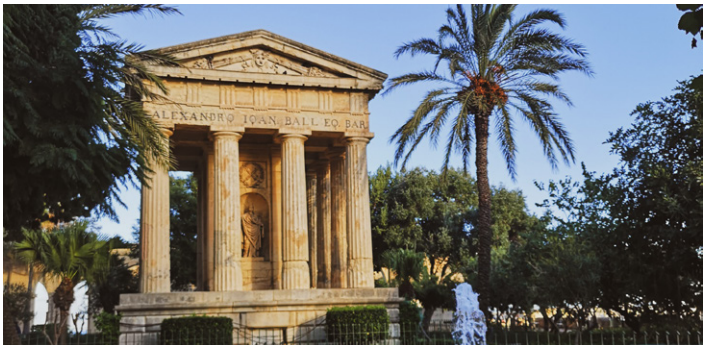
HTPD

Extended program book

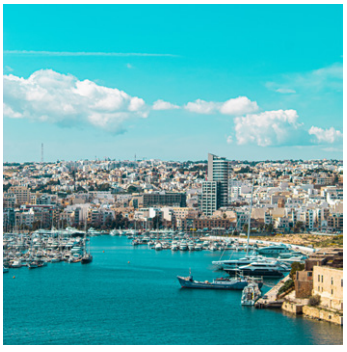
HIGH-THROUGHPUT PROCESS DEVELOPMENT

VALLETTA, MALTA | OCT 30–NOV 2 | 2023



6th

INTERNATIONAL CONFERENCE



VALLETTA, MALTA
OCTOBER 30–
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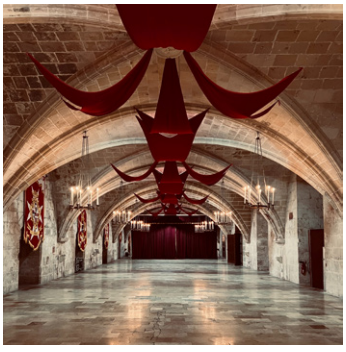

Photos by Madalina Calin, Lucas Klein, Anette Muscat, Theo Pruvot, and Joseph Buhagiar on Unsplash

Welcome to the Sixth International Conference on High-Throughput Process Development 2023

Welcome!

We are delighted to continue our conference series devoted to devoted to High-Throughput Process Development (HTPD) and smart PD. After meetings in Krakow, Poland, in 2010, in Avignon, France, in 2012, in Siena, Italy in 2014, in Toledo, Spain 2017, in Porto, Portugal 2019, we are now - after a small pandemic break - meeting in Valletta, Malta, yet another beautiful city on the UNESCO world heritage site list, in October 2023.

Over a decade after the first meeting in the conference series, high-throughput methods are now widely used in all areas of process development from upstream, through downstream to stable formulations. With HTPD, model-based process development, and advanced process analytical technologies, we have not only become faster, but also created the capability to evaluate more process scenarios than ever before, thus gaining a deeper understanding of process dynamics. If not obvious before, the COVID-19 pandemic also clearly demonstrated the importance to be able to move quickly in a safe and robust way. It was also demonstrated the importance of integrating research, as decades of laboratory research laid the groundwork for the rapid development of mRNA vaccines.

The goal of this scientific conference has not changed markedly – rather expanded – since the first meeting in 2010: to provide a leading forum for discussion and exchange of ideas surrounding the challenges and benefits of employing high-throughput techniques, *in-silico* PD and other approaches in the development of production processes for biological products.

Cytiva is the principal sponsor of the High-Throughput Process Development conference series, with the active involvement of industry and academia experts, ensuring this conference provides an excellent opportunity to discuss and influence the future of high-throughput process development methods in our industry.

We are looking forward to your participation in HTPD 2023
and we welcome you to Valletta, Malta!

Aaron Noyes, Jennifer Pollard, and Mats Gruvegard

General information

Venue

The conference will be held in The Mediterranean Conference Center (MCC) in Valletta, Malta, in the Michel' Angelo Grima Hall.

Registration

The registration desk is open as follows:

Monday, October 30,	9.00–16.00
Tuesday, October 31	7.30–12.00 13.30–19.00
Wednesday, November 1	8.00–12.00 13.30–15.30
Thursday, November 2	8.30–12.30

Please, come to the desk if you need any assistance.

Program and abstract book

A program overview with time slots and presentation titles will be available at the registration desk. An extended abstract book will be available as a pdf on the conference webpage htpdmeetings.com

Oral sessions

All oral presentations will take place at The Mediterranean Conference Center in Michel' Angelo Grima Hall. Speaking slots are scheduled to 25 minutes plus 5 minutes for Q&A. Consult the program for the presentation times of the different sessions. Ensure to give your presentation to the technician well in advance of your presentation.

Poster session

Posters should be mounted Michel' Angelo Grima Hall on Monday afternoon between 15.00 and 18.00 or Tuesday morning before 8.00. Poster boards are labelled with a number corresponding to the abstract number in the program book. The poster session is scheduled for Tuesday evening at 17.00–19.00. Refreshments will be available during the poster session. Posters presenters are urged to be available near their posters during the poster session. All posters will be on display throughout the conference and should be taken down by 12.00 on Thursday.

Lunch and Coffee breaks

Lunch will be provided at the MCC in the Sacra Infermeria Hall. Complimentary coffee will be available during coffee breaks outside the conference room. Consult the program for times.

Welcome reception

A welcome reception will be held on Monday October 30 at the terrace at the MCC, starting at 17.40. This is a time to make new friend and reconnect with old ones, while enjoying a glass of wine or beer.

Walking Tour

A walking tour of Valletta on Wednesday November 1 is included in the registration package. The tour will start after the panel discussion outside the Congress Centre and will last about 90 minutes. Please come prepared this day with comfortable walking shoes.

Conference gala dinner

A conference closing gala dinner will be held on Thursday November 2 at the Mediterranean Conference Center

Dress code

The meeting and setting promote communication between participants and informal dress is suggested. For the closing conference dinner smart casual attire is recommended.

Contact information

Practical questions

Opus agency

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Venue

Mediterranean Conference Centre

Old Hospital Street, Valletta

VLT 1645, Malta

Organizing committee

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Jack Kramarczyk
Moderna Therapeutics, US

Michael Doherty
Ring Therapeutics, US

Felix Wittkopp
Roche, Germany

Sheng-Ching Wang
Merck & Co, US

Program

Monday October 30

Pre-conference day / Start of conference	
9.00–16.00	Registration desk open at Mediterranean Conference Center (MCC)
10.00–15.00	Chromatography Modeling Day (lunch included)
16.00	Conference start. Opening remarks
16.15	**Opening keynote** **Scale-down tools for rapid upstream process development: fundamentals and scaling approaches** ***Dr Martina Micheletti***, University College London, London, United Kingdom
17.40	Welcome drink and opening reception at MCC

Tuesday October 31

Session 1 – Smart Process Development – Modeling	
8.00–8.15	**Session intro** Session chairs: ***Jürgen Hubbuch***, Karlsruhe Institute of Technology / ***Tobias Hahn***, Cytiva
8.15–8.45	101 **Adapting High-throughput Technologies for Mechanistic Modeling: Construct Model with the Combination of Kp and RoboColumn as a Novel Calibration Tool** *Yanru Zhang* Chugai Pharmaceutical Co., Ltd., Tokyo, Japan
8.45–9.15	102 **Accelerating downstream process development using *in-silico* process optimization with mechanistic models** ***Gabriela Sanchez**, Julie Robinson, Michael Hartmann, Ashley Shu, Rebecca Chmielowski, Francis Insaidoo, John Welsh*, Hong Li*, David Roush, Jennifer Pollard** Merck & Co., Inc., Kenilworth,NJ USA, *Previous employees who contributed to the research
9.15–9.45	103 **Mechanistic modeling of virus surrogate removal by anion exchange chromatography** ***Lukas Döring**[1,2], Johannes Winderl[1], Dietmar Lang[1], Matthias Kron[1], Jürgen Hubbuch[2]* 1) Rentschler Biopharma, Laupheim, Germany 2) Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany
9.45–10.15	Coffee
10.15–10.45	104 **A chromatography system modeling strategy for precise *in silico* process scaling** ***Tatjana Trunzer**, Lena Enghauser, Sabrina Stahlberger, Florian Grau, Tobias Hahn* Cytiva, Karlsruhe, Germany

10.45–11.15	105 **Creation of a Phase I/II digital twin for a mAb MMC_AEX unit operation in flow-through mode** *Erik Hinze* CSL Behring Innovation GmbH, Marburg, Germany
11.15–11.45	106 **Simplifying the mechanistic modeling workflow with precharacterized columns – the story from their development to application** ***Max Edin**[1], Patricia Roch[1], Eggert Brekkan[1], Lalita Kanwar Shekhawat[1], Lena Enghauser[2], Daniella Ekström[1], Tatjana Trunzer[2], Gunnar Malmquist[1], Tobias Hahn[2]* 1) Cytiva, Uppsala, Sweden; 2) Cytiva, Karlsruhe, Germany
12.00–13.00	Lunch

