ISOTOPICS Newsletter – Issue 3

ISOTOPICS: Isotopic labeling for drug innovation

ISOTOPICS is a H2020 – Marie Sklodowska Curie Action – Innovative Training Network. This European research and training project gathers 5 academic organisations and 3 pharmaceutical companies. The main objectives of the ISOTOPICS project are to develop innovative isotopic labeling chemistry and to train 15 Early Stage Researchers (ESRs) in this scientific field. The interdisciplinary ISOTOPICS network provides then cutting-edge research and first-class training to mentor highly skilled young researchers specialized in labeling chemistry with a dual academic/industrial culture.

In this Issue:

ISOTOPICS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 675071.

4th ISOTOPICS Meeting

All the ISOTOPICS consortium and the 5 members of the Advisory Board attended this 1,5-day meeting organised by the Karolinska Institutet and AstraZeneca beneficiaries in September 2018 at Stockholm (Sweden). The management team informed about the administrative follow-up of the project and the 15 ISOTOPICS ESRs presented their research results and communication actions.

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 ESRs had also the opportunity to define the content of the scientific deliverables, which will be submitted in 2019.

"The titles of the scientific deliverables defined concrete expectations, current needs and problems of the scientific and industrial world considering isotope labelling chemistry which were stated at the beginning of all PhD works. Astonishingly, to the present day, the biggest part of those demands could be accomplished and filled with interesting scientific results which gave already the one or the other real practical solution to the addressed problems. Several new published methods, new labelled complex molecules and new attractive feedstocks for isotope labelling reactions could be delivered by the ESR´s and presented at the 4th ISOTOPICS meeting. For this reason, the upcoming deliverable library is going to be a detailed overview of the principle achievements of our consortium and a must-read for every organic and radiochemist". **ESR1 - Viktor PFEIFER (CEA)**

"I enjoyed the 4th ISOTOPICS meeting in Sweden which was a great experience. The advisory board gave us many useful advices. I was really impressed with the quality of all the ESRs presentations and the progress we did from the beginning of the project. Impressive results were presented. Discussions with people from different backgrounds are always beneficial giving us new visions on the research. Approaching the end of the PhD, this kind of meeting is very important and helpful for us." **ESR11 - Donia BOUZOUITA (CNRS)**

"Last meeting in Stockholm witnessed, as usual, extraordinary discussions about radiochemical research. All ESRs presentations have been highly stimulating and have been followed by a profound question session between the presenting ESR and the public. It has been enormously inspiring to see the huge progresses that each one of us has made during these two years, and how some of these progresses are already applied for industrial needs. The 4th ISOTOPICS meeting of Stockholm has been a wonderful occasion to exchange opinion and point of view about science." **ESR2 - Alberto PALAZZOLO (CEA)**

"Stockholm welcomed us with frosty weather, but it was good to meet everyone after a longer no see (the last meeting was almost a year earlier in November 2017). Listening to the ESRs presentations you could clearly see that everyone has made incredible progress with their research and attended multiple interesting conferences. I think you could really feel that we are on our way to complete the scientific objectives of the project." **ESR7 - Mateusz IMIOLEK (UOXF)**

During the meeting, 2 plenary lectures were given by members of the advisory board. Dr. Gilles Tamagnan (XingImaging LLC; Beijing, China) talked about imaging biomarkers development and some applications in PET imaging of neurodegenerative diseases. Prof. Bengt Långström (University of Uppsala, Sweden) gave insights on Carbon-11 radiopharmaceuticals development and emphasised the current need to improve isotopic labelling techniques and associated technology.

"Dr. Tamagnan gave a clever overview of the latest discoveries in Bioimaging, especially discussing the application of the most important isotopes used in the field, showing how immense could be the applications for diagnosis. Sharing his huge practical experience spread in different continents, there were given several examples of how to translate what is done in the lab to patients, emphasizing the importance of data interpretation.

Prof. Långström is a living legend in the field of radiochemistry, especially in Carbon-11 chemistry and its applications. His lecture retraced the historical development of PET imaging, emphasizing how important was the evolution of technical manifolds through the years and how such huge development can have a direct impact on people's life. For his birthday, Prof. Långström gifted us his passion and energy, inspiring new generation to go deeply into a problem to solve it within conventional and unconventional ways."

ESR3 - Antonio DEL VECCHIO (CEA)

A social event was organised at "Den Gyldene Freden" restaurant in Stockholm old town. All the participants enjoyed a Swedish home cooking dinner. The restaurant premises are historic and have welcomed famous Swedish singers and writers. The members of the Swedish Academy (which makes the annual decision on who will be the laureate for the Nobel Prize in Literature) are used to eat in this restaurant every week.

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Group ISOTOPICS

4th Training session

All the ISOTOPICS ESRs attended this 5-day training in Karolinska Institutet premises (Stockholm, Sweden) to have an overview of the synthesis of radiotracers and their *in vivo* evaluation *via* PET imaging during pre-clinical animal experiments. They had also advice on CV writing and project management.

