5th Annual

PEGS EUROPE

Final Agenda

Protein & Antibody Engineering Summit

4–8 November 2013 • Lisbon, Portugal

There is still time to join the largest PEGS Europe ever!

Antibody Engineering

Novel Antibody Constructs & Alternative Scaffolds *4–5 November*

Cancer Biotherapeutics *6–7 November*

Development of Novel Biotherapeutics *7–8 November*

Protein Expression

High-Throughput Protein Expression *4–5 November*

Optimizing Protein Expression *6–7 November*

Difficult to Express Proteins *7–8 November*

Record Participation! – 50% more attendees, presentations and exhibitors

Keynote Speakers:

Luis Borges, Ph.D., Amgen, Inc.

Yves Durocher, Ph.D., National Research Council of Canada

Dominic Esposito, Ph.D., SAIC-Frederick

Robert Lutz, Ph.D., ImmunoGen, Inc.

Andreas Plückthun, Ph.D., University of Zurich

Martine Piccart, M.D., Ph.D., ESMO (European Society for Medical Oncology)

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Agenda Presentations

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

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Sponsor will select invitees from the conference pre-registration list for an evening of networking at the hotel or a top local venue. CHI will extend invitations, conduct follow-up and monitor responses. Reminder cards will be placed in the badges of delegates who will be attending.

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Exhibitors will enjoy facilitated networking opportunities with highly-qualified delegates making it the perfect opportunity to speak face-to-face with prospective clients and showcase your latest product, service, or solution.

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To customize your participation at PEGS Europe, please contact:

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Conference-at-a-Glance *A two-stream, six-conference, five-day event*

	Antibody Engineering Stream	Protein Expression Stream
Monday AM	Pre-Conference Short Courses*	
Monday PM	Novel Antibody Constructs & Alternative Scaffolds	High-Throughput Protein Expression
Tuesday AM	Novel Antibody Constructs & Alternative Scaffolds	High-Throughput Protein Expression
Tuesday PM	Novel Antibody Constructs & Alternative Scaffolds	High-Throughput Protein Expression
	Plenary Session	
Wednesday	Cancer Biotherapeutics	Optimizing Protein Expression
Thursday AM	Cancer Biotherapeutics	Optimizing Protein Expression
	Plenary Session	
Thursday PM	Development of Novel Biotherapeutics	Difficult to Express Proteins
	Dinner Short Course*	
Friday	Development of Novel Biotherapeutics	Difficult to Express Proteins

Conference Short Courses*

Monday, 4 November | 9:00 – 12:30

SC1: From Understanding of Aggregation to Devising of Prevention Strategies

Instructor: Tudor Arvinte, Ph.D., CEO, Therapeomic, Inc.; Professor, University of Geneva

Attend this half-day workshop to gain a critical overview of the available techniques for detection of aggregation and impurities (leachables) and how these methods can be applied. Delegates will learn about strategies for combining analytical methods to ensure detection of aggregates across a range of particle sizes. High-throughput analysis (HTA) and high-throughput formulation (HTF) platforms will be presented. Using case studies, potential causes of aggregation and prevention strategies will be discussed.

- Causes and avoidance of impurities and aggregates
- Impact of impurities and leachables
- New technologies for characterization
- Prevention strategies

Discussion to include experiences of the participants regarding aggregation.

SC2: Measures to Enhance Half-Life and Stability

Instructors: Arne Skerra, Ph.D., Professor, Chair, Biological Chemistry, Technical University Munich; CEO, XL-protein GmbH

Javier Chaparro-Riggers, Ph.D., Associate Research Fellow, Protein Engineering, Rinat-Pfizer, Inc.

This half-day workshop will provide an overview on the current state of the art in protein engineering, targeted at the improvement of half-life of antibodies and other proteins, which are key points to consider in the development of biopharmaceuticals. Current technologies to prolong the circulation of biologics, such as PEGylation, fusion with biological polymers (PASylation etc.), Ig Fc fusion and others will be covered and discussed.

- Renal filtration of biologics and the basics of pharmacokinetics (PK)
- Management of short plasma half-life, a problem of most biopharmaceuticals
- Current and new technologies to prolong the circulation of biologics: PEGylation vs.PASylation
- Short introduction into special aspects of antibody PK
- Increasing T(1/2) by decreasing non-specific elimination
- Increasing T(1/2) by decreasing antigen-specific elimination
- Application to Fc-fusion proteins: FcRn and pH switch

SC3: Alternate Display Technologies

Instructors: John Löfblom, Ph.D., Assistant Professor, Molecular Biotechnology, AlbaNova University Center, Royal Institute of Technology (KTH)

Birgit Dreier, Ph.D., Senior Scientist, Laboratory of Prof. Dr. A. Plückthun, Department of Biochemistry, University of Zurich

John Löfblom, Ph.D., Assistant Professor, Molecular Biotechnology, AlbaNova University Center, Royal Institute of Technology (KTH)

Birgit Dreier, Ph.D., Senior Scientist, Laboratory of Prof. Dr. A. Plückthun, Department of Biochemistry, University of Zurich

Phage and yeast display have become the industry standard for those looking to isolate high affinity protein ligands against nearly any receptor through directed evolution. But what happens when phage and yeast display fall short? This course will cover the development of new display systems to address shortcomings of phage and yeast display, constructing libraries and assessing library quality, and screening and selection methods for generation of new affinity proteins as well as for epitope mapping purposes.

- Development of new display systems to address shortcomings of phage and yeast display
- Constructing libraries and assessing library quality
- Screening and selection methods for generation of new affinity proteins as well as for epitope mapping purposes
- Coverage of bacterial display, *E. coli* display, and ribosome display

SC4: What if I can't patent my molecule or treatment?

Instructors: Alan Feeney, Esq., Principal, Feeney Law Group,

Donald J. Fruge, MPH, Executive Director, Feeney Law Group

Enactment of the America Invents Act and issuance of several key decisions from the U.S. Supreme Court have turned the world of U.S. patenting upside down. What you thought you knew about patenting is no longer true. The course will address the basics of U.S. patent law and how the recent changes impact the patenting process with particular emphasis on the biological arts.

Thursday, 7 November | 17:35 – 20:30

SC5: Dinner Short Course: Troubleshooting and Engineering of Antibody Constructs

Instructors: Jonas V. Schaefer, Ph.D., Head, High-Throughput Laboratory, Biochemistry, University of Zurich

Annemarie Honegger, Ph.D., Senior Scientist, Biochemistry, University of Zurich

Recombinant antibodies vary widely in their biophysical characteristics, from stable monomers to metastable aggregation-prone oligomers. In particular, antibody variable domains differ in their intrinsic thermodynamic stability and often require labor-intensive engineering. It is critical to understand how the poor stability of individual variable domains not only limits the biophysical properties of small fragments, but also affects the production yield, stability and homogeneity of full-length IgGs containing these domains.

Attend this short course to:

- Recognize potentially troublesome antibody variable domain sequences
- Know how to choose the appropriate framework and to improve its stability while humanizing non-human antibodies
- Use structure-based engineering to optimize your antibody's biophysical properties
- Optimize your choices of the best possible format for your antibody
- Improve your expression strategies for different immunoglobulin products

**Separate registration required*

5th Annual NOVEL ANTIBODY CONSTRUCTS AND ALTERNATIVE SCAFFOLDS

Engineering, New Targets and Lead Selection

MONDAY, 4 NOVEMBER

12:00 Registration

FOCUS ON TARGETS AND LEAD SELECTION

14:00 Chairperson's Opening Remarks

Arne Skerra, Ph.D., Professor, Technische Universität Munich; Co-Founder, Pieris AG, Germany

14:05 Doing It the Other Way Round: Using High-Throughput Human Monoclonal Antibody Generation to Identify New Drug Targets

Stefan Dübel, Ph.D., Director, Biotechnology and Bioinformatics, Institute of Biochemistry, Technische Universität Braunschweig

Current high content screening methods failed to deliver the expected abundance of new drug targets. Our capability to rapidly generate panels consisting of hundreds to thousands of different monoclonal human antibodies for research allows one to overcome these limitations, by comparing not only expression but also the role of individual posttranslational modifications and, most important, the spatial "togetherness" of >100 different proteins per individual healthy vs. disease sample with 40nm resolution.

14:35 Deep Sequencing of Phage Display Panning Output Pools to Guide Antibody Lead Selection

Stefan Ewert, Ph.D., Senior Investigator, NIBR Biologics Center, Novartis Pharma AG

The presentation will show examples how Deep Sequencing of Phage Display panning output pools could guide antibody lead selection with focus on achieving diversity regarding e.g. antigen cross-reactivity profile and biophysical properties.

15:05 Controlling Cellular Signaling with Ultraspecific Binding Proteins

Shohei Koide, Ph.D., Professor, Biochemistry and Molecular Biology, University of Chicago

Using two alternative scaffold platforms, FN3 monobody and affinity clamp, we have developed a series of binding proteins to targets involved in cell signaling. Intracellular expression followed by mass spectroscopy-based proteomics establishes that these binding proteins are exquisitely specific to a single target in the cell. We use these binding proteins to precisely dissect and control cellular signaling, including cancer progression and stem cell development, and determine drugability of targets.

Sponsored by RETROGENIX®

15:35 Discovering Novel Antibody Targets, Antibody Off-Targets, and Uncovering Receptors for Protein Ligands Using Retrogenix's Powerful Deconvolution Technology

Jim Freeth, Ph.D., Managing Director, Retrogenix, UK

Selecting antibodies by phenotype, rather than against a pre-determined target, leads to novel, disease-relevant antibody targets. Retrogenix's Cell Microarray technology overcomes the target deconvolution hurdle, with high success rates. The technology also provides a powerful approach to identify potential off-target activities to guide lead selection, and to identify previously unknown receptors of protein ligands.

Sponsored by CHEMICAL COMPUTING GROUP

15:50 A Unified Framework for Computer-Aided Biologics Design

Andrew Henry, Chemical Computing Group

Protein engineering plays a pivotal role in modulating the function, activity and physical properties of biologics. Representative strategies employed in protein engineering include rationale protein design and directed evolution. In general, disparate work has been done in applying computer-aided biologics design (CABD) to protein engineering for the development of novel biological therapeutics. Here, we establish a unified framework of protein engineering tools and investigate its applicability to modulation of protein properties: affinity and stability.

