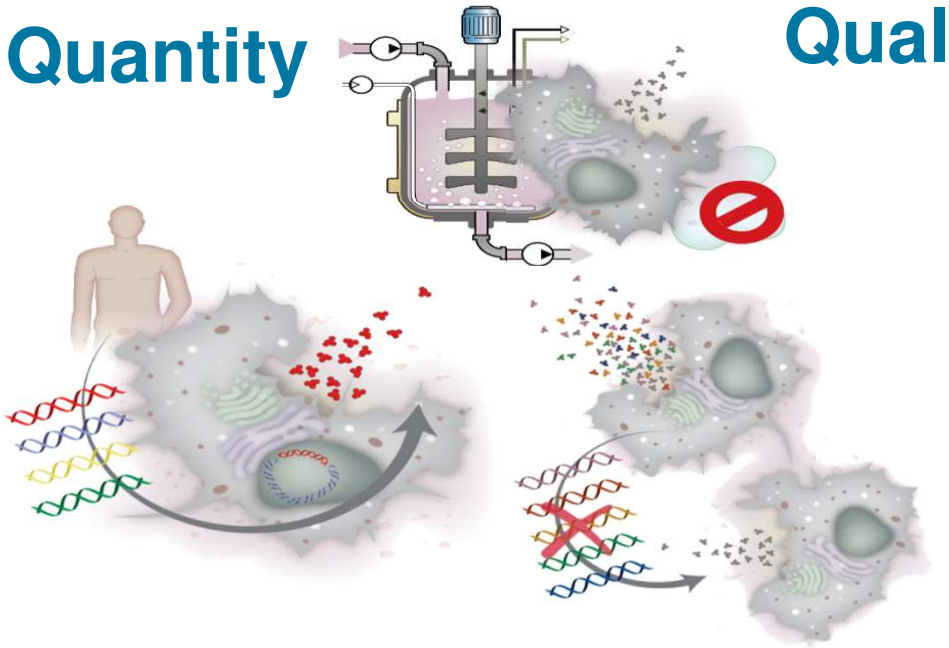
Bjørn Voldborg
Head of The National Biologics Facility
Technical University of Denmark

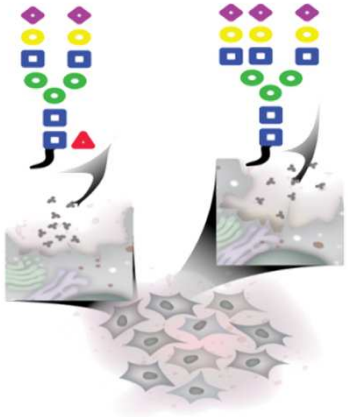
The National Biologics Facility: Research and Development in the Interspace between Academia and Industry

The DTU CHO Program: Control the protein production

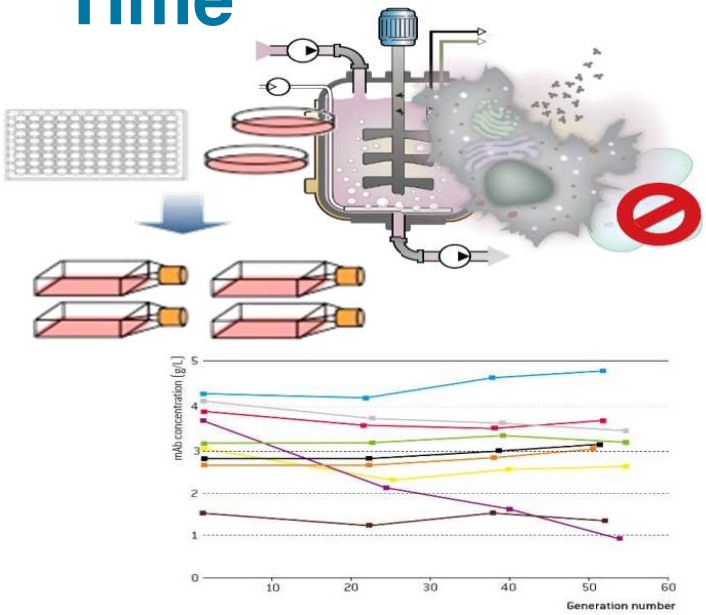
Quantity



Quality



Time



High Titers (Cost)

- Transgene expression
- Translation
- Transport
- Effective folding
- Cell viability, density, longevity

Purity (Safety and Cost)

- Immunogenicity
- Degradation
- Purification loss
- Contamination

Controlled PTMs (Safety and Efficacy)

- Proteolysis
- Glycosylation
- Charge variants
- Disulfides
- Etc

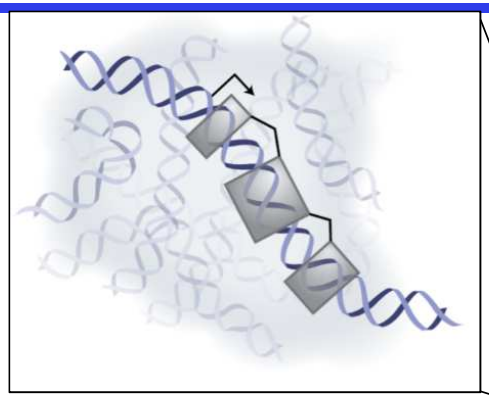
Development time

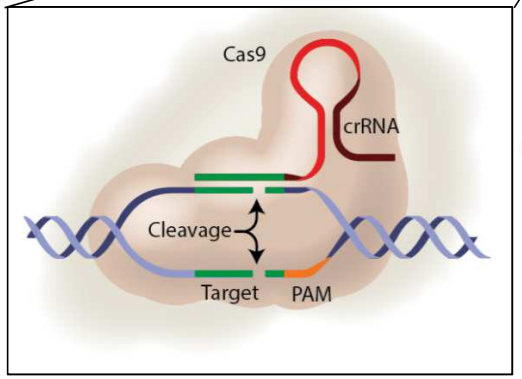
- Targeted integration
- Predictable yield

