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Cambridge Healthtech Institute's Fourth Annual

August 20-23, 2012 | Renaissance Boston Waterfront Hotel, Boston, MA

THE BIOPROCESSING SUMMIT

Practical Solutions for Today's Laboratory Challenges

CONCURRENT PROGRAMS

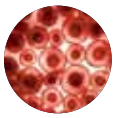
AUGUST 20-21


Optimizing Cell Culture Technology


Overcoming Purification Challenges


Higher-Order Protein Structure

AUGUST 22-23


Optimizing Cell Line Development


Scaling Up & Down with Optimized Bioreactors


High-Concentration Protein Formulations

AUGUST 20

Pre-Conference Short Courses

(SC1) Optimizing Media – Achieving Super Soup

(SC2) Design and Interpretation of Accelerated Stability Studies of Biologics

(SC3) Protein Expression in Non-Mammalian Host Systems – *E. coli*, Baculovirus & Yeast

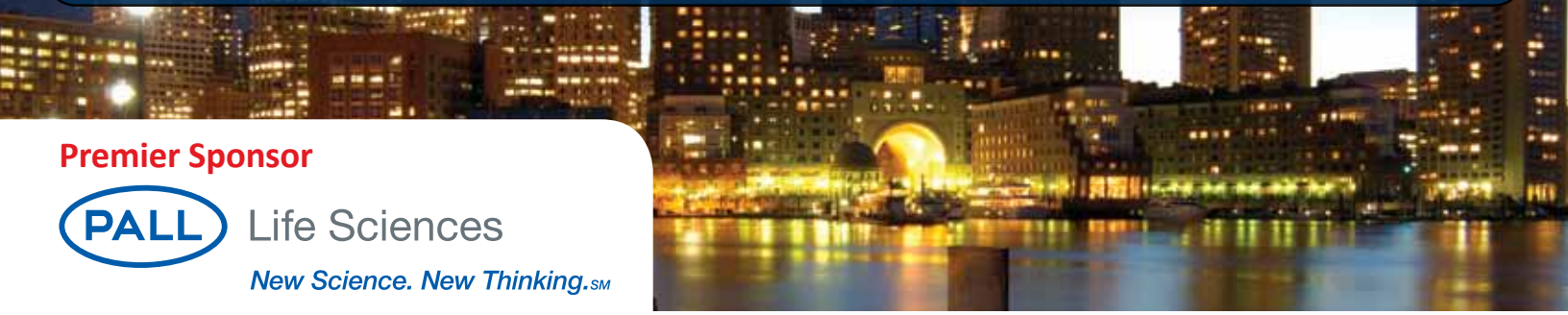
AUGUST 21

Dinner Short Courses

(SC4) Sub-Visible Particle Analysis in High-Concentration Protein Formulations

(SC5) Connecting the Dots: Understanding Your Bioprocess Data

(SC6) Transient Protein Production in Mammalian Cells: A Short Story



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BioprocessingSummit.com

The Bioprocessing Summit brings together international leaders to discuss today's bioprocess issues from cell line selection to manufacturing. The Summit provides practical details in a relaxed, congenial atmosphere that promotes information exchange and networking. This year, a "Formulation Foci" has been added to delve into protein structure and formulations.

This leading bioprocess meeting is hosted by Cambridge Healthtech Institute (CHI) in Boston each summer along the lively and cosmopolitan harbor waterfront with its restaurants, cafes, museums and art galleries, and within easy reach of historical sites, Faneuil Hall and the famed North End.

Conference-at-a-Glance

Monday Morning (August 20)	Pre-Conference Short Courses*		
Monday Afternoon	Optimizing Cell Culture Technology	Overcoming Purification Challenges	Higher-Order Protein Structure
Tuesday Morning (August 21)	Optimizing Cell Culture Technology	Overcoming Purification Challenges	Higher-Order Protein Structure
Tuesday Afternoon	Optimizing Cell Culture Technology	Overcoming Purification Challenges	Higher-Order Protein Structure
	Dinner Short Courses*		
Wednesday Morning (August 22)	Optimizing Cell Line Development	Scaling Up & Down with Optimized Bioreactors	High-Concentration Protein Formulations
Wednesday Afternoon	Optimizing Cell Line Development	Scaling Up & Down with Optimized Bioreactors	High-Concentration Protein Formulations
Thursday Morning (August 23)	Optimizing Cell Line Development	Scaling Up & Down with Optimized Bioreactors	High-Concentration Protein Formulations

**Separate registration required*

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Sponsor & Exhibitor Opportunities

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space and branding, as well as the use of the pre- and post-show delegate lists. Sponsorship allows you to achieve your objectives before, during, and long after the event. Any sponsorship can be customized to meet your company's needs and budget. Signing on earlier will allow you to maximize exposure to hard-to-reach decision makers.

Sponsored Presentations

Showcase your solutions to a guaranteed, highly-targeted audience. Package includes a 15 or 30-minute podium presentation within the scientific agenda, exhibit space, on-site branding and access to cooperative marketing efforts by CHI.

Breakfast & Luncheon Presentations

Opportunity includes a 30-minute podium presentation. Boxed lunches are delivered into the main session room, which guarantees audience attendance and participation. A limited number of presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Invitation-Only VIP Dinner/ Hospitality Suite

Sponsors will hand-pick their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects. Evening will be customized according to sponsor's objectives (e.g. purely social, focus group, reception style or plated dinner, plated dinner with specific conversation focus).

CHI Lead Generation

CHI can help you with lead generation throughout the year. Our internal database includes over 800,000 prospects in the life sciences. By leveraging the database and mining for your specific requirements, we can produce multiple custom projects which will deliver your prospective buyers.

- Web Symposia
- Podcasts
- White Papers
- Custom Market Research Surveys
- And More!

Exhibit Information

Exhibitors will enjoy facilitated networking opportunities with qualified decision makers at The Bioprocessing Summit, making it the perfect platform to launch a new product, collect feedback and generate new leads. Exhibit space sells out quickly, so reserve yours today!

Additional promotional opportunities available!

For additional information, please contact:

Suzanne Carroll
Senior Business Development Manager
781-972-5452
scarroll@healthtech.com

Reserve your exhibit space by May 18 & SAVE $300!

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Selexis SA
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Thomson Instrument Co.

Monday Pre-Conference Short Courses*
August 20, 2012 • 8:30 - 11:30am

SC1 Optimizing Media – Achieving Super Soup

To grow mammalian cells, researchers need to provide an optimal *in vitro* environment. The key feature of successful cell growth is the culture medium. "Achieving Super Soup" requires finesse and know-how in order to combine the right ingredients at the right times under the right conditions to achieve high titers. This workshop will provide a foundation for optimizing cell culture media presented by real-world experts who will also tailor a portion of the course to fit concerns and challenges faced by the workshop participants.

- Feed strategies
- Media formulation
- Oxygen
- Providing optimal conditions
- Process optimization
- Analytical tools
- Increasing cell densities
- High-throughput protocols

Instructors:

Robin Ng, Ph.D., Senior Bioengineer, Cell Culture Process Development, Shire Human Genetic Therapies

Albert Shkurti, Manufacturing Manager, Media and Buffer Prep, Shire Human Genetic Therapies

Michael Butler, Ph.D., Professor, Microbiology, University of Manitoba

Jörg von Hagen, Ph.D., Head, Process Development, Merck KGaA

SC2 Design and Interpretation of Accelerated Stability Studies of Biologics

Large molecule drugs are sensitive to environmental factors and require advanced analytical capabilities integrated with cGMP-compliant stability programs to evaluate their quality with time stored under various conditions. Stability studies for biologics and biosimilars can require a diverse range of analytical techniques conducted in accordance with GLP or cGMP requirements. Alternative analytical techniques may also be required to investigate post-translational modifications.

- Understanding stability study requirements per ICH guidelines
- Understanding analytical methodology challenges pertaining to monitoring stability, particularly for product registration purposes
- Utilizing advanced analytical technologies in terms of what insights they give us and how they may be incorporated in a cGMP-compliant stability study
- Designing stability protocols that take into account the idiosyncrasies of biologics as well as formulation, analytical, manufacturing, and regulatory knowledge gained during development

Instructors:

Danny Chou, Ph.D., Former CSO, Protein Characterization, NorthStar Bio

Sheila Magil, Ph.D., Senior Consultant, Bioprocess Technology Consultants, Inc.

Olivier Brass, Ph.D., Scientist, Discovery, Sanofi Pasteur

SC3 Protein Expression in Non-Mammalian Host Systems – *E.coli*, Baculovirus & Yeast

Specialized protein expression systems offer the potential for cheaper production, quicker results and simpler sourcing of raw materials. Yet, there is often a resistance to move into an expression system that is unfamiliar or not considered "mainstream." This course will provide an overview of the most popular non-mammalian expression systems.

- Selecting the right host system
- Mastering the system to achieve productivity
- Host cell engineering to improve product quality
- Development of protein expression assays
- Development and optimization of protein purification processes
- Automating high-throughput protein expression and purification
- Scaling up production

Instructors:

Dominic Esposito, Ph.D., Director, Protein Expression Laboratory, SAIC-Frederick, Inc.

Donald L. Jarvis, Ph.D., Professor, Molecular Biology, University of Wyoming

Piotr Bobrowicz, Ph.D., Director, Technology and Platform Development, Adimab, LLC

Tuesday Dinner Short Courses*
August 21, 2012 • 6:00 - 9:00pm

SC4 Sub-Visible Particle Analysis in High-Concentration Protein Formulations

The need to monitor, measure and control sub-visible particulates in bio-pharmaceutical formulations has been emphasized in recent publications and comments by regulators. Some of these particulates can be highly transparent, fragile and unstable. In much of the size range of concern, a practical measurement method with adequate sensitivity and repeatability has been difficult.

- Development and qualification of a method or complementary methods for sub-visible particle counting for a high concentration protein formulation
- Overcoming the issues inherent in high-concentration formulations and container-closure systems
- Understanding the latest tools, technologies and methodologies
- How to ensure that the resulting method is robust, reproducible, and suitable for use in a QC environment

Instructor: Kevin Mattison, Ph.D., Principal Scientist, Bioanalytics, Malvern Instruments

Mary Beth Pelletier, Ph.D., Scientist, Analytical Technology, Biogen Idec

Wei Qi, Ph.D., Research Associate, University of Colorado, School of Pharmacy

SC5 Connecting the Dots: Understanding Your Bioprocess Data

Bioprocess data is the key to understanding and optimizing your processes – both in development and in continuous improvement. Looking at a simple spreadsheet is no longer sufficient. We need more powerful tools to enable us to see the big picture and to make sense of all the available data.

This introductory course is specifically aimed at biologists, process engineers, managers and others actively involved in the process and does not require any mathematical understanding or knowledge. It will provide a seamless comprehension of the most important principles and introduce the most effective tools.

- Fundamentals of successful bioprocess data analysis
- Common methods explained: Understanding the statisticians
- Nuts & bolts of applied process data analysis
- Root cause analysis
- Leveraging all the data
- Seeing is believing: Convincing your colleagues

Instructor: Juergen von Frese, Ph.D., Managing Director, Data Analysis Solutions, DA-Sol GmbH

SC6 Transient Protein Production in Mammalian Cells: A Short Story

This short course will introduce the fundamental concepts needed to establish transient protein production in mammalian cells. This will allow for the rapid generation of milligram to gram quantities of recombinant proteins for therapeutic, functional, and structural studies. The course will combine instruction and case studies in an interactive environment.

