SYMPOSIUM AND WORKSHOP SESSIONS

WORKSHOP
SUNDAY 5TH MAY 9:30-11:00 · AUDITORIUM 10

www.CHOgenome.org: where we are and where we might go

organized by Nicole Borth, Kelvin Lee and Mike Betenbaugh

This workshop will be dedicated to the benefits of organism/cell line specific websites and the tools that currently are available at www.CHOgenome.org and tools/features that you may want to see implemented in the future. The workshop will include tutorials and a discussion on what the most important and urgent needs of the scientific community are with respect to CHO-omics. To help prepare this please fill in the survey on what your needs are: link (to follow).

WORKSHOP STRUCTURE:

- **9:30-10:00 Introduction and Keynote. Multi-omic resources for detailed discovery in mammalian cells**
  Kimberly Robasky, University of North Carolina at Chapel Hill

  We will discuss emerging resources wherein detailed data and tools are being released to gain insights into mammalian cells. These include NCI's Genomic Data Commons Portal (GDC), NIH's Genotype-Tissue Expression (GTEx), and NHLBI's Trans-Omics for Precision Medicine (TOPMed), as well as the Alliance for Genome Resources (AGR) and emerging single-cell atlas initiatives. We will provide examples for using these resources and for integrating omics data.

- **10:00-10:10 CHOgenome.org: Resources and Tools for the CHO Community**
  Madolyn Macdonald, University of Delaware

  This presentation will focus on how to use CHOgenome.org to access genome information for the Chinese hamster (CH) and CHO cells. CHOgenome.org currently hosts multiple genome assemblies for CH and CHO as well as several tools to search and visualize this data. We will provide an overview of the available CH and CHO genome assemblies with emphasis on the most recent reference genomes and annotations. We will then demonstrate how to find sequence, annotation, and protein information for a gene of interest from a particular assembly. We will also describe how to use the CHOgenome.org BLAST tool and the JBrowse viewer to gain further information. In addition, we will discuss and invite comments for future plans for the website.

- **10:10-10:20 The CHOmine and epigenome databases**
  Heena Dhiman, Austrian Center of Industrial Biotechnology

  This presentation will lead the audience through different additional available CHO specific websites to demonstrate how information can be extracted. One example is the CHOmine, an intermine toolbox that links different information databases available for genes, including different reference genomes, protein databases, KEGG and Gene ontology information. It enables linking between different gene IDs and thus help in quickly collecting all information for a gene from a single site. The epigenome database, on the other hand, enables a detailed look at the regulation of activity across a genome by providing data for 6 related CHO-K1 cell lines, including transcriptome, DNA methylation, calls for small mutations and larger scale structural variants such as translocations.

- **10:20-10:30 Resources for Metabolic Modelling**
  Nathan E. Lewis, University of California San Diego

  Biotherapeutic production in mammalian cells is a bioenergetically demanding task, wherein we culture the host cells to rapidly grow to high densities, all while requiring cells to produce large quantities of recombinant protein drugs. Given these demands, mammalian host cells are cultured in rich medium to provide ample nutrients for high growth and protein production. Systems biology models provide a framework to describe the uptake of these nutrients and quantify the metabolic fluxes as resourced are driven to growth and protein production. Here I will discuss a variety of tools that are publicly available to build and run models of mammalian metabolism to deepen ones understanding of and optimize mammalian metabolism.
- **10:30-11:00 A look into the future: Survey Results and Discussion**
  Moderator: Nicole Borth, BOKU University and Austrian Center of Industrial Biotechnology

  Briefly, a summary of the results of the survey on the use of CHO resources and the perceived needs of the scientific community in this field for the future, followed by discussion

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ESACT/ACTIP WORKSHOP SUNDAY 5TH MAY 9:30-11:00· AUDITORIUM 11

The digital transformation of animal cell culture technology

Prof. Dr. Michelangelo Canzoneri (Sanofi, ESACT representative) and Christine Mitchell-Logean (UCB, ACTIP representative)

The ongoing digital transformation is influencing the way process scientists approach the development of manufacturing cell lines and industrial cell culture processes. Recent advances made in the field of process miniaturization, parallelization, automation and control are implemented into highly efficient process development workflows. This workshop provides insights by experts from the biopharmaceutical industry about their ways of leveraging digitalization and machine learning. Key challenges around experimental designs, data and knowledge management strategies, statistical process models and decision-making tools in the development of manufacturing cell lines and cell culture processes will be highlighted. The presenters will illustrate their concepts with example case studies and will discuss about future outlooks and opportunities in this context.

