Cell Line Development and Engineering US

June 18-20, 2019
Park Central Hotel
San Francisco, CA

REVOLUTIONIZE CELL LINE DEVELOPMENT & ENGINEERING TO IMPROVE PRODUCT QUALITY, REDUCE TIMELINES & INCREASE TITRES

Practical strategies to optimize CHO, advance early clone selection and improve production of antibodies and complex molecules using novel and established cell lines.

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Intellectual Property Lawyer, MPEG LA

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CELL LINE ENGINEERING IMPROVING THE HOST CELL TO IMPROVE THE PRODUCT

MODULATING THE PROTEIN FACTORY

8:15am **KEYNOTE: A Systems Approach To Engineering Protein Production in Mammalian Cells**

The majority of biotherapeutics are produced in mammalian cells. To facilitate cell line development, we are mapping the pathways involved in mammalian cell growth and protein production. We have used these with genome editing techniques to develop cell lines with improved traits for protein production.

Nathan Lewis, PhD, Associate Professor, Department of Pediatrics & Bioengineering, **UNIVERSITY OF CALIFORNIA, SAN DIEGO**

8:45am **KEYNOTE: CHO Cells - Too Good To Be Wrong**

Alan Dickson, Professor, **THE UNIVERSITY OF MANCHESTER**

GENETIC ENGINEERING APPROACHES & OPTIMISING CELLS

9:15am **Horizon Discovery Spotlight Presentation**

Spotlight presentation

9:45am Networking Refreshment Break

10:30am **Generation of Improved Host Cell Lines for Biomanufacturing using Vector and Cell Line Engineering Technologies**

A toolbox of vector elements and novel engineered CHO cell lines were developed, which resulted in an increase of titer and improved product quality. By integrating these vector and cell line engineering technologies, we are aiming for further reducing time lines during cell line development.

Dennis Pfaff, Investigator, **NOVARTIS**

11:00am **CRISPR/Cas9 Platform Development for Drug Target Discovery and Validation**

- Adaptation of CRISPR/Cas9, a bacterial genome defence system, for eukaryotic molecular genetics has ushered in a new phase of the genomics revolution.
- Here, I will present the framework of a CRISPR/Cas9-based platform for drug target discovery and validation and how this platform can be exploited for single gene to genome-scale experimentation.

Benjamin Haley, Senior Scientist, **GENENTECH**

11:30am **Development of CHO Informatics To Support CHO Cell Line Characterization**

Omics-based approaches have provided key tools to understand the underlying biological processes critical to bioprocessing. Developing effective bioinformatics tools for the analysis and integration of complex omics is essential. Case studies will be presented to highlight how we develop sophisticated and state-of-the-art pipelines for the in-depth characterization of recombinant CHO cell lines expressing biotherapeutic targets.

Wei Wei, Principal Scientist, **PFIZER**

12:00pm **Small Scale Perfusion-Mimic Processing in Ambr 15 Cell Culture Micro Bioreactor System; Improving Screening Capability for Intensified Processes**

With the growing trend in the Biopharma market towards development of intensified processes, high throughput tools offer many advantages to speeding up development timelines. Identifying key parameters for optimisation and selecting the best media and feeds for intensified processes, utilizing small scale models, cannot only save considerable time, but also presents a cost-effective way of understanding which conditions should be implemented at larger scale.

Current tools are insufficient to effectively screen intensified process parameters at the micro bioreactor scale in an automated fashion. The newly launched capabilities of the ambr 15 offer many advantages for screening conditions, media and feeds, due to automation, parallel operation and low working volumes. In this talk the capabilities of the ambr 15 system will be discussed.

Alison Rees-Manley, ambr 15 Product Manager, **SARTORIUS STEDIUM BIOTECH**

12:30pm Luncheon

1:45pm **Genome Engineering to Reduce Viral Particle Release by CHO Cells:**

CHO cells are known to express endogenous viral elements embedded in their genome, and to release retroviral-like particles in the culture supernatant. This complicates the detection of potential contamination by viral adventitious agents, and, despite the lack of evidence of infectivity of these particles, raises safety and regulatory concerns.

Using Next generation sequencing approaches, we characterized several families of endogenous retroviral elements (ERVs) present in CHO-K1 cell genome.

We focused on one highly conserved ERV group of the Gammaretrovirus gender, as it was potentially functional, giving rise to viral-llike particle containing viral genomic RNA. Transcriptome and viral particle analysis validated the functionality of ERVs from this group, and it further indicated that the mRNA and viral genome are expressed from few (approximately 4) ERV sequences.

Using CRISPR-Cas9-mediated CHO genome engineering, we mutagenized the conserved ERV sequence group. Comparison of genomic and viral particle sequences allowed the identification of one ERV that encodes the viral genome of corresponding retroviral particles. We show that particular mutations within this ERV suffice to decrease the release of genome-loaded viral particles by several orders of magnitude.

