ManuCyte – Self-learning modular manufacturing platform for flexible, patient-specific cell production

SPECIFIC TARGETED RESEARCH PROJECT

Final Report

Publishable Summary

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Project Website address:	www.manucyte-project.eu

1 Project key data

Project Acronym:	ManuCyte
Project Title:	Self-learning modular manufacturing platform for flexible, patient-specific cell production
Project Website:	www.manucyte-project.eu
Consortium:	Fraunhofer IPA
	ABO Akademi
	Primacyt
	Chipman Technologies
	mta automation
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2 Executive Summary

The ManuCyte project aimed at the development of an integrated, intelligent, flexible and modular automation platform for cell cultivation in order to enable patient-specific cell cultivation in an industrial scale.

In order to achieve this, various platform components have been developed during the project such as bioreactors (cell culture vessels capable for automated handling), an optical monitoring plug-in for cell status recognition, an incubation plug-in, handling systems and a hybrid workplace to support man-machine interaction.

Unfortunately, not all components could be developed sufficiently, so e.g. the liquid handling system was not finalised till the end of the project. Furthermore there appeared some serious issues with purchased handler components so that the integration of the overall ManuCyte platform was not completed at the end of the project. This had also a major impact on the demonstration runs which were planned to be executed which was only possible by means of work-arounds then.

However, the exploitation of the singular developments is going on quite well. Some of the partners have already integrated their components to their product portfolio.

3 Project context and objectives

The rapid development of methodologies in personalised medicine provides great potential to revolutionise the future treatment of a wide range of diseases. Exploitation of this great potential requires the cultivation / production of (human) cells patient specific and on industrial scale.

At present, industrial-scale cultivation of cells is not possible on an individual patient basis. Cell cultivation is currently performed by manual processing, or at best use of a semi-automated processing, on laboratory scale. Results of these small scale methodologies are heavily reliant on human intervention and assessment restricting accuracy, reproducibility, and efficiency of the process. Ensuring processed cells meet stringent quality criteria constantly is a key factor; with present cell production processes this is virtually impossible.

The ManuCyte project aims at the development of an integrated, intelligent, flexible and modular automation platform for cell cultivation which enables to cultivate cells patient-specific.

4 Scientific achievements

In a first step, the consortium specified use cases and requirements on an automation platform for patient-specific cell cultivation. This was achieved by combining know-how from biology, process automation, and IT. Afterwards, the detailed design and prototypes were developed for the platform components. In detail, the achievements are as follows:

- The module framework is the basis for the realisation of a modular and scalable concept for the setup of cell cultivation platforms and allows the flexible composition of process equipment (plug-ins) as well as easy extension of capacities. Its design was completed and it was assembled during the 2nd period of the project. The control for the included handling system has been implemented as well as related mechanical and electrical interfaces to the plug-ins and assisting robot and the integrated RFID equipment. However, there arose issues with the commercially available gripper which has been chosen as it turned out to suffer from a software bug which resulted in the gripper not completely closing.

- The liquid handling component has been planned to be able to compose the cell culture medium individually for each cell culture. Therefore, several mixing tests have been executed in order to choose the most appropriate mixing principle. Furthermore, a prototype has been built up to test the system functionality together with the cell vessels developed within the project – the bioreactors – and to proof that the system can be sterilised and is cross-contamination free.
  This is also supported by especially developed connectors which also enable to avoid contamination from the environment by providing the possibility to sterilise the liquid handling and bioreactor contact points before putting them together.
  However, beyond this prototyping work, the integration of the overall liquid handling with the incubation slots and overall ManuCyte platform has not been executed successfully due to considerable delays.

- Bioreactors have been developed which are suitable for handling and identification within automated systems as well as automated connection to the liquid handling system for medium exchange. Therefore, several material, liquid flow, and cell cultivation tests have been executed and the prototype developed has been improved iteratively in order to overcome issues with leakages, damages due to high temperatures during sterilisation of the bioreactors, etc.
  Besides this, several sensor technologies have been integrated to the bioreactor in order to enable inline measurement of several physical and biochemical parameters.

- In order to enable measurement and evaluation of cell status of the cell types which are used within the system, respective tests and classification cycles have been undertaken by means of adapting an already existing optical cell monitoring system. Furthermore, this cell monitoring system has been redesigned in order to fit automation needs from a mechanical, electrical and especially software point of view.

