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Isotopics – Isotopic labeling for Drug Innovation - H2020

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Impact Objectives

- Develop new methods for the chemical labelling of drug candidates with the ultimate aim of streamlining drug innovation and decreasing drug attrition
- De-risk the field of drug discovery and development (DDD) by allowing more drug candidates to be evaluated during preclinical studies
- Train the next-generation of first-class radiochemists with specialist knowledge and expertise in labelling chemistry, in addition to dual academic-industrial culture

Tomorrow's treatment

Dr Christophe Dugave is involved in an innovative training network coordinated by the French Alternative Energies and Atomic Energy Commission. Here he discusses the importance of the network for the drug discovery and development landscape



Could you begin by introducing your background and key research interests?

I obtained my PhD in molecular pharmacology in 1990 from the

Pierre and Marie Curie University, France, under the guidance of Professor Andr e Marquet, studying the vitamin K-dependent carboxylations that are involved in blood coagulation and calcification processes. I then moved to the University of Sherbrooke, Canada, for a postdoc in organic chemistry under the supervision of Professor Pierre Deslongchamps, synthesising macrocycles as potential precursors of steroid analogues.

In 1992, I joined the French Atomic Energy Commission (CEA) in Saclay close to Paris, first as a researcher and then as a group leader from 1997. I later obtained my agreement to supervise research. I was mainly interested in the synthesis of unnatural amino acids, pseudopeptides and their use for exploring structure transitions in peptides and proteins, and related pathologies. I also used pseudopeptides and rhenium metallopeptides for inhibiting the enzymatic activity of peptidyl cis-trans isomerases involved in AIDS, cancer and neurodegeneration.

In 2003, I started a research programme devoted to the development of new integrated technetium and rhenium complexes for the early diagnosis and

treatment of cancer. In 2012, moving to another research unit of CEA, I became more deeply involved in deuterium and tritium labelling of molecules and biomolecules (in particular peptides) using metal nanoparticles catalysed reactions and their applications to the study of biomolecules and drug-like molecules.

Can you describe the key goals of the Isotopic Labelling for Drug Innovation (ISOTOPICS) project?

As an innovative training network (ITN), ISOTOPICS aims to train 15 Early Stage Researchers (ESRs) who are working on the development of new chemical strategies for the isotopic labelling of drug candidates and biologics. All ESRs are preparing a PhD in associated universities when the partner's entity is not empowered to award the doctoral degree. ISOTOPICS includes a cutting-edge research programme developed in partner research units for the development of new reactions usable for the isotopic labelling of organic molecules (especially drugs), but also a first-class training programme that includes five schools, workshops and conference cycles given by recognised experts.

What do you find most interesting about this work and about research on drug discovery and development (DDD) in general?

First, the challenges are really exciting from a human point of view because by securing DDD, ISOTOPICS is expected to play a key

role in the development of new drugs, which will undoubtedly strongly impact on human health and wellbeing. Participating in the development of tomorrow's treatment is something really motivating. Moreover, the application of efficient isotopic labelling techniques to biologics (antibodies, siRNAs), the importance of which is growing in therapy, is also very exciting.

Can you discuss your research plan?

Our global research plan is relatively simple in its principle. ISOTOPICS is aimed at the development of straightforward, late-stage and efficacious labelling methods applicable with a high specificity and an unprecedented selectivity to drug molecules. Consequently, as stated in the proposal, ISOTOPICS is anticipated to address the most pressing questions in isotopic labelling for DDD and to meet the needs of pharmaceutical companies.

What do you think the future of research in this area looks like?

I foresee exciting new challenges and applications for isotopic labelling, in particular isotopically-labelled drugs for diagnosis and treatment of diseases. This urges the training of new generations of young talented chemists specialising in this field, and consequently, we hope the ISOTOPICS training structure will be perpetuated in a further project and through the building of a continuous training structure on a European-wide scale.



