ACTIP

Animal Cell Technology Industrial Platform

Position Paper on Research and Innovation of Animal Cell Technology

in support of Europe's biopharmaceutical industry

Since the late 1980s, Animal Cell Technology has evolved from a fringe technology into a mainstream application, now accounting for more than 60 % of all new drugs being brought to market. Industrial Animal Cell Technology focuses on the active use and application of animal cell-based technologies in the development and production of biopharmaceuticals, virus-based biologics, gene therapeutics, in vitro tissues and organs and other preventative or therapeutic approaches. It encompasses mammalian cells including human cells and cells from animals such like birds, insects and others. The spectrum of cell types comprises continuous cell lines, diploid cells and cell lines as well as primary cells and stem cells.

Despite Animal Cell Technology having become a well-established platform for biopharmaceutical production, substantial issues remain, fuelling the need for research and innovation. Many fundamental questions in cellular and systems biology, physiology and bioprocess science relevant for technological applications remain unresolved. The complex higher eukaryotic cell and its specific interactive properties still remain largely unknown.
A sustainable future, however, is only secured by increased fundamental and applied research, since only a steady stream of new knowledge generates new product concepts and the establishment of new SMEs. Both SMEs and larger pharmaceutical companies, the members of ACTIP, recognize the importance of pure and mission-oriented fundamental research; they therefore propose long-term approaches/developments in research with interest for applications, whereby research support should be extended to a pre-industrial level.

ACTIP Interests

Research and innovation is the driver for growth. The denial of a sustainable support for fundamental research and training of scientists can have serious consequences. Today the European biopharmaceutical industry still suffers from the aftermaths of the aversion against technology innovation in the 1990s. This situation was recognized as a misjudgment not until the turn of the millennium. And also today a repetition is threatening. Beside the US, especially Asia and also the South American countries continue their efforts in supporting biotechnology and its application-oriented research. It is necessary to accept that the race against the clock is ongoing. For instance, the Indian biotechnology sector became a five billion-dollar industry by 2010.
India is ranked among the top 12 biotech destinations in the world and is the third biggest in Asia-Pacific in terms of the number of biotech companies. And the other countries are also pushing their investment activities. Europe should not stay behind.

Therefore, ACTIP encourages a specific stimulus to support the biopharmaceutical industry, in particular a balanced approach encompassing both fundamental and applied research. This would improve the competitiveness of Europe's biopharmaceutical industry on a global stage and would ensure that high-quality jobs will remain in Europe.

ACTIP Needs for Sustainable Research and Development in Animal Cell Technology

Despite major achievements over the past 20 years, there is a continuing requirement for intensive research and development in animal cell technology to support improving human health and European competitiveness. The dramatic increase in the cellular productivity and in protein yields from titers of 0.2 g per liter 10 years ago to more than 10 g per liter today for monoclonal antibody production gives a powerful example of the impact research and innovation can have in industrial applications. This is exemplified by the monoclonal antibodies which is the biggest present class of new biotechnologically generated therapeutics. Based on their molecular structure and associated binding properties, which give them the attribute of recognizing a nearly unlimited amount of antigens and markers, they have an almost inexhaustible therapeutic potential. For the year 2015 it is estimated that the monoclonal antibody market will have a volume of 64 billion US$. This amount comprises 38 % of the total biotechnological pharmaceutical market, which antibodies share with other proteins and vaccines and which will cover about 170 billion US$. From 38 billion US$ in 2009 a doubling of growth is prognosticated for the antibody market until 2015 (Business Insights, 2010).

Full social and economic as well as ecological benefits of technologies in development can only be achieved against a background of solid scientific infrastructure and the ability to identify, promote and translate science to products. ACTIP endorses the following further arguments in favor of an EU-wide effort:

- Clinicians and scientists from industry are calling for more animal cell based approaches and products. These products and approaches are used:
  - for the production and safety testing of biopharmaceuticals and vaccines;
  - in the development and production of virus-based biologics;
  - in tissue engineering;
  - in cell and gene therapy approaches;
  - in advanced research programs;
  - in human and other genome projects;
  - in support of personalized medicine approaches.

- A further development of basic skills and appropriate tools is essential in order to ensure continuous innovation achieve continuous innovation. This is exemplified by the explosive development of the single use technology to industrial scales.

- The development and manufacturing of cell-based processes for biologics is still far away from being predictable and reliable. Therefore the reliability of manufacturing and quality across the entire industry has to be enforced. An example is the Biomanufacturing Research Programme of the MIT to improvethe predictability and reliability of the biomanufacturing process.

- To take full advantage of the progress made in genomics and other ‘omics’ sciences, a more profound scientific understanding of cell biology, physiology and biochemistry.

