FLIX

FLow chemistry for Isotopic eXchange

FLOW CHEMISTRY FOR ISOTOPIC EXCHANGE

THE FLIX CONCEPT

Isotopes are variants of the same chemical element having the same number of protons but a different number of neutrons (and atomic weight or molecular mass). Uncommon isotopes can be substituted for standard ones in molecules of interest. The equal protons (and electrons) make them almost the same chemically. Then, molecules containing the substituted isotopes can be detected with analytical methods like mass spectroscopy and nuclear magnetic resonance (NMR).

FLIX is a radically new concept for the creation of isotope-labelled molecules using a late-stage isotope labelling approach. High added-value molecules (drugs, biologics, smart materials) with stable isotopes will be obtained in an easier, faster, and more effective way, using new generations of catalysts along with flow chemistry for the selective exchange of predetermined atoms and chemical motifs of end-use organic compounds. Success will have tremendous impact on fields from synthetic chemistry to biomedical diagnostics to materials research.

AMBITIOUS SPECIFIC OBJECTIVES

1) Develop new generations of organometallic catalysts for isotope exchange reactions;

2) Screen catalysts for the isotope 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;

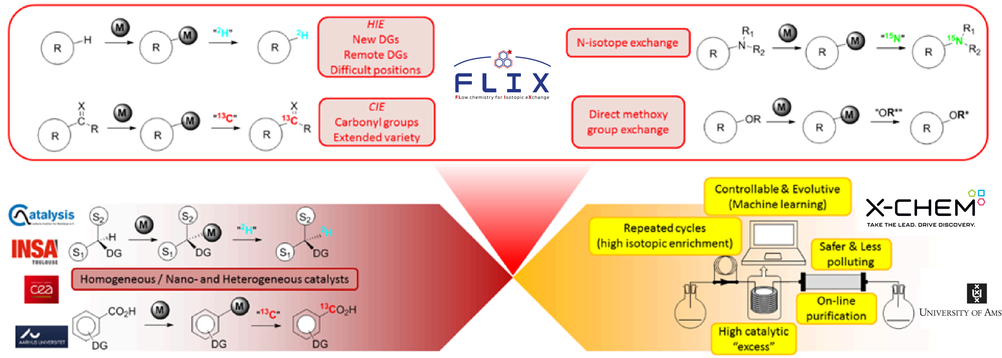
4) Design and build an adaptable multi-module machinery for combinable chemical exchange labeling.

3.5 M€ **2020/2024** **7 partners**

TECHNOLOGICAL APPROACH

FLIX is is expected to revolutionize the isotope labelling approach with stable isotopes using a flow chemistry system which should help finding new reactions that are out of reach using batch chemistry techniques. 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 isotope labeling of complex chemicals and biologics.

The 'FLIX machinery' uses a combination of specialized reactor modules operating under continuous flow conditions, either in closed-loop or open systems for the on-line H/D, C-12/C-13, N-14/N-15 isotope exchanges with an unprecedented efficacy and without any chemical alteration of the molecules.



WORK DISTRIBUTION

CEA :
- Coordination & Management.
- Development of innovative isotope labeling techniques and catalysts in batch and flow chemistries.
- Leading the design and synthesis of new organometallic catalysts for carbon isotope exchanges ($^{12}C/^{13}C$).

INSA TOULOUSE :
- Focusing on nano- and heterogeneous catalysts for the $^{1}H/^{2}H$ isotope exchange.
- Working on the multi-labelling of proteins with $^{15}N/^{13}C/^{2}H$ for biomolecular NMR spectroscopy.