ESACT WORKSHOP ON EXTRACELLULAR VESICLES: SUNDAY 5TH MAY 9:30-11:00 · AUDITORIUM 12

EVs – the next generation complex biopharmaceutical

Co-chaired by Scott Estes, Ivan Wall, and Johannes Grillari

Extracellular vesicles have raised a strong interest recently as novel biopharmaceuticals. Thereby, 2 different lines of research and development are crystallizing, on the one hand the use of EVs as therapeutics per se, and on the other their use as drug delivery vehicle.

In regard to their use as complex biopharmaceutical, there is accumulating evidence for therapeutic activity in various disease models including stroke, myocardial infarction, osteoarthritis, or bone regeneration. They even have been used in a human graft versus host disease patient with extremely positive result. It is hypothesized that beneficial effects that were observed in clinical trials using e.g. mesenchymal stem cells (MSCs) might well be due to the secretome of these MSCs as opposed to direct incorporation of allogeneically transplanted MSCs. Considering more than 500 ongoing clinical trials using MSC based therapies, we can envision an ever increasing necessity of production systems for EVs.

Similarly, the use of EVs as drug delivery/targeting vehicles has by now produced promising results in animal models.

In order to give key insights into this fast evolving field, we here apply for a workshop to be held at ESACT2019 in Copenhagen, as we see a benefit for all experts in EV based biology and in animal cell culture technology to convene and discuss in order to boost and inspire the respective fields in the quest to produce, purify and finally bring EVs as novel biopharmaceuticals to the patients. Thereby, IW will introduce the basic biology of EVs and their isolation and processing; JG will outlined the potential cross-talk between different cells and tissues by EVs; BG will show their therapeutic potential and finally, SEA will highlight the EV potential as a drug delivery vehicle.

WORKSHOP STRUCTURE:

- **Advancing Bioprocessing of Exosomes**
  Ivan Wall, UK
- **Cross-talks in aging and age associated diseases: from EV biology to application**
  Johannes Grillari/BOKU/Evercyte, Vienna, Austria
- **MSC-EVs in regenerative Medicine: Heterogeneity of MSCs and resulting EV preparations**
  Bernd Giebel, University clinics Essen, Germany
- **Bioengineered EVs as a versatile platform for biomedical applications**
  Amir El Andaloussi, Karolinska Institutet, Stockholm, Sweden
- **Questions to the panel**

ESACT FRONTIERS WORKSHOP SUNDAY 5TH MAY 9:30-11:30 · ROOMS 69/70

Design Thinking to foster innovation and creativity

Speaker and moderator: Guilherme Martins Vitorino (NOVA Information Management School, Portugal)
Chairs: Ana Filipa Rodrigues (iBET, Portugal) and Paulo Fernandes (Autolus, UK)

Design Thinking is a method to foster innovation and creativity by following a user-centric approach. Designing is giving form to an idea to conceive a more desirable product, service, process or organization and refining it into something that can be delivered reliably and efficiently. In addition to the consumer-related aspects, Design Thinking can leverage several aspects of technology, research and development, including creating new products and tools, conceiving new applications for old products, shortening product development cycle or establishing new models for productivity and collaboration.

ESACT Frontiers invites you to join a Design Thinking session especially conceived for the 26th ESACT meeting in Copenhagen. In this session, participants will be guided through the fundamental steps of Design Thinking with insightful explanations and examples. Dynamic exercises will engage participants to address challenges and identify opportunities for innovation, collaboration or unexpected value creation. As major outcome of the session, participants will recognize the use of Design Thinking as a useful methodology to create new technologies, capabilities, relationships, activities and materials in their own practice while contributing to shape the future of academia-industry interaction in the field of animal cell technology.

