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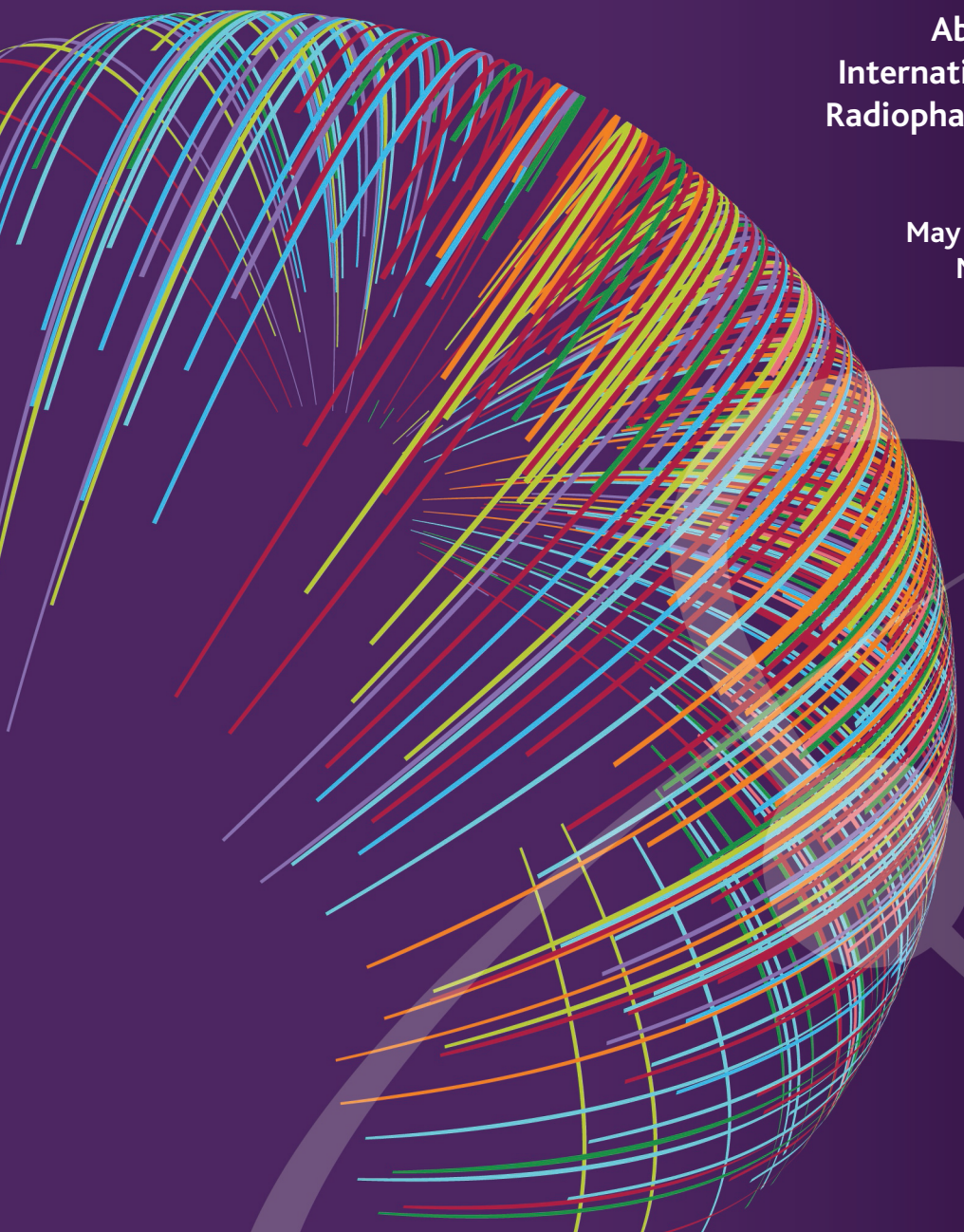
NUCLEAR MEDICINE AND BIOLOGY

FROM BENCH TO CLINICAL TRANSLATION

Molecular Targeting · Validation In Vitro & In Vivo · Radiotherapy



Abstracts of the International Symposium on Radiopharmaceutical Sciences iSRS 2022

