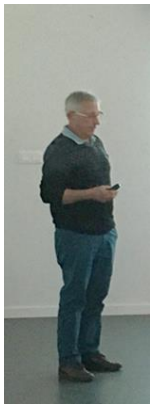
# ISOTOPICS Newsletter - Issue 4

## ISOTOPICS: Isotopic labeling for drug innovation

ISOTOPICS is a H2020 – Marie Sklodowska Curie Action – Innovative Training Network which gathers 5 academic partners and 3 pharmaceutical companies. The main objective of the ISOTOPICS project is to develop innovative and general isotopic labeling chemistry and radiochemistry and to train 15 Early Stage Researchers (ESRs) in this area. ISOTOPICS is expected to meet the need of industry by providing new researchers specialized in labeling chemistry with a dual academic/industrial culture.



Website: www.isotopics-project.eu

## In this Issue:

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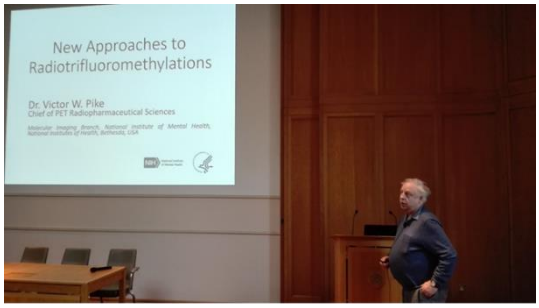
## 5th ISOTOPICS Meeting

All the ISOTOPICS consortium and the 3 members of the Advisory Board attended this 2-day meeting organised by Oxford beneficiary in March 2019 at Oxford (UK).

The management team informed about the administrative follow-up of the project and the 15 ISOTOPICS ESRs presented their research results and communication actions.





"Oxford was an interesting experience. It is impressive to see the progress made by everyone, the presentations always lead to interesting discussion between the people from the academia and industry. It was the last meeting for some students and Oxford was a great opportunity to wish everyone the best for the future. " **ESR14 – Malvika SARDANA (AZ)**

Dr. Victor Pike (NIMH, USA) and Pr. Heinz Coenen (Institut für Neurowissenschaften und Medizin Universität zu Köln Jülich – GERMANY), two highly experienced researchers and members of the project Advisory Board, gave plenary lectures (1h of talk and 15 minutes of questions/discussion) to present several examples of research works carried out during their career.

"We were privileged to hear all these inspiring talks by the experts within the isotopic labeling chemistry field. These talks expanded our knowledge and gave an opportunity to participate in the discussion." **ESR10 – Kaisa HORKKA (KI)**

"Dr. Viktor Pike gave a very interesting plenary lecture about possible synthesis of $CF_3$, mostly as gas, using carbon isotope such as carbon-11, but also fluorine isotope such as fluorine-18. This $CF_3$ synthesis methodology have allowed him to reach high specific activities in the synthetized products. These products could be used in the next steps in various reaction patways." **ESR15 – Mégane Valero (SAN)**

The progresses of the PhD projects and the different dissemination and communication actions realised by the ESRs confirmed the fruitful research works of the consortium.

"The meeting in Oxford was a particular stimulating experience for all of us. In addition to the high-level research we had the pleasure to listen to, we presented our work in the wonderful and picturesque frame of Merton College, in the auditorium named after Nobel laureate poet TS Elliot, former Merton scholar. A very pleasant social event was organised in the Savile room of Merton College, where, among painting by Picasso and Chagall, we had the chance to spend a nice evening, all together. "**ESR5–Francesco IBBA (UOXF)**

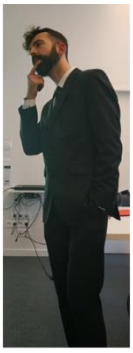
A social event was organised in the beautiful Savile room in Merton College.

"A unique experience of Oxford's style dinner surrounded by fine art and accompanied with even better food let us reconnect with participants of the meeting on a lighter note." **ESR7 – Mateusz IMIOLEK (UOXF)**


## Final ISOTOPICS Meeting

The final ISOTOPICS meeting was organised by CNRS-INSA beneficiary in Toulouse (France) in November 2019. This 1.5-day Meeting gathered PIs, 10 ESRs and 5 members of the Advisory Board. The Project management team informed about the project implementation. Then ESRs gave an oral communication in order to present their PhD project results, their short-term perspectives and their communication and dissemination.





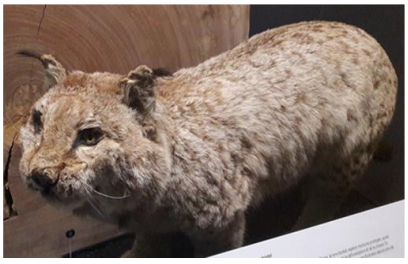

Dr. Pascal George a highly experienced researchers and member of the project Advisory Board, gave a plenary lecture to present several examples of research works carried out during his career.

All AB members congratulated the consortium members for their worked and thanked the management team for its input. They also noticed that within the consortium, communication was really efficient and outstanding; and that ESRs' communication skills really upgraded.

"The advisory board gave valuable feedback, and it was a relief to hear about ESRs' progress. I can truly agree on that the performance of the ESRs improved enormously during the project." **ESR10 - Kaisa HORKKA (KI)**

"The final meeting in Toulouse had a bittersweet taste, being the end of a wonderful experience. It was interesting to see how every project developed over these years. The meeting was very successful thanks to the organisation of two enjoyable social events. In the afternoon a visit to the exhibition *Extinction the end of the world,* shed a light to some very pressing issues, while at dinner time a social event was organised at "Les caves de la Maréchale" which is an original Toulouse cellar dating back from the Roman occupation. Special thanks goes to Professor Bruno Chaudret for the excellent choices." **ESR5–Francesco IBBA (UOXF)**

"We were showed around by a knowledgeable guide, which allowed us to fully experience this thought provoking exhibition. Interesting points were being raised as we discussed possible scenarios for immediate and long term future. The choice of the topic was particularly apt considering this was out last meeting. " **ESR7 – Mateusz IMIOLEK (UOXF)**


## 5th Training session

All the 15 ESRs of the ISOTOPICS project attended this 3-day training session. It was organised in **Oxford (UK) before the 5th ISOTOPICS meeting.**
The training was composed of several lectures, divided in 5 sessions, given by UOXF and Oxford staff.
A visit of UOXF laboratories (Chemistry research laboratories) was organised after the 5th Meeting.