Nicolas Mermod, Director, Laboratory of Molecular Biotechnology, **UNIL**

2:15pm **Glycoengineering CHO Cells For The Production Of Therapeutic Glycoproteins**
At CFB we have used our high throughput cell engineering pipeline to generate a panel of engineered CHO cells with improved properties for the production of recombinant therapeutic proteins.
We now have a large collection of cell lines generating tailored glycoprofiles, and we have used these to produce a therapeutic protein with a defined N-glycan profile, matching the current plasmas derived product.
Bjørn Voldborg, Director of CHO Cell Line Development, DTU, **BIOSUSTAIN NOVO NORDISK FOUNDATION CENTER FOR BIOSUSTAINABILITY**

GENETIC ENGINEERING APPROACHES & OPTIMISING CELLS

2:45pm **CRISPR-based Engineering of CHO Cell Lines for Improved Biologics Development**
CHO cells continue to be the gold standard for biotherapeutic development. With the publication of the CHO genome and the advances in CRISPR-mediated gene editing, the engineering of custom CHO cell lines is feasible. Rapid, cost-effective generation of custom CHO lines requires efficient delivery of CRISPR machinery for precise gene editing and high, post engineering cell viability.
Joseph Abad, Field Applications Scientist, **MAXCYTE**

3:15pm Networking Break

NEW HOST & VECTOR DESIGNS TO OVERCOME BOTTLENECKS IN BIOPROCESSING

4:00pm **Optimization of Expression Vector Design to Streamline the Transition from Research to Clinical Cell Line Development:**
Expression vector design plays a key role for efficient recombinant protein expression in Chinese Hamster Ovary cell lines. Here we evaluated vector design strategies including signal peptide and codon editing choices as well as vector construction approaches that accelerated the transition of lead molecules from Research and optimized clinical cell line development.
Yizhou Zhou, Scientist II, Cell Culture Development, Protein Development, **BIOGEN**, *USA*

4:30pm **Glycoengineering Of The Human Embryonic Kidney FreeStyle 293-F Cell Line Towards Prolonged Bioavailability of Recombinant Coagulation Factor VII**
Rico Uhler, PhD Candidate, Cell Line Development and Engineering, **MANNHEIM UNIVERSITY OF APPLIED SCIENCES & OCTAPHARMA BIOPHARMACEUTICALS,** *Germany*

5:00pm Networking Reception in Poster & Exhibit Hall

AGENDA

DAY TWO: WEDNESDAY, JUNE 19TH

CELL LINE DEVELOPMENT TECHNIQUES & TECHNOLOGIES

PROGRESSIONS IN CLONE SCREENING & DETECTING EARLY CELL VIABILITY

8:15am **Introducing ddPCR to Facilitate Clone Screening & CharacterizatioDroplet Digital PCR Assays for CHO Expression Vector Engineering, Stable Clone Screening and Characterization**
Generating a robust, stable, and high-titer production cell line is a critical requirement for all successful biologics FIH (First-in-Human) programs. Traditionally, quantitative PCR (qPCR) technologies were used to determine the biologics' (mostly monoclonal antibody) expression levels and copy numbers. However, data obtained from qPCR assays could be highly variable and non-reproducible. In this presentation, we will describe the optimization and implementation of droplet digital PCR (ddPCR) assays, for the determination of mAb expression levels and copy numbers. We will present how to utilize ddPCR assays to facilitate expression vector optimization, CHO stable clone screening, and FIH production clone characterization.
Bo Jiang, Principal Scientist, **MERCK BIOLOGICS PROCESS R&D**

8:45am **Rethinking Cell Line Selection: Screening Strategies for CHO & Beyond**
CHO cells are the prevalent host for protein production with much of the industry using automation and high throughput methods in their cell line development workflows. As other organisms re-emerge with potential to produce biologics at high volumes and low cost, new screening approaches will need to be developed for these systems and host selection will be key to ensuring success for a given molecule.
Christina Alves, Scientist, **BIOGEN**

9:15am **Clone Screening Technology for Early Viable Cell Identification**
Spotlight Presentation
- Use improved vectors to skew clonal distribution for high producers
- Combination with VIPS™ all-in-one system for high efficiency single cell cloning
- Discuss optimisation methods for clonal outgrowth
- Discuss workflow benefits of fewer plates per project and significantly shorter timelines from "transfection to ambr"
- New concepts for earlier selection of top clones based on key attributes

