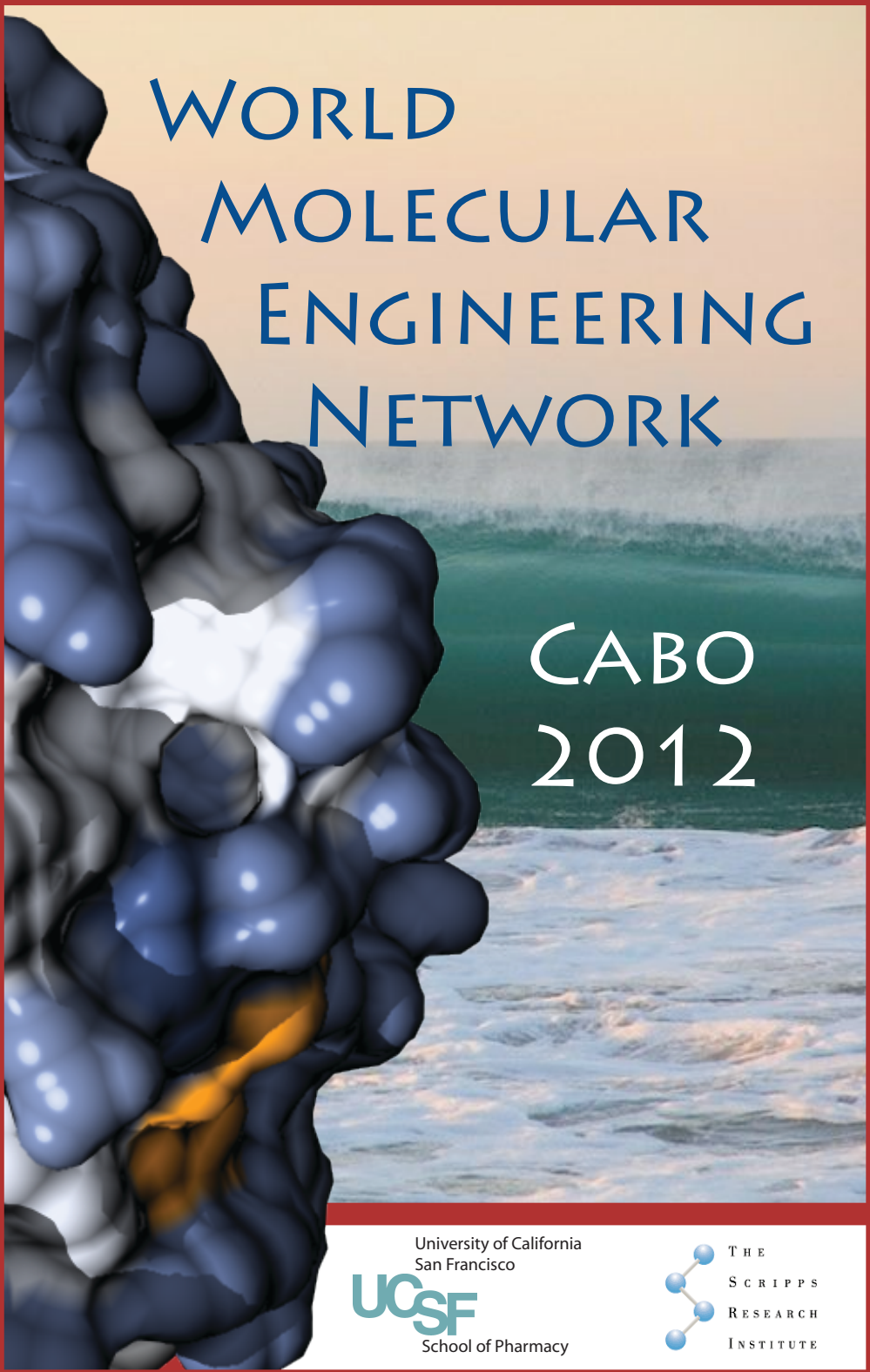
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Our History

The WMEN conference has been held for the past 22 years during the month of May in Los Cabos, Mexico. The meetings originated from a grant from the Rockefeller Foundation supporting research collaborations between scientists at UCSF, MRC Cambridge and The Scripps Research Institute, now called TSRI. Drs. Daniel Santi and Ian Wilson started the meetings and created the unique scientific ambience. The meeting style has remained unchanged but, twelve years ago, the venue moved from Cabo San Lucas to an all-inclusive resort in San Jose del Cabo. The 2012 meeting was held at a new venue, the Barcelo Los Cabos Palace, an attractive resort with excellent conference facilities and very attentive staff. Each year, the meeting attracts approximately 60 academic, industrial, and biotech participants, as well as venture capitalists and patent attorneys. The majority of the attendees are professors, laboratory heads or research directors, but we also encourage participation of the next generation of scientists through selecting a number of the top graduate students and postdoctoral fellows from UCSF, TRSI, UC Berkeley and Stanford. The spirit of scientific research is enhanced and refreshed in this stunning setting with a stellar list of participants.