All the courses and workshops are summarised hereafter:
-'**Pre-clinical and clinical development of novel radiosensitising drugs**' (0.21 day; Dr Geoff Higgins, Department of Oncology, UOXF)

-'**Problem Session** (0.25 day, Dr Florion Guibbal, Department of Oncology & Department of Chemistry, UOXF):
"In this interesting and well-packaged session we were given the opportunity to solve some problems about labeling of small molecules for PET." **ESR10 – Kaisa HORKKA (KI)**

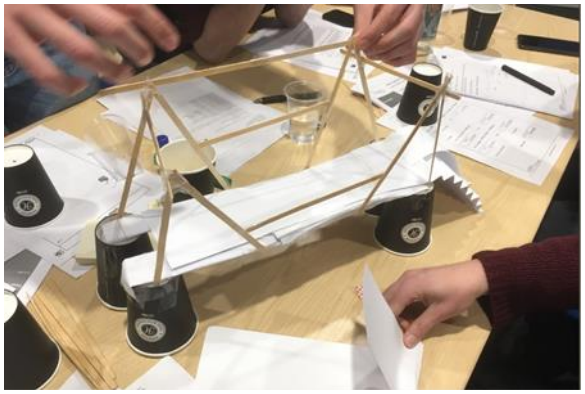
-'**The technical side of setting up a Radiopharmacy and what is required before making medication for patients**' (0.29 day; Dr Rebekka Hueting, Department of Oncology, UOXF).

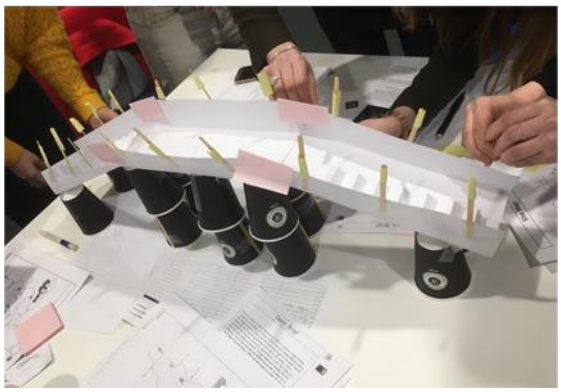
**-'Labeling of Biologics'** course (0.5 day; Prof. B. Davis, UOXF):
"One of the most striking aspect of ISOTOPICS, in my opinion, was the opportunity of attending great lectures, dedicated to a very small audience. It was definitely the case when we met and listened to Professor Ben Davis speaking about labeling of biologics. His energy and passion for the topic was tangible, an experience everybody will remember." **ESR5–Francesco IBBA (UOXF)**

-'**DNA Imaging repair**' (0.25 day, Dr Bart Cornelissen, Department of Oncology, UOXF)

**-'Scientific Project Set-up and Management'** Workshop (1 day; Justin Hutchence MPLS, Oxford):
"Great workshop that let us practice our leadership skills. Divided in groups we solved an intricate case study, assuming different roles and ensuring that we can work as a coherent group to manage the project. " **ESR7 – Mateusz IMIOLEK (UOXF)**

-'**Proposal Writing'** Workshop (0.5 day; Justin Hutchence MPLS, Oxford):
"In the class hold by Justin Hutchence, the Early-Stage-Researchers were taught how to point out new ideas and how to attract interest on their scientific proposals. The lecturer shared many of his experiences in submitting successful and unsuccessful manuscripts. Important points to be fulfilled in order to obtain a positive feed-back may be an innovative and future-oriented research project but also the feasibility of the work-package within a certain time period" **ESR01 - Viktor PFEIFER (CEA-Saclay)**



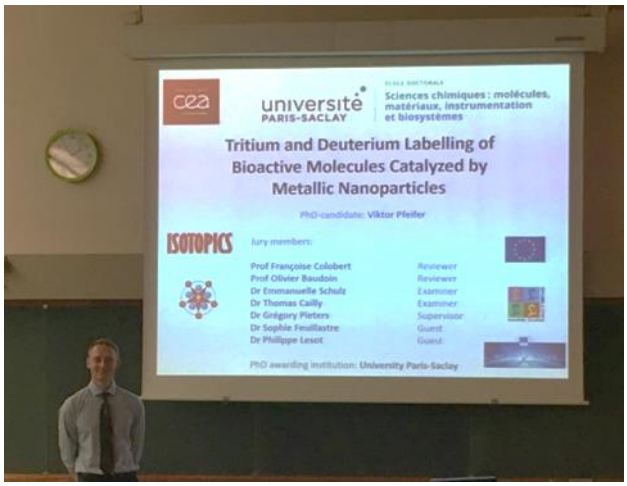


## Photo gallery



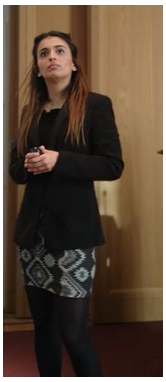

Project Manager relay in Mai 2020


*(Left: Dr. E. Nehlig, right: t Dr. K. Hinsinger With Coordinator Dr. C. Dugave)*





cea
New Methodologies for the Late-Stage Labeling of Drug Candidates
DE LA RECHERCHE À L'INDUSTRIE
Antonio Del Vecchio
Frédéric Joliot
SHFJ
SANOFI



# Secondment experiences

**ESR 06 – Anna Chiara Vicini (University of Oxford) hosted by SANOFI (France) for 3 months**

*What was the purpose of your secondment? What are the research results?*

Unfortunately, I can't give too many details, because the research is confidential until its publication (a draft is ready, so it will be soon, hopefully!). What I can say it's that SANOFI had the expertise to demonstrate that the novel catalytic concept we developed in the Gouverneur group (Hydrogen Bonding Phase-Transfer Catalysis, HB-PTC) can be applied to an industrial setting. This was very exciting to me, because I really wanted to find an application for my research. And what is better, it worked nicely!

*What is the impact of this experience on your future career?*

First, it helped me in clarifying what I want to do in the future, and in particular what fuels my curiosity and motivation to do research. Secondly, I think that an experience outside of the academic world is invaluable regardless of the future career path. Finally, it was a great learning experience as I had the chance to work side by side with engineers, which strengthened my ability to communicate with people with different expertise. And of course, I learnt some basic chemical engineering.

