



# MEDICIS-PROMED

## WP3: Theranostic radiopharmaceuticals for imaging/treatment cancer



Medicis



Advanced  
Accelerator  
Applications

A Novartis Company



ÉCOLE POLYTECHNIQUE  
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UNIVERSITÉ  
DE GENÈVE  
FACULTÉ DE MÉDECINE



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UNIL | Université de Lausanne  
Faculté de biologie  
et de médecine



7<sup>th</sup> supervisory meeting – Januar 17th, 2019  
Vienna (Medauston)

# WP3-Overview of ESR deliverables

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Deliv/ESR number	Researcher	Location	Deliverables title / due date in months
D3.1 ESR-8	Alice D'Onofrio	IST (Lisboa, C2TN radiopharma)	Cell nucleus targeting with bioligands for Auger Therapy / <b>M36</b>
D3.2 ESR-1	Annie Ringvall Moberg	CERN-Isolde (Geneva)	Laser molecular break-up in RFQ cooler for beam purification / <b>M30</b>
D3.3 ESR-6	Roberto Formento	AAA/Arronax (Nantes)	Cyclotron production and mass separation of SC-47/48/49 <b>M36</b>
D3.CH1 ESR-CH2	Francesco Cicone	Lausanne University Hospital (CHUV)	Preclinical imaging and animals model – clinical translation on cancer / <b>M36</b>
D3.5 ESR-14	Ioanna Prionisti	University of Geneva (HUG)	New approaches and delivery methods for the treatment of glioblastoma through brachytherapy / <b>M41</b>
D2.5 ESR-12	Alexandra Litvinenko	UNIGE, Faculty of Medicine, HUG	Investigation of imaging probes for ovarian cancer in animal models / <b>M24</b>

# WP3- ESR milestone status (I)

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Milestone number	ESR in charge	Milestone title	Due date (in months)	Current progress at January 2019
MS11	Alice D'Onofrio (ESR8)	Synthesis of cold Tb bifunctional complexes, characterization of their DNA binding	24	<b>70%</b> Waiting for Tb isotopes
MS12	Annie Ringvall Moberg (ESR1)	CO+ injection in a RFQ-Cooler and conditions for molecular break-up	15	<b>90% (24 months)</b>
MS13	Roberto Formento Cavaier (ESR6)	<ol style="list-style-type: none"> <li>1. Development of a Gadolinium target for the production of Terbium radionuclides</li> <li>2. Development of a natural titanium-based target for 47/48/49Sc production</li> </ol>	20	<b>100% of milestone 1</b> <b>100% of milestone 2</b> <b>(35 months)</b>

# WP3- ESR milestone status (II)

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Milestone number	ESR in charge	Milestone title	Due date (in months)	Current progress at January 2019
MS15	Francesco Cicone (ESR-CH2)	<p>1. Labelling of anti-Tumor Endothelial Marker 1 (TEM1) with radioiodine. Immunobinding assays and biodistribution in mice. Micro SPECT/CT imaging of I-123-antiTEM1</p> <p>2. Labelling of anti-Tumor Endothelial Marker 1 (TEM1) with radiometals. Immunobinding assays and biodistribution in mice. Micro PET/CT imaging of Tb-152-antiTEM1</p> <p>3. Radioimmunotherapy of Sarcomas in mouse xenografts (I-131 vs Tb-161 vs Tb-149)</p>	M16	<p><b>66% (at October 2018)</b></p> <p>(100% milestones 1 and 2)</p>
MS10	Ioanna Prionisti (ESR-CH3)	In vivo implantation glioblastoma model for brachytherapy	M20 (->M29)	<p><b>60%</b></p> <p><b>(24 months)</b></p>
MS14	Alexandra Litvinenko (ESR-CH1)	Multi-modality imaging techniques (PET, CT and MRI) at different phases of ovarian cancers in small animals models	M20	<p><b>40%</b></p> <p><b>(25 months)</b></p>