- A brief overview of protein expression systems
- An in-depth introduction to mammalian transient expression systems
- Examination of the key elements necessary for the establishment of a mammalian transient production system
- Scalable transient protein production
- Optimizing the transient protein production process

Instructors:

Richard Altman, M.S., Research Scientist, Alexion Pharmaceuticals

Dominic Esposito, Ph.D., Director, Protein Expression Laboratory, SAIC-Frederick, Inc.

Henry C. Chiou, Ph.D., Senior Manager, Molecular Biology, Life Technologies Corporation

**Separate Registration Required*

Optimizing Cell Culture Technology

Enhancing Knowledge for Growing Mammalian Cells

MONDAY, AUGUST 20

8:00 am Pre-Conference Registration and Morning Coffee

8:30 - 11:30 Recommended Short Courses*

SC1 Optimizing Media – Achieving Super Soup

SC3 Protein Expression in Non-Mammalian Host Systems – *E.coli*, Baculovirus & Yeast

Separate registration required, please see page 3 for details

11:30 am - 5:30 pm Main Conference Registration

OPTIMIZING CELL CULTURE PROCESSES

1:00 Chairperson's Opening Remarks

» 1:10 OPENING KEYNOTE PRESENTATION:

Implementation of Risk Mitigation Strategies for Upstream Operations

Ayda Mayer, Ph.D., Director, Process Development, Human Genome Sciences, Inc.

Case studies on implementing risk mitigation strategies and methods to achieve operational excellence in manufacturing will be presented. These initiatives are critical to continuously produce safe and quality products, further understand and improve the production process, and enhance the robustness of the product supply chain.

» 1:45 FEATURED PRESENTATION:

Technology for Accelerating Cell Line Selection and Increasing Fed-Batch Production

James M. Piret, Ph.D., Professor, Chemical & Biological Engineering, Genome Science and Technology, University of British Columbia

Production cell line selection is typically the longest step in the development of new mammmalian cell manufacturing processes. To accelerate this step, we have developed a microfluidic platform for the clonal culture and the antibody productivity assessment of suspension-adapted mammalian cells. The robustness, flexibility and scalability of this microfluidic platform provide unique advantages for the rapid generation of clonal cell lines.

2:15 The Challenges Associated with Establishing Product Quality Comparability while Making Process Modifications

Natarajan Vijayasankaran, Ph.D., Engineer II, Late Stage Cell Culture, Genentech, Inc.

This presentation will focus on a case study of the development of a chemically defined cell culture process for production of a monoclonal antibody that is in later stages of clinical development. The challenges associated with matching product quality attributes to protein synthesized from an earlier version of the process will be discussed. Process and culture medium modifications combined with mathematical modeling approaches, when appropriate, used to establish product quality comparability.

2:45 Refreshment Break

OPTIMIZING UPSTREAM PROCESSING

3:15 Tackling the Challenges of Designing a Platform USP for the Next Generation Bispecific Antibody Format, the Kappa/Lambda-Body

Laura Di Grazia, M.S., Head, Upstream Processing, Manufacturing, NovImmune SA

Novimmune has recently developed a novel therapeutic bispecific antibody format, the Kappa/Lambda-body, which displays the innovative particularity of presenting two different light chains (one Kappa and one Lambda), with a common heavy chain: thus, generating a unique fully human bispecific product that is indistinguishable from a standard IgG. The talk will address the manufacturability of this format using a chemically defined, animal component free process, by demonstrating the successful expression of Kappa/Lambda-bodies in semi-stable CHO pools and stable CHO cell lines, both in shake flask and bioreactor models. Cell line screening approaches for selecting high bispecific Ab-producing cell lines were optimized and challenges were overcome using innovative analytical techniques to distinguish the bispecific from the monospecific format, based either on differential antibody charge/hydrophobicity or using a specific ELISA format. The impact of cell line Kappa/Lambda chain ratio on downstream processing will also be discussed. Overall, cell cultures presented comparable total mAb productivities and growth characteristics to those expressing the corresponding kappa or lambda monospecific antibodies.

3:45 Effect of Raw Materials and Processing Technologies of Dry Powder Media on Titer and Beyond

Jörg von Hagen, Ph.D., Head, Process Development, Merck KGaA

In the area of mammalian cell culture, media solubility, homogeneity, batch-to-batch consistency, and other classical physico-chemical properties are fundamentals. In different cases, the effect of solubility and the processing of critical ingredients will be presented. Moreover, the presentation will capture the bridging impact of raw material selection and treatment on the critical quality attributes of new biological entities. As platform media and feed are established in the biopharmaceutical industry, there is a need for media suppliers to allow for high-concentrated liquids converted from dry powder. These aspects are addressed and important steps to achieve high-concentrated soluble feeds are presented.

4:15 Small-Group Breakout Discussions

This session provides the opportunity to discuss a focused topic with peers from around the world in an open, collegial setting. Select from the list of topics available and join the discussion to share ideas, gain insights, establish collaborations or commiserate about persistent challenges. Then continue the discussion as you head into the lively exhibit hall for information about the latest technologies.

5:15 Breakout Group Summaries

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 End of Day

TUESDAY, AUGUST 21

8:00 am Registration and Morning Coffee

CHO CELL CULTURE

8:25 Chairperson's Remarks

» 8:30 FEATURED PRESENTATION:

Novel Approaches for the Prediction and Isolation of Highly Productive Recombinant CHO Cell Lines

Mark Smales, Ph.D., Professor, Biotechnology, School of Biosciences and Centre for Molecular Processing, University of Kent

The ability to generate high producing recombinant mammalian cell lines has been greatly enhanced in recent years through the development of approaches such as high-throughput screening technologies. Despite this, the ability to predict the phenotypic behavior of specific cell lines in the bioreactor early in the cell line development process remains challenging. We have developed new screening and predictive performance approaches that allow the prediction of a cell line's performance at the bioreactor scale early in the cell line construction process. Here this approach and its application to cell line construction will be discussed.

9:00 Cell Culture Platform Application in an Early-Stage mAb Project

Yao-Ming Huang, Ph.D., Principal Engineer, Biogen Idec, Inc.

9:30 Towards Dynamic Metabolic Flux Analysis in CHO Cell Cultures

Maciek R. Antoniewicz, Ph.D., Assistant Professor and DuPont Young Professor, Chemical & Biomolecular Engineering, University of Delaware

The metabolism of Chinese hamster ovary (CHO) cells changes dramatically during a fed-batch culture as the cells adapt to a changing environment and transition from an exponential growth phase to stationary phase. In this talk, I will highlight progress on 13C-metabolic flux analysis in CHO cells and discuss novel techniques for dynamic metabolic flux analysis. Application of these new tools may allow identification of intracellular metabolic bottlenecks at specific stages in CHO cell cultures and eventually lead to novel strategies for improving CHO cell metabolism and optimizing biopharmaceutical process performance.

10:00 Characterization of a High-Throughput Micro Bioreactor: Process Control, Consistency and Comparability in CHO Clone Ranking and Process Optimization Studies

Sponsored by TAP Biosystems

Tim Ward, Director, Strategic Product Marketing, TAP Biosystems

The ambrTM system combines the benefits of single use labware and automated liquid handling to provide a high-throughput microscale bioreactor system with capability for both batch and fed-batch cell cultures. This talk introduces the ambr, its potential in bioprocess development and, through discussion of field data gathered to date, demonstrates its effectiveness in CHO cell culture applications: clone screening, process optimization, and design of experiments.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing

OPTIMIZING THROUGH NEXT-GENERATION TECHNOLOGIES

11:00 Dynamic Transcriptome Profiling for Cell Culture Process Comparisons

Karthik P. Jayapal, Ph.D., Staff Scientist, Cell Culture Development, Global Biological Development, Bayer HealthCare Pharmaceuticals

Existing literature on genomics for mammalian cell culture pertains primarily to non-producing cells or those in exponential growth phase which may not have direct relevance to commercial manifacturing. In this study, we employed DNA microarrays to analyze the temporal transcriptome dynamics of commercial recombinant protein-producing cells in two processes – (1) a long-term high-flow non-mAb perfusion process and (2) a ~2 week mAb fed-batch process. In the former case, despite the presumable steady-state nature of the perfusion process, we identified certain subtle changes in the cell's transcriptome which correlated with cell age while, at the same time, demonstrating the utility of genomics technologies for scale-down model validation. In the latter example, we show a preliminary investigation of lactate production and consumption phenotypes to identify clusters of genes correlated with lactate production.

11:30 Mammalian Cell Fluid Mechanics and Scale-Up Considerations

Jeffrey J. Chalmers, Ph.D., Professor, Chemical & Biomolecular Engineering, Ohio State University

Suspension animal cell culture is now routinely scaled up to bioreactors on the order of 10,000 liters, and greater, to meet commercial demand. However, the concern of the "shear sensitivity" of animal cells still remains, not only within the bioreactor, but also in the downstream processing. The perception of "shear sensitivity" has historically put an arbitrary upper limit on agitation and aeration in bioreactor operation; however, as cell densities and productivities continue to increase, mass transfer requirements can exceed those imposed by these arbitrary low limits. This presentation will mainly focus on publications from both academia and industry regarding the effect of hydrodynamic forces on industrially relevant animal cells, and on general observations with respect to scale-up.

12:00 pm Accelerating Bioprocess Optimization through the Use of Next-Generation Genomics Technologies

Len van Zyl, Ph.D., Research Assistant Professor, College of Natural Resources, North Carolina State University; CEO, ArrayXpress, Inc.

In this presentation, we explain the financial and scientific benefits of incorporating Next-Generation Genomics (NGG) technologies into standard practices for research and development of therapeutic biologics and their manufacturing development and optimization. We will give experience-based examples of how a systems biology approach improved our understanding of a production organism's biology, and provided detailed insight of how the cell's genetic machinery responded to changes in Critical Process Parameters. The results directly contributed to improved product yields, product quality, and overall process stability.

12:30 Luncheon Presentation: A New Bench Scale Single Use Bioreactor System

Sponsored by PALL Life Sciences

Charles Golightly, Ph.D., Director of Marketing, Pall Life Sciences

Development of a new bench scale "rocker style" single use bioreactor will be described, with discussion of physical parameters for design space definition and performance measurement; with comparison to industry standard systems. Presentation will conclude with results from CHO batch culture trials for design validation, showing significant increases in achievable cell densities and cell productivity.

ANALYTICAL TOOLS TO ENHANCE PRODUCTIVITY

1:55 Chairperson's Remarks

2:00 Assessing and Controlling the Raw Material Variability in Mammalian Cell Culture

Seongkyu Yoon, Ph.D., Assistant Professor, Chemical Engineering & Director, BioManufacturing Center, University of Massachusetts, Lowell

Biologics manufacturers are facing challenges due to lot-to-lot variations of critical raw material, lack of appropriate measurements of intermediate process parameters, and even inappropriate analytical test methods of final product quality attributes. The presentation will illustrate how to characterize raw material variations and its impact in cell culture processes. Raw materials and media will be analyzed for lot-to-lot variation characterization using analytical spectroscopies. The collected data will be used to develop multivariate regression models between raw material and cell-culture performance for prediction of viable cell density and cell viability. These models can be used for subsequent batches to compensate raw material variabilty and accurately predict the cell-culture performances.

