FRANCE-BIOIMAGING

WORK PACKAGE 3 (WP 3)

PROBE DEVELOPMENT, OPTOMANIPULATION & OPTOGENETICS

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18 September 2015, 16:00-17:30

Purpose of the session

The purpose of this session is to provide an overview of the current activity in the field covered by WP 3 in French groups. The speakers have been asked to give flash presentations providing an overview of their activity and highlighting on a specific development. They will be available for further discussions during the FBI meeting.

The abstracts of the presentations are given in the following pages.

MOLECULAR MATERIALS FOR BIOPHOTONIC

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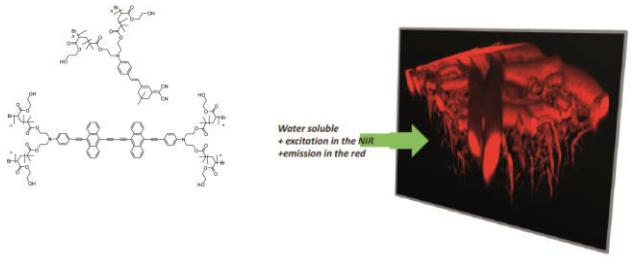
Abstract

Our activity is based on the design of materials with optimized spectroscopic properties for diagnostic or therapy with an improved resolution, using linear or nonlinear multi-photonic irradiation:

(a) Ln complexes for in-depth imaging of strongly scattering thick tissues by two-photon scanning microscopy in a NIR-to-NIR configuration, combining good stability and efficiency in water (1). Recently we showed peculiar properties of Ln for biosensors or FRET detection in cellulo or in-vivo (2).

(b) nanoplatforms for dyes transport in biological media: (a) nanocarriers, consisting in either chromophores encapsulated in the liquid core of gold shells conferring high photostability and brightness (3), or shells of luminescent polymers grafted on gold bipyramids or stars nanoparticles, triggering the cell death with a similar efficiency of the polymer conjugate alone, but with advantage of high loading of photosensitizers (70 000/particle) combined with high efficiency(4). Optimized structures led to observe the efficient emission enhancement with anisotropic nanoparticles.

(c) efficient agents for non-invasive intravital imaging of brain vasculature in the motor cortex with a maximum observation depth of 360 µm through a thinned-skull window, and 620 µm after a craniotomy (5).



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DEVELOPMENT OF PHOTOTRANSFORMABLE FLUORESCENT PROTEINS FOR SUPER RESOLUTION MICROSCOPY

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Abstract

The Pixel team of the Institute for Structural Biology has joined the advanced bioimaging community through a side door. As crystallographers, we were originally interested in the structural aspects of fluorescent proteins. Our interests into the photophysical mechanisms by which phototransformable fluorescent proteins (PTFPs) photoactivate, photoconvert or photoswitch, quickly brought us into the field of super-resolution microscopy. We now combine single-crystal and single-molecule approaches to rationally engineer PTFPs with advanced properties,[1] and we use these in biomedically relevant projects,[2] employing quantitative PALM.[3] We are notably interested in developing photostable variants with reduced photobleaching[4,5] and or photoblinking.[6] We also design superfolding variants that reversibly photoswitch and are thus suitable for the nanoscale investigation of oxidative cell compartments such as the bacterial periplasm, that hitherto have remained blind to super-resolution techniques.[7]