- As there are many process steps which are special for a certain cell types or occur only with low frequency, it was decided that the automation platform should have an integrated working place to execute process steps manually. Therefore, a hybrid workplace was implemented which integrates a laminar flow bench in order to ensure

sterile working conditions as well as an enhanced user interface that provides a digital lab book and guidance / working instructions for the process steps to be executed.
This hybrid workplace is connected to the process automation system via an assisting robot which handles the bioreactors between both systems and also can support laboratory workers at the hybrid workplace by means of man-machine interaction. For this reason, the assisting robot was developed as a redundant system while considering comprehensive security issues.
Equivalent to the handling system of the module framework, there arose issues with the commercially available gripper which has been chosen as it turned out to suffer from a software bug which resulted in the gripper not completely closing.

- To control the overall ManuCyte platform, an existing MES which originally was implemented for the semiconductor industry has been modified to fit cell-biology process needs. Therefore, the process steps have been analysed and modelled and specific links and dependencies among them have been introduced to the software system. Communication protocols to all automation components have been implemented in a generic way, which makes them reusable, and have been tested by using emulators representing the process and handling components of the automation platform.
  In order to enable the evaluation and optimisation of cell cultivation processes, a cell behaviour model has been designed which consumes process parameters and measurement results from the MES and gives suggestions for process step parameterisation back. Therefore, well-known algorithms from cell analytics have been combined with self-learning mechanisms from the IT domain.

Cell cultivation tests were executed during the whole development phase of the project in order to generate data sets for the cell behaviour model, to evaluate the applicability of the bioreactor and the sensor technologies used for cell monitoring (optical, physical, and biochemical), and to execute research on further biochemical indicators for cell status (division, stress, death).

The integration of the ManuCyte automation platform with regard to hardware, software, and process components in Primacyt’s laboratories was not completely finished until the end of the project as one plug-in was integrated only with regards to hardware. Thus, test runs and demonstrations of the system could not be executed completely. However, the demonstrator system with related process plans and automation procedures was set up as far as the integrated components allowed this. E.g. cell growth under standard and under stress induced conditions could be monitored by the optical monitoring system.

5 Expected final results, their impact and use

The results of the research executed within the ManuCyte project has been planned as a scalable, intelligent automation platform for cell cultivation. As nowadays 75% of cell cultivation effort is caused by manual process execution, there is a considerable potential to increase efficiency of such processes by automating cell cultivation steps. This potential is to be exploited by the ManuCyte cell cultivation platform.

But not only efficiency is an argument for automated cell production, quality and constancy in process outputs is an even more important advantage, because each company, laboratory or even laboratory assistant has its own “best practice” and / or standard operating procedures in setting up process parameters. Due to the low level of automation and software integration, those parameters are often only verified within each laboratory which may lead to rejections, depending on the experience and qualification of the assistant. A hard- and software integrated cell cultivation system which controls the cell processes and monitors cell status would decrease rejections and variations in quality to a minimum.

The possibility of cultivating cells patient-specific in industrial scale enables enlarging application areas for individual cell-biologics such as personalized medicine which includes personalized pharmaceutical screenings (e.g. for cancer therapy. Besides this, it has turned out during the execution of the project that a similar demand in automated cell culture may also exist in research institutions and companies who are differentiating stem cells into a variety of differentiated cells. These differentiation processes undergo specific phases, whereby each phase or step during the differentiation is characterized by having its own requirements with regard to media composition. So stem cell research organisations are also potential applicants of the ManuCyte system.

However, the overall benefits could not be demonstrated completely during the project duration (including two months demonstration extension). The overall concept could only be evaluated partially, i.e. by means of prototypes which did not cover the whole cell cultivation process flow. Nevertheless, feedback from interested potential applicants was positive, even if mainly restricted to certain application cases or aspects of the overall platform.

In addition to the potential applications described above for the overall ManuCyte platform, and considering that the overall platform could not be finalised and demonstrated during the project as planned, there were several components of the platform identified as exploitable results independently from the exploitation of the overall platform. Examples therefore are the mini-NVD which enables accurate dosing and dispensing of liquids in various applications (e.g. gluing), the module framework which is going to be exploited in other industries where flexible processes (e.g. 3D-printing) are applied.

These singular components have potential to improve the competitiveness of European SMEs since they strengthen their market position in interdisciplinary application fields. Examples therefore are the developed valves and dispenser of the liquid handling which is also applicable to other industries, the automation-enabled optical monitoring, or the MES which now is also applicable for the life science industry (before mainly semiconductor and photovoltaics). This helps the respective project beneficiaries to extend their field of customers, or to approach existing customer fields with an improved product portfolio.