

# CHO+PLUS

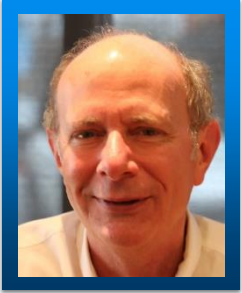
HI-PERFORMANCE CELL LINES

**Presentation to B2DG**

August 17, 2021

**Contact:** Larry Forman, Founder and CEO | **Email:** [Larry@CHO-Plus.com](mailto:Larry@CHO-Plus.com) | **Phone:** +1 (845) 380-6993  
**WeChat:** LarryForman | South San Francisco, California | USA

# CHO+Plus Team



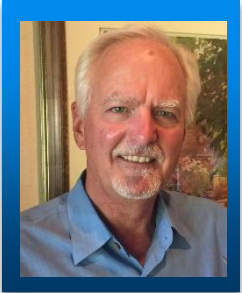
## **Lawrence Forman, Founder and CEO**

40+ years cell culture process development;  
Genentech, CuraGen; process development consultant,  
GMP manufacturing



## **Lawrence Chasin, Co-Founder & Chief Scientific Advisor**

Professor of Biological Sciences, Columbia University  
Pioneered field of mammalian cell genetics;  
Created two CHO cell lines used by most of  
biopharmaceutical industry



## **James Panek, COO**

40+ years in the biopharmaceutical industry;  
Management roles included:  
SVP Product Operations at Genentech;  
CEO at VaxGen;  
Co-CEO at Celltrion



## **T. Shantha Raju, VP and Head of Protein Sciences**

25+ years in the biopharmaceutical industry;  
Management roles included:  
Head of R&D at Venn Therapeutics  
Senior Director at Medimmune  
Scientific Director at Janssen Pharmaceuticals



## **Kathy Ngo, Senior Scientist. Cell Engineering**

Aridis Pharmaceuticals;  
SME for development of CRISPR-based technology for mAb  
production enhancement in CHO cell lines;  
Developed microfluidics-based HTS technology for CHO  
clonal selection

# **WE'RE HIRING!**

## **Senior-level Molecular Biologist**

# Market

## Therapeutic proteins

- Antibodies used to treat human diseases like cancer and rheumatoid arthritis
- Other proteins used to treat heart disease and other disorders
- Rapidly growing \$150 Billion dollar market



PROMISING NEW TREATMENTS  
FOR A RANGE OF DISEASES

# Problem

- High production costs
- High infrastructure costs
- Capacity limitations associated with commercial production

# Industry Solution

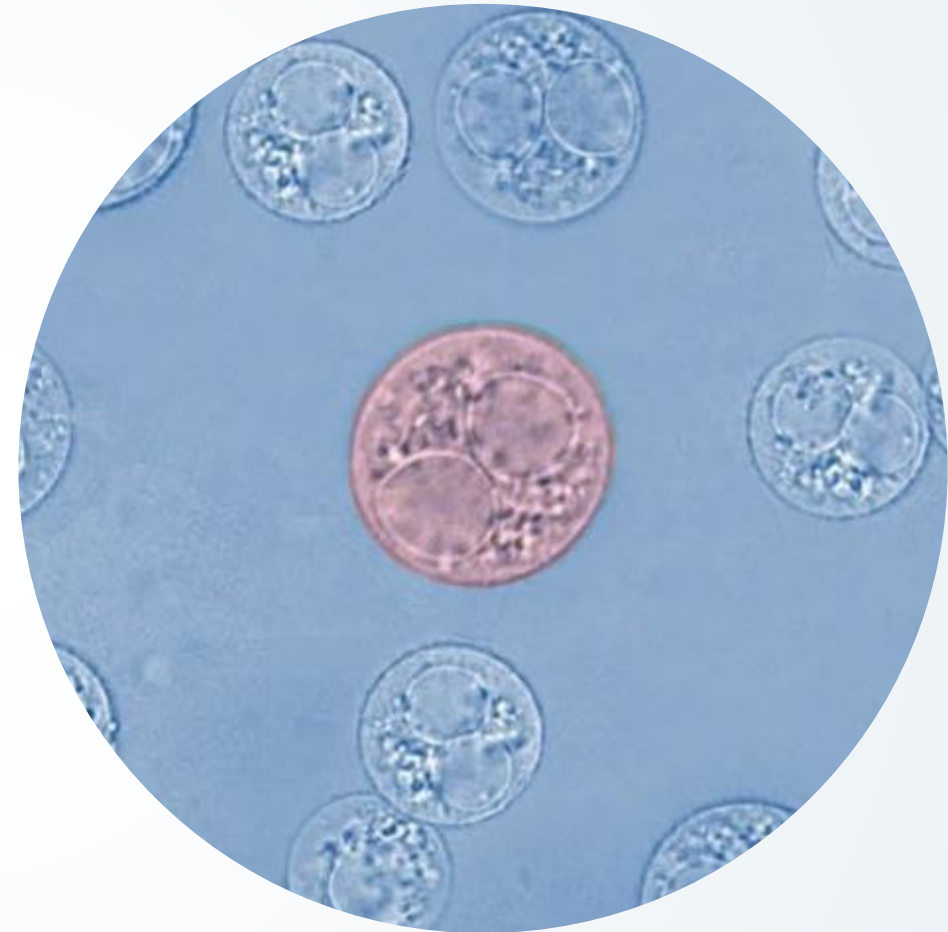
Pharmaceutical companies are constructing billion-dollar factories to keep up with increasing demand



EXPENSIVE INFRASTRUCTURE

# CHO+Plus Solution

- Patented and patent-pending technologies
- Improve productivity at the cell level
- Have a top-five pharmaceutical company partner
- In negotiations with others



HIGH-PERFORMANCE CELLS

# Business

Technology Provider:

- Create cell lines for pharma customers
- Annual technology license fees
- Royalties on product sales
  
- Small scale operation with high profit margins
  
- High likelihood of being acquired



HIGH-MARGIN,  
LABORATORY-SCALE OPERATION

# Vast Worldwide Biologics Market

## CHO+Plus Target Customers

Pharmaceutical Companies and Contract Manufacturers of Therapeutic Proteins

**\$316  
Billion**

## Rapidly Growing Worldwide Therapeutic Protein Revenues

100 new proteins per year approved by FDA  
2,000 new active INDs worldwide each year  
>10,000 new cell lines every year

**\$150  
Billion**

## Target Proteins

Antibodies, Enzymes, Hormones/Growth Factors  
Biosimilars, Hard-to-Produce Proteins, Blood Clotting Factors, Antibody-Drug Conjugates

**2018**

**2025**

# Problem: Expensive Factories, Stagnant Productivity



EXPENSIVE INFRASTRUCTURE

High-cost facilities and processes limit capacity of therapeutic protein production

