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ICM User Group Meeting 2018

San Diego, CA November 8-9.

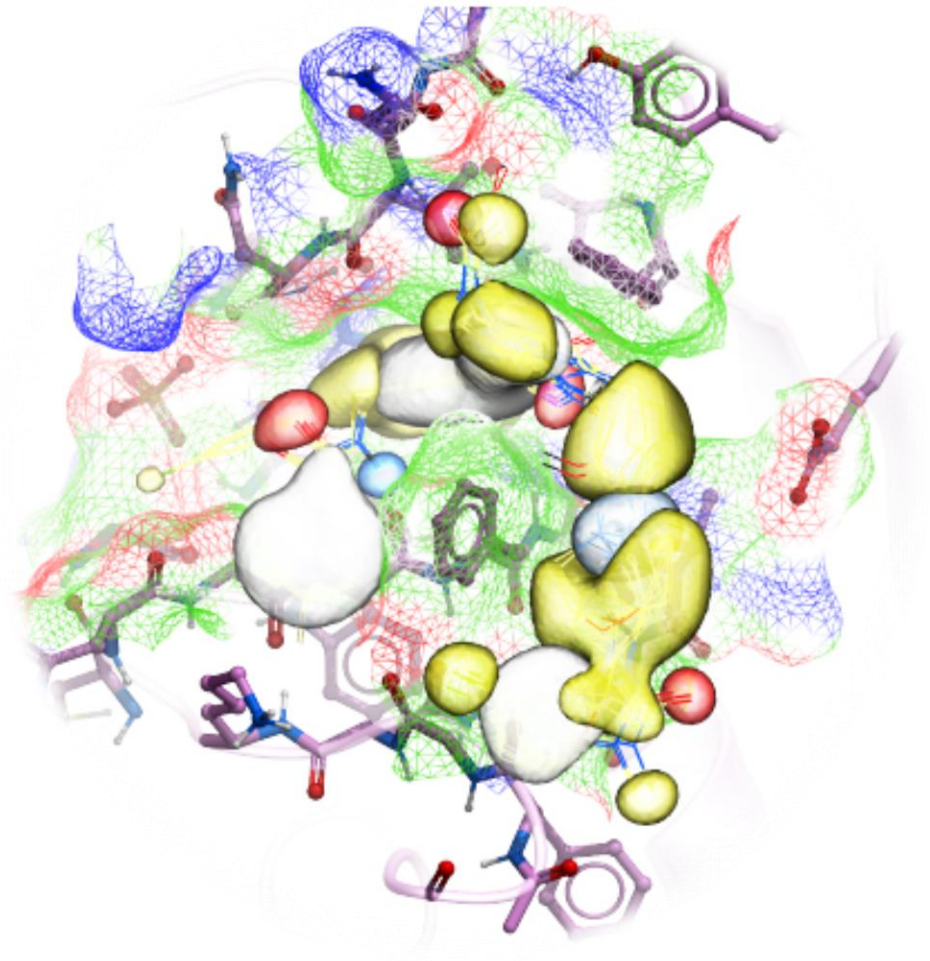

Image taken from Lam *et al* (2018) JCAMD – Structure/Ligand-based Docking
ICM Ranked 1st Place for Ligand Docking Accuracy and Affinity Prediction – D3R Grand Challenge 3

Message to Meeting Participants

We would like to welcome all of you to the 2018 ICM User Group Meeting (UGM) and we hope that it will be an enjoyable and informative experience. Thank you to all our UGM speakers! We have speakers from all over the world who will be presenting on a wide range of subjects. We have speaker sessions on Protein Structure Analysis, RNA Drug Discovery, Modeling of Membrane Proteins, Latest ICM Developments, Structure-Based Drug Design, Chemical Biology and Cheminformatics, ICM for Teaching and Communication, Protein-Protein Docking, and Lead Discovery. All the speakers are to some extent users of the ICM software, so we are looking forward to hearing how they put ICM and other Molsoft applications to good use in their research.

In addition to the presentations, we have a number of events scheduled throughout Thursday and Friday. The events are designed to provide opportunities to interact and exchange ideas as well as chances to speak to the speakers and MolSoft's scientists and developers about their areas of expertise. Most of these events include some element of food, refreshments, and exercise - we hope you can join us!

Extracurricular Events

Thursday Lunchtime at Torrey Pines Beach. Have lunch and take the opportunity to swim at the beach or hike the trails at the Torrey Pines State Reserve.

Friday Lunchtime at La Jolla Shores – Salad and Pizza at the beach with volleyball and swimming.

Friday Evening: Wine and Cheese reception at MolSoft.

Thank you for participating.

MolSoft User Group Meeting Organization Committee

MolSoft LLC
11199 Sorrento Valley Road, S209
San Diego
CA 92121
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THURSDAY 8th Nov

8:30 – 9:00 Meeting registration.

LATEST ICM DEVELOPMENTS

9:00 - 9:25 **Prof. Ruben Abagyan, Ph.D.**

Professor, University of California San Diego, and MolSoft Founder

"Internal Coordinate Mechanics: new ideas and new applications."

