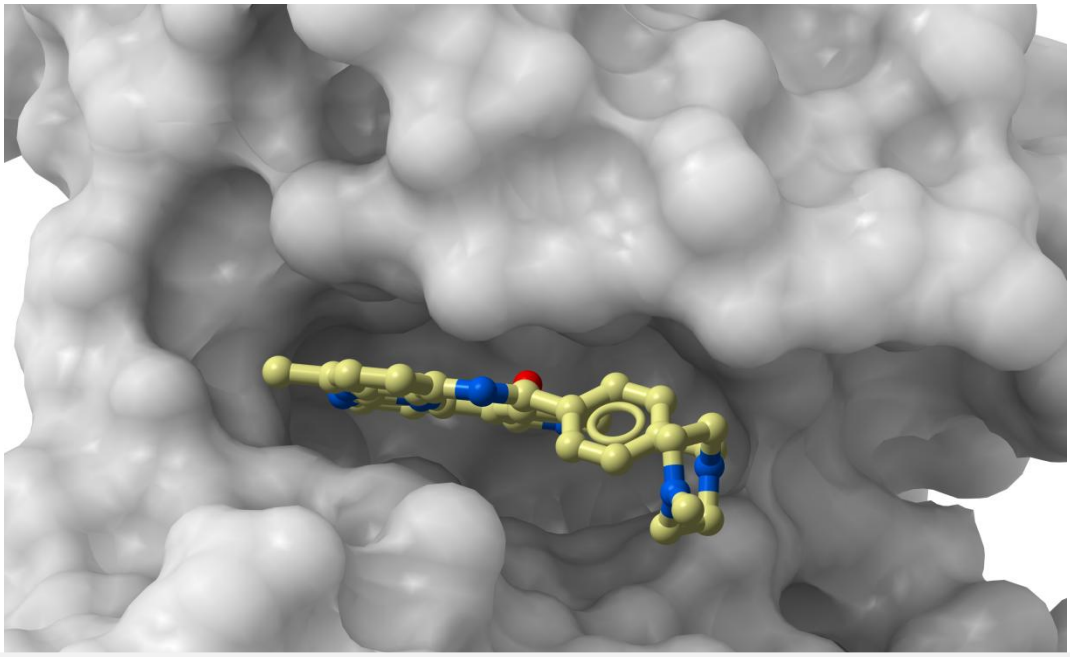
April 4-5 San Diego, CA



MolSoft Workshop

Next Generation ICM Desktop Computational Biology and Chemistry Tools

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Workshop Conducted By

Ruben Abagyan Ph.D.	Professor	UCSD, MolSoft Founder
Maxim Totrov Ph.D.	Principal Scientist	MolSoft LLC
Eugene Raush M.Comp.Sci.	Principal Software Developer	MolSoft LLC
Polo Lam Ph.D.	Senior Research Scientist	MolSoft LLC
Andrew Orry Ph.D.	Senior Research Scientist	MolSoft LLC

Attendees

Andrew Stelzer Ph.D.	Research Scientist	Nymirium
Andrew Bordner Ph.D.	Senior Associate Consultant	Mayo Clinic
Badry Bursulaya Ph.D.	Research Investigator II	GNF
Brian Marsden Ph.D.	Principal Investigator	SGC Oxford
Donovan Chin Ph.D.	Senior Investigator I	Novartis
Doreen Tivon B.Sc.	Research Associate	NYU
Han Choe Ph.D.	Associate Professor	Uni. of Ulsan College of Medicine
Hua Li Ph.D.	Scientist	BASF
Laurence Miller M.D. Ph.D.	Director of Research	Mayo Clinic
Lutz Tautz Ph.D.	Research Assistant Professor	Sanford Burnham
Mark Shenderovich Ph.D.	Principal & CSO	Mol3D Research
Rosa Buonfiglio B.Sc.	Graduate Student	University of Bologna
Ryan Brady Ph.D.	Drug Discovery Researcher	Monash University
Vsevolod (Seva) Katritch Ph.D.	Assistant Professor	The Scripps Research Institute
Thomas Coudrat M.Sc.	Graduate Student	Monash University
Tim Cardozo M.D. Ph.D.	Associate Professor	NYU
Wadud Bhuiya Ph.D.	Senior Scientist	Conagen Inc
Weirong Xing Ph.D.	Assistant Professor	Loma Linda University
William Bisson Ph.D.	Assistant Professor	Oregon State University

