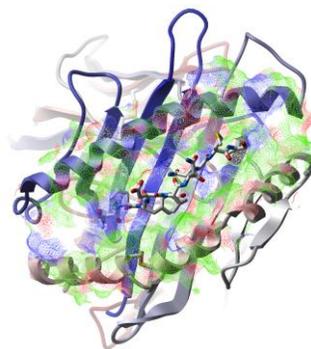
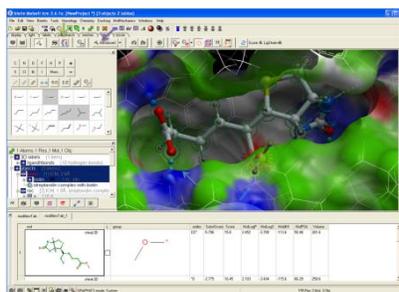
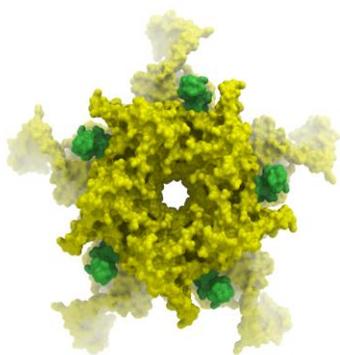


Challenges in Protein Structure Prediction and Drug Discovery



ICM User Group Meeting La Jolla CA USA

April 9th – 10th, 2009



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 25 speakers from all over the world who will be presenting on a wide range of subjects including molecular modeling, docking and screening, cheminformatics, and molecular visualization. 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 talks we have a number of events scheduled throughout Thursday and Friday. The events are designed to give everyone opportunities to interact and exchange ideas as well as chances to personally ask our speakers about their areas of expertise. Most of these events include some element of food, refreshments, and exercise - we hope you can join us!

Thanks for participating.

The MolSoft User Group Meeting Organization Committee

MolSoft LLC 3366 N. Torrey Pines Court Suite 300 La Jolla CA 92037

858 625 2000 x102

www.molsoft.com

List of Extracurricular Events

Thursday Lunchtime: Lunch at the Beach – join us at Del Mar’s Powerhouse Park for pizza, boat rides with the Del Mar Lifeguards, and beach volleyball.

Thursday Evening: Sundowner Reception at MolSoft

Friday Morning: Early morning walk at Torrey Pines State Park for early birds and jet lagged people!

Friday Evening: Wine and Cheese reception at the Abagyan Lab

For more information on each event, pick up a flyer during registration

or speak to Andy, Crystal or Rita from MolSoft

THURSDAY 9TH APRIL - MORNING SESSION

- 8:00am - 8:30am Meeting registration.
- 8:30am - 9:05am **Welcome by Prof. Ruben Abagyan, Ph.D.**
Professor, The Scripps Research Institute, and MolSoft Founder
"ICM – Past, Present and Future"
- 9:05am - 9:40am **Keynote Speaker: Maxim Totrov, Ph.D.**
Principal Scientist, MolSoft LLC
"Atomic Property Fields (APF): methodology for ligand and receptor superposition and comparison"

PROTEIN STRUCTURE MODELING AND ANALYSIS

- 9:40am – 10:05am **Irina Kufareva, Ph.D. (The Scripps Research Institute)**
"Identification, characterization, and targeting of protein kinase exosites"
- 10:05am - 10:25am **Break** - Refreshments provided by MolSoft
- 10:25am -11:00am **Keynote Speaker: Prof. Michael Sundström, Ph.D.**
Managing Director, Novo Nordisk Foundation Center for Protein Research, University of Copenhagen
"Chemical bioprobes for structural and functional studies of medically relevant proteins"
- 11:00am - 11:25am **Timothy Cardozo, M.D., Ph.D. (NYU)**
"Deciphering conserved structures in dynamic or unstable protein surfaces."
- 11:25am - 11:50am **Bengt Persson, M.D., Ph.D. (Linköping University & Karolinska Institute)**
"Prediction of mutant severity using structural calculations in ICM"
- 11:50am - 2:30pm **Lunch provided at Del Mar Powerhouse Park**

THURSDAY 9TH APRIL AFTERNOON SESSION

2:30pm – 2:55pm **Lutz Tautz, Ph.D. (Burnham Institute for Medical Research)**

“Structure-based design of tyrosine phosphatase inhibitors”

2:55pm – 3:30pm **Keynote Speaker: Brian Marsden, Ph.D.**

Structural Genomics Consortium, University of Oxford, UK

“Structural Biology Data Visualization for the Masses”

MEMBRANE PROTEIN MODELING AND DRUG DESIGN

3:30pm - 3:55pm **Aina Westrheim Ravna, Ph.D. (University of Tromso)**

“Molecular modeling and docking studies of drug transporters using ICM”

3:55pm - 4:10pm Break – Refreshments provided by MolSoft

4:10pm – 4:35pm **Lars Brive, Ph.D. (University of Goteburg)**

“A hybrid receptor/ligand-based approach for dopamine receptor agonist selectivity.”

4:35pm - 5:00pm **Vsevolod “Seva” Katritch, Ph.D. (The Scripps Research Institute)**

“Structure based selectivity profiling for GPCR ligands”

5:00pm - 5:25pm **Polo Lam, Ph.D. (MolSoft LLC)**

“Modeling the Secretin Receptor”

Evening **Sundowner Reception at MolSoft LLC**

FRIDAY 10TH APRIL MORNING SESSION

7:00am- 8:15am Early morning walk at Torrey Pines State Reserve for early birds and jet lagged people! See flyer for more details.

CHEMICAL BIOLOGY AND CHEMINFORMATICS

8:30am - 9:05am **Keynote Speaker: Dr. Eric Martin, Ph.D.**
Novartis Institute for Biomedical Research
“Interactive Drug Design Using the ICM 3D Ligand Editor”

9:05am- 9:30am **Valérie Campagna-Slater, Ph.D. (Structural Genomics Consortium, Toronto)**
“Out of the box computational chemistry -> Outside the box applications”

9:30am - 9:55am **Olga Lomovskaya Ph.D. (MPex Pharmaceuticals)**
“Overcoming multi-drug resistance in bacteria”

9:55am - 10:10am Break – Refreshments provided by MolSoft

10:10am - 10:45am **Keynote Speaker: Donovan Chin, Ph.D.**
Novartis Institute for Biomedical Research
“FOCUS: A Software Platform For Virtual Medicinal Chemistry”

10:45am - 11:10am **Professor Katherine Kantardjieff, Ph.D. (Cal State University - Fullerton)**
“Exploiting Structural Information for Modeling and Simulation: Guiding Principles from Chemistry”

11:10am - 11:35pm **Eugene Raush, M.Sc. (MolSoft LLC)**
“Overview and recent development of Molsoft ActiveICM.”