May 29 to June 2 2022
Nantes, France

The publication of this abstract book was sponsored by the Society of Radiopharmaceutical Sciences

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AIMS AND SCOPE

Nuclear Medicine and Biology publishes original research addressing all aspects of **radiopharmaceutical science:** synthesis (automated and manual), *in vitro* and *ex vivo* studies, *in vivo* biodistribution by dissection or imaging, radiopharmacology, radiopharmacy, and translational clinical studies of new targeted radiotracers. The importance of the target to an unmet clinical need should be the first consideration.

These multidisciplinary studies should validate the mechanism of localization whether the tracer is based on binding to a receptor, enzyme, tumor antigen, or another well-defined target. The studies should be aimed at evaluating how the chemical and radiopharmaceutical properties affect pharmacokinetics, pharmacodynamics, or therapeutic efficacy. Ideally, the study would address the sensitivity of the tracer to changes in disease or treatment, although studies validating mechanism alone are acceptable as well.

If the synthesis of a new radiopharmaceutical is submitted without *in vitro* or in vivo data, then the uniqueness of the chemistry must be emphasized and should provide a substantial improvement over existing methodologies.

Radiopharmacy practice, addressing the issues of preparation, automation, quality control, dispensing, and regulations applicable to qualification and administration of radiopharmaceuticals to humans, is an important aspect of the developmental process, but only if the study has a significant impact on the field.

Contributions on the subject of therapeutic radiopharmaceuticals also are appropriate provided that the specificity of labeled compound localization and therapeutic effect have been addressed.

Further Information on the Aims and Scope of Nuclear Medicine and Biology

Graphical abstract

A Graphical Abstracts is mandatory for this journal, please find more details here *https://www.elsevier.com/journals/nuclear-medicine-and-biology/0969-8051/guide-for-authors*

Introduction:

In keeping with the goal of translating the preclinical studies to the clinic, the introduction of your manuscript should contain the potential impact of the tracer on a particular disease.

Materials and Methods:

Given that validation of new targeted radiotracers is a primary goal of the journal, all new tracers should minimally have radiochemical yield (RCY), radiochemical purity (RCP), molar activity (MA) , for reference see the publication 'Consensus nomenclature rules for radiopharmaceutical chemistry—Setting the record straight'. If not commercially available, for small molecules and peptides the precursor and cold reference should have identity (minimally 1H-NMR, 13C-NMR, HRMS) and purity (minimally HPLC) reported, while for metal complexes and biologicals alternative analyses should be provided.

Identity of a new tracer is crucial information and should be assessed via minimally HPLC where the retention time is compared to a cold reference (eg ^{19}F analog of the ^{18}F tracer). In case a radionuclide does not have a stable isotope available, a surrogate element should be used instead (eg Re to use as surrogate of ^{99m}Tc).

In vivo evaluation of new tracer should minimally include assessment of the biodistribution and the metabolism of a new tracer, if not applicable this should be justified in the discussion of the manuscript.

All metrics should have an associated average value, standard deviation and number of studies. For small-animal images, the amount injected, the anesthesia used and the image duration should minimally be included in the figure caption so comparisons can be easily made. Correlation with tissue dissection data is recommended.

Manuscripts on pharmacy including those on automation that focus on the apparatus and the computer program should present substantially improved RCY, RCP, MA; shorter reaction time; or improved analytical techniques compared to the present state of the art. All new pharmacy approaches should be referenced as complying with standard applicable regulations Radiation-absorbed dose (dosimetry) studies in humans should contain the full data set published as supplementary data. A comparison with small-animal dosimetry data is encouraged.

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May 29 to June 2, 2022

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Introduction to this Abstract Supplement

We are delighted to finally hold the 24th International Symposium on Radiopharmaceutical Sciences in-person in Nantes, France, May 29 to June 2, 2022.

