ISOTOPICS Newsletter – Issue 2

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

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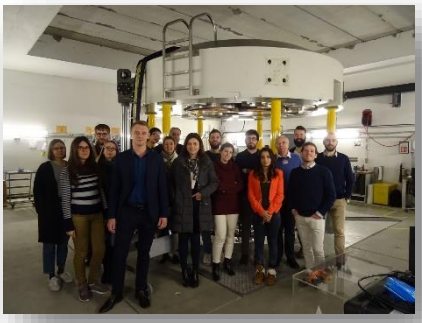

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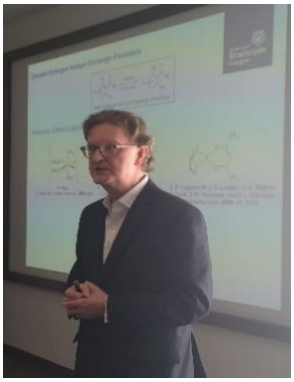
2nd ISOTOPICS Meeting

All the Principal Investigators, the 15 Early Stage Researchers (ESRs), the Advisory Board and the management team attended this event organised in April 2017 in Frankfurt (Germany) by the SANOFI Beneficiary. This 2-day meeting allowed us to discuss about the administrative and scientific progresses of the project. Each ESR gave a little talk about the context of their PhD project and their first results.

"During the meeting, the ESRs were able to present their first results, and it was delightful to notice how well everyone were advancing."
ESR10 - Kaisa HORKKA (KI)

"Regarding the presentations performed by ESRs in 2nd ISOTOPICS meeting, I was very impressed with the progress of the research works in such a short period of time. Overall, these research works demonstrate the applicability of the different radioisotopes in the production of novel radiolabeled molecules with potential medical interest using distinct methodologies."
ESR12 - Agostinho LEMOS (ULG)

During the meeting, Prof. William Kerr (University of Strathclyde, UK) was invited to give a plenary lecture. The title of the conference was "Iridium Catalyst Systems of Enhanced Utility in C-H Activation and Hydrogen-Isotope Exchange". This outstanding presentation was valued by all the ISOTOPICS consortium.



"When I first knew that William Kerr would have given us a plenary lecture I was thrilled. Indeed, Professor Kerr is one of the biggest name in H-D exchange through transition metal catalysed C-H activation. As I expected, the lecture was marvelous. The rationality behind his studies astonished me the most, every result was followed by a detailed mechanistic study, so nothing was left unexplained. A beautiful example of scientific coherence." **ESR2 - Alberto PALAZZOLO (CEA)**

The discussions between the ESRs and the PIs were fruitful for envisaging the application of the studied synthetic methodologies within the network and help to refine the secondments plan.

"The discussion with the PIs was extremely inspiring, many ideas came out to improve our research. I think that sharing of ideas within the network is the crucial point of ISOTOPICS project."
ESR5 - Francesco IBBA (UOXF)

"The oral presentations and discussions were very beneficial. Discussions with people from different backgrounds: academic and industrial allow us to have different visions on research and to precise our PhD objectives. We get new ideas and helpful advices for the rest of the thesis. Hearing the presentations of all the ESRs was very inspiring, knowing more about their projects. They all presented in a clear way with excellent skills. Isotopic meetings are very useful, they guide us through our research". **ESR11- Donia BOUZOUITA (CNRS)**

A social event was organised at the Eberbach Monastery (Eltville am Rhein; 40 min by bus from Frankfurt). All the participants enjoyed first a wine-tasting tour in the wine cellars of the world-famous Steinberg vineyard and then a nice dinner at the Monastery.

3rd ISOTOPICS Meeting

This event corresponded to the Mid-term Review of the project. The Project Officer, an external scientific expert, a REA legal Officer, all the ISOTOPICS consortium, the Advisory Board and the management team attended the meeting at the University of Liège (Belgium).


Each ESR had to present its personal background, explain the research results obtained so far and answer the questions of the scientific expert and the Advisory board.

