Our History

The WMEN conference has been held for the past 18 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, The Scripps Research Institute (TSRI) and the MRC, Cambridge. 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, that are a mixture of laboratory heads, postdocs and students from UCSF, UC Berkeley, TSRI and UCLA combined with representatives from biotech, big pharma, scientific equipment companies, VCs and patent lawyers. The spirit of scientific research is enhanced and refreshed in this stunning setting as well as by the interesting and eclectic mix of participants. This format has worked well and we look forward to many more successful meetings in the years to come.

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

29 April – 3 May 2007, San Jose del Cabo, Baja, Mexico

For the first time, the schedule this year was a little delayed on Sunday evening due to the late arrival of the San Diego flight. But we accomplished the entire evening's talks and finished up a little later than the intended schedule , but nevertheless in fine style!

Sunday Evening, 29 April

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

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

Kirk Clark	Novartis
Mary McGrath	Gilead
Daniel Santi	Kosan/UCSF
David Stevens	Wilson Sonsini Goodrich & Rosati

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

Joshua Chappie	TSRI	Understanding dynamin's basal GTPase activity
Graham Johnson	TSRI	Automated visualization of subcellular environments
Donald Kerkow	TSRI	Understanding the molecular interactions controlling post-transcriptional regulation of the *C. elegans* transformer 2 gene
Chris Kimberlin	TSRI	Structural studies of the prion replicative interface
Gabriel Lander	TSRI	Effects of pressure on packaged DNA structure in phage lambda

	Dena Marrinucci	TSRI	Investigating drug targets on circulating tumor cells
	Anke Mulder	TSRI	Functional studies of medically important serine hydrolases
	Sherry Niessen	TSRI	Defining the role of KIAA1363 in cancer biology
	Theresa Tiefenbrunn	TSRI	Structural studies and antiangiogenic activity of synthetic thrombospondin-1 type 1 repeat analogs
	Sarah Voytek	TSRI	Emergence of a continuously evolving ribozyme
	Andrew Ward	TSRI	Structural dynamics of the ABC transporter MsbA
	Craig Yoshioka	TSRI	Computer vision and 3D electron microscopy
		Break	
	Mark Burlingame	UCSF	A facile one-pot synthesis of disulfide monophores
	Elisabeth Humphris	UCSF	multi-specificity of protein interfaces
	Maki Inada	UCB	Ultraconserved nonsense for regulation of gene expression in the SR protein family
	Yannet Interian	UCB	Towards a phylogenomic approach to pathway reconstruction.
	Kathy Ivanetich	UCSF	Overview of Northern California water quality research projects
	Sami Mahrus	UCSF	Global profiling of proteolysis in apoptosis
	Eswar Narayanan	UCSF	Large-scale protein structure modeling and applications
20:30 – 21:00	**Reception**		**In the Main Garden**

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Monday Morning, 30 April — Advances in Proteomics (Chair: Todd Yeates, UCLA)

09:00	Kimmen Sjolander	UCB	Construction of the PhyloFacts phylogenomic encyclopedias
09:20	Steven Brenner	UCB	Ultraconserved nonsense: Pervasive unproductive splicing of SR proteins associated with ultraconserved DNA elements
09:40	Gary Siuzdak	TSRI	Metabolomics for elucidating gene function
10:00	Break		
10:30	Ian Wilson	TSRI	Structural genomics and new opportunities
10:50	Marc Elsliger	TSRI	Structural genomics and its application to structural biology
11:10	Ray Stevens	TSRI	Structural proteomics of protein therapeutics
11:30	Bridget Carragher	TSRI	An automated pipeline for macromolecular microscopy

Monday Afternoon — Immunology and Virology (Chair: Ray Stevens, TSRI)

17:00	Jim Paulson	TSRI	Self-assembly of macromolecular complexes on B cells
17:20	Erica Olmann-Saphire	TSRI	Antibodies against the Ebola virus: Structural analysis
17:40	Mark Yeager	TSRI	Structure of full-length HIV-1 CA: A model for the mature capsid lattice
18:00	Break		

SPONSORS I – Advances in Technology for Structural Biology

18:30	Sue Byram	Bruker-AXS	Bruker instruments for structural biology
18:50	Joe Ferrara	Rigaku	Homelab vs Synchrotrons: The truth might surprise you

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Tuesday Morning, 1 May			**SPONSORS II – (Chair: Dan Santi, Kosan/UCSF)**
09:00	Jay Pandit	Pfizer	Structure-based design of PDE-10 inhibitors
09:20	Niek Dekker	Astra Zeneca	Purified membrane proteins in drug discovery
09:40	Michal Vieth	Eli Lilly	It is all about fragments - from characterizing target space to design
10:00	Duncan McRee	Active Site	Fishing for fragments with the ACTOR robot
10:20	**Break**		
10:40	Brian Atwood	Versant Ventures	Hedge Funds, Gigafunds, and the Dreaded Binary: Biotech VC in the 21st Century
11:00	**Panel Discussion**	Alta Partners	***Panel Leaders: Jean Deleage, David Mack***

Title: Building a Business in Biotech: What it Takes to Launch, Fund, and Grow a Successful Company

Tuesday Afternoon			**Nucleic Acids and Proteins (Chair: Tanja Kortemme, UCSF)**
16:30	Joel Gottesfeld	TSRI	Chromatin therapeutics for neurological diseases
16:50	David Millar	TSRI	Ribonucleoprotein assembly at the single-molecule level
17:10	Robert Fletterick	UCSF	Repression by DAX-1
17:30	**Break**		
			Enzymes
17:50	Jack Kirsch	UCB	Evolutionary strategies to change protein specificity
18:10	Rashid Syed	Amgen	Crystal structure of hypoxia-inducible factor prolyl hydroxylase 2 (HIF-PH2)
18:30	Adam Renslo	UCSF	New small molecule inhibitors of cysteine proteases in trypanosomes

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Wednesday Morning, 2 May — **Assemblies, Computation, and Chemistry (Chair: Kimmen Sjolander, UCB)**

08:30	Todd Yeates	UCLA	Piecing together the structure of the carboxysome shell
08:50	Andrej Sali	UCSF	The molecular architecture of the nuclear pore complex
09:10	Daniel Minor	UCSF	Structural biology of ion channel regulation
09:30	Ron Milligan	TSRI	Depolymerizing kinesins
09:50	Break		
10:10	Tanja Kortemme	UCSF	Design of selective and multi-specific interfaces
10:30	Ron Zuckermann	UCB	Bio-inspired polymers as nanoscale building materials
10:50	Phil Dawson	TSRI	Control and assembly of macromolecules using rapid and dynamic chemical reactions
11:10	**Close**		

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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

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Overview: This year was again a terrific meeting. The central core was molecular structure characterization engineering ultimately aimed at drug design. These were flanked by a variety of different talks, all relevant to this broad audience touching on different areas of interest. This year had some amazing presentations of EM/multi-scale work, though unfortunately not as many as last year. The company research presentations (and this year the VC Presentations) continue to be a distinctive and appealing characteristic.

