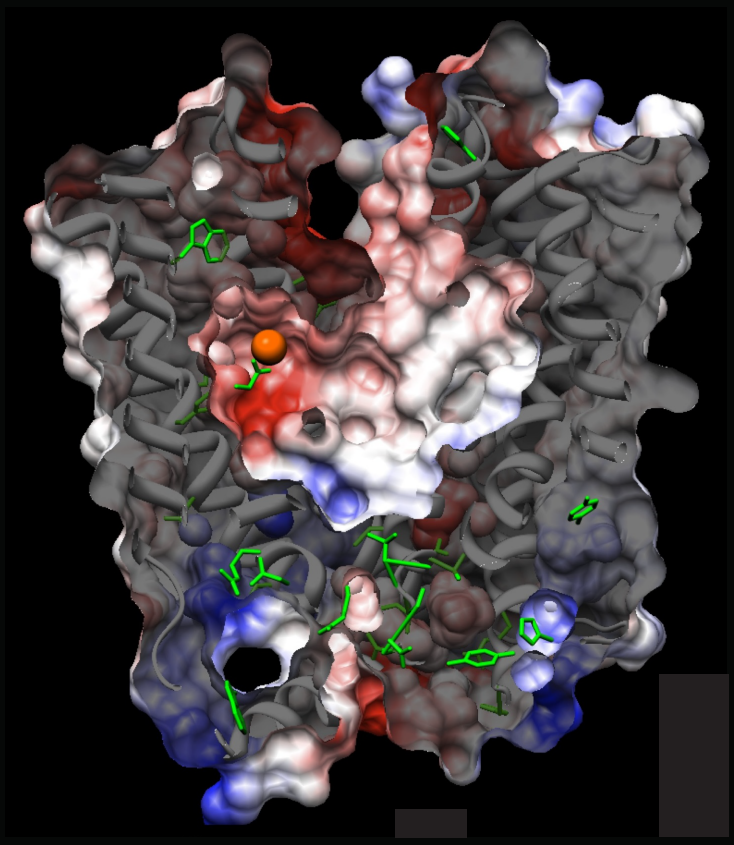
World Molecular Engineering Network



CABO 2011

UCSF
University of California
San Francisco

The Scripps Research Institute

Our History

The WMEN conference has been held for the past 21 years during the month of May in Los Cabos, Mexico. The meetings originated from a grant from the Rockefeller Foundation supporting research collaborations between scientists at UCSF, MRC Cambridge and The Scripps Research Institute, now called TSRI. Drs. Daniel Santi and Ian Wilson started the meetings and created the unique scientific ambience. The meeting style has remained unchanged but, eleven years ago, the venue moved from Cabo San Lucas to the all-inclusive El Presidente Hotel in San Jose del Cabo. This venue has been attractive as the conference facilities are excellent and the staff very attentive. Each year, the meeting attracts approximately 60 academic, industrial, and biotech participants, as well as venture capitalists and patent attorneys. The majority of the attendees are professors, laboratory heads or research directors, but we also encourage participation of the next generation of scientists through selecting a number of the top graduate students and postdoctoral fellows from UCSF, TRSI, UC Berkeley and Stanford. The spirit of scientific research is enhanced and refreshed in this stunning setting with a stellar list of participants.

Cabo XXI Program
World Molecular Engineering Network Twentieth-First Annual Meeting on Structural Biology

1-4 May 2011, San Jose del Cabo, Baja, Mexico

Sunday Evening, May 1

17:00	Andrej Sali and Ian Wilson	**Introduction and Welcome**
17:15	Irwin D. (Tack) Kuntz	**Keynote Lecture-Design:The Long View**

17:45–20:00 ***Self-Introductions***

Scott Forrest	TSRI
Eric Schneider	UCSF
Liang Tang	Bayer
Jaume Pons	Rinat
Pavel Strop	Rinat

Short Presentations (5+1 min.) by TSRI, UCSF, UCB Graduate Students, Postdoctoral Fellows *et al.* (Chair: Ian Wilson)

Daniel Bachovchin	TSRI	Discovery and characterization of a remarkable class of protein phosphatase methylesterase-1 (PME-1) inhibitors
Gira Bhaba	TSRI	Dynamics in enzyme catalysis
Cory Dambacher	TSRI	A robust temporal control switch for synthetic biology
Damien Ekiert	TSRI	From broadly neutralizing antibodies to a universal influenza vaccine
Robert Kirchdoerfer	TSRI	VLR species specificity for bacillus spores
Jingun (Jeff) Liu	TSRI	Investigating ligand mediating dynamic changes of GPCR using 19F NMR
Dmitry Lyumkis	TSRI	Structural characterization of ribosomal signaling in non-stop protein decay
Crystal Moran Gutierrez	TSRI	Probing structural transitions and dynamics in intrinsically disordered α-synuclein to determine function
Crystal Moyer	TSRI	Functional genetic and biophysical analyses of membrane penetration by human adenovirus

	Cory Rillahan	TSRI	High-throughput synthesis and glycan microarray screening identifies high affinity sialoside analogs for siglec targeting
		Break	
	Gloria Olivier	LBL	Peptoid nanosheets as protein mimetic materials for molecular recognition
	Edgar Deu Sandoval	Stanford	Development of a novel 'fragmenting hybrid' approach for the delivery of protease inhibitors to the malaria parasite
	Homin Kim	UCSF	Function of C-termini in AAA+ ATPase of 26S proteasome
	David Barkan	UCSF	A divide and conquer approach for protein-peptide docking
	John Pak	UCSF	The overexpression of human integral membrane proteins in mammalian cells
	Elena Dolgikh	UCSF	Predicting binding to P-glycoprotein and related transporters by flexible receptor docking
	Jennifer Liu	UCSF	Understanding microtissue maintenance in synthetic MCF-10A acini
20:15–21:30	**Reception**		**Poolside**

Monday Morning, May 2

Advances in Structural Biology (Chair: James Fraser)

09:00	Andrej Sali	UCSF	Small molecule docking against protein structure models
09:20	James Fraser	UCSF	Protein cryo-crystallography quenches functional hidden alternative conformations
09:40	J Michael Sauder	Lilly	Engineering proteins for structural biology
10:00	Rick Harkins	Bayer	Identification of novel protein scaffolds from public databases
10:20	**Break**		

Cellular Biology and Visualization (Chair: Larry Gerace)

10:40	Graham Johnson	TSRI	Applications of subcellular modeling and visualization software
11:00	Zv Gartner	UCSF	Total synthesis of 3D living tissues
11:20	Larry Gerace	TSRI	Endoplasmic reticulum nanodomains in

			regulation of cholesterol biosynthesis
11:40	Jeff Kelly	TSRI	Enhancing proteostasis for disease intervention

Monday Afternoon

Immunology and Biomedicine (Chair: Jim Paulson)

16:30	James Paulson	TSRI	Controlling the immune response with nanoparticles decorated with siglec ligands
16:50	Dan Santi	UCSF/Pro Lynx	Predictably extending drug duration
17:10	Carlos Barbas	TSRI	Chemically programmed immunity
17:30	Ian Wilson	TSRI	Broad neutralization of HIV-1
17:50	**Break**		

Chemical Biology (Chair: Matthew Bogyo)

18:10	Dennis Wolan	TSRI	Structure-based mechanism of streptopain and insights into inhibitor design
18:30	Matthew Bogyo	Stanford	Applications of small molecule probes to study protease function
18:50	Ronald Zuckermann	LBL	Protein mimicry with peptoid polymers

Tuesday Morning, May 3

Sponsors I (Chair: Dan Santi)

09:00	Roger Durst	Bruker	Advances in x-ray source and detection technologies
09:20	Glen Spraggon	GNF	Crystal structure of PCSK9 in complex with the Low Density Lipoprotein receptor
09:40	Rob Kania	Pfizer La Jolla	Structure-based design of axitinib and crizotinib
10:00	**Break**		
10:30	Arvind Rajpal	Rinat	From donor-derived antibody phage

			libraries to antibody repertoire analysis to synthetic library design - coming full circle in our efforts to understand and recapitulate functional diversity of antibodies
10:50	Stephen Doberstein	Nektar	Optimizing pharmacodistribution of small molecule drugs through polymer conjugation
11:10	Alicia Berger	Versant Ventures	Trends in venture capital

Tuesday Afternoon

Nucleic Acids and Nucleic Acid Binding Proteins (Chair: Jamie Williamson

16:30	David Millar	TSRI	Nucleic acid - protein interactions at the single molecule level
16:50	Jamie Williamson	TSRI	Dynamics of ribosome assembly in cells
17:10	Pilgrim Jackson	Celgene	Histone tales and the modifications that tell them (a story of JMJD2C)
17:30	**Break**		

