Our History

The WMEN conference has been held for the past 19 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 and 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 nine years ago the venue moved from Cabo San Lucas to the all-inclusive El Presidente Hotel in San Jose del Cabo. The meeting includes approximately 60 selected participants, 40 of which are laboratory heads. The spirit of scientific research is enhanced and refreshed in this stunning setting.

FINAL SCHEDULE
World Molecular Engineering Network Eighteenth Annual Meeting on Structural Biology

4-8 May 2008, San Jose del Cabo, Baja, Mexico

Sunday Evening, 4 May

17:00 – 17:15 Andrej Sali and Ian Wilson **Introduction and Welcome**

17:15-20:00 ***Self-Introductions by Non-Presenting Sponsors***

Hans Parge	Pfizer
Daniel Santi	UCSF
Sammy Farah	Versant Ventures
Heather Preston	TPG

Short Presentations (5 min.) by TSRI and UCSF Graduate Students, Postdoctoral Fellows *et al.*

Mark A. Burlingame	UCSF	The SMDC and advances in disulfide monophore synthesis
Abram Calderon	UCSF	Using structure-based drug design to direct NMR screening of an RNA target
Ranyee Chiang	UCSF	Evolutionarily conserved substrate substructures for automated annotation of enzyme superfamilies
David Eramian	UCSF	TSVMod: Prediction of the absolute accuracy of protein models
Franz Gruswitz	UCSF	Conduction through the ammonia channels- faculty talk??
Kathryn Ivanetich	CSU Chico	Quantification of human-derived fecal *Enterocci* in environmental waters
Sriram Sankararaman	UCB	Predicting catalytic and specificity residues in proteins
Fumiaki Yumoto	UCSF	Critical nuclear receptor in ES cell
	Break	
Katy Barglow	TSRI	Activity-based proteomic and structural analysis of the nitrilase family of

			enzymes
	Russell Burge	TSRI	Interaction of the double-stranded RNA-binding zinc finger protein JAZ with the adenoviral VA1 RNA
	Graham Johnson	TSRI	Automated visualization of subcellular environments
	Donald Kerkow	TSRI	A novel RNA-binding domain I the nuclear export factor (NXF) family
	Chris Kimberlin	TSRI	Structural studies of Ebola virus VP35
	Gabriel Lander	TSRI	A look at bacteriophage evolution via high-throughput automated cryoEM
	Anke Mulder	TSRI	Biding of kinesin 13 heads to curved microtubule protofilaments
	Peter Smith	TSRI	Genetic SAR: a new method for identifying critical enzyme/inhibitor interactions.
	Megan Thielges	TSRI	Exploring the energy landscape of antibody-antigen complexes: Protein dynamics, flexibility, and molecular recognition
	Theresa Tiefenbrunn	TSRI	Structural investigations of synthetic antiangiogenic thrombospondin type 1 repeat analogs
	Andrew Ward	TSRI	ABC transporters and novel detergents
20:00–21:00	**Reception**		**Poolside**

Monday Morning, 5 May

Advances in Proteomics (Chair: Robert Stroud, UCSF)

09:00	Ian Wilson	TSRI	The expanding protein universe
09:20	Andrej Sali	UCSF	Integrative methods for protein structure determination
09:40	Kimmen Sjolander	UCB	New methods for enzyme active site prediction
10:00	***Break***		
10:30	Dennis Wolan	UCSF	Small molecule activators of the executioner caspases
10:50	Ray Stevens	TSRI	GPCR structure and implications for drug discovery
11:10	Andrew Krutchinsky	UCSF	Studying dynamics of protein assemblies in cells with fluorescence microscopy

11:30	Peter Kuhn	TSRI	Circulating tumor cells in cancer management – from bedside to bench and back

Monday Afternoon

Immunology , Virology, and Glycobiology (Chair: Sherry LaPorte, Rinat/Pfizer)

16:30	Jim Paulson	TSRI	Functional Glycomics
16:50	Carlos Barbas	TSRI	Chemically programmed immunity
17:10	Tobin Dickerson	TSRI	Applying phage escape technology to high throughput screening and the modeling of viral evolution
17:30	Matija Peterlin	UCSF	Host cellular complexes on HIV regulatory and accessory proteins

17:50 **Break**

SPONSORS I – Advances in Technology for Structural Biology (Chair: Robert Fletterick, UCSF)

18:20	Andy May	Fluidigm	Diffraction-capable microfluidic crystallization chips for screening and structure determination
18:40	Roger Durst	Bruker	X-ray source and detector technologies for micron-sized crystals

Tuesday Morning, 6 May

SPONSORS II – (Chair: Dan Santi, UCSF)

09:00	Joseph Ferrara	Rigaku	Advances in X-ray instrumentation for the home lab
09:20	Michal Vieth	Eli Lilly	Kinase bioprints-prospective modeling of kinase selectivity
09:40	Sherry LaPorte	Rinat/ Pfizer	Snapshots of the IL-4 receptor ternary complexes: An opportunity to visualize the basis of cytokine receptor pleiotropy in the immune system

10:00	**Break**		
10:30	Todd Appleby	Gilead Sciences	Introduction to Gilead Sciences
10:40	Peter Munson	WSGR	Biotechnology Startups: Intellectual property & commercial development
11:00	**Panel Discussion**	***Panel : Ray Stevens (lead), , Sammy Farah , Jim Paulson, Andrej Sali, Dan Santi, Robert Stroud, Andrew Ward, Jamie Williamson, Dennis Wolan***	

