Marie Skłodowska-Curie Actions (MSCA)
Innovative Training Networks (ITN)
H2020-MSCA-ITN-2014

Annex 1 to the Grant Agreement (Description of the Action) Part B

Table of Contents

List of Participants

Consortium Member	Legal Entity Short Name #	Academic	Non-academic	Award PhD	Country	Dept./ Division / Laboratory	Scientist-in-Charge	Role of Partner Organisation
Beneficiaries								
European Organization for Nuclear Research	CERN **1**	**X**			**EU**	Engineering Dpt Source Target Interaction Group Radioactive Beam Sources	Dr. T. Stora	
University of Manchester	Graphene inst. **2**	**X**		**X**	**UK**	University of Manchester, National Graphene Institute	Prof. K. Novoselov	
University of Mainz	JOGU **3**	**X**		**X**	**DE**	Johannes Gutenberg Universitaet Mainz, LARISSA Group	Prof K. Wendt	
Advanced Accelerator Applications	AAA **4**		**X**		**FR**	Systems engineering department	Dr. L. Macioco	
Instituto Superior Técnico	C2TN **5**	**X**		**X**	**PT**	Centro de Ciências e Tecnologias Nucleares Radiopharmaceutical sciences	Prof. I. Santos	
Centro Nazionale di Adroterapia Oncologica	CNAO **6**	**X**			**IT**	Directorate	Prof. R. Orecchia	
Lemer Pax	PAX **7**		**X**		**FR**	Direction	Dr. J.M. Lemer	
University of Leuven	KUL **8**	**X**		**X**	**BE**	Dept Physics Astronomy Instituut voor Kern- en Stralingsfysica	Prof. P. van Duppen	
Partner Org.								
Lausanne University Hospital	CHUV	**X**		**X**	**CH**	Dept of nuclear medicine and molecular imaging	Prof. MD J. Prior	36months ESR paid by CH: ESRCH2 preclinical studies ovarian cancer
Geneva University	UNIGE	**X**		**X**	**CH**	Faculty of Medicine	Prof MD P. Morel	2x36months ESR paid by CH: ESRCH1, ESRCH3 Surgery/translational imaging
Swiss Fed. Inst. of Tech., Lausanne	EPFL-ISREC	**X**		**X**	**CH**	School of Life Science Swiss Experimental Cancer Research Center	Prof. D. Hanahan	36months ESR paid by CH: ESRCH4 Molecular oncology Bioligand for preclinical studies
Medaustron	Medaustron		**X**		**AT**	Injector - Therapy Accelerator Team	Dr. P. Hurschuetz	Carbon Ion Hadron therapy
Oxford university consulting	Oxford consult		**X**		**UK**	Said Business School	Ms. F. Reid	Complementary Training
ARRONAX GIP	ARRONAX	**X**			**FR**	R&D Department	Prof. F. Haddad	Medical isotope cyclotron production
Institut Laue Langevin	ILL	**X**			**FR (EU)**	Radioisotope production	Dr. U. Koester	Medical isotope reactor production

1. Summary

MEDICIS-PROMED aims to develop a network of academic, medical and industrial partners providing an extensive doctoral program to 11 ESRs and 4 Swiss-supported ESRs (ESRCH)[1] in the field of new personalized treatments using radioisotope beams, notably for treatment of the deadly ovarian cancer, exploiting the newly discovered tumour endothelial marker 1 (TEM1/endosialin) for targeting the cancerous tissues. In this scheme, CERN, the European Organization for Nuclear Research is the coordinating partner, and collaborates with local hospitals which are able to exploit short-lived isotopes produced in the newly constructed CERN-MEDICIS facility. It fits within an extended network of high-technology companies and leading academic research institutes which will design new components for the development or tests of innovative radiopharmaceuticals and imaging agents for personalized treatment. It brings world-class researchers together in the field of lasers and isotope mass separation, accelerators, material science, oncology, entrepreneurial radiopharmaceutical production, and imaging, to propose new solutions to the 2nd deadliest cancer for women. In addition, the network will benefit from the coaching of the pioneer of personalized PET-imaging aided carbon hadron therapy recently tested in Japan

2. Excellence

2.1 Quality, innovative aspects and credibility of the research programme

- Introduction, objectives and overview of the research programme

The field of molecular oncology and nuclear medicine is rapidly evolving, with the recent marketing of new drugs exploiting new radioisotopes and radioactivity such as Xofigo® [1,2] This field is expected to expand rapidly and provide **new types of treatments combining imaging and personalized treatment** with the same radiopharmaceutical and different types of isotopes, emitting positron or gamma light for imaging on one side, and Auger electron, beta and alpha radiation for treatment on the other side, known as theranostics pairs [3]. In addition, positron emitting isotopes such as ^{11}Carbon can personalize hadron therapy treatments by imaging the dose distribution of the implanted ions [4,5] . This domain can now rapidly progress on a European level thanks to the present training network proposal where leading academic, medical institutes and high-tech companies will contribute to a multidisciplinary coordinated program, as shown in Figure 2.1a. This will build on the new CERN-MEDICIS medical radioisotope beams facility that can produce unique batches of innovative isotopes, such as ^{149}Terbium [6]. Figure 2.1b displays the present supply chain of radioisotopes for medicine on top, and at the bottom the new supply chain which is expected, resulting from MEDICIS-PROMED. It is going beyond the present common practices, thanks to the expected results of the ambitious R&D program, and to the new generation of young scientists trained in the relevant fields.

The program will develop along three R&D work packages integrating multidisciplinary intersectorial training teams, Table 2.1a:

- Development of new radioisotopes and techniques using isotope mass separation for medicine and based on CERN-MEDICIS (WP1)
- Development and test of ^{11}Carbon PET-aided hadron therapy (WP2)
- Synthesis & tests of radiopharmaceuticals to diagnose & treat ovarian cancer (WP3)

---

[1] ESR positions in Swiss partner organizations will be supported by Switzerland and are quoted as ESRCH1-4 following euresearch recommendations www.euresearch.ch (section 6)

[1] Nuclear Physics for Medicine, NuPECC report (2013), in the press ; www.nupecc.org; NuPECC is an Expert Committee of the European Science Foundation.
[2] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, *Cell*, 144(5), 646-674 (2011).
[3] LE Kandalaft, DJPowell, N Singh, G Coukos Immunotherapy for ovarian cancer: what's next? *J Clin Oncol* 29:925. (2011)
[4] U. Amaldi et al, Accelerators for hadron therapy: From Lawrence cyclotrons to linacs, *Nuclear Instruments and Methods in Physics Research* A620 563–577 (2010).
[5] T. Mendonca et al., Intense post-accelerated ^{11}Carbon beams for hadron therapy: Treatment and at the same time 3D dose mapping by PET imaging, CERN-ACC-NOTE-2014, in the press. http://cds.cern.ch/
[6] R. Augusto et al. CERN-MEDICIS (MEDical Isotopes Collected from ISOLDE): A new facility, CERN-ACC-NOTE-2014-0019, http://cds.cern.ch/

Figure2.1a
Left: Change in therapies following a PET/CT functional imaging using ^{18}F-based FDG radiopharmaceutical (N=22976). Reprinted from Hillner et al., JCO 2008. From bottom to top gray code: Major change in management; Major change in mode of therapy, minor change in nontreatment, minor change in therapies, no change.
Right: # of patients/year traited in the world by hadron therapy and number of operating centers. The Proton to Carbon treatment ratio is 9:1. Insert: European map, large circles represent carbon hadron therapy centers [1,4].

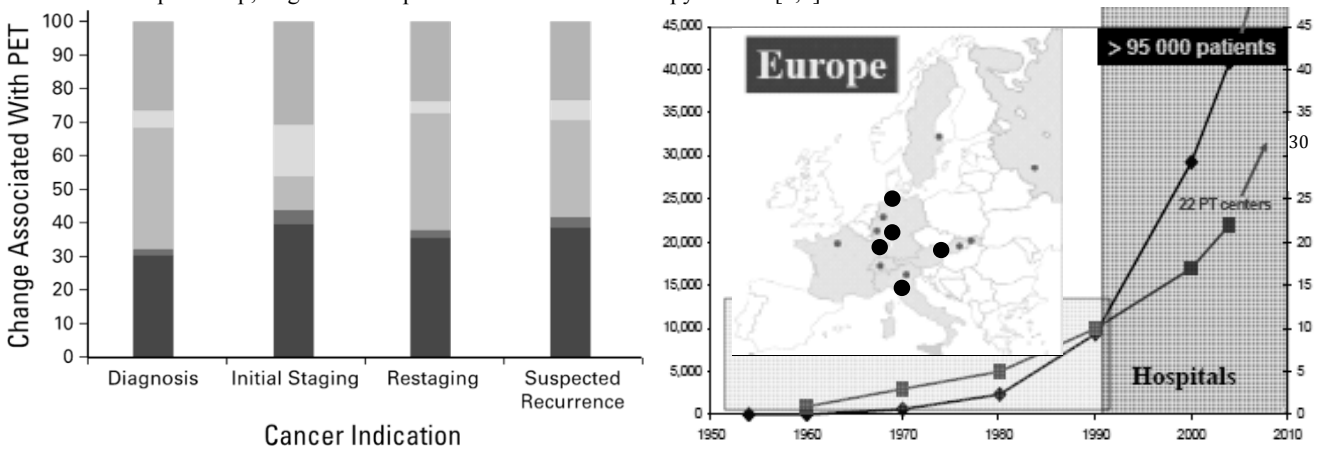
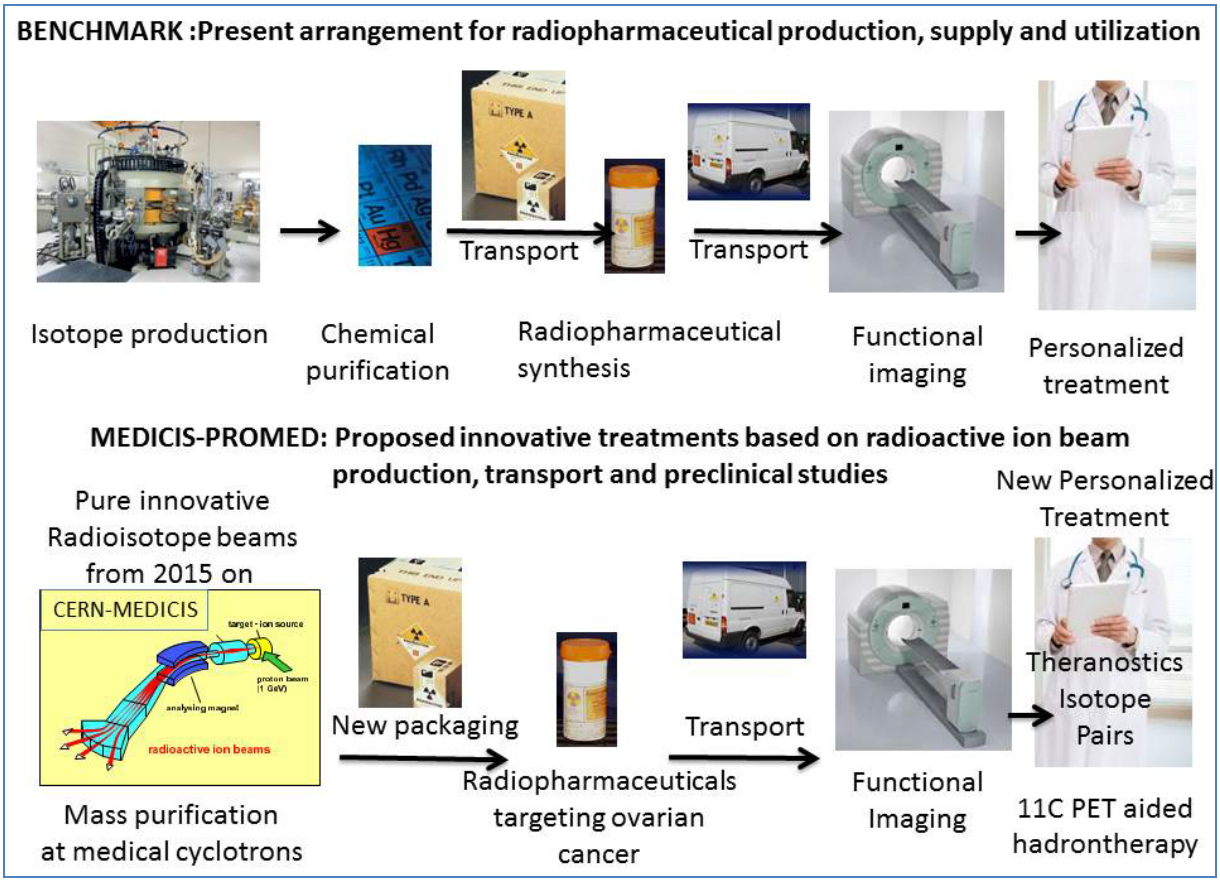


Figure 2.1b: Field of training and expected impact of MEDICIS-PROMED on the radioisotope-based personalized medicine supply chain in Europe.



