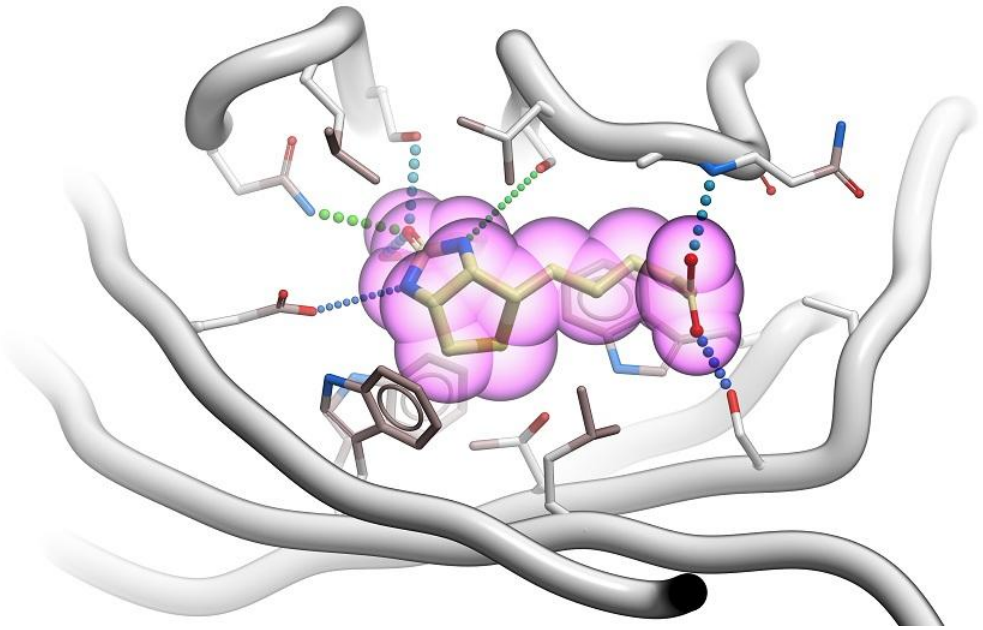
# ICM User Group Meeting 2012

March 29-30

San Diego, CA USA



**Presented by:**

MolSoft
molecules *in silico*

## Message to Participants

We want to welcome all of you to this ICM User Group Meeting and hope that it will be a good learning experience for everyone. We have 29 speakers from all over the world who will be presenting on a wide range of subjects. We have speaker sessions on Protein Structure Analysis, Modeling of Membrane and Immune Response Proteins, Latest ICM Developments, 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 ask our speakers personallay about their areas of expertise. Most of these events include some element of food, refreshments, and exercise - we hope you can join us!

Thank you for participating.

MolSoft User Group Meeting Organization Committee

MolSoft LLC 11199 Sorrento Valley Road, S209 San Diego CA 92121

858 625 2000 x108

www.molsoft.com

## 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

Torrey Pines State Reserve and Beach

## THURSDAY 29th MARCH - MORNING SESSION

| | |
|---|---|
| 8:00am - 8:30am | Meeting registration. |
| 8:30am - 8:55am | **Prof. Ruben Abagyan, Ph.D.** |
| | Professor, University of California San Diego, and MolSoft Founder |
| | ***"ICM and Molsoft : the state of the technology and applications"*** |
| 8:55am - 9:20am | **Maxim Totrov, Ph.D.** |
| | Principal Scientist, MolSoft LLC |
| 9:20am – 9:45am | **Brian Marsden, Ph.D.** |
| | Principal Investigator, Research Informatics, at SGC, University of Oxford |
| | ***"activeICM and iSee in data dissemination: Where are we now?"*** |
| 9:45am - 10:10am | **Michael Sundstrom, Ph.D.** |
| | Vice President, Discovery Research, at Karolinska Development |
| | ***"Understanding Protein Function and the Proteome"*** |
| 10:10am – 10:25am | **Break -** Refreshments provided by MolSoft |

## PROTEIN STRUCTURE ANALYSIS

| | |
|---|---|
| 10:25am -10:50am | **Bernhard Rupp, Ph.D.** |
| | Founder and CEO at q.e.d. life sciences discoveries |
| | ***"Ligands in macromolecular models: approach with caution"*** |
| 10:50am - 11:15am | **Irina Kufareva, Ph.D.** |
| | *Project Scientist at University of California, San Diego* |
| | ***"Pocketome: an encyclopedia of small-molecule and peptide binding sites in 4D"*** |
| 11:15am - 11:40am | **Gerard Van Westen, MSc** |
| | Leiden/Amsterdam Center for Drug Research |
| | ***"Consensus Structures Reveal Concealed Protein Properties"*** |
| 11:40am - 2:30pm | **Lunch provided by MolSoft at Torrey Pines State Beach** |
| | Eat, hike and swim. |

## THURSDAY 29TH MARCH AFTERNOON SESSION

### MEMBRANE PROTEIN MODELING

2:30pm – 2:55pm **Patrick Sexton, Ph.D.**

Professor of Pharmacology at Monash University

***"Loop modeling and ligand-directed modeling of G protein-coupled receptors"***

2:55pm – 3:20pm **Andrew Bordner, Ph.D.**

Assistant Professor of Pharmacology at the Mayo Clinic, Phoenix, Arizona

***"Derivation and testing of an implicit solvation model for membrane proteins"***

3:20pm - 3:45pm **Vsevolod "Seva" Katritch, Ph.D.**

Assistant Professor of Molecular Biology at The Scripps Research Institute

***"Structure-based discovery of GPCR modulators"***

3:45pm - 4:00pm **Break** – Refreshments provided by MolSoft

### MODELING IMMUNE RESPONSE PROTEIN INTERACTIONS

4:00pm – 4:25pm **Carlo Boutton, Ph.D.**

Associate Director Technology & Information Management at Ablynx

***"Nanobodies through the eyes of a computational biologist"***

4:25pm - 4:50pm **Lutz Tautz, Ph.D.**

Research Assistant Professor at Sanford-Burnham Medical Research Institute

***"Chemical Genomics Approaches in T cell signaling"***

4:50pm - 5:15pm **Evgeny Shmelkov, MSc.**

New York University

***"In silico Prediction of the Neutralization Range of Human Anti-HIV Monoclonal Antibodies"***

### LATEST DEVELOPMENTS AT MOLSOFT

5:15pm – 5:25pm **Break** – Refreshments provided by MolSoft

5:25pm – 5:50pm **Yelena Arnautova Ph.D.**

Senior Research Scientist MolSoft LLC

***"AQUASITES"***

| | |
|---|---|
| 5:50pm – 6:15pm | **Slava Brover** |
| | Senior Software Developer, MolSoft LLC |
| | ***"ICMDB" presentation with Brian Marsden Ph.D. (SGC Oxford)*** |
| 6:15pm - 6:30pm | **Arman Sahakyan** |
| | Senior Software Developer MolSoft LLC |
| | ***"Advanced ICM Graphical User Interface Developments"*** |

## FRIDAY 30TH MARCH MORNING SESSION

### LATEST DEVELOPMENTS AT MOLSOFT (Contd.)

8:30am - 8:55am **Eugene Raush, M.Comp.Sc.**

Principal Software Developer MolSoft LLC

**"New linker and scaffold substitution tool in the 3D ligand editor"**

### CHEMICAL BIOLOGY AND CHEMINFORMATICS

8:55am - 9:20am **Terry Stouch, Ph.D.**

President, Science For Solutions, LLC

**"Making sense of antisense: ICM customization for rapid evaluation of RNA-based therapeutics"**

9:20am - 9:45am **Rashmi Hedge, Ph.D.**

Professor, Cincinnati Children's Hospital Medical Center

**"A chemical biology approach to uncovering cellular function"**

9:45am - 10:10am **William Bisson, Ph.D.**

Senior Research Scientist and Lecturer at University of Geneva

***"Computational chemistry and drug design: key players in a interdisciplinary team aiming for success"***

10:10 – 10:25 **Break** – Refreshments provided by MolSoft

10:25am - 10:50am **Gennadiy Poda, Ph.D.**

Chemist, Cheminformatics and Computational Chemistry at Ontario Institute for Cancer Research, Toronto

