

## **New therapeutic molecules - A challenge for biopharmaceutical production**

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Recent developments in molecular modeling, genetic engineering, process engineering, and increased knowledge of human physiology have led to new therapeutic approaches. Recombinant proteins derived from microbial or mammalian expression systems are currently under clinical evaluation or already approved for treatment of various diseases. Frequently recombinant proteins are connected to various chemical agents, such as toxins or Polyethylenglycol (PEG), further broadening its therapeutic applications. In addition viral vectors and plasmid DNA (pDNA) are frequently used in gene therapy.

Biopharmaceutical production processes have become highly productive and can be reproducibly controlled in a narrow range. Therefore these production processes are capable of producing high quality biomolecules and fulfill all regulatory requirements. Bacteria, yeasts, filamentous fungi and mammalian expression systems are utilized as production platforms. Ongoing developments in transgenic plants and animals provide additional possibilities for expression of recombinant proteins.

In my presentation I will focus on large scale, cGMP production of antibody fragments and plasmid DNA (pDNA).

Currently more than 300 monoclonal antibodies (mAbs) are in preclinical or clinical development. Those mAbs are produced in mammalian expression systems. Those are limited by high production costs, long production time, risk of viral contamination and broad IP protection. Non-glycosylated antibodies or antibody fragments differ in functionality and physico-chemical properties from mAbs. Specificity, affinity and physico-chemical properties can be improved by genetic engineering. Alternative expression systems are evaluated for production of full length antibodies or antibody fragments.

Gene therapy and genetic vaccines promise to revolutionize the treatment of inherited (e.g. cystic fibrosis) and acquired (e.g. cancer) diseases. Since viral vectors are generally associated with numerous disadvantages when applied to humans, the administration of naked DNA, or DNA packed into lipo- or polyplexes emerge as viable alternatives. pDNA is produced in *E.coli* cells by batch or fed-batch fermentation. Cells are disintegrated by alkaline lysis in a batch or semicontinuous lysis system. Purification is based on a combination of different chromatographic principles. Undesired plasmid forms (oc-, linear) and other impurities (RNA, gDNA, host cell proteins and endotoxins) are removed effectively.