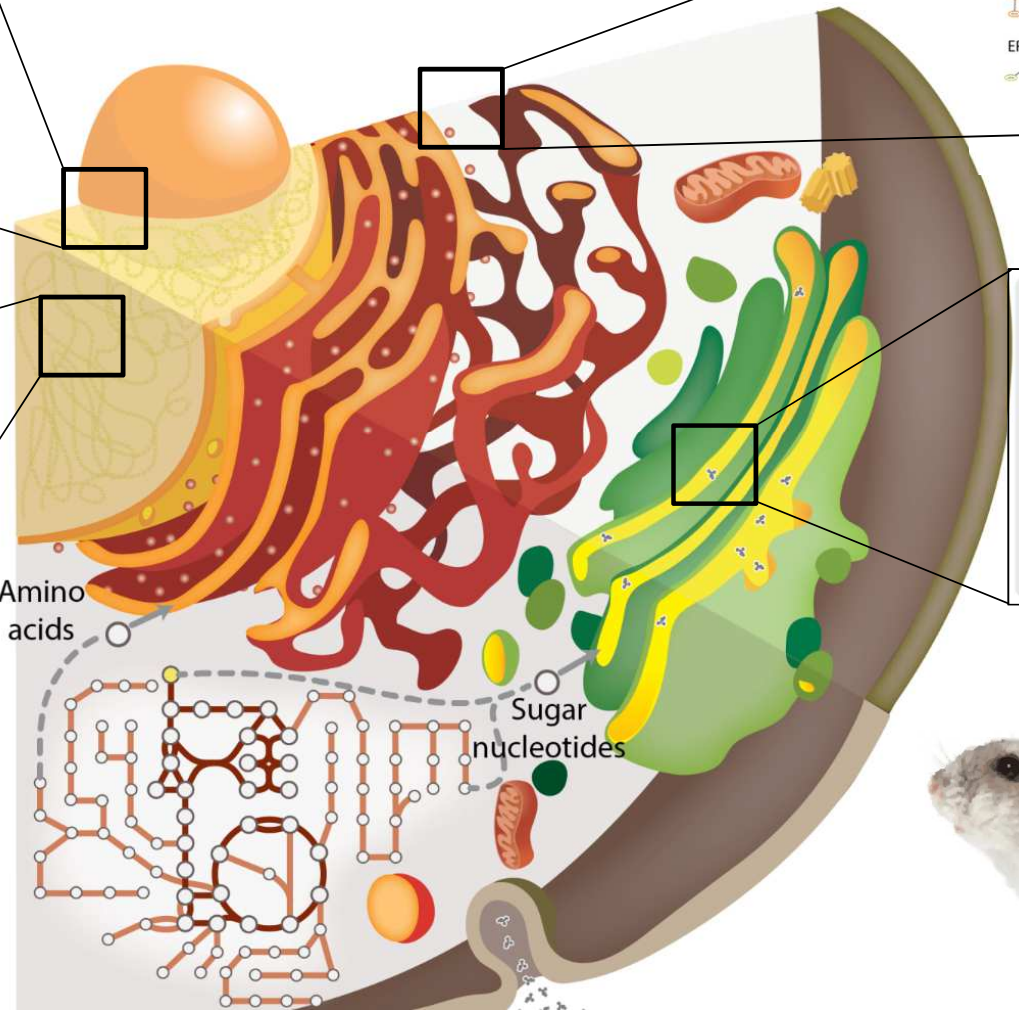
Stable expression

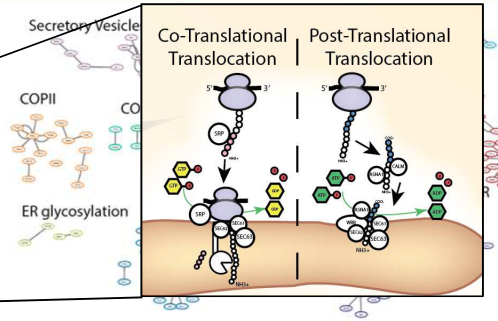
- Stable yield
- Genome stability
- Selective sweeps

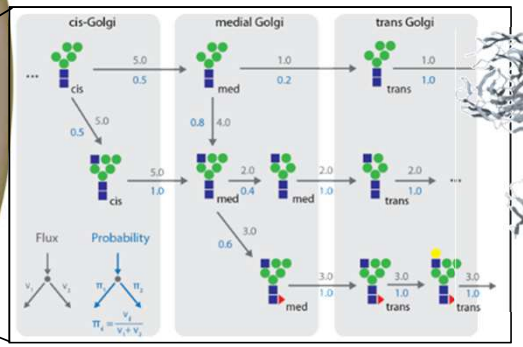
CHO Cells as engineerable entities

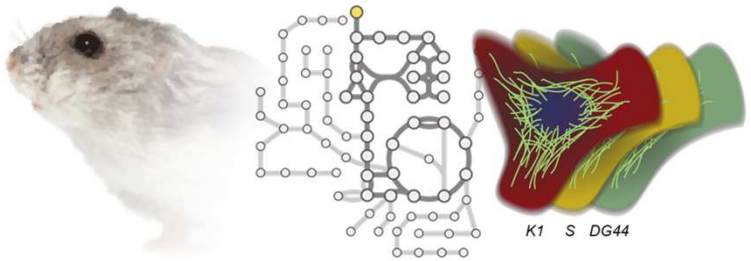






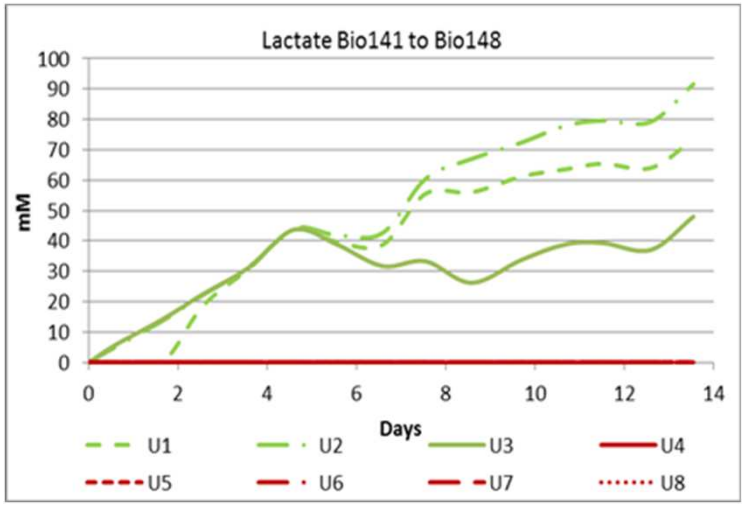


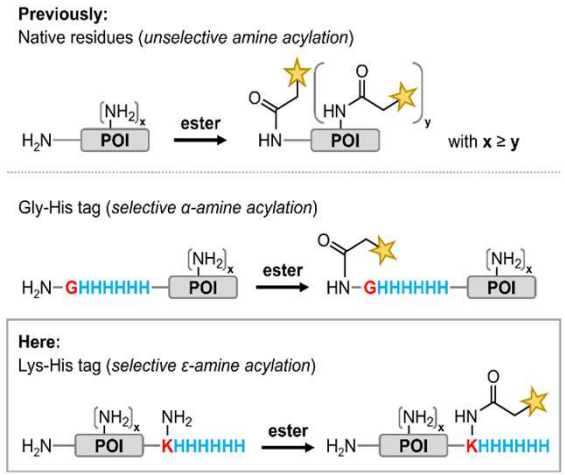


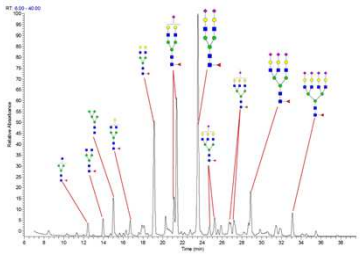


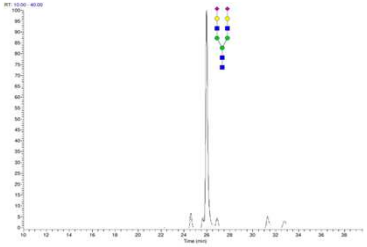
Platform Cell Lines for controlled production of biopharmaceuticals

