AGENCE NATIONALE DE LA RECHERCHE

Presentation of the funded projects in 2010 for the Program Blanc Inter SVSE 5

ACRONYM and project title **Page**

Blanc Inter SVSE 5 Program

Edition 2010

Titre du projet	**BioPol folders** – Biocompatible poly(amphiphiles) to fold and stabilize engineered antibody fragments for in vivo molecular imaging in cancer
Abstract	Unstability and aggregation of fragments of recombinant antibodies limit the therapeutic and diagnostic developments of this important class of bioproducts. Solubilisation under a native-like form would address both cost and safety issues. We develop non covalent complexes between scFv fragments and synthetic (biocompatible) copolymers to form soluble complexes in aqueous solutions. Compositions and architectures of the copolymers are adjusted by synthesis to optimize their binding on scFv models produced in bacteria. We will evaluate specifically hydrophobic binding that occurs with unstable folding intermediates, and must be balanced by hydrophilic moities, sp. biocompatible ones (PEO, phosphocholine). We will study binding isotherms with native and partially unfolded states of scFv (fluorescence correlation spectroscopy, circular dichroïsm, capillary electrophoresis, FFF, ELISA assays) and eventually the localisation of contact with the polymers by NMR (cross-saturation, 15N relaxation, deuterium exchange). The project gathers a polymer chemist and a company, both developing polymer cargoes for drug delivery, biochemists experts in antibodies and imaging, and a physico-chimists specialize in protein/polymer complexes. Promising complexes will be tested for tagging cancer cells with a new scFv targeted against endothelin receptors.
Partners	ENS-UMR 8640 Dept Chimie et Fac de Pharmacie (Canada) CEA de Saclay (iBiTec-S)- Laboratoire d'Ingénierie des Anticorps pour la Santé Supratek pharma (Canada)

Coordinator	Christophe TRIBET - ENS-UMR 8640 christophe.tribet@ens.fr
ANR Funding	320 000 €
Start Date and Duration	36 mois
Reference	ANR-10-INTB-1501
Cluster Label	Medicen

Titre du projet	**NMVASC** – Nanofabrication and magnetic active cell patterning for vascular engineering

Abstract

This project intitled «Nanofabrication and magnetic active cell patterning for vascular engineering», acronyme NMVASC, is submitted to the ASTAR/ANR Joint Call for Proposals in Nanotechnology area. This projet will associate 4 partners from France (2) and Singapore (2). - Partner 1: Inserm U698, Cardiovascular Bioengineering Group - France - Partner 2: CNRS UMR 7057, Biological Physics Group - France - Partner 3: National University of Singapore, Bioengineering, Regenerative Nanomedicine Lab - Singapore - Partner 4: Institute of Materials Research and Engineering (IMRE), Nanoimprinting Group – Singapore Development of a functional small-diameter vascular graft for the treatment of vascular disease remains a challenge for coronary arterial bypass surgeries and lower limb peripheral arterial disease. Recent evidence indicates that endothelialization of bypass grafts by establishment of a confluent and stable endothelial cell layer in the lumen of vascular grafts is critical for long-term patency of small-diameter vascular grafts. In vivo, cells are surrounded by topographical and biochemical cues in their microenvironment with native extracellular matrix comprising nanoscaled features in the form of nanofibers, nanopores, and nano-ridges. Therefore, we hypothesize that by creating well-defined nano-textured patterns on a vascular graft surface, we could create a nano-environment suitable for endothelial cell adhesion and migration that would lead to improved graft patency. In this context, we intend to develop novel nano- and microfabrication technique to enhance endothelial cell-substrate interactions on materials that have been previously developped by Partner 1. These materials, based on natural polysaccharides and synthetic polyvinyl alcohol, have proven to be effective as vascular grafts in a rat model. However, incomplete endothelialization of the lumen surface was obtained. Addition of nanotopographical cues on these biomaterials will be investigated by partners 3 and 4 for creating an optimal microenvironment for endothelial cells, using nanofabrication technologies, such as solvent casting

and nanoimprinting lithography. Since physical signals sensed by cells, such as the mechanical properties of the matrix (local rigidity, adhesiveness, architecture, etc.) are increasingly emerging as determinants of cell survival, proliferation, migration and differentiation, we intend to examine the influence of the physical and mechanical properties of nano- and micro-patterned substrates on cell adhesion. Endothelial cell responses, such as cell proliferation and migration as well as cytoskeleton organization, to these nanostructured materials will be evaluated by partners 1 and 3. The development of micro-organized magnetic substrates by partner 2 will allow us to control the geometry of cell assembly in either two or three dimensions, on both non-patterned and patterned substrates. We will create these mechanical constraints by inducing cells to internalize magnetic nanoparticles and then submitting them to a magnetic field gradient. Finally, we will prepare tubular scaffolds from the nanopatterned materials, we will apply controlled and modulable local magnetic constraints permitting structured cell assembly in order to culture cells into tubular grafts and we will investigate these tubular scaffolds as vascular replacement in a rat model (all partners).

