Presentation of the funded projects

in BIOTECS 2010 programme

Programme BIOTECS

Edition 2010

Project title	**BLOODSECUR** – Securisation of blood components towards prion transmission during blood transfusion
Abstract	Variant Creutzfeldt-Jakob Disease (vCJD) is linked to the transmission of Bovine Spongiform Encephalopathy (BSE) agent to human, presumably through the oral route. According to the initial projections, up to half a million of consumers could have developed this disease first identified in 1996 in United Kingdom. The number of undiagnosed contaminated bovine which entered into the human food chain has been estimated close to 2 millions. The human exposure to the risk has been very heterogeneous: cases reported up to now (over 215 cases worldwide) would correspond to the few ones exposed to the highest infectious doses. Besides them, ten- to hundred-thousands-fold more people would have been exposed to ten- to hundred-thousands-fold lower infectious loads, and their situation towards infection (healthy, carriers or under incubation) remains to be elucidated. In parallel to primary contamination through consumption of BSE-contaminated food products, secondary human-to-human transmission was rapidly suspected via contaminated surgical equipment, tissue transplantations as well as through blood or blood products, according to the presence of infectivity in peripheral organs of vCJD patients. Theoretical risk turned to real, since four likely vCJD transmissions via blood transfusion (red blood cell concentrate) were reported in the UK. For one of them, blood donation was performed three years before the donor developed clinical signs: this suggests that donors under incubation may present a risk for a long period before onset of disease without being suspected, since no blood diagnostic test is available up to now. In addition to these four cases, the Health Protection Agency in the United Kingdom (UK) reported in February 2009 the evidence of vCJD infection in a hemophiliac patient, suggesting that even after processing and dilution, plasma may also be infectious and constitute a potent source of contamination. This finding extends the risk to all plasmatic derivatives which were initially thought to be not concerned because of very low infectious doses theoretically involved. This

concern was due to high dilution factors in the plasma batches and due to methods of purification used in the industrial processes. In this context, the current risk related to new cycles of infection by blood transfusion necessitates rapid implementation of measures to ensure that blood products are prion-free, notably by developing methods to eliminate infectivity when preparing these products in the absence of available diagnostic techniques for screening donors, as it has been recently recommended by a UK independent experts panel. In a previous RIB-2005 Project called PRIONSECUR, a device (P-CAPT filter) was validated to remove prion potentially present into red blood cell concentrate. The present project aims to enforce blood security by completing the validation of P-CAPT device on endogenous infectivity in a unique primate model of prion disease, which is considered as the most pertinent model of human situation towards prion. In parallel, we propose to develop and validate, according to the same strategy used for developing P-CAPT device, new devices to remove prions from plasma. Indeed, safety of plasma and derivatives towards prion is currently heterogeneous since it relies on various techniques. Moreover, we recently observed that, in a primate model of human prion disease, exposure to low doses of BSE induces, after extensive incubation periods, atypical forms of vCJD that would remain undiagnosed with current methods. These animals are modeling low doses-exposed consumers, suggesting a major health problem if similar situation in human exists. We proposed in the frame of this project to confirm or infirm the transmissibility of those new forms through blood, and evaluate the ability of the aforementioned devices to remove prions linked to those atypical forms.

Partners	MACOPRODUCTIONS CEA - DSV/iMETI/SEPIA - EmmanuelComoy
Coordonator	CHRYSLAIN SUMIAN - MACO chryslain.sumian@macopharma.com
ANR funding	980 829€
Starting date and duration	November 2010 - 48 months
Cluster label	

Programme BIOTECS

Edition 2010

Project title	**DbaitTherap** – Clinical proof of concept of a first-in-class inhibitor of DNA double strand break repair in cancer therapy
Abstract	Since 2000, the rapid growth of structural data (from 10 000 structures in 2000 to 64 000 now) are at the origin of several success stories in the study of complex biological systems and in the discovery of new drugs by computer design. The analysis and comparison of structures give the chemical basis which allow to identify and design interactions with ligands. Nevertheless, most of the existing tools can only compare structures on a global analogy basis (tertiary structure), which does not always gives an explanation to observed functional differences. In this project, BIONEXT S.A., in collaboration with high-level academics, propose to develop, enhance and give the experimental proofs of the virtual screening processes based on the comparison of structural regions. This novel description of molecular structures in contiguous regions allows to identify the fine differences between binding sites and to explain why chemically near molecules may not share a same function, while chemically different molecules can share a same function. The screening of molecular regions gives several advantages: (1) regions are the smallest functional units of molecules; (2) it is possible to retrieve all the molecules that share a functional region, independantly of their size or sequence similarity or secondary or tertiary structures; (3) it becomes possible to retrieve molecular partners (proteins and RNA included) by looking for molecules that possess complementary regions; (4) the identification of a « structural code » from these regions allows to characterise functionally a molecule from its structure only by localisaing its binding sites and associated partners. The concretization of this project will lead to a new way of performing molecular analysis and to the marketing of innovative solutions answering major issues of academic and industrials, such as: (1) what is the specificity (the frequency) of a molecular region in a cellular context (problem of efficacity in drug design); (2) what are the molecular targets of a compound (molecular mechanisms of drugs); (3) what are the molecular causes of some toxicity (REACH reglementation).