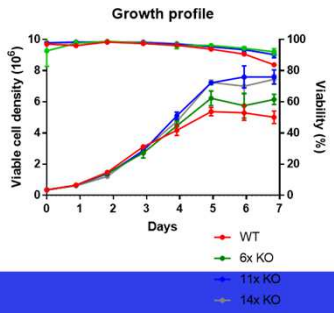
- Fully Documentated (LIMS)
- CHO-S based (GMP “ready”).
- Engineered:
  - GS selection (CLD)
  - Quality (Glycosylation & Bioprocess)
  - Zero Lactate (CHOZela) (Bioprocess)
  - Glyco-engineered (geCHO) (Glycosylation)
  - HCP reduced (cleanCHO) (Downstream)
  - Targeted Integration (CLD & Bioprocess)
- Targeted Protein Acylation

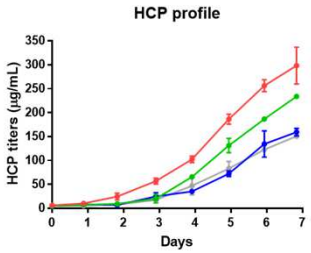






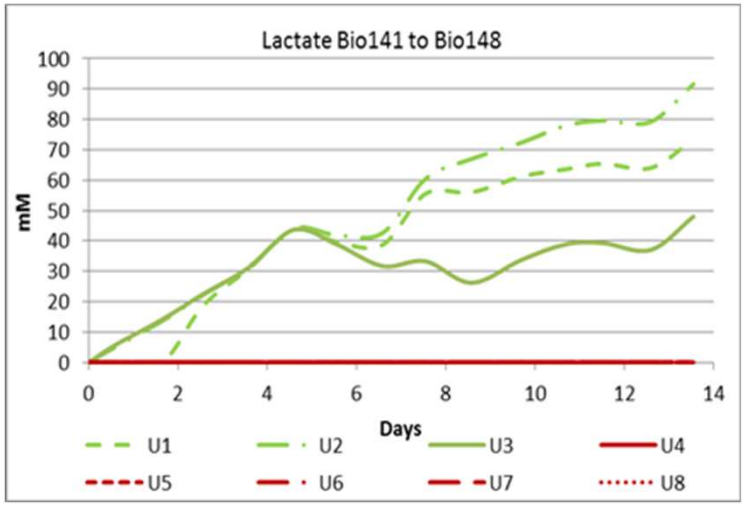


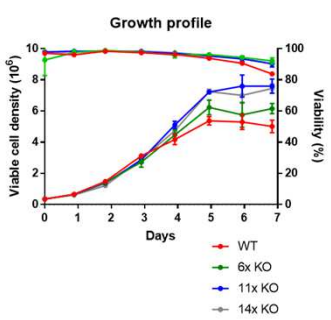


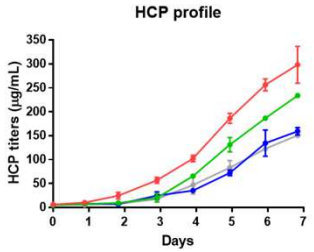


Platform Cell Lines for Biopharmaceutical production

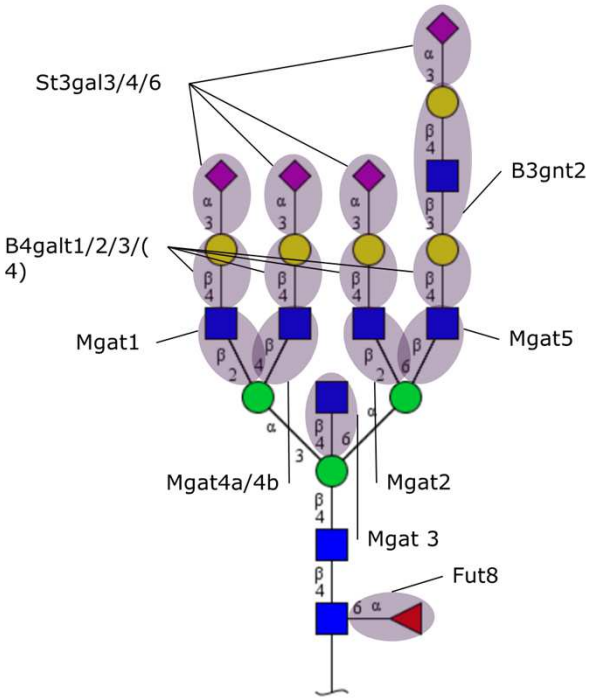
- Full Documentation (LIMS)
- CHO-S based (GMP “ready”).
- Engineered:
  - GS
  - Quality
  - ZeN/ZeLa
  - Glyco-engineered
  - HCP reduced
  - Targeted Integration
- Acylation





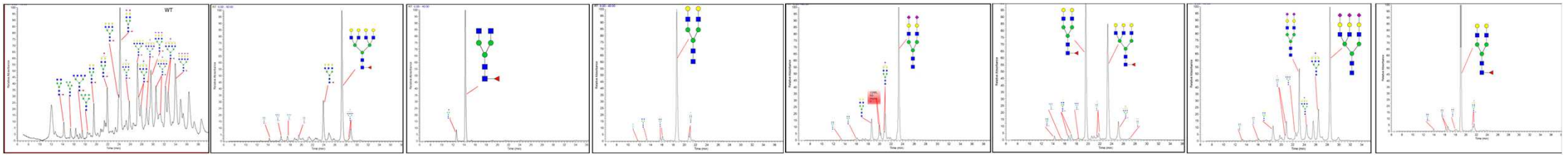


Glyco-engineered geCHO Cell Lines for accurate control of glycosylation of drug candidates



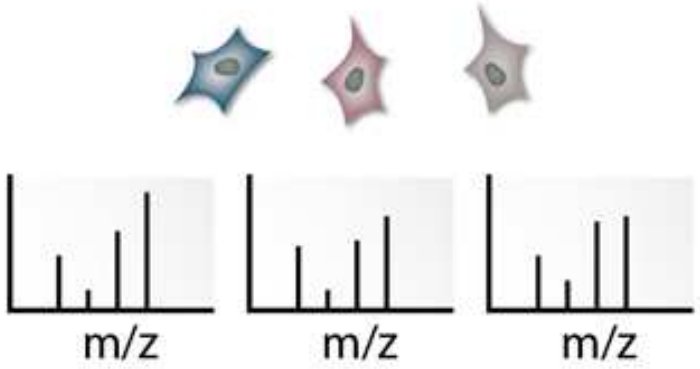
”geCHO panel”

	Mono-antennary	Bi-antennary	Tri-antennary	Tetra-antennary
	✓	✓	✓	✓
No Core Fucose	✓	✓	✓	✓
No Sialic acids	✓	✓	✓	✓
No Galactoses	✓	✓	✓	✓
No Fucose/sialic acids	✓	✓	✓	✓
No Fucose/galactoses	✓	✓	NA	NA
Human sialic acids	✓	✓	✓	✓
Human sialic acids No Fucose	✓	✓	✓	✓



