FLow chemistry for Isotopic eXchange

Project funding from the EU's Horizon 2020 Program

NEWSLETTER

FLIX Newsletter °1 - April 2021

We are delighted to present the first newsletter of the EU funded project - FLIX.
In the first issue of the newsletter, we want to introduce you to the main idea of the FLIX project as well as to present its first key results and the consortium

About The Project

FLIX is a radically new concept for the late-stage chemical isotopic labeling of high added-value molecules (drugs, biologics, smart materials) with stable isotopes (^{2}H, ^{13}C and ^{15}N). It utilizes the unique properties of new generations of catalysts, which specifically and selectively exchange predetermined atoms and chemical motifs of end-use organic compounds. The ultimate outcome of the project is to devise and build a modular and adaptable flow chemistry system for the straightforward and combinable isotopic labeling of complex chemicals and biologics.

The 'FLIX machinery' will use a combination of specialized reactor modules operating under continuous flow conditions, either in closed-loop or open systems for the on-line $^{1}H/^{2}H$, $^{12}C/^{13}C$, $^{14}N/^{15}N$ and methoxy group direct isotopic exchanges with an unprecedented efficacy and without any chemical alteration of the molecules.

The project's objectives are to:

1) Develop new generations of organometallic catalysts for isotopic exchange reactions;
2) Screen catalysts for the isotopic exchange on a relevant portfolio of organic molecules in batch and flow chemistries and assess catalyst robustness;
3) Devise and validate the 'combinable isotope labeling' concept;
4) Design and build an adaptable multi-module machinery for combinable chemical exchange labeling.

The project is expected to have a multi-billion Euro positive **impact on** all sectors using stable isotopes in particular:

1) Drug innovation, by accelerating preclinical studies, de-risking clinical trials and fostering the development of novel deuterated 'heavy drugs';
2) Design of new tracers for diagnostic imaging with improved biological properties;
3) Streamlining the production of multi-labeled complex molecules for NMR studies;
4) Development of novel isotopically-enriched materials.

Advisory Board Committee

The FLIX Management Structure includes an Advisory Board formed by prominent scientists who have expertise in fields related to the project.

The role of this board is to provide advice to the management, implementation and strategy of the project as well as ethics issues that may arise. It is based on i) reading of annual reports, ii) attending the first Scientific Meeting and the Mid-term Meeting, iii) participating in teleconferences or Skype meetings on demand of the Central Management Team, Supervisory Board or individual Consortium Members to address a particular issue and, if available, attending the regular Consortium Webinars.

Advisory Board members have expertise related to the project:

- Pr. Jacques Lebreton (University of Nantes / Atlanchim)
- Pr. Thomas Wirth (Cardiff University)
- Pr. Ruben Martin (ICIQ, Barcelona University)

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FLIX Partners

FLIX representatives at the kick-off meeting

CEA - French Alternative and Atomic Energy Commission, France

CEA is a French public government-funded research organization in the areas of energy, defense and security, information technologies and health technologies. The CEA maintains a cross-disciplinary culture of engineers and researchers, building on the synergies between fundamental and technological research. As a part of the Fundamental Research Division of CEA, the Molecular Labeling and Bio-organic Chemistry Unit (SCBM) regroups more than 50 people. It is one of the world leaders in the field of isotopic (radio)labeling in particular for deuterium /tritium and carbon-13/carbon-14 labeling, organic synthesis and chemical biology. At CEA, SCBM has a long-term and extensive experience in isotopic labeling of chemicals (especially drugs) and biologics (nucleotides, peptides), in organic synthesis as well as in purification and characterization of chemicals.

INSA TOULOUSE - National Institute of Applied Sciences of Toulouse (INSAT), France

INSA Toulouse is an international, pluridisciplinary French engineering school. Its courses are supported by the activity of 8 leading-edge research laboratories, backed by large industrial groups. INSAT is also strongly involved in the research policy of the "Université of Toulouse Midi-Pyrénées" and closely collaborates with partner engineering universities within the INSA Group.