From 2015 CERN-MEDICIS will be the first worldwide facility dedicated to **mass-separated radioisotope beams for medical applications**. Its **network**, consisting of university hospitals, hadron therapy centers and isotope distribution entrepreneurial companies across France, Italy and Switzerland, is **leading the field of oncological research, imaging and personalized treatments**. It will act as the seed for the extended **MEDICIS-PROMED** network and **train** a new generation of **entrepreneurial scientists** to develop systems for **new personalized treatments throughout Europe**.

- Research methodology and approach

The project will be structured into 6 Work Packages as shown on Table 2.1a:

Table 2.1a: Work Package List

WP No	Work Package Title	Activity Type	Lead Participant No	Lead Participant Short Name	Start Month	End month	ESRs involvement
1	Mass separation of innovative medical isotopes using CERN-MEDICIS	Research	3	JOGU	4	48	2,4,5,7,10
2	^{11}Carbon PET-aided hadron therapy	Research	6	CNAO	4	48	3,9,11 + CH1,4[3]
3	Theranostic radiopharmaceuticals for imaging/treatment of ovarian cancers	Research	4	AAA	4	48	1,6,8 + CH2,3[3]
4	Training	Training	1	CERN	4	48	1-11 +CH1-4[3]
5	Management	Management	1	CERN	1	48	N/A
6	Communication	Communication	5	C2TN	6	48	1-11 +CH1-4[3]

The research plan will follow the steps:

- Familiarization with the field of research, by making a literature survey and getting hands-on training with direct supervision
- A project development plan is devised, and first investigations, combining simulation tools and experimental approaches are followed.
- The ESR is coached to develop innovative approaches to the problems, test them, and use the results as feedback to evolve the prototype.
- Evaluation of the research progresses are made on a yearly basis. If there is no foreseen breakthrough within the timeframe of the project, an alternative, secure project is followed. In such an event, the European Project Officer is informed for his agreement. This is addressed further in 4.2 Risk Management.
- If conclusive results have been obtained from disruptive approaches, IPR is first evaluated, and the project is evolved within the network and eventually outside to promote the step from the successful demonstrator to an industrial up scalable system.
- These results are subsequently disseminated.
- The thesis manuscript is finally written and submitted to the doctoral school, followed by the thesis defence.

The network will specifically train young researchers in R&D topics that cover the disciplines required in this new integrated field of mass-separation of radioisotopes for medicine, specifically addressing the ovarian cancer. This is, to name but a few, targets for medical radioisotope production, ion sources to produce an accelerated radioactive ion beam, laser-based purification techniques, operational safety procedures and shipping technologies, multifunctional radiopharmaceutical synthesis, pre-clinical studies with innovative isotopes and dual imaging, robot-assisted surgical brachytherapy (Table 2.2a) . More precisely for WP1, ESR 4, 7 will develop new

[3] ESR positions in Swiss partner organizations are directly supported by Switzerland and are quoted as CH1-4 following euresearch recommendations www.euresearch.ch

[7] L. P. Gaffney et al. Studies of pear-shaped nuclei using accelerated radioactive beams, *Nature* 497,199–204 (2013)
[8] T. Stora, High intensity ^{6}He beam production, *Europhysics News* 43(5), (2012)
[9] Y. Blumenfeld, T. Nilsson, P. Van Duppen, Facilities and methods for radioactive ion beam production, *Physica Scripta*152, 014023 (2013), proceedings Nobel Symposium 152: Physics with Radioactive Beam.

production targets possibly leading to new isotopes, ESR7 new pure and efficient laser ion sources leading to higher collected quantities, ESR2 will develop an integrated safe isotope collection system at MEDICIS, and ESR10 the relevant transport technologies that were up-to-now lacking. For WP2, ESR11 works on the mass separated $^{11}CO^{+}$ beam production as the required first step in PET aided ^{11}Carbon therapy, ESR3 develops the next charge breeding scheme required for acceleration, while ESR9 performs the full acceleration and treatment ^{11}Carbon hadron therapy test and planning. ESRCH4 further develops bioconjugates suitable for imaging and treatment of the ovarian cancer therapeutic target defined in MEDICIS-PROMED, while ESRCH1 develops multimodal imaging methodologies for the treatment planning. In WP3, ESR1 works on novel methodologies to provide pure theranostics isotopes at CERN-MEDICIS, ESR6 focuses on the industrial production of theranostics radiopharmaceuticals at cyclotron centers, and ESR8 specifically on cancerous DNA-targeting radiopharmaceuticals. ESRCH2 integrates these new drugs and diagnostics into preclinical tests using multimodal imaging and ESRCH3 extends the disruptive therapeutic approaches, testing robotic-assisted surgical modes of operation. The contributions of the ESR to the MEDICIS-PROMED research program can also be seen in Figure 4.1a (sect 4.1).

- Originality and innovative aspects of the research programme

MEDICIS-PROMED proposes to significantly advance the use of radioisotopes for personalized medicine in Europe [1]. This will be done in three interconnected and coherent scientific intersectorial Work-Packages, with 11 Early Stage Researchers hired by the beneficiaries and 4 recruited in Swiss partner organizations, as shown in Table 2.2a. In Work Package 1 , the field of medical isotope production will be significantly impacted by the introduction of a new method of medical isotope production, that is isotope mass separation, which was up until then only developed for fundamental research studies [7-9]. It will be supported by the construction of CERN-MEDICIS, the first facility of this kind dedicated to the production of medical isotope batches [6]. Before CERN-MEDICIS, medical isotopes were exclusively produced at medical cyclotrons or at nuclear reactors [1]. The purification step was achieved by radiochemical methods. Recently, ISOLDE, the isotope mass separation online facility at CERN, has shown that new isotopes, and their combinations, can be used to address important problems to treat cancers at the preclinical stage [10]. With the construction of CERN-MEDICIS, not only new isotopes will be regularly produced for medical studies, but in addition the technique of mass-separation will be further developed to meet the needs of possible transfers to isotope production units in hospitals and private industry. In particular, after the recent development that was driven at Isolde, CERN, using nanomaterials for the production of new isotopes [11], we propose to explore in MEDICIS-PROMED the possibility of coating metallic target materials with graphene as protection layers with the **Nobel Prize laureate K. Novozelov**, **opening up the possibility to produce isotopes that were up-to-now inaccessible by mass-separation**. Indeed up until recently, no refractory isotopes could be produced this way [9,12]. It is expected that their production via volatile multicarbonyl molecules will now become possible, thanks to the graphene protective layer [13].

CERN-MEDICIS will also serve as a platform to test a **new approach for hadron therapy** as defined in Work Package 2. Hadron therapy centers are developed in USA, Japan and Europe, Figure 2.1a[6][4]. Most of the centers use protons, and combined cyclotrons or Linear injector and a circular synchrotron to reach the variable required beam energies to penetrate deeply in human tissues. More recently, hadron therapy with carbon ions, that is treatment using stable ^{12}Carbon ions instead of protons, has shown benefits for some families of radioresistant tumours. The present treatment planning however suffers from an important missing information which is the exact three dimensional dose exposure of the tissues, coming from eventual movement of the target or changes in

[10] C. Müller, et al. A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α- and β-radionuclide therapy: An in vivo proof-of-concept study with a new receptor-targeted folate derivative. *J Nucl Med* 53 1951(2012).
[11] Y. Kadi, et al., EURISOL High Power Targets, *Nucl Phys News,* 18(3) (2008).J.P. Ramos, et al. Intense $^{31-35}$ Ar beams produced with a nanostructured CaO target at ISOLDE, *NIMB*320, 83-88 (2014).
[12] T. Stora Recent developments of target and ion sources to produce ISOL beams. *NIMB*317, 402-410 (2013).
[13] J. Even et al., Rapid synthesis of radioactive transition-metal carbonyl complexes at ambient conditions*, Inorg. Chem.*, 51(12), 6431-6433 (2012).I. Usoltsev et al., decomposition studies on the stability of tungsten- and molybdenum carbonyl complexes performed at Riken (JP), Annual report, Lab. Radiochemistry Environmental Chemistry, Paul Scherrer Institute, p.3 (2013)
[14] K. Parodi, PET monitoring of hadrontherapy, *Nuclear Medicine Review* 15, C37–C42(2012)
[15] T. M. Mendonca, et al., production and release of ISOL beams from molten fluoride salt targets, *NIMB*329, 125 (2013).

blood irrigation of the exposed tissue during treatment. This is extremely important since exposition of healthy tissues and organs can lead to secondary effects, and sometimes to severe complications eventually engaging and compromising the survival diagnostics. Some attempts have been made to use the ion fragmentation and isotopes that are left on the ion track to map the distribution, however this is made difficult by the different reaction channels and isotopes that are produced in this way [14]. In this Work Package, we propose to develop the required production, mass separation and pre-acceleration accelerator elements to test the **direct use of PET ^{11}Carbon ion beams for hadron therapy [5]**. They present the dual function of treatment, because of similar properties as ^{12}Carbon ions, and in addition as imaging ions, because they emit positrons and can then be used to image the deposition pattern, using for instance PET-CT scanners. The development of the different elements in the acceleration chain has progressed significantly in the past few years, with for instance the development of new Sodium fluorine-based salt targets and the successful post-accelerated carbon isotope beams using electron beam ion sources [15]. CNAO and Medaustron, two European centers performing hadron therapy with carbon ions, are directly involved in this Work Package.

Work-Package 3 addresses the development of innovative treatments, using **theranostic pairs**, exploiting the developments of new isotopes made possible in WP1 & 2 and by CERN-MEDICIS. The use of theranostic isotope pairs and the development of personnalized treatment require a proper selectivity of the tissue or metabolic activity that needs to be monitored. This can be done only if biologically relevant molecules, enzymes or proteins can be associated with the tissue. **For ovarian cancers in that respect, a new protein target has recently been identified, the tumor endothelial marker 1 (TEM1) and an antibody fragment has shown high binding affinity to TEM1 [16]** . In MEDICIS-PROMED, new bioligands will be synthesized to chelate radioisotopes and both perform imaging studies and treatment for ovarian cancers in pre-clinical studies. The possible breakthrough is expected to originate from the combination of the new identified TEM1 targets, new functional ligands, and diverse combinations of radioisotopes that can provide imaging capabilities by emitting photons and positrons, treatment at mm-scale for large tumors with isotope emitting beta radiation, and small metastasis and single cell treatment capabilities using isotopes emitting alpha particles and Auger electrons [17-20]. To successfully address this task, leading university hospitals situated at close proximity of CERN, will highly contribute to this work package. In particular, the network will benefit from a series of training by the **Medical Doctor Prof. G. Coukos, recent Advanced ERC in immunotherapy**.