***"Identification of Epigenetics modulators for early state anti-cancer drug discovery efforts"***

### ICM FOR TEACHING AND COMMUNICATION

10:50am - 11:15am **Charles Grisham, Ph.D.**

Professor of Chemistry, University of Virginia

***"Teaching Students in an Undergraduate Biochemistry Course to Create Molsoft Molecular Documents"***

11:15am - 11:40pm **Katherine Kantardjieff, Ph.D.**

Dean, College of Science and Mathematics at Cal State University at San Marcos

***"Computational Biochemistry in Undergraduate Education and Research using ICM: A Report from the Trenches"***

11:40am - 12:05pm **Julie Ealy, Ph.D.**

Associate Professor of Chemistry, Penn State Lehigh University at Lehigh Valley

***"Bioinformatics for Undergraduates and the Use of ICM Pro"***

12:05pm – 3:00pm **Lunch Provided by MolSoft at La Jolla Shores Beach**

Eat, Swim, Play Volley Ball, Walk along the boardwalk

## FRIDAY 30TH MARCH AFTERNOON SESSION

## PROTEIN-PROTEIN DOCKING

3:00pm – 3:25pm **Juan Fernandez-Recio, Ph.D.**

Research Group Leader at Barcelona Supercomputing Center

***"New challenges for protein docking in the interactomics era"***

3:25pm – 3:50pm **Badry Bursulaya, Ph.D.**

Research Investigator, II at Genomics Institute of the Novartis Research Foundation

***"Protein-protein interfaces: hot spot analysis and disruption"***

## LEAD DISCOVERY

3:50pm - 4:15pm **Anton Filikov, Ph.D.**

Scientist II NCI Frederick

***"Antagonistic androgen receptor structure: Useful models despite low homology"***

4:15pm – 4:25pm **Break** – Refreshments provided by MolSoft

4:25pm - 4:50pm **Timothy Cardozo, M.D., Ph.D.**

Associate Professor NYU Langone Medical Center

***"A Novel VLS Approach Targeting The Malaria Glideosome"***

| | |
|---|---|
| 4:50pm - 5:15pm | **Jianghong An, Ph.D.** |
| | Staff Scientist at the Genome Sciences Centre, BC Cancer Agency |
| | ***"Identification of Autophagy Inhibitors for Novel Cancer Therapies by Targeting both Active and Allosteric Sites of ATG4B"*** |
| 5:15pm - 5:40pm | **Giovanni Bottegoni, Ph.D.** |
| | Istituto Italiano di Tecnologia |
| | ***"Computational hit discovery of a novel anandamide transport inhibitor"*** |

**ROUND TABLE DISCUSSION**

| | |
|---|---|
| 5:40 – 6:15 | **Questions and answers with MolSoft developers and scientists** |
| 6:15 - onwards | **Wine and cheese reception at MolSoft** |

Thursday 8:30am - 8:55am

**Ruben Abagyan, Ph.D.**

Professor, University of California San Diego, and MolSoft Founder

**ICM and Molsoft : the state of the technology and 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.

Thursday 8:55am - 9:20am

**Maxim Totrov, Ph.D.**

Principal Scientist MolSoft LLC

***"Recent developments in ICM methodologies and applications"***

**Abstract**

A range of developments in ICM modeling algorithms will be reviewed: The new forcefield (ICMFF) for peptide and protein modeling. ICMFF application for protein loop prediction. ICMFF extension to glycan modeling. New features in the grid docking protocol. AquaSites - discrete water displacement analysis in binding sites. Highlights from a case study on aminergic GPCR modeling and prospective VLS will be discussed.

**Biography**

Maxim Totrov is 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 Mosloft ICM.

Thursday 9:20am – 9:45am

**Brian Marsden, Ph.D.**

Principal Investigator, Research Informatics at SGC, University of Oxford

***"activeICM and iSee in data dissemination: Where are we now?"***

## Abstract

In the last three years, the use of the activeICM plugin in the iSee platform to disseminate the SGC's unrivalled human structural biology output has continued to grow. In addition, the technology and iSee concept has expanded into peer-review publishing with a number of different journals. Now, the activeICM plugin is being used as the basis of web applications to aggregate and disseminate protein family structural information. Dr. Marsden's talk will summarize the state of play, what we've learned while working with publishers over the last three years and attempt to predict where the iSee concept is going.

## Biography

After a degree in Natural Sciences at Cambridge and a DPhil at Oxford simulating the dynamics of extracellular modules, Brian was fortunate to spend 2 and a half years in the Abagyan lab at TSRI. Here he spent far too much time building Linux clusters, writing ICM scripts and nothing like enough time learning the ins and outs of *in silico* drug discovery. Despite this, he was lured back to the UK to run the computational chemistry group at BioFocus (now Galapagos) before moving back to Oxford to build and run the Research Informatics group at the SGC. In addition to bioinformatics, computational chemistry and systems administration, his group specializes in LIMS platforms and novel methods of disseminating structural biology data to the masses.

Thursday 9:45am - 10:10am

**Michael Sundstrom, Ph.D.**

VP Discovery Research at Karolinska Development *& CEO KDev Discovery (Stockholm, Sweden)*

***"Understanding Protein Function and the Proteome"***


**Abstract**

The presentation will focus on work performed at the Novo Nordisk Foundation Center for Protein Research (CPR) where Dr. Sundstrom held the position as Managing Director until October 2011.

The Novo Nordisk Foundation Center for Protein Research was established at the Faculty of Health Sciences, University of Copenhagen, to promote basic and applied discovery research on human proteins of medical relevance. The establishment of the Center was made possible by a significant donation from the Novo Nordisk Foundation and additional contributions from the University of Copenhagen for the building of new laboratories. The Center now comprises a wide range of expertise and skills, with activities in the areas of disease systems biology, proteomics, high throughput protein production and characterization, chemical biology, disease biology, and protein therapeutics, with a clear ambition to promote biomedical translational research.

In addition to providing an overview regarding the research efforts at CPR, the talk will also provide a brief overview of prioritized projects and activities at Karolinska Development.


**Biography**

**Current Positions**

**VP Discovery Research, Karolinska Development:** Dr. Sundstrom's work duties are focused on identification and evaluation of novel biomedical research projects for considerations regarding funding and company formation by Karolinska Development. As part of this duty, he also manages Karolinska Development´s early drug discovery company, KDev Discovery.

**CEO KDev Discovery :** In his role as CEO, Dr. Sundstrom oversees the strategic direction and operational activities at the company. KDev Discovery has around 15 staff members, with expert level skills, resources and infrastructure in protein science, target validation, assay development, screening and cheminformatics/chemistry.

**Previous Management Experience**

- Managing Director: NNF Center for Protein Research (University of Copenhagen) 2007 - 11
- Chief Scientist: Structural Genomics Consortium (University of Oxford, UK) 2003-07
- Director: In-Licensing, Biovitrum AB (Large Biotech, Stockholm, Sweden) 2002-03
- Head of Research: Actar AB (Small Biotech, Stockholm, Sweden) 2001-02
- Director: Structural Chemistry & Informatics, Pharmacia (Milan, Italy) 1998-2001
- Head: Protein Crystallography, Pharmacia (Stockholm, Sweden) 1995-97

**Other Work Experiences and Education**

- Scientist: Protein Crystallography, Pharmacia (Stockholm, Sweden) 1993-95
- PostDoc: Center for Structural Biochemistry (Karolinska Institute, Sweden) 1992-93
- PhD Student: Dept. of Molecular Biology (Uppsala University, Sweden) 1988-92
-

**Selected Recent Publications**

- Kotzsch A *et al* (2011). A Secretory System for Bacterial Production of High-Profile Protein Targets. *Protein Science*
- Vernet E *et al* (2011). Screening of genetic parameters for soluble protein expression in Escherichia coli. *Protein Expression and Purification.*
- Sundstrom M *et al* (2008*).* A coordinated pilot project to generate affinity reagents to human proteins. *Nature Methods.*
- Soundararajan M *et al* (2008). Structural diversity in the RGS domain and its interaction with heterotrimeric G protein alpha-subunits. *PNAS*
- Fedorov O *et al* (2008). Systematic Analysis of Ser/Thr Kinase Inhibitor Binding Profiles. *PNAS 2008.*
- Ng SS *et al* (2007). Crystal structures of human histone H3K9 and H3K36 demethylase JMJD2A reveal the basis for substrate specificity. *Nature.*
- Vedadi M *et al* (2006). Development and application of chemical screening methods to identify ligands that promote protein stability, protein crystallization and structure determination. *PNAS*

Thursday 10:25am -10:50am

**Bernhard Rupp, Ph.D.**

Founder and CEO at q.e.d. life sciences discoveries

***"Ligands in macromolecular models: approach with caution."***

**Abstract**

Macromolecular models are particularly useful when they include a ligand or transition state analog. Such a ligand structure will represent the binding site in a conformation better suited for drug design than a ligand-free model. In the increased usefulness and impact factor lies (no pun intended) the rationale for the postmodern crystallographer to divine desired molecules into poor and spurious density. As such molecules are not restrained by sensible density, they rely on correct geometric restraint descriptions to remain in plausible conformations. If even those are flawed, entropic chaos triumphs. A few out of thousands of cautionary tales are provided.