The 6 sessions were given by Karolinska Institutet and AstraZeneca staff members but also from related companies. The different subjects were:

'Cyclotron targetry' course [J. SIIKANEN (KI), P. LIDSTROM (General Electrics); 0,5 day]
"The "cyclotron targetry" course was really helpful to learn more about the production of labelled isotopes, such as ^{18}F, ^{11}C, ^{15}O, etc. We learned about the challenges, present and future we need to face in that field. It provided as well, complementary information to the visit of IBA we had in Liege during the previous meeting. **ESR13 – Laura TRUMP (UCB)**

'Radiochemistry Automation' course [P. LARSEN (Scansys), P. LIDSTROM (General Electrics); 1 day] with a visit of KI new PET laboratories.
"The "Radiochemistry Automation" course emphasized the relevance of the fully automated syntheses in the minimization of the radiation exposure to workers and provided general information about the automation processes in synthesizers that can be useful in the production of medicinally relevant radiotracers. The visit of new PET laboratories of Karolinska Institutet was very fruitful and contributed to a clear understanding, from the practical viewpoint, of the different aspects related to the production of novel PET radiopharmaceuticals." **ESR12 – Agostinho LEMOS (ULG)**

'Preclinical PET imaging' course [P. JOHNSTROM (AZ), M. TOTH (KI), T. TRAN (KI); 1 day] with the visit of Karolinska Experimental Research and Imaging Centre (KERIC) and Astrid Fagraeus Laboratory premises
"The visit of the facilities was very instructive and it allowed us to broaden our knowledge beyond radiochemistry. Though it wasn't the main focus of the course, we were once again invited to focus on the ethics of science and in particular, this time, on animal tests. These are an important part in the development of a new drug, but they create a lot of debate in public opinion. For this reason, transparency in animal tests is of the upmost importance to maintain the trust of the general public in science. The Astrid Fagraeus Laboratory does this, allowing the visit of its premises. There ethologists and veterinaries clearly and passionately described to us what steps they took to ensure the wellbeing of the animals hosted. From the design of new challenges for the primates to better mimic the time they spent in the wild to find food, to the best practice on how to inject the radiotracers in mice, all the animals are taken care of at all stages of research." **ESR 6 – Anna Chiara VICINI (UOXF)**

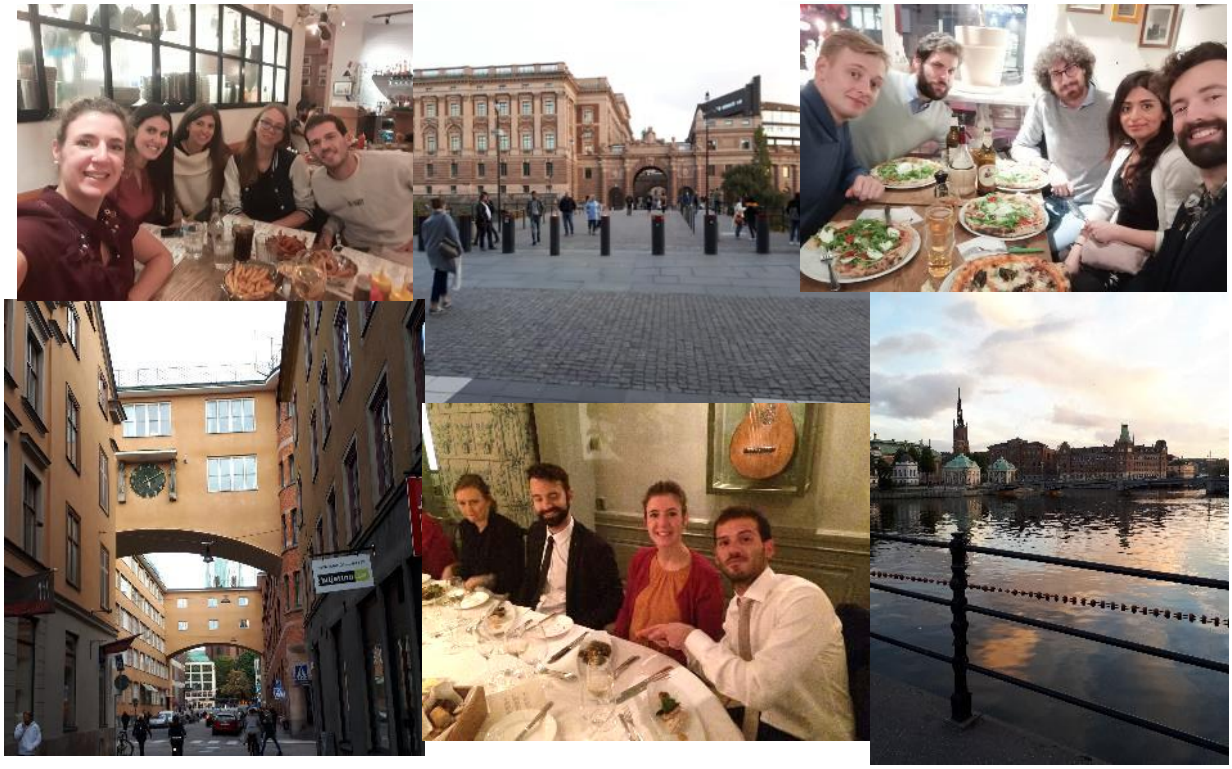
'Open your Mind to Non-Isotopic Labeling' course [P. NILSSON (Linköpings University), M. ZUREK (AZ), N. NAJAFINOBAR (AZ), R. GOODWIN (AZ); 1 day]
"The second last day of our training in Stockholm was fully dedicated to imaging techniques that do not require isotopic labelling. The course explained the fundamental of mass spectrometry, fluorescence and magnetic resonance used to obtain high-resolution images of biological and medicinal relevant targets. Of particular interest for me was the course taught by Richard Goodwin, who beautifully explained the new frontiers of imaging with mass spectrometry and how his group in AZ Cambridge contributes to drug discovery advances. A very interesting and inspiring day for us." **ESR5 – Francesco IBBA (UOXF)**