Membrane Proteins (Chair: Robert Stroud)

18:00	Andrew Ward	TSRI	Structure of P glycoprotein bound to a nanobody inhibitor
18:20	Matt Jacobson	UCSF	The specificity of P-glycoprotein and related transporters
18:40	Robert Stroud	UCSF	To and through the biological membrane
19:00	Natalia Jura	UCSF	Membrane organization and control of signaling in the HER family of receptor tyrosine kinases

Wednesday Morning, May 4

Viruses, Assemblies, Computation, and Drug Design (Chair: Andrej Sali)

08:30	David Stout	TSRI	Progress toward an allosteric inhibitor targeting HIV protease
08:50	Mark Yeager	TSRI/ UVA	Atomic level modeling of the HIV-1 capsid
09:10	Jack Johnson	TSRI	Dynamics and stability in virus

			maturation: The mechanism of a molecular machine
09:30	Yifan Cheng	UCSF	Single particle cryoEM study of macromolecular complexes
09:50	**Break**		
10:10	Arthur Olson	TSRI	Wet docking
10:30	Wayne Fairbrother	Genentech	Mechanism of IAP antagonist-induced activation of cIAP ubiquitin ligase activity
10:50	Sarah Hymowitz	Genentech	Ubiquitin binding to A20 ZnF4 is required for modulation of NF-κB signaling
11:10	Brent Appleton	Novartis	Resistance screen with a novel c-Met inhibitor reveals mutations found in cancer patients
11:30	Ian Wilson and Andrej Sali		**Closing Remarks**

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The following pages are summaries of presentations and comments on the meeting and venue.

WMEN Conference
San Jose del Cabo
El Presidente Hotel

For more information, contact:

Andrej Sali
sali@salilab.org

Ian Wilson
wilson@scripps.edu

Hilary Mahon
hilary@salilab.org

Name: Carlos F. Barbas
Department: The Scripps Research Institute
Mailing address: 10550 N Torrey Pines Road
La Jolla, CA 92037
Email address: carlos@scripps.edu
Phone number: 858 784-9098
Fax number: 858 784-2583

Overview: Overall an excellent meeting. One of the best groups of presenters found at any conference

Presentation: Carlos F. Barbas, III
The Skaggs Institute for Chemical Biology and the Departments of Molecular Biology and Chemistry, The Scripps Research Institute, La Jolla, CA, USA, 92037.
carlos@scripps.edu

Recently, my laboratory has developed a new class of immunotherapeutic agents termed Chemically Programmed Antibodies or CovX-bodies as prepared by Pfizer-CovX Inc. In this presentation, I will attempt to summarize some of our results concerning this promising new class of immunotherapeutic molecules. The success of the antibody molecule as therapeutic agent is based on at least three properties; (i) an Fab moiety that permits antigen binding with high specificity and affinity, (ii) an Fc moiety that mediates effector functions, and (iii) FcRn binding that permits a circulatory half-life of up to 21 days. Although conventional therapeutic agents based on small organic molecules have been successful in many instances, they are clearly limited with respect to their short half-life in circulation and their inability to mediate effector functions. Proposing that a blend of these features will lead to therapeutic agents with superior properties, we have developed chemically programmed antibodies. I will present studies concerning the superior biological activity bestowed upon small molecules and peptides by this approach and describe how four such drugs have now advanced into human clinical trials. In the

later part of my talk I will consider a new approach to vaccines based a chemical approach to vaccinology that has the potential to provide instant immunity.

Impressions: Great meeting! Made new connections and the compelling presentations seeded new ideas in my research

Name: David Barkan
Supervisor: Andrej Sali
Department: UCSF
Mailing address: 1700 4th St, Suite 501
San Francisco CA 94158
Email address: dbarkan@salilab.org
Phone number: 6102209244
Fax number: n/a

Presentation: I gave a 5 minute talk describing my research on development of a new protein-peptide docking algorithm.

Impressions: I thought it was great. The talks were interesting. Most of them were outside of my direct field (Computational Structural Biology), but were still relevant. However, it would be nice to maybe double the number of computational talks in the future, since I think experimentalists would benefit from seeing more of these.

I liked the mix of academics and industry that we saw as I am an advanced graduate student deciding which area to go into. Everyone was really friendly and approachable which I think is important for a conference and not always the case. The highlight for me was probably the chance to interact with students at Scripps to see what kind of research they are doing and get to know them on a professional and personal level.

The resort and the surrounding area were beautiful. The food was not very good but that might be expected in an all

inclusive resort where they have no incentive to make it very good. Wireless internet really should be free (here and at every hotel at this point) but my department reimbursed me so it wasn't a big deal in the end. However, I know that wasn't the case for everyone, so maybe it could be negotiated with the hotel in the future that "all inclusive" includes wifi, or maybe to negotiate a discounted rate for wifi across multiple days.

I would also like to give my compliments to the organizers of the conference from UCSF and Scripps who handled all the logistics. Things went exceptionally smoothly despite having a large number of people from different parts of the US to handle. These people are great at their jobs and should probably get a small monetary bonus to reflect that.

Name: Gira Bhabha
Supervisor: Peter Wright
Department: TSRI
Mailing address: 10550 N Torrey Pines Rd
MB-02
La Jolla, CA 92037
Email address: gbhabha@scripps.edu
Phone number: 858-784-9651
Fax number: 858-784-9822

Presentation: Divergent evolution of enzyme dynamics in dihydrofolate reductase

Impressions: fantastic meeting. almost all talks were very good, with high quality and exciting science, and the meeting was very interactive.

Name: Yifan Cheng
Department: Biochemistry & Biophysics, UCSF
Mailing address: 600 16th Street, GH-S312B, MC 2200, San Francisco, CA 94158
Email address: ycheng@ucsf.edu

Phone number: 415-514-9707
Fax number: 415-514-4145

Overview: Very nice meeting, and I will definitely try to attend again in the future.

Presentation: Single particle cryoEM study of macromolecular complex

Impressions: Very nice meeting, with very impressive presentations. Interactions with other participants are very productive.

Name: Corey M. Dambacher
Supervisor: Peter G. Schultz
Department: The Scripps Research Institute
Mailing address: Department of Chemistry SR202
10550 N. Torrey Pines Road, La Jolla, CA 92037
Email address: cdambach@scripps.edu
Phone number: (858) 784-9345
Fax number: (858) 784-9440

Presentation: Dynamic expression of pathway components is important for achieving optimized exploitation of drug and metabolite production in engineered micro-organisms. To address this, an unnatural amino acid (UAA)-mediated repression/induction switch has been generated. The switch makes use of the LacI repressor protein as a semi-oscillator. A single plasmid containing all necessary components for commercial utilization of the semi-oscillatory switch has been generated (pSTARS: Stop codon-mediated Activation/Repression Switch). Northern blots of total RNA isolated from cells containing a GFP reporter under control of the pSTARS system show that upon amber suppression, this switch can shut off reporter transcript expression very rapidly (in less than 15 minutes). Fluorescent plate reader

measurements taken from cultured DH10B cells containing the pSTARS/GFP plasmid show a 50-fold reduction in total fluorescence in the presence of the UAA as compared to the same cells grown without UAA supplemented in the media. Expression from the lac promoter can be re-initiated by IPTG induction, allowing for a semi-oscillatory pattern of expression. We show the utility of the pSTARS system toward the modulation of individual factors within the ribosomal protein network, and for engineering metabolic pathways in E. coli. This system will allow investigators to exert robust temporal control of gene expression for a variety of applications.

Impressions: This was the first meeting I have attended in which every attendee gives a talk. This was very good for discussion, as at least some of each investigator's research was revealed to the group. I think this meeting was a lot like going to a Gordon conference or a meeting at Asilomar, but with a less rigid meeting structure and an environment more conducive to relaxation and collaboration. I too would put this down as "best meeting attended". I really enjoyed discussing research with the grad students, post docs and faculty from UCSF and others; I was able to make several new connections. There was a large diversity of research presented (not just in the area of structural biology), with most being newly discovered phenomena. I am also a big fan of the non-disclosure agreement because this allows attendees to collaborate before results are made public. The organizers and the specific attendees selected are what ensured a great meeting, and I hope the meeting continues to be a wonderful experience for everyone who attends in the future.

Name: Edgar Deu
Supervisor: Matthew Bogyo
Department: Stanford University, Pathology Department
Mailing address: Edwards Bld, Room R315
300 Pasteur Dr

Stanford, CA94305
Email address: edgardeu@stanford.edu
Phone number: (650) 725-6981
Fax number: (650) 725-7424

Presentation: Development of a novel fragmenting hybrid, approach for the delivery of protease inhibitors to the malaria parasite.