11:35pm - 1:30pm **Lunch on your own**

FRIDAY 10TH APRIL AFTERNOON SESSION

PROTEIN-PROTEIN DOCKING

- 1:30pm – 1:55pm **Juan Fernandez-Recio Ph.D. (Barcelona Super Computing Center)**
"Protein-protein docking with ICM and beyond: current and future challenges"
- 1:55pm – 2:20pm **Andrew Bordner, Ph.D. (Mayo Clinic)**
"Peptide-MHC docking with ICM for epitope prediction".

STRUCTURE BASED DRUG DESIGN

- 2:20pm - 2:45pm **Jianghong An, Ph.D. (BCGSC)**
"Discovery of a novel small-molecule inhibitor of the avian influenza H5N1 virus"
- 2:45pm - 3:00pm Break – Refreshments provided by MolSoft
- 3:00pm - 3:25pm **Giovanni Bottegoni Ph.D. (Istituto Italiano di Tecnologia)**
"The Challenge of Receptor Flexibility in Molecular Docking Studies"
- 3:25pm - 3:50pm **Edmond Ma, Ph.D. (University of Hong Kong)**
"Computer-Aided Drug Design and Lead Optimization: Small Molecule Inhibitor of Beta-Lactamase"
- 3:50pm - 4:15pm **Colin Smith, Ph.D. (University of California at San Francisco)**
"Identifying druggable sites in protein structures and virtual screening-based discovery of PfENR inhibitors"

CLOSING PRESENTATION

- 4:15pm – 5:15pm **Prof. Ruben Abagyan, Ph.D.**
Professor, The Scripps Research Institute, Founder, MolSoft LLC
- Evening **Wine and cheese reception – Abagyan Lab - TSRI**

Prof. Ruben Abagyan Ph.D.

The Scripps Research Institute and MolSoft Founder

“ICM – Past, Present and Future”

Biography

Dr. Ruben Abagyan has been a Professor in the Department of Molecular Biology of The Scripps Research Institute, La Jolla, California, since 1999. He graduated from the Moscow Institute of Physics and Technology in 1980 and received his Ph.D. in molecular modeling and biophysics from the Moscow State University in 1984. In 1990 he moved to Heidelberg Germany and became a staff scientist at the European Molecular Biology Laboratory, where he laid the foundation for a new internal coordinate approach to molecular structure prediction and molecular docking (ICM). In 1994 he moved to New York University where he became the director of computational biology and IT at the Skirball Institute of Biomolecular Medicine. At NYU he received tenure as Associate Professor of Biochemistry and Mathematics at the NYU Medical School and the Courant Institute of Mathematics, respectively. During the same year he co-founded Molsoft LLC to continue the development of the ICM program. From 1999 to 2001 he served as the Director of Computational Biology, Chemistry and IT at the Novartis Institute for Functional Genomics. Dr. Abagyan has co-authored over 130 peer-reviewed publications and book chapters. He has developed an international reputation in the field of proteomics and structure-based drug discovery and received grants from NIH, DOE, DOD and private organizations. He has served on the Board of Directors of Syrrx and Plexus Vaccines, and on organizing committees for conferences on drug discovery. In 2000 and 2002 he accepted CapCure Award for excellence in prostate cancer research, and in 2003 he received the Princess Diana medal in Sydney, Australia. In 2007 Dr. Abagyan was appointed Adjunct Professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego and received an Excellence Award from the UCSD School of Pharmacy.

Keynote Speaker: Dr. Maxim Totrov Ph.D.

Principal Scientist, MolSoft LLC

“Atomic Property Fields (APF): methodology for ligand and receptor superposition and comparison”

Abstract

Alignment or superposition of multiple flexible ligands in 3D is a key step in rational ligand-based drug design, pharmacophore elucidation and 3D QSAR analysis. We have recently introduced Atomic Property Fields methodology, which utilizes continuous Gaussian-based multicomponent potentials to represent the distributions of physico-chemical atomic properties. Calculation of APF pseudo-energy provides a sensitive measure of similarity between these distributions for two or more molecules in 3D. Because the potentials are continuous and smooth, gradient minimization can be used to achieve locally optimal fit, while global sampling is performed using Monte-Carlo to identify globally optimal superposition. The method is shown to successfully identify non-trivial superpositions, and to be effective in VLS and 3D QSAR tests.

The approach is next extended to the superposition and comparison of the binding sites in protein receptors. Atom set forming a shell around the binding site is treated as a 'molecule' to be superimposed. Application of the APF superposition approach to distantly related active sites shows the ability of the method to identify and superimpose common features despite wide overall divergence of the receptor structures. Furthermore, APF pseudo-energy can serve as a measure of similarity between pairs of binding sites. Sites similar to a query are successfully identified in a database of binding sites. Finally, by converting the APF score into a distance measure and applying hierarchical clustering, all binding sites in a database can be clustered into families which correspond well to the established functional classes.

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.

Irina Kufareva, Ph.D.

The Scripps Research Institute – La Jolla, CA

"Identification, characterization, and targeting of protein kinase exosites"

Abstract

The surface of a typical protein kinase has multiple sites of regulatory interactions with other cellular proteins or alternative domains of the same kinase. In contrast to the ATP-binding site targeted by most kinase therapeutics, these sites are called exosites. Small-molecule compounds targeting the exosites have three potential advantages: they (i) are non-ATP-competitive, (ii) more specific, and (iii) may subtly modulate, rather than inhibit, the kinase activity by changing its substrate preferences or subcellular localization.

We built a system of ICM scripts for automatic identification, cataloguing, and annotation of the potential druggable exosites on the protein kinase domains within the existing structural kinome (~140 of 478 protein kinases at the moment). We also developed two structure modeling protocols for exosite compound screening. One protocol generates accurate and specific models of the most famous transient exosite – the so-called hydrophobic “selectivity” pocket – starting from the abundant structures of the activated kinases. Another protocol is designed to improve druggability of transient apo-exosites. Application of the latter protocol to protein kinase CK2 allowed for rational development of exosite modulators of CK2 activity which act by disrupting the CK2 subunit interaction.