Topic: Translational Research - Approaches and right balance for academia

Tuesday Afternoon

Nucleic Acids, Proteins & Enzymes (Chair: Jamie Williamson, TSRI)

16:30	Joel Gottesfeld	TSRI	Chromatin therapeutics for neurological diseases
16:50	David Millar	TSRI	Nucleic Acid – protein interactions at the single-molecule level
17:10	Tom James	UCSF	Molecular recognition entailing RNA: :induced fit virtual screening to find small molecule ligands
17:30	**Break**		
18:00	Jamie Williamson	TSRI	Dynamics of the ribosomal proteome
18:20	Craig Yoshioka	TRSI	Visualizing ribosome assembly
18:40	Robert Fletterick	UCSF	Androgen receptor antagonists

Wednesday Morning, 7 May

Assemblies, Computation, and Chemistry (Chair: Kimmen Sjolander, UCB)

08:30	Qinghai Zhang	TSRI	Chemistry endeavors to solve membrane protein structures

08:50	C. David Stout	TSRI	Crystal structure of a mitochondrial membrane protein: Vitamin D specific cytochrome P450 CYP24A1
09:10	Robert Stroud	UCSF	Gas Channels
09:30	***Break***		
10:00	Floyd Romesberg	TSRI	Efforts to expand the genetic alphabet
	Todd Yeates	UCLA	Ideas for designing topologically interesting protein polymers
10:20			
10:40	Art Olson	TSRI	Extending applications of automated docking
11:00	Ian Wilson and Andrej Sali		**Closing Remarks**

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

WMEN Conference
San Jose del Cabo
El Presidente Hotel

For more information, contact:

Daniel Santi
daniel.v.santi@gmail.com

Ian Wilson
wilson@scripps.edu

Karin Asensio
karin@salilab.org

Name: Prof. Carlos F. Barbas
Department: The Scripps Research Institute
Mailing address: 10550 N. Torrey Pines Road, BCC 550, La Jolla, CA 92037
Email address: carlos@scripps.edu
Phone number: 858 784-9098
Fax number: 858 784-2583

Presentation: CovX-bodies: from Concept to Clinic
Prof. Carlos F. Barbas, III
The Scripps Research Institute, La Jolla, CA, USA, 92037.

Recently, my laboratory has developed a new class of immunotherapeutic agents termed Chemically Programmed Antibodies or CovX-bodies as prepared by CovX Inc. I will present studies concerning the superior in vivo activity bestowed upon small molecules and peptides by this approach and describe how CovX Inc. has now advanced these molecules into several human clinical trials. CovX was recently acquired by Pfizer.

Impressions: Fantastic meeting. Great diverse and intense presentations. Creative science and a great opportunity to bounce around cross-disciplinary ideas.

Name: Katy Barglow
Supervisor: Ben Cravatt
Department: Chemical Physiology/TSRI
Mailing address: 10550 N. Torrey Pines Rd, BCC159, La Jolla, CA 92037
Email address: kbarglow@scripps.edu
Phone number: 858-784-8202
Fax number: 858-784-8023

Presentation: My work focuses on using structurally diverse small molecule libraries into functionally and biochemically characterize enzymes. Recently, we discovered probes for the nitrilase family of enzymes, a poorly understood, highly conserved family of C-N hydrolases. For the nitrilase

ureidopropionase-beta, the probes, discovered de novo from screening, acted as close substrate mimics, implying that probe labeling profiles may offer insight into substrate selectivity for uncharacterized enzymes. Towards that end, we solved the structure of the nitrilase enzyme mouse Nit2 at 1.4Å resolution. Through a combination of probe labeling, mutagenesis, and molecular modeling, we propose a model of probe (and, by extension) substrate binding into the active site of this uncharacterized enzyme.

Impressions: This meeting was terrific! I was able to talk to many interesting colleagues and discuss collaborations. I thought the structure of short postdoc and graduate student talks on the first night, followed by longer PI presentations and sponsor presentations on the following days worked very well, and I particularly also enjoyed the translational research panel. Overall, a great week--thanks to all who made it possible.

Name: Russell G. Burge
Supervisor: Peter E. Wright
Department: Molecular Biology
Mailing address: 10550 N. Torrey Pines Road, La Jolla CA, 92037
Email address: burge@scripps.edu
Phone number: 858-784-8775
Fax number: 858-784-9822

Presentation: Interactions of JAZ with VA1 RNA

We are studying how the human protein, JAZ interacts with adenoviral RNA, VA1 using EMSAs and NMR spectroscopy.

Impressions: This meeting is well organized and the speakers conduct interesting research and on average are very good at conveying their scientific research to the other meetings attendees. The presentations from the sponsors are also of great interest, especially to the students who may also being looking for industry positions.

Name: Mark Burlingame
Supervisor: Adam Renslo
Department: Pharm Chem/UCSF
Mailing address: Byers Hall, MC 2552 1700 Fourth St., Room 504 San Francisco, CA 94158-2330
Email address: mark.burlingame@ucsf.edu
Phone number: 415-514-1367

Presentation: The SMDC and advances in disulfide monophore synthesis.