Impressions: The meeting was well organized and the scientific program was excellent. However, it is fairly tough to presents someone's work in 5 min, and have people remember anything after listening to 20 5min talks in a row. I would suggest splitting the 5min presentation among the different sessions.
Also, some kind of award for the best presentation of students and postdoc would make the meeting more fun and interesting.

Name: Elena Dolghih
Supervisor: Matt Jacobson
Department: Department of Pharmaceutical Chemistry
Mailing address: UCSF, Byers Hall, Room 402, San Francisco, CA 94158
Email address: ldolghih@gmail.com
Phone number: 415-476-8679
Fax number: (415) 476-0473

Presentation: My research focuses on the development of structure-based approach based on flexible receptor docking to predict ligand interactions with P-glycoprotein and Bile Salt Export Pump (BSEP). These and related active efflux transporters are known to affect pharmacokinetic profiles of many clinically relevant compounds by influencing their absorption, elimination, and penetration of the blood-brain barrier. An in silico method could provide a qualitative, quick, and inexpensive way of evaluating potential drug efflux problem at the early stages of drug development.

Impressions: I thoroughly enjoyed the meeting and found it very informative. It was a great opportunity to learn about the latest developments in the field and meet with many interesting scientists.

Name: Damian Ekiert
Supervisor: Ian Wilson
Department: Molecular Biology
Mailing address: 10550 N. Torrey pines Rd.
BCC206
La Jolla, CA 92037
Email address: dcekiert@scripps.edu
Phone number: 858-784-2941
Fax number: None

Presentation: From broadly neutralizing antibodies to a universal therapy for influenza

Impressions: Best meeting that I attended this year! The science presented at Cabo is always to notch and is always followed by good discussions later on the beach, at the bar, or at dinner.

Name: Scott Forrest
Department: Office of Technology Development
Mailing address: 10550 N Torrey Pines RD, TPC-9
La Jolla, CA 92037
Email address: sforrest@scripps.edu
Phone number: 858-784-9388

Fax number: 858-784-9910

Overview: I head the business development group at Scripps and was invited to attend the meeting based on the increased interactions between the Scripps structural biologists and their industry counterparts.

Presentation: A simple introduction and overview of my role within Scripps and, more generally, my role in commercializing academic research.

Impressions: An excellent format for getting to know the presenting scientists (this was probably the single best aspect of the meeting). The presentation formats, allowing for many concise talks each day, was also enjoyable. Enjoyable as well to see raw research from the commercial sector presented.

Name: James Fraser
Department: UCSF
Mailing address: Byers Hall Room 301E (Office), 309 (Lab)
UCSF Mail Code 2530
1700 4th Street
San Francisco, CA 94158
Email address: james.fraser@ucsf.edu
Phone number: 415 493 8421
Fax number: 415 514 9736

Overview: My work focuses on the development and application of biophysical methods, particularly X-ray crystallography, to characterize protein side chain flexibility. We use these tools to study connections between conformational dynamics and enzymatic catalysis, interaction specificity, and allosteric communication. We use directed evolution techniques to examine the emergence and resilience of coupled side chain motions during genetic drift. The broad goal of our research is to describe how the evolutionary pressures on many hierarchies of motion shape protein-protein interaction networks and enzymatic catalytic cycles.

Presentation: Although modern protein crystal structures are based nearly exclusively on X-ray data collected at cryogenic temperatures (~100 K), I discussed how this practice leads to specific and pervasive biases in protein

conformational ensembles. By analyzing available data for 30 different proteins using new computational tools for electron-density sampling, model refinement and molecular packing analysis, we found that crystal cryo-cooling remodels the conformational distributions of more than 35% of side chains and eliminates packing defects necessary for functional motions. These results expose a bias in structural databases toward smaller, over-packed, and unrealistically unique models. Monitoring room-temperature conformational ensembles by X-ray crystallography can reveal motions crucial for catalysis, ligand binding, and allosteric regulation - with important implications for structure-based drug design and protein engineering.

Impressions: This meeting was one of the best meetings I have ever been to. The size of the group and length of the meeting were perfect for having a diversity of scientific interests while maintaining the possibility to actually get to talk to everyone. The location provided an ideal mix of isolation and relaxation. I was incredibly impressed with both the short- and long-form presentations. Because of the interactive nature of the meeting, I felt like collaborations were starting all around me constantly.

Name: Zev Gartner
Department: UCSF Pharm Chem
Mailing address: 600 16th St. Box 2280
San Francisco, CA 94158
Email address: zev.gartner@ucsf.edu
Phone number: 415-514-9962
Fax number: n/a

Overview: My lab is developing technologies for understanding the relationship between form and function at the sub-micron and tissue-level length scales. Specifically, we wish to understand how the structure of tissues contributes to maintaining homeostasis, and how the

organization of receptors at the cell surface affects the intensity, duration, and specificity of signal transduction.

Presentation: I discussed how tissue structure can affect the phenotype of otherwise identical cells. I then discussed an example from the lab of how a Ras-expressing cell's phenotype is affected by the specific context in which it is growing.

Impressions: Very informative and fun. I connected with a ton of interesting people and reconnected with several that I hadn't seen in a great while.

Name: Larry Gerace
Department: The Scripps Research Institute
Mailing address: 10550 N. Torrey Pines Rd.
La Jolla, CA 92103
Email address: lgerace@scripps.edu
Phone number: 858-784-8514
Fax number: 858-784-9132

Overview: This was my first year of attendance at the WMEN meeting.

Presentation: I discussed recent work in which we have defined SPFH domain-containing membrane proteins that provide a platform for controlling the regulatory machinery for cholesterol and fatty acid biosynthesis in the endoplasmic reticulum. I provided a perspective on how SPFH domain proteins, which are widely distributed in all kingdoms of life, could serve as a general organizing principles for membrane nanodomains.

Impressions: I greatly appreciated the perspective of this meeting, involving the functions/design of different cellular macromolecules and macromolecular complexes. The presentations were clear and succinct, and there was plenty of time for informal discussion with meeting participants. I

found the panoramic view of cutting edge approaches discussed at this meeting to be greatly informative.

Name: Crystal Moran Gutierrez
Supervisor: Prof. Ashok Deniz
Department: Molecular Biology/Scripps Research Institute
Mailing address: 10550 N. Torrey Pines Road MB-19
La Jolla, CA 92037
Email address: crmoran@scripps.edu
Phone number: 858-784-2911
Fax number: 858-784-9067

Presentation: Probing Structural Transitions and Dynamics in Intrinsically Disordered-Synuclein

Impressions: I was quite impressed by the professional rigor of such a small meeting. The quality of science presented and the outstanding scientists in attendance, especially in an atmosphere that allowed for many and thorough discussions about the material covered, made for a very rich conference experience. The format seems exceptional for cultivating deeper connections with colleagues, reflecting on the context of one's own work, and exploring potential collaborations.

Name: Rick Harkins
Department: US Innovation Center, Bayer HealthCare
Mailing address: 455 Mission Bay Blvd. South, San Francisco, CA 94158
Email address: rick.harkins@bayer.com
Phone number: 415.437.5881
Fax number: 415.437.5970

Overview: Our group has been involved in the identification and validation of novel protein scaffolds as antibody mimetics. Antibody mimetics represent a novel class of biologics derived from non-traditional antibody-based protein domains or scaffolds. Antibody mimetics can provide the

potency and specificity afforded by monoclonal antibodies, yet are much smaller, typically 10-20 kDa, and easier to produce.

Presentation: We performed a systematic search of public protein sequence and structural databases using a set of selected criteria to identify an ideal antibody mimetics scaffold, notably, protein domains that were small (50-100 amino acids in length), stable (soluble, extracellular), and human in origin. In addition structures were sought that would be amenable to the generation and display of libraries for screening targets, particularly integral membrane proteins, such as GPCRs and ion channels. Thus, protein domains with loops that could be varied in composition and extended in length could be of great value in binding pockets or deep crevices found in certain target proteins.
From approximately 750 protein domains in the SMART database (Simple Modular Architecture Research Tool), the "three fingered" protein domain (TFPD) was identified as a scaffold with specific structural and functional criteria that matched the profile for a novel and robust mimetic. The TFPD is small, comprising 65 to 90 amino acid residues, disulfide-rich comprising about 4 to 5 disulfide bonds, and contains three distinctive ß-sheet containing loops or "fingers". TFPDs are present throughout vertebrates and exhibit broad functional diversity, from potent and lethal snake venoms (e.g α-bungarotoxin) to physiologically important cell surface receptors (e.g. urokinase receptor). We have identified two human TFPDs as candidate scaffolds and demonstrated the ability to generate and display highly diverse libraries, and screen for novel binders against known targets. The goal of the project is to extend these studies and utilize the proprietary TFPD scaffold to identify novel binders to highly relevant but as yet inaccessible drug targets.

