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 February 2013

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

Period covered: from 1st October 2012 to 30th September 2013

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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.

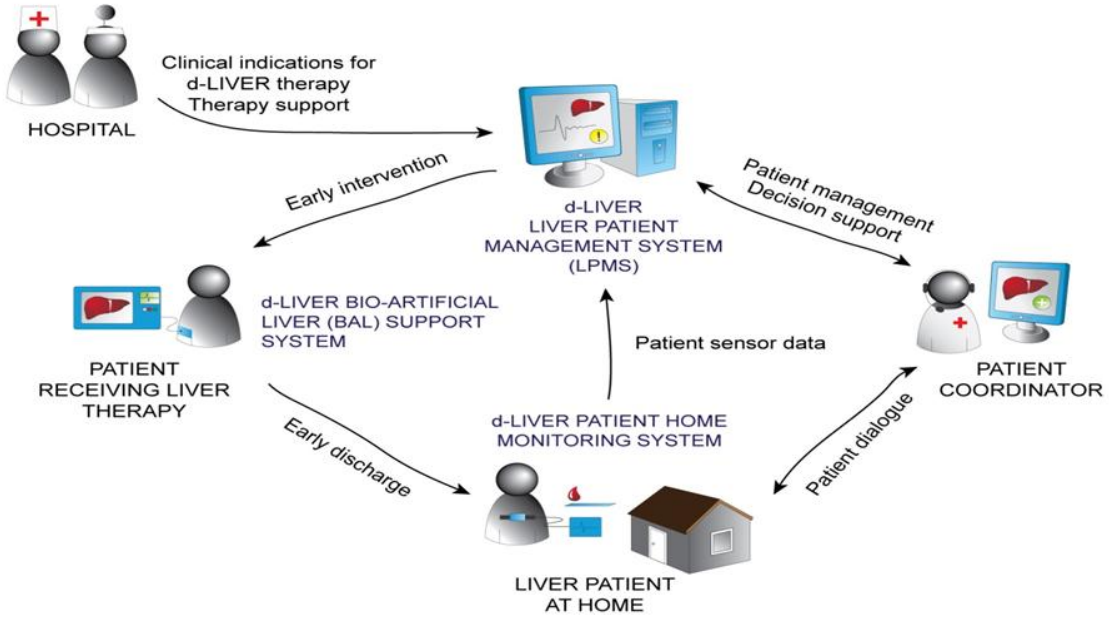

Figure 1: The d-LIVER system concept.

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), enablingMNT 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. 2nd Period Progress

In general, the second period of the project (01/10/2012 to 30/09/2013) was focussed on building upon the excellent groundwork produced during Period 1 which developed the clinical scenarios, elaborated the system specifications, initiated development of both wearable and (bio)chemical sensors and specified initial elements of the ICT security and communication framework.

In Period 1, the project expressed the vision and mission of the d-LIVER concept in terms of a common high level system description with all partners helping to define the design goal specifications (the system requirements specifications) and to develop a vocabulary of d-LIVER technical and clinical terms. During Period 2, key objectives were to review and update the system specifications and project understanding as a result of continual progress in technology development and to outline the applicable regulatory requirements for d-LIVER in order to be able to carry out clinical investigations involving volunteer test subjects later in the project.