Table 2.2 a Recruitment Deliverables per Participant

ESR #	Participant	Start	Duration	Project	WP
1	**CERN**	**6**	**36**	Laser molecular break-up for isotope beam purification	3
2	**CERN**	**4**	**36**	Production of theranostics $^{149/152}$Tb at CERN-MEDICIS and shipping	1
3	**CERN**	**4**	**36**	CO injection fast valve for C-->C^{6+} C-->C^{1+}-->C^{n+} charge breeding	2
4	**Graphene inst**	**4**	**36**	Metallic foil targets with graphene for innovative isotopes	1
5	**JOGU**	**4**	**36**	Laser Ion Source for radiolanthanide purification at medical cyclotrons	1
6	**AAA**	**4**	**36**	Industrial production of β^-/γ therapy radioisotope with mass separation system at high power cyclotrons	3
7	**C2TN**	**4**	**36**	Uranium Carbide nanofibers targets for increased isotope extraction	1

[16] AN Chacko et al., Development of 124I Immuno-PET Targeting tumor Vascular TEM1/Endosialin, *J. Nuclear Medicine* 55, 1-8 (2014).
[17] C. Li et al., Antibody-based tumor vascular theranostics targeting endosialin/TEM1 in a new mouse tumor vascular model, *Cancer Biology&Therapy* 15:4, 1-9 (2014).
[18] O. Ratib, PET/MRI: a new era in multimodality molecular imaging. *Clin Transl Imaging,* 1(1), 5-10 (2013).
[19] GM van Dam et al., Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting:first in-human results,*Nature Medicine* 17(10), 1315-1319 (2011).
[20] Volonte F, Pugin F, Buchs NC, Spaltenstein J, Hagen M, Ratib O, Morel P , Console-Integrated Stereoscopic OsiriX 3D Volume-Rendered Images for da Vinci Colorectal Robotic Surgery. *Surg Innov*. 2012 May 1

8	**C2TN**	**6**	**36**	Multifunctional ^{161}Tb complexes for cell DNA specific targeting	3
9	**CNAO**	**4**	**36**	Personalized ^{11}Carbon PET aided hadron therapy	2
10	**PAX**	**4**	**36**	New shielded packaging container for medical nuclear medicine	1
11	**KUL**	**6**	**36**	Mass separated beams of CO^+, CO_2^+ and CH_4^+ with high efficiency	2
CH1	**UNIGE**	**6**	**36**	Investigation of imaging probes for ovarian cancer in animal models	2
CH2	**CHUV**	**6**	**36**	Preclinical Imaging and Animal Models – Clinical Translation on	3
CH3	**UNIGE**	**6**	**36**	New robot-assisted instruments and delivery methods for brachytherapy	3
CH4	**EPFL**	**6**	**36**	Radiometal and ^{11}Carbon –based bioligands synthesis for target receptors of ovarian cancer	2

2.2 Quality and innovative aspects of the training programme

The training program will consist in cutting-edge research projects done by recruited early stage Researchers across the different institutions of the training network. The Researchers will both develop innovative scientific skills, and follow technical, scientific, and complementary skills courses, at a local and network-wide level, ensuring a high level of employability. Recruitments will be made both in universities delivering doctorates, in international organizations, in industries, and in foundations. Intersectorial secondment in the network is the norm, both within a single Work Package or between Work Packages providing a coherent network. The table of recruitments in the network is shown in Table 2.2a above.

- Overview and content of the training (ETN)

Areas of training, supervision and individual plans

Each Researcher will be assigned a main supervisor who will carry out the career development meeting in the first few weeks of employment. The jointly prepared Career Development Plan will contain a breakdown of the research project, detail the courses the Researcher needs to take as well as more long-term planning. If necessary, the career plans will be submitted for revision in the event of changes.

Each Researcher will be assigned a contact person from the HR Department at the recruiting network participant.

Arrangements for access to a supervisor and monitoring mechanisms

Contact on a daily to a weekly basis with the supervising scientist is the norm. If for some reason the contact were to be insufficient, the administrative and scientific contact persons would be available to help remedy the situation.

Common training credit system throughout the network

All the trainees of the network will be enrolled on a PhD program in doctoral schools at universities, located at or near the project. All organizations and supervisors have experience of joint PhD supervision with academic PhD supervisors. To guarantee an equal treatment and evaluation of the trainees in the network, a **credit system ECTS** will be implemented and followed both locally and at the network management level. From a total of 180 ECTS required during the network training, the following average figure will be planned:

R&D project: 75 ECTS – Secondment: 60 ECTS – Courses, network-wide training: 45 ECTS

The network-wide training will be organized in different modules along the project as shown in Table2.2b.

Table 2.2 b Main Network-Wide Training Events, Conferences and Contribution of Beneficiaries

	Main training events & Conferences	**ECTS**	**Lead Institution**	**Project Month**
1	**Kick-off week – CERN (EU)** All Researchers, supervisors, scientists in charge are invited. It will be organized at CERN and will serve to set and share the training goals of the MEDICIS-PROMED network. All the Researchers had been recruited a few months before. Presentations of the individual research projects will be made by the supervisors and the scientists-in-charge, while the Researchers will make poster presentations. Visits of the neighbouring AAA, UNIGE and CHUV-EPFL will be organized, with concrete lab demonstrations. Two days will be allocated for transferable skills courses, such as creativity, IP aspects and entrepreneurship	5	CERN	6
2	**General training 1 – Manchester (UK)** A selection of the 5 most advanced projects will be selected for oral presentation. Some of the obligatory courses will be delivered at this occasion, such as *Materials and radiation.* Physics Nobel Prize K. Novozelov will deliver his *Scientific innovation and advanced materials* training.	10	Manchester	12
3	**Workshop on functional multimodal SPECT/PET imaging – Lausanne/Geneva (CH)** The workshop is distributed over Geneva and Lausanne (60km distance, 45 min by train) at the CIBM and ITMI imaging platforms. Advanced ERC MD prof Coukos (CHUV) and Dr. P. Lecoq (CERN) deliver a joint training on *Immunotherapy and cancer treatment* and *Detectors and Medical imaging*	10	UNIGE/ CHUV	18
4	**Specialized training 2 – Leuven (BE)** 10 most advanced ESRs give oral presentations and 5 poster presentations. Hands-on training on isotope mass separation and laser techniques is provided; advanced ERC Prof; P Van Duppen (KUL) gives his lecture *Radioactive Ion Beams and Lasers.* Courses on target and ion source for medical isotope production are provided.	5	KUL	24
5	**Summer school 1 at CNAO – Pavia (IT)** PET aided hadron therapy for personalized medicine. The visiting scientist K. Noda-san (NIRS, JP) is invited to deliver his training *PET-aided hadron therapy;* Hands-on training on treatment planning, test on dummy targets is provided, together with theoretical courses on Radiobiology; Monte Carlo simulations for treatment planning, medical accelerators, etc.	10	CNAO	24-36
6	**Visiting scientist training – diverse sites (EU)** The training delivered by the visiting scientists are organized, and coupled to international scientific conferences, such as Electromagnetic Mass Isotope Spectrometry (EMIS), European Association of Nuclear Medicine Meeting (EANM), etc.	5	C2TN-IST	12-36
7	**Summer school 2 at C2TN-IST – Lisbon (PT)** *Radioisotopes for medicine*. The visiting scientist Dr. U. Koester (ILL) is invited. Practical training on radioisotope production in the nuclear reactor and radiopharmaceutical synthesis are provided. Researchers team up to work on case studies for Business Plans for a start-up in personalized medicine engineering systems.	10	C2TN-IST	36-48

For part of the training program, modern tools to provide access on a network-wide basis will be possible. For instance, **Distant training** is now possible at university of Manchester where the training module is organized to minimize the time spent at Manchester, generally a couple of days, while most of the training is done when the Researcher is back home. **Webinars** is another form which fully exploits modern communication networks. CERN has its own video-recording systems in large conference rooms and archiving databases for easy retrieval.

The recruited Researchers will have access to the technical and scientific graduate lectures available in the academic organizations of the network. MEDICIS-PROMED regroups some of the most prestigious technical universities in Europe, such as the University of Manchester, one of the biggest universities in UK, KU Leuven, the Swiss Federal Institute of Technology in Lausanne, ranked amongst the best in Europe for engineering studies, which is reinforced with two University Hospitals. On top of this, CERN, the world´s largest particle physics center, has an extensive training program in the various scientific & technical disciplines, computer & detector technologies, required for the design of machine components, as well as complementary training required in the management of large international scientific collaborations.

Advanced technical and scientific training will be provided locally to the Researchers hired in their respective doctoral schools as well as in the organizations. An overview of possible training is provided in the following Table 2.2c. A set of obligatory, general training, courses will be defined between the Researcher and its supervisor, with assistance of the training office of MEDICIS-PROMED. In addition, optional courses will be defined following the needs of the Researcher.

Table 2.2 c List of scientific trainings

Training	**Knowledge gained**	**Institution**	**WP**
Mass separators	isotope mass separation isotope production targets and ion sources Hands-on training	Isolde, **CERN**	1,2
Materials and radiation	2D materials Graphene Material performance and degradation	Materials for demanding environments New CDT school/ **Univ. Manchester**	1,2
Fluka Monte-Carlo Code	Multiple particle tracking code Radiation protection Hadron therapy treatment planning Shielding and operational safety	**INFN, CERN**	1,2,3
Radiobiology	Biological radiation dose-response curve DNA damage and repair	Univ. Pavia, **CNAO**	2,3
High power Lasers	Laser spectroscopy Atomic transitions Laser ionization	**JOGU**	1,3
5f intermetallic phase diagram	Inorganic synthesis of intermetallic alloys Handling of actinide materials Characterization techniques	**C2TN-IST**	1
Molecular oncology	Molecular biology of normal and cancer cells Hallmarks of cancer Development of anti-cancer drugs	**EPFL-ISREC**	2, 3
Radiopharmaceuticals synthesis	Solid phase peptide synthesis principles Chelators for radiometals Automated modules	**C2TN-IST**	2,3
Radioisotope production	Production cross-sections Energy deposition Isotope separation and target reprocessing	**ARRONAX**	1,2
Nuclear spectroscopy	Properties of exotic nuclei Optical techniques Combining atomic traps and lasers	**KUL**	1,2,3
Ionization in plasma	Classification of plasmas Atomic phenomena Experimental characterization	**EPFL**	1
Robotics and automation	Process definition Programed vs remote controlled Practical cases	**EPFL**	1,2,3
CERN Accelerator School	Basic physics of accelerators Accelerator components Practical cases	**CERN**	1,2,3
Nuclear engineering	Basics of materials for nuclear environments Radiation damage Heat power dissipation	**Univ. Manchester**	1,2
Functional imaging	Principle of PET-SPECT imaging Image treatment softwares	**UNIGE/CHUV**	2,3

Transferable skills

The training of the Researchers will be completed with a selection of transferable skills. They will be offered as network-wide training courses, or offered in the large organizations part of the network, such as University of Manchester (largest single site university in UK), KUL, JOGU, CERN and EPFL. The list introduced in Table2.2d can be further expanded with optional courses. The transferrable skills training program will guarantee a high level of employability of the Researchers in both the private and academic sectors. A partner organization, Oxford University Consulting, participates in the training office of the network and provides advice on the definition of this part of the training.

Table 2.2 d List of transferable skills trainings

Network-wide transferable skills Training	**Goal**	**Days**
Effective communication-Presentation skills(follow-up from kick-off), Chairing and participating in meetings, Rapid Reading, Managing time and stress, Working effectively in team, Report writing, Proposal writing, Job application, Career development in science and technology, Speaking to the public/media, Ethical issues and(inter)national legislation	Improve collaboration skills Improve communication skill Learn about multi-tasking, time management and crisis management Improve efficiency	15
Language courses (English and/or the language of the host country)	Better language proficiency to maximise communication possibilities Improve employment chances	2hours/ week
Project management (PMI)	Learn about effective management of R&D projects including scheduling, budgeting	3
Scientific writing skills	Be effective in scientific written communication, requests, lectures. Learn to develop critical thinking skills Learn about development of analytical and argumentation skills	1
New Product Development (NPD)	Strategic thinking Learn about various stages and subprocesses of NPD which integrates, R&D, marketing and financing Market survey strategies Learn about pricing methods	1
Marketing entry strategies	How to approach the market Learn about existing tools and methods	1
Acquiring private and public funding	Learn about research proposal writing and evaluation National funding organizations functioning Start-up national programs	1
Establishing an enterprise	Learn from gained partners experience Learn about national differences	2
Intellectual Property and KT aspects	Evaluate patentability Strategy based on innovation Patent application process Licensing	2
Entrepreneurship	Market need evaluation Start-up company life cycle Successful vs unsuccessful	3
Creativity and Idea generation	Methods to promote idea generation Individual vs collective processes Idea selection	1

Training provided by the visiting scientists

MEDICIS-PROMED will have the contribution of world renowned visiting scientists such as a young Nobel prize laureate and a young advanced ERC. They will be accompanied by an entrepreneur, former collaborator of Nobel Prize laureate Prof. C. Rubbia, which has successfully launched a company leader in the field of radiopharmaceuticals. They will finally be accompanied by a Japanese accelerator engineer, the first having developed and operated a hadron therapy accelerator chain directly with ^{11}Carbon PET isotopes. The complete list of visiting scientists is presented:

K. Novoselov, Graphene Institute – Physics Nobel Prize 2010 – Scientific Innovation and Advanced Materials

U. Koester, ILL- chairman of the NuPECC[8] working group for *Nuclear Physics for Medicine-Radioisotope production*– Production of medical radioisotopes

P. Van Duppen, KUL – Adv ERC – Radioactive Ion Beams and Lasers

S. Buono, AAA – Radiopharmaceuticals marketing and Entrepreneurship

G. Coukos, CHUV – Adv. ERC – Immunotherapy and cancer treatment

P. Lecoq, CERN – Adv ERC – Detectors and Medical imaging

K. Noda-san – NIRS – PET-aided hadron therapy with carbon ions

The training will serve several purposes and will provide:

a coherent view of the network since the lectures cover the different topics addressed in the 3 Work Packages.

the most advanced state-of-the-art scientific knowledge in the respective fields of research and training.

models to follow for the young Researchers and to provide inspiration.

extraordinary networking opportunities, and career prospects.

exposure to the various research cultures, prevailing in universities, international organizations, companies and hospitals.