Impressions: Location: Very good

Number of participants: Excellent
Length of meeting: Excellent
Comments: This was my first invitation to attend the WMEN conference and I was delighted to be a part of this group for three days. I was impressed by the quality of the presentations, particularly by the postdocs and grad students that were able to convey their research in such a professional and clear manner within the five minute time slots. The friendship and camaraderie within the group was apparent immediately and fostered a relaxed atmosphere for excellent scientific dialogue and discussion. I very liked the fact that everyone spoke and contributed at the meeting and I really enjoyed the mix of academia and industry representation. The sponsor's dinner was terrific.
From a scientific perspective, this was an excellent structural biology meeting.

Name: Sarah Hymowitz
Department: Genentech
Mailing address: Department of Structural Biology
Email address: hymowitz@gene.com
Phone number: 650 225 7819
Fax number: 650 225 3734

Overview: I loved the meeting. Great to learn about so many different areas and see the immense progress over the years on projects. I hadn't realized how much linker work was going on with various protein-drug conjugate scaffolds. My favorite factoid was the H3 length distribution (short in mice, medium in humans, long in cows), which I've shared with several colleagues. I thought the balance between basic research and drug discovery projects was appropriate.

Presentation: Presentations were interesting and largely well paced. The graduate students/post docs did a great job on the short talks. The PIs sometimes were less good at pacing but I think that's expected.

One thing I noticed was that the gender diversity among the PI presenters was a bit skewed (3 women out of ~35). This may not be easily addressable, but might be worth a bit of reflection for next year.

Impressions: Can't believe that I've been in the Bay area crystallography community since 1992 and this is the first time I attended the "Cabo" meeting. I hope to be able to participate more frequently in the next 20 years...

Name: Pilgrim Jackson
Department: Biochemistry/Celgene
Mailing address: 4550 Towne Centre Ct
San Diego, CA 92121
Email address: pjackson@celgene.com
Phone number: 858-795-4803
Fax number: 858-552-8716

Overview: Our group uses structure based drug discovery for oncology and inflammation targets. Currently there is a significant effort on understanding mechanism of action and inhibition of novel epigenetic enzymes.

Presentation: We developed a novel high throughput screen and solved the crystal structure of JMJD2C to advance small molecule inhibitors of its demethylase activity. In addition, it was determined that adjacent histone modifications had a dramatic effect on JMJD2C demethylase activity. Specifically, phosphorylation of H3 Thr11 appears to eliminate JMJD2C demethylation of H3 Lys9 in vitro, creating a discrepancy with published data from cell extracts.

Impressions: The meeting was very enjoyable and productive, providing an ideal environment for communication and in depth discussion. Size, length and location all seemed appropriate.

Name: Matt Jacobson
Department: UCSF Dept. of Pharmaceutical Chemistry
Mailing address: UCSF MC 2540
1700 4th St., Byers Hall, Room 408E
San Francisco, CA 94158-2330
Email address: matt.jacobson@ucsf.edu
Phone number: 415-514-9811
Fax number: none

Overview: Major projects currently include
1) New methods for computer-aided drug design, currently focused on membrane permeability, including the blood-brain barrier, as well as computer-aided design of macrocyclic compounds and antibodies.
2) Assigning enzyme function using computational structural biology (homology modeling, docking).
3) Understanding and predicting allosteric regulation.

Presentation: I presented our work on rationally designing cyclic peptides for oral bioavailability (collaboration with Scott Lokey and Pfizer). The most advanced compound is a ~750 MW N-methylated cyclic peptide with ~30% oral bioavailability. I emphasized the implications for designing drugs outside the usual range of properties, e.g., Lipinski's rules of 5.

Impressions: Excellent in all respects. Very high quality talks by all constituencies: UCSF, Scripps, and industry. Potential future collaborations from the interactions.

Name: Graham Johnson
Supervisor: Olson/Sali
Department: MolecularBiology / Scripps , QB3/ UCSF
Mailing address: 10550 N. Torrey Pines Road, MB-112
La Jolla, CA 92037
Email address: graham@grahamj.com

Phone number: 303-249-3934
Fax number: 8587842209

Presentation: Applications of Subcellular Modeling and Visualization Software

AutoFill is a computational tool that creates 3-D models of complex biological environments, based on 3-D structures or reconstructions of the components, ultrastructural data from microscopy, and biochemical information on concentrations and distributions. ePMV, runs molecular modeling software directly inside of professional 3D animation applications (hosts) to provide simultaneous access to the capabilities of these newly connected systems. Applications of both software packages were shown, as well as combination applications where ePMV can be used both to provide a GUI and to allow users to interact with autoFill results.

Impressions: Good depth and breadth within the discipline of structure and exciting diversity at the boundaries- it was nice to see a hint of formal expansion into adjacent disciplines to reflect trends in broad-scope research.

The mix of social to seminar time works well to aid networking. I made great use of the down time to discuss current/past collaborations and future plans.

This year, the talks ran long, sometimes more than an hour over... it would be great to keep the talks moving, as in past years to keep the allotted time consistent for each participant and minds fresh. Otherwise, it was outstanding as always.

Name: John E. Johnson
Department: Molecular Biology Scripps
Mailing address: Department of Molecular Biology MB31
The Scripps Research Institute
10550 N. Torrey Pines Rd.
La Jolla, CA 9037
Email address: jackj@scripps.edu

Phone number: 858-784-9705
Fax number: 858-784-8660

Overview: Jack Johnson's research includes virus particle dynamics studied by mass spectrometry, cryoEM and spectroscopy as well as crystallographic studies of viruses infecting yeast, bacteria, archea and insects. Johnson has over 300 publications that cover, the structure (at near atomic resolution) and function of 20 different viruses and virus-like particles, as well as cryoEM and solution x-ray scattering studies of particle dynamics.

Presentation: Dynamics and Stability in Virus Maturation: Mechanisms of a Molecular Machine

Assembly of quasi-equivalent virus capsids engages molecular switches to create different interface contacts between the same gene products. The particle often assembles as a fragile, spherical shell in which the subunits are properly positioned on the appropriate surface lattice and then quasi-equivalent subunit contacts differentiate during maturation, creating a robust, faceted particle. Folding of the switch regions of the subunit depends on assembly and maturation that are affected by biochemical cues. NwV is a quasi-equivalent virus, with a T=4 surface lattice, where this process is dramatic (a change in particle size of 100Å during maturation) and can be investigated in vitro. Here we use biochemistry[1], Small Angle X-ray Scattering (SAXS)[2] and electron cryo-microscopy and image reconstruction (CryoEM)[3] to characterize maturation intermediates and an associated auto-catalytic cleavage, the kinetics of morphological change and to demonstrate that regions of NwV subunit folding are maturation-dependent and occur at rates determined by their quasi-equivalent position in the capsid.

1. Matsui, T., Lander, G., and Johnson, J.E. 2009 Characterization of Large Conformational Changes and

Auto-proteolysis in the Maturation of a T=4 Virus Capsid. J Virol 83, 1126-1134.
2. Matsui, T., Lander, G., Khayat, R. and Johnson, J.E. 2010 Subunits fold at position-dependent rates during maturation of a eukaryotic RNA virus. Proc. Natl. Acad. Sci. USA 107:14111-5.
3. Matsui, T., Tsuruta, H., & Johnson, J.E. 2010 Balanced Electrostatic and Structural Forces Guide the Large Conformational Change Associated with Maturation of a T=4 Virus. Biophys J. 98:1337-43.

Impressions: The meeting was excellent. I had not attended for four years due to schedule conflicts. It was my fourth and I was both excited and motivated by the presentations. It is unlike any other meeting in that it is all world class science, but with no particular logic other that it is structural biology and biophysics (for the most part). The week after returning to Scripps I had meetings with two different participants to look into collaborations. The students did an outstanding job in their presentations and the overall quality of the talks was truly exceptional. It is wonderful to have such a great meeting of friends and colleagues.