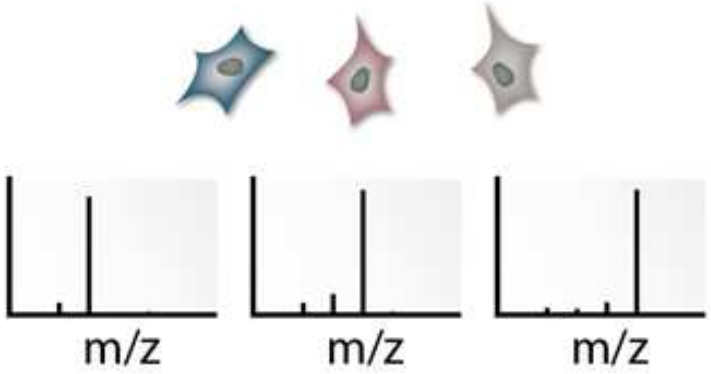
Glyco-optimize your glycoprotein for optimal efficacy: Vaccines, mAbs, Enzymes, etc…

Pick high titer clones from same pool for preclinical assays



Low diversity of heterogeneous glycosylation

Express preclinical material in the 30+ glycoengineered cells

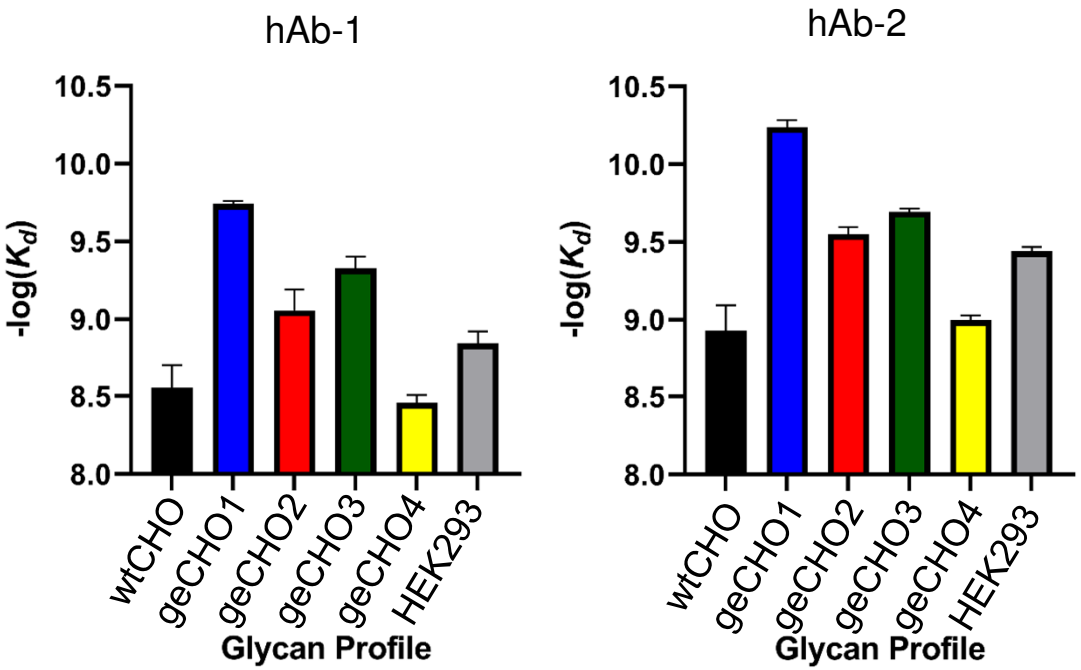


Diversity across the CHO glycosylation space with more homogeneous glycosylation

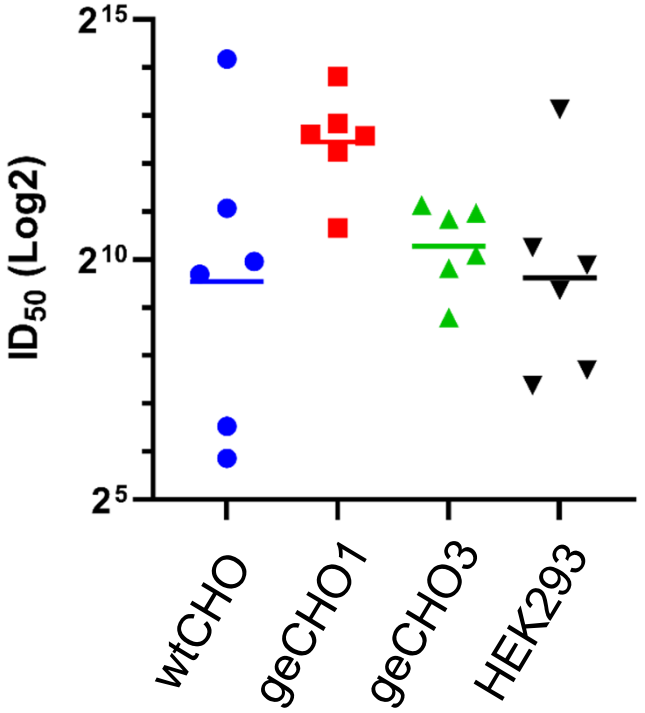
Precision engineering of HepC Vaccine candidate