WORKSHOP STRUCTURE:

- Introduction
- Design Thinking principles
- Exercises:
  1. "Painstroming"
  2. Warm-up
  3. Strategic partnerships
  4. Challenge
- Closing

GE HEALTHCARE SPONSORED WORKSHOP SUNDAY 5TH MAY 11:30-13:00 · AUDITORIUM 10

Intensifying cell culture operations – modern approaches to biopharma commercialisation

Moderator: Andreas Castan, GE Healthcare

Cell line development, process development and process intensification, advanced data analytics and automation are all important strategies manufacturers are using to optimize process efficiency. These steps, along with better approaches to heterogeneity in the pipeline, reductions in costs, and more flexible and agile manufacturing, are all necessary to meet the changing requirements of the biologics industry. During this session, our chairperson Andreas Castan Ph.D, Principle Scientist GE Healthcare Life Sciences, will join seasoned experts to present case studies on these topics and share their insights into overcoming obstacles

WORKSHOP STRUCTURE:

- **Baochuan Huang Ph.D,** Senior Director, Cell Culture Development & Manufacturing, **Kiniksa Pharmaceuticals** will detail media and process development efforts required to realize a high-performing and simplified retrofitted process for producing clinical materials.
- **Patrick Mayrhofer Ph.D**, Department of Biotechnology **BOKU,** Vienna will describe perfusion media and process development, as well as scale-up to pilot scale bioreactors to achieve process intensification.
- **Anurag Khetan Ph.D,** Site Director, Biologics Process Development **Bristol-Myers Squibb** will provide an overview of the process of getting from DNA to drug substance and discuss current challenges in early biologics process development.
- With growing attention on the impact of raw materials on cell culture performance, **Aaron Woolstenholme, GE Healthcare Life Sciences** will describe how installing a seamless connection for data transfer enables development and manufacturing teams to receive real-time data on their cell culture media and its quality.

BERKELEY LIGHTS SPONSORED WORKSHOP SUNDAY 5TH MAY 11:30-13:00 · AUDITORIUM 11

Rapid generation of clonal cell lines with superior titers using the Berkeley Lights Beacon Platform

The development of new antibody therapeutics will require rapid, scalable workflows to generate stable cell lines secreting production-level titers. To date, clone selection approaches are hampered by measurements that are not predictive of titer and stability in the downstream production environment.

In this workshop, Berkeley Lights will introduce how the Beacon platform enables rapid selection of cell lines with titers superior to clones selected with alternative CLD methods. The Beacon CLD workflow enables generation of cell lines >99% monoclonality assurance in under 1 week, removing the need for multiple lengthy rounds of cloning. In addition, the workshop will demonstrate how the Beacon can measure clonal population dynamics in order to analyze and predict clonal stability over a typical 8-week scale up period.

The Beacon platform is rapidly becoming the gold standard for CLD, with expanding adoption at AMGEN, GSK, Teva, Novo Nordisk, Shire, Selexis, Catalent, Sanofi, and several other pharma and CROs. Customers will co-present case studies demonstrating how the Beacon has both accelerated their CLD timelines and improved the yield of top-secreting clones.

MERCK SPONSORED WORKSHOP 1
SUNDAY 5TH MAY 11:30-13:00 · AUDITORIUM 12

Facets of seed train intensification – a biopharma industry perspective

Moderator: Jennifer Campbell, Upstream Technical Specialist, Process Solutions, Merck

Process intensification is gaining traction in the biopharmaceutical industry especially in Upstream where flexibility, speed to manufacture and protein yields per run are triggering the shift from traditional fed-batch to perfusion-based processes. Even though perfusion-based production remains a challenge mainly due to the lack of robustness and reliability of current cell retention technologies, more and more drug manufacturers are considering the implementation of perfusion to intensify their seed train.

During this workshop we will explore different seed train intensification strategies (Perfused seed train and High Volume High Cell Density process intermediates etc., discuss the main challenges associated with them and have an end-user present a case study on how they have successfully intensified their seed train.