Session 2 – Evolution of Mature HTPD Platforms

13.00–13.15	**Session intro** Session chairs: ***John Welsh***, Rivanna Bioprocess Solutions / ***Brian Murray***, Sanofi
13.15–13.45	201 **Integrated Protein A Chromatography and Low pH Viral Inactivation Unit Operations Miniaturised on an Automated Platform** ***Paras Sharma**[1], Lars Robbel[2], Michael Schmitt[2], Duygu Dikicioglu[1], Daniel G. Bracewell[1]* 1) University College London, London, United Kingdom; 2) CSL Behring Innovation, Marburg, Germany
13.45–14.15	202 **High Throughput Screening for resin regeneration conditions** ***Cornelia Walther**, Nadine Royla, Regina Zivkovic, Yvonne Patzold, Christoph Pertl, Cecile Brocard* Boehringer-Ingelheim RCV GmbH & Co KG, Vienna, Austria
14.15–14.45	203 **Improved DOE Workflow for Parallel Screening Experiments on the Ambr® Crossflow TFF system** ***Viktor Sandner**[1], Vishal Parbhakar[2], Samantha Ward[3], Tanja Rau[4]* 1) Sartorius Stedim Austria GmbH, Vienna, Austria; 2) Sartorius Stedim India Pvt. Ltd.; 3) Sartorius Stedim UK Ltd.; 4) Sartorius Stedim Biotech GmbH
14.45–15.15	Coffee
15.15–15.45	204 **High Throughput Models for Process Characterization: Successes and Challenge** ***Brian Murray**, Harry Poppick, Thomas Liao, Thomas Wasylenko, Peter Firmin, Shashi Malladi, Ludivine Profit, Jason Walther* Sanofi, Framingham, MA United States
15.45–16.15	205 **Micro-scale Purification Platform – High throughput tool for BioPharma Manufacturing Investigations** ***Manoj Ganesh**, Elijah Beaudin, Quynh Nguyen, Emily Mosher, Sushil Bhatia, Zizhao Liu* Regeneron Pharmaceuticals, East Greenbush, USA
17.00–19.00	**Poster session**

Wednesday November 1

Session 3 – Integrated PD and Analytics Case Studies

9.00–9.15	**Session intro** Session chairs: ***Jon Coffman***, Astra Zeneca / ***Andrea Rayat*** University College London, London, United Kingdom
9.15–9.45	301 **Automated Raman spectroscopy measurements for integrated chemometric model development** ***Jakob Müller*** Karlsruhe Institute of Technology, Karlsruhe, Germany
9.45–10.15	302 **SpecPlate, the better standard for more efficient plate based UV/Vis absorbance measurements** ***Carsten Radtke*** PHABIOC, Karlsruhe, Germany
10.15–10.45	Coffee
10.45–11.15	303 **Integration of Automated High Throughput Process Analytics to support High Throughput Process Development** ***Nicola Roberts****, Razwan Hanif, Mari Spitali* UCB, Slough, United Kingdom
11.15–11.45	304 **Enhancing Bioprocessing with pH Sensitive Nanosensors: High Throughput Screening and Antibody Production** ***Alison Tang****[1], Greta Csalane Besenyei[1] and Veeran Chauhan[2]* 1) AstraZeneca, Cambridge, UK 2) University of Nottingham, Nottingham, UK
12.00–13.30	Lunch

Session 4 – Panel Discussion

13.30–15.00	**Best Practices in HTPD for Regulatory Filings, Formulations, and More** Facilitator: ***Michael Doherty***, Ring Therapeutics
15.30	**Guided walking tour in Valletta** (included in conference fee)

Thursday November 2

	Session 5 – Calling All Nanoparticles: HTPD with Cells, Viral Vectors, LNPs, Gene Editors, and Vaccines
8.00–8.15	**Session intro** Session chair: ***Jack Kramarczyk***, Moderna Therapeutics
8.15–8.45	501 **Downstream overview of an end-to-end high throughput AAV drug substance process development platform** ***Mahsa Hadidi****, Junfen Ma* Sanofi, Waltham, MA United States
8.45–9.15	502 **Development of High-Throughput Purification Methods for Adeno-Associated Viral Vectors** ***Katerina Farukshina****, Talia Levy, Nathan Sweeney* Cell and Gene Therapy Catapult, London, United Kingdom
9.15–9.45	503 **Towards High-throughput process characterization of gene therapy viral vectors** ***Mathew Petroff****, Jeff Plegaria, Qi Lin, Jon Palmer, Mi Jin* Spark Therapeutics, Philadelphia, PA United States
9.45–10.15	Coffee
10.15–10.45	504 **Breaking boundaries in AAV platform optimisation HT monolith chromatography plate development** ***Nicholas Pearman*** Pharmaron Biologics, Liverpool, United Kingdom
10.45–11.15	505 **Platform for High-Throughput Algorithmic Optimization of *in vitro* Transcription** ***Spencer E. McMinn****, Danielle Miller, Daniel Yur, Shashank Murali, Sheng-Ching Wang, Kevin Stone, Emily Wen* Merck & Co., Inc., Rahway, NJ United States
11.15–11.45	506 **High-throughput Process Development for Antibody-Drug Conjugate (ADC)** ***Benjamin Fabre****, Véronique Chiche, Benjamin Ha, Eric Lacoste* Sanofi, Vitry sur Seine, France
12.00–13.15	Lunch

Thursday November 2

Session 6 – Frontiers in HTPD/Smart PD	
13.15–13.30	**Session intro** Session chairs: ***Felix Wittkopp***, Roche / ***Sheng-Ching Wang***, Merck & Co
13.30–14.00	601 **Advancing High-Throughput Chromatography Development: Leveraging a QSAR Model for Experimental Design and Applying Learnings to High-Throughput Methods** ***Michael Rauscher***[1], *Michael Hartmann*[1], *Sheng-Ching Wang*[1], *John P. Welsh*[2] 1) MSD, Kenilworth, NJ United State 2) Rivanna Bioprocess Solutions, LLC, Charlottesville, VA United States
14.00–14.30	602 **Smart Bioprocessing Grand Challenge** ***Lucie Studená***, *Sean Ruane, Lukas Kuerten, Elaine Speirs* Centre for Process Innovation, Darlington, United Kingdom
14.30–15.00	Coffee
15.00–15.30	603 **Just because you can doesn't mean you should: What makes a successful high-throughput method** *Tobias Hahn* Cytiva, Karlsruhe, Germany
15.30–16.00	604 **Utilising machine learning for preventive maintenance and accelerating data analysis capabilities with digital transformation** *Razwan Hanif* UCB, Slough, United Kingdom
16.00–16.30	605 **Establishment of a High-Throughput Technology Roadmap across a Global Organization to Improve Purification Process Development for Biologics** ***Ludivine Profit***[1], *Brian Murray*[2], *Mélanie Mazenod*[1], *Benjamin Fabre*[1], *Benoit Mothes*[1], *Jason Walther*[2], *Kevin Brower*[2] 1) Sanofi, Vitry-sur-Seine, France 2) Sanofi, Framingham, MA USA
19.00	**Conference Gala Dinner**

Poster list

701 **Advancing Mispair Removal Approach: High-Throughput Techniques for Efficient Bispecific Antibody Downstream Process Development**

Yanru Zhang
Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

702 **A high throughput study of sodium hydroxide cleaning efficiency for protein A resin**

Jelena Vasić, Anna Grönberg, Tomas Björkman, Gunnar Malmquist and Eva Heldin
Cytiva, Uppsala, Sweden

703 **Accelerating Process Development for NANOBODY® Molecules: A High-Throughput Approach for IEX Resin Screening and Automated Data Analysis**

Matthias De Langhe, Wouter Martens, Jurgen Van Impe
Sanofi. Zwijnaarde, Belgium

704 **Exploring practical considerations in resin and condition screening using high-throughput techniques, coupled with Design of Experiments (DoE) – A case study**

Artur Stanczak
Bio-Rad Laboratories, Warszawa, Poland

705 **High throughput process development for optimised control of leached protein A**

Sigrid Hansen, Silvia Pirrung, Patrick Diederich, Florian Dismer
Novo Nordisk, Copenhagen, Denmark

706 **HTPD for late phase development to improve process polish step**

Martina Fischer, Florian Capito
Sanofi Deutschland GmbH, Frankfurt, Germany

707 **HTPD for Efficient Optimization of AAV Full Capsid Purification**

Ayman Ismail, René Gantier, Shelly Para, Tim Schroeder
Repligen Corporation, Waltham, MA United States

708 **Advantage of antibody-based selectivity in the purification of biologics**

Kevin Sleijpen
Thermo Fisher Scientific, Leiden, Netherlands

709 **Improving throughput and quality of results in nephelometric turbidity unit evaluation with SpecPlate, a new UV Vis microwell plate**

Jannik Jungmann
PHABIOC GmbH, Karlsruhe, Germany

710 **High-throughput tools and workflows for purification process development of non-mAb modalities**

Mary Lunson, Carol Abraham, Nicholas Field, Alma Svatos, Vivek Halan, Fathima Shazeena Rauf*, Varsha Yadav, Jean Aucamp*

Lonza Biologics plc, Slough, United Kingdom

711 **The Generation of a highly Predictive SMA mechanistic model for a CEX gradient elution of a novel antibody format**

Neil Watson, Curtis Phippen, Razwan Hanif

UCB, Slough, United Kingdom

712 **Competing brains – Application of Artificial Neural Networks to support a fast calibration workflow of mechanistic chromatography models**

Tinu Koshy, Dominik Hertweck, Dominik Voltmer, Felix Wittkopp

Roche Diagnostics GmbH,Penzberg, Germany

Pre-conference poster list

Doubling process productivity and speeding up process development with mechanistic modeling for chromatography

Pia Graf, Jennifer Reichert, Tobias Hahn, Nora Geng, and John Scibetta

Cytiva, Uppsala, Sweden

Scalability of mechanistic models for ion exchange chromatography under high load conditions

Tobias Hahn, Tatjana Trunzer, Lena Enghauser, and Thiemo Huuk

Cytiva, Uppsala, Sweden

Mechanistic modeling workflow for chromatography simplified with precharacterized *f*(x) columns

Patricia Roch[1], Lena Enghauser[2], Lalita Kanwar[1], Max Edin[1], Tobias Hahn[2], and Gunnar Malmquist[1]

