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 – Year 3

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

Period covered: from 1st October 2013 to 30th September 2014

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Publishable Summary – Year 3

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.

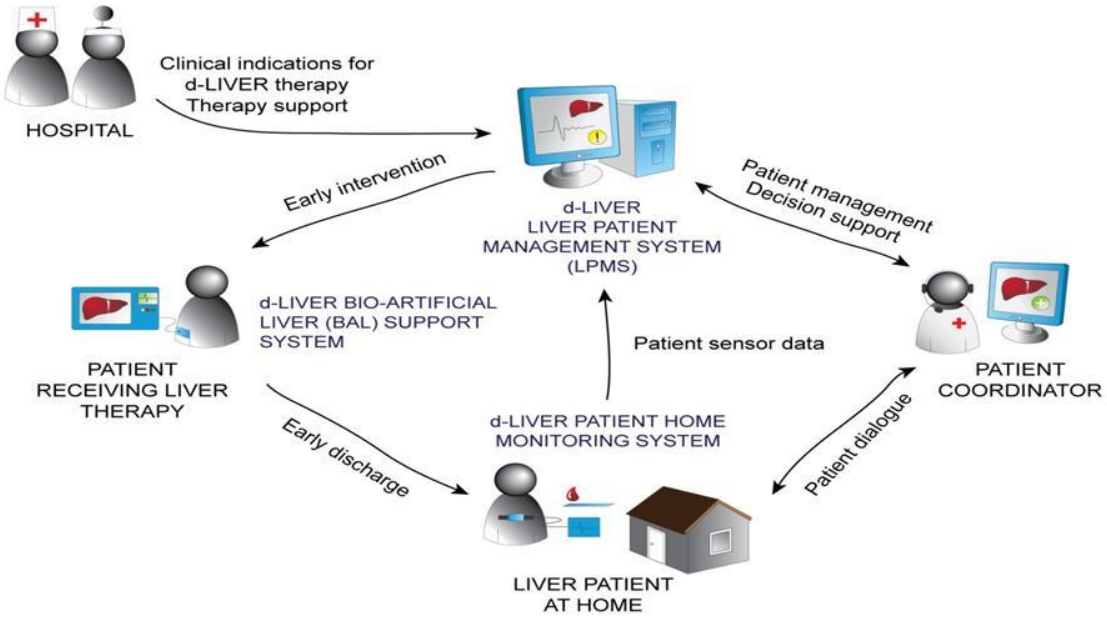

Figure 1: The d-LIVER system concept.

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

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 and FhG-ICT-IMM (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), Humanitas Mirasole SpA (Italy).

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)**

3rd Period Progress

The work carried out in Period 3 of the project (01/10/2013 to 30/09/2014) has built upon that of Periods 1 and 2 which addressed the clinical scenarios and system requirements, developed both the wearable and (bio)chemical sensors, developed strategies for the blood biochemistry instrumentation and cartridge and produced the first prototype of the Liver Patient Management System based on 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 system requirements and to develop a vocabulary of d-LIVER in both technical and clinical terms.

During Period 2, key outcomes were a review and update of the system specifications and project understanding as a result of continual progress in technology development and identification of the appropriate d-LIVER regulatory requirements in order to be able to carry out clinical evaluations of the systems being developed.

In Period 2 the project 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. In Period 3 the clinical centres in the UK and Germany were joined by a new partner from Italy and continued the prospective studies on Quality of Life and Cost Effectiveness to capture individual Quality of Life assessments of chronic liver failure patients over the course of one year. These studies have shown favourable recruitment rates and the expansion to include another European country should lead to robust data to compare the populations. In addition, subsequent to the planning of evaluation procedures of the d-LIVER systems, in both Periods 2 and 3, which involved the elaboration of study protocols in line with European directives and ethical guidelines, Ethics Committee approval has already been obtained for all but one of the d-LIVER clinical evaluation studies. The ethics amendment for the Blood Biochemistry Instrument (BBI) evaluation will be submitted in late 2014.

In the first two periods, physical and biochemical sensors for the monitoring of patient parameters at home and in the Bio-artificial Liver Support Unit (BAL) were characterized and their performance compared with the d-LIVER requirements. By the end of the second period strategies for some sensors were reviewed to make them operational and work on other sensors either focused on integrateability or ceased. Therefore, as a result of decisions taken between the end of the second period and Month 30 as to which blood biochemistry sensors would be integrated in the d-LIVER cartridge and instrument, a well-documented list of all retained sensors and their technical specifications, as well as their integration onto the respective platforms, was produced and submitted to the Commission. The overall effect, in terms of the clinical ramifications of the removal of certain sensors was assessed and no real detrimental impact of these decisions was identified.

