Publishable executive summary

Introduction and overall objectives

The 6th Framework Programme of the European Union introduced new funding instruments aimed at stimulating the development and implementation of specific key technologies within the European Research Area. Integrated Projects belong to these new instruments and group together numerous partners from European research centres to collaborate on a large-scale innovative project. *CellPROM* – with a total volume of € 26 Mio the largest Integrated Project within the thematic priority of NMP, nanobiotechnologies – unites academic and industrial researchers (26 partners) from 12 countries and is coordinated by Prof. Dr. Guenter Fuhr, head of the Fraunhofer Institute for Biomedical Engineering (IBMT) in Germany. The main objective of the project running over four years being non-invasive »reprogramming« of the destiny of individual cells on an industrial scale, the abbreviation »*CellPROM*« stands for »Cell Programming by nanoscaled devices«.

The principle relies on specific reactions of cell surface receptors in response to contact with customised nanostructured surfaces – the *NanoScapes* – whose macromolecular landscapes mimic biological surfaces triggering processes like immune response and stem cell differentiation in the human body. The project started in March 2004 and will be completed in February 2008.

Since the transmission of the reprogramming or differentiation information from the surface receptor to the nucleus of the cell occurs via natural intracellular signal pathways and without further technical interference, this approach promises a minimisation of undesirable side effects of artificial cell imprinting, while its mastery on an industrial scale opens up important areas of application in the fields of biotechnology, medicine, pharmacy and general technological development. The project *CellPROM* gives a strong push to and knits together interdisciplinary research in nanostructuring and signalling processes in cells because large-scale production and use of these *NanoScapes* require the development of suitable tools – e.g. reusable nano-stamps – and their testing with cells as well as the adaptation of current methods of cell handling and characterisation to the technical requirements of the imprinting process. At the end of the project, functional modules are to be provided that already incorporate first solutions to these technical challenges. They can serve as vantage points for further development until the maturity phase as well as for the design of subsequent applications whose aggregated effects will considerably foster the significance of the location Europe in the key market of nano-biotechnologies.

Imprinting of cells will be realised via artificial nano-biotechnological devices, e.g. surfaces generated by nanostructured stamps or beads, these tools are designed according to the natural principles of cellular signalling and differentiation. As nanocomponents are essential to the imprinting process, suitable techniques and principles to form nanoscaled macromolecular patterns on arbitrary surface geometries have to be developed. All components, ranging from the nanoscale of functional interfaces up to the macro level for cell handling, are to be developed as functional modules suitable for further application.

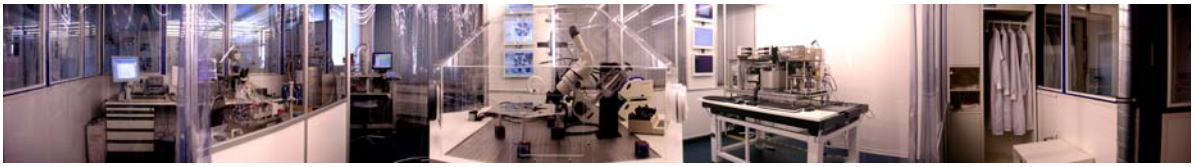
The project features multiple nano- and biotechnological challenges, meeting which will lead to breakthroughs in nanotechnological device development and, moreover, drastically advance our understanding of biological signals relevant to cellular differentiation. A potential device for the mass production of such precisely differentiated cell samples will follow a modular approach. Within this Integrated Project, we will address those modules by highly interlinked workpackages, each of them dedicated to a special module development. Different expertise has to be combined to bridge the gap between biology and

nanotechnology, but at the same time to make the transition from the macro world of a medical device over meso- and micro-fluidic systems to the *NanoScapes*™ well in the nanometre range.

Objectives and results of the third year

At the very beginning of the project two device concepts have been developed and elaborated in the following three years: the magnetic warehouse concept for adherently growing cells and the DEP/fluidic device for suspension cells. Last years results clearly revealed that both directions should be followed. Consequently, the naming was changed reflecting that a transition from concepts to realisations has now been made. The magnetic warehouse approach will now be called MagnaLab crediting the magnetic manipulation of the carriers. The DEP/fluidic device is called NazcaLab, inspired by the layout of the fluidic chip resembling the ancient large scale drawings observed in Peru, South America.

The operational framework of the *CellPROM* application laboratory is now fully established serving as the point of integration for both devices; respective tools and modules are developed by the different partners in the framework of the project and the interplay is evaluated in the application laboratory.

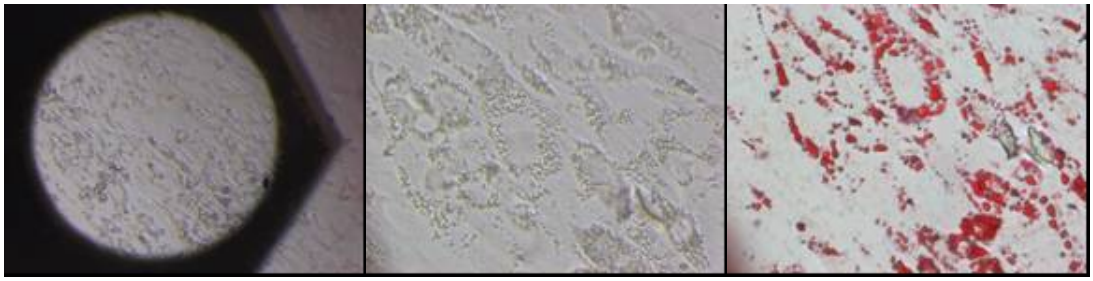


Panoramic view of the *CellPROM* application laboratory.
Image courtesy FhG-IBMT.