Name: Natalia Jura
Department: CVRI and Department of Cellular and Molecular Pharmacology/UCSF
Mailing address: 555 Mission Bay Blvd. South
Cardiovascular Research Building, Rm 452W
University of California at San Francisco
San Francisco, CA 94158
Email address: natalia.jura@ucsf.edu
Phone number: 415-514-1133
Fax number: 415-514-2550

Overview: The research goals in my lab are focused on understanding the molecular mechanisms of activation of the HER and MET families of receptor tyrosine kinases at the

plasma membrane. These receptors are frequently deregulated in human diseases and represent critical and challenging therapeutic targets. Specifically, we use structure-function studies to obtain complete molecular picture of the assembly of the active receptor complexes at the plasma membrane in living cells, and in the reconstituted membrane systems. This will allow us to gain understanding of how conformational changes in these receptors are transmitted across the plasma membrane and initiate signaling events inside the cell, and how we can design the most efficient strategies for targeting these receptors in disease.

Presentation: Activation of the epidermal growth factor receptor (EGFR) involves an asymmetric interaction between the kinase domains of two receptor molecules, in which one kinase domain plays a role analogous to that of a cyclin activating a cyclin-dependent protein kinase (CDK). The mechanism by which engagement of ligands by the extracellular domains of EGFR is transduced into formation of the asymmetric kinase domain dimer has not been understood. We have identified a critical regulatory role that the juxtamembrane segment of the receptor plays in this transition. We show that the portion of the juxtamembrane segment, the juxtamembrane latch, makes a latching interaction between two kinases domains in the receptor dimer. This latching is essential for EGFR activation in response to ligand binding and is conserved among the EGFR family members. In addition, we present structural evidence for the role of the N-terminal juxtamembrane fragments in connecting the activated allosteric kinase domain dimer to the previously obtained structure of the transmembrane domain and the extracellular portion of the receptor. These studies led to a first structural model of the full length EGFR in the active state and identified novel modes for negative feedback regulation that controls ligand-dependent activation of EGFR.

Impressions: This was my first Cabo meeting, and at the same time one of the best meetings that I had the chance to attend in my scientific career! It was highly interactive, with question sessions taking almost the same amount of time as the seminars themselves. What is really great about this meeting is that it brings together researchers with strong background in protein sciences, but working on very different experimental systems. This allows for the flow of expertise and innovation that everyone benefits from. The attendance of the scientists from the industry helped me to reevaluate the application of my research to current clinical challenges, and allowed for great interactions that I tremendously enjoyed. The location is great and really facilitates social collisions, where the most exciting scientific discussions took place. The high ratio of faculty to students/postdocs is very beneficial for both sides and brings down the barrier between them. The five minute format of student/postdoc talks is a great idea - and this was my favorite part of the meeting! The organization was flawless! Looking forward to the meeting next year!

Name: Homin Kim
Supervisor: Yifan Cheng
Department: Biochemistry and Biophysics department
Mailing address: UCSF, Box 2200,San Francisco, CA, 94158
Email address: hohu78@gmail.com
Phone number: 415-514-9708
Fax number: 415-514-4145

Presentation: I'm working on the Proteasome structure by single particle cryoEM to understand the gate opening mechanism of 20S proteasome. From the high resolution structure of yeast 20S with Rpt C-terminal peptides, we could propose the relative location between base of RP and a ring. Furthermore, we could understand the gate opening mechanism of eukaryotic 20S proteasome induced by Rpt C-terminal tail.

Impressions: It was a great chance to extend my knowledge about not only basic biology but also application of that. Particularly, many talks from the company gave me a lot of ideas about the drug discovery based on the protein structure. Nicely organized session also very impressive.

Name: Robert Kirchdoerfer
Supervisor: Ian Wilson
Department: Molecular Biology/The Scripps Research Institute
Mailing address: 10550 North Torrey Pines Road, BCC206 La Jolla, CA 92037
Email address: rkirchdo@scripps.edu
Phone number: 858-784-2945
Fax number: 858-784-2980

Presentation: My research examines the specificity of antibodies of agnathan fish. The agnathans diverged from other vertebrates prior to the evolution of both jaws and an adaptive immune system based on the immunoglobulin fold. However, these fish independently evolved adaptive immunity using variable lymphocyte receptors in place of traditional vertebrate antibodies and T-cell receptors. We examined a particular VLR, VLR4 in its ability to bind and discriminate the immunodominant protein of *Bacillus anthracis* spores. We showed that specificity for *B. anthracis* spores over *B. cereus* or *B. thuringiensis* spores is not the result of amino acid polymorphisms and so likely arises from presentation of the epitope on the surface of the spores or modification of the epitope by post-translation modification.

Impressions: I liked the size of the meeting, not so large so as to inhibit scientific discussion, but large enough to bring a large variety of ideas to the table. I also enjoyed the balance of academic and industrial attendance and found the perspectives on venture capital to be particularly refreshing.

The meeting location was superb and I felt that we were taken very well care of at the Presidente Intercontinental.

Name: Jack F. Kirsch
Department: University of California
Mailing address: 572 Stanley Hall #3220
Email address: jfkirsch@berkeley.edu
Phone number: 510 642-6368

Overview: I am officially retired, but am engaged in a collaborative project on improving enzyme functional annotation from primary sequence and structural data.

Presentation: I did not speak because of my retirement status, but participated actively in the Discussions.

Impressions: This was my 10th attendance at this meeting, and it is the one that I find the most valuable. The speakers do uniformly excellent science, and they in turn chose their topics for general interest. I like the Gordon Conference format in which the talks are concentrated in the morning and evening, leaving the afternoon free for mental and physical recuperation. I generally benefit from both the formal and informal contacts. The students and postdocs add an important dimension to the proceedings. The timing of the presentations was excellent again this year. The session chairs were very efficient at keeping the speakers on track.

Name: Jeffrey Liu
Supervisor: Ray Stevens
Department: TSRI
Mailing address: 10550 North Torrey Pines Rd. GAC 1200 La Jolla, CA 92037
Email address: jjyliu@scripps.edu
Phone number: 858-784-9411
Fax number: 858-784-9020

Presentation: receptor dynamics

Impressions: This meeting is a great forum to discuss scientific ideas and meet other scientists from Scripps, UCSF and the industry. The meeting has a dynamic range of topics, and a good collection of experts of many fields related to structural biology and drug development. Personally, I would like to see more membrane protein structural biologists in the future.

Name: Jennifer Liu
Supervisor: Dr. Zev Gartner
Department: Chemistry and Chemical Biology/UCSF
Mailing address: 600 16th Street
Genentech Hall Box 2280
San Francisco, CA 94158
Email address: Jennifer.Liu2@ucsf.edu
Phone number: 415 476 6251

Fax number: 415-502-4690

Presentation: Three-dimensional (3D) cell culture models are valuable tools for understanding the relationship between genetics, morphogenesis, and microtissue architecture. For example, in laminin-rich extracellular matrix (lrECM), 3D cultures of non-malignant breast epithelial lines, such as MCF-10A cells, develop into growth-arrested and polarized acini, while cultures of transformed MCF-10A cells may grow into structures exhibiting aberrant proliferation and polarity. It remains challenging, however, to study the interplay between healthy and genetically altered cells since acinar structures in current 3D systems are derived from a single initial cell that is either healthy or transformed. Models that incorporate both normal and transformed cells into the same microtissue are needed for interrogating heterotypic intercellular crosstalk as well as for understanding how cellular composition impacts acinus phenotype. Towards this goal, we are using a programmed assembly strategy to build

three-dimensional structures with defined initial compositions. Our method uses chemical means to impart cells with specific adhesive properties by modifying cell surfaces with synthetic, single-stranded DNA. Cells labeled with complementary strands self-assemble into multicellular clusters, and the topology of the resulting structures can be controlled by varying assembly reaction parameters. Furthermore, these assembled structures can be cultured in 3D matrices. We are currently characterizing the morphogenesis of assembled structures synthesized from non-malignant MCF-10A starting cells when cultured in lrECM as well as building assemblies that contain both parental and genetically transformed MCF-10A cells. We can also build larger, more complex structures and are devising methods for synthesizing clusters with an outer layer of myoepithelial cells, which better mimic the bilayered architecture of in vivo mammary acini. These 3D culture models will shed light on how tissue-level composition and organization affect the cancer-associated behaviors of transformed cells. They may also serve as background structures for systematically assessing the effects of cancer-relevant molecular and microenvironmental perturbations.

Impressions: Overall the meeting was very nicely put together with great talks from both students/postdocs, PIs, and sponsors. I really liked the diversity of topics covered; I learned a lot about many research areas. It was nice that every attendee gave a talk, so I think the group size this year was good to allow for everyone to speak. The venue was nice with the exception of not-so-great, all-inclusive food. There were clearly more graduate students invited from TSRI which I found a bit strange since this was the first year that I had heard of this meeting.