The Laboratory of Physic and Chemistry of Nano-objects (LPCNO – UMR5215) is a Joint research Unit operated together by CNRS, INSA Toulouse and Université Paul Sabatier Toulouse III.

The Laboratory of Biological Systems and Processes Engineering (LISBP) is one of the leading industrial biotechnology laboratory in France. LISBP is specialized in biotechnology, systems biology and chemical engineering and covers a wide spectrum of complementary and multi-disciplinary research activities to create a continuum "from gene to process", essential for successful biotechnological innovation.

INSAT has a long experience on one side on the synthesis and reactivity of nanocatalysts and mechanistic studies and on the other side on the determination of complex structures of biomolecules by NMR spectroscopy as well as reactivity studies in solution using various NMR tools including exchange spectroscopy and chemical shift perturbation (CSP).

LIKAT - Leibniz Institute of Catalysis, Germany

The Leibniz Institute for Catalysis is one of the largest publicly-funded research institutes in Europe in the area of applied catalysis. The Department of Applied Homogeneous Catalysis investigates important aspects of homogeneous catalysis, especially of transition metal-catalysts. Fundamental strategic aims of their research are the development of new, environmentally benign catalysts and synthetic protocols as well as their application in industry. The transfer of results from model studies and mechanistic investigations to specific chemical products or processes is a particularly important aspect here.

LIKAT is specialized in the design and development of new (metallic) catalysts (especially homogeneous and nanoparticle catalysts), new catalytic reactions and their application to a broad range of research fields with an impressive track of related publications. The laboratory has an extensive experience in P- and N-ligands synthesis, organometallic chemistry (Pd, Rh, Ru, Fe, Cu, etc.), the development of processes for bulk chemicals, the synthesis of biologically active agents, oxidation processes and high pressure chemistry.

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Aarhus University (AU), Denmark

AU has 39,000 students, with 8,000 employees. In 2020 the university was number 120 at the Leiden Ranking, and number 106 on the Times Higher Education World University Ranking (2021). iNANO, Interdisciplinary Nanoscience Center (www.inano.au.dk), was established in 2002 and at present is a major research and education center based at Aarhus University hosting 60 senior scientists, ~100 PostDocs and ~100 PhD students. The center combines expertise and faculty from Physics, Chemistry, Molecular Biology and Medicine to carry out world-class interdisciplinary research in Nanoscience and Nanotechnology. The center gives access to a broad range of infrastructure, tools and expertise including clean-room facilities. With a 5-year undergraduate nanotechnology programme and nanoscience graduate programme (www.inanoschool.au.dk), the center provides a full educational environment. In addition to the large base of basic research, the center has a large number of ongoing industrial projects and partnerships.

University of Amsterdam (UvA), The Netherlands

The Noel group is embedded in the Van 't Hoff Institute for Molecular Sciences (HIMS). The mission of HIMS is to push the boundaries of chemistry by performing internationally recognized scientific research that is curiosity driven as well as application driven. HIMS strives at utilization and expansion of its knowledge and expertise by engaging in collaborative research efforts that address challenges in society and industry. The Sustainable Chemistry cluster in Amsterdam, which includes the flow chemistry research group of Prof Noel, provides an excellent research environment for the current projects. Sustainable Chemistry is a Research Priority Area of the UvA, and its quality and value are officially recognized by the University Board.

ComInnex, Hungary

ComInnex is a chemistry service organization with strong interest and background in the development of chemical technologies. ComInnex's staff has served its partners for over 12 years synthesizing novel or known marker compounds or other organic molecules. The current infrastructure enables ComInnex's scientists to prepare final targets from mg to 50 g scale in purity up to 98%.

ComInnex's chemists paired with ComInnex's state-of-the-art flow reactors provide a second-to-none combination of know-how and technology for quality custom synthesis of commercially non-available compounds. With capabilities of -70 to +1000°C and from vacuum to 400 bar, their team are technologically equipped to handle even the most challenging of chemistries professionally and safely.