### Achievement and current progress

- **36 months of PhD at CHUV, milestone 1 and 2** are achieved. Labeling of anti-Tumor Endothelial Marker 1 (TEM1) with  $^{125}\text{I}$ ,  $^{111}\text{In}$  and  $^{152}\text{Tb}$  was successful. *In vitro* immunobinding assays and *in-vivo* biodistribution were completed. Micro SPECT/CT imaging of  $^{123}\text{I}$ -antiTEM1 and micro PET/CT imaging of  $^{152}\text{Tb}$ -anti TEM1 were acquired.
- **Milestone 3** “Radioimmunotherapy of Sarcomas in mouse xenografts. ( $^{131}\text{I}$  vs  $^{161}\text{Tb}$  vs  $^{149}\text{Tb}$ )” has not been achieved by the end of the contract due to the unavailability of  $^{161}\text{Tb}$  and/or  $^{149}\text{Tb}$ . A therapeutic experiment with  $^{177}\text{Lu}$ -antiTEM1 was attempted but would need further improvements which are beyond the scope of the MEDICIS-PROMED project.
- **Publications.** Two publications are in the writing phase and are expected in 2019 from the *in-vitro* and *in-vivo* experiments that were carried out during the duration of the contract.
- **Secondment status.** It was decided not to proceed with the organization of a secondment as it would have not been pertinent to Francesco’s experiments. Moreover, it was agreed that a secondment is not mandatory for Swiss-funded ESRs.

## Scientific production/international conferences/events/trainings

### Conferences (MEDICIS-related):

- 23rd IRIST (International Research group in Immunoscintigraphy and Therapy) International Meeting, Lausanne 2016. **Presentation:** “Labeling with halogens/metals and first preclinical evaluation of an anti-TEM1 antibody fragment”
- European Association of Nuclear Medicine (EANM 2017) 21-25 October 2017, Vienna. **Presentation:** “Preclinical evaluation of a single-chain variable anti TEM-1 fragment labelled with  $^{111}\text{In}$  and  $^{152}\text{Tb}$ ”.
- 6<sup>th</sup> Faculty and Staff Cancer Retreat of the Swiss Cancer Center Lausanne (14-15 November 2017), Lausanne. **Presentation:** “Preclinical evaluation of a single-chain variable anti TEM-1 fragment labelled with  $^{111}\text{In}$  and  $^{152}\text{Tb}$ ”.
- MEDICIS-Promed Lemman School on Preclinical and Clinical Imaging with radioisotopes, Lausanne, CH (12 March 2018). **Invited Talk:** Physics in Nuclear Medicine.

### Scientific production :

- It is worth noting that Francesco contributes to a large amount of ongoing research that lead to the production of 18 articles in peer-reviewed journals since January 2016. One article he co-authored (Sjögreen Gleisner K et al. (2017) EJNMMI Phys.;4:28) has received the Springer Prize: EJNMMI Physics Best Paper- Award during the last EANM congress (Dusseldorf 2018)
- He is reviewer for the leading journals in the field of nuclear medicine and molecular imaging (EJNMMI, JNM etc.)

## Scientific production/international conferences/events/trainings

He is co-editor of two thematic issues titled: “Perspectives in small animal radionuclide imaging” (<https://www.frontiersin.org/research-topics/6866/perspectives-in-small-animal-radionuclide-imaging>) and “Nuclear Medicine in the context of Personalized Medicine” (<https://www.frontiersin.org/research-topics/8806/nuclear-medicine-in-the-context-of-personalized-medicinein>) in the journal Frontiers in Medicine, which are open for submissions.

### Academic achievements.

- On 09/04/2018 Francesco has received the National Habilitation to Associate Professorship in Radiodiagnostic and Radiotherapy from the Italian Ministry of Instruction, University and Research, available at:
  - <https://asn16.cineca.it/pubblico/miur/esito/06%252FI1/2/4>
- In parallel, Francesco was Graduated with a **PhD title** from "Sapienza" University of Rome in "**Angio-Cardio-Thoracic Pathophysiology and Imaging**"

### Outreach

- Participation to the article “CERN to produce radioisotopes for health”, in CERN courier.
- Francesco has participated to the recent media visit of 29<sup>th</sup> November at CERN MEDICIS
- Participation to the recording of the “MEDICIS contest outreach video” at CHUV, Lausanne