Ian Taylor, Director, **SOLENTIM**

9:45am Networking Refreshment Break

ADVANCEMENTS IN CLD TECHNOLOGY TO ACCELERATE TIME TO CLINIC, INCREASE PRODUCT QUALITY OR ACHIEVE HIGHER TITRES

10:30am **KEYNOTE: Improving the Transfection Process Using Synthetic Vectors & Synthetic DNA**
- How do you create synthetic vectors?
- Advantages & Disadvantages of using synthetic vectors instead of traditional vector systems
- How can the use of synthetic biology be used to reduce timelines?
- Moving from microbial to mammalian

Roderick Slavcev, Associate Professor/CSO, Executive Director, **WATERLOO INSTITUTE OF NANOTECHNOLOGY/ MEDIPHAGE BIOCEUTICALS**

11:00am **Examining The Role of PKM1 in Lactogenic Behaviour and Metabolic Shift in CHO Cells, A Case Study**
Our studies revealed that pyruvate kinase muscle-1 (PKM1) expression correlates with lactogenic behaviour in CHO cells and deletion of PKM1 or PKM gene in CHO cells reduces lactate production and results in a metabolic shift in these cells. For certain deletion configurations, this resulted in an increase productivity, which is likely due to the observed metabolic shift.
Shahram Misaghi, Senior Scientist, **GENENTECH**

11:30am **A Genomic Case of Structure-Function Relationship: The Leap-In Transposase System**
The Leap-In transposase system provides substantial speed and cost advantages over alternative cell line development platforms. Leap-In obviates the need for the highly automated equipment required to make random integration approaches effective. In combination with instrumentation providing reliable monoclonality assurance, Leap-In enables execution of multiple projects in short development timelines using minimal resources.
Ferenc Boldog, Director of Cell Line Development, **ATUM**

12:00pm Luncheon

1:15pm **Improving Clone Performance: A Case Study from Amgen**
Fides Lay, Scientist, Cell Line Development & Genetic Characterization, **AMGEN**

1:45pm **Understanding CHO Population Dynamics In Relation To Master Cell Banks**
Cell free protein synthesis is powerful new paradigm for the production of biopharmaceuticals. One extract cell line can be used to produce multiple products. I will discuss some of the work that has been done to tailor our E. coli strains for cell free protein synthesis including 1) Stabilizing components of the cell free reaction 2)Eliminating RF1 for NNAA incorporation 3) Identification and expression of chaperones for high yield IgG synthesis.
Jennifer Lin, Senior Scientist, **PFIZER**

THE FUTURE OF CELL LINES

2:15pm **Creating A Cell Line To Go Cell Free**
Cell free protein synthesis is powerful new paradigm for the production of biopharmaceuticals. One extract cell line can be used to produce multiple products. I will discuss some of the work that has been done to tailor our E. coli strains for cell free protein synthesis including 1) Stabilizing components of the cell free reaction 2)Eliminating RF1 for NNAA incorporation 3) Identification and expression of chaperones for high yield IgG synthesis.
Dan Groff, Principal Scientist, SUTRO BIOPHARMA

2:45pm Networking Refreshment Break

3:15pm **Human Derived Cell Lines: Compatibility & Stability**
Since 2000 Glycotope's GEX technology allows production of various therapeutic proteins with a fully human glycosylation profile. Challenges regarding regulatory approvement and our approaches to overcome these will be discussed. Advantages of using a human cell line for production will be presented based on case study data.
Vicky Goralczyk, PhD, Director Cell Line and Bioprocess Development, **GLYCOTOPE GMBH**

3:45pm **PANEL DISCUSSION: Which Expression System Is Best For Which Molecule?**
- Some molecules demonstrate an obvious preference for a particular cell line – what data demonstrates this?
- Discussing cell free, human, microbial and plant cell lines – what are the pros and potential cons of these cell lines
- Why are they beneficial over CHO cells?
- If there is no obvious preference for a product – how can we tell which host cell to use?
- Why do some proteins express better in certain cell lines more than others?
- Do glycosylation patterns play a role?

Christina Alves, Principal Scientist, **BIOGEN**
Dan Groff, Principal Scientist, **SUTRO BIOPHARMA**
Somen Nandi, Adjunct Professor, **UNIVERSITY OF CALIFORNIA, DAVIS**
Rico Uhler, PhD Candidate, MANNHEIM UNIVERSITY OF APPLIED SCIENCES & OCTAPHARMA BIOPHARMACEUTICALS

4:45pm End of Day Two

CELL LINE DEVELOPMENT FOR COMPLEX MOLECULES & CLONAL STABILITY

THE OUTSIDE PERSPECTIVE INVOLVING CELL LINE DEVELOPMENT

8:15am **KEYNOTE: Landscape of CRISPR**
- Will industry be able to use CRISPR?
- When will industry be able to use it?
- What are the implications of using it?
- Will it become more freely accessible?