"Attending the third meeting in Liege, the midterm one, was a great experience. Finally, we had the opportunity to show our results and give them an organic structure; all the ESRs put them in the first line to exploit in the best way their thesis. Everybody from Tritium to Carbon passing through Fluorine, really worked hard to achieve impressive results. I enjoyed and appreciate a lot this moment." **ESR4 – Gianluca DESTRO (CEA)**

The 3rd ISOTOPICS meeting was a great opportunity for all of us, not only to present ourselves and the PhD results obtained so far, but also to share ideas and receive very useful input and advice from the audience. In doing this, all the participants showed great interest and continuous support for our work that although challenging can bring priceless scientific accomplishments. **ESR 08 - Alexandra GAFITESCU (UOXF)**


At the end of the meeting, Prof. Troels Skrydstrup gave an exceptional plenary lecture entitled "New Directions in Transition Metal Catalyzed Carbonylation Chemistry for Synthesis and Isotope Labeling". He answered afterwards several questions from the ISOTOPICS researchers and ESRs.

"Prof. Skrydstrup gave an excellent presentation in regards to late-stage labeling with carbon monoxide. It was nice to see how CO-gas can be used in a safe manner, as well as in equimolar amounts. The latter is of great concern for using radioactive labeled CO. He complemented this by highlighting the different CO-labeling strategies, which has been published by his group." **ESR14 – Malvika SARDANA (AZ Gothenburg)**

A social event was organized at the Atelier de Selys restaurant to continue the discussions in a more relaxed environment.


After this Mid-Term Review, the Project officer underlined that the project is very well managed and that the ISOTOPICS consortium is working on very innovative methods for radiolabeling.

"After a certain time period, it was already an obvious conclusion for most of us that the project as a whole was shaping up nicely from different point of views. Owing to the high facility given to the ESRs to communicate and to move across all Europe, suitable collaboration partners could be easily figured out and scientific research progressed quickly. Thus, many ISOTOPICS members started to consider each other as direct colleagues very soon and geographic distances lost in significance surprisingly fast." **ESR1 - Viktor PFEIFER (CEA)**

"The Project officer asked several questions to all of us to make sure that our project is in progress. He also provided us some helpful advices which personally will guide me through my research project. In overall, all projects are well-managed and on track for the development of new radiotracers by using some innovative methods. I am convinced that our research work will have a huge impact on the radio-pharmaceutical industry" **ESR9 - Mélodie FERRAT (KI)**

2nd Training session

The 15 ISOTOPICS ESRs were gathered in SANOFI premises (Frankfurt, Germany) after the 2nd meeting (April 2017) to have a 4-day training session. This session presented some applications of the isotopic labeling to medicinal chemistry in pharmaceutical industry.

The training was composed of 5 sessions divided in distinct lectures given by several members of the SANOFI staff:

- 'Introduction to SANOFI and the pharmaceutical industry' workshop with a visit of the SANOFI premises (Laboratory of Isotope Chemistry & Metabolite Synthesis).
- 'Fundamental Ease in Medicinal Chemistry' course
- 'Industrial application of isotopic labeling' course
- 'Open your mind to imaging methods' workshop
- 'Research Ethics' workshop

"The training in Frankfurt was really interesting. It was nice to see more about another pharmaceutical industry, the numerous speakers allowed us to learn more about medicinal chemistry and the interest and use of isotope labelling in industry." **ESR13 - Laura TRUMP (UCB)**

"The 2nd training in Frankfurt was given by Sanofi scientists about medicinal chemistry, industrial application of isotope labeling, imaging methods, research ethics; a visit of the labs was also included. It is each time a great opportunity for the ESRs to go to one of the Beneficiary place and see how is work doing there but also to keep good relation between the ESRs, visit the city and enjoy time together." **ESR15 – Mégane VALERO (SANOFI Germany)**

3rd Training session

The University of Liège organised the training in November 2017. This 4,5-day session involved theoretical course, workshop with pharmaceutical company staff and visit of laboratories:

- 'Good Manufacture Practices (GMP) for Radiopharmaceutical Production' Course
- 'Use of isotopes in Quantitative Analysis of Biomolecules' Course
- 'Drug discovery and development process: Application to Epilepsy disease at UCB Biopharma' Workshop
- 'PET Imaging' Workshop
- 'Intellectual Property' Workshop
- 'Enterprise, Entrepreneurship' Workshop and visit of IBA Cyclotron assembly plant.

