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EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Addendum to the ISOLDE and Neutron Time-of-Flight Committee

# IS528 **Novel diagnostic and therapeutic radionuclides for the development of innovative radiopharmaceuticals**

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**Abstract**

We propose the exploration of novel radionuclides with diagnostic or therapeutic properties from ISOLDE. Access to such unique isotopes will enable the fundamental research in radiopharmaceutical science towards superior treatment, e.g. in nuclear oncology. The systematic investigation of the biological response to the different characteristics of the decay radiation will be performed for a better understanding of therapeutic effects. The development of alternative diagnostic tools will be applied for the management and optimization of radionuclide therapy.
We request 11 shifts to pursue our work with the quadruplet of diagnostic and therapeutic Tb isotopes ($^{149,152,155,161}$Tb). We request 12 shifts to collect $^{140}$Nd and $^{134}$Ce which should serve as long-lived *in-vivo* PET generators. We request 3 shifts for exploratory studies with other novel radioisotopes. We request 6 off-line shifts for an off-line mass separation to obtain $^{169}$Er with high specific activity, thus enabling a preclinical therapy study with this radiolanthanide.

**Requested shifts (in total)**: 26 online shifts plus 6 offline shifts

The present Addendum follows the status report INTC-SR-528.

## Motivation, experimental setup and technique

The enormous diversity of radioisotopes that are readily available at ISOLDE and the high quality of these mass-separated beams ("carrier-free", i.e. close to the ultimate specific activity) provide a unique toolkit for new applications in nuclear medicine and can overcome the bottleneck of radioisotope availability.

The radioisotopes are collected at ISOLDE by implantation into a temporary matrix (e.g. Zn or salt coated noble metal foils), then shipped in shielded containers to the receiving laboratory. Upon arrival the matrix is dissolved and the radionuclides are used either directly or after an additional radiochemical purification step for labeling of experimental radiopharmaceuticals. These serve for preclinical *in vitro* and *in vivo* studies.

## Addendum

### A) $^{149}$Tb-cm09 dose escalation study, detailed comparison with $^{161}$Tb-cm09

In our previous work the *in vitro* and *in vivo* behavior of the new folate conjugate cm09 has been well characterized and enables now quantitative studies of the therapeutic efficacy of cm09 radioconjugates in tumor bearing mice as function of activity and emitted radiation ($\alpha$ versus $\beta$). $^{149}$Tb is the ideal alpha emitter for this purpose as it has the same chemical behavior as the beta emitter 161Tb which has been used with cm09 extensively [Mue13]. However, with the $^{149}$Tb activities available in the previous runs only 3 groups of mice could be treated with activities of 1.1+1.3 MBq, 2.2 MBq and 3.0 MBq respectively and the number of mice per group was low (3 or 4). Such a setting did not allow investigation of an optimum activity and had much more the character of a pilot-study. To consolidate these preliminary results and to study in detail also possible longterm kidney toxicity, we need at least 6 groups with 6 mice each and injected activities up to 6 MBq. Given the unavoidable decay losses during transport to PSI, radiochemical purification and labeling, this translates to 8 collections (midnight to 08:00) and shipments of 100 to 150 MBq $^{149}$Tb each.

### B) $^{149}$Tb pilot study with peptides

After the successful validation of the therapeutic efficacy of $^{149}$Tb folate radioconjugates we want to apply it also for a pilot study of $\alpha$-PRRT (peptide receptor radionuclide therapy). Peptides show generally a different uptake and excretion pattern than cm09. Hence they present a second independent system that has to be validated for targeted $\alpha$ therapy. The efficacy and possible side effects will be investigated in a pilot study with 3 groups of mice which requires 3 collections (midnight to 08:00) and shipments of 100 to 150 MBq $^{149}$Tb each.

## C) $^{152}$Tb/$^{155}$Tb imaging isotopes for longitudinal biodistribution studies

During collection of $^{149}$Tb in GLM we intend to collect in parallel also the imaging isotopes $^{152}$Tb and $^{155}$Tb respectively in GHM. These will be used to prepare and assist the $^{149}$Tb therapy studies by PET and SPECT biodistribution measurements over time. This data is essential for accurate dosimetry calculations in the comparison of $^{149}$Tb and $^{161}$Tb efficacy.