Cabo XXII Program
World Molecular Engineering Network Twenty-Second Annual Meeting on Structural Biology

6-9 May 2012, San Jose del Cabo, Baja, Mexico

Sunday Evening, May 6

17:00	Dan Santi and Ian Wilson	**Introduction and Welcome**
17:15	William Rutter	**Keynote Lecture- What Am I Doing?**

17:45–18:00 ***Self-Introductions***

Wenwu Zhai	Rinat/Pfizer
Jack Kirsch	UCB
Seth Harris	Genentech
Eric Schneider	UCSF
Neil Kumar	Third Rock Ventures

18:00-20:00 **Short Presentations (5+1 min.) by TSRI, UCSF, UCB Graduate Students, Postdoctoral Fellows *et al.* (Chair: Dennis Wolan)**

Dmitry Lyumkis	TSRI	Single-particle electron microscopy reveals extensive conformational variability of the Ltn1 E3 ligase
Peter Lee	TSRI	Head-hunting: targeting the hemagglutinin receptor-binding site
Ashley Pratt	TSRI	Mechanistic insights into framework destabilization of Cu, Zn-superoxide dismutase ASL mutants
John Chen	TSRI	Heterodimer formation of two forms of Charco-Marie Tooth associated mutant forms of glycyl-tRNA synthetases that restores aminoacylation
Eugene Chun	TSRI	New fusion partners for G protein-coupled receptor crystallization
Robert Kirchdoerfer	TSRI	Organization of influenza replication machinery
Denis Malyshev	TSRI	Replication without H-bonds: the structure of a DNA polymerase replicating an expanded genetic alphabet

	Katherine Petrie	TSRI	Modeling fitness landscapes *in vitro*: mutagenesis and genetic drift
	Kimberly Hartfield	TSRI	New strategies toward crystallization of complex forms of cytochrome P450 240A1
	Josephine Leung	TSRI	Towards crystallization of *Thermus thermophilus* transhydrogenase
		Break	
	Avner Schlessinger	UCSF	Structure, function, and evolution of solute carrier (SLC) transporters
	David Shaya	UCSF	Voltage-gated sodium channel protein dissection creates a set of functional 'pore-only' proteins
	Louis Metzger	UCSF	Structures of a hinging membrane enzyme access membrane resident lipid to produce lipid X in the synthetic path to lipid A
	Sabine Mocklinghoff	UCSF	Protein crosstalk in transcriptional control - strategies to identify novel regulatory complexes
	Jason Porter	UCSF	Two halves are better than the whole: development of an inducible PTEN phosphatase
	Justin Farlow	UCSF	Imaging single Notch receptors at the cell surface with self-assembling monovalent quantum dots
	Greg Lee	UCSF	Determining binding modes of cruzain inhibitors via NMR spectroscopy
	Martijn Verdoes	Stanford	Non-peptidic cathepsin S activity-based probe for noninvasive optical imagining of tumor associated macrophages

20:15–21:30 **Reception** **Poolside**

Monday May 7 — Advances in Structural Biology (Chair: James Fraser)

09:00	Bridget Carragher	TSRI	EM automation: the next decade
09:20	Roger Durst	Bruker	Developments in source and detector technology
09:40	John Tainer	TSRI	Advanced SAXS and a dawn for a mechanistic structural systems biology
10:00	Jane Dyson	TSRI	NMR studies of large and difficult proteins
10:20	Peter Wright	TSRI	Exploring protein energy landscapes by

			NMR relaxation
10:40	Break		
11:00	Graham Johnson	UCSF	autoFill: applications of mesoscale modeling and visualization software
11:20	Tom Ferrin	UCSF	Advances in chimera for modeling and animation
11:40	Robert Fletterick	UCSF	Structures in stem cell biology
12:00	Ray Stevens	TSRI	Structural genomics of the human GPCR superfamily

Immunology and Biomedicine (Chair: Ian Wilson)

16:30	James Paulson	TSRI	Siglecs as sensors of self
16:50	Charles Craik	UCSF	Antibody-assisted structure determination
17:10	Andrew Ward	TSRI	Broad neutralization of influenza virus
17:30	Sherry LaPorte	CytomX	Probodies: Protease-activated antibodies for disease-specific targeting
17:50	Break		

Chemical Biology (Chair: Zev Gartner)