The meeting will take place in the form of invited keynote presentations, 15-minute oral abstract presentations (including three minutes for Q&A), 3-minute thesis presentations, poster presentations, and 1–2 min videos submitted as part of a Radiopharmaceutical Sciences Olympiad competition. Of course, there will be plenty of opportunities for informal interaction, including an opening party in the exhibit hall, various breaks, and an afternoon excursion.

Since some presenters could not know of their ability to attend before abstracts needed to be submitted to the publisher, leadership decided to publish all confirmed oral presenter abstracts and all abstracts accepted for poster presentation. Undoubtedly, some abstracts in the supplement will not be available for poster viewing (due to institutional, COVID-related restrictions), but we still thought that there was benefit to publishing all the poster abstracts.

Sandrine Huclier, PhD
Subatech and Arronax
Nantes, France
iSRS 2022 Program Chair

CONTENTS

affinity in mouse and human plasma was studied using an ultrafiltration assay. Biodistribution and SPECT/CT imaging studies were performed in FR-positive KB tumor-bearing nude mice.

Results: FR-binding affinity of the folate radioconjugates was in the nanomolar range (1.7–4.7 nM) with a trend of higher affinity for the 6*S*-5-MTHF-based radioconjugates. This was in line with the higher cell uptake (48–56%) of the 6*S*-5-MTHF-based radioconjugates as compared to 6*R*-5-MTHF-based (30–45%) and folic acid-based radioconjugates (25–43%). The albumin-binding affinity was enhanced for AMBA-containing radioconjugates. Folate radioconjugates modified with 4-(*p*-iodophenyl)butanoate (Groups 1 and 3) showed an up to 11-fold increased albumin-binding affinity than those equipped with 4-(*p*-iodophenyl)pentanoate (Groups 24 and 25). Consequently, radioconjugates of Groups 1 and 3 showed higher retention of activity in the blood pool (up to 8.7% IA/g; 24 h p.i) than those with the weak albumin binder (Groups 24 and 25: <0.2% IA/g; 24 h p.i). Importantly, the 5-MTHF-based radioconjugates exhibited enhanced blood retention (up to 8.7% IA/g; 24 h p.i.) compared to the folic acid-based counterparts (<1% IA/g; 24 h p.i.). On the other hand, kidney retention was lower for folate radioconjugates with the strong albumin binder (Groups 1 and 3: 12–70% IA/g; 24 h p.i.) than for those with the weak albumin binder (Groups 24 and 25: 33–143% IA/g; 24 h p.i.). Within the same group, kidney uptake was 1.7- to 2.9-fold increased for the 6*S*-5-MTHF radioconjugates compared to the other two candidates. Tumor uptake was more favorable for 5-MTHF radioconjugates than for folic acid radioconjugates (26–47% IA/g vs. 14–20% IA/g; 24 h p.i.), whereas the incorporated albumin binder had only a minor impact (Figure 1B) [3]. SPECT/CT studies with tumor-bearing mice confirmed these findings.

Conclusion: The selection of each functional unit and their interplay had a decisive impact on the distribution pattern of these novel folate radioconjugates. It remains to be demonstrated clinically, which features are most relevant to enable a safe and effective application of folate radioconjugates for therapeutic purposes.