Thursday April 4th

9:00 - 10:00	**ICM Methods and Success Stories** Presentation by Ruben Abagyan Ph.D. (MolSoft Founder)
10:00 - 10:15	Break
10:15 – 11:00	**New Features in the ICM 3D Ligand Editor** Andrew Orry Ph.D. - Fragment Based Drug Design - Ligand Based Screening via APF - Multiple Receptor Docking - Covalent Docking
11:00 -12:00	**Overview of the new features in the Graphical User Interface** Andrew Orry Ph.D.
12:00 - 2:00	Lunch at Torrey Pines State Beach
2:00 – 2:45	**ICMPages & ICMdb: New ways of capturing and mining data in ICM** Brian Marsden Ph.D. (SGC Oxford)
2:45 - 3:15	**Methods for Incorporating Receptor Flexibility in Ligand Docking** Presentation by Max Totrov Ph.D.
3:15 - 4:30	**Hands on Multiple Receptor Docking Examples** Max Totrov Ph.D. - How to prepare an ensemble of structures for 4D docking - Multiple Receptor Conformation Docking - Partially Explicit Receptor Docking
4:30 - 4:45	Break
4:45 - 5:15	**Covalent Ligand Docking and Screening** Max Totrov Ph.D.

Friday April 5th

9:00 - 10:15	**ICM Molecular Modeling** Ruben Abagyan Ph.D. - Linking sequence to structure - ICM Biased Probability Monte Carlo (montecarlo command) - Methods for building multiple receptor conformations - Model refinement - Model selection
10:15 - 10:30	Break
10:30– 11:30	**ICM-Scripting - Advanced Data Types and Operations** Eugene Raush M.Comp.Sci - Working with Chemical Spreadsheets - Filter expressions and related functions - Commands, column formulas, plots, data trees - Chemical arrays + related functions and
11:30 – 12:00	**Overview of the latest development in ICM scripting language** Eugene Raush M.Comp.Sci - New data type: Collection - Logical expression "short-circuit" - conditional expression support a?b:c - Incorporating ICM into KNIME
12:00 - 1:00	Lunch
1:00 - 1:30	**Introducing MolScreen - New Product Launch** Polo Lam Ph.D.

Friday 5th User Group Meeting

1:30 - 1:55	Donovan Chin Ph.D. (Novartis) Cloud *Super* Computing for Chemical Diversity
1:55 - 2:20	Laurence Miller M.D. Ph.D. (Mayo Clinic) Roles of ICM in elucidation of structure of class B GPCRs: Focus on the prototypic secretin receptor.
2:20 – 2:30	Break
2:30 - 2:55	Lutz Tautz Ph.D. (Sanford Burnham) Less competitive may be a better option, novel strategies for targeting the human PTPome.
2:55 – 3:20	Tim Cardozo M.D. Ph.D. (NYU) Inhibition of the protein interface governing degradation of the tumor suppressor p27 by the SCF-Skp2 ubiquitin ligase.
3:20 – 3:45	Andrew Stelzer Ph.D. (Nymirium) Utilizing RNA Dynamics to Discover Novel Therapeutics
3:45 – 4:05	Break
4:05 - 4:30	Andrew Bordner Ph.D. (Mayo Clinic) Predicting the biophysical effects of residue substitutions using ICM
4:30 – 4:55	William Bisson Ph.D. (Oregon State University) Computational Chemogenomics in Drug Design and Discovery : Recent Applications
4:55 – 5:30	**Questions and Answers with MolSoft's Scientists and Developers**
5:30-	**Wine and Cheese Reception**

User Group Meeting Abstracts and Bios

Donovan Chin Ph.D. (Novartis)

Cloud *Super* Computing for Chemical Diversity

Bio

Donovan is a member of the CADD group at Novartis in Cambridge MA, and has been a drug hunter for 15+ years. Prior to Novartis he was at Biogen Idec, Transform Phramaceuticals (now part of J&J), 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.