Impressions: Once again, the WMEN meeting was extremely stimulating scientifically bringing together a diverse set of scientists addressing biology and medicine through a common ground of protein structure. I found the panel discussion a particularly interesting and insightful examination of the roles of venture capitalists, Pharma, and Academia in developing new drugs and drug targets.

Name: Abram Calderon
Supervisor: Thomas L. James
Department: University of California, San Francisco
Mailing address: Box 2280, 600 16th Street 522, University of California, San Francisco CA 94143-2280
Email address: abram.calderon@ucsf.edu
Phone number: (415) 476-4378
Fax number: (415) 502-8298

Presentation: Using Structure-Based Drug Design to Direct NMR Screening of an RNA Target

Impressions: This was my first time at the conference. I liked that the talks from the students and post-docs were short. This made it easy to get an overview of the research that different people are doing.

Name: Ranyee Chiang
Supervisor: Patricia Babbitt
Department: Biopharmaceutical Sciences/UCSF
Mailing address: UCSF MC 2550, Byers Hall N508, San Francisco, CA 94158-2550
Email address: rchiang@cgl.ucsf.edu
Phone number: 415-502-1248
Fax number: 415-514-4797

Presentation: Evolutionarily Conserved Substrate Substructures for Automated Annotation of Enzyme Superfamilies

Impressions: People should do a better job of keeping the talks to the allotted time. I really enjoyed the panel discussion and more of those would have been even better. Making time for people to have dinner on the first day would be good.

Name: Robert Fletterick
Department: Biochemistry UCSF
Mailing address: UCSF MC 2240, Department of Biochemistry, Genentech Hall Room, S 412E, 600 16 th Street, San Francisco CA 94158-2517
Email address: flett@msg.ucsf.edu
Phone number: 415 476 5080
Fax number: 415 476 1902

Overview: The meeting was swell. The conference setting helped foster interactions. The science interchange was impressive.

Presentation: I spoke about prospects for making a new class of therapeutics for the human androgen receptor which might be developed into clinical drugs. Current drugs used to treat prostate cancer bind weakly because they were designed to fit the hormone binding pocket of the receptor. These drugs do not have a perfect fit so they cause the receptor to fold incompletely into a state that will not permit

the required cofactor proteins to bind. Our idea, which was backed by chemical and biological assays of a small library of compounds, was to discover a compound which binds much tighter than the current drugs or natural hormones. We showed that this was possible by placing a large hydrophobic extension on a steroid hormone. Appropriate additions to the 11 position of the steroid ring not only bind tighter than hormones, but create receptors which are not able to be activated and which are degraded by the cancer cells. We speculated that this paradoxical pairing of tight binding with destabilization of the protein was due to enhance hydrophobic interactions between the receptor and the compound.

Impressions: Great venue. The small meeting was perfect to allow people to discuss the science outside of the meeting room The meeting room was fine, though often slightly too cold from air conditioning. The mixer was perfect to greet colleagues. The food at the hotel was marginal, though the staff were accommodating.

Name: Joel Gottesfeld
Department: The Scripps Research Institute, Department of Molecular Biology
Mailing address: 10550 N. Torrey Pines Road, MB-27, La Jolla, CA 92037
Email address: joelg@scripps.edu
Phone number: 858-784-8913
Fax number: 858 7848965

Overview: Research in our laboratory concerns the development of small molecules to regulate gene expression. We are using both DNA binding molecules and enzyme inhibitors to regulate the expression of clinically significant genes. Our recent efforts have focused on histone deacetylase inhibitors as potential therapeutics for neurodegenerative diseases.

Presentation: My presentation this year focused on the

development of HDAC inhibitors as therapeutics for the neurodegenerative diseases Friedreich's ataxia (FRDA) and Huntington's disease (HD). FRDA is caused by hyper-expansion of GAA•TTC repeats in the first intron of a nuclear gene that encodes the mitochondrial protein frataxin. Expanded triplet repeats cause gene silencing either by altering DNA or chromatin structure. We examined the chromatin structure of the frataxin gene in cell lines derived from a FRDA patient and a normal sibling of this patient using antibodies to the various modification states of the core histones and chromatin immunoprecipitation methods. We find that gene silencing at expanded frataxin alleles is accompanied by hypoacetylation of histones H3 and H4, and methylation of histone H3 at lysine 9, consistent with a heterochromatin-mediated repression mechanism. We screened commercially available histone deacetylase inhibitors for their effects on frataxin transcription in the FRDA cell line, and identified one compound, BML-210, that partially reverses silencing in the FRDA cell line. Based on the structure of this compound, we synthesized and assayed a series of derivatives of BML-210 and identified histone deacetylase inhibitors that reverse frataxin silencing in primary lymphocytes from Friedreich's patients. We showed that these molecules act directly on the histones associated with the frataxin gene, increasing acetylation at particular lysine residues on histones H3 and H4. Using a chemical proteomics approach, we identified the target of our HDAC inhibitors as HDAC3. Unlike many triplet-repeat diseases (for example, the polyglutamine expansion diseases such as HD and the spinocerebellar ataxias), expanded GAA·TTC triplets do not alter the coding potential of the frataxin gene; thus, gene activation would be of therapeutic benefit. Animal studies have established the bioavailability and efficacy of these molecules as potential FRDA therapeutics. In the case of HD, we find that our molecules reverse neurodegeneration in a transgenic mouse model, without apparent toxicity.