9:25 - 9:50 **Maxim Totrov, Ph.D.**

Principal Scientist MolSoft LLC

Keynote Speaker

9:50 – 10:15 **John Van Drie Ph.D.**

Van Drie Research LLC

"The use of virtual screening in the discovery of the first drug-like inhibitors of histone acyltransferases."

10:15 - 10:30 **Break** - Refreshments provided by MolSoft

RNA Drug Design

10:30 – 10:55 **Christine Hajdin Ph.D.**

Associate Director of Screening and Computational Sciences, Ribometrix

"Utilizing computational methods to understand the principles for drugging RNA with small molecules."

10:55 -11:20 **Sarah Sirin Ph.D.**

Computational Chemist, Arrakis Therapeutics

"Targeting RNA with Small Molecules."

Membrane Proteins – Molecular Modeling and Drug Design

11:20 - 11:45 **Irina Kufareva Ph.D.**

Associate Adjunct Professor, UCSD

"Experiment-guided modeling to understand CXC chemokine receptor signaling"

11:45 - 2:25 **Lunch provided by MolSoft at Torrey Pines State Beach**

Eat, hike and swim. (Weather permitting)

2:25 – 2:50 **Vsevolod "Seva" Katritch, Ph.D.**

Assistant Professor USC

"Structure based virtual ligand screening and design for new GPCR probes"

2:50 – 3:15 **Wilnelly Martinez Ortiz**

PhD Student, NYU

"Contact Area defines scoring function and modeling restraints for Voltage-Gated Ion Channels."

3:15 - 3:40 **Olga Lavinda Ph.D.**

NIH NRSA Postdoctoral Fellow at NYU Langone

"Treat Me Covalently" – New Tools to Improve Covalent Drug Design For Advancement Of Cancer Treatments"

3:40 – 3:50 **Break** – Refreshments provided by MolSoft

Antibacterial Drug Design

3:50 - 4:15 **Shozeb Haider Ph.D.**

Excellence Fellow in Computational Medicinal Chemistry, UCL

"Identifying allosteric sites in β-lactamases."

4:15 – 4:40 **Trevor Zandi**

PhD Student at The Johns Hopkins University

"Modeling mycobacterial L,D-transpeptidases: Insights into antibacterial design"

ROUND TABLE DISCUSSION

4:40 – 5:05 **Q&A Session with MolSoft's Developers and Scientists.**

FRIDAY 9th November

LATEST ICM DEVELOPMENTS

9:00 - 9:25 **Eugene Raush**

Principal Developer, MolSoft LLC

"New Features in the Latest Release of ICM"

9:25 - 9:50 **David Damerell Ph.D.**

Structural Genomics Consortium

"SCARAB – Data Capture, Integrator and Minor" Presented Online

Keynote Speaker

9:50 – 10:15 **Michael Sundström Ph.D.**

Scientific Director, SGC - Karolinska University Hospital and Karolinska Institutet

"Data capture and management in pre-clinical research: From hypothesis to target-disease association."

10:15 - 10:30 **Break** - Refreshments provided by MolSoft

Protein Modeling and Structure-Based Drug Design (Part 1)

10:30 – 10:55 **Lutz Tautz Ph.D.**

Research Associate Professor at Sanford Burnham Prebys Medical Discovery Institute

"Allosteric Inhibitors of the SHP2 Phosphatase as Novel Cancer Therapeutics"

10:55 -11:20 **Matthieu Schapira Ph.D.**

Principal Investigator, SGC Toronto

"Systematic analysis of atomic protein-ligand interactions in the PDB"

11:20 - 11:45 **William Bisson Ph.D.**

Assistant Professor, Oregon State University

"Computational Chemical Genomics in Precision Cancer Medicine: Recent Applications"

11:45 - 2:30 **Lunch provided by MolSoft at Torrey Pines State Beach** Eat, hike and swim. (Weather permitting)

ICM in Education

2:30 – 2:55 **Charles Grisham, Ph.D.**

Professor of Chemistry, University of Virginia

"*PSAFE: A Free Online Project for Teaching Macromolecular Structure-Function Relationships to Undergraduate Students with Molsoft ICM BrowserPro*"

Protein Modeling and Structure-Based Drug Design (Part 2)

2:55 – 3:20 **Lea Lough Ph.D.**

Research Assistant at New York University School of Medicine

"Targeting the Amino Acid Response Pathway in Leukemia"

3:20 - 3:45 **Hariprasad Vankayalapati Ph.D.**

Arrien Pharmaceuticals & TGen

"Computational Approaches to Small Molecule Immunotherapeutics"

3:45 – 4:10 ***Ruben Abagyan Ph.D.***

Professor, University of California San Diego, and MolSoft Founder

"ICM Future Directions – Round Table Discussion"

4:10 – **Wine and cheese reception at MolSoft**

Schedule is Subject to Change

Abstracts and Speaker Bios

Ruben Abagyan, Ph.D.

