

Presentation of the funded projects in 2010 for the « TecSan » Program

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APSIC - Training and Fitting Amputees during Situations of Daily Living

Abstract

The project concerns motor disability. In particular, it deals with amputee people locomotion. It is commonly known that lower limb amputation results in lifelong disability. In their everyday life, level walking is just one of the situations people with amputation have to cope with, while stair and slope ascent and descent, for instance, are much more difficult tasks. Indeed, joint functionalities necessary for level walking are different from those needed in these other situations. Lower limb prosthesis are the only way to restore joint functions in people with amputation. After amputation, most of the patients come back home. To guarantee a correct social reintegration, patients have to reach a sufficient level of autonomy. However, the current prosthetic components are optimized specifically for level walking and, often, they are not adapted to walking in other conditions, offering a limited level of autonomy to people with amputation. The project aims at proposing innovative prosthetic devices in order to increase the ability of people to realize current tasks during their everyday life. To complete the range of functionalities offered by the already available products, the prosthesis developed during the project will be both totally new designed and conceived from innovating prosthetic apparatus using existing prosthetic components. Besides, optimal use of prosthesis cannot be reached without specific rehabilitation orientated toward targeted situations. To develop such a rehabilitation program, taking advantage of the whole environment of the patient, is a therapeutic innovation that would help clinicians to better restore gait functions. Nowadays, very few patients benefit from a prosthesis specific rehabilitation and very few researches took both aspects of the prosthetic management into account at the same time, even if they are obviously connected. The project will take advantage of non invasive gait analysis systems to develop rehabilitation processes useful during clinic routine. From a scientific point of view, the project will allow to gain knowledge about gait mechanisms in the considered conditions. Moreover, the information associated with the modeling work will lead the partners to better understand the influence of geometrical and mechanical characteristics of the prosthesis on the patient's gait.

Partners

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ANR funding

790 k€

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January 2011 – December 2013 – 36 months

Reference ANR-10-TECS-014

Cluster label

ASIMUT - Advanced Surgery with Interstitial capacitive Micromachined Ultrasonic Transducer for conformational thermal ablation of brain tumors

Abstract

More and more surgical techniques are evolving toward the use of minimally invasive technologies to reduce the morbidity of operations, reduce levels of pain, shorten hospital stays, and reduce associated costs. Currently, percutaneous radiofrequency (RF) or laser probes, guided in real-time by ultrasound or MRI imaging, are frequently used clinically for the successful treatment of bone, lung, liver and kidney metastases. The ASIMUT project's main objective is to replace RF or laser by high intensity focused ultrasound (HIFU), which can be focused in 3D to produce thermal injury that more closely conforms to the target tumor geometry. ASIMUT offers an innovative approach to exploring this new therapeutic technique by using interstitial transducers incorporating capacitive micromachined ultrasound transducers (cMUTs). The clinical objective of this project is to use cMUTs in HIFU arrays to develop a device for interstitial thermotherapy that allows conformational treatment of brain tumors under local anesthesia with real-time MRI imaging guidance. The consortium set up for the ASIMUT project includes 3 partners: Unit 556 of INSERM, a specialist in HIFU research for 20 years; Vermon, a company that has significant expertise in cMUT and ultrasound transducer technology for over a decade; and CarThera, a startup company whose primary mission is to develop innovative medical technology and to translate it to clinical practice. ASIMUT will include significant advances in both medical and technological contexts: • the realization of treatments that are more effective, less invasive, cost less, and that are more applicable to a significant number of patients by allowing for a single outpatient procedure that includes both diagnosis and ablation of specific brain tumors by using a MRI-guided interstitial probe. • an innovative approach is utilized that involves interstitial ultrasound transducers incorporating cMUTs to control the local ablation of brain tumors or cancerous tissue and utilizes a miniature probe to enable this technology to produce thermal injury to the conformational target tumor without the need for cooling of the probe during treatments (these 3 features are innovations of CMUT probes compared to other research projects involving HIFU probes) For the 3 years of the project, ASIMUT should lead to the achievement of preclinical testing in animals through the implementation of the 6 following tasks : • Task 1: Requirements definition and clinical conditions • Task 2: Design of the cMUT device for interstitial HIFU • Task 3: Fabrication and characterization of the cMUT devices • Task 4: Manufacturing of prototypes and experimental preclinical testing • Task 5: Experimental Validation & Qualification • Task 6: Preclinical Evaluation In the longer term, ASIMUT is part of a more ambitious project that aims to validate clinically the use of cMUT technology for other HIFU applications. This research will also take place under the proposed consortium with INSERM parties controlling the development of HIFU devices, Vermon ensuring the design and manufacture of transducers, and CarThera providing clinical expertise and implementation of preclinical trials.

