European Organization for Nuclear Research
Organisation européenne pour la recherche nucléaire

CERN MEDICIS – 3rd Collaboration Board meeting

CERN, 20th March 2019
Minutes by N.-T. Vuong, T. Stora - DRAFT
Link to the agenda and MEDICIS proposals: https://indico.cern.ch/event/797974/

Agenda:

- Introduction, Approval minutes 2nd board
- Facility Report
- Update on the MoU
- Financial Reporting
- Report on MED007
- Coffee Break
- Report on MED014 with cold Tb isotopes
- New project proposals:
  rev MED 004 from IST, MED 017 from PSI, MED 018 from PSI, MED 019 from PSI, MED 020 (IRMA V) from KU Leuven, MED 021 from IST, MED 022 from HCUGE, MED 023 from HCUGE
- Future EU Project
- AOB

Participants:

Present:

Giovanni Anelli, CERN – IPT-KT, invited
Frank Brucherseifer, JRC-Karlruhe
Irwin Cassels, SCK.CEN, invited
Frederik Cleeren, KU Leuven, invited
Thomas Cocolios, KU Leuven
Michel Forni, Fondation pour l'innovation sur le cancer
Vadim Gadelshin, JGU Mainz, invited
Simone Gilardoni, CERN – EN-STI
Dante Gregorio, CERN – EN-FAP, invited
Peter Ivanov, NPL
Michael Lassmann, Scientific Liaison Officer, EANM
Gerda Neyens, CERN
Karine Martinez, HCUGE
Antonio Paulo, IST Lisbon
Fabio Pozzi, CERN – HSE-RP, invited
Joao Pedro Ramos CERN – MEDICIS Run Coordinator
Sunniva Siem, UiO Univ. of Oslo
Simon Stegemann, KU Leuven
Thierry Stora, CERN
Zeynep Talip, PSI, invited
Nick Van der Meulen, PSI
Nhât-Tân Vuong, CERN, invited
Martin Walter, HCUGE

By remote connection:

Ferid Haddad, GIP Arronax
Ulli Koster, ILL
Susanta Lahiri, SINP Kolkata
Kirsten Leufgen, SCIPROM
Nathalie Michel, GIP Arronax
John Prior, CHUV
Maija Radzina, Riga Stradins Univ.
Jose Sanchez-Segovia, FABIS
Alice D'Onofrio, C2TN IST Lisbon

Introduction, Approval minutes 2nd board – T. Stora

T. Stora presents the agenda of the meeting. Eight project proposals were received for the 3rd MEDICIS collaboration board meeting.
A typo in the drafted minutes is corrected: affiliation of Guy Bormans is corrected into KU Leuven. There were no further comments.

Facility Report – J.P. Ramos

J. P. Ramos, the MEDICIS facility run coordinator reports on: 2018 operation, the current technical stop, and plans during CERN Long Shutdown 2 (LS2).
J. P. Ramos gives a brief overview of the MEDICIS facility. The present time required from End Of Beam (EOB) to isotopes lasts for 4 hours. Targets can be ready for isotopes extraction 4 hours after the end of irradiation. There are three possible modes of irradiation: 1) standard mode through the ISOLDE target, 2) through the ISOLDE neutron converter, 3) with a new mode of irradiation directly on the MEDICIS target deflecting the beam below the ISOLDE target. The last mode of irradiation increases the number of interaction by a factor 10 with respect to the first mode. As the beam scatters spreads out after going through the target or the converter (in mode 1 and 2), a larger MEDICIS target container is being designed to reach the highest interaction probability.
2018 operation: 15 targets were produced since the beginning of MEDICIS in October 2017 and 12 were produced in 2018. 2 targets are currently in Arronax for source importation for operation in 2019. 26 irradiations took place and 19 separations for isotope extraction were performed.
Technical stop: A metal plate will be added to the magnet to improve the mass resolution at high mass. Extraction electrodes based on a new design from the SPES facility will be installed on MEDICIS and ISOLDE Front-Ends. The connection of the ventilation is causing a delay of ~ 1 month in the reception of the Radiochemistry shielded fume-hood. MELISSA laser will be operational, within a week, when the laser safety system will be connected to CERN safety system and an operation console will be available.
Radiochemistry operation: Commissioning is progressing well, and is expected to start after an external audit will issue positive recommendations. First production of Tb-155 and its associated radiochemistry is planned.
Documentation: the operation of the facility is documented thanks to reports which synthesizes the relevant information for each isotope collection.
Operation during LS2: Tb isotopes will be produced from Gd target irradiated at Arronax. It will require a radiochemistry target separation step before mass separation. Cold separation tests have been performed in different conditions: TbO is more volatile than elemental Tb. In favourable conditions, TbO ions are much more extracted than Tb ions. Er169: A new sample transfer method to avoid contamination has been developed and will be used for the next collections in 2019. Laser ionization is prepared for the next collections in 2019.
Schedule: The schedule for 2019 foresees two to three operation cycles per month after the resteart of the facility, and a technical stop at the end of the operation period.
Developments:

Some development work took place on the isotope separation methods. It covers the use of Rhenium ion source, molecular scandium ion formation ScFx from Titanium foils, Tm ion separation from Tm target, Iron (Fe) isotopes from Y2O3 and AlNi targets (at KULeuven), Pt isotope production and extraction.

Open days participation:

CERN open days will take place on 14th -15th September 2019. (http://opendays.cern). MEDICIS will be open for visits, and will organize demonstration with its lasers systems.

Outlook and conclusions:

The Operation schedule is being prepared for 2019. It will mainly depend on the consolidation of the facility and the importations of the sources from Arronax and ILL. A standardization and normalized activity from source needs to be defined. It is proposed to take 3hours post EOB (End Of Beam) normalized for 1e18poT. For external sources, time of arrival at CERN + 8 hours.

MEDICIS-Promed final conference:

The MEDICIS-Promed network will organize its final conference in Erice on 30th April-4th May. It will notably cover techniques of isotope acceleration, medical physics, and research in oncology. It will also serve to start-up a network of facilities at the European scale (topics introduced later in the meeting).

Comments:

S. Gilardoni mentions that the ISOLDE and MEDICIS facilities operate in a similar way. The Class A laboratory was constructed to operate with open radioactive sources. The issue found with a malfunction of the extraction electrode in the beamline will have consequence on the design of the infrastructures for both facilities, ISOLDE and MEDICIS.

T. Stora mentions that the schedule will need to accommodate new constraints with respect to the schedule last year, as no proton beam is available at CERN during LS2. The output of MEDICIS will therefore also depend on the proper organization of the source importation from partners on one side, mainly ARRONAX and ILL Grenoble, and with possible interferences with CERN services as ongoing consolidation programs of CERN infrastructures takes place during LS2.

F. Haddad asks the confirmation that the schedule is to be prepared with J.P. Ramos, as MEDICIS run coordinator. He also warns with possible issues arising from radiation protection aspects for the handling of radioactive sources at ARRONAX. The targets prepared for Terbium production will be highly radioactive and their dose rate will be much higher than what is classically handled. It will require working and finding on a solution for an optimized handling.

Update on the MoU – G. Anelli

The costs for the operation of the facility are covered by the MEDICIS collaboration and therefore requires financial contributions of the members. The high-energy physics program is the priority and mandate of CERN. A new MoU is to be prepared beyond its approved phase A with a targeted date September 2020. The board will need to focus on a better definition of the contributions and on how much each member will benefit from the MEDICIS facility.

A dedicated meeting is proposed on 17th September, the day before the next collaboration board, to allow anticipation of discussion and to speed up the signature process. The KT Group will prepare a drafted MoU accordingly. The preparation meeting requires the presence of the institutes representatives who hold signature rights or at least proper delegates that can take decisions.

Comments:

G. Neyens: The contributions to MEDICIS are already defined in the Annex of the MoU. She reminds that cost of operations are also clearly defined, 400 kCHF for staff and 250 kCHF for material for a regular year of operation during Phase A. In Phase B: Upgrade of the facility, a preliminary cost estimate of 600 kCHF has been defined. That includes two additional isotope collection points, a new target design and a better radiochemistry infrastructures. The operation costs for Phase B should not be affected by this.

The preparation discussion and the dedicated meeting for the new MoU is agreed by the board.