Presentation: Presentations were of outstanding quality. The postdocs' 5-minute talks were remarkable for compressing a tremendous amount of discovery and excitement in to a comprehensible and compelling brief Presentation. In many ways these are the highlight of the meeting. The more traditional faculty Presentations were consistently of high caliber, lucid, and suitable for this audience. A great learning experience.

Impressions: Overall, an enjoyable and significant meeting. The allotted time for interaction is highly beneficial. The location is, of course, beautiful and the all-inclusive arrangements do encourage people to see each other informally throughout the duration (though at a financial cost related in part to the unlimited quaffables on offer). The flawless AV support is remarkable.

Name: Mark Burlingame
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Overview: The Small Molecule Discovery Center (SMDC) is a new core facility at UCSF designed to bring HTS and Med chem capabilities to researchers at UCSF.

Presentation: "A facile one-pot synthesis of disulfide monophores"

Impressions: Great meeting excellent talks and nice atmosphere for meeting and discussion of science with other attendees. Excellent Facilities.

Name: Bridget Carragher
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Overview: Our lab is developing a pipeline to automate the processes involved in solving macromolecular structures using cryo-electron microscopy. One of the goals of the pipeline is to enable much higher data throughputs and improve the resolution of single particle reconstructions. We are also using the pipeline to help understand what currently limits resolution in these maps and to expand the utility of cryoEM to a wider range of investigators.

Presentation: I presented an Overview of the methods used in cryo-electron microscopy (cryoEM) and some of the technology we have developed to automate these methods. Several “case studies” were then presented to: (i) demonstrate the use of the pipeline to routinely generate 3D

maps of icosahedral viruses in under 24 hours; (ii) show that our current methods enable reconstructions to ~5A for well behaved particles, and (iii) show how these methods could be used for very practical characterization studies for bio-pharmaceuticals.

Impressions: This was my first Cabo meeting and I would love to become a regular participant! The format is very conducive to multidisciplinary and interdisciplinary communication and the atmosphere and organization leave plenty of time and opportunity for informal interactions. I thought this was a great meeting.

Name: Josh Chappie
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Overview: My research focuses on understanding how dynamin, a large GTPase capabale of self-assembly, regulates the process of clathrin mediated endocytosis. Specifically, I am interested in deciphering the mechanisms of dynamin's basal and assembly stimulated GTPase activites and determining how they influence endocytic uptake. To understand these processes, I am employing a combination of techniques including protein engineering, site-directed mutagenesis, x-ray crystallography, and cryo-EM.

Presentation: To investigate the mechanism of dynamin's basal GTPase activity, we have generated a minimal fusion protein consisting of the GTPase and GED domains. This construct is soluble and reconstitutes a high basal GTPase activity comparable to the full length protein. We have been utilizing this construct for mutagenesis screening to identify catalytic residues and for high-resolution structural studies.

Impressions: The meeting was fantastic. The location and scheduling of events was great and highly conducive to a large amount of interaction with faculty and industry researchers. I enjoyed the wide variety of research topics and scientific perspectives that were presented at this year's meeting.

Name: Phil Dawson
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Overview: My lab focuses on the use of synthetic chemistry to understand protein function. By chemically synthesizing proteins, we have used non coded elements to study the role of hydrogen bonding and electrostatics in protein folding kinetics and enzyme catalysis. In addition, we are using these techniques to design mimics of the HIV surface glycoproteins and to develop sensitive imaging agents.

Presentation: The ability to chemically modify biological macromolecules in a specific manner underlies many of the methods and technologies used in modern research. This specific tailoring of macromolecules has been enabled by the development of highly chemoselective ligation (conjugation) chemistries that are characterized by their chemoselectivity, reactivity and compatibility with neutral aqueous buffers. We have demonstrated that the aromatic amine, aniline is a potent nucleophilic catalyst for imine ligations that form stable oximes and hydrazones from aldehyde and amine-labeled precursors. We have used this catalyst to optimize imine reactions that achieve ligation with rates over 1000 M-1 s-1, several orders of magnitude faster than currently used ligation approaches. Such fast conjugation rates are essential if chemical approaches are

ever to compete with the rapid labeling possible using non-covalent interactions such as biotin or antibodies.

Impressions: This was an extremely stimulating meeting with the usual strong presentations by all participants. Indeed, the students and postdocs set a high standard for the meeting on the first night, facilitating interactions throughout the meeting.

Investigator: Niek Dekker
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Overview: My section is responsible for the production of (labeled) crystallization-grade human proteins for NMR and crystallography to support lead generation in AstraZeneca's drug discovery with structural information.

Presentation: Membrane proteins constitute a considerable fraction of drug targets but are poorly structurally characterized. Available crystal structure information in the pdb is limited to prokaryotic membrane proteins and eukaryotic membrane proteins that are abundantly available in their natural source. The first examples of crystal structures of recombinantly expressed eukaryotic membrane proteins have only recently reported. Expression, extraction and purification of G-protein coupled receptors (GPCRs) and ion channels (ICs) is challenging due to various factors such as low expression levels, intrinsic low stability and the presence of lipids and detergents. The membrane protein initiative at AstraZeneca aims at the production of purified GPCRs and ICs in functional form for drug discovery. Applications of these reagents are many fold, for example for crystallography, biophysics, affinity screening, and for the generation of therapeutic antibodies. Examples of the

expression, purification, crystallization and functional characterization of a number of GPCRs and ICs were presented.

Impressions of the meeting:
Location: Wonderful to escape wet Sweden for a few days
Number of participants: Good
Length of meeting: Good
Highly interesting presentations by PI's of the various groups mainly from UCSF and Scripps on structure in biology. Small size of the meeting allowed for close interaction with many of the participants.

Name: Robert Fletterick
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Overview: The hotel staff performed perfectly, the lecture room and presentation equipment was effective and we lost almost no time between speakers. The climate control worked well, so that transitions between breaks and meeting room did not require accommodation to different temperatures.

Presentation: My talk was the first public **Presentation** of the structure of the DAX-1 nuclear receptor. The structure was a trimer of two DAX-1 molecules and one LRH-1 molecule. DAX-1 is well known clinically, since according to gene dossage DAX-1 can change the the gender from male to female in XY humans. I showed that DAX-1 protein operates like a repressor, blocking coacttivators from binding to other nuclear receptors that are targeted by DAX-1.I also showed that DAX-1 does not respond to hormones directly since protein chain fills the expected hormone binding

pocket. That DAX-1: LRH-1 interactions are unique in the trimer was proven by functional analysis of mutants at the three protein interfacesused by DAX-1 or LRH-1 molecules.