Professor, University of California San Diego & MolSoft Founder

"Internal Coordinate Mechanics: new ideas and new applications."

Abstract
An overview of the main ideas, directions, benchmarks and challenges.

Biography Dr. Ruben Abagyan is a Professor in the Skaggs School of Pharmacy at the University of California, San Diego, which he joined in 2009. He received his Ph.D. in molecular modeling and biophysics from the Moscow State University. At the European Molecular Biology Laboratory in Heidelberg, Germany, he completed the first version of internal coordinate mechanics program (ICM), its global optimization engine and its scripting language, which was followed by the next, C-version, of ICM co-developed with Max Totrov. He co-founded Molsoft in mid-nineties. He has written and contributed to over 200 papers and book chapters, received an Excellence Award from the UCSD School of Pharmacy, two CapCure awards, and the Princess Diana medal in Australia.

Maxim Totrov, Ph.D.

Principal Scientist MolSoft LLC

Biography Maxim Totrov is the Principal Scientist at Molsoft LLC, La Jolla, CA. His areas of research include computer-assisted drug design (CADD) with a focus on the development and application of protein– ligand and protein–protein docking methods; biophysics of protein–ligand interactions and binding affinity prediction; protein-structure analysis, visualization and modelling. In 2001, after postdoctoral studies at The Scripps Research Institute, Dr. Totrov joined Molsoft. Dr. Totrov began working with Ruben Abagyan in the early 90‟s to extend and rewrite many parts of the internal coordinate mechanics (ICM) code, which formed the basis of the current version of ICM.

John Van Drie Ph.D.

President, Van Drie Research LLC

"The use of virtual screening in the discovery of the first drug-like inhibitors of histone acyltransferases."

Abstract Many cancer drugs target histone deacetylases (HDAC's), but drugs which target the reverse process – histone acetylation – have long been sought. The discovery of the first drug-like inhibitors of p300 HAT was recently reported by Abbvie and Acylin [Lasko et al, Nature, 2017; Michaelides et al, ACS Med Chem Lett], which began with chemical matter discovered by virtual screening. In this talk, I describe how normal mode analysis and Monte Carlo loop modeling applied to the public Xray structure were used to predict an alternate possible protein conformation, to direct a virtual screen, which identified two distinct molecules, one of which led to the advanced candidate A-465.

Biography John H Van Drie is a veteran drug-hunter, with over 30 years experience in drug discovery, at Novartis, Vertex, and Pharmacia (originally Upjohn). He is currently President of Van Drie Research, a

company he founded in 2007, to provide in silico services and advice to drug discovery organizations, mainly biotechs working on small-molecule drugs. He has contributed to the discovery of HIV-protease inhibitors, oxazolidinone antibiotics, Hepatitic C protease inhibitors, and Cystic Fibrosis protein-folding correctors. He was trained as a theoretical chemist at Caltech, studying molecular quantum mechanics with W. A. Goddard, and also studied as a BAEF Fellow in the lab of I. Prigogine at the Univ. Libre de Bruxelles. He was Chair of the Gordon Conference on Computer-Aided Drug Design in 2003, and was one of the founders of BioCAD (later part of Accelrys), developers of the Catalyst software for drug design.

Christine Hajdin Ph.D.

Associate Director of Screening and Computational Sciences, Ribometrix

"Utilizing computational methods to understand the principles for drugging RNA with small molecules."

Abstract RNA molecules are essential for cellular information transfer and gene regulation, and RNAs have been implicated in many human diseases. Messenger and non-coding RNAs contain highly structured elements, and evidence suggests that many of these structures are important for function. Targeting these RNAs with small molecules offers opportunities to therapeutically modulate numerous cellular processes, including those linked to 'undruggable' protein targets. However, identifying which RNA and regions within them to target has been a long standing challenge. This talk will discuss principles for recognizing targetable regions of the RNA and the correlations between these targetable regions and the drug like properties of the small molecules that bind them.

Biography Christine Hajdin, an expert in RNA structure and chemoinformatics, is the AD of Screening and Computational Sciences at Ribometrix. Christine earned her PhD at the University of North Carolina at Chapel Hill with Kevin Weeks in 2013. After graduation, she worked as a data scientist at Explorys, now IBM Watson Health Care, and then as an Investigator at Novartis. Christine has worked across disease areas and throughout the drug discovery pipeline performing target ID, library selection and compound optimization. She now oversees the informatics and screening teams at Ribometrix.

Sarah Sirin Ph.D.

Computational Chemist, Arrakis Therapeutics

"Targeting RNA with Small Molecules."

Abstract This presentation will give a general overview of targeting RNA using small molecules and present structural analysis of RNA binders. I will present insights from ligand based virtual screen benchmarks and illustrate how we are using virtual screening to advance projects. Lastly, I'll present our Molcart implementations and illustrate how we are using ICM tools lower the barrier for querying structure activity relationships and enhance collaborations.