European Dimension of the FLIX Consortium

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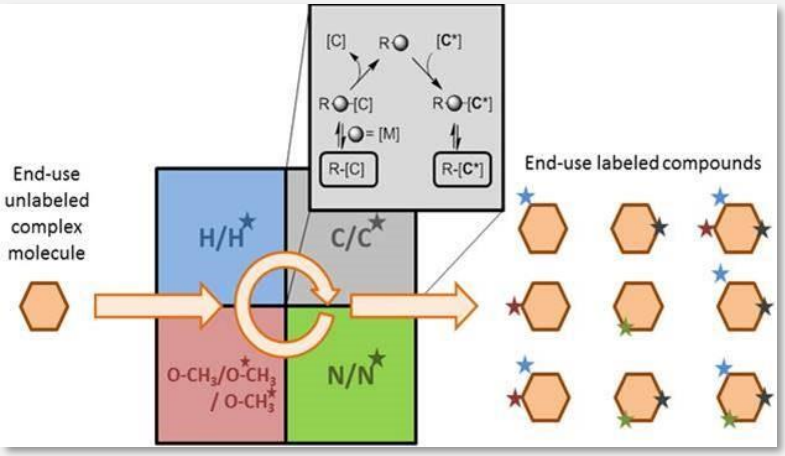
Key Results

The project kicked off in the beginning of January 2020. According to the research plan, a special effort was done during the first year of implementation for devising new isotopic routes utilizing the late-stage labeling paradigm (WP2), and for constructing a modular and adaptable flow-chemistry machine (WP3) capable of labeling complex molecules with an unprecedented specificity, selectivity and efficiency.

The consortium focused its research potential for discovering new catalysts for $^{1}H/^{2}H$ and $^{12}C/^{13}C$ isotopic exchange (respectively called HIE and CIE), through either direct metal-catalyzed isotopic exchange process or indirect pathways, in order to perform a late-stage or even last-stage H and C-labeling of end-use molecules. In a parallel approach, smart screening and analytical strategies were developed in order to identify and characterize the best catalysts usable in flow chemistry. Therefore, a series of free and supported metal catalysts capable of performing HIE of specific C-H moieties in complex molecules (drug-like compounds) and biological derivatives (amino acids, fatty acids etc.) were selected and added to the portfolio of existing flow chemistry catalysts (CEA, INSA, LIKAT, UVa).



A new approach using the transient directing group exchange was developed in order to smartly orientate the HIE catalyst selectivity (LIKAT). The consortium was also interested in the use of new catalyst supports (in particular abundant and sustainable supports such as carbon and cellulose) (CEA, LIKAT). A new photocatalyzed CIE reaction was also devised and its scope was exemplified on more than 40 molecules (CEA). In a parallel approach, the depropionylation /reproprionylation concept permitted the efficient carbon labeling of propionyl amine compounds (AU). Catalysts accelerating the previously developed metal-catalyzed CIE were also optimized using a new stress and compatibility test (CEA). On the other hand, innovative isotopic sources alternative to $^{2}H_2$ and CO_2 were also proposed for hydrogen (CEA, LIKAT, AU) and carbon isotopic exchange (CEA, AU). The construction of catalytic modules was also initiated for HIE and tested towards a series of deuterium labeling reactions benefiting from the flow chemistry advantages such as local high catalyst concentration and possible repeated reaction in closed-loop with a controlled recirculation of substrates (TU/e then UvA, COMINNEX and CEA). In the CIE field of research, the continuous flow labeling of ureas using the catalysed Staudinger/Aza-Wittig reaction was successfully explored.

In summary, despite the Covid-19 pandemic, resulting in lockdowns and work limitations which strongly impacted the experimental progress in most of the participating countries, the project is implemented in a satisfactory way with many innovations in the fields of HIE and CIE. The consortium now benefits from an impressive portfolio of available specific, selective and efficacious catalysts usable for flow chemistry HIE and CIE. N-isotopic exchange and O-methyl group isotopic exchange have to be now tackled (WP2) and modules for the newly-developed CIE reaction will be developed soon (WP3). The second year of project implementation will also see the initiation of WP4 devoted to the application of our strategy, in particular for the labeling of complex molecules (drugs, small biologics, smart material components) and the proof-of-concept of multiple combined isotope incorporation. The general architecture of the labeling machine will be also designed taking advantage of experience acquired in WP2 and the first feed-back from WP4.

