Grant Agreement no. 287596

d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

INSTRUMENT: Collaborative Project (Integrating Project)

OBJECTIVE: ICT-2011.5.1

Project Periodic Report – Publishable Summary

Annex I dated: 8th June 2012

Periodic report: 1st ■ 2nd □ 3rd □ 4th □

Period covered: from 1st October 2011 to 30th September 2012

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1. Publishable Summary

1.1. Project Description

The d-LIVER project originates from clinical needs and applies a scenario driven development methodology in response to FP7 ICT Objective ICT-2011.5.1: Personal Health Systems. This emphasizes research that aims for disease management and also targets rehabilitation and treatment at the point of need with a focus on specific diseases and in particular the requirement to address the need for ICT-enabled artificial liver systems to facilitate detoxification as remote transient therapy at the point of need, offering continuous care from hospital to home settings, as stated in Target Outcome a3) Liver Failure.

There is a clear, unmet need for an ICT-enabled bio-artificial liver (BAL) in combination with liver patient management and support systems with associated monitoring and control for the remote management of patients with chronic liver disease outside the hospital. The overall goal of the project is to provide safe and cost-effective systems for continuous, context-aware, multi-parametric monitoring of both patient and BAL system parameters in order to: enhance the quality of medical treatment and management; improve the quality of life for patients; reduce the incidence and duration of hospitalization and consequently reduce the health economic burden of chronic liver disease. d-LIVER will facilitate improved treatment whilst enabling patients to spend more time at home under constant, albeit remote, medical supervision.

The d-LIVER system concept is illustrated in Figure 1. Central to this concept is the pursuit of more efficient bio-artificial liver support devices, with significant detoxification capability and synthetic metabolic activity, as well as high biocompatibility and safety. These systems will be capable of constantly communicating the status of both the patient and the BAL remotely to central clinical services, in a secure and confidential manner, such that patient monitoring is continuous and intervention can be both swift and beneficial.

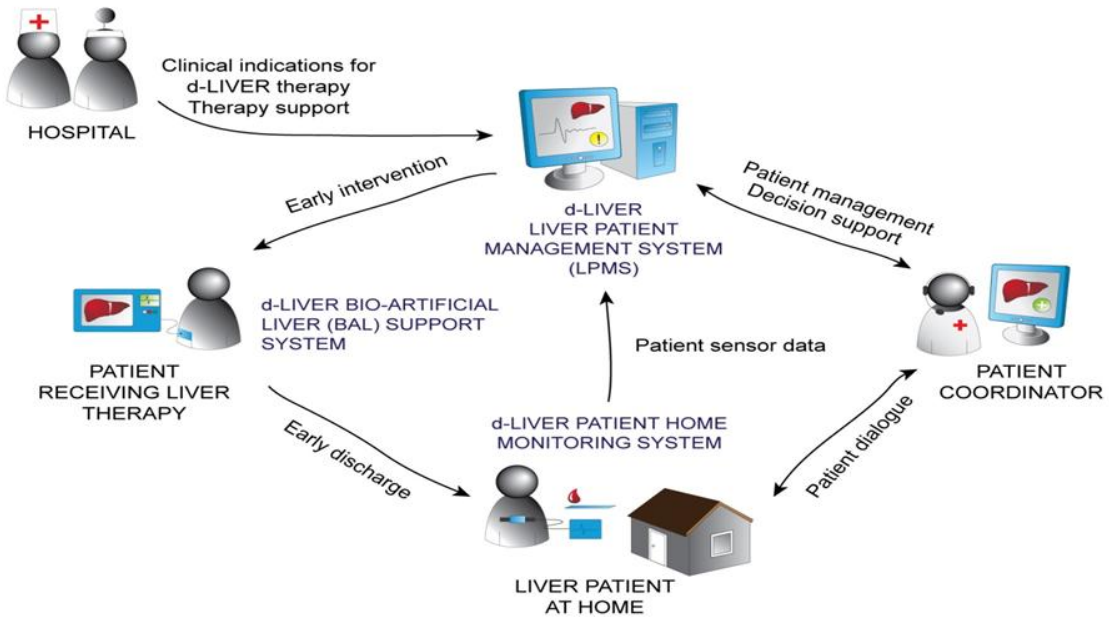

Figure 1: The d-LIVER system concept.