'Career' workshop [K. BECKENIUS (KI), A. RENNERMALM (Search4S); 1 day]
"In my opinion, the Career Workshop lead by Dr Anna Rennermalm was a very positive experience, mainly because it focused on two very important aspects. Firstly, it brought to our attention the variety of careers available to us upon completion of our doctoral studies. We can choose to either pursue a career in fundamental chemistry research or take advantage of skills built up during this PhD programme and become professionals in a tangential field. Secondly, we received great advice on how to stand-out in a very competitive job-market and how to promote our strengths in future job interviews." **ESR8 – Maria Alexandra GAFITESCU (UOXF)**

'Management principles' workshop [A. KARLSTROM (LILS); 0.5 day]
"For the last training session, Anders Karlström, a specialist in leadership and management on life sciences, made us evaluate ourselves as coworkers. By recognising our own features and preferences in working life, we learned about typical behavioral patterns for different personalities. We received some advice on how to cope with our own personal features and how to adapt them with colleagues who might behave in a different way. It was certainly an eye-opening lesson about the reasons why some people are more productive together while others encounter problems." **ESR10 – Kaisa HORKKA (KI)**

Photo gallery

- **4th Meeting and Training**



- **ESRs during secondments or communications**

Secondment experiences

ESR 4 – Gianluca DESTRO (CEA) hosted by Karolinska Institutet for 1 month

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

I joined Kaisa (ESR10) and the group of Prof. Christer HALLDIN at Karolinska Institutet in order to expand my knowledge about carbon radioisotopes, moreover to face another challenge; indeed, we decided to apply the idea of carbon isotope exchange on carbon-11. Thanks to the close collaborations with Kaisa and also Dr. Magnus SCHOU (AstraZeneca) the results will be disclosed in a new publication.

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

I think that flexibility is a crucial skill that a PhD needs to develop, for sure this secondment helps to increase this ability, then meet new scientists is always stimulating.

What was your favourite moment during this secondment?

There were many enjoying time together in the lab and in the office, I really liked how was easy sharing ideas and plans for the chemistry, then the dinner all together was a cosy moment outside the worktime.

ESR 14 – Malvika SARDANA (AstraZeneca) hosted by Dr. Davide AUDISIO and Dr. Fabien CAILLÉ (CEA) for 6.5 months

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

The secondment took place at the French Alternative Energies and Atomic Energy Commission (CEA) in Paris-Saclay, France. The work in France was focused on the reduction of $^{14}CO_2$ to ^{14}CO using two routes: elecotrochemical and fluoride catalyzed reduction with disilanes. The electrochemical reduction proved to be difficult for the reduction of stoichiometric amounts of labeled CO_2. Fortunately, the method using disilanes, was more successful.

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

The secondment provided an academic experience during the PhD. Additionally, I received the opportunity to work with fluorine-18, which is a radio isotope with a half-life time of 109.7 min, making this an attractive PET radioisotope. As I work mainly with long lived isotopes (C-14, half life time 5490 years), it was an excellent opportunity to expand my capabilities with PET-chemistry.

What was your favourite moment during this secondment ?

During my stay in France I moved between labs, this increased my ability to adapt between labs and experience the different work culture. Moreover, it was a great opportunity to live in Paris and be there in the summer. Lastly, the opportunity to work in a PET lab, expanded my skills set.

Malvika among the team of Dr. Davide AUDISIO in front of CEA

ESR interviews

ESR 9 –Mélodie FERRAT (KI), group of Prof. Christer HALLDIN

Could you tell us about your background?

My name is Mélodie, I come from France and I describe myself as an organic chemist with knowledge in inorganic chemistry and biology. Years ago, I moved from Nice, my hometown, to Paris in order to pursue my studies. I have received both my bachelors' degree in chemistry at the University of Versailles-Saint-Quentin-en-Yvelines and my master's degree in R&D pharmaceutical chemistry at the University of Paris-Saclay. During my academic career, I had the opportunity to be part of an inorganic-chemistry team by working with a project namely "Metal organic framework" (MOF 14 and MOF 177), then I worked in the field of pure organic chemistry by doing catalysts derived from Alkaloids followed by a project regarding organocatalysis. My latest internship dealt with the discovery and the

synthesis of new antimicrobial drugs against Staphyloccocus. Currently I am doing my PhD at Karolinska Institutet (Stockholm, Sweden) in the field of radiochemistry.