Impressions: Superb. I thought the chairs did a good job of promoting discussion but I would like to see more accurate timing and even more discussion questions. Most of the science was absolutely first rate on the strongest international scale.

Name: Joel Gottesfeld
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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. In the first approach, pyrrole-imidazole polyamides can be programmed by chemical synthesis to recognize a wide range of DNA sequences with affinities and specificities that are comparable to eukaryotic transcriptional regulatory proteins. In previous studies, we have shown that polyamides bind their cognate DNA sequences in the context of cellular chromatin, both in simple model systems and in the nucleus of cultured cells. We have used these molecules as either activators or repressors of gene expression. More recently, our efforts have focused on histone deacetylase (HDAC) inhibitors as potential therapeutics for neurodegenerative diseases.

Presentation: My Presentation this year focused on the development of HDAC inhibitors as therapeutics for the neurodegenerative disease Friedreich's ataxia (FRDA). FRDA is caused by hyper-expansion of GAA•TTC repeats in

the first intron of a nuclear gene that encodes the mitochondrial protein frataxin. We examined the chromatin structure of the frataxin gene in cell lines derived from a FRDA patient and a normal sibling of these 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. Unlike many triplet-repeat diseases (for example, the polyglutamine expansion diseases such as Huntington's disease 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.

Impressions: 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: Elisabeth Humphris
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Overview: I am a 3rd year graduate student working on extending our lab's current computational methods for the prediction and design of protein-protein interfaces.

Presentation: I have developed a "multi-state" design algorithm, which allows multiple selective pressures to be present during our computational optimization process, and used it to examine the properties of promiscuous binding interfaces. Additionally, I presented preliminary data that incorporating a new backbone flexibility move--the backrub--into computational design improves our ability to correctly predict sequence plasticity at protein-protein interfaces.

Impressions: I really enjoyed the short presentations by the post docs and graduate students--it was a great way to introduce everyone. The PI talks were both interesting and relevant to my own work. The long afternoon break was a great chance to interact as well as to enjoy the scenery.

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Overview: My research examines an unusual mode of gene regulation, which involves alternative splicing associated with some of the most conserved regions of the human genome. We have observed that a surprisingly large fraction of human genes are processed via alternative splicing to include premature translational stop codons. These transcripts are predicted to be recognized and degraded by a cellular error-control pathway known as nonsense-mediated decay. We show that an entire family of RNA-processing genes called SR proteins is alternatively spliced to introduce premature termination codons. Strikingly, their alternative regions are among the most extensively conserved regions of the human genome known as ultraconserved DNA elements, suggesting that alternative splicing is essential for proper regulation of these genes.

Presentation: see above

Impressions: This meeting was very enjoyable. I particularly liked the format with the great short postdoc and graduate student talks to kick things off. There was lots of high quality presentations. The conference room was freezing cold, but the weather outside was gorgeous!

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Overview: I presented an Overview of Northern California water quality projects, focusing on the San Francisco Bay area and newly developed or under development microbial source tracking assays.

Presentation: The Presentation focused on two projects: 1)

Identification of San Francisco Bay sites with elevated levels of fecal pollution and 2) Development and validation of quantitative PCR assays specific for human fecal pollution and application to the San Pedro Creek Watershed. For the first project, primary sites of pollution were found near Oyster Point and in Islais Creek, with the vast majority of sites tested on the Bayside in San Francisco and San Mateo Counties showing insignificant levels of fecal pollution. The second project focused on development and validation of quantitative human specific microbial source tracking assays and reference assays for fecal pollution.

Impressions: The meeting was excellent, with numerous outstanding presentations and opportunities to interact with colleagues from Scripps, UCSF, other institutions and the sponsoring entities. As in recent years, my only criticism has been of the quality of the food at the Presidente.

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Presentation: Automated Visualization of Subcelluar Environments:

We plan to use commercial software to automate the 3D modeling and ultimately the animated simulation of sample molecular realms using collections of varied data (protein database files, EM averaged maps, tomography maps, local protein concentrations, conformation ratios, etc.) The software plug-ins we develop can export these models into more universal file formats, allowing clients to create visualizations in the form of static images, animations, plastic models, and interactive viewers for use in data analysis, peer communication, education, and outreach.

We will utilize techniques of illustration to suppress visual noise, clarify time dilation and thus summarize an event while quietly presenting/retaining the hurricane of underlying interactions. Movies can thus be created from the modules to make the process pedagogically useful in classroom. Simultaneously, underlying data will be retained in a quantifiably accessible manner for use in the virtual lab.

Impressions: This meeting gave me an unprecedented opportunity to discuss topics of overlapping interest with many potential collaborators and provided a helpful survey of efforts from labs with goals similar to my own. Compared to other meetings, our luxurious breaks gave me time to digest the science as well as time to follow up with birds of a feather. Although it demanded intense focus (arguably difficult in the land of surf and sun), the rapid fire, highly concentrated presentation format really helped to keep the science exciting for me as a rookie attendee.

Name: Jack F. Kirsch
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Overview: Most of our laboratory effort is concerned with the mechanism of action and directed evolution studies of pyridoxal phosphate-dependent enzymes. The enzymes studied are aspartate aminotransferase, which catalyzes the interconversion of the dicarboxylic amino acids, aspartate and glutamate, with their corresponding α-keto acids, oxalacetate, and α-keto glutarate, and aminocyclopropane carboxylate synthase, which is the committed enzyme in the biosynthesis of the gaseous plant hormone, ethylene. We have identified and mutated most of the important amino acid side chains surrounding the pyridoxal phosphate

cofactor. These studies together with the structural ones have led to a detailed understanding of the mechanisms of action. We are also using ion-cyclotron mass spectrometry to address problems in proteomics, and are involved with rational design of novel enzyme activity.

Presentation: I presented our work on the redesign of the enzyme, malate dehydrogenase (MDH) to have the activity of lactate dehydrogenase (LDH). The design used five mutagenic changes that were identified by a debiased evolutionary tree analysis that was incorporated into Venn Diagrams. Although the two enzymes share only 28% sequence similarity, these few introduced mutations sufficed to produce a LDH with 3% of wild-type activity, and a strong preference for lactate over malate as substrate. The methodology is general, and may be useful for other enzyme design project.

Impressions: This was my 9th 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: Donald Kerkow
Supervisor: James Williamson
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Overview: I am currently studying the RNA binding capabilities and specificities of C elegans NXF-2. NXF-2 is a unique member of the NXF family of nuclear export proteins in both putative function and RNA binding abilities. In C elegans, NXF-2 functions in an alternative mRNA nuclear export pathway independent from the normal NXF-1/TAP mediated pathway. Based on our findings it seems possible that other NXF family members, of other organisms, could also be participating in or controlling alternate mRNA export pathways.