Name: Dmitry Lyumkis
Supervisor: Bridget Carragher
Department: TSRI

Mailing address: 10550 North Torrey Pines Rd. CB 129
La Jolla, CA 92037
Email address: dlyumkis@scripps.edu

Phone number: 858-784-9208
Fax number: 858-784-9208

Presentation: My work focuses on the structural characterization of a recently identified gene product called Listerin and its interaction with stalled ribosomes. Listerin is an E3 ubiquitin ligase that ubiquitinates nascent chains that were inappropriately translated through a stop codon, resulting in their degradation within the proteasome. I presented single-particle EM reconstructions of free Listerin in various conformational states, indicating the importance of the proteins flexibility for its biological function. I also presented some preliminary work on cryo-EM studies that aim at identifying the ribosomal footprint for Listerin recruitment.

Impressions: This is my second time at the WMEN meeting, and it is my favorite meeting to attend. Because of the combination of academic and industry scientists, this meeting presents a unique opportunity to learn about the type of work going on in both areas. For example, several of the speakers talked about their ongoing work to directly translate findings in their laboratories into relevant clinical applications. On the other hand, there were also a number of interesting presentations with regard to basic questions in structural biology, along with the incorporation of hybrid techniques to address them. This broad spectrum of speakers and topics is what I enjoy most about this meeting.

Name: David P. Millar

Department: The Scripps Research Institute
Mailing address: 10550 N. Torrey Pines Rd
La Jolla, CA 92036

Email address: millar@scripps.edu
Phone number: 8587849870
Fax number: 8587849067

Overview: My laboratory develops and applies single-molecule fluorescence techniques for biophysical studies of proteins, nucleic acids and macromolecular assemblies. Our major projects include: (a) Molecular biophysics of DNA replication. We are developing single-molecule fluorescence methods to visualize dynamic conformational changes that occur as a DNA polymerase replicates or proofreads DNA. (b) Ribonucleoprotein assembly in the HIV system. We are studying the mechanism of oligomeric assembly of HIV-1 Rev on the Rev Response Element (RRE) RNA. (c) We are developing single-molecule FRET methods to detect transient protein-protein interactions during GPCR signaling.

Presentation: I described our recent studies of the Rev-RRE system from HIV-1. The Rev protein regulates nucleocytoplasmic export of viral mRNA by assembling as an oligomeric complex on the RRE. We have developed a single-molecule fluorescence assay that allows us to visualize the assembly process one Rev monomer at a time, revealing the mechanism of assembly (sequential monomer binding) and the microscopic rate constants for each step of assembly. Using this assay, we have shown that the cellular RNA helicase DDX1 promotes oligomerization of Rev on the RRE, by suppressing non-productive nucleation events and accelerating the binding of the first few Rev monomers to the RRE. Interestingly, our results suggest that DDX1 targets the Rev protein rather than the RRE RNA to promote oligomeric assembly. Our results explain why DDX1 serves as a cellular cofactor to promote the RNA export function of Rev.

Impressions: This was another successful and highly enjoyable meeting. The Cabo meeting is one of the most informative meetings that I typically attend, and has become

a highlight of the scientific year for me. The breadth of topics and the quality of the science presented are always outstanding. This meeting provides a unique opportunity to learn about exciting new areas of research at both Scripps and UCSF. I also enjoy the chance to interact with Scripps and UCSF colleagues in a friendly, relaxed atmosphere. The El Presidente Hotel continues to provide a convenient venue for the meeting.

Name: Crystal Moyer
Supervisor: Glen Nemerow
Department: Immunology/TSRI
Mailing address: 10550 N. Torrey Pines Rd.
IMM-19
La Jolla, CA 92037
Email address: cmoyer@scripps.edu
Phone number: (858) 784-9182
Fax number: (858) 784-8472

Presentation: My research focuses on understanding the proteins and mechanisms involved in adenovirus endosomal escape during cell entry. We've identified the internal capsid protein VI as the viral lytic factor, and showed that specific mutations in the critical N-terminal amphipathic α-helix alter protein secondary structure and perturb membrane insertion. These changes at the molecular level are ultimately linked to a reduction in endosome escape and virus infectivity.

Impressions: Overall, the meeting was excellent. The location is very suitable, and the size of the meeting was perfect to allow for plenty of interaction, while still maintaining a large diversity of scientific interests.

Name: Gloria Olivier
Supervisor: Ron Zuckermann
Department: Molecular Foundry, Lawrence Berkeley National Lab
Mailing address: 1 Cyclotron Rd,

Berkeley, CA 94720
Email address: gkolivier@lbl.gov
Phone number: 510-486-6907
Fax number: 510-495-2376

Presentation: My research aims to develop functional, synthetic protein mimics from peptoid nanosheets. Like proteins, peptoids are linear, information-rich polymers in which the information content is encoded by a precise sequence of monomers. The Zuckermann lab has successfully made a variety of folded protein mimetic polypeptoids, including highly stable helical bundles and planar sheets. I am currently working to fold polypeptoid chains into atomically-defined crystalline structures, and then engineer binding and catalytic sites into the sequence code to imbue functionality.

Impressions: The 2011 WMEN conference exceed my expectations! This was my first year in attendance and I was impressed with the caliber of research talks and attendees. From an intellectual standpoint, I gained a lot from hearing a diversity of research & industry-sponsored talks, and from having the opportunity to speak directly with some of the presenters after their presentations. The size of the meeting (and relaxed atmosphere) was very helpful for networking with the other postdocs and PIs. My lab is working to establish collaborations with several of the people we met at this conference. This was a well-organized and truly memorable meeting!

Name: Arthur Olson
Department: Molecular Biology, The Scripps Research Institute
Mailing address: MB-5
The Scripps Research Institute
La Jolla, CA 92037
Email address: olson@scripps.edu

Phone number: 858 784-9702
Fax number: 858 784-2860

Overview: My laboratory focuses on computational structural molecular biology. We develop software for molecular modeling and visualization. We also apply molecular modeling, especially docking technology for biomedical application including drug design and chemical biology applications.

Presentation: This year I presented a new algorithm that enables the inclusion of water molecules in docking and virtual screening computations. The approach is able to predict waters that stabilize the interaction of ligands with target protein receptors. This work was not published at the time of the meeting, and is currently submitted for publication.

Impressions: The presentations at this year's meeting were excellent. There were a number of talks that described both new approaches and new results in the area of structural molecular and cellular biology. The science was first rate, and the interactions among the participants was both stimulating and rewarding.

Name: John Pak
Supervisor: Robert Stroud
Department: Biochemistry
Mailing address: 600 16-th St
Genentech Hall Rm S414
Email address: john.pak@msg.ucsf.edu
Phone number: 415-476-3937
Fax number: 415-476-1902

Presentation: The overexpression of human membrane proteins in human cells.

Impressions: I really like this meeting a lot. The quality of the talks was outstanding - much better than I anticipated. I also appreciated the smaller scale to this conference as it makes it easier to converse with the participants.

Name: James Paulson
Department: Department of Chemical Physiology
Mailing address: 10550 N. Torrey Pines Road
La Jolla, CA 92037
Email address: jpaulson@scripps.edu
Phone number: 858 784-9634
Fax number: 858 784-9634

Overview: Our group investigates the roles of carbohydrate binding proteins that mediate cellular processes central to immune regulation and human disease. Our main interests are in the siglec family of glycan binding proteins that are expressed on most white blood cells, and both mediate cell-cell interactions and regulate cell signaling receptors. I am also the Principle Investigator of the Consortium for Functional Glycomics, a large NIH funded consortium that comprises 540 investigators worldwide.

Presentation: The presentation this year focused on the roles of B cell siglecs in peripheral tolerance. The siglec CD22 is a negative regulator of B cell receptor signaling, and recognizes sialic acid containing glycans on adjacent cells as 'self ligands'. We found that treatment of mice by iv administration of liposomal nanoparticles containing both an antigen and glycan ligands of CD22-induced apoptosis of the B cells that recognized the antigen. This signal is caused by the physical ligation of CD22 to the B cell receptor, abrogating normal signaling by engagement with the antigen. As a result, the animals were tolerized to the same antigen on subsequent challenge. The results have significance for treatment of autoimmune disease and allergies caused by a B cell response to a known antigen.

Impressions: This has been my 10th meeting, and as always, the meeting exceeded my high expectations. It is a wonderful format where everyone presents, and the mix of students, postdocs, faculty and representatives of pharma, technology and venture companies is unique. The meeting is sustained by the high level of science and the breadth of topics ensures that one will hear something new in every session. Although the economy of past few years has somewhat 'stressed' the meeting attendance, the energy was very high this year, evident from the very first session with student and postdoc presentations. Will block my calendar as soon as the meeting is announced for next year.