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ANR funding 991 k€

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Reference ANR-10-TECS-011

Cluster label Medicen

Abstract

The BB EEG platform project aims at developing an Internet portal providing telemedicine and e-learning services in the field of the electroencephalographic (EEG) signals of the newborn. The EEG consists in recording the spontaneous electrical activity of the brain through several electrodes placed on the scalp. It is a functional review that provides additional results to brain imaging data (MRI tomography). The neonatal period is a high risk neurological damage period because of the immature nature of the brain for the premature births and/or because of non optimal conditions at birth (anoxia, infection ...). The consequences can be severe and cause permanent and severe disabilities. The EEG enables the assessment of the brain function. It monitors the brain maturation during the first weeks of life if the child is born premature. The EEG makes possible the evaluation of the degree of brain damage in cases of difficult birth (e.g. cerebral anoxia). It can also detect possible seizures and monitor their evolution under treatment. In this case we must couple the EEG with a synchronized video of the patient in order to properly identify abnormal clinical manifestations. The techniques of neuroprotection starting to be commonly used, as for example the controlled hypothermia for cases of cerebral anoxia, require that an accurate assessment of the severity of brain damage be done. The EEG allows the physiological assessment but requires trained personnel for both the acquisition of EEG signals and their interpretation. The neonatal EEG requires highly specialized personnel. The French expertise is recognized but its daily practice suffers from a growing shortage of specialists. The Video EEG signals are recorded in digital form by a technician and visually analyzed by a doctor after their acquisition. They can also be analyzed by tools of signal processing in order to complement, accelerate or intensify the visual analysis. These characteristics prove that the EEG signals will fit well to telemedicine activities. Thus some members of the consortium have developed in Loire Valley for several years a EEG signals transport mean between hospitals Laval and Le Mans. In Bourgogne there is also an telemedicine activity around the EEG. In the Pays de la Loire region there are adapted facilities that enable the transmission of large amount of data. However, technical constraints (transport of medical data) and organizational (type of economic exploitation, work organization conditions for different personal) are hampering the application of EEG telemedicine activities on an industrial scale. Moreover, it is very important to ensure that the development of remote interpretation is not accompanied by a loss of competence. The BB EEG project will thus pave the way for the industrial development of the telemedicine activities and will contribute to maintaining the recognized excellence of the French school in this area. Our consortium brings together all the players necessary to tackle these barriers. It combines several hospitals in the region of Pays de la Loire with industry specializing in the secure transport of medical data, the

work flow organization and its potential applications for learning strategies, with researchers in mathematics and signal processing fields. The hard goal of the BBEEG project is to provide a portal offering a combination of different services for a much rapid and secure diagnostic and for the newborn EEG training. The target audience are hospitals that do not have the competence of physicians who request a second opinion and professionals (doctors and technicians EEG) who wish to gain competence in this area. Our project will constitute a methodological framework for other initiatives in other medical fields.

Partners

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ANR funding

613 k€

**Starting date
and duration**

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Reference

ANR-10-TECS-009

Cluster label

Images & Réseaux

Bone printing - Laser-Assisted Bioprinting for bone tissue engineering

Abstract

Parallel to standard Tissue Engineering, technological advances in the fields of automation, miniaturization and computer-aided design and machining have led to the development of Bioprinting. This later concept has been defined recently as the “the use of computer-aided transfer processes for patterning and assembling living and non-living materials with a prescribed 2D or 3D organization in order to produce bio-engineered structures serving in regenerative medicine, pharmacokinetic and basic cell biology studies”. As compared to traditional approaches in Tissue Engineering, bioprinting represents a paradigm shift. Indeed, its principle is not more to seed cells onto a biodegradable scaffold but rather to organize the individual elements of the tissue during its fabrication step (before its maturation) through the layer-by-layer deposit of biologically relevant components. Moreover, while giving a better control on the cell distribution into 3D constructs, such automatized processes should also minimize contamination issues during tissue engineering process and should reduce the duration for manufacturing a fully functional engineered-tissue. In the framework of the project Bone printing, we will focus on the development and the evaluation of new technologies through the application of the Bioprinting principle to bone tissue engineering. Regarding basic research, the main outcome will be gaining further understanding of the influence of the local microenvironment of human mesenchymal stem cell (hMSC) on the functionality of 3D tissue-engineered constructs. This will be addressed by investigating effects of hMSC patterns and biomaterials properties such as composition and stiffness on tissue function. In this aim, CMCP will focus on the design of novel collagen-based materials through innovative cross-linking procedures. Regarding experimental developments, this project will consist in realizing the second generation of Laser-assisted Bioprinter which will permit the deposit of living cells and biomaterials in vitro, in vivo and through a safe, sterile and automatized process. As for laser-assisted technologies for biofabrication, main industrial developments concern laser sintering, photo-polymerization and, to our knowledge, no company has proposed an integrated LAB system yet. ALPhANOV and INSERM U577, in collaboration with one subcontractor (e.g. ES Technology) specialized in integrating laser machines for different kind of applications, will thus develop such a system. Regarding the preclinical aspect, we will evaluate the interest of bioprinting in vivo, what could pave the way to new perspectives in robotized surgery and medicine. The benefit of this new approach compared to the implantation of engineered tissues elaborated in vitro will be addressed in this project. To summarize, this project is related to the “tissue engineering and biomaterials” theme of TecSan 2010 program. It aims at developing new innovative technologies for bone tissue reconstruction through an original 3D laser printing technology. Bioimaging will play also a key role in this program for investigating the newly formed tissue in an experimental model of bone defect in small animal. This project includes also an automation of the bioprinting process for producing a controlled and reproducible regenerated

tissue. The realization of a second generation Laser-Assisted Bioprinter should open new perspectives in regenerative medicine as well as in other biomedical area by furnishing organotypic cultures. Moreover, a spin-off (company) creation for commercialization of 3D Laser-Assisted Bioprinter, with support from the "Route des Lasers" competitiveness cluster is envisaged before the end of this project. Objectifs globaux, verrous scientifiques/techniques.