*What was your favourite moment during this secondment?*

Everybody in SANOFI was very welcoming and I really must thank Cathy Aubert, Sebastien Roy, Jorg Blankenstein and all the people in their team for making the experience of working in their laboratories enjoyable and fruitful. The best moment though, was the coffee at 8.30 am with Philippe Courtes, trying to speak French while still not completely awake.

**ESR 13 – Laura TRUMP (UCB) hosted by ULG beneficiary for 6-8 months**

*What was the purpose of your secondment? What are the research results?*

The secondment performed at ULG was more than just a secondment as it was also one of the main parts of my thesis. Indeed, my PhD was performed in very close collaboration with the ULG and ESR 12, and I have spent around 6-8 months at the ULG, over several periods of 1-2 weeks. The purpose of this secondment was to adapt the difluoromethylation methodology developed in UCB in fluorine-19 chemistry into fluorine-18 chemistry. The $^{18}$F-difluoromethylation was successfully developed, resulting in a publication in Angewandte, but also automated on a commercially available synthesizer, the AllinOne from Trasis, resulting in another publication, accepted in OPR&D.

*What is the impact of this experience on your future career?*

Thanks to this experience, I was fully trained to work with fluorine-18, confronted to its subtilities and challenges. Additionally, I had the possibility to develop new engineering skills, in order to develop the photoredox reaction onto a commercially available synthesizer, and to fully automate the 3 step-synthesis. It also allowed me to enlarge my network, as the ULG is surrounded by many radiopharmaceuticals industries (IBA, Trasis, Nucleis, etc…).

Finally, and most importantly, thanks to this experience, I was granted a position as a radiochemist in the radiopharmaceutical company Trasis (permanent position, Liège).

*What was your favourite moment during this secondment?*

My favourite moment was the automation of the 3-step synthesis. The automation of a synthesis in fluorine-18 is essential, in order to be used in clinic as high amounts of radioactivity are at stake, preventing any manual intervention. It was really a new experience, and even if it took a lot of time, the first time the synthesis was perfectly running, entirely automated, was really satisfactory, and at the end, all the efforts totally worth it.

# ESR interviews

**ESR 11 – Donia BOUZOUITA (CNRS), group of Dr Bruno CHAUDRET**

*Could you tell us about your background?*

I obtained my engineering degree in chemistry in 2015 at the INSAT of Tunisia. I carried out my master internship in the LPCNO of Toulouse under the supervision of Bruno Chaudret and Simon Tricard. It was about the self-assembly of Pt nanoparticles with organic ligands for electronic applications. After that, I did my PhD in the LPCNO at Toulouse in order to broaden my knowledge in nanoparticle synthesis and in the world of catalysis.

*What is your PhD project about?*

My PhD focuses on the isotopic labeling of molecules with biological interest through C-H activation catalyzed by metal nanoparticles. The main objectives were the synthesis of nanoparticles with different properties in order to find a direct, simple and easy method for the labelling of complex biomolecules.

*According to you, what are the strengths of the ISOTOPICS project?*

In my opinion, the main strength of the ISOTOPICS project is the different collaborations we had elaborated between the various industrial and academic partners. The interactions between the beneficiaries with different backgrounds during the trainings/meetings are also of huge importance as it gives us the opportunity to learn and get relevant advices.

**ESR 02 – Alberto PALAZZOLO (CEA), group of Dr. Grégory PIETERS**

*Could you tell us about your background?*

I received my master degree in medicinal chemistry from the University of Catania in 2015 working on the synthesis of new therapeutic agents. Thereafter, I moved to the polytechnic university of Milan as a research assistant. Herein I developed some new techniques to modify carbon materials using conventional organic reactions. Finally, in fall 2016 I moved to the CEA to do my PhD thesis.

*What is your PhD project about?*

In this three years my research have been focused in the development of new methods to synthesize deuterated and tritiated compounds using metallic nanoparticles catalysis. I especially worked on the modification of the activity of some catalysts throughout switching and/or adding organic ligands.

*According to you, what are the strengths of the ISOTOPICS project?*

I think that the strongest point of the ISOTOPICS project is the relationship within the consortium. The strongest connections between team permitted to create and develop new catalysts, methodologies and devices. We all worked together as a unique team of researcher with the common objective of pushing further the science of radiolabelling.

**ESR 12 – Agostinho LEMOS (ULG), group of Prof. A. LUXEN**

*Could you tell us about your background?*

I completed my Bachelor's Degree in Biochemistry in 2013 at the Faculty of Sciences of University of Porto. As part of my undergraduate studies, my Bachelor project was focused on biochemical and biological evaluation of steroid derivatives as potential aromatase inhibitors for the treatment of oestrogen-dependent breast cancer. Afterwards, I pursued a Master's Degree in Pharmaceutical Chemistry at Faculty of Pharmacy of University of Porto. The research project performed in master thesis was based on the synthesis, biological evaluation, and *in silico* studies of xanthone derivatives as potential antitumor agents *via* activation of the p53 pathway. After finishing the Master's in 2015, I earned a research fellow position (5 months) in a project focused on computational studies to understand the mechanism of signalling of G-protein coupled receptors. In 2016, I was selected for the Early Stage Researcher position at GIGA Cyclotron Research Centre in University of Liege, under the supervision of Prof. André Luxen.

*What is your PhD project about?*

My PhD project is mainly focused on the radiosynthesis of $^{18}$F-labeled compounds as reagents for the introduction of [$^{18}$F]difluoromethyl moieties in organic substrates.

*According to you, what are the strengths of the ISOTOPICS project?*

I strongly believe that the partnership between academy and industry in the ISOTOPICS project is advantageous for the progress of scientific works and the production of high-quality research articles. The different ISOTOPICS trainings allow the fellows to strengthen their theoretical skills. The ISOTOPICS meetings constitute a useful opportunity to put in practice our communication skills, to track the research progresses of the different fellows, and to receive valuable advices and constructive opinions from the advisory board members.