## D) $^{140}$Nd versus $^{134}$Ce as long-lived PET tracer: understanding the daughter delabeling

$^{134}$Ce and $^{140}$Nd have long half-lives (3.2 and 3.4 d) and offer delayed positron emission after electron capture (EC) decay via their $^{134}$La and $^{140}$Pr daughters respectively. However, the abundant Auger electron emission accompanying the EC decay can induce an unwanted delabeling from the chelator as we already observed for $^{140}$Nd-DOTA. Applying these isotopes optimally as *in vivo* PET generators requires a more comprehensive understanding of the effects of EC on different chelators, which we intend to study systematically with more $^{134}$Ce and $^{140}$Nd samples from ISOLDE. Alternative, more robust labeling systems are envisioned, such as embedded labeling of nano-particles, giving access to long-lived PET tracers combined with well understood chemistry. The availability of a reliable long-lived PET tracer is particularly important for the radiolabeling of newly developed monoclonal antibodies (mAbs) for the diagnosis and therapy of life-threatening *Aspergillus fumigatus* (MATHIAS project, EU-FP7 [MATHIAS]) or *Echinococcus multilocularis* (DFG project) infections in animal models.
We ask for 6 shifts to test different mAbs with different chelators with $^{134}$Ce and $^{140}$Nd respectively. The optimized chelator and labeling method will then be used for the immuno-PET or theranostic studies requiring 6 shifts. Please note that these shifts can be scheduled with the same Ta target as A) to C), thus filling the daytime gaps between the $^{149}$Tb collections.

## E) Offline mass separation of $^{169}$Er for in vivo therapy study

Among all radiolanthanides with clinically useful half-life, $^{169}$Er ($T_{1/2}$=9.4 d) has the lowest beta energy ($E_{av}$ = 100 keV) and practically no gamma radiation, hence it is predicted to provide best targeting (i.e. highest tumor-to-normal-tissue absorbed dose ratio) for a wide range of tumor sizes [Uus06]. Unfortunately production of $^{169}$Er is hampered by the low neutron capture cross section of $^{168}$Er(n,γ) leading inevitably to low specific activity $^{169}$Er. We propose combining irradiation in the high flux reactor of Institut Laue-Langevin (Grenoble) with an off-line mass separation at ISOLDE to provide high specific activity $^{169}$Er for a preclinical proof-of-principle therapy study. Irradiation of highly enriched $^{168}$Er in the high flux position ($1.5 \cdot 10^{15}$ n./cm$^2$/s) of the ILL reactor provides $^{169}$Er at a specific activity of 4 MBq/µg, i.e. each radioactive $^{169}$Er is diluted by 700 stable $^{168}$Er atoms. An additional mass separation step is required to increase the specific activity by at least two orders of magnitude. The resulting high specific activity $^{169}$Er will be labeled to the well known DOTATOC peptide and therapeutic efficacy and possible kidney damage will be directly compared to $^{177}$Lu-DOTATOC, the “gold standard” in peptide receptor radionuclide therapy.

**F) Exploratory studies with other promising radioisotopes**

In addition to the radioisotopes discussed so far, there are other innovative radioisotopes with promising properties for imaging, as element-specific radiotracers or for targeted therapy. For a validation of the suitability of these radioisotopes initially basic studies are needed, namely phantom imaging studies and image reconstruction optimization, radiochemical trials and *in-vitro* experiments. We intend to collect samples of $^{71,72,74}$As, $^{73}$Se, $^{84}$Rb, $^{117m}$Sn, $^{200,203}$Pb or $^{203\text{-}206}$Bi, allowing to perform initial tests. We ask for 3 shifts to perform these collections "opportunistically", i.e. to be scheduled when another experiment demands the respective target/ion source combination.

## Future plans with all <u>requested</u> shifts (including available shifts):

(i) Envisaged measurements and requested isotopes

A) 8 shifts for collection of 149Tb

B) 3 shifts for collection of 149Tb

C) 152Tb and 155Tb collected at GHM in parallel to A) and B)

D) 12 shifts for collection of 134Ce and 140Nd

E) 3 shifts for exploratory studies with other promising radioisotopes

F) 6 shifts for off-line mass separation of 169Er (could be scheduled during PSB shutdown or on one separator while the other is used online)

(ii) Have these studies been performed in the meantime by another group?

No.

(iii) Number of shifts (based on newest yields) required for each isotope

The given yields were observed in the last beam time, averaged over several hours of collection.

| Isotope | Cumulative yield (/uC) | target – ion source | Shifts (8h) |
|---|---|---|---|
| 149Tb | 8E7 | Ta foil + W or Re surface ionizer and Dy RILIS | 11 |
| 152Tb | 1E9 | Ta foil + W or Re surface ionizer and Dy RILIS | Included in $^{149}$Tb shifts (see above) |
| 155Tb | 1.6E9 | Ta foil + W or Re surface ionizer and Dy RILIS | |
| 140Nd | 2E8 | Ta foil + W or Re surface ionizer | 12 |
| 134Ce | 3.4E7 | Ta foil + W or Re surface ionizer | |

| | | | |
|---|---|---|---|
| 71,72,74As<br>73Se | | ZrO2 or Y2O3 + VD5 | 3 |
| 84Rb | | UCx + surface ionizer; Nb + surface ionizer; etc. | |
| 117mSn | | UCx + Sn RILIS | |
| 200/203Pb<br>203-206Bi | | UCx + Pb or Bi RILIS respectively<br>Alternatively from UCx + surface ionizer or VD7 as decay daughters of Fr or Rn beams | |
| 169Er | | Off-line mass separation with W or Re surface ionizer, optionally with Er RILIS | 6 offline |

**Total shifts:** **26+6**

**Available:** **10**

**New request:** **16+6**

## References:


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