North American UGM & Conference 2021

Wednesday, Sep 22: Moderator: Alain Ajamian **09:00 AM - 10:15 AM**

Antibody Modeling and Protein Engineering

Freya (Klepsch) Trasischker, Senior Applications Scientist, Chemical Computing Group (AT)

Moderator: Alain Ajamian | Morning Session - Virtual Workshops

Freya Trasischker
Senior Applications Scientist, Chemical Computing Group

Protein Engineering / Protein Properties / Developability / Hot Spot Analysis / Antibody Modeling / Humanization / Molecular Surfaces The course covers approaches for structure-based antibody design and includes protein-protein interactions analysis, in silico protein engineering, affinity modeling and antibody homology modeling. The interaction of a co-crystallized antibody-antigen complex will be studied by generating and examining the molecular surfaces and visualizing protein-protein interactions in 3D and 2D. Antibody properties will be evaluated using specialized calculated protein property descriptors and analyzing protein patches. The application of protein engineering tools for homology modeling and conducting property optimization of antibodies in the context ...

Wednesday, Sep 22 **09:00 AM - 12:00 PM**

[Parallel Q&A Session] Ask Support a Question :)

Morning Session - Q&A Discussions

Wednesday, Sep 22: Moderator: Alain Ajamian **10:30 AM - 11:45 AM**

Biologics: Protein Alignments, Modeling and Docking

Will Long, Principal Scientist, Chemical Computing Group

Moderator: Alain Ajamian | Morning Session - Virtual Workshops

Will Long
Principal Scientist, Chemical Computing Group

Protein Alignments and Superposition / Loop and Linker Modeling / Homology Modeling / Protein- Protein Docking The course covers methods for aligning protein sequences, superposing structures, homology modeling fusion proteins and conducting protein-protein docking. In particular, an approach for aligning and superposing multiple structures will be described for determining structural and surface protein variations in relation to protein property modulation. A method for grafting and refining antibody CDR loops as well as using a knowledge-based approach to scFv fusion protein modeling using the MOE linker application will be described. An approach to generate homology models of a murine antigen structure ...

Wednesday, Sep 22 **12:00 PM - 01:00 PM**

Posters & Group Discussions

Poster Session

(Poster details to be added)

Wednesday, Sep 22: Chair: TBA **01:15 PM - 01:20 PM**

Opening Remarks

TBA

Chair: TBA Afternoon Session - Scientific Presentations

Wednesday, Sep 22: Chair: TBA **01:20 PM - 01:50 PM**

An Introduction to Biopharmaceutical Informatics

Sandeep Kumar, Distinguished Research Fellow (Biotherapeutics) and Group Leader, Boehringer Ingelheim

Chair: TBA Afternoon Session - Scientific Presentations

Sandeep Kumar
Distinguished Research Fellow (Biotherapeutics), Boehringer Ingelheim

In this talk I shall provide an overview of an emerging field called Biopharmaceutical Informatics Biopharmaceutical informatics calls for syncretic use of computational biophysics, standardized experiments and information technology (data, databases and learning) to make biologic drug discovery and development more efficient, faster, and affordable.

Wednesday, Sep 22: Chair: TBA **01:50 PM - 02:20 PM**

Targeting Stem Cell Pathways With Constrained Peptides

Rami N. Hannoush, Senior Principal Scientist, Group Leader, Genentech

Chair: TBA Afternoon Session - Scientific Presentations

Rami N. Hannoush
Senior Principal Scientist, Group Leader, Genentech

TBA

Wednesday, Sep 22: Chair: TBA **02:20 PM - 02:50 PM**

FLT201: An AAV Mediated Gene Therapy for Type 1 Gaucher Disease Designed to Target Difficult to Reach Tissues

Fabrizio Comper, Scientific Director, Freeline Therapeutics Limited

Chair: TBA | Afternoon Session - Scientific Presentations

Fabrizio Comper
Scientific Director, Freeline Therapeutics Limited

Background: Mutations in the GBA1 gene result in deficiency of β-Glucocerebrosidase (GCase) and cause Gaucher disease Type 1 (GD1). Enzyme replacement therapy (ERT) and substrate reduction therapy currently are standard of care for the treatment of GD1. However, significant unmet needs remain; frequent intravenous (IV) infusion is required because of the short half-life of ERTs. A liver-directed, adeno-associated virus (AAV)-mediated gene therapy may address unmet needs for GD patients by providing sustained, endogenous production of GCase following a single IV infusion. Here we report preclinical characterisation of FLT201, an investigational liver-directed AAV gene therapy for the treatment of GD1. Method: ...

