Apotekarsocieteten
Swedish Pharmaceutical Society

The Scheele Symposium

Gathering scientists to explore and celebrate groundbreaking research within drug discovery and drug development.

The Scheele Symposium in honour of the Scheele award laureate.

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The Scheele Symposium 2023

Adventures in chemical biology – basic science translating into patients

November 9 in Stockholm

Professor Peter G. Schultz

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Thomas Lundbäck


Sara Mangsbo


Christian Hedberg


Fredrik Frejd


Simon Elsässer


Anna Falk


Amelie Eriksson Karlström


Ola Engkvist

Short Biography & Abstract

Christian Hedberg is Professor of Organic Chemistry at Umeå University, and his research is focused on innovate approaches in chemical biology and medicinal chemistry, with the overall application to infection biology.

Identification of bacterial toxin protein targets during intracellular infection via co-substrate-mediated covalent capture

Christian Hedberg, Umeå University

Abstract

This project has the *purpose* to conceptualize ***R****eactive* ***P****rotein – **P**roteome **P**rofiling* " ***RP³*** ". The goal is to create a robust method for absolute substrate profiling of bacterial toxins against cellular target proteins employing **covalent nucleotide co-substrates** resulting in covalent ternary complexes. During infection, pathogenic bacteria tweak their eukaryotic hosts by translocating toxins. Toxins display catalytic activity against host cell proteins, targeting key functions, often using a metabolite as co-substrate. *No tools exist for the proteomic evaluation of the absolute substrate profile of a given toxin.* Non-covalent affinity enrichment gives biased results depending on the reagent and relative target abundance. We have developed a new concept based on covalent and subsequently cleavable capture of the target proteins by the reactive co-substrate of the toxin. We have used the workflow to target profile a number of AMPylating bacterial toxins, as well as in preparative mode made covalent ternary toxin-nucleotide-substrate complexes for structural biology. This provides a unique opportunity to capture transient structures, not accessible by classical methods.

Short Biography & Abstract

Simon Elsässer is an Associate Professor at Karolinska Institutet where he heads the Laboratory of Chemical and Synthetic Systems Biology. Dr. Elsässer read biochemistry at Tübingen and Harvard University before joining David Allis' lab at Rockefeller University for his PhD in Chromatin Biology. In 2012, he moved to MRC Laboratory of Molecular Biology to work in Synthetic Biology with Jason Chin and since 2015 he is a group leader at Karolinska Institutet and SciLifeLab.

Expanding the chemical biology toolbox for mammalian cells

Simon Elsässer, Karolinska Institutet

Abstract

Engineering proteins with non-canonical amino acids (ncAAs) provides exciting opportunities for controlling and probing protein function in mammalian cells. I will present our recent efforts to create a comprehensive, modular and efficient toolbox available to the community for incorporating one or more ncAAs into proteins in mammalian cells, and I will discuss opportunities and challenges of genetic code expansion. I will showcase application of our tools in fluorescent labeling and imaging, proteomics and the study of posttranslational modifications.

Short Biography & Abstract

Amelie Eriksson Karlström is Professor of Molecular Biotechnology at KTH and her research is focused on protein engineering, affinity technologies and bioconjugation chemistry for diagnostic and therapeutic applications.

PNA-pretargeted affibody-based radionuclide therapy

Amelie Eriksson Karlström, KTH Royal Institute of Technology

Abstract

In targeted radionuclide therapy tumor-specific radiolabeled molecules are used to deliver cytotoxic radiation to tumor cells. To avoid unwanted exposure of non-tumor organs, a pretargeting strategy can be used, where the tumor-targeting step is uncoupled from the delivery of the toxic radionuclide. We have developed and evaluated a system for pretargeting based on the high selectivity and high affinity of peptide nucleic acid (PNA) hybridization. A tumor-targeting affibody molecule is conjugated to a primary PNA probe, which binds with high affinity to a secondary radiolabeled PNA probe. The primary agent is administered first and the secondary, radiolabeled agent is administered after the primary agent has accumulated in the tumor and cleared from non-tumor tissue. We have demonstrated that the PNA-based affibody-mediated pretargeting system gives high tumor-to-normal tissue contrast in vivo and can mediate radionuclide therapy of HER2-expressing tumors in a mouse model.

