthetized DOTA-NI was labelled with cyclotron produced $^{44}$Sc and with $^{68}$Ga, which was obtained from a $^{68}$Ge/$^{68}$Ga generator. After purification the octanol/water partition coefficient (logP) of the radiotracers was determined as -3.3 for $^{44}$Sc-DOTA-NI, and -3.5 for $^{68}$Ga-DOTA-NI. We made in vitro stability measurements of the radiotracers. After two hours they were stable in tested conditions. A small animal PET/MRI study was performed in KB tumour-bearing CB17 SCID mice. Images were obtained at 90 minutes and 4 hours after tail vein injection of radiotracer. Ex vivo biodistribution studies of both radiotracers were also performed.

Results
We realized the synthesis of $^{44}$Sc-DOTA-NI and $^{68}$Ga-DOTA-NI. According to PET/MRI study both radiotracer uptake were intense. Standardized uptake values (SUVs) were calculated for $^{44}$Sc-DOTA-NI (tumour SUVmean: 1.46 ± 0.32, tumour-to-muscle ratios (T/M) SUVmean: 62.26±10.51) and for $^{68}$Ga-DOTA-NI (tumour SUVmean: 0.79 ± 0.10, T/M SUVmean: 25.17±6.17) at 90 min postinjection. Biodistribution studies showed both radiotracer clearance mainly occurs through the kidney.

Conclusion
The preclinical studies confirmed that $^{44}$Sc-labelled DOTA-NI is a promising radiotracer for the detection of tumour hypoxia and superior compared to $^{68}$Ga-DOTA-NI.
Development of fluorescent probes as diagnostic tools to track bcl-2 dependency in breast cancer

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Breast cancer remains the leading cause of death by cancer among women. In particular, triple negative breast cancers (TNBCs) and Luminal B (LumB) cancers are difficult to treat with standard chemotherapy although this is almost systematically used as a first line of treatment. For these cases, initial results may be promising but progression and dissemination are not prevented in the long term.

Juin et al. currently study the BCL family of proteins which act at the core of the therapeutic response of cancer cells and significantly contribute to their adaptation to stress.1 Anti-apoptotic members of this family, which include BCL-2, BCL-xL and MCL-1, exert a survival activity that relies on their ability to bind and antagonize pro-apoptotic members by engaging a network of intracellular interactions. The binding interfaces have been targeted through the use of small-molecules BH3 mimetics (ABT-737/navitoclax dual BCL-2/BCL-xL, ABT-199/venetoclax selective BCL-2). Their ex vivo studies with breast tumors slices suggest that BCL-2 inhibitors would be useful for the treatment of breast cancers that are refractory to the acute effects of chemotherapy.

There is thus a need to confirm that responsive tumors encompass chemosensitive ones and to define tools that could diagnose BCL-2 dependency to stratify patients. To this aim, we have synthesized several fluorescent probes which have been evaluated for their efficacy to modulate the interaction between Bcl-2 and its intracellular partners. Work is in progress to develop new probes based on fluorescent and radiolabeled BH3 mimetics.

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