ANNEX A

PUBLIC SELECTION BASED ON QUALIFICATIONS AND INTERVIEW FOR THE AWARDING OF NO. 1 EARLY STAGE GRANT LASTING 12 MONTHS FOR CONDUCTING RESEARCH PURSUANT TO ART. 22 OF LAW NO. 240/2010 AT THE DEPARTMENT OF MANAGEMENT, INFORMATION AND PRODUCTION ENGINEERING (SC 09/G2 - BIOENGINEERING - SSD ING-IND/34 - BIOENGINEERING (CUP: F56C18000450006) TYPE B (GRANT AGREEMENT N. 825159)

announced with decree of the Chancellor Rep. no. 63/2019 of 28.01.2019 and posted on the official registry of the University on 28.01.2019

RESEARCH PROJECT

"Computational fluid dynamics of a microstructured substrate for cell culture"

Research structure: Department of Management, information and production Engineering
Duration of the grant: 12 months
Scientific Area: Industrial and information engineering
Academic recruitment field: 09/G2 - Bioengineering
Academic discipline: ING-IND/34 - Bioengineering
Scientific Director: Prof. Andrea Remuzzi

The activities of the present research project are instrumental for the development of the ERC project ERC-2018-PoC (MOAB - Miniaturised optically accessible bioreactor for drug discovery and biological research), a collaborative project between the Politecnico of Milano and the University of Bergamo. The problem addressed by the ERC-PoC project is related to the difficulties of the pharmaceutical industry to develop new drugs. The development of a new drug lasts ten years and costs around one billion euro, thus most companies are not able to sustain such a huge investment effort. In fact, development of a radically new therapeutic agent, either a traditional chemical drug or an advanced bio-drug like a stem cell-based therapy, is subjected to regulatory approvals based on three phases: 1) lab discovery in vitro, 2) pre-clinical test in animals and 3) clinical test on patients. This process may take even longer than ten years. Currently, among ten thousand new therapeutic agents, only one arrives to the market. Thus, drug development is currently a process with 96.4% failure in the pre-clinical testing phase, meaning that the drug efficacy measured in vitro is almost never confirmed in animals. Most technologies currently used to test therapeutic agents in vitro is obsolete. It's often a flat culture dish, in which a single cell population is cultured on the bottom, the drug to be tested is added to the culture medium and the expected activation of specific cell markers is measured on cells. However, in this simplified in vitro culture condition, the drug elicits a cell response that is not representative of the in vivo response, which is based on cell interactions that occur a) in three-dimensional (3D) non-flat environments and b) between several cell populations and never limitedly to the one addressed by the drug.
The aim of the ERC-PoC project is to generate a more realistic in vitro tool to test the response to drugs by an affordable yet highly-performing new device that allows to culture live 3D tissue-equivalents instead of isolated cells. The system is based on a novel nano-engineered 3D micro-scaffold for stem cell culture (named "nichoid") in a millifluidic optically accessible bioreactor (named the "MOAB"). There are already evidence in the literature that the nichoid micro-scaffold, nanofabricated on the bottom of a culture well, is capable of guiding the self-organization of several types of stem and progenitor cells into organoids mimicking functions, very hard to mimic in vitro and crucial for testing new drugs. The MOAB allows to maintain alive 3D tissue-equivalents in vitro, of few millimetres in size, under continuous perfusion of culture medium and under infusion of the drug to be tested, and diagnostics of cell response both optically in real time and also post-cultivation. The goal of this PoC proposal is to perform a technical and commercial feasibility to move the MOAB-nichoid to the market. If successful, he MOAB-nichoid could drastically reduce the time to market and costs of newly- developed drugs and bio-drugs, drastically reducing the use of laboratory animals.
The aim of the present project is to confirm the technical feasibility and performance of the MOAB system. The goal is to increase the maturity level of the MOAB-nichoid device further characterizing the

fluid-dynamics of the culture chamber that accommodate the nichoid substrate. The activities will consist in the following steps.
1)Implementation of a computational fluid dynamics model that will include the culture chamber with the nichoid substrate integrated into it. Using microscopic imaging, at optical and electronic level, micro-geometry models of the nichoid microstructured cell scaffold in the culture chamber will be constructed numerically and validated. These numerical models will be imported into a CFD software (OpenFOAM, https://openfoam.org) to solve the flow field at different and increasing flow rate values.
2)In a subsequent phase the CFD simulations will include geometric models of cell populations to estimate the local shear forces acting on cell membrane and affecting cell function and structure. To this aim 3D images of the nichiod substrate seeded with mesenchymal stem cells will be imaged by flourescnet labeling and confocal microscopy. Using these 3D images, numerical models of the microstructured scaffold and the cells within i twill be processed to obtain numerical surface models, at different cell culture times.
3)The results of the CFD analyses will be used to optimize the millimetric geometry of the assembly of the MOAB and the nichoid scaffold.
The activities of the project will be instrumental to the final design of the MOAB system as well as for its characterization for the commercial use of the system. On the basis of the data obtained, the potential users will be able to choose the best optimal conditions for the use of this bioreactor for investigations on cell functions and screening of chemical compounds. The project will have a total duration of one year. The results will be published in accordance with the experimental and numerical techniques compatibly with the protection of the intellectual property of the systems developed within the ERC-PoC MOAB project.