Partners	DNA Therapeutics Institut Curie – Véronique DIERAS Hopital Cochin - Marie-Françoise AVRIL Hopital Ambroise Paré – Philippe SAIAG
Coordonator	Jian-Sheng SUN - DNA Therapeutics sun@dna-therapeutics.com
ANR funding	772 504€
Starting date and duration	January 2011 - 24 months
Cluster label	Medicen

Programme BIOTECS

Edition 2010

Project title	**DEMENAGE** – Delivery of Meganucleases for Genome Engineering
Abstract	The DEMENAGE partners are experts in designing and using sequence specific endonucleases (meganucleases) for gene targeting in mammalian cells. Meganucleases have a broad potential for inactivating genes or precisely inserting DNA sequences into the genome for biotechnological or therapeutic purposes. DEMENAGE focuses on therapeutic gene transfer and will develop meganucleases, as well as specialized vectors for their delivery, in order to achieve targeted integration of therapeutic transgenes. DEMENAGE partners will develop an approach whereby therapeutic sequences will be systematically targeted to a dedicated locus (safe harbor) in the human genome. For this we will characterize a safe harbor in the human genome, where insertion of the transgene would be without unwanted toxic consequences and develop a meganuclease that allows targeting it. In parallel, the issues of efficiency and toxicity of meganuclease delivery into the target cell will be addressed. Advanced meganuclease design will be incorporated into viral vectors derived from Lentiviruses or Parvoviruses (AAV). A central goal of the project is to deliver the nuclease transiently, preferably under the form of a protein, into the target cell. Accordingly, the nuclease will solely perform its hit-and-run function without the potential toxicity due to a sustained exposure of the genome. Lentiviral-based vectors will be tested ex-vivo in hematopoietic stem cells and in keratinocytes, whereas the AAV vectors will be used for in toto delivery to the liver. DEMENAGE should bring out advanced reagents for safe and efficient delivery of meganucleases, that will be valuable for gene therapy applications and beyond.
Partners	Cellectis SA Inserm U-845 – Olivier Danos
Coordonator	Frédéric Pâques - Cellectis SA

ANR funding	748 108€
Starting date and duration	November 10 - 36 months
Cluster label	Medicen

Programme BIOTECS

Edition 2010

Project title	**DERMATHER** – Dermaseptine B2 : a new molecule against tumoral growth and angiogenesis
Abstract	For the last 15 years, the role of tumor angiogenesis in growth and dissemination of tumors has been increasingly studied. It is now considered indisputable that angiogenesis is a crucial mechanism mediated numerous factors, leading to the formation of new blood vessels. Therefore, inhibiting this dynamic process or the biological activity of angiogenic factors should stop tumour progression and possibly induce their regression. Among new therapies developed to improve the management of cancer, in addition to the use of cytotoxic reagent, molecules targeting the angiogenesis are promising molecules. In this context this program aims to explore the combined action of antitumoral and antiangiogenic effects of Dermaseptin B2 (Drs B2), a peptide purified from the skin secretions of an Amazonian frog. This peptide targets both tumor and activated endothelial cells leading to a direct blockage of the tumor growth as well as angiogenesis, without effect on the non-tumoral cells. From this duality of effect, in several in vitro and in vivo experimental models, this molecule induces an inhibition of the tumoral growth and even in certain cases the complete eradication of the tumor. The whole properties of DersB2 were patented by CNRS in July 2009. The aim for this project is to complete our studies relating to the research of a minimal bioactive structure, to elucidate the mechanism of action and to determine clinical biomarkers that could be up or down regulated in the most sensitive types of tumor under Drs B2 treatment. This project could help AnyGenes to move through a full pharmaceutical development up to and including a formal Phase I/ Phase IIa clinical trial to demonstrate the ability of Drs B2 or an analog peptide to treat cancer patients.
Partners	AnyGenes EAC CNRS 7149 – José COURTY
Coordonator	Ben Youssef NAIMI - AnyGenes ben.naimi@anygenes.com