Impressions: For a non-structural molecular biologist, with interests in structure-function relationships in DNA-binding

proteins, this meeting is very valuable in learning the nuances of biophysical approaches to this field. As in previous years, I am continually impressed by the quality of structural data that comes from the institutions represented at this meeting. I think the mix of senior PI's, more junior PI's and postdocs and students is excellent. There are far too few meetings where such a mix is possible. I would favor longer presentations by some of the more advanced postdocs and graduate students. These could be in place of some of the talks given by the PI's who have spoken at previous meetings. Perhaps PI's should only speak every other year, and I would be willing to speak on such a schedule. I think the location and length/scheduling of the meeting is outstanding and I hope to be included in future years.

Name: Franz Gruswitz
Supervisor: Bob Stroud
Department: Biophysics/UCSF
Mailing address: 600 16th St S412
Email address: gruswitz@msg.ucsf.edu
Phone number: 4155135585
Fax number: 4154761902

Presentation: Plugging the Ammonia Channel: How nitrogen supply is linked to carbon and nitrogen availability in  E. coli

Impressions: I really liked the quality of the talks and the panel discussions. Some natural connections were made during social times, but it would be great if there were some dinner activity on the first night and lunch activity the next day the had even greater means of enhancing networking within the group. I think this is primarily about attendance. Some of the senior PIs and industrial sponsors chose not to participate in many social activities. Many PIs were extremely involved and huge kudos to them. This made the meeting for me.

Name: Thomas L. James
Department: Department of Pharmaceutical Chemistry, UCSF
Mailing address: Mail Code 2280, Genentech Hall, 600 16th St, San Francisco, CA 94158-2517
Email address: james@picasso.ucsf.edu
Phone number: (415) 476-1916
Fax number: (415) 502-8298

Overview: Major goals of our research are (a) to investigate small molecule-macromolecule interactions as well as biomolecular structure and dynamics using NMR, and (b) to use three-dimensional nucleic acid structures with computational search algorithms and subsequent NMR screening to discover novel ligands. The subjects for study are often chosen to be targets for subsequent drug design.

Presentation: Molecular Recognition Entailing RNA: Induced Fit Virtual Screening to Find Small Molecule Ligands. Due to the paucity of unique three-dimensional RNA structures, the typical conformational malleability of RNA, and the success of using protein targets in developing clinically useful drugs, there has been little effort to discover drugs rationally RNA structures. There is precedent in that RNA-binding drugs have probably been used by most of us, however. Techniques of structure-based drug discovery applicable to proteins are not directly applicable to RNA. Nevertheless, we and others have recently been developing or modifying methods to find small molecule ligands that will bind with some specificity to selected RNA targets with the view that these ligands may contribute to developing novel drug leads.
We have developed a strategy to discover ligands for RNA targets based on three-dimensional RNA–structure-based computational screening of 105 - 106 commercially available compounds for binding, followed by NMR binding screens of computational “hits”. The starting point for such a study is to determine the structure of a potentially useful target. The

human ribonucleoprotein telomerase is a validated anticancer drug target, and hTR-P2b is a part of the human telomerase RNA (hTR) essential for its activity. Interesting ligands that bind hTR-P2b were identified using the tandem docking/NMR screening approach. An important key to success was our development of the program MORDOR which can be used for virtual screening of a small molecule database to find binders with both ligand and receptor permitted to be flexible with consequent induced fit binding.

Impressions: Location: Excellent
Number of participants: Just right
Length: Just right

The presentations and quality of science presented were first-rate. The size of the meeting, focus of interests, location in an isolated setting conducive to strong interactions among participants, and quality of the science presented made this one of the best meetings I have attended. Although I had some notion of the research areas of my colleagues, it was good to have those updated as well as learn much more about the exciting research at Scripps, at UC Berkeley, and at the industrial labs represented.

Name: Graham Johnson
Supervisor: Art Olson
Department: Molecular Biology/TSRI
Mailing address: 10550 N. Torrey Pines Road, La Jolla, CA 92037
Email address: graham@scripps.edu
Phone number: 3032493934
Fax number: 858-784-2860

Presentation: Automated Visualization of Subcellular Environments

Impressions: Fantastic. The balance of scientific talks with networking conversation time before and after each session block really allows attendees to expand their knowledge and

establish collaborations. This years meeting was well organized and relatively punctual...it seemed to run very smoothly.

Name: Don Kerkow
Supervisor: James Williamson
Department: Department of Molecular Biology/The Scripps Research Institute
Mailing address: 10550 North Torrey Pines Rd, La Jolla, CA 92037
Email address: dkerkow@scripps.edu
Phone number: 858-784-8743
Fax number: 858-784-2199

Presentation: Talk Title: "The Novel NXF NTF2-Like RNA Binding Domain"

Impressions: Once again, a superb meeting! I especially enjoyed hearing about the new advances in home xray sources, the possibility of shooting crystals within a fluidigm chip, the UV screener for crystals and the novel "facial" detergents and their applications. Additionally, the projects described in the talks were all very interesting and provided me with some new methods for my own work. My least favorite aspect of the conference was the panel discussion because it often results in pointless and irresolvable arguments. I feel the time spent on this could be better served by more sponsor or professor talks.

