Project:

Rapid development of pharmaceuticals by multimodal in-vivo biodistribution quantification (RapidPharma)

Technological key words:

Organ Biodistribution, Fluorescence-mediated Tomography, Image Fusion, Automated Segmentation, Fluorescent Fusion Proteins, Orthotopic Tumors, Transgenic Tumor Models.

Industrial sectors addressed:

Pharmaceutical Drug Development, Medical Imaging, Preclinical Medical Research

Total project costs: 1,545,965.00 Euros

Partners' descriptions:

- Institute for Experimental Molecular Imaging (ExMI), RWTH Aachen University Clinic, Germany. Academic research institute. ExMI focuses on the development of novel contrast agents, imaging techniques and therapeutic approaches. ExMI is responsible for leading and managing the project and executing two work-packages (WPs), to improve the hybrid optical imaging protocol and to perform pre-clinical in-vivo studies to evaluate the consortium developments. (www.exmi.rwth-aachen.de)

ExMI

- Royal Philips, Germany. Large industry. Philips is focused on improving people's lives through meaningful innovation in the areas of Healthcare, Consumer Lifestyle and Lighting. Philips Healthcare is dedicated to developing innovative health-care solutions, to improve patient outcomes, provide more and better value, and expand access to care. In this consortium, Philips will

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develop organ segmentation methods with visualization and structured reporting capabilities. (www.philips.de)

- Protein Technologies Ltd (PTL), is based the Manchester, UK. PTL is a SME specialising in protein engineering offering contract research services and also undertakes original new product development. PTL's particular speciality is the discovery, development and formulation of fluorescent proteins (FPs). Within RapidPharma, PTL will lead WP #3 (Fluorescent probes) where they will design, validate and produce near-infrared antibody fusions and recombinant FPs. (www.protein-technologies.com)

- Di.V.A.L Toscana SRL, Italy, Small industry. DIVAL is a Florence-based spin-off that develops genetically modified mouse models; non-oncological, oncological and transgenic models. They also provide pharmacodynamics, preclinical in vitro analysis, and produce monoclonal antibodies. In RapidPharma, DIVAL will be leading WP4 (Mouse models) where they will generate transfected tumor cells and mouse models for atherosclerosis and orthotopic and transgenic pancreatic tumors. (www.divalsrl.com)

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Project abstract:

Determination of the organ-biodistribution of novel pharmaceuticals is an important step in pharmaceutical research since undesired accumulation in organs must be precisely evaluated in pre-clinical studies. State of the art invasive methods require large numbers of mice, i.e. via quantification in excised organs. Main purpose of the project is to significantly reduce the number of animals required for pre-clinical studies by using modern imaging technology. Non-invasive in-vivo measurement of a drugs' biodistribution using fluorescent labeling is an important biomedical improvement for pharmaceutical research, because it allows longitudinal measurement within the same subject. However, the overall procedure, dye selection, quantitative signal reconstruction and organ segmentation must be improved before this technology is accurate, efficient and therefore widely applicable for clinical drug development.

Previously, we found a clear need to improve fluorescence reconstruction to enhance accuracy and sensitivity of fluorescence-mediated tomography. To achieve this mathematically and computationally challenging goal, we will develop innovative reconstruction algorithms combining advanced numerical optimization methods such as automated differentiation with massively parallel processing power. Furthermore, we need to fully automate the FMT and µCT image fusion in a robust way. To minimize the manual effort in data analysis, which currently dominates the overall amount of work per scan, efficient interactive or automated organ segmentation will be developed. Furthermore, we will investigate a recently discovered class of fluorescent proteins which strongly emit in the near infrared range and as such hold particular promise in µCT-FMT imaging. Moreover, optimized mouse models, particularly nude mice, will be developed addressing different diseases. Finally, we strive to apply our method to investigate several promising drug candidates in preclinical therapy studies.

We strongly believe that this method for in-vivo biodistribution determination is the most sensible approach to characterize novel drugs where it will save money and time for pharmaceutical companies on early drug screening and provide deeper understanding of drugs' biodistribution and kinetics monitoring. Therefore, we expect to provide highly sensitive drug biodistribution determination that will significantly improve clinical translation of novel drugs.

RapidPharma

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Expected results and exploitation plan:

- The expected results are: reconstruction software, software for automated organ segmentation and quantification, an optimal fluorescent dye platform and innovative transgenic and orthotopic animal models.
- The developed segmentation software will be integrated into the Philips Imalytics Research Workstation, which is a commercial product of Philips Research.
- The proposers will produce a set of standardized 'off-the-shelf' probes for use in combination µCT-FMT which will be marketed on their website and other media. These will be supported by data sheets and standard operating protocols. The proposers will also offer a custom development service, where individual probes can be fused to biologics and/or tailored to particular imaging systems.
- The new developed models and services (GLP) will be introduced to the market and made available to the pharmaceutical industries. Hybrid optical imaging will be commercialized as service, including analysis and report generation.

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