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Starting date and duration November 2010 – October 2013 – 36 months

Reference ANR-10-TECS-001

Cluster label Route des Lasers

CancerSensor - Molecularly imprinted polymer-sensor of urinary modified nucleosides for non-invasive therapy control of cancer

Abstract

Colorectal cancer is the second cause of cancer-related deaths. Once colon cancer spreads beyond the colon, into the lymph nodes or into other areas of the body, it is then harder to treat. It is thus very important to can detect as earlier as possible a cancer, to treat it fast, to check for the efficacy of treatments and for any recurrence. The therapeutic drug monitoring of antineoplastic agents is at this time restricted by several factors, such as the lack of established therapeutic concentration ranges, a considerable inter- or intra-individual pharmacokinetic variability, a relationship linking toxicity to systemic exposure, and complicate pharmacodynamics of drug toxicity. To circumvent those limitations and evaluate the success of chemotherapy is to correlate a cancer treatment with the amount of tumour markers, a substance that can be found in the body when cancer is present. It has been reported that cancer patients excrete in their urine an abnormal increased amounts of modified nucleosides, which are formed at the post-transcriptional stage by chemical modification of normal nucleosides within the RNA. These modified nucleosides cannot be reutilized or further degraded, but they are excreted in the urine as intact molecules. The elevated levels of modified nucleosides in the urine samples have served as potential cancer biomarkers in many studies. Although different analytical techniques have been reported for determination of nucleosides levels, they are practically difficult to use as a routine tool for therapy control of colorectal cancer. Goals of this proposal are to develop and validate a quantitative, non-invasive diagnostic tools to follow-up the chemotherapy of colorectal cancer and monitor the disease response to chemotherapeutics. A methodology will be developed making use of a combination of the probably most exciting recent advances in the field of acoustic-biosensor based on molecularly imprinted polymers (MIP). It includes advances which will take the sensitivity down to a low-concentration single-molecule level. Apart from detecting and identifying tumour markers in the urine samples, the effect of circadian chemotherapy on the amount of cancer markers, using the developed tools will be explored. This is to date an almost unexploited dimension of diagnostic information. By combining and supporting these novel optical methods with state-of-the-art affinity molecule MIP technology, tumour biomarkers, acoustic biosensor, will be exploited to extract a maximum amount of information out of very small amounts of sample material. Given the high incidence of colorectal cancer, this project has a very high relevance. Those tools will be used, within the frame of this project, to analyze more than 3000 urinary samples from patients under chemotherapy for colorectal cancer and to correlate the chemotherapy treatment with the circadian time of infusion and the circadian variations of clearance. The need for development of rapid, sensible, easy-to-use and cost effective sensors for surveillance of pre-

and post-operative CRC is evident and of huge interest. This approach could deeply modify the manner of checking near each person the effectiveness of the chemotherapy treatment of colorectal cancer. At the end of this project, we will offers diagnostic products for colorectal cancer follow-up in the European market. It will have the ability to detect and recognize the expression of tumour-associated biomarkers in patients with metastatic cancer. To obtain the level and width of expertise required, we have thus formed a consortium involving highly recognized teams: Organic and medicinal chemistry (Pr Agrofoglio – Orléans), Biosensor technology (Pr Rebière – Bordeaux), Bioanalysis (Dr Bénech - CEA), Oncology and circadian biology (Dr Lévi – INSERM, Hôpital Paul Brousse - Villejuif), Polymers and product development (Dr Vidal - MERCK Chimie – ESTAPOR)

Partners

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ANR funding

778 k€

Starting date and duration

February 2011 – January 2014 – 48 months

Reference

ANR-10-TECS-004

Cluster label

CHITOART - Chitosan physical hydrogel-based bioartificial vascular substitute

Abstract

The overall objective of this collaborative project is to develop, from chemistry to the device, a tissue-engineered vascular conduit that remains in-situ physiologically functional on the long term, containing the core elements of a vascular tissue. Such development will be carried out from in vitro building to in vivo evaluation in small animals. In our project, 5 partners from hospital department or academic research and 2 companies bring together their knowledge, know-how and expertise from macromolecular science, physico-chemistry of the elaboration of natural polymer systems, cellular and tissue biology, to in vivo implantation and evaluation. The material study and device design is the starting point of the project. The investigated systems result from the association of different chitosan-based hydrogels. Chitosan is a natural bioresorbable and biocompatible polysaccharide well suited for tissue engineering. Such hydrogel associations (the ChitoArts) will bring the combined mechanical and biological properties required for the application. The chitoart architectures are specifically designed as templates for tissue engineering, and in a second step will be bio-functionalized with the pertinent cell types to rebuild in a combined in vitro and in vivo approach, multilayered vascular conduits with a resulting tissue organization inspired from natural blood vessels. The methodology used here will rely on the optimization of each component of the ChitoArt architectures, in relation with coordinated in vitro and in vivo evaluations of their mechanical and biological properties.

Partners

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ANR funding

852 k€

Starting date and duration

December 2010 – November 2013 – 36 months

Reference

ANR-10-TECS-017

Cluster label

CIRDO Recherche industrielle - Smart Companion Responding to Eye and Finger

Abstract

CIRDO Industrial Research is a project to develop a « Smart Companion Responding to Eye and Finger », which is a product of increased social e-Link and automated integration of innovative services (automatic recognition of speech and analysis of situations (scenes) in an uncontrolled complex environment) to empower and support for caregivers, patients with chronic diseases or Alzheimer's disease or related. In addition, this project will allow the validation of generic technologies, a psychological and ergonomic evaluation on the use of the services developed (on the usefulness, usability and accessibility, acceptance, ethical, economic model, ...) but also critical investigation of knowledge acquired by human services offered by caring agency, which will then be transferred to the whole sector. The CIRDO Industrial Research project is solution-based e-Lio (e-Link social, telecare), plus a nutrition service management (telemonitoring) through CIRDO Training project.