Biography

Irina Kufareva received a MS in mathematics and a PhD in computer science, both from Tomsk State University, Russia. She is currently a senior research associate at The Scripps Research Institute, 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.

Keynote Speaker: Prof. Michael Sundström, Ph.D.
Managing Director
Novo Nordisk Foundation Center for Protein Research
University of Copenhagen, Sweden

“Chemical bioprobes for structural and functional studies of medically relevant proteins”

Abstract

The major goal for structural biology is to provide the 3D structures of human proteins and protein complexes and provide insights regarding their structure/function relationships. However, as large scale structural biology/genomics initiatives can be considered the major academic ‘producers’ of recombinant proteins of medical relevance, an enormous opportunity exists to better utilize this resource for the identification and development of low molecular weight compounds that bind to the proteins and have the ability to modulate their function. To date, this ‘protein bank’ has been under utilized by academic researchers, in large part due to resource restraints for translational research and due to lack of knowledge of the requirements for drug discovery and development. However, recent work in combining Structural and Chemical Biology has now started to yield results that clearly show a path forward, e.g. by the use of systematic interaction studies versus larger collections of recombinant enzymes.

Biography

Managing Director, NNF Center for Protein Research

Michael Sundström assumed the position as Managing Director for the Novo Nordisk Foundation, Center for Protein Research at the University of Copenhagen, in Sept 2007. Funding (~100 M€) for the centre spans over 10 years, with an explicit goal to establish it as a leading international research centre with focus on protein target identification and validation. Currently, the centre employs 25 staff members, but expects to grow to ~150 staff members in 2011/2012. Particular focus areas are disease systems biology, proteomics, protein production and characterization, interactome analyses as well as disease biology.

<http://www.cpr.ku.dk>

Previous Management Experience

Chief Scientific Officer, Structural Genomics Consortium (Oxford) 2003–07

Director, In-Licensing, Biovitrum AB (Stockholm) 2002–2003

VP Research, Actar AB (Stockholm) 2001–2002

Director, Structural Chemistry & Informatics, Pharmacia (Milan) 1998–2001

Head, Protein Crystallography Pharmacia (Stockholm) 1995-1997

Thursday, 11:00AM

Timothy Cardozo, M.D., Ph.D.

New York University

"Deciphering conserved structures in dynamic or unstable protein surface."

Abstract

The surface envelope glycoprotein (gp120) of the HIV virus mediates infection via its specific recognition of human cellular receptors. gp120 consists of a sequence-conserved, well structured core buried under sequence variable and dynamic variable loops. A critical protein interaction surface for infectivity is formed by the third variable loop of gp120. Accordingly, conserved structures that mediated host receptor engagement are preserved in this variable loop despite frequent sequence variation and dynamic structure that promote immune system escape. We use ICM ab initio folding to detect conserved structures in this dynamic, sequence variable loop and draw structure activity relationships that are useful for protein design.

Biography

Currently an Assistant Professor at NYU School of Medicine, Dr. Cardozo trained in Ruben Abagyan's lab for his PhD and received his MD concurrently. Since his training, Dr. Cardozo has been pursuing collaborative protein design and drug design projects in academia centered on HIV vaccine design and protein interface drug discovery.

Bengt Persson, M.D., Ph.D.

Linköping University & Karolinska Institutet

"Prediction of mutant severity using structural calculations in ICM"

Abstract

A structural model of human steroid 21-hydroxylase (CYP21) was calculated using ICM in order to enhance our knowledge of structure–function relationships and to better understand the molecular causes of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. A total of 60 disease-causing mutations and six normal variants were individually modelled. A structural explanation for the corresponding phenotype was found for all but two mutants for which available clinical data do not correlate with in-vitro enzyme activity. We found an inverse correlation between the calculated stability of the protein and clinical severity of the mutant. Furthermore, the ICM model allowed us to identify putative structurally important residues involved in haem- and substrate-binding, redox-partner interaction and enzyme catalysis using docking calculations and homology with structurally determined cytochrome P450s.

The stability measure of mutated structures calculated using ICM has also been used as basis for a method to predict the effects of mutations in the p53 cancer suppressor gene, believed to be involved in over 50% of all human cancers. The new method takes both structural features and sequence properties into account. For each mutant, a severity score is reported, which can be used to classify them into deleterious and non-deleterious. The method has a prediction accuracy of 77% on all mutants and 88% on breast cancer mutations on the WAF1 promoter. When compared to earlier methods, using the same dataset, our method clearly performs better.

Biography

Bengt Persson is professor of bioinformatics at Linköping University and Karolinska Institutet, and director of National Supercomputer Centre, Linköping, Sweden.

Lutz Tautz Ph.D.

Burnham Institute for Medical Research

“Structure-based design of tyrosine phosphatase inhibitors”

Abstract

Tyrosine phosphorylation is a rapidly reversible post-translational modification, catalyzed by protein tyrosine kinases (PTKs) and reversed by protein tyrosine phosphatases (PTPs). The human genome contains 103 PTP genes with 81 encoding for active phosphatases. Disturbances of PTP function have been implicated in diverse human diseases including cancer, diabetes, and autoimmune disorders. Targeting PTPs with small molecules is still a challenge yet to be mastered. Structure-based, rational approaches can help to develop compounds that are both potent and selective for the phosphatase of interest.

Biography

Lutz Tautz received his Ph.D. in Organic Chemistry and Biochemistry in 2002 from Karlsruhe University, Germany, under the direction of Prof. Janos Retey. He then joined Prof. Tomas Mustelin's group at the Burnham Institute for Medical Research La Jolla, CA, where he worked as a postdoctoral associate, and later as a Staff Scientist. Since 2009 he has been holding the position as a Research Assistant Professor at the Burnham Institute. His research focuses on protein tyrosine phosphatases (PTPs) and their modulation by small molecules in cell signaling events. He applies methods such as HTS, (Q)SAR, and structure- and ligand-based approaches to identify new lead compounds for particular PTPs, as well as assays to characterize compounds in vitro and ex vivo.

Brian Marsden, Ph.D.

Structural Genomics Consortium, University of Oxford, United Kingdom

“Structural Biology Data Visualization for the Masses”

Abstract

The SGC is an international public-private partnership (UK charity number 1097737) that aims to determine three dimensional structures of medically important human proteins, including integral membrane proteins, and proteins from human parasites. All structures, results and related reagents created by the SGC are made freely available via public databases in a prompt manner without IP constraints.