Limited productivity advancements in the last 20 years

Current capacity will not meet future needs

## Current Therapeutic Protein Production Solution

Build more factories, costing up to \$2 Billion each



Productivity Has Plateaued

0.1 g/l

1985

1995

2005

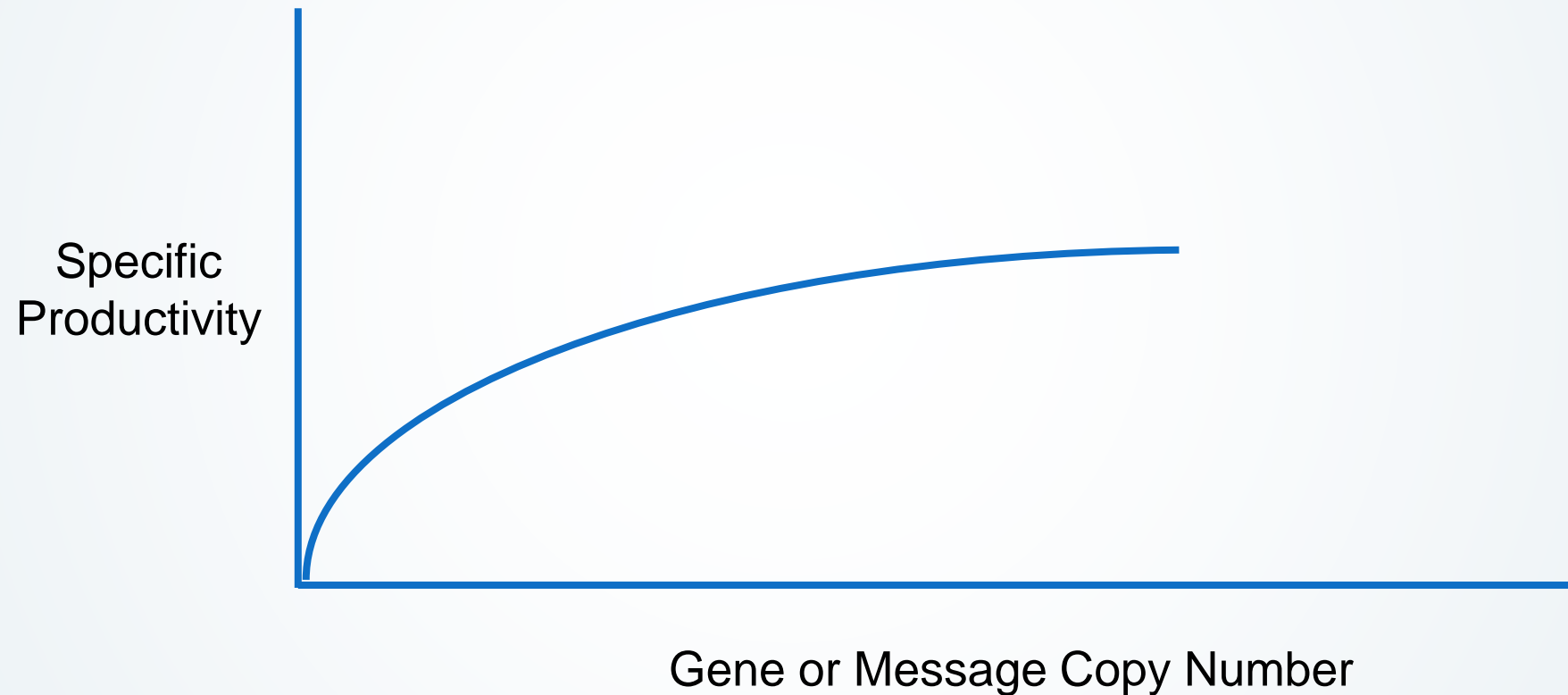
2015

4 g/l

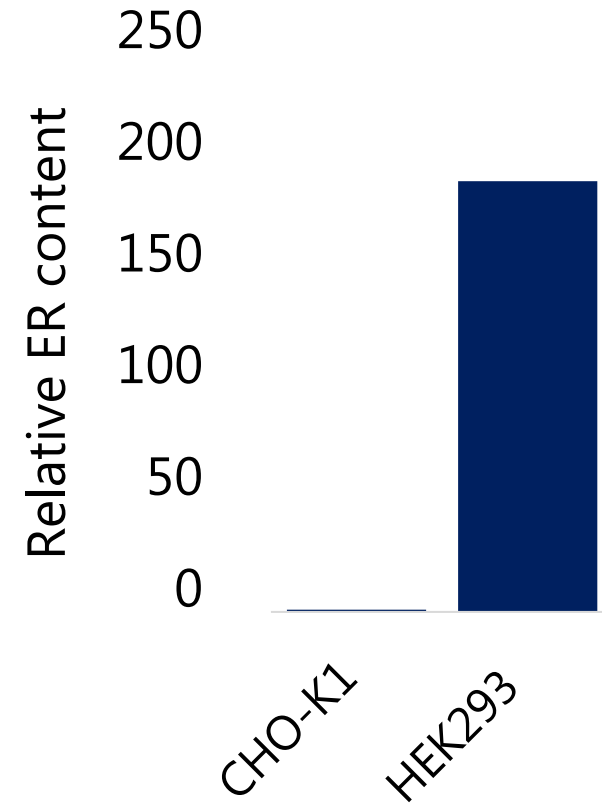
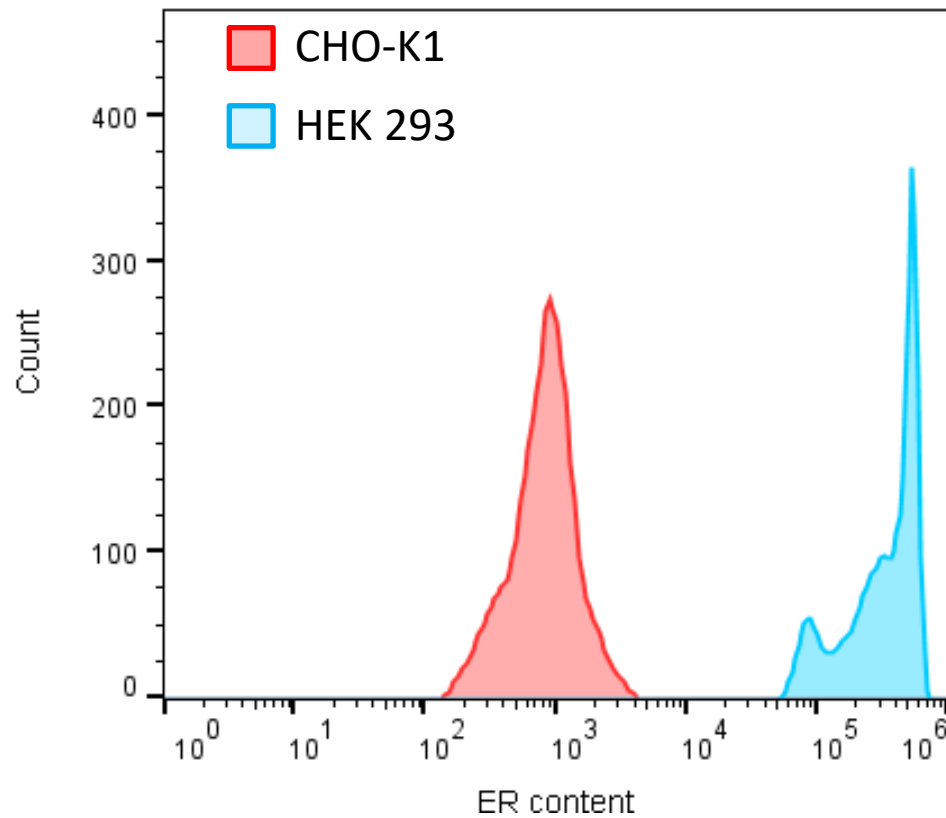