2:30 Control of Glycosylation Profiles in Cell Bioprocesses

Michael Butler, Ph.D., Professor, Microbiology, University of Manitoba

The glycosylation profile of proteins secreted from mammalian cells in culture

is dependent upon critical parameters associated with the host cell line, the culture media, the mode of culture and the specific protein synthesized. It is important to control these parameters in an industrial bioprocess to ensure consistency of the final product and maximum bioactivity. The critical culture parameters will be discussed in the context of bioprocesses in which fine control is necessary to synthesize glycoproteins for the production of highly efficacious biopharmaceuticals with consistent structural profiles.

3:00 Permittivity Measurements in Cell Culture Processes

Sven Ansorge, Ph.D., Development Scientist I, Alexion Montréal Corp.

In routine cell culture operations, process characterization and supervision relies primarily on offline sampling and analysis resulting in extended response times to process events and variations. Further efforts are thus needed to implement *real time* monitoring tools that allow for advanced and rationalized process control strategies. We provide here insights into the recent progress made concerning the use of *in situ* permittivity-based sensors in cell culture processes. Published and unpublished findings from several groups including work on CHO, insect (Sf-9) and HEK293 cell lines are presented and discussed. It is demonstrated that this technology allows tracking of the biovolume content (i.e., cell growth), the metabolic activity and, in particular in the case of viral productions, product release.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing

NEW DIMENSIONS FOR CELL CULTURE

4:15 Taking Cell Culture to the Third Dimension

Chi Zhang, Ph.D., Research Scientist, Credo Biomedical Pte. Ltd.

Highly functional *in vitro* cultured cells are of great usefulness in various applications such as cell-based testing, constructing large tissues and pathological research. The key to culturing functional cells *in vitro* is to recapitulate an *in vivo*-like cellular microenvironment which allows extensive mechanical support as well as cell-cell, cell-matrix and cell-soluble factor interactions. The development of 3D cell culture devices has made possible the controlling of cellular microenvironments, phenotypes and behaviors under novel experimentations. Microfluidic systems are believed to be advantageous over other systems in terms of a more controllable microenvironment, however, few attempts to engineer a soluble microenvironment for extensive cell-soluble factor interactions within these microfluidic systems are reported. Hence, there is a great need to develop an *in vitro* model with well-controlled soluble microenvironment to primarily supplement *in vivo* animal models, thus reducing the cost and ethical issues surrounding animal experimentation.

4:45 A Scaffoldomics Approach to Optimizing Synthetic 3D Cell Niches

Carl G. Simon, Jr., Ph.D., Biologist, Polymers Division, Biomaterials Group, National Institute of Standards & Technology (NIST)

We have developed scaffold library approaches to systematically screen the effect of scaffold properties on cell function in 3D. Our most recent work has focused on the effect of 3D scaffold structure on the morphology and differentiation of primary human bone marrow stromal cells (hBMSCs). We have found that some scaffold structures promoted hBMSC differentiation while others enhanced proliferation. Microarray screening revealed that each scaffold structure induced a unique and reproducible gene expression signature, indicating that hBMSCs had a precise response to each architecture. Hierarchical cluster analysis showed that treatments sorted by scaffold structure and not by composition, suggesting that structure was more important than chemistry. The effects of scaffold structure appeared to be mediated by cell shape, where substrates that induced differentiation also induced a similar hBMSC morphology.

5:15 End of Conference

Hotel & Travel Information

Conference Venue and Hotel:
Renaissance Boston Waterfront Hotel
606 Congress St.
Boston, MA 02210
Phone: 617-338-4111

Hotel Reservations:
Online: www.bioprocessingsummit.com
Discounted Room Rate: $199 s/d
Cut-off Date: July 23, 2012

Please make your reservation online or call the hotel directly to reserve your sleeping accommodations. Identify yourself as a Cambridge Healthtech Institute conference attendee to receive the discounted room rate. Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted on a space- and rate-availability basis. Rooms are limited, so please book early.

Flight Discounts:
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- Call Hertz at 1-800-654-3131 and use Hertz Convention Number 04KL0003
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Inaugural

Overcoming Purification Challenges

Conquering Bottlenecks to Achieve Pure Protein

August 20-21

MONDAY, AUGUST 20

11:30 am - 5:30 pm Main Conference Registration

CONQUERING CHALLENGES

1:00 pm Chairperson's Opening Remarks

» 1:10 OPENING KEYNOTE PRESENTATION:

Addressing Challenges of Membrane Protein Expression, Purification and Stabilization

Lawrence J. De Lucas, Ph.D., Director, Center for Macromolecular Crystallography (CMC), University of Alabama, Birmingham

This presentation will compare strategies using a variety of protein/peptide tags to provide an early quality assessment for protein expression, potential yield, purity and homogeneity of integral membrane proteins (IMPs). In addition, several examples will be presented for high-throughput self-interaction chromatography used as a method to improve membrane protein solubility and stability.

1:45 Expression and Purification of Diacylglycerol Acyltransferases

Heping Cao, Ph.D., Principal Research Scientist, Southern Regional Research Center, U.S. Department of Agriculture

Diacylglycerol acyltransferases (DGATs) are integral membrane proteins that catalyze the last and rate-limiting step of triacylglycerol biosynthesis in eukaryotic organisms. DGAT knockout mice are resistant to diet-induced obesity and lack milk secretion. DGAT genes have been identified from at least 83 organisms, but none of the enzymes from any organism had been expressed and purified from bacterial expression systems. We developed the first procedure for producing full-length recombinant DGAT proteins from any species using an *E. coli* expression system.

2:15 Talk Title to be Announced

David W. Wood, Ph.D., Associate Professor, Chemical & Biomolecular Engineering, The Ohio State University

2:45 Refreshment Break

AFFINITY PURIFICATION

3:15 The Exploitation of *S. cerevisiae*: A Comprehensive Design of Affinity Tags and Overview of Microbial Applications

Carissa Young, Ph.D., Research Scientist, Delaware Biotechnology Institute, Department of Chemical and Biomolecular Engineering, University of Delaware

To improve the functional production of secreted or membrane proteins (e.g., ligand-binding yields indicative of active receptors), we have generated versatile yeast expression cassettes that incorporate numerous tags for identification and purification, and to assess protein interactions, protein structure/function, and intracellular localization. To reference selective organelles in *S. cerevisiae*, endogenous proteins were designed with codon-optimized fluorescent protein variant resulting in a valid assessment of heterologous protein subcellular localization. Furthermore, we have established methodologies to investigate the role of cellular quality control and its modulation during heterologous protein expression, focusing specifically on the unfolded protein response (UPR), autophagy, and ER associated degradation (ERAD) pathways.

3:45 Analyzing Cell Signaling Pathways with Affinity Purification-Mass Spectrometry

Alexey Veraksa, Ph.D., Assistant Professor, Biology, College of Science & Mathematics, University of Massachusetts, Boston

The study of cell communication mechanisms has been facilitated by the advances in protein complex purification and analysis. In my laboratory, we use affinity purification followed by mass spectrometry to map the structure of signaling networks, with follow-up functional studies in model systems. I will present the evolution of preferred tags used in my lab for affinity purification of protein complexes from higher eukaryotic cells and tissues, and will discuss the advantages and potential limitations of this approach.

4:15 Small-Group Breakout Discussions

This session provides the opportunity to discuss a focused topic with peers from around the world in an open, collegial setting. Select from the list of topics available and join the discussion to share ideas, gain insights, establish collaborations or commiserate about persistent challenges. Then continue the discussion as you head into the lively exhibit hall for information about the latest technologies.

5:15 Breakout Group Summaries

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 End of Day

TUESDAY, AUGUST 21

8:00 am Registration and Morning Coffee

BREAKTHROUGH TECHNOLOGIES

8:25 Chairperson's Remarks

» 8:30 FEATURED PRESENTATION:

Protein Adsorption and Transport in Polymer-Derivatized Ion Exchangers

Abraham Lenhoff, Ph.D., Allan P. Colburn Professor of Chemical Engineering, Chemical and Biomolecular Engineering, University of Delaware

Incorporation of hydrophilic polymers has become widely used by many adsorbent manufacturers in seeking increased capacity and improved performance of particulate, membrane and monolithic ion exchangers for use in bioprocessing. While such adsorbents are used in much the same fashion as their underivatized counterparts, the mechanisms involved and some features of the performance attained may differ in important ways. This presentation will provide an overview of the structures of the derivatized materials and of similarities and differences in performance relative to their more conventional counterparts, with the goal of providing guidance for both adsorbent selection and design of new materials.

9:00 mAb-Aggregate Analysis in Two Minutes: Application of Tandem and Parallel Interlaced HPLC

Patrick Diederich, Ph.D., Scientist, Institute of Process Engineering in Life Science, University of Karlsruhe

Analytical techniques that match a high-throughput process development approach are still not common or well characterized and often come along with lower precision. Quantitatively precise analytics such as HPLC techniques usually require long assay times. In this talk, methods are presented that show how HPLC analytics nevertheless can be utilized as high-throughput compatible analytics. Most promising, the potential of combining interlaced sample injection with parallel, isocratic operation of two chromatography columns on a single HPLC system is demonstrated. By this methodology, the assay time for antibody aggregate analysis by size exclusion chromatography was reduced to less than two minutes per sample without sacrificing precision.

9:30 Rescue of Non-Expressing Protein Targets via Fusion to Maltose Binding Protein: Perspectives from a High-Throughput Protein Expression and Purification Pipeline

Stephen Nakazawa Hewitt, Ph.D., Senior Scientist, Department of Medicine,

Division of Allergy and Infectious Diseases, School of Medicine, University of Washington

Poorly expressing and insoluble protein expression are major obstacles for purification of recombinant proteins. We have developed several strategies for attempting rescue of these targets in a high-throughput manner in the context of a structural genomics effort. By modifying the cloning vector to include the highly soluble maltose binding protein expressed as a fusion tag, we are able to quickly attempt rescue of expression by simply moving PCR amplified inserts between various vectors.

10:00 Novel Hollow Fiber Membrane Adsorber, QyuSpeed™ D, Expands the Options Available in the Purification Tool Box

Sponsored by AsahiKASEI ASAHI KASEI BIOPROCESS

John Fisher, Senior Manager, Science & Technology, Asahi Kasei Bioprocess Inc.

Membrane adsorbers are a powerful tool for polishing steps in downstream biopharmaceutical processes due to their high flux, ease of use, and simple scale-up. QyuSpeed™ D (QSD), a DEA ligand-grafted reusable hollow fiber adsorber provides high-throughput, robust impurity clearance over a range of pH values and salt concentrations. Scalability of this magnitude coupled with the ability of QSD to capture high molecular weight protein targets more effectively than existing anion exhange resins make QyuSpeed™ D the ideal choice for eliminating impurities from biotherapeutics or plasma-derived products.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing

ANTIBODY PROCESSING

11:00 Debottlenecking Antibody Manufacturing Through the Use of Simplified Buffer Systems

Natraj Ram, Ph.D., Senior Group Leader, Purification, Technical Operations, Abbott Bioresearch Center

One of the key materials used in the manufacture of proteins are buffers. Buffer preparation requires a significant amount of space, time, and resources and could potentially be a bottleneck when dealing with high titer processes. In this presentation, the concept of using simplified buffer systems is introduced and demonstrated, as a means of reducing facility foot print, buffer volumes, buffer raw materials and possibly reducing manufacturing time.

