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## Frontiers in radionuclide imaging and therapy, a chemical journey from naturally radioactive elements to targeted theranostic agents

It gives us great honour to welcome you to the 2017 *Dalton Transactions* themed issue: *Frontiers in Radionuclide Imaging and Therapy, A chemical journey from naturally radioactive elements to targeted theranostic agents*. This special issue recognises the contributions of Professor Isabel Santos from the Instituto Superior Técnico at the University of Lisbon, to the advancement of science in the field of radiopharmaceutical chemistry on the occasion of her recent retirement. Professor Santos has been working over the years on the coordination chemistry of *f*-elements, namely actinides (U(III/IV)) and lanthanides (e.g. Sm, Ho), as well as of *d*-transition metal compounds, mainly Re and  $^{99m}\text{Tc}$ . Some of those metal complexes featured interesting properties for applications in molecular imaging, targeted radionuclide therapy and theranostics. She has published more than 200 publications, and has been responsible for numerous research projects. Professor Santos has been the head of the Radiopharmaceutical Sciences Group for several years, and between 2013 - 2015 she was the first President of the "Centre for Nuclear Sciences and Technology" (C<sup>2</sup>TN) in Lisbon, a national research facility rated as "Excellent" by the Portuguese Science Foundation. We would like to emphasise that Professor Santos not only made outstanding contributions to the inorganic chemistry community, but also pioneered in Portugal and Europe a move towards inclusion of women in science, where gender equality is currently a relevant concern in the academic environment worldwide. Indeed, she has been a role model for many of her female students and co-workers, not to mention her national and international collaborators. The recognized inter-/multi-disciplinary nature of the research domains proposed in this themed issue reflects Professor Santos' varied scientific interests, which span basic research in inorganic/organometallic chemistry to more application oriented studies. Indeed, this issue provides a broad spectrum of studies and views on radiometal-based molecular complexes and nanoplatforms for molecular imaging, systemic radiotherapy and theranostics, with approximately 30 papers, authored by well-known experts in their field. There are articles focused on the production and radiochemistry of radiometals, such as those by Abrunhosa and co-workers (*Fast and cost-effective cyclotron production of  $^{61}\text{Cu}$  using a natZn liquid target: an opportunity for radiopharmaceutical production and R&D*) and Jurisson and co-workers (*Chemistry and Radiochemistry of Arsenic, Rhenium and Rhodium Isotopes Relevant to Radiopharmaceutical Applications: Development of High Specific Activity Radionuclides for Imaging and Treatment*). Within this framework, the study presented by Oehlke and co-workers (*Measurement of reaction kinetics of [ $^{177}\text{Lu}$ ]Lu-DOTA-TATE using a microfluidic system*) is also particularly innovative as it demonstrates that microfluidic synthesis techniques can become a viable alternative to the conventional, batch-wise radiolabelling techniques. Also, in the context of new radiolabelling procedures, Reid and co-workers report on a new radiofluorination method through Cl/ $^{18}\text{F}$  halide exchange (*[AlCl<sub>3</sub>(BnMe<sub>2</sub>-tacn)] – a new metal chelate scaffold for radiofluorination by Cl/ $^{18}\text{F}$  exchange*). The introduction of innovative bifunctional chelators for stabilization of radiometals such technetium, gallium, copper or other relevant radioisotopes for molecular nuclear imaging or targeted radiotherapy applications has been explored by the research groups of Abram (*Thiourea Derivatives as Chelating Agents for Bioconjugation of Rhenium and Technetium*), Maina-Nock (*DOTA-to-DATA Chelator-Switch for  $^{68}\text{Ga}$ -Labeling of [Tyr<sup>3</sup>]Octreotide*).

Preclinical Comparison of the Radioligands), Dénat (MANOTA: a promising bifunctional chelating agent for copper-64 immunoPET), Blower (copper complexes with dissymmetrically substituted bis(thiosemicarbazone) ligands as a basis for PET radiopharmaceuticals: control of redox potential and lipophilicity) and Orvig (H4octapa: Synthesis, Solution Equilibria and Complexes with Radiopharmaceutically Useful Metal Ions).

Novel rhenium and technetium organometallic complexes potentially useful as targeted imaging probes by employing bioorthogonal chemistry or complexes useful as theranostic molecular tools using the matched pair  $^{99m}\text{Tc}/\text{Re}$  have been introduced by Valliant's (Preparation of tetrazine-containing [2 + 1] complexes of  $^{99m}\text{Tc}$  and in vivo targeting using bioorthogonal inverse) and Alberto's (Structure and Reactivities of Rhenium and Technetium bis-Arene Sandwich Complexes [M( $\eta^6$ -arene) $_2$ ] $^{\pm}$ ) groups, respectively.

