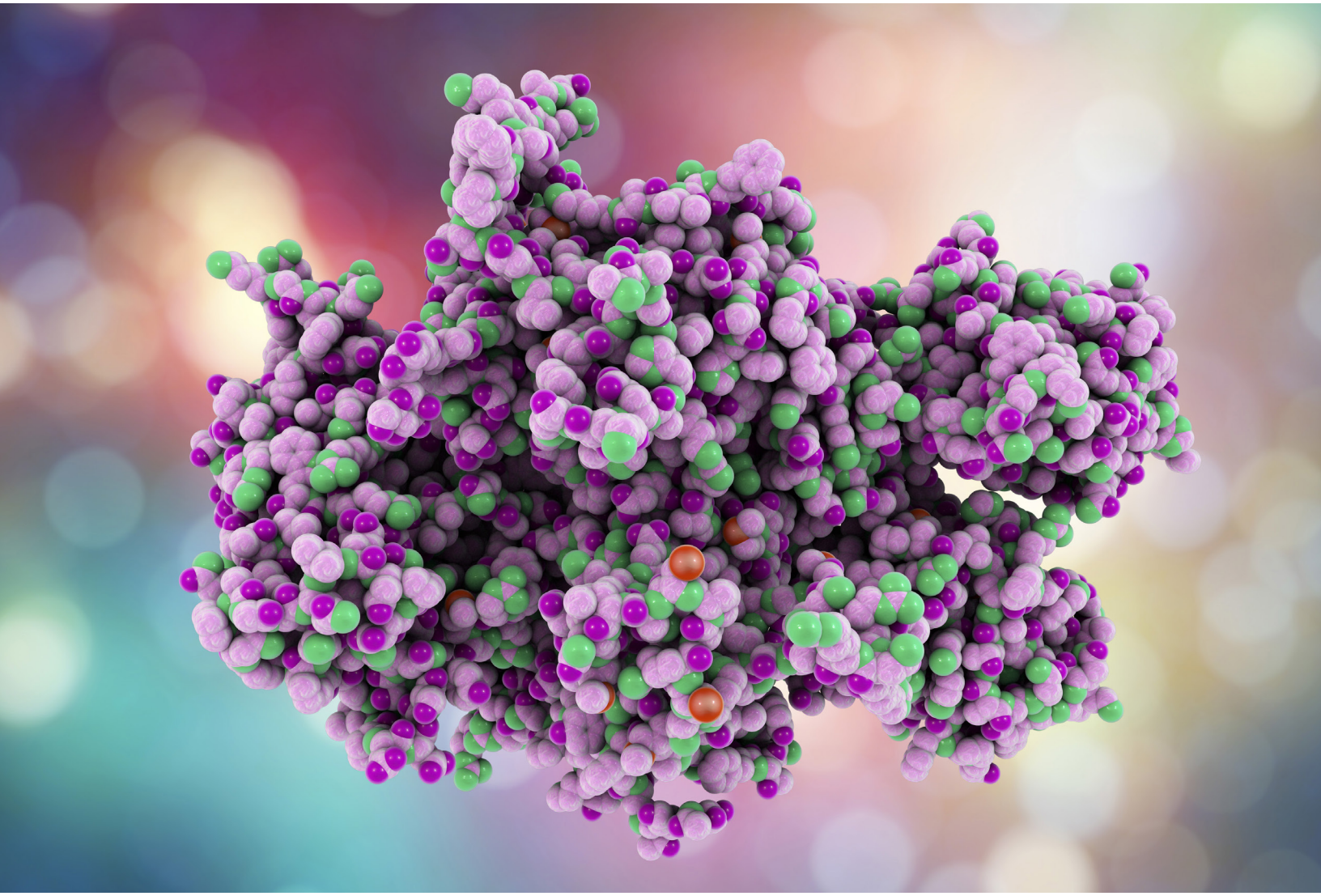
LakePharma
The Biologics Company

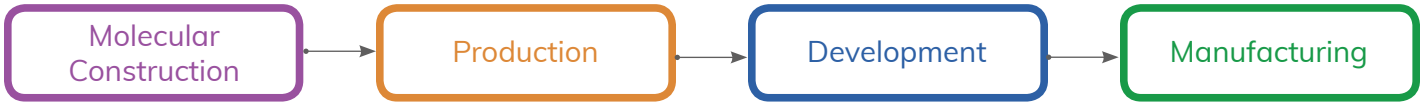


Mammalian Recombinant Protein Production and Manufacturing Services

- Molecular Biology
- Transient Protein Production & Purification
- Stable Cell Line Development
- Process Development and microBiomanufacturing™

Integrated Solutions from Molecular Construction to GMP Manufacturing

Recombinant proteins are an important category of biologics. LakePharma offers integrated solutions for mammalian recombinant proteins including molecular construction, transient and stable protein production, research cell bank (RCB) and master cell bank (MCB) development, process development, and GMP manufacturing utilizing the microBiomanufacturing approach.



- Gene synthesis
- Vector construction and molecular cloning
- Plasmid DNA production and purification

- Transient mammalian expression
- Purification

- Stable cell line development
- Upstream, downstream, formulation, and bioassay development

- Process transfer and engineering run
- microBiomanufacturing

25,000+	expression vectors constructed
23,000+	protein purifications performed
700+	cell lines generated
500+	organizations served

Molecular Biology Services

Molecular construction is the first step of making recombinant proteins. LakePharma offers various starting points for clients including gene synthesis and plasmid construction as well as reconstructing vectors for antibody expression via hybridoma sequencing.

Gene Synthesis and Molecular Cloning