1) Cytiva, Uppsala, Sweden; 2) Cytiva, Karlsruhe, Germany

Optimizing AAV full/empty separation using mechanistic modelling

Tatjana Trunzer[1], Patricia Roch[2], Pia Graf[1], Åsa Hagner McWhirter[2], Thiemo Huuk[1], Tobias Hahn[1]

1) Cytiva, Karlsruhe, Germany; 2) Cytiva, Uppsala, Sweden

Software-implemented workflows for model-based downstream process development

Alexander Gutzler, Thiemo Huuk, Tobias Hahn

Cytiva, Karlsruhe, Germany

Understanding ion exchange chromatography with the colloidal particle adsorption (CPA) model

L. Enghauser, T. Trunzer, T. Hahn, T. Huuk, J. Reichert, J. Scibetta, and N. Whitelock

Cytiva, Uppsala, Sweden

Session 1

Smart Process Development – Modeling

Session chairs

***Jürgen Hubbuch**, KIT, Germany*

***Tobias Hahn**, Cytiva, Germany*

Smart PD: knowledge is power! With HTPD, model-based process development, and advanced process analytical technologies, we can not only become faster, but also evaluate more process scenarios than ever before and thus gain a deeper understanding of the process dynamics. The employed models are divided into white-box, grey-box and black-box models. White-box models in particular allow us to explain cause and effect, but also machine learning approaches allow us to develop new hypotheses. In this session we will discuss how knowledge can be generated with smart PD methods, how digital twins can be implemented in real-world scenarios and how the cost-benefit ratio can be optimized to work smarter and cheaper at the same time.

101

Adapting High-throughput Technologies for Mechanistic Modeling: Construct Model with the Combination of Kp and RoboColumn as a Novel Calibration Tool

Yanru Zhang

Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

Mechanistic modeling is becoming indispensable in the realm of smart process development, particularly for optimization and acceleration of downstream processes development. One of the challenges in developing such mechanistic models lies in the need for extensive calibration runs. In this work, we successfully constructed a mechanistic model for mixed-mode chromatography using the combination of high-throughput technologies, partition coefficient (Kp) screening and miniaturized pre-packed chromatography columns (RoboColumn) data. This approach replaces the conventional chromatography operation using ÄKTA™ system. The RoboColumn system enabled the simultaneous execution of multiple calibration runs, significantly reducing the time required compared to the traditional ÄKTA™ system. Furthermore, by combining the use of Kp data for isotherm calculations, we were able to significantly improve model prediction in high molecular weight species (HMWS), leading to a more efficient approach. As a result, the process time required for traditional ÄKTA-based calibration runs was reduced by approximately 75% with equivalent model accuracy. The model constructed by Kp screening and RoboColumn showed its potential to predict the levels of HMWS and yield. This approach paves the way for more efficient and rapid construction of mechanistic models in the future, contributing to the advancement of smart process development, specifically in downstream process optimization.

102

Accelerating downstream process development using *in-silico* process optimization with mechanistic models

***Gabriela Sanchez**, Julie Robinson, Michael Hartmann, Ashley Shu, Rebecca Chmielowski, Francis Insaidoo, John Welsh*, Hong Li*, David Roush, Jennifer Pollard**

Merck & Co., Inc., Kenilworth, USA
*Previous employees who contributed to the research.

The biopharmaceutical industry is undergoing a revolution in oncology and other complex diseases, thanks to a wave of innovation and new drug modalities. Antibody-based therapeutics such as multi-specifics, fusion proteins, and protein conjugates allow access to therapeutic targets inaccessible by traditional mAbs. But these new modalities may contain multiple functional domains and are often vulnerable to in-process and *in vivo* biotransformation, creating a more diverse profile of impurities that need to be removed. Apart of having non-standard formats that challenge the well-established downstream platform, the industry is shifting to building more efficiency on its manufacturing operations (e.g., continuous protein A capture) creating more pressure on the process development teams to enable robust processes and reduce time-to-market. But despite the increased complexity, downstream strategies for process development still rely on the traditional mAb platform fit and trial and error wet-lab optimization.

This talk presents a new rationale for rapid process design, with a systematic data capture and the use of mechanistic models to identify optima in the design space of chromatography steps in the downstream process. Mechanistic models typically allow more accurate extrapolation compared to data driven empirical models, making them a useful tool for rapidly designing and optimizing processes as well as for risk analysis and establishing parameter ranges. The use of mechanistic modeling of chromatography in process development (PD) will be discussed, emphasizing case studies of diverse molecules at different development stages with their respective rigor. The case studies will present the implementation of mechanistic models to accelerate process development for complex, non-platform applications such as a continuous protein A capture step and a polishing step for an engineered mAb, that will become an Antibody Drug Conjugate (ADC). This work, will show how placing resources strategically in modeling can address PD challenges and can increase process understanding, reduce experimental burden, and expedite process development timelines.

103

Mechanistic modeling of virus surrogate removal by anion exchange chromatography

Lukas Döring[1,2], *Johannes Winderl*[1], *Dietmar Lang*[1], *Matthias Kron*[1], *Jürgen Hubbuch*[2]

1) Rentschler Biopharma, Laupheim, Germany
2) Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

Mechanistic modeling has evolved into a valuable and well understood tool for development and characterization of biopharmaceutical downstream processes (DSP). Product-related impurities like high and low molecular weight species and charge variants, have been shown to be described accurately by these models. However, process-related impurities like host cell proteins and DNA still pose a challenge in DSP and no mechanistic models that describe virus removal have been published so far. The recent revision of the virus safety guideline (ICHQ5a) allows a modular approach for claiming virus clearance based on previous data and deep process understanding. This makes mechanistic modeling of viral clearance a highly interesting tool i) to predict viral safety, ii) to enable lean bioprocessing and iii) to improve bioprocesses.

A mechanistic model for Minute Virus of Mice Virus-Like Particle (MVM-VLP) on an anion exchange resin suitable to elucidate and to optimize critical parameters is presented. We focus on the calibration of models for describing desorption and dispersion behavior on a logarithmic scale to accurately predict logarithmic reduction values in specific process steps. Furthermore, we demonstrate the applicability of these models in the context of a platform approach, using MVM-VLP viral clearance data in presence of monoclonal antibodies.

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A chromatography system modeling strategy for precise *in silico* process scaling

Tatjana Trunzer*, Lena Enghauser, Sabrina Stahlberger, Florian Grau, Tobias Hahn*

Cytiva, Karlsruhe, Germany

Chromatographic purification processes for biopharmaceutical products are often developed at laboratory scale and need to be scaled up for production or scaled down for efficient process characterization. While the biopharma industry performs this exercise on a regular basis, the basic understanding of flow rate effects on mass transfer and adsorption/desorption phenomena when scaling up or scaling down are limited and can be challenging. Even when applying mechanistic modeling, system and column effects are rarely distinguished, which challenges the determination of scale-dependent and scale-independent effects.

We examined the impact of different, individually configured elements in the flow path of chromatography systems to enable *in silico* scale-up and scale-down. In our extensive study, we investigated different flow paths in ÄKTA pure™, ÄKTA avant™, and ÄKTA pilot™ 600 chromatography systems. We also studied different flow rates and compared their effects for traditional, packed-particle columns and fiber-based Fibro™ PrismA prototypes.

Our study showed that there is no one-size-fits-all model for chromatography systems. The modeling of flow-through conditions with different system configurations provided detailed insights into the dependency of dispersion and mixing effects on the number and volume of different flow path items. A complex model was derived for a fully equipped ÄKTA avant™ system, and reduced models containing fewer flow path items were developed for a simple, basically configured ÄKTA pure™ system and the larger ÄKTA pilot™ system. Based on these models, we identified a flow rate-dependent tubing and device-specific calibration strategy. This strategy allows to precisely distinguish between scale-dependent mass transfer effects and scale-independent thermodynamics as demonstrated in a case study with model proteins.

105

Creation of a Phase I/II digital twin for a mAb MMC_AEX unit operation in flow-through mode

Erik Hinze

CSL Behring Innovation GmbH, Marburg, Germany

In the biopharmaceutical industry, chromatographic processes play a pivotal role in the production of high-quality biological drugs. To optimize and enhance these processes, digital twins are gaining increasing importance as an innovative solution throughout product- and process development. Digital twins allow for the virtual representation, simulation, and optimization of real processes prior to their implementation in production and beyond. The complexity of biopharmaceutical processes, coupled with variable input raw materials and production conditions, makes prediction of optimal process parameters challenging. Conventional empirical or statistical (e.g. DoE) approaches are time-consuming and only valid within limited ranges.

Here, we present a mAb case study describing the development of a mechanistic model for a multi-modal anion exchange resin (MMC_AEX) operated in flow-through mode. We demonstrate our workflow covering all aspects of model building from experimental design to calibration including model selection and experimental verification. After successful verification we used the model to predict process improvements outside of the experimental design space and experimentally confirmed the model-based prediction. The experimental design was focused on potential Critical Quality Attributes (e.g. HMWS, HCP) as key drivers during process development as well as assessment of the influence of potential Critical Material Attributes (e.g. resin ionic capacity) on process performance.

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Simplifying the mechanistic modeling workflow with precharacterized columns – the story from their development to application

Max Edin[1], *Patricia Roch*[1], *Eggert Brekkan*[1], *Lalita Kanwar Shekhawat*[1], *Lena Enghauser*[2], *Daniella Ekström*[1], *Tatjana Trunzer*[2], *Gunnar Malmquist*[1], *Tobias Hahn*[2]

1) Cytiva, Uppsala, Sweden
2) Cytiva, Karlsruhe, Germany

Mechanistic models describe the physical phenomena of chromatographic separations and need input parameters that physically relate to the biomolecules, the column, and the resin involved. Determination of column and resin characteristics, such as porosity, ligand density, and accessible surface area, is a vital step prior to model calibration. These properties are typically determined experimentally and must be measured with sufficient accuracy to ensure successful modeling. This accuracy is especially needed if planning to transfer the model across scales and between columns or resin types.