Short Biography & Abstract

Sara Mangsbo is a professor of antibody drugs at Uppsala University and will serve as a guest professor at SLU in the field of comparative medicine from 2024. With a Ph.D. in clinical immunology and over 15 years of experience in immuno-oncology, Sara Mangsbo has been instrumental in the development of innovative antibody and peptide-based immunotherapeutics. Her expertise extends from the laboratory to clinical testing, bridging the gap between research and practical application. Additionally, she has introduced an advanced method for predicting immunotoxicity responses to biologics by repurposing an ex vivo human blood assay. As an entrepreneur, she has co-founded ventures such as Immuneed AB, Vivologica AB, and Strike Pharma AB.

The Adaptable Drug Affinity Conjugate (ADAC) technology, towards precision immunotherapy

Sara Mangsbo, Uppsala University

Abstract

The Adaptable Drug Affinity Conjugate (ADAC) technology is a pioneering advancement in modular and targeted drug delivery. This innovative approach addresses the challenges of traditional drug therapies, offering enhanced specificity, reduced off-target effects, and improved therapeutic outcomes.

ADACs consist of engineered molecules with a bispecific antibody design, allowing for modular cargo loading through a binding moiety specific to a tag linker. The high affinity of this binding moiety to the tag linker tethers a fully loaded ADAC, improving payload half-life and enabling cell-specific payload delivery. Furthermore, ADACs' targeting moieties are adaptable to different diseases and cell types, making this technology suitable for a wide range of conditions, from cancer to autoimmune disorders. ADACs can incorporate various therapeutic agents, including small molecules, biologics, and nucleic acids, making them a versatile platform for precision medicine.

The initial ADAC protein, STRIKE2001, offers peptide payloads, specifically neoantigen-based peptide drug therapeutics. It targets CD40 to stimulate the CD40 pathway, ensure antigen presentation, and activate T cell responses to specific neoantigenic peptides. STRIKE2001-KRASm targets KRAS-mutated non-small lung cancer (NSCLC), colorectal cancer (CRC) and pancreating cancer using subdermal administration, thus maintaining an excellent safety profile by choice of administration route.

The adaptable nature of STRIKE2001 via the ADAC technology fosters innovation and opens doors to personalized medicine. Researchers can fine-tune STRIKE2001 to optimize drug release kinetics and targeting efficiency, tailoring treatments to individual patient profiles. This approach promises to revolutionize medicine by introducing highly effective, low-toxicity treatments.

In conclusion, Adaptable Drug Affinity Conjugate technology represents a transformative advancement in targeted therapies. Its adaptability, precision, and reduced toxicity make it a promising candidate for various medical applications. As ADACs continue to evolve, they have the potential to redefine disease treatment, ultimately with the goal to improve patient treatment worldwide.

Short Biography & Abstract

Fredrik Frejd received his Ph.D. from the Swiss Federal Institute of technology, ETH, in Zurich on phage display and combinatorial engineering of antibody repertoires for tumor therapy. Dr. Frejd is now adjunct professor in cancer precision medicine at the department for Immunology, Genetics and Pathology at Uppsala University, with a special focus on tumor biology, phage display and development of minimized tumor targeting agents for payload therapy. Fredrik Frejd is also the Chief Scientific Officer of Affibody AB and has over 25 years of experience in translational life science research with expertise in biologics drug development and therapeutic protein engineering of alternative scaffolds. Fredrik is a member of the board of Akiram Therapeutics AB and Immuneed AB.

Affibody Protein Tweezers: IL-17 AA Capture and Clinical Translation

Fredrik Frejd, Affibody, Uppsala University

Abstract

Several signaling molecules that drive autoimmune disease are of dimeric nature. A challenge in drug development is to selectively target specific forms of dimeric proteins when there are several variants present. Interleukin-17 (IL-17) AA is an important homodimeric driver of several autoinflammatory conditions whereas heterodimeric IL-17 AF and IL-17 FF homodimers are believed to be important for epithelial barrier defense and should therefore not be blocked. Izokibep is a novel Affibody molecule engineered to develop a potentially best-in-class highly selective IL-17AA blocking ligand trap with femtomolar binding affinity and complete blocking ability. The small robust three helical bundle scaffold allows the generation of a drug that has only 18.6 kDa size and yet antibody like half-life by virtue of an integrated albumin binding domain. The potency, albumin distribution and high dose ability translates to high therapeutic efficacy in patients with psoriasis, psoriatic arthritis and hidradenitis suppurativa. Excellent three-year safety and efficacy data support both the IL-17 program as well as the Affibody drug class in general. Izokibep is now in late-stage clinical development.

