COST EMF - MED (Action BM1309):
European network for innovative uses of EMFs in biomedical applications

STSM Report:

Immune response modulation by EMF: Review, concepts and research potentials

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Abstract:

As a part of the COST-Action the WM "Immune response modulation" this STSM aims to substantiate the activity by developing one or more drafts/outlines for possible publications, research proposal(s), and new ideas in order to further the WM´s goals. During the 14 days STSM a pilot study to investigate the physical/biophysical mode of action on cellular level has started, we identified new research areas for future grant applications, generated an interinstitutional MoU, initiated a special journal issue for the COST-EMF-MED-Action, and started a review article in cooperation with other members of the Action. The STSM thus successfully provided with the opportunity to initiate valuable and for the Action highly relevant activities that are subjects for more long-lasting and intense collaborations.

A. Purpose of the STSM

The objectives of the present STSM application are to

- Develop a concept how to identify new research areas with potential to be included or applied in the H2020 program as well as in other transnational research foundations.

- Draft/outline one (or more) review articles. These paper(s) will provide the state of the art on immune response modulation by EMF, and attention will be paid to both possible molecular mechanisms and immune-modulating therapies focusing on specific signals/frequencies/ exposure times.

B. Work Description

The STSM grant recipient Myrtill Simkó planned the work prior to the site visits and subsequently performed site visits at CNR-IREA, Naples, ITA and at ENEA, Division of Health Technologies, Rome,

ITA during the period 12-26 March 2016. During the visit to Dr. Maria Rosaria Scarfi and her team and the applicant Dr. Myrtill Simkó, worked on the following issues:

1. identification of possible project application themes such as specific biological effects to be investigated in a cooperative way
2. with regard to topic 1, identification of possible grant application themes
3. drafting a Memorandum of Understanding (MoU) between our Institutes
4. planning on a "Special Issue" in a peer reviewed journal covering "Medical applications of EMF" (as a working title)
5. conceptual work/draft of a review article on immune response modulation by EMF

The STSM included a visit to ENEA in Rome, Italy as well, meeting with Dr. Claudio Pioli and Dr. Carmela Marino to discuss about the content of a review article in a peer reviewed Journal. We (the host and the visitor) have agreed on a working concept.

C. Results / Deliverables

1. Initiation of a cooperative research project

After intense discussions regarding how to give insight into the mode of action ~~on~~ of EMF exposure on cellular level, we have identified a new EMF research area with the potential to give hints and possible explanations about physical and biophysical processes during EMF exposure on cellular level. However, the main requirement for this study is to design precise experimental and exposure conditions. Thus, we developed a concept to build a temperature-controlled equipment that can be used during EMF exposure under a confocal microscope where we plan to study "live" cell culture conditions. This work is still ongoing in cooperation with the Hungarian COST Partner Dr. György Thuróczy. The challenge for the heating system is that the confocal microscope is equipped with laser beams, those power is adjusted on the basis of the adopted fluorescent molecule by possibly causing temperature change in the sample. Therefore we have to develop a heating-cooling system keeping the temperature constant. The next challenge is to keep the temperature constant during the exposure to EMF, to avoid interference with the lasers and the used molecules/dyes, and to use a surface for the cells that is transparent for the light, keeping stable temperature, without interfering with the fields. The work has been theoretically developed during the STSM and is still in progress. Several solutions have been explored for the equipment and materials to be used by requesting information and quotations to various specialized companies. We hope that in the next future this equipment can be used for the planned studies.

We have also started some specific pilot studies that are independent of the exposure. We think that if the EMF exposure related studies show the expected outcome this research area with several aspects of basic research, will have a strong potential to be supported by grant holders such as H2020.

2. Identification of relevant subject areas for transnational collaborative grant applications

We have also identified the research area "Electromagnetic fields and bystander effects" for research application by common discussions and literature study. This concept is relatively well described for ionizing radiation (IR). It has been shown that if the cell culture medium was taken from IR exposed cells and transferred on non-irradiated cells, cell death was induced in the non-IR-targeted cell culture. The action mechanisms of the caused bystander effects are not totally understood yet. However, the bystander effects seem to be primarily a low dose phenomenon with a saturation of around 0.2(-0.5) Gy (see Nagasawa & Little, 1992; Prise et al. 2005). It seems that the release of specific cytokines are involved in intercellular bystander signaling events (Prise & O'Sullivan 2009) and also calcium as a mediator of intracellular signaling has been shown to trigger this effect (Mattson & Chan 2003). Some of the signal pathways described is similar to those that are discussed to be involved in the field of immune

modulation of EMF. Mothersill et al. (2007), exposed cells to Magnetic Resonance Imaging (MRI) 10 min and detected a bystander response. There are a few more studies showing the presence of bystander effects also in combination with chemicals and EMF. However the mode of action is not clear yet.