"Countless steps down a steep stair, a narrow corridor than turns, turns and seems to never finish… and finally here it is: the cyclotron! Our work would not be possible without this machine that produces the radioactive ^{18}F isotope by proton bombardment of $H_2{}^{18}O$. We surround the cyclotron, listening fascinated to Simon Zaremba (IBA) who explains us that in fact the cyclotron accelerates negative ions, before turning them into protons and finally producing ^{18}F. His eyes are bright while he describes us all the features of the first cyclotron produced at IBA (Ion Beam Application SA) and you can feel the passion in his speech, the same passion that we caught in Yves Jongen's description of IBA foundation and development. The story of IBA originally a spin-off of the catholic university of Louvain-la-Neuve and now counting more than 1500 employees, is a successful example of entrepreneurship, which would not be possible without the desire of its founder to push the boundaries, improving what at the time was the accepted state of the art on ion beams. It's this message of not being satisfied with the current knowledge, but the desire to continuously improve it that I'm taking home as a scientist."

ESR6 - Anna Chiara VICINI (UOXF)

"Our 3rd training session organized in such a professional manner at the University of Liège was again a powerful experience aimed to round up our formation as scientists with expertise in isotopic labeling of future drug molecules. Among all the courses, I enjoyed the most our visit at UCB Pharma where we had the opportunity to test a virtual reality system for better visualization of a target. I have to say that "being" inside of a protein was a rather exciting experience!"

ESR8 - Alexandra GAFITESCU (UOXF)

Photo gallery

Germany

Belgium

Interviews of ESRs

ESR6 – Anna Chiara VICINI (UOXF), group of Prof. Véronique GOUVERNEUR

Could you tell us about your background?

I have studied chemistry at the University of Bologna (Italy) completing my Bachelor (Industrial Chemistry) in 2014 and my Master (Chemistry) in 2016 prior to join the Gouverneur group at the University of Oxford in the same year. My interest for Organic Chemistry dates back to the first undergraduate course and therefore I decided to carry out my Bachelor project in the field of Asymmetric Organocatalysis under the supervision of Prof. Luca Bernardi and Dr. Maria Francesca Fochi (University of Bologna). Having developed an interest in medicinal chemistry, I took part in the Erasmus exchange project to complete my Master Thesis and I joined the group of Prof. Roland J. Pieters at the department of Chemical Biology and Drug Discovery at Utrecht University (The Netherlands). I was there when I decided to continue my education and I applied to ISOTOPICS, which brought me to the UK.

What is your PhD project about?

My PhD project aims to develop a new organocatalytic nucleophilic fluorination employing inexpensive fluoride sources, ideally in an asymmetric fashion. Once the methodology would be validated with the natural abundant fluorine isotope (^{19}F), I will try to extend the protocol to radiofluorination.

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

Science at advanced level is like those discovery expeditions of the XIX Century: it can't be done by a single person but it needs different expertise to really make an impact in the field. ISOTOPICS does this. Through the trainings I had the possibility to learn about topics I would have never covered during my PhD. The secondment in SANOFI would give me the possibility to experience how it is doing research in an industrial environment, thus helping me in better planning my future career. More generally the building of a network between Industry and Academia, the space of discussion between experienced researchers and ESRs are the main strength of ISOTOPICS.

ESR10 – Kaisa HORKKA (KI), group of Prof. Christer Halldin

Could you tell us about your background?

I am Finnish with a background in Organic chemistry. I obtained my BSc degree in Chemistry and MSc in Organic chemistry from the University of Helsinki. I completed my Master's thesis at the Complutense University of Madrid with Prof. María Luz López Rodríguez. During the last years of my studies I worked in the field of synthetic chemistry at the University of Helsinki with Dr. Sami Heikkinen. I achieved experience also on biochemistry (with Prof. Perttu Permi, Helsinki Institute of Biotechnology) and wood chemistry (with Prof. Ilkka Kilpeläinen, University of Helsinki).

What is your PhD project about?