The central part of the MagnaLab is a large fluidic chip manufactured from different layers of polycarbonate and connected by laser-welding. The current layout features 15 cultivation chambers allowing different cell suspension additives to be supplied to the cells. Thus a parallel cultivation of different cell models in the same chip is possible.

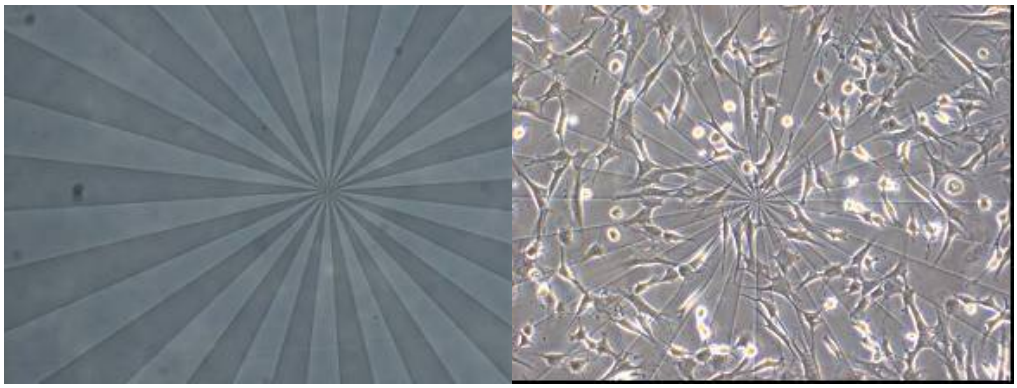
Different polycarbonate foils prior to assembly, MagnaLab fluidic chip after bonding (middle) and fluidic experiment with coloured fluids representing different cell suspension additives (right).
Image courtesy LEISTER and FhG-IBMT.

The cells are grown adherently on small, value added glass carriers (1 mm x 2 mm), those carriers are manipulated magnetically through the MagnaLab to undergo different processing steps. Long term cell cultivation under those conditions could be shown with adult pancreatic stem cells for 20 days, first results for differentiation in the chip with soluble growth factors are promising.



Adipogenic differentiation of adult pancreatic stem cells (CEsub2b) on carriers inside the MagnaLab with soluble growth factor (IGF-1) at day 20 (unstained in left and middle pictures, Oil-red-O staining on the right).
Images courtesy FhG-IBMT.

Nano-structurisation and functionalisation for the *NanoScapes™* has been matured. Different features with sizes down to 50 nm have been reproduced in polymers and inorganic layers on glass. Various roads for the immobilisation of signal factors have been established. The systematic study of those substrates in the MagnaLab will be the main focus of the last project year.



Radial topological structure in a thin titanium dioxide layer on glass produced by a sol-gel embossing technique (left). Cells show varying behaviour grown on the structures (right).
Images courtesy INM and FhG-IBMT.

Partners and consortium

Europe has an excellent background in nano-, microsystem- and bio-technology in many countries, but in order to maximise the overall impact it needs to strengthen and reinforce that excellence by focusing on specific goals well into reach to be carried out in a 4-year project but showing future perspectives for continued technical development for the rapidly growing biotechnology market. Complementary specialist groups from all over Europe come together to share their different expertise and results in various areas of nano(bio)technology: material science, biology, biotechnology, nanotechnology, manufacturing technology, cell handling and clinical testing. Each of the partners has specific knowledge in his field and internationally recognised expertise. The collaboration in the *CellPROM* project, based on the complementarity principle, will lead to long-lasting co-operations between the partners.

Project co-ordination is with the Fraunhofer-Gesellschaft, one of the key players in applied research in Europe. The technical and scientific problems to be solved on the way to the *CellPROMs* have been decomposed into manageable units like well-defined workpackages, each of which is headed by a partner with a strong expertise in the respective field. To assure quality and sustainability of the project's results, knowledge management strategies have been further detailed and clear decision-making procedures implemented. The project co-ordinator and three subproject leaders form a board of four persons to perform and strengthen the high level decision-making. Thereby, vertical and horizontal connections are introduced to ensure high quality of management in each step.

The universities of Lausanne (Switzerland), Barcelona (Spain), Saarbruecken (Germany), Vienna (Austria), Kaiserslautern (Germany), Pavia (Italy), Ljubljana (Slovenia), Tel-Aviv (Israel) and Vilnius (Lithuania) form the scientific backbone of the consortium. The non-profit research institutes of Fraunhofer-Gesellschaft (Germany), Royal Institute of Technology (Sweden), Institute of Experimental Biology and Technology (Portugal), Institute Pasteur (France), Institute of Spectrochemistry and Applied Spectroscopy, Institute for New Materials, Georg-Speyer-Haus and Max-Planck-Institute for Biophysical Chemistry (all Germany) with their expertise in applied research bridge the gap between basic research towards technical development. The companies Evotec Technologies (Germany), Leister Process Technologies (Switzerland), GeSIM (Germany), Sysmelec (Switzerland), Eurogentec (Belgium), Silex (Sweden) and AMO (Germany) with their product portfolio in the nano-, micro- and bio-technology field stand for competitive developments in line with market requirements. The start-ups Eurice and tp21 (both Germany) bring in their expertise in project administration, knowledge dissemination and training, since management is an issue for Integrated Projects of this size, educational perspectives are applied on a European scale, and new skills and expertise are expected to be created in Europe.

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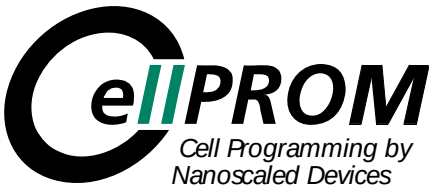
Project logo



Project website

http://www.cellprom.net