Biography Sarah Sirin is a computational chemist at Arrakis Therapeutics, a biopharmaceutical company pioneering the discovery of small-molecule medicines that directly bind and modify the biological function of RNA to treat disease. Prior to joining Arrakis, she was at AbbVie, where she used structure-based design to advance small molecules, antibody drug conjugates, and biologics projects. She has extensive background in structure-based design, computational chemistry, and informatics. She completed postdocs at MIT and Schrodinger and received her doctorate from NYU School of Medicine.

Irina Kufareva Ph.D.

Associate Adjunct Professor, UCSD

"Experiment-guided modeling to understand CXC chemokine receptor signaling"

Abstract Chemokine receptors are key drivers of cell migration in physiology and disease. Their interaction network is remarkably complex, with many chemokines targeting multiple receptors and triggering different, often biased downstream responses. Structural principles of receptor agonism, selectivity and bias were partially revealed by the recently crystallized receptor-chemokine complexes; however, these structures remain incomplete and no structures yet exist for CXC subfamily complexes. Using experiment-guided molecular modeling in ICM, we revealed the principles of ligand interaction and activation in two receptors of the CXC family: a canonical GPCR CXCR4 and an atypical receptor ACKR3. These receptors, together with their mutual endogenous chemokine ligand CXCL12, drive tumor progression and metastasis in a broad variety of cancers.

Biography Dr. Kufareva received a Master of Science in Mathematics and a Ph.D. in Computer Science in 1994 and 1999, respectively, both from Tomsk State University, Russia, where she went on to serve as a faculty for 2 years prior to moving to the USA. Between 2004 and 2009, she trained in computational biology as a research associate with Ruben Abagyan's group at the Scripps Research Institute, La Jolla. In 2009, she was employed by the UCSD Skaggs School of Pharmacy and began growing her independent research program. She became an Associate Adjunct Professor in 2018. The goal of her lab is to elucidate the structural, molecular, and architectural principles of cell signaling by combining computational predictions with experimental validation. Dr. Kufareva has co-authored over 60 papers, reviews and book chapters, leading to her international recognition as an expert in the field of molecular modeling and computational structural biology.

Vsevolod "Seva" Katritch, Ph.D.

Assistant Professor USC

"Structure based virtual ligand screening and design for new GPCR probes"

Biography Dr. Seva Katritch received his Ph.D from Moscow Institute of Physics and Technology, followed by postdoctoral training at Rutgers University and Scripps Research Institute, a stint in a biotechnology startup and a faculty position at the University of California, San Diego.
His current group at UCS is focused on deciphering molecular mechanisms of G protein-coupled receptors (GPCRs) and on using this knowledge to discover ligands and tool compounds with new functional properties.

Wilnelly Martinez Ortiz PhD

Student, NYU

"Contact Area defines scoring function and modeling restraints for Voltage-Gated Ion Channels."

Abstract The super resolution revolution has recently and rapidly catapulted cryo-electron microscopy (cryoEM) to the forefront of state-of-the-art structure determination techniques, given its capacity to routinely achieve atomic or near atomic 3D structures of complex macromolecules such as voltage-gated ion channels (VGIC). Recently, several VGIC's have been resolved at near atomic resolution by single-particle non-crystalline cryoEM. Despite the numerous tools available to determine the relative resolution

and overall model fitness to raw experimental data, to-date, there are no tools capable of assessing the quality of the residue assignment in the resultant structural models. To address this void a bioinformatics metric and method has been developed, which scores the accuracy of 3D models of the pore-forming subunit of the VGIC's based on the preservation of evolutionarily conserved functional contacts within the voltage-sensing-domain (VSD) structural fold. The metric calculates the contact area of a VSD conserved motif to rapidly assess the accuracy of all reported VGIC structures independent of the source of the raw data, allowing its use for comparison of cryo-EM and X-ray crystal structures. The use of the metric to unambiguously reveal subtle molecular modeling errors in VGIC-VSD models and to define modeling constraints capable of refining VGIC near-atomic cryoEM data to atomic resolution will be discussed.

Biography Wilnelly Martinez-Ortiz is a trained chemist and computational protein modeler, with a Bachelors degree in Chemistry from the University of Puerto Rico and a Masters degree in Molecular Pharmacology and Biophysics from NYU. She worked with Dr. Ming-Ming Zhou performing de-novo organic synthesis and with Dr. James Gallo in PK/PD compound profiling during her tenure in Mount Sinai's PREP program. And is currently completing her PhD at NYU in Dr. Timothy Cardozo's lab, where her research has focused on computational molecular modeling of complex protein structures.

Olga Lavinda Ph.D.

