Laboratoire d'excellence SynOrg

Des molécules pour le vivant

JOURNÉE DU LABEX SYNORG

PROGRAMME

jeudi 30 septembre 2021

Université d'Orléans
Amphi n°1, UFR STAPS
Campus de la source

www.labex-synorg.fr

PROGRAMME

- **9h - 9h45**
  Accueil des participants à l'Amphi 1 des STAPS) / Vérification du pass sanitaire

- **9h45 - 10h15**
  Bilan du LabEx SynOrg / Mot d'accueil
  (AC Gaumont, P Jubault, S Routier)

- **10h15 - 11h**
  Conférence #1 *O Baudoin* - (modérateur : *S. Routier*)

- **11h - 12h :** (modérateur : *F. Suzenet*)
  11h Communication #1. *J. Decaens*
  11h15 Communication #2. *S. Kassamba*
  11h30 Communication #3. *Q. Ibert*
  11h45 Communication #4. *AG. Diallo*

- **12h00 - 13h30** Repas *(salle 111 des STAPS)*

- **13h30 - 14h15** Conférence #2 *G. Evano* (modérateur : *I. Gillaizeau*)

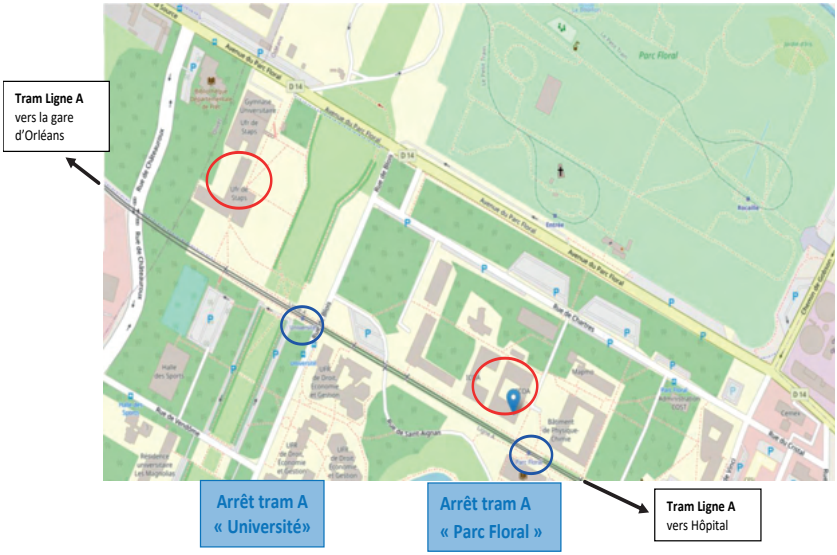
- **14h15 - 15h00**
  14h15 Communication #5. *P. Bonnet*
  14h30 Communication #6. *S. Vertueux*
  14h45 Communication #7. *A. Cador*

- **15h00 - 15h30** Pause Café

- **15h30 - 16h15** (modérateur : *P. Jubault*)
  15h30 Communications #8. *V. Flon*
  15h45 Communication #9. *D. Bretagne*
  16h00 Communication #10. *T. Brisker*

- **16h15 - 16h45**
  Mot de fin et clôture de la journée.

Venir à l'ICOA et à l'amphi n°1 de l'UFR STAPS (All. Du Château, 45100 Orléans)



- **Venir en train :** Vous pouvez arriver en gare d'Orléans ou des Aubrais, ensuite prenez le tram ligne A (L'arrêt du tramway se trouve à la sortie des gares) et descendez à l'arrêt ***Université pour aller à l'amphi 1 des SATPS*** (10 min à pied de l'ICOA). L'ICOA est à l'arrêt Parc Floral (plan du campus universitaire d'Orléans).