## Achievement and current progress

**36 months of PhD at C2TN, milestone** is well advanced:

- First clickable tetrazine containing chelators have been synthesized and successfully labelled with cold In and with  $^{111}\text{In}$ . Click reaction with TCO was performed successfully.
- Completed the pre-clinical evaluation (cellular uptake and internalization in +/- and hu/mu TEM1 cell lines) of four mAb fragments towards TEM1 receptor by labelling with  $^{125}\text{I}$ . None of the previous mAb fragment showed promising pre-clinical behavior, currently working on a new mAb fragment.
- Pre-clinical *in-vitro* and *in-vivo* evaluation of the new radioiodinated mAb fragment is completed and confirmed that is the most-promising candidate for further studies

## Next steps toward the scientific milestone

- Conjugation with TCO-mAbFc still to be optimized. On-going radiolabelling and biological evaluation of the clickable radioimmunoconjugates.
- Due to the no availability of Tb-161, the project was re-oriented towards the development of clickable radioimmunoconjugates as theranostic agents for TEM1 pre-targeting.



### Secondment done

- **CHUV:** August - October 2018 - SPECT imaging and pre-targeting approach of mAb fragments directed towards TEM1 receptor with  $^{111}\text{In}$  performed with poor results, investigations on-going to optimize TCO binding to mAb.

### Scientific production/international conferences/events/trainings

- Radiopharmaceutical Science group, C2TN, Lisbon, November 2015. **Presentation:** "Design, synthesis and pre-clinical evaluation of multifunctional  $^{161}\text{Tb}$  complexes for cell specific targeting of DNA"
- ICTR-PHE, 15-19 February 2016, Geneva. **Poster:** "MEDICIS-produced radioisotope beams for medicine applications Marie Curie Innovative Training Network"
- Cancéropôle Grand-Ouest Workshop at Le Bono, France. September 2016. **Presentation:** "Design, synthesis and pre-clinical evaluation of multifunctional  $^{161}\text{Tb}$ -complexes for DNA-Targeted Radioimmunotherapy"
- Radiopharmaceutical Science group, C2TN, Lisbon, October 2016. **Presentation:** "Design, synthesis and pre-clinical evaluation of Clickable  $^{161}\text{Tb}$  complexes for DNA-Targeted Radioimmunotherapy – Experimental Part"
- C2TN Thematic Strand Workshop - C2TN, Lisbon, October 2016. **Presentation:** " $^{161}\text{Tb}$ -Complexes for DNA-Targeted Radioimmunotherapy"
- Chemistry Doctoral School in the Instituto Superior Tecnico of Lisbon, November 2016. **Presentation:** "Design, synthesis and pre-clinical evaluation of multifunctional  $^{161}\text{Tb}$  complexes for cell specific targeting of DNA".
- Phd Open Days at Instituto Superior Tecnico, Lisbon 5-6 April 2017. **Poster and Pitch Presentation:** "DNA-Targeted Radioimmunotherapy with clickable  $^{161}\text{Tb}$ -complexes".

Design, synthesis and pre-clinical evaluation of multifunctional  $^{161}\text{Tb}$  complexes for cell specific targeting of DNA

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## Scientific production/international conferences/events/trainings

- Encontro Ciencia 2017, Lisbon 3-5 July 2017. **Poster**: "Towards clickable radioimmunoconjugates as theranostic agents for TEM-1 targeting"
- 2ECQUL – University of Lisbon PhD Chemistry Meeting organized by Colegio de Quimica at Rectory of Universidade de Lisboa, Lisbon 4-5 December 2017. **Poster** and **Flash Presentation**: "Clickable Radioimmunoconjugate – Theranostic agents for TEM1 targeting".
- C2TN Annual Workshop, C2TN, Lisbon 6 December 2017. **Poster**: "Towards clickable radioimmunoconjugates as theranostic agents for TEM-1 targeting".
- Escola Superior Tecnologias da Saude, Lisbon – 23 March 2018 – **Presentation** – "MEDICIS-Produced radioisotopes for medicine".
- Instituto Superior Tecnico – Keep in Touch – 23 May 2018 – **Posters** – "MEDICIS-Produced radioisotopes for medicine" and "Clickable Radioimmunoconjugate – Theranostic agents for TEM1 targeting".
- World Molecular Imaging Conference, Seattle, September 2018. **Poster** "Clickable Radioimmunoconjugates: Theranostic Agents for TEM1 pre-targeting."
- CancéropôleGrand-Ouest Workshop, France, September 2018. **Presentation**: "Clickable Radioimmunoconjugates: Theranostic Agents for TEM1 pre-targeting."
- C2TN Annual Workshop, C2TN, Lisbon 11 December 2018 **Presentation**: "Development of TEM1/Endosialin Targeted Radioimmunoconjugates for Cancer Theranostics"