NIH NRSA Postdoctoral Fellow at NYU Langone

"Treat Me Covalently" – New Tools to Improve Covalent Drug Design For Advancement Of Cancer Treatments"

Abstract Covalent inhibitors (CIs) are a special class of medicinal compounds that are capable of forming covalent bonds within the target-binding pocket resulting in potent inhibitory action. Even though 26% of marketed drugs have covalent mechanisms of action, the majority of them were discovered by chance. CIs offer significant advantages over conventional therapeutics: a covalent bond is irreversibly formed between a drug molecule and a binding pocket. The benefits of completely neutralizing the target protein include increased duration of inhibition, decreased dosing, and safeguarding against drug resistance. In addition, CIs possess enormous potential to become the solution for "undruggable" targets due to their selectivity and specificity for the target.

While highly beneficial, the mechanism of discovering and designing covalent drug prototypes can be challenging. The evaluation of previous work done in the field of covalent drug design, and current software tools utilizing many complex algorithms, suggest an error in more than 40% cases of prediction of covalently bonding drugs. In our work we aim to investigate the complex mechanism of covalent bonding among different molecules and their targets. Specifically, we investigate the covalent bonding mechanism and fundamental aspects of the reaction steps that are unique from other drug approaches, and look at how these unique features can be used to our advantage in drug design. Our findings demonstrate that proper assessment of pre-binding non-covalent features can improve identification of covalent inhibitors and scoring.

Biography Dr. Olga Lavinda is a NIH-NRSA Post-Doctoral fellow at the Department of Biochemistry and Pharmacology at NYU Langone School of Medicine in New York, where she has been employed since 2016. Dr. Lavinda currently collaborates with the O. Perlman Department of Dermatology, where she leads drug discovery efforts in the specialized fields of oral cavity squamous cell carcinoma and pigmentation disorders. She received her PhD in organic synthesis and computational chemistry from Biomedical

Chemistry Institute at New York University, where she refined her skills in applying interdisciplinary methodologies to intractable scientific questions. Her current work with pigmentation focuses on structure-based drug discovery and homology modeling, which has led to the discovery of several promising molecules that can restore pigmentation in OCA2-null cells. Her primary scholarship area lies in the development of methods to improve ligand-receptor scoring for covalent inhibitor screening, and application of these methods to find cure for the treatment of oral cancer. She is particularly interested in exploring covalent warheads with unusual reactivity that can be used to target sites devoid of traditional reactive residues, such as cysteine or serine. Dr. Lavinda is passionate about integrating her organic chemistry background with computational drug discovery to provide unique insight and experimental methodologies for the clinical community.

Shozeb Haider Ph.D.

Excellence Fellow in Computational Medicinal Chemistry, UCL

"Identifying allosteric sites in ß-lactamases."

Abstract The presence of ß-lactamases (e.g., PDC-3) that have naturally evolved and acquired the ability to break down ß-lactam antibiotics (e.g., ceftazidime and ceftolozane) leads to highly resistant and potentially lethal *Pseudomonas aeruginosa* infections. We show that wild-type PDC-3 ß-lactamase forms an acyl enzyme complex with ceftazidime, but cannot accommodate the similar but larger ceftolozane due to a specific structural moiety (R2 side chain). A single amino acid substitution from a glutamate to a lysine at position 221 in PDC-3 (E221K) causes the tyrosine residue at 223 to adopt a new position poised for efficient hydrolysis of both cephalosporins. The importance of the mechanism of action of the E221K variant, in particular, is underscored by its evolutionary recurrences in multiple bacterial species. Understanding the biochemical and molecular basis for resistance is key to designing effective therapies and developing new ß-lactam/ß-lactamase inhibitor combinations.

Biography Dr Shozeb Haider is a Associate Professor in Computational Chemistry and the Drug Discovery lead at UCL School of Pharmacy, London. His research focuses on using Computational methods to study Anti-Microbial Resistance, G-quadruplex complexes, protein-nucleic acid and protein-protein interactions. He is also a Fellow of the Royal Society of Chemistry.

Trevor Zandi PhD

Student at The Johns Hopkins University

"Modeling mycobacterial L,D-transpeptidases: Insights into antibacterial design"

Abstract Biosynthesis of the peptidoglycan portion of the bacterial cell-wall is a major target of antibiotics. Notable among these antibiotics are the beta-lactam inhibitors of peptidoglycan cross-linking, which include penicillin. The chemical composition of the peptidoglycan layer varies between and within bacterial species. Uncovering the chemical and structural features governing enzymatic cross-linking of these diverse peptidoglycan in mycobacteria, a species wherein the majority of peptidoglycan cross-links are generated by an evolutionarily and mechanistically distinct family of enzymes, L,D transpeptidases, can assist in the design of next-generation beta-lactam antibiotics. Penems and carbapenems are the only sub-classes of beta-lactams known to inhibit L,D transpeptidases and possess anti-mycobacterial activity. The design of penem drugs in the Townsend lab is currently guided by known bactericidal penems, the structure of the

mycobacterial peptidoglycan, and covalent docking against crystal structures/homology models of L,D transpeptidase enzymes

Biography Trevor Zandi is a PhD candidate in the Program in Molecular Biophysics and George E. Owens Fellow at Johns Hopkins University under the supervision of Professor Craig Townsend. His research involves drug design and synthesis, informed by the chemical and structural basis of enzyme-substrate recognition. He was trained in structural bioinformatics in the lab of Professor Ruben Abagyan at UC San Diego, where he received a B.S. in computer science with a specialization in bioinformatics.