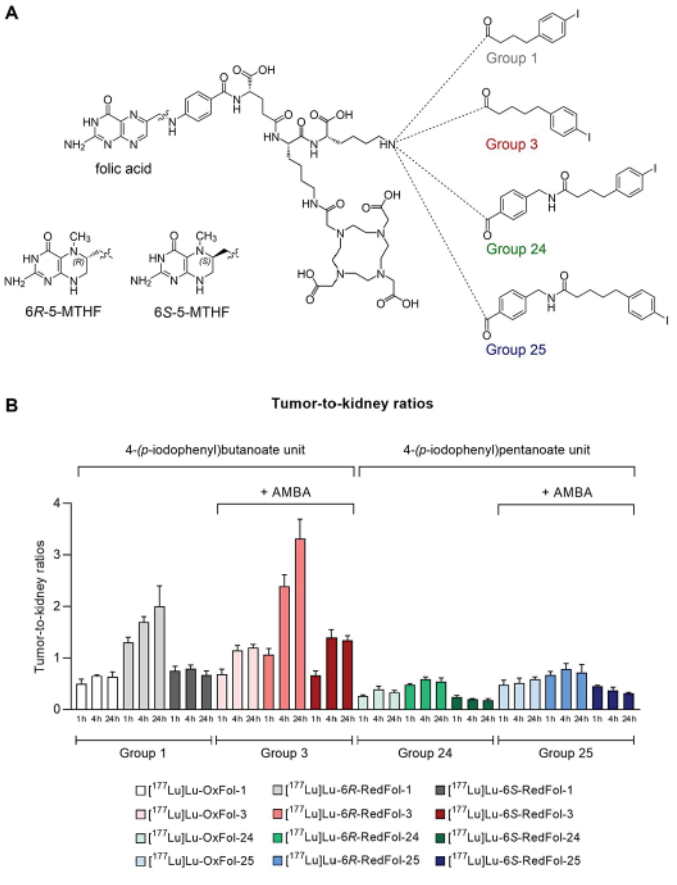


Figure 1: (A) Chemical structures of the novel folate conjugates. **(B)** Tumor-to-kidney ratios determined based on biodistribution data obtained at 1 h, 4 h and 24 h after injection of respective radioconjugates.

References:

[1] Dumelin et al., Angew. Chem. Int. Ed. Engl. 2008;47:3196-3201
[2] Deberle et al., Bioconjug Chem 2021;32:1617-1628
[3] Guzik et al., *EJNMMI* 2020;48:972-983

O-14

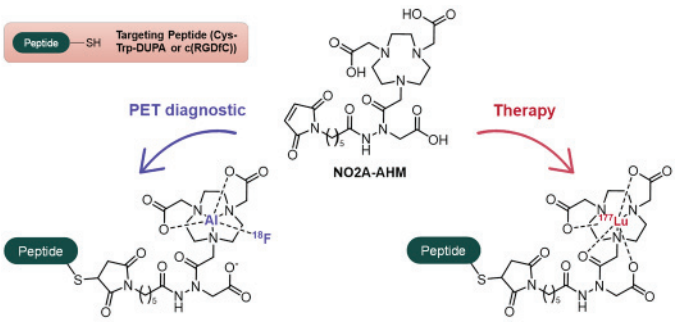
Design and synthesis of a new bifunctional chelating agent for ^{18}F-Al/^{177}Lu radiolabelling: theranostic approach

Laurène Wagner[1], Raùl Losantos[1], Céline Frochot[1], Gilles Karcher[2], Antonio Monari[3], Charlotte Collet[1], Samir Acherar[1]
[1]Université de Lorraine, France, [2]Nancyclotep, Plateforme d'imagerie moléculaire, France, [3]Université de Paris, France

Objectives: Theranostic and personalized medicine are blooming as strategies to improve patients health care and provide early treatment [1]. Access to ^{18}F-radiochemistry for theranostic application is attractive due to imaging property of fluorine-18. However, to perform diagnosis by PET with fluorine-18 and β^- therapy with lutetium-177, the use of two different chelating agents (NOTA and DOTA respectively) was required [2]. To overcome this issue, we propose herein to develop a new general chelating agent named NO2A-AHM, labelled with different types of emitters (β^+, β^- and γ) using the mismatched pair (^{18}F-Al/^{177}Lu). Moreover, this agent can be coupled to targeting units containing a thiol function such as peptides. Experimental and computational chemistry was performed to confirm the capacity of our chelating agent to label aluminum-fluorine and lutetium.

Methods: Different strategies to synthesize the original chelating agent NO2A-AHM were realized. Complexation ability of the new chelator was also evaluated using molecular modeling approaches at DFT level of theory. Experimental complexation study was also performed with aluminum-fluorine-19 and lutetium-175. Thiol-maleimide click chemistry was used to couple NO2A-AHM to the targeting agents Cys-Trp-DUPA and c(RGDfC).