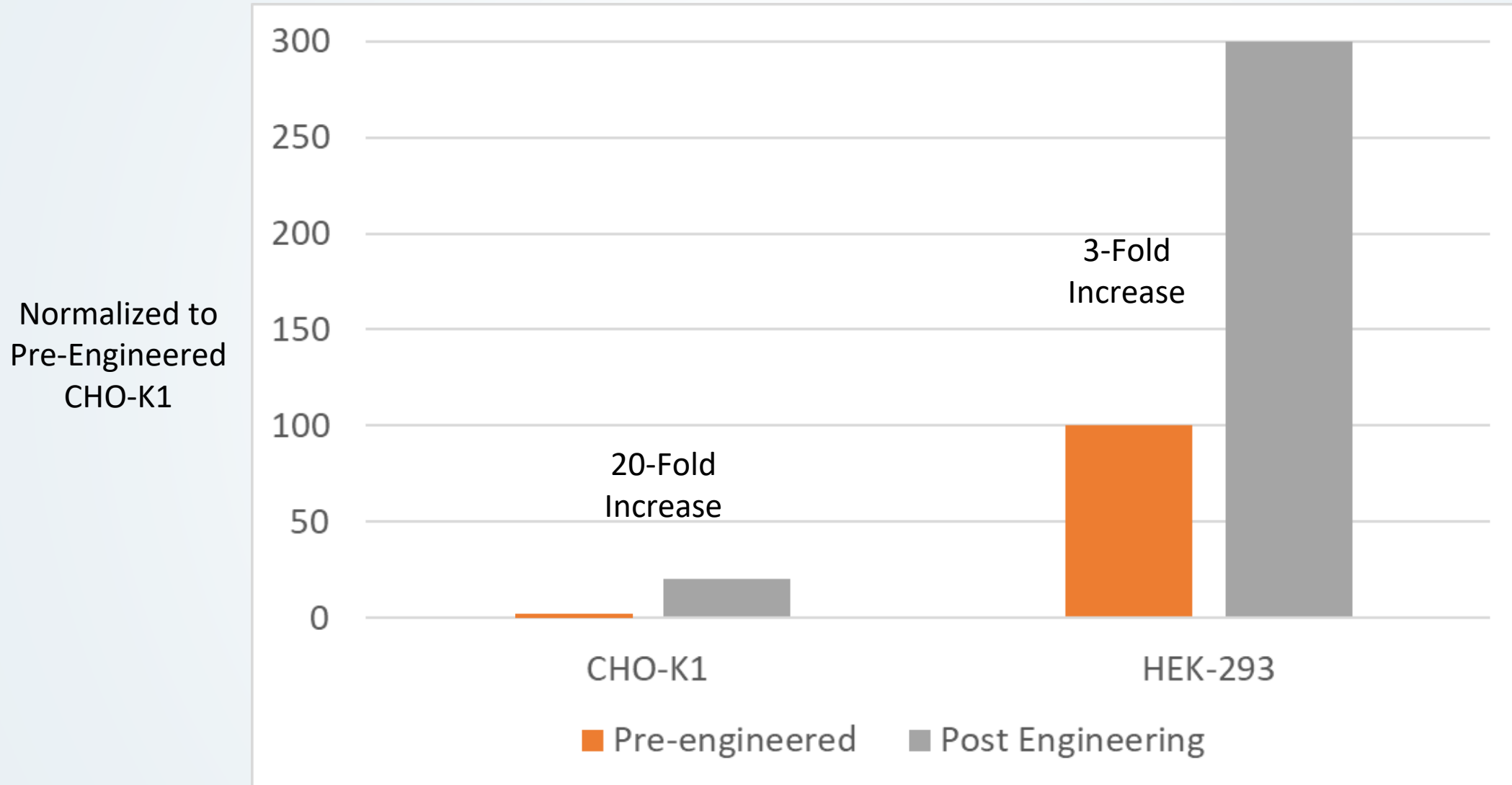
# Cellular Bottlenecks: Specific Productivity for Un-engineered Cells



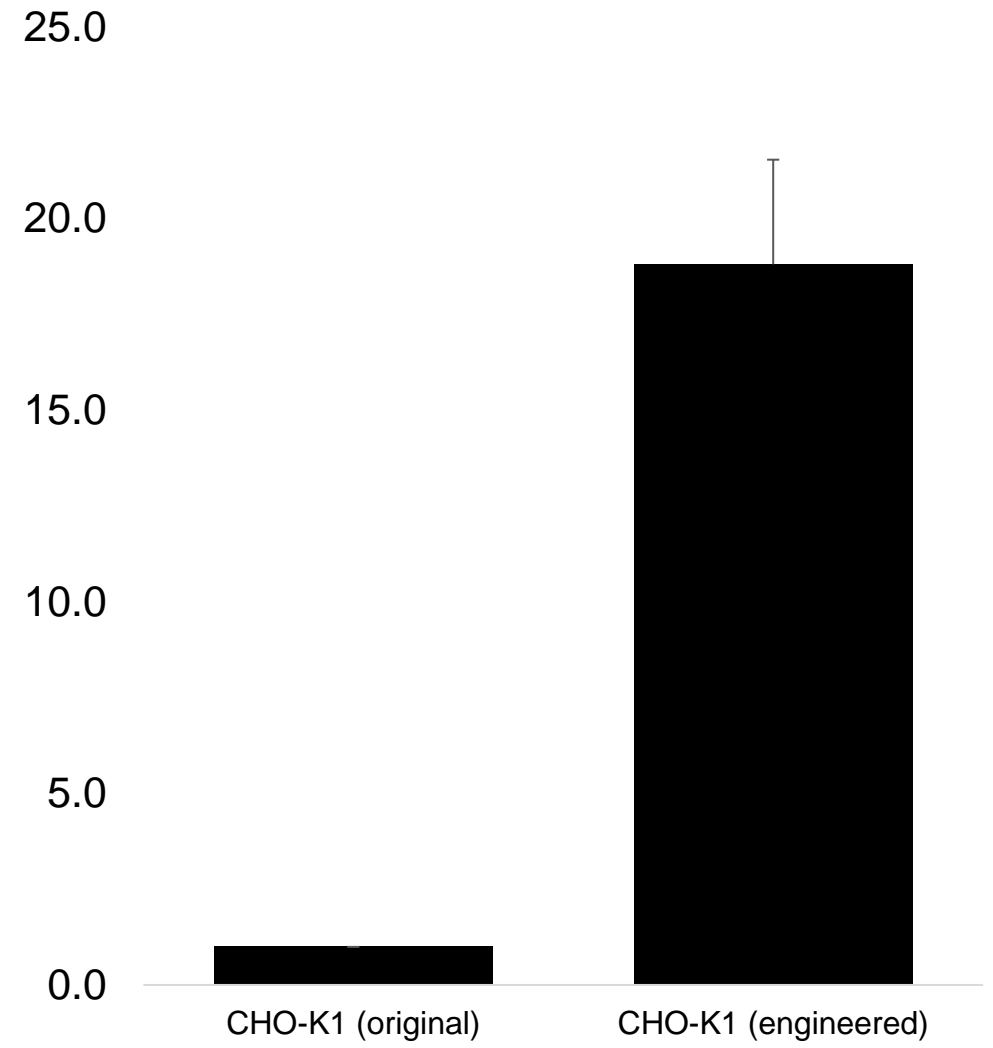
# Un-Engineered HEK-293 Cells Have >100-fold More ER than CHO-K1 Cells (by ER-Tracker™ Green Staining)