Even though column-characterization experiments are usually seen as rather trivial, studies exploring the validity of the results and how they may differ under various experimental conditions are generally lacking.

In this work, we studied the effect of tracer molecule choice, concentration, and flow rate when determining porosities of chromatography columns. Additionally, we studied the behavior of polymer, tentacle-like ligands versus traditional monomer ligands at different ionic strengths and how the apparent accessible surface area of the packed resin is affected. Furthermore, we performed a simulation-based sensitivity analysis to study the impact of measurement uncertainty on the model calibration results and the model's predictive performance.

Our results demonstrate that the conditions used for column characterization experiments are important. The conditions are especially significant when comparing different resin structures and ligand modalities. The increased knowledge of the underlying mechanisms of column and resin characterization will lead to a faster and more reliable model calibration workflow by enabling smarter choices of experimental conditions and more informed troubleshooting.

We also highlight how the use of pre-characterized *f*(x) columns can accelerate process development by simplifying the mechanistic modeling workflow. In our case study, a mAb polishing step was optimized using combined offering from Cytiva of GoSilico™ chromatography modeling software and a pre-characterized *f*(x) column. The optimized model was then transferred to a second *f*(x) column that was twice the size and had different column-specific properties. The outcome of this experiment was accurately predicted by the model, showing that the effects of material properties were correctly accounted for.

Session 2

Evolution of Mature HTPD Platforms

Session chairs

***John Welsh**, Rivanna Bioprocess Solutions*

***Brian Murray**, Sanofi*

Over a decade after this conference's first meeting, this session will focus on the evolution and current status of mature high throughput process development platforms. Specifically, this session will highlight: (i) the development of HT technologies to enable mature HTPD platforms and (ii) applications of these platforms. For enabling mature platforms, examples involving technology development (e.g. software, hardware, automation) or overcoming challenges to facilitate implementation across diverse modalities are encouraged. For applications of mature HTPD platforms, case studies from later stages of process development such as bioprocess control strategy development using high throughput tools or lessons from regulatory interactions around HTPD are welcome. Lastly, this session is interested in the development of novel data applications for bioprocess development that are enabled by having a mature HTPD platform (e.g. digital workflows).

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Integrated Protein A Chromatography and Low pH Viral Inactivation Unit Operations Miniaturised on an Automated Platform

Paras Sharma[1], *Lars Robbel*[2], *Michael Schmitt*[2], *Duygu Dikicioglu*[1], *Daniel G. Bracewell*[1]

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High throughput process development (HTPD) is established for time- and resource-efficient chromatographic process development. However, integration with non-chromatographic operations within a monoclonal antibody (mAb) purification train is less developed. An area of particular importance is the development and optimisation of low pH viral inactivation (VI) that typically follows protein A chromatography and its effect on the aggregation behaviour of the mAb product. However, the lack of pH measurement devices at the miniature-scale represents a barrier to implementation. Furthermore, many HTPD strategies lack integration of the surrounding unit operations within the purification sequence, limiting process interactions and overall process knowledge.

This study is based upon the design and testing of a HTPD platform for the integration of protein A chromatography and low pH VI operations, to assess the effect of pH on the aggregation behaviour of mAb product during low pH VI. This was achieved by translating laboratory-scale protocols to the miniature-scale using a workflow design and simulation software before execution on an automated liquid handling platform. The protein A chromatography and low pH VI operations were successfully translated to the miniature-scale, as assessed by comparative analysis of step yields and aggregate contents. Upon integrating the two operations, comparisons between the miniature-scale platform and laboratory-scale system were made. The processing time of the miniature-scale sequence (4.75 hours) was less than for the laboratory-scale sequence (7.75 hours), which translates to increased labour efficiency for the miniature-scale. Furthermore, the miniature-scale platform allowed for greater throughput while minimising human error across repeat low pH VI runs, compared to the laboratory-scale system. This not only highlights the economic advantages of the miniature-scale platform, but also the opportunity for further integration within the mAb purification sequence, which can be utilised as a rapid assessment tool for mAb candidates.

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High Throughput Screening for resin regeneration conditions

***Cornelia Walther**, Nadine Royla, Regina Zivkovic, Yvonne Patzold, Christoph Pertl, Cecile Brocard*

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A major cost driver in the production of biopharmaceutical products is the utilized chromatography resins. Therefore, reusing the resins is essential for cost efficient production and affordable drugs. Efficient resin regeneration procedures are necessary to enable the reuse of resins. Insufficient or improper cleaning procedures can result in the best case in loss of performance and in the worst case in loss of production batches. However, the design of an efficient regeneration procedure is often neglected.

Efficient regeneration procedures depend on the stage of the corresponding chromatography in the production process or the resin type. The conditions for a well-designed process differ based on these parameters and cannot be easily transferred from one resin to the other.

We set up a high throughput screening in batch format on our liquid handling station where in a first step, regeneration solutions and combinations thereof can be tested. The regeneration itself, as well as a blank elution after the regeneration and the resin, is analyzed for each condition. Well-working conditions are then transferred to RoboColumn scale where further parameters such as flow rates and holding times can be tested. In this scale, the regeneration and a blank elution can be analyzed. Moreover, influences on ligand density or dynamic binding capacity can be evaluated. The best conditions can then be tested in a short life cycle study where the performance of the resin can be evaluated after a certain number of chromatography cycles.

With this screening setup, the development of an efficient resin regeneration procedure is possible with reduced amounts of material, in shorter time, and with fewer resources in the lab.

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Improved DOE Workflow for Parallel Screening Experiments on the Ambr® Crossflow TFF system

Viktor Sandner[1], *Vishal Parbhakar*[2], *Samantha Ward*[3], *Tanja Rau*[4]

1) Sartorius Stedim Austria GmbH
2) Sartorius Stedim India Pvt. Ltd.
3) Sartorius Stedim UK Ltd.
4) Sartorius Stedim Biotech GmbH

The use of high-throughput and semi-automatic robotic devices allows for the rapid processing of biological samples, such as proteins, antibodies, and vaccines. The ambr crossflow allows operators to efficiently screen and optimize ranges of process parameters, including different buffers, buffer strength, conductivity, and pH to find the best operating parameters for any given system.

The built-in functionalities of the ambr crossflow software facilitates the use of DOE tags for numerical and categorical process parameters as well as simple and nested calculations, e.g. average flux in a specific phase during diafiltration. These workflows are important steps that strongly improve data handling and analysis before initiating lab work and especially during post-process analysis. In this study, we tested a scenario in which IgG was subject to different process conditions and improved flux, yield and aggregate levels were modeled with the ambr crossflow software in combination with DOE.

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High Throughput Models for Process Characterization: Successes and Challenge

***Brian Murray**, Harry Poppick, Thomas Liao, Thomas Wasylenko, Peter Firmin, Shashi Malladi, Ludivine Profit, Jason Walther*

Sanofi, Framingham, MA United States

At Sanofi, an active area of focus is implementing higher throughput models for process characterization. Process characterization is a resource-intensive activity, often requiring dozens to hundreds of experiments, and is required to establish the proven acceptable ranges for manufacturing process parameters. Typically, determining these ranges requires two categories of experiments: (1) small-scale model development and qualification, to ensure the small-scale model is representative of the manufacturing-scale process, and (2) using the small-scale model to perform univariate and multivariate characterization experiments, the data from which are then analyzed to define the proven acceptable ranges.

Here, we will share results from characterizing the chromatography operations for an enzyme manufacturing process using both traditional small-scale models (bench-scale columns) and the high throughput minicolumns. Through replicating the experimental designs with both systems, we found that, despite some differences in the data and statistical models, the control strategies developed using the two models were highly similar.

While a similar control strategy was developed in this case, additional analysis examined the causes of dissimilarity in the data and statistical models. Two main causes were identified: (1) increased transition band broadening, which was impactful for specific phases of some unit operations, and (2) increased variability of the minicolumn system relative to the traditional bench-scale system. Through experimentation and statistical simulations, we have shown that the increased variability of the minicolumn system, despite assuming a perfectly-accurate model, can lead to signficantly different proven acceptable ranges under process-relevant scenarios. While these effects can be impactful, we have designed and implemented guidance for our small-scale model qualification and process characterization experiments to minimize this effect. Here, we will present evidence for these challenges along with our overall guidance on using minicolumns for process characterization.

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Micro-scale Purification Platform – High throughput tool for BioPharma Manufacturing Investigations

***Manoj Ganesh**, Elijah Beaudin, Quynh Nguyen, Emily Mosher, Sushil Bhatia, Zizhao Liu*

To accelerate small-scale investigation and raw material screening studies, efforts have been made to evaluate liquid handlers (Tecan & Hamilton) to perform high-throughput micro-scale purifications. The end goal is to establish a fully automated micro-scale high-throughput purification platform, which can be leveraged to provide fast turnaround results.

This presentation will present the work focused on comparing micro-scale column purification using Tecan to lab-scale ÄKTA performance and discuss critical case studies of applications to manufacturing support in aiding with root cause investigations and raw material screening. Details on high-throughput micro-scale harvest and VI (Viral Inactivation) step will also be presented. We would also share our methodology of monitoring RoboColumn integrity prior to performing the purification; pre-column assessment to check for NGHETP and Skewness to see column integrity, which are critical steps to be automated to achieve a fully automated workflow. Experience and lessons learned of working on automating downstream processing steps will also be shared.