The d-LIVER project is application-orientated and based on four inter-linked scenarios, defined by clinicians, which drive ICT and sensor technology development in order to meet exactly the needs for continuous clinical support, monitoring and therapy of liver patients at the point of need from hospital to home settings. These scenarios are:

- Chronic liver failure
- Chronic cholestatic itch
- Bridging therapy before liver transplantation
- Acute liver failure

On the basis of these scenarios, a full set of both physical and biochemical parameters have been defined in d-LIVER which will be required to be measured either at regular intervals (patient status monitoring) or continuously (BAL efficacy monitoring). Each scenario has its own most appropriate sub-set of these essential parameters which will be required to be measured and communicated with the ICT LPMS. Monitoring will fundamentally focus on five main branches:

1. Indication/ decision/ timing/ planning for bio-artificial liver support sessions
2. Basic remote monitoring during d-LIVER bio-artificial liver support therapy
3. Evaluation of therapy success after liver support / detoxification
4. Remote monitoring of patient liver function/ toxin level/ general condition until the indication for the next session
5. Actual recommendations for patients at home regarding personal life-style and behaviour based on patient data monitored by the LPMS

1.2. The d-LIVER Consortium

Newcastle University (UK), Commissariat à l'Energie Atomique et aux Energies Alternatives (France), Charité - Universitätsmedizin Berlin (Germany), Centre Suisse d'Electronique et de Microtechnique (Switzerland), Fraunhofer Gesellschaft zur Förderung der angewandten Forschung e.V., FhG-IBMT (Germany), Institut für Mikrotechnik Mainz GmbH (Germany), iXscient Ltd. (UK), Stiftelsen SINTEF (Norway), Universitat Rovira i Virgili (Spain), AT4 wireless, S.A. (Spain), Stem Cell Systems GmbH (Germany), 4M2C Patric Salomon GmbH (Germany), STAR Healthcare Management GmbH (Germany).

1.3. Objectives of the Project

The specific objectives of d-LIVER are to:

- Define the clinical requirements for patient management and bio-artificial liver unit operation in the chosen clinical scenarios **(Month 7)**
- Develop wearable sensing technologies for remote continuous monitoring of patient physical status **(Month 32)**
- Develop biochemical sensor technologies for accurate analytical measurements of patient blood biochemistry and bio-artificial liver unit quality parameters **(Month 32)**
- Produce model bio-artificial liver unit based on primary human or porcine hepatocytes integrated with multi-parametric sensor systems and closed loop control **(Month 36)**
- Develop instrumentation hardware platforms **(Month 36)**
- Develop Liver Patient Management System (LPMS) and integrate with hardware platform **(Month 40)**
- Clinically evaluate d-LIVER system for use at Point-of-Need in a clinical environment according to the defined scenarios **(Month 42)**
- Develop and evaluate clinically high risk bio-artificial liver technology **(Month 42)**
- Encompass innovation management ensuring exploitation of the developed technology **(Month 48)**
- Promote wide sectoral and geographical dissemination of the project results **(Continuous)**
- Integrate multidisciplinary education, training and skills development with research activities **(Continuous)**

1.4. 1st Period Progress

In general the first period of the project was focussed on the development of clinical scenarios, the elaboration of system specifications, the development of both wearable and (bio)chemical sensors and the specification of the ICT security and communication framework. The project has put substantial emphasis on establishing a shared terminology and understanding of the mission, components and actors involved in each facet of the project. This is in particular important in projects involving many partners with different professional backgrounds. The project has therefore developed several easy-to-comprehend clinical scenario descriptions illustrating central aspects of the project to be developed. Further, a shared concept description has been developed and a vocabulary of d-LIVER technical and clinical terms has been defined. In all of this work, particular attention has been paid to establishing procedures for system quality, manufacturability and traceability according to international standards for medical devices.

One key task in the 1st period was commencing the formal evaluation of Quality-of-Life (QoL) in chronic liver disease patients living at home, and the factors impinging on it. Key issues are the impact of current management strategies and the degree to which the d-LIVER monitoring and support systems may be able to improve this situation. The study has been designed and Ethics approval has been obtained in the UK with an application prepared for submission in Germany.