- Client can provide sequences or templates as starting materials
- Available cassette option
  - In-house
  - Commercially available
  - Client-provided
- Deliverable includes miniprepped DNA and sequence confirmation of the gene of interest
- Turnaround time: 1- 3 weeks

Plasmid DNA Production

- pDNA production at various scales from 0.5 mg to >50 mg with three endotoxin level options
  - Transfection grade (<100 EU/mg)
  - Low-endo grade (<10 EU/mg)
  - Endofree grade (<1 EU/mg)
- Standard quality control includes sequence confirmation and agarose gel electrophoresis
- Additional add-on services
  - Additional sequencing & aliquoting
  - Glycerol stock generation
  - Restriction enzyme analysis
- 23-hour DNA purification service from the receipt of bacterial pellet to delivery is available at multiple scales

Hybridoma Variable Region Sequencing

- Client can provide frozen hybridoma cell pellete or purified mRNA
  - 1 week turnaround time
  - Constant region sequencing also available
- A variety of isotypes and species available:
  - IgG, IgM, IgA
  - Mouse, rabbit, hamster, transgenic mouse, primate B cells

Mammalian Transient Protein Production with Proprietary TunaCHO Platform

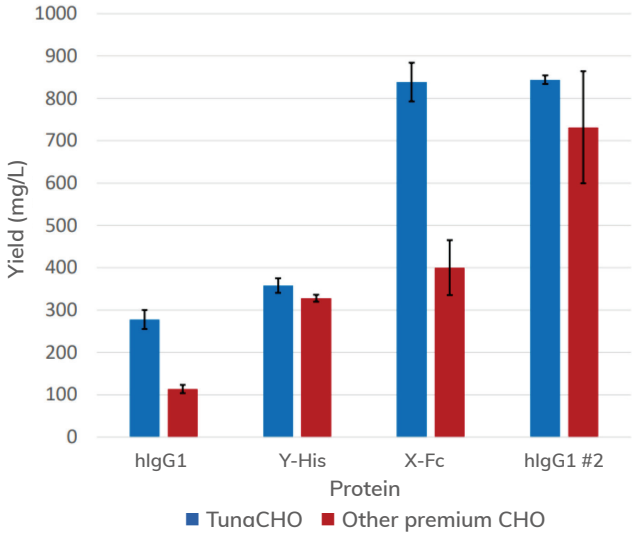
In this stage, typically small quantity of recombinant proteins are needed quickly for various optimizations and testing. To meet this need, LakePharma offers the proprietary TunaCHO™ transient protein platform—derived from the CHO-K1 parental line—which provides high yield, robust performance, and consistency.

