Biomanufacturing 2020 (bioMFG2020): Development of Innovative high throughput analytical tools and methods to characterize cell culture fluid during development and commercial cell culture processes

Kupers Luc

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Need for public-private collaboration

- Although the industrial Animal Cell Technology has become a well-established platform for biopharmaceutical production, substantial issues remain. Fundamental questions in cellular and systems biology, physiology and bioprocess science relevant to animal cells remain unresolved. A better control and higher prediction of cellular behaviour in the development and manufacturing of biopharmaceuticals demands a **multidisciplinary** approach.
- The poor understanding of how bioprocesses impact cell and protein quality and the lack of suitable ‘easy-to-use’ and fast predictive tools/methods, asks for the development of innovative analytical technology that lead to faster, leaner, more controllable, cost-effective and finally more industrious production. These novel tools/methods to measure cell culture parameters and product quality attributes should lead to increased efficiency of the animal cell production platform, and provide a basis for process understanding.

Need for public-private collaboration

- As these developments are not the core business of the biomanufacturing companies, there has been less innovation in this field. Consequently, most methods currently used for monitoring and controlling the cell culture process are the same as 20 years ago and not well adapted to the challenges given the increase in complexity of cell culture processes, the variability of the raw materials and the move to disposable technology. Most innovation in this area comes from academia and SMEs.

Objectives

- The overall objective is to develop a better understanding of the production cell and its environment, and how this is correlated to productivity and product quality.
- To enable novel, easy-to-use, fast, high-throughput, analytical and/or feedback control methods for the parameters that can be measured during development of biopharmaceuticals.
  - High-throughput methods
    - Small testing volumes leading to miniaturisation and automatic sample preparation to enable fast (at-line, online) testing, eliminating time-consuming testing in laboratories away from the bioreactors.
  - Novel methods
    - Novel technologies for online non-invasive testing, such as spectrophotometric methods and technologies to test cell culture conditions (cell density, viability, sugars, amino acids, metabolites, trace elements, vitamins, lipids, titer, molecule attributes and contaminants).

Objectives (cont.)

- Feedback control
  - Once the analytical method has been developed, parameters that have an impact on the attribute can be adjusted to bring the attribute to the desired level. The automated controls, algorithm or data analysis needed to perform such modelling and feedback control would be beneficial for a better control of manufacturing operations.
- Data Management
  - Finally, all these efforts result in an increasing amount of biochemical data that calls for the development of knowledge and data management tools essential to maximally explore these datasets and to push strategies for future concepts.

Pre-competitive nature

- Fundamental questions in cellular and systems biology, physiology and bioprocess science relevant to animal cells remain unresolved. A better control and higher prediction of cellular behaviour in the manufacturing of biopharmaceuticals can only be secured by increased basic and applied research.
- The cell culture process for the production of biopharmaceuticals has a big impact on quality and safety of the final product. This is well established for almost all quality attributes of biological molecules. Such attributes can relate to the molecule and its heterogeneity or to other process impurities:
  - Molecule heterogeneity originates from different proteolytic processing, post-translational modifications resulting in multiple glycoforms, diverse phosphorylation, additions, isomerisation, amino acid changes, oxidation, deamidation, acetylation, pyro-glutamate formation…
  - Process related impurities are host cell proteins, lipids and DNA; process reagents or process components that are challenging to remove such as antifoam, shear stress polymers (poloxamer), or media additives.

Expected impact

- This should lead to more effective products manufactured by predictive, economic and competitive processes and thus to more cost savings that benefit both industry and healthcare systems, whilst ensuring safety.
- The innovative analytical tools guarantee a more effective control and execution of the production phase and will lead to the qualitative and consistent manufacturing of biopharmaceutical therapies, increase supply chain reliability and reduce drug shortages, securing the delivery of these therapies to patients that need them.
- The biomanufacturing industry will be taken to the next higher level of competitiveness where biopharmaceuticals can be produced in a more efficient and cost effective way substantially increasing the significance the biopharmaceutical industry.

Suggested architecture of the project

- To be agreed with the Consortium is known
- Workpackages to be defined
- Duration of the project
  - The project is expected to last 48 months
- Budget
  - Total budget: 9.4 million euro

Expected contributions of the applicants

- develop innovative, automated highly-sensitive measurement tools and high throughput measurement methods for proteins, lipids, growth factors, amino acid, vitamins, nucleotides, CO2, O2, lactate, glutamate, ammonium, Lactate Dehydrogenase (LDH);
- develop high throughput tools to measure product quality attributes like purity, binding/activity, aggregation, glycosylation, phosphorylation, de-amidation, oxidation, MW, isomers;
- develop innovative micro-Scale Fed-Batch Cultures;
- develop rapid spectrophotometric methods for cell culture monitoring (Raman, NIR, Fourier Transform InfraRed spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR)) for In-Line CHO Cell Culture Monitoring;

Expected contributions of the applicants

- develop process analytical technology for biopharmaceutical products;

- are specialized in high-throughput screening (HTS) assays;
- are specialized in ‘omics’ method development (proteomics, metabolomics, glycomics…);
- are specialized in management, interpretation and modelling of complex data sets;
- are specialized in development and manufacturing of online probes and of devices for aseptic at-line sampling and rapid sample preparation.

The industry consortium is composed of the following companies:

- Sanofi
- GSK
- UCB
- Rentschler Biotech
- Pfizer
- Bayer
- Synthon

innovative medicines initiative

Expected (in kind) contributions of industry consortium

The expertise brought by the industry consortium to the project includes: high throughput, biopharmaceuticals, cell line development, robotics analytical testing, Quality by Design, sample preparation, sample technology, data handling tools, modelling, feed-back control.

- Program management
- Technical expertise and support
- Scientific knowledge
- Testing of the tools in the real conditions
- Qualification and Validation expertise
- Resources

What's in it for you?

Through this project, innovative analytical tools developed by academic partners and SMEs can get translated, validated and implemented at larger companies for commercial purposes, making the partners stronger in a highly competitive environment.

- Connection to and collaboration with leading companies that are experienced in the production of proteins using animal cells at large scale
- Conditional access to companies infrastructure
- Translation and validation of new technologies by testing in real conditions

innovative medicines initiative

Key deliverables of the full project

- Methods for high-throughput testing, novel analytical methods or feedback control and related elements that measure key attributes of cell culture processes (preferably technologies that are mature enough to be applied without the need of a dedicated scientist in the field of this application, and technologies that are GMP and designed to facilitate their validation);
- Novel miniaturized microfluidic-based technologies that allow real-time, automated, high-throughput product quality target product profile (QTPP) monitoring and control of cell culture processes;
- Online/at-line or in-line tools for parameter measurement;
- New technologies for cell culture development and the selection of these technologies so that they can be applied in GMP manufacturing to allow for PAT control for full scale;
- Best suited instruments and/or tools to perform the analytical methods;

Key deliverables of the full project

- Tools to measure Critical Process Parameters;
- Better process understanding;
- High-performance single-use sensors for the disposable bioreactors;
- Data management tools: tools for the integration of data and data management enabling the efficient use of the raw measurement data that will be generated by the new technologies and new applications of existing technologies;
- Knowledge database and the appropriate statistical tools to make useful knowledge of the data generated and to make use of this data to gain more in depth knowledge of the cell culture process, metabolic pathways and quality of product to be expected.

Questions?

Contact the IMI Programme Office
infodesk@imi.europa.eu • www.imi.europa.eu

www.imi.europa.eu
@IMI_JU