MITIGATE NEWSLETTER

CLOSED-LOOP MOLECULAR ENVIRONMENT FOR MINIMALLY INVASIVE TREATMENT OF PATIENTS WITH METASTATIC GASTROINTESTINAL STROMAL TUMOURS

EDITION 3 * 09/2016

Dear Readers,

For the MITIGATE consortium the past year started with a review of results obtained from pre-clinical studies conducted since the beginning of the project. Consequently, in September 2015 during our Intermediate Meeting, several important decisions concerning the planned diagnostic clinical trial were made. A number of substances, all with a potential for GIST-specific imaging, were tested with respect to specificity and patient safety. The substance displaying the best pre-clinical results was chosen for the recently opened diagnostic clinical trial, conducted at the Medical University of Innsbruck, Austria. Based on MITIGATE's approach of focusing on progressive tumour lesions, several eligibility criteria for participation in the trial were published on the MITIGATE website. We truly hope that in the near future GIST patients can benefit from better diagnosis through an improved tumour volume definition and better detection of the disease. As a result, alternative treatment options such as minimally invasive interventional therapies or stereotactic radiation therapy could be applied with greater precision. In the future, these therapy concepts may also be translated to other types of cancer.

With the completion of the third year of the project, we are pleased to report on research conducted within two of the project's work packages (WPs): WP5 and WP6. WP5-studies are mainly concerned with the discovery of a new GIST-specific radiotracer. This included the development of standard radiolabelling procedures together with in vitro and in vivo evaluation of specificity of the synthesised radiopharmaceutical. Alongside research on modelling of human bio-distribution and absorbed doses, a database of GIST mass spectrometry signatures was created.

In WP6, the main activities are focused on the preparation and timely launch of the clinical trial. Substantial regulatory and administrative work was completed last year. The Medical University of Innsbruck, a leading partner in this WP, was responsible for the preparation of the ethics committee proposal, study documents, submission to the competent authorities and planning of the patient's recruitment.

Also in this newsletter, the Medical University of Innsbruck (MUI) and the European Institute for Biomedical Research (EIBIR), our partner for project management and dissemination, will be presented.

As for the future, MITIGATE efforts will focus on the translation of pre-clinical results into clinical practice. Among other things, evaluation of the results of the clinical trial, further development of new GIST-specific radiotracers and an assessment of new functional and metabolic MR imaging methods of GIST tumours are the key accomplishments for the last year of the project.

More details are available on the website www.mitigate-project.eu.

Enjoy the read!

Prof. Stefan Schönberg
MITIGATE Scientific Coordinator

Dr. Pamela Zolda
MITIGATE Project Manager

FIRST-IN-HUMAN APPLICATION OF THE DIAGNOSTIC TRACER ^{68}GA-NEOBOMB1: CONSIDERATIONS ON SAFETY, TOLERABILITY AND TARGETING IN A CLINICAL STUDY

The final aim of MITIGATE`s work package 6 is to assess the diagnostic value of NeoBOMB1 in GIST patients, and to demonstrate its safety and tolerability. According to national law and European guidelines concerning good clinical practice and use of medicinal products in humans, several steps have to be taken before any pharmaceutical substance can be routinely used in humans.

Every early phase study design, especially our combined phase I/IIa study, has to adhere to these special requirements. Throughout the study, measures to assess and provide safety – i.e. the lack of severe adverse events – and tolerability – i.e. the lack of less severe side effects – will take centre stage. Every patient will undergo extensive medical screening and observation concerning clinical, physiological and biochemical findings before, during and after the administration of NeoBOMB1.

In the second phase, the focus will shift to providing focused information on the targeting properties of NeoBOMB1 in patients with known lesion receptor-profiles. Patients will be followed up closely for 24 hours and will be seen again twice in the timeframe of one week. A final telephone interview will be performed up to three weeks later to confirm the patient's wellbeing and to detect any delayed adverse events.

Why is such a complicated process required for a diagnostic investigation? While there is a need to increase the diagnostic sensitivity and specificity of current imaging modalities to detect GIST in its early and advanced stages, this alone would make it difficult to justify such a study. There are some significant benefits beyond that, though. Not only should such a specific tracer like NeoBOMB1 allow for an improved characterisation of tumours and thus provide the team of physicians with more accurate information about the biological state of the tumour, but also it can serve as a better foundation on which to plan minimally invasive treatment approaches such as radiofrequency ablation, microwave ablation, irreversible electroporation or targeted radiation therapy.