Laurence Miller M.D. Ph.D. (Mayo Clinic)

Roles of ICM in elucidation of structure of class B GPCRs: Focus on the prototypic secretin receptor.

Bio

Dr. Miller trained at Jefferson Medical College and did his residency in Internal Medicine and fellowship in Gastroenterology at Mayo Clinic. He did his postdoctoral training in Cell Biology at Yale University School of Medicine. His subsequent career has been at Mayo Clinic in Rochester, MN and at Mayo Clinic in Scottsdale, AR, where he moved to set up the Cancer Center and to be Dean of Research in 2002. He has had a longstanding interest in the structure, function, and regulation of GPCRs and in use of these insights for drug development.

Abstract

G protein-coupled receptors (GPCRs) are the largest superfamily of receptor molecules in the genome and the predominant target of existing drugs. We now know much about the structure of the class A GPCRs, with the solution of crystal structures of more than a dozen such molecules. The class B GPCRs represent a small, but potentially important group of GPCRs that have been predicted to possess structural differences from the class A GPCRs. In this talk, we will review the characteristics of this family of receptors and of the experimental approaches used to elucidate their structure and the molecular basis of natural ligand and drug binding and activation of these molecules. This has relevance for drug development and optimization of drug candidates targeting these receptors.

Lutz Tautz Ph.D. (Sanford Burnham Medical Research Institute)

Less competitive may be a better option, novel strategies for targeting the human PTPome.

Bio

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

Abstract

Protein tyrosine phosphatases (PTPs) are important signaling molecules and implicated in many human diseases, ranging from cancer to cardiovascular, immunological, infectious, neurological, and metabolic diseases. Consequently, the development of specific PTP inhibitors is of great interest, as such molecules may be used as tool compounds for exploring aberrant PTP function in cells and in vivo, or may lead to the development of novel therapeutics. However, because of the highly conserved active site among the members of the PTP superfamily, lack of inhibitor selectivity has posed a major hurdle in past and current efforts. Novel strategies to overcome this main obstacle will be discussed.

Tim Cardozo M.D. Ph.D. (NYU)

Inhibition of the protein interface governing degradation of the tumor suppressor p27 by the SCF-Skp2 ubiquitin ligase.

Bio

Dr. Timothy Cardozo, MD-PhD, is Associate Professor of Biochemistry and Molecular Pharmacology at NYU School of Medicine (NYUSOM). He is an active clinician, educator and computational structural biologist specializing in drug/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 medicine, biology, surgery, chemistry and computer science, Dr. Cardozo was 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. He also 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.

Abstract

In the ubiquitin proteasome system, the E3 ligase SCF-Skp2 and its accessory protein, Cks1, promote proliferation largely by inducing the degradation of the CDK inhibitor p27. Overexpression of Skp2 in human cancers correlates with poor prognosis, and deregulation of SCF-Skp2-Cks1 promotes tumorigenesis in animal models. Skp2, however, is a challenging target for drug discovery because it contains no enzymatic active site, and executes its functions solely through protein-protein interactions. We identified small molecule inhibitors specific to SCF-Skp2 activity using in silico screens targeted to the binding interface for p27. These compounds selectively inhibited Skp2-mediated p27 degradation by reducing p27 binding through key compound-receptor contacts. In cancer cells, the compounds induced p27 accumulation in a Skp2-dependent manner and promoted cell-type-specific blocks in the G1 or G2/M phases. Our approach may be applicable to other functional protein interfaces, and designing SCF-Skp2-specific inhibitors may be a novel strategy to treat cancers dependent on the Skp2-p27 axis.