Participation in International conferences and other ongoing training/research programs

The participation in international conferences and in other EU-funded projects public events is an integral part of the training. It allows the Researchers to submit scientific abstracts and be evaluated by their pairs, to present their work to a larger community, often not directly active in that field, to learn up-to-date scientific progresses in related research areas – an important process to generate new ideas or find technical solutions to existing open issues, and to develop their network. We provide in the following a non-exhaustive list of such opportunities: EMIS (International Conference on Electromagnetic Isotope Separators and Technique Related to their Applications), EANM (European Association of Nuclear Medicine meetings), E-MRS (Eur. Material Research Society meetings), ACS (American Chemical Society meetings), IPAC (International Particle Accelerator Conference), open events of FP7-projects ARDENT, LA^{3}NET, ENTERVISION&ULICE (& eventual follow-up), …

[8] An expert committee of the European Science Foundation, www.NuPECC.org

- Role of non-academic sector in the training programme

The non-academic partners, i.e. private companies, will contribute to the training in hosting trainees for industrial-oriented engineering system development PhDs, in providing secondment for the trainees located at academic organizations. They will also provide network-wide training lectures, for instance to illustrate how private industry can develop following a strategy of industrial innovation and entrepreneurship as Lemer Pax or AAA companies. Both P.M. Lemer and S. Buono, CEOs of Lemer-Pax and AAA, have demonstrated successful **entrepreneurship achievements** in the field of radioisotope transport engineering and production of radiopharmaceuticals. They will serve as **models for the young Researchers**. They will in particular help the network to address the methodology of bridging academic innovation into industrial demonstrator and marketed product. To further reinforce this dimension of the training, **Oxford University Consulting** will develop a specific obligatory training program for the Researchers.

2.3 Quality of the supervision

The supervision approach and quality will follow the guidelines of the European Charter for Researchers.

The supervisors have been identified for each of the ESRs and their names are displayed in section 5. When co-supervision is required in a doctoral school, several universities have been identified, most of them at proximity of the host institution or with which past doctorates had been co-supervised. The trainee will have regular meetings with his supervisor, from a daily to a weekly basis depending on the needs. Furthermore, the trainee is part of a larger research laboratory, where monitoring tools for PhD projects and trainees are in place, such as regular presentation in group seminars and written reports.

- Qualifications and experience of supervisors

All supervisors identified in the network organizations have **long experience in directly supervising or co-supervising PhD students.** They have a proven track-record of high-impact scientific publications, and sometimes completed with patents and proven transfer of the academic innovations into marketed products. Supervisors have published in highly cited journals in scientific disciplines relevant to the objectives of MEDICIS-PROMED, such as Nature, Advanced Materials, Physical Review Letters, Review of Scientific Instruments, Nuclear Medicine Communication, Nature Medicine, Advanced Drug Delivery Reviews (as defined in sect. 5) and have filed patent applications. They also hold professorship and scientific/technical managerial positions in their home institutions. This will ensure a very high level of supervision.

- Proposed joint supervision arrangements

An Ombudswoman is designed in network. **Ms. S. Datta-Cockerill**, formerly in the CERN HR department, is presently Ombudswoman at CERN and will serve the network for confidential matters dealing with the Researchers and Supervisors, helping settling-up gender issues, conflicts, private difficulties; to name but a few.

The ESRs hosted outside universities will be assigned **two supervisors** each –one from the host organisation and one from a doctoral school. The supervisors have experience of joint supervision. A typical arrangement will follow the practice of the CERN doctoral program, where the Personal Project Development Plan is defined by both supervisors - the local supervisors monitor the progress of the project and local training courses, whereas the university supervisors will maintain regular contacts with the Researchers, are responsible for all aspects related to courses and credits for PhD enrolment, submission of requested documentations, and the final PhD defense. The proper definition and follow-up of the supervision scheme is overviewed at the network level by the Supervisory Board and the local HR department contact.

- Non-academic contribution to supervision

The responsibility of the non-academic supervisors will be to directly supervise both the seconded ESRs and, in the case they are beneficiaries, their own ESRs. The supervisors at Lemer Pax and AAA worked in academic research laboratories prior to taking over their industrial positions, and have **experience in PhD supervision**. They will in particular be looking into properly integrating the R&D activities into an industrial environment. Oxford Consulting, a non-beneficiary, will organize network-wide training courses, such as entrepreneurship, to enforce the coherence and mutual vision throughout MEDICIS-PROMED. They will act at the network

management level, to provide advise to the Researchers when they will define their **Personal Career Developments Plans**.

2.4 Quality of the proposed interaction between the participating organisations

- Contribution of all participants to the research and training programme

All participants contribute to the research and training programme, by providing either supervisory skills, secondment capacity, doctoral schools which deliver PhD diplomas, visiting scientists, network-wide training lectures/courses and complementary skills. The contributions of the beneficiary and partner organizations of MEDICIS-PROMED are shown in the following table:

- *Table 2.4a :Contribution of Organizations to the Training in MEDICIS-PROMED*

Name	Supervision	Secondment	Award PhD	Visit scientist	Network-wide training	Complementary skills
CERN	X	X		X	X	X
Graphene inst.	X		X	X	X	X
JOGU	X	X	X		X	
AAA	X	X		X		
C2TN	X	X	X		X	
CNAO	X	X				
PAX	X	X				
KUL	X	X	X	X	X	X
CHUV	X	X	X	X	X	
UNIGE	X	X	X		X	
EPFL-ISREC	X	X	X		X	X
Medaustron	X	X				
Oxford Consulting					X	X
ARRONAX	X	X				
ILL	X	X		X		

- Synergies between participants

Clear synergies between the participants of the MSC-ETN can be outlined. Innovative medical isotope production will take place in hospitals (UNIGE), private company (AAA) and research organizations (ARRONAX, ILL, CERN), thus methodologies can be compared, and the most efficient approaches developped and used throughout the network. The design of engineering components for isotope mass separators, that being laser ion sources, dipole magnets or new types of targets are integrated in groups of different scientific and technological cultures at Univ. Manchester, JOGU, KUL, CERN, C2TN or ARRONAX. Secondments of the ESRs through the network will clearly exhibit the synergies between these institutes, for instance going from a prototype isotope production target system developped at C2TN evolved into a fully operative system at ARRONAX.

- Exposure of researchers to different (research) environments, and the complementarity thereof

The composition of the network is made of large universities (KUL, JOGU, University of Manchester), of Engineering School (EPFL), of foundations (CNAO), of international organizations (CERN, ILL), of companies including SMEs (AAA, PAX), and of university hospitals. The Researchers will be interacting with the other organizations in the network during secondments, during the regular contacts within their respective Work Packages, or during network-wide events. They will be confronted not only to staff having a largely different

background; hence different ways of interacting, dealing with problems and progressing in research, but also to the administrative structures themselves, which varies significantly from one type of organization to the other. The Researchers will be able to participate in both international scientific conferences, as well as in industrial fairs, where the principle of interactions (posters, information stands, oral presentations) can significantly change. The visiting scientists, during their training and implication in the network activities, because of their diverse professional backgrounds and cultures, and as leaders in their respective fields, will help the Researchers understand the concrete meaning of the "different (research) environment". Oxford University Consulting partner has been invited in the network to specifically address this point and provide the required tools to the Researchers to fully benefit from the diverse environments made available in MEDICIS-PROMED.

3. Impact

MEDICIS-PROMED will train a new generation of scientists, bringing together a network of world renown researchers and entrepreneurs in isotope mass-separation and lasers, accelerators, material science, oncology, robotics and imaging, to bring new solutions to the 2nd deadliest cancer for women, around a newly build facility CERN-MEDICIS. This is done by the design and engineering of subsystems along the supply chain and tests of radiopharmaceuticals, and PET-aided hadron therapy. This is expected to become an expanding field for such newly trained scientists.

3.1 Enhancing research- and innovation-related human resources, skills, and working conditions to realise the potential of individuals and to provide new career perspectives

First of all, the development of mass-separated radioisotope beam devices for personalized medicine treatments demands a broad range of interdisciplinary skills and advanced technologies, such as advanced materials synthesis, lasers, electromagnetic separator design and operation, Monte carlo simulations, radiochemistry, robots and imaging with animals. It is thus an excellent training ground and a solid basis for careers in academia and research. The collaboration of the Graphene Institute, CNAO or UNIGE in this network represents significant added value for training and research in that respect:

- The training requires unique, leading edge infrastructure and expertise, which is not available at a single place. The availability of experts on graphene, laser ion sources, radioisotope packaging and radiopharmaceutical design and tests cannot clearly be found in a single site. The training network will significantly simplify this access and the trainees will work at the best suited places.
- The development of medical isotope mass separation subsystems is achieved in CERN-MEDICIS, JOGU, KUL, C2TN and can as well be used in therapy centers such as CNAO and Medaustron. The trainees will learn to work in such a team in open collaboration and competition with the best scientists in the field.
- Through responsibilities, from their individual project to the participation in the network-wide events such as taking care of the MEDICIS-PROMED young scientist award, the Researchers will be trained in important aspects of scientific, entrepreneurial and administrative leadership within a large international collaborative effort.
- The Researchers will have the opportunity to become known of, e.g. prof Novozelov, prof van Duppen, Dr. Stefano Buono, or Prof D. Hanahan. As clear leaders in their respective fields of research (advanced materials, nuclear physics, radiopharmaceutical marketing and molecular oncology), this will give the Researchers a boost in their career, with possible invitation to workshops and conferences at an early stage of their scientific career, helpful to gain international recognition.
- Intersectorial mobility between universities, national centers, European organizations, foundations, companies' sites will give the Researchers an in-depth view of innovation and how cutting-edge research is addressed in different environments. They will very much profit from the world-wide links between the scientific and technological communities, and be able to work in very different areas, such as industrial robotics

(automobile industry, intervention in hostile environments), in chemistry (design of composites, polymers and plastics, environment), in imaging softwares (environmental satellite surveys), to name but a few.

- Through research and personal contacts at workshops and conferences the Researchers will establish links to colleagues in other academic or applied research laboratories, for instance CERN has privileged contacts with ESA and JRC international organizations. This will also promote and reinforce long term collaborations at an international level.
- The involvement of the trainees in a broad spectrum of scientific and technological activities will enhance the intersectorial interaction and transfer of technologies, preparing Researchers to work in many different professional environments, such as in start-ups to possibly make commercial exploitation of the results of their own research projects, or joining prestigious international organizations, for instance at the European Molecular Biology Organization (EMBO).
- By the very nature of the large international scientific collaborations, all trainees will be immersed in a pool of networking possibilities. For instance, Researchers attending ICIS (International Conference on Ion Sources) will directly become connected with people in private companies designing industrial ion implanters, plasma generators or academic researchers designing a new generation of propulsions for satellites.
- The mentoring by internationally-recognised scientists and the systematic training in soft skills (presentations, chairing of meetings, writing of publication, reports and proposals, teaching at workshops, student supervision, etc.) is an additional bonus for a career in academia and industry. Most of the staff in HR departments of large Organizations, such as CERN or Michelin (multinational tyres manufacturer), were engineers an scientists prior to joining their present functions.

All the above elements will help the young Researchers realize their potential and significantly improve their career prospects. Europe will gain a batch of entrepreneurial researchers capable of contributing effectively to the knowledge-based economy. The expertise gained by the Researchers can directly be transferred and exploited in the nuclear electricity and engineering, industrial lasers and robotics, ion beam treatments and cutting of advanced materials, to name but a few.

3.2 Contribution to structuring doctoral / early-stage research training at the European level and to strengthening European innovation capacity, including the potential for:

The network comprises major universities, international organizations, large research institutes with excellent international reputations, and small to medium size high tech companies. The activities of the network partners significantly contribute to the implementation of the Lisbon objectives for making Europe the most dynamic and competitive knowledge-based economy in the world.

Fragmented R&D programs will decrease due to the joint program proposed in MEDICIS-PROMED. The facilities will be used in a more coherent way, and will promote greater European cohesion and improve transfer of knowledge. The organisation of the “CNAO PET-aided hadron therapy for personalized medicine” summer school will be the first of a series which will treat the specificities of hadron therapy accelerators operated with radioisotope beams, whose number is expected to constantly increase across Europe. The program of training in MEDICIS-PROMED will be integrated into a **new doctoral school**, whose objective is to train young PhD in the broad field of target, sources, beam devices for accelerators, imaging and treatment systems. This new school will deliver credits distributed amongst lectures given at universities, practical training at accelerator laboratories, and hands-on training session in the private partners. **Future extension** of the MEDICIS-PROMED network to accommodate new relevant partners is highly likely.