Key advantages:

- **High productivity**—yield can reach 2 g/L
- **Consistent and scalable performance** —similar results observed from 10 mL to 20 L production scale
- **High-throughput**—can be used in 96-block production of antibodies

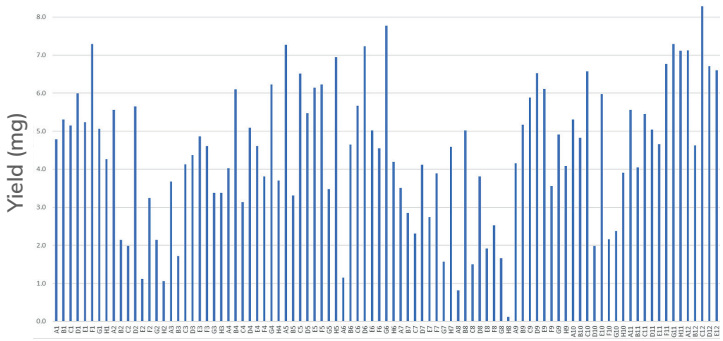
Other available cell lines include:

- LakePharma's proprietary Tuna293™
- ExpiCHO™
- Expi293™



Higher yield of recombinant human IgG1, Fc-fusion protein, and His-tagged non-antibody protein were observed in the TunaCHO process.

High-throughput Antibody Production using TunaCHO platform



Shown here are 85 recombinant antibodies produced in 10 mL TunaCHO process with Protein A purification. The average yield observed is 4.2 mg per 10 mL culture.

Custom Protein Purification Service

- Affinity tagged and tagless protein purification
- Purification from crude extracts/serum/tissues
- Proteolytic Digestion for affinity tag removal
- Scale-up capabilities
  - Up to 300 L of conditioned media
  - Up to 100 L of cell paste
  - Columns from 1 mL to 30 L
- Endotoxin options: <100, < 10, < 1 EU, and < 0.1 EU/mg

Proprietary CHO-GSN Package for Stable Cell Line Development

CHO lines have been preferred due to advantages in culture condition adaptability, gene plasticity, and ability in post-translational modifications. LakePharma's CHO-GSN™ parental cells, a GS knockout derived from CHO-K1, offers robust performance. Together with proprietary vectors and strong expertise in stable cell line development, LakePharma's complete CHO-GSN package offers fast stable cell line development in 24-34 weeks.

CHO-GSN™ Parental Cells +

- Suspension adapted
- Animal product-free culturing
- Compatible with chemically defined commercial media

Proprietary Stable Expression Vectors +

- High expression stable expression vectors
- Bicistronic vectors for antibodies
- Monocistronic vectors for proteins
- Vectors for 3+ chain molecules available

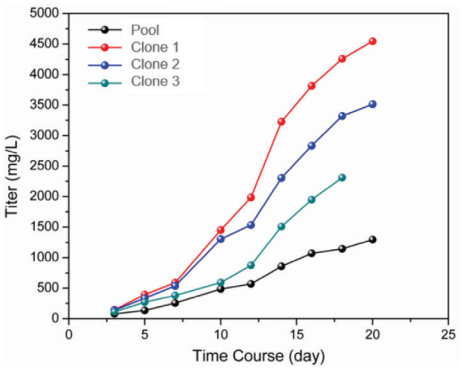
Stable Cell Line Generation Expertise =

- Proprietary methods for cell line development & stable pool selection
- Experience in selecting and maintaining stability