Short Biography & Abstract

Anna Falk is leading a research team that uses cellular reprogramming and iPS cells to create and study models of human brain development and for creating novel cell therapies. Dr Falk is heading the IndiCell project, a Vinnova milieu for iPSC derived cell therapy and is the director of Lund University ATMP center and Lund Cell and Gene Therapy Core.

iPS cells for disease modelling and cell therapy

Anna Falk, Lund University

Abstract

The challenges in studying the human brain development have over recent years been addressed by multiple technology discoveries, to mention some, somatic cell reprogramming, establishment of induced pluripotent stem cells (iPSC), brain organoids, genome editing using CRSIPR. Today, we can faithfully design and create cellular models of the healthy and diseased human brain using patient specific iPSC and/or by CRISPR editing the genome in iPSC. iPSCs are the superstar among stem cells, they can be expanded unlimited, and they have the potential to differentiate to any type of cell in the body, which make them the perfect starting material for both brain model creation and for cell therapy development. Currently we cannot take full advantage of the potential of iPSC and their clinical applicability is limited due to the need for undefined conditions for iPSC cultivation, which increase the risk of immunogenicity, result in batch-to-batch variability and finite scalability. These limitations may be circumvented by xeno-free, defined culture conditions. However, biological processes that preserve robust, homogenous iPSCs in defined conditions remain to be characterized. We have compared gene expression data from over 100 iPSC cell lines cultivated in undefined and defined culture conditions. Defined culture conditions significantly reduced intra-iPSC line variability, highlighting the importance of standardization to minimize iPSC biases. This variability is concurrent with decreased germ layer differentiation and increased expression of Ca^{2+}-binding proteins. The significance of tightly controlled Ca^{2+} signaling in iPSC pluripotency in defined culture conditions was also confirmed. A deeper understanding of these processes may aid in standardizing defined iPSC culture conditions and the possibility to utilize their full potential for regenerative medicine.

Short Biography & Abstract

Ola Engkvist, Head of Molecular AI department at AstraZeneca, Professor of ML/AI Chalmers University of Technology, Trustee Cambridge Crystallographic Data Centre.

Applying AI to drug design

Ola Engkvist, AstraZeneca, Chalmers University of Technology

Abstract

Artificial Intelligence has become impactful during the last few years in chemistry and the life sciences, pushing the scientific boundaries forward as exemplified by the recent success of AlphaFold2. In this talk I will provide an overview of how AI have impacted drug design in the last few years, where we are now and what progress we can reasonably expect in the coming years. The presentation will have a focus on deep learning based molecular de novo design, however, also aspects of synthesis prediction, molecular property predictions and chemistry automation will be covered.

Short Biography & Abstract

Peter G. Schultz did his undergraduate and graduate work at the California Institute of Technology. In 1985, after postdoctoral studies at the Massachusetts Institute of Technology, he joined the faculty of the University of California at Berkeley, where he was Professor of Chemistry, Principal Investigator at Lawrence Berkeley National Laboratory and an Investigator of the Howard Hughes Medical Institute. Schultz joined the faculty of Scripps in 1999 where he is currently the Scripps Family Professor of Chemistry and President of Scripps.

Scheele award lecture: An Expanding Genetic Code

Peter Schultz, The Scripps Research Institute, USA

Abstract

The maturation of chemical synthesis during the 20th century has elevated the discipline from a largely empirical into a rational science. Recently, we have witnessed another major advance in the field in which chemists use chemical and biological “synthetic” methods together to alter the structures and properties of biological macromolecules in ways heretofore unimagined. This interdisciplinary approach to synthesis has even allowed us to expand upon the genetic code, the DNA-protein relationship that defines the characteristics of living organisms at the molecular level. In this lecture I will describe recent advances in the field and their application to chemical, molecular and cellular biology.