A live Q&A session will allow for an interactive exchange between the workshop attendees and the subject matter experts.

WORKSHOP STRUCTURE:

- **Intensified Seed: driving value towards the evolution of upstream processes**
  Habib Horry, Upstream Integration Marketing, Process Solutions, Merck
- **Seed train process intensification by using a novel high cell density cryopreservation approach. (detail of abstract-presentation from AMGEN see below)**
  Korbinian Morgenstern, Amgen Research GmbH, Munich, Germany
- **Advantages of specific cell culture media for expansion and N-1 perfusion.**
  Melanie Brandl, Proprietary Media, Process Solutions, Merck
- **Seed train process intensification by using a novel high cell density cryopreservation approach**
  Korbinian Morgenstern, Till Reinhardt, Rüdiger Neef, Mathias Käfer
  Process Sciences, Amgen Research (Munich) GmbH, München, Germany

Background and novelty: In the majority of mammalian cell culture processes, seed train unit operation accounts for the most part of the production period. The time increases substantially with production scale since additional expansion steps with increasing cell culture volumes are required to generate sufficient amount of cell mass for the next scale up step. While an extended pre-culture expansion time is a key source for process variability and pose a higher risk for contamination, process intensification strategies can help to reduce cycle time, process variability and contamination risk to a minimum.

The high cell density cryopreservation (HCDC) plays an important role in seed train process intensification by freezing cells at high concentration in specialized single-use bag assemblies. With the use of these frozen seed train intermediates the production cycle time, batch-to-batch variability and risk of contamination can be substantially reduced. As single cell source the seed train intermediates can be used at multiple stages in drug process development and manufacturing campaigns enabling a shorter turnover time and a higher flexibility.

Experimental approach: In this study, we determined the optimum conditions in terms of cell densities, freeze and thaw temperatures, and DMSO exposure for internally used CHO cell lines. A high cell density culture was generated in a perfused N-1 bioreactor and filled into customized single use bag assemblies at different conditions. The frozen N-1 seed train intermediates were then used to inoculate small scale batch and perfusion bioreactors to directly compare cell culture growth and productivity to a reference perfusion process using a standard seed train.

Results and discussion: In this study, we demonstrate that production bioreactors inoculated from frozen N-1 seed train intermediates in HCDC bags achieve an equivalent growth and production performance when it is compared to a reference perfusion process. Optimum conditions for bag fill, freeze and thaw were evaluated with a shake flask culture cryovial freezing experiment beforehand. In addition, the fill and freeze procedure was adjusted as well resulting in a more simplified handling of the HCDC bag assemblies.

SARTORIUS SPONSORED WORKSHOP
SUNDAY 5TH MAY 13:30-15:00 · AUDITORIUM 10

Driving value through intensified bioprocessing

Moderator: Miriam Monge (Sartorius)

Summary: Cell culture Process Intensification is a hot topic, especially because it enables commercial scale production from flexible and low cost single-use facilities. As indicated in the BPOG technology roadmap, in many cases perfusion approaches are used for cell culture intensification, e.g. to generate high volume, high cell density cell banks, to minimize the number of seed train steps, or to inoculate the main bioreactors at high cell density to improve its volumetric productivity. Perfusion approaches are also used in the final N-stage bioreactors, dramatically increasing volumetric outputs and even achieving over 50 g/L (cumulative titer) in around 3 weeks.

However, to efficiently develop all these different perfusion approaches, especially when switching from regular Fed Batch approaches in early development, to perfusion enabled intensified approaches in late development requiring comparable product quality, has been cumbersome so far, in particular due to the lack of representative high throughput scaled-down perfusion process development tools.

Recently, suppliers like Sartorius Stedim Biotech, have launched new tools and services for efficient perfusion cell culture development and implementation at large scale.