16:05 Refreshment Break

NOVEL PRODUCTS AND CREATIVE ENGINEERING

16:35 Isolation and Optimization of Novel Anti-GPCR Antibodies

Julie Douthwaite, Ph.D. Senior Scientist, Antibody Discovery and Protein Engineering, MedImmune LLC

G protein coupled receptors (GPCR's) represent a challenging target class for the isolation and optimization of therapeutic biologics. In this work we have used a combination of immunization and phage display to isolate antibodies capable of potently blocking the activity of the formyl peptide receptor (FPR). Using combinatorial mutagenesis approaches, significant improvements to both affinity and species cross-reactivity of the lead molecules are demonstrated, resulting in antibodies that show significant potency in cellular disease assays.

17:05 Hexavalent TRAIL-Receptor-Agonists with Enhanced Therapeutic Properties: Underlying Engineering Concept and *in vivo* Activity Profile

Oliver Hill, Ph.D., Vice President, Molecular Biology, Apogenix GmbH

Apogenix has engineered a TRAIL mimetic with three Apo2L/TRAIL protomer subsequences fused into one polypeptide chain. This trivalent single-chain-TRAIL-receptor-binding-domain (scTRAIL-RBD) was fused to the Fc-part of human IgG1 to create a hexavalent scTRAIL-RBD-FC fusion protein. *In vitro,* the hexavalent agonist induces superior clustering of TRAIL-Rs and subsequent apoptotic cell death of sensitive tumor cell lines. In contrast to bivalent agonistic TRAIL-R2 antibodies, its potent anti-tumor efficacy *in vivo* is independent of Fc-receptor based multimerisation events.

17:35 Improving PK and Cholesterol Lowering by a pH-Sensitive Anti-PCSK9-Antibody

Javier Chaparro-Riggers, Associate Research Fellow, Protein Engineering, Rinat-Pfizer, Inc.

Target-mediated clearance and high antigen load can hamper the efficacy and dosage of many antibodies. pH-sensitive binding of the antibody to its antigen can improve the PK and PD in such cases. We improve the PK and extend cholesterol lowering in rodents and non-human primates by engineering a pH-sensitive anti-PCSK9 antibody variant and we can show that this effect is FcRn dependent.

18:05 Welcome Reception in the Exhibit Hall with Poster Viewing

19:05 End of Day One

TUESDAY, 5 NOVEMBER

07:30 Registration

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

ENGINEERING OF BI- AND MULTI-SPECIFIC PRODUCTS

08:30 Chairperson's Remarks

Stefan Dübel, Ph.D., Director, Biotechnology and Bioinformatics, Institute of Biochemistry, Technische Universität Braunschweig

08:35 Anticalins: A Versatile Non-Ig Scaffold for the Design of Bifunctional Biotherapeutics

Arne Skerra, Ph.D., Professor, Technische Universität Munich; Co-Founder, Pieris AG, Germany

Anticalins are based on the small lipocalin scaffold (160-180 aa) that displays four hypervariable loops on a robust beta-barrel. These single-chain proteins, which can be generated against a wide variety of medically relevant targets, from small haptens to large antigens, are ideally suited for functionalization: either in a fusion protein approach (e.g. as Duocalins) or via chemical conjugation. We will present data for an anti-VEGF Anticalin tested in a Phase 1 clinical trial, for an anti-hepcidin Anticalin currently under development for the treatment of anemia, and novel strategies to couple radiometal chelators, drugs or toxins to tumor-specific Anticalins for cancer treatment or *in vivo* imaging.

09:05 Efficient Generation of Stable Bispecific IgG1 by Controlled Fab-Arm Exchange

Janine Schuurman, Ph.D., Director, Strategic Research, Genmab B.V.

We will present a technology for the efficient generation of IgG1 bispecific antibodies. The platform generates antibodies with normal IgG structures, regular Fc-mediated effector functions and *in vivo* stability typical of IgG1 antibodies. The platform is amenable to both antibody drug discovery and development. Technical background and proof-of-concept studies will be presented.

09:35 Engineering Bispecificity into a Single Albumin-Binding Domain Aimed for Drug Targeting and *in vivo* Half-Life Extension

Johan Nilvebrant, Ph.D., Post-Doctoral Researcher, Protein Technology, Royal Institute of Technology, Alba Nova University Center, Stockholm

We have engineered a 46 amino acid albumin-binding domain as a scaffold for bispecific affinity proteins. By diversification of the non-albumin binding side of this small domain, followed by display of the resulting libraries on phage or on cells, bispecific single-domain proteins with high affinities for several targets have been isolated. These molecules approach the size limit of bispecific, folded proteins and have many interesting properties for biotherapeutical applications.

10:05 Novel Discovery Platform for Bispecifics

Sponsored by AB CHECK

Vera Molkenthin, Ph.D., Chief Scientist, AbCheck s.r.o

Wouldn't it be nice to skip reformatting steps between antibody discovery and lead development and to address key features like folding yield and stability already during antibody discovery? The potential of a novel recombinant antibody discovery platform allowing display and selection of complex molecules in combination with a smart bioinformatics approach for library design will be demonstrated. Besides being compatible with full-length IgG the platform holds special and unique advantages to address bispecific formats.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

11:15 Engineering Stable Bispecific Antibodies in the Final Therapeutic Format

Robert Mabry, Ph.D., Associate Director, Antibody Discovery and Bispecific Engineering, Adimab LLC

Bispecifics assembled from individual components frequently do not retain affinity and structural stability of parental antibodies. We have presented large libraries of full-length bispecific antibody formats on the surface of yeast to select for significant affinity and biophysical improvements over antibody assembly. These molecules express well in mammalian hosts, and detailed biophysical characterization demonstrates a consistent pattern of generating stable bispecifics.

11:45 F-star: Advancing Novel Bispecific Antibody Biologics in Oncology

Haijun Sun, Ph.D., VP, Biological Products, f-Star

F-star's Modular Antibody Technology uses straight forward "mix-and-matching" of antibody components to create unique mAb2 bispecific antibodies and allows rapid exploration of their novel biology. An Fcab against a single target, with a site introduced in the constant region, can either be developed as a therapeutic agent or be combined with the variable regions of different existing antibodies to create a panel of bispecific antibodies. F-star's mAb2 bispecific antibodies retain all conventional antibody properties such as Fc-mediated effector function, manufacturability, stability, and PK and can be progressed from Fcab to *in vivo* pharmacology testing in very short periods of time. F-star is now developing a preclinical oncology product pipeline based on this next generation biologics technology platform.

12:15 Bispecific Antibody Derivatives that Bind Cell Surface Targets and Capture Payloads

Ulrich Brinkmann, Ph.D., Senior Principal Scientist, Pharma Research and Early Development (pRED), Large Molecule Research, Roche Penzberg

Antibody Derivatives that bind cell surface targets and capture payloads via hapten binding moieties can be generated in various formats. Various payloads such as fluorophores, small compounds, proteins, peptides, nucleic acids or nanoparticles can be complexed with such delivery vehicles. These antibody complexes deliver payloads specifically to target cells that are recognized by the targeting moieties of the delivery vehicles.

12:45 Strategies for the Directed Engineering of Antibodies

Sponsored by morphosys

Jan Van Den Brulle, Ph.D., Director, Discovery Alliances Technologies, MorphoSys AG

The properties required for antibody candidates on their way to an approved therapeutic agent are getting more and more ambitious. We therefore have established a technology platform (arYla) to engineer antibody candidates with respect to defined properties like affinity, immunogenicity and biophysical behavior. Successfully conducted case studies will be presented.

ENGINEERING OF BI- AND MULTI-SPECIFIC PRODUCTS (Continued)

14:00 Chairperson's Remarks

Janine Schuurman, Ph.D., Director, Strategic Research, Genmab B.V.

14:05 Human Bispecific Antibodies with a Common Light Chain: Combining Superior Functionality and Developmental Reliability in the Well-Established Full Length IgG Format

Ton Logtenberg, Ph.D., CEO, Merus B.V.

A common light chain (cLC) transgenic mouse for human mAbs and CH3-engineering have been used for the efficient discovery of full length IgG human bispecific antibodies. Screening of thousands of bispecific antibodies against combinations of RTKs in cell-based assays uncovered bispecific antibodies with superior activity vis-a-vis 'best in class' comparators. cLC bispecific antibodies, like conventional therapeutic IgG antibodies, have attractive features: they recruit immune effector functions, have excellent stability and give high yields during manufacturing.

14:35 Novel Hybridoma-free Technology for the Development of Recombinant Monoclonal Antibodies

Sponsored by ICOSAGEN CELL FACTORY

Mart Ustav, Ph.D., CEO, Icosagen Cell Factory

Continuously growing need for therapeutic monoclonal antibodies forces the search of novel and efficient methods to accelerate the development process. Classical hybridoma-derived method is time consuming, laborious and not efficient way to generate monoclonal antibodies. Icosagen has developed novel hybridoma-free method for the generation of recombinant antibodies from different hosts: chickens, mice or rabbit using direct isolation of antibody variable region encoding cDNAs from a spleen or bone marrow of the immunized animal and generation of scFv antibodies. From scFv, generation of expression vectors for different subtypes and origin of antibodies in high throughput format is validated. For the production of reconstructed antibodies, mammalian stable episomal expression technology (QMCF Technology) is used.

15:05 Problem Solving Roundtable Discussions

Table 1: How to Get What You Want from Antibody Phage Display

Moderators: Stefan Dübel, Ph.D., Director, Biotechnology and Bioinformatics, Institute of Biochemistry, Technische Universität Braunschweig

Stefan Ewert, Ph.D., Senior Investigator, NIBR Biologics Center, Novartis Pharma AG

Table 2: Measures to Increase Half-Life and Stability of the Product

Moderator: Arne Skerra, Ph.D., Professor, Technische Universität Munich; Co-Founder, Pieris AG, Germany

Table 3: Engineering of Bispecific Antibodies

Moderator: Robert Mabry, Ph.D., Associate Director, Antibody Discovery and Bispecific Engineering, Adimab LLC

Table 4: Immuno-Oncology: The Next Big Thing?

Moderator: John Haurum, CEO, F-star

16:05 Refreshment Break in the Exhibit Hall with Poster Viewing

» PLENARY SESSION

16:55 Designing Receptor Binding Proteins with Highly Potent Biological Function

Andreas Plückthun, Ph.D., Director and Professor, Biochemistry, University of Zurich

Non-IgG molecules, unless armed with toxins or other effector units, are usually thought to be limited in the biological responses they can elicit. However, Designed Ankyrin Repeat Proteins (DARPins) are particularly versatile, because of their favorable biophysical properties, and they can be engineered into many formats. Using DARPins generated against members of the EGFR family, and a combination of x-ray crystallography, signaling studies, and *in vivo* experiments, it will be demonstrated how molecules could be engineered to selectively induce apoptosis in tumors, and their mechanism of action has been deduced. New intracellular sensors will be described for such studies.