Partners

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ANR funding

733 k€

Starting date and duration

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Reference

ANR-10-TECS-012

Cluster label

Minalogic

DIADOMI Development of a diamond dosimeter for measuring absorbed dose in the mini-fields used in stereotactic radiotherapy

Abstract

In the eyes of statistics: 2 800 000 new sickness events and 1 700 000 death per year in Europe, cancer is one of the main public health concern, and is the main death cause in France. At the present time radiotherapy, used all alone or combined with other treatments, is the heart of cancer treatment. Innovative technologies using small fields are currently used in cancer treatment occurring in sensitive area. The clinical efficiency of these techniques have been proved but critical risks due to non well known beam characteristics curb the use of such techniques. For example, the measurement of absolute dose is not possible actually due to the lake of suited detectors to these measurements. The aim of this project is to develop a diamond specific detector for accurate absolute dose measurement during treatment using small fields. This work will lead to a very small size (with an active area <math><1\text{mm}^3</math>), high sensitivity (signal to noise ratio~1000) and tissue equivalence (diamond atomic number: $Z=6$, packaging is water equivalent) device. Precise specifications will permit to reveal technological and clinical constraints associated to the dosimeter after that, the dosimeter will be scaled, optimized and realized. Clinical environment and standard tests will allow us to probe the diamond detector response in standard and small fields irradiation tests. To improve dose measurements accuracy in every particular point of the volume and for every treatment, Monte-Carlo simulation tools will complete small fields diamond detector measurements and hospital ordinary dosimeters measurements. This project is based on partner assessments: • CEA-LIST on built-in, simulation and characterization of the dosimeter in standard conditions • IRSN on medical dosimeters in particular its know-how concerning the use of dosimeters in small field dosimetry • Hospitals to perform measurements in clinical environment and to set specifications: Pitié Salpêtrière (APHP - Paris) hospital academic centre, Alexis Vautrin (Nancy), René Gauducheau and Léon Bérard (Lyon) cancer centres. • In final part, the private company will perform a detector pre-industrialization. These ones will benefit from improvements gained during clinical testing.

Partners

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ANR funding 832 k€

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Reference ANR-10-TECS-002

Cluster label

EMBOLTER - Mean time ambulatory emboly counting for stroke risk evaluation.

Abstract

The cerebral infarctus (stroke) are caused by emboli generated eg carotid stenosis. These strictures emboligenic emboli produce more or less continuous even for some low significant stenosis and asymptomatic. Asymptomatic stenosis will generally not treated except in cases where the embolic nature is proved. The difficulty is that embolic nature is difficult to evaluate, take time in costly equipment and specialized operator required to monitor the record and reposition the sensor. The result is not always reliable. Work in progress show that 2 sessions of 8 hours of monitoring generation of emboli by transcranial Doppler are necessary for this diagnosis. The project objective is to propose a prototype of Holter embolus, with a recorder of transcranial Doppler signals and a tracking system offsetting movements of the sensor. An analysis workstation performs post processing of record, with optimizations that can be made through the coercion of real time. The proposed algorithm has some post-processing, supported by the U930, a Doppler electronics / control and software supported by Atys, a mechanical part supported by Atys with the support of a specialist subcontractor micro-mechanism and a clinical validation part supported by the team of the University Hospital of Lille. The highlight of this project is the complementary expertise of three partners who can meet all challenges.

Partners

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ANR funding

474 k€

Starting date and duration

February 2011 – January 2015 - 48 months

Reference

ANR-10-TECS-006

Cluster label

GINSENG - Global Initiative for Sentinel E-health Network on Grid

Abstract

The GINSENG project is part of an experimental development for a "light" grid infrastructure dedicated to e-health and epidemiology. This network aims to collect distributed medical data in order to perform original data analysis thanks to the innovative technologies of grid computing. This project includes the following research areas: medical informatics, epidemiology joined with a socio-economic modeling. This network aims to federate distributed and existing medical databases, in particular cytopathologic data, to make them available to regional and national epidemiologic structures. Thanks to the distributed architecture of the grid, the network should become interoperable with any medical centre which would need of those medical data. This project follows the Sentinel Network for Cancer Screening project (RSCA) for which we developed a prototype to share cytopathologic medical data between labs and cancer screening associations in the Auvergne region.

Partners

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MAAT

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ANR funding

776 k€

Starting date and duration

April 2011 – March 2014 - 36 months

Reference

ANR-10-TECS-008

Cluster label

Project title**IDS - INTELLIGENT DIABETIC SOCKS :
Embedded Device for Diabetic Foot
Prevention****Abstract**