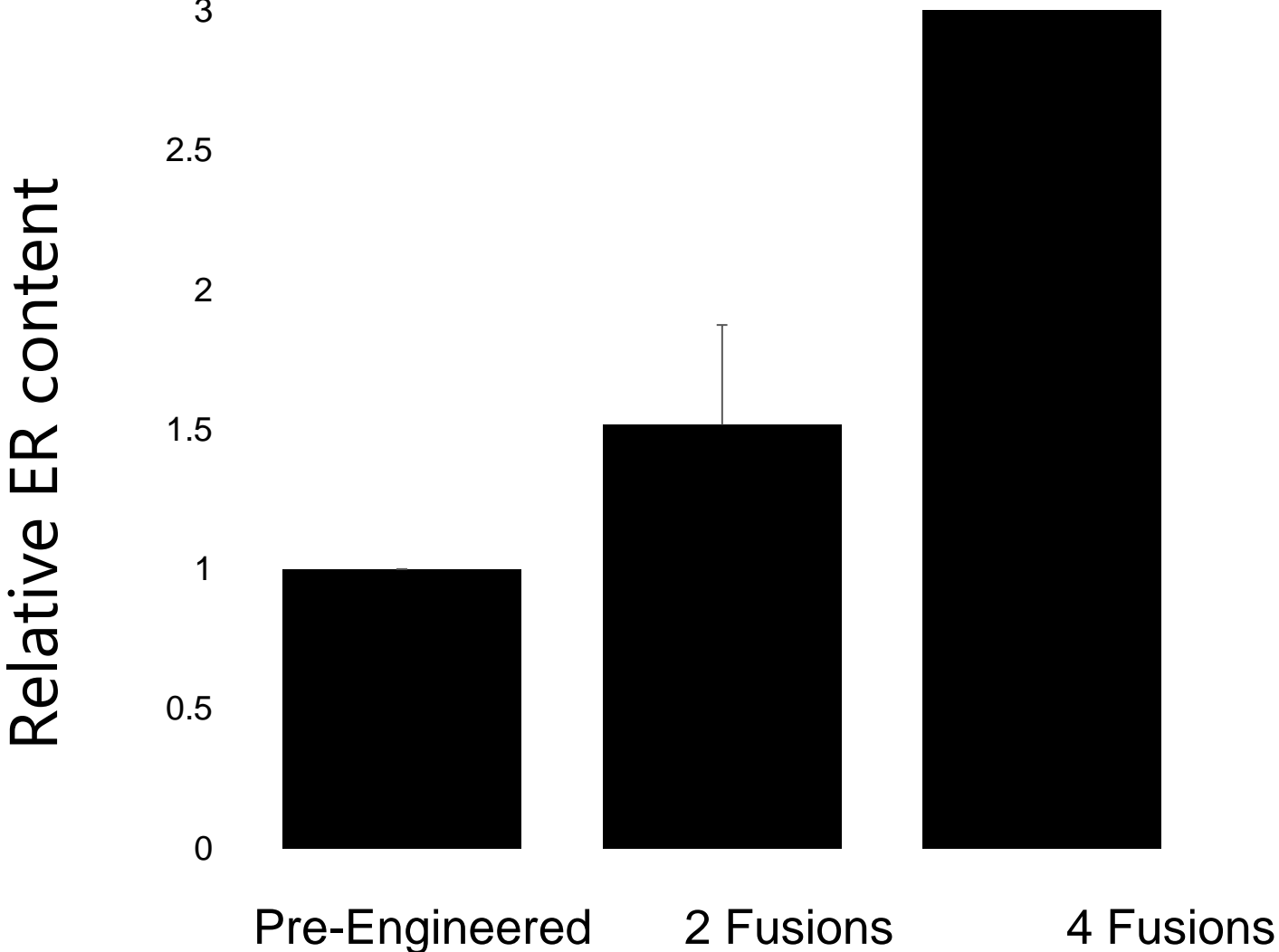
# Pre- and Post-Engineered ER Content



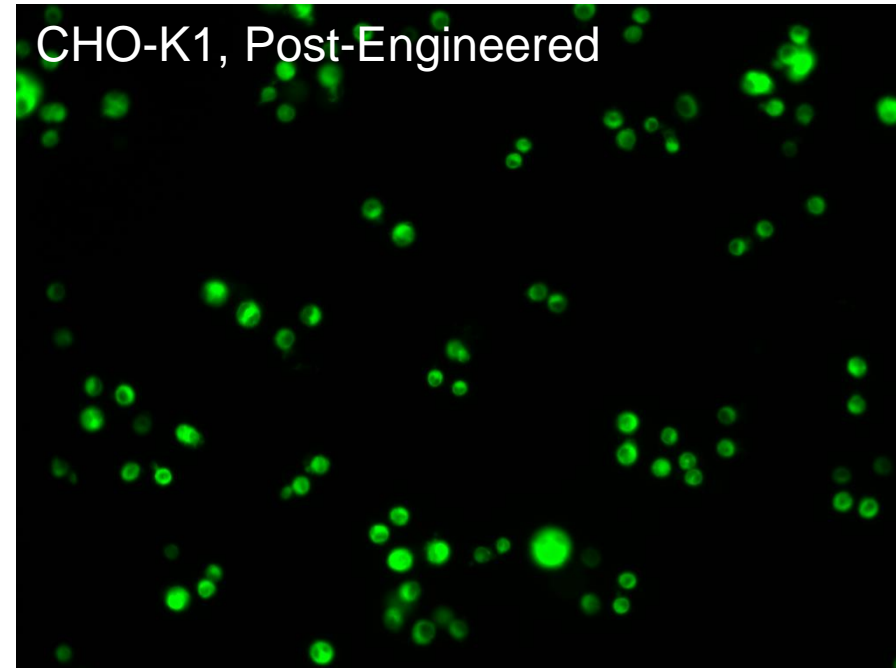
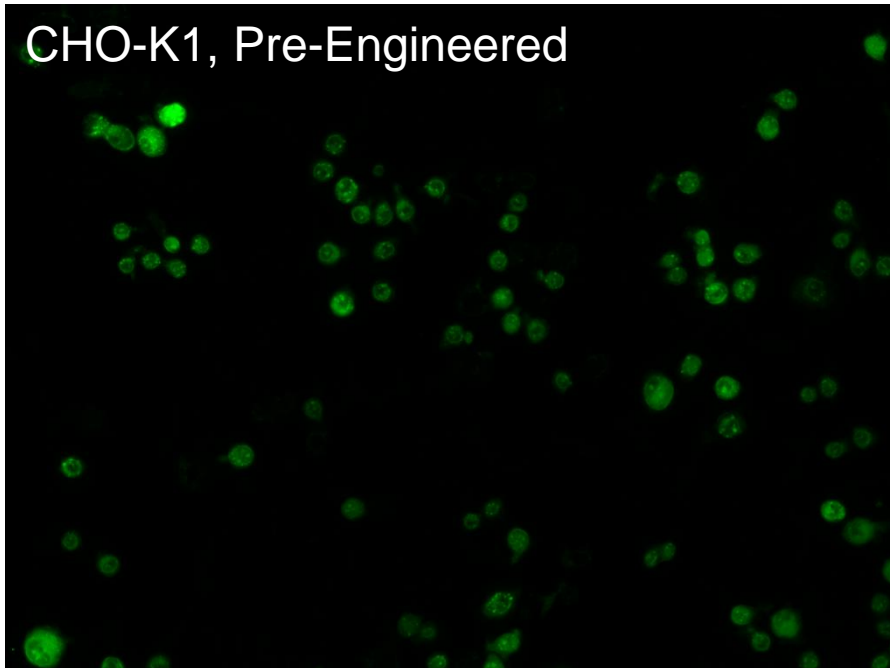
Relative ER content