The Innovation Radar

The Innovation Radar (IR) is a European Commission initiative to identify high potential innovations and innovators in EU-funded research and innovation projects. The IR goal is to allow every citizen, public official, professional and business person to discover the outputs of EU innovation funding and give them a chance to seek out innovators who could help to launch and develop newly created companies exploiting the project outputs.

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INNOVATION 1

Autonomous machine for H/C/N specific and combined isotopic exchanges on organic molecules

The aim is to is to build a modular and adaptable flow chemistry system for the straightforward and combinable isotopic labeling of complex chemicals. This 'FLIX machinery' will use a combination of exchangeable specialized reactor modules operating under continuous flow conditions for the on-line $^{1}H/^{2}H$, $^{12}C/^{13}C$, $^{14}N/^{15}N$ and methoxy group direct isotope exchanges with an unprecedented efficacy (in terms of specificity, selectivity, reproducible and scalable yields) and without any chemical alteration of the molecules. The labeling machine is expected to propose a reliable, adaptable and easy-to-use automated system for the isotopic labelling of complex and high-value added molecules such as drug candidates, heavy (deuterated) drugs, diagnostic agents, complex biolocal molecules and smart materials that are of paramount importance for the academic stakeholders operating in the medicinal chemistry sector, pharmaceutical industry, organic materials etc.

INNOVATION 2

Flow chemistry process for reactions that are out of reach using batch chemistry technology

The labelling of organics with stable and radioactive isotopes (such as ^{3}H and ^{14}C) is of paramount importance in numerous fields of application as drugs (drug preclinical studies, clinical Phase 0 trials, deuterated drugs), diagnostics (MRI hyperpolarized tracers, stabilized PET tracers, development of new $^{11}C/^{13}N$-labeled tracers for PET diagnostic imaging using straightforward microfluidic techniques in modular reactors), biology, toxicology and materials (smart materials, organic material encryption) for instance.

This flow chemistry process could impact industry fields using those complex labelled organic molecules. Industrials could therefore be interested by the innovation developed: the pharmaceutical industry sector, diagnostic imaging by MRI or mass spectrometry specialized companies, preclinical/clinical studies-specialized companies, smart-material research.

FLIX PUBLICATIONS

- Sara Kopf, Helfried Neumann, Matthias Beller (2021). ***Manganese-catalyzed selective C–H activation and deuteration by means of a catalytic transient directing group strategy***, Chem. Commun., 2021, 57, 1137 https://pubs.rsc.org/en/content/articlepdf/2021/cc/d0cc07675a
- Victor Babin, Alex Talbot, Alexandre Labiche, Gianluca Destro, Antonio Del Vecchio, Charles S. Elmore, Frederic Taran, Antoine Sallustrau, Davide Audisio (2021). ***A Photochemical Strategy for Carbon Isotope Exchange with CO2***, ACS Catalysis 2021, 11, 2968–2976 https://pubs.acs.org/doi/full/10.1021/acscatal.0c05344#
- Marco Lepron, Marion Daniel-Bertrand, Gabriel Mencia, Bruno Chaudret, Sophie Feuillastre, and Grégory Pieters (2021). ***Nanocatalyzed Hydrogen Isotope Exchange***, Accounts of Chemical Research https://pubs.acs.org/doi/full/10.1021/acs.accounts.0c00721
- Minghao Feng, Joao De Oliveira, Antoine Sallustrau, Gianluca Destro, Pierre Thuéry, Sebastien Roy, Thibault Cantat, Charles S. Elmore, Jorg Blankenstein, Frédéric Taran, and Davide Audisio (2021). ***Direct Carbon Isotope Exchange of Pharmaceuticals via Reversible Decyanation***, Journal of the American Chemical Society https://pubs.acs.org/doi/pdf/10.1021/jacs.1c01923

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