11:30 Strategies to Streamline Two-Column Monoclonal Antibody Purification Platforms

Yun (Kenneth) Kang, Ph.D., Principal Scientist & Head, Purification Team, Bioprocess Sciences, ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company

In two-column mAb purification platforms, traditional Q column or, increasingly, Q membrane adsorber is used as a polishing step in a product flow-through mode. For mAbs with a low pI (< 7.0) or solubility issues under low ionic strength solution conditions, however, poor process performance is expected. We have developed a robust mAb purification platform which demonstrates high process yield and efficient clearance of impurities (HCP, HMW, host DNA, leached protein A) for those challenging antibodies.

12:00 pm Countercurrent Tangential Chromatography: New Single Use Technology for mAb Capture

Andrew L. Zydney, Ph.D., Department Head and Walter L. Robb Family Endowed Chair, Chemical Engineering, The Pennsylvania State University

Countercurrent Tangential Chromatography (CTC) is a new column-free purification and capture technology that holds great promise for purification of high-value recombinant proteins like monoclonal antibodies. CTC provided high-resolution antibody purification at very low pressures (< 7 psi) with excellent protein recovery. In addition, CTC is no longer limited by the constraints of packed columns, allowing the use of smaller chromatography beads with improved binding kinetics and throughput. These results clearly demonstrate the potential of using Countercurrent Tangential Chromatography for low-cost commercial antibody purification.

12:30 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

ANALYTICAL STRATEGIES

1:55 Chairperson's Remarks

2:00 Gaining Efficiency and Value During Process Characterization

Rick St. John, Ph.D., Senior Engineer, Purification Development, Biologics Department, Genentech, Inc.

2:30 Model-Based Rational Strategy for Chromatographic Resin Selection

Marcel Ottens, Ph.D., Assistant Professor, BioSeparation Technology, Department of Biotechnology, Faculty of Applied Sciences, Delft University of Technology

In this presentation, a model- based rational strategy for the selection of chromatographic resins is proposed and illustrated by evaluating three mixed mode adsorbents for the separation of a ternary model mixture of BSA, ovalbumin and amyloglucosidase. The main question addressed is selecting the most optimal chromatographic resin from a few promising alternatives. The methodology starts with chromatographic modeling, parameters acquisition and model validation, followed by model based optimization of the chromatographic separation for the resins of interest. Finally, the resins are rationally evaluated based on their optimized operating conditions and performance metrics such as product purity, yield, concentration, throughput, productivity and cost. The proposed model based approach could be a suitable alternative to column scouting during process development, the main strengths being the fact that resins are evaluated under their ideal working conditions, enabling a fair comparison. This presentation also demonstrates the application of column modeling and optimization to mixed mode chromatography.

3:00 Monitor and Control Critical Purification Attributes of Viral Glycoproteins as Vaccine Product Candidates

Julie Q. Hang, Ph.D., Senior Scientist and Group Leader, Vaccine Protein Biochemistry, MedImmune

Many recombinant viral surface glycoproteins are subunit vaccine targets in pre-clinical and clinical trials to induce humoral immune responses. Due to the complex nature of glycosylation, oligomerization and aggregation, purification products could introduce the product biophysical characteristics depending on purification processes. The changes showed impact on the vaccine immunogenicity. The strategies and case examples will be presented on how to use protein characterization tools to identify the critical purification attributes, and how to establish robust purification process to achieve consistent production specifications.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing

SPEEDING PURIFICATION PROCESSES

4:15 Three-Phase Partitioning in Micro- and Macro-Scale Protein Purification

William Ward, Ph.D., Associate Professor, Biochemistry and Microbiology, Rutgers University

Three-phase partitioning (TPP) was introduced in 1997, but this powerful protein purification technique has received only moderate recognition. Unlike any protein purification method known, TPP will semi-selectively release recombinant proteins from *E. coli*, purify the released protein to 80% homogeneity and remove all chromosomal DNA, scatter, turbidity, and viscosity. Simultaneously, TPP removes lipids, cell walls, and most pigments while concentrating the sample as much as 50-fold. All this is accomplished in less than 60 minutes and with minimal equipment. TPP is applicable to protein mini-preps and large scale purification processes.

4:45 The Protein Miniprep: High Purity Protein in 60 Minutes

David O'Connell, Ph.D., Senior Scientist, School of Medicine, University College Dublin

In protein preparation, the purification of highly purified functional protein is rarely described as very quick and very easy. This presentation shows novel approaches to gently purify proteins very quickly in a highly simplified manner, accessible to the novice and expert alike. This approach has the potential to become a staple protocol for all sizes of laboratory, academic to industrial. This novel and powerful approach will be highlighted with interesting case studies of protein preparations of different functional proteins.

5:15 End of Conference & Registration for Dinner Short Courses

6:00 - 9:00 pm Recommended Dinner Short Course*

SC6 Transient Protein Production in Mammalian Cells: A Short Story

Separate registration required, please see page 3 for details.

Inaugural

Higher-Order Protein Structure

Characterization and Prediction

August 20-21

MONDAY, AUGUST 20

8:00 am Pre-Conference Registration and Morning Coffee

8:30 - 11:30 Recommended Short Courses*

SC2 Design and Interpretation of Accelerated Stability Studies of Biologics

*Separate registration required, please see page 3 for details

11:30 am - 5:30 pm Main Conference Registration

EFFECT OF CONFORMATIONAL STABILITY ON FORMATION OF HIGHER-ORDER ASSEMBLIES

1:00 pm Chairperson's Opening Remarks

Bruce Kerwin, Ph.D., Scientific Director, Drug Product Development, Amgen

» 1:10 OPENING KEYNOTE PRESENTATION:

Higher-Order Structure of Protein Products – Who Needs It?

Emily Shacter, Ph.D., Consultant, ThinkFDA, LLC; Former Chief, Laboratory of Biochemistry, Division of Therapeutic Proteins, Office of Biotechnology Products, CDER/OPS, FDA

Proteins are defined by their amino acid sequence and higher-order structures. The bioactivities, biodistribution, immunogenicity, and clinical safety and efficacy profiles of proteins depend on proper synthesis and folding; transcriptional, translational, and post-translational modifications; and exposure to external stresses during manufacture and storage. The FDA's regulatory expectations for evaluation of protein higher-order structure are evolving as advanced analytical tools become more available. This talk evaluates why and when protein higher-order structure should be analyzed.

1:45 Differential Scanning Calorimetry (DSC) for Biopharmaceutical Development: Versatility and Thermodynamic Power at Work

Sorina Morar-Mitrica, Ph.D., Investigator, Biopharmaceutical Technologies, GlaxoSmithKline R&D

This talk focuses on the use and application of DSC for structure and stability investigations of biopharmaceuticals, with an emphasis on monoclonal antibodies, in both early development and late stage products. Case studies presented will show how DSC analysis is used in formulation development, forced degradation, or comparability studies. From thermogram shape to identification of structural transitions, from melting temperatures (Tm) to Tm-based stability ranking, DSC allows for more confident biopharmaceutical development at a faster development pace.

2:15 Hydrogen Exchange Mass Spectrometry (HDX) for Studying Protein Structure and Dynamics

Joseph Costanzo, Chemical Engineering, University of Virginia

Aggregate structures are difficult to characterize because of their heterogeneity, large size, and sometimes multiphase nature. Hydrogen-deuterium exchange detected by mass spectrometry (HDX) is emerging as a new approach that can provide relatively high-resolution structural information, even in complex environments. In this talk, an overview of the physical basis and experimental methods for HDX will be given. Examples of the different kinds of information that can be obtained from aggregating protein systems will be provided.

2:45 Refreshment Break

» 3:15 FEATURED PRESENTATION:

Influence of Electrostatics on Higher-Order Structure and Assembly

Christopher Roberts, Ph.D., Associate Professor, Department of Chemical Engineering, University of Delaware

This talk focuses on experimental characterization of the effects of pH and salt concentration on the formation of a range of aggregate sizes, morphology, and structure (local to larger scale). Examples include monoclonal antibodies and smaller, model proteins. The conditions are typical of therapeutic protein formulations, and highlight the importance of electrostatic inter- and intra-protein interactions, as well as more traditional views that emphasize hydrophobic and hydrogen bonding interactions. Phenomenological models also help to guide formulation design to account for these features.

3:45 Implementation of Sub-Visible Particle Analysis in Developmental Stability Studies

Robert Simler, Ph.D., Staff Scientist, BioFormulations Development, Genzyme

Subvisible particle analysis is often utilized in late stage development to aid in thorough drug product characterization. Short timelines and material constraints can make early implementation of subvisible particle analysis challenging. This talk will present a case study summarizing the preliminary liquid formulation development effort for a monoclonal antibody, highlighting the role of subvisible particle analysis.

4:15 Small-Group Breakout Discussions

This session provides the opportunity to discuss a focused topic with peers from around the world in an open, collegial setting. Select from the list of topics available and join the discussion to share ideas, gain insights, establish collaborations or commiserate about persistent challenges. Then continue the discussion as you head into the lively exhibit hall for information about the latest technologies.

5:15 Breakout Group Summaries

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 End of Day

TUESDAY, AUGUST 21

8:00 am Registration and Morning Coffee

EFFECT OF STRUCTURAL CHANGES AND INTER-PROTEIN INTERACTIONS

8:25 Chairperson's Remarks

Erinc Sahin, Ph.D., Research Investigator, Biopharmaceutics, Drug Product Science & Technology, Bristol-Myers Squibb

8:30 Case Study: Use of DSC in Higher-Order Structure Characterization and Prediction

Jie Wen, Ph.D., Senior Scientist, Global Cellular & Analytical Resources, Amgen

Differential scanning calorimetry (DSC) has been widely used by the biopharmaceutical industry for protein thermal stability and higher-order structure characterization. It is very sensitive to changes caused by the manufacturing process. At Amgen this technique has been successfully applied as a predictive tool for candidate screening and formulation development. This presentation will share the lessons learned from the case studies and discuss the qualification of this technique for protein thermal stability and higher-order structure characterization.

9:00 Higher-Order Structure Comparison of Biopharmaceuticals by Circular Dichroism: Definition of Unbiased Acceptance Criteria of Spectral Data

Horst Bierau, Ph.D., Scientific Advisor & Relation Manager, Analytical Development Biotech Products, Merck Serono

The use of Circular Dichroism for the analysis of higher-order structure of biopharmaceuticals is highlighted by case studies. One approach proposes to define unequivocal acceptance criteria, which eliminates operator bias associated with visual assessment of sample versus reference spectra. It is

based on statistical analysis which distinguishes inherent variation in a given set of reference spectra from genuine structural differences that may be present in a sample. The proposed approach is generic and may readily be adapted to analyze spectral data obtained from techniques other than CD.

9:30 Effect of pH and Light on Aggregation and Conformation of an IgG1 mAb

Bruce Kerwin, Ph.D., Scientific Director, Drug Product Development, Amgen

An IgG1 mAb at pH 3.5, 5 and 8 was exposed to UV light at multiple protein concentrations. The exposure resulted in a pH-dependent formation of high molecular weight species where the degree of oligomerization increased with increasing pH. The opposite trend was observed for conformational changes suggesting that different strategies will be required to stabilize the protein against these modifications during processing.

10:00 Sponsored Presentation *(Opportunity Available)*

10:15 Coffee Break in the Exhibit Hall with Poster Viewing

11:00 The Characterizing Role of a Hydrophobic Patch in Antibody Clustering

Thomas Scherer, Ph.D., Scientist, Late Stage Pharmaceutical Development, Genentech

It is well-known that relatively small discrepancies in protein surface electrostatics and hydrophobic area can lead to large differences in the strength of non-specific interactions and a protein's structural stability, particularly at high concentrations. We have used biophysical, structural and analytical methods to improve our understanding of the issues encountered at high protein concentrations and their relationship to the macromolecular surface. Our current research on therapeutic antibodies has strong implications for using novel formulations to overcome common downstream drug product processing and delivery problems.

