



Keystone™ Expression System

RESPONSIVE. RELIABLE. RESOURCEFUL.

Cytovance® Biologics is a leading contract development and manufacturing provider of both mammalian and microbial service offerings to the biopharmaceutical industry.

R&D Services include cell line development using Freedom® CHO-S® (Life Technologies), microbial strain development using GeneGPS™ Codon Optimization Technology (DNA2.0) and Cytovance® Biologics' Keystone™ Expression System, research cell bank production, process development, process optimization using statistical Design-of-Experiments (DoE), technology transfer, scaled-down model development and process characterization using a QbD framework.

Each customers' project is customized to match the required scope and clinical phase. In-house mammalian and microbial platform processes enable efficient movement from development to commercialization.

A strong **Analytical Development** team is integrated into R&D Services and ensures a seamless transition into Quality Control for in-process and release testing. Core competencies include method development, method transfer, method optimization, method qualification, preformulation development, and product characterization. For early phase customer needs Cytovance offers Manufacturability Assessments for antibodies, other mammalian expressed proteins and Expression Feasibility Studies for microbial expressed proteins.

Since its inception 10 years ago in Oklahoma City Cytovance® Biologics has successfully manufactured a wide array of biological products for our customers in the U.S., European, and Asian markets.

Cytovance® Biologics are your partners for mammalian and microbial process development and cGMP biopharmaceutical manufacturing from the bench to commercialization.



Our Services

Product Types

Monoclonal Antibodies, Recombinant Proteins, Enzymes, Transgenics, Fragment Antibodies, Fusion Proteins, Scaffold Molecules, Vaccines, and PEGylated Proteins

Expression Systems

Mammalian, Microbial

Expression Platforms

Freedom® CHO-S® (Life Technologies), Keystone™ Expression System

Mammalian Cell Line Development

Transfection, Clone Screening & Selection

Microbial Cell Lines

Bacterial & Yeast Cell Lines
Strain Screening & Selection

Process Development

Batch/Fed-Batch Development, Scale Up & Harvest Optimization, Purification Development

Analytical Method Development

Impurity Testing, In-process testing, Assay development/Transfer, Qualification

cGMP Cell Banking

Microbial & Mammalian

cGMP Manufacturing for Mammalian Production

100L Mammalian Bioreactor Suite
500L Mammalian Bioreactor Suite
1000L Mammalian Bioreactor Suite
5000L Mammalian Bioreactor Suite*
50L, 200L, 250L & 1000L SUBS

cGMP Manufacturing for Microbial Production

10L Microbial Fermentation Suite
200L Microbial Fermentation Suite
1000L Fermentation Suite

cGMP Fill/Finish

Automated Liquid Vial Filling

Process Characterization

Process Characterization Master Plan, Risk Assessment, Scale-Down Model Development & Qualification, Design-of-Experiments (DoE)

Process Validation

Process Validation Master Plan

Supporting Services

ICH Stability Studies, Regulatory, CMC Support & Project Management

*coming soon

Keystone™ Expression System

***E. coli* platform designed by Cytovance personnel based on extensive lessons learned from 10 years of contract biomanufacturing experience.**

- Quality by Design approach from gene construction to GMP manufacturing
- Proprietary vectors, hosts, and platform fermentation processes are designed to fit each other for efficient and robust scale-up
- Efficient work-flow enables MCB initiation with growth and titer data from a fed-batch process that is scalable and manufacturable

Cytovance’s Toolbox Approach

HOSTS
 Each Keystone™ host was built to be robust and circumvent common scale-up problems (such as genetic instability and nutrient deficiencies).