ANR funding	584 732€
Starting date and duration	March 2011- 36 months
Cluster label	Medicen

Programme BIOTECS

Edition 2010

Project title	**HIFI-ASSAYS** – High Throughput Filtering Assays for Multiplexed Blood Group Genotyping and Human Serology
Abstract	The HiFi-assays project aims at developing high throughput and multiparametric analysis tools dedicated to the characterisation of biological samples. The proposed technology is to use an innovative filtration array (HiFi) together with a cost-efficient colorimetric staining/detection of positive results (Patent No. FR09356049.8 and US61/227 666). In this concept, different molecular probes can be immobilised as medium density (100 spots) microarrays (HiFi-array) on the external face of a microtiter plate bottom modified with a porous polymeric membrane. The samples are then incubated/filtrated through the plate bottom, optimising the interaction between target and probe molecules. The plus of the technology are: - A generic platform for multiplexed high throughput assays (DNA, protein and peptide based assays). - A quantitative detection of interactions levels on each spots (image greyscale quantification over three decades). - A filtering protocol increasing interactions between targets and immobilised probes and lowering the assay background. Two applications of the innovative technology, with strong impact onto health security, will be investigated during the project: - A DNA microarray genotyping assay for extended blood group systems characterisation of blood donation samples. - A proteins and peptides microarray based test for the serological investigation of hepatitis infection (diagnosis) and evolution to liver cancer (prognosis). In both case, the project will aim at developing a complete solution, from sample preparation (DNA extraction and PCR multiplex, for example) to protocol automation and treatment of data results. Each application will be validated at medium scale (between 1'000 and 10'000 samples), during a specific on-site demonstration/validation task. The project is an industrial project, coordinated by the company AXO Science SAS, aiming at the maturation of a product meeting the In Vitro Diagnosis (IVD) standards. As a final deliverable and thanks to coordination by the

	supporting SME, a final product prototype named HiFi will be produced at a pre-industrial scale and used for project validation. Two different products named HiFi Blood 96 and HiFi Sero 96 (Trademarks already registered at the INPI), for blood genotyping and hepatitis serology, respectively, are planned to be developed following the project completion. Here, the presence in the consortium of two end-users (Etablissement Français du Sang and Institut Albert Bonniot INSERM-UJF U823) will strongly increase the project impact.
Partners	AXO Science Institut de Chimie et Biochimie Moléculaires et Supramoléculaires – UCBLI - Christophe MARQUETTE Etablissement Français du Sang - Jean-Charles BRES Institut Albert Bonniot – Inserm – Patrice MARCHE
Coordonator	Othello CHARTIER - AXO Science othello.chartier@axoscience.com
ANR funding	768 589€
Starting date and duration	January 2011 - 36 months
Cluster label	LYON BIOPOLE

Programme BIOTECS

Edition 2010

Project title	**HLA** – Monochain HLA class I mice, epitopes identification and preclinical tetramer calibration of interest in human diseases.
Abstract	HLA class I monochain transgenic mice expressing the transgenic HLA molecules in a totally H-2 class I negative context and representative of 9 of the most frequent HLA class I alleles (A01.3, A02.01, A24.2, B08.1, B27.5, B35.1, B44.2 et Cw7.1) in all human populations, have been created. They will be used for the identification of epitopes of potential vaccine interest in the Muc1 Tumor Associated Antigen (non small cell lung cancer) and the identification of potential autoimmune epitopes in ? cell autoantigens (GAD, IA-2, IGRP, ZnT8 and preproinsulin) associated with human type 1 diabetis. Tetramers corresponding to these HLA class I molecules and these candidate epitopes will be preclinically validated with these mice. The human relevance of the candidate epitopes identified with the HLA transgenic mice will be evaluated with peripheral blood lymphocytes of cancer or diabetic patients.
Partners	Transgene INSERM U986 – Roberto MALLONE
Coordonator	Ronald ROOKE - Transgene rooke@transgene.fr
ANR funding	600 000 €
Starting date and duration	February 2011 - 48 months
Cluster label	