11:30 Structural Footprinting of a Homotetramer Using Chemical Cross-Linking and Mass Spectrometry

Jie Nan, Ph.D., Wenner-Gren Fellow, Department of Molecular Biology, Uppsala Biomedical Center

The structure of arginyltransferase is unknown and only distant homologs are found in the structural databases. Yeast arginyltransferase (yATE1) was recombinantly expressed and formed a stable homotetramer of ~400 KDa. Given no crystals after screening, chemical cross-linking and high-resolution mass spectrometry was applied to probe the structure. Over 200 unique cross-linked sites and nearly 90 single modification sites were identified. Further studies examining intra- and inter-protein cross-links provided distance restraints for structural modeling and tetramerization contacts.

SOLUBLE AND INSOLUBLE AGGREGATES: ANALYTICAL CHALLENGES

» 12:00 PM FEATURED PRESENTATION:

New Methods for Therapeutic Protein Higher-Order Structure Characterization

Henryk Mach, Ph.D., Senior Investigator, Bioprocess Analytical and Formulation Sciences, Merck Research Laboratories

Changes in the process or formulation of therapeutic proteins and vaccines may bring unexpected changes in the propensity to aggregate despite favorable chemical and spectroscopic comparability. Development of precise and efficient methods to characterize the higher-order structure behavior during production and administration often requires adaptations of the existing hardware.

12:30 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:55 Chairperson's Remarks

Christopher Roberts, Ph.D., Associate Professor, Department of Chemical Engineering, University of Delaware

2:00 Protein Aggregation: Experimental Approaches, Cautionary Observations & Kinetic Modeling

Erinc Sahin, Ph.D., Research Investigator, Biopharmaceutics, Drug Product Science & Technology, Bristol-Myers Squibb

Protein aggregation is recognized as one of the most significant stability problems that limit shelf life of biopharmaceuticals. Aggregates, being products of a continuum of oligomerization reactions, can vary between dimers to large polymers as well as soluble to insoluble materials. The variability in the length scales and solubilities of aggregates present formidable technical difficulties. This presentation includes experimental cases and cautionary observations that aim to challenge the way we look at aggregates, their characterization and formulation selection process.

2:25 Effect of polyols and mechanical stress on protein aggregation: How useful is DSC analysis?

Devendra (Davy) Kalonia, Ph.D., Professor of Pharmaceutics, Department of Pharmaceutical Sciences, University of Connecticut

2:50 Early Vaccine Functionary and Stability Prediction and Adapted Formulation Strategies

Oliver Brass, Ph.D., Scientist, Discovery, Sanofi Pasteur

The presentation will focus on how to develop vaccine formulation with innovative predictive tools. This will be illustrated by case studies on antigenic protein, adjuvanted glycoprotein, and lived attenuated virus. Rational predictive approaches for vaccine functionality and stability assessment, is a permanent challenge in order to assume an optimal time between product development and clinical trials and market launch.

3:15 Effects of Stress and Post-Translational Modifications on Protein Higher-Order Structure

Carl Jone, Ph.D., Director, Analytical Development UCB

The growing interest by regulators in protein higher-order structure, and whether protein structural variants are clinically relevant is driving a re-evaluation of current analytical methods and the development of novel techniques. The presentation will show how recent developments in higher-order structure analyses can reduce operator bias, facilitate understanding of structural changes of stressed molecules and demonstrate that post translational modifications may lead to changes in higher-order structure and influence biological activity.

3:40 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 NIST Standards for Counting and Characterization of Protein Particles: Status and Prospects

Dean Ripple, Ph.D., Leader, Bioprocess Measurements Group, National Institute of Standards and Technology

To support the characterization of particles in protein therapeutics, NIST is developing polymer particle standards that closely mimic the optical properties of protein particles. We have created three types: 1) a polydisperse mixture of irregular particles formed by abrasion, 2) monodisperse particles formed by lithography, and 3) an optical 'target' with low-optical contrast features. These standards range in size from 1 µm to 300 µm, covering the design, formulation, stability and use, and characterization of each type.

BIOPHYSICAL CHARACTERIZATION FOR BIOSIMILARS

4:45 Biophysical Characterization for Biosimilars: Comparability Studies and Technical Proof of Similarity

Otmar Hainzl, Ph.D., Lab Head, Biophysical Characterization, Analytical Characterization, Sandoz, Hexal AG

Technical development of biosimilars requires continuous comparison with the originator product. As HOS analysis involves ensemble methods which show the overall status of a protein, as well as methods which can detect subtle differences between the product and originator material, it delivers comprehensive information on the protein. In a "technical proof of similarity" exercise, the analytical results are used to demonstrate required high similarity to the originator product, where HOS and binding studies may significantly improve understanding of the molecule and its mode of action.

5:15 End of Conference & Registration for Dinner Short Courses

6:00 – 9:00 pm Recommended Dinner Short Course*

SC4 Sub-Visible Particle Analysis in High-Concentration Protein Formulations

*Separate registration required, please see page 3 for details

TUESDAY, AUGUST 21

6:00 - 9:00 pm Recommended Dinner Short Course*

SC6 Transient Protein Production in Mammalian Cells: A Short Story

**Separate registration required, please see page 3 for details*

WEDNESDAY, AUGUST 22

8:00 am Registration and Morning Coffee

FACILITATING THE SUCCESS OF BIOLOGICS

8:25 Chairperson's Opening Remarks

» 8:30 OPENING KEYNOTE PRESENTATION:

Evolution of Cell Line Development Technologies

James P. Fandl, Ph.D., Vice President, Protein Expression Sciences, Regeneron Pharmaceuticals, Inc.

Flow cytometry presents unparalleled capabilities for cell line development and is the basis for Regeneron's VelociMabTM suite of technologies. These technologies will be described with special emphasis on how they evolved from each other in response to the changing resource-limited demands of a growing biotechnology company.

» 9:00 FEATURED PRESENTATION:

Optimizing Development Before Starting the "Process": Addressing Key Challenges in the Development of Biopharmaceuticals

Jesús Zurdo, Ph.D., Head, Innovation, Biopharma Development, Lonza Biologics plc

The extremely high attrition rate observed in pharmaceutical development, linked to dwindling R&D productivity and spiralling development costs, are putting pressure on how process development is conducted. New strategies aimed to reduce risks in the manufacturing process, as well as clinical development, are being introduced in early stages of development. These approaches need to be combined with innovative ways of developing host cells that can facilitate the transition into the clinic. Finally, the new paradigm for biopharmaceutical development needs to incorporate a more holistic definition of product design, in which elements of administration and delivery are incorporated alongside mode of action or safety.

9:30 Efficient Cell Line Selection Strategy to Anticipate for Optimal Cell Line Development

Kirsten Hegmans, M.S., Scientist and Team Leader, Cell Technology, Protein Sciences, Crucell

The seeds for a successful cell line development program are already planted in the early phase of a cell line generation approach. The success rate can be managed by implementing a cell line selection strategy that considers parameters key for optimal production, such as stability of production and compatibility of the cell lines in the anticipated production process. For the PER.C6® platform, we have turned the traditional paradigm from selecting only high producing cell lines, to deselecting cell lines based on harsh criteria which are crucial in the foreseen production process.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

CHO CELL LINE DEVELOPMENT

10:45 Engineering Novel Lec1 Glycosylation Mutants in CHO-DUKX Cells: Molecular Insights and Effector Modulation of N-Acetylglucosaminyltransferase I

Xiaotian Zhong, Ph.D., Principal Scientist/Lab Head, Global Biotherapeutics Technologies, Pfizer Biotherapeutics Research and Development

The complexity and heterogeneity of glycosylation modification offers both an opportunity and a challenge to biotherapeutics drug discovery. Glyco-engineering through cell line engineering has provided a new approach to facilitate the development of next-generation of biotherapeutics with optimized glycoforms and therapeutic utilities. The presentation will talk about a study utilizing chemical mutagenesis and lectin selection strategy to engineer new Lec1 mutants in dhfr- host cells. The resulting cell lines allow an effective methotrexate selection for a quick stable pool expression of recombinant proteins such as antibodies with relatively homogenous Man5GlcNAc2 glycans modification for biotherapeutic and structural purpose. The data has revealed some molecular insights into these novel mutations as well as new mechanistic details and potential effector modulation function of the GnTI enzyme.

11:15 Proteomic Analysis of a Sustained Productivity (SQp) Phenotype in mAb-Secreting CHO Cells

Niall Barron, Ph.D., Program Leader, Mammalian Cell Engineering, National Institute for Cellular Biotechnology, Dublin City University

The ability of mammalian cells to sustain cell specific productivity (Qp) over the full duration of bioprocess culture is a highly desirable phenotype, but the molecular basis for sustainable productivity has not been previously investigated in detail. In order to identify proteins that may be associated with a sustained productivity phenotype, we have conducted a proteomic profiling analysis of two matched pairs of monoclonal antibody-producing Chinese hamster ovary (CHO) cell lines that differ in their ability to sustain productivity over a 10-day fed-batch culture.

11:45 Bio-layer Interferometry (BLI): Instant Dip and Read™ Label-Free Protein Quantitation and Binding Kinetics

Sponsored by PALL Life Sciences

Sriram Kumaraswamy, Ph. D., Director, Marketing Field Applications, Pall ForteBio

The presentation will describe the use of label-free binding assays on the Octet and BLItz platforms for cell line development. These systems are used routinely to perform titer assays for primary and secondary screening of cell lines, scale-up culture and cell line stability monitoring, and bioreactor titer performance monitoringforMAbs, as well other Protein A binding protein drug candidates. Assay results, turnaround time and labor will be compared with HPLC titer assay as well as ELISA.

12:00 pmThe Reality of Fully Scalable Transient Gene Expression (TGE) in CHO Cells for Gram-Scale Antibody Production

Sponsored by MaxCyte

James Brady, Ph.D., Director of Technical Applications, MaxCyte

Transient gene expression in CHO cells greatly shortens the time line of antibody development by eliminating the need for transient HEK systems. Data is presented demonstrating rapid gram-scale antibody production using the MaxCyte® STX™. Titers exceeding 400 mg/L allow for production of over a gram of antibody from a total culture volume of only two liters.

12:15 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

CELL LINE DEVELOPMENT

1:55 Chairperson's Remarks

2:00 Cell Line Development of Multiple Molecules to De-Risk Programs

Marguerite Campbell, Scientist, Biologics Research, Janssen Research & Development

Advances in molecule selection, cell line development technology and platform processes have not eliminated the risk of project failure in pre-clinical development. This talk will discuss a front-loaded and flexible strategy to increase success rates by developing cell lines for multiple molecules and delay the selection process until adequate data is available to intelligently select the molecule and clone. Decision processes and case studies will be presented to demonstrate the effectiveness of this approach.