We plan to investigate this interesting phenomenon in the human neuroblastoma cell line SH-SY5Y and a set of experiments was designed in details. Moreover, we also discussed the possibility to evaluate RF-induced adaptive response in several healthy and cancer cell lines. A set of experiments was planned to test the induction of AR in SH-SY5Y cells. The results will be used to evaluate possible therapeutic applications by optimizing the balance between induced damage in healthy and cancer tissues for chemo- and radio-therapy.

We think that such results will provide new possibilities to explore this scientific area and it will be possible to identify research grant within the H2020. The difficulty in this area is to identify possible cooperation (consortium) partners and an appropriate research hypothesis, since this research community is relatively small at the moment.

3. Memorandum of Understanding (MoU)

The MoU is in progress and awaits final signatures from our respective Institutes representatives. It includes:

Purpose:

AIT and IREA-CNR are linked by common scientific and research interests. This collaboration is intended to start a scientific cooperation in fields of shared interest and expertise. The activities undertaken pursuant to this Memorandum of Understanding (MOU) reflect a spirit of cooperation and reciprocity intended to be of mutual benefit to both parties and contribute to an enduring scientific relationship between the Parties.

Objectives, scope and major activities:

The following forms of collaboration will be explored:

A. The development of programs designed to promote cooperation in fields of mutual research interests;

B. The development of projects and programs in specific areas of mutual research interest;

C. The development of formal award courses and professional development courses, as mutually agreed by the Parties;

D. Research Collaboration and Exchange of scientific materials;

E. Abroad programs of experienced and early stage researchers.

The MoU furthermore includes agreements regarding:

- Implementation and funding
- Duration and option to amend
- Extend or terminate
- General terms
- Intellectual property rights
- Confidentiality
- Financial regulations

4. Identification of a topic for a special issue on “Medical applications of EMF”

Regarding to Dr. Scarfi´s idea on a “Special Issue” the negotiation process has started with specific journals. In our discussions we have realized that “immune modulation by EMF” will not lead to enough submissions therefore we increased the scope of possible manuscripts, and introduced the tentative title “Special Issue - Medical applications of EMF: in vitro studies”.

Outlining and first draft of a review article

A two day meeting was performed at Dr. Pioli`s lab in Rome where Dr. Mattsson was attending as well, to discuss and outline a review article related to the WM "Immune response modulation". This brain storming leads us to develop an interesting and new concept (view) for a review article about immune response and electromagnetic fields. We acknowledge the cooperation of Dr. Mattsson and Dr. Savelkoul, who have already agreed to take part as coauthors. We have outlined the preliminary structure of the Manuscript with the present working title is: "Change of perspective in EMF and immune system: from health concerns to immune regulation?" whereby Dr. Pioli has the lead. Our goal is the focus on immune modulation findings covering the entire spectrum of EMF, to identify possible pathways and activation processes that could be affected/modulated by EMF. We think that this paper will further the knowledge of EMF-induced immune modulation (if any) and allow generating a different view in this area. Furthermore we aim to open new research areas by identifying knowledge gaps. For a face-to-face meeting we will use the coming BioEM-conference in Ghent.

In summary, our activities are continuing after the site visits and have resulted in further work on the initiated research project, including recruitment of additional EMF-MED members. The draft MoU has been subjected to legal scrutiny and is now undergoing signing by the leaders of the involved institutes. The writing of the review article is underway and also one physical author group meeting has been set. The additional initiated activities have been followed up and are expected to be emphasized in the next phase of the STSM-related work.

D. Future collaboration with host institution

The basis for the future collaboration is manifested by a MoU between our institutes (CNR-IREA and AIT). According to our common agreements and result (as described in C.) we will continue with our cooperative research activities.

E. Expected Publications

With regard to the Special Issue on Medical applications of EMF, we expect several publications, specifically by the COST Action members. Furthermore one review publication is expected on the "Immune modulation and EMF" area.

F. Other Comments

No other comments.

Confirmation by the host institution of the successful execution of the STSM:

We confirm that Dr. Myrtill Simkó has performed the research work as described above.

Contact Person of Host Institution	Name of researcher
Dr. Maria Rosaria Scarfi	Dr. Myrtill Simkó
Signature	Signature