18:10	Dennis Wolan	TSRI	Proteomic interrogation of the human distal gut microbiome
18:30	Matthew Bogyo	Stanford	Imaging proteolysis during inflammation using small molecule probes
18:50	Dan Santi	UCSF/ ProLynx	A chemical approach to half-life extensions of therapeutics
19:10	Jim Wells	UCSF	The NEDDylator: a catalytic tagger for cell biology

Tuesday , May 8

Sponsors I (Chair: Dan Santi)

09:00	Peter Hirth	Plexxikon	Developing a new therapy for metastatic melanoma harboring the v600 B-Raf mutation
09:20	Jennifer Riggers	Nektar	The design of novel and improved therapeutics utilizing Nektar's advanced polymer conjugation technology

09:40	Javier Chaparro-Riggers	Rinat/ Pfizer	A pH-sensitive anti-PCSK9-antibody: improving PK and cholesterol lowering by increasing antibody-antigen binding cycles and reducing target-mediated clearance
10:00	Manoj Desai	Gilead	Cobicistat: a potent and selective pharmacoenhancer
10:20	Break		
10:40	Dana Ault-Riche	Reflexion	Mirror image proteins as novel anti-angiogenic agents
11:00	Albert Stewart	Pfizer La Jolla	Examples of strategies for targeting protein-protein interfaces: Hif-1A/ARNT PasB heterodimer
11:20	Steven Bartz	Merck	Accessing external innovation
11:40	Craig Muir	Third Rock Ventures	Third Rock Ventures: Investment models on the west coast

Nucleic Acids and Lipid Binding Proteins (Chair: Robert Fletterick)

16:30	David Millar	TSRI	A new fidelity checkpoint in DNA polymerase I
16:50	Floyd Romesberg	TSRI	Successful expansion of the genetic alphabet
17:10	Jamie Williamson	TSRI	Structural genomics of RNA binding proteins in T-cell activation
17:30	Dirk Bussiere	Novartis	Designing compounds against lipid kinases: NVP-BKM120 - a pan-class I PI3K inhibitor
17:50	Break		

Membrane Proteins (Chair: Andrew Ward)

18:10	David Stout	TSRI	Transhydrogenase
18:20	Dan Minor	UCSF	Structure and mechanism of a voltage-dependent enzyme
18:50	Robert Stroud	UCSF	Surviving the heavy metal onslaught
19:10	Zev Gartner	UCSF	Building relationships between structure and function in epithelial tissues

Wednesday, May 9

Assemblies, Computation, Design and Drug Discovery (Chair: Sherry LaPorte)

08:30	Philip Dawson	TSRI	Assembly of peptide functionalized nanoparticles for biological imaging
08:50	Bill Degrado	UCSF	Analysis and design of proteins
09:10	James Fraser	UCSF	The evolution and function of protein conformational dynamics
09:30	Jacob Corn	Genentech	Rationally engineering conformational dynamics to modulate ubiquitin-deubiquitinase interactions
09:50	Break		
10:10	Dinesh Patel	Prota-gonist	Peptide therapeutics: from 'identity crisis' to 'exceptional opportunities'
10:30	Peter Kuhn	TRSI	Fluid biopsy in solid tumors, how HD-CTCs can provide real-time drug response and stratification
10:50	Joshua Salafsky	Biodesy	Second-harmonic generation (SHG) for allosteric drug discovery: conformational change in real time
11:10	Alan Cheng	Amgen	Leveraging thermodynamics for data mining and drug discovery
11:30	Ian Wilson and Dan Santi		**Closing Remarks**

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

WMEN Conference
San Jose del Cabo
Barcelo Los Cabos
Palace Hotel

For more information, contact:

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Overview: I am a regionally based scout for the Merck Research area. I perform search and evaluation for tools and technologies and drug/biologic opportunities for all Merck's areas of interest. Opportunities that align with Merck's interests are forwarded to colleagues who specialize in a specific disease area to assess whether we will move to further collaboration/partnering discussions. In performing this role, I interact and build relationships with the Biotech companies, Academic Institutions, VC/Angel groups etc. to find opportunities but also to inform these groups of what Merck is interested in.

Presentation: My presentation covered what Merck is doing to stimulate investment in the early space (target ID/validation to phase I). Many or most large pharma have had to cut research budgets and reduce workforces, and this has resulted in looking to external sources for the early space innovative research. However, many VC's have shifted to funding later stage projects. In addition, a major source of new targets for pharma and biotech is the scientific literature. However, recent studies by Bayer and Amgen have reported on the lack of reproducibility of the results in the scientific literature. While this is not surprising to most, it means that pharma/biotech must screen through many targets just to get to a few that are robust enough to move forward. To address these issues Merck has put in 3 initiatives:

1. Early space academic collaboration dollars. Merck will identify specific labs to collaborate with to "robustly" validate targets.