**Biography**

Dr. Rupp leads a small business specializing in autonomous robotics for high throughput crystallography. He is well respected in the crystallographic community for his textbook '*Biomolecular Crystallography: Principles, Practices and Application to Structural Biology'* and somewhat less popular through his validation work uncovering highly implausible crystal structures.

Thursday 10:50am - 11:15am

**Irina Kufareva, Ph.D.**

*Project Scientist at University of California, San Diego*

***"Pocketome: an encyclopedia of small-molecule and peptide binding sites in 4D"***

## Abstract

Transient intermolecular interactions drive all biological processes and mediate most normal, pathological, or therapeutic responses. The inherent conformational plasticity of interaction sites is of primary importance because it allows them to accommodate a variety of binding partners; however, it also encumbers prediction or rationalization of these interactions. To promote understanding of flexible transient interactions, we developed the Pocketome (www.pocketome.org), an encyclopedia of experimentally solved conformational ensembles of druggable binding sites in proteins and protein assemblies. The ensemble nature adds an extra, fourth dimension to the otherwise three-dimensional Pocketome data, which is critical for understanding interaction principles and specificity. Pocketome currently contains ~2000 binding site ensembles and is constantly growing. With its unique molecular visualization and analysis tools, Pocketome represents a universal resource for elucidation of principles of transient flexible molecular interactions as well as for understanding and predicting ligand specificity and polypharmacology. The latter application is illustrated by design and implementation of Pocketome-based multi-conformational 3D-activity models for the family of nuclear receptors.

## Biography

Irina Kufareva received a MS in Mathematics and a Ph.D. in Computer Science in 1994 and 1999, respectively, both from Tomsk State University, Russia. She currently holds a position of a project scientist in UCSD Skaggs School of Pharmacy, La Jolla, CA. The focus of her work is protein-ligand complex structure prediction and drug design. Her research expertise is in the field of novel, particularly challenging targets involving transient and conformationally variable interfaces, protein-protein interactions, and allosteric sites.

Thursday 11:15am - 11:40am

**Gerard Van Westen, MSc**

Leiden/Amsterdam Center for Drug Research

***"Consensus Structures Reveal Concealed Protein Properties"***

## Abstract

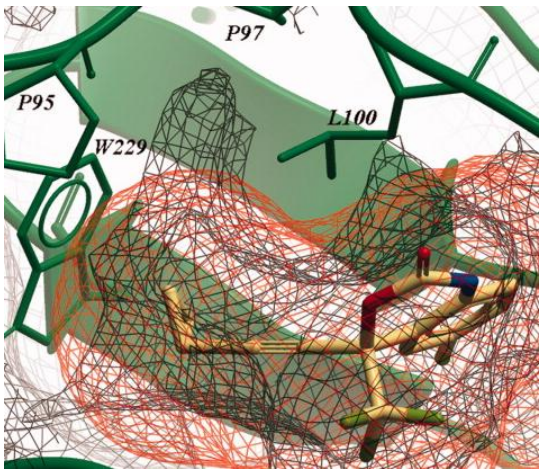
G.J.P. van Westen[1]; J.K. Wegner[2], A.P. IJzerman[1], H.W.T. van Vlijmen[2], A. Bender[1]

[1]Division of Medicinal Chemistry, LACDR, Einsteinweg 55, 2333 CC, Leiden, The Netherlands

[2] Tibotec BVBA, Turnhoutseweg 30, 2340 Beerse, Belgium

Crystal structures of proteins have become an invaluable tool in rational drug design. The high degree of detail enables the scientist to rationally optimize the chemical structure of a drug in order to maximize both activity and selectivity. Concurrent with the appearance of rational drug design – and one of the drivers behind it – is the growth of the Protein Databank (PDB).[1] The PDB contained 78,191 unique structures in 2011 and has been growing by approximately 10 – 20 % per year over the last ten years. However, at the same time techniques relying on these structures, such as docking algorithms, have shown varying (and sometimes very little) success.[2] One of the reasons is that a crystal structure provides only a static snapshot of the dynamic structure that a protein represents. This static image cannot depict parts of the protein that are flexible (and in which way), or provide a solid basis for a docking calculation involving conformational flexibility ('induced fit').

The following problem therefore needs to be addressed, namely: How can large crystal structure databases such as the PDB be mined efficiently, and how can confidence in algorithms relying on crystal structures for drug design be increased?




Several techniques aiming to resolve this problem have appeared but no definite answer has been found.[3] In our approach, termed 'Consensus Structures', we pool the information contained in multiple crystal structures, where each of the crystal structures is treated as a single snapshot depicting part of the conformational space accessible to the protein.[4] The combined snapshots thereby provide a dynamic view of the conformational space that is accessible to the protein and enable the scientist to take protein dynamics into account when designing novel potential drugs.

'Consensus Structures' provide the scientist with a ligand pharmacophore *and* a protein pharmacophore which contain basic information about the interaction between both, such as volume and information

concerning hydrogen bond donors and acceptors. In addition it provides information about which features of these pharmacophores are conserved among the different crystal structures and which are unique for a single structure. In this manner, 'Consensus Structures' are highlighting features in the pocket that are not yet targeted by current ligands, and thereby they are able to guide the rational design of drugs in novel ways.


1. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE (2000) The Protein Data Bank Nucleic Acids Res. 28:235-242.

2. Kellenberger E, Rodrigo J, Muller P, Rognan D (2004) Comparative evaluation of eight docking tools for docking and virtual screening accuracy. Proteins: Struct., Funct., Bioinf. 57:225-242.

3 Totrov M (2008) Atomic property fields: generalized 3D pharmacophoric potential for automated ligand superposition, pharmacophore elucidation and 3D QSAR. Chem. Biol.Drug Des.71:15-27

4. van Westen GJP, Wegner JK, Bender A, IJzerman AP, van Vlijmen HWT (2010) Mining protein dynamics from sets of crystal structures using "consensus structures". Protein Sci 19:742-752.


**Biography**

Gerard van Westen is a PhD student at the Leiden Amsterdam Center for Drug Research (LACDR) currently doing research in the field of proteochemometric modeling. He studied Biopharmaceutical Sciences at Leiden University from September 2001 until September 2007. During his master he has done two major internships. The first was within the LACDR on a biochemical research project in the field of atherosclerosis. The second one was something completely different on a computational project at Tibotec in Mechelen, Belgium. This project was in the field of HIV inhibitor research. It was here that he discovered the challenging side of computational research. The productive cooperation has led to a close collaboration with Tibotec, who are currently funding his PhD at the group of Medicinal Chemistry at Leiden University. In May this year Gerard will move to the European Bioinformatics Institute in Hinxton (Cambridge, UK) to start working on a 3 year EIPOD postdoc.

Thursday 2:30pm – 2:55pm

**Patrick Sexton, Ph.D.**

Professor of Pharmacology at Monash University

***"Loop modelling and ligand-directed modelling of G protein-coupled receptors"***

## Abstract

Although protein crystallography has provided recent significant advances in understanding of receptor structure and ligand interaction at the superfamily of G protein-coupled receptors, we are still in our infancy in this field. Molecular modelling can provide a gateway to further our understanding of GPCR structure and, in particular, to build models that may be predictive of ligand binding. Key areas for development in GPCR modelling include predicting the structue of interhelical loops, and the ability to generate models predictive of agonist binding. We have been benchmarking the effectiveness of the ICM HPC method for loop modelling and also the application of ligand-directed modelling with agonists to inactive state structures to generate agonist predictive models.

## Biography

Patrick Sexton a leading international researcher in the field of G protein-coupled receptors (GPCRs), and in particular with respect to allosteric modulation of receptors and in the structure/function of Class II GPCRs and accessory proteins. His research crosses industry and academic boundaries through elucidation of fundamental biology and the intersection of this with drug-receptor interactions. He has authored over 170 publications, with major contributions to understanding of the distribution of receptors, the structural interface between peptide ligands and receptors, modulation of receptors by accessory proteins, detection and quantification of small molecule allosteric drug effects and ligand-biased signaling.