Using geCHO for antibody binding and neutralization assays

Antigenicity Comparison



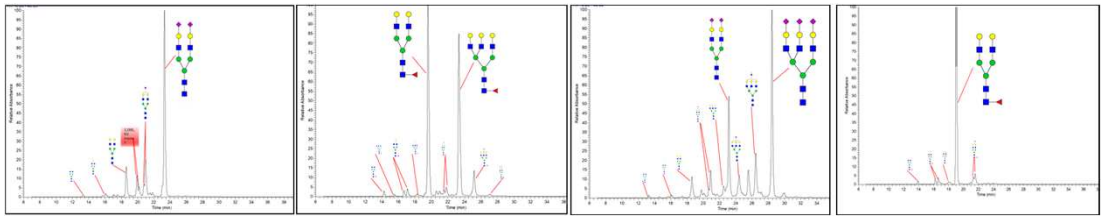
Neutralization

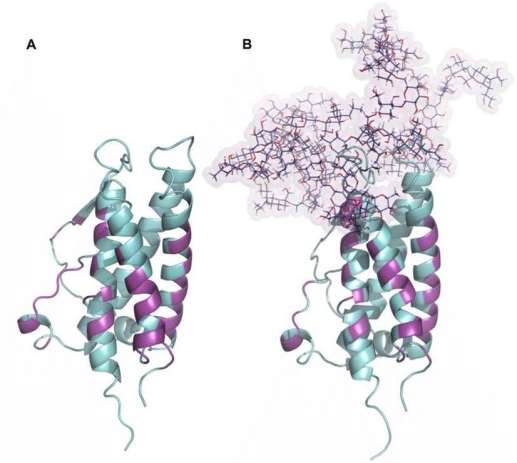


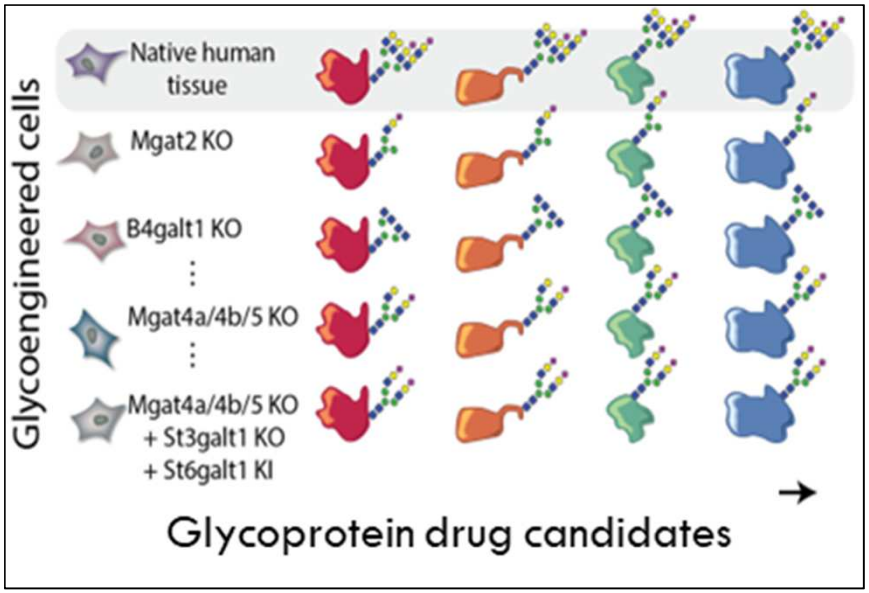
Optimal glycans enhance immune response

NBF will make the optimal variant of your glycoproteins for you

- **Production of Glycovariants (NBF)**
  - Send aa seq/expression plasmid to CLPPF
  - Transient expression in part of, or the full glycopanel
  - Purification (tag or non-tag based)
  - Glycoprofiling
  - Activity analysis
  - Timeframe 3-6 weeks
  - No License needed
- **Establishment of Production Cell Line (CLPPF or Client)**
  - Generation of stable pool expressing POI
  - Glycoprofiling
  - Generation of monoclonal high expression clones
  - Stability assays, glycoprofiling etc…