In this workshop, we will demonstrate, through industry use cases, the comprehensive product and services toolbox developed by Sartorius Stedim Biotech enabling rapid development of robust intensified processes, including n-1 perfusion and n-stage perfusion approaches such as intensified Fed Batch or continuous perfusion. Results will be shared on the new ambr15, for clone and media screening in 'perfusion' mode, as well as ambr250 HT perfusion process development results. Furthermore, (very) high cell density seed train data from RM perfusion bioreactors up to 100 L scale (!) will be shared. Having a perfusion filter sheet welded into the bottom of the RM bag, these systems present a highly cost efficient seed train intensification alternative.

WORKSHOP STRUCTURE:

- **The latest tools for upstream process intensification and integration**
  Gerben Zijlstra (Sartorius)
- **Reduction of Unit Operations in Animal Cell Culture Processes**
  Detlef Eizenkraetzer (Roche Diagnostics)
- **A Versatile Cell line Generation Toolbox for the Development of Intensified CHO Processes**
  Dirk Mueller (Sartorius)
- **Simple and robust large-scale high-density perfusion seed culture expansion in an internal membrane-filtration single-use bioreactor**
  Viviane Salou (Novartis)

INFORS HT SPONSORED WORKSHOP
SUNDAY 5TH MAY 13:30-15:00 · AUDITORIUM 11

Very large-scale screening in micro-wells, smart data and a new digital solution – paths to the future.

Abstract: The topics which INFORS HT will present are about creating bridges to the future. Bioprocesses use very sophisticated equipment. That capability can be used to speed up product development and this is already happening. However, biotechnology has yet to fully embrace some concepts driving other industries.

In this session, we will present how new, very large-scale screening solutions push the need for better digitalization of bioprocesses. We will describe how bioprocessing data can be collected in a single repository and transferred through smart modeling tools to create information, support decision taking and create an automated process control feedback.

WORKSHOP STRUCTURE:

- **From Screening to Scaleup, a Platform for Handling a Range of Cell Culture Needs**
  Andrew Magno (INFORS HT, USA)
- **Moving bioprocess data towards smart data and into the cloud, the first steps**
  Eric Abellan (INFORS HT, CH)
- **Transforming bioprocess data into valuable information and proactive decision support through hybrid modeling**
  Michael Sokolov (Datahow AG, CH)

MERCK SPONSORED WORKSHOP 2
SUNDAY 5TH MAY 13:30-15:00 · AUDITORIUM 12

Upstream Bioprocess Development: Getting it Right the First Time

The first challenge in developing a new biologic drug is to select a partner who will develop the production cell line. The workhorse for biologic drug manufacture is the CHO cell line and the number of cell lines derived from CHO cells illustrate the diversity of the CHO-based systems. However, not all CHO cells are created equal, and the search for the best-producing clone is often compared with looking for a needle in a haystack. Certain strategies can be employed in the process of engineering CHO cells to increase the cells' productivity, with the goal being the selection of a clone that produces a high titer, high quality protein product. As time and cost are of essence in the quest to meet development timelines and advance to the next phase in the development lifecycle, to achieve the desired result, the need to establish the product's structural and functional characteristics is as important as the need to develop a high-expressing cell line. Collaborating with a partner that is able to provide a well optimised cell line development platform coupled with comprehensive bio analytical tests is a key to successful biological drug development.

This session will review strategies that can be applied in the process of cell line development, to improve cell productivity and achieve high titers, including expression cassette design and statistical methodologies, and investigate a few of the analytical approaches that may be applied during the various stages of the cell line development process. From defining the core structure, measuring impurities and glycan profiling with high-throughput techniques, such as CE-LIF, during the establishment of stable cell pools, to assessing the binding, structural and functional characteristics via sensitive SPR, Mass Spectrometry analytics and cell-based methods at the wider and final clone selection stage. In addition to this, the session will also attempt to interactively understand what future testing requirements may be, considering the conventional and new promising technologies that may be implemented during this process.

WORKSHOP STRUCTURE:

- **High-titer expression in CHO cells, importance of the cell type, expression cassette design and statistical approach**
  Murielle Verges, Upstream Process Development, BioReliance® End-to-End Solutions, Merck
- **Selecting the right candidate during clone characterisation with various analytical approaches**
  Daniel Galbraith, Product Characterization Strategy, Merck