Presentation: "Characterizing Novel Modes of RNA Recognition and Binding by the Putative C. elegans Nuclear Retention Factor NXF-2."

Impressions: This is my second trip to Cabo for this meeting and I thoroughly enjoyed it once again. The talks are great, the networking is great and the location is awesome!

Name: Tanja Kortemme
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Overview: Our research program focuses on simulation, analysis, design and evolution of proteins, protein interactions and networks. We combine computational protein design, biochemistry and cell biology to create and characterize simple biological assemblies made up of sets of protein-protein interactions. Despite the significant approximations made in computational protein design methods, these strategies may contribute to the quantitative analysis of protein signaling assemblies in biological systems.

Presentation: We have made progress towards improved models in two respects, (1) to more accurately model changes in protein conformation in response to sequence perturbations predicted by design simulations, and (2), to optimize protein sequences for multiple fitness criteria, such as function within a network of proteins where correct interactions should be favored and unwanted interactions avoided. We have applied such a “multi-constraint” design method to analyze whether and how protein networks place constraints on naturally occurring protein interface sequences to form desired interactions. We identify two strategies to achieve multi-specificity, where promiscuous interfaces use either (i) shared or (ii) distributed “multi-faceted” binding hot spots to recognize multiple partners. These findings suggest routes to target each type of interface: Shared interfaces may be better small molecule targets, whereas multi-faceted interactions may be more “designable”, both by evolution as well as for synthetic applications to design proteins with altered interaction patterns.

Impressions: The science, informal exchange of ideas, size of the meeting and location were all excellent. The student/postdoc presentations were a definite highlight. This was my second year at the CABO meeting, and it was wonderful to see people again and continue the discussions!

Name: Gabriel Lander
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Overview: Evolutionary Optimization of Pressure and Structure in Bacteriophage Lambda

Presentation: The double-stranded DNA packaged within bacteriophages is highly stressed and exerts pressures of tens of atmospheres on the capsid walls. It has been hypothesized that these great pressures aid in ejection of the phage genome into the cell upon infection, as well as play a structural role by doubling the strength of the capsid wall. We have examined the inter-strand spacing of packaged DNA within phage lambda for mutants containing 50%, 78%, 94%, and 100% of the wild type genome by high-throughput cyroEM. We have shown that even a slight change in the amount of DNA that has been packaged induces a dramatic reorganization of the inter-strand spacing of the DNA within the phage, suggesting that there is an evolutionary correlation between genome length and capsid size. It has also been shown previously that the addition of polyvalent salt ions significantly decreases the internal pressures within the phage by stabilizing the DNA-DNA-interactions. Through examination of these specimens by cryoEM, we show that these polyvalent ions introduce further stabilization by ordering internal DNA that would otherwise be disordered.

We have additionally begun work towards asymmetric reconstructions of the empty and fully packaged lambda phage, in which we see an intact three-dimensional view of the concentrically-spooled DNA within the capsid shell, as well as how the tail assembly is attached to the capsid. A comparison between central slices of the asymmetric wild type and empty particles show clear density depicting the dsDNA and portal proteins, and evidence that upon completion of packaging, a plug-like gene product or conformational change of the portal shuts the tail entrance. This unequivocally disproves the theory that there is DNA within the lambda tail after completion of DNA packaging.

Impressions: One of my favorite conferences of the year - the relaxed atmosphere and small size of the meeting provided a perfect stage for interesting discussions with people from a wide range of backgrounds, an aspect that 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.

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Overview: ActiveSight is a Structure-Based Drug Design services company specializing in fragment-based screening and co-crystallography structures. We help our clients find early leads using fragment-based screening (FBS) of targets. The hits from the screening can be either elaborated into leads using their own chemistry or in collaboration with ActiveSight. Recently, we hired Vicki Nienaber as our CSO. She is one of the inventors of fragment-based screening and is well-known for leading several drug discovery collaborations in the pharmaceutical industry using FBS. For later lead development, we offer co-crystallography services with our clients lead compound bound to the protein target of the compound. We have full capabilities from gene-to-structure including protein cloning, expression, purification, crystallization and structure determination. See htpp://www.active-sight.com for more info.

Presentation: We described the background and theory behind FBS and how it is being implemented at ActiveSight. We described the results of the screening on a collaborative project with led by Art Olsen at Scripps on protease resistance in HIV. In this project, we are looking for novel inhibitors that cover as much of the protease binding site as possible. These will be used in an *ex vivo* evolution system to test the rate at which protease becomes resistant. We hope to answer the question of how resistance evolves and whether certain classes of inhibitors are more or less resistant to resistance.

ActiveSight has a pre-formulated library for sale at our website at http://www.active-sight.com/products. This library has been designed as a general purpose fragment-screening library. It comes ready-to-soak in shape diverse mixtures. It has been a very popular product with biotechs, pharmas and academic labs involved in translational research.

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

I have been returning to this meeting year after year. It is a great place to see first-class cutting-edge science, to learn new techniques, to meet collaborators and even venture capitalists for kicking off that new company you have always dreamed of starting.

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Overview: Topic: Global Profiling of Proteolysis in Apoptosis

Presentation: We have recently developed a novel strategy for proteomic profiling of proteolysis in complex samples that makes use of an engineered peptide ligase termed subtiligase, a variant of the serine protease subtilisin. This enzyme is used to selectively label protein N-termini created following proteolysis, allowing for affinity purification and subsequent MS-based identification of corresponding N-terminal peptides. We have utilized this method to profile

the proteolysis carried out by caspases during apoptosis (programmed cell death). Based on diverse studies of apoptosis in different organisms and cell types, there are currently approximately 400 known caspase substrates. Using a single experimental system of one cell type and one apoptotic inducer, our studies have thus far resulted in identification of 50 reported and an additional 200 previously unreported caspase substrates.

Impressions: This meeting was excellent. I very much enjoyed the mixture of talks from academia and industry, as well as the thought-provoking panel discussion on venture capital and biotech. Many of the shorter talks by students and postdocs were as impressive as the longer talks by faculty. The meeting was very well organized and the location was amazing.

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Overview: Our research focuses on detecting and characterizing circulating tumor cells isolated from the blood of metastatic cancer patients.

Presentation: The biological and clinical significance of circulating tumor cells.

Impressions: This was my first time at the Cabo meeting and I thought the meeting was fantastic. I was quite impressed with the diversity of high caliber research presented by graduate students, PI's, and sponsors. Thank you for inviting me!

Name: David Millar

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Overview: My laboratory develops and applies modern fluorescence spectroscopic methods, including single-molecule and time-resolved techniques, for biophysical studies of nucleic acid folding processes and protein-nucleic acid interactions. The major projects in our laboratory 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) RNA folding and ribonucleoprotein assembly. We are studying the assembly pathway of the signal recognition particle (SRP) and the oligomerization of HIV-1 Rev on the Rev Response Element (RRE) RNA using both bulk and single-molecule fluorescence methods.