What is your PhD project about?
My PhD project is about the development of new methodologies for rapid and efficient introduction of carbon-11 into carbonyl group to make radioactive tracers for PET studies. This would broaden the tracer toolbox for investigating new aspects of human pathophysiology.

According to you, what are the strengths of the ISOTOPICS project?
The strengths of ISOTOPICS project are to have a practical knowledge in both academia and industry, to have the opportunity to do some communication action such as presenting our PhD project in front of researchers and trying to build a scientific network that is useful for our future.

ESR 13 –Laura TRUMP (UCB), group of Dr. Christophe GENICOT

Could you tell us about your background?
My name is Laura Trump, I come from France where I obtained an engineer degree in chemistry, and a master in biomolecules chemistry. I did several internships, mainly in industry (Galapagos, Belgium, 3 months and Sanofi, France, 6 months) which naturally lead me to do my PhD in a pharmaceutical industry within UCB Biopharma.

What is your PhD project about?
My PhD is about developing new methodologies for the insertion of CHF^{18}F to N-heteroaromatics. The point is to be able to develop new PET tracers for clinical imaging. And also to use the methodology to better assess the efficacy/pharmacokinetics of a drug, and thus to reduce drug attrition. The reaction will be using photochemistry, to allow late stage functionalization and flow chemistry to reduce reaction time (crucial parameter for fluorine-18). This is a PhD in collaboration with ESR12 who is labelling the reagent, and the ULG.

According to you, what are the strengths of the ISOTOPICS project?
According to me, the main strength of the ISOTOPICS project is the great networking. We are working with the experts in the field and can learn a lot with them during the trainings/meetings but also during secondments, which can provide great opportunities for the future.

ESR 15 – Mégane VALERO (Sanofi), Isotope Chemistry group headed by Dr. Volker DERDAU

Could you tell us about your background?
I am coming from France and studied mainly in Paris where I achieved knowledges in organic chemistry and biology. When I was looking for a PhD after my Master degree, I was willing to go abroad to challenge myself with the English language and also to discover and adapt to another culture. I am now doing my PhD in Frankfurt, Germany, at Sanofi and I am fully happy to have been ended up there.

What is your PhD project about?
The goal of my PhD is to find efficient, fast and simple methods for labelling of pharmaceutical relevant molecules with a particular focus on complex biomolecules such as peptides or natural products by hydrogen isotope exchange (HIE) using iridium catalysts. This method would allow a direct deuteration or tritiation of the desired target molecule in a single reaction step.

According to you, what are the strengths of the ISOTOPICS project?
The networking opportunities we have via the ISOTOPICS project are huge in my eyes. We meet regularly with the consortium which allows us to interact with the students, the supervisors coming from the different beneficiaries, but also other people involved into the project. These meeting are really helping me to get to know more about other isotope chemistry, to get advises to improve my project and to have interactions with potential future employers. The ISOTOPICS project also gave me the opportunity to attend several conferences where I presented my project and had the opportunity to interact with a broader bench of people involved in science.

Forthcoming events

- 5th ISOTOPICS meeting and training in Oxford (UK), 14-15 March 2019
- 24th Workshop of the IIS-CED in Bad Soden (Germany), 19-20 Sept. 2019
- Final ISOTOPICS meeting in Toulouse (France), October 2019

Dissemination actions

Posters

ESR1 – Viktor PFEIFER (CEA)

"Deuterium and Tritium Labelling of Bioactive Molecules Catalyzed by Ruthenium Nanoparticles, graduate school assembly" *4ème Journée des doctorants de 2MIB*, Oct. 2018, Université Paris-Sud, Orsay (France)

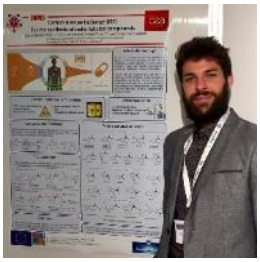
ESR2 – Alberto PALAZZOLO (CEA)

"Deuterium and tritium labelling using Ruthenium nanoparticles catalyzed C-H activation" *22-ICOS conference*, Sept. 2018, Florence (Italy).

ESR3 – Antonio DEL VECCHIO (CEA)

"Late-Stage Carbon Labeling of Pharmaceutically Active Ureas from CO_2" *22nd International Conference on Organic Synthesis*, Sept. 2018, Florence (Italy).

ESR4 – Gianluca DESTRO (CEA)



"CO_2 chemistry for the synthesis of radiolabeled compound", *First International Symposium on Drug Discovery and New Therapeutics,* Apr. 2018, Orsay (France).

"Carbon Isotope Exchange (CIE) for the synthesis of radio-labeled compounds", *22nd International Conference on Organic Synthesis*, Sept. 2018, Florence (Italy).

ESR5 – Francesco IBBA (UOXF)

"Asymmetric Nucleophilic Fluorination under Hydrogen Bonding Phase-transfer Catalysis" *Oxford Synthesis Summer Conference*, June 2018, Oxford (UK).