Financial Reporting – D. Gregorio

In 2018, the CERN&society foundation received a grant from Fondation pour la lutte contre le cancer et pour les recherches medico-biologiques of 50 kCHF and a 200kCHF transfer from a 300kCHF donation of ADAM. Expenses amount to 138kCHF which corresponds to one CERN Staff position distributed over different personnels in the Radio-protection group.
A positive balance of +22kCHF is reported on 31st Dec 2018.
In 2019, 233kCHF financial contribution is expected (based on contributions from partners that have signed and expected donations), while expenses accounted for, up to February, are related to a CERN Staff position, materials expenses and one project associate position.
Prof. T. Cocolios comments that in-kind contributions to the project are not only for material, and can also cover the secondment of staff as already implemented with the position of MEDICIS run coordinator as supported by KULeuven.
It is planned to include in-kind contributions in the next MoU.
T.Stora mentions that there is already two scientific publications in preparation coming from MEDICIS activities, one in the context of MEDICIS-Promed lead by Dr. F. Cicone/CHUV on preclinical use and dosimetry of 152Tb, and a second one lead by B. Webster, NPL related to 155Tb radiochemical purification.

Report on MED007 – S. Stegemann (KULeuven/MEDICIS-Promed)

Some prototype material irradiation took place, and the analysis of 11C release efficiency is ongoing. Release was observed; however it is not quantified yet. The project was completed successfully, with a patent application that has been filed and input provided to the MEDICIS-Promed technical report on 11C-based hadron-therapy.

It is also mentioned that the project MED006-Prof Cocolios is completed successfully: A video in the context of MEDICIS-Promed Marie Curie network has been created, which featured the use of non-conventional isotopes for the medical research. The video is available on the following links : https://videos.cern.ch/record/2671551; https://www.youtube.com/watch?v=5T6RTxSh-rI

Report on MED014 with cold Tb isotopes – F. Cleeren

The MED014 project is part of a recently approved Tb-IRMA-V project by FWO in Belgium (see MED020 proposal thereafter). The teams and infrastructures available for the characterization of radiopharmaceuticals is presented at KULeuven, and UZ Leuven. The principle of bio-conjugation, that is the combination of a ligand, a linker and a chelating group for the selected isotope is introduced, with the aim to match the physical and biological half-lives. The strategy to design and test chelation of heat-sensitive molecules is shown, first with stable 159TbCl3 precursor, and later switching to 161Tb available from SCK and 155Tb foreseen from MEDICIS. First tests are conducted with Human Serum Albumin, and later with anti-CEA nanobodies. The kinetics of chelation with DOTA derivatives is shown with 159TbCl3, and takes less than 30 minutes at 25C. Initial complexation studies with 161Tb are then shown to be quantitative in less than 60 minutes.

Based on this report, the request of 155Tb delivery from MEDICIS is evaluated positively.

New projects

Rev_MED 004 - Clickable Terbium Complexes for Radioimmuno-Imaging & Therapy – A. Paulo

The MED004 revision is introduced. The revised proposal is still focused on the click chemistry as principle for labelling. The anti-TEM1 antibody fragment remains as a focal point of the proposal. After firs evaluations with commercial isotopes, the modified project proposes to focus on 155Tb-based radiobioconjugates. It will allow imaging studies.

The board approves the modified objectives of Rev MED-004.

MED005
This project is closed as the PhD student driving the project had left the group.

MED 021 - 155/161Tb-labeled radioconjugates for cancer therapy with Auger electrons – A. Paulo
This project proposes to synthesize bioconjugates combining a DOTA chelator for 155/161Tb, Design DOTA based 155/161 Tb complexes, a bioactive ligand as BBN analog, a cleavable linker and a DNA-targeting moiety. This aims as demonstrating the augmented therapeutic efficacy of Auger therapy and reduction of administrated doses.

The Board approves the project, asks to first present the results obtained with Tb-155, and present at the next board if Auger positive effects have been identified, together with the strategy to demonstrate an Auger-electron specific efficacy.

MED 017 - 167Tm production at MEDICIS from external PSI target
MED 018 - No-carrier-added 169Er production at MEDICIS from target irradiated at ILL
MED 019 - No-carrier-added 175Yb production at MEDICIS from external ILL target
Principcal co-investogators : Zeynep Talip, Nick Van der Meulen, Cristina Muller
The three proposals are presented together. Isotope requests are made on 167Tm separation at MEDICIS from a cyclotron target irradiated in Injector 2 at PSI, 175Yb and 169Er from ILL, all with high specific activities.