- Contribution of the non-academic sector to the doctoral/research training

The training network comprises important engagement of non-academic organizations at different levels and types of involvement. One of the organizations, Oxford University consulting, will specifically address the organization of network-wide training events, and the **elaboration of the complementary skills program**. They will join-up

with training representatives of the organization in the training office. A **public lecture** will be provided by Dr. S. Buono, CEO of AAA, **on entrepreneurship and radiopharmaceutical marketing**.

- Contribution to developing sustainable joint doctoral degree structures (EJD only).

In the design of particle sources and accelerators there are many common research themes and challenges that are often dealt with independently at numerous institutes scattered around Europe. This approach has the risk to lead to fragmentation and uncoordinated activities. It is therefore very beneficial to have structured activities between these institutes which bundle and focus their research efforts. Such an approach fosters long-term collaboration. In fact the proponents fully expect to have further joint research and training programmes after the completion on MEDICIS-PROMED.

All the MSC-ETN organizations will greatly benefit from the Early Stage Researchers and Visiting Researchers through their contribution to their R&D program. Since the private organizations of MEDICIS-PROMED base their earnings on developing and marketing innovative products, they will naturally continue to host young Researchers for their own benefit, for instance within the foreseen new doctoral school.

European innovation capacity will be boosted by sustainable research training programmes, such as that of the present proposal. Indeed, it is highly probable that the Deliverables in WP1, 2, and 3 will significantly change the fields of innovative medical isotope production, hadron therapy with carbon ions, and theranostics for ovarian cancer treatments. This will create new needs amongst the industry and personalized medicine centers linked to hadron therapy centers and hospitals. The training skills of this network, and the freshly graduated Researchers, will therefore become more and more demanded as this field will further grow the coming years.

3.3 Effectiveness of the proposed measures for communication and dissemination of results

- Communication and public engagement strategy of the project

Besides the PhD thesis inherent to each grant, the results will be disseminated in the form of extended abstracts, conference proceedings and research articles to be published in high-rank indexed journals. The presentation of oral communications in international conferences and COST action meetings covering the different areas of the Program will be strongly encouraged. Highly qualified students will be recruited and, therefore, it is anticipated that at least an average of one conference paper and three international indexed journal papers will be published by each doctoral researcher. Dissemination of results through patent registration is also foreseen due to the basic-applied character of the outlined research themes and its translational potential.

All the partners have a huge culture for promotion and communication in science and technology al local, national or international level (see for instance https://www.youtube.com/watch?v=eEUPvii2UcQ). Efforts of partners will focus in lectures and demonstration towards general public using different strategies to spread high impact scientific results, such as the organization of local events, press and media releases, and divulgation through social networks (e.g. Facebook, Twitter, etc). In this way, the Consortium will promote its scientific activities among young people and general public, facilitating exchanges between scientists and EU citizens.

The Program aims at promoting the emergence of European leaders in R&D, capable of creating cutting-edge knowledge and technologies on the production and biomedical applications of innovative radioisotopes. Therefore, the Program is expected to foster Clinical and Translational research, and promote new business ventures, improving human health and European economic growth.

A list of more specific outreach actions is provided in the following Table 3.3a:

Table 3.3a

Outreach actions
High School and undergraduate classes 1-day visits to CERN-MEDICIS/AAA/UNIGE Several one-day visits will be organized. Particularly, CERN is at 15 min. from Geneva int'l airport, a node for low-cost companies. The CERN visitor's service organize daily visits for >10'000 students every year. We will propose MEDICIS-PROMED visits, extending to AAA (3km from CERN) for radiopharmaceuticals and UNIGE (7km) for PET imaging and surgery, providing a unique set of intersectorial international network's organizations
MEDICIS-PROMED young scientist award Every year, a call for successful research projects of freshly graduated PhDs in the field of engineering systems for personalized medicine will be published on websites and media. The selected candidate will be invited at one of the network-wide meetings and the presentation will be recorded and broadcasted on social media
Public lecture It will be given by Dr. S. Buono, CEO of AAA in the Globe of Innovation (Geneva), on radiopharmaceutical marketing and entrepreneurship**.**
MEDICIS-PROMED contest 2 teams of ESRs (ca 6-8 each) will compete during 24 hours: Their aim is to perform imaging tests as fast as possible, one at CHUV, the other at CNAO. They will start by producing isotopes at CERN-MEDICIS and travel to CNAO for one team, while the second one will travel from ILL to CHUV. They will perform the synthesis of the radiopharmaceutical upon arrival, probe its activity by imaging in a model system. This will be reported by video and a summary will be broadcasted in the local networks. It will be a concrete example of the new medical isotope supply chain as proposed on Figure 2.1b.
Final conference It will be the opportunity to invite scientists and industry, scientific policy makers, journalists, at the final conference where the most important results will be presented.

- Dissemination of the research results

Dissemination of research results in the physics world is most commonly done using journal publications, presentations at conferences (with subsequent publication in proceedings) or seminars. This gives the Researchers ample opportunity to hone their skills in writing or making presentations. More specifically, the MEDICIS-PROMED final conference will be organized to gather a wide community from both the academic and private sectors, active in the wide field of particle accelerators and their medical applications. The dedicated project web site will also be an important source of information and results from this MSC-ETN project.

- Exploitation of results and intellectual property

The general rules for access, use and dissemination of intellectual property, defined in the H2020 Rules for Participation, will be applicable to this MSC-ETN project. Special Partnership Agreements will be concluded between participants and the industrial partners after consultation with the Supervisory Board, ensuring that the IPR policies of the latter are respected in the framework of the MSC-ETN project. That concerns in particular results which may have industrial or commercial applications.

In specific cases, network Researchers, who are hosted by an industrial partner for a secondment, may be requested to sign a non-disclosure agreement with the company in order to protect designs, know-how and procedures owned by the company.

As beneficiaries of MSC-ETN grant, the participating institutions shall ensure that the project results be disseminated as swiftly as possible. Nonetheless, the dissemination activities shall be compatible with the protection of intellectual property of the associated partners involved.

With the nature of the goals defined in Work Packages 1, 2 and 3, as well as those defined at each individual Researchers project level, the developments might lead to engineering systems for medical isotopes production, for new personalized medicine protocoles, and for new candidate drugs qualified for further clinical tests. The aim of the Work Packages is to design demonstrators and prototypes. In the event that a prototype is meeting all requirements for industrialization, for instance a Type B(u) container for isotope transport or a turnkey Laser system for isotope purification, companies will be approached and the prototypes exploited, even after the conclusion of MEDICIS-PROMED. It is indeed possible that the turn-key isotope purification laser system be installed at one of the AAA production premises and used in the isotope production development.

The Network coordinator T. Stora has an intersectorial experience with more than 10 patents and 50 scientific publications in leading scientific journals (Nature, Physical Review Letters, Advanced Materials, Angewandte Chemie), and proven record of technology transfer, such as the biosensor chip HPA used in Biacore ® biosensor devices resulting from one of his research activities. He will use his experience to further push these transfers in the training network.

4. Implementation

4.1 Overall coherence and effectiveness of the work plan

- Fellow's individual projects

Table 4.1 d: Individual Research Projects

ESR 1	**CERN**	**PhD : Y**	**Start : Month 6**	**Duration 36 months**	**D3.2 (WP3)**
Molecular break-up by laser in RFQ cooler					
Objective : To study the impact of the chemical nature of the molecules on their break up in a RFQ-Cooler device before or after mass separation of molecular isotope beams					
Expected Results: **A** :Different types of molecular ions will be injected in a RFQ Cooler, such as LnF+, CO+, CH4+. **B** The efficiencies of transmission, time of residence will be investigated by varying the cooling gas pressure, its nature (He, H2, H2O). **C** The molecular break-up by UV laser light excitation will be investigated. The precise required repetition rate, wavelength, plasma induction will be investigated. **D** The presence of other beam components on the results, such as alkali metals, will be investigated, to decide if the purification step must take place before or after mass-separation.					
Planned secondment: PAX – 5 months –Engineering design for a maintenance-free RFQ cooler/purification device					

ESR 2	**CERN**	**PhD : Y**	**Start : Month 4**	**Duration 36 months**	**D1.5 (WP1)**
Production of $^{149/152}$Terbium theranostics isotopes at CERN-MEDICIS and shipping					
Objective : to define the proper operational conditions and safety boundaries for the production and shipping of radioisotopes from radioactive ion beams					
Expected Results: The CERN-MEDICIS facility is the first facility to start operation for the production of medical istope batches by mass separation. The necessary engineering validation and documentation steps will be elaborated for its safety file. This includes the procedure and design of isotope batch collection chambers, coupling of radiochemical purification modules to the isotope mass separator. The efficiencies for the collection of $^{149/152}$Terbium will be determined, and different engineering systems, such as targets and ion sources will be selected and optimized to achieve the best figures.					
Planned secondment: - ILL – M16-20 – Production of the complementary ^{161}Terbium & mass separation of ^{163}Erbium					

ESR3	**CERN**	**PhD : Y**	**Start : Month 4**	**Duration 36 months**	**D2.2 (WP2)**
CO molecule fast gas injection and C-->C^{6+} and C-->C^{1+} -->C^{n+} charge breeding investigations					
Objective: For different types of treatment ions explore the possibilities and limitations of the charge breeding stage linking the radioactive beam production and post-accelerator					
Expected Results: **A**. Ion throughput capability of the charge breeding system as is for different type of treatment ions and the means of increasing it., by e.g. implementing alternative cooling methods in the Penning trap or using continuous mode injection into the Electron-Beam Ion-Source (EBIS). **B**. In collaboration with ESR1 address the beam purity by $^{11}C^{16}O$ breakup efficiency inside the Penning trap and EBIS, and stable beam contamination. **C**. Establish the operational conditions such as injection repetition rate, extracted pulse length and mass-to-charge ratio.. **D**. Literature study on Electron Cyclotron Resonance Ion Source (ECRIS) alternative charge breeding in collaboration with MEDAUSTRON					
Planned secondment: Medaustron, M22-26 The rotation will allow the student to acquire operational experience from a full-scale treatment facility and extended experience of alternative ECRIS					

ESR4	Graphene Institute	PhD :Y	Start : Month 4	Duration 36 months	D1.1 (WP1)
Metallic foil targets with protective graphene layers to produce innovative isotopes					
Objective: To study the possibility and mechanisms of graphene growth on uranium, thorium and other metals to form a protective layer. To characterised the grown graphene layer and its ageing in difficult environments					
Expected Results: It has been demonstrated recently, that graphene can serve as a completely impermeable membrane on a surface of a metal. Furthermore, as graphene can be grown conformal on a piece of metal of any shape, it can be used as a corrosion protection. We would like to use graphene as a corrosion protection on uranium, thorium and other metals. Different metals allow for different mechanisms of graphene growth. We will investigate a possibility of graphene growth on uranium, thorium and other metals, the mechanisms of such growth and will optimise the process. Growth on Tantalum will first be investigated. The student will get familiar with the basic methods of graphene characterisation (AFM, SEM, Raman, etc). and develop new methods to characterise graphene on uranium.					
Planned secondment: CERN – M25-35 The growth of graphene on radioactive metals such as uranium and thorium, for the production of yet inaccessible isotopes by mass separation, such as ^{99}Molybdenum, will be undertaken at CERN.					