Session 3

Integrated PD and Analytics Case Studies

Session chairs

***Jon Coffman**, Astra Zeneca*

***Andrea Rayat**, University College London*

Analytics have always been a significant bottleneck for HTPD implementation. The number, volume, and format of the samples often prevent a full analysis of the results. We are interested in case-studies for integrating HTPD and analytical methods. We are interested in methods that can be used in control loops during the HTPD, especially those that control PQ or CPPs in a dynamic manner. In these cases, demonstration of a control loop would make an ideal presentation. Multi-attribute methods applied to HTPD without control loops is also challenging and valuable. In-line/on-line/at-line analytical methods for extremely small volumes, such as those found in microfluidics, are also limiting HTPD. Since, many HTPD methods remain a curiosity, we want to see how they are actually being used to develop manufacturing processes. Case studies using these methods in a routine development business process would be highly relevant. A discussion of factors (e.g., technological, business, human factors, etc) preventing the routine use of HTPD would be appreciated.

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Automated Raman spectroscopy measurements for integrated chemometric model development

Jakob Müller

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Multivariate spectroscopic techniques, such as ultraviolet/ visible (UV/VIs), infrared (IR) or Raman spectroscopy, are the most common methods for analyzing complex biological solutions. Particularly Raman spectroscopy has been gaining popularity due to is high selectivity for multiple process parameters and product attributes and its flexibility with regard to sample condition. After data acquisition, multivariate regression methods can then be used to correlate the spectra with analytical reference data to build predictive models for real-time applications. While mathematical methods can be used to correct measured signals in retrospect, automated measurement systems are desired in process development in the first place to characterize the influence of different process parameters. Automated measurement systems enable to reproducibly acquire new data in high-throughput and resemble process operating conditions with only low sample volumes required. Furthermore, the combination of standardized methods for data acquisition, data processing, model building and sophisticated storage solutions such as a database form a bridge to integrated the model development and model life-cycle assessment.

In this study, we demonstrate the concept, implementation and testing of an automated data acquisition tool for Raman spectroscopy for measuring critical quality attributes (cQAs) in real-time by applying hardware automation and multivariate regression methods. We established an experimental setup using a commercial Raman spectrophotometer for data acquisition, an ÄKTA chromatography system for automated sample handling and an external pumping device for measurements under flow. In connection to the establishment of the device communication and conceptualization of a suitable measurement routine we conducted an experimental study using monoclonal antibody solutions containing a variable amount of our cQA of interest. The recorded spectra were subsequently used to build a chemometric model for cQA quantification based on the automated measurement data. The experimental study involves the investigation of the effect of varying flow rates on the measured data and the quality of the resulting chemometrics model. The performance of the model was evaluated upon offline-data as well as spectra collected during a small-scale ion-exchange chromatography experiment.

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SpecPlate, the better standard for more efficient plate based UV/Vis absorbance measurements

Carsten Radtke

PHABIOC GmbH, Karlsruhe, Germany

In the realm of high-throughput process development, a significant portion of experimental insights hinges on the UV/Vis analysis of samples within multiwell plates. While this gold standard approach offers valuable data, it is plagued by susceptibility toerrors stemming from pipetting inaccuracies, the disruptive presence of liquid menisci, and a limited detection range necessitating constant dilution adjustments. Recognizing these shortcomings, we are thrilled to unveil a straightforward solution—PHABIOC's groundbreaking innovation, the SpecPlate.

The SpecPlate arises from an idea conceived several years ago within the research group of Prof. Jürgen Hubbuch at the Karlsruhe Institute of Technology (KIT). Presented as a poster by our esteemed colleague Marie-Therese Schermeyer at the HTPD meeting in 2017, the overwhelmingly positive response compelled us to collaborate with realization partners to mature the concept into a tangible product.

Distinguished by its exceptional attributes, the SpecPlate is redefiningUV/Vis spectroscopy practices. By rectifying the vulnerabilities of conventional multiwell plates, it streamlines concentration determination while eliminating sources of error such as liquid menisci and dilution discrepancies. The SpecPlate's capacity to cover an extensive concentration range underscores its versatility and adaptability.Furthermore, up to four measurement points per samplewith different, physically predefined path lengths enable more precise measurement in high-throughput format.

A prominent advantage lies in the SpecPlate's adherence to international standards for multiwell plates, ensuring seamless integration with standard laboratory equipment including liquid handlers and plate readers. This fosters effortless incorporation into existing workflows.

During the HTPD meeting in 2023, I am excited to showcase compelling case study results that illuminate the potential and flexibility of theSpecPlate. Its implementation has yielded heightened accuracy, reproducibility, and efficiency across diverse applications.

The SpecPlate embodies a success story born at KIT, propelled by the feedback received at a previous HTPD meeting. Through the unveiling of our latest progress, I aim to bring this narrative full circle, underscoring how an innovative idea evolved into a pioneering technology. During my presentation, I look forward to showing you the amazing capabilities of SpecPlate and providing a glimpse into the future of plate-based absorption measurement.

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Integration of Automated High Throughput Process Analytics to support High Throughput Process Development

Nicola Roberts, *Razwan Hanif, Mari Spitali*

UCB, Slough, United Kingdom

Monoclonal antibodies (mAbs) continue to be a growing segment of the drug market with the global market size estimated to reach USD 237.6 billion in 2023. To support the development from candidate selection through to licence application of mAbs in a timely manner, UCB has taken the approach to invest in methodologies to increase efficiency including high-throughput tools. This includes the miniaturization and automation of both the upstream bioreactors for cell culture process development and the downstream purification process using automated liquid handlers such as Tecan's Evo platform. The purification platform has had continued improvement over time and adaptations to workflows to increase robustness and address bottlenecks. The same approach has been applied to the development of appropriate high throughput process analytics (HTPA). To support the high throughput platform established within development, key assays for impurity clearance and product quality analysis have been either fully automated or partially automated to increase efficiencies. Rather than a fully integrated automation platform which can be inflexible for future innovations and very costly, an incremental approach to solve each automation hurdle was applied. Presented here is an overview of how different hardware were integrated and the approach taken for installation, scheduling software and maintenance for HTPA automation.

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Enhancing Bioprocessing with pH Sensitive Nanosensors: High Throughput Screening and Antibody Production

Alison Tang[1]*, Greta Csalane Besenyei*[1] *and Veeran Chauhan*[2]

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2) University of Nottingham, Nottingham, UK

Measuring pH accurately in a high throughput fashion using a small amount of sample has always been a challenge. Traditional micro pH probes can accurately measure pH of very small volumes; however, it is a very labour-intensive activity when there are 96 plus samples and is difficult to incorporate into an automated liquid handling platform. There is a commercially available pH measuring 96-well plate with fluorescence pH sensors, however this technology has very narrow pH detection range and hence not flexible enough for monitoring pH of a MAb purification process.

Despite the progression in bioprocessing technology, accurately monitoring and adjusting pH in high-throughput experimental setups remains a significant obstacle. This limitation hinders efficient screening of downstream experimental conditions and the optimization of antibody production processes. Current pH monitoring techniques fail to demonstrate high reproducibility and struggle to determine differences at low pH. Additionally, existing solutions do not fully capitalize on the possibilities of sample conservation or offer data at a resolution compatible with automated dispensing platforms. To address these gaps, we introduced pH sensitive nanosensors (~30 nm diameter) capable of monitoring pH from 2.5-8.0 ±0.17. These sensors were characterized for high reproducibility, even in challenging conditions such as ATTO dye inclusion at low pH. Further, the nanosensors improved the calibration curve for high pH measurements, showcasing versatility. The nanosensors are fully compatible with the Tecan automated dispensing platform, offering an opportunity to work with extremely low volumes, down to 25 µL. The nanosensors can detect pH of buffers and protein solutions at a nanosensor concentration as low as 1 mg/mL; furthermore, the accuracy of the measurements is agnostic to protein concentration. This allows for substantial improvements in sample conservation. This work has enabled full protein purification platform process to be performed on a liquid handling system, miniaturising the optimisation of bioprocessing operations for AstraZeneca and can be integrated into routine procedures to drive automation of process development.

Session 4

Panel Discussion: Best Practices in HTPD for Regulatory Filings, Formulations, and More

***Facilitator: Michael Doherty**, Ring Therapeutics*

At HTPD 2023, attendees will have the opportunity to explore new possibilities and gain a deeper understanding of bioprocess development while utilizing fewer resources. This conference provides a platform for participants to connect with scientists who share similar challenges and interests, opening the door for future conversation.

During this panel discussion, attendees will hear from experts with diverse backgrounds across a wide spectrum of modalities, offering a glimpse into how HTPD and Smart PD are applied in real-world situations. The panel format allows for a candid discussion about the industry's challenges, successes, and limitations in meeting current and future targets. This session promises to be both practical and thought-provoking and will provide an outlook to HTPD needs and applications for the years to come.

Session 5

Calling All Nanoparticles: HTPD with Cells, Viral Vectors, LNPs, Gene Editors, and Vaccines

***Session chair: Jack Kramarczyk**, Moderna Therapeutics, USA*

Developing dispersions and suspensions of nanoparticles as pharmaceutical products can bring significant challenges, relative to development of soluble products of uniform composition. Nanoparticles are inherently challenging due to their large size, unique behavior, and variability across the population. These complex delivery vehicles and active pharmaceutical agents may require unique unit operations and analytical methods; additionally, the laboratory systems and experimental methodologies used for process design and characterization may require inventive solutions and novel approaches.

This session will review case studies which highlight approaches, strategies, gaps, and opportunities for miniaturization and HTPD designed to address the specific challenges of developing pharmaceutical nanoparticles.

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Downstream overview of an end-to-end high throughput AAV drug substance process development platform

***Mahsa Hadidi**, Junfen Ma*

***Sanofi, Waltham**, MA United States*

The recombinant adeno-associated virus (AAV) has proven to be a safe and effective delivery tool for gene therapy applications. Widespread use of AAV necessitates efficient manufacturing processes delivering high product quality. However, the short process development timelines, material limitations of early-stage development, and inherent complexities of this modality pose significant challenges. One strategic approach is to harness high throughput (HT) methodologies and automation technologies to enhance the efficiency and optimization of AAV process development, encompassing purification processes.