Thursday 2:55pm – 3:20pm

**Andrew Bordner, Ph.D.**

Assistant Professor of Pharmacology at the Mayo Clinic

***"Derivation and testing of an implicit solvation model for membrane proteins"***

**Abstract**

Despite their prevalence and importance as drug targets, relatively few experimental structures of membrane proteins are available, highlighting the need for computational modeling. A key challenge in such membrane protein simulations is accounting for the heterogeneous environment provided by the solvated lipid bilayer. We have derived a computationally efficient implicit solvation model utilizing atomic solvation parameters for membrane proteins in a bilayer, which has been implemented in ICM. We next tested the new solvation model by comparing ICM simulation results with diverse experimental data. First, we predicted the positions and orientations of proteins relative to the bilayer and compared the results with solid state NMR structures. Next, we performed folding simulations for a series of host-guest peptides in hydrophobic and aqueous environments and compared with results with available CD data. We were also able to successfully fold amphipathic peptides and reproduce the experimentally characterized propensities of hexameric peptides to form beta sheets. Finally, we compared calculated relative transfer free energies with data from two different experiments. Overall, these results suggest that ICM simulations using the solvation model are able to accurately account for a wide range of membrane protein properties.

**Biography**

After postdoctoral training in computational biology at the UCSD Department of Bioengineering, Andrew Bordner joined Ruben Abagyan's group at The Scripps Research Institute. He then worked at Molsoft LLC for about one year and as a Research Scientist at Oak Ridge National Laboratory in Tennessee. In 2007, he joined the Mayo Clinic in Arizona as an Assistant Professor in the Department of Molecular Pharmacology and Experimental Therapeutics.

Thursday 3:20pm - 3:45pm

**Vsevolod "Seva" Katritch, Ph.D.**

Assistant Professor of Molecular Biology at The Scripps Research Institute

***"Structure-based discovery of GPCR modulators"***

## Abstract

Within the last 2 years, crystal structures have been determined for 9 distinct G protein-coupled receptors (GPCRs), suggesting exponential growth trend for structural coverage of this important superfamily of clinical targets. The GPCR 3D templates open a unique opportunity for expansion of structure-based drug discovery. Here we will discuss several recent applications of ICM modeling tools to GPCRs, from initial characterization of the binding pockets and subtype selectivity to in-depth ligand discovery programs. In many cases the modeling and VLS take advantage of a ligand guided receptor optimization approach. The examples of successful discovery programs include prospective virtual ligand screening for new antagonist chemotypes for $A_{2A}$ adenosine receptor, and rational optimization of $A_{2A}$AR agonists using fragment screening in an established chemical scaffold. Another line of inquiry led to discovery of new ligands for dopamine D3 receptor with allosteric and bitopic modes of binding. Further applicability of these tools to modeling GPCR subtypes and conformational states will be discussed.

## Biography

Dr. Vsevolod "Seva" Katritch received his Ph.D. in computational biology from Moscow Institute of Physics and Technology (MIPT), while also serving as a visiting scholar at Lausanne University, Switzerland. After completing a postdoc at Rutgers University, NJ and The Scripps Research Institute with Prof. Ruben Abagyan, Dr. Katritch held a position of Associate Director of Structural Genomics at Plexus Vaccine Inc., and as Director of Computational Biology at SIGA Technologies Inc. He returned to academia in 2008 and currently leads computational biology efforts of the GPCR Network program as an Assistant Professor at Scripps. Dr. Katritch's interests are focused on structural and computational biology of membrane proteins, including GPCRs, structure-based drug discovery and application of genomic data to analysis of individual drug response.

Thursday 4:00pm – 4:25pm

**Carlo Boutton, Ph.D.**

Associate Director Technology & Information Management at Ablynx

***"Nanobodies through the eyes of a computational biologist"***

**Abstract**

**Nanobodies® from a structural point of view**

Nanobodies are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occuring heavy-chain antibodies. The Nanobody technology was originally developed following the discovery that camelidae (camels and llamas) possess fully functional antibodies that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3). Importantly, the cloned and isolated VHH domain is a perfectly stable polypeptide harbouring the full antigen-binding capacity of the original heavy-chain antibody. These newly discovered VHH domains with their unique structural and functional properties form the basis of a new generation of therapeutic antibodies which Ablynx has named Nanobodies.

**Biography**

Carlo Boutton obtained a PhD in physical chemistry at the KULeuven (Belgium) in 1999. He started his career at Algonomics (currently Lonza) where he developed software to predict the presence of T-cell epitopes in biologicals. In 2003, he joined Tibotec (subsidiary of J&J) where he contributed to several structure-based drug design programs against HIV and HCV targets.

In 2007, he joined Ablynx as teamleader of the scientific computing group and he is currently associate director of the "technology & information management" group

Thursday 4:25pm - 4:50pm

**Lutz Tautz, Ph.D.**

Research Assistant Professor at Sanford-Burnham Medical Research Institute

***"Chemical Genomics Approaches in T cell signaling"***

**Abstract**

Aberrant T cell signaling and activation is linked to infection, inflammation, autoimmunity, immunodeficiency, cancer, and other disorders and human diseases. Small-molecule chemical probes that modulate the activity of specific signaling molecule, such as protein kinases or protein phosphatases, are invaluable tools for exploring antigen-mediated responses in human T cells or in animal models of human disease. While the development of specific kinase inhibitors has made remarkable progress within the last decade, effective strategies to target specific protein phosphatases are still elusive. Using the tyrosine phosphatases HePTP and LYP as examples, the significance and power of *in silico* docking and structure-guided drug design for the generation of selective chemical probes in human T cells and *in vivo* will be discussed.

**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 Burnham Institute in La Jolla, CA with Dr. Tomas Mustelin, first as a postdoc and later as a staff scientist. In 2009 Dr. Tautz joined the faculty of the Sanford-Burnham Medical Research Institute. Dr. Tautz' area of expertise is the identification and development of small-molecule modulators that function as chemical probes to explore aberrant signaling pathways in human disease, with a focus on those that rely on the phosphorylation and dephosphorylation of signaling molecules.

Thursday 4:50pm - 5:15pm

**Evgeny Shmelkov MSc.**

New York University

***"In silico Prediction of the Neutralization Range of Human Anti-HIV Monoclonal Antibodies"***

## Abstract

Antigenic variation is a primary obstacle to HIV-1 vaccine development since antibodies (Ab) directed against the viral envelope have widely variable and poorly predictable cross-strain reactivity. The breadth of cross-strain reactivity is usually estimated by in vitro neutralization of a broad panel of HIV-1 viral strains by a query antibody. However, this approach is cumbersome and cannot be scaled up to assess the more than 60,000 circulating HIV-1 viruses. To address this issue, we used de novo docking of a flexible peptide, representing the epitope-containing part of a viral gp120, to a static 3D structure conformation of an antigen-combining site of a specific Ab to predict whether neutralization would occur between the pair. To train the method we used a panel of 59 diverse pseudoviruses (psVs) controlled for masking effects. All psVs had an associated experimentally derived IC50 value for neutralization by anti-V3 loop monoclonal Abs 2219 and 447-52D. We optimized the flexible peptide docking procedure for each of these mAbs by determining an optimal docking model (i.e. an optimal length of a docking peptide and an optimal mAb conformation) giving the largest area under the prediction ROC curve (AUC) on the training set of 59 psVs. The prediction accuracy for the optimized method was then estimated: the AUC is equal to 0.96 (95% CI (0.91; 1)) for mAb 2219, and to 0.88 (95% CI (0.79; 0.97)) for mAb 447-52D. Thus, the method accurately predicts the neutralization of any HIV-1 strain by mAbs 2219 or 447-52D based solely on neutralization-assay-independent energetics and 3D structural parameters. The neutralization range of these anti-V3 loop mAbs can therefore be precisely determined in silico. Furthermore, given the fact that mAbs 2219 and 447-52D have completely different binding modes, we anticipate that our approach is extensible to other anti-HIV mAb:viral-epitope complexes with known structure.

## Biography

Evgeny is a PhD candidate in the Computational Biology Program in the Sackler Institute of Graduate Biomedical Sciences at New York University School of Medicine and Courant Institute of Mathematical Sciences. His experience includes computational and wet-lab research in different fields of biomedical sciences, such as diabetes, cancer, and neuroscience. Currently, he works in the field of infectious diseases and HIV-1 vaccine development. Evgeny holds Master's in Computational Biology from New York University, and Bachelor's and Master's in Medical Physics from the Lomonosov Moscow State University.

Thursday 5:50pm – 6:15pm

**Slava Brover** Senior Software Developer, MolSoft LLC

***"ICMDB" (presentation with Brian Marsden Ph.D. (SGC Oxford))***

**Abstract**

ICMdb is a tool to work with databases. Currently ICMdb can work with MySQL and Oracle platforms. ICMdb allows querying and editing existing tables in the databases, installing 3rd party databases, for example, ChEMBL, DrugBank, and creating personal data, for example, lists of identifiers of some entity. The Query Builder allows querying tables by different conditions spanning more than one table which may reside on different databases. ICMdb uses the Molsoft Molcart package functionality to perform chemical searches. ICMdb can visualize experiment data as plots. Queries and personal data can be saved and shared by other ICMdb users.