ESR5	JOGU	PhD : Y	Start : Month 4	Duration 36 months	D1.3 (WP1)
Remotely operated Laser Ion Source for radiolanthanide purification at medical cyclotrons					
Objectives: efficient mono-isobaric ion beam production via elemental selective laser ionization					
Expected Results: Each chemical element needs a defined 2 or 3 –steps laser ionization scheme. Terbium, Lutetium and Erbium isotopes will first be considered, using solid-state diode lasers that are better suited for remote operation. The ion source cavity (length, material, temperature) at the mass separator will afterward be developed to increase the ionization efficiencies. Finally a fully automated control software and monitoring will be implemented fo foresee its transfer at a medical cyclotron.					
Planned secondment: UNIGE M34-39: setting up and test of atomic vapour cell-laser system at UNIGE cyclotron					

ESR6	AAA	PhD : Y	Start : Month 4	Duration 36 months	D3.3 (WP3)
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					
Objectives: feasibility study for a large scale production of selected isotopes using a middle sized high current cyclotron and the CERN-MEDICIS mass separation system					
Expected Results: Perform a explorative study based on theoretical analysis and Monte Carlo simulations in order to identify radioisotopes with favourable characteristics, namely: β- spectrum for therapy; γ emission for SPECT imaging; half-life for logistics and clinical use, corresponding β+ (positron) emitting isotope to be used as companion diagnostic agent; favourable chemistry for targeted radiometabolic therapy suitability; effective production yield, for 30-70 MeV protons, target feasibility, effective extraction yield with the CERN-MEDICIS mass separation system.)					
Planned secondment: CERN-MEDICIS-M11-16: Scandium mass separated isotope beams					

ESR7	**C2TN**	**PhD : Y**	**Start : Month 4**	**Duration 36 months**	**D1.2 (WP1)**
Uranium Carbide nanofibers targets for increased stability and extraction yield of alpha-emitting radioisotopes					
Objectives: Improve the release properties, hence the yield efficiency, of the classical uranium carbide targets, by changing the method of production and the final microstructure.					
Expected Results: Nanofibers are expected to improve both the stability of the target materials and isotope release properties of key radioisotopes, such as heavy alpha emitters such as 211At, 212Bi, and eventually some volatile radiolanthanides. The nanofibers will be produced by electrospinning, changing the precursors, the spinning conditions. The final material will be characterized with XRD, SEM, BET, etc.					
Planned secondment: ARRONAX M19-21 : design of a 47Sc production target for cyclotron; AAA : M36-38 : test production of 47Sc at industrial cyclotron units					

ESR8	**C2TN**	**PhD :Y**	**Start : Month 6**	**Duration 36 months**	**D3.1 (WP3)**
Design, synthesis and pre-clinical evaluation of multifunctional ^{161}Tb complexes for cell specific targeting of DNA					
Objective: ^{161}Terbium Auger-emitting radiopharmaceuticals for the eradication of large tumor masses or small metastases for ovarian cancers					
Expected Results: **A** Synthesis and characterization of macrocyclic bifunctional chelators (e.g. 1,4,7,10-tetraazacyclododecane DOTA) bearing a tumor-specific MAb fragment targeting moiety and a DNA-binding moiety). **B** Synthesis of cold Tb complexes and characterization by spectroscopic techniques. **C** biological evaluation of Tb-161 complexes (Damage in plasmid DNA, Cell uptake using human tumor cell lines, Radiotoxicity and mechanisms of cell death, Biodistribution and SPECT imaging in tumor-bearing mice)					
Planned secondment: CHUV – M39-40 – μPET-SPECT imaging in nude mice EPFL – M21-28 – Synthesis of bifunctional fluorescent-Auger emitting bioligand targetting ovarian cancer DNA					

ESR 9	**CNAO**	**PhD : Y**	**Start : Month 4**	**Duration 36 months**	**D2.3 (WP2)**
Personalized ^{11}Carbon PET aided hadron therapy					
Objective: to adapt the treatment plan according to PET response halfway through the course of hadron therapy, to investigate hypoxia tracers, fluorinated aminoacides or DNA synthesis markers and to validate PET for early response assessment.					
Expected Results: select most suitable PET tracers for adaptive hadron therapy and early response evaluation. New tracers will be investigated including hypoxia tracer (a non exhaustive list is: ^{18}F-MISO, ^{18}F-FAZA, ^{62}Cu-ATSM) other fluorinated aminoacids (^{18}F-FET, ^{18}F-FACBC, etc.) or DNA synthesis markers (18- fluorothymidine). The tools developed for FLUKA will be verified at CNAO in a clinical scenario. Comparisons with the standard ^{12}C treatment plans will be studied in terms of dose, biological effect and ß$^{+}$-emitters distributions					
Planned secondment: CERN M17-19 Monte-Carlo Fluka simulations on ^{11}C ion implantation profile modelling UNIGE M30-32 : PET imaging on small animals at the Institute of Translational Molecular Imaging (ITMI) ;					

ESR10	**PAX**	**PhD : Y**	**Start : Month 4**	**Duration 36 months**	**D1.4 (WP1)**
New shielded packaging container for nuclear medicine isotopes					
Objective: To obtain a new technology type B certified shipping container.					
Expected Results: The typical isotopes (^{149,152,155,161}Tb, ^{177}Lu, ^{47,48,49}Sc, etc) and activities for shipment will first be defined. The European shipping regulations will then be studied in details. First dimensioning of the required shielding, mechanical resistance with be done by Monte-Carlo simulations and by Finite Element Model Mechanical codes. A first prototype will be constructed and checked for effective shielding capacity, leak tightness, shock resistance, etc. A second packaging will be constructed, learning from the prototype, and documentation will be filed to obtain its homologation. Specific innovations, such as direct transfer of the collected isotopes from the separator into the packaging are foreseen.					
Planned secondment: ILL- M12-14 Dr. U. Koester, validation of principle ; CERN, Dr J Vollaire (Radioprotection) M28-30 Monte-Carlo simulations .					

ESR11	**KUL**	**PhD :Y**	**Start : Month 6**	**Duration 36 months**	**D2.1 (WP2)**
Mass separated beams of CO^+, CO_2^+ and CH_4^+ with high efficiency					
Objective: develop compact and turn-key mass separator systems for medical radioisotope production					
Expected Results: The program aims to liaise the development on innovative medical RIB ongoing in Belgium (e.g. the ISOL@MYRRHA project and the University Hospital research groups on medical RIB) with CERN-MEDICIS. Different mass separators are currently operational or under the development at KUL. A new off-line mass separator to study resonance laser ionization of gas-jet based radioactive isotopes and a new laser laboratory are under construction, part of the HELIOS project. The outcome of the program will be 1) an operational MEDICIS mass separator (based on the LISOL system), 2) ion simulation packages to optimize the beam transport with respect to efficiency and mass resolution in order to limit isotope contamination, 3) trained scientists to operate and optimize the RIB production of certain interesting isotopes and 4) active participation in the long-term development of compact and turnkey mass separator systems.					
Planned secondment: CNAO – M32-41 - Hadron therapy tests with $^{13}CO/CO_2/CH_4$					

ESRCH1[9]	**UNIGE**	**PhD : Y**	**Start : Month 6**	**Duration 36 months**	**D2.CH1 (WP2)**
Investigation of bimodal imaging probes for ovarian cancer in animal models					
Objective: Develop and validate preclinical imaging techniques for assessment of bio-distribution and performance of new tracers in animal models for prediction of therapeutic efficacy of new radio-labelled compounds at Institute of Translational Molecular Imaging (ITMI) at UNIGE					
Expected Results: Development of methodology and validation of preclinical techniques. The ESR will be responsible of seeking new methodological techniques and experimental protocols that are suitable for the new compounds that are being evaluated. It will also include the development and validation of biological models that allow quantitative assessment of the efficacy and performance of the tracers as well as their potential efficacy of treatment of the given tumours.					
Planned secondment: CNAO – M26-28 - PET-aided hadron therapy					

[9] The deliverable associated to the Swiss hosted fellows ESRCH1-4 have been defined for the coherence of the proposal. They will be precisely defined at the consortium agreement with the definition of the Swiss financial participation

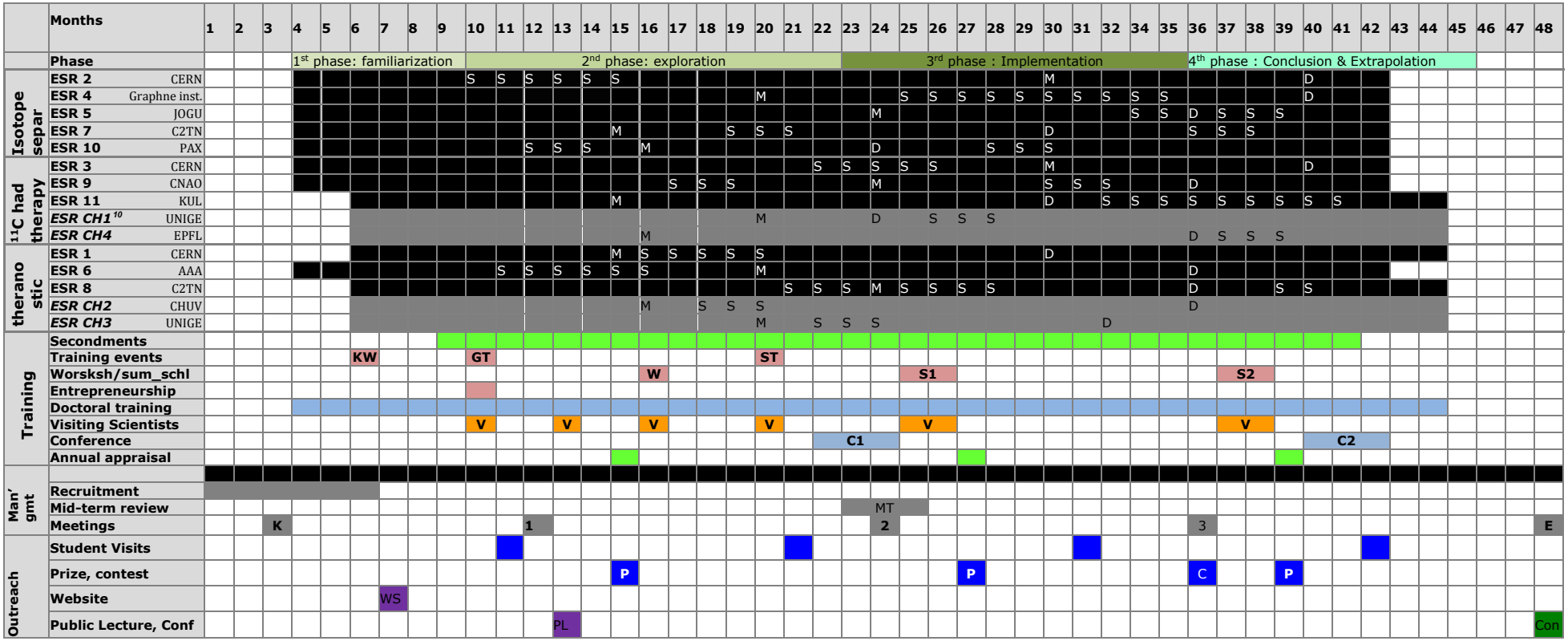
ESRCH2	**CHUV**	**PhD : Y**	**Start : Month 6**	**Duration 36 months**	**D3.CH1 (WP3)**
Preclinical Imaging and Animal Models – Clinical Translation on ovarian cancer					
Objective: Develop translational imaging and therapy with monoclonal antibodies for ovarian cancer					
Expected Results: The ESR will be in charge of performing the translation from a successful preclinical model for diagnosis to a first study in humans, firstly from a diagnostic point of view, and secondarily, as a preclinical therapeutic radioimmunotherapy and then, if feasible into a therapy in humans; His supervisor, Dr. Melita Irving, (Ludwig Center for Cancer Research, University of Lausanne, Biopôle III) will train him performing molecular biology and preclinical antibody research on ovarian cancer in mice. At CHUV, preclinical imaging will be done in nuclear medicine with μPET/SPECT/CT, and for clinical trials, PET/CT and SPECT/CT clinical scanners and radiation shielded beds for clinical therapy.					
Planned secondment: EPFL-ISREC – M18-20 – tests on pancreatic cancer in mice					

ESRCH3	**UNIGE**	**PhD : Y**	**Start : Month 6**	**Duration 36 months**	**D3.CH2 (WP3)**
New robot-assisted instruments and delivery methods for brachytherapy					
Objective: Develop and validate new delivery techniques for brachytherapy in computerized and large animal models					
Expected Results: The aim of this project is to establish new instruments and delivery methods for brachytherapy using stereotactic, endoscopic ultrasonographic-guided or robotic-assisted surgery for the treatment of non-resectable brain, ovarian and pancreatic cancers. New isotopes with specific types of emission, tissue penetration and half-life will be developed at CERN-MEDICIS. For brain tumors, we will use stereotactic and/or image-guided placement of coated particles, based on magnetic resonance imaging. For ovarian and pancreatic cancers, we will evaluate endoscopic ultrasonographic guided delivery of seeds and will establish the Da Vinci robot-assisted system for intra-organ placement of seeds.					
Planned secondment: C2TN – M22-24 – brachytherapy in small animals					

ESRCH4	**EPFL**	**PhD : Y**	**Start : Month 6**	**Duration 36 months**	**D2.CH2 (WP2)**
Bifunctional fluorescent and PET/treatment bioligand for ovarian cancer					
Objective: Develop and validate new bifunctional fluorescent and radioactive bioligand for ovarian cancer					
Expected Results: These reagents will consist of three major parts – 1) a bioligand for targeting of ovarian cancer; 2) a fluorophore for optical readout; 3) and a chelator for radiolanthanide such as Terbium (Tb). The first application of these probes would be to study their specific binding to ovarian cancer cells first in cell culture followed by biodistribution studies in animal models of ovarian cancer. The initial studies will be focused on folate receptor-alpha targeting moiety because several studies revealed that it is increased in 90–95% of patients with epithelial ovarian cancer. Moreover, the absence of folate receptor-alpha on healthy cells provides high tumor-to-normal ratios making this targeting moiety a good target for both imaging and therapeutic. Indocyanine green (ICG) will be a first choice of fluorescent reagent because of its extensive use in clinic. Terbium is known to possess excellent chelation properties to diethylene triamine pentaacetic acid (DTPA) and therefore this compound will be used in the construction of the final conjugates. In some biodistribution studies the chelate will be replaced with ^{11}C isotope.					
Planned secondment: AAA - M37-39 - radiopharmaceutical synthesis automated production modules					