Programme BIOTECS

Edition 2010

Project title	**INNODIAG** – Innovation in molecular diagnostic in health using the latest development in Nanotechnology: Application to breast cancer prognostic.
Abstract	The project entitled "INNODIAG" focuses on two complementary axes. On one hand; it deals with the selection and validation of new biomarkers genes in the treatment of breast cancer through the application of novel learning methods using fuzzy logic developed by the group DISCO LAAS. This tool used for the first time on data sets of tumors of breast cancer was found to have a gain rose 10% on the reliability of prognosis compared to those obtained by other existing tests, including in particular the using DNA microarray "Mammaprint®" fabricated with 70 genes selected by methods of hierarchical classification. Alongside this work, a prototype next-generation microarray, designed by the application of innovative technologies by soft lithography and detection by optical diffraction free of labeling will be build up. This development will represent a major breakthrough in bringing the microarray to the Market diagnosis by reducing its manufacturing costs, simplification of the reading system and speed in acquiring information. It will be used to design a first pre-prototype biochips to test the prediction of breast cancer carrying the biomarker genes previously identified and validated by 'classical' microarray methods. Because of its simplicity, robustness , and low cost it will be made available to clinical laboratories, and this new type of microarray is expected to fully enter into personalized medicine and help the clinician and oncologist to determine the most appropriate treatment for cancer and, more broadly, it should bring the current microarray as a tool of diagnosis. This project will be in a strategic context for the integration of converging technologies BIO-NANO-INFO in the field of Life Sciences in making the best use of potential public and private research for economic development regionally and nationally. This project covers both the component 'Experimental development' (developing a new technology for

	manufacturing biochips generic, up to the market between 2 and 4 years) and 'Industrial research' (pre-clinical research with the ability develop a new test this prediction based on DNA microarray previously developed and may lead to the market within 5 to 10 years). In addition, this project fits perfectly with the thematic focus 3 “Tools and innovative products in health diagnosis” and focus theme 4 "Technology Tools".
Partners	Dendris Centre Pierre Potier -Jean-Marie François Innopsys – Stephane Lebrun Laboratoire d'Architecture et Analyse des Systèmes laboratoire d'Architecture et Analyse des Systemes Laboratoire d'Ingénierie des Systèmes Biologiques et des Procédés Institut Claudius Regaud
Coordonator	Michel Corbarieu - Dendris michel.corbarieu@club-internet.fr
ANR funding	949 425 €
Starting date and duration	February 2011 - 36 months
Cluster label	Cancer-Bio-Santé

Programme BIOTECS

Edition 2010

Project title	**Onco-kappaB** – Compounds targeting NF-kappaB activation as cancer therapeutics by inhibiting IkappaBalpha binding to beta-TrCP
Abstract	NF-kB is a pivotal transcription factor which activates the transcription of a great number of genes, including growth factors, angiogenesis factors, cell adhesion molecules, and anti-apoptotic factors . NF-kB controls the inflammatory response and other stressful situations. Activation of NF-kB is also the hallmark of the innate immune response and, owing to the subsequent induction of cytokines, chemokines, specific enzymes and anti-microbial peptides, NF-kB helps to construct the first line of defence against pathogens. Furthermore, NF-kB has an important role in the development of the acquired immune system, mainly as a result of its anti-apoptotic effect. Abnormally high constitutive activation of NF-kB is implicated in all chronic inflammatory syndromes, and inhibition of NF-kB activation pathways is one of the favourite targets for the development of a new generation of anti-inflammatory molecules. NF-kB is also a key player in the etiology of human cancers. NF-kB is constitutively actived in various solid tumors (e.g. breast, ovarian, colon, pancreatic tumors), and hematopoietic malignancies (e.g. B and T-cell lymphomas) .It has been shown to promote tumor cell survival and reduce the effectiveness of conventional anticancer therapies . Hence, targeting NF-kB activation pathways would help also to develop new anti cancer drugs and/or new treatments potentiating the sensitivity of tumors to radiotherapy and chemotherapy. Proteasome inhibition has already been shown to block the chemotherapy-induced activation of NF-kB in vitro, and has been correlated with enhanced chemosensitivity and increased apoptosis in xenografted tumor cells in mice. Similarly, inhibition of NF-kB activation increases radiation-induced apoptosis and enhances the radiosensitivity of cancer cells, such as colorectal cancer cells both in vitro and in vivo.It thus appear that one crucial step in NF-kB activation is IkBs/b-TrCP protein-protein interaction. Our project main goal is to develop new inhibitory molecules