Eugene Raush

Principal Developer, MolSoft LLC

"New Features in the Latest Release of ICM"

Biography Education: MS in Computer Science and Applied Math from Tomsk State University 1994 Eugene Raush began working with Ruben Abagyan in late 90's. He is principal Software Engineer at Molsoft since 2002.

David Damerell Ph.D.

Structural Genomics Consortium

"SCARAB – Data Capture, Integrator and Minor" Presented Online

Abstract David will give a detailed overview of the ICM-Scarab ELN/LIMS product which is the result of a long-standing collaboration between the SGC and Molsoft which dates back to the founding of the SGC. ICM-Scarab has been purposely designed to bridge the world between ELN and LIMS and also to make it easy to integrate and mine data held in distinct databases. As well as directly integrating experiment write-up with the other Molsoft ICM technologies. Much of the talk will focus on the new web-based version of ICM-Scarab.

Biography David is the senior informatician at the Structural Genomics Consortium's Oxford University site, with a keen interest in developing tools and data management solutions to simplify the capture, mining, and reporting of SGC output.

Michael Sundström Ph.D.

Scientific Director, SGC - Karolinska University Hospital and Karolinska Institutet

"Data capture and management in pre-clinical research: From hypothesis to target-disease association."

Abstract Preclinical studies with conventional models of disease often fail to translate into clinical realities. This holds true for most therapeutic areas, ranging from anti-infectives to oncology. In addition, the path from discovery to clinical trials and ultimately approval is long. For example, a recent analysis of the history of first-in-class kinase inhibitors revealed that often more than a decade transpired between the first published conclusive target-disease association and the initiation of clinical studies. This delay occurred despite the fact that clinical success rates for kinase inhibitors and other targeted therapies are higher compared to classical small-molecule medicines. One of the reasons for this is likely that multiple sources of data from multiple research groups need to over time provide converging and supporting disease-link evidence before industry is convinced of embarking on costly drug discovery and development programmes. However, there are also examples where the use of disease models based on patient cells have provided the necessary and supporting validation data. For example, anti-TNF therapy for rheumatoid

arthritis was developed with significant support from data using synovial cell samples from patients, enabled by the development and optimization of new more advanced cell culture conditions. Thus, applying specific and high-quality probes as small molecules or antibodies to patient-derived test systems, holds an enormous potential for target discovery and interrogation.

However, patient samples are not always easily obtainable, involves direct collaboration with hospitals and clinicians, and also requires the cooperation and consent from the patients themselves. In addition, samples are of limited size or volume, remain in a near native state for short time, and often do not constitute the foundation for the generation of a renewable resource such as stem cells and organoids. In addition, there is significant variability between donors/patients, which combined with the relatively low number of patient samples normally available, results in observed trends rather than rigid statistical significance of effect. Hence, regular access to samples from multiple patients is required to allow sufficient amounts of data to be generated and analysed.

The talk will provide an overview of our hospital and patient-based collaborations have been organized, preliminary results will be presented and a general outline provided on how the generated data and results from these precious cell sources is managed and analysed.

References Preclinical target validation using patient-derived cells. Edwards AM, Arrowsmith CH, Bountra C, Bunnage ME, Feldmann M, Knight JC, Patel DD, Prinos P, Taylor MD and **Sundström** M. Nature Reviews Drug Discovery. 2015 Mar;14(3):149-50

Knapp S, Sundström M. Recently targeted kinases and their inhibitors—the path to clinical trials. Current Opinion in Pharmacology. 2014;17:58-63.

Biography Michael Sundstrom received his PhD from Uppsala, followed by PostDoctoral studies at the Karolinska Institutet. From 1993-2000 he was at Pharmacia as Director for structure-based drug design and oncology R&D portfolio management, mainly focused on the development of kinase inhibitors. Between 2001 and 2003 he held senior positions at the Swedish Biotech's Actar and Biovitrum. In 2003, he joined the Structural Genomics Consortium (SGC) at the University of Oxford, as Chief Scientist, where efforts were focused on structure-function relationships for metabolic enzymes, integral membrane proteins and protein kinases. His team at Oxford has since been the largest contributor worldwide of 3D-structures for these protein families. In 2007 he assumed the position as Managing Director for the Novo Nordisk Foundation Center for Protein Research (Copenhagen), with main research areas covered were protein production and characterization, proteomics and systems biology. From end of 2011, he was VP Discovery Research at Karolinska Development in Stockholm, mainly working with in-licensing of pre-clinical research projects. He then re-joined the SGC since mid-2014 as Scientific Director, with primary focus on leading its IMI funded ULTRA-DD project and the SGC Tissue Platforms; focused on target definition and validation in oncology, neurodegenerative and inflammatory diseases. He is since 2007 adjunct Professor at the University of Aalborg (DK), and regularly works with the Swedish Foundation for Strategic Research regarding their research and leadership programs.