As a future goal, this study should prove a stepping-stone for the application of NeoBOMB1 coupled to a therapeutic radioactive agent. This could provide patients without the possibility of surgical cure and ineffectiveness of tyrosine-kinase-inhibitors with a novel and highly specific systemic treatment option, which certainly is a goal worth pursuing!

MITIGATE is currently recruiting participants for the clinical diagnostic study. An online recruitment form was developed in close collaboration with representatives of patient organisations and clinicians. The form introduces the study and the eligibility criteria for participants. Please visit our website for details.

MITIGATE PROJECT FACTS

Name: Closed-loop Molecular Environment for Minimally Invasive Treatment of Patients with Metastatic Gastrointestinal Stromal Tumours

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Partners: Ruprecht-Karls-University Heidelberg, DE, Coordinator (UHEI)
European Institute for Biomedical Imaging Research, AT (EIBIR)
Medical University Innsbruck, AT (MUI)
University of Torino, IT (UNITO)
IPA Fraunhofer, DE (FHI)
Mannheim University of Applied Sciences, DE (HM)
Cage Chemicals*, IT (Cage)
Advanced Accelerator Applications*, FR (AAA)
Rapid Biomedical*, DE (Rapid)
Stemcell Technologies*, FR (SCT)

**SME (Small and Medium Enterprise)*

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EUROPEAN INSTITUTE FOR BIOMEDICAL IMAGING RESEARCH

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MAJOR ACTIVITIES IN TWO WORK PACKAGES

WORK PACKAGE 5: NEOBOMB1, A NEW GENERATION BOMBESIN ANALOGUE FOR GRPR TARGETING: IN VITRO/IN VIVO CHARACTERISATION IN GIST ANIMAL MODELS AND DEVELOPMENT OF A GMP DIAGNOSTIC KIT FOR HUMAN USE

The MITIGATE project aims to develop alternative diagnostic and therapeutic options for GIST patients. Targeted radiopharmaceuticals would provide an effective, non-invasive tool for personalised diagnostic/treatment options.
NeoBOMB1 is a new generation bombesin analogue, which binds with high affinity/specificity to the gastrin release peptide receptor (GRPR) expressed in GIST. Using the tumour models developed by MITIGATE partners, in vitro and in vivo characterization of the NeoBOMB1 was performed. In vitro studies performed by MUI using GIST cell lines (T1, 882 and 430) confirmed expression of the GRPR in these tumour models, as well as high affinity and low internalization of the NeoBOMB1, consistent with its antagonistic behaviour.
In vivo studies with ^{68}Ga-labelled NeoBOMB1 were performed at the MITIGATE partner Advanced Accelerator Applications (AAA) in mice bearing the GIST tumour xenografts. The GIST-882 cell line was shown to be the optimal model for 68Ga-labelled NeoBOMB1 PET visualisation. Using the standard radiolabelling procedure set up by AAA, mice bearing the GIST-882 xenograft were evaluated for tumour uptake after injection of NeoBOMB1. A direct comparison with the standard PET tracer ^{18}F-FDG was also performed, showing higher uptake for ^{68}Ga-labelled NeoBOMB1 (Figure 1). This indicates that there might be an advantage in using this tracer over the established clinically used compound.
After assessment of the NeoBOMB1 imaging performance, the safety of the peptide was also evaluated within WP5. Overall, no signs of toxicity were observed in rats, indicating that the peptide is well tolerated at a dose several hundred times higher than the maximum peptide dose for diagnostic use in humans.
All the pre-clinical studies described above were performed with the kit approach, developed by AAA, for the preparation of NeoBOMB1 solution for injection. The kit allows a standardised and controlled ^{68}Ga-labeling procedure based on the direct reconstitution of a pre-formulated GMP vial.
The kit developed by AAA will now be tested in the Phase I/IIa clinical trial at the University of Innsbruck to evaluate safety, bio-distribution, dosimetry and preliminary diagnostic performance of NeoBOMB1 in patients with advanced TKI-treated GIST.