"Hydrogen Bonding Mediated Asymmetric Nucleophilic Fluorination: Structure and Mechanism", *22nd International Symposium on Fluorine Chemistry*, July 2018, Oxford (UK).

ESR7 – Mateusz IMIOLEK (UOXF)

"Tryptophan selective trifluoromethylation of native residues in proteins" *Gordon Research Conference&Seminar in Bioorganic Chemistry*, June 2018, New Hampshire (USA).

ESR8 – Maria Alexandra GAFITESCU (UOXF)

"Synthetic approaches to elucidate structure-activity relationships in glycoproteins", *Pfizer sponsored Organic Chemistry and Chemical Biology Symposium*, Oct. 2018, Oxford (UK).

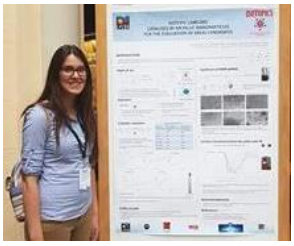
ESR9 – Mélodie FERRAT (KI)

"In-loop carbonylation – a novel and simplified method for carbon-11 labeling of drugs and radioligands" *EANM18*, Oct. 2018, Düsseldorf (Germany).

ESR10 – Kaisa HORKKA (KI)

"Rapid and efficient BEMP-mediated synthesis of 11C-labelled benzimidazolones using [11C]carbon dioxide" *EANM18*, Oct. 2018, Düsseldorf (Germany).

ESR11 – Donia BOUZOUITA (CNRS)



"Isotopic labelling catalysed by metallic nanoparticles for the evaluation of drug candidates" *TrapCat meeting*, Oct. 2018, Tarragona (Spain).

"Isotopic labelling catalysed by metallic nanoparticles for the evaluation of drug candidates" *Stable Carbene Symposium*, Nov. 2018, Toulouse (France).

ESR13 – Laura TRUMP (UCB)

"Development of a flow photoredox reaction for the addition of $CHF^{18}F$ to N-heteroaromatics", *MedChem2018 symposium*, Nov. 2018, Namur (Belgium).

"Development of a flow photoredox reaction for the addition of $CHF^{18}F$ to N-heteroaromatics", *BMIC meet industry event*, Nov. 2018, Braine L'Alleud (Belgium).

ESR14 – Malvika SARDANA (AZ)

"Visible-light Enabled Aminocarbonylation of Unactivated Alkyl Iodides", *4th Annual Doctoral School 2MIB*, Oct. 2018, Orsay (France).

ESR15 – Mégane VALERO (SAN)

"C-H functionalization: Highly Selective Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Aliphatic Amides" *BOSS XVI symposium*, July 2018, Brussels (Belgium).

"C-H functionalization: Highly Selective Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Aliphatic Amides" *Nikas 2018 conference*, Sept. 2018, Göttingen (Germany).

ACS Catalysis Best Poster Award

"Highly selective directed iridium-catalyzed hydrogen isotope exchange (HIE) of unactivated C(sp3) centers in aliphatic amides" *Doctoral school assembly "4ème Journée de l'Ecole Doctorale ED2MIB",* Oct. 2018, IUT d'Orsay (France).

Oral communications

ESR1 – Viktor PFEIFER (CEA)

"Deuterium and Tritium Labelling of Bioactive Molecules Catalyzed by Ruthenium Nanoparticles", *13th International Symposium on Synthesis and Applications of Isotopes and Isotopically Labelled Compounds*, June 2018, Prague (Czech Republic).

ESR2 – Alberto PALAZZOLO (CEA)

"The Late Stage Deuterium and Tritium Labelling of Nucleobases Catalyzed by Ruthenium Nanoparticles", *IIS 2018*, June 2018, Prague (Czech Republic),.

ESR3 – Antonio DEL VECCHIO (CEA)

"CO_2 Fixation for Late Stage Labeling of Drug Candidates", *First International Symposium on Drug Discovery and New Therapeutics*, Apr. 2018, University of Paris-Saclay Paris, (France).

"CO_2 Fixation for Late Stage Labeling of Drug Candidates", (oral communication), *IIS 2018*, June 2018, Prague, (Czech Republic).

J. Label. Compd. Radiopharm. Award for Junior Scientists 2018

"New Methodologies for the Labeling of Drug Candidates", *Journée de l'Ecole Doctorale 2MIB*, Oct. 2018, Orsay (France).

ESR4 – Gianluca DESTRO (CEA)

"CO_2 chemistry for the synthesis of radiolabeled compound", *IIS 2018*, June 2018, Prague, (Czech Republic).

J. Label. Compd. Radiopharm. Award for Junior Scientists 2018

ESR5 – Francesco IBBA (UOXF)

"Merging Hydrogen Bonding and Phase-transfer Catalysis", *ACS Fall National Meeting*, Aug. 2018, Boston (USA).

ESR7 – Mateusz IMIOLEK (UOXF)

"Selective radical trifluoromethylation of native residues in proteins" *22nd International Symposium on Fluorine Chemistry*, July 2018, Oxford (UK).