17:45 Immunotherapy with BiTE® Antibodies

Luis Borges, Ph.D., Scientific Director, Therapeutic Innovation Unit, Amgen, Inc.

BiTE® antibodies are potent bispecific single-chain antibodies that redirect T cells to kill tumors. They engage a tumor target and a constant region of the T cell receptor to recruit and activate polyclonal T cells to eliminate tumors. They have demonstrated potent efficacy in various preclinical tumor models and have now transitioned to clinical studies. Blinatumomab, a CD19xCD3 BiTE® antibody, is in clinical development and has shown high single-agent response rates in patients with refractory or relapsed B-ALL and B-NHL.

18:30 End of Novel Antibody Constructs and Alternative Scaffolds

CANCER BIOTHERAPEUTICS

Inaugural ADCs, Multi-Specifics, Combined Therapies and Immunotherapy

TUESDAY, 5 NOVEMBER

» PRE-CONFERENCE PLENARY SESSION

16:55 Designing Receptor Binding Proteins with Highly Potent Biological Function

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18:30 End of Day

WEDNESDAY, 6 NOVEMBER

07:45 Registration and Morning Coffee

08:30 Chairperson's Opening Remarks

Jason Baum, Ph.D., Principal Scientist, Research, Merrimack Pharmaceuticals, Inc.

MULTI-SPECIFIC ANTIBODY PRODUCTS

08:35 Two-in-One Antibody Targeting EGFR and HER3 and Platform Update

Germaine Fuh, Ph.D., Senior Scientist, Antibody Engineering, Genentech, Inc.

Mutation at the antigen binding sites of a mono-specific antibody may recruit a second binding specificity such that each Fab arm exhibits dual binding function and IgG with this dual action Fab (DAF) can be produced as conventional IgG. Proof-of-concept is a HER2/VEGF Two-in-One antibody; EGFR/HER3 Two-in-One DAF antibody is in clinical phase II trial for treating epithelial cancer. The talk will cover the generation and development of the EGFR/HER3 DAF antibody including preclinical and clinical phase I data.

09:05 MM-141, a Bispecific Antibody Co-Targeting IGF-1R and Erbb3, Overcomes Network Adaptation by Blocking Redundant Survival Pathways

Jason Baum, Ph.D., Principal Scientist, Research, Merrimack Pharmaceuticals, Inc.

An integrated Network Biology approach was used to design and optimize MM-141 to overcome limitations of first generation IGF-1R therapies by also blocking heregulin-mediated compensation through ErbB3. MM-141 potentiates the activity of both targeted therapies and chemotherapies through the combined inhibition of PI3K/Akt/mTOR signaling as well as control over feedback loops triggered by these agents.

09:35 Bispecific κλ-bodies for Selective Inhibition of CD47 in Cancer Cells

Nicolas Fischer, Ph.D., Head, Research, Novimmune SA

We have used our κλ-body platform to generate CD47-neutralizing bispecific antibodies. These fully human antibodies are composed of a CD47-specific arm and a targeting arm, specific to a tumor associated antigen (TAA). The preferential neutralization of CD47 on TAA-expressing cancer cells should therefore show better pharmacological properties and a broader therapeutic window as compared to non-targeted anti-CD47 monoclonal antibodies. The presentation will also highlight how light chain diversity can be exploited to create bispecific antibodies with favorable manufacturability and stability profiles that facilitate their development path.

10:05 ADAPTIR™ Molecules: Unique Biology From A Flexible Bispecific Platform

Sponsored by emergent biosolutions

John W. Blankenship, Ph.D., Principal Scientist, Applied Research, Emergent Biosolutions

ES414 is the lead candidate from Emergent's ADAPTIR™ (modular protein technology) platform of bispecific protein therapeutics that are modular in design and have unique and distinguishing properties. In preclinical studies, ES414 redirects T cells to kill PSMA-expressing tumors, has prolonged serum half-life, and induces minimal cytokine release compared to other formats. ES414 is progressing toward clinical development.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

11:05 Targeting Tumor Microenvironmental Signals with Bispecific Antibodies

Alessandro Angelini, Ph.D., David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology (MIT)

We have developed bispecific antibodies that locally contravene soluble signaling factors that establish the supporting tumor microenvironment that enables tumor survival and growth. Soluble factors such as VEGF, TGF-β, and IL-8 play a demonstrated role in tumorigenesis, and enhanced interdiction of these signals within the tumor should enhance the therapeutic index of cancer therapy.

11:35 Novel Multi-Targeting Antibody Mixtures: Mode of Action and Advantages Over Other Approaches

Michael Kragh, Ph.D., Director, Antibody Pharmacology, Symphogen A/S

This talk will present the selection of antibodies against tumor-related antigens to obtain synergistic combinations, the benefits of simultaneous targeting of multiple receptors, and examine pan-HER (EGFR, HER2 and HER3) targeting to address tumor heterogeneity and plasticity.

12:05 High-Throughput Design, Production, and Evaluation of Multi-Specific Antibodies

Maria Wendt, Ph.D., Scientific Consultant, Biologics, Genedata

With the advent of multi-specific antibodies, today's biotechs must evaluate increasing numbers of next-generation antibody molecule formats (e.g. bi- and n-specifics, tandem-scFv-Fc, DVD-Ig, Diabodies) and parametric variants (e.g. linkers, V-domain order, Fc). A significant bottleneck are high-throughput molecular biology and cloning processes required for systematically generating DNA constructs to express the desired molecules. Here, we present a new workflow system for HT molecule design, DNA synthesis, and verification. Integrated into a comprehensive data management system for samples, assays, and analytics results, our platform enables the systematic evaluation of large panels of multi-specific antibodies.

12:35 Luncheon Presentations *(Sponsorship Opportunities Available)* **or Lunch on Your Own**

ADVANCES WITH CANCER IMMUNOTHERAPY

14:00 Chairperson's Remarks

Andrea van Elsas, CSO, BioNovion B.V.

14:05 Cancer Immunotherapy Using Immune Modulating Antibodies

Andrea van Elsas, CSO, BioNovion B.V.

Immune rejection of human cancer has been an elusive goal until recently. T cell modulating antibodies targeting CTLA-4 and the PD-1 pathway induced clinically meaningful responses and long-term benefit in patients with metastatic cancer.

Successful immune rejection can come with significant immune related adverse events. Immune oncology agents do not directly tumor cells but treat the patient's immune cells. In this presentation, the discovery of immune modulating antibodies and their translation into clinical success will be discussed.

14:35 Immunocytokines: A Novel Potent Class of Armed Antibody

Laura Gualandi, Ph.D., Philochem A.G.

Antibodies are effective tools that can deliver molecules with potent therapeutic activity, such as Cytokines, to the tumor site, minimizing toxic effects. Aspects like molecular format, valence and the chosen target antigen contribute to the efficacy of the immunocytokines *in vivo*. Combinatory therapeutic strategies with other agents have also been recently investigated. This talk will cover advanced preclinical and clinical data on armed antibodies discovered and developed by the Philogen group.

15:05 NKTT320: A Humanized Monoclonal Antibody for Cancer Immunotherapy

Robert Mashal, CEO, NKT Therapeutics

Activation of iNKT cells has been shown to have therapeutic effects both in preclinical models and in patients with cancer, and represents an important pathway for the immunotherapy of cancer. iNKT cells have an invariant T cell receptor (iTCR). NKT Therapeutics is developing NKTT320, a humanized monoclonal antibody which specifically recognizes the iTCR present exclusively on iNKT cells, and has been shown to activate iNKT cells both *in vitro* and *in vivo*.

15:35 Refreshment Break in the Exhibit Hall with Poster Viewing

16:15 Novel Tumor-Targeted, Engineered IL-2 Variant (IL-2v)-Based Immunocytokines for Immunotherapy of Cancer

Ekkehard Moessner, Ph.D., Group Leader, Protein Engineering, pRED, Roche Glycart A.G.

A novel class of immunocytokines will be discussed that are based on Fc containing and also on non-Fc containing building blocks. The IL2 component is optimized for improved performance in tumor targeting. Enhancement of *in vivo* efficacy, when combined with ADCC competent antibodies, will be discussed.

ANTIBODY-DRUG CONJUGATES AND PAYLOADS

16:45 Next-Generation ADCs: Enabling Higher Drug Loading, Alternative Payloads, and Alternative Targeting Moieties

Timothy B. Lowinger, Ph.D., CSO, Mersana Therapeutics, Inc.

The application of polymers to antibody-drug conjugate (ADC) design can provide numerous advantages, including significantly higher capacity for drug payload; utilization of alternative payloads not suitable for direct conjugation; improvement of physicochemical properties; and utilization of protein recognition scaffolds beyond the commonly used IgGs. Examples of these benefits achieved using Mersana's polyacetal-based conjugation system to create next-generation ADCs will be presented.

17:15 Problem Solving Roundtable Discussions

Table 1: Engineering of Bispecific Antibodies

Moderator: Nicolas Fischer, Ph.D., Head, Research, Novimmune SA

Table 2: Antibody-Drug Conjugates: Linkers and Payloads

Moderators: Robert Lutz, Ph.D., Vice President, Translational Research & Development, ImmunoGen, Inc.

Timothy B. Lowinger, Ph.D., CSO, Mersana Therapeutics, Inc.

Table 3: Site-Specific Conjugation of ADCs

Moderator: Pavel Strop, Ph.D., Associate Research Fellow, Protein Engineering, Rinat-Pfizer, Inc.

Table 4: Cancer Immunotherapy: Reaping the Benefits

Moderators: Andrea van Elsas, CSO, BioNovion B.V

Luis Borges, Ph.D., Scientific Director, Amgen, Inc.

Table 5: Cancer Biotherapeutics in the Clinic

Moderators: Jason Baum, Ph.D., Principal Scientist, Research, Merrimack Pharmaceuticals, Inc.

Martine Piccart, M.D., Ph.D., Head, Medical Oncology, Jules Bordet Institute; Chair, ESMO (European Society for Medical Oncology)

18:15 Networking Reception in the Exhibit Hall with Poster Viewing

19:15 End of Day One

THURSDAY, 7 NOVEMBER

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

08:30 Chairperson's Remarks

Robert Lutz, Ph.D., Vice President, Translational Research & Development, ImmunoGen, Inc.