PATHOLOGICAL CONTEXT: Diabetic Foot is the consequence of the long-term chronic complications of diabetes affecting the lower limbs, namely peripheral neuropathy and angiopathy. When both complications are associated to an external trivial trauma, they determine the progression of the pathology from a non-ulcerated condition of a foot at risk, to an acute syndrome characterised by the classic diabetic foot ulcer, followed by a chronic condition in the post-ulcerative phase, which can lead to amputation. **SOCIETAL AND ECONOMICAL CONTEXT:** A limb is lost every 30 seconds on planet Earth because of diabetes. In addition to causing pain and morbidity, foot lesions in diabetic patients have substantial economic consequences: \$11 billion and £3 billion respectively from US and UK health expenditures both in 2001. However, in addition to the direct costs of foot complications, there are also indirect costs relating to loss of productivity, individual patients and family costs and loss of quality of life. **EFFECTIVENESS OF PREVENTION:** Studies have suggested that follow Team Care behaviour could reduce foot ulcer and amputation from 50% to 80%. This monitoring strategy is largely based on renewed vigilance of the diabetic patient which mainly consists in making a daily inspection of his feet. Unfortunately, studies have shown that patient vigilance decreases over time. Complications which appear after some time are directly correlated with the increasing lack of vigilance. Other studies have provided insoles prototypes based on a real time measurement of the pressures between the plantar foot and the shoes but they are developed in the context of gait analysis and need a wire connection between the insole and an electronic acquisition card. Moreover, these prototypes are unable to detect overpressures in the dorsal surfaces of the toes and the feet. That is why IDS (Intelligent Diabetic Socks) project proposes to develop the first smart wearable device able to monitor and assist the diabetic patient to help him maintaining alertness against foot overpressures both in real-time and in a daily use. **ORIGINALITY, INNOVATIONS AND AMBITIOUS NATURE OF THE IDS PROJECT:** Originality and innovations of the IDS project lie in the final wearable device, the Intelligent Diabetic Socks, dedicated to real-time foot ulcers prevention for diabetic people. This scientific and technological innovation, based on a textile able to measure pressure, will alert the patient as soon as overpressures and/or internal stresses are observed in the foot or the ankle. In addition to this warning, some advices concerning ways to reduce the corresponding risks will be proposed to the patient. Once warning validated by the patient, the device provides recommendations through a media like the "smart phone" (or a "watch") that is able to deliver simple messages like "Stop as soon as possible", "Remove the pebble in your shoe" or more elaborate ones like the display of the full pressure cartography. The ambitious nature of the project lies in the discretion and the comfort of the IDS device. First with a diabetic sock which looks like any other sock, but also with a real-time measurement

of pressures and stresses that can generate very simple alerts or more complex messages. After consulting the information transferred to his smart phone, the patient will be able to see areas that were most pressurized during the day. In particular are highlighted the areas that the patient can check himself or the areas to be treated promptly by his doctor. **RELEVANCE OF THE PROPOSAL IN RELATION TO THE CALL THEME:** The IDS project both concerns the principal focus of the call theme about development of innovative technologies and services for functional substitution of impairment and for autonomy in general and the priority focus of the call theme about development of innovative technologies and services to favour autonomy of patients with chronic diseases.

Partners TIMC-IMAG
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Reference ANR-10-TECS-013

Cluster label TECHTERA

Project title

MATRIXCELL - MATRIX compounds associated to CELL therapy in serum free media for regeneration of ischemic tissues.

Abstract

Cardiovascular diseases remain the leading cause of death in developed countries. Conventional treatments usually fail and these diseases represent a main target for cell therapy. Clinical trials of first generation have been performed with heterogeneous cell populations. They showed a poor efficiency with transient improvement of functional parameters, probably related to a paracrine effect of the injected cells. The current trend is to use more homogeneous cell populations and also to take into consideration the environment of injected cells. Our project will be developed in this context. We will regenerate the vascular system in ischemic diseases by a cell therapy approach and by repairing the extracellular matrix, highly degraded in these diseases. For this "matricial therapy", we will use synthetic GlycosAminoGlycans (GAG), mimicking the properties of natural GAGs, key elements of the extracellular matrix. These molecules bind themselves to growth factors and cytokines and increase their efficacy. Industrial Partner 3 has identified two lead GAG mimetics, active on mature endothelial cells (EC). Preliminary results (Partners 1 and 2) showed that these leads can increase the formation of circulating endothelial progenitors (EPC) derived colonies. The extracellular matrix of endothelial cells also stimulates the formation of these colonies. The project takes into account these concepts and preliminary data. It aims to create a new generation of therapy products associating cells and matrix compounds in a serum free medium. Le projet s'articule autour de ces concepts et données préliminaires. Il a pour but de créer une nouvelle génération de produits thérapeutiques associant cellules et composés matriciels dans un milieu sans sérum. The EC will be produced by partner 2, from adult peripheral blood (autologous to the patient) or from cord blood, if the quantity and quality of adult cells are not optimal. The cord blood EPC-derived EC are allogeneic, but they generate more colonies and have a capacity of proliferation significantly higher than their adult equivalent. The matricial products will be composed of first-generation lead GAG mimetics or of second generation GAG mimetics taking in account the structure of natural GAGs (partner 2) isolated from EC or ischemic tissues in regeneration. These last molecules will be selected on their significant activity on the formation of colonies derived from EPC and on the proliferation of EC derived from it. The serum-free medium, produced by industrial partner 4 will be supplemented with GAG mimetics of first and second generation produced by partner 3, and the potentiating effect of GAGs on heparin binding growth factors will be analyzed by partner 2. The effectiveness of this medium containing GAG mimetics will be evaluated by partner 2 on EC derived EPC, and by partner 5 in animal models of cardiac and hind limbs ischemia. In these animal models, partner 5 will analyze the efficacy of cell therapy by measuring cardiac and vascular functions. EC will be produced in GMP conditions,

enabling a rapid transition to clinical trials. For this, cells will be grown in a closed system in an optimized culture medium containing the most active GAG mimetic. The objective is to generate a maximal number of colonies, with high proliferation potential. This will enable the production, preferably from adult EPC, of a cell dose compatible with therapeutic use, while limiting the number of passages, which may affect cell integrity by generating genomic instability. The integrity of the genome of these cells will be analyzed. Overall, incorporating endothelial cells derived from EPC, serum-free medium and matrix elements (GAG) will generate new products for in vitro cell culture and in vivo therapies.

