FLIX Project Press Release No: 1

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Text:

FLIX ***(*FLow chemistry for Isotopic eXchange*)*** is the European project supported by the European Commission under the Innovation Action Theme of the HORIZON2020 Program for Research and Innovation with funding of € 3 469 740.

Isotopic labeling permits the reliable tracking and identification of compounds in complex media since it does not alter the chemical integrity of molecules. For this reason Isotopic labeling is of paramount importance in large panel of scientific and industrial activities such as chemistry (mechanistic studies) biology (proteomic & metabolomics studies), medicine (including drug discovery development, 'heavy drugs', diagnostic imaging agents with improved metabolic stabilities and toxicology studies) and development of new organic materials (OLED emitters, anti-counterfeiting encryption) which have huge human, economic and societal impacts at a multi-billion dollar scale.

Isotope labeling has been intensively investigated during the past century and therefore, numerous labeling methods have been developed to date, most of them relying on the step-by-step transformation of precursors. However these strategies are based on time-consuming and waste-generating multi-step synthesis. For one decade, the metal-catalyzed late-stage isotopic substitution on end-use molecules or final precursors has been thoroughly investigated however, it is more challenging due to technical difficulties.

FLIX is a radically new concept for the ultimate-stage chemical isotopic labeling of high added-value molecules (drugs, biologics, smart materials) with stable isotopes. 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 and methoxy group direct isotopic exchanges with an unprecedented efficacy and without any chemical alteration of the molecules.

The project is expected to have a multi-billion Euro positive impact on all sectors using stable isotopes in particular: drug innovation, by accelerating preclinical studies, de-risking clinical trials and fostering the development of novel deuterated 'heavy drugs'; design of new tracers for diagnostic imaging with improved biological properties; streamlining the production of multi-labeled complex molecules for NMR studies and the development of novel isotopically enriched materials.

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As a new paradigm, **FLIX** combines synergistically the recent progresses in catalyst engineering, automated flow chemistry developments and machine learning systems to develop a revolutionary approach of smart isotopic labeling of complex organic molecules using final compounds instead of precursors or derivatives.

The **FLIX** consortium is made of seven high-profile European partners selected for their acknowledged excellence as well as both their complementarity and trans-nationality in order to provide the necessary skills, expertise, and state-of-the-art background required to ensure the success of the **FLIX** project as well as the sustainability of the expected results.

We are currently in the 42nd month of the project and despite delays related to the Covid pandemics and resulting lockdowns, the project is progressing as originally planned.

We designed, develop new catalysts able to accelerate the isotopic exchange reactions while using various and safe isotopic sources (such as deuterated water) under flow chemistry conditions. The robustness of the catalyst was screened. A particular effort was done for the development of catalysts made of cheap and abundant metals (instead of rare earths, such as platinum, palladium etc.) and recyclable supports (such as starch) in order to ensure sustainability. The conception of FLIX-Boxes was also undertaken in order to exploit the properties of catalysts in the best experimental conditions. Until now, the $^{1}H/^{2}H$ and $^{12}C/^{13}C$ exchange have been successfully studied however the $^{14}N/^{15}N$ exchange and O-methyl exchange for deuterium and carbon-13 labeling are actively investigated. All these catalyst are able to label specifically and selectively complex molecules at the late-stage of their synthesis or even to employ end-use molecules (last-stage labeling). These methods have sky-rocketed the potential of isotopic labeling since it considerably minimize the number of steps, synthesis times, chemical wastes and production costs.

The FLIX-Machine is under construction. It is composed of interchangeable catalytic modules (FLIX-Boxes and a series of continuous flow chemistry systems that permit either open-loop or closed-loop reactions. This latter system enable to perform several catalytic cycles in order to increase the yields of isotopic labeling but also to detect new but low-yielding reactions that have to be optimized. Therefore, the FLIX-Machine is expected not only to ameliorate already known reactions but also to discover totally new processes that would be ignored in non-continuous flow conditions. This is mainly due to the repeated reactions achieved in closed-loop but also to the very high local catalyst/substrate ratio which strongly accelerates difficult chemical reactions.

Therefore, the complete FLIX machinery is expected to streamline and accelerate the labeling processes of complex organic molecules such as drug candidates. The system is also boosted by inclusion of a machine-learning system based on artificial intelligence capable of orientating synthetic choices, to decide of preferred synthetic routes and to optimize the chemical reactions rationally, based on previous

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knowledge but also on reactions previously performed by the system. It is clear that the FLIX concept should benefit to all the scientific community in particular researchers working on structural biology (i.e. protein NMR) but also pharmaceutical companies since stable isotopes are widely used for the drug discovery and development. The FLIX-Machine should also be used as basis for the design of a miniaturized version working in continuous microfluidic chemistry with increased security for labeling of organic molecules with radioactive isotopes such as tritium and carbon-14, but also very-short period emitters such as carbon-11 and fluorine-18 currently used for medical imaging by positron emission tomography (PET).

The consortium is balanced in terms of partner's profiles from 5 countries (France, German, Denmark, Netherlands, Hungary), with:

- Five world-class technical research centres (CEA, INSA, LIKAT, AU, TUE) offering proven cutting-edge technical and scientific background, as well as capabilities and ability to disseminate through high-ranked scientific journals and conferences.

- Two SME (Absiskey, X-Chem) with significant state-of-the-art background in the field, experience in ambitious European R&D projects, demonstrated dissemination and exploitation capabilities, a strong product orientation, as well as access to targeted markets where they have leading positions

The project implementation has been planned for 54 months.

FLIX project was officially launched on 01/01/2020

Links:

Visit the FLIX Project website at: https://flix-h2020.eu/

For more information, contact:

Dr. Sophie Feuillastre

Email: sophie.feuillastre@cea.fr

or

Dr. Christophe Dugave

Email: christophe.dugave@cea.fr

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