2:30 Tailoring Product Quality Attributes Though Cell Line Development and Process Optimizaton

Anne B. Tolstrup, Ph.D., Director, Cell Culture II, Process Science, Boehringer Ingelheim Pharma GmbH & Co. KG

Boehringer-Ingelheim is faced with the multi-faceted challenge of developing CMC processes for therapeutic proteins, both for NBEs and for biosimilar molecules. The desired product quality attributes of a given therapeutic molecule vary depending on its desired effector function. For example, antibodies aimed at targeting cancer cells should typically exhibit high ADCC activity, while a biosimilar molecule should match the profile of its originator molecules. The BI-HEX platform comprises several elements allowing efficient tailoring of the product quality in a given direction, such as CHO host cell lines varying in their glycoprofiles, automated screening and analytics procedures during cell line development, and DoE-based cell culture process development. Examples will be given on how these elements are combined to select production clones generating optimal molecules.

3:00 Immortalization of Tissue/Organ-Specific Human Cells: Airway, Bone Marrow, Parotid, Mammary, Thyroid, and Parathyroid Cell Line Development

Dieter C. Gruenert, Ph.D., Professor, Department of Otolaryngology - Head and Neck Surgery, Professor, Department of Laboratory Medicine, University of California, San Francisco, and Head and Neck Cancer Lab, Mt. Zion Cancer Center

The development of human cell culture systems has been an integral component of understanding normal cell function and disease mechanisms, as well as the screening and development of therapeutic interventions (pharmacological and genetic) and protein production. While primary cell systems have a certain appeal, they have a limited lifespan and are often difficult to manipulate. The immortalization of human cells, in particular epithelial cells, has proven to be a significant contribution to the repertoire of reagents for the development of novel human therapies and for the generation of human proteins. To further this technology, cells from specific tissues/organs (airway, bone marrow, parotid gland, mammary gland, thyroid and parathyroid) have been immortalized. These immortalized cells display tissue-specific features in terms of gene expression, protein/hormone production, and function that will be beneficial for tissue-specific drug screening and therapeutic development.t

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing

HIGH THROUGHPUT CELL LINE DEVELOPMENT

4:15 A Fully Automated Approach to Cell Line Development

Gregory Keil, Scientist I, Protein Expression Technologies, MRL Bioprocess Development, Merck

Production cell line development for manufacturing therapeutic recombinant proteins involves screening hundreds or thousands of transfected cells to ultimately select the best clone with the desired protein productivity and quality attributes. Traditionally, this process was mostly conducted manually, was very labor intensive, and was limited in throughput. Here, we have streamlined the process by fully automating most of the steps to increase the operational efficiency and accuracy. First, we used surface-capture technology and FACS to isolate high producers into 96 well plates. Then, we used a Genetix Clone Select Imager™ integrated with a robotic arm to automatically monitor and select wells with colonies grown from a single cell with documented monoclonality. The population data derived from this microscopic screening are fed into a TECAN™ system to perform fully automated sampling and ELISA assay for product levels. The selected clones based on growth and titer are then harvested and scaled up into 24-well plates. Productivity and binding affinities of the product in 24 well plates are then confirmed by the use of a ForteBio Octet™. Cells from selected 24 wells were transferred into 50 ml conical spintubes for growth and productivity evaluation in agitated suspension culture. A custom designed TECAN™ system was then employed to automatically perform long-term semi-continuous suspension culture for evaluating stability of the clones. Fed-batch evaluations were carried out at different cell ages by using AMBR 48 microbioreactor system™ under more controlled conditions for mimicking large-scale production conditions. By orchestrating process instruments, this automatic cell line development scheme has drastically increased the efficiency and throughput of cell line development. It also provides better traceability, documentation of cell line history and reduced error-prone steps.

4:45 High-Throughput Cell Line Development Using Deep-Well Screening and Product Quality Assessment

Brian S. Majors, Ph.D., Scientist, Cell Engineering, Biogen Idec, Inc.

The biopharmaceutical industry has made great strides to increase productivity on recombinant protein expression, decrease cell line development timelines, and improve the product quality of complex biotherapeutic proteins. At Biogen Idec, we have implemented a high-throughput cell line development workflow that allows improved efficiency and shortened timelines, without compromising the quality of cell line generation. Implementation of deep-well culture technology into the cell line development workflow allows for screening of cell lines in a suspension system that more closely reflects the eventual manufacturing process. In addition, deep-well screening in 24-well plates allows for both analysis of culture growth and production characteristics, but also sufficient cell culture supernatant for purification and product quality analysis. Such early information about the characteristics of the cell lines and the protein they produce leads to more informed decisions when it comes to choosing cell lines for downstream processes. This presentation will give an overview of the cell line development process at Biogen Idec and the challenges we have faced in the implementation of high-throughput technologies.

5:15 Networking Reception, Last Chance for Exhibit and Poster Viewing

6:45 End of Day

THURSDAY, AUGUST 23

8:00 am Morning Coffee

ENGINEERING DESIRED QUALITIES

8:25 Chairperson's Remarks

8:30 Gene Editing Approaches for Viable Commercial Production

Eric Rhodes, Chief Technical Officer, Horizon Discovery Ltd.

There are now several technologies available to engineer stable genetic changes into the genome of mammalian cell lines. Each has its own strengths and weaknesses and the choice of which approach is best suited is dependent on a number of factors. Among the factors to be considered are: the nature and complexity of the desired modifications; the expertise required to achieve the end result; any safety and regulatory concerns; freedom to operate issues; and downstream commercial costs. An overview of the available technologies in light of these factors will be discussed.

9:00 Optimizing Recombinant Glycoprotein Production in the Baculovirus-Insect Cell System

Donald L. Jarvis, Ph.D., Professor, Molecular Biology, University of Wyoming

The baculovirus-insect cell system is widely used to produce recombinant proteins with eukaryotic modifications, such as glycosylation. However, this platform is constrained by the fact that the insect cell lines used as hosts for baculovirus expression vectors have relatively primitive protein glycosylation pathways that cannot produce sialylated glycoproteins. We have addressed this problem by glycoengineering the baculovirus-insect cell system to humanize the protein N-glycosylation pathway. In this presentation, I will report the results of our latest glycoengineering efforts and their impact on our efforts to optimize the baculovirus insect cell platform for recombinant glycoprotein production.

9:30 Ensuring Cell Line and Process Stability in Dynamic R & D and Regulatory Environments

Tiffany D. Rau, Ph.D., Consultant, Rau Associates

10:00 Coffee Break

TRANSFECTION & ELECTROPORATION

10:30 Lighting the Way for Biologists: Optical Transfection

Frank Gunn-Moore, Ph.D., Professor of Molecular Neurobiology, School of Biology, University of St. Andrews

The plasma membrane of a eukaryotic cell is impermeable to most hydrophilic substances, yet the insertion of these materials into cells is an extremely important and universal requirement for the cell biologist. To address this need, many transfection techniques have been developed including viral, lipoplex, polyplex, capillary microinjection, gene gun and electroporation. The current discussion explores a procedure called optical injection or photoporation, where a laser field transiently increases the membrane permeability to allow species to be internalized. If the internalized substance is a nucleic acid, such as DNA, RNA or small interfering RNA (siRNA), then the process is called optical transfection. This contactless, aseptic, cell transfection method provides a key nanosurgical tool to the microscopist—the intracellular delivery of reagents and single nanoscopic objects. The experimental possibilities enabled by this technology are only beginning to be realized. This presentation will discuss our new and novel optical transfection technology which is being developed with the end-user in mind.

11:00 The Road Toward Scalable Transient Gene Expression in Mammalian Cells

Lucia Baldi Unser, Ph.D., Senior Scientist, Laboratory of Cellular Biotechnology, EPFL

Transient gene expression (TGE) was established as a faster alternative to stable cell lines for the production of r-proteins. With TGE, no cloning after transfection is necessary. Although mainly considered as a research tool, and not yet a standard production platform for industrial manufacturing, TGE is raising a growing interest in the industrial biotechnology R&D departments. In this talk, I will describe how the limitations to successful large-scale TGE in HEK293 and CHO cells were surpassed during the last 15 years, and how we can use today's state-of-the-art technology for the production of gram-amounts of r-protein.

11:30 Impedance Analysis of Adherent Cells after *in situ* Electroporation: Non-Invasive Monitoring during Intracellular Manipulations

Joachim Wegener, Ph.D., Institute of Analytical Chemistry, Chemo and Biosensors, University of Regensburg

In this study adherent animal cells were grown to confluence on circular gold-film electrodes of 250 µm diameter that had been deposited on the surface of a regular culture dish. The impedance of the cell-covered electrode was measured at designated frequencies to monitor the behavior of the cells with time. The gold-film electrodes were also used to deliver well-defined AC voltage pulses to the adherent cells in order to achieve reversible membrane electroporation (*in situ* electroporation = ISE). Cells recovered from the electroporation pulse within less than 90 min. When membrane-impermeable, bioactive compounds like N3– or bleomycin were introduced into the cells by *in situ* electroporation, concomitant impedance readings sensitively reported on the associated response of the cells to these toxins as a function of time.

12:00 pm End of Conference

Scaling Up & Down with Optimized Bioreactors + Disposables

TUESDAY, AUGUST 21

6:00 - 9:00 pm Recommended Dinner Short Course*

SC5 Connecting the Dots: Understanding Your Bioprocess Data

**Separate registration required, please see page 3 for details*

WEDNESDAY, AUGUST 22

8:00 am Registration and Morning Coffee

BIOPROCESS DEVELOPMENT

8:25 Chairperson's Opening Remarks

» 8:30 OPENING KEYNOTE PRESENTATION:

What Scales Up Must Scale Down – Spinning Wheels?

Beth Junker, Ph.D., Senior Scientific Director, BioProcess Development, Merck Research Laboratories

Scale-down models have been and remain essential to process development, process performance qualification, and troubleshooting of scaled-up process operations. Practicality dictates that most process development experiments are conducted at the small scale. However, scale-down model fidelity varies considerably for different bioprocess steps, expression systems, and protein products. This talk presents the current state of scale-down models, offers an explanation about why this state exists despite decades of scale-up experience, and what advances need to be undertaken to "let the spinning wheel fly".

» 9:00 FEATURED PRESENTATION:

From Micro to Small Scale Fermentation – Combining Cell Line and Process Development

René Brecht, Ph.D., Vice President, Process Science & Manufacturing, ProBioGen AG

The development of new cell lines and cell culture processes has to fullfil the demand for high productivity, shortened timelines and robustness. Therefore, effective screening of clones has to be combined with process optimisation work early on. Micro and small scale bioreactors covering a range from a few millilitres up to ten litres are used and need to be understood in terms of transferability of parameters to the next scale. Different case studies will be presented to illustrate the strategies we employ.

9:30 Consistent Fed-Batch Bioprocess Development in the µL to L-Scale

Stefan Junne, Ph.D., Group Leader, Process and Systems Biotechnology, Chair, Bioprocess Engineering, Institute of Biotechnology, Technische Universität Berlin

From concept to market, it typically takes from 5 to 10 years for the development of biotechnological processes. The step from bench-scale to pilot- and production-scale is crucial, since multidisciplinary approaches are necessary to circumvent typical problems of the scale-up process. One factor causing issues is the inconsistency of the process mode. Therefore, we have developed *in situ* susbtrate delivery systems, which allow a fed-batch procedure in any scale. In combination with state-of-the-art experimental design approaches, a fast and consistent process development in well-plates on liquid-handling systems becomes possible. Therefore, also microsensor integration and scale-down reactor concepts in the L-scale are considered.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

MODELING PROCESSES

10:45 Qualification and Application of a Bioreactor Scale-Down Model for a Microcarrier Perfusion Cell Culture Process

Caroline DiCesare, Process Engineer 1, Commercial Cell Culture Development, Genzyme Corp.