Further to the initial development of clinical application scenarios during Period 1, the project has commenced a number of clinical needs studies including: investigation of patient quality of life at home; definition of suitable outcome variables; investigation of economic burden of chronic liver disease; and identification of potential clinical variables for the initiation of the d-LIVER treatment and BAL support sessions. The clinical centres in the UK and Germany initiated a prospective study to capture individual quality of life assessments of chronic liver failure patients over the course of one year and these studies have shown favourable recruitment rates. Continuation of the Quality of Life and Cost Effectiveness studies, with possible expansion to include other European countries, should lead to more robust data to compare the populations. Based on liver demographic clinical and biochemical function parameters, biological indices and certain test methods, work on defining outcome variables could allow a comprehensive model for the prediction of morbidity and mortality to be elaborated. In addition, work commenced for the planning of evaluation procedures of the d-LIVER system which involved the preparation of study protocols in line with European directives and ethical guidelines. In the first period, physical and biochemical sensors for the monitoring of patient parameters at home and in the BAL were characterized and their performance compared with the d-LIVER requirements. At the end of the first period, 8 sensors out of 11 were operational and 6 met the project requirements. During the second period, strategies for some sensors were reviewed to make them operational and work on other sensors focused on integrateability and further characterization. The overall objective was to make a decision at the end of the period on which blood biochemistry sensors would be integrated in the d-LIVER cartridge and instrument. The potential impact, in terms of the clinical consistency of the overall system, for sensors which are not being pursued for integration at this time was assessed.

The ideal goal for the blood biochemistry system is to be able to measure all biochemical parameters in a single microfluidic cartridge using a finger-prick blood sample. In Period 1, 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. As a consequence, work in this area in Period 2 concentrated on the top-level concept design of the development of the functional fluidic component modules and their separate testing. The outcomes if this work included: development of the microfluidic scenarios and first designs of the cartridge; successful realization and testing of the serum generation and integrated sample mixing and dilution solutions; and establishment of injection moulding and hot embossing processes for small scale production.

A model bioreactor with a capacity of 8ml was built as a demonstrator in the second period. To operate the bioreactor, commercial sensors and actuators were used in different control loops.

They enabled the observation of vital cell parameters. In particular temperature, pH, flow rates of liquids and gases were regulated. To monitor the cell quality and functionality, impedance and ammonium sensors were designed and integrated along with an oxygen sensor into the system. To operate the bioreactor, software was developed which supervised all control loops and monitored operating parameters including oxygen content on a display. Additionally hardware and software to monitor and evaluate the sensor signals was also developed. In initial tests, the functionality of the system could be demonstrated.

During the second period of the project, all tasks in support of the design, development and build of the instrumentation platforms that will service the requirements of d-LIVER were commenced. These included the blood biochemistry instrument and the wearable system for continuous collection of physiological patient parameters.

In Period 2 the first basic LPMS prototype was developed. This supports a set of commercial Continua certified off-the-shelf devices and can partially or initially interact with simulators of d-LIVER devices or with early device prototypes. The system platform further includes a first version of the Care Flow Engine that executes personalised treatment plans of patients and, as part of the basic functionality, modules for initial medication management, patient inquiries as well as one cognitive test were implemented.

In all of the technical development Workpackages particular attention has been paid to establishing procedures for system quality, manufacturability and traceability according to international standards for medical devices even allowing for the fact that, at this stage, there are no regulatory issues which will prevent evaluations taking place within the framework of the project.

Within the work on a potential new source of hepatocytes for the BAL, seeding an experimental pancreatic progenitor cell into bioreactors has been completed and a manuscript describing the work has been accepted for publication. A procedure for the isolation of human progenitor cells from human pancreas has been developed and these cells have been successfully expanded and differentiated to hepatocytes in culture. Because human pancreas tissue has been in short supply, several fall-back options have continued to be investigated, including the use of human pancreatic cell lines, human induced pluripotent stem cells (hiPSCs) and use of a novel polymer matrix to promote a hepatic phenotype.

The project continued to disseminate results of d-LIVER to a broad audience via the website, flyers, factsheets, workshops and conferences. Issues around background and foreground IP were explored with the intention to identify and manage the intellectual property developed and to ensure that suitable initial exploitation plans were produced by each partner with the support of the Exploitation Committee.

An initial element of the d-LIVER project video was produced by TRiBECA Knowledge Ltd. This was designed to cover the aims of the project and to include interviews with patients affected by chronic liver disease. The final version of the first video was shown to all the partners at the Year 2 Annual General Assembly and will be shown to the Commission Reviewers at the 2nd Annual Technical Review prior to being included on the project public website.

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