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EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Letter of Intent to the
ISOLDE and Neutron Time-of-Flight Experiments Committee
for experiments with HIE-ISOLDE

Innovative radioisotopes for preclinical and clinical studies in nuclear medicine

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Abstract

We propose exploiting innovative radioisotopes from ISOLDE for R&D towards optimized diagnostics and therapy procedures in nuclear medicine.

1. Introduction

Radionuclide diagnosis and therapy are indispensable tools in oncology, cardiology and psychiatry. Advantages are the high sensitivity and the low side effects for the patients. At the moment

radionuclide diagnosis and therapy is performed based on a limited selection of available radionuclides. However, there exists consensus among the radiopharmaceutical research community that radionuclides with more suitable decay properties could improve diagnosis and therapy significantly. R&D in this field is hindered since innovative radioisotopes are not available in adequate quality and quantity.
A large selection of high-quality radioisotopes is an important asset in R&D towards improved diagnostics and therapy in nuclear medicine. Some of these isotopes can be produced also at small accelerators, but may require years of development (optimization of target, projectile energy, chemical separation, etc.) to achieve satisfactory quantities and specific activity. Other isotopes can only be produced with high energy protons (or heavy ions) at large accelerators.
Most of these isotopes are readily available at ISOLDE and will be available with improved intensities at **HI**E-ISOLDE.
We launched a new collaboration that intends performing experiments with innovative radioisotopes produced at the unique facilities of (HIE-)ISOLDE, ILL Grenoble, PSI Villigen and Arronax Nantes. The collaboration is still growing and aims for a joint Pan-European research project covering this purpose.

2. Science case

This proposal aims to change the current situation and will provide optimal radionuclides for diagnosis and therapy, by selecting radioisotopes that are optimized with respect to half-life, decay mode and chemical properties.
Dozens of different isotopes with different decay properties (emission of gamma rays or positrons for imaging or of betas, alphas or low-energy conversion or Auger electrons for therapy) are of interest for medical studies and are available at ISOLDE already today. ISOLDE could provide over 1000 different radioisotopes in carrier-free quality, i.e. with specific activities close to the theoretical optimum. Moreover, ISOLDE offers the possibility to collect elements with similar chemical properties (e.g. different lanthanides) from the same target quasi-simultaneously, i.e. by just changing the mass selection with the separator magnet. Hence, different radiotracers can be collected for simultaneous (multi-tracer and multi-agent) in-vitro or in-vivo studies.

3. Experimental setup

The infrastructure required for first preclinical experiments consists of the ISOLDE collection chambers (already existing) that are usually placed at the GLM or GHM beamlines
For collections of higher activities and for collections of isotopes used in later clinical studies we propose to design a dedicated collection chamber that allows remote-handled introduction and removal of a suitable catcher to perform the implantations under sterile conditions. This system will be, except for the connection through a differential pumping channel towards the ISOLDE beamlines, a “closed” system that guarantees best protection against contamination, i.e. against introduction of germs into the chamber and against release of activity from the chamber. This additional “barrier” should allow increasing the permissible activity levels with respect to the usual radioactive “class C lab” limit of the ISOLDE hall and is essential to make full use of the **HI**E-ISOLDE intensities.
A close-by radioactive laboratory is required for handling and packing the activity before shipping it to the users located at different radiochemical and radiopharmaceutical labs in Europe.
In certain cases activity and dose rate of the shipped activity can be substantially reduced by performing a chemical separation (removal of isobars and other masses introduced by molecular sidebands) before shipping. We propose to install a small radiochemical lab in an auxiliary building close to the ISOLDE experimental hall. This lab would also be used for simple labeling of bioconjugates (antibodies, peptides). In particular for short-lived nuclides and slow labeling processes there may be significant decay losses in this step. Labeling before shipping minimizes the activity to be shipped and quality control can be performed during shipment, hence optimizing the time management and efficiency of the overall process. To remain compatible with the higher activities available from **HI**E-ISOLDE, this lab should fulfill Class B specifications.

4. Beam requirements

Typical examples of current R&D interests are:

- PSI: ^{152}Tb as long-lived PET tracer and ^{155}Tb as long-lived SPECT tracer for biodistribution studies of peptides and antibodies and for personalized dosimetry of Tb-based radiotherapy. ^{149}Tb as alpha emitter for comparative studies of the therapeutic efficiency with the electron emitters ^{161}Tb and ^{177}Lu.
- Mainz: ^{149}Tb for preclinical studies on alpha-immuno-therapy in comparison to the longer lived alpha emitter ^{225}Ac and to longer lived beta emitters.
- Risø: ^{71}Ge, ^{131}Cs and ^{165}Tm/^{165}Er as low-energy electron emitters of highest specific activity for fundamental radiobiology experiments on the efficiency of therapy with low-energy electron emitters.
- Nantes: comparative studies of tracer and SPECT imaging qualities of ^{203,204,205,206}Bi as longer-lived tracer for biodistribution studies of bismuth in view of ^{213}Bi therapy.
- Grenoble: ^{71}Ge and ^{117m}Sn with high specific activity as low-energy electron emitters for R&D on therapy with internalizing peptides.
- Genève: various isotopes for simultaneous multi-tracer SPECT studies with CZT detectors.
- PSI/Genève/Grenoble: Test of SPECT and PET imaging qualities of unconventional radiotracers: ^{200,203}Pb (SPECT), ^{71,72,74}As, ^{84}Rb and ^{202}Bi (PET).
- Tübingen : carrier-free long-lived PET tracers ^{140}Nd/^{140}Pr and ^{134}Ce/^{134}La to follow the biodistribution of antibodies over longer time.
- Garching: R&D towards ion-implanted stents for brachytherapy applications.

For comparative multi-tracer studies it is important to collect different isotopes simultaneously (e.g. GLM and GHM) or subsequently (e.g. during few hours).
Compared to other ISOLDE applications, our proposed applications are less challenging for ISOL targets and ion sources since the isotopes of interest are longer-lived (hours to days) and the beam purity is less crucial due to chemical post-separation.
For specific cases (e.g. ^{117m}Sn) the RILIS will be required to provide additional isomeric separation, optimizing the specific activity of the isomer.
Typical activities required are several 100 MBq for preclinical studies with PET (10-20 MBq per mouse) or SPECT (10-40 MBq per mouse) tracer, and several 100 MBq for preclinical studies with alpha (5 MBq/mouse) or low-energy electron (10 to 50 MBq per mouse) emitters. Such activities can be collected today at ISOLDE within few hours and are covered by the authorization limit of the ISOLDE hall (class C lab). Later clinical studies will require higher activities (**HI**E-ISOLDE) that are achievable with an increase of the primary proton beam intensity and/or beam development (boost of ionization efficiency with improved RILIS schemes). Beam development is requested to optimize the intensity of ^{149}Tb (via RILIS of Tb or Dy precursor respectively) and to ionize Sn with isomeric selectivity.
Typically several campaigns per year should be performed for few hours to few days each. The most frequently needed targets are likely Ta+WSI (partly complemented by RILIS), UC_x+WSI (complemented by RILIS for different elements) and ZrO_2 or Y_2O_3+VD5.
We ask for 4 shifts for test collections with such targets to determine the presently achievable yields and beam purities of some isotopes of interest.
Low beam energy (30-60 keV) is generally sufficient. There are no particular requirements with respect to energy resolution, beam emittance or time structure of the beam.

5. Safety aspects

A radiochemical “class C” (later “class B”) laboratory is required for dry and wet chemical separations. Radiochemical laboratories at CERN that previously allowed performing chemical off-line separations of isobars are no longer operational and have to be renewed.