Presentation: My talk focused on the Rev/RRE system from HIV-1. Rev is a key regulatory protein from HIV-1 that controls the transition from the early to late phases of viral gene expression. Rev binds to the RRE within the viral RNA, where it assembles as an oligomeric RNP. The formation of the oligomeric complex is essential for the subsequent export of unspliced viral mRNA from the nucleus to the cytoplasm. Hence, the binding of Rev to the RRE and the subsequent oligomerization are potential targets for new therapeutic agents for the treatment of AIDS. We have developed a novel single-molecule imaging method to visualize the binding and oligomerization of Rev on individual RRE molecules immobilized on a surface. This approach has allowed us to dissect the assembly pathway in great detail, revealing that the Rev-RRE complex assembles via the sequential binding of Rev monomers to the RRE. Moreover, we have quantified the microscopic association

and dissociation rates at each step of the assembly pathway. Interestingly, oligomerization of Rev on the RRE exhibits significant negative cooperativity, which may play a role in the biological function of Rev.

Impressions:
Location: Excellent.
Number of participants: Good size and mix of faculty, postdocs and graduate students.
Length of meeting: Just right.

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.

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Overview: We use cryo-electron microscopy and image analysis to study the structure and mechanism of action of several macromolecular assemblies. Current interests include actin-myosin and microtubule-kinesin complexes, proteins that affect microtubule dynamics, AAA proteins and membrane proteins. We use the three-dimensional maps

calculated from electron images of the machines together with biochemical data and high-resolution x-ray structures of the individual components to provide insight into molecular mechanisms.

Presentation: The Kinesins: How nature engineered a range of molecular motors and a depolymerizing machine.

I described how plus-end directed and minus-end directed kinesins execute powerstrokes while attached to their microtubule tracks. This mechanochemical activity was then considered in terms of three coupled cycles: an ATPase cycle, an attachment cycle and a mechanical cycle. I explored the various ways these cycles could be coupled, emphasizing that all four possibilities have been explored by nature, resulting in plus and minus end directed kinesins, and forward and backward myosins. Finally I presented data that suggest depolymerizing kinesins are designed to bind two adjacent protofilaments, thereby maximizing their destabilizing activity at microtubule ends.

Impressions: size of the group - excellent
location of the meeting- excellent
attendees and presenters- excellent
length of the meeting -excellent

All the presentations were of very high quality. I found the student presentations particularly useful.

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Overview: My lab studies the structure and function of ion channel proteins and the molecules that regulate their function.Our work in ion channels covers two broad areas:

structural investigation of ion channel architecture and function, and the development of new methods to identify and map the sites of action of ion channel regulatory molecules. Ion channel proteins are central to the function of the brain, heart, and nervous system. Understanding how ion channels work at the molecular level should facilitate the development of a range of potential therapeutics for treatment of cognitive disorders, cardiac diseases, and pain.

Presentation: My talk covered my laboratory's recent work on the structural and functional characterization of a voltage-gated potassium channel regulatory complex, the Kv4.3 T1 domain/KChIP1 complex. Kv4 channels play important roles in the regulation of excitability in the brain and heart. The interaction with KChIP calcium sensors is central to Kv4 channel function. Exactly how KChIPs bind to and modulate Kv4 channels has been a controversial topic with three groups presenting three mutually exclusive models based on different types of structural and biochemical studies. Our co-crystal structure and small-angle X-ray scattering analysis (SAXS) of the Kv4.3 T1 domain/KChIP1 complex defines the molecular basis for how KChIP1 interacts with the pore forming subunit and resolves the issue for how the channel and regulatory protein interact. Our data show that the complex forms a cross-shaped octamer in which each KChIP protein interacts with two channel subunits via two distinct sites, termed 'Site 1' and 'Site 2'. This arrangement was not anticipated by any of the previously published models. Our functional studies demonstrate that the two sites of channel/KChIP interaction have two separable roles. Site 1 is critical for calcium-dependent formation of the complex and regulates channel trafficking to the plasma membrane. Site 2 is the modulatory site. Mutations in Site 2 leave KChIP/Kv4 association and trafficking properties in tact, but abolish the modulatory effects of Kv4 on channel biophysical properties.
This work resolves how Kv4 channels and KChIP proteins interact and serves as a platform for further dissection and modulation of Kv4 channel function.

Impressions: The meeting was excellent. The combination of a great location, a small group, concise Impressions, and outstanding scientific content created a unique atmosphere for both learning and networking. The participation of the biotechnology community provided a good balance of scientific viewpoints. This is the only meeting I have been to where there is such good interaction between academic and biotechnology scientists. The opportunity to forge new scientific interactions with both academic and industrial scientists in a relaxed environment is invaluable.

Name: Eswar Narayanan
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Overview: My research focus is on the development of methods and algorithms for large-scale protein structure modeling and their application to biological problems requiring high-throughput structural data.

Presentation: I have developed a completely automatic protein structure modeling pipeline, called MODPIPE that can calculate comparative models on a genome-scale. The pipeline consists of several state-of-the-art modules for fold-assignment, target-template alignment, model building and model evaluation. Application of the pipeline to several genomes indicates that domains in approx. 50% of all sequences in any genome can be modeled at useful accuracy and folds can be assigned to an additional 10%. Two most recent sample applications of MODPIPE are: (i) MODPIPE has been used to calculate models for all

ribosomal proteins in Canine 80S ribosome that were subsequently docked into a low-resolution cryo-electron density map to interpret the structural model of the mammalian ribosome at a molecular level. (ii) Models for approximately 5000 uncharacterized amidohyrolase sequences were calculated and used for in sillico docking of known substrates. The high-scoring complexes were then used to classify the sequences into specific subfamilies.

Impressions: The meeting was well organized with a lot of interesting talks and panel discussions. The confluence of scientists from academia and industry provided for many enlightening discussions. The all-inclusive resort location kept all participants together that helped maximize social interaction during the ample unstructured time provided. Overall I would recommend a similar format for future meetings.

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Overview: Many metabolic enzymes, including lipases, oxidoreductases, and glutathione S-transferases, are believed to make key contributions to primary tumor progression, invasion, and metastasis. As such, there is an urgent need for elucidating the precise roles that metabolic enzymes play in cancer biology, so as to uncover new potential therapeutic targets and biomarkers.