08:35 A Universal Chemically Driven Approach for Constructing Homogeneous ADCs

David Jackson, Ph.D., Principle Scientist, ADC Discovery, Igenica, Inc.

Current ADCs in clinical development are heterogeneous mixtures that differ in both DAR (drugs/antibody) and their conjugation sites. Igenica has invented novel site-specific linkers to enable the synthesis of homogeneous ADCs. The linkers are compatible with a variety of drug payloads and can be applied to any antibody. Homogeneous ADCs were synthesized using the novel linkers and compared to heterogeneous ADCs made with conventional linkers. Analytical data and activity of the ADCs in tumor models will be presented.

09:05 Location Matters: Site of Conjugation Modulates Stability and Pharmacokinetics of Antibody-Drug Conjugates

Pavel Strop, Ph.D., Associate Research Fellow, Protein Engineering, Rinat- Pfizer, Inc.

To understand the role of conjugation site, we developed an enzymatic method for site-specific antibody-drug conjugation. This allowed us to attach diverse compounds at multiple positions and investigate how the site influences stability, toxicity, and efficacy. We show that the conjugation site has significant impact on ADC stability and pharmacokinetics in a species-dependent manner. With this method, it is possible to produce homogeneous ADCs and tune their properties to maximize the therapeutic window.

09:35 Development of Second Generation Duocarmycin ADCs with Superior Therapeutic Window

Marion Blomenröhr, Ph.D., Program Manager Biopharmaceuticals, Synthon Biopharmaceuticals

The first generation ADCs have successfully exploited the mAb-driven tumor cell targeting for optimization of efficacy, but have failed to reduce off-target toxicities. This presentation will highlight Synthon's second generation Linker-Drug technology and its complementarity with novel proprietary duocarmycin payloads yielding highly stable and potent ADCs, with an improved *in vivo* therapeutic window.

Sponsored by PolyTherics enabling better biopharmaceuticals

10:05 Producing Better Antibody-Drug Conjugates (ADCs) Using ThioBridge™ Conjugation

Antony Godwin, Ph.D., Director, Science & Technology, PolyTherics Ltd

Next-generation antibody-drug conjugates will be required to be less heterogeneous and have better stability. PolyTherics has developed ThioBridge™ for improved conjugation of a cytotoxic payload at the disulfides bonds of antibodies, antibody fragments and other targeting proteins. With ThioBridge™, the resulting ADC has the benefit of reduced heterogeneity, as the drug to antibody ratio is limited to a maximum of 4 with little DAR 0 species. Stability is also enhanced, as unlike single thiol conjugation approaches at disulfides, ThioBridge™ is not prone to drug deconjugation reactions in serum. *In vitro* and *in vivo* data for mAb and Fab conjugates with an established payload confirms specific binding and activity.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

12:35 End of Cancer Biotherapeutics

5th Annual

DEVELOPMENT OF NOVEL BIOTHERAPEUTICS

Developability, Enhanced Product Properties and Therapeutic Application

THURSDAY, 7 NOVEMBER

10:00 Registration

» PLENARY SESSION

11:05 Medical Treatment of HER2 Positive Breast Cancer: Two Decades of a Fascinating History and More to Come

Martine Piccart, M.D., Ph.D., Head, Medical Oncology, Jules Bordet Institute; Chair, ESMO (European Society for Medical Oncology)

The talk will cover multiple aspects of anti-HER2 treatment in breast cancer. It will present a summary of the clinical results obtained with trastuzumab and several other anti-HER2 drugs in breast cancer (lapatinib, TDM1, pertuzumab). Issues like the treatment duration, biomarkers of resistance to treatment will be debated. Finally it will discuss future promising research strategies: neoadjuvant trials, comparison between anti-HER2 agents, combinations of these drugs and functional imaging.

11:50 Antibody-Drug Conjugates: From Bench to Bedside and Back

Robert Lutz, Ph.D., Vice President, Translational Research & Development, ImmunoGen, Inc.

Antibody-drug conjugates are emerging as an exciting approach to the development of antibody-based therapeutics. The growing preclinical and clinical experience with maytansinoid conjugates such as Kadcyla (T-DM1) is leading to an enhanced understanding regarding critical attributes for target antigens, antibodies, payloads and linkers. The translational knowledge is being incorporated into research and development efforts for the next generation of ADC candidates.

12:35 Enjoy Lunch on Your Own

13:30 Chairperson's Opening Remarks

Syd Johnson, Ph.D., Vice President, Antibody Engineering, MacroGenics, Inc.

MEASURES TO AVOID DEGRADATION AND AGGREGATION

13:35 *In silico* Prediction of Degradation Hotspots in Antibody Variable Regions

Hubert Kettenberger, Ph.D., Principal Scientist, Large Molecule Research, Roche Pharma Research and Early Development (pRED)

Besides function, chemical stability is an important selection criterion in the discovery of therapeutic proteins. Importantly, degradation "hotspots", i.e., amino acids which degrade quickly during manufacturing, storage or *in vivo*, should be avoided whenever possible. By combining mass spectrometry, structural biology and machine learning, we developed a reliable, high-throughput *in silico* approach to predict Aspartate and Asparagine degradation hotspots in the variable regions of monoclonal antibodies.

14:05 Unique *in silico* Tools for Prediction of Propensity to Aggregate and for Viscosity for Monoclonal Antibodies and Therapeutic Proteins

Bernhard Helk, Ph.D., Head, New Technologies, Biologics, Novartis Pharma AG

Four *in silico* tools and their practical application to the prediction and characterization of protein-protein interaction are demonstrated: SAP (Spatial Aggregation Propensity) identifies hydrophobic patches and is applied to engineer mAbs and ADCs with increased stability. DI (Developability Index) predicts aggregation propensities based on SAP and net charge. SCM (Spatial Charge Map) ranks mAbs according to viscosity. SIM (Spatial Interaction Map) predicts hot spot residues for specific protein-protein interaction sites.

14:35 Engineering Aggregation Resistance in IgGs based on Lessons Learned from Comparative Expression

Jonas V. Schaefer, Ph.D., High-Throughput Laboratory, Biochemistry, University of Zurich

Aggregation is an important concern for therapeutic antibodies as it increases the risk of immunogenicity. Our comprehensive studies have systematically investigated the impact of certain sequences on these properties of IgGs using various biophysical methods and showed that their aggregation susceptibilities can be readily engineered. Our data offer an improved insight into the molecular processes causing aggregation and an understanding of the influence of certain intramolecular interactions on this process.

15:05 Refreshment Break in the Exhibit Hall with Poster Viewing

ENHANCEMENT OF PRODUCT PROPERTIES BEFORE ENTERING THE CLINIC

15:50 Rapid Design of Optimized Site-Specific ADCs and Manufacture by Cell-Free Protein Synthesis

Trevor J. Hallam, Ph.D., CSO, Research & Development, Sutro Biopharma, Inc.

Sutro has developed a scalable cell–free protein synthesis platform for production of full IgGs, bispecific antibodies and ADCs in hours from DNA. Expression of many non-natural amino acid positional variants enables data-driven selection of site-specific candidate ADCs that are optimal for antigen binding, suppression efficiency, folding, thermal stability, conjugation efficiency, internalization and cell killing. The same synthetic platform can be used for production of chosen variants for larger scale or cGMP manufacture within days.

16:20 CTLA4 – Fc Fusion: Engineering for Increased Affinity to CD80 and CD86 for the Treatment of Inflammatory Diseases

Katherine Vousden, Ph.D., Senior Scientist, Antibody Discovery & Protein Engineering, MedImmune LLC

CTLA4 is a selective co-stimulatory modulator capable of inhibiting the stimulation of T-cells via engagement with its binding partners CD80 and CD86. A recombinant construct of the CTLA4 extracellular domains fused to immunoglobulin IgG Fc is approved for the treatment of inflammatory diseases. In this work we have used combinatorial evolution and ribosome display to greatly enhance the affinity of CTLA4 for its binding partners. The resultant constructs exhibit greatly enhanced potency in cellular assays. They therefore represent a potential next-generation of molecules for the treatment of inflammatory diseases.

16:50 Understanding the Efficacy & Safety Issues in Developing Dual- and Multi-Specific Biologics

Tariq Ghayur, Ph.D., Senior Research Fellow, DVD – Ig & Novel Biologics, Abbvie, Inc.

17:20 End of Day One

17:20 Short Course Registration*

17:35 – 20:30 Dinner Short Course: Troubleshooting and Engineering of Antibody Constructs

** Separate registration required, see page 2 for details*

FRIDAY, 8 NOVEMBER

PRECLINICAL DEVELOPMENT

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

08:30 Chairperson's Remarks

Katherine Vousden, Ph.D., Senior Scientist, Antibody Discovery & Protein Engineering, MedImmune LLC

08:35 Development of Leptin and Interleukin 22 Antagonists and Potential Use in Therapy of Cachexia and Autoimmune Diseases: A Novel Approach for Development of High-Affinity Cytokine Antagonists

Arieh Gertler, Ph.D., Professor, Institute of Biochemistry, Food Science and Nutrition, Hebrew University in Jerusalem

We developed high affinity antagonists of leptin and IL-22 which compete with the respective agonists for binding to receptor. Our approach has several advantages over an antibody approach, as it manipulates the endogenous agonist, ensuring proper binding to the receptor to induce full antagonism. Another major disadvantage of monoclonal neutralizing Ab is that their use is commonly associated with development of B and T cell allo-response, producing side effects and limiting the efficacy of treatment with time.

09:05 RG7116, a Novel Therapeutic Antibody that Locks HER3 in the Closed Conformation, Potently Blocks HER3 Signaling, and is Optimized for Immune Effector Activation

Birgit Bossenmaier, Ph.D., Principle Scientist, Discovery Oncology, Roche

HER3 has emerged as an attractive therapeutic target in oncology due to its central position in the HER signaling network. RG7116 is a novel anti-HER3 monoclonal antibody designed to block HER3 activation, down-regulate HER3, and enhance ADCC. These different modes of action are demonstrated by biochemical studies, X-ray crystallography, detailed analyses of the effects on HER3 signaling and ADCC assays. They translate into convincing preclinical efficacy data in different xenografts, as well as first signs of efficacy in the clinic.

09:35 Problem Solving Roundtable Discussions

Table 1: Engineering to Maintain Affinity and Specificity

Moderator: Katherine Vousden, Ph.D., Senior Scientist, Antibody Discovery & Protein Engineering, MedImmune LLC

Table 2: Specific Issues to Address when Moving from Preclinical to Clinical

Moderator:Tariq Ghayur, Ph.D., Senior Research Fellow, DVD – Ig & Novel Biologics, Abbvie, Inc.