Name: Cory Rillahan
Supervisor: James Paulson
Department: Chemical Physiology/The Scripps Research Institute
Mailing address: MEM L71, 10550 N Torrey Pines Rd La Jolla, CA 92037
Email address: rillahan@scripps.edu
Phone number: 858 784 9637
Fax number: 858 784 9690

Presentation: High throughput synthesis and glycan microarray screening identifies high affinity sialoside analogs for selective cell targeting.

Impressions: I thought the meeting was very good this year. There was a great mix of topics and speakers, which help to keep things interesting and lively. I would recommend a similar program for next year.

Investigator: Andrej Sali
Dept./Institution: Dept of Biopharmaceutical Sciences, UCSF
Mailing Address: UCSF MC 2552, Byers Hall Room 503B, 1700 4th Street, San Francisco, CA 94158-2330, USA
Email Address: sali@salilab.org

Phone: (415) 514 4227
FAX: (415) 514 4231

Overview: We are using computation grounded in the laws of physics and evolution to study the structure and function of proteins. We aim to improve and apply methods for: (i) predicting the structures of proteins; (ii) determining the structures of macromolecular assemblies; (iii) annotating the functions of proteins using their structures. This research contributes to structure-based functional annotation of proteins and thus enhances the impact of genome sequencing, structural genomics, and functional genomics on biology and medicine.

Presentation: To determine a macromolecular assembly structure by single particle electron microscopy (EM), a large number of two-dimensional (2D) particle images need to be collected, aligned, averaged, clustered and finally assembled via reconstruction into a three-dimensional (3D) density map. This process is limited by the number and quality of the particle images, the accuracy of the initial model, and compositional and conformational heterogeneities. We developed a computational method that bypasses single particle reconstruction by translating 2D images into spatial restraints, adding other spatial restraints (e.g., molecular docking, cross-linking, proteomics derived protein interactions), and modeling against all restraints as implemented in our Integrative Modeling Platform (IMP) package (http://salilab.org/imp). The method was described, benchmarked, and illustrated by its application to a 7-member Nup84 complex, part of the Nuclear Pore Complex.

Impressions:
Location: Good
Number of participants: Perfect
Length of meeting: Just right

There was plenty of time to be engaged in free format discussions with other participants. A large fraction of presentations were inspiring and informative.

Name: Daniel Santi
Department: UCSF/ProLynx
Mailing address: Daniel Santi, M.D., Ph.D.
Associate Dean, Recall Professor
Box 2240 , 600 16th Street N457B
University of California, San Francisco
San Francisco, CA. 94143 - 2240
Email address: Daniel.V.Santi@gmail.com
Phone number: 415 533 5775
Fax number: None

Overview: My UCSF work involves developing and managing an Industry Outreach Program that strives to bring UCSF and Industry scientists together. At this meeting, I described ongoing work at ProLynx, a young biotech company I recently co-founded.

Presentation: I described a new format for polyethylene glycol (PEG) and other macromolecule-drug conjugates that has been developed at ProLynx. Our technology platform uses a set of novel linkers that cleave, via β- elimination reactions, at different, pre-programmed rates to allow the controlled sustained release of native, active drugs – peptides, proteins and small molecules –from macromolecular conjugates. Importantly, at steady state the apparent half-life of the released drug is identical to that of the PEG-linker-drug conjugate. Hence, employing a set of linkers with a range of β-elimination rates allows the effective half-life of a drug to be predictably controlled and adjusted. Using our technology, we can sustain steady state levels of such drugs for periods of a few hours to a few weeks that can be specifically tailored for a particular drug.

Impressions: As usual, the science and environment were terrific. This year's meeting seemed particularly good, and the quality of the science presented was outstanding. The size and length of the meeting was ideal, as was the general location. My only constructive is that the quality of the food and hotel service left much to be desired.

Name: J. Michael Sauder
Department: Structural Biology, Lilly Biotechnology Center
Mailing address: 10300 Campus Point Dr, Suite 200, San Diego, CA 92121
Email address: michael.sauder@lilly.com
Phone number: 858-638-8802
Fax number: na

Overview: I provide bioinformatics, protein engineering, and project management support for structural biology targets, supporting structure-based drug discovery research at Eli Lilly and Company. From 2006-2011, I have also served as the project leader for the New York SGX Research Center for Structural Genomics (NYSGXRC), one of the NIH-funded large scale centers funded during the second phase of the Protein Structure Initiative.

Presentation: I discussed the protein production and crystallization challenges in structural biology and provided some examples of construct design and protein engineering that lead to structures during the NIH-funded structural genomics project.

Impressions: The meeting was excellent. The smaller size fostered informal discussions, and the fact that every attendee gave a summary of their research also facilitated interaction. The quality of the science presented was excellent.

Name: Glen Spraggon
Department: Genomics Institute of the Novartis Research

Foundation
Mailing address: 10675 John Jay Hopkins Drive
Email address: gspraggon@gnf.org
Phone number: 858 812 1567
Fax number: 858 812 1746

Overview: As part of the Novartis Institute of Biomedical Research (NIBR), the Genomics Institute of the Novartis Research Foundation (GNF) focuses on the discovery of new molecules and technologies to address unmet medical needs.
My group is focused on the use of structure to guide the development of novel small molecules and biotherapeutics and is dedicated both to obtaining atomic resolution information on target molecules using X-ray crystallography and to developing and employing new technologies in X-ray crystallography. Projects, generally involve collaborations between many groups and range from the determination and optimization of protein function from structure, via protein engineering, to the development of novel inhibitors by structure-aided drug design. These activities are coupled with the development of new technologies for various structural genomics projects, taking advantage of GNF's automated protein expression, purification, and crystallization facilities.

Presentation: Low density lipoprotein cholesterol (LDL-c) homeostasis in vertebrates is largely governed by the Low Density Lipoprotein Receptor (LDLR). A number of effector molecules are able to control the concentration of LDLR at the cell surface and thus affect plasma LDL-c levels. One such molecule, PCSK9, has been shown to disrupt LDLR recycling and redistribute LDLR for degradation in the lysozome. Naturally occurring mutants of PCSK9 have been identified which correlate with plasma levels of LDL-c and consequently with occurrence or resistance to coronary heart disease. Understanding the nature of the interaction between PCSK9 and LDLR, how LDLR is inhibited, and the

tertiary structure of cell-surface LDLR are among the major goals of cardiovascular research. The presentation reports the crystal structure of a complex of PCSK9 with LDLR and the first of LDLR at a cell-surface pH. The crystal structure, at low resolution (7 Angstroms), demonstrates the capability of X-ray crystallography to accurately define the quaternary structure of the complex at this resolution when high resolution structures of the individual domains are known. The structure enhances the current model of LDLR inhibition by PCSK9, showing that PCSK9 potentially stabilizes the open LDLR form by locking the conformation of the â-propeller/EGFC domains and thus inhibiting the closed ring conformation of LDLR at endosomal pH.

Impressions: The meeting was a great mix of academic and industrial presentations and well worth attending. I particularly liked the format of WMEN; the meeting being of sufficient size to cover a wide range of scientific disciplines but small enough that all attendees could orally present their work. Coupled with the location, these features provided an ideal setting for education, collaboration and active discussion within the multi-disciplinary sciences represented at the conference.

Name: C. D. Stout
Department: Molecular Biology, TSRI
Mailing address: 10550 N. Torrey Pines Rd., MB8
La Jolla, CA 92037
Email address: dave@scripps.edu
Phone number: 858 784 8738
Fax number: 858 784 2857

Overview: We use X-ray crystallography to study the structure and function of the membrane bound mitochondrial enzyme, transhydrogenase, understand the mechanism of the vitamin D metabolizing cytochrome P450, CYP24A1, and enable drug design against HIV protease. Collaborative projects focus on the mechanism of O2 reduction by

cytochrome ba3 oxidase, and the basis of substrate specificity in cytochrome P450's.

Presentation: A fragment screen employing crystallography against HIV protease (PR) in the closed, inhibited form identified two surface binding sites, the exo site and the flap site, each with the potential to alter PR conformational preferences. Based on the initial fragment hits, higher affinity molecules are being developed using methods of structure based drug design. Fragments bound in the flap site appear to favor the closed form, consistent with allosteric inhibition. Drugs based on these fragments could act in synergy with FDA-approved PR inhibitors to restore potency against multi-drug-resistant PR mutants.

Impressions: The Cabo meeting is unique in the very high quality of the science presented and the breadth of important problems addressed within the context of structural biology and drug discovery. The opportunities to interact are excellent, and the fact that all attendees speak benefits the interaction. The location and facilities are excellent. This size of the meeting is ideal for allowing all attendees to present while having time for discussions outside the formal program.