2. CALIBR: Merck, with other non-profits, has established the California Institute for Biomedical Research. Projects will be sourced globally. For example, a scientist with an interesting new target selected to enter will have a completed funded project. The project will have a small molecule HTS campaign or biologics support, med chem, pharmacology etc. and a defined exit, which is animal proof of concept. At exit, Merck has the right to license, or if not interested, the asset may return to the home institution or may be attractive to a VC or Angel group.

3. The Merck Research Venture fund,which is dedicated to the formation of companies in the early space.

Impressions: The quality and content of the meeting was very impressive. Not being a structural biologist, I learned a lot from this meeting, and am following up with a few PI's on potential collaborative opportunities. The small size of the meeting also means there is ample opportunity to network.

Name: Matthew Bogyo
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Overview: Overall a great meeting. The range of topics is good with a strong emphasis on structural biology, but not too many pure structure talks.

Presentation: It is great to have all the postdocs and grad students present short talks on the first day so that it opens discussion during the rest of the meeting. I think that the faculty talks are a good length but could even to make a tiny

bit shorter to open up time for slightly longer postdoc and grad student talks.

Impressions: Overall I really enjoy attending this meeting. It has lead to several good collaborations between my lab at Stanford and UCSF/Scripps. I thought the meeting site was much more fancy and nice than the old site but felt that it was somewhat too big of a venue and preferred the old site only because it had more a feel that we owned the place.

Name: Bridget Carragher
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Fax number: 858-784-9090

Overview: An excellent meeting that stands out in being quite different from almost every other meeting I attend. One of the most impressive aspects is the high level of interaction among the participants, with the industry attendees and especially with the students. This student and postdoc interaction is given an enormous boost on the first night with the short format talks, which work astonishingly well and get them immediately integrated into the meeting.

Presentation: The presentations are on the whole outstanding. The short talks format is a great idea and I hope this never changes. It is great that every participant has a chance to present.

Impressions: A scientifically very interesting and friendly meeting that I think encourages interesting interactions between academia and industry and gives students a unique opportunity to present their work.

Name: John Chen

Supervisor: Paul Schimmel/Xianglei Yang
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Presentation: Charcot Marie Tooth (CMT) disease is a neurodegenerative disease with a variety of gene mutations. Glycyl tRNA synthetase (GlyRS) is found to contain over 10 mutations implicated in CMT. Two mutations, C157R and P234KY, are shown to form a tight homodimer that facilitates increased tRNA binding. This enables the C157R monomer to perform aminoacylation.

Impressions: The meeting was a positive environment for sharing science and potentially facilitating new collaborations. The venue was very welcoming, and overall I enjoyed it immensely. One adjustment I'd propose would be finishing all presentations by early afternoon so we have more time for outside activities.

Name: Alan Cheng
Department: Amgen
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Overview: I am a scientist at the Amgen San Francisco research labs, where I work with chemists and biologists on the discovery of new medicines for oncology, neuroscience diseases, and metabolic diseases. My primary scientific interest is in computer-aided drug design.

Presentation: I presented a computational approach based on binding thermodynamics and protein structure to estimate the small-molecule druggability of a protein pocket. We can

complement this computational approach with a 19F-NMR fragment-screening approach. In beta-secretase drug discovery targeting Alzheimer's disease, we have used a structure-based drug design approach to design a new scaffold that captures additive free energies of binding while retaining favorable pharmacokinetic properties.

Impressions: A good meeting that impressively hosted talks from so many well-respected research leaders in a beautiful setting.

Group size and mix: Excellent size for encouraging new interactions and catching up, and included a well-balanced mix of students, post-docs, faculty, and industry. Nearly every one presented.

Meeting length: Just right. I thought the student/post-doc 5-minute talks on the first day covering very recent and in-progress work were very effective and well done.

Meeting location: The Barcelo was a great venue right on the beach of San Jose del Cabo. The resort had a variety of areas that allowed for informal meetings, but was small enough so that you run into most attendees outside the formal meeting room.

Name: Jacob Corn
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Overview: My lab works on the molecular determinants of affinity and specificity at protein-protein interactions. We are especially interested in how the evolution and maintenance of dynamics shapes protein interfaces. We use computational and experimental means to both explore the

mechanisms of natural interactions and to engineer new ones.

Presentation: I presented our work on the development of proteins with altered timescales of conformational dynamics. These engineered molecules have greatly increased affinity and specificity for their targets, but NMR experiments reveal that their primary changes relative to wild type are in the speed of their motion. Despite having almost identical structures and surfaces compared to wild type, slowed variants are unable to complement in vivo, highlighting the functional importance of macromolecular dynamics in living cells.

