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HoT in RS course for pilot on Moodle

Lead Beneficiary: IST

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Authors:	António Paulo, Lurdes Gano

For the Lead Beneficiary	**Reviewed by Work package Leader**	**Approved by Coordinator**
António Paulo	**Mojmír Němec** 	**Mojmír Němec** 

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CO	Confidential, only for Beneficiaries of the A-CINCH project	

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Project information

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EC Project Officer:	Kateřina Ptáčková
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Coordinator contact:	+420 224 358 331, mojmir.nemec@fjfi.cvut.cz
Administrative contact:	+420 245 008 599, cinch@evalion.cz
Online contacts:	http://www.cinch-project.eu/

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EXECUTIVE SUMMARY

The preparatory course for a hands-on training in “Synthesis and Analytical Control of Radiopharmaceuticals” was elaborated. The materials for the hands-on training have been prepared to the extent that the trainings could be conducted. IST has already conducted the training with 4 students and their feedback was very positive.

The course was designed as an experimental teaching. It offers a preparatory phase before the actual practical teaching based on the "Basic Radiochemistry Course" developed by the University of Helsinki and provided by the A-CINCH project. This allows participants to get used to the topics discussed at their own pace and save a lot of time on site.

CONTENT

1. INTRODUCTION

Nuclear medicine modalities involve the administration of radiolabeled drugs, called radiopharmaceuticals, which are used for diagnostic or therapeutic applications depending on the physical properties of the labelling radionuclide. The implementation of nuclear medicine as an autonomous specialty relied strongly on SPECT imaging studies with ^{99m}Tc radiopharmaceuticals since the early 1970s, which was followed by a fast development of PET imaging due to the increasing availability of ^{18}F-labeled tracers in the early 1980s, namely [^{18}F]-2-FDG that still remains the leading PET tracer in oncology. Currently, an exponential expansion of radiotherapeutics in oncology (Figure 2), it is expected ,which has been fostered by the recent approval of [^{177}Lu]Lu-DOTA-TATE (Lutathera) and [^{177}Lu]Lu-PSMA-617 (Pluvicto^{TM}) by the FDA and/or EMA agencies for the treatment of neuroendocrine tumors and prostate cancer, respectively. Numerous clinical trials involving novel radiotheranostics are running nowadays, due to the very encouraging preclinical results obtained in the past few years for antibodies and their fragments, peptides or peptidomimetics, radiolabeled with alpha- or beta emitters. The aim of the HoT is to present a general overview of the most relevant aspects involved in the design, synthesis, characterization and preclinical evaluation of radioactive compounds with potential interest as radiopharmaceuticals.

2. Structure of the course

The course includes a theoretical part addressing the design and types and clinical applications of radiopharmaceuticals (e.g., diagnostic versus therapeutic agents; perfusion versus target-specific agents), fundamentals of radiopharmaceutical chemistry (classical PET radionuclides, radiohalogens, radiometals), analytical and quality control of radiopharmaceuticals, preclinical investigation of radiopharmaceuticals (cellular studies and animal imaging). The theoretical part is based on the e-course "Basic course in Radiochemistry" developed by the University of Helsinki and provided by the A-CINCH project, which is available at https://eshop.cinch-project.eu/products/Basic-course-in-Radiochemistry/42. All the participants in the HoT had to attend this e-course before assisting to the hands-on training.

The HoT itself was scheduled for a week (5 working days). In the morning of the first day, the HoT was introduced and two theoretical lectures on preclinical studies of radiopharmaceuticals were given. Then, several practical sessions focused on the synthesis, analytical control and biological evaluation of a target-specific radiopharmaceutical took place.

3. Hands on Training in Lisbon (CTN campus/IST)

The IST conducted the hands-on training on "Synthesis and Analytical Control of Radiopharmaceuticals" in the facilities of the Group of Radiopharmaceutical Sciences from IST at CTN/IST, from 17th to 21th July 2023.