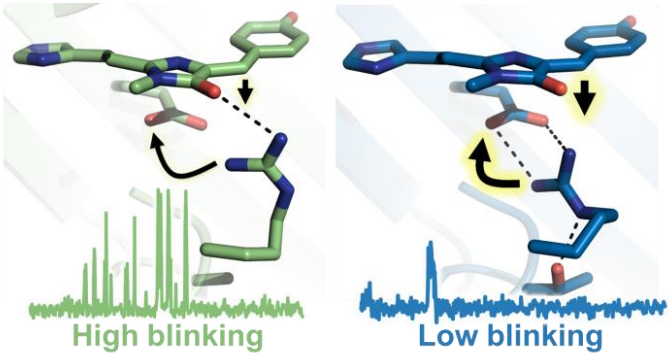

Figure: understanding the mechanisms behind photoblinking in PTFPs

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TWO-PHOTON OPTIMIZED PROBES FOR THE CELLULAR BIOLOGY

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Abstract

To understand the mechanism of recognition and response between receptors and ligands or probing the signaling pathways of the cell there is an increasing need for the development of highly specific molecular probes.[1] Some experimental interventions require sub-micrometer and sub-millisecond resolutions, corresponding to the spatiotemporal scale of physiological processes such as synaptic transmission and intracellular second messenger signaling. The challenge consists of perturbing the biological system with a concentration jump of the physiological ligand, a cofactor or an antagonist, with timing and spatial dimensions that mimic the physiological process, leading to kinetic and mechanistic information. "Caged compounds" have been developed to address this issue with the first publication of "caged" ATP by Kaplan et al. in 1978.[2] Photolysis with one-photon excitation (by UV light) is limited by light scattering. Thus, two-photon (TP) excitation with near-IR photons is privileged since scattered photons do not excite. However, probes that respond efficiently to two-photon activation are elusive: the often poor aqueous solubility of probes with high cross-sections and the fact that irradiation often requires laser beam parameters inaccessible with commercially available lasers.

We are developing 2-hydroxymethylene-dimethylaminoquinoline (DMAQ) derived photolabile protecting groups which show fast fragmentation kinetics in physiological solutions on irradiation by UV (OP), or, NIR (TP) light, high uncaging sensitivity, high solubility and low fluorescence.[3] Photorelease of L-glutamate, GABA, glycine and kaïnate by the most efficient derivatives strongly and efficiently activated receptors, generating large, fast rising responses similar to those elicited by glutamate photoreleased from the widely used MNI-caged glutamate.

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FLUOROGEN-BASED REPORTERS FOR FLUORESCENCE IMAGING

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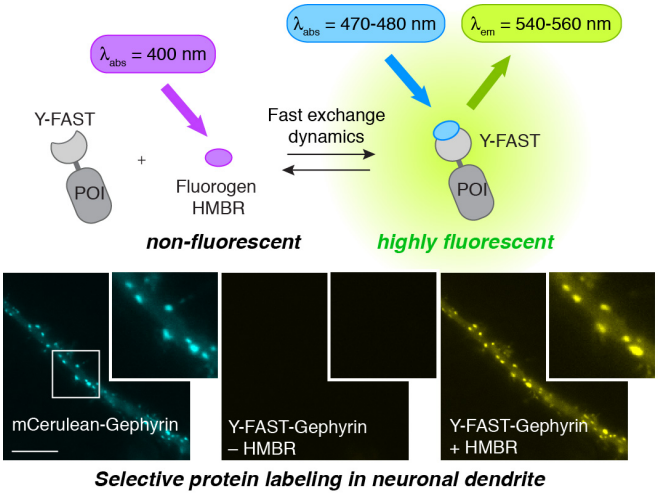
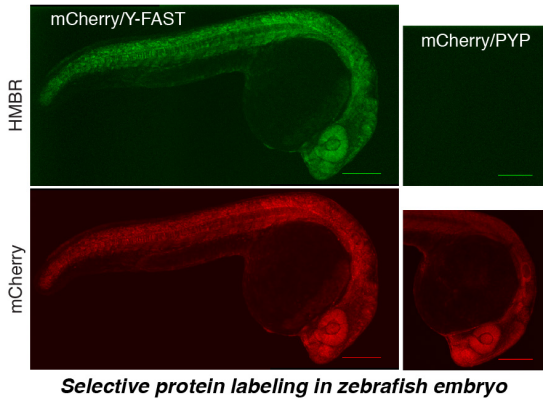
Abstract

Selective labeling with fluorogenic probes represents a general strategy for highlighting proteins in living systems. In this approach, a protein of interest (POI) is fused to a protein tag that binds a fluorogenic ligand and activates its fluorescence. As the fluorogenic ligand is non-fluorescent by its own and becomes strongly fluorescent only upon binding its target, unspecific fluorescence background in cells remains minimal even in the presence of an excess of fluorogen, thus ensuring high imaging contrast. Here, we present Y-FAST, a small protein tag enabling to fluorescently label proteins through the specific and reversible binding of a cell-permeant and non-toxic fluorogenic ligand HMBR. Y-FAST is a monomeric 14-kDa protein engineered from the Photoactive Yellow Protein (PYP) by directed evolution. Y-FAST is photostable, as bright as common fluorescent proteins, and allows for imaging proteins in various subcellular locations and in a large variety of systems, from mammalian cells (including neurons) to microorganisms and zebrafish. Y-FAST distinguishes itself from other labeling systems because the binding of the fluorogen is not only instantaneous and specific but also highly dynamic: the exchange dynamics is characterized by a binding/unbinding frequency of about 10 Hz enabling in particular (i) to rapidly switch the fluorescence on and off at will by addition or withdrawal of the fluorogen, opening new perspectives for multiplexing imaging, and (ii) to envision various applications for sub-diffraction-limit imaging using Single-molecule Localization Microscopies (SLM) or Super-resolution Optical Fluctuation Imaging (SOFI).