Presentation: Using activity based protein profiling (ABPP), an advanced proteomic technology that assesses the activity of many enzymes in parallel within native proteomes, we have identified the serine hydrolase KIAA1363 as being

highly elevated in numerous pathogenic human cancer cell lines. These included cell lines from several tumorigenic origins including the breast, ovary, and skin. Moreover, this enzyme was found to be raised in a number of primary human tumors compared to their corresponding normal tissues. Together, these data suggest an important role for KIAA1363 in human tumorigenesis. Using retroviral gene transfer in combination with either RNAi or overexpression technology we have demonstrated that KIAA1363 is not only necessary but also sufficient to support several of the in vitro and in vivo pathogenic properties of both breast and ovarian human cancer cell lines. The overexpression of KIAA1363 leads to an augmentation of the in vitro proliferation and migration potential and the in vivo tumor growth of cancer cells. Moreover, a reduction of KIAA1363 activity decreased both the migration potential and the in vivo tumor growth of cancer cells. Importantly, KIAA1363's ability to regulate these properties was entirely dependent upon its catalytic activity. The molecular mechanism by which KIAA1363 regulates the pathogenic properties of human cancer cell lines was addressed using a global metabolite profiling strategy in combination with metabolic labeling studies to determine that KIAA1363 serves as a central node in an ether lipid signaling pathway that bridges the platelet-activating factor (PAF) and lysophosphatidic acid (LPA). Biochemical studies revealed that KIAA1363 regulates this network by hydrolyzing the metabolic intermediate 2-acetyl monoalkylglycerol to monoalkylglycerol (MAGE). Perturbation of KIAA1363 levels or catalytic activity in human cancer cell lines directly correlates with changes in the concentration of these metabolites. The significance of ether lipids, such as LPA in cancer biology, is demonstrated by the fact that LPA is an established biomarker of ovarian cancer being elevated nearly 10 fold in ascites fluid and LPA has been shown to regulate many of the pathogenic properities of cancer cell lines. Significantly, we have found that KIAA1363-regulated cellular migration is dependent on the bioactive lipid LPA, as the addition of as little as 10 nm alkyl-LPA rescued the migratory defect induced by an inhibition of KIAA1363 activity. These findings indicate that KIAA1363 is

an important molecule in human cancer biology.

Impressions: The meeting was a lot of fun.
Both student and PI talks were really well done and it was great being exposed to so many different aspects of science. Thank you for the opportunity.

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Overview: Our group investigates the roles of glycan binding proteins that mediate cellular processes central to immune regulation and disease. In particular, we are interested in the siglec family of glycan binding proteins that are expressed on most white blood cells and mediate cell-signaling events.

Presentation: CD22, a member of the siglec family, is a regulator of B cell receptor signaling with an extracellular domain that recognizes sialic acid containing glycans of cell surface glycoproteins as ligands. Our current focus is to understand how the glycan-binding domain of CD22 modulates its function as a modulator of B cell signaling.

This year, we reported the development of a hetero-bifunctional molecule comprising a CD22 ligand coupled to an antigen that assembles a decavalent IgM-CD22 complex on the surface of a B cell. Once formed, the immune complex is a target for complement mediated cell killing. This result suggests a novel approach to development of therapeutics for B cell leukemias by targeting the ligand binding domain of CD22.

Impressions: Location: Excellent facilities as always
Number of participants: Maybe add 5-10 faculty next year
Length of meeting: Just right

The meeting has consistently maintained high standards of good science with a great mix of basic, translational and applied research in the structural biology arena. The industry/sponsors and venture representatives are a key element in making the meeting unique. The students continue to amaze by conveying their project and exciting results in 5-7 minutes.

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Overview: The Small Molecule Discovery Center (SMDC) is a QB3 core facility at UCSF providing UC biomedical researchers with modern small molecule discovery technologies, including high-throughput screening and medicinal chemistry optimization capabilities. We assist investigators in performing biochemical and cell-based high-throughput screens using an array of modern instrumentation and employing a screening library of around 170,000 lead-like small molecules. The SMDC medicinal chemistry group selects a subset of these targets/assays for follow-up optimization studies, with the ultimate goal of identifying cell-active, patentable lead series that could be further developed by industry partners.

Presentation: Cysteine proteases represent promising therapeutic targets in important but neglected parasitic diseases such as Chagas disease in Central and South America and sleeping sickness in Africa. The SMDC

medchem group has become involved in an effort to identify and optimize inhibitors of the parasitic proteases cruzain and rhodesain. Lead compounds for this effort have largely come from screening of cathepsin inhibitor libraries garnered from the pharmaceutical industry. To complement this approach, and with the aim of identifying non-peptidic inhibitors, we have recently applied in silico methods to screen virtual inhibitors incorporating vinyl sulfone or aminoacetonitrile warheads. This work was done in collaboration with Rafaela Ferreira in the Shoichet and McKerrow labs at UCSF. A set of commercially available carboxylic acids was joined in silico to the warheads and the resulting library of virtual inhibitors docked to a published cruzain structure using the program DOCK. In the docking study, artificial charges were introduced to insure that the electrophilic sites on the inhibitor structures were located near the active site cysteine residue. Using this approach, we identified non-peptidic inhibitors that afforded reasonable enzymatic activity against cruzain. In a separate search for non-covalent (reversible) inhibitors of cruzain, a similar docking study was implemented to screen the ZINC database of commercially available lead-like small molecules. Out of this virtual screen, we identified novel small molecules that inhibit cruzain in a biochemical assay. The SMDC chemistry team is currently synthesizing analogs of these novel cruzain inhibitors with the aim of mapping their SAR and identifying more potent derivatives.

Impressions: This was a really interesting and well organized conference. The scope of work presented was quite broad, attendance at the sessions was very good, and lots of good discussions were fostered. I especially enjoyed the panel discussion on the topic of translational science and venture capital funding of new companies. The setting was perfect and the hotel was very well run. I look forward to attending again in the future.

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Overview: My current research is focused on the mechanisms of regulation of nuclear receptors.

Presentation: At the meeting, I presented the first three-dimensional structure of Dax-1 in a functional complex with its target, nuclear receptor LRH-1, and showed its mechanism as a corepressor. Unexpectedly, Dax-1 binds LRH-1 using a newly discovered functionality, a repressor helix built from a family conserved sequence motif. Mutations in the repressor helix are found in humans with endocrine syndromes and are shown to attenuate Dax-1 function *in vitro*.

I**mpressions**: The meeting is very well organized, optimal in size and with superb presentations. The format of the meeting gives a lot of possibilities to communicate and discuss science in non-formal settings. For the future meetings, no changes are necessary.

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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: Nuclear pore complexes (NPCs) are ~50 MDa proteinaceous assemblies that selectively transport cargos across the nuclear envelope (NE). To determine the molecular architecture of the NPC, we collected a large and diverse set of proteomic data and developed a method for using this data to define the relative positions and proximities of the NPC's constituent proteins. Our structure reveals that half of the NPC is made of a core scaffold, which is structurally analogous to vesicle coating complexes. This scaffold forms an interlaced network that coats the entire curved surface of the NE membrane within which the NPC is embedded. The selective barrier for transport is formed by large numbers of proteins with disordered regions that line the inner face of the scaffold. The NPC consists of only a few structural modules that resemble each other in terms of the configuration of their homologous constituents, thus providing clues to the ancient evolutionary origins of the NPC.