A vast quantity of data is generated by the SGC and published in many forms, including many co-crystallised structures with small molecules, and chemical biology data . However, much of this data is disseminated in a manner that is not accessible to non-structural biologists. In collaboration with Molsoft, we have pioneered an approach, called iSee, to present our structural work to the non-expert in an intuitive and interactive manner. iSee datapacks contain expert annotations of protein structures with emphasis on the insights in biological function the structures have given. To date we have made available over 500 datapacks to the public and are now embarking on a project to have many of these peer reviewed and published.

The aforementioned amount of data we generate also has a clear impact in the accessibility of the SGC’s web sites. Hundreds of structures, limited available screen area, lots of metadata – how does a visitor find anything of interest? We have begun the development of a web 2.0 platform to provide the visitor the ability to filter down through the available structural information in an interactive manner.

Finally, we are developing novel web-based applications for non-structural biologists using activeICM to leverage our structural and chemical biology data for the purposes of generating chemical probes for epigenetics-related protein targets. A sneak-preview of one of these applications will be given.

Biography

Brian completed his D.Phil. in the NMR lab of Prof. Iain Campbell at the University of Oxford on molecular dynamics of fibronectin modules, and then made a fateful decision to join a certain Prof. Abagyan's lab at TSRI in La Jolla. Here he learned much about ICM, did some methods-development on structural alignments and built a number of large Linux clusters. A spell at Biofocus in Saffron Walden, UK as a team leader in computational chemistry taught him the benefits and follies of industrial life (and a bit about drug-discovery) but then was asked to run the Informatics group at a fledgling academic organisation known as the Structural Genomics Consortium (SGC). He has been there ever since and is responsible for providing LIMS, computational chemistry, cheminformatics, bioinformatics and also IT systems. His main interests focus around the development of more accessible informatics platforms and also in the dissemination of multi-disciplinary data to the non-expert.

Aina Westrheim Ravna, Ph.D.

University of Tromsø, Norway

“Molecular modeling and docking studies of drug transporters using ICM”

Abstract

Homology modeling of membrane proteins such as transporters involved in drug abuse and depression, and transporters involved in multidrug resistance, represent special challenges; there are few templates and homology may be low. Still, experimental data may be reproduced in molecular modeling and docking studies. The dopamine (DAT), serotonin (SERT) and noradrenalin (NET) transporters are molecular targets for different classes of psychotropic drugs. The crystal structure of Aquifex aeolicus LeuT(Aa) has been used as a template for molecular modeling of DAT, SERT and NET, and two putative drug binding sites (pocket 1 and 2) in each transporter have been identified. Cocaine was docked into binding pocket 1 of DAT, corresponding to the leucine binding site in LeuT(Aa), and clomipramine was docked into binding pocket 2 of DAT, corresponding to the clomipramine binding site in a crystal structure of a LeuT(Aa)-clomipramine complex. The structures of the proposed cocaine- and tricyclic antidepressant-binding sites may be of particular interest for the design of novel DAT interacting ligands. Multidrug resistance (MDR) is a limitation to cancer chemotherapy, antibiotic treatment and HIV medication. Molecular models of the ABC transporters ABCB1 (P-glycoprotein), ABCC4 (multidrug resistance protein 4 (MRP4)) and ABCC5 (MRP5), which are involved in MDR, has been constructed and are currently being used in docking studies which may aid in the development of drugs inhibiting anticancer agents efflux.

Biography

Dr. Ravna received her Ph.D. in pharmacology from the University of Tromsø, Norway, in 2003. Her thesis was titled: "Molecular modelling of secondary transporters and their interactions with cocaine and SSRIs". Dr. Ravna is currently working in a post doctoral position (granted by The Norwegian Cancer Society) doing molecular modeling studies on ABC transporters involved in multidrug resistance.

Lars Brive, Ph.D.

University of Goteburg, Sweden

"A hybrid receptor/ligand-based approach for dopamine receptor agonist selectivity."

Biography

1998 Ph D in Chemistry, Gothenburg University, Sweden

1999-2001 Postdoc with Kathryn Ely, The Burnham Inst, La Jolla

2001-2003 Postdoc with Ruben Abagyan, The Scripps Research Inst, La Jolla

2003-2004 Postdoc repatriation, Biophysics, Gothenburg University

2004-2008 Assistant Professor, Cell & Molecular Biology, Gothenburg University

2009-current Associate Professor, Dept Biomedicine, Sahlgrenska Academy, Gothenburg University

Vsevolod “Seva” Katritch, Ph.D.

The Scripps Research Institute

"Structure based selectivity profiling for GPCR ligands"

Abstract

More than 800 seven-transmembrane (7TM) proteins of GPCR family are involved in signaling and regulation in CNS, cardiovascular, immune and other major systems in our bodies. Moreover, GPCRs are targets for almost half of the existing drugs in clinic, and the range of novel targets and investigational drugs in this field are rapidly expanding. Unfortunately, 3D modeling of GPCRs was long hampered by the lack of relevant structural data, with rhodopsin (Rho) being the only GPCR with crystal structure solved. The situation is rapidly changing thanks to the recently determined high resolution structures of β -adrenergic (β 2AR, β 1AR) and adenosine A2a receptor (AA2AR), which opens an opportunity for accurate 3D analysis of the whole families of clinically relevant GPCRs.

In this talk Dr. Katritch will illustrate several recent applications of the ICM molecular modeling to analysis of different aspects of GPCR interactions with small molecule ligands: (i) analysis of agonist-induced conformational changes in β 2AR, (ii) blind prediction of the antagonist-AA2AR complex structure, and (iii) modeling of the adenosine receptor subtype selectivity. He will also discuss the benefits of ligand guided optimization approach in development of GPCR models for drug discovery.

Biography

Dr. Vsevolod “Seva” Katritch received a B.Sc. in physics and applied math and a Ph.D. in computational molecular biology from Moscow Institute of Physics and Technology (MIPT), while also serving as a visiting scholar at Lausanne University, Switzerland. He got his postdoctoral training at Rutgers University, NJ and The Scripps Research Institute with Prof. Ruben Abagyan. Dr. Katritch served as Associate Director of Structural Genomics at Plexus Vaccine Inc, and as Director of Computational Biology at SIGA Technologies Inc. His works on molecular modeling have been published in more than 25 scientific papers, including three in the Nature Journal. Dr. Katritch also coauthored a book on conformational modeling of biopolymers and more than 5 patent applications. Current interests focused on (i) structural and computational biology of membrane proteins, including GPCRs, (ii) structure-based drug discovery and (iii) application of genomic data to analysis of individual drug response.