- **Gantt chart**

Reflecting ESR recruitments, secondments, training events, management & dissemination / public engagement activities



K = Kick-off meeting E = End of project S=secondment M=Milestone D=Deliverable

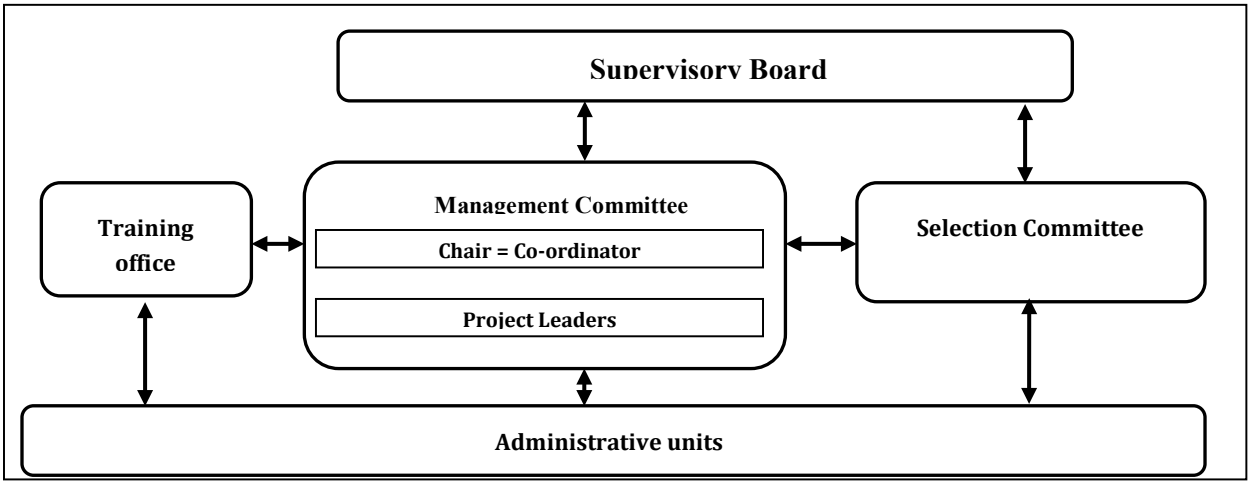
[10] ESR positions in Swiss partner organizations are directly supported by Switzerland and are quoted CH1-4 following Euresearch recommendations www.euresearch.ch

4.2 Appropriateness of the management structure and procedures

- Network organisation and management structure

The management structure of the network and the roles and responsibilities in the management are presented below:

Management Structure:



- Joint governing structure

Supervisory Board (SB) 2 meetings/year, All represented. 1 ESR elected 1x/year	• Approving and overseeing implementation of the training programme for scientific, technical and complementary skills, and co-ordination of the network-wide training activities; • monitoring and evaluating overall progress of the research training programm • ensuring exchange of best training practice with the partners, and in particular with the industrial members.
Management Committee (MC) 4-6 meetings/year	• overall management of the research programme; • initiate and follow-up recruitment; approve job definition; • implementation of the training activities with the associated partners; • monitoring and follow-up of the progress of the individual research projects; propose corrective measures if required; • ensure frequent contact and exchange of ideas among the partners; • overview of the integration of the Researchers into the research team(s); • review of the Personal Career Development Plans; • organization of the outreach actions • dissemination of project results.
Project /Network Coordinator Dr. T. Stora	• coordination of the MSC-ETN research training programme; • overall responsibility for the financial management; • organizing and chairing the Management Committee meetings; • communication to/from the associated partners; • communication and reporting to the European Commission.
Selection Committee	• selection and appointment of the Researchers; • monitoring of gender balance and equal opportunities.

Training Office	• organization, coherence of the courses and network-wide training event progr • administration of the ECTS training credits for the recruited ESRs.
Administrative Units [1 per institutions.]	• administrative support to the Management and Selection Committees; • organization of the Supervisory Board meetings; • financial follow-up and reporting; creation of budget codes and all necessary monitoring tools and other financial arrangements; financial auditing; • administrative formalities and support to the recruited Researchers; • Assist Coordinator and independent expert(s) in conflict resolution.

The Management Committee is chaired by the MEDICIS-PROMED Project Coordinator – the other members are appointed for one year periods by the Supervisory Board. Experts with non-voting rights are invited in the Committee, such a training advisor and a HR advisor. The Training Office provides support to the MC for the organization and monitoring of the training. It is composed of a training officer and his deputy, nominated by the MC, Oxford University Consulting representative, and one Researcher elected for one year terms.

Dr. T. Stora (CERN) will be the Project Coordinator. Dr. Stora, senior physicist, is target and ion source development team leader at CERN-ISOLDE, and is project leader of CERN-MEDICIS. He is coordinating a JRA in the FP7 ENSAR proposal, and has supervised several Marie Curie fellows and had coordinated a WP in FP6 EURISOL-DS project.

MD. PhD J. Prior (CHUV) will specifically address the medical aspects in the network. He is presently Head of Nuclear Medicine, Molecular Imaging and Therapy department at the Lausanne Hospital. He is President of the Swiss Nuclear Medicine Society. He is the initiator of FP7 ENDOTOF-PET with a consortium of 13 institutions for developing an endoscopic PET-ultrasound probe for molecular imaging.

Dr. T. Stora and MD PhD J. Prior have been collaborating together for 4 years in developing the CERN-MEDICIS collaboration.

- Supervisory board

All partners, including partner's institutes, are represented on the Supervisory Board. The executive decisions for the implementation of the research training programme will be taken by the Executive Board. Any changes in the research and/or training programme will have to be approved by the Supervisory Board. Where such changes may have impact on the contractual obligations of the MSC-ETN, the EC Project Officer in charge of the MSC-ETN will be informed in due course.

- Recruitment strategy

Introduction - Charter and Code of Researchers

All participating institutions recognise the value of all forms of mobility as a means for enhancing the professional development of researchers. They recognize that the mobility of researchers is one of the strengths of international research collaborations, where international recruitment and/or mobility, on the basis of excellence, is part of their mission.

The recruitment policy, employment conditions, and staff career development prospects of the institutions participating in this network are in good compliance with the Researchers' Charter and Code for Recruitment.

The recruitment process

The recruitment process comprises the following steps: (1) definition of the job, (2) advertisement of the vacancy, (3) selection of the researcher, (4) employment and induction into the network. The

process is run locally by the HR department of the recruiting network participant and is followed by the Executive Board of the network. The recruitment will preferably be launched in September to attract the best students that have freshly graduated from the major schools and universities.
Job descriptions, prepared locally, will be approved by the EB. All positions will be advertised on the Cordis mobility and Euraxess portals, the network web site, the participating institutions´ local (electronic) recruitment tools, e.g. e-RT at CERN, as well as via networks inside the project and its participants and partners. Each position will have an application deadline, in conformity with rules in places, which will be respected strictly. Information on MEDICIS-PROMED programme would also be made available to the public at outreach events.
Concerning the selection process, applicants will submit their applications to the appropriate recruitment office. Following screening of applications by the human resources departments, applicants will undergo a rigorous selection on grounds of quality and potential, as well as a matching of their scientific profile and interests with job specifications. Assessment is made according to academic qualifications, experience, achievements, and other elements including language knowledge and mobility. This assessment will be done by a board comprising the local HR co-ordinator, a representative of the local network participant (normally the supervisor for the position) and two representatives of the Executive Board, namely the Network Co-ordinator and the Recruitment Co-ordinator.

- Progress monitoring and evaluation of individual projects

The Supervisory Board will oversee the dissemination of best practice between the network participants. In particular, it will encourage all partners:
- to follow closely the milestones and deliverables of the individual research projects;
- to prepare well-structured career development plans for each recruited Researcher;
- to provide the Researchers with a certain degree of independence in carrying out their research projects;
- to stimulate the Researchers to make workshop and conference talks and presentations;
- to strengthen the networking and collaborative activities, even beyond the scope of this project;
- to keep a good record and documentation of the obtained results;
- to submit the publications, resulting from the project, to open access repositories and journals, in line with the recommendations of the EC on open access to scientific information.

At the level of individual ESRs and supervisors, Project Development Plans are drafted and followed on the network website. While Researchers will post monthly update of their project, the Supervisors will submit a progress report every 6 months. It will help decide if the research project is progressing as expected, and make yearly assessment for possible reorientation of the project, as described in the following section Risk management. The evaluation criteria will be clearly published on the network wide level.
Personnel Career Development Plans will be elaborated for each of the Researchers and will help define the content of their local, optional and complementary skill training, as well as their participation to external meetings and conferences

- IPR

Any background IP which a partner wishes to include in the project and provide access rights thereto, will be listed in the Consortium Agreement in a specific Annex. Any other background not included in the list shall be automatically excluded from project use, although a partner has an option to add background during the project, as it sees fit, for the attainment of the project objectives. Such inclusion of background shall be made in writing by the right holder.

Regarding ownership, the rules be clarified in the Consortium Agreement. The details will be spelled out in the agreements concluded between the Researchers and the beneficiaries. To help out the Management board in this task, technology transfer units available in the different organizations will assist in the evaluation of the inventory activities and in an eventual patent application. All the

organizations and scientists in charge of MEDICIS-PROMED have already gone through IP assessment and patent filling procedures.

- Gender aspects

In the present project, the promotion of gender balance in will be addressed by encouraging explicitly applications from female individuals at all levels within the MSC-ETN. Gender distributions will be monitored, and efforts will be made to invite female Researchers to present talks at the network's meetings in order to provide positive role models to young female scientists.

4.3 Appropriateness of the infrastructure of the participating organisations

The infrastructures made available by the organizations will allow a proper integration of the Researchers and development of the activities of MEDICIS-PROMED. CERN, Graphene Institute, JOGU, C2TN, KUL, CHUV, UNIGE, EPFL-ISREC, ILL, ARRONAX GIP are large research institutes that have world-class research infrastructure, administrative units such as HR dept with housing and mobility student/staff support offices, finance dept., communication services, technology transfer, libraries, IT dept, to name but a few. The research infrastructures are detailed further in section 5. Lemer-Pax, AAA, and CNAO, while of a smaller size than the other beneficiaries, are science and high-technology oriented organizations, and already hosts young scientists on other European programs. Lemer-Pax has a long tradition of industrial and engineering innovation-based development, and use up-to-date computer assisted design platforms, a design office, and a prototyping facility. AAA, some of its personnel having been working with Physics Nobel Prize Winner C; Rubbia, have 2 R&D premises and many more production sites distributed in Europe and beyond. It therefore already hosts the appropriate support, delocalisation, communication services to host the Researcher. The partner organization Oxford University consulting, a smaller structure, specifically joins the network to undertake the transferable skills training program, and is used to work with both universities and large academic research organizations, including CERN.

4.4 Competences, experience and complementarity of the participating organisations and their commitment to the programme

- Consortium composition and exploitation of partners' complementarities

The consortium comprises institutes that can cover all the requested R&D activities relevant for the isotope production chain, target development, mass separation, laser purification, ion sources, radiopharmaceutical synthesis, transport technology, biodistribution studies in cells, development of PET ions acceleration for therapy and imaging, imaging on small animals, pre-clinical tests on animal for ovarian cancer tumours. The advanced target materials developments is done in two leading institutes for graphene (graphene institute) and uranium materials (IST).