In my project, I develop methods to label molecules with ^{11}C-carbon dioxide. The project is divided into two parts. In the first part I synthesize ^{11}C-benzimidazolones and in the second part I intend use Ni catalyst to carboxylate unactivated precursors. Finally, the methods will be applied into labelling of potential or existing PET radiotracers.

What are the strengths of ISOTOPICS?

The most important strengths are the possibility to be part of a multidisciplinary group and learn by following other groups' work and by secondments, as well as to network with other researchers.

Secondment experience

ESR3 –Antonio DEL VECCHIO (CEA)

Secondments at Karolinska Institutet from 21/10/2017 to 26/11/2017

"The Secondment at Karolinska Institutet gave me the opportunity to access to a different carbon isotope field, learning its problems and duties. Working closely with Dr Magnus Schou as hosting supervisor, I was introduced to the most common methodologies for the valorization of [^{11}C] in the labelling of therapeutically and diagnostically relevant compounds".

Dissemination and communication actions

Posters

ESR1 – Viktor PFEIFER (CEA):

- "Deuterium and tritium labelling of bioactive molecules catalyzed by ruthenium nanoparticles" Journée des Doctorants de l'Institut Joliot, July 2017, CEA-Saclay, FR.
- "Deuterium and tritium labelling of bioactive molecules catalyzed by ruthenium nanoparticles", Journée de l'ED2MIB, October 2017, Paris-Saclay University, FR.

ESR2 – Alberto PALAZZOLO (CEA):

- "Deuterium and tritium labelling of peptides, small proteins, oligonucleotides and alcohol-containing biomolecules", Journée des Doctorants de l'Institut Joliot, July 2017, CEA-Saclay, FR.
- "Deuterium and tritium labelling of alcohols and nucleotides", Journée de l'ED2MIB, October 2017, Paris-Saclay University, FR.

ERS3 – Antonio DEL VECCHIO (CEA): "New Methodologies for the labeling of drug candidates" Journée des Doctorants de l'Institut Joliot, July 2017, CEA-Saclay, FR.

ESR5 – Francesco IBBA (UOXF): "Organocatalytic nucleophilic fluorination", 17th Annual RSC Fluorine Subject Group Postgraduate Meeting, September 2017, Leicester, UK.

ESR6 – Anna Chiara VICINI (UOXF): "Organocatalytic nucleophilic fluorination", 17th Annual RSC Fluorine Subject Group Postgraduate Meeting, September 2017, Leicester, UK.

ESR14 – Malvika SARDANA (AZ): "Late-stage labeling enabled by carbonylation with CO", 26th IIS Symposium (UK Group), November 2017, Cambridge, UK.

Oral Communications

ESR15 – Mégane VALERO (SAN):

- "Iridium-catalyzed hydrogen isotope exchange and applications of isotopically labelled compounds for drug discovery", September 2017, IIS-Workshop, Bad Soden, Germany.
- "Iridium-catalyzed hydrogen isotope exchange and applications of isotopically labelled compounds for drug discovery", September 2017, AdBOC2017 conference, Sheffield, United Kingdom.

Publications

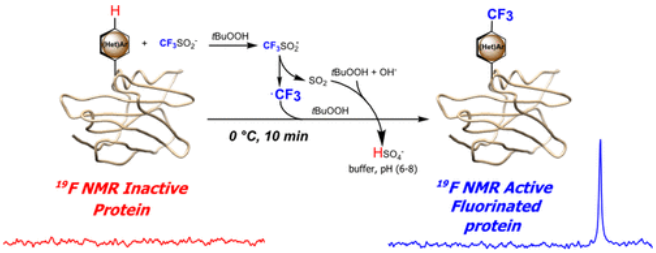
- "ISOTOPICS – Isotopic labeling for drug innovation – H2020" (Tomorrow's treatment. Enhancing European pharmaceutical innovation), Christophe Dugave, Karen Hinsinger; Impact, Volume 2017, Number 8, October 2017, pp. 52-54. (DOI: 10.21820/23987073.2017.8.52)

"This is an outreach action from the management team of ISOTOPICS to advertise about our project. We wanted to communicate the objectives, planned impact and relevance of research to a large public" **Project manager - Karen HINSINGER (CEA)**