Results: This new bifunctional chelating agent for theranostic applications is based on a hydrazine moiety functionalized by a NOTA cycle, a chelating arm, and a linker with a maleimide function. This design was chosen to allow the formation of 5 to 7 coordination bonds with a metal. The complexation of aluminum-fluorine, gallium and lutetium has been confirmed by molecular modeling justifying our chosen approach. NO2A-AHM was synthesized in 6 steps with an overall yield of 10%. Coupling of the bifunctional chelating agent with cysteine containing targeting agent was realized thanks to thiol-maleimide click reaction leading to the two precursors NO2A-AHM-Cys-Trp-DUPA and NO2A-AHM-c(RGDfC) with a yield of 77% and 77% respectively. Complexation was realized with non-radioactive cation metals (aluminum-fluorine-19 and lutetium-175) on NO2A-AHM and on peptide-precursor compounds (NO2A-AHM-Cys-Trp-DUPA, NO2A-AHM-c(RGDfC)) with yields of 70-80%.



Chemical structure of NO2A-AHM coupled with targeting peptide and labelled with aluminum-fluorine-18 or lutetium-177 for theranostic approach

Conclusions: The proof of concept of the ability of NO2A-AHM to complex aluminum-fluorine for further PET imaging applications and lutetium for therapeutic applications has been successfully achieved and is encouraging for the development of the theranostic approach. Further investigations will be performed using gallium to obtain ^{68}Ga-radiotracer for PET imaging applications. Radiolabelling of this new chelating agent with aluminum-fluorine-18 and lutetium-177 is under investigation.

Acknowledgments: We thank the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation and Nancyclotep for PhD funding.

References:

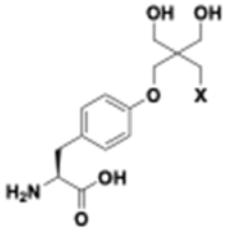
[1] Yordanova et al. Theranostics in Nuclear Medicine Practice. OncoTargets Ther. 2017, 10, 4821–4828, doi:10.2147/OTT.S140671.
[2] Notni et al. Thinking the Role of Radiometal Isotopes: Towards a Future Concept for Theranostic Radiopharmaceuticals. J. Label. Compd. Radiopharm. 2018, 61, 141–153, doi:10.1002/jlcr.3582.
[3] McBride et al. Radiofluorination Using Aluminum-Fluoride (Al18F). EJNMMI Res. 2013, 3, 36, doi:10.1186/2191-219X-3-36.

O-15
At-211-labeled L-tyrosine derivatives via neopentyl scaffold for targeted α-therapy

Yuta Kaizuka[1], Hiroyuki Suzuki[1], Tadashi Watabe[2], Yoshifumi Shirakami[2], Kazuhiro Ooe[2], Takahiro Teramoto[3], Atsushi Toyoshima[2], Tomoya Uehara[1]
[1]Chiba University, Japan, [2]Osaka University, Japan, [3]IRS, Osaka University

Objectives: L-Type amino acid transporter 1 (LAT1) is up-regulated in various tumors. Therefore, radiolabeled amino acid derivatives transported by LAT1 have been developed for tumor diagnosis and used in clinical stages. Astatine-211 (^{211}At) is an α-emitter and belongs to halogen as same as fluorine-18 (^{18}F) and radioiodine. So, ^{211}At-labeled amino acid derivatives have been developed as radiotherapeutic agents. However, deastatination from ^{211}At-labeled amino acid derivatives has been observed, and its improvement is desired. Recently, we reported neopentyl glycol as a platform to prepare ^{211}At-labeled compounds with high *in vivo* stability against deastatination [1]. In this study, to develop a ^{211}At-labeled amino acid derivative, we designed, synthesized, and evaluated neopentyl glycol conjugated amino acids as a candidate for targeted α-therapy.

Methods: Since the substituent modifications of the hydroxy group in the tyrosine side chain would be tolerant for the recognition by LAT1, a neopentyl scaffold was introduced into the hydroxy group to prepare NpTyr (Figure). Before evaluating [^{211}At]At-NpTyr, [^{125}I]I-NpTyr was also prepared and evaluated the amino acid transport mechanism using C6 cell line and the biodistribution in C6 tumor-bearing mice because ^{211}At-Np derivatives showed similar properties to ^{125}I-Np derivatives. Finally, the biodistribution of [^{211}At]At-NpTyr in normal mice was compared with [^{125}I]I-NpTyr.