Impressions: Fantastic! The 5 minute talks were jam-packed with great info, the PI talks were a great high-level overview, and the location was stellar. I hope I get the opportunity to attend next year.

Name: Charles Craik
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Overview: The research interests of the Craik lab focus on defining the roles and the mechanisms of enzymes in complex biological processes and on developing technologies to facilitate these studies. The primary emphasis of our work has been on enzymes in infectious disease and cancer. Our studies have evolved to encompass numerous proteases and their endogenous inhibitors as well as protease receptors and have recently found practical applications in translational research in oncology and

infectious diseases.

Our ability to recombinantly manipulate and then biophysically characterize proteolytic enzymes and their endogenous inhibitors coupled with our understanding of the determinants of molecular recognition, provide a basis for structure-based inhibitor design. Our original studies on HIV protease serve as a model for inhibitor design efforts on proteases and on other enzymes in general and have evolved into a full-fledged program targeting human herpes virus proteases. Significant efforts are also made towards developing technologies for determining the extended substrate specificity and for selectively inhibiting key enzymes of the innate immune response, identifying a new class of membrane bound proteases implicated in various forms of epithelial cancers and monitoring caspase activity at the single molecule level. We recently developed a promising strategy for using the activity of these tumor-related proteases for early cancer detection and for blocking their function without compromising the vital workings of the bodyís own normal proteases using antibodies that target the active conformation of the protease. These antibodies can help stratify patient populations for aggressive cancer phenotypes and may provide therapeutic potential in addition to their prognostic value. More information can be found at the following website: http://www.craiklab.ucsf.edu/

Presentation: A methodology for identifying high value antibodies for structural studies and in vivo imaging studies of membrane bound proteins was presented. Rapid identification of antibody fragments that can recognize native protein structure makes phage display a valuable method for structural studies of membrane proteins. Methods that speed the reliable characterization of phage display selected antibody fragments are needed to make the technology more generally applicable. A phage display biopanning procedure was described to identify Fabs for both soluble and membrane proteins. It was also shown that Fabs can be

rapidly grouped based on relative affinities using ELISAs and unpurified Fabs. The procedure greatly speeds the prioritization of candidate binders to membrane proteins and aids in subsequent structure determinations. Identification of Fab/protein complexes facilitated high-resolution single particle electron microscopy studies of small proteins that are below the resolution limit (< 100 kilodaltons). Examples were presented from a collaboration with Yifan Cheng where the synthetic Fab facilitated structural analysis of small protein complexes by both negative staining and cryoEM. Finally, Fabs that bind to the active form of membrane bound proteases were fluorescently and radiolabeled to create multimodal probes for monitoring proteolytic activity associated with metastatic cancer in vivo. Examples were shown for anti-matriptase antibodies that monitored proteolytic activity associated with metastatic colon cancer in patient derived xenograft models of cancer.

Impressions: Outstanding meeting with terrific talks. Great mix of structure, chemical biology, mechanism and practical applications for business opportunities. Fantastic setting and excellent facilities.

Name: William DeGrado
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Overview: This was a terrific meeting. I liked that students spoke early so we could connect more easily. I liked the mix of industry and academics.

Presentation: All the presentations were very well prepared and delivered.

Impressions: This is one of the very best meetings I have ever attended.

Name: Roger Durst (sponsor)
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Presentation: Developments in Source and Detector Technology

Impressions: The venue was very nice. The program of talks was excellent. I personally do not like the 5 min student presentations as the short time is simply not sufficient to give a coherent presentation in most cases. Would rather see a student poster session as this would give more of a chance to interact.

Name: Jane Dyson
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Overview: The Cabo meeting is intensive, with lectures throughout the morning and late afternoon. The lectures were really the only time that the participants met as a group, except for the reception on the first evening.

Presentation: I very much enjoyed all the presentations from the UCSF and TSRI participants, and from some of the

pharma speakers. Several of the pharma speakers did not really make the effort to engage a non-industry audience, which was unfortunate. Technical details and comparisons between drugs are not in general of great interest to academic scientists.

Impressions: In general the meeting was very well attended, with most of the participants attending most of the lectures. Question time was lively. It was definitely an advantage to meet new people under relatively informal conditions.