Keystone™ hosts include:

1. BL21 derivatives enhanced for periplasmic expression
2. BLR(DE3) with repaired nutrient deficiency
3. The only available non-DE3 K-12 compatible with the T7 promoter
4. Platform K-12 host with multiple protease knockouts

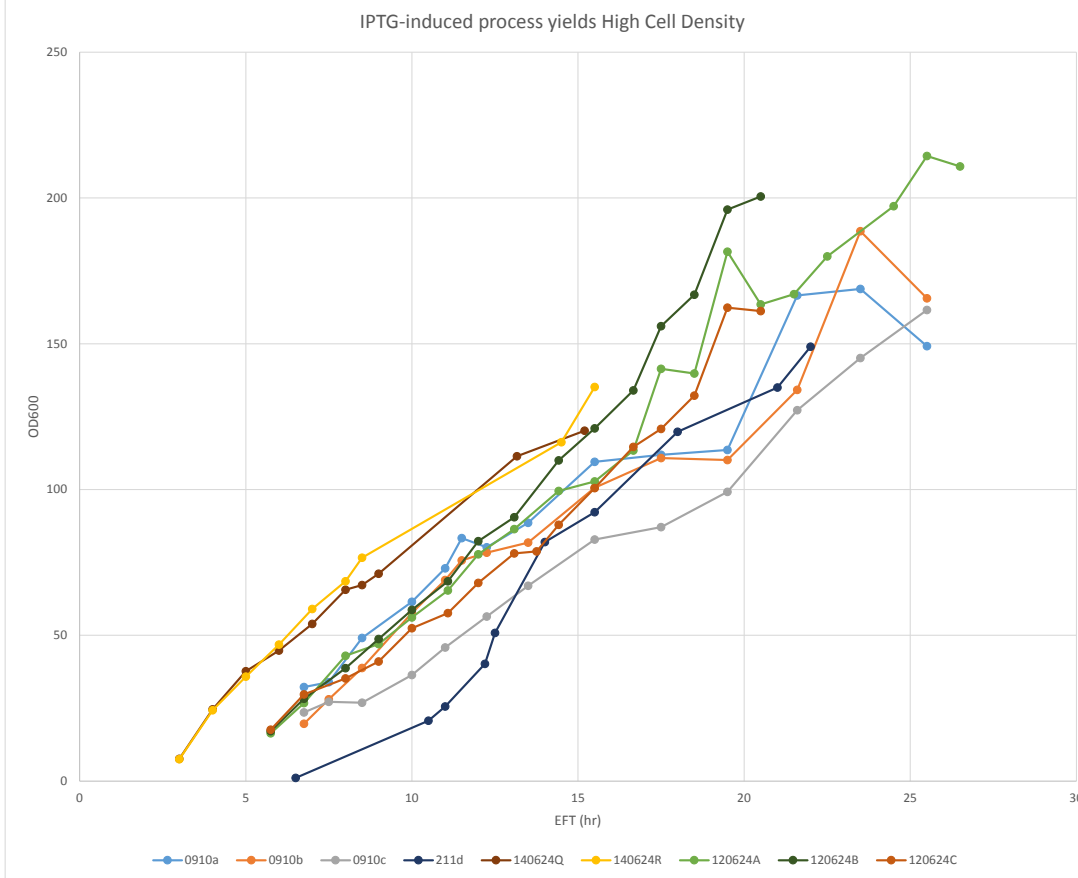
Platform fed-batch processes yields high cell density with a variety of products and enable choice of a strain for cGMP MCB production and initiation of process development with fed-batch titer and growth data.

DNA

- Keystone™ Vectors were custom-built by Cytovance
- Two Promoters can be tuned to accommodate a variety of products
- Efficient primary screen is performed in a 24-well dish (3 mL culture volume)
- Platform fermentation screening processes fit each promoter and yield high cell density

Sample *E. coli* Strain Development Project

- Design 12 plasmids: 2 promoters, 2 compartments, 2 periplasmic leaders, 2 copy number
- DNA2.0 synthesize codon-optimized genes with GeneGPS™ and perform Electra™ cloning using Keystone™ vectors
- Transform 2 *E. coli* hosts per plasmid; B and K-12 lineages
- Evaluate 24 strains in 24-well dish by SDS-PAGE (soluble, insoluble, media fractions)
- Advance 8 best strains to shake flask screening for confirmation
- Advance 4 best strains to platform fed-batch fermentation processes
- Based on fed-batch data, advance best strain to process development and cGMP MCB production





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