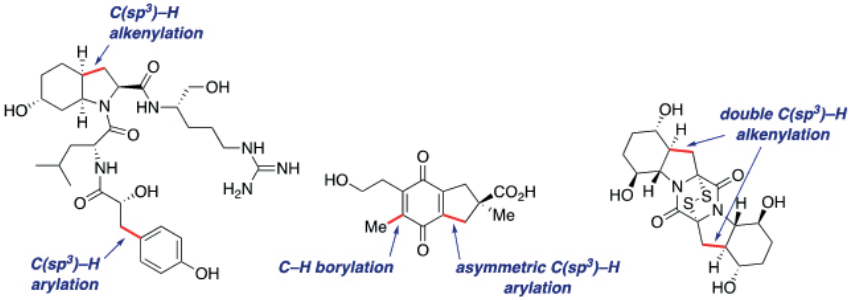
- **Venir en voiture :** Sortez de l'A71 à Orléans-sud (sortie 2) en direction d'Olivet et d'Orléans la Source. Après le péage, allez tout droit, direction Orléans la Source. Vous traverserez une ZAC et deux feux tricolores. Au deuxième feu tournez à gauche vous arrivez sur le campus, à la hauteur de l'IUT. Ensuite tournez à la première rue à droite (rue d'Issoudun) puis à la première rue à gauche (rue de Blois), puis au bout de la rue à droite (rue de Chartres). Lorsque vous arrivez devant le bâtiment d'enseignement général (Bâtiment vert sur votre droite) garez-vous sur les parkings de gauche. L'ICOA est juste derrière le bâtiment d'enseignement général.

Constructing Small Rings by Palladium(0)-Catalyzed C(sp3)-H Activation

Olivier BAUDOIN
University of Basel, Department of Chemistry, St. Johanns-Ring 19, CH-4056 Basel, Switzerland, olivier.baudoin@unibas.ch

Research efforts from our group in the past decade have focused on the construction of carbo- and heterocycles via palladium(0)-catalyzed intramolecular C(sp3)-H activation from a diversity of sp2 electrophiles.[1]

This method was integrated into a multiple C-H functionalization strategy[2] to streamline the access to complex natural products.[3] This lecture will present some of the most recent aspects of this chemistry.



[1] O. Baudoin, Acc. Chem. Res. 2017, 50, 1114.
[2] O. Baudoin, Angew. Chem. Int. Ed. 2020, 59, 17798.
[3] a) D. Dailler, G. Danoun, O. Baudoin, Angew. Chem. Int. Ed. 2015, 54, 4919; b) R. Melot, M. V. Craveiro, T. Bürgi, O. Baudoin, Org. Lett. 2019, 21, 812; c) P. Thesmar, O. Baudoin, J. Am. Chem. Soc. 2019, 141, 15779.

Recent Advances in the Chemistry of Ynamides

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Organic synthesis clearly is today a central science with deep implications in various domains such as biology, medicine or material science. Considering the extent of chemical methodology's contributions to other disciplines, there is a high and growing demand for efficient procedures to assemble complex molecules or pharmaceuticals from simple building blocks. This drive for shorter and more efficient synthetic procedures, as well as the quest for molecular diversity, has fueled the development of new reactions, and catalysts that efficiently contributed to the selective syntheses of ever larger and more complex systems with increased efficiency. In addition to the design of these new processes, novel ways to assemble molecules and the development of new building blocks are also important drivers for organic synthesis.
Nitrogen-substituted alkynes, and especially "ynamides", clearly fall into this category: the chemistry of these compounds, which display an exceptional reactivity, has been extensively investigated recently and they have clearly emerged as remarkably useful and versatile building blocks enabling the design of unique transformations.

We have been involved for almost fifteen years in the development of various synthetic strategies, mostly based on copper catalysis, for the synthesis of a broad variety of ynamides as well as in the study of their reactivity and in the design of new chemical transformations from these building blocks, which will be highlighted in this lecture with selected examples.

Enantioselective synthesis of functionalized cyclopropanes with fluorinated moieties.

Jonathan DECAENS, ***Philippe JUBAULT.***
COBRA UMR 6014

Fluorine atom have unique properties, it is the smallest atom after hydrogen and the most electronegative atom. These properties lead to decrease the pKa of vicinal functions and a variation of the molecule's lipophilicity. Around 25% of pharmaceutical molecules and 40% of agrochemical molecules approved by the FDA contain at least one fluorine atom. Cyclopropane is the smallest cycloalkane, constituted with only three carbons. The introduction of cyclopropyl moieties in a biomolecule influences its physico-chemical and its pharmaco-kinetic properties.

Therefore, the combination between cyclopropane and fluorine atom is very interesting because the introduction of a fluorocyclopropane in a molecule allows the modification of several parameters of this molecule.