**ESR 7 – Mateusz IMIOLEK (UOXF), group of Prof. DAVIS**

*Could you tell us about your background?*

Originally, from Poland, I did my undergraduate degree in Natural Sciences at University of Warsaw (BSc in Chemistry and Physics). Then, I continued my education enrolling in a Master in Organic Chemistry at the same university. In the meantime, I was working part-time in a pharmaceutical company, occasionally also tutoring IB students. As part of my studies, I took advantage of the ERASMUS+ programme, through doing an internship at University in Strasbourg as well as choosing to spent semester at University of Barcelona. That led to my current positions as a DPhil Student at University of Oxford.

*What is your PhD project about?*

My DPhil project's main aim is the discovery of new methodologies for the chemical modification of proteins. Particularly, I am interested in radical reactions that can be readily used for fluorination. Fluorine can serve as a great probe to investigate biological events (through protein observed $^{19}F$ nuclear magnetic resonance or $^{18}F$ positron emission tomography). Additionally, I have explored the potential of this chemistry as a new technique for bioconjugation.

*According to you, what are the strengths of the ISOTOPICS project?*

ISOTOPICS project has had a tremendous impact on the development of my academic career particularly because, it allowed me to present the results of my research early on, in front of peers and experts in the field. That was essential for defining goals and getting feedback that matters. Moreover, creating a network of collaborations my DPhil project could evolve in many directions. Finally, exposure to the industrial partners gave a unique perspective and helped me to place my research in context of potential applications.

## Dissemination and communication actions

**Posters**

ESR5 – Francesco IBBA (UOXF)

"Hydrogen Bonding Phase-Transfer Catalysis: Discovery and Mechanistics Insights", 26th Annual Review Meeting, Catalysis and Enabling Technologies for Synthesis, London (UK), December 2019.

ESR–Anna VICINI (UOXF):

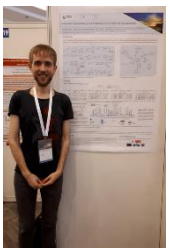
"Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of beta Fluoroamines", (awarded poster) 2nd Chem East Organic Symposium in Norwich (Uk), May 2019.

"Hydrogen Bonding PhaseTransfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of β Fluoroamines", 26th International Symposium: Synthesis in organic chemistry, Cambridge (UK), July 2019.

ESR7 – Mateusz IMIOLEK (UOXF)

"Site-Selective Protein C-Formylation via Sequential Difluoromethylation-Hydrolysis", Pfizer Organic Chemistry and Chemical Biology Symposium, Oxford (UK), October 2019.

ESR12–Agostinho LEMOS (ULG):

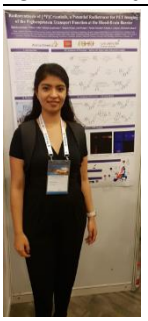


"Automated radiosynthesis of 2-[18F]BTSO2CF2H in a GE FASTLab synthesizer", The 23rd International Symposium on Radiopharmaceutical Sciences (ISRS 2019), Beijing (China), May 2019.

ESR13 – Laura TRUMP (UCB)

"Late stage 18F-difluoromethylation via a flow photoredox reaction to N-heteroaromatics", The 23rd International", Symposium on Radiopharmaceutical Sciences (ISRS 2019), Beijing (China), May 2019.

ESR14 – Malvika SARDANA (AZ)

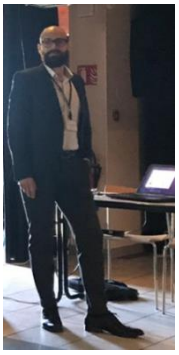


" Radiosynthesdis of [18F] Crizotinib, a Potential Radiotracer for PET Imaging of the P-glycoprotein Transport Function at the Blood Brain Barrier", The 23rd International Symposium on Radiopharmaceutical Sciences (ISRS 2019), Beijing (China), May 2019.

"Visible-light enabled late-stage aminocarbonylation of alkyl iodides with carbon monoxide", 21st edition of European Symposium on Organic Chemistry, Vienna, (Austria), July 2019

**Oral communications**

ESR2 – Alberto PALAZZOLO (CEA)



"Development of novel techniques for the deuterium and tritium labelling of nucleosides, nucleotides and oligonucleotides", 56ème Semaine d'étude en Chimie Organique (SECO56), La Clusaz (France), May 2019.

"Development of novel techniques for the deuterium and tritium labelling of nucleosides, nucleotides and oligonucleotides", Doctoral school assembly "5ème Journée de l'Ecole Doctorale ED2MIB", (Université of Paris-Saclay), Evry, University d'Evry (France), June 2019.

ESR3 – Antonio DEL VECCHIO (CEA)

"Cascade Reactions for the Late Stage Labeling of Drug Candidates", 47th IUPAC World Chemistry Congress, (IUPAC2019Paris), July 2019.

ESR4 – Gianluca DESTRO (CEA)

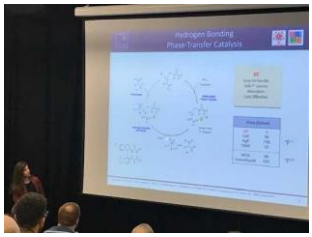
"Dynamic carbon isotope exchange enabled labeling of pharmaceuticals with *CO2", 56ème Semaine d'étude en Chimie Organique (SECO56), La Clusaz (France), May 2019.

ESR5 – Francesco IBBA (UOXF)

"Mechanistic Insights on Hydrogen Bonding Phase-Transfer Catalysis: an NMR investigation", 18th RSC Fluorine Subject Group Postgraduate Meeting, Southampton, (UK), April 2019.

"Asymmetric Nucleophilic Fluorination under Hydrogen Bonding Phase-transfer Catalysis" Astra-Zeneca Graduate Symposium, University of Oxford, Oxford (UK), May 2019.

ESR–Anna VICINI (UOXF):



"Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of beta-Fluoroamines", 18th RSC Fluorine Subject Group Postgraduate Meeting, Southampton, (UK), April 2019.

"Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of beta-Fluoroamines", Astra-Zeneca Graduate Symposium, University of Oxford, Oxford (UK), May 2019.

"Hydrogen Bonding Phase-Transfer Catalysis (HB-PTC) with Alkali Metal Fluorides: Enantioselective Synthesis of β-Fluoroamines", 3rd international Symposium on Synthesis and Catalysis (ISySyCat 2019), Evora (Portugal), September 2019. She won a prize as one of the best two oral communications.