Enhancing European pharmaceutical innovation

ISOTOPICS combines researchers and industry in an innovative effort to de-risk drug development, create new tools for medicine and train first-class radiochemists with dual academic-industrial expertise

At present, not only is drug discovery and development time-consuming and expensive, it is also riskier than ever, with only one in 10 products that enter clinical trials reaching the market. This is referred to as the 'attrition' of drug candidates and links to poor efficacy and unexpected adverse effects detected in phase 2 clinical trials. New strategies are required to de-risk drug innovation and one international research project might just offer a solution.

Isotopic Labelling for Drug Innovation (ISOTOPICS) is a European research project involving five academic partners and three pharmaceutical companies spanning five European countries. It is funded by the European Commission and will run for four years. It is coordinated by the French Alternative Energies and Atomic Energy Commission (CEA, Institute of Biology and Technology at Saclay) and involves the French National Research Agency (CNRS, National Institute of Applied Sciences in Toulouse, France); the Department of Chemistry at the University of Oxford, UK; the Karolinska Institute PET Centre in Stockholm, Sweden; and the Cyclotron Research Centre of the University of Liège, Belgium. The pharmaceutical companies involved are UCB-BioPharma, Belgium; AstraZeneca, Sweden; and the Sanofi Group (Sanofi Aventis Deutschland GmbH, Germany and Sanofi-Recherche, France).

NEW LABELLING TECHNIQUES

The goal is to develop new methods for the chemical labelling of drug candidates, thereby streamlining drug innovation and decreasing drug attrition, which is needed given less than 10 per cent of druggable compounds currently reach the market. The aim is to provide industry and research bodies with new labelling techniques, which will be patented and published in high impact factor journals. Dr Christophe Dugave explains how the project arose: 'The ISOTOPICS project came about in 2014, following intensive discussions with my colleagues Dr Bernard Rousseau (tritium labelling), Dr Frédéric Taran (carbon-14 labelling) at CEA and Professor Véronique Gouverneur (fluorine-18 labelling) and Professor Ben Davis (chemistry of biologics) from the University of Oxford. As the project took shape, we associated Professor Christer Halldin (Carbon-11 labelling) at Karolinska Institute, Professor Bruno Chaudret (Nanoparticles for tritium labelling) from CNRS and Professor André Luxen (Fluorine-18 labelling) at University of Liège.' As Dugave explains: 'Everyone considered the development of new isotopic labelling strategies for drug candidates as a prerequisite to the de-risking and renewal of drug innovation.'

INVOLVING INDUSTRY

Next, the industrial partners – specifically, large pharmaceutical companies such as

UCB BioPharma (Dr Christophe Genicot), AstraZeneca (Dr Chad Elmore and Dr Magnus Schou) and Sanofi-Aventis (Dr Jens Atzrodt and Sébastien Roy) – came on board. 'After a first presentation of the proposal to the 2015 Horizon 2020 (H2020) projects call, we finally got the grant in 2016 with financial support of around 4 million euros for four years,' states Dugave.

Importantly, ISOTOPICS is also training 15 PhD students; equipping them to meet the needs of the industry by providing specialist knowledge and expertise in labelling chemistry with a dual academic and industrial culture. 'ISOTOPICS should train a new generation of young talented scientists specialising in isotopic labelling. All Early Stage Researchers (ESRs) will also perform at least two secondments in the academic and industrial sectors in partners' premises to be exposed to the industrial sector (for academic ESRs) and academic research (for industrial students),' explains Dugave. 'The emergence of new concepts and techniques on the one hand, and researchers with a dual academic/industrial experience on the other hand, should therefore meet the needs of industry, but should also foster the creation of start-ups and the development of small and medium-sized enterprises (SMEs) specialising in isotopic labelling, an activity that is more and more frequently subcontracted by the big companies.'