Partners	INSERM ADR Paris VII-UMR_S 698 CNRS Paris B- UMR 7057 NUS-Division of Bioengineering (Singapour) IMRE-Patterning and Fabrication Group (Singapour)
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ANR Funding	216 716 €
Start Date and Duration	36 mois
Reference	ANR-10-INTB-1502
Cluster Label	

Titre du projet	**NTS-Polyplex** – Neurotensin-polyplex: Tool for a novel gene therapy of Non Small Cell Lung Cancer

Abstract

Lung cancer is the main cause of death from cancer with 5-year survival across all stages at 15-20%. About 80% of these tumors are from non–small-cell histological type (NSCLC), including adenocarcinomas, squamous cell, and large cell carcinomas. Surgery is generally accepted as the best treatment option for NSCLC. Unfortunately, only 1/3 of patients with NSCLC are candidates for curative resection. The remaining patients have more advanced stages: multifocal or bulky N2, unresectable IIIB, or metastatic disease. Patients with non-surgical stage III disease are treated with chemo-radiotherapy. The remainder, representing the majority of cases, is treated with chemotherapy or supportive care depending on age, and performance status. Lung cancer remains fatal even with only localized disease at presentation (Stage IA 5 year survival 80%). A 2008 meta-analysis, performed to take into account the new therapeutic regimens, demonstrated a benefit of chemotherapy for advanced NSCLC, improving survival by 9% at 12 months, increasing survival rate to 29% versus 20%. The benefit seen due to the changes in the lung cancer population and drug the regimens used, remained very small. The limited impact of currently available treatments for inoperable NSCLC and the trend towards fewer or no improvement over time should prompt searches for new therapeutic strategies. We discovered a ligand/receptor complex implicated in all steps of cancer progression. Neurotensin (NTS), a 13 amino acid peptide, and its high affinity receptor, NTSR1 lead to cell proliferation, survival, mobility, and invasiveness in specific cancer cell types and facilitates tumor growth and metastasis process. NTSR1 expression level is associated with poor prognosis in patients with ductal breast cancer and head and neck squamous cell carcinomas, and in stage I primary lung adenocarcinoma. NTS-polyplex is a non-viral gene transfer system using NTSR1

endocytosis to facilitate the entrance of the polyplex molecule carrying a plasmid expression vector, into the cell. It was developed to evaluate gene transfer to neuronal cells and neuroblastoma tumors. We demonstrated that intravenous injection of the NTS-polyplex reached and transfected neuroblastoma tumor cells. NTS-polyplex transfection is therefore more efficient in the tumor cells than in healthy cells of organs known to express the NTSR1. The transfection of the thymidine kinase (HSVTK) suicide gene followed by ganciclovir (GCV) treatment decreased the size and weight of neuroblastoma tumors by 30% to 50% and increased apoptosis when compared to controls. These conclusive results call for further development of this approach for lung cancer therapy. In this project, we propose to clarify the contribution of NTS/NTSR1 complex in lung tumor progression, and to identify the NSCLC patients eligible for cancer gene therapy using NTS-polyplex. The evaluation of NTSR1 expression status will be developed on stage IIIB and IV NSCLC patients included in therapeutic protocols. We propose to develop experimental tumors expressing or not NTSR1 and/or NTS to evaluate a possible gene therapy on advanced lung tumor and their metastasis. The Mexican industrial partner, Psicofarma, will be responsible for developing the products for human therapy. The scientific strengths of this project lie with the combination of basic and translational research (French partners), the continued collaboration in experimental research (between the French and Mexican laboratories), and the future biotechnology development (Psicofarma).

Partners	INSERM Delegation Paris VI-UMR_S 938 INSERM Delegation Paris VI-UMR 938 INSERM Delegation Paris VI-UMR 707 CINVESTAV (Mexique) Psicofarma (Mexique)
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ANR Funding	292 206 €
Start Date and Duration	36 mois

Reference ANR-10-INTB-1503