

ProBioCen
Intelligent Biopharmaceutical Solutions

•• Welcome to ProBioGen

ProBioGen is a renowned Contract Development and Manufacturing Organization (CDMO) and Technology Provider, with extensive expertise in cell line engineering, process development (upstream- and downstream process) and GMP manufacturing of biopharmaceuticals.

We are the partner of choice to assist you to successfully develop and manufacture your biopharmaceutical drug product candidate.

ProBioGen provides individual, state-of-the-art service packages (from cell lines to comprehensive biopharmaceutical manufacturing programs) coupled with proprietary technology platform offerings, to permit the optimization of biopharmaceutical production processes. Our technology innovations offer enhancement of cellular productivity and yield and improvements in product potency, quality and safety.

Our cutting-edge development services in combination with our quality manufacturing solutions enable your drug candidates to reach their full potential reliably and in a rapid timeframe.

We at ProBioGen are a knowledgeable and dedicated team with decades of biopharmaceutical, engineering and scientific experience. Our goal is to smoothly and successfully advance the development of your drug candidates. Our motivation is your success.





Product Characterization



Robust
Process
Development



Preclinical
Material
Manufacturing



GMP
Manufacturing



Release

•• Proprietary Core-Technologies Available

Designer Cell Lines: Platform replacing primary chicken cells in vaccine production

Designed cell lines, originating from the Muscovy Duck (**AGE1.CR®**) allow production of a wide spectrum of vaccine strains and viral vectors. An additional modification enhances the susceptibility and yield for some highly attenuated viruses (**AGE1.CR.pIX®**).

- Directed immortalization according to the defined risk guidelines of the FDA
- Development performed in GMP environment
- Master Cell Bank available
 - Extensively characterized according to EU and US guidelines
 - Free of adventitious agents and particle associated reverse transcriptase activity
 - Full documentation is available for source, cell history and raw materials
- High yield, fully scalable and chemically-defined production processes for vaccine viruses established
- Successful technology transfers and developments
- Permissive for wide spectrum of animal and human viruses, including influenza and pox viruses
- Customized packaging cell lines for replication-deficient vectors

GlymaxX®: Elegant Glyco-Engineering to boost the ADCC activity of antibodies

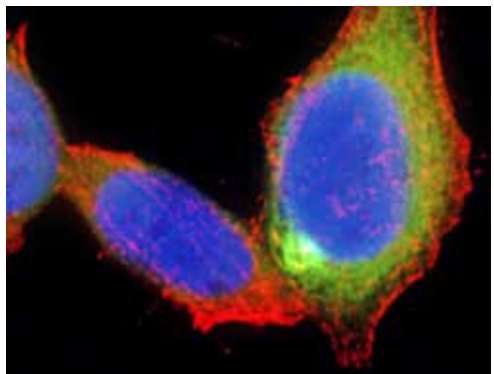
This technology is based on the heterologous, cytosolic expression of a bacterial enzyme that redirects the *de-novo* fucose synthesis pathway towards a sugar-nucleotide that cannot be metabolized by the cell. The enzyme mediates the secretion of antibodies that are devoid of core-fucose. The resulting modification of the glycostructure of IgG1 antibodies enhances their binding to NK cells – the dominating effector cells in ADCC. Consequently, the potency of the modified antibodies, directed against tumor or infected cells, is substantially increased.

- Enables production of fucose-depleted antibodies from preexisting producer clones
- No adverse effect on production parameter
- No culture additives necessary

Human Artificial Lymph Node: Prediction of immune responses to drug candidates

The proprietary human Artificial Lymph Node (HuALN) model is used for testing of immune reactivity and immunotoxicology *in vitro*. The model emulates both humoral and cellular immune responses and serves as meaningful system, providing additional information in lead optimization and preclinical testing (e.g. risk evaluation and dose-finding).

- Comparative immune reactivity of peptides, proteins, DNA vaccines, etc.
- Adjuvant testing
- Immune modulation
- Vaccine potency



•• Cell Line Development

Stable, High-Yield Mammalian Producer Cell Lines

ProBioGen's pharmaceutical cell line development platform is based on proprietary expression vector technology, optimized clone selection and screening workflow complemented by an in-house chemically defined cell culture media platform.

