Click Chemistry Based Labeling of Biomolecules with ^{18}F: a New Method to Produce PET Molecular Tracers.

David Thonon, Cécile Kech, Christian Lemaire, André Luxen
Cyclotron Research Center, Liege University, B30 Sart-Tilman 4000 Liege

The aim of molecular imaging is to in vivo characterize and measure biological process at the cellular and molecular level. The success of this new discipline will benefit considerably to the biomedical research community. By example, molecular imaging creates the possibility of in vivo imaging gene expression, optimizing drug therapy and imaging drug effect at a molecular and cellular level or detecting pathology at a « predisease » state[1].

Basically, molecular imaging requires two elements: a molecular probe whose concentration and/or spectral properties are altered by the biological process investigated and imaging systems able to monitor these probes in vivo. Thanks to its high sensitivity (10^{-9} -10^{-12} M) and "quantitativety", positron emission tomography (PET) is ideally suited to image molecular process. Among a number of positron-emitting nuclides, fluorine-18 appears to be the best candidate for labeling biomolecules in regards of its favorable physical and nuclear properties.

The challenge for the radiochemist is to introduce a short half-life radioisotope (18-fluorine, $t_{1/2}$ 109.7 min) onto biomolecules which are specific to the biological process studied. In this context, the goal of our work is to develop a general and simple method that permit to label a large library of biological compounds.

To achieve this aim, we have selected a fast, selective and efficient reaction that permits to graft ^{18}F tagged molecules onto compounds of biological interest (peptides, oligonucleotides, lipids, …). « Click » reactions and more particularly Huisgen 1,3 dipolar cycloaddition of alkynes with azides are well adapted to the preparation of radiopharmaceuticals as they require only benign reaction conditions, simple workup and purification procedures (Fig. 1). In principle, this cycloaddition can be performed in the presence of water and oxygen and is orthogonal to any functional groups and so can be performed without the protection of other functional groups[2]. This strategy implies the introduction of either alkyne or azide groups onto the biomolecules and to prepare a bifunctional tracer featuring the complementary function.

Results obtain in the functionalization of small peptides and an original four steps, fully automatized radiosynthesis of an ^{18}F labeled azide will be presented. Finally preliminary results obtained in « Click » chemistry will be demonstrated.

These results confirm that « Click » chemistry for fluorine-18 labeling in well selected conditions has the potential to develop into a universal labeling tool thanks to its rapidity and selectivity. The next step must be in vivo studies to determine both stability and toxicity.

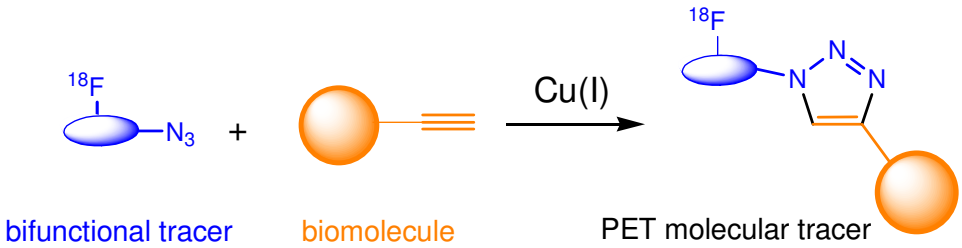

Fig. 1

1. Massoud, T.F. Gambhir,S.S. Molecular Imaging in Living Subjects: Seeing Fundamental Biological Processes in a New Light. Genes & Development. 17, 545, 2003.
2. Bock,V.D., Hiemstra,H., Van Maarseveen, J.H. Cu^{I} Catalysed Alkyne-Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective. Eur.J.Org.Chem. 51, 2006.