IFIGENEIA

Innovative Facility for Isotope GENeration with Efficient Ion Accelerator

T4.3 Investigate best ligands for development within excellence hub

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Kick-off meeting
3-4 April 2025
Thessaloniki, Greece

This project has received funding from the European Union's Horizon Europe Framework Programme for Research and Innovation under grant agreement no 101186921.

T4.3 Description

T4.3 Investigate best Ligands for development within excellence hub (M5-M42) [Leader: UL]

- The aim of T4.3 is to
- **investigate the relevance of several promising cancer targets**.
- In this regard, we will examine **promising targets in various cancer types.** Targets of interest will be selected and evaluated in the literature.

- Native ligands and their shorter variants will be **subsequently designed** and synthesized by means of classical organic chemistry and solid-phase support techniques. Such pharmacophores will be further equipped with radionuclide-tailored chelating ligands.
- The ultimate aim is to develop highly stable, affine, and specific radiotracers and radiopharmaceuticals for the most promising targets strongly and commonly over-expressed in cancer tissues.

T4.3 Investigate best Ligands for development within excellence hub

Start Date:	**M5**	**Task Leader:**	**UL**
End Date:	M15-42-48	**Task Contributors:**	UL, GNP

Del.	Deliverable Title	Lead Partner	Diss. Level	Due On
D4.2	Report for the identification of the best candidate isotopes for each of the three application areas: theranostics, therapy and diagnostics	UL	SEN - Sensitive	15 (42)

Mx	Milestone Title	Lead Partner	Mean of verification	Due On
4	Pilot pre-clinical studies finalization	6 - GNP	D4.3	48

T4.3 Methodology

80 % of isotopes still come from aging reactors

Target Selection and Literature Evaluation (M5–M10)

- **Systematic review of current literature** to identify cancer targets with:
  - Strong and selective overexpression in tumors
  - Existing ligands or known binding motifs
  - Previous validation in imaging or therapeutic contexts
- **Utilize databases and tools** (e.g., The Human Protein Atlas, TCGA, IUPHAR/BPS Guide to Pharmacology) to support selection.
- **Select 3–5 (?) top-priority targets** based on expression profiles, feasibility, and clinical relevance (e.g., PSMA, GRPR, CXCR4, HER2, integrins).

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Radionuclide Candidates

Ligand Design and Optimization (M10–M20)

- **Design ligand candidates**:
  - Based on native ligands, mimetics, or peptidomimetics
  - Shortened variants with retained binding affinity
- **Perform in silico modeling and docking** to refine ligand structure and predict binding affinity.
- **Involve AI-assisted design platforms** (optional) to speed up optimization and suggest novel scaffolds.

T4.3 Timetable - Resources

- Timeline for T4.3 (M5–M42) – Activities & Resources:

Phase	Timeframe	Activity Description
1. Target Selection	M5–M10	Literature review & prioritization of 3–5 top cancer targets
2. Ligand Design	M10–M20	In silico ligand modeling, docking, design of mimetics
3. Synthesis	M20–M30	Solid-phase & organic synthesis of ligand candidates with chelators
4. Evaluation	M30–M40	In vitro testing: stability, affinity, specificity
5. Reporting & Handover	M40–M42	Documentation, data sharing with T4.4–T4.5, contribution to WP4 deliverables





T4.3 Timetable - Resources

- **Key Inputs:**
- **From WP3:** LINAC energy profile, target irradiation simulations
- **From WP4 (T4.3–T4.5):** Preclinical and radiochemical feasibility
- **To WP1 & WP5:** Planning, safety, and scale-up integration

Interactions with other Tasks - 1

- **Task Collaboration & Data Flow:**
- **WP3 (LINAC design):**
  Provides energy range, target types, beam intensity – vital to estimate production yields and validate radionuclide production feasibility.
- **T4.1 (Regulatory Framework):**
  Alignment with legal and ethical aspects of radionuclides handling, transportation, and waste.
- **T4.3 (Ligands):**
  Coordination on radionuclides suitable for coupling with ligands for cancer-targeted applications (e.g., Lu-177 with PSMA ligands).

Interactions with other Tasks - 2

- **T4.4 (Preclinical validation):**
  Provides feedback on biological behavior, biodistribution, toxicity of proposed radio-labelled molecules (as potential radiopharmaceuticals).
- **T4.5 (Pilot production):**
  Task 4.2 feeds selected radionuclides and target specifications into small-scale test productions.

- **Deliverables Supported:**
- **D4.1:** Specification report for radionuclide lab
- **D4.2 / D4.3:** Radionuclide selection protocols and production strategy