One of the current manufacturing challenges for cell culture processes that were developed decades ago is the ability to improve process robustness and troubleshoot problems. To overcome this challenge, a qualified scale-down model is crucial in order to conduct studies that can be translated to the larger scales. For this purpose, a cell culture scale-down model using 12-liter bioreactors was developed and subsequently qualified for a microcarrier-based perfusion cell culture process. For qualification, statistical equivalency needs to be established by comparing selected process performance parameters in the 12L scale to the large scale using a two one-sided test (TOST) analysis. The results showed that cell culture performance and product quality attributes were within the specification range in the scale down model. The qualified model can be used for example to evaluate new cell bank candidates for future implementation in manufacturing, to analyze the effect of media additives on cell culture performance, and for continuous improvement support.

11:15 Computational Methods Supporting Process Intensification

Ulrich Krühne, Ph.D., Senior Researcher, Center for Process Engineering and Technology (PROCESS), Department of Chemical and Biochemical Engineering, Technical University of Denmark

The talk presents a number of case studies, where computational methods have been used for gaining a more detailed understanding of complex interactions in biochemical applications. The cases will comprise scenarios across scales reaching from microfluidic examples to pilot plant scale setups. Computational fluid dynamic (CFD) models coupled with biological models will be presented for shedding light on reactor design, determination of material properties and optimization routines.

» POSTER HIGHLIGHT:

11:45 Integrating and Utilizing Computational Fluid Dynamics in the Cell Culture Scale Up Work Flow

Toby Blackburn, Engineer, Technical & Cell Culture Development, Biogen Idec, Inc.

As part of an effort to further understand scale up considerations and assumptions, computational fluid dynamics models were developed for all bioreactors at all scales at Biogen Idec. Various methods of model standardization and validation were discussed. The final approach involved utilizing fluid mixing characteristics, including Np, Kolmogorov mixing length and turbulent energy dissipation rate, as an independent tool in conjunction with experimental mix time and mass transfer to minimize impact to cell culture processes upon scale up. CFD simulations were run for all reactors across the operational range, but at RPMs fixed across the scales by P/V. Initially this P/V was calculated using a "book value" power number. Throughout the course of the data analysis, this power number appeared to overestimate system efficiency in dual impeller cases, leading to a revision in scale-up approach when transferring between single and dual impeller systems.

12:00 pm Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

BIOREACTOR OPTIMIZATION

1:55 Chairperson's Remarks

2:00 Bioreactor Scaling Up and Down: How to Perform Successful Process Development

Aurore Lahille, Ph.D., Specialist, New Technologies and Manufacturing Support, Merck Serono

Manufacturing planning depends on performances derived from process development data. This presentation will provide guidelines to reach a successful bioreactor process scale-up and down. My talk will span either disposable or reusable small process development bioreactors (15mL to 3L) to more than 1000L bioreactor, illustrating Merck's biodevelopment way forward.

2:30 Topology Optimized Bioreactors — A Design Example with Immobilized Yeast

Krist V. Gernaey, Ph.D., Associate Professor, Center for Process Engineering and Technology (PROCESS), Department of Chemical and Biochemical Engineering, Technical University of Denmark

This work exploits the increased design flexibility offered by microsystems for optimizing the operation of a microbioreactor. In this optimization project, the production of a recombinant protein in a continuous culture of immobilized *Saccharomyces cerevisiae* was used as a case study. A topology optimization methodology was applied to a mathematical model of the *S. cerevisiae* microbioreactor, in order to obtain the spatial distribution of immobilized yeast that maximizes protein concentration at the outlet. Compared to a stirred tank reactor, productivity improvements of up to a factor ten were predicted.

3:00 Insights into Large-Scale Bioreactors

Andreas Lübbert, Ph.D., Professor, Center for Bioprocess Engineering, Institute of Biochemistry and Biotechnology, Martin-Luther-University

In recent years we learned much about the transport properties of large bioreactors. Here we discuss the most important aspects, for instance, the improvements in our understanding of the oxygen mass transfer in stirred tank bioreactors, the problem of CO_2 accumulation in large-scale cell culture bioreactors and its solution. We will focus on the mechanistic understanding of the effects and the validation of the corresponding engineering models by means of physical measurements.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 Enhancing Infrastructure Flexibility – Design of a Novel Automated Methanol Feed System for Pilot-Scale Fermentation of *Pichia pastoris*

Kristie R. Apgar, Ph.D., Research Chemical Engineer, Bioprocess Clinical Manufacturing Technology, Merck Research Labs, Merck & Co., Inc.

Industrial fermentation of Pichia pastoris requires a large volume of methanol feed during the induction phase. However, a large volume methanol feed is difficult to employ in the processing suite due to the inconvenience of constant monitoring, manual manipulation steps, and fire and explosion hazards. To optimize and improve safety of the methanol feed process, a novel automated methanol feed system has been designed and implemented for industrial fermentation of P. pastoris. Details of the design of the methanol feed system are described. The main goal of the design was to automate the methanol feed process and to minimize the hazardous risks associated with storing and handling large quantities of methanol in the processing suite. The methanol feed system is composed of two main components: a Bulk Feed system and up to three portable Process Feed systems. The Bulk Feed system automatically delivers methanol from a central location to the portable Process Feed system. The Process Feed system provides precise flow control of linear, step or exponential feed of methanol to the fermenter. Large-scale fermentations with linear and exponential methanol feeds were conducted using two Mut+ (methanol utilization plus) strains, one expressing a recombinant therapeutic protein and the other a monoclonal antibody. Results show that the methanol feed system is accurate, safe, and efficient. The feed rates for both linear and exponential feed methods were within ± 5% of the set points and the total amount of methanol fed were within 1% of the targeted volume.

4:45 Scaling-Down a Process: Lessons in Correcting Your Assumptions in Order to Create a Small-Scale Bioreactor Model

E. Todd Sorensen, M.S., Development Associate 4, Alexion Pharmaceuticals, Inc.

The need for robust, reproducible large-scale cell culture bioreactor performance for the production of recombinant proteins and monoclonal antibodies led us to develop reliably predictable small-scale bioreactor models. During the exercise of creating a small-scale bioreactor model for our 10,000L Bioreactors, not only did we discover how to operate our bioreactors, we also learned that several of our initial assumptions were incorrect. Our approach started by defining requirements for our model such as retaining product quality attributes across scales and matching trends in growth and productivity. Next, we employed computational fluid dynamics (CFD) software in conjunction with a series of experiments to characterize each scale, focusing on: magnitude of shear forces, mixing time, bubble size distribution and liquid addition dispersion. We explored the impact of modifying a host of operating conditions including: agitation rate, pH setpoint, dissolved oxygen setpoint, sparge rate, location of liquid additions (i.e. feed and alkaline solution) and timing of liquid additions. Ultimately, we engineered our model to go from outperforming the large-scale by nearly 50% in terms of productivity to closely matching final titer while preserving product quality. We will discuss the lessons learned by going through this process.

5:15 Networking Reception, Last Chance for Exhibit and Poster Viewing

6:45 End of Day

THURSDAY, AUGUST 23

8:00 am Morning Coffee

DISPOSABLES

8:25 Chairperson's Remarks

8:30 A Single-Use Purification Process for the Production of a Monoclonal Antibody Produced in a PER.C6 Human Cell Line

Blanca Lain, Ph.D., Senior Scientist, Downstream Process Development, Percivia LLC

9:00 Disposable Bioreactors: Adaption of Process Sensors and New Applications

Sascha Beutel, Ph.D., Scientific Advisor and Substitute Director, Institute for Technical Chemistry, Leibniz University of Hannover

Disposable bioreactors become more and more established in modern biotechnological industries. The major drawback is currently the adaption and integration of process analytical technology, especially online-sensors to monitor cultivation processes in time. In our current research we adapted various sensor elements to rocking-motion disposable bioreactors, as T-, pH-, DO-probes and others. We also investigated the usability of these reactor-systems for the cultivation of strict anaerobic bacteria, microalgae and fungi, comparability to conventional stainless steel fermenters and the possibility of up-scaling for chosen processes.

9:30 Use of Disposable Optical Sensor Patches (pH, DO, pCO2, Temperature and Conductivity) for Cell Culture, Purification and Media Preparation Applications

Janani Ravindhar, M.S., Engineer I, Manufacturing Sciences, Biogen Idec

Currently, there are no means to take internal measurements in bioprocess bags during manufacturing operations. This has been identified as an area of increasing need for both upstream and downstream

processing because of the increasing use of disposable bags, and the benefits of monitoring both physical and chemical parameters in real time. The use of optical sensor patches integrated to the bags offers to be a promising solution due to its capacity to provide continuous online data and enable future process control improvements. Additionally, the use of these sensor patches can aid with trouble shooting, proactively identify issues before proceeding to subsequent processing steps and ultimately save batches.

10:00 Coffee Break

SCALING UP

10:30 Scale-Up Methodology for Viral Vaccines Processes

Ludovic Peeters, Scientist, Cell Culture & Viral Process Development, GSK Vaccines

This case study will focus on the current GSK Vaccines approach to perform the scaling-up of cell based viral vaccines. Practical examples will cover adherent and non-adherent cell substrates and describe the specificity of stainless steel and single-use bioreactor technologies. The specificity of vaccine process constraints will also be covered.

11:00 Rapid Design and Manufacturing of Novel Engineered Protein Therapeutics

Trevor J. Hallam, Ph.D., CSO, Sutro Biopharma

Sutro has developed a scalable cell-free protein synthesis platform for the efficient production of therapeutic proteins. The process is separable into two phases, the production of a ribosome-rich cell extract and the subsequent production of therapeutic product. Once selection of the desired protein variant is made, scale-up to >100g scale can occur within days using the same process used at research scale with no reformatting required. Sutro plans to move to continuous extract production with subsequent disposable technologies capable of making hundreds of grams of API in 10-12 hours. The platform enables production of protein sufficient for GLP tox and clinical studies within a few weeks from first synthesis of DNA sequence.

11:30 Importance of End of Run Studies for a Scale-Up of Commercial Cell Culture Processes

Sofie Goetschalckx, M.S., Manufacturing Cell Culture Science Lead, Technology, Genzyme Belgium

We have learned a great deal from end of run studies for improving cell culture performance and bioreactor design. In order to investigate the homogeneity of the culture and to improve the bioreactor configuration, End of Run (EOR) studies were performed at the end of the harvest phase. These analyses included stratification studies, cone dip-tube positioning, sparger performance and mixing studies.

12:00 pm End of Conference

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Inaugural

August 22-23

High-Concentration Protein Formulations

Overcoming Challenges in Stability and Aggregation

TUESDAY, AUGUST 21

6:00 - 9:00 pm Recommended Short Course*

SC4 Sub-Visible Particle Analysis in High-Concentration Protein Formulations

**Separate registration required, please see page 3 for details*

WEDNESDAY, AUGUST 22

8:00 am Registration and Morning Coffee

LYOPHILIZATION AND RECONSTITUTION OF HIGHLY CONCENTRATED PROTEIN FORMULATIONS

8:25 Chairperson's Opening Remarks

Jennifer Maynard, Ph.D., Assistant Professor, Chemical Engineering, University of Texas at Austin

» SPECIAL KEYNOTE CO-PRESENTATION: Fundamentals of Reconstitution Times with Highly Concentrated Monoclonal Antibody Systems

8:30 Part 1: Freeze-Drying of Highly Concentrated Protein Formulations: Formulation, Process Considerations and Reconstitution Issues

Serguei Tchessalov, Ph.D., Associate Research Fellow, Pharmaceutical Sciences, BioTx R&D, Pfizer

An increase in protein concentration allows a significant decrease in drying time without notable effect on product quality (moisture, stability and cake appearance). While dryer overload could become a limiting factor, process optimization paired with lyophilizer characterization should minimize this problem. However, reconstitution time of lyophilized material significantly increases with concentration. Effect of formulation, process conditions, reconstitution media and container closure configuration will be reviewed in this presentation.