# Annie Ringvall Moberg, ESR1

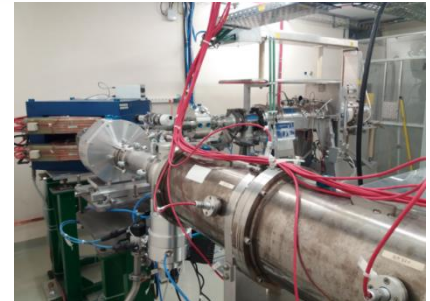
(I)

Studies of bunched atomic and molecular beams in the ISOLDE RFQ cooler and buncher

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## Achievement and current progress

- **24 months of PhD at CERN:** New beam instrumentation based on secondary-electron multiplication (SEM) has been designed, built and commissioned with the purpose to detect bunched ion beams from the ISOLDE-HRS RFQ ion-beam cooler. In April 2018 Time-of-Flight (ToF) measurements were conducted using the new SEM detector in order to study beam dynamics and bunching in the RFQ. Using ToF measurements, the longitudinal beam emittance and transmission efficiency were investigated and optimized. Molecular formation and dissociation in the RFQ with respect to buffer gas and radio-frequency were also investigated. Furthermore, the Offline 2 facility is in its commissioning state
- Successful Time-Of-Flight measurements for ions/molecules extracted from the RFQCB at ISOLDE took place in June 2018. The data has been analysed and it was presented at the EMIS conference and a conference proceeding will be submitted.
- Development of the RFQCB at ISOLDE, e.g. the bunching mode and fast switching was also done in June.
- The commissioning of Offline 2 has started and the first ion beam has been produced at the facility.



## Next Step

- The RFQcb is still under construction and commissioning will proceed until the Offline 2 facility is fully ready.

### Secondment status

- **The GUNILLA facility at the University of Gothenburg:** 2 months during Jan-Mar 2019.
- **DESIREE facility at Stockholm University:** 6 weeks during Nov-Dec 2017, may return for further experiments.
- **RaySafe in Gothenburg:** professional visit during two weeks in June 2017.

### Scientific production/international conferences/events

- ISOLDE Workshop – December 2018. **Poster presentation:** Time-of-Flight study of cooled molecular beams
- EMIS – The International Conference on Electromagnetic Isotope Separators and Related Topics (Geneva) from 16th-21<sup>st</sup> of September 2018. **Poster presentation:** “Time-of-Flight study of molecular beams extracted from the ISOLDE RFQ cooler and buncher”
- She gave a presentation of ISOLDE, CERN-MEDICIS and MEDICIS-Promed at Stockholm University for the Atomic Physics group.
- ARIS – Advances in Radioactive Isotope Science, Keystone, Colorado (USA) from May 28 to June 2, 2017. **Poster presentation:** “The development of the new Off-line 2 isotope mass separator at ISOLDE, CERN within MEDICIS-Promed”.
- Annie was a part of the tour and a partial guide for the MEDICIS facility during the official CERN visit from Ms Elke Sleurs (State Secretary for Combating Poverty, for Equal Opportunities, for Disabled People and for Science Policy). During the visit she presented a poster briefly explaining the MEDICIS production of the radioisotope beam for medical applications. (2016)

### Events/trainings

- She organized a visit to CERN for third year students at the University of Gothenburg, high schools teachers and staff of a science center in Sweden. The visit included e.g. a visit/guided tour to ISOLDE and Offline 2. During the visit Annie presented her project with the MEDICIS-Promed (2018).
- She organized a visit at ISOLDE and Off-line 2 for third year students at the University of Gothenburg, high schools teachers and staff of a science center in Gothenburg. During the visit Annie presented her project with the MEDICIS-Promed (2017).
- Internal training at CERN. Training performed within Medicis-Promed and CERN.
- Attended the CERN Accelerator School (CAS) – Introduction to accelerator physics (February 2017).
- Attended the CAS – Beam injection, extraction and transfer (March 2017).
- High Voltage electrical habilitation, CERN (2016).
- Radioprotection formation for Controlled Area, CERN (2016).
- Project Management with OpenSE (2016).
- First Aider – Level 1 (2016).