Selective protein labeling in neuronal dendrite



Selective protein labeling in zebrafish embryo

Reference: A small fluorescence-activating and absorption-shifting tag for tunable protein imaging in vivo. *Proceedings of the National Academy of Sciences,* under revision. Plamont, M.-A., Billon-Denis, E., Maurin, S., Gauron, C., Specht, C. G., Shi, J., Querard, J., Pimenta, F. M., Pan, B., Rossignol, J., Volovitch, M., Chen, Y., Triller, A., Vriz, S., Le Saux, T., Jullien, L. & Gautier, A.

SWITCHABLE FLUORESCENT PROBES FOR TARGETED TWO-PHOTON CELLULAR IMAGING: FROM DNA TO PROTEIN LABELING

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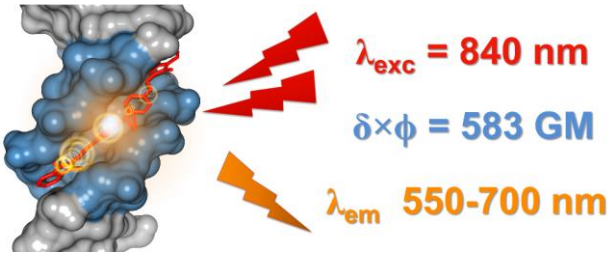
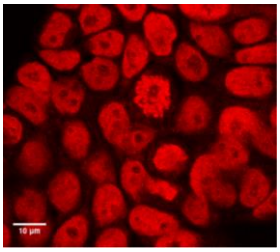
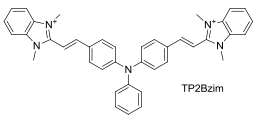
Abstract

Given the remarkable developments of multiphotonic microscopy, we recently turned our attention towards the design of fluorophores optimized for biphotonic absorption and compatible with the labelling of biomolecules (low molecular weight, water-solubility, chemical function for bioconjugation). Novel DNA markers have been elaborated, which combine criteria rarely met in usual markers: i) low quantum yield in the free state and red-emission with a high brightness when bound to DNA; ii) two-photon absorption cross sections larger than that of usual markers (up to 1080 GM) iii) high photostability. The vinyl triphenylamine series (TP) represent a novel family of robust probes for optical tracking of DNA in cells by confocal and multiphotonic microscopy.[1,2] Other series such as vinyl-carbazoles[3] and vinyl-acridines[4] have also been developed.





Confocal microscopy imaging of fixed HT29 clles incubated with TP2Bzim (100nM) λexc=800nm



Structure modifications enabled to switch from DNA probes (cationic TP-pyridinium series) to protein probes (anionic TP-rhodanine series) without affecting the optical properties.[5] Finally most TP compounds appear cell-permeant and show an intracellular localization consistent with their in vitro target specificity.

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NEW PERSPECTIVES FOR NEAR-INFRARED IMAGING IN LIVING CELLS AND SMALL ANIMALS WITH LANTHANIDES: NANO-MOFS, POLYMETALLIC DENDRIMER COMPLEXES AND METALLACROWNS

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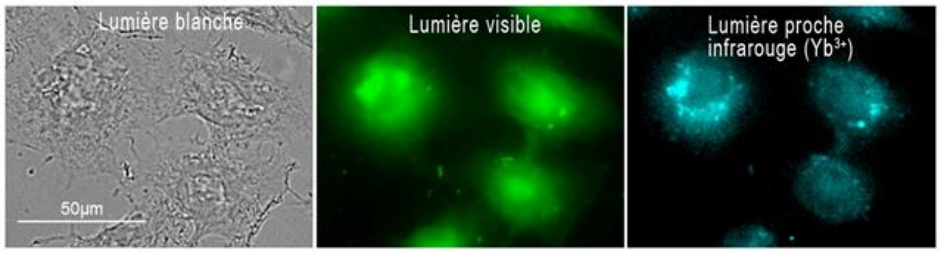
Abstract