Chun Hung “Polo” Lam, Ph.D.

MolSoft LLC

“Modeling the Secretin Receptor”

Abstract

In this talk, Dr. Lam will summarize aspects of the recent progress in the modeling of Secretin Receptor, including transmembrane domain and loop modeling, peptide docking guided by distance restraints, and dimerization modeling.

Biography

Polo Lam graduated from Virginia Tech in 2004, worked on asymmetric syntheses in a number of areas, including Tryptophan, Benzodiazepine analogs and Taxol dimers. He joined Dr. Ruben Abagyan’s lab at TSRI after graduation and subsequently joined Molsoft LLC in 2006. For the last few years, he has been working on different projects, including homology modeling and virtual screening in Family A and B GPCRs, acetylcholinesterase, phosphodiesterase. He is currently a research scientist at Molsoft.

Keynote Speaker: Dr. Eric Martin, Ph.D.

Novartis Institute for Biomedical Research

“Interactive Drug Design Using the ICM 3D Ligand Editor”

Abstract

Interactive Drug Design Using the ICM 3D Ligand Editor, *Mika Lindvall*¹, *Donovan Chin*², *Peter Hunt*³, *Nikolaus Stiefl*⁴, *Yongjin Xu*¹, *Eugene Raush*⁵, *Andrew Orry*⁵, *Max Totrov*⁵, *Ruben Abagyan*⁵, *Novartis Institutes for BioMedical Research: 1Emeryville CA, 2Cambridge MA, 3Horsham England, 4Basel Switzerland 5Molsoft: La Jolla CA*

The most effective single tool in drug design is the intuition of experienced medicinal chemists. Their ability to combine estimates of synthetic feasibility, toxicological liabilities, metabolic liabilities, physicochemical properties, and effective ligand/protein interactions is unmatched by any computational methods. The ability to bring this experience effectively to bear within the confines of a 3D ligand binding site, however, is limited by the available tools for interactive 3D drug design.

Colin McMartin and Regine Bohacek pioneered interactive 3D ligand editing within a protein binding site. [McMartin, C., Bohacek, R. J. QXP: Powerful, rapid computer algorithms for structure-based drug design. *Computer-Aided Mol. Design* 11(1997): 333-344] Drawing on years of practical experience doing drug design with QXP/FLO+, a team of Novartis scientists worked with Molsoft to design an interactive 3D editor within ICM. This implementation employs many powerful features and innovations, while maintaining a simple intuitive interface that facilitates the capture of medicinal chemists' thinking. It can be used side-by-side with a professional modeler, or easily operated directly by medicinal chemists. The philosophy and use of the 3D ligand editor will be demonstrated, and its strengths and weaknesses discussed.

Biography

Eric Martin has a Ph.D. in physical organic chemistry from Yale University. He has worked in computational chemistry, analytical instrumentation, drug design and herbicide design for 25 years. He is best known for starting the field of combinatorial library design in 1993. His recent research focuses on iterative medium-throughput screening employing docking with target-customized scoring functions, and on data-driven modeling methods that treat individual kinase drug targets as members of a family, rather than as idiosyncratic protein targets.

Primary Current Research Interests:

- “AUTOSHIM”: creating highly predictive target-customized docking functions by generating interaction features for an ensemble of crystal structures, parameterizing regression models on the features against activity data (“shimming”), and iteratively refining the pose selection with model parameterization.

- Kinase-target family modeling:

“2D profile-QSAR models”: highly predictive activity models, including cellular activity, for new kinases from combining historical activity data for 100,000s of compounds against 70 kinase enzyme assays and 32 cellular assays.

“Surrogate docking”: AUTOSHIMMING a “universal kinase model”, i.e. an ensemble of crystal structures from diverse kinases, to predict the binding of new kinases with no crystal structure. Pre-docking a compound archive makes this 3D docking method as fast as 2D QSAR.

- Interactive structure-based drug design.
- High-throughput computing on Beowulf clusters.
- Conformational analysis and active-analog approaches for drug discovery using ab initio quantum methods.
- Targeted, structure-based and property-tailored combinatorial library design.

Valérie Campagna-Slater, Ph.D.

Structural Genomics Consortium – University of Toronto

“Out of the box computational chemistry -> Outside the box applications”

Abstract

A quick overview will be given of three applications which utilize virtual screening techniques to extract information from chemical or protein databases. First, the World Drug Index (WDI) was screened in a virtual chemical genetics approach that interfaces the biological and pharmacological spaces. Validation against seven targets, including 4 enzymes and 3 nuclear hormone receptors, shows that VLS of the WDI is able to recapitulate known biology for many of the targets tested, and uncover unknown biology. In the second project, compounds of interest are docked to thousands of pockets from the PDB to predict their pharmacology. Last, a pharmacophore approach was used to search the entire human PDB for novel pockets possessing pre-defined chemistry.

Biography

Valérie Campagna-Slater completed her B.Sc. in chemistry at the University of Ottawa (1999-2003). She then completed a Ph.D. in chemistry at Dalhousie University (2003-2007) under the supervision of Dr. Donald F. Weaver, focusing on the development and application of methods for molecular modeling and drug design. She joined the Structural Genomics Consortium at the University of Toronto in January 2008, where she works as a postdoctoral fellow in the group of Dr. Matthieu Schapira.

Friday 9:30AM

Olga Lomovskaya, Ph.D.

Mpex Pharmaceuticals, Inc.

“Overcoming multi-drug resistance in bacteria”

Biography

Dr. Lomovskaya has extensive experience in microbiology and molecular genetics, antibiotic resistance mechanisms, and drug discovery, and is a leading expert in the field of bacterial efflux pump biology. At Mpex, she is responsible for discovery biology, including lead discovery and optimization. In addition, she is a project leader for the company's IV EPI program. Previously, Dr. Lomovskaya was Associate Director of Biology at Essential Therapeutics (previously Microcide Pharmaceuticals) where she coordinated efforts in the discovery and evaluation of antibiotics and antibiotic potentiators from natural products and synthetic libraries. She received her Ph.D. in molecular genetics from the Institute of Molecular Genetics, Russian Academy of Sciences and her M.S. in molecular biology from Moscow State University, with research appointments at MIT, Cal Tech and Stanford. Dr. Lomovskaya is an inventor on several patents, authored numerous original papers and review articles and is serving as a member of editorial boards of several scientific journals.

