



## **CERN MEDICIS – 11<sup>th</sup> Collaboration Board meeting**

CERN, 6<sup>th</sup> December 2023

Minutes by C. Duchemin, T. Stora / DRAFT

Link to the agenda and MEDICIS proposals: <https://indico.cern.ch/event/1351618/>

Link to the MEDICIS proposals: <https://medicis.cern/approved-projects>

### **Agenda:**

- Collaboration matters: MoU, financial, review updates
- Facility technical reports
- New proposals
- AOB

### **Participants (tbc):**

*Present:*

*Charlotte DUCHEMIN*

*Thierry STORA*

*Alessandro RAIMONDO*

*Edgars MAMIS*

*Karine MARTINEZ*

*Lurdes GANO*

*Zeynep TALIP*

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*Cyril BERNERD-CERN*

*Frank BRUCHERTSEIFER- JRC(EU)*

*Sean Collins – NPL (UK)*

*Sean FREEMAN-CERN (Isolde collaboration)*

*Simone GILARDONI-CERN*

*Lurdes Gano-CTN-Univ Lisbon (PT)*

*Eugenia Hatziangeli – CERN (ATS Medical applications)*

*Muhammad INZAMMAM – PAEC(PK), seconded at MEDICIS*

*Peter IVANOV-NPL (UK)*

*Qaiser KHAN– PAEC(PK)*

*Susanta LAHIRI-*

*Laura LAMBERT-CERN*

*Michael LASSMANN-EANM*

*Nick van der MEULEN-PSI (CH)*

*Fabio POZZI-CERN*

*John PRIOR-CHUV (CH)*

*Agata ROZYCKA-CERN*

*Dr. SHABANA-PAEC (PK)*

*David VIERTL – CHUV (CH)*

*Toms TORIMS-RTU (LV)*

**Approval of minutes of the 10<sup>th</sup> Board & Agenda – Thierry Stora, CERN**

Minutes of the previous board are approved, with minor typos corrected and the following comments included:

NvdMeulen: no discussion had actually taken place on PSI side for the raise of the contribution a raise to 25kCHF should be addressed with the legal service.

Brussels university should read 'Vrije', it should say 'VUB' or 'Vrije Universiteit Brussel'.

Sean Freeman is affiliated to CERN, Alessandro Raimondo should be added to the list of participants

Thierry Stora : as MEDICIS is celebrating its 10<sup>th</sup> anniversary this year, a vin chaud and other events will be organized with Stefano Marzari along the year 2024..

### **MoU Update, MEDICIS budget and financial report - Agata Rozycka, Alessandro Raimondo**

Agata Rozycka presents the expenses until 30 November 2023, as well as the financial contribution for the year 2023 at the same date and donations. Some information was still lacking at this stage, notably on the PRISMAP contribution.

The year started at 4kCHF and finished with a positive balance of 97kCHF. With expected further contributions and commitments of +49 kCHF and of -38kCHF.

CERN contributions covered 321 for both personal and material, with an additional 12 kCHF commitment.

The sum of purchases amount to 176967CHF on the collaboration budget code, with further budget redistribution between CERN and the collaboration expected by the end of the year. On CERN budget codes, expenses and commitments are shown for a total of 163070 CHF for material, and of 26 985CHF for personnel as the RP staff (1 Eq FTE) of 169919 CHF is now accounted on a different budget code.

The contribution of 212000CHF for 2023 is shown, and a donation of 20000CHF (and a further 25000CHF expected), completed with a contribution from PRISMAP of 24000CHF.

The overall operation was shown together for the past years, with diverse contributions from the collaboration, CERN, donations and European projects. The in-kind contributions were finally shown.

Simone commented on the future fundings and way of managing that will be discussed later.

Alessandro said that we should also address legal aspects related to shipping radioisotopes to institutes not signing the MoU. A letter is being prepared to cover these aspects to be signed by the receiving institute when it is not signing the MoU. Likewise, KULeuven is signing on behalf of a Belgium consortium, and these differences will be taken into account. T. Cocolios mentions that there is legal document that describes the consortium and the association of other Belgium universities with the funding agency. This scheme is similar, eg, as the one used for the Isolde collaboration in that respect. T. Stora mentions that we have already shipments in the context of PRISMAP and this is already taken care of.