The luminescence of lanthanide-based probes has several complementary advantages over the fluorescence of existing organic fluorophores and semiconductor nanocrystals, such as sharp emission bands for spectral discrimination from background emission, long luminescence lifetimes for temporal discrimination and strong resistance to photobleaching. In addition, several lanthanides emit near-infrared (NIR) photons that can cross deeply into tissues for non-invasive investigations and that result in improved detection sensitivity due to the absence of native NIR luminescence from tissues and cells (autofluorescence). The main requirement to generate lanthanide emission is to sensitize them with an appropriate chromophore.

Different concepts for such sensitization of NIR-emitting lanthanides are explored. The current limitation of low quantum yields experienced by most mononuclear lanthanide complexes is compensated for by using a large number of lanthanide cations and by maximizing the absorption of each discrete molecule, thereby increasing the number of emitted photons per unit of volume and the overall sensitivity of the measurement. To apply this concept, we have created different types of NIR emissive i) metal organic frameworks (MOFs) and ii) polymetallic dendrimer complexes.The structure of metallacrowns is another promising approach in which the lanthanide is surrounded by a number of chromophoric ligands and well protected from vibrations, leading to high quantum yields.



"HeLa" cells after incubation with nano-MOFs.[2] Near-infrared imaging allows the fluorescence signal emitted by the nano-MOFs to be located more precisely without parasitic autofluorescence light in the visible domain

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INORGANIC CELLULAR CHEMISTRY: IMAGING METAL COMPLEXES IN CELLS OR TISSUE

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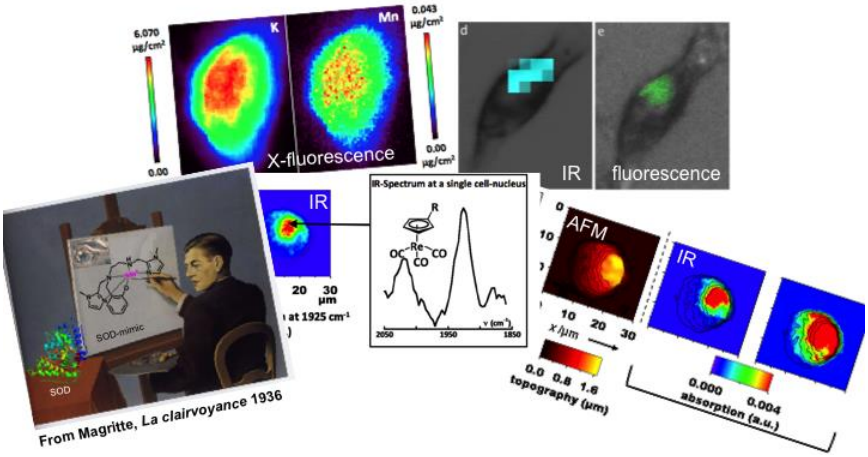
Abstract

Inorganic complexes are increasingly used for biological applications, as metallodrugs or metalloprobes. We design and synthesize metal complexes with controlled physico-chemical properties,[1] including tuned cell-penetration and organelle targeting. We focus on two main topics.

(a) Bio-active metal complexes: Mn-complexes showing an antioxidant activity are designed to rescue cells from oxidative stress and studied in cellular models, with the aim of correlating their bio-activity, with quantification, speciation and location.[2-5]

(b) Metal-based probes: $Re(CO)_3$ complexes are developed as multimodal probes, to be used as organelles trackers or tags. They are easy to conjugate to any kind of bio-molecule and can be imaged by a variety of spectroscopies, including IR, (sub-cellular to tissue scale).[6-9]

Innovative techniques to quantify these metallic species, investigate their speciation, and determine their cellular-location are used, leading to key information about their behavior in cells. Controlling inorganic complexes inside cells is an emerging field that we called "cellular inorganic chemistry" as it involves translation of knowledge acquired in round-bottom flask into cells.