Partners

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ANR funding

800 k€

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Reference

ANR-10-TECS-010

Cluster label

Project title

MELASCAN - Innovative solution allowing to detect and characterize progress over time of a skin cancer, using a standardized methodology and equipment, for the use of specialized and general physicians.

Abstract

The melanome, under its malignant shape, is recognized as being the most severe shape of skin cancer. Its impact to the human population grows for several decades and doubles approximately every 10 years. The diagnosis is at present made by a clinician from the visual inspection of the lesion, sometimes by means of dermatoscope or of digital images, in application of ABCDE rule: Asymmetry, Edge, Color, Diameter, Evolution capacities. However, the identification of a mélanome by these clinical examinations remains difficult for the small-sized melanoma (< 6 mm) and for the circular forms which do not go into the field of the ABCDE rule. Furthermore, the sensitivity and the specificity of this identification depends strongly on the level of experience and training of the physician, as well as in the interpretation of the colors of this last one dependent on its visual acuteness and on its sensitivity in the chromatic nuances. The current dermoscopie examines the skin with a tool eliminating the reflections of the stratum corneum and allowing a significant magnification. This technique increases the performance to differentiate pigmented melanocyte from and none melanocyte. However, in the case of differential diagnosis between a melanoma and an atypical naevus, the dermoscopie do not bring sufficient diagnostic accuracy and resolution to avoid an chirurgical procedure and do not improve the practice of therapeutics. The essential reasons are that: - The current computerized tools base themselves on the visual information of the acquired image, with results not better than the ones obtained by the visual analysis performed by the physicians." -No standardization of the imaging process is currently available. The reproducibility between devices and the repetability of the acquisition with the same device are not guaranteed. The MELASCAN project suggests realizing the acquisition of the same zone by means of monochromatic lightings or in weak spectral range covering the wavelengths of the UV until the IR by means of a standardized device and a methodology. The integration of a multi-spectral light will allow to reveal to the physicians properties of the until then not visible skin characteristics (haemoglobin, melanin, collagen, others) and to observe the cutaneous in-depth layers. Wavelengths in the IR range penetrates more than the wavelengths of the visible spectrum." The collection of these data within a community base certified by a group of experts will allow to end in a decision-making tool by a classification in malignant / not malignant. The MELASCAN output provides to the physician a diagnostic based on a sophisticated measurement tools combined with data collected in the field using the "close relations" lesson including criterias of the human eye analysis (shape, contrast, colorimetry) associated to the "standard" diagnoses and the tracking of the progress over time.

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ANR funding	952 k€
Starting date and duration	December 2010 – December 2013 - 36 months
Reference	ANR-10-TECS-018
Cluster label	LYON BIOPOLE

Project title

MICO - COgnitive MIcroscope: A cognition-driven visual explorer for histopathology. Application to breast cancer grading.

Abstract

Within the last decade, histopathology became widely accepted as a powerful exam for diagnosis and prognosis in mainstream diseases such as breast cancer. Currently, analysis of medical images in histopathology largely remains the work of human experts. For pathologists, this consists of hundreds of slides examined daily. Such a tedious manual work is often inconsistent and subjective. The cognitive microscope (MICO) aims at radically modifying the medical practices by proposing a new cognitive medical imaging environment able to improve reliability of decision making in histopathology. Our goal is to realize a generic, open-ended, semantic digital histology platform including a cognitive dimension. MICO combines visual perception, context, cognition and experience to reinforce a visual diagnosis assistance following an approach centered on user behavior. MICO will be a pervasive adaptation platform through learning mechanisms facilitating fast, incremental and continuous learning of explicit and implicit medical knowledge. MICO will be able to adapt to the context at different levels, including specific domain knowledge, information about the patient, partial interpretation of the visual content and subjective feedback from the user. A major issue plaguing current computer-aided diagnosis systems is the opaqueness of their mechanism, making the users untrustworthy and the results hard to validate. MICO aims at moving a step forward in medical practice by proposing the foundations of a new confluent cognitive medical imaging technology using context in an intelligent way. Our platform will be capable of cognitive functions ranging from active perception to symbolic description, from symbolic manipulation to communication, and from an ad hoc approach to a capitalization of previous experiences. MICO will behave in a cognitively consistent way with standard medical practice, following a uniform representation of image analysis, reasoning and context elements. This transparency throughout the whole process is exploited in order to permit confluence between the user and the platform, and medical validation of the results through technologies of content-based semantic image retrieval. The platform will be fully configurable and operable through a knowledge explorer allowing, in an incremental way, new medical knowledge capture, representation, use and discovery. In order to have a structural flexibility, MICO has a modular structure. In order to allow a semantic communication between the different modules, a middleware relying on semantic web technology will be used. The middleware will link together the production base, the domain knowledge base, the rule base, the user interface and the digitization device, while using available state-of-the-art technologies and domain ontologies. This distributed structure will enable easy development, incremental evolution, self-adaptation and remote applications. Breast cancer grading will be developed, tested and validated in the frame of project MICO in order to demonstrate the viability and relevance of the

system. Being part of a long term process, initiated by the experience of the industrial and university partners, MICO will be an open system, easily deployable into several specific medical domains such as histopathology, cytopathology and hematology. Besides computer-aided diagnosis, the platform opens the way to a wide range of applications requiring manipulation of medical knowledge such as telepathology, datamining, teaching and education assistance.