- "Hydrogen Bonding Phase-Transfer Catalysis (HB-PTC) with Alkali Metal Fluorides: Enantioselective Synthesis of β-Fluoroamines", 6th Winter Process Chemistry Conference, in Birmingham (UK), December 2019. 'Young Chemist Award'.

ESR7 – Mateusz IMIOLEK (UOXF)

"Radical fluoroalkylations for selective modification of native residues in proteins", Astra-Zeneca Graduate Symposium, University of Oxford, Oxford (UK), May 2019.

"Selective modification of proteins with fluoroalkyl radical precursors"and "Probing and exploiting the reactivity of C● radicals for selective protein editing", ACS National Meeting, San Diego, (USA) August 2019.

ESR8 – Maria Alexandra GAFITESCU (UOXF)

University of Oxford, Oxford (UK), "Site-selective strategies for the biological investigation of glycoproteins", Astra-Zeneca Graduate Symposium, May 2019.

"Elucidating glycogen biosynthesis through palladium-mediated enzyme control", ACS National Meeting, San Diego (USA), August 2019.

ESR9 – Mélodie FERRAT (KI)

"In-loop carbonylation - a novel and simplified method for carbon-11 labeling of drugs and radioligands", 23rd International Symposium of Radiopharmaceutical Sciences (ISRS), Beijing (China), May 2019.

ESR10 – Kaisa HORKKA (KI)

"Rapid and efficient BEMP-mediated synthesis of 11C-labelled benzimidazolones using [11C]carbon dioxide", 23rd International Symposium of Radiopharmaceutical Sciences (ISRS), Beijing (China), May 2019.

ESR11 – Donia BOUZOUITA (CNRS)

- ACS Spring 2019 National Meeting in Orlando, (United states), May 2019: "Tuning the Catalytic Activity/Selectivity of Water-Soluble Bimetallic RuPt Nanoparticles by Modifying their Surface Metal Distribution" and "Surprising differences of alkane C-H activation catalyzed by ruthenium nanoparticles".

ESR13 – Laura TRUMP (UCB)

"Late stage 18F-difluoromethylation via a flow photoredox reaction to N-heteroaromatics", 23rd International Symposium of Radiopharmaceutical Sciences (ISRS), Beijing (China), May 2019.

"Late stage C-H $^{18}$F-difluoromethylation of N-heteroaromatics for PET imaging", 19th European Symposium on Fluorine chemistry, Warsaw (Poland), August 2019.

"Late stage C-H $^{18}$F-difluoromethylation of N-heteroaromatics for PET imaging", UCB PhD day, London (UK), September 2019.

"Late stage C-H 18F-difluoromethylation of N-heteroaromatics for PET imaging", 26th Young chemists in industry, Slough (United Kingdom), November 2019.

ESR15 – Mégane VALERO (SAN)

**"**C-H Functionalization: highly selective directed iridium-catalyzed hydrogen-isotope exchange reactions", IIS-CED – 24th International Isotope Society - Central European Division Workshop, Bad Soden (Germany)**,** September 2019


*On the left: Laura, Malvika, Mélodie and Agostinho at the gala dinner of the 23rd International Symposium of Radiopharmaceutical Sciences (ISRS), Beijing (China), May 2019. One the right, Donia at the* ACS Spring 2019 National Meeting in Orlando (USA), May 2019.

**Recent Scientific publication**

**CH-Functionalization - Prediction of Selectivity in Iridium(I) Catalyzed Hydrogen Isotope Exchange Competition Reactions**

Mégane Valero, Thomas Kruissink, Jennifer Blass, Remo Weck, Stefan Güssregen, Alleyn T. Plowright, Volker Derdau *Angew. Chem. Int. Ed.* **2019**, accepted (DOI: 10.1002/anie.201914220).

**NHC-Stabilized Iridium Nanoparticles as Novel Catalysts in Hydrogen Isotope Exchange Reactions of Anilines**

Mégane Valero; Donia Bouzouita; Alberto Palazzolo; Jens Atzrodt; Christophe Dugave; Simon Tricard; Sophie Feuillastre; Grégory Pieters; Bruno Chaudret; Volker Derdau, *Angew. Chem. Int. Ed.* **2020**,132, 1-7.

**Hydrogen Isotope Exchange Catalyzed by Ru Nanocatalysts: Labelling of Complex Molecules Containing N-Heterocycles and Reaction Mechanism Insights**

Viktor Pfeifer, Marie Certiat, Donia Bouzouita, Alberto Palazzolo, Sébastien Garcia-Argote, Elodie Marcon, David-Alexandre Buisson, Philippe Lesot, Laurent Maron, Bruno Chaudret, Simon Tricard, Iker del Rosal, Romuald Poteau,* Sophie Feuillastre, Grégory Pieters*, *Chem. Eur. J.* **2019***,accepted).*.

**Development of a general automated flow photoredox <sup>18</sup>F-Difluoromethylation of N-heteroaromatics in an AllinOne synthesizer**

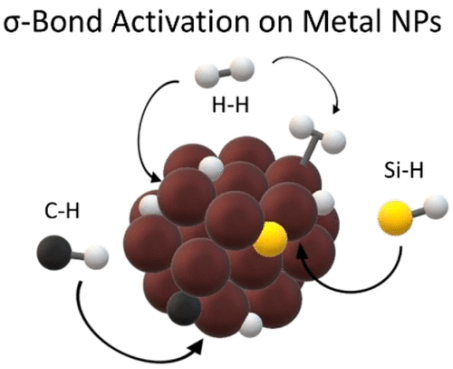
Trump, Laura; Lemos, Agostinho; Jacq, Jérôme; Pasau, Patrick; Lallemand, Bénédicte; Mercier, Joël; Genicot, Christophe; Luxen, André; Lemaire, Christian, *Org. Process Res. Dev*, **2019**, accepted (DOI: 10.1021/acs.oprd.9b00442).

**Visible-Light Enabled Aminocarbonylation of Unactivated Alkyl Iodides with Stoichiometric Carbon Monoxide for Application on Late-Stage Carbon Isotope Labeling**

Malvika Sardana, Joakim Bergman, Cecilia Ericsson, Lee Peter Kingston, Magnus Schou, Christophe Dugave, Davide Audisio, and Charles S. Elmore, *J. Org. Chem.***2019**, 84, 24, 16076-16085.