Another goal was to complete a detailed study of the acceptability of the proposed approach by potential future d-LIVER users and to identify possible barriers to the uptake of the d-LIVER system in practice. With the input of patient groups (LIVErNORTH, UK and Deutsche Leberstiftung, Germany), clinical partners identified important potential issues concerning the d-LIVER system. As a result, a first version of a questionnaire targeting the individual opinions of patients and carers on the proposed system was designed. The main focus was on familiarity with the use of novel technology, security of data transmission in the ICT setting, and acceptability of different levels of decision making (active/ passive decision support).In general, it was found that there was a broad acceptance of the d-LIVER concept among the target population.

Within the first period specifications and concepts for all the wearable physiological sensors and blood biochemistry sensors were defined and analytical characterization studies carried out, bearing in mind the suitability of the sensors for final integration into the overall d-LIVER systems. Currently, 8 out of the required 11 sensors are fully operational and most of these meet the requirements of the project in terms of performance. Further optimisation, improvement and integration will be continued in the 2nd period.

The ideal goal for the system is to be able to measure all eight blood biochemical parameters in a single microfluidic cartridge using a finger-prick blood sample. This commenced with microfluidic cartridge designs for various cases, including so-called ‘best case’ and ‘worst case’ fluidic scenarios. The scenarios outlined the need for new microfluidic functions, which would simplify the cartridge significantly. Accordingly, the development of the relevant microfluidic functions such as serum generation and dilution of liquids on chip was commenced. Initial work on sensor integration was also carried out.

Concepts for the integration of the different sensors for the online control of the bio-artificial liver support unit (BAL) were specified and developed. Fabrication processes were established that allowed integration of impedance sensors inside the BAL to monitor cell viability and quality. As a result, suitable parameters for the closed-loop control of cell culture conditions were specified and first measurement setups for the quality control of cells prior to their use in the BAL were established.

The instrument requirements and acceptance criteria have been clearly defined. The system design, that was originally planned for the 2nd period of the project, has already commenced.

In the 1st period concepts were developed for the Communication Architecture and Security Framework and for the Liver Patient Management System and Patient Client System. Bearing in mind that security is essential in systems dealing with medical information, an analysis of the security requirements for the d-LIVER architecture was performed as part of the security framework design. This security analysis covered different aspects, such as privacy, authentication, access control and security of communications. The mechanisms and techniques to achieve the required security level were based on international standards.

Within the work on a potential new source of hepatocytes for the BAL, a rat progenitor cell line which is readily expandable and produces quantitatively functional hepatocytes with a single hormone, was successfully seeded into an experimental bioreactor and differentiated into hepatocytes. The cells remained viable and functional for the length of the study. These pilot results demonstrated that it should be possible to produce bioreactors with functional human hepatocytes from an equivalent human progenitor.

The project website was launched and is updated regularly. Logos, clip-art, templates, and other dissemination materials were produced and distributed. Finally, a project factsheet and project overview slide were supplied to the Commission for dissemination purposes.

1.5. Expected End Results & Impacts

The liver is a complex organ with various vital functions in synthesis, detoxification and regulation; its failure therefore constitutes a life-threatening condition. As of today, liver transplantation is still the only curative treatment for liver failure due to end-stage liver diseases. Donor organ shortage, high cost and the need for immunosuppressive medications are still the major limitations in the field of liver transplantation. Many patients, especially those who are not listed for high urgency transplantation, may not survive until a suitable donor organ is available. The expected impacts of d-LIVER will therefore be to:

- Use technology to move management of end-stage liver disease (ESLD) patients out of the clinic and into the home or near-home setting
- Improve quality and length of life by dynamic management of complications (daily not monthly)
- Improve quality of life for patients and carers through avoiding burdensome clinic visits
- Reduce costs of hospitalisation and improve disease management and treatment at the point of need, through more precise assessment of health status and quicker transfer of knowledge to clinical practice
- Improve links and interaction between patients and doctors facilitating more active participation of patients in care processes
- Accelerate the establishment of interoperability standards and of secure, seamless communication of health data between all involved stakeholders, including patients

For more information, see the project website: www.d-liver.eu