Partners

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LIP6
TCF
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ANR funding

1 160 k€

**Starting date
and duration**

February 2011 – January 2014 - 36 months

Reference

ANR-10-TECS-015

Cluster label

Medicen

Project title**PANsABIO - Elaboration of a "smart" anti-biofilm dressing for chronic wounds****Abstract**

Already frequent (> 950 000 per year in France), chronic wounds from escarres, ulcers, diabetes and cancers will expand in the next decades due to population ageing and diabetes increase. Infection of these wounds by pathogen bacteria leads to a decline of the patients' health, to a growth of the treatment expense, to longer cares and sometimes to the necessity of the patient's hospitalization. At the present time, the used antibacterial agents are efficient but only on the short-term as bacteria rapidly develop a protective biofilm. Caring the wounds is particular and painful for the sick person; moreover nurses have to intervene frequently over long periods of time. Improvement in this field would be a great help for the personal in hospital and mainly for the numerous patients. It will also provide an answer to a question arising in all developed countries. We propose to control the biofilm level by the combined use of various agents preserving the commensal flora of the wound. We also wish to avoid bacterial infection by mastering specifically the growth of some pathogen bacteria. The PANsABIO project consists in realizing a systematic study of bacterial contamination, biofilm formation and infection on various types of chronic wounds. Such data are not available today. Then using these data, we will focus on the creation and development of a smart anti-biofilm dressing for chronic wounds. This dressing must be efficient and easy to use, must facilitate the care of chronic wounds, limit patients' hospitalization and avoid bacterial infection. In addition a file will be created to connect the macroscopic characteristics of the wound to the data obtained through various analyses at different scales. The dressing here developed will control the biofilm level and if necessary destroy pathogen bacteria. It will be a new type of product with smart drug delivery properties. The project will join the efforts of medical staff, of academic researchers and of a start-up, all of them being recognized specialists of their respective fields. All steps have been separately studied and the whole program should be realized in the next 4 years. Finally, this project is of real interest for all developed countries.

Partners

ERRMECE
PBS
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CURIE
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ANR funding

1 098 k€

Starting date and duration

January 2011 – December 2014 - 48 months

Reference ANR-10-TECS-019

Cluster label Medicen

Plas'O'Soins - Platform for the monitoring and coordination of home care activities

Abstract

In order to meet the challenges of homecare, there is a need to establish a strong coordination between the health stakeholders. The homecare organizations have different work practices, and there is a need to help them put the patient at the center of the homecare process. The goal of the project is to develop a technological platform allowing for the orchestration of homecare processes, with the aim to improve this type of care and to face unforeseen events that are frequent in this type of processes. This platform is meant to answer the needs of homecare or home hospitalization structures, in terms of coordination, planning and monitoring of the care plans, and of the stakeholders activities. The system needs to provide for : - The rendering of real-time state of the care process, either globally or on a per-actor basis - The timely transmission of information (alerts, schedule changes...) towards the appropriate stakeholder - The planning and coordination of activities, and their dynamic re-planning - The managing of coherence and traceability of activities - The help to the decision process by providing statistic data

Partners

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ANR funding

1 100 k€

Starting date and duration

April 2011– March 2014 - 36 months

Reference

ANR-10-TECS-016

Cluster label

Cancer-Bio-Santé

Project title

SonInCaRe -Controlled cell Sonoporation by In-vivo Cavitation Regulation: from fundamental understanding to in-vivo applications

Abstract

Drug delivery and gene therapy have recently opened new perspectives for managing an array of complicated diseases that may have substantial societal dimensions. Among the possible applications, the administration of a therapeutic gene (transfection) can help in treating pathologies like monogenic hereditary diseases (mucoviscidose, Duchenne myopathy ...), cancers, vascular and metabolic diseases. Amongst transfection methods, viral methods can lead to cytopathy, cytotoxicity and an unpredictable immune response, while nonviral methods (electroporation, microinjection or gene gun) also present limitations, in particular in terms of efficiency. In this framework, sonoporation could appear as an alternative method particularly promising for in-vivo applications, since ultrasound treatments are low-invasive, well-tolerated by the patients and cost-effective. Furthermore, focused ultrasound system could ensure targeted extracorporal treatments within the body with a millimeter precision. Currently, the compromise between transfection and cell viability remains insufficient, and sonoporation mechanisms misunderstood. The aim of the project SonInCaRe is to design, implement and validate a controlled sonoporation system applied to the in-vitro and in-vivo transfection of cells. In order to achieve a reproducible and efficient treatment, the monitoring of sonoporation will be implemented during insonification to ensure spatial and level control. To reach this objective, a transverse field group unifying biologists, physicists and in-vivo clinical applications specialists has been set up. The fundamental mechanism underlying sonoporation will be investigated through the combination of numerical simulations, theoretical analysis and sonoporation experiments. Theoretical modeling and numerical simulations will be engaged to study the interaction between cavitation microbubbles and cell membranes. Experimental works will be engaged to analyze sonoporation of known-properties lipid layers, by using nanorheology and atomic force microscopy (AFM) methods. Different sonoporation devices will be designed and validated in-vitro on different cell lines, ex-vivo on tissues and in-vivo on several animal tumor models. Two French laboratories and two Taiwanese university hospital laboratories approached to conduct in-vivo experiments. Within these researches, the SonInCaRe project put forward new technological developments for which a French industrial partner and a Taiwanese one are also involved.