The aim of these 3 proposals is to make a systematic study on beta-to-Auger contributions for therapeutic effects.
The board comments that no imaging component exists for 175Yb and thus the clinical application might be difficult, making the theranostics approach difficult. Further to this, gamma emission might limit the possibilities to handle these isotopes with high activities, not a concern for 169Er a pure electron emitter already shown to be provided in high specific activities by MED-011 and published (https://doi.org/10.1016/j.nimb.2019.04.022).
The boards recommends to proceed with MED-018 as the technical feasibility is already demonstrated. The feasibility of MED-019 needs to be established, with 90GBq/mg possible at ILL. The ILL irradiation capacity will be 8x in the summer period of June-July-August, and 6-7x in September.
MED-017 seems more challenging. The board recommends to present the strategy for imaging and systematic auger-to-beta dosimetry in September.

MED 022 - Non-invasive imaging of radioactive platinum chemotherapeutics for patient stratification - M. Walter
MED 023 - Imaging of iron metabolism – M. Walter
These two proposals share in common a strategy to make imaging of chemotherapeutic compounds that do not provide imaging compounds. In MED-022, the goal is to produce radioactive cis-Platinum for patient follow-up, and possibly identify efficacy and toxicity. In MED-023, bacteria responses to antibiotics could be imaged.
The board mentions that related projects are already ongoing in different groups such as in South Africa, the Netherlands, Strasbourg or Montpellier. Furthermore Pt isotope has never been produced as seperated isotopes and will require significant technical developments if at all possible. 52Fe has already been produced as 1st beams at ISOLDE., but the activity is not matching the needs. Ongoing developments such as the development of NiAl superalloy might meet this request. 59Fe could be available from cyclotrons. Since not very high specific activity is required for imaging

proof-of-concepts, it is proposed to supply 195mPt from ILL, while technical feasibility is explored at CERN. These two projects are seen as high risks, high benefits type of projects.
MED-022 is approved by the board, while MED-023 is pending technical feasibility results in September.

MED 020 - Tb-IRMA-V: Terbium ISOL Radioisotopes for Medical Applications in Flanders- T. Cocolios
The Tb-IRMA-V project is presented. 2.2 M€ from Research Foundation Flanders (FWO) has been granted to the consortium KU Leuven (coordinator)- CERN - SCK.CEN. 161Tb is to be provided by BR2 at SCK.CEN. MED-014, part of this project, is already expecting 155Tb from MEDICIS. A financial support of 290kCHF is provisioned for MEDICIS.
Additionally, 149Tb is required, and will be available from 2021 onward from MEDICIS. The transport limit values have been computed by P. Bertreix/CERN-RP and by M. Maietta (Lemer-Pax , MEDICIS Promed). Prof. Cocolios asks for a copy of the thesis of M. Maietta. It is also noted that the delivery of 149Tb to Belgium could be done with a minimum of 2 half lives decay before dispatch.

Future EU Project – T. Stora, K. Leufgen
A new call INFRA-2-2020. For integrating infrastructures for starting communities will be open later in 2019. 5 M€ budget is recommended per project. The details of the call was presented. SCIPROM K. Leufgen. Partners are interested to participate to this new project. A kick-off meeting will take place on 30th April in Erice, MEDICIS-Promed Final Conference. The consortium should define a number of Transnational large and major infrastructures, networking activities and joint research activities. A follow-up meeting is foreseen on 19th September after the next board.

AOB
M. Radzina / RSU asks criteria to take part in the INFRA programme. The cyclotron energy limitation is addressed: No precise layout has been defined at the moment. Since TNA are major infrastructures, small infrastructures could be federated in one virtual TNA. Clinical strategy and project shall also be discussed.

Next dates
The schedule for 2019 operations is to be circulated and a first part up to September will be released.
A topical meeting for the next MoU will take place on **17th September 2019**.
The next collaboration board meeting will take place on **18th September 2019**.
The kick-off meeting to launch a new European project in the INFRA-2-2020 call will take place on 30th April 2019 in Erice, IT, and a next meeting will take place at CERN on **19th September 2019**.