Since few years, our research team is interested in the synthesis of fluorinated cyclopropanes. Herein, we will present the enantioselective synthesis of new fluorinated cyclopropanes from di-acceptors diazo compounds by rhodium catalysis.

Acces to substituted Germoles by zinc mediated Intramolecular Hydrogermylation

Seydou KASSAMBA, ***Muriel DURANDETTI.***
COBRA UMR 6014

Carbon, silicon and germanium atoms have structural similarities (valence and geometry), which are at the origin of an isostery between them. The presence of silicon or germanium atom are known to increase the lipophilicity, the biological, photophysical and electronic properties of silylated or germylated compounds compared to their carbon analogs. The synthetic chemistry of organogermanium compounds is not widely developed and this goes back to the fact that organosilicon compounds and its unexpected properties are not entirely determined. Here we present germoles which are five-membered heterocyclic derivatives of cyclopentadiene bearing a germanium atom and diene moiety. As is known, germoles can be obtained through C—Ge bond-forming processes which requires transition-metal catalyst such palladium,1 ruthenium,2 rhodium3 which are turn based on Ge—H, Ge—C(sp3) or Ge—H/C—H bonds activation. Now, we present new methodology to access to germoles compounds via intramolecular hydrogermylation based on germanium-hydrogen bond (Ge—H) activation (scheme 1) using diethyl zinc. An attractive feature of this approach is that a wide range of substituted germoles C could be accessed upon functionalization of the vinylzinc intermediates B arising from cyclisation of A.

R = Me, Et, *n*Pr, *t*Bu, TMS, Ph

[1] O. Baudoin, Acc. Chem. Res. 2017, 50, 1114.

[2] O. Baudoin, Angew. Chem. Int. Ed. 2020, 59, 17798.

[3] a) D. Dailler, G. Danoun, O. Baudoin, Angew. Chem. Int. Ed. 2015, 54, 4919; b) R. Melot, M. V. Craveiro, T. Bürgi, O. Baudoin, Org. Lett. 2019, 21, 812; c) P. Thesmar, O. Baudoin, J. Am. Chem. Soc. 2019, 141, 15779.

Use of the PIDA/NH3 couple in organic synthesis: towards the synthesis of primary ureas and diazirines

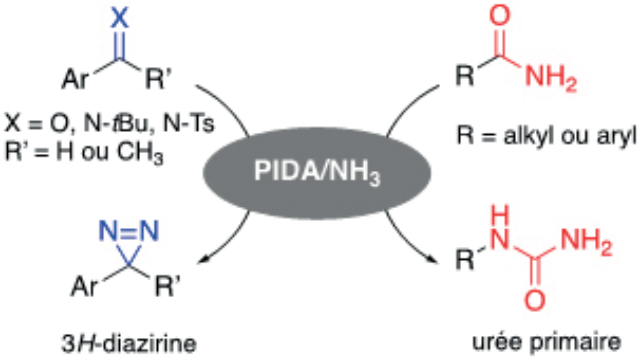
Quentin IBERT, ***Vincent REBOUL.***

LCMT

La combinaison de l'ammoniac (NH3) avec un réactif à iode hypervalent, le PIDA (Phenyl Iodine Diacetate), conduit à des espèces électrophiles azotées permettant des réactions d'amination. Ce couple a surtout été utilisé sur des composé soufrés afin de former des fonctions possédant une double liaison S=N. Plus récemment, nous avons mis au point une nouvelle application avec la synthèse de 3H-diazirines, en un seul pot, à partir d'acides aminés.

Ce type d'hétérocycle ayant de nombreuses applications en biologie (Photoaffinity Labelling) et hyperpolarisation (lors de l'emploi de 15N2-diazirines), nous avons voulu développer une nouvelle méthode de synthèse à partir de dérivés carbonylés (aldéhydes, cétones et imines), permettant l'accès à des diazirines plus variées, comme les diazirines aromatiques. Au cours de ces recherches, nous avons également pu montrer la possibilité de transformer une fonction amide en fonction urée primaire, toujours en utilisant ce couple.

L'optimisation des conditions réactionnelles de ces deux nouvelles réactions ainsi que leurs mécanismes de formation seront présentées et discutées.