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 the presentations were inspiring and informative.

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Overview: My laboratory combines structural, biochemical, and immunological techniques to understand the pathogenesis of viral hemorrhagic fevers, and to develop vaccines and immunotherapeutics against them.

Presentation: I presented the crystal structure of an antibody termed 13F6-1-2, in complex with its Ebola virus GP epitope. 13F6-1-2 was raised against the Zaire subtypes of the Ebola virus, and protects against 1000x lethal dose of Ebola virus in an animal model. The antibody is encoded by rare genes. Of particular interest is the lambda x light chain, of which no structure was previously available. The unusual protein sequences in this antibody adopt unusual structural features in both framework and complementarity determining regions. The conformation of the GP peptide in the antigen binding site likely mimics the expected extended structure of this region as it appears in the heavily glycosylated mucin-like domain of the intact GP on the viral surface.

Impressions: Good mix of content, good opportunity to find collaborations at TSRI and elsewhere

Name: Gary Siuzdak
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Overview: The venue and the opportunity to discuss science in an informal atmosphere was wonderful. The meeting has impacted my lab in a couple of ways already.

Presentation: I enjoyed the student rapid presentations and I believe it was also a good experience for them. A

minute or two extra might have been useful and perhaps spreading it over two evenings. The faculty were also good, although many were well out of my field for me to have a reasonable understanding. The discussion on biotech was excellent.

Impressions: It seemed like all the attendees appreciated the opportunity to talk about their science. And the interactions of the students with the faculty also made it more interesting. Overall, a good meeting.

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Overview: My lab works on computational method development for protein structure prediction, phylogenetic tree construction, phylogenomic inference of protein function, multiple sequence alignment, and other related tasks.

Presentation: I presented an Overview of the PhyloFacts resource my group has developed (funded by the NSF and NIH) for genome-scale phylogenomic analysis, and associated algorithms.

Impressions: Excellent mixture of exciting talks on different topics, which I really enjoyed. The setting was excellent, as usual, and the hotel staff provided professional support for the meeting. The setting is also very conducive to informal discussions outside of the formal meeting sessions. I shared a memorable dinner with five scientists from different top pharmaceutical companies, for instance, in which we discussed how big pharma view bioinformatics (my field) and the challenges in their work.

Overall, fantastic meeting. This is now my second year and I'd rank this meeting in the top 5% of meetings I've attended over the past 15 years.

Name: Raymond Stevens
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Overview: The Stevens' laboratory is primarily focused in the area of structural neurobiology, with efforts in both basic science, as well as applied. Over the past few years, we have developed technologies to help speed up structural biology to further increase the impact of the field in all areas of biomedical research including structural genomics, structure based drug discovery, and more traditional structural biology projects.

Presentation: Recently, we have been focused on converting our basic science knowledge of enzymes involved in neuronal signaling or neuronal signaling disruption towards the development of novel therapeutics. Specifically, we have developed an enzyme replacement therapeutic to treat phenylketonuria (PKU) as well as creating a new version of botulinum toxin. Both of these therapeutic development projects were highlighted at the Cabo meeting.

Impressions: Location as always is spectacular, as are the scientific discussions between academics, industry, VC's and even lawyers. There is no other meeting quite like this one and it is definitely worth continuing.

Name: Theresa Tiefenbrunn

Supervisor: Philip Dawson

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Overview: I work on the synthesis of derivatized peptides for site-specific labeling of proteins and on the chemical synthesis of proteins with biological activities.

Presentation: My talk focused on my efforts to chemically synthesize the second thrombospondin-1 type 1 repeat (TSR2) along with analogs that will provide information about the factors stabilizing this unique domain. Additionally, data on the antiangiogenic activity of my synthetic TSR2 were presented.

Impressions: I thought the meeting was a great forum for being able to interact scientifically and socially with professors in a more intimate setting than I've been in before. I was exposed to many interesating topics that I hadn't previously heard much about. The venue was great, and the setting was perfect. I also appreciated the scheduling of some down time in the afternoon.

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Overview: A family of synthetic RNA enzymes has been made to evolve in a continuous manner using a simple serial transfer procedure that can be carried out indefinitely. In these experiments, it is possible to evolve ribozymes that catalyze template-directed 3', 5'-phosphodiester ligation under adverse conditions including extreme pH, and low divalent salt concentrations. This research aims to further explore ribozyme differentiation and strain evolution using a population of multiple ribozyme families, which compete for limited resources. To this end, a stringent selection procedure was used to obtain a second family of ribozymes that have the ability to catalyze ligation, and subsequently amplify, under continuous *in vitro* evolution conditions. Future continuous coevolution experiments will address evolutionary principles with the potential to discover synergy (mutualism) or antagonism (competition, predation, parasitism) when selection pressure is applied to the system.

Presentation: Emergence of a Continuously Evolving Ribozyme

Impressions: This was my first year at the meeting, and I now understand why it is so popular. I really enjoyed interacting with both faculty and the sponsor scientists in an informal setting. The breath of topics discussed was phenomenal, especially given the length of each. This served to highlight the most exciting results from each discipline without getting bogged down with non-essential details. I found preparing my five-minute talk to be quite challenging, though surely this gets easier each year with repeated invitations to the meeting.

Name: Andrew Ward
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Overview: I study the structure/function relationship of ATP Binding Cassette (ABC) transporters using x-ray crystallography and electron microscopy. ABC transporters are responsible for translocating a wide variety of substrates across membranes. The transport of antibiotics and chemotherapeutics can lead to multidrug resistant phenotypes in bacteria and cancer cells. Multiple structures of the bacterial ABC homologue, MsbA, have allowed us to describe the gross conformational changes that accompany transport. Direct visualization of these conformational changes illustrate how accessibility to either side of the membrane is mediated by an alternating access mechanism that utilizes ATP binding and hydrolysis to drive these changes.

Presentation: Structural Biology of the ABC Transporter MsbA

Impressions: I had a great time at the meeting. It was a good balance of science and fun. It is especially nice to be able to interact with so many great scientists in a casual relaxed setting.

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Overview: Our lab works on immune recognition of microbial pathogens, in particular HIV-1 and influenza virus. We investigate the structural basis of neutralization of microrganisms by the innate and adaptive immune systems, including antibodies, T-cell receptors, TLRs and other

pattern recognition receptors. We are also involved with several large consortia including the Joint Center for Structural Genomics (JCSG), the 1918 flu consortium, The International Aids Vaccine Initiative and the Consortium for Functional Glycomics.