Friday 10:10AM

Keynote Speaker: Dr. Donovan Chin, Ph.D.

Novartis Institute for Biomedical Research

“FOCUS: A Software Platform For Virtual Medicinal Chemistry”

Abstract

This talk will showcase the use of ICM as a software platform (which we call FOCUS) to facilitate the analysis of data and the design of new compounds by medicinal chemists. We have integrated tools, methods and databases across the global NIBR intranet along with the usual ICM technologies into a customized user interface. This user interface extends the ‘molecular document’ concept with the Molsoft internal development GUI language in a way that creates simple workflow widgets that are used by casual and expert users to simplify complex workflows.

Concepts driving the development of FOCUS are 1) iterative hypothesis-driven design 2) easy access to validated CADD methods & models 3) one stop shop for tools focused on drug discovery.

Biography

Donovan is a member of the CADD group at Novartis in Cambridge MA, and is the originator and project leader for FOCUS. Prior to Novartis he was at Biogen Idec, Transform Pharmaceuticals and Moldyn. He did his post-doc with George Whitesides at Harvard, and his PhD was in computational polymer science from the University of Massachusetts.

Katherine Kantardjieff, Ph.D.

California State University Fullerton

“Exploiting Structural Information for Modeling and Simulation: Guiding Principles from Chemistry”

Abstract

Users and consumers of crystallographic information must remember that a biomolecular crystal structure is a hypothesis based upon model agreement with the diffraction data. Provided they are fully validated by established criteria, such models present an opportune starting point for additional computation that may provide further insights into biochemical function and mechanism, as well as successfully guide drug discovery efforts, including target selection, synthesis, and design modification to optimize binding affinity and pharmacokinetic properties. Crystal structures also provide the basis for comparative protein structure modeling which, by matching accuracy with intended use, may be used for virtual screening, defining antibody epitopes, protein engineering, rational mutagenesis, molecular replacement phasing, and fitting low resolution electron density. Given a structure, molecular dynamics or QM/MM approaches may further elucidate catalytic mechanism and contribute meaningfully to inhibitor design. It is also important to remember that, in the early stages of the drug discovery process, we choose a strategy able to generate new chemical leads that will exhibit desirable biochemical activity. Successful screening efforts should aim to select stable, non-covalent ligands and eliminate protein-reactive compounds from consideration as drug leads early in the process. As we shall see in this presentation, exploiting biomolecular crystal structure and compound collections for modeling and simulation can be quite powerful in addressing a research problem or learning about fundamental chemistry. However, *caveat emptor*.

Biography

Katherine Kantardjieff is Professor of Chemistry and Biochemistry at California State University Fullerton, where she is Director of the W.M. Keck Foundation Center for Molecular Structure, a research and training laboratory in X-ray diffraction analysis, molecular modeling and simulation, and a core facility for the California State University Program for Education and Research in Biotechnology. Her research interests are in protein structure and function, biophysics, structural biology, crystallography, structural genomics, computational biochemistry, and structure-guided drug design. Kantardjieff developed the University Bioinformatics Certificate Program, and she is currently leading a CSU-wide effort to develop high-performance computing infrastructure. Kantardjieff received the Andreoli Faculty Service Award in 2009, the highest honor bestowed upon faculty by CSUPERB. She is Faculty Coordinator for Academic Technology at Cal State Fullerton, and she is Chair of the United States National Committee for Crystallography (NAS/NRC).

Eugene Raush, M.Comp.Sc.

MolSoft LLC

“Overview and recent development of Molsoft ActiveICM.”

Abstract

ActiveICM was developed in 2008 as a tool for dynamic 3D molecular structure visualization that can be embedded into web-pages and Microsoft Office applications. It is a successful alternative to JMol and Accelrys ActiveX controls widely used by the scientific community. ActiveICM has multiple advantages over both. It fully preserves the visualization capabilities of Molsoft Browser, it can be embedded in a MS PowerPoint presentation, and it is free. The embedded unit for ActiveICM is an ICM binary project file created by the user in the complete ICM environment that, in addition to molecular objects, may contain views, ICM slides, and/or ICM scripts. In the recent months, we implemented new functionality that allows (i) automatic transition between molecular views within the ActiveICM control embedded in a PowerPoint slide; (ii) one-way communication between existing active controls on a PowerPoint slide or a web-page and the embedded ActiveICM control. We also created a tool for conversion of ICM project files with HTML content into complete web-pages. The new functionality is actively employed by ICM users all over the world.

Biography

Education: MS in Computer Science from Tomsk State University 1994

Consultant for Molsoft LLC since 1999

Senior Software Engineer at Molsoft since 2002

Juan Fernandez-Recio, Ph.D.

Barcelona Super Computing Center

"Protein-protein docking with ICM and beyond: current and future challenges"

Abstract

Computational docking aims to predict the structure of a complex formed by two interacting proteins starting from the structures of the individual components. Many different docking methods have been reported, with mixed success. The recent CAPRI experiments (<http://www.ebi.ac.uk/msd-srv/capri/>) provide an objective assessment of current docking methods and their successes and limitations. One of the most successful methods in the first two CAPRI editions was ICM-DISCO [1], which used a two-step approach: i) pseudo-Brownian Monte-Carlo rigid-body search on grid-based potentials with an essential evaluation step based on Coulombic electrostatics (with distance-dependant dielectric constant), truncated (soft) van der Waals (ECEPP parameters), empirical hydrogen bonding and ASA-based desolvation; and ii) refinement of selected docking poses with ICM optimization of ligand interface side-chains [2,3]. A simplification of the rigid-body evaluation scheme (considering only electrostatics and desolvation) was later implemented in pyDock [4] in order to rescore docking sets generated by a variety of methods, which yielded top results as scorer tool in the most recent CAPRI edition [5]. Further use of distance restraints from sequence conservation [6] or end-to-end distance of flexible peptide segments [7] helped to improve docking. These approaches have been applied to different interactions of biological and therapeutical interest, such as in the recently reported ICM-based modelling of transient interactions in electron transfer between FNR and its redox partners ferredoxin and flavodoxin [8]. Finally, future directions of the protein-protein docking field will be discussed.