Selected Publications

- *Arrowsmith CH et al (2015)* The promise and peril of chemical probes. *Nature Chemical Biology. 21;11(8):536-41*
- Edwards AM *et al* (2015). Preclinical target validation using patient-derived cells. *Nature Reviews Drug Discovery. 14(3):149-50*
- Knapp S and Sundström M (2014). Recently targeted kinases and their inhibitors – the path to clinical trials. *Current Opinion in Pharmacology. 8;17C:58-63.*

- Francavilla C *et al* (2013). Functional proteomics defines the molecular switch underlying FGFR2b trafficking and response. *Molecular Cell.* S1097-2765*(13)00575-3*
- Fedorov O *et al* (2007). Systematic Analysis of Ser/Thr Kinase Inhibitor Binding Profiles. *Proc Natl Acad Sci U S A. 104(51):20523-8*
- Ng SS *et al* (2007). Crystal structures of human histone H3K9 and H3K36 demethylase JMJD2A reveal the basis for substrate specificity. *Nature. 5;448(7149):87-91.*

Lutz Tautz Ph.D.

Research Associate Professor at Sanford Burnham Prebys Medical Discovery Institute

"Allosteric Inhibitors of the SHP2 Phosphatase as Novel Cancer Therapeutics"

Abstract The protein tyrosine phosphatase SHP2 is a key regulator of growth factor and cytokine signaling, controlling important cellular processes such as proliferation, survival, apoptosis, adhesion, and migration. SHP2 function has been found upregulated in many cancers, including prostate, colorectal, breast, and lung cancer, glioma, glioblastoma, melanoma, and leukemia. Inhibition of this phosphatase could be a novel approach for targeted cancer therapy.

Biography Dr. Tautz earned his Ph.D. in Organic Chemistry and Biochemistry from the University of Karlsruhe (Germany) with Dr. Janos Retey in 2002. He continued his research in chemical biology at the Sanford Burnham Prebys Medical Discovery Institute (SBP, La Jolla, CA) with Dr. Tomas Mustelin, investigating the role of protein tyrosine phosphatases in signaling and human disease. In 2009 Dr. Tautz joined the Faculty at SBP. He currently holds the position of Research Associate Professor at the SBP NCI-designated Cancer Center. His area of expertise is the development of small-molecule chemical probes of protein phosphatases as tool compounds and novel therapeutics.

Matthieu Schapira Ph.D.

Principal Investigator, SGC Toronto

"Systematic analysis of atomic protein-ligand interactions in the PDB"

Abstract We compiled a list of 11 016 unique structures of small-molecule ligands bound to proteins in the Protein Databank - 6444 of which have experimental binding affinity - representing 750 873 protein-ligand atomic interactions, and analyzed the frequency, geometry and impact of each interaction type. We find that hydrophobic interactions are generally enriched in high-efficiency ligands, but polar interactions are over- represented in fragment inhibitors. While most observations extracted from the PDB will be familiar to seasoned medicinal chemists, less expected findings, such as the high number of C-H···O hydrogen bonds or the relatively frequent amide-π stacking between the backbone amide of proteins and aromatic rings of ligands, uncover underused ligand design strategies.

Biography Matthieu holds a Ph.D in biochemistry from Ecole Normale Superieure, Paris. After graduating in 1995, he completed a couple post-docs in protein crystallography and computational chemistry at New York University Medical Center. He joined Molsoft in 2000, and later moved to Lyon, France, to lead structure-based drug design at Aptanomics/Imaxio, a drug discovery start-up. In 2007, he joined the Structural Genomics Consortium in Toronto as head of research informatics, and holds an Associate Professor cross-appointment with the Department of Pharmacology and Toxicology at University of Toronto.

William Bisson Ph.D.

Assistant Professor, Oregon State University

"Computational Chemical Genomics in Precision Cancer Medicine: Recent Applications"

Biography Dr Bisson completed in 2003 his PhD in Medicinal and Computational Chemistry at the ETH Zurich, Switzerland. In 2004 he joined as a Research Fellow the Scripps Research Institute in La Jolla, CA. Later in 2006, Dr. Bisson started as a Research Associate at the nearby Sanford-Burnham Medical Research Institute. In 2008 Dr. Bisson joined as a Research Associate the Oregon State University and in 2010 he came back to Switzerland, at the University of Geneva as Senior Research Scientist. From 2013, Dr. Bisson is Assistant Professor at Oregon State University working successfully in multi-disciplinary cancer research projects combining computational chemical genomics and molecular biology.

Charles Grisham, Ph.D.

Professor of Chemistry, University of Virginia

"PSAFE: A Free Online Project for Teaching Macromolecular Structure-Function Relationships to Undergraduate Students with Molsoft ICM BrowserPro"

Biography Charles M. Grisham is a biochemist and a professor of chemistry at the University of Virginia in Charlottesville, Virginia. He received his B.S. from the Illinois Institute of Technology and his Ph.D. in chemistry from the University of Minnesota. Grisham is a Research Career Development Awardee of the National Institutes of Health and is a member of the American Society for Biochemistry and Molecular Biology. Grisham has co-authored the textbook entitled Biochemistry with Reginald H. Garrett.