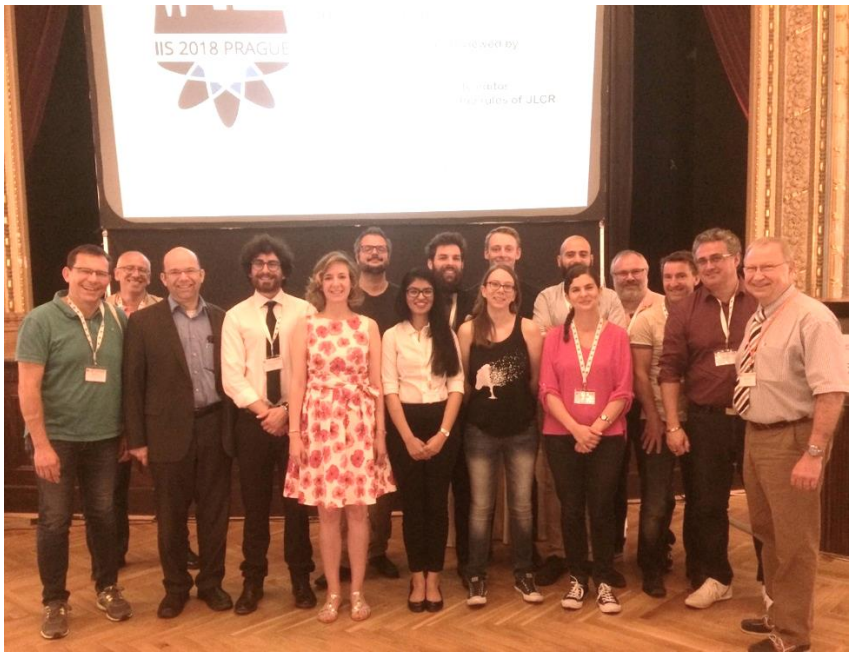
ESR14 – Malvika SARDANA (AZ)

"Visible-light enabled carbonylation of alkyl iodides", *13th International Symposium on the Synthesis and Application of Isotopically Labelled Compounds*, June 2018, Prague (Czech Republic).

ESR15 – Mégane VALERO (SAN)

"Iridium-catalyzed Hydrogen Isotope Exchange (HIE) Method of aliphatic sp3-centers in unactivated amides" *IIS 2018*, June 2018, Prague (Czech Republic).

J. Label. Compd. Radiopharm. Award for Junior Scientists 2018

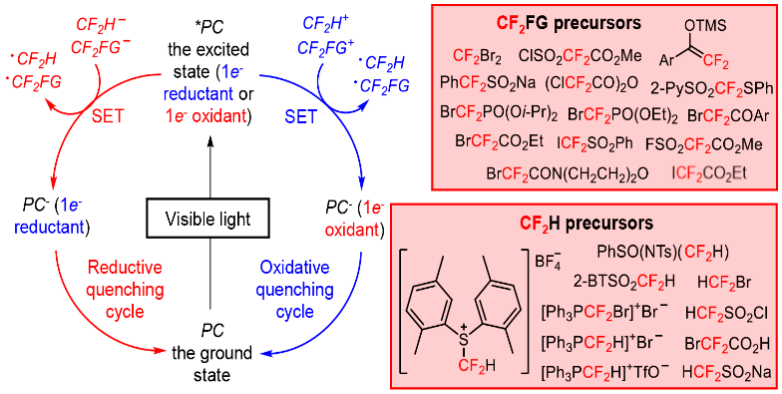


Several ISOTOPICS members at the 13th International Symposium on the synthesis and application of isotopically labelled compounds (IIS 2018), June 2018, Prague (Czech Republic).

Recent scientific publications

Progress in difluoroalkylation of organic substrates by visible light photoredox catalysis

Agostinho Lemos, Christian Lemaire, André Luxen*, *Adv. Synth. Catal.* **2019**, *in press* (DOI: 10.1002/adsc.201801121).



"This review provides a comprehensive overview concerning to the synthetic approaches for visible light-mediated difluoroalkylation of organic molecules reported in the literature since 2014. To date, we have witnessed to an increasing progress in the development of transition metal-photocatalyzed methodologies for introduction of difluoroalkyl motifs (CF_2H and CF_2FG, FG = a functional group) into various building blocks, involving a myriad of difluoroalkylating reagents (see Graphical Abstract). The use of organophotocatalysts in difluoroalkylation reactions has also deserved a special attention, particularly in the area of pharmaceutical industry, due to the need of minimizing the amount of metal catalysts in the production of pharmaceuticals. In this manuscript, we underlined the importance of difluoroalkyl motifs in pharmaceutical research and drug development because of their ability to potentially enhance properties related to the biological activity of molecules. In addition, we emphasized the relevance of visible light photoredox catalysis as a sustainable approach for the obtention of CF_2-containing derivatives from the viewpoint of safety, cost, availability, and "green" chemistry. Owing to the attractive features of visible light photoredox catalysis and the late-stage introduction of difluoroalkyl groups, we expect that the manuscript could be useful to inspire organic chemists in the exploration of additional synthetic routes for installation of these chemical moieties." **ESR12 – Agostinho Lemos (ULG).**

Dynamic Carbon Isotope Exchange of Pharmaceuticals with Labeled CO_2

Gianluca Destro, Olivier Loreau, Elodie Marcon, Frédéric Taran, Thibault Cantat*, Davide Audisio*, *J. Am. Chem. Soc.* **2019**, *141* (2), 780–784.

