NanoBrain kick-off meeting
February 14-15, 2013

Program

Brain tumors and neurodegenerative pathologies such as Alzheimer's disease (AD) represent the major disorders of the central nervous system (CNS). The lack of reliable diagnostic markers and pharmacological therapies for these diseases is mainly ascribable to the blood-brain-barrier (BBB) that isolates the brain from the rest of the body. Consequently, most CNS-active agents are unable to reach the brain tissue in therapeutically active concentrations, and biomarkers of disease penetrate in very tiny amounts outside the BBB.

Our project will deliver novel sensors for diagnosis and nano-sized carriers for drug delivery to the brain. Our goal is to foster the collaboration of three Institutes devoted to development of nanotechnology with the top CNR institute devoted to neuroscience research. The NanoBrain partnership is strongly interdisciplinary and the program of the meeting is tailored to promote convergence and synergy between nanotechnology and living matter.

The talks will be divided in two different typologies: each session will include background talks (title in boldface) that will cover the basic neurophysiology and physics involved in the project. These will be followed by talks specific to the aims: these talks may take the form of a multiple-speaker talk followed by a general discussion. The interdisciplinarity of our partnership is remarkable and each speaker should make the best possible effort to reach across to the colleagues of the other side.

The meeting will occur in the seminar room of NEST, Piazza San Silvestro 12, Pisa. The lab is at a very short ride from either the airport and the train station.

Thursday February 14, 2013

12:00-12:20	Opening : Lucia Sorba (Director of Nano), Gimmi Ratto (Nanobrain Coordinator)
Session 1: neurophysiological background.	
12:20-13:10	Background Talk 1. **1.1) The blood brain barrier: friend and foe (Paolo Fabene, Verona University)** The brain is biochemically and immunologically isolated from the body by the Brain Blood Barrier (BBB), a complex structure formed by the cells that form the vessel walls and the surrounding astrocytes. As a result of this, most circulating factors are excluded from the brain parenchyma and, conversely, factors released in the brain

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	extracellular space are not allowed to diffuse away from the Central Nervous System (CNS). This fact influences both the capacity of delivering drugs to the brain (only about 2% of the possible CNS therapeutic compounds can cross the BBB reaching their pharmaceutical targets) and the capacity of reading the presence of biomarkers of brain pathologies outside of the BBB. These facts have been known for long time and have strongly limited our capacity of early diagnostic and treatment of brain disease. ***Food for thought**: Is it conceivable to cause a transient opening of the BBB to allow for the collection of analytes in the blood stream?*
13:15-14:15	Lunch @NEST
14:15-15:00	Background talk 2 **1.2) Alzheimer for dummies: from the disease to the diagnostic (Nicola Origlia, IN, Pisa)** Here we will cover the basic cell biology and biochemistry of Alzheimer disease and we will present the animal and cellular models available. The biochemistry of β amiloid and of hyperphosphorylated Tau protein will be reviewed in view of their potential prognostic value. ***Food for thought**: Is it conceivable to generate an in vitro model for the production of supernatant to be used during the phase 1 validation of the sensing platform?*
15:00-15:45	Background talk 3. **1.3) Glioblastoma for dummies: from the disease to the diagnostic (Matteo Caleo and Carlo Sala, IN)** Gliomas are primary central nervous system tumors that arise from astrocytes, oligodendrocytes, or their precursors. There is a clear and present need of novel tools for the early diagnosis and therapy of these tumors. Here we will present the hypothesis that the sustained activation of intracellular Rho GTPases might offer a new therapeutic strategy. Rho GTPases control a variety of cellular events ranging from actin reorganization, gene transcription, proliferation and survival, and can be blocked in the activated state by the bacterial toxin CNF1 (Cytotoxic Necrotizing Factor 1). Given the high affinity of these toxins, they represent an ideal cargo for a nanoscopic delivery vector. ***Food for thought**: Is it conceivable to generate an in vitro model for the production of supernatant to be used during the phase 1 validation of the sensing platform?*
Session 2: nanotech and diagnostic	
15:45-16:45	Background talk 4. **2.1) Physics of ultrasensitive detection for dummies (Filippo Romanato, IOM; Paolo Facci, Nano)** These background talks will cover the basic physics of the sensing devices. It will be provided an overview of the most promising technologies for which preliminary results have been obtained within the partnership. A preliminary list of technologies that will be covered includes measures performed on the basis of the following approaches: plasmonic resonance, atomic force microscopy, electrochemical,