Wednesday, Sep 22: Chair: TBA **02:50 PM - 03:20 PM**

Developability Assessment and Property Prediction by pH-Dependent Conformational Sampling

David Thompson, Senior Applications Scientist, Chemical Computing Group (US)

Chair: TBA | Afternoon Session - Scientific Presentations

David Thompson
Senior Applications Scientist, Chemical Computing Group

mAb candidates identified from high-throughput screening or binding affinity optimization often present liabilities for developability, such as aggregation-prone regions or poor solution behavior. In this work, we developed a method for modeling proteins and performing pH-dependent conformational sampling, which can enhance property calculations such as hydrophobic patches, charge and pI. A retrospective data analysis demonstrates that these 3D descriptors, averaged over conformational sampling and stochastic titration, can accurately predict pI values, screen candidates and enrich libraries with favorable developability properties for a range of biotherapeutics. The clinical landscape of antibodies is also analyzed and its property profile and insights thereof ...

Wednesday, Sep 22: Chair: John Gunn **03:20 PM - 03:50 PM**

Break | MOE Showcase: Antibody Structural Analysis, Developability Assessment & More

Maximilian Ebert, Scientific Services Manager, Chemical Computing Group

Chair: John Gunn | Afternoon Session - Scientific Presentations

Maximilian Ebert
Scientific Services Manager, Chemical Computing Group

Building and analysing a model for an IgG4 antibody, calculating properties and identifying aggregation prone regions
Another MOE biological modeling topic, selected from attendees' suggestions

Wednesday, Sep 22: Chair: John Gunn **03:50 PM - 04:20 PM**

Avidity Driven Bifunctionality

Bellos Hadjivassiliou, Senior Principal Scientist, Bristol-Myers Squibb

Chair: John Gunn | Afternoon Session - Scientific Presentations

Bellos Hadjivassiliou
Senior Principal Scientist, Bristol-Myers Squibb

Therapeutic antigens of interest that are also expressed on healthy tissues require a selective targeting strategy to only target the antigen on diseased tissue. This selectivity is necessary in order to minimize toxicity and to ensure good pharmacokinetic properties. We have developed a detuning strategy to engineer bispecifics that selectively bind to a ubiquitously expressed effector antigen on target cells. We used a crystal structure of the effector antigen bound to a high affinity Fab to guide the construction of an in silico library of Fab variants predicted to have a range of lower affinities, good stability, and low immunogenicity. ...

Wednesday, Sep 22: Chair: John Gunn **04:20 PM - 04:50 PM**

Predicting Antibody Developability Profiles Through Early Stage Discovery Screening

Essam Metwally, Principal Scientist, Merck Research Labs

Chair: John Gunn | Afternoon Session - Scientific Presentations

Essam Metwally
Principal Scientist, Merck Research Labs

Monoclonal antibodies play an increasingly important role for the development of new drugs across multiple therapy areas. The term ‘developability’ encompasses the feasibility of molecules to successfully progress from discovery to development via evaluation of their physicochemical properties. These properties include the tendency for self-interaction and aggregation, thermal stability, colloidal stability, and optimization of their properties through sequence engineering. Selection of the best antibody molecule based on biological function, efficacy, safety, and developability allows for a streamlined and successful CMC phase. An efficient and practical high-throughput developability workflow (100 s-1,000 s of molecules) implemented during early antibody generation and screening ...

Wednesday, Sep 22: Chair: John Gunn **04:50 PM - 05:20 PM**

Predictive Process Development: A Computational Biophysics and Machine Learning Strategy

Francis Insaidoo, Associate Principal Scientist, Merck & Co., Inc.

Chair: John Gunn | Afternoon Session - Scientific Presentations

Francis Insaidoo
Associate Principal Scientist, Merck & Co., Inc.

A large and diverse set of data is critical for most predictive algorithms. For biologics and specifically with regards to monoclonal antibody, there is a limited set of data that can be leveraged for a robust predictive algorithm. Irrespective of the absence of predictive tools, there is significant success in the development of monoclonal antibodies. Yet, as the type of molecules in discovery change and new modalities are exploited to discover and develop novel biotherapeutics, the current platform for biologics development will be challenged. The development of predictive algorithms based on first principles that is modality agnostic would be beneficial. ...