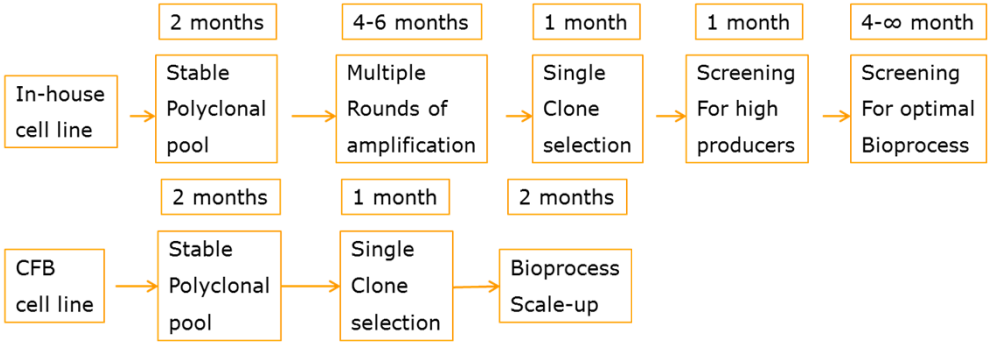


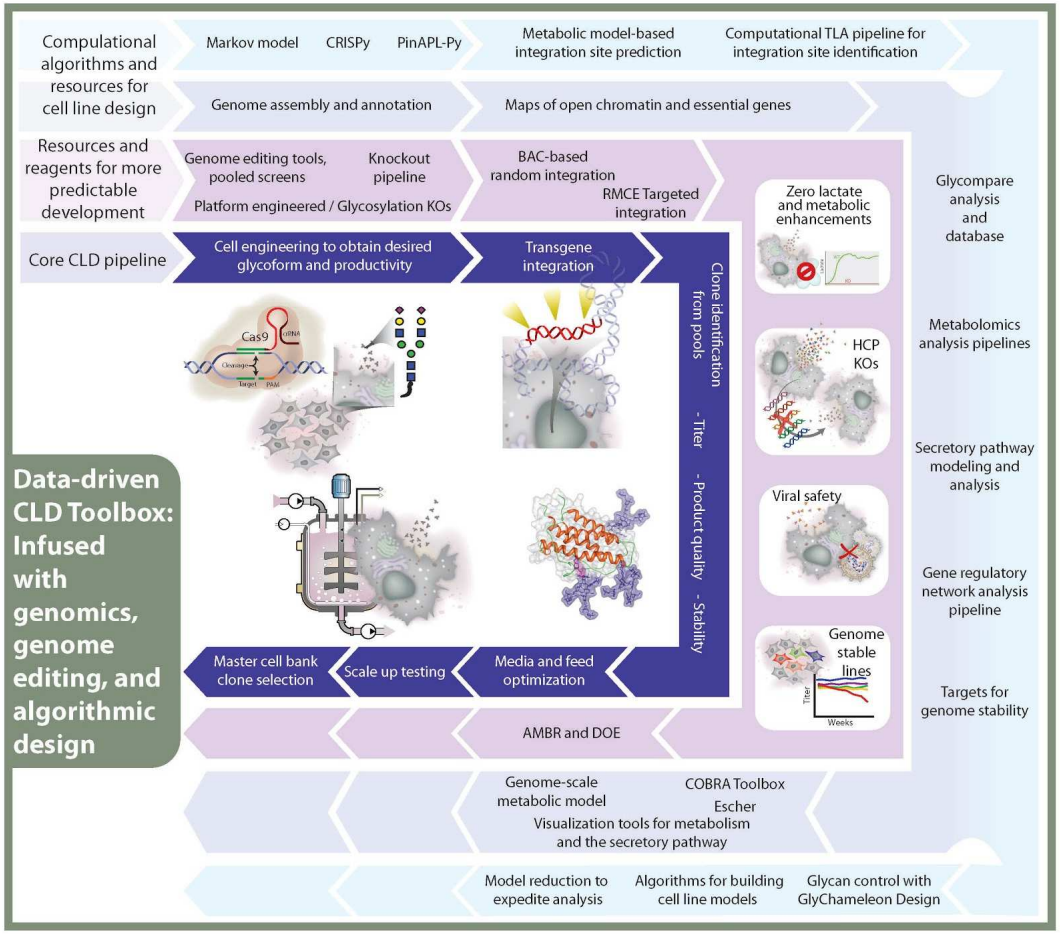


Summary

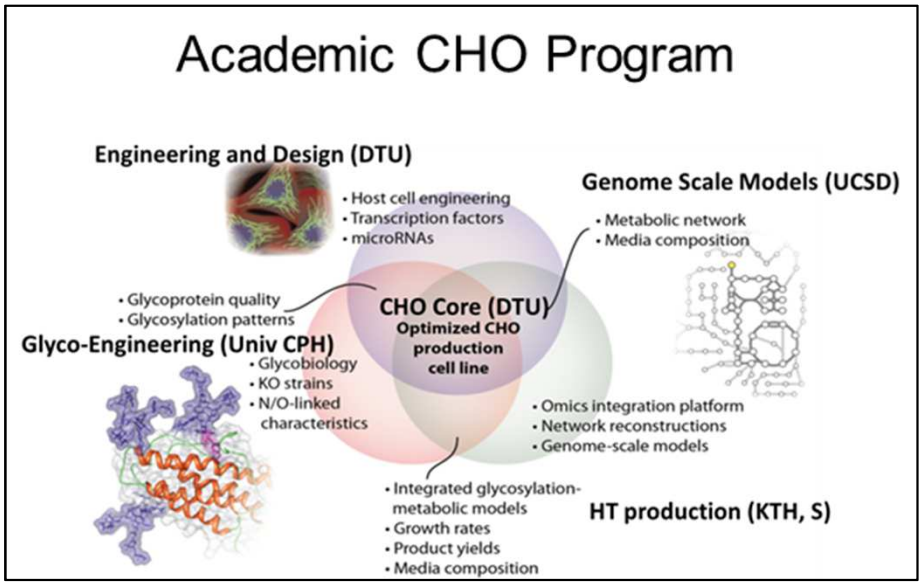
Research and data driven toolbox for fast and controlled development of optimized therapeutic products and improved CHO cell lines, resulting in:

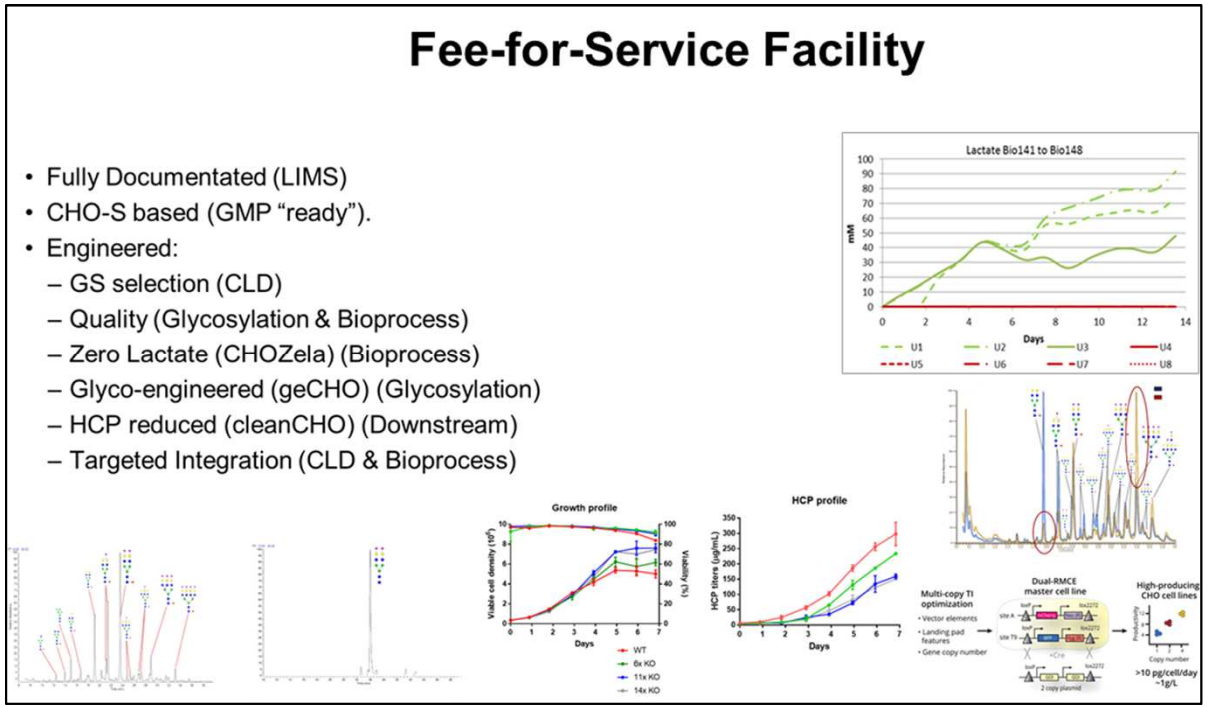
- Better protein based drugs
- Proteins that can not be made in CHO today
- Proteins with designed glycoprofiles.
- Faster from bench to pharmacy
- Cheaper development
- Cheaper production



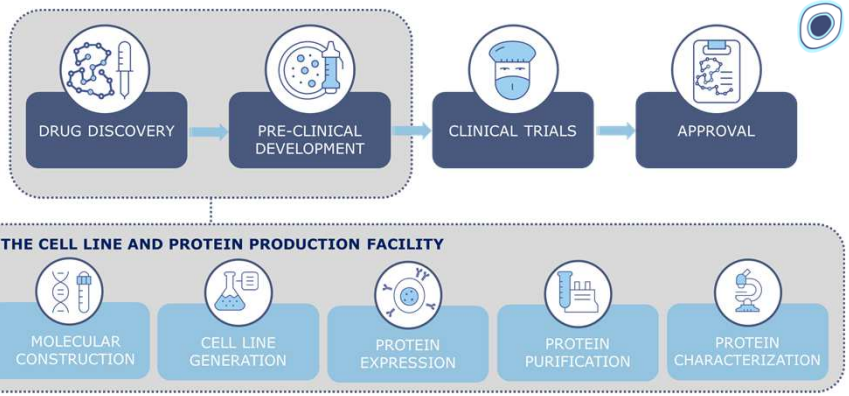


Academic results for industrial service: The National Biologics Facility





Since 2020: the National Biologics Facility (NBF)

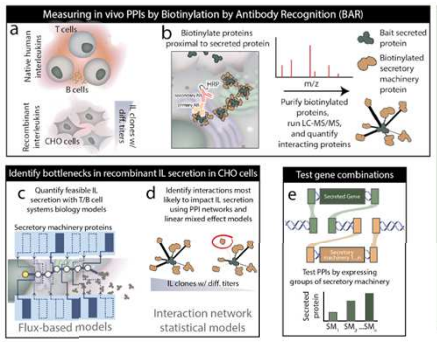


NBF NATIONAL BIOLOGICS FACILITY

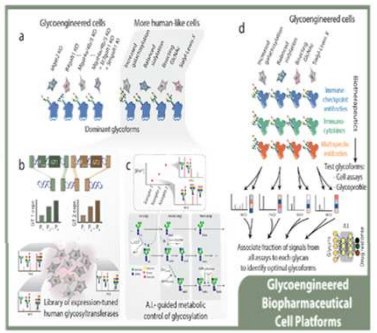
bioneer your trusted life science partner