Guenter Blaich, Ph.D., E.R.T., Scientific Director, Global Preclinical Safety, Development Sciences, Abbvie, Inc.

Table 3: Developability Concerns

Moderator: Syd Johnson, Ph.D., Vice President, Antibody Engineering, MacroGenics, Inc.

Table 4: Engineering of Bispecific Antibodies

David Urech, Ph.D., Chief Scientific Officer and co-CEO, Numab AG

10:35 Coffee Break

11:00 Targeted Fas-Mediated Treatment of B-Cell Lymphoma by Hexameric CTLA4-FasL

Noam Shani, M.D., KAHR Medical, Hadassah Medical Center, Jerusalem

CTLA4-FasL (KAHR-102) is a bispecific fusion protein that combines the extra-cellular domains of CTLA4 and FasL. In this lecture we will present data showing that CTLA4-FasL naturally forms a stable homo-hexamer which combines high affinity B7-targeting with highly efficient Fas-mediated apoptosis. We will also demonstrate the mode-of-action and preclinical efficacy of this molecule in two B-cell lymphoma animal disease models, and describe our near future clinical trial plans.

11:30 Optimization of Bispecific DART Proteins for Clinical Use

Syd Johnson, Ph.D., Vice President, Antibody Engineering, MacroGenics, Inc.

Manufacturability, stability and pharmacokinetics have been challenges to effective development of bispecific antibodies for clinical use. We have developed and optimized several formats of our highly stable Dual-Affinity ReTargeting (DART®) proteins that address these issues. Multiple examples will be presented of DART proteins approaching the clinic for oncology, autoimmunity or infectious disease applications. Challenges of nonclinical toxicology for these highly potent molecules in relevant species will also be discussed.

12:00 Pro-Apoptotic and Anti-Angiogenic Tumor Therapy Approaches with Novel DARPin Formats

Ignacio Dolado, Ph.D., Program Leader, Research Oncology, Molecular Partners A.G.

The DARPin platform enables novel therapeutic concepts in which efficacy, PK, and mechanism of action are tailored to address unmet medical needs, resulting in the generation of best- and first-in-class products. We will highlight various preclinical programs exploiting the unique properties of DARPins to generate novel multi-specific approaches against key drivers of tumor angiogenesis (e.g. VEGF) and survival (e.g. Her2, Her3).

12:30 TRIBODIES: Building Trispecificity by Fab-scFv Fusions

Nico Mertens, Ph.D., Director, Antibody Research, Development, Biotecnol, Inc.

Tribodies are antibody fragment based scaffolds by fusions to Fab-chains. The molecular structure allows easy engineering of bispecific, bivalent bispecific, but also trispecific or multivalent reagents. Tribodies behave superior as compared to smaller fragment constructs, due to better PK properties of these intermediate sized molecules and multivalent/multispecific targeting. Tribodies are eligible to be developed as a new generation of biopharmaceuticals, as they can target multiple antigens with a single molecule.

13:00 Luncheon Presentations *(Sponsorship Opportunities Available)* **or Lunch on Your Own**

13:30 Session Break

NOVEL PRODUCTS IN THE CLINIC

14:00 Chairperson's Remarks

Ignacio Dolado, Ph.D., Program Leader, Research Oncology, Molecular Partners A.G.

14:05 Towards Predictability in Discovery and Engineering of Bi-Specific Therapeutics

David Urech, Ph.D., Chief Scientific Officer and Co-CEO, Numab AG

14:35 Exploring Antibody Domains as Effective Candidate Therapeutics

Steven Grant, Ph.D., Manager, Biopharm Discovery, Biopharm Research & Development, GSK (Domantis)

This talk will provide an update on the preclinical and clinical data of domain antibody-based drugs that are currently in development. It will cover library design and lead discovery process, the advantages over conventional monoclonal antibody-based therapies focusing on topically delivered dAbs and the AlbudAb™ platform.

15:05 Plant-Derived Pharmaceuticals; A New Era for Medicine

Kathleen Hefferon, Ph.D., Scientist, Cell and Systems Biology, University of Toronto

The proposal deals with the newly emerging field of rapid and large scale production of vaccines, monoclonal antibodies and other therapeutic proteins in plants. Clinical trials are outlined and the current state of commercialization is detailed.

15:35 End of Development of Novel Biotherapeutics

HIGH-THROUGHPUT PROTEIN EXPRESSION

Inaugural

Screening, Miniaturization, and Engineering for Success

MONDAY, 4 NOVEMBER

12:00 Registration

14:00 Chairperson's Opening Remarks

SCREENING AND ANALYSIS

14:05 Screening for High-Yielding *Pichia pastoris* Clones: The Production of G-Protein Coupled Receptors as a Case Study

Bernadette Byrne, Ph.D., Professor, Division of Molecular Biosciences, Imperial College London

The *Pichia pastoris* system has a particularly good track record for the expression of G protein coupled receptors (GPCRs). Generation and screening of expression clones with this system uses standard molecular biology techniques. Multiple clones can be generated and screened in a matter of a few weeks making this similar to *E. coli* expression in terms of speed. In addition, basic buffer components and the lack of expensive equipment make small-scale expression screening in *P. pastoris* very cost-effective. Here we describe the procedures used for small scale GPCR expression screening.

14:35 Automating the Ribosome Display Technology and High-Throughput Screenings

Jonas Schaefer, Ph.D., Head, High-Throughput Laboratory, Department of Biochemistry, University of Zurich

Selecting specific affinity reagents by automated Ribosome Display technology and various High-Throughput screenings, we screen up to 20,000 clones per week, including various steps from small-scale expression in microtiter plates to large-scale purifications for biophysical analyses. Therefore, my talk will highlight recent improvements of HT expression miniaturization as well as optimizations in the automation process, leading to a further increased throughput of our protein selection and screening pipeline.

15:05 From Factorial Approaches to Domain Boundary Screening: Methods to Optimize Protein Expression in *E. coli*

Bruno Coutard, Ph.D., Architecture et Fonction des Macromolécules Biologiques (AFMB), UMR CNRS and Aix-Marseille University

This presentation will describe the tools that were devised to produce viral proteins for functional and structural studies, and that could be, for most of them, applied to any kind of soluble protein. The first part will present how both expression level and solubility level can be optimized using Design of Experiments (DOE) for the bacterial cultures. The second part will be devoted to the deletion library screening enabling the design of single domains suitable for the production and purification of soluble and stable proteins.

15:35 Combining Analytical Technologies to Augment Understanding of Protein Therapeutics

Sponsored by Malvern

E. Neil Lewis, CTO, Malvern Instruments & Head, Malvern Bioscience Development Initiative

To more fully understand the developability, formulability and manufacturability of a protein therapeutic requires the non-invasive and non-destructive measurement of numerous physicochemical properties of protein formulations such as formulation viscosity, protein structure, hydrodynamic size and morphology. To meet these measurement challenges, measurement techniques that uniquely combine optical microscopy (flow and static), dynamic light scattering (DLS) and Raman spectroscopy to provide both structural, thermodynamic and kinetic insights into the mechanisms of protein aggregation and the factors that influence protein stability in formulation are discussed.

16:05 Refreshment Break

AUTOMATION, CLONING AND CONSTRUCTION

16:35 Applying HT-Protein Approaches to Biological Discovery

Scott Lesley, Ph.D., Director, Protein Sciences and Biotherapeutics, Genomics Institute of the Novartis Research Foundation

17:05 FX Cloning: A Versatile High-Throughput Cloning System for Characterization of Enzyme Variants

Eric R. Geertsma, Ph.D., Department of Biochemistry, University of Zurich

Diverse disciplines in biology critically depend on the ability to clone large numbers of open reading frames (ORFs) into expression vectors. Here I detail FX cloning, a unique high-throughput cloning system that allows the straightforward transfer of a sequence-verified ORF to a variety of expression vectors, while avoiding the common but undesirable extension of target ORFs with cloning-related sequences. FX cloning is robust, highly efficient and economical in its use.

17:35 High-Throughput Construction and Small Scale Expression Screening of Multi-Tag Vectors in *Escherichia coli*

Louise E. Bird, Ph.D., Division of Structural Biology, Henry Wellcome Building for Genomic Medicine, University of Oxford

18:05 Welcome Reception in the Exhibit Hall with Poster Viewing

19:05 End of Day One

TUESDAY, 5 NOVEMBER

07:30 Registration

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

HT LIBRARY GENERATION AND STRUCTURAL STUDIES

08:30 Chairperson's Remarks

08:35 Multiple Chromosomal Gene Integration for Production of Pharmaceutical Proteins in S. cerevisiae

Malene Møller Jensen, Protein Expression, Novo Nordisk

09:05 High-Throughput Construct Screening and Rational Strategies for Structural Platform Establishment: Case Studies of Difficult Kinases

Jacques Dumas, Ph.D., Head, Protein Production, Vitry Biologics SCP, Vitry Research Center, sanofi

sanofi has a long experience in kinases for medicinal projects, with more than 90% success in crystallization. However several kinases are still very difficult to obtain. We present case studies for which we spent variable time to find the right construct. For the last cases we started a collaboration with EMBL Grenoble which established a platform called ESPRIT (Expression of Soluble Proteins by Random Incremental Truncation) allowing the selection of tracks of soluble constructs in *E. coli*. We further pursue within sanofi our efforts in expression and purification optimizations. For both projects, structures were solved at 2.0Å.

09:35 High-Throughput Expression in Mammalian Cells

Trevor Wilkinson, Ph.D., Associate Director, Protein Sciences, MedImmune, Ltd.

The use of high content protein microarrays for the screening of novel and or unplanned target interactions is very powerful. We have optimized the approach for very sensitive determination of the specificity and promiscuity of many important classes of proteins in the biotherapeutic pipeline. This presentation highlights solutions to key concerns for the industry in developing attritional strategies for candidate protein molecules through optimized assay protocols on new generation proteome chips.