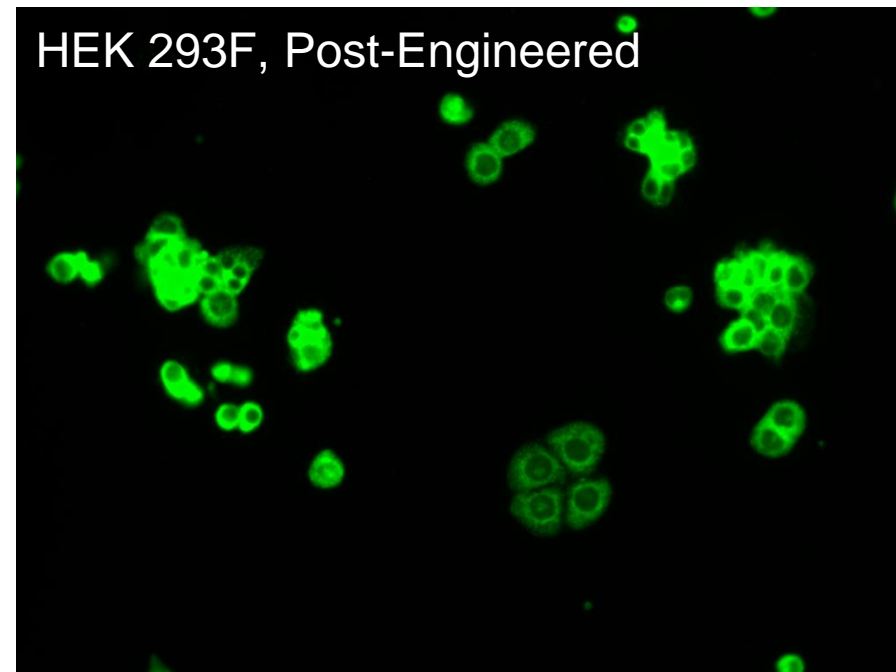
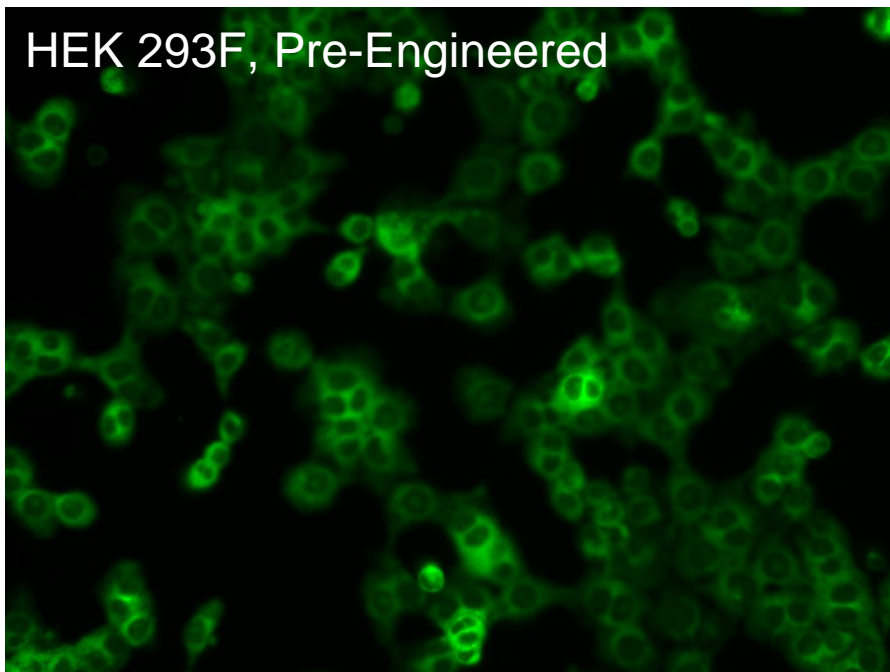
# ER Content for Another CHO Cell Line