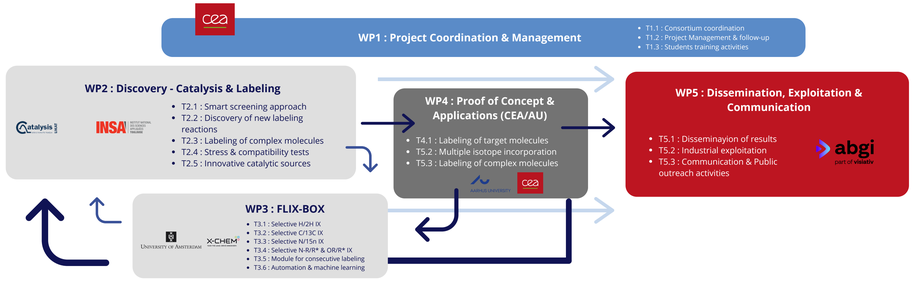
LIKAT :
- Research on homogeneous and heterogeneous catalysts.
- Evaluating new synthetic methods for isotope labeling.AU (Aarhus University)
- Development of innovative techniques for the $^{1}H/^{2}H$ and $^{12}C/^{13}C$ isotope exchange.
- Design and utilization of safer isotopic sources.

UvA (University of Amsterdam) :
- Expertise in flow chemistry for designing the FLIX-BOX.
- Development of machinery and automation, integrating machine learning.
- Development of innovative techniques for the $^{12}C/^{13}C$ isotope exchange.

X-CHEM :
- Specific machinery technology for the FLIX project.
- Software development for automation and optimization of synthesis processes.
- Development of innovative techniques for the $^{12}C/^{13}C$ isotope exchange.

AU :
- Development of isotopic labeling techniques for $^{12}C/^{13}C$.
- Design and utilization of safer isotopic sources.

ABGi :
- Management of communication and dissemination of project results.
- Responsible for the exploitation management of developed innovations.



IMPACTS

The project is expected to have an impact on all sectors using stable isotopes in particular:
- **Revolutionizes isotope labeling** with stable isotopes, expanding the scope of achievable chemical reactions and laying foundational work for radiolabeling with ^{12}H and ^{14}C for drug trials.
- **Systematically uses stable isotopes** in drug development, integrating isotope labeling with mass spectrometry imaging to significantly reduce drug attrition rates.
- **Develops 'heavy drugs'** and deuterated PET imaging agents with enhanced biological stabilities, improving therapeutic efficacy and safety.
- **Creates ^{2}H, ^{13}C, ^{15}N hyperpolarized organic tracers for MRI,** providing new tools for medical diagnostics and advancing biological research.
- **Reduces reliance on radio-isotopes**, addressing safety, environmental, and cost concerns while promoting environmentally friendly chemical processes through continuous flow systems.
- **Facilitates advanced toxicology studies** and the development of deuterated smart materials for anti-counterfeiting, improving safety assessments for food-related chemicals and enhancing product security.
- **Enables the development of new $^{11}C/^{13}N$-labeled tracers** for PET diagnostic imaging through fast, adaptable microfluidic techniques.
- **Contributes to the competitiveness of the European pharmaceutical sector** and impacts multi-billion dollar markets across drugs, diagnostics, biology, and materials.
- **Enhances research and innovation capacity across Europe,** promoting gender balance and training the next generation of scientists, thus improving employability and fostering entrepreneurship through academic and industrial collaboration.

RESULTS

- Development and screening of new catalysts compatible with flow chemistry isotope labelling of organic molecules such as engineered metal nanoparticles or heterogeneous catalysts, homogeneous and immobilized transition metal catalysts;
- Design of new catalytic reactions for deuterium/hydrogen isotope exchange, carbon-13/carbon-12 isotope exchange and nitrogen-15/nitrogen-14 isotope exchange, validation on multifunctional molecules combined with stress and compatibility tests;
- Development of innovative isotopic sources;
- Design, building and development of FLIX-BOX (catalytic modules) for hydrogen and carbon IE that will operationalize flow chemistry innovations, enabling scalable and precise isotope labeling
- Construction of a preliminary FLIX-MACHINE system with associated automation system software;
- Application to the late-stage isotope labeling of complex real-life molecules (mainly drugs) through direct HIE and CIE in order to make the proof of concept of the FLIX paradigm in both batch and flow chemistries conditions.
- Dissemination of the project results led to the publication of numerous publications in peer-review journals.
- Communication actions has been done with the publication of 3 newsletters and communicating results using the Project's website and social media.

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