Palladium-mediated enzyme activation suggests multiphase initiation of glycogenesis

Matthew K. Bilyard, Henry J. Bailey, Lluís Raich, Maria A. Gafitescu, Takuya Machida, Javier Iglésias-Fernández, Seung Seo Lee, Christopher D. Spicer, Carme Rovira, Wyatt W. Yue* & Benjamin G. Davis*, *Nature* **2018**, 563, 235–240.

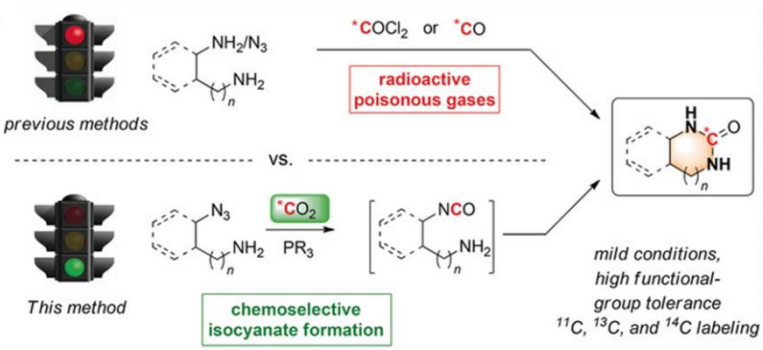
Surprising Differences of Alkane C-H Activation catalyzed by Ruthenium Nanoparticles": Complex Surface-Substrate Recognition?

Niels Rothermel, Donia Bouzouita, Tobias Röther, Iker de Rosal, Simon Tricard, Romuald Poteau, Torsten Gutmann,* Bruno Chaudret,* Hans-Heinrich Limbach* and Gerd Buntkowsky*, *ChemCatChem* **2018**, *10*, 4243-4247.

Late-Stage Isotopic Carbon Labeling of Pharmaceutically Relevant Cyclic Ureas Directly from CO_2

Antonio Del Vecchio, Fabien Caillé, Arnaud Chevalier, Olivier Loreau, Kaisa Horkka, Christer Halldin, Magnus Schou, Nathalie Camus, Pascal Kessler, Bertrand Kuhnast, Frédéric Taran, Davide Audisio*, *Angew. Chem. Int. Ed.* **2018**, *57*, 9744.

Abstract: A robust, click-chemistry-inspired procedure for radiolabeling of cyclic ureas was developed. This protocol, suitable for all carbon isotopes (11C, 13C, 14C), is based on the direct functionalization of carbon dioxide: the universal building block for carbon radiolabeling. The strategy is operationally simple and reproducible in different radiochemistry centers, exhibits remarkably wide substrate scope with short reaction times, and demonstrates superior reactivity as compared to previously reported systems. With this procedure, a variety of pharmaceuticals and an unprotected peptide were labeled with high radiochemical efficiency.



Recent Developments in Heterocycle Labeling with Carbon Isotopes

Antonio Del Vecchio, Gianluca Destro, Frederic Taran, Davide Audisio*, *J. Label. Compd. Radiopharm*. **2018**; 1-20.

Visible-Light-Driven Reduction of CO2 to CO and Its Subsequent Valorization in Carbonylation Chemistry and ^{13}C Isotope Labeling

Philipp Gotico, Antonio Del Vecchio, Davide Audisio, Annamaria Quaranta, Zakaria Halime*, Winfried Leibl, and Ally Aukauloo*, *ChemPhotoChem* **2018,** *2*, 715.

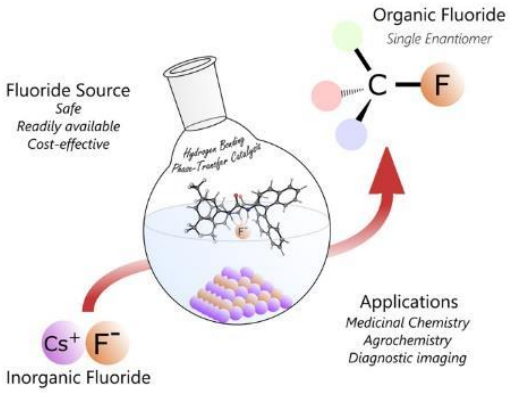
New trends and applications in carboxylation for isotope chemistry

Ryan A. Bragg, Malvika Sardana, Markus Artelsmair, Charles S. Elmore*, *J Label. Compd. Radiopharm.* **2018**, 1–15.
"Recently, the Journal of Labelled Compounds and Radiopharmaceuticals has chosen to highlight advances in carbon isotope labelling with a special edition of the journal. The paper that our group produced focuses on carboxylations utilizing CO_2. It provides perspectives on recent Carbon-12 methodologies which, potentially, could be translated for use with radioisotopes (Carbon-14)." **ESR14 – Malvika SARDANA (AZ).**

Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis

Gabriele Pupo, Francesco Ibba, David M. H. Ascough, Anna Chiara Vicini, Paolo Ricci, Kirsten E. Christensen, Lukas Pfeifer, John Richard Morphy, John M. Brown, Robert S. Paton, Véronique Gouverneur*, *Science* **2018**, *360* (6389), 638-642.