Kristin Neuman, Intellectual Property Lawyer, **MPEG LA**

THE IMPORTANCE OF CLONAL STABILITY & MONOCLONALITY

8:45am **How to Ensure Clonality: A Case Study by Amgen**
- What is acceptable or not acceptable?
- What are the limits of monoclonality?
- How relevant is monoclonality?
- Next generation sequencing and clonality confirmation
- How clonal is a 'clonal' population?
- Duration of genome identity over generations
- Will the FDA require a Next Generation Sequencing analysis?

Jonathan Diep, Scientist, **AMGEN**

9:15am **Incorporating Targeted Integration & Single Cell Seeding**
Spotlight Presentation

9:45am Networking Refreshments

10:30am **Tools for Supporting Clonal Origin of Cell Line Development**
Juhi Ojha, Bioinformatics Research Scientist, **BAYER PHARMACEUTICALS**

11:00am **High-throughput RNA Sequencing reveals extensive alternative splicing induced by temperature shift in Chinese Hamster Ovary Cells**
Mild hypothermia is a commonly used practice in bioproduction of recombinant proteins, but the molecular mechanisms underlying the increased yield is poorly understood. We applied RNAseq to study gene expression at hypothermic cell cultures and enrich the CHO transcriptome annotation. Our results reveal the pervasive role of alternative splicing and indicate key pathways regulating hypothermic adaptation.
Ioanna Tzani, Postdoctoral Researcher**, NIBRT**

OPTIMISING MEDIA & CULTURE CONDITIONS

11:30am **N-Glycan Sample Preparation and Analysis Workflows for Screening and Characterization of Biotherapeutics**
N-glycans on biotherapeutics can affect immunogenicity, pharmacokinetics and pharmacodynamics, making characterization of N-glycans an essential in the development process. We present N-glycan sample preparation and analysis workflows for biotherapeutics, including released glycan labeling with a choice of fluorophores for characterization by liquid chromatography (LC), mass spectrometry (MS), and capillary electrophoresis (CE) including the Gly-Q integrated system for rapid screening.
John Yan, Application Scientist, **Prozyme**

12:00pm Luncheon

THE SOLUTIONS TO MANUFACTURING COMPLEX PROTEINS & BIOSIMILARS

1:30pm **Immunoglobulin Domain Interface Exchange as a Platform Technology To Engineer and Manufacture Bispecific Antibodies**
Glenmark Pharmaceuticals' BEAT® platform is a robust and versatile bispecific antibody platform based on heavy chain heterodimerization. The technology relies on biomimicry wherein the protein-protein interfaces of two different immunoglobulin constant domain pairs are exchanged to design new heterodimeric CH3 domains. In transient transfections, at equimolar chain ratios, engineering allows for ≥ 95% heterodimerization in the bispecific Fab scFv and the Fab Fab common light chain antibody formats. Using our platform, we have engineered and in-house manufactured two clinical stage bispecific antibodies. Engineering concept, manufacturing, and latest improvements to the platform will be presented.
Stanislas Blein, Senior Director, Head Antibody Engineering, **GLENMARK BIOTHERAPEUTICS**

2:00pm **Cell Line Development of Bispecific and Trispecific Molecules: Vector Design and Cell Line Screening**
Valentina Ciccarone, Principal Scientist, Cell Line Development, **MACROGENICS**

2:30pm **Venturing from Scaling Out To Scaling Up In Novel Proteins**
- How to scale up production instead of scaling out?
- What are the maximum production levels?
- Are different bioreactors required?
- High through-put cell screening to monitor correct assembly of protein
- Multi-chain product – one chain might express higher than the other – how to address the balance and prevent resulting impurities?
- How to maintain the right product quality?

3:00pm Networking Refreshment Break

3:30pm **High-throughput Screening of Bi-Specifics**
The production of bispecific antibodies adds a challenge to scientists for the cell line screening process since many other product related assemblies of antibodies can be produced by the cells. In this presentation, we will discuss a high throughput screening using Octet platform that can help identify the best transfectant pools and clones expressing the bi-specific antibody in cell line development.
Eva Rubio-Marrero, Scientist I, CLD, Drug-Substance Biologics, **CELGENE**

4:00pm **Transient and Stable Bispecific Antibody Expression: Case Studies and Lessons Learned**
Bispecific antibodies possess a unique set of format and molecule specific challenges. Here, I present protein expression and purification strategies used to advance Celgene's BsAb preclinical programs.
Jeffrey Johnson, Principal Scientist, **Celgene**

4:30pm End of Conference

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- Connect one-on-one with the scientists who would be implementing your tools to generate interest and gain insight.
- Showcase your expertise and demonstrate thought leadership to industry leaders and decision makers.
- Learn about the latest developments in the industry so you can better anticipate future needs of the market.
- Uncover new potential clients and partnership opportunities to grow your business.
- Highlight your company as a member of the community in an intimate setting to grow relationships.

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