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Biography

Dr. Juan Fernández-Recio. Director of the Protein Docking and Interactions group at the Barcelona Supercomputing Center (BSC). He did a PhD in Biochemistry at the University of Zaragoza (1995-1999). Since that time, he has spent almost six years in the internationally renowned laboratories of Prof. Ruben Abagyan (NYU Skirball Institute in New York, US; Scripps Research Institute in San Diego, US) and Prof. Sir Tom Blundell (University of Cambridge, UK), in which he has acquired expertise in molecular recognition between proteins and has contributed to develop computational tools that are state-of-the-art

in the protein-protein docking field. In 2005, he joined the Barcelona Science Park (PCB) and the Institute for Research in Biomedicine (IRB), which made possible to start pioneer research lines in Spain in the field of molecular modeling of protein-protein interactions. Dr. Fernández-Recio was awarded a Curie European Reintegration Grant and two consecutive Plan Nacional I+D+i grants, and recently he joined the BSC as a Group Leader in the Life Sciences Department. He has published more than 40 research articles in international peer-review scientific journals, has presented his work in a more than 20 scientific talks in international conferences (most of them as invited and plenary lectures), has filled 1 international patent, has been involved in teaching in several Master and Courses on Computational Biology and Bioinformatics (MSc Univ. Cambridge; MSc UB-UPF; Doctorate UB; Summer Courses in Univ. Zaragoza and Univ. Complutense Madrid), has organized three international scientific conferences, one EMBO course on docking, and is supervising several PhD students (2 awarded and 4 ongoing theses). He has established a large number of collaborations throughout the world in order to analyze the binding mode of many systems of biological and therapeutical interest.

Andrew Bordner, Ph.D.

Mayo Clinic

"Peptide-MHC docking with ICM for epitope prediction".

Abstract

The binding of short protein fragments to class I and II MHC is required for initiating a cytotoxic or helper T-cell immune response. Because there are > 1000 MHC types and each one binds a distinct subset of peptides the prediction of which peptide binds a particular MHC, based on limited experimental data, is a challenging problem. Commonly used sequence-based methods use machine learning to find characteristic patterns in binding versus non-binding peptide sequences. However, structure-based methods that use docking and scoring have the potential to identify binding peptides with non-standard motifs not present in the training set. Furthermore, because they employ a physical energy function, they can make predictions for different MHC types than those used to train the model. We discuss methodology and results for docking peptides to both class I and class II MHC and using the docked structures to predict peptide epitopes. The discovery of such epitopes has potential biomedical applications in vaccine design and understanding autoimmunity.

Biography

Andrew Bordner began his postdoctoral computational biology training at the UCSD Department of Biomedical Engineering in 1999. He then joined Ruben Abagyan's group at The Scripps Research Institute in 2001 and also worked at Molsoft for about one year. In 2005 he became a Research Scientist at Oak Ridge National Laboratory in Tennessee. He is currently an Assistant Professor in the Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic in Arizona.

Jianghong An Ph.D.

Genome Science Center, Vancouver, British Columbia, Canada

“Discovery of a novel small-molecule inhibitor of the avian influenza H5N1 virus“

Abstract

Computational molecular docking provides an efficient and innovative approach to examine small molecule and protein interactions. We have utilized this method to identify potential inhibitors of the H5N1 neuraminidase protein. Of the twenty compounds tested, one compound, NSC89853, demonstrated the ability to inhibit viral replication at a level comparable to the known neuraminidase inhibitor oseltamivir (Tamiflu). It demonstrated efficacy across a number of cell-lines assays and in both the H1N1 and H5N1 viruses. The predicted binding of the compound to the known H5N1 neuraminidase structure indicates a binding interface largely non-overlapping with that of oseltamivir or another neuraminidase inhibitor zanamivir (Relenza). These results indicate that this compound or similar molecules would remain effective in the presence of virus mutations conferring resistance to either oseltamivir or zanamivir and also vice-versa.

Biography

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

Giovanni Bottegoni Ph.D.

Italian Institute of Technology

"The Challenge of Receptor Flexibility in Molecular Docking Studies"

Abstract

One of the greatest obstacles against a truly unbiased use of molecular docking in computer assisted drug design is the fact that almost every standard protocol currently employed freezes completely or almost completely the receptor conformation during simulations. Overlooking protein flexibility means to belittle the pivotal role conformational rearrangements play in basically every biological event proteins are involved in. Two different but potentially paired approaches aimed at implementing receptor flexibility in ligand docking will be here presented. Both the reported protocols were built on top of well established and optimized ICM docking and scoring algorithm to a single static receptor. The SCan Alanines and Refine (SCARE) algorithm produces gapped versions of a single pocket conformer, docks a flexible ligand to each of the variants, and, after optimization and re-scoring, selects the best energy pose. SCARE proved particularly useful when the binding event is associated to a localized but pronounced rearrangement of one or more side chains. The Four-Dimensional Docking approach is a general ensemble docking protocol that represents receptor flexibility as the fourth dimension of the sampling space. 4D Docking achieved the accuracy of a traditional ensemble docking paradigm, employing on average only one fourth of the time during the ligand sampling phase.

Biography

Pharmaceutical biotechnologist by trade, in 2005 Giovanni Bottegoni received his doctoral degree in medicinal chemistry from the University of Bologna, Italy. Soon after he joined as a post-doc the group of Professor Abagyan at the Scripps Research Institute, La Jolla, CA – USA where, for two years, he studied and developed advanced methodologies in docking and virtual ligand screening. Presently, he is a senior post-doc in the group of Dr. Cavalli at the Dept. of Drug Discovery and Development (D3), Istituto Italiano di Tecnologia (Italian Institute of Technology), Genoa – Italy.

Edmond Ma, Ph.D.

University of Hong Kong

“Computer-Aided Drug Design and Lead Optimization: Small Molecule Inhibitor of Beta-Lactamase”

Abstract

The increasing emergence of β -lactamases in the bacteria family is a worrying clinical problem. These bacterial enzymes can inactivate many clinically useful β -lactam antibiotics with extremely high efficiency, and constitute the major antibiotic-resistant mechanism in the bacterial world. This clinical pressure has spurred up extensive efforts on the discovery of new and potent inhibitors against classes A and C β -lactamases, which are commonly encountered in many clinical cases of bacterial infection. In particular, class C β -lactamases have received increasing attention in recent years because of lack of potent inhibitors against these destructive enzymes. With the aid of computer-aided drug design, we have built up an *in silico* protein model from the class C AmpC β -lactamase for virtual drug screening. We have successfully made use of the *in silico* AmpC model to design a series of 50 new flavone derivatives (through ligand docking), which are non- β -lactam organic compounds. Our preliminary *in vitro* enzyme activity studies have shown that some of the flavone derivatives can inhibit the hydrolytic activity of the AmpC β -lactamase. These encouraging results prompted us to further investigate the potencies of the flavone derivatives designed *in silico*.