X=^{125}I: [^{125}I]I-NpTyr
^{211}At: [^{211}At]At-NpTyr

Figure. Structure of the evaluated agents

Results: [^{125}I]I-NpTyr and [^{211}At]At-NpTyr were obtained in 47% and 48% radiochemical yields, respectively, and over 98% radiochemical purities after HPLC purification. [^{125}I]I-NpTyr was incorporated into the cells in a time-dependent manner. In the presence of 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH), an inhibitor of system L transporter or alpha-methyl-$_L$-tyrosine (AMT), LAT1 substrate, the uptake of [^{125}I]I-NpTyr was reduced to 15% and 19%, respectively. Tumor accumulation of [^{125}I]I-NpTyr in C6 tumor-bearing mice was comparable to that of 3-[^{125}I]iodo-α-methyl-$_L$-tyrosine ([^{125}I]IMT). Both [^{125}I]I-NpTyr and [^{211}At]At-NpTyr exhibited low accumulation in the stomach and the neck and similar biodistribution profiles in normal mice.

Conclusions: [^{125}I]I-NpTyr was transported into C6 cells with the involvement of LAT1, and the tumor accumulation of [^{125}I]I-NpTyr *in vivo* was comparable to the conventional amino acid tracer. [^{125}I]I-NpTyr and [^{211}At]At-NpTyr exhibited similar pharmacokinetics in normal mice. These findings suggest that [^{211}At]At-NpTyr is a good candidate for targeted α-therapy.

Acknowledgment: This work was supported in part by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science, grant number 19K08222. ^{211}At was supplied through the Supply Platform of Short-lived Radioisotopes, supported by JSPS Grant-in-Aid for Scientific Research on Innovative Areas, grant number 16H06278.

References:

[1] H. Suzuki, Y. Kaizuka, et al., J. Med. Chem. 2021, 64, 15846-15857

Scientific Session 4: Nanomedicine

O-16
Tetrazine ligation based pretargeting strategy for core-labeled polymeric micelles

Emanuel Sporer[1], Christian Poulie[2], Jesper Jørgensen[2], Andreas Kjær[2], Matthias Herth[2], Andreas Tue Ingemann Jensen[3]
[1]Technical University of Denmark, Denmark, [2]University of Copenhagen, Denmark, [3]LiPlasome Pharma A/S, Denmark

Objectives: Polymeric micelles (PMs) can be used to deliver therapeutic substances and radionuclides to tumor lesions. The most common targeting strategy is passive accumulation via the enhanced permeability and retention effect (EPR). However, the EPR effect only results in limited and slow accumulation, and cannot target micrometastases. For these reasons, EPR is not compatible with targeted radionuclide therapy. Here we present a new strategy for active targeting of PMs via biorthogonal pretargeting. PMs consisting of polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA) co-polymers were surface modified with tetrazines (Tz). These Tz-PMs can be injected three days after a transcyclooctene (TCO) modified antibody has been administered and accumulated in the tumor (Figure 1). The PMs then accumulate in the tumor via the Tz-TCO ligation.

Methods: *Synthesis:* NH_2-PEG(5k)-PLGA(10k) was modified with either 2,5-dioxopyrrolidin-1-yl 2-(4-(1,2,4,5-tetrazin-3-yl)phenyl) acetate or DOTA, via their NHS derivatives. PEG(5k)-PLGA(10k)-NH_2 was modified with 2,5-dioxopyrrolidin-1-yl 3-(trimethylstannyl) benzoate (Figure 2). After synthesis, the resulting functionalized polymers were mixed in DMF in different ratios, along with unmodified PEG(5k)-PLGA(10k). Slow addition of water caused formation of PMs, which were purified by sequential concentration on centrifuge filters. To monitor PMs in vivo, we co-labeled them with copper-64, as well as with iodine-125 via a recently developed covalent core-labeling strategy that is also applicable to astatine-211.