	that will target abnormal NF-kB activation through the inhibition of IkBs/b-TrCP interaction. Hopefully, such an approach should provide means to develop new strategies for therapeutic intervention in carcinogenesis and inflammatory diseases. The project is built on a collaboration between : - a biotechnology company, based at Genopole, CellVir (partner 1), Start up Biopharma specialized in the development of new drugs by inhibition of protein-protein interactions ; - and two academic laboratories : that lead by Véronique Baud (partner 2) at the Institut Cochin, recognized as a world expert on the NF-kB activation pathways, member of the NF-kB study group in the Cancéropole Ile de France, and that of Gildas Bertho (partner 3), at UMR 8601 in Paris Descartes University, specialized in the structural study by NMR of the binding of small ligands to proteins and that has worked for several years with Richard Benarous to study by NMR techniques the binding of substrates to b-TrCP, including IkBa. This industrial R&D program is validated by in vitro and in cellulo proof of concept previously obtained by the three partners of the project (see below), that the inhibition of the interaction between IkBa and its ubiquitin ligase b-TrCP results indeed in the blocking of the activation of NF-kB by potent stimulating agents such as TNFa. The partners will be helped by subcontractant experts in high content in cellulo screenings (Biophenics), and in xenotransplantation of human tumors in mice (Xentech).
Partners	BIODIM INSERM –Véronique Baud UPD – Nathalie Evrard
Coordonator	Richard Benarous - BIODIM richard.benarous@mutabilis.fr
ANR funding	904 781€
Starting date and duration	January 2011- 36 months
Cluster label	Medicen

Programme BIOTECS

Edition 2010

Project title	**PEPTOMED** – Innovative drugs from peptide toxins
Abstract	Animal venoms are composed of molecular entities (toxins) used for killing and paralyzing prey. These biologically active molecules are endowed with high selectivity and efficacy, exquisitely optimized by the evolution process. Toxins are both molecular tools for the study of their receptors and potential lead molecules for the development of novel therapeutics. Their receptors are involved in various human pathologies. Venoms thus represent the natural equivalent of the large chemical libraries used by the pharmaceutical industry for drug discovery. They however offer the advantage of containing only biologically active molecules. The mission of the PEPTOMED project is the discovery and development of novel therapeutics from venom peptides. The vision developed is to explore the enormous structural and pharmacological wealth of animal venoms, using an innovative technology. This will lead to the development of drugs more efficacious (high affinity) and with less side effects (high selectivity). Our long term objective is to achieve a leadership position in the field, based on systematic, large-scale investigation of animal venoms, and correlated with the selection of molecular targets involved in important human pathologies such as pain, cancer or central nervous system diseases.
Partners	VENOMETECH SAS CEA Saclay – Nicolas GILLES CNRS – Emmanuel BOURINET
Coordonator	Pierre Escoubas - VENOMETECH SAS escoubas@venometech.com
ANR funding	955 234€
Starting date and duration	January 2011 - 36 months
Cluster label	EuroBioMed (ex ORPHEME)

Programme BIOTECS

Edition 2010

Project title	**Prostirna** – Proof of concept of the effect of SXL01, an interfering RNA targeting the androgen receptor, in the treatment of castration-resistant prostate carcinomas.
Abstract	Prostate cancers are the second leading cause of death by cancer in men. Hormonal ablation efficiently inhibits the growth of invasive or metastatic tumors at the initial stage of the disease. However, within a few months tumors recur and only palliative treatments are available. Over 200,000 people die every year from prostate cancer (10,000 in France). There is thus an unmet medical need for efficient treatments for castration-resistant prostate carcinomas (CRCaP). The androgen receptor (AR) is still expressed in tumors that no longer respond to hormonal ablation and is mandatory for cell survival, proliferation, and migration. Inhibition of AR synthesis by RNA interference proved in several models to inhibit the development of CRCaP. The corresponding siRNA, SXL01, was patented. The main goal of this proposal is to establish the proof of concept of the therapeutic effects of SXL01 in patients suffering from CRCaP conducting a phase I/IIA clinical trial. The proposal is innovative both in view of the target, AR in CRCaP, and the methodology used, RNA interference by systemic route. Only 3 clinical trials for siRNAs in oncology are ongoing, none in Europe and none for prostate cancers. The proposal is based on solid preclinical data which notably demonstrate - The specific antitumor effect of systemic administration of SXL01 (120µg/kg/day in saline) on CRCaP - The complete absence of stimulation of the innate immune system (TLRs, IFN, cytokines) by SXL01, even at high doses. - A preferential biodistribution of SXL01 in the prostate, a significant concentration in skin and bones, and almost none in muscles and heart. The regulatory preclinical and toxicity studies, and the clinical protocol planned for the clinical trial of SXL01 to treat CRCaP have been submitted and pre- approved by the French regulatory agency (AFSSAPS). A task in this proposal is dedicated to the development of innovative systemic drug delivery methods for siRNAs. Due to the large therapeutic applications of siRNAs, which allow targeting genes coding

