MITIGATE NEWSLETTER

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

EDITION 4 * 09/2017

Dear Readers,

Welcome to the 4th MITIGATE newsletter, in which we are pleased to provide you with information on research activities of the MITIGATE consortium in the final phase of our project.

In the past year we have successfully fulfilled one of the most important MITIGATE milestones: the opening of the clinical trial on the diagnostic GIST-specific radiotracer at the Medical University Innsbruck. So far, several patients have participated in the trial and further examinations are planned until the end of the project. The results obtained provided us with significant input for novel protocols and guidelines towards better diagnosis and treatment for patients with GIST. We are also glad to announce that further investigations, i.e. efficacy study on the GIST theranostic substance, are being carried out and will continue beyond MITIGATE.

To fulfil our dedication to personalised medicine, pre-clinical studies on GIST subtype classification and imatinib resistance - as well as new possible specific GIST-targeting imaging compounds - have also progressed in the past year.

In this newsletter we report on studies conducted in two work packages: WP7 and WP8. The efforts of WP7 concentrated on the development of a protocol for minimally invasive treatment and studies on robotic assistance. Within WP8, the assessment of new MR imaging methods of GIST tumour models into clinical practice has been investigated. Finally, we are pleased to introduce the company profiles of two MITIGATE industry partners involved in WP7 and WP8: Rapid Biomedical and Cage Chemicals.

Next to the scientific activities our great efforts are now directed towards dissemination and exploitation of all results obtained, assuring that our research will be continued in the future.

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

MAJOR ACTIVITIES IN TWO WORK PACKAGES

WORK PACKAGE 7: MINIMALLY INVASIVE THERAPY

This work package focuses on minimally invasive therapies other than radiopharmaceuticals, including radioactive seed placement, external radiation therapy, thermal and non-thermal ablation. The aim is to develop a methodology to tailor the treatment plan individually to the patient. The first objective is to design a concept to investigate combinations of treatment and have this protocol approved. The next objective is to develop a strategy and the tools to integrate the new markers for PET-CT imaging into the combination treatments. The final objective is to apply these new treatment strategies to carefully selected patients within the concept study protocol. Patients with progressive disease shown on conventional imaging techniques will receive a PET-CT examination with the new tracer. If necessary, unclear findings will be re-evaluated by diagnostic biopsy. This approach helps to avoid under- and over-treatment.

Patients will be treated by current state of the art endoradiotherapy or image guided minimally invasive treatment options.
The purpose of the assisting technology is to support physicians performing minimally invasive treatments in planning, execution, and monitoring of the intervention. To meet the requirements of a complex minimally invasive treatment the following concept was developed.

- A software tool allowing the user to combine and view medical imaging data and to select target points and entry points for the needle-based treatment.
- A manipulator or robot to provide positioning and orientation of a needle guide. The KUKA LBR iiwa MED is selected for its design purpose: a component for medical products.
- A registration method to determine the robot position and orientation in image coordinates.
- A communication protocol to send target and entry points from the planning software tool to the robot.

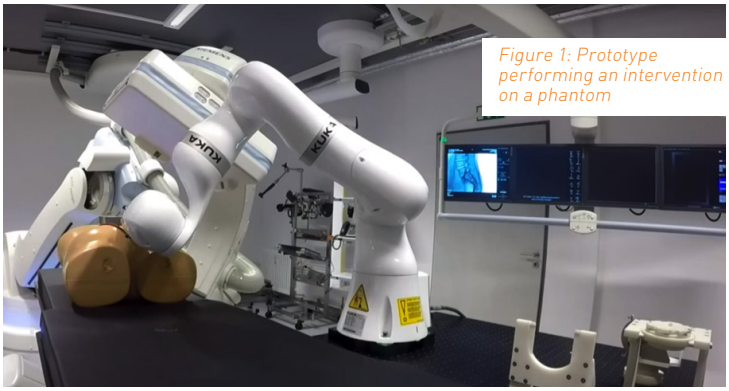

Figure 1: Prototype performing an intervention on a phantom

WORK PACKAGE 8: MULTIMODAL THERAPY CONTROL

Work package 8 aims at developing multi-modality imaging protocols, MRI sequences and hardware for the MRI-based functional assessment of GIST tumour microenvironment and for evaluating the therapeutic effect on GIST tumour murine models upon imatinib treatment. This work-package involved several academic institutions (UNITO, UHEI, HM) and commercial partners (RAPID, CAGE, AAA). Despite physical challenges, sodium imaging has the large advantages to be non-invasive and without ionizing radiation. The tissue sodium concentration could be quantified which enables measurement of tissue viability and assessment of therapeutic effectiveness on a cellular level and optimises monitoring of GIST patients. A clinical 1H/23Na RF coil system was designed and constructed by RAPID. This coil allows accelerated 23Na imaging of the torso with an optimum SNR combined with the ability for 1H overview images. The coil assembly was developed in close collaboration with the clinical partner at the University Medical Center Mannheim. Here a clinical workflow for multimodal therapy control was set up and used to scan volunteers. The 1H and 23Na images were combined to yield a true 23Na concentration quantification based on linear fit from reference vials. High resolution anatomical information from proton MR imaging (grey scale) is combined with functional data from sodium MR scans (colour scale).
At the preclinical level, CAGE Chemicals worked in close collaboration with UNITO for improving the early detection of GIST response to treatment upon imatinib administration on GIST430 (imatinib-resistant), GIST-T1 and GIST882 (imatinib-sensitive) xenograft murine models. A multimodal imaging approach was established for evaluating tumour volumetric changes (T2w), cellularity (DWI), acidosis (pH-imaging CEST) and vascularization (DCE-MRI) by MRI technique in combination with FDG-PET imaging (metabolism). The wide range of the obtained functional parameters may provide new insights in the early identification of GIST response to therapy.