ENSURING EFFICACY

The project is extremely important given the issues facing DDD in terms of drug safety. It is hoped ISOTOPICS will assist with de-risking DDD by enabling more drug candidates to be evaluated during preclinical studies and phase 0 trials in order that the most efficacious and selective compounds can be selected, and the drug development process can therefore be secured. However, as Dugave emphasises: 'this implies the pharmaceutical companies are able to (radio) label much more drug candidates for dosing and in vivo imaging, but also for producing new deuterated drugs with higher metabolic resistance and better efficacy. ISOTOPICS doesn't just concern DDD, but is anticipated to help in the development of new carbon-11 and fluorine-18 labelled drugs usable for diagnostic purposes.'

The project has the potential to have an important impact, as Dugave highlights: 'If ISOTOPICS succeeds in securing DDD, it will help Europe to be the leader in this area and it is obvious this will permit the industries to invest in neglected research areas, such as diseases in Third World countries or orphan diseases,' he states. 'Moreover, by studying more compounds at the very beginning of preclinical trials, ISOTOPICS should help paradoxically to reduce animal experiments, which are strongly challenged.'

AN IMPRESSIVE START

Although the project is still in its infancy, the researchers have unearthed a number of initial results to date. First, the use of decorated ruthenium nanoparticles, which were synthesised by CNRS, have shown promise as catalysts deuterium and tritium labelling of a variety of chemicals in select drugs. 'The very specific and selective deuterium/hydrogen exchange through C-H activation allows using final drugs rather than derivatives and labelling precursors. Tuning the nanoparticles in terms of metal, size, poisoning and coating, as well as changing the reaction solvent, enables us to modulate the reactivity, specificity and selectivity of nanoparticles, which have proven to be more efficacious than existing homogeneous catalysts,' Dugave details. 'Moreover, use of a heterogeneous nanoparticle catalyst should avoid the metal contamination of products (often resulting from catalyst

leaching), which is a permanent concern for drug synthesis,' he extrapolates. 'It is noteworthy that such nanocatalysts are made of ruthenium, a metal which is by far less rare and expensive than the palladium and platinum used in many catalysts. Additionally, nanoparticles can be recovered and reused for the preparation of other batches of labelled products. All these advantages are of great interest for our industrial partners, particularly at Sanofi-Aventis, even if they carry out their own research to achieve similar goals.'

Furthermore, the carbon-14 labelling team has unearthed another result: 'This concerns the derivatisation of carbon-14 labelled carbon dioxide into the corresponding isocyanate, an important intermediate in the synthesis of many drugs, especially those containing a cyclic urea and carbamate chemical motif,' explains Dugave. 'Of course, the reaction process will be applied with carbon-11 in collaboration with our Swedish Partners at Karolinska and AstraZeneca.' Additional, similar results have been obtained in the field of fluorine-18 labelling by Oxford, the University of Liège and UCB-BioPharma.

ONGOING GOALS

Looking ahead, Dugave believes efforts should focus on theranostic tools (therapeutic agents usable for diagnostics) for personalised medicine. 'This should experience an unprecedented development in the next decade by using Positron Emission Tomography (PET)-emitters for real-time whole-body medical imaging,' he explains. 'Another challenging area related to the diversification of nanomedicines is the labelling of nanotherapeutics, which poses specific problems resulting from the size and complexity of such systems. Needs in the area of nanotherapeutics labelling are equal to the hopes nanomedicine arouse.'

With developments and progress already made despite being in its early stages, ISOTOPICS looks set to have a big impact on DDD and succeed in accelerating the discovery of new therapeutic solutions to existing and emerging diseases, and ultimately enhance European pharmaceutical innovation.

Project Insights

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Dr Christophe Dugave obtained his PhD in molecular pharmacology from the Pierre and Marie University, France. After a postdoc in chemistry at the University of Sherbrooke, Canada, he integrated the CEA. He is coordinating the ISOTOPICS project with the support of Dr Karen Hinsinger as a Project Manager.