Wednesday, Sep 22 **05:20 PM - 05:30 PM**

Closing Remarks

Chris Williams, Director of Scientific Support, Principal Scientist, Chemical Computing Group

Afternoon Session - Scientific Presentations

Wednesday, Sep 22 **05:30 PM - 06:30 PM**

Social Interactions | Further Discussions

(Bring Your Own Beverage)

Thursday, Sep 23: Moderator: Alain Ajamian **09:00 AM - 10:15 AM**

Small Molecule Virtual Screening

Sarah Witzke, Applications Scientist, Chemical Computing Group

Moderator: Alain Ajamian | Morning Session - Virtual Workshops

Sarah Witzke
Applications Scientist, Chemical Computing Group

MOE Databases / Descriptors / Fingerprints / QSPR Modeling / Pharmacophore Modeling / Template-Forced Docking / Scaffold Replacement / MedChem Transformations The course covers the suite of MOE applications which can be applied to small-molecule virtual screening. Topics include the preparation of small molecule databases for virtual screening, filtering databases based on substructure matching and property values, building QSAR/QSPR models and fingerprint similarity models as database filters, pharmacophore query creation and searching, and small-molecule docking. These tools are used in conjunction to present a complete virtual screening workflow. The creation of de novo structures using the MOE Scaffold Replacement and ...

Thursday, Sep 23 **09:00 AM - 12:00 PM**

[Parallel Q&A Session] Ask Support a Question :)

Morning Session - Q&A Discussions

Thursday, Sep 23: Moderator: Alain Ajamian **10:30 AM - 11:45 AM**

Advanced Structure-Based Drug Design

Nadia (Huifang) Li, Applications Scientist, Chemical Computing Group

Moderator: Alain Ajamian | Morning Session - Virtual Workshops

Nadia (Huifang) Li
Applications Scientist, Chemical Computing Group

Pharmacophore Modeling / Docking / Fragment-based Design / Scaffold Replacement / R-Group Screening / Project Search / Protein-Ligand Interaction Fingerprints The course describes advanced SBDD workflows in drug discovery projects and encompasses a range of topics from pharmacophore query generation to protein-ligand interaction fingerprints. More specifically, the course will cover the application of pharmacophores in the context of protein-ligand docking, scaffold replacement and R-group screening. A method for querying a 3D project database will also be presented along with the generation and analysis of protein- ligand interaction fingerprints (PLIF).

Thursday, Sep 23 **12:00 PM - 01:00 PM**

Posters & Group Discussions

Poster Session

(Poster details to be added)

Thursday, Sep 23: Chair: Alain Deschenes **01:15 PM - 01:20 PM**

Opening Remarks

Alain Deschenes, Vice President, Chemical Computing Group

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Thursday, Sep 23: Chair: Alain Deschenes **01:20 PM - 01:50 PM**

Artificial Intelligence in Drug Discovery – Revolution, Evolution, or Complete Nonsense

Pat Walters, Senior Vice President Computation, Relay Therapeutics

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Pat Walters
Senior Vice President Computation, Relay Therapeutics

Many have claimed that Artificial Intelligence (AI) will bring about a revolution in drug discovery and development, while others have argued that we are reaching the zenith of a hype cycle that will lead to a period of disillusionment. As is often the case, the truth lies somewhere between these extremes. This presentation will focus on areas where AI is having a real impact on drug discovery and highlight factors that are necessary to increase its utility.

Thursday, Sep 23: Chair: Alain Deschenes **01:50 PM - 02:20 PM**

Discovery of a TRPA1 Clinical Candidate for the Treatment of Asthma

Huifen Chen, Senior Principal Scientist, Genentech

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Huifen Chen
Senior Principal Scientist, Genentech

Transient Receptor Potential Ankyrin 1 (TRPA1) is a non-selective cation channel expressed in sensory neurons where it functions as an irritant sensor for a plethora of electrophilic compounds and is implicated in pain, itch, and asthma. To study its function in various disease contexts, we sought to identify novel, potent and selective small molecule TRPA1 antagonists. Due to the lack of TRPA1-ligand complex structures for structure-based design, we relied heavily on ligand-based modeling and data analysis to guide the design and optimization of TRPA1 antagonists. In this presentation I am going to highlight the challenges, opportunities and lessons learned in ...

Thursday, Sep 23: Chair: Alain Deschenes **02:20 PM - 02:50 PM**

A Small-Molecule Inhibitor of C5 Complement Protein

Keith Jendza, Scientific Technical Leader I, Novartis

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Keith Jendza
Scientific Technical Leader I, Novartis

The complement pathway is an important part of the immune system, and uncontrolled activation is implicated in many diseases. The human complement component 5 protein (C5) is a validated drug target within the complement pathway, as an anti-C5 antibody (Soliris) is an approved therapy for paroxysmal nocturnal hemoglobinuria. Here, we report the identification, optimization and mechanism of action for the first small-molecule inhibitor of C5 complement protein.