**σ-H–H, σ-C–H, and σ-Si–H Bond Activation Catalyzed by Metal Nanoparticles**

Juan M. Asensio, Donia Bouzouita, Piet W. N. M. van Leeuwen, and Bruno Chaudret, *Chem. Rev.* **2020**, 120, 2, 1042-1084.




**Abstract:** Activation of H–H, Si–H, and C–H bonds through σ-bond coordination has grown in the past 30 years from a scientific curiosity to an important tool in the functionalization of hydrocarbons. Several mechanisms were discovered via which the initially σ-bonded substrate could be converted: oxidative addition, heterolytic cleavage, σ-bond metathesis, electrophilic attack, etc. The use of metal nanoparticles (NPs) in this area is a more recent development, but obviously nanoparticles offer a much richer basis than classical homogeneous and heterogeneous catalysts for tuning reactivity for such a demanding process as C–H functionalization. Here, we will review the surface chemistry of nanoparticles and catalytic reactions occurring in the liquid phase, catalyzed by either colloidal or supported metal NPs. We consider nanoparticles prepared in solution, which are stabilized and tuned by polymers, ligands, and supports. The question we have addressed concerns the differences and similarities between molecular complexes and metal NPs in their reactivity toward σ-bond activation and functionalization.

**"In-loop" carbonylation – a simplified method for carbon-11 labeling of drugs and radioligands**

Mélodie Ferrat, Kenneth Dah,l Christer Halldin and Magnus Schou, *J. Label. Compd. Radiopharm*. **2020**, 1-8.

**Tuning the Catalytic Activity and Selectivity of Water-Soluble Bimetallic RuPt Nanoparticles by Modifying their Surface Metal Distribution**

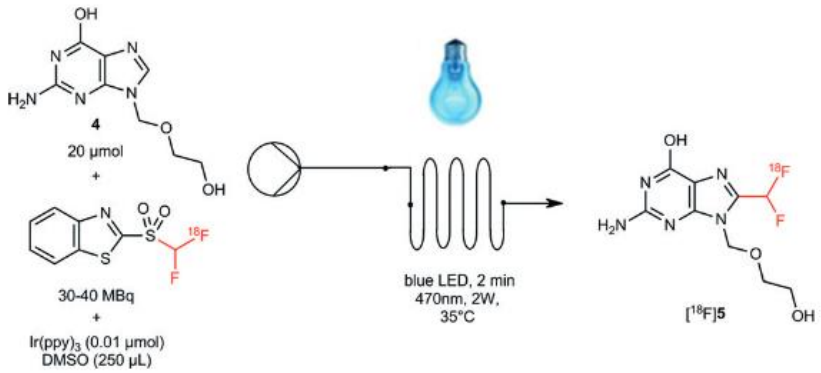
Donia Bouzouita, Guy Lippens, Edwin A. Baquero, Pier F. Fazzini, Gregory Pieters, Yannick Coppel, Pierre Lecante, Simon Tricard, Luis M. Martínez-Prieto, and Bruno Chaudret, *Nanoscale*, **2019**, **11**, 16544-16552.

**Comparison of Iridium(I) catalysts in Temperature mediated Hydrogen Isotope Exchange Reactions**

Mégane Valero, Anurag Mishra, Jennifer Blass, Remo Weck, and Volker Derdau, *ChemistryOpen* **2019**, 8, 1183-1189

**Late stage 18F-difluoromethyl labeling of N-heteroaromatics with high molar activity for PET imaging**

Laura Trump, Agostinho Lemos, Bénédicte Lallemand, Patrick Pasau, Joël Mercier, Christian Lemaire, André Luxen and Christophe Genicot, *Angew. Chem. Int. Ed.* **2019**,131, 13283-13288




**Abstract:** Despite a growing interest in CHF2 in medicinal chemistry, there is a lack of efficient methods for the insertion of CHF18F into druglike compounds. Herein described is a photoredox flow reaction for 18F-difluoromethylation of Nheteroaromatics that are widely used in medicinal chemistry. Following the two-step synthesis for a new 18F-difluoromethylation reagent, the photoredox reaction is completed within two minutes and proceeds by C@H activation, circumventing the need for pre-functionalization of the substrate. The method is operationally simple and affords straightforward access to radiolabeled N-heteroaromatics with high molar activity suitable for biological in vivo studies and clinical application.

## Highlights in C(sp$^3$)-Hydrogen Isotope Exchange

Mégane Valero and Volker Derdau, *J. Label. Compd. Radiopharm*. **2019**,1-15.

## The Emergence of Carbon Isotope Exchange

Karen Hinsinger and Grégory Pieters, *Angew. Chem. Int. Ed.* **2019,** 58, 9678-9680.

**Abstract**: Significant progress in C–C bond activation with transition metals has recently enabled the development of several carbon isotope exchange reactions. These methods are based on C–C bond decarboxylative carboxylation reactions in the presence of selected transition metals and labelled carbon monoxide or carbon dioxide.


## Rapid and Efficient Synthesis of 11C-Labeled Benzimidazolones Using [11C] Carbon Dioxide

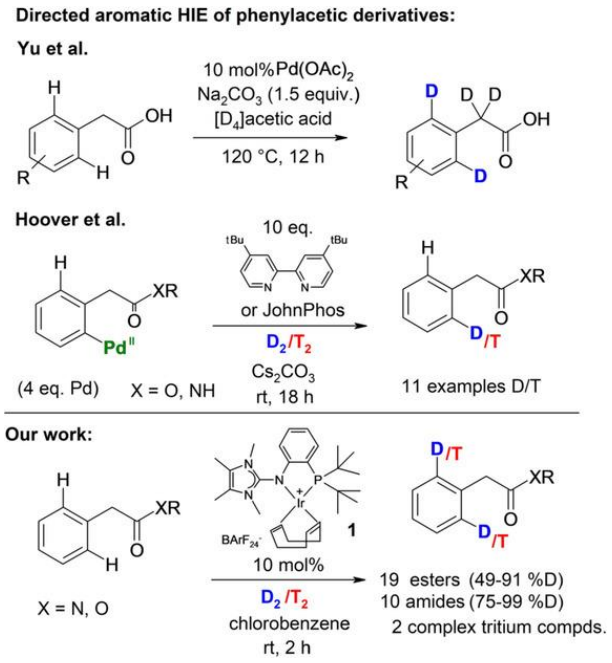
Kaisa Horkka, Kenneth Dahl, Jonas Bergare, Charles S. Elmore, Christer Halldin, and Magnus Schou, *ChemistrySelect.* **2019**, 4, 1846 –1849.