This work focuses on downstream AAV purification within an end-to-end HT process development platform. It presents the application of HT methodology alongside advanced HT analytics to accelerate the exploration of AAV stability and purification process parameters utilizing various HT modules (including mini-columns, resin tips, and 96-well plates). This integration accelerates the identification of optimal conditions leading to improved yields and shortened timelines, facilitating realization of gene therapies from research to clinics.

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Development of High-Throughput Purification Methods for Adeno-Associated Viral Vectors

***Katerina Farukshina**, Talia Levy, Nathan Sweeney*

Cell and Gene Therapy Catapult, London, United Kingdom

High-throughput process development for AAV products is challenging; the upstream process generates an AAV containing cell lysate in which many CQAs cannot be assessed due to low titre and sample complexity. Furthermore, downstream processing typically requires a high volume of starting material and includes filtration and chromatography steps that are slow and low throughput (one sample purification takes >10 h). We have developed high-throughput direct capture chromatography methods using RoboColumns and 96-well capture plates, both of which allow for rapid concentration and cleanup of AAV-containing lysates. The titre and purity in eluates are sufficient for most analytical methods, thus enabling characterisation of yield and quality from milli-scale upstream process development experiments employing high-throughput multiwell plates or bioreactor systems. To assess CQAs from small elution volumes, we implemented advanced high-throughput characterisation techniques with low sample volume requirements such as dynamic light scattering, HPLC, mass photometry and automated qPCR.

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Towards High-throughput process characterization of gene therapy viral vectors

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Spark Therapeutics, Philadelphia, PA United States

High-throughput process characterization of viral vectors may address both resource burdens and understanding gaps in Gene Therapy drug substance processes. However, before HT-PC can be realized, significant progress is required in adapting Gene Therapy specific concerns into a HT-PC framework. Towards this, we first present efforts to understand the HT scale down model. We then show HT case studies towards informal assessment of process robustness. Finally, we end by suggesting a HT-PC approach that may balance concerns of limited historical regulatory exposure and challenges in Gene-Therapy scale down models.

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Breaking boundaries in AAV platform optimisation HT monolith chromatography plate development

Nicholas Pearman

Pharmaron Biologics, Liverpool, United Kingdom

Pharmaron has established a multi-faceted purification toolbox approach using small-scale downstream processing (DSP) high throughput (HTP) systems, to deliver rapid process optimisation and manufacture of a wide range of Adeno-Associated Virus (AAV) serotypes and products. The use of an automated liquid handling robot in downstream purification (DSP), allows Pharmaron to conduct an early assessment of purification performance for a specific gene therapy product. This approach allows for the determination of platform fit and subsequent rapid optimisation through a combination of targeted HTP screening and Design of Experiment (DoE), to assess the optimal binding and elution conditions for separating full/partial, from empty AAV capsids.

The integration of monolith-based chromatography into Pharmaron's DSP purification toolbox, required creation of a scale down model capable of assessing a product's fit to the platform and optimisation of the process to attain specific performance targets. To achieve this model, small-scale, HTP methods for utilising monolith plates on the Biomek i7 liquid handling platform were developed.

The results demonstrated that AAV can be bound and eluted from monolith plates using similar conditions to those used at larger scale, with AEX plates achieving separation of full/partial species, from empty particles. This demonstrated that the Biomek i7 robot could successfully model large scale monolith chromatography at small, HTP scale. This innovative approach is invaluable in maximising productivity and drastically reducing development timelines and costs for their customers with the ultimate aim of providing life changing medicines to patients.

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Platform for High-Throughput Algorithmic Optimization of *in vitro* Transcription

Spencer E. McMinn*, Danielle Miller, Daniel Yur, Shashank Murali, Sheng-Ching Wang, Kevin Stone, Emily Wen*

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The recent success of non-viral, mRNA vaccines have shown that new vaccine technologies can be used to target emerging diseases as well as diseases not previously thought to be remediable by vaccines (1). One of the key advantages of mRNA vaccine technology is the ease of editing the coding region of mRNA via *in vitro* transcription (IVT) to quickly address a new target without changing the fundamental development process (2). While the optimization of IVT has received much recent attention, the challenge remains that the optimal conditions for one sequence do not translate to another. Therefore, a robust platform is required to quickly optimize the IVT reaction for new mRNA sequences of interest. Here we describe the integration of algorithmic optimization tools with a robotic liquid handler to enable a high-throughput platform for the optimization of the IVT reaction for mRNA synthesis. We selected the SARS-CoV-2 Delta variant as a relevant mRNA sequence to demonstrate the application of our platform. The IVT process was optimized for yield and purity utilizing machine learning models. The population of these models with *in silico* experiments provided additional insights into this complex biochemical reaction

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High-throughput Process Development for Antibody-Drug Conjugate (ADC)

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Sanofi, Vitry sur Seine, France

To deliver on our commitment to bring first-in-class treatment, we aim at accelerating the introduction of our biologics into clinical trials. To that end, we are leveraging high-throughput capabilities integrating miniaturization, automation, and parallelization to provide a systematic approach, reduce time, material, and resource requirements, and increase efficiency to develop a manufacturing process at both early- and late-stages.

In the context of Antibody-Drug-Conjugate (ADC), we develop a high-throughput platform to screen and optimize reaction conditions. We demonstrate the use of 96-well plate format to screen parameters and build predictive models to be used at lab-scale. This presentation highlights our strategy and methodologies to develop such a platform, using a 2-positions liquid dispenser. We share our statistical methodologies to study our HT system (*i.e.* precision, accuracy, edge effects) and to compare HT and lab-scale. Some critical points such as the evaporation or the distribution settings are discussed. Finally, we share a case study showing the development of a monoclonal antibody reduction step, a critical unit operation within the overall conjugation process, where we leverage models build at HT-scale. Overall, this presentation exemplifies the setting of a HT platform for chemical steps, found in various modalities: protein conjugates, lipid conjugates, nanoparticles conjugates...

Session 6

Frontiers in HTPD/Smart PD

Session chairs

***Felix Wittkopp**, Roche, Germany*

***Sheng-Ching Wang**, Merck & Co, US*

High-throughput process development (HTPD) has been successfully applied in many academic and industrial labs before and during the pandemic, in end-to-end CMC development, and across therapeutic modalities. More recent challenges include the support of a) connected and continuous process development, and b) the next level of accelerated CMC development in order to fight the pandemic.

This session invites speakers to present the latest trends and concepts in HTPD including learnings from the pandemic. How could high-throughput-related platforms, workflows and development strategy help to accelerate CMC timelines even further without compromising patient safety? How do high-throughput platforms perform regarding environmental sustainability? How can we reduce waste and improve waste management? In addition, contributions addressing innovative approaches to develop and characterize new unit operations, to support health authority submissions by HTPD as well as any other novel approaches such as further miniaturization, are enthusiastically welcomed.

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Advancing High-Throughput Chromatography Development: Leveraging a QSAR Model for Experimental Design and Applying Learnings to High-Throughput Methods

Michael Rauscher[1], *Michael Hartmann*[1], *Sheng-Ching Wang*[1], *John P. Welsh*[2]

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High-throughput experimentation is a well-established approach for accelerating development of chromatographic processes for biological products. However, complex modalities such as multi-specifics, fusion proteins, and protein conjugates are increasingly common, presenting new separation challenges across a wide range of process- and product-related impurities. Resins can be screened in a microplate format to assess partitioning of product and impurities at a range of mobile phase conditions, but a bottleneck can still exist due to the potential breadth of screening space. *In silico* resin screens using empirical models trained on historical data sets can help narrow down the design space that should be screened experimentally. This work presents a Quantitative Structure-Activity Relationship (QSAR) model that has been developed and trained with a high-throughput data set of ~8000 data points across 30 therapeutic proteins and 40 resins. Calculated descriptors for proteins and resins afford predictions of product binding and optimal screening regions for separation. General strong binding and elution behavior, as classified by specific partition coefficient values, can be predicted with ~95% accuracy. This model has been applied in early stage development of complex biological molecules and is now a routine part of the process development workflow in our group. At the same time, key learnings from the QSAR model development have motivated the maturation of the high-throughput platform by increasing method standardization and automation in order to ensure better comparability across a large data set. New instrumentation and analytical methods are being employed to increase the diversity and precision of data that can be gleaned from a screen, verifying process parameters and leveraging microfluidics-based analytics when feasible. Complementary high-throughput chromatography methods also are leveraged to provide information that plate-based screening cannot provide. Importantly, this work showcases the iterative relationship of *in silico* and experimental high throughput screening and demonstrates how innovations *in silico* have helped to drive the evolution of the HTS experimental workflow to better handle the unique challenges presented by an increasingly complex pipeline.

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Smart Bioprocessing Grand Challenge

***Lucie Studená**, Sean Ruane, Lukas Kuerten, Elaine Speirs*
Centre for Process Innovation, Darlington, United Kingdom

The current approach to bioprocess development and scale-up is based on extensive experimentation, usually employs ad-hoc solutions applied under time and financial pressures and needs to be rebuilt from the ground up for each new molecule. This approach is both inefficient in itself and results in inefficient processes entering production because there is little time to reach the optimal parameters.

The Smart Bioprocessing Grand Challenge aims to revolutionise the development of bioprocesses by using modelling and automated processes. We aim to be able to develop bioprocesses largely *in silico*, resulting in a drastic decrease in development costs and a significant improvement in the quality of the resulting processes.