# Roberto Formento Cavaier, ESR6

(I)

Large scale production of innovative radioisotopes for theragnostic using a middle sized high-current cyclotron and the CERN-MEDICIS mass separation system

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## Achievement and current progress

- **35 months of PhD at AAA/Arronax**
- **Production of very high specific activity Er-169: Irradiation at ILL (FR) reactor, mass separation at CERN (CH). This was the first worldwide production of high specific activity Er-169 with a usable dose produced (18 MBq)**
- **milestone 1 – Sc production:** CFD validations under completion. Meanwhile together with Cern the logistic and the planning for the first proof of concept is ongoing.
- **milestone 2 – Tb production:** Natural gadolinium targets have been purchased, everything is ready at Arronax for the irradiation, waiting for the availability of MEDICIS mass separator (2<sup>nd</sup> of April 2019 ?). Cross-section experiment and analysis performed to evaluate production yield for Tb-149, Tb-152 and Tb-155.

## Next steps toward the scientific milestone – remaining 1 month

- **Thesis defense the 12<sup>th</sup> of February 2019**

## Secondment status

- **CERN** 6 months: started on October 2017 for 2 month, from February 2018 to May 2018
- **JOGU (Mainz)** 2 month: started on November 2017, ongoing until end of December 2017, one week in May 2018

Large scale production of a beta-/gamma emitter radioisotope for therapy using a middle sized high-current cyclotron and the CERN-MEDICIS mass separation system

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## Scientific production/international conferences

- ICTR-PHE, 15-19 February 2016, Geneva. **Poster:** “MEDICIS-produced radioisotope beams for medicine applications Marie Curie Innovative Training Network”
- 24th Conference of Application of Accelerator in Research and Industry, 30th October- 4th November 2016, Fort Worth, Texas. **Presentation and Poster:** “MEDICIS-produced radioisotope beams for medical applications – a Marie Curie Innovative Training Network”
- 6<sup>th</sup> Symposium on Medical radioisotopes/Challenges in production, transport and applications, Mechelen, May 11<sup>th</sup>. **Poster:** “Cyclotron produced terbium radionuclides for theranostic applications”.
- 9th International Conference on Isotopes & Expo, 12 – 16 November 2017, Doha (Qatar), **Presentation:** “High Specific Activity production of Scandium Sc-47”
- 17th International Workshop on Targetry and Target Chemistry (WTTC17), ICNAS (PT), **Presentation: Arronax non-standard radionuclides and radiopharmaceuticals production**
- The International Conference on Electromagnetic Isotope Separators and Related Topics (EMIS), CERN from 16th to 21st September 2018, **Presentation:** “very high specific activity production of Er-169”

Large scale production of a beta-/gamma emitter radioisotope for therapy using a middle sized high-current cyclotron and the CERN-MEDICIS mass separation system

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## Publication

- Terbium Radionuclides for Theranostics Applications: A Focus On MEDICIS-PROMED, Physics Procedia 90 ( 2017 ) 157 – 163, Roberto *et al.*
- Proceeding NIMB for the conference EMIS on Erbium-169 production, authors review ongoing

## Events

- JED Journée de l'école doctoral, 30 June 2017, Angers. **Presentation:** “ Cyclotron produced terbium radionuclides for theranostic applications”

## Trainings

- Training performed within Medicis-Promed.
- High Voltage electrical habilitation, CERN, October 2017
- Radioprotection formation for Controlled Area, CERN, November 2017
- Laser user and expert, CERN, April 2018
- Ansys UDF and Ansys Fluent, October 2018

## Seminar

- RADIONUCLIDES PRODUCTION FOR THERAGNOSTIC APPLICATIONS, Politecnico di Torino, 22<sup>nd</sup> May 2018