Four students, with different levels of education (one PhD, two PhD students and one master's student) and from three different countries, were selected out of eight applications.

In the morning of the first day the students assisted to two theoretical lectures on topics related with the preclinical evaluation of radiopharmaceuticals: **T1**, In vitro Evaluation: Cell-Based Assays; **T2**: In vivo Evaluation: Animal Models, Biodistribution, Metabolism Studies. Thereafter, the students followed several practical sessions, as summarized and illustrated below (**Figure 1**).

- **Session 1 (S1)** – **Measurement of the Activity of a Medical Radionuclide (e.g., ^{111}In)**: Measurements using the dose calibrator and the gamma-counter, including the demonstration of the calibration of the equipment.
- **Session 2 (S2)** – **Analytical Techniques for Radiochemical Purity Determination**: Running of radio-HPLC and radio-ITLC assays, namely using common radioactive precursors such as $^{111}InCl_3$.
- **Session 3 (S3) – Synthesis and Characterization of Cold Precursors and Surrogates:** Synthesis and characterization of a cold surrogate (M-DOTA-PSMA617, M = ^{nat}In) of a PSMA derivative by mass spectrometry (ESI-MS).
- **Session 4 (S3) – Synthesis and Purification of a Radiopharmaceutical:** Labelling of a PSMA derivative (DOTA-PSMA$_{617}$) with $^{111}InCl_3$; Purification of the radioconjugates using Sep-Pak C18 cartridges; Radionalytical control (HPLC and ITLC) of the final radioconjugate (M-DOTA-PSMA$_{617}$, M = ^{111}In), including its chemical identification by HPLC co-injection with the cold congener and analysis by γ-detection and UV-vis detection, respectively.
- **Session 5 (S5) – In Vitro Evaluation of a Radiopharmaceutical:** determination of the *in vitro* stability of a radiopharmaceutical (M-DOTA-PSMA$_{617}$, M = ^{111}In) under physiological conditions and in the presence of cell medium; assessment of its lipophilicity through the determination of the n-octanol/water partition coefficient (log P) by the shake flask method.
- **Session 6 (S6) – Cell lines and cell culture:** Demonstration of basic cell culture protocols (e.g. cell growth and propagation, cell subculture, contamination and biosafety, optical microscope observation, growth media, sera and reagents).
- **Session 7 (S7) – Cellular Studies of a Target-Specific Radiopharmaceutical**: cellular uptake assays of a radiopharmaceutical (M-DOTA-PSMA$_{617}$, M = ^{111}In) in human tumor cell lines, including blockade experiments.
- **Session 8 (S8) – Biodistribution and Metabolism Studies of a Target-Specific Radiopharmaceutical**: Evaluation of the biodistribution and metabolic stability of a radiopharmaceutical (M-DOTA-PSMA$_{617}$, M = ^{111}In) in normal mice.

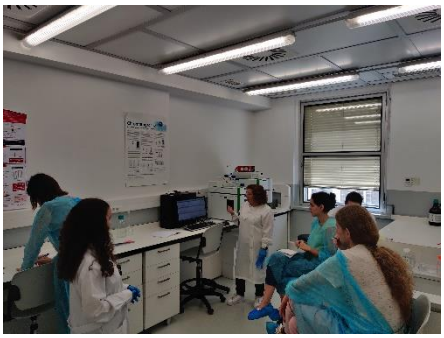

Figure 1. *The students in the laboratory with their supervisors Célia Fernandes (left) and Lurdes Gano (right).*

4. CONCLUSIONS

The online part of the Basic course in Radiochemistry" developed by the University of Helsinki and made available by the A-CINCH project allowed participants of the HoT "Synthesis and Analytical Control of Radiopharmaceuticals"to gain basic scientific knowledge before the face-to-face classes, allowing for a more efficient use of time and resources during traditional laboratory exercises and lectures. According to the final discussion on the last day of the HoT, which was attended by all trainees and supervisors, the face-to-face phase was quite successful in terms of participant satisfaction.