Name: Robert M. Stroud
Department: Department of Biochemistry & Biophysics, UCSF
Mailing address: S- 412C Genentech Hall, 600 16th Street, San Francisco, CA 94158-2517
Email address: stroud@msg.ucsf.edu
Phone number: 415 476 4224
Fax number: 415 476 1902

Overview: The project I described was titled 'Insertion Folding and Assembly of Membrane Proteins'. The work from my laboratory discussed the mechanisms that determine correct targeting of membrane proteins and

receptors, highlighted by the structural determinations of membrane protein structures at high resolution by X-ray crystallography. Particularly, I discussed the signal recognition system and the structure of the translocon through which membrane proteins get inserted into their membrane.

Presentation: The mechanism of signal-dependent targeting was described in reference to a high resolution structure of the SRP in complex with its receptor SR that directs targeting to the translocon pore in the target membrane. The structure of the translocon, a three-protein complex was presented and revealed a partially opened pore that enables lateral movement of membrane proteins into the membrane during folding. The C-terminus was shown to be a key trigger to the interaction with the ribosome. Alongside, two human membrane proteins, expressed heterologously, were defined for the first human Rh factor, and for an Aquaporin from human brain that is a target for drugs against the damage in the brain following stroke. These Protein crystal structure reveal key roles in the understanding of an essential process in cell biology.

Impressions: Location: Excellent.
Number of participants: Good size
Length of meeting: Just right

Convenient for access from California, and sufficiently remote to concentrate people's time and attention. Cabo San Lucas is excellent after refinement of location over the years.
Number of participants: A comfortable size for the meeting is about 40 people, with 20 speakers. Attendees and presenters were excellently chosen from the superb groups in structural biology at Scripps and at UCSF.
Length of meeting: The meeting of 3 days length is quite adequate and more would probably be too much.

The science presented was absolutely first rate with many important new breakthroughs in the fields of immunology,

drug design, chemical basis for inhibition, chemical basis for understanding enzyme mechanisms and cell surface receptor interactions.

Name: Andrew Ward
Department: Molecular Biology/The Scripps Research Institute
Mailing address: 10550 N. Torrey Pines Rd., CB163Q, La Jolla, CA 92037
Email address: abward@scripps.edu
Phone number: 8587847320
Fax number: 8587849985

Overview: A good diversity of science, though focused on structure and drug discovery. A bit less bioinformatics/computational biology than previous years but that made room for more cell biology.

Presentation: I presented the x-ray structure of the ABC transporter P-glycoprotein with a bound nanobody inhibitor. This works follows up the recently published structure of P-glycoprotein and provides another structural intermediate in the highly dynamic transporter. Flexibility provides a variety of looks for the drug binding pocket and may account for the polyspecificity.

Impressions: Another successful year with great presentations and interactions. The industrial partners provided a nice overview of where the private sector is focused. A few of the speakers/sessions went well over time.

Name: Jamie Williamson
Department: Dept. Molecular Biology, TSRI
Mailing address: 10550 North Torrey Pines Road, MB-33 La Jolla, CA 92037
Email address: jrwill@scripps.edu
Phone number: 858-784-8740

Fax number: 858-784-2199

Overview: This was probably the best Cabo meeting I have attended, of approximately 8. There was good representation from both TSRI and UCSF, and good representation from industry. There were some new faces present, which was excellent. The students and postdocs did extremely well in their presentations, and there were many new stories, even from the standard attendees. The sponsors are an excellent addition to the meeting, in particular.

Presentation: I gave a great talk!

Impressions: This is an excellent overview of structural biology, biophysics, and computation. The format is relaxed but engaging, and it was a highlight of my 15 meetings this year. The venue is excellent, and there is plenty of time for informal discussions and recreation in addition to the talks. Very high scientific value!

Name: Ian A. Wilson
Department: Molecular Biology
Mailing address: The Scripps Research Institute, 10550 N Torrey Pines Road, BCC206
La Jolla, CA 92037
Email address: wilson@scripps.edu
Phone number: (858) 784-9706
Fax number: (858) 784-2980

Overview: My laboratory works on the structural basis of immune recognition of microbial pathogens. We work extensively on influenza virus and HIV-1 and, in particular, broadly neutralizing antibodies that interact with multiple strains and subtypes. The human antibody crystal structures have revealed fascinating new ways and mechanism of virus neutralization. We also investigate other components of the human immune system, such as TLRs,

VLRs and TCRs and their interaction with antigens. I also direct the Joint Center for Structural Genomics which is a multi-institutional consortium of NIH PSI:Biology. We have developed many methods and approaches for high throughput crystallography and NMR and have determined over 1200 novel protein structures.

Presentation: Broadly Neutralizing Antibodies to HIV-1. I presented our recent work on exciting new broadly neutralizing antibodies to HIV-1 and the novel modes of interaction through extended CDR H3 loops of up to 28 residues. The "hammerhead" antibody has the longest human CDR H3 known and adopts a very ordered structure with a towering H3 that has two lobes at its tip that contain sulfated tyrosines. I also presented our work on the new, highly potent IAVI PGT antibodies that have been characterized by the Burton group (virology) and by our group (structural biology). These antibodies seem to have novel epitopes that include carbohydrate.

Impressions: Once again, a terrific meeting with a high quality presentations and great interaction with all of the participants whether from academic or industry.

Name: Dennis Wolan
Department: Molecular and Experimental Medicine
Mailing address: The Scripps Research Institute, MEM L43
10550 North Torrey Pines Road
La Jolla, CA 92037
Email address: wolan@scripps.edu
Phone number: 858.784.7936
Fax number: 858.784.7950

Overview: Our group is interested in the discovery of small molecules that target the inhibition of extracellular proteases secreted from bacteria. Such inhibitors could be applied as tools to understand the biological significance of the target proteases and as potential foundations for therapeutics.

Presentation: Structure-based mechanism of streptopain and insights into inhibitor design

Impressions: As always, a fantastic meeting. I liked how the meeting was organized; however, I would prefer the session chair not have his/her talk within the same session. That setup seemed to result in time management issues. I also miss the "round table" discussion - I found the topics within past years to be useful - particularly to the younger attendees.

Name: Ronald Zuckermann
Department: Molecular Foundry, Lawrence Berkeley National Lab
Mailing address: 1 Cyclotron Rd.; MS 67-5110
Berkeley, CA 94720
Email address: rnzuckermann@lbl.gov
Phone number: 510-486-7091
Fax number: 510-495-2376

Overview: I study the folding of non-natural polymers into protein-like structures. To what extent can protein structure be recapitulated in a synthetic polymer? My lab studies the effect of sequence control on polymer structure. We developed a family of polymers called peptoids that can be synthesized cheaply and efficiently from primary amine building blocks. Through a combination of design, computation, combinatorial synthesis and screening we are identifying new rules that dictate the folding of peptoids into defined higher order structures.

Presentation: We identified a sequence pattern of peptoid residues that results in the self-assembly of ultra-thin nanosheets. The peptoid nanosheets are composed of fully extended peptoid chains, aligned parallel to one another over long distances (over 100 micron square) and yet are

only two molecules thick. We interrogated the structure by a variety of methods to establish the ordering of peptoid chains in the material. The well-defined structure serves as a soluble 2D platform upon which to display conformationally constrained loops at defined distances from one another, ultimately serving as a platform for molecular recognition.

Impressions: The work presented at this meeting was of exceptionally high quality. I found it to be a truly inspiring experience. The size of the meeting was just right: large enough to cover a diversity of topics, and small enough to make connections with new people.

“Discussions at the meetings have helped nucleate one new effort in my lab and provided key direction to another.”
Steven E. Brenner, Ph.D.

“This is one of the best meetings of the year. Very high caliber talks, from academic PI’s, from the grad students and postdocs, and from the people from industry : all uniformly high.”
Ken A. Dill, Ph.D.

“I sincerly hope that future generations of young scientists will be afforded the chance to participate in a similarly formatted conference.”
Michael J Evans, Advisor: Benjamin Cravatt III, Ph.D

“The atmosphere of the meeting was very friendly and scientifically stimulating. The meeting provides an excellent forum for discussion and fostering of new ideas and collaborations.”
Molly He Sunesis Pharmaceuticals

“I particularly liked the fact that most of the presented research was unpublished, which makes this meeting very unique.”
Tanja Kortemme, Ph.D.

“The Cabo meeting is one of the most informative meetings I typically attend and has become a highlight of the scientific year for me. The breadth of topics and the quality of the science presented are always outstanding.”
David P. Millar, Ph.D.

“The science presented was absolutely first rate with many important new breakthroughs.”
Robert M.Stroud, Ph.D.