The objectives of this project are to

- (i) synthesize the new flavone derivatives,
- (ii) investigate the effects of the flavone derivatives on the hydrolytic activity of the AmpC β -lactamase,
- (iii) examine the effects of the flavone derivatives on the anti-antibiotic activities of bacterial strains capable of producing the AmpC enzyme, and
- (iv) study the AmpC/flavone interactions by X-ray crystallography.

Biography

Dr. Edmond Ma is specialized in molecular modeling, virtual ligand screening and drug design & flexible receptor docking. After his training at The University of Hong Kong under Prof. Chi-Ming Che, he undertook the post of postdoctoral fellow (2005–2008) at Hong Kong Polytechnic University (supervisor: Prof. Kwok-Yin Wong). In 2007, he went to The Scripps Research Institute (supervisor: Prof. Ruben Abagyan) as a visiting scientist. For the past three years, Dr. Edmond Ma has actively participated in the drug discovery by computational structural biology approach and published seventeen papers in international journals. Recently, Dr. Edmond Ma and several collaborators from The Scripps Research Institute (USA), The University of Hong Kong, and The Hong Kong Polytechnic University, using the predictive power of computers to uncover new and potentially powerful anti-cancer, anti-bacteria, anti-Parkinson or anti-virus therapeutics from a library of natural products or Drug-like compounds.

Colin Smith, Ph.D.

University of California at San Francisco

"Identifying druggable sites in protein structures and virtual screening-based discovery of PfENR inhibitors"

Abstract

There is a dire need for novel therapeutics to treat the dangerous malarial parasite, *Plasmodium falciparum*. Recently, the X-ray crystal structure of enoyl-acyl carrier protein reductase (ENR) in complex with triclosan has been determined and provides an opportunity for the rational design of novel inhibitors targeting the active site of ENR. Here we report the discovery of several compounds by virtual screening and their experimental validation as high potency PfENR inhibitors.

Meeting Participants
(As of printing)

Margarita Abagyan
Director of Operation
MolSoft LLC
La Jolla, CA

Ruben Abagyan, Ph.D.
Professor of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Jianghong An, Ph.D.
Staff Scientist
Genome Science Center
Vancouver, British Columbia
Canada

Andrew Bordner, Ph.D.
Assistant Professor
Mayo Clinic
Scottsdale, AZ 85259

Giovanni Bottegoni, Ph.D.
Post Doctoral Researcher
Italian Institute of Technology (IIT)
Genoa, Italy

Lars Brive, Ph.D.
Associate Professor
University of Goteburg
Sweden

Valérie Campagna-Slater, Ph.D.
Post Doctoral Researcher
Structural Genomics Consortium
Toronto, Canada

Timothy Cardozo, MD, Ph.D.
Assistant Professor
Department of Pharmacology
New York University
New York, NY

Donovan Chin, Ph.D.
Research Investigator II, CADD,
Novartis Institute for Biomedical Research
Cambridge, MA

Crystal Crawford
General Counsel
MolSoft LLC
La Jolla, CA

Victoria Feher, Ph.D.
Principal Scientist
Takeda San Diego, Inc.
San Diego, CA

Juan Fernandez-Recio Ph.D.
Director of the Protein Docking and Interactions
Group
Barcelona Supercomputing Center (BSC)
Spain

Therese Fuller, M.Sc.
Coleman College
San Diego, CA 92123

Veli-Pekka Jaakola, Ph.D.
Post Doctoral Researcher
Department of Molecular Biology
The Scripps Research Institute
La Jolla CA 92037

Claudio Joazeiro, Ph.D.
Assistant Professor
Department of Cell Biology
The Scripps Research Institute
La Jolla, CA

Katherine Kantardjieff, Ph.D.
Professor of Physical Chemistry
California State University - Fullerton
Fullerton, CA

Vsevolod "Seva" Katritch, Ph.D
Scientific Associate
Department of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Irina Kufareva, Ph.D.
Senior Research Associate
Department of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Olga Lomovskaya, Ph.D.
Vice President of Biology
Mpex Pharmaceuticals, Inc.
San Diego, CA

Brian Marsden, Ph.D.
Principal Investigator
Research Informatics
Structural Genomics Consortium
Oxford, United Kingdom

George Nicola, Ph.D.
Post Doctoral Researcher
Department of Molecular Biology
The Scripps Research Institute
La Jolla, CA

So-Jung Park, Ph.D.
Post Doctoral Researcher
Department of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Michael Pique
Department of Molecular Biology
The Scripps Research Institute
La Jolla, CA

Eric Scheeff, Ph.D.
Research Associate
Salk Institute
La Jolla, CA

Keren Klein
PhD Student
Department of Pharmacology
New York University
New York, NY

Chun Hung "Polo" Lam, Ph.D.
Research Scientist
MolSoft LLC
La Jolla, CA

Edmond Dik-Lung Ma, Ph.D.
Assistant Professor
University of Hong Kong

Eric Martin, Ph.D.
Director, Computational Chemistry
Novartis Institute for Biomedical Research
Emeryville, CA

Andrew Orry Ph.D.
Senior Scientist
MolSoft LLC
La Jolla, CA 92037

Bengt Persson, M.D., Ph.D.
Professor of Bioinformatics, Director of NSC
(National Supercomputer Centre)
Linköping University & Karolinska Institutet,
Linköping, Sweden

Eugene Raush, M.Comp.Sc.
Senior Software Engineer
MolSoft LLC
La Jolla, CA

Colin Smith
Graduate Student
University of California at San Francisco
San Francisco, CA

Sujata Sovani
Research Technician
Department of Molecular and Experimental
Medicine
The Scripps Research Institute
La Jolla, CA

Vyachesav "Slava" Brover, M.S.
Senior Software Engineer
Molsoft LLC
La Jolla, CA

Michael Sundström, Ph.D.
Managing Director
Novo Nordisk Foundation Center for Protein
Research
Copenhagen, Denmark

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

Maxim Totrov, Ph.D.
Principal Scientist
MolSoft LLC
La Jolla, CA

Aina Westrheim Ravna, Ph.D.
Post Doctoral Researcher
University of Tromso
Norway

Lily Wu, Ph.D.
Postdoctoral Fellow
Department of Pharmacology
New York University
New York, NY