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 Periods 1 and 2, the microfluidic cartridge designs for various cases, including so-called ‘best case’ and ‘worst case’ fluidic scenarios were elaborated and by the end of Period 2 functional fluidic component modules had been designed and tested. In Period 3 the modules were continuously reviewed and optimized and four different feasible microfluidic designs were adapted and transferred to an injection moulding process for the ultimate manufacture of cartridges with consistent quality in order to realize the clinical evaluation studies. Protocols for the integration of the different sensors were produced and "pre-final" microfluidic cartridges were delivered to the partners for preliminary on-cartridge sensor fluidics testing and for optimization of the BBI.

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.

In Period 2 all tasks related to design, development and build of the d-LIVER instrumentation platforms were commenced. These included the blood biochemistry instrument and the wearable system for continuous collection of physiological patient parameters. By the end of Period 3 the BBI hardware had been finalised from a mechanical and electronic perspective and the system software including a user interface and communication protocols programmed. The BBI is therefore on schedule and now ready for testing. In addition, work on the design and development of the integrated Wearable Device demonstrated excellent progress and this device is now ready for clinical evaluation.

At the end of Period 2, a basic prototype of the LPMS became available. During Period 3, internal project evaluation by clinical partners provided valuable feedback about improvements which were required to be included. This resulted in the development of an extended version of the LPMS, LPMS 2.0, a prototype of which was produced in May 2014. This also included further novel features such as patient-doctor interaction tools. Further progress was made with the integration of additional off-the-shelf devices and the d-LIVER instruments in the LPMS. The integration of commercial devices was accomplished by interfacing Bluetooth devices through a proprietary vendor specific SPP communication protocol to the Device Manager. The outcome of this was the creation of LPMS version 3.0 which was demonstrated successfully to the clinical partners during the Period 3 project General Assembly. This version will be used in the clinical evaluation of the systems in the next Period.

The bioreactor system for the BAL showed excellent correlation of online parameters with routine offline parameters and demonstrated the suitability of real-time surveillance in experiments performed with the B-13 cell line or with primary porcine liver cells. Sensor-based monitoring via integrated impedance, ammonia and oxygen sensors showed sensitive responses to induced toxic stress in bioreactor cultures and could thus be used as a fast, non-invasive method to evaluate the cell quality in the BAL. The results in Period 3 also showed that changes in the cell behaviour could be graded into different states dependent on the toxin concentration. This allows measures to be taken for cell recovery or culture and/or therapy termination dependent on the actual state of the cells. Finally, it was demonstrated that primary porcine hepatocytes could be used in the bioreactor for the establishment of a clinical-grade BAL.

As a pilot, 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. 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 pancreatic tissue has been in short supply, several fall-back options have continued to be investigated, including the use of human pancreatic cell lines and human induced pluripotent stem cells (hiPSCs). The most promising approach for the production of human hepatocytes was through using an engineered human pancreatic cell line. This cell line, after treatment with glucocorticoid, expressed the highest levels of liver proteins and readily tolerated high levels of toxins found in sera from patients with liver failure and will be available for testing in the BAL within the time-frame of the project.

The project has continued to disseminate d-LIVER results to a broad audience via publications in high quality international journals, workshops conferences, flyers, factsheets and the website. The website has been extended to target health professional and is now available in Italian as well as English and German. A news article on d-LIVER was broadcast by Euronews in November 2014 along with press articles on CORDIS and Digital Agenda for Europe (http://ec.europa.eu/digital-agenda/en/news/d-liver-eu-project-designs-home-care-system-liver-patients). The Euronews video

is available on the FUTURIS website (http://www.euronews.com/2014/11/03/longer-life-for-damaged-livers) and has also been placed on the project website along with a Twitter feed.

Issues around background and foreground IP were further defined in Period 3 in order 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. IP for encephalopathy management, which relies on a cognitive test and a patient enquiry, has been secured through a UK patent application and a clinical trial in a home setting is about to commence. Some five additional patent applications arising directly from the work carried out in d-LIVER are in the process of being filed.

The initial d-LIVER project video, covering the clinical need, was produced by TRiBECA Knowledge Ltd. and shown to all the partners at the Year 2 Annual General Assembly and to the Commission Reviewers at the 2nd Annual Technical Review. The video is now included on the project website. The next stage of the project video, which covers animation of the various components of the d-LIVER system, is currently being produced.

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