Name: Peter Kuhn
Department: cell biology/tsri
Mailing address: 10550 n Torrey pines Rd, GAC1200, La Jolla, CA 92037
Email address: pkuhn@scripps.edu
Phone number: +1 858 784 9114
Fax number: +1 858 784 8996

Overview: Circulating tumor cells in blood circulation has

become a mainstream research and diagnostic approach over the last few years. Our ability to find and characterize these cells has impact on both, basic research and clinical fields.

Presentation: The presentation focused on our ability to find and characterize circulating tumor cells in patients with breast, colon, lung and prostate cancer. The morphologic and protein expression characterization will enable us to identify the origin of these cells and monitor/guide treatment regiments.

Impressions: This was again a very successful and productive meeting with a great round table discussion that engaged in particular the student participants.
The VC community clearly missed out by not being represented very well as i believe that those who were present really contributed and gained from the meeting.

Name: Gabriel C Lander
Supervisor: Jack Johnson/ Bridget Carragher
Department: Mol Bio/Cell Bio - TSRI
Mailing address: CB129,10550 N Torrey Pines Rd, La Jolla, CA 92037
Email address: glander@scripps.edu
Phone number: 858-784-9208
Fax number: 858-784-9090

Presentation: Phage head stabilization viewed by automated cryoEM
We report the cryoEM structure of bacteriophage lambda and the mechanism for stabilizing the 20Å thick capsid containing the dsDNA genome. The crystal structure of the HK97 bacteriophage capsid fits most of the T=7 lambda particle density with only minor adjustment. A prominent surface feature at the 3-fold axes corresponds to the cementing protein gpD, necessary for stabilization of the capsid shell. Its position coincides with the location of the covalent cross-link formed in the docked HK97 crystal

structure, suggesting an evolutionary replacement of this gene product in lambda by autocatalytic chemistry in HK97. The crystal structure of the trimeric gpD, in which the fourteen N-terminal residues required for capsid binding are disordered, fits precisely into the corresponding EM density. The N-terminal residues of gpD are well ordered in the cryoEM density adding a strand to a beta-sheet formed by the capsid proteins and explaining the mechanism of particle stabilization.

Impressions: The relaxed atmosphere and small size of the meeting provided a perfect stage for interesting discussions with people from very diverse fields, an aspect I found most enjoyable. The schedule was well planned, and at no point did I feel worn out from long days of talks and discussions, as is the case at many other conferences I have attended. The panel discussion this year was far superior to those from years past. Having slides to go off of kept the discussion focused and directed, it was a great idea.

Name: Anke Mulder
Supervisor: Ronald Milligan and Bridget Carragher
Department: Cell Biology
Mailing address: 10550 N Torrey Pines Rd. CB227, La Jolla, CA 92037
Email address: mulderam@scripps.edu
Phone number: 619-309-5779
Fax number: 858-454-8811

Presentation: Binding of Kinesin-13 Heads to Curved Microtubule Protofilaments

Impressions: A wonderful, relaxed atmosphere that encouraged open discussion between students and established researchers. This is a fantastic meeting from a student's perspective. There is no other meeting, to my knowledge, where communication between senior scientists and student researchers is so open and honest. I think this meeting fills a very important niche.

Name: James C. Paulson
Department: Departments of Chemical Physiology and Molecular Biology
Mailing address: 10550 N. Torrey Pines Road, MEM-L71, La Jolla, CA 92037
Email address: jpaulson@scripps.edu
Phone number: 858-784-9634
Fax number: 88-784-9690

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 400 investigators worldwide.

Presentation: Functional glycomics. This year I gave an overview of the Consortium for Functional Glycomics, with emphasis on the problems that confront this field in describing biology at a structural level. The primary focus is how glycan binding proteins recognize and distinguish glycan ligands from all other glycan structures, and how such recognition can impact cell surface biology. The talk gave a broad overview of the types of biology mediated by protein-glycan interactions, and then focused on the resources that are being developed by the CFG to address these problems. The CFG is in its 7th year of 10 years of funding, and is developing a database that integrates diverse datasets to help the biologist access the data needed to elucidate the role of the glycan binding protein of interest. (http://www.functionalglycomics.org)

Impressions: Over the years the meeting has kept its basic format, but is always fresh with the gradual addition of new faculty, industry and venture participants, and the active

contributions of the students and postdocs. The quality of the presentations continue to set a high standard, and the formal and informal discussions in this beautiful setting once again made for a rewarding and memorable meeting.

Name: B. Matija Peterlin
Department: Medicine/UCSF
Mailing address: Box 0703, 533 Parnassus Ave UCSF, San Francisco, CA 94143-0703
Email address: matija.peterlin@ucsf.edu
Phone number: 5021905
Fax number: 5021901

Overview: Excellent meeting at the intersections of structural biology, drug design, new therapies and pathophysiology

Presentation: I presented data on our studies of interactions between HIV and the host, especially those between viral accessory and regulatory proteins and cellular machineries involved in transcription, signaling and trafficking of organelles. These protein: protein and nucleic acids: protein interactions are amenable to further structural studies as well as specific intervention with new drugs.

Impressions: A meeting that brings diverse groups together is extremely useful, as new ideas and collaborations invariably emerge. Personally, I came away with new projects and new contacts. Some of these might lead to clinical applications in our fight against AIDS.