### **Feedback from PRISMAP - Thierry Stora**

Thierry presents an update on the PRISMAP project. The 6<sup>th</sup> consortium meeting happened last week in Lisbon, hosted by CTN and the medical faculty. The consortium, the radionuclides and the inclusion of medical institutes is shown. In this project, radionuclides need to be shipped to other institutes, and a related agreement has been developed to account for this. 32 projects (from 45) have been selected for reception of radionuclides, from 33 research teams. The share from MEDICIS in PRISMAP the good coordination and efficient development of the facility towards PRISMAP. In addition, efforts in standardization and data generation is significant, together with the shipping with a dedicated private jet, allowing a 4hours door to door delivery from MEDICIS to DTU (DK). While shipping was expensive, this is actually justified in view of the production costs already committed from the facilities. From the respective Key Performance Indicators, we delivered 16 radionuclides (10 defined as threshold), a user selection panel had met 4 times and selected for funding 23 research projects, and a platform that was organized to receive requests such as combined 203Pb/212Pb available from MEDICIS and ARRANAX production centers,

already as this is performed in MEDICIS. For more advanced research, supply of radionuclides should be supported through other schemes, and contacts are already done with EFPIA federation, big pharma and SME's.

From the 5 objectives set at the start, all objectives are progressing : Provide access to new radionuclides and new purity grades for medical research, create a common entry port and web interface for the starting research community, enhance clarity and regulatory procedures to promote research with radiopharmaceuticals, unlock the biomedical research through better data on radionuclides, ensure the long-term sustainability of PRISMAP

On this last point, exchanges at the highest point between the European Commission and CERN to express PRISMAP views on research radionuclides in biomedicine. This is also expressed in the European Radioisotopes Valley Initiative which is setting the long term perspectives from the commission.

Views on PRISMAP+, the follow up programme for PRISMAP, is being elaborated in a white paper. With a 1<sup>st</sup> dedicated mass separation facility for biomedical research in operation, operation constraints eg linked with high radionuclide activities and traceability is a major development at MEDICIS, which is foreseen to be joined up in the coming years by facilities in SPES-INFN, Myrrha-SCK, Tatroo-PSI, Smile-Subatech, possibly also IFIN, a unique mass separation consortium setting worldwide.

### **MEDICIS operation in 2023 – Charlotte Duchemin**

Charlotte provides an update of the MEDICIS programme in 2023. The technical stop was followed by the restart mid March. 3 new projects were accepted. 10 new targets and 6 were reused. The MELISSA ion source was used for 80% of the operation for many radiolanthanide collections. Scheme development for Dy and Sc, as well as a new laser ion source based on Raman-based diamond has been used for the 1<sup>st</sup> time at MEDICIS for the Ra production. 18 irradiation slots have been used this year, for Ba-128, Ra-224, Ac-225, Tb-155, Tm-165, Tm-167 and for Sc-47 as PhD work. 25% of poT of total PSB proton beam for 2023 was delivered for the MEDICIS programme (to HRS 45 % direct and 10% indirect, to GPS 45%). The beam steering was cross-checked with gafchromic films. 6 weeks with external samples (Sc-43/44, Sm-153, Er-169 from PSI, SCK and ILL) were performed. Shipments went to CHUV, DTU PAEC, KULeuven, IRA-CHUV, NPL, PSI, Univ. Bordeaux, Heidelberg Hospital. Worth mentioning >100MBq Ra-224/Ra-225 collections and >1 GBq Sm-153 collections. In PRISMAP, 3 User projects received Tb-155, Tm-165 and Ac-225, as well as Ra-224/Pb-212 developments, with a dedicated private jet deliveries 4hrs door-to-door to DTU. An overall 3.8GBq total activity was collected, with a 40% separation efficiency for Ra, and 1.2GBq Sm-153 delivery that allowed >99% radiolabeling yield testing of the radiobioconjugate there.

### **Update on MEDICIS international review board - Simone Gilardoni**

A review of MEDICIS happened few weeks ago. The purpose of the review was to assess the relevance of the operation of MEDICIS up to 2025 and beyond. LS3 will happen in 2026-2027. The international review panel members were Cathy Cutler (BNL, USA), Rachel Eloirdi (EC), Ratib Osman (HUG) and Ilyes Zahi (Novartis), independent, outside of Europe. In particular, since the collaboration could not fund the MEDICIS operation, CERN management wanted to assess the relevance and see how the future funding must be foreseen. The outcome was in general positive. There will be a presentation of the review outcome in January 2024 to the next planned CSMAC (CERN Medical Applications Steering Committee). This committee selects, prioritizes, approves and coordinates all proposed medical application projects and their execution with the available budget. There will be a discussion with the management for future beyond 2025, since the current deadline for MEDICIS is considered as the end of the PRISMAP program.

## **Options for MEDICIS developments - Simone Gilardoni, Thierry Stora**

The efforts to obtain the lacking financial resources from the MTP from last year were after all rather successful. The previous discussions we raised on the possible financial schemes for the collaboration should again be considered, or any new other input raised. The next board could be an ideal framework for this. At JRC, there is also restructuring and discussions along the elections of the new commission next year. So far, this activity is expected to be maintained or even reinforced in a large sense. But unfortunately in the background, a staff reduction is ongoing at JRC and how this may impact the programme will be seen. K. Martinez from HUG indeed reiterates the wish to reinforce the support from HUG towards MEDICIS. A forthcoming meeting with prof Garibotto and Dr. Bois is planned. Finally, CHUV indeed is promoting the preclinical demand, while the clinical input from Prof Prior was already expressed during the review process.