Andrew Stelzer Ph.D. (Nymirium)

Utilizing RNA Dynamics to Discover Novel Therapeutics

Bio

Andrew Stelzer uses his expertise in molecular modeling, structural biology, and RNA-small molecule recognition to discover novel lead compounds that bind a target RNA and abrogate cellular malfunction. Andrew is an experienced researcher with 6 years experience in small molecule drug discovery with expertise in biophysics, computational chemistry and biochemistry. During his PhD tenure at the University of Michigan, Andrew co-invented a technology aimed at RNA-targed drug discovery. This technology was licensed out of the University and formed the core technology of Nymirum, a biotech based in Ann Arbor, MI. While working at Nymirum, Andrew has been instrumental in all aspects of the business from the bench/desk to strategic partnerships, to IP portfolio development.

Abstract

RNAs are increasingly being shown to exhibit fundamental roles in regulating biological processes. Numerous studies investigating RNA biological function indicate that many RNAs regulate biology through their three dimensional structure and dynamics, which leads to varying degrees of interaction with other critical biomolecules such as proteins, RNA, DNA, and small molecules. At Nymirum, we are focused on elucidating the RNA structures that regulate biology and exploit RNA structure and dynamics for drug discovery purposes. The core Nymirum technology combines nuclear magnetic resonance spectroscopy (NMR) and molecular dynamics (MD) to generate dynamic ensembles of target RNAs. The RNA conformers from the ensemble are interrogated to identify putative binding pockets, which provide insight into RNA biological function and have identified key RNA-small molecule interactions that afford biological activity. Libraries of small molecules are virtually screened against the binding pockets and top scoring diverse putative small molecule binders are selected for downstream experimental testing. Here we show that using the Nymirum approach, novel small molecules have been identified to bind the HIV-1 TAR RNA, displace the cognate TAR-binding protein Tat, and inhibit viral replication by binding the HIV-1 TAR RNA. We also show the NMR-MD ensemble of the CUG RNA, which is implicated as a toxic species

in DM1 patients, revealed minor groove binding pockets that were successfully exploited to identify novel CUG-binding small molecules that alleviate CUG-mediated splicing defects in a cell-based minigene assay.

Andrew Bordner Ph.D. (Mayo Clinic)

Predicting the biophysical effects of residue substitutions using ICM

Bio

Andrew Bordner is currently a senior associate consultant in the Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic in Arizona. His research interests include molecular modeling of proteins, computational immunology, bioinformatics, and clinical informatics. He has previously worked at Oak Ridge National Laboratory, Molsoft LLC, The Scripps Research Institute, and UCSD.

Abstract

Residue substitutions can change the stability of proteins as well as their binding affinities to other molecules. Computational prediction of these effects has application to diverse biomedical problems. We begin by discussing how ICM molecular mechanics simulations can be used to predict these quantities. Next, we will describe two different applications of these techniques to designing proteins or peptides with altered binding affinities. One application is discovering competitive peptide antagonists of the secretin receptor while the other is engineering MHC proteins with enhanced binding to T cell receptors. Finally, we describe a current project in which we are applying large-scale prediction of the the effects of disease-associated mutations on human proteins, including their stability and binding to other proteins and DNA.

William Bisson Ph.D.

Computational Chemogenomics in Drug Design and Discovery : Recent Applications

Bio

Dr Bisson completed in 2003 his PhD in Medicinal and Computational Chemistry at the ETH Zurich, Switzerland. In 2004 he joined as a Research Fellow the Scripps Research Institute in La Jolla, CA. Later in 2006, Dr. Bisson started as a Research Associate at the nearby Sanford-Burnham Medical Research Institute. In 2008 Dr. Bisson joined as a Research Associate the Oregon State University and in 2010 he came back to Switzerland, at the University of Geneva as Senior Research Scientist. Currently, Dr. Bisson got appointed Assistant Professor at Oregon State University working successfully in inter-disciplinary projects mostly in cancer using computational chemogenomics. He recently got selected for the international initiative in carcinogenesis called the Halifax Project involving 26 countries worlwide as one of 12 Leaders coming also from Stanford, Yale, Duke Medical Schools. Specifically Leader of the Team ''Biomarker and Disruptive Validation''.