ER-Tracker™ Green

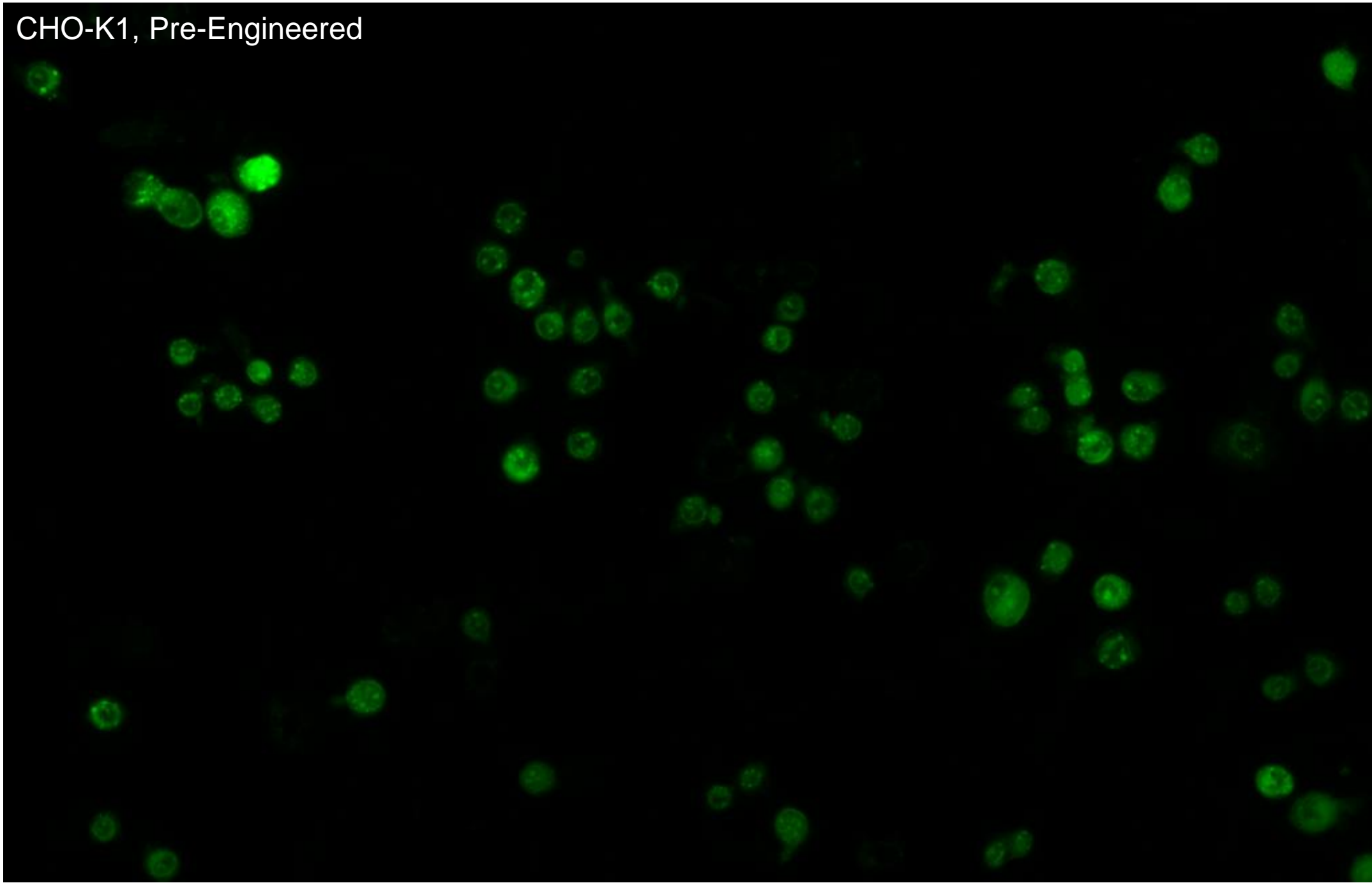


ER-Tracker™ Green



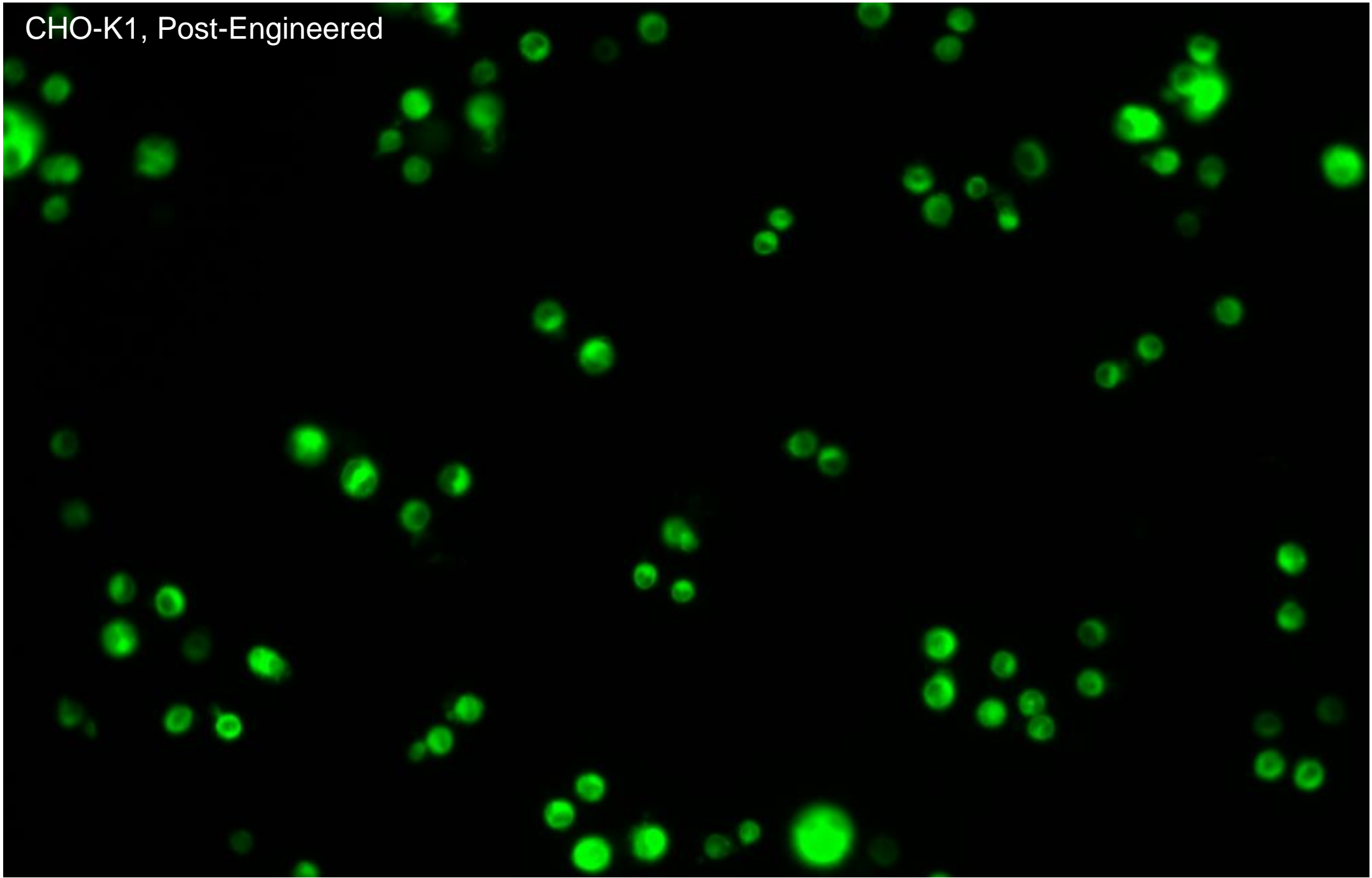
ER-Tracker™ Green

CHO-K1, Pre-Engineered



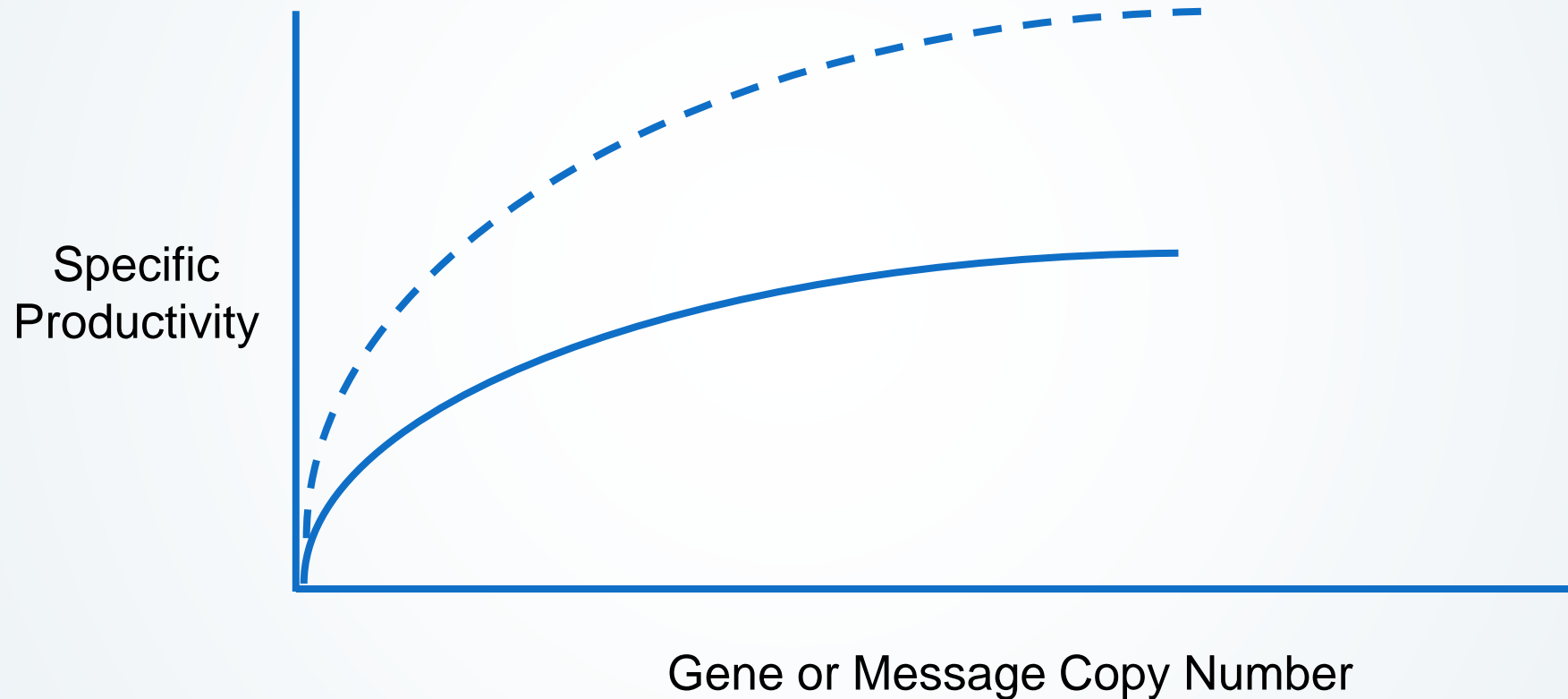
ER-Tracker™ Green

CHO-K1, Post-Engineered



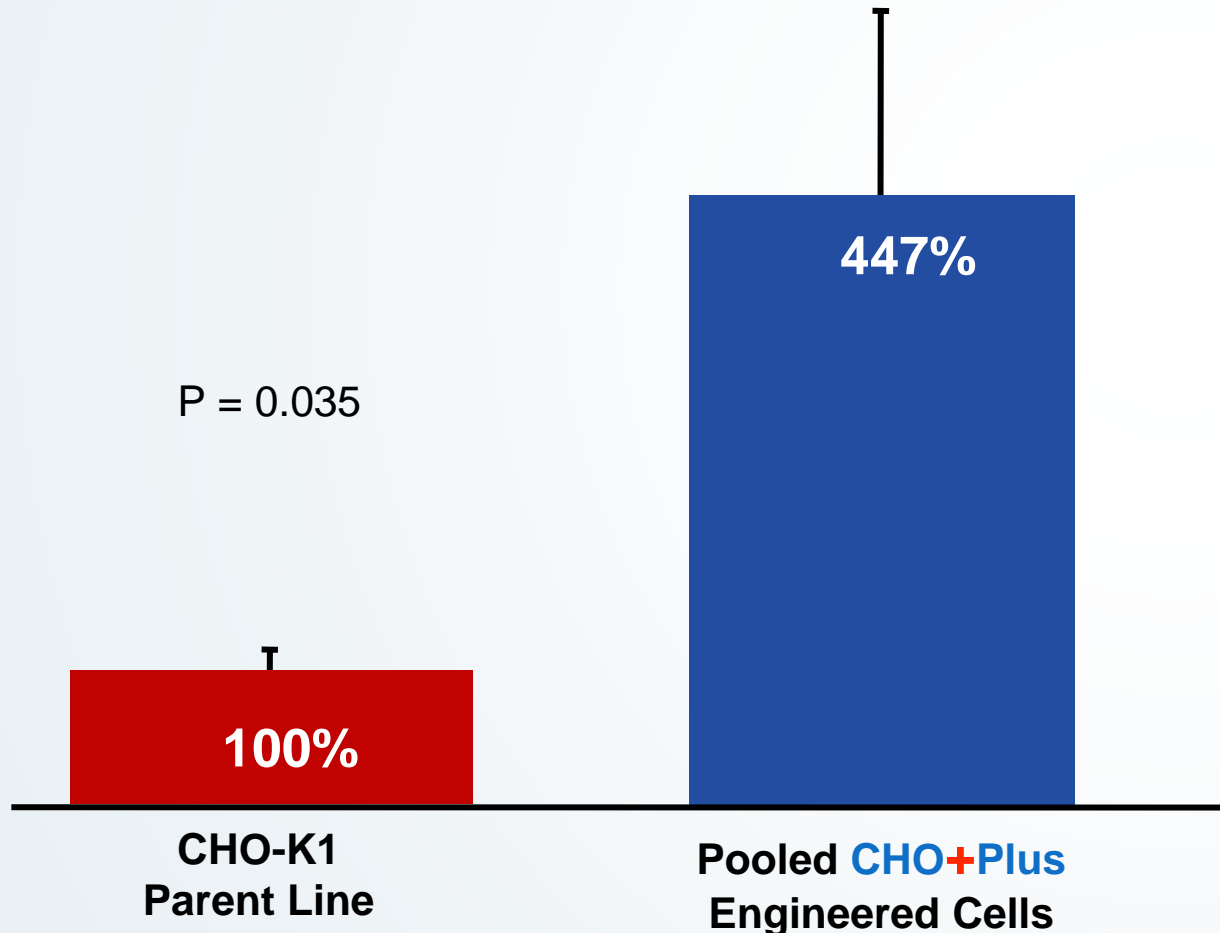


# Cellular Bottlenecks – Specific Productivity for CHO Plus Engineered Cells



# CHO+Plus Proof-of-Concept: 4.5x Higher Productivity

## Relative Specific Productivity (%)



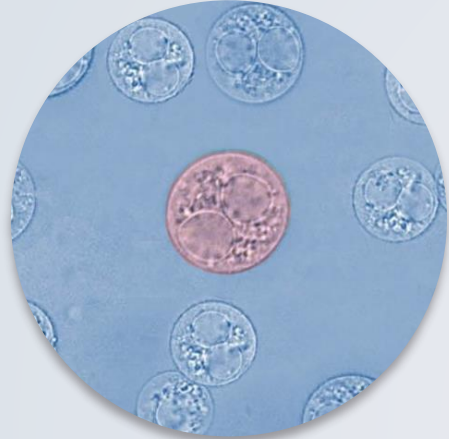
## Experimental Methods

- Secreted r-hu embryonic alkaline phosphatase
- Transient transfection
- Two experiments
- Time points in triplicate
- Multiple data points over multiple days

### Use in Antibody Production

Additional evidence gives a very high level of confidence that this technology will work for stable human antibody production.

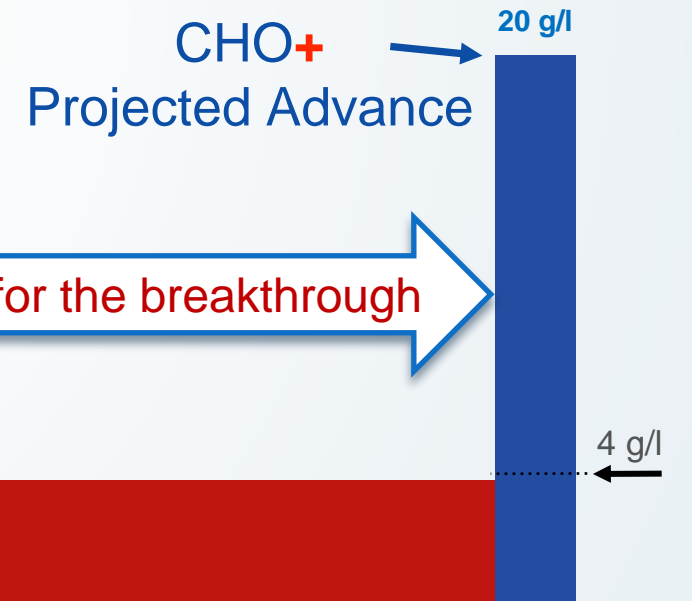
# Solution: CHO+Plus High-Productivity Cells



## HIGH-PERFORMANCE CELLS

- Highly-engineered parental cells
- Regulatory agency compliant
- Higher protein productivity per cell

Genetically Engineered CHO Cells to Increase Protein Productivity  
**5x Target Improvement, 20 g/l**; Patents issued and pending,  
Lower COGS, Fewer factories required



Industry is ready for the breakthrough

0.1 g/l

1985

1995

2005

2015

# Kathy and the Multitron



# CHO+Plus Technology - Overview

- For all eukaryotic cells; initially focusing on mammalian cells
- Proof of Concept indicates 4.5-fold specific productivity increase
- Cells engineered via:
  - Repeated cell-cell fusions, giving rise to genome shuffling and random amplification of genes and whole chromosomes
  - Cells screened for growth and higher ER, Golgi, other phenotypes
- Higher ER density alleviates translation bottlenecks for high-level production of therapeutic proteins; other phenotypes to increase production of other pharmaceutical agents
- No foreign genes or viruses; compliance with regulatory requirements

# CHO+ Technology: US Patent

(12) **United States Patent**  
**Forman**

(10) **Patent No.:** US 10,329,594 B1  
(45) **Date of Patent:** Jun. 25, 2019