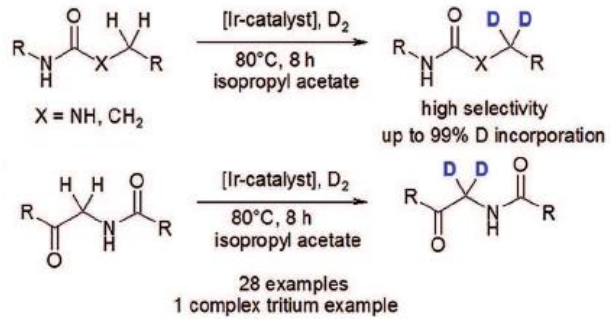
Highlighted in *Chemical and Engineering News*, **2018**, *20* (96), 8. – Fetching fluoride with hydrogen bonding.



"Procedures for the construction of carbon-fluorine bond are in continuous demand because of the value of the products across applied chemistry and due to its central role in radiochemistry being Fluorine-18 one of the radionuclides most widely used in positron emission tomography (PET). In the past ten years, chemists have made remarkable progress in this area in part due to the availability of fluorine reagents of tailored reactivity. Among these reagents anionic sources of fluoride, such as alkali metal fluorides (CsF, RbF, KF, NaF, LiF), are the most convenient due to their cost efficiency and safety in handling, nevertheless their use in a synthetic contest (*nucleophilic fluorination*) is complicated by their poor solubility in organic solvent and generally low reactivity and selectivity. At the University of Oxford, we developed a new activation mode for fluoride that allows for the first time an *organocatalytic asymmetric fluorination* using alkali metal fluorides. Key for the success was to merge phase-transfer catalysis, in which a fluoride salt is transported from the solid phase to the solution, and the hydrogen bonding ability of chiral ureas, that guide the fluoride in solution. This new concept in catalysis, named Hydrogen Bonding Phase-transfer Catalysis (HB-PTC), was applied to the fluorination of episulfonium ions affording enantiopure β-fluoro sulfides." **ESR5- Francesco IBBA (UOXF).**

Highly Selective Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Aliphatic Amides

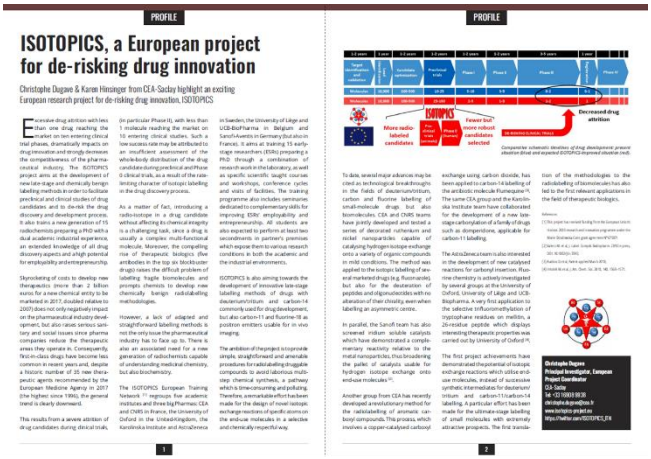
Mégane Valero, Remo Weck, Stefan Güssregen, Jens Atzrodt* and Volker Derdau*, *Angew. Chem. Int. Ed.* **2018**, *57*, 8159.



A process for the synthesis of carbon labeled organic compounds

Destro G, Audisio D, Cantat T, **2018**, EP18305407 (patent)

Communication actions

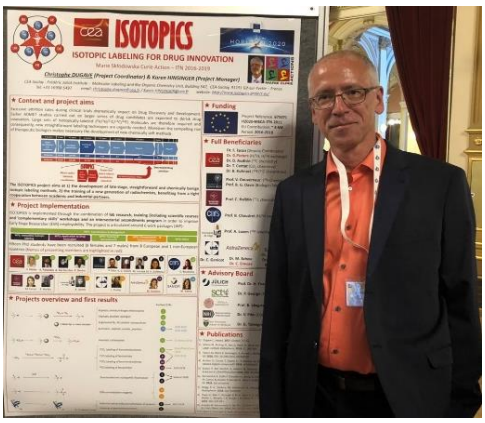

PROFILE

ISOTOPICS, a European project for de-risking drug innovation

Christophe Dugave & Karen Hinsinger from CEA-Saclay highlight an existing European research project for de-risking drug innovation, ISOTOPICS

PROFILE

The management team has published an article in the OPEN ACCESS GOVERNMENT journal to highlight the expected impact of ISOTOPICS in de-risking drug innovation and to inform about last research results.
You can have access to this article on the ISOTOPICS website.



Dr. Christophe DUGAVE, ISOTOPICS project coordinator, presented a poster and a flash communication during the 13th International Symposium on the synthesis and application of isotopically labelled compounds (IIS 2018; June 2018; Prague, Czech Republic).

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