Noteworthy, reports on radiometal complexes aimed at targeting organs such as the heart (Liu and co-workers,  $^{99m}\text{Tc}(\text{III})$  Complexes as Radiotracers for Myocardial Perfusion Imaging and  $^{99m}\text{Tc}$ -3Cboroxime: A Novel  $^{99m}\text{Tc}(\text{III})$  Complex [ $^{99m}\text{TcCl}(\text{CDO})(\text{CDOH})_2\text{B}-3\text{C}$ ] ( $\text{CDOH}_2 = \text{Cyclohexanedione Dioxime}$ ;  $3\text{C}-\text{B}(\text{OH})_2 = 3\text{-(Carbamoylphenyl)boronic Acid}$ ) with High Heart Uptake and Long Myocardial Retention), cell-membrane transporters (Correia and co-workers, Technetium- $^{99m}$  complexes of L-arginine derivatives for targeting amino acid transporters) and thrombus (Caravan and co-workers, Fibrin-Targeting Probes for Thrombus Imaging) are also included in this issue. Moreover, imaging of inflammation and infection *in vivo* is also a subject of relevant interest as addressed by Kniess and co-workers ( $^{99m}\text{Technetium}$ -based Small Molecule Radiopharmaceuticals and Radiotracers Targeting Inflammation and Infection) and by Drlica and co-workers (Fluoroquinolones as imaging agents for bacterial infection) in the corresponding Perspectives. Two Perspectives papers describe innovative methodologies towards the development of novel peptide-based molecular probes for targeting E-selectin (Iranzo and co-workers, A computational and experimental study to develop E-selectin targeted peptides for molecular imaging probes) and provide an overview on the use for metal complexes for multimodal imaging, which is currently considered a hot topic (Tóth and co-workers, Metal complexes for multimodal imaging of misfolded protein-related diseases).

Apart from the molecular-based approaches, this special issue also comprises two full articles in which radiolabelled gold-based nanoparticles (AuNp) have been studied. For example, in the paper by Paulo and co-workers it has been demonstrated that thiolated bombesin-containing AuNp are potentially useful as target-specific GSH-mediated drug delivery systems (In Vitro/In Vivo "Peeling" of Multilayered Aminocarboxylate Gold Nanoparticles Evidenced by a Kinetically Stable  $^{99m}\text{Tc}$ -label: Implications for Glutathione-mediated Drug Release). The work presented by Khoobchandani and co-workers (Mangiferin Functionalized Radioactive Gold Nanoparticles (MGF-  $^{198}\text{Au}$ NPs) in Prostate Tumor Therapy: Green Nanotechnology of Production, In Vivo Tumor Retention and Evaluation of Therapeutic Efficacy) shows that a  $^{198}\text{Au}$ -labeled Np (beta emitter) promotes tumour reduction in a preclinical model of prostate cancer.

Concerning the development of novel theranostics, another hot topic, the articles by Bodio and co-workers (In vitro and in vivo trackable titanocene-based complexes using optical imaging or SPECT) and Gomez Quiroga and co-workers (Combining Imaging and Anticancer Properties with New Heterobimetallic Pt(II)/M(I) ( $M = \text{Re}, ^{99m}\text{Tc}$ ) Complexes) are exquisite examples of such type of approach, where (bi)metallic complexes containing simultaneously a cytotoxic unit and a nuclear or optical imaging probe were synthesized and evaluated biologically with relevant results for further application.

We would like also to highlight the contributions with an higher clinical component, that is the case of the Perspective by Costa and co-workers (*Radionuclides in oncology clinical practice – review of the literature*), which discusses clinical applications of therapeutic radionuclides commonly used in the clinical practice of oncology; or the full article by Müller and co-workers (*Clinical evaluation of the radiolanthanide terbium-152: First-in-human PET/CT with <sup>152</sup>Tb-DOTATOC*), describing the first-in-human PET/CT with <sup>152</sup>Tb-DOTATOC; and the full article by Brechbiel and co-workers (*Comparative Studies on the Therapeutic Benefit of Targeted  $\alpha$ -Particle Radiation Therapy for the Treatment of Disseminated Intraperitoneal Disease*), which reviews the use of the  $\alpha$ -emitting particles radionuclides for radioimmunotherapy. These contributions were organized and written to reach the broader audience of the inorganic chemistry/organometallic community interested in biomedical applications of radiometals.

Finally, we would like to thank the editorial staff at *Dalton Transactions* for making this themed issue possible. All the authors as well as reviewers are also acknowledged for their efforts and relevant contributions, and we hope this special issue will encourage further developments in this exciting research field.

Please enjoy and get inspired!

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Cardiff University, Guest Editor

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