

GMP Production

The Fast-track to Product Development

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About Product Development

A key asset in the pursuit of new therapies is the production of drug substances for timely entry into preclinical and clinical studies, and later for in-market supply of products.

At Cytos Biotechnology, production of Good Manufacturing Practice (GMP) and technical quality Immunodrugs™ is essential not only for Cytos Biotechnology's own R&D programs, but also for those of its partners. The team at the heart of production employs about 35 scientists, engineers and technical experts with a track record of delivery over 10 years.

Achievements include:

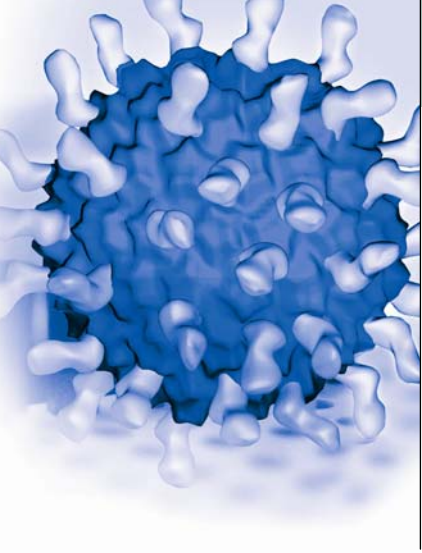
- development of manufacturing processes for four biogenetics, which were subsequently licensed to partners;
- development of manufacturing processes and analytical tools for Immunodrugs™ and Active Pharmaceutical Ingredient (API) production for preclinical and clinical studies;
- GMP and technical quality Immunodrug™ production for Cytos Biotechnology's own preclinical and clinical trials and supply to its corporate partners.

Cytos Biotechnology's GMP System

Cytos Biotechnology has its own GMP infrastructure, including a pilot facility for GMP compliant API development. The facility occupies an area of 380 m² including space for an 80 m² clean room class C. Regular inspections are performed by the Health Authorities and the company's corporate partners. Cytos Biotechnology holds a manufacturing license for Immunodrugs™ for clinical trials (phase I-III) from the Swiss Agency for Therapeutic Products (Swissmedic).

Pilot scale chromatography column

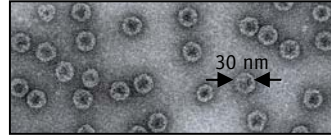




The Expression Technology

The VLP proteins are expressed in genetically-engineered *E.coli* cells where 180 capsid monomers spontaneously self-assemble into each VLP. Hence, VLPs produced through recombinant DNA technology lack viral/bacteriophage genomes and are replication incompetent. Assembly takes place in the cytoplasmic space of the *E.coli* bacterium. Production of the VLPs in a prokaryotic system ensures high yields and a timely and economic manufacturing process.

Electron micrograph of VLPs



(Electron micrograph by T. Bächli, University of Zurich)

3-Step Production

Immunodrugs™ are built around protein scaffolds, so called virus-like particles (VLPs), which are derived from certain viruses or bacteriophages (viruses able to infect bacteria). Such VLPs are then decorated *in vitro* with different antigens (see the companion backgrounder “Immunodrugs™ –The Technology Platform”).

Cytos Biotechnology’s approach involves an economic three-step production process:

- (1) bacterial fermentation,
- (2) VLP purification, and
- (3) coupling with the antigen of choice.

The Upstream Process

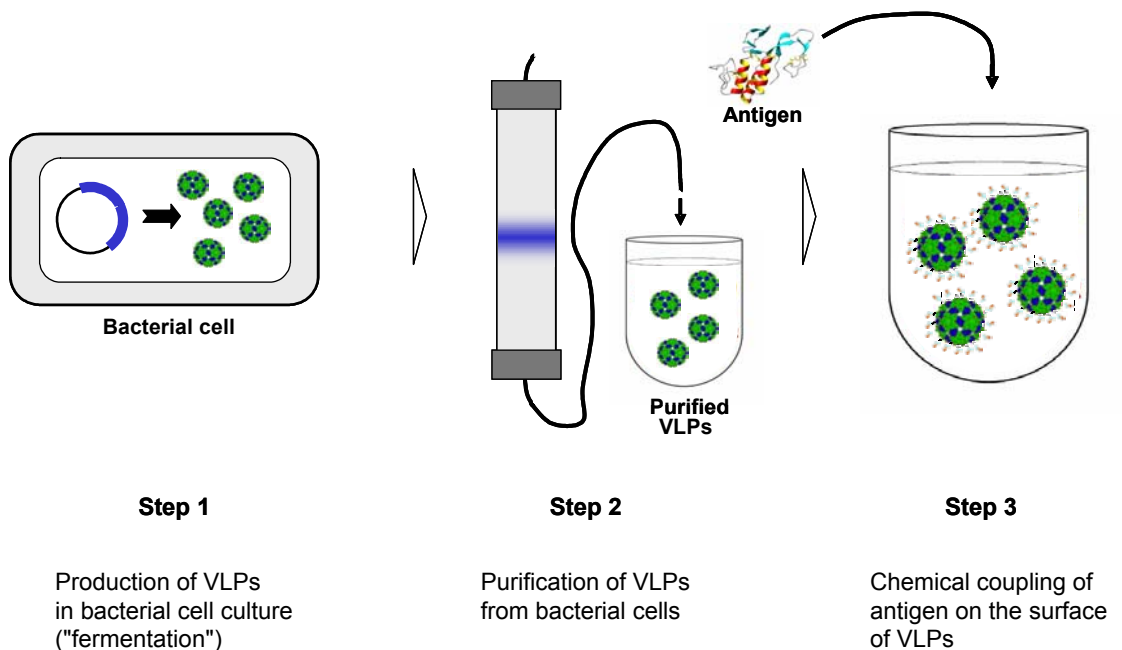
Through continuous improvement and long-term experience, Cytos Biotechnology has developed a carefully controlled, stable and highly consistent process for fermentation of VLPs in bacteria. A 50 liter-scale process with a process time of 28 hours has recently been implemented. Total yield of correctly folded and assembled VLPs from *E.coli* culture is approximately 8 grams per liter.

The Downstream Process

Bacterial cells containing VLP product are disrupted using high pressure homogenization. After clarification, the VLP material is further purified by chromatography. Purity of the product is > 99%.

Antigen Coupling

Using an optimized chemical coupling process, Cytos Biotechnology is able to couple recombinant proteins, synthetic peptides, and low molecular weight organic compounds such as nicotine. Antigens coupled to VLPs through covalent linkage maintain the accessibility and conformation necessary to evoke a strong, specific immune response *in vivo*.



Characterization and Controls

The development of the necessary analytics tools for characterization and control of Immunodrug™ production is a key factor in manufacturing a high fidelity product. A team of about 20 experts is dedicated to the characterization of API and manufacturing intermediates, and performs release of analytics under GMP.

Stability

The stability of each API batch is routinely monitored over an at least two year period under different storage conditions. Particle size as determined by light scattering techniques and integrity monitoring through HPLC methods have demonstrated the robust nature of Cytos Biotechnology's Immunodrug™ carrier.

GMP Production

Cytos Biotechnology has a dedicated team of experts who are responsible for production of API for its own clinical trials and those of its partner companies. The team adheres to the principles of GMP within Cytos Biotechnology's manufacturing facility. Overall quality and adherence to regulatory guidelines is assured by a small, highly experienced Quality Assurance (QA) group. The final decision concerning release of API batches is taken by the responsible person according to the Swiss Law on Therapeutic Products.

50-litre bioreactor



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