Our downstream approach is centred around powerful analytical platforms that explore the full contaminant profile of a sample, as well as the desired product. By taking measurements before and after the purification processes, the reduction in individual contaminants can be identified. By using standardised platforms, transferability issues can be greatly reduced, and the properties measured in each platform are strongly related to the mechanisms used in the relevant process, increasing their predictive power. Standardisation also allows us to build large datasets of platform data comparable across products and scales, greatly increasing the predictive powers of any model built thereof and ensuring the transferability of process insights.

We are combining this platform measurement approach with a Smart Automated Development laboratory which allows us to refine and validate model predictions directly, adding real-world confirmation and real-time feedback to our modelling approach.

The ultimate goal of the grand challenge is a product-agnostic system, in which process behaviour can be roughly predicted by platform measurements of an initial sample, allowing experimentation to be focused on proving and fine-tuning processes, and greatly shortening process development times.

The study is currently in a Proof-of-Concept stage, where CPI, working with Innovate UK, is developing and proving two analytical platforms, the first focused on clarification and filtration, and the second on downstream chromatography. CPI is also building large datasets of platform measurements, developing models based on the platform data, and constructing the digital and process infrastructure to support work going forward.

As an innovation centre, CPI is uniquely positioned to perform large collaborative projects with multiple partners, and so CPI is interested in seeking pharmaceutical and digital partners to join the wider project once the Proof-of-Concept phase is complete. The full grand challenge will build platforms and datasets to explore the full upstream and downstream process and will involve a large consortium of collaborative partners.

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Just because you can doesn't mean you should: What makes a successful high-throughput method

Tobias Hahn

Cytiva, Karlsruhe, Germany

Since the first International HTPD Meeting, methods and technologies have evolved tremendously, and some prototypes and ideas have become commercial products or established processes. However, this is by no means true of all HTPD approaches, and some self-proclaimed Smart PD solutions are not as clever as they seem on second glance.

- When does miniaturisation no longer solve problems but create new ones?
- Where is a good trade-off between quantity and quality in data collection?
- What if tried and tested laboratory procedures are simply incompatible with a certain new technology?
- Do we know what we don't know, especially with respect to mechanistic modelling? And if we do, what do we conclude from this?

In this presentation, conference papers from the past years from the HTPD community, but especially from the author himself, will be critically examined to identify what distinguishes the ultimately successful methods from the less successful ones. The goal is to learn from the past and focus our research on what promises sustainable success in the future.

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Utilising machine learning for preventive maintenance and accelerating data analysis capabilities with digital transformation

Razwan Hanif

UCB, Slough, United Kingdom

The downstream process development for antibody-based biopharmaceuticals has been applying a platform approach for many years. Although this has proved to be a very effective approach, optimisation of processes for ever increasing complexity of feedstreams and new innovative antibody formats has meant that process platform adaptation is required prior to clinical manufacture. The adoption of microscale techniques with automation allows for process development throughput to be accelerated and is a step towards realising industry 4.0.

Industry 4.0 is part of the fourth industrial revolution circa 2010, implementing artificial intelligence (AI) trending towards the internet of things (IoT), automation, digital twins and cloud-based infrastructure. It is estimated that AI will generate $13 trillion of value by 2030 (McKinsey forecast 2018), yet there are many examples of failed AI projects, which makes formulating a sound strategy difficult. However, for successful implementation it is necessary to combine AI model building with scientific and engineering understanding with tools that are appropriate for science, engineering and data science methods. The key is starting with smaller projects to better understand how an AI project will evolve to help build a platform for further expansion. The benefit of automated microscale techniques is however bottlenecked by the ability to obtain meaningful analytical data from the large number of samples taken and to examine large and historical data sets. In this regard, there is tremendous potential to use AI for machine learning, simulation and data analytics to improve product quality and process efficiency.

In this example, ~1500 SEC samples are performed per month, which is ~18000 samples per year and requires 135 litres of buffer. The SEC columns cost £2500 with their unmonitored use varying considerably. The current system requires the operator to manually monitor operational metrics of the chromatography run for anomalies, and their expertise is required to detect and take preventative action. Therefore, this system gathers operational data, but not expertise on how to leverage data to run what-if analysis in a scalable way. MATLAB® machine learning models were used to pre-process data and extract features to monitor column health and to isolate root cause of failures, variability and predict time-to-failure and remaining useful life (RUL).

605

Establishment of a High-Throughput Technology Roadmap across a Global Organization to Improve Purification Process Development for Biologic

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To accelerate the development of Sanofi's biologics mammalian pipeline, we aim at streamlining purification process development through implementation of high-throughput (HT) capabilities. To enable continual improvement, we have developed a HT technology development roadmap to align our global organization on both our short- and long-term vision. This presentation highlights 3 projects as part of this roadmap.

On short-term, we have been focusing on HT tangential flow filtration (TFF) to overcome material limitation during the development of Ultrafiltration/Diafiltration (UF/DF) step. Benchtop TFF systems commonly used as scale-down model are material consuming and can only conduct one experiment at a time. To address this, the use of the ambr® crossflow system as a scale-down model has been evaluated and successfully implemented for process development to benefit from miniaturization, automation, and parallelization.

On long-term, we are developing a HT process development lab with HT cell culture equipment co-located with an integrated purification and analytical suite. In addition, we aim for complete integration and automated execution of chromatography development experiments with high throughput analytical assays. Improvements towards automating the sampling and data workflow have also been made.

On longer term, the implementation of Next-Generation in-line sensors for data acquisition could maximize the use of minicolumns for HT chromatography. Up until now, only partial information about protein concentration is acquired by fractionation into 96-wells plates and UV measurement only at the end of the experiment. We are currently working on the design of UV in-line measurements on 8 minicolumns in parallel, using liquid handling system, to gain more precise information about each small-scale experiment.

By defining collectively one engaging trajectory with high level overview of the timelines, detailed objectives and deliverables, our HT technology development roadmap ensures that the team move efficiently and share the same vision of the current state and path forward. It is an essential tool for visualizing, sharing and adapting our plans for our global HT platform.

Posters

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Advancing Mispair Removal Approach: High-Throughput Techniques for Efficient Bispecific Antibody Downstream Process Development

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High-throughput technologies have become a key technology as extremely useful for accelerating the development of bio-pharmaceutical downstream processes. Although numerous reports exist on the application of high-throughput technologies in the development of standard antibody downstream process, there are limited reports on their use in the development of complex molecules such as non-common L-chain (ncLc) bispecific antibody which offer more innovative modes of action for medical treatment and address unmet medical needs. However, these antibodies present challenges due to the formation of multiple mispair variants, which need to be efficiently removed during the downstream process. The development of efficient mispair removal processes for these antibodies is another time-consuming challenge. In this work, partition coefficient (Kp) screening and miniaturized pre-packed chromatography columns (RoboColumn) were sequentially employed to efficiently explore the separation conditions for mispairs in the ProL affinity elution process development for ncLc bispecific antibody. Integration of icIEF analysis in the Kp screening step enabled efficient condition exploration in the subsequent RoboColumn step, and the entire optimization process was completed within a few weeks. Furthermore, we intend to showcase the construction of an automated data platform to accumulate and analyze high-throughput process development (HTPD) data, which can be efficiently used for mechanistic model development. By employing this approach, we successfully developed a HTPD platform that could efficiently explore the optimal condition for complex biopharmaceutical molecules in a very short period.

702

A high throughput study of sodium hydroxide cleaning efficiency for protein A resin

Jelena Vasić, Anna Grönberg, Tomas Björkman, Gunnar Malmquist and Eva Heldin

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Protein A affinity chromatography is the main technique for capture of antibodies or Fc-fusion proteins and is commonly used in purification platforms. To prevent fouling and carryover between cycles, and to extend the resin lifetime, protein A resins are cleaned with sodium hydroxide (NaOH) between cycles. Protein A resins available on the market vary in properties like material of base matrix and type of protein A ligand, influencing how well they can tolerate high NaOH concentration.

High NaOH concentrations work as a sanitizer to prevent and reduce bioburden. Cleaning with high NaOH concentration can speed up the cleaning-in-place (CIP) step, which helps reduce the cycle time. Finding the highest concentration possible that a given protein A resin can tolerate is important for optimizing process efficiency. To speed up the experiments, a high throughput approach was used both for fouling the resin and analysis of foulant.

We have previously found that 0.3–0.5 M NaOH cleans more efficiently than 0.1 M NaOH. These results show that more of the fouled protein was removed from the resin with higher NaOH concentrations. Here, we explore CIP with NaOH concentrations up to 1.0 M and study the influence of CIP contact time in high throughput format.

703

Accelerating Process Development for NANOBODY® Molecules: A High-Throughput Approach for IEX Resin Screening and Automated Data Analysis

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Sanofi. Zwijnaarde, Belgium

NANOBODY® molecules are based on single variable antigen-binding domains derived from camelid antibodies that still attain similar target affinity properties as conventional antibodies whilst benefitting from a smaller size. Due to their variability in pI, charge and/or MW roughly 5 weeks of the Process Development (PD) of a novel NANOBODY® molecule are spent on the Ion Exchange chromatography (IEX) strategy and the corresponding data processing and analysis. We discuss the possibility to expedite this resource-intensive process by employing a semi-automated and high-throughput approach at miniature scale for IEX screening. Additionally, we aimed to automate the data processing and analysis through the use of R / RStudio and custom analysis dashboards designed in TIBCO Spotfire®. Here we propose such a semi-automated and high-throughput approach and show that it remains comparable to its bench-scale counterpart.