- Continue research, education and innovation into production and use of therapeutic proteins.
  - **CRO work** in protein production and CLD broadly speaking (in alliance with Bioneer)
  - **Research** in enhancing secretory pathway, glycosylation and Bioprocessing
  - **Educate** graduate and continuing education (Life Long Learning)

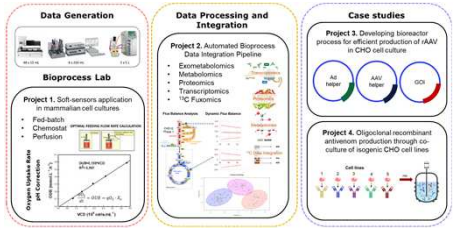
Enhance CHO cell productivity with rational engineering



Human-like glycosylation in CHO



Big Data approaches & bioreactor engineering

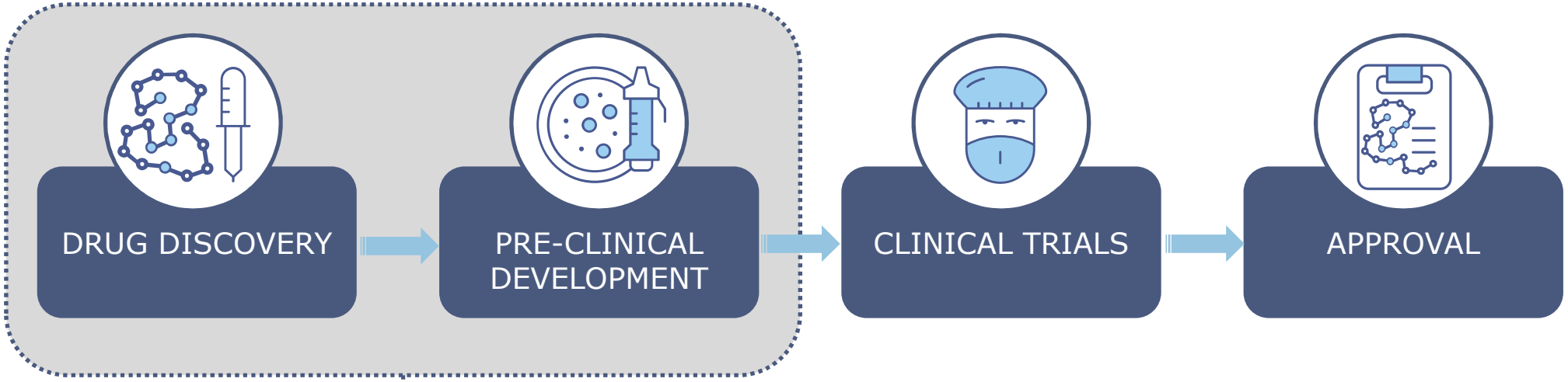


Industry input & interests

People	*Courses*
PhD Postdoc MSc BSc	MSc Biomanufacturing – theoretical – 5 ECTS MSc Mammalian cell culture engineering – practical – 5 ECTS Life long learning - Current topics in biomanufacturing - 5 ECTS

Biopharmaceutical Drug Development pipeline

We are your partner from early drug discovery to pre-clinical development



THE CELL LINE AND PROTEIN PRODUCTION FACILITY

- Experts in in Molecular Construction, Cell Line generation, Protein Production and Characterization for Drug Discovery and Preclinical phases
- We deliver everything from Expression Constructs over Purified Proteins to Production Cell Lines that are ready to move to a CMO for GMP validation and GMP production

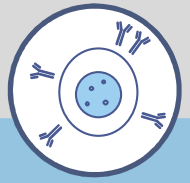
THE CELL LINE AND PROTEIN PRODUCTION FACILITY

MOLECULAR CONSTRUCTION

Cloning
High throughput
Protein Variants
Expression Vectors

CELL LINE GENERATION

Targeted Integration
Engineering
Stable Integration
Clonality
High producer
Characterization
Banking



PROTEIN EXPRESSION

Transient
Stable Pools
Producing Clones
Shake Flasks
Batch/Fedbatch
3 ml – 30 L scale

PROTEIN PURIFICATION

Tagged Protein
Untagged Protein
DSP Development
µg to g scale

PROTEIN CHARACTERIZATION

Purity
Identity
Affinity
Interaction
Activity
Glycoprofile

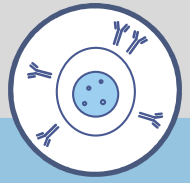
Flexible entry and exit points

PROTEIN OR DNA SEQUENCE	EXPRESSION CONSTRUCT	EXPRESSION CONSTRUCT OR CELL LINE	PROTEIN CONTAINING SUPERNATANT	PURIFIED PROTEIN

THE CELL LINE AND PROTEIN PRODUCTION FACILITY


MOLECULAR CONSTRUCTION


CELL LINE GENERATION


PROTEIN EXPRESSION


PROTEIN PURIFICATION


PROTEIN CHARACTERIZATION

EXPRESSION CONSTRUCT	EXPRESSION CELL LINE	PROTEIN CONTAINING SUPERNATANT	PURIFIED PROTEIN	CHARACTERIZED PROTEIN

How to start a project in CLPPF.

- **Step 1**
  A presentation of the capabilities and competences of NBF, and a presentation of the project in non-confidential terms.
- **Step 2**
  Meeting with team of scientific staff (either under CDA or not), to present and discuss the project in detail to align expectations and deliverables. NBF project leader appointed
- **Step 3**
  Delivery of the necessary information on e.g., the protein(s), identity, available starting material and delivery/QC requirements.
- **Step 4**
  The NBF team put together a project plan which will form the basis of the timelines and costs of the project.
- **Step 5**
  Draft of the project plan is sent for approval. If accepted, the project is ready to start.

Extensive industrial and academic experience in molecular biology, cell line development, recombinant protein production and characterisation.

- **Director: Bjørn Voldborg**
  - 20+ years experience in recombinant protein production
  - 8 years experience in cell line engineering and development
  - 10+ years experience in managing Core facilities
  - 9 years experience from Industrial Biotech
- **Molecular Biologist: Sara Petersen Bjørn**
  - 30+ years experience in molecular biology
  - 20 years experience from industrial biotech
  - 10 years experience from protein production/cell line development core facilities
- **Cell Biologist: Johnny Arnsdorf:**
  - 25+ year's experience with cell biology and drug discovery
  - 10+ year's experience from Big Pharma and Biotech
  - 12+ years Leadership experience
- **Protein Chemist: Sanne Schoffelen**
  - 15 years experience in protein engineering, purification, characterization and chemical modification
  - 10+ years experience in intact protein mass spectrometry and peptide mass fingerprinting
  - 5+ years experience in protein activity analysis
  - 15 years experience in management and dissemination of research projects

- Laboratory Technicians:
  - **Karen Kathrine Brøndum:**
    - 7 years experience in FACS sorting
    - 9 years experience in cell biology
    - 4 years experience in Nextera MiSeq library preparation
    - 1 year experience in Nextera RNAseq library preparation
  - **Karoline Fremming:**
    - 6 years experience in CHO cell line engineering and protein production.
    - 5 years experience in MiSeq and RNAseq library preparation.
    - 1 year experience in protein purification.
  - **Daniel Dunn**
    - Experience with CHO cells in industrial facilities for clinical purposes.
    - Experience with protein purification on ÄKTA systems.
    - Experience with recombinant protein expression in research.