- Gaining an understanding of the characteristics of critical manufacturing paths and medium ingredients is needed to increase the likelihood of successful processes. This is also perceived by the US Food and Drug Administration which launched an initiative by offering a grant to research projects that improve reliability, speed and quality of biopharm production processes in July 2011.

- A bundled European education concept for training of young scientists specialized in pharmaceutical biotechnology is a fundamental demand for a successful bio-industry and needs to be intensified consequently and systematically. This concept should also contain measures to increase the inflow of youngsters into the beta sciences.

Annex 1. Main ACTIP Research Interests (2011)

Cell Biology

- Development of new, mammalian regulatory-friendly cell lines (i.e. non-transformed and virus-free as well as virus-replicating for virus-based products and virus-non-replicating for protein products).
- Identification of factors involved in the immortalization of cells; establishment of conditional immortalization procedures.
- Improving stem cell technology.
- Development of new continuous cell lines from other vertebrates (e.g. avian) and alternative cell lines from invertebrate species (e.g. insects, crustaceans, sponges) for increasing product quality and efficiency as well as extending product applicability.
- Development of methods allowing isolation or induction of cell lines that keep their differentiated characteristics and that can be grown in large scale culture.
- Development of efficient methods for site-specific modifications in mammalian cells (other than embryonic stem cells).
- Improvement of efficient expression systems, especially for toxic proteins.
- Development of reverse genetics as a tool to develop defined RNA and DNA viruses for use in vaccinology and gene therapy programs.
- Systems biology and metabolic pathway engineering.
- Identification and removal of the bottlenecks in cellular secretion pathways including intracellular transport, intracellular degradation and folding.
- Identification of new regulatory elements and promoters for improved gene expression.

Process Technology

- Development of new rapid expression systems allowing predictable productivity combined with a short development time.
- Development of improved reliable process monitoring, minimum invasive measurement and control technologies.
- Development of improved bio-separation and product purification systems.
- Development of methods that permit the viable preservation of very large numbers of animal cells or organs.
- Development of technologies for the production of virus vectors and virus-like particles for the production of gene therapeutics.
- Development of reliable support systems for tissue and organ-like cell culture.
- New probes and reliable monitoring and control for single use cultivation systems. Classification of bags and ports etc. in categories for realization of standards.
- Improving understanding of manufacturing scale-up to improve reliability of pharmaceutical product manufacturing and quality.

Cells and Products

- Study of the *in vivo* function of posttranslational modifications in proteins including *N*- and *O*-linked glycosylation.
- Transdisease vaccinology with emphasis on both prophylactic and therapeutic vaccines.
- Continuing study of the immunology of vaccination.
- Development of new efficient adjuvants.
- Further development of nucleic acid vaccination for both human and veterinary applications.
- Identification of vaccine targets. Studies on host-pathogen interactions.

Gene and Cell Therapy

- Development of cell-targeted specific vectors.
- Development of safe, immune nonreactive cells.
- Development of new packaging technologies.
- Further development of expansion technologies for primary cells.
- Methods for the storage and *in vitro* and in vivo expansion of stem cells to be used in human therapy.
- Further development of cell-mediated gene transfer.
- New efficient downstream process technologies for the isolation of therapeutic virus-like particles.

Artificial Organs and Organ Replacement

- Studies leading to the development of artificial tissues and organs such as liver, pancreas etc.
- New bioreactor concepts of the generation of tissues *in vitro*.

Functional Genomics and Proteomics

- Methodology to translate genomics into diagnosis and therapies including improving methods of gene expression from newly discovered chromosomal DNA (verification of genes, exploration of gene function) and improvement of knock-out technology on cells to explore gene function.

In vitro Methodologies

- Development of new *in vitro* methods for the study of drug metabolism and pharmacokinetics.
- Development of cellular models for metastasis induction, tumor and normal function.
- Studies on cellular signal transduction pathways leading to the development of *in vitro* models that are used for the identification of lead compounds.
- Development of tools that will facilitate High Throughput Screening and assay development in today's drug discovery programs; preferably, this should be non-animal based methods, such as *in-vitro* and *in-silico* methodologies.

Virtual Methodologies

- Establishment of a virtual database of certified cells and vectors used in the industrial production of marketed therapeutics and diagnostics to foster R&D, exchange of material, standardization of cell lines and regulatory procedures.
- Extending genetic engineering for taming the complexity of living cells towards reliable synthetic tools by strictly characterizing the genetic sequences that perform needed functions, combining them into devices to achieve more complex functions, and inserting the devices into cells. As all life is based on roughly the same genetic code, synthetic biology could provide a toolbox of reusable genetic components leading to cells with a predictable property and behavior.

Annex 2. Educational Interests

A bundled European education concept for academic training of young scientists specialized in pharmaceutical biotechnology is a fundamental demand to ensure growth and competitiveness of Europe's biopharmaceutical industry. Education efforts need to be intensified consequently and systematically.

ACTIP, January, 2012