(54) **CELL LINES FOR HIGH LEVEL PRODUCTION OF PROTEIN-BASED PHARMACEUTICALS**

(71) Applicant: **CHO Plus Inc.**, San Francisco, CA (US)

(72) Inventor: **Lawrence Forman**, San Francisco, CA (US)

(73) Assignee: **CHO Plus, Inc.**, San Francisco, CA (US)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 118 days.

(21) Appl. No.: **15/254,852**

(22) Filed: **Sep. 1, 2016**

## Related U.S. Application Data

(60) Provisional application No. 62/213,880, filed on Sep. 3, 2015.

(51) **Int. Cl.**  
**C12P 21/00** (2006.01)  
**C07K 16/00** (2006.01)  
(Continued)

(52) **U.S. Cl.**  
CPC ..... **C12P 21/00** (2013.01); **C07K 16/00** (2013.01); **C12N 5/16** (2013.01); **C12N 5/163** (2013.01);  
(Continued)

(58) **Field of Classification Search**  
CPC ..... C12P 21/00; C12P 21/005; C07K 16/00; C07K 2317/14; C07K 2317/51; C07K 2317/515; C12N 5/16; C12N 5/163; C12N 2510/02; C12Y 301/03001; G01N 33/5005; G01N 33/5076; G01N 33/56966; G01N 2333/916

See application file for complete search history.

(56) **References Cited**

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## OTHER PUBLICATIONS

Bandaranayake et al., Recent Advances in Mammalian Protein Production, vol. 588, No. 2, NIH Public Access, Jan. 21, 2014, pp. 253-260.

(Continued)

*Primary Examiner* — Gailene Gabel

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

This invention provides improved cell lines for manufacture of protein-based pharmaceutical agents, considerably reducing the cost of commercial production. The cell lines are obtained by fusing cells from one or more parental cell populations. The hybrid cells are then selected for one or more characteristics that support protein production on a non-specific basis, such as the level of endoplasmic reticulum, Golgi apparatus, and/or other desired phenotypic features, compared with other hybrids or parental cells in the starting mixture. A gene encoding a therapeutic protein is transfected into the cells before or after one or more cycles of fusion and selection. Depending on the protein product being expressed, cell lines may be obtained that produce as much as eight grams or more of protein per liter of culture fluid.