10:05 BLI Technology is Broadly Applicable in Drug Discovery

Sponsored by fortéBIO A Division of Pall Life Sciences

Marijn van der Neut Kolfschoten, Ph.D., Senior Scientist, Crucell Vaccine Institute, Janssen Center of Excellence for Immunoprophylaxis

Octet instruments make use of BioLayer Interferometry (BLI) to measure molecular interactions real-time and label-free. These instruments can be used for both quantitative and qualitative binding assays. Within the Crucell Vaccine Institute the Octet instruments are broadly used to support drug discovery activities. Examples of these applications, such as protein quantitation, binding characteristics (breadth of binding, kinetics etc), competition experiments, qualification of drug candidates and mechanism of action experiments, will be presented.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

11:15 Insights into How to Design Assays and Correctly Plan for Candidate Profiling in the Most Cost-Effective, Rapid and Dynamic way

David O'Connell, Ph.D., Director, Masters Programs in Biotechnology, School of Biomolecular & Biomedical Research, University College Dublin; Conway Institute of Biomolecular & Biomedical Research, UCD Belfield

The use of high content protein microarrays for the screening of novel and or unplanned target interactions is very powerful. We have optimized the approach for very sensitive determination of the specificity and promiscuity of many important classes of proteins in the biotherapeutic pipeline. This presentation highlights solutions to key concerns for the industry in developing attritional strategies for candidate protein molecules through optimized assay protocols on new generation proteome chips.

11:45 Poster Spotlight Presentation: The Protein Factory within the Human Protein Atlas Project - High-Throughput Protein Production and Purification

Katarina Malm, Research Engineer, Proteomics, KTH Royal Institute of Technology

12:15 High-Throughput Analytical Gel Filtration Screening of Integral Membrane Proteins for Structural Studies

Christian Löw, Ph.D., Medical Biochemistry and Biophysics, Karolinska Institute

Structural studies of integral membrane proteins (IMPs) are often hampered by difficulties in producing stable homogenous samples for crystallization. We have developed a screening approach that prioritizes IMP targets based on three criteria: expression level, detergent solubilization yield and homogeneity as determined by high-throughput small-scale immobilized metal affinity chromatography (IMAC) and automated size-exclusion chromatography (SEC). Our screening strategy is rapid, cost efficient and can easily be adapted to other challenging proteins and protein complexes. Results for nutrient uptake systems will be discussed.

12:45 Luncheon Presentations *(Sponsorship Opportunities Available)* **or Lunch on Your Own**

USING THE TOOLS SUCCESSFULLY

14:00 Chairperson's Remarks

14:05 Searching for Microbial Protein Over-Expression in a Complex Matrix Using Automated High-Throughput MS-Based Proteomics Tools

Michael Akeroyd, Ph.D., DSM Biotechnology Center, The Netherlands

We present a sensitive, generic workflow for high-throughput screening of successful microbial protein over-expression in microtiter plates containing a complex matrix based on mass spectrometry techniques. MALDI-LTQ-Orbitrap screening followed by principal component analysis and peptide mass fingerprinting was developed to obtain a throughput of ~12,000 samples per week. We show that this generic workflow can effectively reduce large expression libraries from fungi and bacteria to their minimal size by detection of successful protein over-expression using MS.

14:35 POSTER SPOTLIGHT PRESENTATIONS

pCoofy Protein Expression Vectors for Fast,Efficient and Background Free Parallel Cloning

Sabine Suppmann, Ph.D., Head, Recombinant Protein PRoduction, EMBL Heidelberg

High Throughput Methods for *Pichia pastoris* Pave the Way for Rapid Process Development, a Case Study: Production of Novel Therapeutic Proteins Fused to Human Serum Albumin as Half-Life Extension

Simon Stammen, Ph.D., Scientist, Process Science, Boehringer Ingelheim RCV GmbH & Co. KG

15:05 Problem Solving Roundtable Discussions

Table 1: Use of High Content Microarrays for Determining Specificity

Moderator: Trevor Wilkinson, Ph.D., Associate Director, Protein Sciences, MedImmune, Ltd.

Table 2: High Throughput Screening of Membrane Proteins for Structural Studies

Moderator: Christian Löw, Ph.D., Medical Biochemistry and Biophysics, Karolinska Institute

Table 3: Automating High Throughput Screening

Moderator: Jonas Schaefer, Ph.D., Head, High-Throughput Laboratory, Department of Biochemistry, University of Zurich

16:05 Refreshment Break in the Exhibit Hall with Poster Viewing

16:55 Targeted MS Quantification of IVT Protein Expression

Manuel Fuentes, Ph.D., Scientist, Medicine, Centro de Investigacion Del Cancer(CIC) – University of Salamanca, CSIC

Due to the lack of immunogenicity of antigens or haptens of molecular weight under 1000-3000 Da; in general, it is necessary to chemically conjugated them to macromolecules highly immunogenic. However, this strategy has not been widely used because poor results have been obtained when the hapten is a short peptide corresponding with point mutation. Here, it will be presented a novel strategy of chemically modified carrier proteins with short specific peptides. This strategy has been successfully used to develop monoclonal antibodies against clinical point mutations which are clinically relevant in gastrointestinal stromal tumor (GIST) and mastocitosis. Epitope mapping of these antibodies has been successfully tested by self-assembled protein arrays containing all the point mutations, wild-type, amino and carboxy deletions.

17:30 Application of Modular Expression Toolboxes in High-Throughput Protein Expression

Ernst Weber, Ph.D., Group Leader, Protein Engineering and Assays, Bayer AG

Rapid, parallel expression optimization is essential in drug development to ensure production of high quality target proteins. Therefore we set up a modular expression toolbox, consisting of standardized elements influencing expression levels, which allow the generation of complex expression libraries. Here we will discuss advantages and implications of a modular cloning system, outline the strategy and design of an expression toolbox, and present case studies were such libraries were expressed and analyzed.

18:00 End of High Throughput Protein Expression

6th Annual OPTIMIZING PROTEIN EXPRESSION
Driving Results with Smarter Strategies

WEDNESDAY, 6 NOVEMBER

07:45 Registration and Morning Coffee

08:30 Chairperson's Opening Remarks

» 08:35 KEYNOTE PRESENTATION:
Optimizing Vector Components for Improved Protein Production from Insect and Mammalian Cells

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

I will discuss a series of technologies we have developed for improving the performance of expression vectors for insect cell and mammalian cell protein production. In insect cells, we have heavily modified the commonly used Bac-to-Bac vector system for baculovirus generation to dramatically reduce the time needed to generate expression clones, and improve the quality of downstream baculovirus production. For mammalian expression, we have used our combinatorial cloning platform to identify promoters, transcriptional and translational enhancers, and fusion tags to improve production of intracellular and secreted proteins. A number of experimental case studies will be presented to demonstrate the utility of these new technologies and their application in small-scale screening for optimized protein production.

STRATEGIES FOR SUCCESS FROM THE BEGINNING

09:05 Toward System-Level Understanding of Baculovirus-Host Cell Interactions: From Molecular Fundamental Studies to Large-Scale Proteomics Approaches

Paula M. Alves, Ph.D., Director, Animal Cell Technology Unit, Instituto de Biologia Experimental e Tecnológica Oeiras, Portugal

We have recently established an Sf9 cell line using a recombinase-mediated cassette exchange (RMCE) strategy which has similar development timelines to baculovirus expression, providing a stable yet versatile alternative that avoids the lytic viral effect on cell growth and protein quality. I will present the development of this master cell line and its capacity to express different complex proteins; a comparison to the Sf9 BEVS technology in terms of production levels and protein quality will be shown.

09:35 Optimizing Heterologous Protein Production in the Periplasm of *E. coli*

Jan-Willem de Gier, Ph.D., Associate Professor, Center for Biomembrane Research, Stockholm University; CSO, Xbrane Bioscience AB

10:05 Twin-Strep-tag®: The More Efficient Strep-tag® for Protein Purification from Cell Culture Supernatants *Sponsored by* iba

Thomas Schmidt, Ph.D., COO, IBA GmbH

The widely used Strep-tag®II provides highly pure and functional proteins from crude lysates of any host. A further development of Strep-tagII is the Twin-Strep-tag which combines its high specificity and mild conditions with higher affinity. This enables more efficient purification directly from cell culture supernatants usually containing the recombinant target protein at low concentration only. A novel biotin blocking solution has been developed for simple removal of eventually present biotin at a reasonable price. Furthermore, the WET FRED device will be presented for the convenient application of large sample volumes (e.g. cell culture supernatants) to Strep-Tactin gravity flow columns in a highly parallel mode without the need for supervision. These recent improvements make the Strep-tag system particularly attractive for the purification of proteins secreted by mammalian or insect cells.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

CELL LINE CHOICES

11:05 Use of an Anti-Apoptotic CHO Cell Line for Transient Gene Expression

Athena Wong, Ph.D., Scientist, Early Stage Cell Culture, Genentech, Inc.

Here, we describe the development of a polyethylenimine (PEI) transient transfection system using an anti-apoptotic host cell line. The host cell line, referred to as the Double Knockout (DKO), was generated by deleting two pro-apoptotic factors, Bax and Bak, in a CHO-K1 cell line using zinc finger nuclease mediated gene disruption. DKO cells expressed ~3-4 fold higher antibody titers than parental CHO-K1 cells. As evidence of their anti-apoptotic properties post-transfection, DKO cells maintained higher viability and had reduced levels of active caspase-3 compared to parental CHO-K1 cells.

11:35 Generation and Optimization of a Suspension CHO-EBNA Expression System to Express Multiple Different Classes of Proteins

Robert Roth, Ph.D., Associate Principal Scientist, Reagents and Assay Development, AstraZeneca, Sweden

Transient gene expression (TGE) in mammalian cells has steadily gained popularity over the past few years as a method for producing protein reagents to support drug discovery research. We will describe the generation and optimization of a suspension CHO cell line for the purpose of TGE. Data will be presented on how the conditions for the transfection with polyethyleneimine were optimized with the help of factorial experimental design and the effect of genetic modifications to improve protein expression. Examples on protein expression of secreted, intracellular and membrane proteins will be shown.

12:05 Scaling from the Bench to Biomanufacturing: Large Scale CHO Transient Transfection Using Flow Electroporation *Sponsored by* MaxCyte

Peer Heine, Ph.D., Field Applications Scientist, MaxCyte Inc.

Flow electroporation (FEP) streamlines antibody development by enabling large scale transient gene expression (TGE) directly in CHO cells, eliminating the need to change cell backgrounds during scale up to biomanufacturing. FEP is fully scalable and produces antibody titers >1g/L with optimization and can also be used to rapidly generate high yield stable cell lines.