### Achievement and current progress

- **24 months of PhD at UNIGE**
- **Milestone MS10** is well advanced and will be completed in time (given the new timeline). Established bibliography for the CNS immune system, glioblastoma and radiation therapy. A review of the literature is completed and will be submitted in due course. The basic plan for animal experiments has been established.
- A pilot animal experiment has been performed in July 2017
- Training in immunostaining and imaging techniques and establishing the immunostaining protocols

### Next steps toward the scientific milestone – remaining 11 months

- Ethical approval for animal experiments
- The 1<sup>st</sup> phase of animal experiments will be implemented in spring of 2019

### Secondment status

- **IST:** probably 2~3 months – in discussion, not until May 2019

### Scientific production/international conferences/events/trainings

- RESAL Module 1: Introductory course in laboratory animal science, 13-22 March 2017, Geneva
- Attending animal experimentation seminar “Material exchange between donor and host photoreceptors: A new way of looking at retinal cell transplantation”, 24 April 2017, Geneva
- Attending animal experimentation symposium “ Reverse engineering the developing brain” 18-20 September 2017
- Attending animal experimentation symposium Louis-Jeantet “The genetic evolution of cancer”, 10 Octobre 2017
- Attending the advanced course “The molecular stratagem of GBM”, 5-12 May 2018
- Radioprotection training course, 14-18 May 2018
- Registering in the Lemanic Neuroscience Doctoral School (LNDS) at the University of Geneva, Faculty of Science
- Training performed within Medicis-Promed

# Alexandra Litvinenko, ESR-CH1

Investigation of imaging probes for ovarian cancer in animal models

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## Achievement and current progress

- **25 months** of PhD at UNIGE.
- **Chemistry:** Dual-modality imaging tracer (PET and fluorescence) design is completed, synthesis is in progress.
- **Biology:** *In vitro* library is completed, cell models with inducible expression of folate receptor are established and characterized.

## Next steps toward the scientific milestone – remaining 11 months

- Complete tracer synthesis, and quality control.
- Radiolabeling, and *in vitro* testing.

## Secondment status

- **EPFL:** “Basics of optical imaging techniques” (December 2016 - November 2017).

## Scientific production/international conferences/events/trainings

- 02/17 - present: French course
- 03/17 - 05/17: Doctoral course “Animal models in biomedical research”
- 03/17: Module 1 RESAL training on animal experimentation
- 06/17 - 07/17: Doctoral course “Academic writing for doctoral students”
- 06/17 - present: Trainings within Medicis-Promed program
- 10/17 - 12/17: Doctoral course “Advanced biomedical imaging methods and instrumentation”
- 10/17: Symposium “Frontiers in Metabolism”
- 11/17: Radioprotection course, CHUV
- 10/18: Doctoral course: “Light microscopy and imaging”

# WP3, general comments

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- Secondments period have been completed or will be finalize almost for all ESRs. Only for one of the ESR the team did not succeed in organizing this period.
- The achievements are well in line with deliverables timing and show some nice advancement in the field of:
  - **radioisotopes production**; first PoC for the coupling of irradiation / mass separation achieved and show great promises, understanding in progress for the improvement of molecular beams physics,
  - **Radiochemistry**; interesting progress in the click-chemistry with ongoing work toward clickable radioimmunoconjugates as theranostic agents for TEM1 pre-targeting,
  - **Preclinical study**; labeling of anti-Tumor Endothelial Marker 1 (TEM1) with  $^{125}\text{I}$ ,  $^{111}\text{In}$  and  $^{152}\text{Tb}$  was well successfully performed with *in vitro* immunobinding assays and *in-vivo* biodistribution analyses, completed by micro SPECT/CT imaging of  $^{123}\text{I}$ -antiTEM1 and micro PET/CT imaging of  $^{152}\text{Tb}$ -anti TEM1, in another PhD, dual-modality imaging tracer (PET and fluorescence) study is progressing and in a last PhD still on progress for the next 12 months (at least) preclinical study to establish treatment of glioblastoma through brachytherapy is under evaluation
- In summary, this project is very successful in many aspects among which:
  - Creating a large range of Scientific expert around the production and use of radiopharmaceuticals thanks to a thorough training program as well as high level PhD project
  - Allowing improvement of innovant technologies that will be expected to favor entry of new theranostics compounds in nuclear medicine with final goal to improve patients lives!