704

Exploring practical considerations in resin and condition screening using high-throughput techniques, coupled with Design of Experiments (DoE) – A case study

Artur Stanczak

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Purification process development can sometimes be a challenging endeavor. Prior knowledge can prove useful in many cases. However, there can be substantial diversity in the physicochemical properties of proteins, even within the same family. This variability can render the development process non-intuitive, protracted, and more expensive. Screening multiple resins with various modalities using high-throughput techniques can expedite the selection of the best-performing resins. A conditions screening study can yield valuable insights when employing the DoE approach. High-throughput techniques, combined with the DoE, can swiftly identify significant factors and interactions between them. Two case studies, involving monoclonal antibodies (mAbs) and immunoglobulin M (IgM), serve as examples of harnessing high-throughput techniques, such as 96-well plates, in conjunction with the DoE. Practical considerations related to handling small volumes, inherent limitations of small-scale studies, as well as certain aspects of scaling up, will be discussed.

705

High throughput process development for optimised control of leached protein A

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The reduction of leached protein A is essential to any drug substance manufacturing process utilising protein A affinity chromatography. It has earlier been described that protein A leakage occurs both due to proteolytic activity in the harvested cell culture fluid and in an intact form during the acid elution1. This causes the leaked protein A to exist as a mixture of fragments as well as intact protein A. Intact protein A and its fragments will interact with the monoclonal antibody as well as the resins used in the purification process. Hence, the removal of protein A involves understanding of the source of the impurity, the intermolecular interactions, and chromatographic behaviour of both individual molecules, their fragments, and their conjugates.

This work aims to identify conditions that can both lower the amount of leached protein A in the collected capture pool and improve reduction further downstream. To be able to choose from several possible process conditions that can be applied to control the protein A level in drug substance, we utilised the high capacity of automated small-scale screening.

We apply a previously described fluorescence-based method where the protein A ligand is labelled (*in situ*) with a fluorescent dye1. This enables high throughput quantification of leached protein A and its fragments in process pools with high sensitivity.

The poster will describe the applied analytical methods, the screening approach, and a selection of results based on the methodology.

706

HTPD for late phase development to improve process polish step

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Here we show process improvement for a phase 2 nanobody project with regards to robustness and product quality.

Using a resin screening with Minicolumns on Tecan freedom EVO applying different pH and conductivity conditions as well as buffer systems, a chromatography resin in the legacy downstream process was replaced, thereby avoiding a pH adjustment step while improving purity and yield.

Screening of selected resins included evaluation with 96 buffer conditions each taking 5 days by integrated automatic buffer preparation on the Tecan robotic platform. The generated pseudo chromatograms identified a promising good separation for one column material which could be confirmed on labscale column. The broad elution condition screen indicated the area to be chosen for pH and conductivity speeding up step elution optimization. Using HTPD supported acceleration of the development of a smooth and robust process change with improved yield and purity fulfilling requirements for market production.

707

HTPD for Efficient Optimization of AAV Full Capsid Purification

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During the recent years Gene & Cell Therapies have becoming an important market segment for the bioprocessing industry. Adeno associated viral (AAV) vectors are meanwhile functioning as the leading gene-delivery vehicle, which is driving the demand for advanced, accelerated process development with the goal to reduce process impurities while maintaining yield.

In particular the removal of empty capsids during the polishing step of AAV vectors is essential to ensure final product quality and safety. However, the lack of time and experience often hampers the screening of numerous chromatography resins and conditions for process optimization with advanced HT equipment, leading to sub-optimal processes being used.

In this study, we developed a method utilizing miniaturized pre-packed columns, an automated liquid-handling system, and UV-based analytics to rapidly select the best resins and conditions for AAV full capsids purification.The approach allowed for a more efficient screening process, using only small amount of AAV material, before scaling up to bench top operation.

Results are showing that different AAV serotypes and virus preparations require distinguished combinations of resin and separation conditions to achieve optimal purification, which emphasizes the necessity of running HTS experiments during AAV purification development.

708

Advantage of antibody-based selectivity in the purification of biologics

Kevin Sleijpen

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Advances in bio-therapeutics are generating an increasing range of complex molecules that present unique and often complex purification challenges. By taking advantage of antibody based selectivity, heavy-chain antibody fragments (VHHs) have proven to be a reliable affinity chromatography solution in the downstream process of biologics.

For the manufacture of challenging antibody formats, the production of therapeutic recombinant proteins, or the development of gene therapy vectors, Thermo Scientific™ CaptureSelect™ affinity products provide a scalabble purification solution for the most demanding bio-therapeutics. For instance, our antibody purification product portfolio consists of four resins that each target a specific domain of the human antibody. The affinity resins provide high target purity in a single step, independent of feedstock. Resins can be used during process development in a RoboColumn format and easily scaled up for cGMP manufacturing.

709

Improving throughput and quality of results in nephelometric turbidity unit evaluation with SpecPlate, a new UV Vis microwell plate

Jannik Jungmann

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The UV/Vis examination of samples in multiwell plates is crucial for gaining experimental insights in the field of high throughput process development. This gold standard method provides useful data, but it is hampered by mistakes that can result from pipe tting errors, the disruptive presence of liquid menisci, and a small detection range that requires ongoing dilution adjustments. We are excited to introduce the SpecPlate, a ground breaking invention from PHABIOC, as a simple remedy for these flaws.

The SpecPlate, distinguished by its remarkable characteristics, is reinventing UV/Vis spectroscopic procedures. It simplifies concentration determination while reducing sources of error such as liquid menisci and dilution differences by addressing the weak nesses of conventional multiwell plates. The SpecPlate's ability to span a wide concentration range demonstrates its flexibility and versatility. In addition, up to four measurement locations per sample with distinct, physically established path lengths al low for more exact measurement in a high throughput manner.

During the HTPD meeting in 2023, I am excited to showcase a novel approach to enhance the throughput and quality of turbidity evaluation th rough abso rption using SpecPlate Turbidity measurement is vital in various applications, including water quality testing and biological sample analysis. In this study, I introduce an efficient method , with a low volume sample approach using the SpecPlate and a microplate reader. The SpecPlate embodies a success story born at KIT, propelled by the feedback received at a previous HTPD meeting.

710

High-throughput tools and workflows for purification process development of non-mAb modalities

Mary Lunson, Carol Abraham, Nicholas Field, Alma Svatos, Vivek Halan, Fathima Shazeena Rauf*, Varsha Yadav, Jean Aucamp*

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Non-mAb modalities are increasingly being used as therapeutic agents. The diversity of these new modalities pose unique challenges for downstream development and in turn on the CMC timelines. At Lonza, we identified three main process development challenges having major impact on the CMC timelines:

The structural complexity of these new modalities often results in solubility and stability issues in the process buffers and can lead to high levels of aggregates, clips, and inactive species.

These modalities do not have affinity capture resins available for supporting sample clean-up of high throughput upstream samples and require resource intensive capture step development.

The diversity in the product-related impurity profiles also necessitates product specific purification process development.

High throughput tools and workflows were developed in house to resolve these process development challenges. The first tool is a solubility and stability screen to rapidly identify buffers compatible with the product; dynamic light scattering is used to generate colloidal and thermal stability data for 48 buffer conditions in four days. The second tool is an automated ÄKTA-based workflow for purification of 48 samples from the micro-scale bioreactors with inline load conditioning. This workflow has a wide range of applications from clean-up of upstream process samples to upstream process characterization during late stage development. The third tool is a user-friendly, flexible platform for high throughput chromatography screening using micro-columns. A cloud-based software solution was integrated with a liquid handling system to enable an efficient end-to-end screening workflow including screen design, screen execution, and data visualisation. Screening workflows were defined for affinity capture, non-affinity capture, ion exchange/ mixed mode polishing and hydrophobic interaction polishing steps. Implementation of these high-throughput tools reduced downstream process development timelines and helped in creating Lonza's robust bispecific antibodies and other recombinant non-mAb DNA-to-IND offerings.

711

The Generation of a highly Predictive SMA mechanistic model for a CEX gradient elution of a novel antibody format

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The characterization of chromatography processes is typically based on statistical models. These models are resource intensive and can be time consuming to generate, even when fractional factorial methods are applied. Additionally, the subsequent models may not predict parameter interactions and or be statistically weak. Mechanistic models' main advantage over the statistical approach is that the models themselves can be used to generate statistically valid proven acceptable ranges.

The polishing step of a complex tri-specific complex molecule involves the removal of both High and Low molecular weight species by use of an increasing salt gradient. By using the GoSilico software, a simple SMA model was generated using only 6 lab-based experiments. The model demonstrated R2 values of over 90% for model fit for all the molecule species detected. We then tested the predictive power of the model by using the software to suggest conditions to maximise monomer recovery and minimising both low and high molecular weight species. The results when compared to that predicted were statistically valid.

712

Competing brains – Application of Artificial Neural Networks to support a fast calibration workflow of mechanistic chromatography models

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Complex protein formats and fast-to-market strategies increased the pressure on bioprocess development groups over the last years. Additionally, a high degree of fermentation automation led to a bottleneck in downstream processing. Two technologies were identified to be crucial for modern DSP development: The application of robotics with small scale chromatography columns and the usage of the available data by the application of modeling approaches.

The efficient application of mechanistic modeling in DSP is supported by data sharing initiatives as well as the availability of commercially available modeling software solutions. However, the shortage of modeling talents remains a hurdle. Highly complex purification processes with multiple impurities and other CQAs require experienced modeling experts and even then, the initial calibration of a model remains the main bottleneck in an efficient utilization of DSP models (1). The potential impact of better calibration workflows is significantly high, as models usually are not calibrated once, but instead continuously if new data for instance from new batches or different scales is available.

One solution to improve the mechanistic modeling workflow is the application of Artificial Neural Networks (ANNs). These machine learning models can make the connection between the wet lab chromatography data and the mechanistic model parameters (2). Our group applied a multi-step calibration workflow based on ANNs to predict SMA model parameters at low as well as high protein load densities. Also, protein mixture samples were investigated. The poster will show two case studies as well how the ANN workflow is connected to the the GoSilico™ Chromatography Modeling Software.

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