Lea Lough Ph.D.

Research Assistant at New York University School of Medicine

"Targeting the Amino Acid Response Pathway in Leukemia"

Abstract Cellular stress signals activate specific kinases of the mammalian integrated stress response (ISR). Amino acid deprivation is one of four types of cell stresses that converge at the phosphorylation of eIF2α to alleviate the cell stress. Drug-like, potent and selective chemical inhibitors targeting major ISR kinases have been previously identified, with the exception of GCN2. Asparaginase (ASNase) is a standard treatment for acute lymphoblastic leukemia (ALL) that results in a drug induced amino acid starvation and apoptosis; however, this amino acid deprivation can be overcome by GCN2 and potentially lead to resistance. We synthesized and evaluated a series of GCN2 inhibitors based on a triazolo[4,5-*d*]pyrimidine scaffold. Several compounds potently inhibited GCN2 *in vitro* and displayed good selectivity over the related kinases PERK, HRI, and IRE1. The compounds inhibited phosphorylation of eIF2α in HEK293T cells with an IC_{50} < 150 nM, validating them as chemical probes for cellular studies. These probes were screened against the National Cancer Institute (NCI-60) human cancer cell line panel. Uniform growth inhibition was observed in all the leukemia cell lines. Growth inhibition in the most sensitive cell lines coincided with high GCN2 mRNA expression levels. In addition we used these compounds and normal mode to generate and identify a GCN2 homology model that can be used for virtual ligand screening (VLS) to identify better chemotypes.

Biography Lea Lough holds and M.S. in biochemistry and is currently a PhD candidate at NYU School of Medicine. She is interested in cell stress pathways and in taking a drug discovery approach to

understand the role that GCN2 has on leukemia. During her free time, Lea enjoys learning about business development in the pharmaceutical industry.

Hariprasad Vankayalapati Ph.D.

Arrien Pharmaceuticals & TGen

"Computational Approaches to Small Molecule Immunotherapeutics"

Biography Dr. Hari is currently serving as a Research Associate Professor of Medicinal Chemistry at the Applied Cancer Research and Drug Discovery Division of Translational Genomics Research Institute (TGen) in Phoenix, AZ since Oct 2017. His research focuses on early discovery, and to IND stage of development of small molecule targeted therapeutics particularly; targeting kinase signaling, immunokinases, epigenetics, nuclear hormone receptors, immune therapeutics - A target class in treating cancer, inflammation, autoimmune, and neurodegenerative diseases.

Prior to TGen, Dr. Hari was serving as Assistant Professor/Chief Scientist of Medicinal Chemistry at the Center for Investigational Therapeutics (CIT) of The Huntsman Cancer Institute (HCI) & School of Medicine of University of Utah in Salt Lake City (Nov 2009 to Sep 2017). With a support from Huntsman Cancer Institute, Dr. Hari established a Medicinal. Organic, Computational Chemistry capabilities and successfully executed the translational research in search for novel cancer therapeutics. His researches at HCI lead to three spin-off Pharmaceutical companies and clinical stage three agents. From 2006-2009 Dr. Hari served as Chief Scientist at the SuperGen/Astex Pharmaceuticals (now Otsuka Pharmaceuticals). From 2003-2006 he was serving as program director of Medicinal Chemistry for early discovery, development and was key in creating several pipeline pre-clinical programs, CLIMB technology and co-founded Montigen Pharmaceuticals in year 2003. Later in year 2006 Montigen was acquired by SuperGen Inc., for 40 million where Dr. Hari played a key role in bringing science/technology in this deal transaction. Dr. Hari's involvement over the years in Drug Discovery/Development, and his leadership lead to the discovery of first-in-class three clinical phase drug candidates; Amuvatinib/MP-470, SGI-1776 and SGI-110.

In addition, Dr. Hari is also serving as Chief Scientific Officer of Arrien Pharmaceuticals (where he successfully completed ARN-6039 Phase 1 trials and partnered on ARN-3261 IND approved by FDA in Sep 2018 for Phase 1 trials in ovarian cancer patients to begin in Q1 2019), Oncolexis Therapeutics and a scientific advisor for few startup Pharmaceutical companies. He is an author of more than 70 peer reviewed scientific publications & presentations in Medicinal, Organic, Computational Chemistry and drug discovery areas. He is an inventor of over 23 published/issued US/WO patents. He holds PhD. and M. Pharm degrees in Medicinal Chemistry from the Institute of Chemical Technology (formally UDCT) of University of Mumbai and University of Karnatk in India. He completed his Post-Doctoral training in Organic Chemistry from University of Sunderland in England and Medicinal Chemistry with Prof. Laurence H. Hurley from University of Arizona Cancer Center in Tucson, USA.