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DEVELOPMENT OF TOOLS FOR THE PHOTOCONTROL AND MONITORING OF PROTEIN-PROTEIN INTERACTIONS AT THE SYNAPSE

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Abstract

Complex and dynamic protein-protein interactions are the core of protein-based networks in cells. At excitatory synapses, the postsynaptic density (PSD) is a prototypical example of protein-based network whose nanoscale structure and composition determines the cellular function. The regulation of PSD composition and receptor movement into or out of the PSD are the base of current molecular theories of learning and memory. However, the mechanisms that dynamically govern the respective synaptic retention of the various receptors remain poorly understood partly due to the lack of tools to monitor or disrupt and control specific endogenous interactions.

The presentation will give an overview of the various approaches we develop in order to monitor or modulate specific protein interactions with the final aim of investigating molecular mechanisms underlying synaptic plasticity. These approaches combines rational design and selection strategies to generate molecular binders that display the desired properties with respect to their target(s). Part of our research interest also goes into implementing to our binders caging and optogenetic strategies in order to generate tools whose activity can be triggered by the use of light.

Design and Applications of Photochemical Tools.

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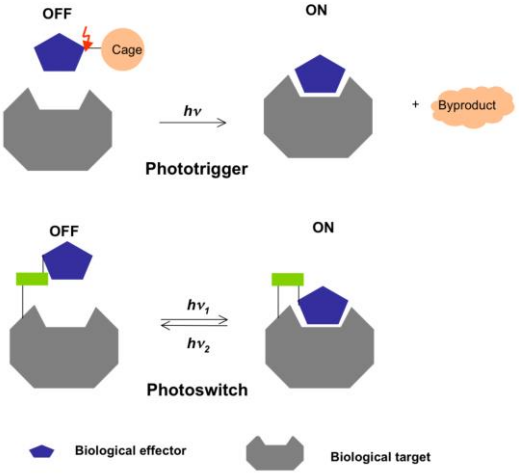
Abstract

Biological processes are very complex phenomena ruled by series of precise spatio-temporal events. To reveal intimate mechanism of these phenomena, cellular process needs to be precisely controlled and tuned with the help of orthogonal tools. Light is an ideal orthogonal external trigger since in many cases the biological environment did not react to light. Photoswitches and Phototriggers provide the capability to rapidly cause the initiation of wide range of dynamic biological processes.[1] The first strategy is referring to synthetic photochromic systems (“photoswitch”), which conditionally activate a protein by attaching an photoisomerizable ligand. The second strategy is based on spatio-temporal delivery pattern of biomolecules. In this context, recent efforts prompted the development of photoremovable groups that have increased photochemical efficiencies for two photon excitation to allow more sophisticated applications.[2] Two-photon excitation produces excited states identical to standard UV excitation while overcoming major limitations when dealing with biological materials, like higher spatial resolution (3D resolution in particular along the z-axis), higher tissue penetration and less toxicity. We have developed a new series of photoremovable groups: an o-nitrophenethyl derivative, which exhibits the necessary properties for a satisfactory caging group including a fast and efficient photolytic reaction at near-UV irradiation.[3] Molecular engineering of the two-photon uncaging cross-sections was performed on this platforms leading to photoremovable groups with ultra-efficient uncaging cross-section.[4] The development and the new opportunities of our two-photon sensitive photoremovable groups and photoswitches will be discussed here, including applications in neuro,[4-5] cellular- biology[6] and in material sciences.[7]



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IMAGING TOOLS FOR BIOLOGICAL APPLICATIONS

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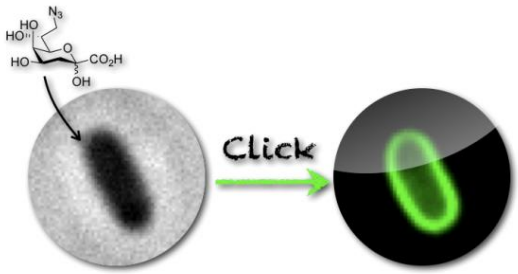
Abstract

The design and synthesis of new tools and responsive probes for imaging biological events is a major preoccupation of the Chemical Biology department at ICSN. We are focusing on various complementary approaches for applications which include *in vivo* visualization of small reactive species or disease-related enzymatic activity, detection of living microorganisms, and mechanistic investigations of the mode of action of new plant hormones or growth promoters. Our tools are currently based on fluorescence or IRM imaging, but we have also interest in using luminescence imaging modes. The development of photoactive probes would be a natural extension of our expertise.

This short communication will present our strategies and skills that could be relevant to the FBI project.



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