- "Evaluation of a P,N-Ligated Iridium(I) Catalyst in Hydrogen Isotope Exchange Reactions of Aryl and Heteroaryl Compounds", Mégane Valero, Annina Burhop, Kristof Jess, Remo Weck, Matthias Tamm, Jens Atzrodt, Volker Derdau J Label Compd Radiopharm. 2017. (DOI: 10.1002/jlcr.3595)

"We have developed a novel and efficient iridium-catalyzed hydrogen isotope exchange (HIE) reaction method with secondary and tertiary sulfonamides at ambient temperatures. Furthermore N-oxides and phosphonamides have been successfully applied in HIE reactions with moderate to excellent deuterium introduction." **ESR15 – Mégane VALERO (SANOFI Germany)**

- "Selective radical trifluoromethylation of native residues in proteins", Mateusz Imiolek, Gogulan Karunanithy, Wai-Lung Ng, Andrew J. Baldwin, Veronique Emilie Gouverneur, and Benjamin G. Davis; J. Am. Chem. Soc., 2018 (DOI: 10.1021/jacs.7b10230) Link to the blog: https://chembites.org/2018/01/23/a-radical-way-***to-label-proteins/***



"In January 2018, thanks to collaborative efforts of Davis', Baldwin's and Gouverneur's groups we were able to publish the first results of my research in a publication: 'Selective Radical Trifluoromethylation of Native Residues in Proteins'. At the beginning of my DPhil project I was investigating various radical reactions that could be used for modification of native residues in proteins with fluorine containing groups. I chose this chemistry bearing in mind its suitability with my ultimate goal – (radio)fluorination. One of the tested protocols based on Langlois' reagent/oxidant proved to be reactive under mild, biocompatible conditions. Although we have observed high reactivity towards many native residues (hetero(aromatic) and cysteine) we were not sure how the system would behave in presence of 'sea' of other functional groups provided by the protein. Competition experiments on small molecule models strongly pointed towards dominant tryptophan trifluoromethylation. Origin of this selectivity was attributed to electronic effects, as protonation of other relatively electron rich heteroaromatic system – imidazole – resulted in hugely diminished reactivity. Having established correct conditions (short time, high conversion) for a peptide and various proteins, we embarked on uneasy task of proving the selectivity in such complex system. Fortunately, fluorine itself, with its nuclear spin of ½, helped us to achieve this aim. Through series of careful denaturative experiments we were able to confirm the MS results, proving conserved tryptophan selectivity. Moreover, we demonstrated that this fluorination protocol, owing unique NMR visibility of the trifluoromethyl group, equips scientists with a fantastic platform for Protein Observed NMR studies which allow e.g. ligand binding screenings and assays. The article has already sparked some interest in the community, as it was chosen to be 'digested' by ChemBites – scientific blog featuring latest research."

ESR7 – Mateusz IMIOLEK (UOXF)

Forthcoming events

13th International Symposium on the synthesis and applications of isotopes and isotopically labeled compounds (3rd-7th June 2018; Prague, Czech Republic)

4th ISOTOPICS Meeting & training (September 2018; Stockholm, Sweden)

22nd International Symposium on Fluorine Chemistry (22nd-27th July 2018; Oxford, UK)

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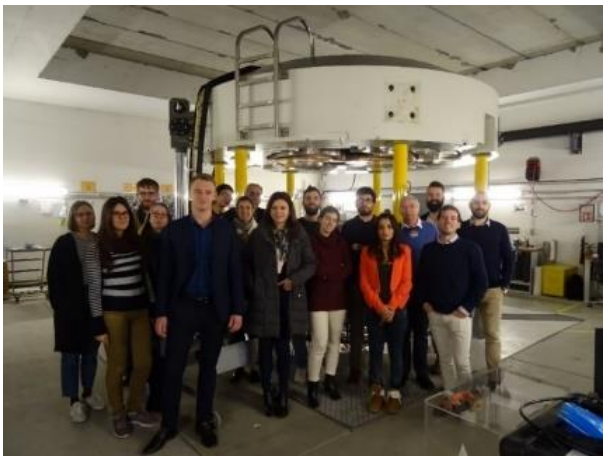

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