LUNCH BREAK

### **Laura Lambert**

Laura presented the start of operation and radiochemistry performed with a new glovebox commissioned end of 2022, notably for the handling of alpha emitting collections such as Ac/Ra225 and Ra-224 collections. She presented the improvements on ampoule decontamination done for importations of sources from ILL, and investigations of thermal release for Scandium radionuclide production. Finally the elaboration of technical specifications for the procurement of new equipment is considered, notably for an ICP-OES. This goes along considering upgrading the ageing fume hoods in 179-R002 class A laboratories (eg used for ampoule decontamination) mutually shared with other activities at CERN (ISOLDE, n TOF) and lab space allocation.

T. Cocolios asked if the ampoule from ILL could be cleaned directly there. PSI is facing the same issue with ampoule decontamination. N. vdMeulen commented that ILL does not have a chemical lab and does not have means to do that.

### **Inzamiam Miam - PINSTECH**

The radiochemistry activities were reported, notably covering the development of a simple generator for Ra-224/Pb-212 delivery in the newly commissioned glovebox, and its dispatch for testing in a partner institute. Charlotte commented that the fact we now have a HP Ge detector in-site allows us to perform this kind of research and development activities (Ra-224/Pb-212 and Sc release study).

### **MED-038 – David Viertl**

David presented the results he obtained on the in-vivo generator Ba/Cs-128 and its application for the treatment of osteosarcoma. Metrological data were reported, notably with a new T<sub>1/2</sub> determined by IRA and NPL metrology institutes. Limited uptake in different osteosarcoma models and cell lines have been measured so far, whereas the underlying principle was the analogy with calcium. Injection in nude mice allowed PET image acquisition, with possibly aiming at predicting dosimetric contribution for Auger electron emitting contributions. Strong localization in the kidney was also witnessed, while not identified in related biodistribution studies.

Different hypothesis were tested, and the anesthetic protocole was seen to influence the kidney accumulation.

This project has been completed by deliveries of Cs-129 to study the uptake of Ba and Cs separately in the kidneys, and confirmed that Ba is preferentially incorporated in bone tissues, while Cs incorporate in the kidneys.

Outlook is to find a suitable in vitro model, consolidate the PET imaging and biodistribution, along with recruitment of a future PhD student to consolidate these findings and progress from there.

U. Koester: Ba-128 or Ba-135m gamma lines could be used in SPECT imaging to differentiate between the decay and diffusion of Cs-128 and the observed ex-vivo and in-vivo differences. T. Stora finally commented that the differences of Ba uptakes in cell lines with respect to expectation for a Calcium surrogate could in turn be used to induce selectivity towards metabolic pathways or specific cell lines once this effect is understood better.

### **MED-027 Strengthening theranostics or radionuclide therapy in Pakistan - Progress report**

Dr Infan Khan-INMOL presented the status and plans in Pakistan to reinforce research and use of theranostics. This covers the possibility to perform peptide synthesis in Pakistan, plans for the development and use of Cu-64/Zr-89 with monoclonal antibodies to perform radioimmuno-PET, the development of conjugates based on Lu-177 or Ac-225. In the long term, the acquisition of a new cyclotron is foreseen. A number of ligands are accessible, and synthesis with Cu-64-Cu-67 or Tb-155 is possible. In particular, a new clinical CZT-based SPECT imaging scanner has been acquired at INMOL. M. Lassmann asked about the feasibility to make proper calibration of the images with Tb-155 in particular, as several gamma lines are produced. A first delivery of Ra/Ac-225 was performed at INMOL. Successful dissolution and labelling with an automated set-up was obtained. Quality control showed appropriate level of labelling. Strong interest to move in the clinical phase is now expressed.

Ra/Ac-225 was dispatched to PINSTECH, where different columns and resins were used to perform a radiochemical purification, with a local resin and a LN resin test sample. The LN resin supplied from Triskem (FR) undergoes a ban for its exportation to PK because precursors originating from USA used in the synthesis of the resin. The separation of Ra and Ac is quantitative, and several extractions are ongoing to check the radiolabeling yields, notably with the

### **MED-015 44Sc production and study for clinical use - Progress Report**

E. Mamis presented progresses in MED-015. Ti and V foils were activated and release performed by gamma spectroscopy. In addition, developments with a number of target units took place in 2022 and 2023, with preliminary data on extraction figures and confirmation of suppression of long lived contaminants such as Sc-46 and Sc-48. Additional tests were performed with a source provided by NvdMeulen-PSI, as well as investigations of molecular beam formation and laser ionization scheme development. At present, the foreseen conditions for optimal separation of Sc is with TiC targets (1/2 charge tested) and extraction as molecular beam.