	spectroscopic, and gravimetric methods. ***Food for thought**: is it possible to estimate the sensitivity of these methods in comparison of the classic assays such as ELISA? What are the possibilities of multiplexing the sensor, i.e. detecting several different ligands within the same device? To increase the probability of detection a large reactive surface is desirable. Is this requirement compatible with the proposed devices?*
16:45-17:15	Coffee break
17:15-18:00	Workshop 1. 2.2) Selecting meaningful markers for Alzheimer and Glioblastoma. Preparation and management of the sample bank (Coordinated by Laura Baroncelli, IN) In this session we will cover the following task: 1) management of the experimental model (cellular and murine). 2) Creation of glioblastoma models in vivo by transplant of tumour cells tagged with green fluorescent protein. 3) Collection of blood and cerebrospinal fluid from animal model (organized in a bank in order to follow the progression of the pathology along the life span of the animal model). 4) Selection of suitable antibodies for the functionalization of the POC sensors. ***Food for thought**: given the special status of the olfactory epithilia should we consider to collect sample by irrigating the nasal cavities? Is there any indication in literature suggesting that markers present in the brain liquor can be found in the olfactory mucosa?*
20:30	Dinner Somewhere Pretty Cool A bus will leave from nearby NEST (Lungarno Buozzi) at 18:30 for the dinner location and will drive back to the same place. Our guests staying at the Hotel are strongly encouraged to check in upon arrival because there will be not enough time between the end of the sessions and the bus departure.

Friday February 15, 2013

09:30-10:20	Workshop 2. 2.3) Functionalization of the sensor active surface (Coordinated by Paolo Facci and Valentina Arima, Nano) In this workshop the strategies to immobilize the selective antibodies on the sensing devices with the correct spatial orientation be discussed. This will require the strict interaction between the “functionalization people” and the “sensing people”. Here methods to improve sensitivity and selectivity of the reagent-antibody interaction will also be discussed. ***Food for thought**: can we design a single functionalization procedure that could be used with all the available sensors? Functionalization and multiplexing: would it be possible to obtain a spatially organized deposition of different ABs on the sensors?*
10:30-11:00	Coffee Break
11:10-12:00	Workshop 3. 2.4) Engineering the device: the microfluidic reaction chamber (Marco Cecchini,

	Nano). The microfluidic platform will be designed to handle and screen macroscopic quantities of solution optimizing its presentation to the detecting sensor to maximize the probability of interaction between analyte and probe. Here the available technologies will be discussed in view of the strict interaction between the PIs of the microfluidic and sensing packages. Mixing technologies relevant for increasing the binding efficacy and the rejection of unwanted unspecific binding will be discussed.
Session 3: drug delivery	
12:10-13:00	Background talk 5. **3.1) Based strategies to enhance neuronal function in Huntington's disease (Marta Valenza, University of Milan)** Here we will discuss the potential of nanoparticles-based strategies to brain targeted delivery of molecules that are not per se blood-brain barrier (BBB) permeable but are of interest from a therapeutic standpoint in neurodegenerative disorders. The example of g7-NPs loaded with cholesterol in a transgenic mouse model of Huntington's disease (HD) will be presented. These pilot studies may create the proof-of-principle to promote new research fields based on the development and optimization of specific NPs crossing the BBB and delivering drugs or molecules in specific regions or cells affected by neurodegeneration not only in HD but also in other brain disorders such as Parkinson's disease or Alzheimer's disease.
13:10-14:20	Lunch @NEST
14:30-15:20	Workshop 4. 3.2) Fabrication and functionalization of polymeric carriers (Loretta del Mercato and Ilaria Palamà, Nano) Here the preparation and properties of polymeric microparticles and nanocomplexes for sensing and drug delivery will be presented. Strategies for their use within the central nervous system will be discussed.
15:30-16:20	Workshop 5. 3.3) Delivery of NPs in vivo (Claudia Lodovichi, IN and Gimmi Ratto, Nano) In this session we will discuss the task of delivering and tracking NPs within the central nervous system. Two different ways of entry to the organism will be discussed: nasal delivery and through the blood circle. ***Food for thought****: is the crossing through the BBB bidirectional? Could we use NPs permeable through the BBB to harvest analytes within the brain to be collected outside of the BBB?*
16:30-17:30	Summary and business meeting.

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