**Biography**

M.Sci. in Operations Research from Rutgers University.

Different projects in data analysis. Bioinformatics, database, data analysis and software support for high-throughput cDNA sequencing, SNP detection. GenBank submissions.

Thursday 6:15pm - 6:30pm

**Arman Sahakyan**

Senior Software Developer MolSoft LLC

***"Advanced ICM Graphical User Interface Developments"***

**Abstract**

Images and sound applications introduce another level of explicitness into ICM. Both mediums are useful for making annotations, visual and audio explanations and tutorials in general. ICM built-in image editor and sound recorder along with respective viewing and playback capabilities make this all possible for ICM users. The user group demonstration will show these features in practice.

Friday 8:30am - 8:55am

**Eugene Raush, M.Comp.Sc.**

Principal Software Developer MolSoft LLC

**"New linker and scaffold substitution tool in the 3D ligand editor"**

## Abstract

The Ligand Editor is a powerful tool for the interactive design of new lead compounds in 3D. It allows you to make modifications to the ligand and see the affect of the modification on the ligand binding energy and interaction with the receptor.

The most popular operations are re-dock and minimize ligand, fast building of heavy atom neighbors, find the best group replacement and others. The convenient undo and redo modification feature makes the Ligand Editor very easy to use.

Recently we developed a new function in the Ligand Editor that allows finding the best scaffold replacement or linker fragment. It lets you interactively select two or more points of connection or replacement and search for possible fragments in the 3D database. The result is returned as a "standard" Ligand Editor hit list where results can be easily browsed and compared.

## 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 has been the Principal Software Engineer at Molsoft since 2002.

Friday 8:55am - 9:20am

**Terry Stouch, Ph.D.**

President, Science For Solutions, LLC

**"Making sense of antisense: ICM customization for rapid evaluation of RNA-based therapeutics"**

## Abstract

ICM functions and scripting were used to build and evaluate RNA hybrids of custom RNA-based therapeutics. Residue templates for custom RNA nucleotide monomers were developed that provided for rapid builds of new oligonucleotides. Base-pair matching and ICM's internal coordinate mechanics were used to rapidly build models of hybrids of the custom oligonucleotides with native RNA. These models served as starting points for evaluation of the stability of the hybrids. The models also provide for investigation of the effects of structural and stereochemical modifications of the custom nucleotide monomers on the properties of the oligonucleotides, such as solubility, and their ability to hybridize. These processes are partly automated within ICM and in the process of being fully automated. The automation makes possible rapid hypothesis testing of large numbers of oligonucleotides of varying composition and sequence in order to optimize properties and function. This can save substantial amounts of time over the synthesis of the custom nucleotide monomers. Since the oligonucletides can range to over 20 residues in length, it is impossible to experimentally study even a small fraction of the possible combinations of custom nucleotides; however, the automation of the modeling can make tractable the study of huge numbers of possibilities.

## Biography

Dr. Terry Richard Stouch has 25 years experience in drug discovery research in large pharma and biotech with specialization in drug design, molecular property prediction, molecular and biomolecular structure, computational sciences, pharmaceutical data evaluation and modeling, and scientific software design. He has participated in placing 8 compounds into human clinical trials. He consults for large and small pharmaceutical and biotechnology companies, biomolecular and chemical database organizations, and chemical and biomolecular software companies, among others.

He is president of Science For Solutions, LLC, a consulting firm specializing in molecular and computational sciences; Senior Editor-in-Chief of the Journal of Computer-Aided Molecular Design; and Adjunct Professor Department of Chemistry and Biochemistry, Duquesne University. He is a Fellow of the American Academy for the Advancement of Science and a Fellow of the International Union of Pure and Applied Chemistry (IUPAC).

Previously he was Director, Computational Chemistry and Structural Biology at Lexicon Pharmaceuticals; Consultant at the Protein Data Bank; Adjunct Professor Department of Pharmaceutical Sciences, School of Pharmacy, University of Kentucky; Principal Scientist in Macromolecular Structure at Bristol-Myers Squibb; and an Office of Naval Technology Postdoctoral Fellow at the Naval Research Laboratory. Both his Ph.D. in chemistry with Professor Peters Jurs and B.S. in biochemistry were earned at the Pennsylvania State University.

He is author of over 70 publications and has presented over 130 invited lectures.

Friday 9:20am - 9:45am

**Rashmi Hedge, Ph.D.**

Professor, Cincinnati Children's Hospital Medical Center

**"A chemical biology approach to uncovering cellular function"**

**Abstract**

Eyes Absents (EYA) are cell-fate determining proteins that form part of the Retinal Determination pathway. In flies eya is critical for eye development, however no eye phenotype has yet been reported for any *Eya* deletion in mice. We have been investigating the biochemical activities of the EYAs and how they correlate with their cellular functions. The EYAs are multifunctional proteins with separable transactivation, threonine phosphatase and tyrosine phosphatase activities. We have shown that the tyrosine phosphatase activity promotes the motility of mammary epithelial cells, correlating with evidence that EYA2 is overexpressed in breast cancers and is associated with a poor prognosis. We now show that lowering EYA levels in endothelial cells leads to significant reduction in motility and the ability to form capillaries. To specifically query the role of the tyrosine phosphatase activity we identified and characterized small molecule inhibitors that are potent and specific towards the EYAs (versus the large family of classical protein tyrosine phosphatases). Treatment of endothelial cells with these compounds led to a reduction in migration and tubulogenesis. Prompted by these observations we generated a conditional knockout of Eya3 in vascular endothelial cells and analyzed the retinal vasculature. A marked reduction in both branching and extension was observed, demonstrating that Eya3 contributes to retinal angiogenesis. These studies not only uncover a role for the EYA proteins in ocular development, but also raise the possibility that EYA represents a novel and druggable target for the development of therapeutics for retinal vasculopathies such as retinopathy of prematurity, diabetic retinopathy and AMD. The EYA inhibitors used here are lead compounds that have already been shown to have specificity, potency, in vivo activity and low toxicity.

**Biography**

**Education**

**1982 B.S.** in Pharmacy Bombay University, Department of Chemical Technology, India
**1989 Ph.D.** in Medicinal Chemistry University of Pittsburgh Pittsburgh, Pennsylvania USA

**Postdoctoral Training**

**1989 - 1994 Postdoctoral Fellow** in Molecular Biophysics & Biochemistry Yale University New Haven, Connecticut USA Mentor: Dr. Paul Sigler

**Academic Appointments**

**1994 - 2000 Assistant Professor** Structural Biology Program Department of Biochemistry Skirball Institute for Biomolecular Medicine, New York University School of Medicine

**2001 - 2007 Associate Professor**

**2008 - present Professor** Cincinnati Children's Hospital Research Foundation Department of Pediatrics Department of Developmental Biology Cincinnati Children's Hospital Medical Center University of Cincinnati School of Medicine

**2011 – present Director** Graduate Program in Molecular & Developmental Biology Cincinnati Children's Hospital Medical Center University of Cincinnati School of Medicine

Friday 9:45am - 10:10am

**William Bisson, Ph.D.**

Senior Research Scientist and Lecturer at University of Geneva

***"Computational chemistry and drug design: key players in a interdisciplinary team aiming for success"***

## Abstract

Chemical Genomics (CG) represents a convergence of biology and chemistry in the era of global approaches to target identification and intervention. The concept of computational CG originated by the fact that the effect of small compounds in the cell is often initiated by direct interactions with proteins. Thus, it is a valuable tool to generate and investigate these interactions at a molecular level.

In academic drug discovery, computational CG can be used on a wide range of applications complementing well *in vitro* and *in vivo* techniques in an inter-disciplinary context.
Recent successful applications involving a variety of disease-related protein targets will be presented. Future outlooks will be discussed.