Name: Floyd Romesberg
Department: Chemistry/TSRI
Mailing address: 10550 N. Torrey Pines Road, CB262R, La Jolla CA, 92037
Email address: floyd@scripps.edu
Phone number: 858-784-7290

Overview: Great meeting. I especially like the 20 min format because it gets to the bottom line of a lot of science quickly. The time between talks is always filled with more detailed discussions.

Presentation: My presentation was titled 'Efforts to Expand the Genetic Alphabet'

Impressions: again it was great. Only one comment. A lot of people talked about 'protein dynamics' maybe next year we could have a special session on the protein dynamics as it related to biological function and drug design. I would be happy to help organize it.

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: We developed a method for structure characterization of assembly components by iterative comparative protein structure modeling and fitting into cryo-electron microscopy (cryoEM) density maps. Specifically, we calculate a comparative model of a given component by

considering many alternative alignments between the target sequence and a related template structure while optimizing the fit of a model into the corresponding density map. The method is being implemented in our program MODELLER for protein structure modeling by satisfaction of spatial restraints and will be applicable to the rapidly increasing number of cryoEM density maps of macromolecular assemblies.

Impressions of the meeting:
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: Sriram Sankararaman
Supervisor: Kimmen Sjolander
Department: UC Berkeley
Mailing address: 324, Stanley Hall, UC Berkeley, CA - 94720
Email address: sriram_s@cs.berkeley.edu
Phone number: 510-813-9888
Fax number: 510-813-9888

Presentation: Enzyme active site prediction

Computational methods for predicting enzyme active sites are an important tool in characterizing the function of enzymes. I will present two methods for active site prediction. The first method relies on protein sequence information alone. It exploits the evolutionary patterns of variation seen in protein families to identify such positions. The second method integrates heterogeneous types of information from sequence and 3d structure to obtain further improvements in active site prediction over current methods. I will also talk about the biologically interesting predictions

made by these methods.

Impressions: The meeting was very stimulating. The format is fine the way it is.

Name: Kimmen Sjolander
Department: QB3/UC Berkeley
Mailing address: 308C Stanley Hall #1762, UC Berkeley, Berkeley, CA 94720-1762
Email address: kimmen@berkeley.edu
Phone number: 510-642-9932
Fax number: 510-642-5835

Overview: Excellent meeting, as usual. Very good mix of people from industry and academia. I had a great time, as did my student who also attended (Sriram Sankararaman).

Presentation: Improving functional residue prediction using evolutionary and structural information (and improving comparative model accuracy using evolutionary information)

Impressions: Excellent mix of senior and junior investigators from academia and industry. Very friendly environment. Outstanding organization.

Name: Raymond Stevens
Department: The Scripps Research Institute
Mailing address: Department of Molecular Biology, 10550 North Torrey Pines Road, La Jolla, CA 92037
Email address: stevens@scripps.edu
Phone number: +1 858 784 9416
Fax number: +1 858 784 9483

Overview: The Stevens lab is focused on studying neuronal signal transduction at the molecular level, primarily using the techniques of NMR and protein crystallography. We have determined the structures of enzymes involved in neurotransmission, toxins that perturb neuronal signal

transduction, as well as the receptors that pick up the neurotransmitter signals. All of this work is done at the basic science level, as well as in the development of therapeutics that are now commercially available, or in human clinical trials.

Presentation: Our laboratory recently solved the structure of the human beta2 adrenergic receptor, one of the model systems to study G-protein coupled signal transduction. We have followed up the initial structural work, with a number of co-crystals structures to help us understand how the binding of a small biogenic amine to a membrane protein receptor can have such an amazing affect on cellular signaling.

Impressions: Probably the best meeting I have attended over the past several years, there just seemed to be a real nice integration of all of the science going on at UCSF and Scripps which was amazing. Panel session also seemed to really spark some interesting discussions. Only downside was that UCSF was not there in larger numbers. The discussion about including more UC-Berkeley or Stanford people I think would be counterproductive. UCSF and Scripps are quite similar to one another which is why we connect so well, and we need to help one another go through the natural evolution of change that is occurring right now in science. Adding a more traditional academic institution would be distracting at this point in time.

Name: C. David Stout
Department: Molecular Biology, The Scripps Research Institute
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: Our research is focused on the structure and function of membrane bound enzymes, and the development

of methods for membrane protein crystallization. A major effort in the past four years has focused on crystallization of E. coli transhydrogenase, a homologue of the mitochondrial respiratory enzyme complex that couples proton translocation with hydride transfer. A structure is a prerequisite to experiments to probe the mechanism of proton pumping, which entails conformational change in the absence of net redox. Through collaborations, we also work on a number of cytochrome P450s, cytochrome oxidase, and nanodiscs for solubilizing integral membrane proteins.