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Presentation: In my presentation, I was using a novel means of synthesizing monovalent quantum dots to label the receptor, Notch. I wish to understand the process through which Notch is activated at the cell surface. The organization of the molecules themselves appears to provide some regulation of this process - but imaging single receptors has proven difficult. We have used phosphorothioate-DNA to produce monovalent quantum dots via steric exclusion. These dots are then linked to the Notch receptor via a SNAP tag fusion and a complementary strand-benzyl guanine. Together, this allow me to tag single Notch receptors with single quantum dots in order to study the dynamics of individual Notch receptors over their lifetime at the cell-surface.

Impressions: Densely packed with interesting science. Small enough to be intimate - large enough to have a diverse set of people. It felt very much like this event has taken place before - it was well planned, well balanced, and well-suited to its mission. I learned a lot. As a student, the close interactions with a number of professors, postdocs and industry people was enlightening and beneficial for my own career. I feel fortunate for having had the opportunity to attend.

Name: Tom Ferrin
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Overview: My research focuses on developing software tools and advanced web-based resources for the visualization and analysis of molecular structure at scales ranging from the atomic to the supramolecular.

Presentation: I presented work covering some of the recent advances we have made with our UCSF Chimera molecular visualization application. This includes work in four key areas: “cloud” based services, integrative modeling, generating simple animations, and dissemination of results via “WebGL” technology. These advances are especially relevant given the dramatic growth in recent years in the availability of sequence and structure data. For example, the PDB now has more than 81,000 structures available, including structures such as the ribosome (1FKA and 1FFK) with 47 proteins and long chains of RNA. Similarly, UniProt now has more than 22,000,000 entries. Given this large and ever-growing body of data, how can researchers most efficiently access this data, generate hypotheses, perform simulations, generate models, and analyze and disseminate results? I discussed features in Chimera that attempt to

address these problems using an interactive and richly visual approach. Additional details can be found on the Chimera web site: www.cgl.ucsf.edu/chimera

Impressions: I am very impressed by the breadth and depth of molecular engineering topics covered during the three days. The 5-minute time limit for postdocs and 20-minute time limit for PIs forced people to put careful thought into preparation of their presentations and the result were talks that got right to the point, covered the most important issues, and didn't go too far astray. The discussion elicited by nearly every talk was enlightening. I very much appreciated the inclusion of talks by leaders from industry, and I learned a great deal from these speakers about current approaches and state-of-the-art technology in commercial therapeutic research. Lastly, the inclusion of free time in the middle of the day provided plenty of opportunity to "catch up" with old friends and meet new ones. All in all, this was an excellent meeting in all respects and I hope to have the opportunity to attend again in the future.

Name: Robert Fletterick
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Overview: The meeting was notable for having exceptional scientists presenting work from numerous disciplines. The talks were well done as if they were prepared for the diverse group. There was lots of time to meet people and learn details of their presentations. I enjoyed especially the talks by the sponsors and industrial scientists.

Presentation: I spoke about a new program to determine structural data for transcription factor complexes. The

unifying goal was that these should determine major changes in the cell program, such as converting fibroblasts to induced pluripotent stem cells or to cardiac myocytes. I focused on the integrated collaboration with the Joint Center for Structural Genomics. The JCSG has powerful robots for expression of proteins, their purification and crystallization that are employed to enable the work to proceed at amplified rates. I stressed the difficulty with working with complexes of one or more protein domains. JCSG scientists perform thousands of operations to bring a target project to structure determination.

One complex was presented in detail, that of the DNA binding domain of Sox9 with its AMH promoter. This complex was altered by adding one to three domains from the transcription factor SF-1 in efforts to assemble larger complexes, and to possibly bring structural order to the disordered segments of the polypeptide chain. I showed that the complexes exist in solution, but three different crystal forms were show to have lost the SF-1 components. Other domains, including a winged helix motif and a RNA recognition motif were shown. The winged helix motif was shown to be unusual in not binding DNA, but rather mediating protein interactions. The RRM was show to bind a particular RNA, allowing an RNA protein complex to be assembled for further structural studies.

Impressions: I appreciated the effectiveness of the meeting room and found the staff to be helpful and unobtrusive. I would often prefer just a bit more time for questions, but there were a few to several excellent questions for most talks.

The hotel was excellent, and there was lots of time between the science sessions to meet with people and learn more about projects. I can only think of one complaint! Please serve more vegetables for the arrival dinner!

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Overview: My research focuses on the discovery, function and evolution of protein conformational dynamics. We are developing new methods to visualize alternative conformations of proteins using X-ray crystallography and comparing these results to NMR methods. We exploit the knowledge of these hidden states to alter protein function with mutations that are remote from active sites.

Presentation: I highlighted some recent methodological developments for calculating allosteric pathways within proteins. I also gave a brief preview of an exciting collaboration that started at last year's Cabo meeting. Hopefully at next year's meeting we will present that collaboration as a finished story.