12:35 Luncheon Presentations *(Sponsorship Opportunities Available)* **or Lunch on Your Own**

NEW TOOLS FOR OPTIMIZATION

14:00 Chairperson's Remarks

14:05 GlycoDelete Technology: Shortcutting Mammalian Cell N-Glycosylation to Produce Therapeutic Proteins with Simplified Sialylated N-Glycans

Francis Santens, Researcher, Department for Molecular Biomedical Research, VIB

We present a novel technology to produce glycoproteins with radically simplified and uniform glycans. This was introduced in HEK 293 cells and tested on several glycoproteins. We compared the glycoproteins form the glycodelete technology with normal glycosylated proteins.

14:35 Production of Minicircles for Gene Therapy and Transient Protein Expression

Michaela Simcikova, Ph.D., Researcher, Prazeres Laboratory, Department of Bioengineering, Instituto Superior Técnico

Minicircles are promising vectors for human gene delivery and transient protein expression applications. Here we describe production systems based on a modified *E. coli* strain which rely on the expression of ParA resolvase from a helper plasmid or from the *E. coli* chromosome to promote recombination of parental plasmids into minicircles. The impact of ribosome-binding sites on the expression of ParA resolvase and efficiency of minicircle generation is also evaluated.

15:05 The Novel Fh8 Fusion Tag: A Comparison with Other Fusion Systems for Efficient Soluble Over-Expression and Purification of Recombinant Proteins in *Escherichia coli*

Sofia Costa, M.S., Researcher, Centre of Biological Engineering, University of Minho

The Fh8 fusion system (Hitag®) was initially used to increase protein expression in *Escherichia coli*, and it is now established as an effective

solubility and purification tag for recombinant protein production in this host cell. The Fh8 was ranked among the best solubility enhancer tags as Trx, MBP or NusA, being easily removed from the target protein without compromising its solubility. The Fh8's low molecular weight and its dual solubility enhancing and purification functionality make this tag a valuable tool for efficient recombinant protein production in *E. coli*.

15:35 Refreshment Break in the Exhibit Hall with Poster Viewing

16:15 SINEUPs: A New Versatile Tool to Increase Protein Synthesis of Your Gene of Interest

Stefano Gustincich, Ph.D., Associate Professor, Neurobiology, SISSA

We have recently identified a group of natural and synthetic antisense non-coding RNAs that activate translation of their sense protein-encoding genes. These molecules have been named SINEUPs since their function requires the activity of an embedded inverted SINEB2 element to UP-regulate translation. By synthesizing the overlapping sequence antisense to the gene of interest, SINEUPs can increase protein levels at will.

16:45 Optimization of Protein Expression in *K. lactis*: A Case Study of a Difficult Expression Problem Solved

Isaura Simoes, Ph.D., Molecular Biotechnology Unit, CNC/Biocant

Redirecting a protein for secretion is particularly useful considering high value-protein expression in heterologous systems like yeasts, by greatly facilitating recombinant protein handling and processing. In this work, we demonstrate the positive impact of manipulating vacuolar sorting signals in two plant proteases for improved secretion in *K. lactis*. This resulted in the development of a new synthetic plant-based rennet which emerges as an alternative/innovative coagulant for the cheese-making industry.

17:15 Problem Solving Roundtable Discussions

Table 1: Improving Performance of Expression Vectors for Insect Cell and Mammalian Cell Protein Production

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

Table 2: Solving Problems of Protein Expression in *K. lactis*

Isaura Simoes, Ph.D., Molecular Biotechnology Unit, CNC/Biocant

Table 3: Evaluating Metabolic Stress and Plasmid Stability in Plasmid DNA Production by *Escherichia coli*

Filomena Silva, Ph.D., CICS-UBI–Health Sciences Research Centre, University of Beira Interio

Table 4: Use of an Anti-Apoptotic CHO Cell Line for Transient Gene Expression

Athena Wong, Ph.D., Scientist, Early Stage Cell Culture, Genentech, Inc.

18:15 Networking Reception in the Exhibit hall with Poster Viewing

19:15: End of Day One

THURSDAY, 7 NOVEMBER

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

VECTORS, PLASMIDS AND PROMOTERS

08:30 Chairperson's Remarks

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

08:35 Development of Alternative Scaffold Proteins as Novel Therapeutics

Subinay Ganguly, Ph.D., Scientific Director, Team Leader CMC, Janssen R & D, Johnson & Johnson

09:05 Evaluating Metabolic Stress and Plasmid Stability in Plasmid DNA Production by *Escherichia coli*

Filomena Silva, Ph.D., CICS-UBI–Health Sciences Research Centre, University of Beira Interior

This review highlights major *E. coli* biological alterations caused by plasmid maintenance and replication, possible causes for plasmid instability and discusses the ability of currently employed bioprocess monitoring techniques to provide information in order to circumvent metabolic burden and plasmid instability, pointing out the possible evolution of these methods towards online bioprocess monitoring.

09:35 Expression Kinetics and Cellular Mechanism in Production of Difficult-to-Express Fc-fusion Protein in CHO Cells

Yusuf Johari, Chemical and Biological Engineering, University of Sheffield

10:05 BAC-Based Expression System Technology for Mammalian Cells

Katalin Zboray, Ludwig Boltzmann Gesellschaft Gmbh

10:35 Coffee Break in the Exhibit Hall with Poster Viewing

11:05 A Comparative Analysis of the Properties of Regulated Promoter Systems Commonly Used for Recombinant Gene Expression in *Escherichia coli*

Simone Balzer, Ph.D., Faculty of Natural Sciences and Technology, Department of Biotechnology, NTNU

The choice of expression system needs to be evaluated for each specific case, but we believe that the standardized vectors developed for this study can be used to more easily identify the nature of case-specific bottlenecks. By then taking into account the relevant characteristics of each expression cassette it will be easier to make the best choice with respect to the goal of achieving high levels of protein expression in functional or non-functional form.

11:35 Technology Toolbox for Cell Line Development

Holger Laux, Ph.D., Principal Scientist, Integrated Biologics Profiling, Novartis Pharma Services AG, Basel

Chinese Hamster Ovary (CHO) cells are widely used for the large scale production of recombinant biopharmaceuticals. These cells have been extensively characterised and approved by regulatory authorities for production of biopharmaceuticals. Our strategy for further optimising yield and reduce screening efforts of our CHO platform includes new vector approaches. Some novel vector technologies that we have evaluated to improve our platform towards high yielding fast processes will be presented. Furthermore we will present that applying transcriptomics derived approaches supported the identification of the root cause of cell growth inhibition and low productivity of a difficult to express therapeutic protein and how state of the art cell line engineering tools enabled the high expression of this therapeutic protein in CHO cell lines.

12:05 End of Optimizing Protein Expression

6th Annual

DIFFICULT TO EXPRESS PROTEINS

Strategies for Solving "Finicky" Protein Problems

THURSDAY, 7 NOVEMBER

12:00 Registration

14:00 Chairperson's Opening Remarks

» 14:05 KEYNOTE PRESENTATION:
A New Platform for the Rapid Generation of Stable CHO Pools and Clones

Yves Durocher, Ph.D., Protein Expression Team Leader, Life Sciences, NRC Human Health Therapeutics Portfolio, National Research Council Canada

Large-scale transfection of HEK293 cells is a highly valuable tool for the fast generation of mgs to grams quantities of r-proteins required for R&D purpose. More recently, new CHO-based platforms have been developed with some success, even though productivity is often lower compared to HEK293 cells. This is especially problematic when large quantities of difficult-to-express r-proteins are needed for various studies. We will present data describing our new CHO platform that allows the generation of stable pools capable of producing up to 500 mg/L of monoclonal antibodies in less than 5 weeks post-transfection. This platform represents a viable alternative to large-scale CHO transfection or stable cell line development for manufacturing large quantities of r-proteins candidates.

MEMBRANE PROTEINS AND COMPLEXES

14:35 Total Protein Engineering Solution for GPCRs through Stabilization and Construct Optimization

Markus Koglin, Ph.D., Associate Director, Protein Engineering, Heptares Therapeutics

Here we demonstrate that protein quality when expressed in mammalian or insect cells drastically improves with increasing thermostability. Although this increased quality produces material suitable for biophysical technologies like SPR or NMR, StaR generation alone normally does not provide suitable material for crystallization. Further construct optimization including N- and C-terminal truncations and PTM removal can have a dramatic effect in expression quantities and qualities. The combination of StaR technology and systematic construct design delivers a powerful approach in expression and purification of protein with suitable crystallization qualities.

15:05 Refreshment Break in the Exhibit Hall with Poster Viewing

15:50 Expression and Stabilization of Pathologic GPCR Mutations and Arrestin Complexes for Structural Studies

Joerg Standfuss, Ph.D., Senior Scientist and Group Leader, Biomolecular Researcher, Paul Scherrer Institute, ETH

We have solved GPCR Structures with full and partial agonists to understand the activation mechanism and the pharmacology of GPCRs in detail. Thermostabilization of receptors has enabled biophysics and detailed pharmacological characterization of a number of GPCRs. GPCR structure can now be used for fragment-based drug design.

16:20 Recombinant Expression of Full-Length Complement Protein C1q and its Globular Domains

Uday Kishore, Ph.D., Director, Centre for Infection, Immunity and Disease Mechanisms, Brunel University

C1q is the IgG- and IgM-recognizing subcomponent of the classical complement pathway that is important in a range of conditions including SLE, cancer, allergy, and transplantation and epilepsy. C1q, which is composed of three chains (A, B, C)having N-terminal collagen region and binds a number of self and non self-ligands via C-terminal globular region. To make recombinant forms of full length heterotrimeric C1q as well as globular region has been a real challenge in the field for over decades. Various strategies to express and characterize C1q will be discussed.

16:50 New Tools for Difficult Expression Problems: Endotoxin-Free Proteins, Biotinlyated Proteins, and More

Sponsored by Lucigen Simplifying Genomics

David Mead, CEO, Lucigen Corp.

Lucigen will present novel competent *E. coli* cells lacking lipopolysaccharide (LPS) for endotoxin-free protein and DNA production, as well as new systems for fast expression and isolation of pure proteins via highly efficient *in vivo* biotinylation.

17:05 Corynex®: A Novel Protein Expression System that Delivers Better Results

Sponsored by AJINOMOTO

Yoshimi Kikuchi, Ph.D., Principal Researcher, AJINOMOTO CO., INC.

Corynex® is a microbial protein expression system that can secrete active proteins directly into media with high purity. Corynex® has already succeeded in producing numerous difficult-to-express proteins which could hardly be produced in other systems.

