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IN SCIENCE AND TECHNOLOGY

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Subject | Minutes of the WG meeting "*Medical Requirements for MFH*" application Meeting of COST Action TD1402 - Multifunctional Nanoparticles for Magnetic Hyperthermia and Indirect Radiation Therapy (RADIOMAG)

Faculty of Sciences, University of Lisbon, Lisbon (Portugal)
16-17th of April 2015

1. Welcome to participants

The participants were welcomed by the local organisers Maria de Deus Carvalho and Liliana Pires Ferreira. Next, the Action Chair Simo Spassov welcomed the participants and opened the meeting.

2. Adoption of the agenda

A small change of the meeting programme was announced. The presentation of the RADIOMAG webpage was switched with the poster flash presentations, *cf.* meeting programme.

3. Meeting content

1st day, 16th of April
Morning
The session was arranged by members of WG 3 (Sophia Costa-Lima, Franck Couillaud, Spiridon Spirou, Alessandro Lascialfari) giving oral presentations with the focus on medical requirements and human constraints for magnetic hyperthermia (MFH) and external radiotherapy (ERT). The WG3 leader (Claire Billotey) prepared the presentation but was represented by Franck Couillaud.

Overview of topics
- NP administration, vascular distribution, excretion pathways, and physio-pathological context
- lung filter and impact on NP coating, intra-venous injection vs. intra-arterial injection
- blood vessel types/blood brain boundary
- discussion on the importance of the EPR effect for humans
- types of ERT
- cell-killing effect of radioactive radiation (direct/indirect), comparison repair rates normal cells vs. tumour cells

- radio-sensitisation to address the problem of hypoxia in tumour regions
- overview of ERT, effect of heat and radiation on different tumour types/growth stages and resulting synergies between MFH and ERT
- overview of MFH: physical basis (Néel/Brown relaxation), SAR, clinical studies done so far, problems of MFH, problems of inhomogeneous heat distribution in tumours due to non-optimal NP distribution
- NP toxicity at cell scale, pros/cons of cellular studies
- environmental conditions of cell line maintenance
- cell-NP interactions and pathways of NP uptake
- regulatory constraints, definition and risks of nano-medicine
- timeline for medical products from R&D to granted marketing authorisation
- safety and quality assessment

The round table was skipped due to lack of time and shifted to the afternoon session.

Afternoon
The session started with individual WG meetings in separate rooms discussing the individual WG strategies as laid down in the morning session. Next, the WG representatives (Thanh Nguyen, Silvio Dutz, Alessandro Lascialfari and Olivier Sandre) presented the discussion outcome and animated the plenary debate.

WG1: presentation of infrastructure and possibilities
WG2: presentation of WG strategy and problems to be tackled – request from WG2 and 4 for standard ferrofluid for comparing MFH testing devices (*cf.* afternoon 2nd day)
WG3: presentation and debate on problems of MFH
WG4: planning of writing a technical note to properly measure magnetic field intensity of MFH set-ups

Discussed topics during plenary debate
- tumour models: rat vs. mouse model: rat model less optimal due to larger size which would require an adoption of commercially available MFH testing devices which are currently optimised for mice.
- it was suggested to set up a database of existing cell lines and tumours models for testing new NPs for MFH application combining also MRI and MFH. Sofia Costa-Lima would provide such list
- SAR determination by means of AC susceptibility / hysteresis curve measurements
- thermometry for monitoring temperatures during MFH application: luminescence / MRI, input from WG2 about length scales required
- phantom tissue: gelatine (or Matrigel™) vs. agarose for tumour simulation. A database of thermal tissue properties is available at the ETH Zürich as well as 3D tumour models.
- legal definition of a ferrofluid for MFH application: medicinal product (*i.e.* drug) rather than medical device. EMA should be involved as early as possible when planning to merchandise a ferrofluid for MFH
- the units of SAR and magnetisation. Silvio Dutz clarified the terms magnetic moment and magnetisation. The use of SI is demanded.

The afternoon session closed around 6 PM with flash presentation of 1-2 slides advertising the posters. Twenty-six posters were exposed, covering a broad spectrum of topics related to the scientific expertise of RADIOMAG.

2nd day, 17th of April

Morning

The session was devoted to oral presentation of WG1, WG2 and WG4 by Thanh Nguyen, Silvio Dutz and Olivier Sandre focusing on:

- the expertise of WG1
- state of the art and physical aspects of MFH
- overview of commercial versus laboratory made MFH testing devices and very recent technical advancements of MFH applicators for SAR measurements, *in-vivo* applications, thermometry and the field/frequency calibration of MFH applicators

An extensive coffee break was allowed for the poster presentations/discussions.

Robert Muller presented then an outline of the future RADIOMAG web-page. It was convened that the web-page will be developed and maintained by a commercial partner. Within the next three weeks input from the network is required for proposing an action logo. In case of several logo propositions a doodle vote will be initiated. Until the end of June the written content has to be finalised.

Afternoon

Two semi-plenary parallel discussions were planned for the afternoon; however it was decided to have a full plenary session occupying the whole afternoon. Due to requirement of a standard ferrofluid for MFH test device SAR calibration, a lively debate was hold, animated by the Action Chair, on:

- the properties and the reproducibility of the calibration ferrofluid,
- magnetic and non-magnetic characteristics to be provided with the ferrofluid (magnetic moment, core grain size, etc.)
- the laboratories in charge of the fabrication,
- the laboratories in charge with carrying out the calibration
- storage conditions and applicable field/frequency for calibration procedure.

It was convened that WG2 leaders will chose the three laboratories which have multi-frequency MFH testing devices who will receive the samples in order to choose an appropriate field/frequency combination. A calibration protocol will be set up and send out to four other laboratories for the actual SAR determination The results should be delivered to WG2 members as $T(t)$-curve and as SAR $[W/g]$ with g being the mass concentration of magnetic NPs. Further details see Annex 13.
The question whether the laboratories in charge of the synthesis of calibration ferrofluids could be reimbursed on the COST budget for the delivery of samples by regular mail or delivery service was raised and the Chair planned to ask to the COST office about this possibility.

4. Next Meeting

The next meeting will take place on the 27th -29th of October 2015 in Limassol, Cyprus.

5. Closing

The Action Chair thanked the local organisers for the excellent organisation of the meeting, the participants for their contribution, and closed the meeting closed around 5 PM.

List of Annexes

Annex 1: Meeting agenda
Annex 2: Signed COST Attendance list
Annex 3: Summary expertise WG1: WG1.Nguyen.summary
Annex 4: Oral presentation Silvio Dutz: WG2.Dutz
Annex 5: Concrete research strategy of WG2: WG2.Dutz.strategy
Annex 6: Oral presentation Claire Billotey: WG3.Billotey.part1
Annex 7: Oral presentation Claire Billotey legal aspects: WG3.Billotey.part2
Annex 8: Oral presentation Sofia Costa-Lima: WG3.Costa-Lima
Annex 9: Oral presentation Alessandro Lascialfari: WG3.Lascialfari
Annex 10: Oral presentation Spiridon Spirou: WG3.Spirou
Annex 11: Oral presentation Olivier Sandre: WG4.Sandre
Annex 12: Website proposition by Robert Muller: WG5.muller.webpage
Annex 13: Protocol debate standard ferrofluid: debate.ff
Annex 14: List of poster presentations: poster.list
Annex 15: Flash poster presentations: poster.flash