## References

1. Gambacorti-Passerini C, Mologni L, Scapozza L, **Bisson WH**, Goekjian P, et al. (WO/2012/XXXXXX) Alpha-carboline inhibitors of NPM-ALK, Ret and Bcr-Abl. *Deposited*.
2. **Bisson WH**, Sengupta S, Mathew LK, Kolluri SK, Tanguay RL. Alternate glucocorticoid receptor ligand binding structures influence outcomes in an *in vivo* tissue regeneration model. *Submitted*.
3. Pimple S, **Bisson WH**, Ratib O, Scapozza L, Seimbille Y. Synthesis and biological evaluation of EGFR /HER-2 inhibitors: Analogs of 5-substituted-4-anilinoquinazoline and 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile – screening for development of novel PET tracers. *Submitted*.
4. Goodale BC, La Du JK, Bisson WH, Janszen DB, Waters KM, Tanguay RL. AHR2 mutant reveals functional diversity of aryl hydrocarbon receptors in zebrafish. *PLoS One* 2012 7:e29346.
5. Chavez JD, Wu J, Bisson WH, Maier CS. Site-specific proteomic analysis of lipoxidation adducts in cardiac mitochondria reveals chemical diversity of 2-alkenal adduction. *J Proteomics* 2011 74, 2417-29.
6. Smith KJ, Murray IA, Tanos R, Tellew J, Boitano AE, Bisson WH, Kolluri SK, Cooke MP, Perdew GH. Identification of a high-affinity ligand that exhibits complete aryl hydrocarbon receptor antagonism. *J Pharmacol Exp Ther.* 2011 338, 318-27.
7. Benninghoff AD, Bisson WH, Koch DC, Ehresman DJ, Kolluri SK, Williams DE. Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. *Toxicol Sci.* 2011 120, 42-58.
8. Murray IA, Flaveny CA, Chiaro CR, Sharma AK, Tanos RS, Schroeder JC, Amin SG, Bisson WH, Kolluri SK, Perdew GH. Suppression of cytokine-mediated complement factor gene expression through selective activation of the Ah receptor with 3',4'-dimethoxy-α-naphthoflavone. *Mol Pharmacol.* 2011 79, 508-19.

## Biography

Dr. Bisson completed in 2003 his doctorate in Medicinal and Computational Chemistry with a thesis on the nicotinic Acetylcholine Receptor at the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland. In 2004 he joined as a Swiss National Science Foundation (SNSF) Postdoctoral Research Fellow the group of Dr. Abagyan at the Scripps Research Institute in La Jolla, CA. There, he worked on finding novel antagonists against the Androgen Receptor (AR) through *in silico* Structure-Based Drug

Design (SBDD) and molecular biology. Later in 2006 Dr. Bisson joined as Research Associate the group of Dr. Pellecchia at the nearby Sanford-Burnham Medical Research Institute where he achieved experience in combining SBDD with NMR technologies against cancer and viral protein targets. In 2008 Dr. Bisson joined Oregon State University in Corvallis, OR as a Research Associate leading intra- and inter-departmental Computer-Aided Drug Design (CADD) projects on a variety of drug discovery targets. In 2010 he was appointed Senior Research Scientist and Lecturer of the course ‘ *’Structural bioinformatics and molecular modeling’’* for graduate students in the School of Pharmaceutical Sciences of the University of Geneva, Switzerland. Currently, Dr. Bisson leads and works in a variety of disease-related CADD research projects forming successful academic inter-disciplinary teams in Switzerland and abroad. He is member of the American and Swiss Chemical Society and recipient of the SNSF Prospective Researcher Award in 2003 and Basel Award 2005 and 2009.

Friday 10:25am - 10:50am

**Gennadiy Poda, Ph.D.**

Chemist, Cheminformatics and Computational Chemistry at Ontario Institute for Cancer Research, Toronto

***"Identification of Epigenetics modulators for early state anti-cancer drug discovery efforts"***

**Abstract**

Mechanisms of epigenetic regulation consist of DNA methylation and post-translational modifications (PMT) of histones. The trimethylation of lysine 4 on histone H3 (H3K4me3) is performed by several histone methyl transferases (HMTs), including SET1a, SET1b and MLL-4. For their activity they require an effector protein, WD repeat-containing protein 5 (WDR5). Rearrangement of the MLL gene is associated with acute myeloid/ lymphoblastic leukemias (ALL). Therapeutic intervention of the WDR5/MLL interaction may lead to possible novel therapeutic agents for MLL-dependent leukemias.

As a part of collaborative effort with the Structural Genomics Consortium (SGC), Toronto, Gennadiy is going to present the computational aspects of the WDR5 probe development that includes creation of the improved screening set, hit characterization and optimization *via* a structure-based focused library design and virtual screening of a 6M collection of commercially available compounds.

**Bibliography**

Dr. Gennadiy Poda received MSc from the Moscow Institute of Physics and Technology (MIPT) in Molecular and Chemical Physics, PhD in QSAR & Computational Chemistry at the Institute of Bioorganic Chemistry, National Ukrainian Academy of Sciences. After postdoctoral training in France and USA, Dr. Poda joined Pharmacia Corporation (now Pfizer, Inc.) in 2001 as a Computational Chemist. Recipient of the Pfizer Team Award, Top 10 Poster Recognition Award at Pfizer Technical Conference, Individual Performance Awards. Currently, Gennadiy is responsible for Cheminformatics and Computational Chemistry in the drug discovery group at the Ontario Institute for Cancer Research in Toronto, Canada. Co-author of 41 publications, 2 book chapters, 4 patents and 21 presentations.

Friday 10:50am - 11:15am

**Charles Grisham, Ph.D.**

Professor of Chemistry, University of Virginia

***"Teaching Students in an Undergraduate Biochemistry Course to Create Molsoft Molecular Documents"***

**Abstract**

One of the learning outcomes of any undergraduate biochemistry course should be an appreciation of the beauty and complexity of protein structures. The availability of state-of-the-art modeling software provides an opportunity to achieve this goal in interesting ways. The Protein Structure and Function Exploration (PSAFE) project was developed at the University of Virginia to introduce undergraduate biochemists to the beauties of protein structure and the nuances of scientific writing. The PSAFE project utilized the molecular document capability of ICM Browser Pro, created by Molsoft LLC, to accomplish its goals. Students in two large introductory biochemistry lecture courses were each assigned a particular protein to study and characterize throughout the semester. The students progress from learning the basics of protein structure early in the course to a thorough analysis of their proteins, in text and graphic presentations, by the end of the semester. The majority of students in these courses report that the PSAFE project was a challenging but highly satisfying experience that great enriched their understanding and appreciation of protein structure.

**Biography**

Charles M. Grisham was born in Minneapolis, Minnesota. He received his B.S. in chemistry from the Illinois Institute of Technology and his Ph.D. in chemistry from the University of Minnesota. Following a postdoctoral appointment at the Institute for Cancer Research, he joined the faculty of the University of Virginia, where he is professor of chemistry. His research career has been devoted to magnetic resonance studies of membrane and enzyme structure and function. His work has been supported by the NIH, the NSF, the Muscular Dystrophy Association, the Research Corporation, the American Heart Association, and the American Chemical Society. He is a Research Career Development Awardee of the NIH, and in 1983 and 1984 he was a Visiting Scientist at the Aarhus University Institute of Physiology in Denmark. In 1999, he was Knapp Professor of Chemistry at the University of San Diego. With Reginald Garrett, he is coauthor of *Biochemistry*, a university-level textbook published by Cengage and now in its 5$^{th}$ edition. He teaches introductory chemistry, biochemistry, and physical chemistry at the University of Virginia.

Friday 11:15am - 11:40pm

**Katherine Kantardjieff, Ph.D.**

Dean, College of Science and Mathematics at Cal State San Marcos

***"Computational Biochemistry in Undergraduate Education and Research using ICM: A Report from the Trenches"***

**Abstract**

Computational biochemistry approaches examine the structure and function of biomolecules with the objective to interpret the information, understand life at the most fundamental molecular level based on physical and chemical principles, and put the information into a predictive framework that can be applied to drug design or engineering of biomolecules with desired or novel properties. Recognizing that the fields of biology and biochemistry have become increasingly quantitative and computational in the post-genomic era, we began incorporating more advanced computation principles into the biochemistry curricula as well as undergraduate research projects at several California State University campuses. The primary instructional tool for these efforts has been Molsoft ICM. This presentation will describe the curriculum development, pedagogy, and assessments, as well as results from selected research projects conducted by undergraduate students as part of advanced coursework, senior theses, and NSF-sponsored international collaborations.

**Biography**

***Katherine A. Kantardjieff*** is the founding Dean of the new College of Science and Mathematics at California State University San Marcos and Director of the Keck Center for Molecular Structure (CMolS). Kantardjieff's previous academic appointments have been Professor and Chair of Chemistry at California State Polytechnic University Pomona and Professor of Chemistry and Biochemistry at California State University Fullerton. Her research utilizes combined experimental and computational approaches to better understand how structure controls chemical and physical properties of biomolecules, and applies this knowledge in drug design and development, as well as in engineering molecules with defined properties. While at CSU Fullerton Kantardjieff developed an innovative computational curriculum for biochemistry majors, which utilizes a Molsoft educational license to bring contemporary tools and practical experiences to students. She has been a pioneer in remote enabling of instrumentation in chemistry as well as synchronous online instruction. Kantardjieff is past chair of the Stanford Synchrotron Radiation Lightsource User Organization Executive Committee and immediate past Chair of the United States National Committee for Crystallography. She is Vice Chair of the National User Facility Organization Steering Committee and Co-Editor of the Journal of Applied Crystallography.