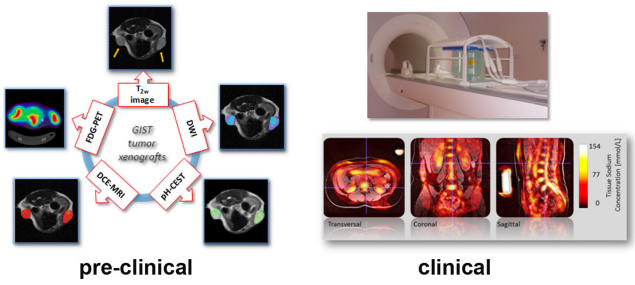

Figure 2: Multimodal imaging approach

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THE MITIGATE CLINICAL STUDY

Within the MITIGATE project the novel radiopharmaceutical 68Ga-NeoBOMB1 was selected for translation into clinical application in GIST patients with advanced stage of their disease. It targets specifically Gastrin releasing peptide receptors expressed in GIST for Positron Emission tomography (PET). Partner AAA provided a pharmaceutically compatible kit formulation for this clinical trial that allows straight forward radiolabelling with 68Ga, a short lived positron emitter at the clinical trial site at the Medical University Innsbruck (MUI). The Clinical Trial "A Phase I/IIa study to evaluate safety, biodistribution, dosimetry and preliminary diagnostic performance of 68Ga-NeoBOMB1 in patients with advanced TKI-treated GIST using positron-emission tomography/computer tomography (PET/CT)" (EudraCT 2016-002053-38) was initiated in December 2016 and the first patient was successfully recruited in January 2017.

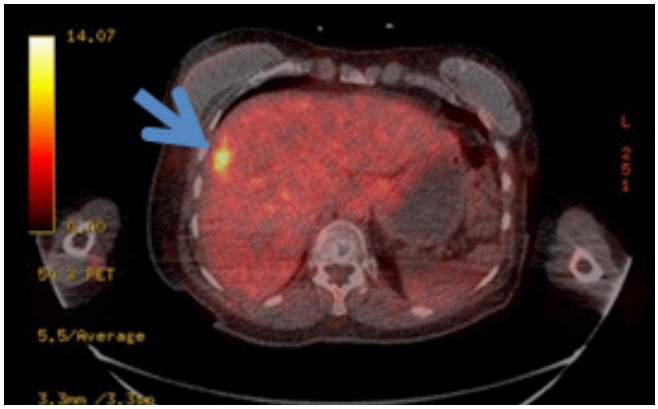

Figure 3: PET/CT image from a patient with advanced TKI resistant GIST, 1h after injection of 68Ga-NeoBOMB1. A liver metastasis is clearly delineated in early images due to binding of the radiopharmaceutical to GRP receptors expressed on GIST.

In the initial part of the study dynamic PET scans in three patients with advanced GIST – most of them resistant to TKI treatment – were included. All study related investigations could be performed as planned. In particular safety monitoring parameters were included, whereby no severe adverse events due to the administration of 68Ga-NeoBOMB1 were found. Physiological enhancement of 68Ga-NeoBOMB1 was observed most strongly in the pancreas. Also rapid renal clearance was observed. Tumour enhancement increased over the time course of the study giving high contrast images at later time points. Pharmacokinetics` investigations revealed a high metabolic stability of 68Ga-NeoBOMB1.

A report detailing these initial results was again evaluated by the ethical committee and no objections were made. Based on this vote, patient recruitment is now continuing and two more patients shall be included until late July 2017. All these first data indicate a very good safety profile of 68Ga-NeoBOMB1 showing excellent image quality in PET. The study is currently moving into its second phase to provide additional data on specific receptor targeting in GIST patients and study completion is planned until end of 2017. Overall the study is expected to provide the basis for further development of the promising novel imaging agent for the benefit of GIST patients in an advanced stage of disease, but also to open other applications in oncological patients.

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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PROJECT PARTNER RAPID BIOMEDICAL (RAPID)

RAPID Biomedical specialises in RF coils that are customised to the individual needs of the scientific MR community. Through attentive alliances with the MR system manufacturers and high level RF expertise we offer full compatibility for the coil solutions - standard or customised. In nearly 20 years RAPID Biomedical has delivered over 1400 different coil designs all over the world. We have thorough experience in designing RF-coils for human and animal scanners from 0.2T up to 21T. The range of non-proton solutions counts 11 different nuclei (so far). All the products are manufactured in Rimpar, Germany. Currently, R&D work concentrates on PET/MR compatible coils, coil packages for hyperpolarised nuclei, human 7T coils, dual tuned coils and multi array coils for parallel MRI. RAPID Biomedical's sister company RAPID MR International, LLC (www.rapidmri.com) is contact partner for customers in North and South America. In MITIGATE RAPID is partner in WP8.

PROJECT PARTNER CAGE CHEMICALS (CAGE)

CAGE Chemicals is a small company founded in 2006 and located in Novara (Italy). The activity of CAGE Chemicals is mainly dedicated to the research and development of products and processes for pharmaceutical and chemical industries. Moreover, CAGE Chemicals has an established experience in the design, synthesis and characterisation of chelating agents and metal complexes used as diagnostic probes in several Molecular Imaging techniques (MRI, PET, SPECT, optical imaging). In MITIGATE, CAGE Chemicals is partner for the development of imaging probes to be used in the research of novel diagnostic approaches and multi-modality imaging assessment of treatment response for GIST patients.

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