Publishable Summary

Summary report

The aim of CoMMiTMenT is the development of a novel tool for the detection, selection and complex characterisation of the vulnerable sub-population of red blood cells in the blood of patients with rare anaemia. This objective will be performed using the novel combination of microfluidics, optical devices and electrical read-outs. This chain of devices makes use of cellular properties like their labelling with fluorescent molecular biomarkers (e.g., antibodies or fluorophores), secondary cellular characteristics, such as the cell shape, or other alterations of cellular morphology and structure. By utilising a smart combination of the above mentioned techniques, positively identified cells can be placed on an adhesive substrate, after which the surface topology of the cell will be determined using Scanning Ion Conductance Microscopy (SICM). The combination of these imaging approaches will lead to the development of a modular device structure, the µCOSMOS, where the "µ" indicates the scale of cellular dimensions. With this µCOSMOS concept, a proof-of-principle for therapeutic interventions in rare anaemias is planned to be given for the treatment of sickle cell disease. The techniques rely on molecular detection: microfluidics and microscopy rely on molecular biomarkers, and scanning ion conductance microscopy on functional imaging of molecular structures. µCOSMOS will allow for the exploration, diagnosis and development of therapeutic interventions for several rare anaemias. Hereditary xerocytosis, overhydrated hereditary stomatocytosis, familial pseudohyperkalemia, cryohydrocytosis, certain types of spherocytosis, hereditary spherocytosis, sickle cell anaemia, thalassemia and phosphofructokinase deficiency are going to be tested. The non-invasive nature of the combined imaging technologies enables to probe the function of molecular effectors and facilitates the testing of medications and their dosage in a personalised manner. For some of the rare anaemias, CoMMiTMenT will provide explanations how molecular defects result in altered cellular functions and finally in the symptoms of the disease. Based on these results, pharmacological targets will be identified and initially tested. Once drugs become available, personalised medical interventions can be explored by the clinical partners within the project or trough a strong relationship with the European Network for Rare and Congenital Anaemias (ENERCA).

Description of the work performed since the beginning of the project and the main results achieved so far.

The CoMMiTMenT partners defined the final overall specifications of the µCOSMOS device chain and first prototypes of individual modules were designed, built, installed, and tested at laboratories of academic/clinical partners. This holds true for the OMiCS, further microfluidic and the SICM. Measurements in the labs of industrial and academic partners are ongoing. At the same time, guided by arivis, software concepts have been developed to unify the different data entities in a common platform/database.

Furthermore, hardware interfaces between the different modules have been developed, allowing a smooth integration of these modules into the µCOSMOS device later on.

Clinical and academic partners headed by the ENERCA members Hospital „CLÍNIC I PROVINCIAL“ in Barcelona and the Medical Centre of the University of Utrecht jointly revised the catalogue of putative rare anaemias to investigate. Additionally, patients with undiagnosed anaemia were identified. The academic/clinical partners designed study protocols including standard assays, like complete blood cell counts, electrophoresis, ektacytometry and osmotic fragility tests, but also investigations of cellular metabolism, enzymatic assays, ion flux measurements, Calcium handling, electrophysiological properties and such complementing the expertise of the different partners to gain an overall picture. Their measurements are ongoing, based on the shipping of blood samples between the partners. Different transportation conditions have been experimentally tested for their usability relative to the study protocols and the results were published.

Further results were published in scientific journals, and dissemination activities were performed through press releases for the general public and scientific presentations at the meetings of the European Red Cell Society (ERCS) and other conferences. Further progress can be followed on the project's website http://rare-anaemia.eu .

Description of the expected final results and their potential impacts and use

The pathophysiology of the majority of rare anaemia is poorly understood, the appropriate treatment is often ineffective or even lacking. It is unacceptable to the CoMMiTMenT partners that the pain and suffering caused by clinically severe rare anaemia has been neglected as a result of lack of reliable high-throughput tools for scientific understanding and clinical diagnosis. The partners are committed to systematically working through the list of anaemia-linked medical conditions in order to generate knowledge that will lead to effective targeted therapies. Thus, the project will ensure an effective therapy with diminished undesirable adverse effects, largely replacing splenectomy. Furthermore, CoMMiTMenT acts as a bridge between the technology-driven SMEs and ENERCA and, as such, supports the competitiveness of Europe in this area. It is clear that this project will result in differing degrees of knowledge gain and success with respect to both the identification of diagnostic targets and the development of drugs and personalised medication. However, the technological concepts that will be used, the complementary expertise and the determination within the CoMMiTMenT participants will substantially contribute to the overall aim of IRDiRC to deliver novel diagnostic modalities and 200 new therapies for rare diseases within the duration of the project. For example, partners of the consortium recently identified the NMDA receptor as a source of Ca^{2+} entry into RBCs in sickle cell disease, and this receptor was presumably responsible for the vaso-occlusive crisis in the patients. Interestingly, there is already an approved antagonist that blocks NMDA receptor-associated channel activity (memantine), which was developed and approved to treat Alzheimer's disease. This fact will encourage rapid progress in the implementation of this treatment. CoMMiTMenT will have access to a phase II clinical study (performed and funded outside of CoMMiTMenT), in which the concept of personalised medications can be tested. This test will be accompanied with the µCOSMOS technology that will be developed within CoMMiTMenT.