Presentation: I presented the first crystal structure of a mitochondrial cytochrome P450, CYP24A1, at 2.0 A resolution. This class of P450 enzymes is involved in the metabolism of hormones; CYP24A1 regulates the active form of vitamin D3 through a 6-step oxidation and degradation of the seco-steriod side chain. Vitamin D and related analogs exhibit potent anticancer properties, but toxicity and drug-resistance, partially attributed to altered CYP24A1 activity in the disease-state, have limited clinical use of these compounds. Hence, CYP24A1 is a target for drug design. At the same time understanding of related mitochondrial P450s will be aided by structural knowledge of CYP24A1. The structure displays an open conformation of the P450 fold with distinctive features, including a short, well defined F' helix linking the F and G helices, a well defined, 3-turn B' helix, and an extensive hydrophobic and presumed membrane-associated surface comprised of the F' and A' helices, and loops of the β-sheet subdomain. The N-terminal residues 33-49, preceding the proline-rich motif of the canonical fold, are disordered. Residues from the B', F and I helices, BC-loop, β1-4 strand, and β4 loop surround the active site. Three copies of the detergent CHAPS are observed in the electron density, the first bound directly above the heme, the second at the entrance to the active site cavity, and the third on the protein surface, intercalated between Trp64 and Trp75. These sites suggest a possible pathway of substrate diffusion into the active site. A potential exit channel for products is defined by the E and I helices and C-terminal β4 strands. A striking

concentration of positive charge on the proximal face of the protein suggests a binding site for adrenodoxin. Current experiments are focused on the structure of the vitamin D3 bound form of the enzyme, expected to exhibit a more closed conformation. This information will characterize the enzyme's active-site architecture, the molecular basis of sec! osteroid recognition, and the chemical mechanism.

Impressions: The breadth of scientific problems addressed, and diversity of disciplines represented, make the Cabo meeting highly stimulating and enriching. The panel discussion concerning funding trends in the Biotech industry was very useful. In general, the Cabo meeting is unique in providing a venue for both academic and industry-associated researchers. It is also unique in anticipating upcoming research trends and applications in biotechnology. The meeting format is ideal, and the venue is superb for fostering interactions among colleagues and graduate students, allowing the time and place for extensive and in-depth discussions.

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

Overview: The main project in my laboratory discussed concerned the structural determinations of the ammonia channel and its regulation by GlnK alongside new progress on two water conducting channels that are drug targets.

Presentation: The mechanism was defined in structures that show how the channel works to conduct ammonia in the gas form. Protein crystal structure has a key role in the

understanding of an essential process in cell biology. New water channels from the malaria parasite and from human brain are basis for drug design.

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: Megan Thielges
Supervisor: Floyd Romesberg
Department: Chemistry
Mailing address: CB 262R, 10550 N. Torrey Pines Rd., La Jolla, CA 92037
Email address: mthielges@scripps.edu
Phone number: 858-784-7418
Fax number: 858-784-7472

Presentation: My research seeks to elucidate of the role of protein dynamics in biological function, and in particular, its role in the evolution of molecular recognition in the immune system. We used ultrafast spectroscopic techniques,

primarily three photon echo peak shift spectroscopy, to investigate the dynamics of a panel of antibodies that bind the chromophoric antigen, fluorescein, with varying thermodynamic behavior. From these experiments, antibodies could be ranked in terms of their flexibilities, and their corresponding energy landscapes could be compared. The correlations found between the dynamics, conformational entropy of binding, and extent of somatic mutation in the antibodies suggest an important role for protein dynamics in biological recognition.

Impressions: I enjoyed this meeting very much. The presentations by both the students and faculty were excellent, as well as the organization of the meeting. I think the addition of a section on dynamics, and the effect of small molecules on protein dynamics, would be interesting. Thanks for the great conference.

Name: Theresa Tiefenbrunn
Supervisor: Philip Dawson
Department: Cell Biology & Chemistry, TSRI
Mailing address: 10550 N. Torrey Pines Rd, CB 256D, La Jolla, CA 92037
Email address: theresat@scripps.edu
Phone number: 858-784-7050
Fax number: 858-784-7319

Presentation: Structural Studies of Synthetic Antiangiogenic Thrombospondin-1 Type 1 Repeat Analogs

Impressions: I really enjoyed the variety of topics presented during the meeting this year, and I think the talk length for professors is ideal - long enough to tell a coherent story, but not too long to get bogged down in the gory details (perfect for a meeting with such a diverse group of people presenting). I liked the mix of academic and sponsor presentations as well.

Name: Andrew Ward
Supervisor: Geoffrey Chang
Department: TSRI
Mailing address: 10550 N. Torrey Pines Rd., CB105, La Jolla, CA 92037
Email address: abward@scripps.edu
Phone number: 858-784-2018
Fax number: 858-784-9985

Presentation: I presented my ongoing work studying membrane bound ABC transporters in the presence of novel detergents. I detailed some of the new detergents and showed preliminary small angle x-ray scattering (SAXS) data that confirmed the promise of these detergents.

Impressions: Another wonderful, well rounded meeting. As usual I had some great discussions with a variety of the scientists there and came back to the lab excited to implement some of the new things that I learned.

Name: James R. Williamson
Department: Molecular Biology, TSRI
Mailing address: MB-33, 10550 North Torrey Pines Road, La Jolla, CA 92037
Email address: jrwill@scripps.edu
Phone number: 858-784-8740
Fax number: 858-784-2199

Overview: The Cabo meeting continues to be a unique combination of basic science with emphasis on structure and function, with venture and commercial perspectives.

Presentation: Despite the fact that many of the PI's were multiple repeat performers, most made an effort to present new stuff. The presentations by the students/postdocs continue to be a highlight. Only a few klinker talks.