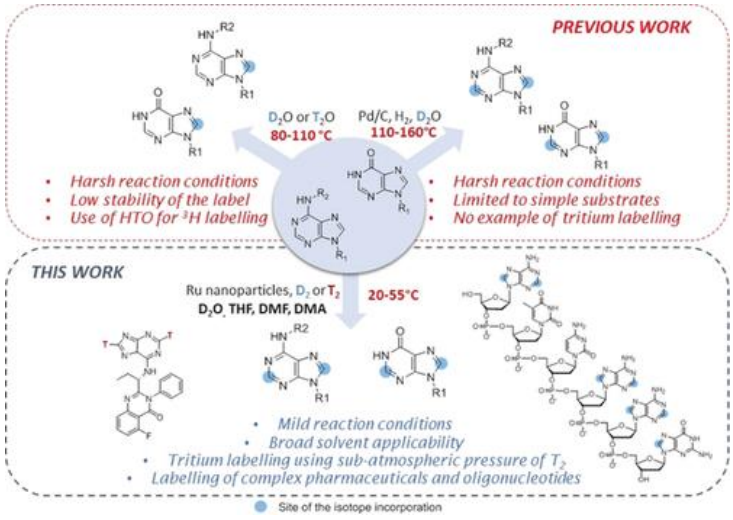
## Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Phenylacetic Acid Esters and Amides

Mégane Valero, Daniel Becker, Kristof Jess, Remo Weck, Jens Atzrodt, Thomas Bannenberg, Volker Derdau, Matthias Tamm, *Chem. Eur. J.* **2019**,*25,6517 –6522.*

Abstract

For the first time, a catalytic protocol for a highly selective hydrogen isotope exchange (HIE) of phenylacetic acid esters and amides under very mild reaction conditions is reported. Using a homogeneous iridium catalyst supported by a bidentate phosphine-imidazolin-2-imine P,N ligand, the HIE reaction on a series of phenylacetic acid derivatives proceeds with high yields, high selectivity, and with deuterium incorporation up to 99 %. The method is fully adaptable to the specific requirements of tritium chemistry, and its effectiveness was demonstrated by direct tritium labeling of the fungicide benalaxyl and the drug camylofine. Further insights into the mechanism of the HIE reaction with catalyst **1** have been provided utilizing DFT calculations, NMR studies, and X-ray diffraction analysis.



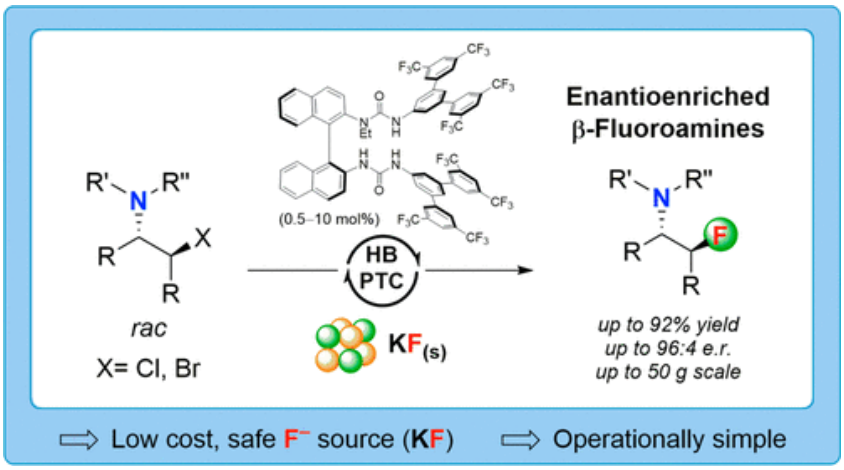

## Efficient access to deuterated and tritiated nucleobase pharmaceuticals and oligonucleotides using hydrogen isotope exchange

Alberto Palazzolo, Sophie Feuillastre, Viktor Pfeifer, Sébastien Garcia-Argote, Donia Bouzouita, Simon Tricard, Céline Chollet, Elodie Marcon, David-Alexandre Buisson, Sophie Cholet, François Fenaille, Guy Lippens, Bruno Chaudret, Grégory Pieters, *Angew. Chem. Int. Ed.* **2019**, *58*, 4891-4895. « Hot paper ».

State-of-the-art HIE for purine derivatives and their features compared to the new method using Ru nanocatalysts.

## Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of β-Fluoroamines

Gabriele Pupo, Anna Chiara Vicini, David M. H. Ascough, Francesco Ibba, Kirsten E. Christensen, Amber L. Thompson , John M. Brown , Robert S. Paton and Veronique Gouverneur, *J. Am. Chem. Soc.* **2019**, *141* (7), 2878–2883.




**Public action engagement**

**→ March 2019-Anna Chiara Vicini (ESR6 – UOXF)**

Anna was a Chemistry demonstrator for "ATOM Science and Festival" as part of OxHOS events (Oxford hands on Science). She was developing free science activities in the open air for all the family.

**→ Mai 2019-Anna Chiara Vicini (ESR6 – UOXF)**

Anna was a Tech me Out Event Manager of Pint of Science 2019, Oxford. She had a logistic role in the organization of the event from finding a good venue to contacting the speakers.

**→Novembre 2019-Davide Audisio (PI – CEA)**

Davide participated at a Pint of Chemistry event: "Gotta catch 'em all! Gathering the chemical elements", organised by the European Young Chemist's Network (from Pint Of Science France) in Paris. He talked about 11, 12, 13, 14 carbon isotopes, and their applications.

## Message from the ISOTOPICS Coordinator – Dr. Christophe DUGAVE (CEA)

The ISOTOPICS project ended with year 2019 after four years of intensive work including not only experimental but also teaching, learning, active dissemination of results and fruitful exchanges inside and outside the consortium. These four years of implementation followed two years of preparation. It is now time to overview the project output.