Presentation: The JCSG is one of only 4 production center funded by the NIGMS Protein Structure Initiative. We have determined more than 400 novel structures (i.e. <30% identical to structures in the PDB) in the past 6 years and are currently on a pace of about 150/year. Most of our effort is in understanding the protein fold space through determination of first structures of large Pfam families as well as more recent exploration into the exciting world of metagenomic targets, such as the Global Ocean Sampling (GOS). We have set up a very efficient pipeline for high throughput structural biology and much of the methodology and technology can be transferred and utilized in individual investigator's labs. Many salvage pathways have been refined to increase protein production and crystallization, as well as to rapidly determine protein structures. We are also interacting with the general biological community, as well as genome sequencing centers, to enhance the value of our structures.

Impressions: A superb meeting as usual with extensive interactions from the diverse set of participants from academia, industry, and funding sources, such as VCs. The first day was exciting with all the student and postdoc that were succinct, but extremely informative. The interaction of the sponsors with the academic participants was another highlight. The hotel did a great job with the meeting room set up and catering.

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Summary of research:

Macromolecular assemblies visualized by electron cryo-microscopy and image processing

In our laboratory, a major theme is the use of electron cryo-microscopy (cryo-EM) and image analysis to examine the structure of large, multicomponent, supramolecular complexes. In electron cryomicroscopy, biological specimens are quick frozen to preserve their native structure and functional properties. A special advantage of this method is that we can capture dynamic states of functioning macromolecular assemblies, such as open and closed conformations of membrane channels and viruses actively transcribing RNA. Three-dimensional density maps are obtained by digital image processing of the high resolution electron micrographs. The rich detail revealed in the density maps demonstrates the power of this approach to reveal the structural organization of complex biological systems that can be related to the functional properties of such assemblies. For our work in structural virology, maps at low resolution (~20 Å) reveal the overall shape and symmetry of the protein capsid layers, as well as the location, shape, dimensions, quaternary arrangement and stoichiometry of the component proteins. For the structure analysis of membrane proteins, electron crystallography of highly ordered, two-dimensional crystals enables a higher resolution analysis (~ 6 Å resolution) from which the secondary structure of the protein within the lipid bilayer can be discerned.

Research projects under way include the structure analysis of (1) membrane proteins involved in cell-to-cell communication (gap junctions), water transport (aquaporins), ionic transport (potassium channels), transmembrane signaling (integrins), and viral recognition (rotavirus NSP4); (2) viruses responsible for significant human diseases (retroviruses, hepatitis B, rotavirus, astrovirus); and (3) viruses used as model systems to understand mechanisms of pathogenesis (arenaviruses, reoviruses, nodaviruses, tetraviruses and sobemoviruses).

Presentation:

Structure of Full-length HIV-1 CA: A Model for the Mature Capsid Lattice

The capsids of mature retroviruses perform the essential function of organizing the viral genome for efficient replication. These capsids are modeled as fullerene structures composed of closed hexameric arrays of the viral CA protein, but a high-resolution structure of the lattice has remained elusive. A three-dimensional map derived by electron cryo-crystallography combined with high-resolution domain structures yielded the first unambiguous model for full-length HIV-1 CA, which revealed three important protein-protein assembly interfaces required for capsid formation. Each CA hexamer is composed of an inner ring of six N-terminal domains and an outer ring of C-terminal domains that form dimeric linkers connecting neighboring hexamers. Interactions between the two domains of CA further stabilize the hexamer, and provide a structural explanation for the mechanism of action of known HIV-1 assembly inhibitors.

Impressions of the Meeting:

My Impressions are unchanged. This continues to be one of my favorite meetings! The size and informal workshop format is similar to a Gordon conference with the advantages of a broad scientific scope and resort location. Frankly, I think the quality of the science presented at this meeting is outstanding. I also appreciate the participation of scientists in industry in order to gain insight into translational research and the potential for commercial applications of basic research.

I have launched two scientific collaborations as a consequence of discussions at this meeting. On the basis of conversations this year, I hope to launch two more. Consequently, this meeting continues to be of substantial personal value.

I have been fortunate to have attended about a dozen of the total of 18 meetings. This is the first year that I can recall in which there was a significant problem. A plane carrying many of the Scripps participants was delayed by several hours. Although the Sunday evening session was postponed a few hours, the students did an excellent job

keeping on time. Even though the session went well in to the evening, the meeting got right back on track. In fact, I liked the format of taking a break to have the patio reception and then continue the second half of the first set of presentations

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Overview: Making Electron Microscopy Easier

Presentation: My work is in technology development and is largely centered around creating and improving the tools available to people interested in structural work using electron microscopes. The two new developments that I discussed at the meeting were targeted at automating techniques used for initial model building, and particle picking; two problems that are very difficult, time-consuming and/or tedious to perform manually.

Impressions: The meeting was excellent. I am especially impressed by the quality and format of the talks given by the graduate students and post docs. The PI talks were excellent and served as a basis to not only educate, but to also create new ideas and partnerships. The sponsor talks where also interesting, though I was a little disappointed that Fluidigm was not there!

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Overview: The Molecular Foundry at Lawrence Berkeley National Laboratory is a User Facility charged with providing support to research in Nanoscience underway in academic, government and industrial laboratories around the world. The Foundry provides users with instruments, techniques and collaborators to enhance their studies of the synthesis, characterization and theory of nanoscale materials. Its focus is on the multidisciplinary development and understanding of both “soft” (biological and polymeric) and “hard” (inorganic and microfabricated) nanostructured building blocks and the integration of those building blocks into complex functional assemblies. We are looking for collaborators and users to spend time at the Foundry to investigate problems in nanoscience. These can be students, post-docs, faculty or staff scientists in industry or government labs.

Presentation: I presented the story of peptoids - a novel class of non-natural biopolymer based on an N-substituted glycine backbone that are ideally suited for nanomaterials research. This bioinspired material has many unique properties that bridge the gap between proteins and bulk polymers. Like proteins, they are a sequence-specific heteropolymer, capable of folding into specific shapes and exhibiting potent biological activities; and like polymers they are chemically and biologically stable and relatively cheap to make. Peptoids are efficiently assembled via automated solid-phase synthesis from hundreds of chemically diverse building blocks allowing the rapid generation of huge combinatorial libraries. This provides a platform to discover nanostructured materials capable of protein-like molecular recognition and function.

Impressions: This was an outstanding meeting. The quality of science was very high, and there was a nice diversity of subjects presented. The setting was extremely enjoyable, and there was plenty of time for casual interactions with other conferees. This was a fantastic opportunity for me to interact with top structural biologists and tell them about my

research and the capabilities of the Molecular Foundry. I made many invaluable contacts that will likely turn into long-term collaborations. It was a privilege to attend.