	for proteins undrugable by antibodies or small molecular entities, the potential social and economic impact of this proposal thus extends well beyond that offered by SXL01 applications in oncology. A major problem for prostate carcinomas is their ability to metastasize. A task of this project is dedicated to assess the capacity of two patented siRNAs to inhibit tumor dissemination in response to hypoxia induced by castration or by antiangiogenic drugs. Applicants have strong and complementary assets allowing them to be at the forefront of the competition today. The proposal involves two biotech companies, SeleXel and BioAlliance Pharma, a CNRS academic group, and two medical departments from the Institut Claudius Regaud and the Hôpital Européen Georges Pompidou. This collaborative project will be determinant to develop new efficient treatments in oncology, increase the scientific knowledge, reinforce the participants' position and strengthen their intellectual property. The results obtained would open important industrial developments and employment opportunities.
Partners	SeleXel Institut Claudius Regaud - Jean Pierre Delord INSERM U589 – Florence Cabon Hopital Européen Georges Pompidou (ARTIC) –Stéphane Oudard Bioalliance Pharma – Aude Michel
Coordonator	Pierre Attali - SeleXel fcabon@selexel.com
ANR funding	1 681 303€
Starting date and duration	February 2011 - 48 months
Cluster label	Medicen Cancer-Bio-Santé

Programme BIOTECS

Edition 2010

Project title	**SAFE-BETA** – Preclinical development of molecular imaging antibodies targeting the ZnT8 protein for the diagnosis and follow-up of diabetes
Abstract	Diabetes results from an absolute or relative decline in pancreatic beta cell mass (BCM) leading to insufficient insulin secretion and hyperglycemia. In type 1 diabetes, hyperglycemia occurs when the beta cells are selectively destroyed by an autoimmune process. In type 2 diabetes, metabolic stress results in insulin resistance and increased insulin demand. Measurement of insulin secretory capacity is currently used as a surrogate measure of BCM, an imprecise reflection of BCM. Because the pancreas is a heterogeneous hard-to-biopsy organ, there is no reliable measure of BCM available: it is currently not possible to distinguish reliably between anatomical versus functional defects of insulin secretion. There are major efforts to develop strategies for the in vivo imaging of pancreatic BCM as a clinical and investigational tool. Imaging agents are needed that are specific for the beta cell or its function. According to the World Health Association (WHO), the current rates of diabetes are at epidemic levels. In 1985, an estimated 30 million people worldwide had diabetes, and that number continues to grow. The number was up to 135 million by 1995, and by 2005 it was estimated at 217 million. By 2030, the WHO predicts that at least 366 million people will be affected. The increasing prevalence of T2DM will fuel most of this growth - the increasing prevalence of T2D parallels that of obesity, defined as a body mass index over 30 kg•m-2 (11,3% en 2003), a condition frequently associated with T2D - but a dramatic increase in the incidence of T1D is also seen. Diabetes accounts for approximately 10% of the total healthcare budget in many countries, as in the USA and in France. The American Diabetes Association has estimated that the total cost of diabetes in the United States in 2002 was approximately $132 billion. Costs could rise as high as $192 billion by 2020. Therefore, improvements in basic knowledge in

	diabetes, new biomarkers for clinical classification and therapeutic stratification in its different forms and new therapeutic strategies are urgently needed to improve the lives of diabetic patients and reduce the skyrocketing costs associated with the disease. This requires an increased ability to identify people before they become fully hyperglycemic, new ways to monitor therapy, and a greater understanding of the pathogenesis and natural history of diabetes. SAFE-BETA builds an innovative approach related to the discovery of the zinc transporter ZnT8, a new diabetes biomarker specifically expressed in the pancreatic islet and mainly in the beta cells. ZnT8 has 2 extracellular loops which showed to be reachable by antibodies, thus enabling to image beta cells while they are secreting insulin. MELLITECH is the expert in ZnT8 modulators identification and ZnT8 potential as a target for BCM evaluation. Gathering this ZnT8 expertise and the knowledge of its partners in the fields of diabetes (INSERM U986 & U859), immunology (CEA/SPI & INSERM U986) and optical/SPECT imaging (UJF/INSERM U823 & U877), the consortium aims at developing an antibody-based imaging technology targeting a protein which is highly islet-specific and mainly expressed in the beta cell: the ingredients are here to overcome the challenge of functional beta cell sorting and to provide new tools for treatment optimization and therapeutic orientation/follow-up in order to better prevent and treat diabetes.
Partners	MELLITECH SAS U986 – Christian Boitard Université Lille II / INSERM U859 – François PATTOU SPI – Nathalie MOREL UJF/INSERM U823 – Véronique JOSSERAND UJF / INSERM U877 – Pascale PERRET
Coordonator	Fabrice CHIMIENTI - MELLITECH contact@mellitech.com
ANR funding	1 226 891€
Starting date and duration	October 2010 - 36 months
Cluster label	