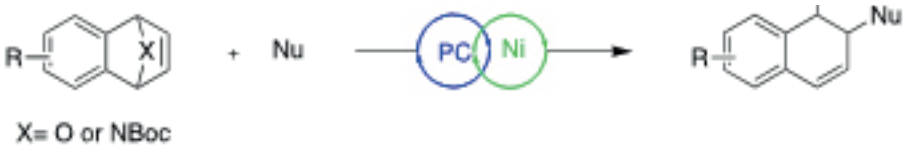


Ring opening reactions of oxabicycles by merging photoredox and nickel catalysis

Abdoul-Gadiry DIALLO, ***Jean-Luc RENAUD.***

LCMT

Over the last few decades, the need for sustainable and environmentally friendly processes has led researcher to an increasing interest in photoredox chemistry and new processes appear very frequently in the literature.1 There is also a continuing need for designing new reactions with absolute control of the regio and enantioselectivity. One approach that has attracted attention is to utilize desymmetrization reactions of meso compounds since many stereocenters can be established rapidly and efficiently in one step.2 The oxabenzonorbornadienes 1a, can be cited as a relevant example. Several metal-catalyzed ring-opening reactions of such substrates have been developed with high yields and high enantiomeric excesses using various nucleophiles, such as amines, alcohols, boronic acids or organometallic reagents.3 The application of visible-light-induced photoredox catalysis to the design and development of a variety of chemical transformations has gained an increasing attention over the past decades. More importantly, the combination of photoredox and organometallic catalysis helps designing numerous transformations which were impossible or not easily accessed thermally under remarkably mild conditions. As the ring opened products are also useful building blocks in the synthesis of several biologically active compounds, the goal of this project was to use the dual photoredox and nickel catalysis tool in order to design new ring opening reactions with new and synthetically versatile nucleophiles to greatly expand the utility of this transformation.



Scheme 1: Oxabenzonorbornadienes ring opening reaction using dual photoredox catalysis.

References:

1. Chemical Review Special issue “Photochemistry in Organic Synthesis”: Chem. Rev. 2016, 116, 9664-10341 (b) K. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2011, 45, 788-802.

2. a) M. Lautens, K. Fagnou, S. Hiebert, Acc. Chem. Res. 2003, 36, 48. b) D. K. Rayabarapu, C.-H. Cheng, Acc. Chem. Res. 2007, 40, 971.

3. for recent review see: Chem. Soc. Rev., 2021, 50, 3013-3093

5. A. G. Diallo, D. Roy, S. Gaillard, M. Lautens, J.-L. Renaud Org. Lett. 2020, 22, 2442.

Application of Frags2Drugs for the fragment-based drug design of macrocyclic kinase inhibitors

Gautier PEYRAT, ***Pascal BONNET.***
Pascal KREZEL, Stéphane BOURG, Samia ACI-SECHE
ICOA UMR 7311

Macrocycles are molecules composed of at least 12 atoms in a ring architecture. Macrocycles are able to inhibit challenging targets and they sometimes present a better affinity and selectivity than linear kinase inhibitors1.
The dysfunction of protein Anaplastic Lymphoma Kinase (ALK) can lead to several cancers. In 2018, the FDA approved the macrocyclic lorlatinib to treat patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer. We focused on the discovery of novel ALK macrocyclic inhibitors to validate Frags2Drugs (F2D) as a tool for the design of novel macrocycles.

Starting from the 2-aminopyridine seed from co-crystallized lorlatinib, we obtained 592 macrocycles. After applying several filters based on PAINS (pan assay interference compounds substructure removal)2, synthetic accessibility estimation3 and molecular docking for binding mode confirmation, we selected 153 ALK macrocycles. None of these inhibitors are similar (Tc > 0.7 using FCFP4 fingerprints) to compounds present in the ChEMBL, ZINC, PKIDB or Ambinter databases.

Among the 153 new macrocyclic inhibitors, 9 have a quantitative estimation of drug-likeness score4 > 0.7 suggesting potential lead compounds after few optimization steps. The suggested macrocycles will be synthesized and evaluated on ALK and on a panel of protein kinases for selectivity.

References

(1) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. The Exploration of Macrocycles for Drug Discovery — an Underexploited Structural Class. Nat. Rev. Drug Discov. 2008, 7 (7), 608–624. https://doi.org/10.1038/nrd2590.