UKoester mentions that eventually V foils with MELISSA laser ionization could be an interesting back up option for elemental Sc release.

TTorims confirms the satisfaction of Latvia about its contribution to the MEDICIS programme, and in return the possibility for MEDICIS to provide some input for the development of nuclear medicine in Latvia. Besides the nice result obtained so far, the completion of MED-015 expected in 2024 would allow the graduation of one of the few MEDICIS/Latvia PhD programme and possibly PRISMAP label students. It also acknowledges the long standing links between Latvia and CERN-MEDICIS way before Latvia became Associate Member of CERN and MEDICIS started operating.

### **MED-034 Determination of 227Ac impurity in 225Ac using alpha spectrometry - Written report**

TStora presents the report on behalf of IRA/CHUV. IRA is an expert center in Switzerland for dosimetric studies. It received batches of Ac225-Ac227 for development of methodology and incorporation measurements. Ac225-Ac227 is not yet used at clinical scale, and it is expected that workers will need to be followed for incorporation measurements. This extends the scientific

mission of MEDICIS into this important workers health monitoring, radioprotection and dosimetric field. In addition TECocolios mentions that the methodology is being compared with data produced at KULeuven for intercomparison.

### **MED-036 Clinical and Pre-clinical Evaluation of Tb155/161 Theranostic Pair for Imaging and Radionuclide Targeted Therapy of Tumors in Pakistan**

PINSTECH is submitting a new project for the investigation of the theranostic imaging and treatment pairs Tb155/Tb161. It will also involve other institutes in Pakistan, such as INMOL. The proposal is to develop the synthesis of radiopharmaceuticals incorporating Tb161 produced in Pakistan and Tb155. Needs to access to chromatographic resin Tb-155 and Tb-161 is required, as well as mass-separated Tb155. Answering the question of UKoester, indeed the preclinical phase can proceed with Tb161, while Tb155 will be required at a later stage going into the clinical phase. Imaging properties MLassmann then went on in the need to perform calibration studies to obtain meaningful imaging. While the production at present is on the low side, some efforts will be required to reach meaningful clinical doses. However, test batches could already be delivered for testing dispatch and perform phantom studies.

As a conclusion, the board recommends to perform a test shipment to be done for Tb-155 and then progress report to see how to move forward with this project.

Regarding the possible shipment of Ra/Ac225 for clinical research in Pakistan, a new project proposal is required. Not anticipating on the outcome of the evaluation by the MEDICIS board, a strategic decision will be issued from a high level committee at CERN foreseen to take place next year within a couple of months.

### **MED-037 Alphamet LoI - metrology needs with alpha emitters – Sean Collins**

Sean Collins presents on behalf of Ana Denis-Bacelar at NPL. AlphaMET is a new project approved by the European Commission and aims to address the unique and unmet metrological challenges of alpha emitters in nuclear medicine. This is a collaboration involving eight European National Metrology Institutes NMI/Dis and BIPM. The State of the Art is standards on Ra-223, which has been reviewed and corrected by 9%, a large number in the field. Different Work Packages will look into standards, in-vivo imaging and adsorbed dose quantification.

Require high purity 100 MBqs Ra-225 and Ra-225. NPL will isolate Ac-225 and Pb-212 at NPL. Two productions of Ra-225 and Ra-224 in 2024 and 2025 in the 100 MBqs range will be required. Radionuclidic purity of better than  $1e-5$  will be required.

The project received support from the board, especially since the radionuclides will be produced in Europe for a EU project.

### **Program 2024 – Charlotte DUCHEMIN**

MEDICIS received the mandate to operate in 2024. The technical stop will last from December to end March 2024. Faraday Cup will be fixed, a new slit system will be implemented, a new kromek detector for high activity monitoring will be included, the laser beam path checked, robot handling trajectories checked, a new target exchange point implemented, and a new safe point as the decay point. A new generation of scanner will be implemented.

Targets will be build (Sm-153 for clinical project, Ta roll target, ThC for Ra-224-225).

The facility will move back into operation in end of March, just before easter. Stable beam test and commissioning are foreseen before the operation run from Arpil to December (November with external sources only) both with target irradiation and external sources.

Foreseen radionuclides are Ra-224, Ra/Ac-225, Tb-155, Ba/Cs128, Sc43/44/47, Sm-153, Tm165 and Tm167 (about 50% for PRISMAP projects).

**AOB**

The CMASC CERN committee is foreseen for end of January. The next board should take place around the restart of the facility.

Thomas Cocolios is involved in the next NuPECC Long Range Plan. There will be a dedicated chapter on medical applications, as well as mass separation. MEDICIS is foreseen to be very visible.