Everyone familiar with project writing knows that it is tempting, easy and therefore ordinary to overestimate goals and impact of the anticipated results in order to secure the grant. When highlighting the potential of late or even last-stage labeling, efficient labeling of non-activated chemical positions (especially C-H moieties) an chemically benign engineering of complex molecules, I was wondering if I did not oversold the project, even though the consortium gathered prestigious research institutions with first-class partners. I must finally admit that all results produced by ISOTOPICS researchers reached the expected goals in most cases beyond my expectations.

If hydrogen isotope exchange was already documented, ISOTOPICS considerably enlarged this research field and filled the chemist's toolbox with highly specific and selective catalysts, the utility of which was demonstrated on a variety of drugs and drug-like molecules. Translating this concept to carbon isotopes was not obvious since breaking C-C bonds specifically was considerably different from classical C-H activation. This was done however. The concept developed on model molecules was even applied to existing drugs, thus demonstrating that this new paradigm was not only a chemical curiosity but was also an extremely attractive and promising concept. "$CO_2$" exchange was even the basis for the building of both granted ERC-advanced project (FASTLabEx) and an ongoing FET-OPEN project (FLIX).

An innovative late-stage labeling of drugs through "CO-NH" bond building was also done with the particular concern of making it totally compatible with the requirements and limitations of $^{11}C$ and $^{14}C$ labeling of chemically complex and structurally fragile molecules. This was realized by adapting cutting-edge chemistry to the particular environment of radiolabeling of drugs.

The labeling of non-activated C-H positions with fluorine and polyfluorinated chemical groups ($CHF_2$ and $CF_3$) was also successfully implemented and provided considerable advances in $^{18}F$ PET chemistry which is also a very active research field nowadays. The stereoselective fluorination concept undoubtedly opens new perspectives for producing stereochemically complex molecules. It also offers new solutions for labeling fluorine-containing drugs with $^{18}F$ without altering their structure, even when fluorine is located on a position that is notably difficult. The modification of drugs and biomolecules with pending difluoro- and trifluoromethyl groups efficiently attached on C-H motifs is also a noticeable progress with a very broad domain of applications.

All this work was awarded by an impressive number of 29 publications (February 2020), including famous articles in high impact factor journals, thus demonstrating the scientific radiance of ISOTOPICS with an average IF of 11. But let's not forget a crucial aspect, far beyond the paper-producing question which validates the scientific value of the work but is not an end in itself. All the research was implemented with the permanent concern of easy applicability, transferability to the particular drug discovery and development (DDD) environment, and its capacity to be translated to the specific needs of *in vivo* assays and finally clinical trials. The very active support of the three active industrial beneficiaries testifies this. I have no doubt that ISOTOPICS findings and methods will be applied for helping the pharmaceutical industry to overcome some technical obstacles reducing their research efficiency and considerably increasing drug attrition. In this respect, ISOTOPICS is really expected to have significant human, industrial and societal impacts.

ISOTOPICS not only produced first-class research but also trained a new generation of young researchers specialized in (radio)labeling chemistry but also familiar of medicinal chemistry and aware of the particular DDD world. Most of them have been also immersed in the industrial environment through intersectorial secondments. This was an opportunity for them to discovering new countries, new routes in addressing scientific issues and new ways of life. The ISOTOPICS training also provided the 15 students not only with scientific courses and workshops but also with complementary skills, which should be decisive for exploiting and promoting their results. In particular, everyone inside the consortium has noticed the students progresses in terms of presentation and capacity to discuss about their

results, but also the emergence of a self-criticism spirit which is essential in science. As all of Consortium members, they also benefited from the precious input of the advisory board, the five members of which regularly demonstrated their implication and trustworthiness.

I also would like to sincerely and warmly thank the two Project Managers who daily helped me follow up the project, organized its proper implementation and regularly solved problems. Nothing was possible without them.

The ISOTOPICS project is now over but is not an end. On the contrary, project completion, marked by several thesis defenses, is now the beginning a scientific life as independent researcher for each of the 15 students. On behalf of the whole consortium, I would like to wish them good luck for finding rewarding jobs and positions, and many successes in their starting professional lives.

## PhD Defence

**- Defended:**

ESR1– Viktor PFEIFER (CEA)
"Tritium and Deuterium Labelling of Bioactive Molecules Catalyzed by Metallic Nanoparticles", 16/09/19.

ESR2– Alberto PALAZZOLO (CEA)
"Development of new methods for the hydrogen isotope exchange catalyzed by metallic nanoparticles", 27/09/19.

ESR3– Antonio DEL VECCHIO (CEA)
"New Methodologies for the Late Stage Labeling of Drug Candidates", 18/10/19.

ESR4– Gianluca DESTRO (CEA)
"CO2 chemistry for the synthesis of radio-labelled compounds", 13/09/19.

ESR11–Donia BOUZOUITA (CNRS)
"Isotopic labelling catalyzed by metallic nanoparticles", 14/10/19.

ESR13–Laura TRUMP (UCB)
"Late stage 18F-difluoromethylation of N-heteroaromatics", 13/12/19.

ESR15–Mégane VALERO (SAN)
"Iridium-Catalyzed CH-Functionalization: Development and Applications of Innovative Strategies for Hydrogen Isotope Exchange on Small Molecules and Biotherapeutic Drugs for Drug Discovery", 17/01/20.

- **Planned in 2020**:

ESR14–Malvika Sardana (AZ)
"Development of new method for labeling of alkyl halides with labeled carbon monoxide", 14/03/20.

ESR5 – Francesco IBBA (UOXF)
"Hydrogen Bonding Phase-transfer Catalysis: a new approach to asymmetric fluorination", first quarter 2020.

ESR10–Kaisa HORKKA (KI)
"Late-stage $^{11}$C-carbonylations of drug-like molecules for PET", 08/20.

## Editorial team

Donia BOUZOUITA (CNRS/INSA Toulouse), Francesco IBBA (University of Oxford), Kaisa HORKKA (Karolinska Institutet), Mateusz IMIOLEK (University of Oxford), Agostinho LEMOS (University of Liège), Alberto PALAZZOLO (CEA), Viktor PFEIFER (CEA), Malvika Sardana (Astra Zeneca), Laura TRUMP (UCB), Mégane VALERO (Sanofi), Anna Chiara VICINI (University of Oxford) and Dr. Emilie NEHLIG (project Manager, CEA).

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- February 2020 –