(2) Baell, J. B.; Holloway, G. A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. J. Med. Chem. 2010, 53 (7), 2719–2740. https://doi.org/10.1021/jm901137j.

(3) Ertl, P.; Schuffenhauer, A. Estimation of Synthetic Accessibility Score of Drug-like Molecules Based on Molecular Complexity and Fragment Contributions. J. Cheminformatics 2009, 1 (1), 8. https://doi.org/10.1186/1758-2946-1-8.

(4) Bickerton, G. R.; Paolini, G. V.; Besnard, J.; Muresan, S.; Hopkins, A. L. Quantifying the Chemical Beauty of Drugs. Nat. Chem. 2012, 4 (2), 90–98. https://doi.org/10.1038/nchem.1243.

Development of chemiluminescent probes for enzymatic detection

Steven VERTUEUX, ***Pierre-Yves RENARD.***
K SOLMONT, A HAEFELE
COBRA - UMR 6014

Over the last few decades, the need for sustainable and environmentally frien-Chemiluminescence is a phenomenon that can be employed to avoid biological auto fluorescence in fluorescence imaging, thus improving the sensibility of fluorescent probes. 1,2-dioxetane is one of the moieties that, upon decomposition, can generate an excited state on a connected fluorophore, giving rise to its intrinsic luminescence. The aim of our project is to develop new phenol based probes for in cellulo and in vivo bio imaging to unblock three bottlenecks: pKa of phenol, hydro solubility, quantum yield efficiency and emission in the near-infrared spectral range. In this project, two different approach are follow; the chemiluminescent platform connecting to a hydro soluble lanthanide complex or a connected fluorophore by a conjugated linker. A water-soluble version of this platform should be the next step for in vivo bio imaging application.

Relevant descriptors for the innovation in chemical reactivity : an ad hoc selection

Ael CADOR, ***Laurent JOUBERT.***
V. Tognetti and P.L.A. Popelier
COBRA UMR 6014

It is well-known1 that unsaturated rings can open through thermal or light activation, affording dienes in the case of cyclobutenes. When a substituted cyclobutene is subjected to a thermal opening, the substituents will rotate in a conrotatory fashion and can rotate inward or outward of the ring. It has been observed2 that substituents usually favor only one mode of rotation; this phenomenon is called torquoselectivity. The inward or outward preference of substituents is usually explained through orbital interactions, notably by invoking the interactions of empty orbitals (on EWGs) with filled orbitals (on EDGs) between the substituent and the rest of the molecule.

The aim of this theoretical study is to explain this torquoselectivity through two approaches: an NBO3 (Natural Bond Orbitals) analysis based on localized bond orbitals (and their interactions) defined with a maximum occupancy criterion or an IQA4,5 (Interacting Quantum Atoms) analysis invoking a partition of the molecular energy of the system into intra-atomic and inter-atomic components. To extract the most relevant interactions, we use a method called REG6 (Relative Energy Gradient) which was developed in the few last years in the group of Pr Popelier at the University of Manchester. This simple and robust method allows for an easy selection without any bias of the discriminating terms which govern a reaction mechanism. This allows us to rationalize the influence of the substituents over the course of the reaction.

References

[1] K. Rudolf, D.C. Spellmeyer, K.N. Houk, J. Org. Chem. 1987, 52, 3708–3710.

[2] S. Niwayama, E.A. Kallel, D.C. Spellmeyer, C. Sheu, K.N. Houk, J. Org. Chem. 1996, 61, 2813–2825.

[3] A. E. Reed, L. A. Curtiss, F. Weinhold, Chem. Rev. 1988, 88, 899-926.

[4] M. A.Blanco, A. M. Pendás, E. Francisco, J. Chem. Theory Comput. 2005, 1, 1096–1109.

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[6] J. C. R. Thacker, P. L. A. Popelier, Theor. Chem. Acc. 2017, 136:86.

Probes for the chemoselective labeling of secondary metabolites in crude fungal extracts.