Friday 11:40am - 12:05pm

**Julie Ealy, Ph.D.**

Associate Professor of Chemistry, Penn State Le High University

***"Bioinformatics for Undergraduates and the Use of ICM Pro"***

## Abstract

Bioinformatics utilizes information freely available on the Internet to solve biological questions, and allows students to understand the overlap of molecular biology, genomics, molecular evolution, drug design, and gain information about proteins. Additionally in Dr. Ealy's course the use of ICM Pro is integrated so students can gain firsthand knowledge about proteins using research level computational software. Each student is assigned a specific protein that has a disease associated with it and has a crystal structure combined with a small drug that is accessible through the Protein Data Bank. Integrated with learning about bioinformatics, the students also complete tutorials on the following using ICM Pro: 1) understanding protein structure and how it relates to function, 2) investigation of hydrogen bond interactions, and 3) docking of a drug into the active site of a protein. Assessment requires their use of ICM Pro to investigate their own protein using the skills they have learned in the course. A culmination of the semester results in a poster presentation by each student to the campus based on their individual protein.

## Biography

Julie B. Ealy, Associate Professor of chemistry at Penn State University Lehigh Valley campus, has taught for 41 years from middle school science to graduate school chemical education. Presently she teaches general chemistry, organic chemistry, and bioinformatics. Students in her bioinformatics class not only use free Internet sources to gain information about proteins, but also use ICM Pro to investigate a protein associated with a disease and for which there is an available or potential drug. Her research at Penn State is both in chemical pedagogy and chemistry/biology with the focus primarily in the use of molecular modeling in almost all aspects. Her research in chemistry/biology is on the hydrogen bond interactions of small molecules in the active site of HIV-1 integrase using ICM Pro for the computational research. Undergraduate freshmen and sophomores participate in the research with Dr. Ealy. Sabbatical time spent at Hershey Medical Center in 2010 with Dr. Michael Katzman permitted her to do wet bench research investigating alternative nucleophilic substrates for the endonuclease activities of HIV-1 integrase. The sabbatical has resulted in many positive contributions to the education of her students.

Friday 3:00pm – 3:25pm

**Juan Fernandez-Recio, Ph.D.**

Research Group Leader at Barcelona Supercomputing Center

***"New challenges for protein docking in the interactomics era"***

## Abstract

Proteins interact with other proteins to form functional, highly specific complexes that are essential for the majority of life processes. We need to identify the structural and energetics determinants of molecular recognition in order to understand better protein association mechanism and to eventually be able to target protein-protein interactions with therapeutic purposes. However, after more than a decade of experimental efforts, including structural genomics initiatives, we know the 3D structure of only a tiny fraction of all protein-protein interactions. Fortunately, computer docking predictions can provide useful structural models to complement experimental efforts. The field has witnessed important advances, but several major challenges still remain. The main difficulty is the treatment of flexibility during docking, in which the algorithm of choice may depend on the binding mechanism. Induced fit can be mimicked by a rigid-body and refinement strategy, like ICM-DISCO and other coarser-grained approaches. On the other side, conformational selection mechanism could be mimicked by the use of precomputed unbound ensembles. We have explored here the use of minimization as well as molecular dynamics to generate input structures for docking, using ubiquitin as a model system. The work has been extended to a large set of cases, and we are currently analyzing the use in docking of conformers generated by normal mode analysis. The results bring interesting ideas about protein association mechanism, and we will discuss new ways to improve docking predictions using ICM.

## Biography

After a PhD in Biochemistry (University of Zaragoza, 1999), Juan Fernández-Recio spent almost four years as Research Associate in the laboratory of Prof. Ruben Abagyan at The Scripps Research Institute in La Jolla, US, developing methods for protein-protein docking based on ICM. Then he moved to the group of Prof. Sir Tom Blundell at the University of Cambridge, UK, as a Marie Curie fellow, where he continued developing methods for structural prediction of protein complexes. In 2005, he joined the Institute for Research in Biomedicine of Barcelona through the Ramon y Cajal Program to start an independent research program on prediction of protein interactions. In 2007 he moved to the Barcelona Supercomputing Center as a Research Group Director, where he is leading the Protein Interactions and Docking group at Life Sciences Department. He has published around 70 articles in international peer-review journals and has given around 30 scientific talks in international conferences (most of them as invited speaker).

Friday 3:25pm – 3:50pm

**Badry Bursulaya, Ph.D.**

Research Investigator, II at Genomics Institute of the Novartis Research Foundation

***"Protein-protein interfaces: hot spot analysis and disruption"***

**Abstract**

ICM script was developed for analyzing the protein-protein complexes with a purpose of identifying the hot spots and accessing the druggability of the pockets. Computational methods for disrupting protein-protein interactions by targeting the identified hot spots will be discussed.

**Biography**

Badry Bursulaya received his PhD in Computational Chemistry in 1998 from Carnegie Mellon University. He is currently a research investigator at The Genomics Institute of Novartis Research Foundation, La Jolla, CA.

The focus of his research is protein-ligand and protein-protein interactions and structure-based drug design.

Friday 3:50pm - 4:15pm

**Anton Filikov, Ph.D.**

Scientist II NCI Frederick

***"Antagonistic androgen receptor structure: Useful models despite low homology"***

**Abstract**

Antagonists of androgen receptor (AR) are used in the clinics for treating prostate cancer. To date, no experimental AR structure in antagonistic form is available, which greatly complicates discovery of new AR antagonists. We built homology models of antagonistic AR based on published antagonist-bound structures of estrogen (ER) and glucocorticoid (GR) receptors. Due to very low homology to the templates we used a combination of 3D superposition procedure that ignores sequence alignment for the 3D-conserved part of the protein followed by modeling based on manual alignment for the H12 helix. The models were validated by docking known and in-house antagonists - apparent molecular recognition for several chemotypes let us conclude that the models are probably useful in designing new antiandrogens.

**Biography**

Dr. Anton Filikov is a scientist at the National Cancer Institute (via SAIC-Frederick, Inc.), where he is supporting the drug discovery effort using computational chemistry, cheminformatics and bioinformatics. Prior to joining the NCI he was at ArQule, Syrrx and Xencor.

Friday 4:25pm - 4:50pm

**Timothy J. Cardozo, M.D., Ph.D.**

Associate Professor NYU Langone Medical Center

***"A Novel VLS Approach Targeting The Malaria Glideosome"***

## Abstract

*Plasmodium* species cause malaria and are obligate intracellular protozoan parasites that rely on an unusual form of substrate-dependent motility for their migration on and across host-cell membranes and for invasion and egress. This unusual motility is powered by the "glideosome", an intracellular macromolecular complex powered by the action of an actomyosin system anchored in the inner membrane complex of the parasite. A complex of actin, aldolase, and Thrombospondin-Related Anonymous Protein (TRAP) constitutes the core of the glideosome. Here, we identified several chemical compounds that prevent dis-assembly of the TRAP-aldolase complex within the glideosome using ICM-VLS against rationally modified conformations of the receptor site. Two of the compounds markedly disrupted the gliding and invasive abilities of *Plasmodium* parasites *in vitro* at micromolar concentrations, and none of the compounds were toxic to human hepatocytes. The results validate the glideosome as a malaria drug target. In addition, we have achieved the first case of rational discovery of medically promising compounds designed to enhance, rather than inhibit, a protein-protein interface.

## Biography

Dr. Timothy Cardozo, MD-PhD, is Associate Professor of Pharmacology at NYU School of Medicine (NYUSOM). He is an active clinician, educator and computational structural biologist specializing in drug and vaccine design and protein engineering. His leading project, which has been funded both by the Bill and Melinda Gates Foundation and the NIH, is immunogen design to exploit the sequence variable loops of the HIV virus. He also developed the first known inhibitor of the kinase PERK, a master regulator of the unfolded protein response (Wang et. al. 2010), and his group successfully re-engineered the estrogen receptor to bind a specific ligand (Goyanka, et. al 2010). Several other molecular design projects addressing challenging targets are under development. Because of his diverse background in liberal arts, medicine, biology, surgery, biophysics, chemistry and computer science, Dr. Cardozo was been recognized with a 2008 NIH Director's New Innovator Award. He has published over 40 papers in bioinformatics, molecular modeling, structural biology, immunology/virology, dermatology, genomics, pharmacology, cell biology, cancer biology and microbiology. At NYUSOM, he serves as Graduate Advisor for the Computational Biology Program and directs a graduate course in drug design. He currently serves on the Young and Early Career Investigator Committee for the Global HIV Enterprise. Dr. Cardozo received his PhD from NYU School of Medicine for his work in the laboratory of Dr. Ruben Abagyan.