9:00 Part 2: Underlying Factors that Contribute to Long Reconstitution Times of Highly Concentrated Protein Pharmaceuticals

Robin Bogner, Ph.D., Associate Professor of Pharmaceutics, School of Pharmacy, University of Connecticut

A systematic study of the effects of protein concentration and formulation components revealed that wetting is a major factor in long reconstitution times of a model protein. Formulation can be adjusted to reduce the reconstitution time. The processing conditions, particularly primary drying temperature, can alter the solid state of some formulation components causing a change in the reconstitution time.

» 9:30 FEATURED PRESENTATION

Development of Lyophilized High-Concentration Formulations

Michael Pikal, Ph.D., Pfizer Distinguished Endowed Chair in Pharmaceutical Technology & Professor of Pharmaceutics, University of Connecticut

Formulation development for high concentration actives usually means monoclonal antibodies, where the formulation would consist of the protein, a disaccharide stabilizer, such as sucrose, and perhaps small amounts of buffer and a small molecular weight polyol, to enhance stabilization. Although storage stability increases with increasing amount of stabilizer, a high concentration of protein and the practical processing limits imposed by high solids content means the level of stabilizers need to be limited. Such relationships between formulation and process will be emphasized.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

HIGH-CONCENTRATION LIQUID FORMULATION

10:45 Formulation of Highly Concentrated PEGylated Proteins

Ahmed Besheer, Ph.D., Research Fellow, Pharmaceutical Technology and Biopharmaceutics, Ludwig Maximilians University

Except monoclonal antibodies, the majority of marketed and investigational biopharmaceuticals are small, and thus rapidly eliminated through the kidneys. Currently, PEGylation is the gold-standard for half-life extension. However, a new challenge is the need to administer high doses of proteins subcutaneously for chronic use, raising questions about safety, stability and feasibility. We synthesized and characterized mono-PEGylated anakinra, and evaluated the stability and viscosity of highly concentrated formulations of PEGylated anakinra. The consequences of viscosity and stability for the application of highly concentrated PEGylated protein solutions are discussed.

11:15 High-Throughput High-Concentration Liquid Formulation Developability Assessment Platform for Protein Candidate Screening

Yu Tang, Ph.D., Investigator, Integrated Biologics Profiling, Novartis

Discovery of stable protein therapeutics with good drug-like properties requires an assessment of developability parameters to minimize risk of late stage development failures. However, low material availability and a short timeline necessitates a high-throughput formulation assessment to help discovery select the best candidates for late stage development. This high-throughput formulation developability assessment platform is composed of: 1) high protein concentration formulation process; 2) biophysical and physicochemical analysis; 3) data evaluation. In this talk, case studies will demonstrate the workflow, analytical package, and data readout, as well as the technical challenges.

» FEATURED POSTER PRESENTATION

11:45 A Fast and Simple Method for Determining Protein-Protein Interactions (PPI) at High and Low Protein Concentration using DLS

Martin Skov Neergaard, Ph.D Student, Section for Biologics, School of Pharmaceutical Sciences, University of Copenhagen

12:15 pm Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:55 Chairperson's Remarks

Robin Bogner, Ph.D., Associate Professor of Pharmaceutics, School of Pharmacy, University of Connecticut

2:00 Enhanced Viscosity Screening with Improved Resolution and Throughput

Jennifer Litowski, Ph.D., Senior Scientist, Drug Product Development, Amgen, Inc.

High viscosities pose a significant challenge in the development of highly concentrated protein formulations. Decisions are typically based on experiments targeting a single combination of protein and excipient, but these measurements are highly sensitive to small variations in concentration. Testing a wide concentration range greatly improved data quality, but required a combination of automated sample preparation and high-throughput measurements to be practically achievable. We applied this approach to a screening experiment which successfully identified excipients with lower viscosity and propose an explanation for these differences.

2:45 The Influence of Charge Distribution on Self-Association and Viscosity Behavior of High Concentration Antibody Solutions

Sandeep Yadav, Ph.D., Scientist, Late Stage Pharmaceutical Development, Genentech, Inc

The work emphasizes role of electrostatic surface potential distribution on self-association and viscosity behavior of mAbs which represent two of the most critical consequences of developing a high concentration formulation. Two IgG1's with 92% sequence similarity but widely different self-association and viscosity behavior were studied for charge residue differences in the primary sequence and subsequently the contribution of these sequence specific motifs to intermolecular interaction, structure factor, hydrodynamic interactions and consequently self-associating behavior have been investigated by making site specific mutations to modulate surface charge distribution.

PROTEIN-PROTEIN INTERACTIONS IN HIGHLY CONCENTRATED PROTEIN FORMULATIONS

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 Detection and Quantitation of Protein-Protein Interactions in Highly Concentrated Solution

Allen Minton, Ph.D., Senior Investigator, Physical Biochemistry, NIH

The presence and magnitude of both attractive and repulsive protein-protein interactions in highly concentrated solution may be determined by measurement of the concentration dependence of static light scattering, sedimentation equilibrium, and viscosity. We will summarize recent experimental results and their interpretation.

4:45 Use of Self-Interaction Chromatography and Osmotic Pressure Measurements to Study Protein-Protein Interactions in Highly Concentrated Antibody Solutions

Andrew Zydney, Ph.D., Department Head and Walter L. Robb Family Endowed Chair, Department of Chemical Engineering, The Pennsylvania State University; Editor-in-Chief, Journal of Membrane Science

Elaheh Binabaji, Department of Chemical Engineering, The Pennsylvania State University

Protein-protein interactions can have a critical impact on the behavior of the highly concentrated antibody solutions required in current formulations. Self-interaction chromatography and osmotic pressure measurements have been used to evaluate the magnitude of these interactions for a model monoclonal antibody. Data were obtained over a wide range of solution pH and ionic strength and in the presence of different buffer excipients. These results have important implications for the design of effective ultrafiltration systems for antibody concentration and formulation.

5:15 Networking Reception, Last Chance for Exhibit and Poster Viewing

6:45 End of Day

THURSDAY, AUGUST 23

8:00 am Morning Coffee

PROTEIN AGGREGATION PHENOMENA

8:25 Chairperson's Remarks

Jennifer Litowski, Senior Scientist, Drug Product Development, Amgen, Inc.

8:30 Delivery of High-Concentration Protein Solutions Necessitates a Multi-Pronged Approach: From Molecule to Device Design

Vikas Sharma, Ph.D., Senior Scientist, Early Stage Pharmaceutical Development, Genentech

This presentation will highlight the advances made to-date and attempts to demonstrate that the high concentration/high-dose challenge can be met by adopting a combination of diverse approaches such as (i) development of high-throughput screening tools to enable selection of candidates with desirable viscosity properties, (ii) protein engineering approaches to understand the molecular basis of high solution viscosity, and (iii) enhancement of current and development of new process technologies that enable the production and delivery of high-concentration/high-dose formulations.

9:00 Hydrophobic Interactions: A Key Player in Aggregation of Antibodies at High Concentrations

Ravi Chari, Ph.D., Senior Scientist, Global Formulation Sciences Parenterals, Abbott

Co-developed with Vineet Kumar, Ph.D., Senior Research Scientist, Global Formulation Sciences Parenterals, Abbott

Development of high-concentration formulations of IgG-like bi-specific molecules (dual variable domain IgGs) showed that the molecular forces that govern their aggregation are different in nature and magnitude than those which control monoclonal antibody aggregation. Biophysical characterization and the result of stress studies on the aggregation and physical stability of dual variable domain IgGs versus that of mAbs is presented.

» 9:30 FEATURED PRESENTATION:

Predicting Protein Aggregation Kinetics in High Protein Concentration Solutions: Significance of Unfolding Thermodynamics

Venkatramana Rao, Ph.D., Associate Director, Drug Product Science and Technology, Bristol-Myers Squibb

Co-developed by Atul Saluja, Ph.D., Senior Research Investigator, Drug Product Science and Technology, Bristol-Myers Squibb

Prediction of protein aggregation rate under refrigerated conditions from short-term high-temperature studies is often critical during formulation development. In this work, using a multi-domain protein at moderate to high concentrations, we present data to highlight (i) the pitfalls of employing a simplistic Arrhenius model in rate predictions; and more importantly (ii) the significance of incorporating unfolding thermodynamics in aggregation rate prediction. Guanidinium HCL induced unfolding studies identified the rate-limiting step whereas non-isothermal kinetics indicated the domain/transition critical for the aggregation process. The challenges associated with an accurate prediction of shelf-life and the implications for biologics product development are discussed.

10:00 Coffee Break

ADMINISTRATION CHALLENGES AND CONCERNS OF HIGH-CONCENTRATION FORMULATION

10:30 Challenges in Development and Administration of High-Concentration Formulations for Monoclonal Antibodies

Meera Agarkhed, Formulation Scientist, Imclone Systems, Inc.

Proteins are prone to aggregation when exposed to accelerated conditions, especially at high concentrations due to protein-protein interactions. Protein formulations are usually developed at low concentrations due to availability and cost constraints. However, a formulation optimized at low concentration may not provide the same stability at higher concentrations. A high concentration protein formulation may pose challenges during administration. A case study will be presented on issues encountered in development and administration of high concentration monoclonal antibody drug product.

Sponsored by WYATT TECHNOLOGY

11:00 Analyzing Protein-Protein and Protein-Excipient Interactions via Composition-Gradient Light Scattering (CG-MALS)

Daniel Some, Principal Scientist, Wyatt Technology Corporation

Optimal formulation of biotherapeutics requires a good understanding of the intermolecular interactions that affect stability as well as equilibrium properties such as viscosity and reversible oligomerization. CG-MALS, implemented in Wyatt's Calypso system, is a key tool for achieving this goal. Calypso determines the essential biophysical parameters describing these interactions, at concentrations typical of protein-based drug formulations: A2 for non-specific repulsion or attraction, KD and stoichiometry for quasi-specific association.

11:30 Ultra-High Antibody Nanoparticle Dispersions Retain Activity and *in vivo* Bioavailability

Jennifer Maynard, Ph.D., Assistant Professor, Chemical Engineering, University of Texas at Austin

We introduce a new form of proteins, nanometer-sized clusters, in which proteins are "self-crowded" to favor the compact folded state. The size of these equilibrium nanoclusters may be tuned reversibly by varying multiscale colloidal interactions with an extrinsic crowding agent and pH. Upon dilution, protein molecules released from the clusters are stable, as shown *in vitro* and *in vivo* in mice and exhibit full biological activity in the bloodstream. Antibody nanoclusters present a radical approach to protein formulation with the potential of patient self-administration of these biologics.

12:00 pm End of Conference

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(SC2) Design and Interpretation of Accelerated Stability Studies of Biologics	(SC5) Connecting the Dots: Understanding Your Bioprocess Data
(SC3) Protein Expression in Non-Mammalian Host Systems	(SC6) Transient Protein Production in Mammalian Cells

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