17:20 End of Day One

17:20 Short Course Registration*

17:35 – 20:30 Dinner Short Course: Troubleshooting and Engineering of Antibody Constructs

*Separate registration required, see page 2 for details

FRIDAY, 8 NOVEMBER

07:45 Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

NEW APPROACHES FOR FINICKY PROTEINS

08:30 Chairperson's Remarks

Stefan Schmidt, Ph.D., Vice President, DSP Production, Rentschler Biotechnology

08:35 A Directed Evolution Method for Optimized Production of Membrane Proteins

Fabrizia Fusetti, Ph.D., Research Associate, Biochemistry, University of Groningen

The study of membrane proteins represents a great opportunity for structure-guided drug discovery but it presents several challenges. The current expression strategies are based on a trial-and-error approach, with a large a part of the effort dedicated to the screening and optimization of several expression parameters. Our solution to the problem is to boost the expression host by triggering its adaptation mechanisms to find the best solution for every new protein in any given environmental condition.

09:05 *Lactococcus lactis*: An Alternative and Emerging System for Functional Expression of Difficult Membrane Proteins

Annie Frelet-Barrand, CNRS Researcher, CEA Saclay/iBiTec-S

The Gram-positive *Lactococcus lactis* has emerged in recent years to be a good alternative system to *Escherichia coli*. Indeed, in addition to other biotechnical purposes, it allows the functional expression of prokaryotic and eukaryotic membrane proteins and in particular of difficult membrane proteins such as plant and human proteins but also their functional characterization.

09:35 Problem Solving Roundtable Discussions

Table 1: Solving Issues of Difficult to Express Therapeutic Fusion Proteins

Moderator: Stefan Schmidt, Ph.D., Vice President, DSP Production, Rentschler Biotechnology

Table 2: Utilizing *Lactococcus lactis* to Express Difficult Proteins

Moderator: Annie Frelet-Barrand, CNRS Researcher, CEA Saclay/iBiTec-S

Table 3: Expression of Difficult Protein Therapeutics: Bispecific Antibodies

Moderator: Yves Durocher, Ph.D., Senior Research Officer, National Research Council of Canada

10:35 Coffee Break

MAKING THE IMPOSSIBLE, POSSIBLE

11:00 Expressing Challenging Targets for Drug Discovery

Rick Davies, Ph.D., Team Leader, Global Protein Science and Supply, AstraZeneca R&D Alderley Pk

Targets for drug discovery projects are becoming more diverse and challenging. They are chosen based on evidence linking them to human disease and not on the challenges, which need to be overcome to express these proteins in suitable quantity and quality to support small molecule drug discovery projects. A number of examples of recent AZ projects will be presented, in which difficult expression/purification challenges have been overcome.

11:30 Directed Evolution of G Protein-Coupled Receptors for High Functional Expression in *E. coli* and Stability in Detergents

Pascal Egloff, Scientist, Biochemistry Institute, University of Zurich

In vitro experiments on G-protein-coupled receptors (GPCRs) are hampered by their low functional expression levels in prokaryotes and by their inherent instability when solubilized in detergent micelles. We recently developed directed evolution technologies that allow generation of GPCR variants with up to 60 fold improved functional expression levels in *E. coli* and superior stability in harsh detergent solution. To validate our approach, we determined several x-ray structures of evolved neurotensin receptor 1 variants using signaling-competent constructs.

12:00 Solving Issues of Difficult to Express Therapeutic Fusion Proteins

Stefan Schmidt, Ph.D., Vice President, DSP Production, Rentschler Biotechnology

Therapeutic fusion proteins are a heterogenous group covering receptor-traps, immunotoxins, Fc-fusions and peptibodies. Interestingly most of them are difficult to express, thus rendering fast and cost efficient production a key challenge. In selected case studies we demonstrate how to overcome the typical difficulties such as absence of a traditional platform technology, low titer, lack of an affinity matrix, tendency to aggregate, isolation of isoforms, etc. Strategies in the context of fusion proteins are summarized and practical advice will be given what parameters to consider when optimizing the "manufacturability" of a novel molecule.

Sponsored by

12:30 Native & Full length Membrane Protein Isolation for Antibody Development and Drug Discovery

Anass Jawhari, Ph.D., CSO, Membrane Protein Alliance

Sponsored by

13:00 Luncheon Presentation CaptureSelect Ligand Technology; Unique Platform for Purification of Antibodies, Antibody Fragments and Therapeutic Proteins

Frank J.M. Detmers, Ph.D., Director, Ligand Application, Life Technologies

CaptureSelect ligand technology is based on affinity ligands derived from heavy chain only antibodies. This technology was used to develop ligands and affinity resins at any scale specific for domains of IgA, IgM and IgG, like the Fc region, Kappa light chain, Lambda light chain, and IgG CH1 domain. Besides antibodies, solutions for the purification of proteins like clotting factors, biosimilars and viruses are developed, offering unprecedented specificity, ensuring mild elution conditions for sensitive proteins.

13:30 Session Break

STUDIES IN SUCCESS

14:00 Chairperson's Remarks

14:05 Membrane Protein Expression and Purification at Novartis

Binesh Shrestha, Ph.D., Lab Head, Investigator, Novartis Pharma, Novartis Institute of Biomedical Research

This presentation will outline new successes with the expression of some of the most difficult to express proteins, membrane proteins.

14:35 A Robust and Rapid Method of Expressing Soluble, Stable, and Functional GPCRs

Karolina Corin, Ph.D., Postdoctoral Fellow, Electrical and Information Engineering, and Molecular Medicine and Hematology, University of Witwatersrand

GPCRs and other membrane proteins are difficult to express in sufficient quantities for structure and function studies. Cell-free expression systems can be used to express milligrams of these proteins. The key is to use an appropriate detergent; almost no protein is expressed with certain detergents, while others yield milligram quantities. Over 13 GPCRs were expressed in this manner, and all were soluble, properly folded, and bound their ligands.

15:05 Overcoming Difficulties in Producing Cereblon for Biophysical Studies with Immunomodulatory Drugs

Gilles Carmel, Ph.D., Principal Scientist, Biochemistry & Structural Biology Department, Celgene

Cereblon (CRBN) was recently described as the target for the immunomodulatory drug thalidomide and we were highly interested in characterizing the interactions of thalidomide and related derivatives with CRBN. Of the many constructs of CRBN, only the ones co-expressed with DDB1 produced soluble CRBN. Independent and complementary methods presented herein demonstrate how to produce an important but difficult to express protein (CRBN), and that the IMiD compounds bind human CRBN.

15:35 End of Difficult to Express Proteins

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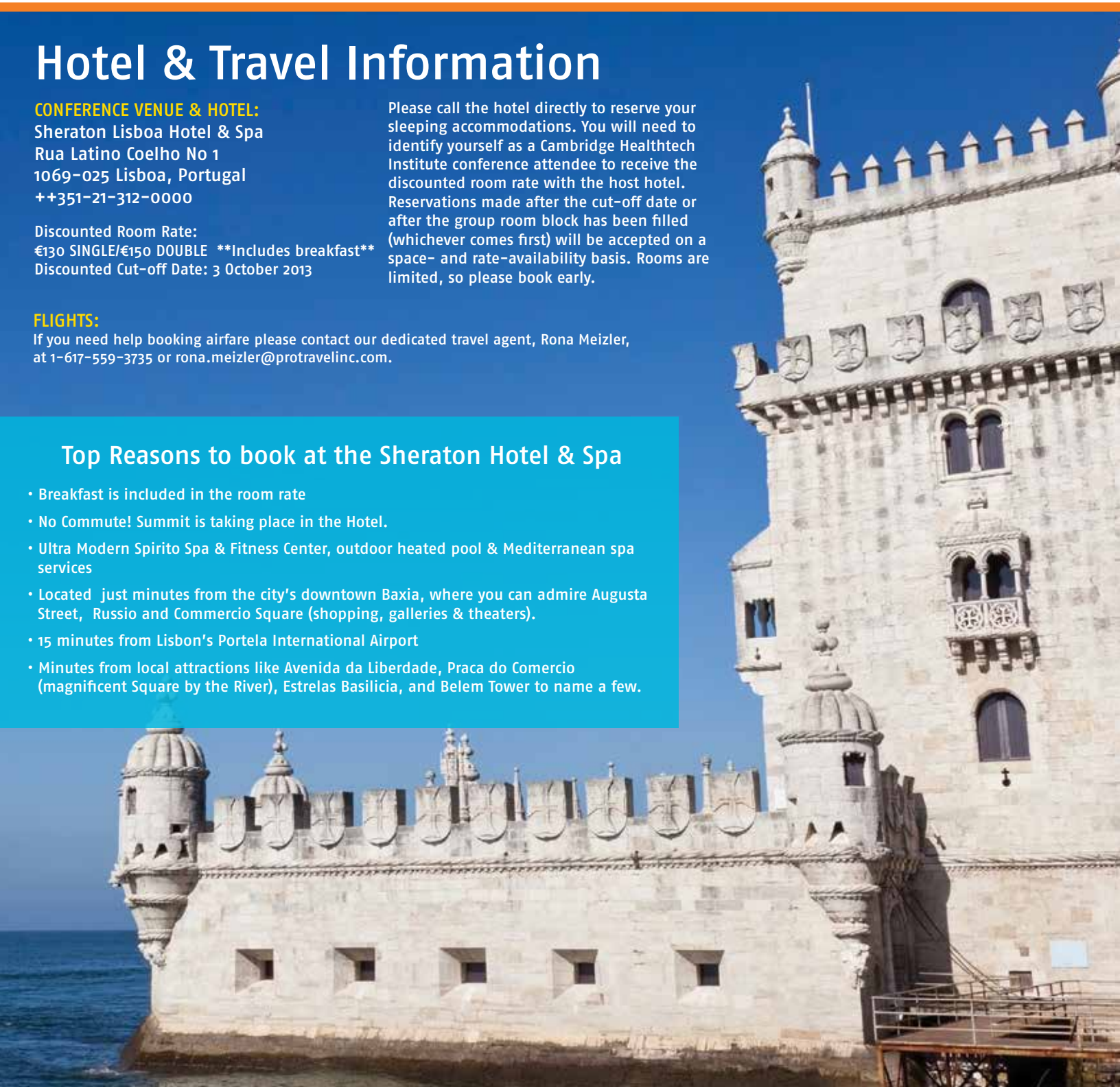

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Dinner SC5: Troubleshooting and Engineering of Antibody Constructs (Thursday evening)

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C1: Novel Antibody Constructs	C3: Cancer Biotherapeutics	C5: Development of Novel Therapeutics
C2: High-Throughput Protein Expression	C4: Optimizing Protein Expression	C6: Difficult to Express Proteins

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