Our preselected CHO host cell lines (based on DG44 and K1 strains) fit perfectly into our rapid up-scale processes and achieve excellent product yields. Stable transgene expression is maintained for at least 60 population doublings.

For products which require manufacturing in human cells, our fully documented, GMP compliant Human Neuronal Precursor (AGE1.HN®) cell line is an available, alternative cell substrate. It supports specific and complex glycostructures (highly sialylated, highly branched) and provides a system for the production of glycoproteins and antibodies with modified activity, stability or susceptibility for proteolysis.

Producer cell lines developed at ProBioGen fully satisfy the requirements of the relevant ICH guidelines (Q5A and Q5B) as well as additional relevant regulations regarding cell substrates and expression constructs applied for GMP manufacturing of biologics. ProBioGen provides full regulatory support to its clients for all aspects pertaining to producer clones.

Services

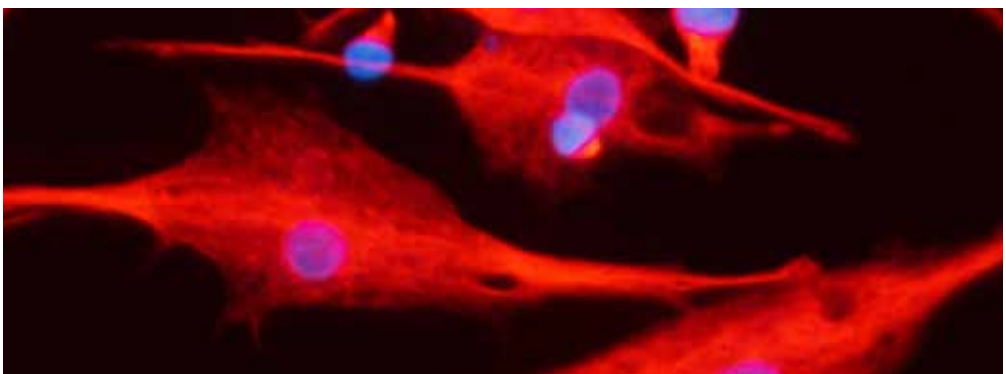
- Gene, transcript and signal peptide optimization and cloning
- Fast Cell Line Development (16–18 weeks)
- Simultaneous generation of producer lines for multiple product candidates
- Full documentation of producer lines
- Analysis of expression stability, gene copy number and RNA level
- Seamless transfer of Cell Line- and Process Development (integrated, Media optimization, early Process Development parallel to Cell Line Development)

Technologies

- Proprietary vector technology
- Automated cloning
- Extensive product analytics including biochemical and structural analytics
- Metabolic profiling/metabolic engineering
- Host cell engineering (Productivity, Product Properties)
- GlymaxX®

Product experience

- Monoclonal antibodies
- Antibody fragments
- Enzymes
- Cytokines
- Fusion proteins
- Growth factors
- Blood clotting factors



•• Process Development & GMP Manufacturing

Economical, Disposable, Transferable Manufacturing Service

A proven track record and experience since 1994 makes ProBioGen a competent partner in the field of contract manufacturing of antibodies and recombinant proteins. Relying on our expertise, state-of-the-art equipment and highly skilled staff, we develop robust and economical processes as a basis for rapid and reliable GMP manufacturing.

ProBioGen possesses the manufacturing authorization from the competent authority and meets the quality standards recommended by EMA and FDA. Multiple inspections and customer audits have confirmed our high quality standards and our compliance to the international GMP requirements.

Services

- Proprietary chemically defined Media Platform
- Cell banking (characterization of MCB and WCB subcontracted)
- Process development
 - High density cell cultivation
 - Cutting edge product yields
- Preformulation
- Stability testing of drug substance
- Manufacturing of preclinical and GMP-grade material
- GMP release testing
- Protein and glycosylation analysis
- Validation and transfer of analytical methods
- CMC documentation
- Regulatory support (for IMPD/IND and MAA/BLA)

Facility capabilities

- Fermentation capacity and capabilities are state-of-the-art
 - Disposable bioreactor technology, stirred tank bioreactors
 - Up to 500L under GMP currently (capacity extension underway)
 - Fed batch processes and ATF