Programme BIOTECS

Edition 2010

Project title	**STROKININ** – Development of the cyclin dependent kinase inhibitor NK-102 as a neuroprotective agent in ischemic stroke
Abstract	Stroke: 3rd cause of mortality, 1st cause of handicap in adults, and 2nd cause of dementia after Alzheimer disease. 1 500 000 strokes occur each year. Today only a single drug, the tPA, is available to treat stroke patients at the acute phase of the disease. However this treatment requires a CT scan or an MRI before treatment to eliminate a cerebral hemorrhage, and therefore can be used to treat only 5% of patients. Moreover, tPA has a short therapeutic window of 3 to 4.5hrs. For all these reasons, there is a need to develop neuroprotective compounds: 1) targeting different cell types, 2) including multiple pathways involved in cell death, and 3) extensively studied in different animal species and experimental models. NEUROKIN develops neuroprotective agents for the treatment of acute neurological diseases. Its data have shown that inhibition of CDKs has a neuroprotective effect in vitro and in rodent stroke models. The most advanced compound, NK-102, has already undergone some preclinical development, no acute toxicity was observed, and it is able to cross the blood brain barrier. INSERM U919 has a large expertise on rodent and primate stroke models. It has an imaging platform that is unique in France (MRI, PET scan). INSERM U615 is specialized in molecular genetics and epidemiology. It has a large expertise in genomic studies in human. The main objectives of this project are 1) to perform extensive pharmacological studies well controlled in rodents using several experimental models of stroke (STAIR guidelines), 2) to validate NK-102 action mechanisms after stroke in the brain of nonhuman primates, and 3) to initiate regulatory preclinical studies on NK-102, in order to increase probability of success in the clinic.
Partners	NEUROKIN S.A. U919 SP2U – Denis VIVIEN INSERM U613 – Serge Timsit

Coordonator	Benedicte Menn - NEUROKIN S.A. menn@inmed.univ-mrs.fr
ANR funding	813 540€
Starting date and duration	March 2011 - 24 months
Cluster label	EuroBioMed (ex ORPHEME)

Programme BIOTECS

Edition 2010

Project title	**TSH testing** – New TSH testing for early diagnosis of hypothyroidism including a therapeutic index for hormone treatment
Abstract	Thyroid diseases are most frequent among endocrine disorders with 100Mn patients in Europe.TSH is the first protein marker prescribed by clinicians. Over the past decades, there has been a long standing debate to validate TSH levels within the normal range and detect the onset of hypothyroidism with high accuracy. The International Federation of Clinical Chemistry has recently estimated to approx. 36% discordance among existing tests. There has been also a need to develop assays calibrated on a molar basis to comply with new regulatory EU Directives. Since those issues are currently unsolved, the TSH testing project aims at establishing new tests and a working group with the IVD Industry to progress in early diagnosis. A clinical validation of new procedures will be developed to measure early raise in TSH (4-10mIU/L) on a molar basis and for the first time, validate a clinical setting for thyroid hormone treatment at 7mIU/L. It is a truly innovative study which will deliver first-in-class tests since no strategic threshold has ever been established worldwide and no Reference Measurement Procedure is known for this marker. Our past EU project showed that during the onset of the disease, TSH is turning to highly sialylated, hypofucosylated, long-lived forms which are more reactive to most monoclonal antibodies than the normal forms. These findings have been patented and a proof of concept (ANR EMPB) performed as a preliminary clinical study. We now aim at establishing a more accurate measurement of the early raise in TSH in subclinical hypothyroidism to develop an early diagnostic. Measuring such glycoforms will deliver a more accurate testing and as a result, will also be able to deliver a threshold that inclines the clinician to treat or not treat the patient with thyroid hormone. The project will be conducted by Pr. C. Ronin - Siamed'Xpress, and organized in 3 main workpackages Bood collections of hypothyroid patients (CHU Lyon Sud): Blood samples will be collected in the Rhône Alpes Region and dispatched as 3 collections: TSH 0.5-4 mIU/L, TSH 4-10 mIU/L and TSH 10-50mIU/L. 1400 patients with slightly elevated TSH will be