Final Stable Cell Lines

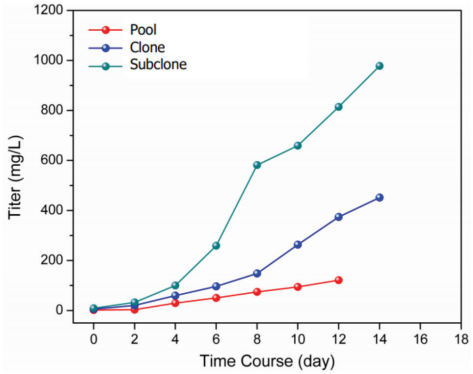
- Demonstrate high titer and robust performance
- Does not require extensive screening to obtain quality clones to move forward
- High tolerance with shear
- Generational stability >80 generations demonstrated

mAb Titer Profile



Titer of mAbs produced using CHO-GSN can reach >3 g/L in shake flasks.

Bispecific A Titer



Higher titer for a difficult-to-express, bispecific antibody was achieved after pool enrichment using CHO-GSN platform.

Bioanalytical Characterization

Full line of protein analytical services to ensure protein identity, quality, stability, and developability.

Primary Structure

- Intact mass
- N-terminal sequencing
- Sequence confirmation

Biophysical Chemical Analysis

- Aggregation
- Thermostability
- pI determination
- Charge variant profiling
- Purity and size

Post Translational Modification

- Glycosylation
- Oxidation
- Phosphorylation

Formulation & Stability Analysis

- Formulation screening
- Excipients screening
- Long-term and accelerated stability studies

End-to-End Services for CHO-GSN Cell Bank Generation

GS STABLE VECTOR SCREENING

LakePharma Proprietary Stable Expression Vectors

- Custom designed for CHO-GSN platform
- Non-CMV promoters
- Thorough QC & sequence confirmation

STABLE POOL GENERATION

CHO-GSN Platform

- CHO-GSN parental cells
- MaxCyte® electroporation
- MSX as high selection pressure

STABLE CLONE GENERATION, LIMITED DILUTION + TITER SCREENING

CHO-GSN High Titer Clones

- High titer clones obtained without intensive screening
- Option to apply the ambr® 15

STABLE SUBCLONE GENERATION, LIMITED DILUTION + TITER SCREENING

CHO-GSN High Titer Clones

- Second round allows for obtaining monoclonality proof without compromising risk of loss of high yield during clone generation
- Use of Solentim™ Cell Metric for confirmation of monoclonality

RESEARCH CELL BANK (RCB)

Final Research Cell Banks

- High titer clones selected
- Monoclonality ensured
- Tolerance to shear force and other bioreactor conditions tested

RCB AND PRODUCT CHARACTERIZATION

RCB Characterization

- Sterility, Mycoplasma, and copy number determination
- Cryopreservation and stability study over 80 generations
- Generate sufficient stability data to support shelf life of clinical material

MASTER CELL BANK

Upstream Process Development

Preliminary Upstream Media and feed screening

Best clone, media, and feed screening

Sartorius ambr® 15 Microbioreactor Clone & Parameter Screening

DoE for media and feed screen

2 L Single-Use Bioreactor Confirmation Run

Stir tank results, DOE Perfusion Testing

50 L Single-Use Bioreactor Scale Up

Scalability

Downstream Process Development and GMP Manufacturing

GMP Process Design & Development

Proof of concept

Small-scale models

Seamless tech transfer featuring single use technology

Analytical Development

A wide range of QC analytical and bioassays to support production and analysis of protein therapeutics

In-process control to monitor yield and quality

GMP Manufacturing

microBiomanufacturing approach: small scale, single use, and flexible

GMP biorepository service for long term sample storage

Working with LakePharma

- Comprehensive technology platform
- Access to integrated solutions from discovery to manufacturing
- Technical consultation with experts specialized in biologics discovery and development
- LakePharma's online client portal—the Data & Process Management System—allows 24/7 access to project information (timelines, data, team communications)
- Strong project management with regular project updates

LakePharma Provides Integrated Solutions for Biologics Development

LakePharma
The Biologics Company

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