- Commitment of beneficiaries and partner organisations to the programme

All beneficiaries and partner organizations are fully committed to the activities of the network. Most of the organizations have already collaborated with the network coordinator on common projects, a large number already collaborating in the development of the CERN-MEDICIS idea and ISOLDE facilities (CERN, Graphene Institute, JOGU, C2TN, KUL, CHUV, UNIGE, EPFL-ISREC, ILL). The complementarity and commitment of the Organizations can be further seen in Table 4.4a

Table 4.4a Competences, experience and complementarity

Name	Competences	Experience	Complementarity/commitment
CERN	Construction of CERN-MEDICIS Target nanomaterials	Leading MEDICIS Part of Isolde collaboration	Coordination/ WP4,5 lead/Training/ Visiting scientist on detectors
Graphene inst.	Graphene on metal	Visit to CERN Collaboration with J. Billowes (part of CERN	Graphene/ General training 1 Visiting scientist on materials/ESR4
JOGU	Laser Ion sources	Part of Isolde collaboration	WP1 lead/ESR 5
AAA	Industrial medical isotope production	Spin off from CERN	WP3 lead/visiting scientist on radiopharma marketting/ESR6
C2TN	Uranium targets	Bilateral CERN-C2TN program/collab/ member of nTOF collab	WP6 lead/ESR7,8/ Summer school 2
CNAO	Hadron therapy with carbon	FP7 ULICE,PARTNER with Medaustron and CERN	WP2 lead/summer school 1/ESR9
PAX	Shielding, isotope packaging	Collab with ILL	ESR10/secondment
KUL	Laser ion sources	Part of MEDICIS, Isolde collaboration	Special. Training/visiting scientist on laser&mass sep/ESR11
CHUV	Preclinical studies Imaging Ovarian cancer	Part of MEDICIS, common CIBM center with EPFL, UNIGE Developments with AAA	Preclinical imaging on ovarian cancer in animals/ ESRCH2/workshop on imaging/visiting scientist on radioimmunotherapy
UNIGE	Robotic surgery Imaging cyclotron	Part of MEDICIS, common CIBM center with EPFL, UNIGE Developments with AAA	Robotic-assisted surgery/translational imaging/ESRCH1,3/ workshop on imaging
EPFL-ISREC	Moleculat oncology	Part of MEDICIS, common CIBM center with EPFL, UNIGE	ESRCH4/molecular oncology training
Medaustron	Hadrontherapy with carbon ECR ion source	Development of ion sources at Isolde, CERN	Secondment for ESR1
Oxford Consulting	Complementary training	Had already collaborated with CERN	Training office / entrepreneurship
ARRONAX	High power cyclotron Targets	Collaboration with PAX, ILL.	Radioisotope production training/secondment
ILL	High flux neutron reactor Medical isotope prod	Part of CERN-Isolde collab., developments with AAA, PAX, ARRONAX	Visiting scientists on medical isotope production/ secondment

6. Ethics Aspects

This chapter has been updated to include the different elements raised by the ethics screening report.

To achieve the main goals of the proposed research program some ethical issues must be taken into consideration namely: *a)* Research on humans including the use of human biological samples and human data collection; *b)* Research on animals (pigs, mice and rats). *c)* Production and handling of short-lived radioisotopes. All researchers involved in the program are aware of the scientific relevance and social impact of getting ethical or legal approvals by competent committees contributing to the quality of their research. Thus, all studies will comply with national and EU legislation and whenever applicable will be previously approved by the National Authorities.

The research program envisages the use and storage of immortalized human cell lines as well as the use of commercially available living animals. Animals are necessary for a better understanding of the in vivo behavior of the new compounds. Studies solely performed in other model systems, like computational or biophysics models or cell lines, do not allow a full preclinical characterization of the compounds to assess their potential usefulness for human use. However animal experimentation will be performed only when there is no other alternative. The choice of different strains of pigs, rats and mice as animal models will allow us to carry out the experiments in the time frame of the ongoing projects.

The laboratory animal facilities and team members responsible by the animal experimentation respect the principles of laboratory animal science on animal care, protection and welfare and are properly accredited by the National Authorities and EU Directives. All the research projects will need to be approved by the national authorities and local ethics committees.

The *Three R Concept* will be rigorously applied to the animal experimentation. Thus, whenever possible alternative methods will be used in order to replace an animal experiment, to reduce the number of animals or to refine the procedures and anesthesia methods so that animal pain or suffering is minimized enhancing their well-being. All compounds will be first evaluated by in vitro techniques and in cell lines. Only the most promising compounds will go on to the in vivo studies. Furthermore, careful experimental design and statistical analysis will contribute to a responsible use of animals.

For Matters concerning research activities based on the production and handling of short-lived radioisotopes in the Organizations of the network, or with the operation of particle beams, namely at CERN, AAA, CNAO, Medaustron, CHUV, UNIGE, EPFL, ARRONAX and ILL, the scientists in charge and the staff involved in these facilities, are well aware of the best practice in place.

Ethics related documents (agreements, template of letters of consent, authorization by the local or national ethics committees, etc.) must be submitted to the external ethical review board and to REA before the initiation of the corresponding research work.

6.1 Ethical institutions and regulations

All partners are perfectly aware of the paramount importance of ethical issues in research, especially in the Health domain.

Local ethical institutions

The activity of UNIGE will take place at the University Hospital of Geneva (Switzerland), the activity of CHUV will be performed at the Lausanne University Hospital (Switzerland), the activity of EPFL/ISREC will be done at the Swiss Federal Institute of Technology in Lausanne (Switzerland), and the work at the Instituto Superior Técnico will be done at the Centro de Ciências e Tecnologias Nucleares in Lisbon (Portugal). It is therefore under the jurisdiction of each institution to comply with ethic committee authorizations.

Non EU countries

Switzerland is already following ICH-GCP on ethical issues according to H2020 and EU regulation. In particular, local ethical boards are already in place in every hospitals and institutes performing tests on humans and animals, as well as SwissMedic, the overseeing authority on use of non-registered pharmaceutics and the Federal Office of Public Health for radioprotection issues and radiation dose delivered to patients.

Regulations

Participants in the project will conform to 1) Current legislation and regulations in the country where the research will be carried out, 2) European legislation, 3) International conventions and declarations. This includes in particular:

- **Directive 95/46 on the protection of personal data**. A particular attention will be paid to Art. 12 concerning the data subject's right of access to data; to Art. 16 and 17 concerning the confidentiality and the security of processing the data; to Art 25 concerning the transfer of personal data to third countries. Section 8 of the present document indicates how these key articles will be applied.
- **Directive 86/609/EEC on the protection of animals** used for experimental and other scientific purposes and Amsterdam protocol on animal protection and welfare.
- **Radiation Protection 118**. Referral guidelines for imaging, October 2001 and **Directive 97/43/EURATOM** on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure.
- **UNESCO 's Universal Declaration on Bioethics and Human Rights**, 19 October 2005.
- **World Medical Association Declaration of Helsinki**, Ethical Principles for Medical Research Involving Human Subjects.
- **World Health Organization's Guideline for Research**.
- **Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work;**
- **The "3 Rs" policy of Refinement, Reduction and Replacement towards the use of animals for scientific procedures (99/167/EC: Council Decision of 25/01/99). These principles of replacement by alternative methods, reduction of the number of animals and the refinement of experiments will be fully applied and P1 will be encouraged to demonstrate that it tries to elaborate/implement alternatives to animal experimentation;**

6.2 Research on humans

Informed consent

All studies performed on patients either for their routine clinical workup or under special protocols, will have to be approved by the local ethic committee after submission of a detail description of the project. All projects require patient consent for undergoing a special study as well as for using existing clinical data and images. Subjects will be provided with oral and written information about the project, the type of treatment and analyses performed, issues related to health risks and data protection, and the nature of informed consent. They will have to sign an agreement.

The following statements will be followed during the project for measurements on subjects:

- The consortium will not collect any data from children, pregnant women or persons not able to give consent.
- No discrimination will be used in terms of race and there will be a balance of gender in the subjects.

Subsequently to acquisition, a report, detailing measurements, post-processed information and medical outcomes, will be provided to volunteers. Informed consent will focus on clarity and investigators will obtain assurance from participants that all queries have been answered to their satisfaction.

Data collection and protection

Patients or subjects may be selected to collect data that are necessary for research proposed in the project. The partners involved in the image acquisition and biological sample collection will follow the

clinical protocols that are operational in their institution and country. Confidentiality, integrity and availability of personal information have to be ensured through protected information. All data will be managed by the research staff in accordance with legal requirements for data. Besides, access to patient data is highly protected and only authorized users can access data that have patient references. All other users in the consortium will receive data anonymously. The patients will know that data are collected anonymously.

Humans

MEDICIS PROMED is expected to involve human participants, and more specifically have activities related to human blood sampling in some of the Swiss partner organizations. Samples will be collected after patient information and approval of the local Ethical Commitees. The participants will be recruited following criteria presently in place, eg based on scientific and medical criteria as done presently in Lausanne university hospital or Geneva university hospital. While it is too early to define each individual activity, as example women with diagnosed ovarian carcinoma will be identified to test radiopharmaceuticals with promising preclinical results for ovarian cancer targeting. The informed consent will be requested in each case according to national regulation rules and Good Common Practice (GCP) rules. Ethics approval will be needed in all cases. In that example, the invasive procedure will consist in inserting a small catheter in one patient's vein to inject radiopharmaceuticals and get blood samples when required. Such protocols have already been performed for instance in Lausanne and Geneva university hospitals, which were approved by the ethics commissions that are already in place for these activities, at the level of the institutions and SwissMedics at the Swiss national level. Any incident will be reported.

Human cells and tissues

Preclinical studies with human cells and tissues will only be performed on animals. At the present stage of the project, no more detailed information of the exact type of cell lines which will be used is available. No human cell lines will be created within this project or acquired from another project. While there are no plans to progress in that direction, human cancer cells might become stored in hospitals databases.

6.3 Research on animals

Only when there is no alternative, animal experimentation will be considered. The minimum number of animal to ensure statistically significant results will be chosen. Particular attention will be given to animal welfare and minimize animal suffering.

The ESR working with animals will be trained on understanding cellular behaviour and will have the possibility to participate in translational studies. Animals will be used in a limited way during this PhD topic and work will be undertaken in accordance with the local guidelines and subject to approval by the licensing authority (regulations on animal experiment under veterinarian and ethical committees).

All experiments will be performed under the national (Swiss for EPFL, CHUV and UNIGE) animal welfare legislation and animal experiments by or under supervision of qualified technicians. Strict application of the 3Rs principle of animal experimentation will be applied (Replacement, Reduction and Refinement).We suggest to indicate the animal species. In our case we just will use mice, rats and pigs.

The laboratory animal facilities and technicians responsible by the animal experimentation are properly accredited by the national authorities. All the research protocols will be also approved by the national authorities. Copies of the relevant authorizations will be provided.

Preclinical studies on animals will be performed on an absolute needs basis with human cell lines. Those are commercially available and will match the tumor studied.

6.4 Research with radioisotopes and particle beams

The International Commission on Radiological Protection (ICRP) has specified in its Recommendation 60 (ICRP, *1990 Recommendations of the International Commission on Radiological Protection*, ICRP Publication 60 (Pergamon, Oxford, 1991) [*Ann. ICRP* **21** (1991) 1], ICRP, *The 2007 Recommendations of the International Commission on Radiological Protection*, ICRP Publication 103 (Elsevier, Amsterdam, 2007) [*Ann. ICRP* **37**(2–4) (2007)]) that any exposure of persons to ionizing radiation should be controlled and should be based on three main principles, namely:

– justification: any exposure of persons to ionizing radiation has to be justified;

– limitation: personal doses have to be kept below legal limits;

– optimization: personal and collective doses have to be kept as low as reasonably achievable (ALARA).

These recommendations are fully incorporated into Organizations radiation and general safety codes. All national and European directives regarding the protection from workers in radioactive environment will be respected; this includes the manipulation of unsealed sources and their application to man and animal in research, as well as the handling of radioactive waste. It follows:

- The Directive 1996/29/EC on the protection of workers in a radioactive environment;

- The Directive 1997/43/EC on the exposure of individuals to ionizing medical radiations.

The transport and handling of short-lived radioisotopes comply with international, ie IAEA best practice regulation, at the international, European, National and laboratories levels. Controlling bodies are in place at the international, European, national and institute levels. The treatment of the generated waste is addressed by optimizing the quantity and the type of waste resulting from the research activities, and by identifying the path to disposal, which is specific for each different country.

Environmental protection and safety

MEDICIS-PROMED will produce short-lived isotopes for preclinical studies. The institutes in charge of isotope productions already comply with national, European and IAEA ethical regulations in that matter. In particular, ALARA principles and controlling bodies are in place to minimize the risk to environment, personnel and the general public.

6.5 External ethical board

An external ethical review board will be created to oversee the MEDICIS PROMED activities. It will be composed of one chair, and five members.

- Prof J. Prior, MD, PhD – CHUV (chair)
- Prof O. Ratib, MD – UNIGE
- Prof L. Buehler MD – UNIGE
- Prof D. Hanahan – ISREC
- Dr. T. Stora – CERN
- Dr. U. Koester – ILL

Marie Skłodowska-Curie Actions (MSCA)
Innovative Training Networks (ITN)
H2020-MSCA-ITN-2014

Annex 1 to the Grant Agreement (Description of the Action) Part B