Thursday, Sep 23: Chair: Alain Deschenes **02:50 PM - 03:20 PM**

Modeling PROTAC-Mediated Targeted Protein Degradation: Case Studies and Recent Developments

Mike Drummond, Scientific Applications Manager, Chemical Computing Group

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Mike Drummond
Scientific Applications Manager, Chemical Computing Group

Targeted protein degradation using bivalent small molecules (such as PROTACs) is a new modality that provides a means to control protein levels in vivo. Despite many clear advantages, numerous challenges exist in PROTAC development, particularly concerning the rational design of efficacious molecules. In this presentation, multiple computational methods that enable the a priori evaluation of putative PROTAC molecules will be discussed. Numerous case studies will be offered, where the application of these computational tools can successfully recommend not only potent PROTAC candidates, but also molecules to avoid. Results from scenarios across different target proteins, E3 ligases, and PROTAC architectures will ...

Thursday, Sep 23: Chair: Alain Deschenes **03:20 PM - 03:50 PM**

Break | MOE Showcase: Data Mining for Medicinal Chemists, High Throughput Docking & More

Maximilian Ebert, Scientific Services Manager, Chemical Computing Group

Chair: Alain Deschenes | Afternoon Session - Scientific Presentations

Maximilian Ebert
Scientific Services Manager, Chemical Computing Group

MOEsaic for mining project activity data and guiding development pathways High Throughput Docking for virtual screening Another MOE small molecule modeling topic, selected from attendees' suggestions

Thursday, Sep 23: Chair: Chris Williams **03:50 PM - 04:20 PM**

Computational Protocols for Modeling Induced Proximity Degrader Ternary Structures

Huan Rui, Senior Scientist, Amgen

Chair: Chris Williams | Afternoon Session - Scientific Presentations

Huan Rui
Senior Scientist, Amgen

A targeted protein degrader (TPD) is a molecule that induces degradation of a target protein leveraging the E3 ligase protein degradation pathway. It contains two moieties connected by a linker. One moiety binds to the target protein and the other binds to an E3 ubiquitin ligase, the role of which is to tag proteins with ubiquitin and flag them down for degradation. The two are linked by a linker. This architecture of TPD allows it to bring target proteins into close proximity of the E3 ligase, increasing their local concentration and therefore allowing targeted degradation. This mechanism makes TPD an ...

Thursday, Sep 23: Chair: Chris Williams **04:20 PM - 04:50 PM**

Modeling the E3-Target Protein Ternary Complex: Application to the Generation of Novel Degraders

Theresa Johnson, Associate Scientific Director, EMD Serono

Chair: Chris Williams | Afternoon Session - Scientific Presentations

Theresa Johnson
Associate Scientific Director, EMD Serono

Use of protein degraders (such as PROTACs -Proteolytic targeting chimeras) to selectively degrade desirable targets has rapidly emerged as a novel therapeutic to add to the arsenal of large and small pharmaceutical companies. To aid the development of these novel molecules, new technologies in structure-based drug design are required. As these degraders are relatively large small molecules which engage two protein targets at the same time, new application of traditional structure-based drug design is required. Using multiple protein-protein docking techniques, we have identified possible binding modes for multiple degrader molecules against several targets. Acknowledging that the initially identified degraders are ...

Thursday, Sep 23: Chair: Chris Williams **04:50 PM - 05:20 PM**

Developing Free Energy Techniques to Help Guide Pharmaceutical Lead Optimization

David Mobley, Professor, Pharmaceutical Sciences and Chemistry, UC Irvine

Chair: Chris Williams | Afternoon Session - Scientific Presentations

David Mobley
Professor, Pharmaceutical Sciences and Chemistry, UC Irvine

I will discuss work in my group on developing alchemical free energy techniques for application in guiding pharmaceutical lead optimization. A key focus will be on lessons learned. In addition to discussing relative and absolute binding free energy techniques, I will also discuss newer work in the group on methods relating to enhanced sampling of ligand binding modes, and nonequilibrium binding free energy calculations. I'll also briefly highlight some of the work going on in the Open Force Field Initiative, and show results from benchmarks with OpenFF force fields.

Thursday, Sep 23 **05:20 PM - 05:30 PM**

Closing Remarks

Anna Lin, Research Group Leader, Chemical Computing Group

Afternoon Session - Scientific Presentations

Thursday, Sep 23 **05:30 PM - 06:30 PM**

Social Interactions | Further Discussions

(Bring Your Own Beverage)