**19 Claims, 1 Drawing Sheet**

# CHO+Plus Technology: US and Other Patents

- Key US patent issued:  
**Cell lines for high level production of protein-based pharmaceuticals**
- Filed PCT application with expanded claims
- Filed US patent continuation to capture expanded claims for US patent
- Several new patent application filings are pending, or are imminent

# CHO+Plus Technology - Targets

- Proteins
  - Therapeutic antibodies
  - Protein-based vaccines
  - Hard-to-produce proteins
    - Blood clotting factors
    - Antibody-drug conjugates
    - Multi-specific antibodies
- Viruses
  - Vaccines
  - Gene therapy
- Others



# CHO+Plus Technology - Applications

- Higher productivity
- Increased sialic acid site occupancy
- Higher final purity; cheaper purification
- Biosimilars
- Improved post-translational modification
- Reduced protease activity

# CHO+Plus Technology - Advantages

- Four- to five-fold increase in cell specific productivity
- Fewer NEW billion-dollar biopharmaceutical manufacturing facilities
- Technology works with existing infrastructure, culture methods, and commercially available media
- Operating facilities can be up to three-fold more productive
- Easier / cheaper purification – Higher feedstock concentration  
Higher product to host-cell-protein ratio  
Higher final purity
- Faster full-scale production ramp-up

# CHO+Plus – Janssen Press Release

## CHO Plus Announces Research Collaboration Agreement With Janssen

*Collaboration will move CHO Plus closer to commercializing its patented cell engineering technology*

SOUTH SAN FRANCISCO, California – December 1, 2020 – CHO Plus ([www.CHO-Plus.com](http://www.CHO-Plus.com)), an early-stage innovation company developing technology to vastly increase the productivity of cells used to manufacture therapeutic proteins, announced today that it has entered into a research collaboration agreement with Janssen Biotech, Inc. (Janssen), one of the Pharmaceutical Companies of Johnson & Johnson. This agreement will allow CHO Plus to demonstrate commercial feasibility of its technology, while also developing several custom projects for Janssen. Under the agreement terms, Janssen will have the non-exclusive right to license CHO Plus technology for production of its therapeutic proteins. The agreement was facilitated by Johnson & Johnson Innovation.

“We are pleased to have entered into this collaboration with Janssen as we advance our technology for use in GMP production of licensed therapeutic proteins,” said Larry Forman, CHO Plus Co-founder and CEO.

Larry Chasin, CHO Plus Co-founder and Chief Scientific Advisor, commented: “It’s great to see this unique technology making its way into the commercial sector, where the expected productivity benefits can quickly be realized.”

CHO Plus laboratories are currently located at the Johnson & Johnson Innovation – JLABS incubator in South San Francisco, CA.

### **About CHO Plus, Inc.**

CHO Plus was founded in 2014 with the mission of increasing the productivity of cells used for manufacturing life-saving therapeutic proteins for treating human disease (such as antibodies for the treatment of cancer). For many years little was done to advance this area. CHO Plus has developed

# BARDA / Blue Knight

- Rapid production of therapeutic proteins and vaccines to address emergent threats to public health
- Technology is regulatory-compliant
- Increase **current** manufacturing capacity three-fold by increasing efficiency; fewer costly manufacturing facilities needed in the future
- Capacity is fungible; less need to displace marketed products
- Collaboration with other Blue Knight / BARDA companies would speed industry implementation and acceptance
- BARDA relationship would accelerate development of our technology into new areas

# Lucrative Business Model: Technology Provider

**\$150 Billion**  
Therapeutic Proteins  
Production

**1% Royalties = \$1.5 B**

**2018**



**HIGH-MARGIN,  
LABORATORY-SCALE OPERATION**

## **Industry Norm:**

**Annual License Fees up to \$700,000**

**1% Royalties on Worldwide Revenue**

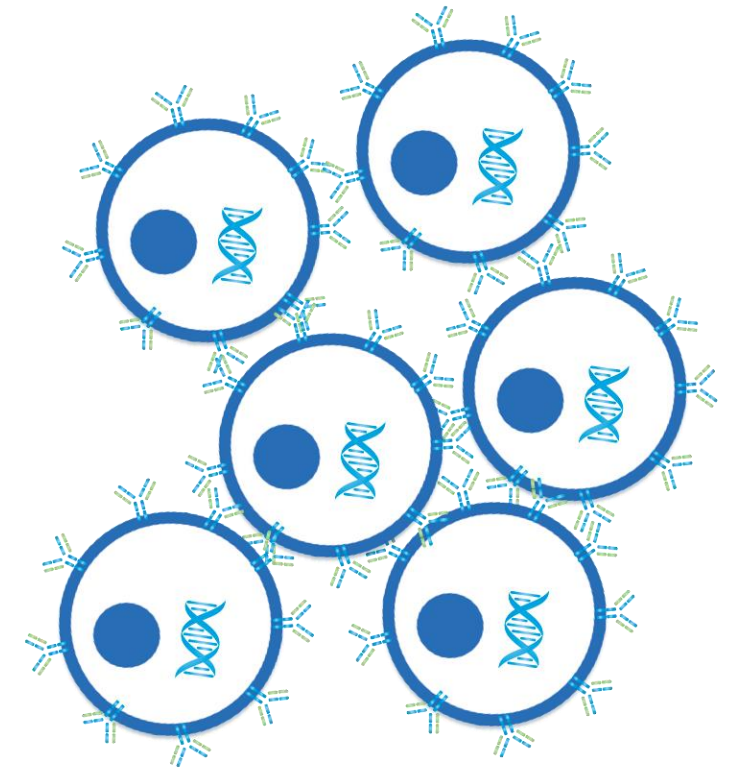
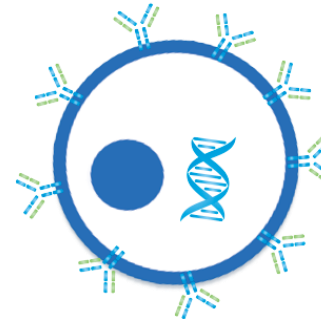
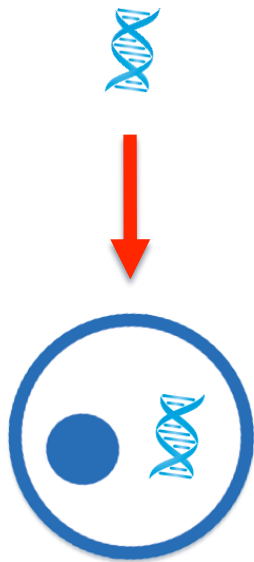
A \$2B/year Protein Production Line = \$20.7M CHO+ Revenue

5 Production Lines = \$103.5M CHO+ Revenue

# CHO+Plus Operating Model Implementation

Customer  
supplies DNA

Confidential  
transfection  
method



1

Proprietary  
CHO+ cells

2

Select  
high-producing clone

3

Expand high producer  
Deliver to customer



**WE'RE HIRING!**

**Senior Scientist / Director / VP**

**Molecular Biologist / Molecular Virologist**

# CHO+Plus Company Overview

- Goal: Increase volumetric therapeutic protein productivity to 15-20 g/l; increase productivity for viruses and other pharmaceutical agents
- Patented technology for engineering mammalian (and other eukaryotic) cells to increase productivity
- CHO Plus team has extensive GMP pharma manufacturing experience
- CHO Plus located in Johnson & Johnson Innovation – JLABS @ SSF
- Research Collaboration Agreement with Janssen Pharmaceuticals
- Accepted into BARDA—Janssen Blue Knight program
- New Research Collaboration Agreement with large pharma (not yet announced)
- Supply agreement with a biotech services company for three cell lines
- We're Hiring: Senior-Level Molecular Biologist / Molecular Virologist