The discussion panel was pretty good this year, and there is clear consensus about "the funding gap". But proposals for

solutions were not forthcoming, having identified the problem correctly. Also, it is not clear this really has a place as a concern in basic research.

Impressions: I think Cabo is in need of infusion of new blood. New companies, new VCs, and we should pick a couple of random investigators from around the country who are top notch to liven things up. It is fine for the UCSF/TSRI crowd to make up the mainstay, but we need to keep the quality of the
presentations high. Not everyone can make a big update every year.

Name: Ian A. Wilson
Department: Molecular Biology/The Scripps Research Institute
Mailing address: 10550 No. 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 lab works on structural biology and structural immunology and we focus on recognition of microbial pathogens by the immune system. We have a large effort in HIV-1 and influenza (1918 and H5N1) and on neutralizing antibodies.

Presentation: In the Joint Center for Structural Genomics, we are exploring the expanding protein universe. The genome sequencing projects have opened up a veritable flood of novel sequences from a broad range of organisms, many of which have unknown functions.

The diversity of proteins is much greater than we anticipated, and the JCSG via the Protein Structure Initiative is investigating novel families, metagenomes (Ocean e.g.), and the human gut microbiome. We are mapping the evolution of large families as they accumulate new functions. The JCSG has developed a high throughput platform that can

produce over 200 novel structures per year. We are now starting to gain many insights into the evolution of these families, as well as the entire proteome of T. maritima.

Impressions: Another very successful and rewarding meeting that had many highlights including the Translational Research round table. The venue is still excellent and the staff very attentive to our needs. The integration of academic, industry, biotech, and other sponsors continues to be a highpoint of this meeting. The student and post-doc presentations were terrific.

Name: Dennis Wolan
Supervisor: Jim Wells
Department: Pharm Chem, UCSF
Mailing address: 1700 4th Street, Byers Hall, 2552, San Francisco, CA 94158
Email address: dennis.wolan@ucsf.edu
Phone number: (415) 514-4506
Fax number: (415) 514-4507

Presentation: Small Molecule Activators of Executioner Caspases

Impressions: This is my fifth Cabo meeting and first as a UCSF postdoc. As always, the meeting was fantastic with great presentations by both UCSF and TSRI attendees. I took away many ideas that I have, or will, implement in my own studies and this is due to the great discussions throughout the conference. I definitely enjoyed the "round table" topic presented by Ray Stevens as to the divide between the academic and industrial components of drug discovery. Hopefully, I will be able to attend next year's 20th meeting!

Name: Todd Yeates
Department: UCLA Dept. of Chemistry and Biochemistry

Mailing address: 611 Charles Young Dr. East, Los Angeles, CA, 90095-1569
Email address: yeates@mbi.ucla.edu
Phone number: 310-206-4866
Fax number: 310-206-3914

Overview: Our work covers the areas of molecular, structural and computational biology. In structural biology, our emphasis is on supramolecular protein assemblies, such as self-assembling protein filaments, layers, and cages. Supramolecular assemblies of interest include both natural and designed structures. Much of our current focus is on bacterial microcompartments, which are giant virus-like structures that serve as primitive organelles inside many bacterial cells. In the areas of computational biology and bioinformatics, recent studies have led to the discovery of unusual microbes that are able to stabilize their proteins at extreme temperatures through mechanisms such as widespread disulfide bonding and topological linking. We are pursuing our interests in unusual topological properties of proteins, and their effects on protein folding, by studying and designing proteins whose backbones are tied in knots.

Presentation: A brief history of proteins bearing knots (and other topologically interesting properties) was presented, followed by a review of some of our recently published work. This included a discussion of topologically linked chains in a thermophilic enzyme, and the discovery and analysis of slip-knots in proteins. These had been overlooked in previous searches for knotted proteins, since a naive computational analysis judges such structures to be unknotted. The presentation finished with a discussion of ideas and early experiments on using knotting to stabilize proteins, with one preliminary success story.

Impressions: The meeting was highly enjoyable. As always it was impressive to see a number of research presentations whose results had such clear biomedical and clinical applications. Presentations on very early ideas still in the formative stage were among the most interesting.

Name: Craig Yoshioka
Supervisor: Ron Milligan / Bridget Carragher
Department: Cell Biology
Mailing address: 10550 N Torrey Pines Rd, La Jolla CA 92037
Email address: craigyk@scripps.edu
Phone number: 858 784 9208

Presentation: Visualizing Ribosome Assembly

Impressions: Another excellent meeting. Of particular improvement this year was the panel discussion which became a referendum for discussing the role of basic science and education in research. Very interesting, and not just more of the same drug A did very well in Phase I trials, etc...

Name: Fumiaki Yumoto
Supervisor: Prof. Robert J. Fletterick
Department: Biophysics and Biochemistry
Mailing address: 600 16th St, Genentech Hall-S416A
Email address: fumiaki.yumoto@ucsf.edu
Phone number: 415-476-5051
Fax number: 415-476-1902

Presentation: I present my project on a nuclear receptor, which relates to ES cell. The status is very preliminary because I just started the experiments on it. This is my first time to present my project in English in a public meeting. I leaned a lot what I should prepare for preparation of a scientific research, and talking in English.

Impressions: I was impressed that there are many interesting talks with very recent progress. The schedule was also nice because I could have resting time between lunch and afternoon session. I sincerely appreciate every member of the meeting especially organizers. Thank you so much.