Partners

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Starting date and duration February 2011 – January 2014 - 36 months

Reference ANR-10-TECS-003

Cluster label

SYSEO - Multimodal and Multimedia Image Analysis and Collaborative Networking for Digestive Endoscopy

Abstract

Up until recently the specialities which claim to be from medical imaging resulted mainly from radiology techniques shelves. Thereby, for the last ten years, the focus was essentially on the setting up of interpreting and storage units software's stations for heavy equipment (MRI, SCANNERS). The value of these solutions is linked to the high price level of the connected appliances and the generated gains by saving on films. This strategy of the rollout predominantly centred on public hospitals ended up penetrating sharply the private companies in reference to the government incentives to archive the patients' radiological films and to swap to digital only. This measure is still relevant today and it brings a real work comfort for the radiologic technicians, and ultimately for the radiologist himself. The non-radiological images production (images and video) and the use of these are more gruelling in some specialisms such as digestive endoscopy where the image is acquired, interpreted and used directly by the doctor in real time and without the help of manipulation. This "real time" operating mode makes tough the setting up of tools for acquisition or images scattering: a global solution, all in one, only could allow their emergence in operating theatre. The Syseo project aims for the creation of a chain of collaborative processes to allow the hepato-gastroenterology endoscopy specialist to produce new images and to archive them easily. The software ergonomics and the use of new devices must take into account the real times constraints in order to extend, on one hand, the span of an examination, improving the quality of the treatment, on the other hand. This concern goes inevitably through the comparison of the acquired images during the examination with the previous images of the patient or those from his radiological or other morphological examinations. If the always more significant images production is an important condition upstream for the support of such systems, the Syseo project intervenes also downstream with the intention of making it collaborative. So, a gastroenterologist must be able to quickly call upon a colleague, either close or remote, to get a supplementary view or access efficiently to images databank in view of diagnosis to consolidate a sensitive observation. As well as, a specialist must be able to archive or submit an unusual image in the aim of an educational purpose. In the manner of the personnel assistants, a comprehensive solution, ergonomic, hyper communicating with real innovation aspects must consent to penetrate the captive and expanding segment of the imaging through gastroenterology, in the home market as well as in the international market. The recommendations of the French Health High Authority (HAS), as far as the patients follow-up is concerned, lead however a lot of practitioners to think on how to arm themselves with tools and their benefits which they could yet be held responsible for. It's a leap that the radiologists took more simply due to the nature itself of their examinations. This is an approach to be achieved by the gastroenterology endoscopy specialists to promote their know-how and to make good use of computer urbanization's projects of their medical institutions.

Partners LIMOS
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Reference ANR-10-TECS-005

Cluster label

Abstract

Novel concepts of nano medicine triggered the development of therapeutic agents of new generations with sizes ranging from nanometers to micrometers and including inventive functions. Local activation of such therapeutic components is an essential function, since it provides a longer therapeutic window and a higher therapeutic index in comparison to classical treatments such as chemotherapy. In addition local delivery minimizes secondary and side effects. Therefore active and targeted delivery opens new perspectives for therapy by providing a controlled release in space, time and on demand. In recent years new promising possibilities for targeted drug and gene delivery have been discovered using ultrasound, gas microbubbles and nanoparticle drugs opening thus new therapeutic strategies. The use of this new therapeutic approach requires the design of new protocols for precise administration of active molecules (control and localization of the treated zones, real time imaging and monitoring). Although this new approach seems promising, it remains today difficult to bring it to a clinical level because of the lack of experimental tools that are essential for an in-vivo validation. For such a validation, it is necessary provide an ultrasound platform that is capable of generating ultrasound of medium intensities (few W/cm^2), in a frequency range between 1 and 5 MHz to target a large spectrum of nanoparticles and microbubbles, and to perform imaging with a higher resolution (20 MHz and higher) in accordance with animal models used routinely (rats and mouse). The objective of the project is to develop an ultrasound theragnostic platform with dual function: therapy and diagnostic and to establish new and appropriate protocols for the activation of microbubbles and nanoparticles. Although such a platform was considered unrealistic 10 years ago, new techniques of ultrasound transduction using cMUT technology (Capacitive Micromachined Ultrasonic Transducers) offer today a solution for such technological breakthrough. A cMUT based probe provides various possibilities to monitor the treated zones using either native imaging or contrast nonlinear imaging in addition to therapy. The project will allow us to reconsider the whole therapeutic procedure by exploiting the recent technological development possible with cMUT and to provide an optimized platform for preclinical validation. The wafer bonding fabrication process has been chosen to develop cMUT probes in this project. The cMUT topology (membrane geometry and gap height) can be locally defined and matched to their role in the probe: low frequency therapy or high frequency (20 MHz) imaging. The platform will be based on a real time high resolution imaging system (15-50 MHz) for which a low frequency electronic card will be added for driving the acoustic emitters for therapy. The experimental platform that will be developed in this project will make use of gas microbubbles and thermosensitive drug nanocarriers. The nanoparticles will be used as a drug carrier where the release is triggered from outside and on demand through focused ultrasound heating. Microbubbles will be used for imaging at high frequency and as a promoter of drug extravasation through the biological barriers and into tumors through

the sonoporation process. The validation of the final platform is also planned in order to evaluate the therapeutic efficacy and the image quality.

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ANR funding 987 k€

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Reference ANR-10-TECS-007

Cluster label Atlanpole Biothérapies