Competences CLPPF

- **Cell Line development** (From *in silico* DNA sequence to production cell line):
  - Random/targeted integration
  - Reduced HCP contaminations
  - Longer FedBatch runs
  - Improved Quality
- **Protein Production** (From aa sequence to purified protein):
  - Transient (quick and flexible): µg to mg
  - Stable Pool/Targeted integration (cheap): mg.
  - Producer cell line (high yield): mg to g
- **Protein Characterization:** (From SDS-PAGE to activity)
  - Purity
  - Identity
  - Glycan profile
  - Activity
  - Assay development
- **Cell Line Engineering** (Engineer the production host):
  - CRISPR/Mad7 based
  - High throughput
  - Targeted gene insertion
  - Removal of contaminating proteins
  - Tailored Glycans
- **Advisory Function** (use the expertise):
  - Protein design
  - Protein production
  - Glycosylation

Case Study (Industry)

- A small startup (non-funded), with a proprietary protein based therapy:
  - Spin out from a University and a Hospital by a medical doctor and an organic chemist
  - POC with protein from stable HEK
  - E.coli product does not work
  - HEK origin unclear and not regulatory acceptable
- Requirement to obtain seed funding:
  - POC with regulatory acceptable product
  - Creadible route towards manufacturing

- Offered services
  - Consultancy
    - Protein production
    - Glycobiology
  - Tasks; Quick and dirty (Cheap) Production for POC
    - Glycoanalysis of previous and produced material
    - Larger scale transient production
  - CLD
    - Generation of stable pool
    - Production from stable pool
    - Development of DSP
    - Generation of stable production cell lines
    - QC

Case Study (Academic moving to industry)

- Tropical Pharmacology Lab at DTU
  - Anti Snake venom mAb's for 3rd world treatment of snakebites
- Production of:
  - Nanobodies
  - Fab's
  - IgG's
- Kinetic measurements
  - Octet RED96
- Cell Line Development
  - Stable pools (with targeted integration)
  - Stable clones GMP "ready".
- Mabs for diagnostics and therapy.

Finding efficient antidotes for snake bite venoms has proved to be a very difficult challenge for modern medicine. Molecular binders, the so called magic bullet-proteins, constitutes a massive step forward in the proces. Photo: Shutterstock

These magic bullet-proteins are revolutionizing modern medicine

A treatment for snake venom, COVID-19 tests and cure for autoimmune disease and cancer. The possibilities of molecular binders are manifold.

Andreas Sixsten Hallstein Rygaard
BSC STUDENT, TECHNICAL UNIVERSITY OF DENMARK, AND UNIVERSITY OF COPENHAGEN

Anne Ljungars
SENIOR RESEARCHER, DEPARTMENT OF BIOTECHNOLOGY AND BIOMEDICINE, TECHNICAL UNIVERSITY OF DENMARK

Thomas Fryer
POSTDOC AT THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CAMBRIDGE

Timothy Patrick Jenkins
ASSISTANT PROFESSOR AT THE DEPARTMENT OF BIOTECHNOLOGY AND BIOMEDICINE, TECHNICAL UNIVERSITY OF DENMARK

The Recruitment Challenge

- **Short term:**
  - LifeLong Learning
    - Specific courses to upgrade existing staff
    - 3-6 ”Mini-Master” program for non-lifetech traines Masters and PhD´s
  - Applied Master projects within industry
  - …….
- **Long term**
  - Development of BSc, Msc and PhD programs within LifeTech and Biopharma manufacturing
  - Tighter integration between academia and CRO/CMO and Pharma industry
  - GMP manufacturing training facility

MEDWATCH

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AGC Biologics opretter headhunter-afdeling og intensiverer jagten på nye medarbejdere

Konkurrencen om medarbejdere hos de producerende life science-selskaber er nu så hård, at AGC Biologics har oprettet en rekrutteringsafdeling, som skal finde mulige medarbejdere.

AGC tog sit første spadestik til sit nye anlæg for snart et år siden. | Foto: Lars Thornblad

Læs også

Novavax trækker sig fra aftale med Fujifilm – betaler milliardbeløb

Del

AF ULRICH QUISTGAARD
Offentliggjort: 01.08.22 kl. 08:57

Mens selskaber som Fujifilm og Novo Nordisk udvider deres fabrikker i Danmark for milliarder af kroner, så er den dansk-stiftede kontraktproduktionsvirksomhed (CDMO) AGC Biologics også ved

En række virksomheder mener, at det er en politisk opgave at skabe bedre rekrutteringsforhold for life science-industrien. | Foto: Jacob Ehrbahn

Del

AF ULRICH QUISTGAARD
Offentliggjort: 30.09.22 kl. 12:07

Manglende arbejdskraft er blevet så massivt et problem for den danske life science-branche, at den fortsatte vækst i industrien reelt er truet af stagnation.

Det slår en undersøgelse blandt erhvervsorganisationen Dansk Erhvervs medlemmer i life science-branchen fast med

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Fujifilm udnytter geografien i kampen om medarbejdere: "Hillerød er et større trækplaster end Kalundborg"

Det bliver en udfordring for Fujifilm Diosynth Biotechnologies at finde 450 nye ansatte, men virksomheden har et geografisk trækplaster, fremhæver topchef Lars Petersen.

Fujifilm Diosynth Biotechnologies skal oven i den almindelige intense kamp om

Læs også

Britt Meelby Jensen: Ambu kunne have klaret sig uden milliardopkøb

DI's life science-chef vil have forskning og knologi på ordenen i ampen

k Erhverv rer nyt netværk gital sundhed

relsesmedlem er hos

MEDWATCH

Øget konkurrence om talenterne presser virksomheder til nye jagt-metoder

Life science-selskaber oplever et øget behov for rekruttering, og i takt med at konkurrencen om kvalificerede medarbejdere bliver intensiveret, opretter flere selskaber interne afdelinger, som alene fokuserer på at jagte nye mulige ansættelser.

Der går ikke mange ledige kvalificerede kandidater rundt uden job i life science-industrien, og derfor jagter virksomhederne i branchen ofte medarbejdere hos konkurrenterne. | Foto: Gregers Tycho/HD

AF ALBERT RØNNING-ANDERSSON, ULRICH QUISTGAARD
Offentliggjort: 21.09.22 kl. 06:56

Det er ude af Andrea Porchias hænder, når andre life science-selskaber kontakter hendes ansatte og forsøger at lokke dem til at skifte arbejdsplads.

Det har hun indset som adm. direktør hos AGC Biologics, hvor hun i højere og højere grad oplever, at konkurrenter jagter hendes medarbejdere med lukrative tilbud om at skrive under på en kontrakt hos dem i stedet.

"Den del af virksomheden kan jeg ikke kontrollere. Når andre virksomheder

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