Impressions: This is a great meeting - and the location was much improved over last year! I always enjoy catching up with the Scripps crew and it offers a rare chance to spend long periods of time dreaming up new collaborations. The Industry presenters this year were highly interactive and presented exciting science.

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Phone number: 415-514-9962

Overview: Fantastic meeting! Great location, speakers, and opportunities for interactions in the afternoon and evening!

Presentation: Excellent meeting room. AV significantly improved from last year. Good coffee and snacks.

Impressions: I met a number of wonderful people from industry and academics. I'll be coming back for sure if invited.

Name: Seth Harris
Department: Genentech
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South San Francisco, CA 94080
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Phone number: 650-467-5187

Overview: My research provides structural support for design of both small molecule and biologic therapeutics, with recent work spanning areas of oncology, neurodegeneration, and infectious diseases. On the technology front, I've worked with my groups to pioneer the implementation of acoustic drop ejection in setting nanoliter scale crystallization trials. Additionally, I develop relational database and informatics tools for streamlining our high-throughput workflow and exploring methods for facile analysis and accessible navigation through large datasets of structures.

Presentation: Brief self-introduction as excluded from program due to time/space constraints...I would have presented on on-going efforts towards the structural alignment and clustering of conformations to identify patterns in structures. Using well-studied kinases as a case study, I would have highlighted the interesting learnings from such multi-structural analysis, demonstrated a self-authored tool

for navigating these data from a web page controlling a PyMOL display, and described applications to improve the convergence of molecular replacement models towards final conformations in cases with highly dynamic proteins.

Impressions: This is a great, convivial meeting that fortifies and extends long-standing ties between structure-focused communities around UCSF, Scripps and affiliated sponsors. Kicking off with the shotgun blast of short talks was energizing and set a good pace for much content in short time. Over the next sessions, it was very stimulating to hear leading edge advances in imaging technologies and methods, membrane protein campaigns, creative ideas from several of the younger investigators starting labs, and also the interesting platform technologies from the industrial sector. I enjoyed exposure to several areas of technology (like tissue organization and quantum dot imaging as well as the impressive visuals of autoFill) that I would not have otherwise readily encountered. Likely it would be good to keep the size under control to ensure a fully inclusive program and format.

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Presentation: The primary aim of my research is structural characterization of a monotopic membrane protein, CYP24A1. In pursuit of crystal structures of this protein in multiple states relevant to understanding its specificity and reactivity, a purification technology has been developed. The approach uses an affinity tagged construct of the redox partner, adrenodoxin, as a substrate for capture of CYP24A1

and purification of the complex. Isolation of this complex presents an opportunity to investigate the physiologically important association of these proteins while improving stability of the membrane protein.

Impressions: This having been the first time I have attended the WMEN meeting, I cannot compare the venue to the previous. However, this year's location seemed pleasant enough (other than the minor chaos inherent in moving to a new location). The length of the meeting seemed appropriate for the amount of content being presented. The number of attendees and presenters, too, seemed about right - the size and remote location contributed to a more intimate feel while still being large enough to have a diversity of presenters. I enjoyed the thematic sessions.

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Presentation: Kinase inhibitors are gaining prominence in the fight to treat a variety of human cancers.

The identification of the BRAF oncogene in 2002 led to efforts to discover RAF pathway inhibitors. Structure-guided optimization yielded PLX4032, a potent and selective inhibitor of oncogenic B-RAF kinase activity. In preclinical cellular and in vivo studies, PLX4032 demonstrates potent anti-cancer activity against tumors bearing oncogenic BRAF mutations, while showing no effect on tumors lacking BRAF mutations. Translated to clinical trials, patients were selected with a companion diagnostic. Given the favorable pharmacology, PLX4032 advanced to human clinical trials in cancer patients. Clinical data now reveal that PLX4032 has

anti-cancer activity in patients with metastatic melanoma. Indeed, significant tumor regressions have been confirmed in patients whose tumors harbor the BRAF oncogene, and the promise of PLX4032 was highlighted in several publications. As with other targeted agents, resistance often causes tumor relapse and emerging data suggests this can occur through a variety of mechanisms. Next generation compounds are aimed to combat the development of resistance.

Impressions: This meeting was a great opportunity to connect with many scientists, many of whom are working on projects or technologies relevant to drug discovery and development. This was an opportunity to learn more about new developments before they appear in the newspaper. Already two very specific opportunities have arisen as a consequence to this meeting and discussions for collaboration projects. I have to thank Dan for nudging me to come to this meeting.

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Overview: In an effort to better comprehend cell function, we have begun to develop visualization standards that can harness, manipulate, and assess the data produced across multiple scientific disciplines- to frame the details of molecular biology on a broader cellular map and to extrapolate predictions where reasonable.