Quality standard

- ISO 9001:2008 certified
- GMP-manufacturing license according to EMA standards

Product experience

- Monoclonal antibodies
- Antibody fragments
- Enzymes
- Cytokines
- Fusion proteins
- Growth factors



•• Cell-based Assays & Services

Product Potency, Functionality, Mode of Action and Cell Characterization

Bioassays provide key information about drug-related bioactivity at an early stage of drug development and lead candidate selection. We can provide what few others will – sophisticated cell-based activity assays, binding assays and cellular analytics supporting product characterization and API release testing. Our testing services can perform qualification and/or full validation for pharmaceutical and cosmetic products.

Antibodies

- Antibody-dependent cellular cytotoxicity assays (ADCC)
- Complement-dependent cytotoxicity assays (CDC)
- Cytotoxicity testing
- Fcγ-receptor binding and ligand binding assays (ELISA format)

Type I Interferons

- Antiviral assays (AVA), according to the European pharmacopoeia
- Commercial and proprietary reporter gene assays
- Anti-proliferation assays

Follicle Stimulating Hormone (FSH)

- Cell-based assay for FSH activity (replacement of the Steelman-Pohley rat ovary test)

Other proteins

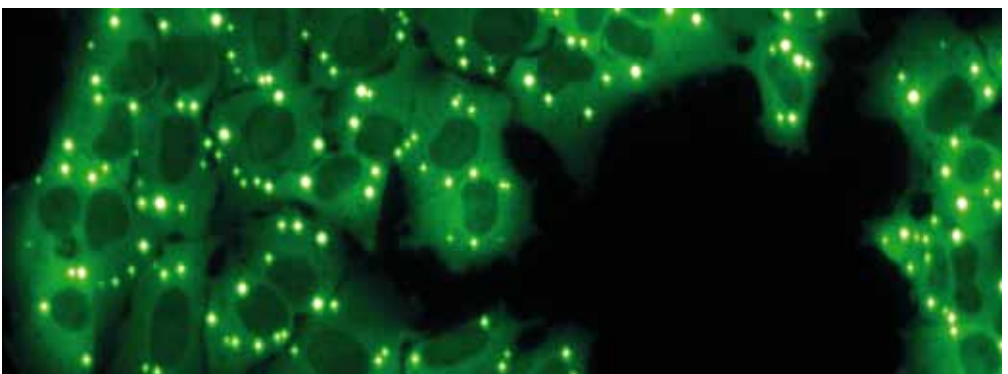
- Cell proliferation assays (e.g. growth factors)

Immune functional testing

- Based on primary human PBMCs and PBMC derived cells:
 - Dendritic cell assays (DC assays)
 - Induced human lymphocyte assay
 - HuALN to predict immunogenicity, immunotoxicity and immunofunction
- Granzyme B ELISPOT
- Immunomodulation (Cellular MHC up-regulation)

Cellular analytics, cell preparation & characterization

- Flow cytometry (CD markers, cell cycle, apoptosis)
- Human primary cells (preparation, separation, characterization)
- Cell line characterization and kinetics according to 'Good Cell Culture Practice' (GCCP)
- Microscopic imaging, immuno-fluorescence services
- Cytotoxicity testing of medical devices according to ISO 10993-5



•• Contact Us

ProBioGen will be pleased to discuss with you possible options for your product development project. We have a well established reputation for our royalty-free, fee-for-service based cell line development services and our robust and economical manufacturing processes, including sophisticated product analyses and cell-based activity assays. We take great pride in our outstanding service quality, scientific excellence, and pragmatic problem-solving skills. We do our part to enable client success.

ProBioGen AG

Business Development
Goethestrasse 54
13086 Berlin
Germany

Phone: +49 (0) 30 924 006-0

Fax: +49 (0) 30 924 006-19

Email: cmo@probiogen.de

www.probiogen.de

Disclaimer

This document contains information that is compiled with the latest scientific and technical knowledge and is believed to be correct at the time of print. ProBioGen does not provide any warranty, express or otherwise, on the accuracy of the content or any results obtained through the use of such information. Furthermore, no information herein is intended or should be constructed as a recommendation to infringe any existing patents.

© 2013 ProBioGen AG, Berlin