recruited and those with TSH> 7mIU/L will be treated with Levothyrox® over 1 month. TSH will be measured and collected again over a period of 1 to 6 months until their TSH is normalized. Appropriate pools will be prepared and sent out to the Manufacturers. Design of new TSH calibrators and new tests (SiaMed'Xpress): Hyperglycosylated TSH will be produced by Siamed based on a proprietary engineering of CHO cells equipped with a 6-sialyltransferase activity. This material will be sent to manufacturers for in house comparison in their analyzers. Monoclonal antibodies against this product will be developped and screened by the company to construct new assays to be validated on blood samples. . Working Group with EDMA (Roche Diagnostics): European Manufacturers will be represented through their European Association. This WP will clarify the right antigen detected by the current tests. To this aim, manufacturers will participate in testing new TSHs in automated assays using a common blood collection. Accordingly, a procedure may be developped to identify which antibodies detect best diseased TSHs. This WP will also seek for the participation of the IFCC Scientific Division and the IFCC-working group Standardization of Thyroid Function testing to help dissemination of the study worldwide The project will deliver a clinical validation of outmost importance to validate new and existing assays according to the recent European Directives. It will provide the Manufacturers with the opportunity of optimizing existing tests or acquiring new tests at will. Since TSH is the first marker to be prescribed among serum protein markers, it is hoped that the project will also deliver a similar strategy to optimize other tests (30 markers).

Partners	SIAMED'Xpress Laboratoire de Médecine Nucléaire (Lyon) – A. Charrié Centre Hospitalier de Chambéry European Diagnostics Manufacturer Association - A-S. Gauchez
Coordonator	Catherine Ronin - SIAMED Catherine.Ronin@univ-provence.fr
ANR funding	851 090€
Starting date and duration	January 2011 - 36 months
Cluster label	EuroBioMed (ex ORPHEME)

Programme BIOTECS

Edition 2010

Project title	**ValiHybritest** – Clinical validation of the early diagnosis test of colorectal cancer "colohybritest"
Abstract	Cancers constitute the first cause of death in the developed countries where they are responsible for a dramatic level of health expenses. The improvement of the forecast and the decrease of the costs generated by the colorectal cancer (CCR), which is became one of the most frequent cancers, passes by the availability of devices, no expensive, allowing to establish early diagnosis. The colonoscopy (of high direct cost), which is the reference method of detection of tumors in the colon or rectum, is proposed to those having a symptom or a positive faecal occult blood test (FOBT). This test is performed within the framework of the mass screening. However, FOBT is very has sever limitations because of the high percentage (50 %) of fault positive and of false negatives. Thus, there is a real opportunity for the creation of tests of molecular diagnosis of the CCR with higher sensitivity and a higher specificity. These tests represent an enormous market. The French group of academic hospitals in Paris (APHP) has patented a new test in the serum based on DNA methylation. This test identifies subjects with high risk of CCR. It is based on the revealing abnormalities of methylation of WIF1 gene in the blood and\or the stools. Profilome, young start-up, prize-winner 2008 of the national competition of new business start-ups, is developing this test in the market. A new Multiplex (targeting several genes) test aims now improving the performances in terms of sensitivity and specificity of the test Monoplex WIF1. This new test has been financially supported by ANR (Bio emergence 2008; Colohybritest project of the Pr. I. Sobhani). It consists in a unique PCR including a very sensitive target and a very specific target of the CCR to obtain better sensitivity without altering specificity of Monoplex WIF1 test. The Profilome Company, in partnership with the APHP, is in charge of leading these tests. During the present project two requirements will be addressed before the phase of marketing. One concerns the use of a validated CEE device for stool sampling (actually calibrated by Mast-Diagnostic Eiken-Japon Company for measuring occult blood by using immunological automated method). Profilome aims to use this device for DNA collect

	from stools prior to Multiplex analysis in clinical trial. The second gaol is to validate on the sensitivity and specificity of the Multiplex in blood in reference to the colonoscopy. So the performances of a test based on the hypermethylation of faecal DNA will be compared with the faecal concentration of occult blood and in reference to the colonoscopy. The partnership with the institutional team of Pr. Sobhani will allow conducting this trial in asymptomatic subjects or in those individuals referred to the colonoscopy because having mild symptoms.
Partners	PROFILOME CHU Henri Mondor - ÉPIDÉMIOLOGIE CLINIQUE – Iradj Sobhani
Coordonator	Claude Hennion - PROFILOME hennion@free.fr
ANR funding	1 046 630€
Starting date and duration	January 2011 - 24 months
Cluster label	