



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

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THE RATIONALE

Gastrointestinal stromal tumour (GIST) is a rare disease and frequently affects young patients with high potential for metastasising, which often results in a short life expectancy of less than 3 years. Currently there is only one class of effective medications, the tyrosine kinase inhibitors (TKI), for systemic GIST therapy and often the tumours develop drug resistance after a few years. No molecular imaging technologies indicating drug resistance, early therapeutic response or disease progression are clinically available. Furthermore, effective targeted agents with other mechanisms of action such as endoradiopharmaceuticals are not designed for treatment of GIST and alternative minimally-invasive treatment options for metastatic disease are not well explored nor has the clinical value of their combined use been established. This leaves GIST patients with very limited treatment options.

THE OBJECTIVES

The overall objective of the MITIGATE project is to develop and validate an integrated closed-loop process to effectively treat metastatic GIST patients resistant to the currently available class of medication, the TKI. This envisaged personalised treatment concept combines innovative strategies for biopsy, inline tissue analysis, molecular tumour characterisation, theranostics by imaging technologies (PET and MRI) and companion radiopharmaceuticals followed by the assessment of biodistribution, dose calculation and measurement of therapeutic effectiveness. In addition, synergistic concepts of minimally-invasive treatment will be applied.

THE EXPECTED OUTCOMES

1. Optimisation of biopsy and tissue preparation in suspected GIST for integrated analysis and subtyping of molecular markers
2. Provision of a large and broadly characterised tumour bank of TKI-responsive and -resistant GIST for generating novel pre-clinical models envisioned to reveal novel markers for TKI-resistance
3. Application of molecular imaging probes for specific GIST features indicating drug resistance, early therapeutic response or progression

4. Development of effective targeted agents with other mechanisms of therapeutic action such as endoradiopharmaceuticals for treatment in patients
5. Combination of this therapeutic approach with alternative, minimally-invasive treatment options for a personalised treatment in the metastatic situation with fewer side effects
6. Non-invasive monitoring of treatment effects in clinical routine

THE CONSORTIUM

MITIGATE's partners representing three European universities, three research organisations and four SMEs will pursue the ultimate goal to develop new protocols and guidelines to effectively diagnose and treat patients with metastatic GIST resistant to current treatment.

- Ruprecht-Karls-Universitaet Heidelberg (coordinator), DE
- EIBIR gemeinnuetzige GmbH zur Foerderung der Erforschung der biomedizinischen Bildgebung, AT
- Medizinische Universitaet Innsbruck, AT
- Università degli Studi di Torino, IT
- Fraunhofer-Gesellschaft zur Foerderung der angewandten Forschung, DE
- CAGE Chemicals, IT
- Advanced Accelerator Applications, FR
- RAPID Biomedizinische Geraete RAPID Biomedical, DE
- STEMCELL Technologies, FR
- Hochschule Mannheim, DE

Eight work packages have been defined that tightly interlink the demands of developing the system platform for minimally-invasive, molecular imaging assisted biopsy, the molecular targeting of tumours, the innovative biotechnology for patient-individualised treatment, the multimodal imaging for therapy planning and monitoring as well as the elaborate exploitation and dissemination of project results.

MITIGATE will run from October 2013-2017, and receives Euro 4.5 M in co-funding from the European Commission under the 7th Framework Programme.



WP4: TARGET ANALYSIS AND MOLECULAR PROBE DESIGN

Starting from known molecules binding to alternative targets WP4 will develop new potential radiopharmaceuticals and synthesise imaging probes recognising specific epitopes on GIST tumour cells. After in vitro evaluation of binding properties the body distribution of the potential radiotracers will be evaluated in vivo in specific animal models by using a small animal PET-CT. Different derivatisation/labeling strategies will be used based on the results of the in vivo and in silico evaluation. A biorepository of naïve and treated/resistant GIST samples will be generated in a viable, cryopreserved state. For patient derived tumourgrafts (PDT) a mouse model of imatinib-resistant GIST will be developed based on highly immunocompromised and/or humanized mice (NSG).



MITIGATE THE WORK PACKAGES

WP1 – Project Management – and WP2 – Dissemination and Exploitation – accompany the project over the entire term.

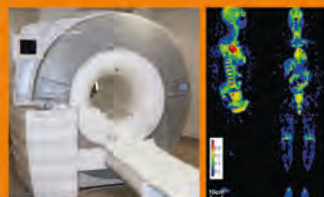
WP3: BIOPSY AND PREPARATION FOR MOLECULAR ANALYSIS



WP3 will develop an endoscopic system that can be navigated to the tumour site, take a tissue sample and transport it to a processing container. An innovative process to isolate tumour cells based on GIST cell specific markers will be designed by the SME partner SCT. WP3 will provide a profile and classification system of TKI-resistant GIST subtypes by mass spectrometry with low noise as well as a database of MS fingerprints that can be correlated with molecularly defined treatments and outcomes.

WP8: MULTIMODAL THERAPY CONTROL

WP8 will develop new metabolic MR methods for early assessment of therapeutic response. A standardised ^{23}Na TSC measurement to cover multiple organs in one scan, along with dedicated resonator systems with high sensitivity will be designed. For multinuclear signal detection (hydrogen and sodium) the X-nuclei MR data will be fused with time-resolved DWI and DCE MRI data sets as well as with DECT perfusion for additional quantification of tumour vascularity and cellularity. Apoptosis induced by therapy of GIST will also be monitored by using a technetium-99m radiocompound for SPECT imaging.



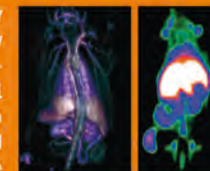
DISSEMINATION
AND EXPLOITATION

WP2

WP1
PROJECT
MANAGEMENT

WP5: PRECLINICAL THERANOSTICS

WP5 will assess the therapeutic potential of radiopharmaceuticals on GIST by preliminary in vivo imaging studies using PET-CT. In comparison with the new radiotracers developed in WP4, two well-established molecules with high affinity for SST and GRP receptors will be tested. Minimally-invasive therapies will be tested preclinically and monitored by non-invasive diagnostics. An in silico PBPK model for the distribution of the tracers in humans will be developed based on the mouse data. Differences in biokinetics of tested substances will be described by PBPK modelling.



WP6: TRANSLATIONAL STUDIES

WP6 will achieve clinical translation with GMP formulation of tracers and radiopharmaceuticals for use in humans. The tracers and radiopharmaceuticals for PET/CT or SPECT-CT, tested in animals with regard to tumour visualisation and therapeutic effectiveness, will be applied to patients after dosimetry for the first time. Optimisation using PBPK modelling will be performed. Treatment of patients according to imaging findings will be complemented by stereotactic thermal ablation.



WP7: MINIMALLY INVASIVE THERAPY

WP7 will comprise a concept study to establish how PET-CT guided thermal ablation and focused beam irradiation as well as percutaneous radioactive seed placement, by a manipulator-assisted needle guidance system can be performed. Based on the new PET-Tracers, the target volumes for minimally-invasive treatment will be adapted. Patient selection for study treatment dependent on mutational status and evaluation of alternative treatment options will be performed.