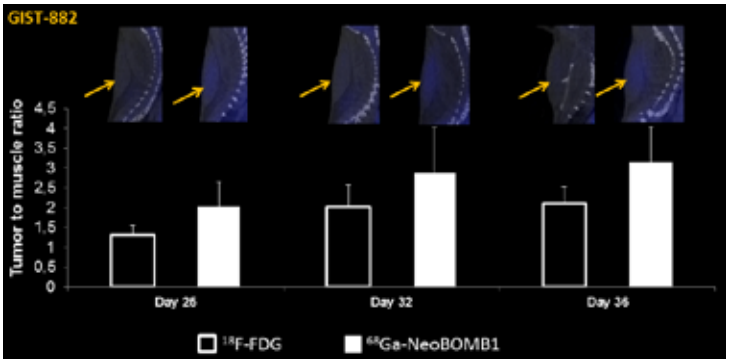

Figure 1: Tumour to muscle ratio for PET imaging of GIST-882-bearing mice at different times after tumour inoculation. The same animal received an injection of ^{68}Ga-NeoBOMB1 and ^{18}F-FDG at different times on the same day.

WORK PACKAGE 6: PREPARATION FOR A FIRST-IN-HUMAN CLINICAL TRIAL

Within work package 6 the main goal over the last six months has been to develop a study protocol for the first-in-human application of NeoBOMB1. To reflect the phase I/IIa nature of the planned study, the protocol was designed to provide both information on the safety and tolerability of 68Ga-labelled NeoBOMB1 as well as to give information on its targeting properties. During the first phase – focused on the tolerability and safety – patients with progressive, as well as with stable or regressive disease will be included to minimize a potential bias through disease burden. In the second phase of the study – focused on tracer-based diagnosis – the focus will be aimed at patients with failure of conventional tyrosine-kinase-inhibitor therapy. These patients will potentially benefit most from alternative, minimally-invasive treatment approaches by interventional radiology or radiation oncology based on improved diagnostic target definition. In cooperation with the Medical Faculty Mannheim a specific, physiology-based pharmacokinetic modelling approach will be employed to further increase the accuracy of the bio-distribution assessment of the peptide.
Last July the local ethical committee approved the study protocol.

PROJECT PARTNER MEDICAL UNIVERSITY OF INNSBRUCK (MUI)

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Located in the heart of the Alps, the Medical University of Innsbruck and its university hospital are dedicated to basic and clinical research, training in various medical disciplines, ongoing student teaching and patient care. In partnership with the Innsbruck State Hospital, its employees provide diagnosis and treatment for over 50.000 individual patients annually from the state of Tyrol, South Tyrol, Vorarlberg and beyond. Furthermore, there are over one million outpatient contacts per year. The university's research focuses on oncology, neurosciences, genetics, and infectious diseases.
The departments of nuclear medicine (Head Prof. I. Virgolini) and for diagnostic and interventional radiology (Head Prof. W. Jaschke) both have a long history of collaboration in several fields ranging from the early days of PET-CT to novel diagnostic and therapeutic approaches in malignancies. Both continue to work together within the MITIGATE project to develop and apply novel diagnostic and therapeutic approaches in patients with GIST.

PROJECT PARTNER EUROPEAN INSTITUTE FOR BIOMEDICAL IMAGING RESEARCH (EIBIR)

EUROPEAN INSTITUTE FOR BIOMEDICAL IMAGING RESEARCH

The European Institute for Biomedical Imaging Research (EIBIR) is a non-profit organisation dedicated to the coordination of biomedical imaging research in Europe. EIBIR`s network of currently 150 members has the mission to strengthen biomedical imaging research throughout Europe by bringing international research expertise together. EIBIR is a multi-disciplinary organisation providing an umbrella for all disciplines related to biomedical imaging and has 12 shareholder organisations that together with the founder, the European Society of Radiology, define EIBIR`s strategic agenda and activities. EIBIR has an excellent track record in projects supported by H2020 and the 7th Framework Programme. In MITIGATE EIBIR is partner for management and dissemination, supports the coordinator in the project`s operational procedures and also coordinates all dissemination and exploitation activities.

Pamela Zolda – Project Manager | EIBIR | Neutorgasse 9, 1010 Vienna, Austria | Phone: +43 (1) 533 40 64-538 | Email: pzolda@eibir.org | www.mitigate-project.eu