Victor FLON, ***Xavier FRANCK.***

COBRA UMR 6014

The discovery of new natural products is of interest in many application sectors: pharmaceuticals, cosmetics and even agri-food, due to their biological activities or innovative physicochemical properties (fluorescence, pigments). Their identification by conventional purification and analytical techniques can be limited by their low concentration in complex media. In collaboration with the team of Prof. Soizic Prado (UMR 7245 MNHN), we aim to isolate and identify new molecules in crude fungal extracts. Using an approach based on chemical reactivity, probes have been developed to jointly contain a reactive chemical function and a tag to increase detection sensitivity. These tagging tools will participate in the discovery of new metabolites by chemoselective reactions in complex natural extracts.

Rational design of S-Glycosyltransferases from Arabidopsis thaliana on demand: from modeling to therapeutic and cosmetic applications

Damien BRETAGNE, ***Richard DANIELLOU.***

ICOA UMR 7311

Glycosyltransferases (GTs) catalyze the glycosylation of a profusion of bioactive natural products Among GT superfamily, GT-B subgroup presents a highly conserved tertiary structure, in which the sugar donor and acceptor substrates bind in separated domains, respectively C-terminal and N-terminal. The enzymatic reaction between the two substrates takes place in the pocket located at the interface between the two domains.

This project aims at providing a new methodology to generate biocatalysts, by selecting the appropriate domains and combining them in a chimeric enzyme. Thus, the engineered GT will be designed according to the nature of the sugar and acceptor structures.

We cloned several GT chimera combining the N-domain and the C-domain from different GT-B with and without interdomain linker. We first demonstrated that the removal of the peptidic linker between domains does not impair either the purification of the chimera, nor the enzymatic activity. Then, by modulating the nature of domains combined, we have widen the substrate specificity of the chimeric enzymes, when compared to the original enzymes. In order to finely understand the molecular mechanisms involved, modelling of domains interaction, as well as cristallogenesis are currently investigated.

This project paves the way for the generation of new enzymes, tailor-designed from the nature of the targeted glycosylated product, that will be used for the synthesis of glycosides with expected applications in cosmetics or as pharmaceuticals.

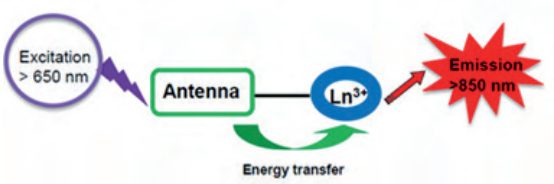
Design, synthesis and characterization of a Near Infrared Fluorophore Antibody Conjugate (AFC) for breast cancer imaging.

Thibault BRISKER, ***Franck SUZENET.***
Marie-Aude Hiebel, Stéphane Petoud, Svetlana Eliseeva , Nicolas Joubert
ICOA UMR 7311

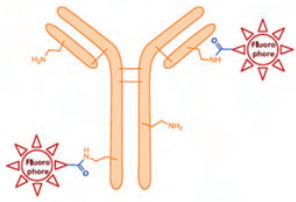
Breast cancer is the most common one among women worldwide. Even though current imaging tools are satisfying, they are expensive, invasive and they are located within hospitals and specific structures. Optical imaging is a great alternative as it is safe, quick and inexpensive while it still has a great resolution. The best optical window for medical imaging is between 700 and 900nm

since tissues and fluids do not absorb much here. This range belongs to the Near Infrared I (below 1000nm), but medical applications can also be run in the Near Infrared II (NIR II) window (1000-1700nm).

Our research labs1,3 have already been working on new near-infrared fluorescent probes that are perfoming well within this NIR optical range. These molecules are made of an already near infrared fluorescent organic scaffold (the « antenna ») and of a amino-carboxylate clip that complexes a lanthanide cation. The antenna absorbs light, transfers the gained energy to the lanthanide cation that emits in return with enhanced fluorescent properties.



Lanthanide based fluorophore.



An Antibody Fluorophore Conjugate

To vectorize them onto the tumor, we linked theses molecules to a fragment of a monoclonal antibody (mAb) which binds specifically to HER2 receptors that are generally overexpressed at the surface of cancerous cells. The whole molecule is an Antibody Fluorophore Conjugate (AFC).

Several original fluorophores have already been synthesized. Some of them have been bioconjugated onto the antibody fragment; we are currently investigating the issues related to this step

Ce travail a bénéficié d'une aide de l'Etat gérée par l'Agence Nationale de la Recherche au titre du programme « Investissements d'avenir » portant la référence ANR-11-LABX-0029-01