Friday 4:50pm - 5:15pm

**Jianghong An, Ph.D.**

Staff Scientist at the Genome Sciences Centre, BC Cancer Agency

***"Identification of Autophagy Inhibitors for Novel Cancer Therapies by Targeting both Active and Allosteric Sites of ATG4B"***

**Abstract**

Autophagy, which means self-eating, is a recycling process used by living cells to degrade intracellular material within a vacuolar/lysosomal system and re-use the breakdown products for nutrients and energy. This mechanism helps cells survive under conditions of low nutrients, hypoxia, and other conditions of cell stress. Similarly, autophagy can have a survival or protective role in tumors exposed to numerous anti-cancer treatments. Moreover, inhibiting autophagy was demonstrated to result in an enhanced tumor response to various chemotherapies, but no specific inhibitors for autophagy currently exist.

Among the more than 20 identified autophagy-related (ATG) genes, ATG4B, which encodes a cysteine protease, plays an important role in the process. ATG4B interacts with LC3 (ATG8), a central autophagy pathway component that mediates autophagosome formation. Fortunately, abundant ATG4B structural data is available, including crystal structures of the free, closed conformation and LC3 complexes with open, active conformations. These structures are suitable for performing molecular docking-based large scale in silico inhibitor screening.

Based on the available biological and structural data, several strategies were applied to identify candidate inhibitors of ATG4B. First, the pocket finder program was applied to all available crystal structures to identify potential small molecule binding sites. For the structures of LC3-ATG4B complexes, we used pockets identified on the LC3-ATG4B interface to conduct inhibitor screening. Those potential binders are predicted to inhibit the biological interaction of LC3 and ATG4B. For the structures with a closed, inactive conformation, we chose pockets where a potential ligand may bind to help stabilize the inactive conformation, which in turn would interfere with substrate interaction. Four pockets were identified in total and molecular docking was conducted against them.

To help identify ATG4B-specific compounds for biological validation, all selected candidates were docked to a pocket database of all human protease and ubiquitin-like proteins for which crystal structures are available. Compounds that docked to those proteins better than to ATG4B were removed.

The final candidates are undergoing testing in cell-free assays (FRET-based LC3 cleavage) to determine effects on enzyme activity, as well as in cell-based assays (GFP-LC3 puncta quantification and p62 degradation) to determine their effects on autophagy activity. At the moment at least one compound was validated for each binding pocket. Further investigations of these and other compounds, as well as the combination of compounds for different binding pockets are in progress. (Supported by CIHR team grant GPG 102167).

**Biography**

Dr. An is a staff scientist of the Genome Sciences Centre, British Columbia Cancer Agency (BCCA, Canada) and his research interests focus on discovery of small molecule inhibitors for therapeutical protein targets through the collaboration with laboratories inside and outside the Agency. Prior to joining the BCCA in 2005, Dr. An was a research associate in Dr. Abagyan's lab at the Scripps Research Institute.

Friday 5:15pm - 5:40pm

**Giovanni Bottegoni, Ph.D.**

Istituto Italiano di Tecnologia

***"Computational hit discovery of a novel anandamide transport inhibitor"***

**Abstract**

The termination of anandamide (AEA) signaling is a two-step process in which AEA is first removed from the synaptic space by a selective transport system, and then it is hydrolyzed by intracellular amidases. In the past, the development of drug-like AEA transport inhibitors had been strongly hampered by a limited characterization of the internalization mechanism at the molecular level. Here, we report the discovery of an important element of anandamide transport, a catalytically-silent variant of the fatty acid amide hydrolase-1 (FAAH-1), which we named FAAH-like anandamide transporter (FLAT). Moreover, we describe the results of a virtual ligand screening campaign carried out on a model of FLAT that led to the identification of ARN272, a competitive antagonist of AEA binding to FLAT. ARN272 presents a remarkable activity profile both in vitro and in rodent models of pain.[1]

[1] Fu J., Bottegoni G., et al. Nature Neuroscience 2011 15(1) 64:9

**Biography**

A pharmaceutical biotechnologist by training, Giovanni Bottegoni received his Ph.D. in Pharmaceutical Sciences in 2005 from the University of Bologna, Italy. He then moved to The Scripps Research Institute (La Jolla, CA, USA), where he spent two years as a postdoctoral research fellow. Since 2008, he has been a senior postdoc at the Drug Discovery and Development Unit of the Italian Institute of Technology.

**Meeting Participants *(As of Printing)***

Ruben Abagyan Ph.D.
Professor
University of California San Diego,
La Jolla, CA

Margarita "Rita" Abagyan
Director of Operations
Molsoft LLC
San Diego, CA

Jianghong An Ph.D.
Staff Scientist
Genome Sciences Centre, BC Cancer Agency
Vancouver, Canada

Yelena Arnautova Ph.D.
Senior Research Scientist
MolSoft LLC
San Diego, CA

William Bisson Ph.D.
Senior Research Scientist and Lecturer
University of Geneva
Geneva, Switzerland

Andrew Bordner Ph.D.
Assistant Professor of Pharmacology
Mayo Clinic
Scottsdale, AZ

Giovanni Bottegoni Ph.D.
Senior Post-Doc
Istituto Italiano di Tecnologia
Genoa, Italy

Carlo Bouton Ph.D.
Associate Director Technology & Information Management
Ablynx
Ghent/Zwijnaarde
Belgium

Slava Brover MSc
Senior Software Developer
MolSoft LLC
San Diego, CA

Badry Bursulaya Ph.D.
Research Investigator, II
Genome Novartis Foundation
La Jolla, CA

Tim Cardozo Ph.D. MD
Associate Professor
NYU Langone Medical Center
New York, NY

Crystal Crawford
General Counsel
MolSoft LLC
San Diego, CA

Lei Du-Cuny Ph.D.
Investigator II
Novartis

Julie Ealy Ph.D.
Associate Professor of Chemistry
Penn State University Lehigh Valley

Juan Fernandez-Recio Ph.D.
Research Group Leader
Barcelona Supercomputing Center
Barcelona, Spain

Anton Filikov Ph.D.
Scientist II
NCI Frederick

Charles Grisham Ph.D.
Professor of Chemistry
University of Virginia
Charlottesville, VA

Rashmi Hedge Ph.D.
Professor
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Katherine Kantardjieff Ph.D.
Dean, College of Science and Mathematics
Cal State San Marcos
San Marcos, CA

Irina Kufareva Ph.D.
Project Scientist
University of California San Diego
La Jolla, CA

Hua Li Ph.D.
Scientist
BASF
Research Triangle Park, NC

Andrew Orry Ph.D.
Senior Research Scientist
MolSoft LLC
San Diego, CA

Eugene Raush M.Comp.Sc.
Principal Software Developer
MolSoft LLC
San Diego, CA

Bernhard Rupp Ph.D.
Founder and CEO
q.e.d. life sciences discoveries

Patrick Sexton Ph.D.
Professor of Pharmacology
Monash University
Melbourne, Australia

Deborah Slee Ph.D.
Head of Research and Development Chemistry at
CendR Inc. and Vice President Chemistry
Aspyrian Therapeutics, Inc. San Diego, CA

Terry Stouch Ph.D.
President
Science For Solutions, LLC

Lutz Tautz Ph.D.
Research Assistant Professor
Sanford-Burnham Medical Research Institute
La Jolla, CA

Vselevod "Seva" Katrich Ph.D.
Assistant Professor of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Polo Lam Ph.D.
Senior Research Scientist
MolSoft LLC
San Diego, CA

Brian Marsden Ph.D.
Principal Investigator
Research Informatics
SGC
University of Oxford
Oxford, UK

Gennadiy Poda Ph.D.
Chemist
Cheminformatics and Computational Chemistry at
Ontario Institute for Cancer Research
Toronto, Canada

Manuel Rueda Ph.D.
Post-doc
UCSD
La Jolla, CA

Arman Sahakyan MSc
Senior Software Developer
MolSoft LLC
San Diego, CA

Evgeny Shmelkov MSc
Ph.D. Candidate
New York University
New York, NY

Michael Storek Ph.D.
Associate Director
Alexion Pharmaceuticals
Cambridge, MA

Michael Sundstrom Ph.D.
VP Discovery Research
Karolinska Development

Maxim Totrov Ph.D.
Principal Scientist
MolSoft LLC
San Diego, CA

Gina Wei Ph.D.
Sr. Scientist II
Halozyme Therapeutics, Inc.
San Diego, CA

Leyte Winfield Ph.D.
AssistantProfessor
Spelman College
Atlanta, GA

Gerard van Westen MSc
Ph.D. Candidate
Leiden/Amsterdam Center for Drug Research
Leiden, The Netherlands