Presentation: Our computational framework autoCell combines existing and novel packing algorithms with multiscale data to generate, visualize and analyze comprehensive 3D models of complex biological

environments, including whole cells, in molecular detail. Along with the code, we release four initial models of biological systems and call upon diverse communities of content experts to iteratively improve these models or to propose new models, through various interfaces under development for this open-source project.

Impressions: Great meeting overall. I have mixed opinions about the new location and frankly prefer El Presidente (didn't have the courage to be only one of two people to raise my hand at the meeting, but I talked to at least a dozen people afterwards who felt the same). Hopefully we can work to offer the best of both worlds. The 2012 accommodations are more comfortable and the quality of the food nearly sells me 100%, but the posh setting and size of the new hotel generates an atmosphere more similar to a large meeting that loses the retreat-like congeniality that several previous Cabo meetings offered. Had I not attended previously and been reunited with several friends/colleagues, I think I would have felt relatively anonymous and isolated trying to navigate my way through the short interaction opportunities. My current position stemmed directly from attending Cabo as a graduate student. In watching the relatively limited interactions that occurred between all participants, especially graduate students and faculty in 2012, I'll suggest that the atmosphere is too grand and distracting to nurture the deeper discussions that used to occur. I prefer not to suffer another week of El Presidente food, but ideally, we'll be able to make some simple modifications to recapture some of the intimacy and opportunity of the pre 2012 meetings. Thank you.

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Presentation: We looked at influenza virus RNA replication complexes using cryo-electron microscopy and combined this structural information with published biochemistry to propose models for viral transcription and RNA replication by the viral polymerase.

Impressions: I enjoyed this years meeting particularly with regards to the diversity of the talks and the extensive interactions with other students and faculty. The size of the group is great (though the meeting room was a bit too small).

The resort is beautiful, but I disliked the way the staff run it. There were complications for a lot of students in getting the double rooms requested. The front desk and lobby staff had never heard of our meeting and couldn't tell us where it was being held; there were no signs directing us. Although the food was much better than the previous resort, it was hard to get a reservation and portions were tiny. The restaurants also had a very strict dress code and turned us away if we didn't meet it. The internet connection was slow and expensive. I had some issues getting hot water for a shower in the morning.

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Overview: This is about my 12th participation. I have always found this meeting to be the most valuable of those that I regularly attend. I don't believe that I have ever skipped a talk, nor have I been bored.

Impressions: Location: Excellent-big improvement over El Presidente

Number of Participants: about right

Length of Meeting: Just right.

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Overview: Enjoyable and informative.

Presentation: Enjoyable and informative.

Impressions: All in all a great meeting.

Name: Sherry LaPorte
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Overview: Our research focuses on protein and antibody engineering to create safer and more effective therapies in a start-up company environment. As part of a small team, we are working to exploit the biology of proteases found

specifically in diseased tissues and use that biology to activate Probodies, protease activated antibodies. These Probody targets are enriched in the disease tissues, but may be present elsewhere in healthy tissue.

Presentation: We have developed a Probody targeting the EGF receptor for cancer. I presented the background of the how technology to create this Probody and how this Probody works to inhibit tumor growth in an animal model as well as to be safely tolerated in a non-human primate.

Impressions: I liked the opportunity to see student, post-doc and faculty presentations along side of industry presentations. All presentations were of high quality. I took many notes and enjoyed follow-up discussions focused around these presentations.

Location: Excellent

Number of participants: Excellent

Length of meeting: If I'm invited in the future, I may plan to arrive earlier to adjust to the heat.

I like that the meeting is relatively small, so that it is easy to approach people and be approached for scientific discussions. The presentations were excellent due to the mixture from two top-notch research institutions, biotech industry leaders and biotech start-up scientists.

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Presentation: My research centers on examining protein-ligand interactions using NMR spectroscopy as my primary method. In particular, I am focusing on validating allosteric inhibitors of human herpesvirus proteases. In addition, I am using NMR to classify binding modes of small molecules that inhibit cruzain, the main cysteine protease associated with Chagas' disease.

Impressions: I really enjoyed the meeting. I especially appreciated the opportunity to meet with the people from Scripps and industry and hearing about their work. The number of participants seemed to be just about the right size -- not too big such that we were lost in the crowd.

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Presentation: My talk was about recognition to the receptor-binding site of hemagglutinin (HA) by antibody S139/1. Despite the the sequence variability of the "head" of HA, S139/1 recognizes a relatively conserved epitope enabling it to bind strains from multiple HA subtypes. Avidity plays a major role in recognition as the bivalent IgG has enhanced binding and neutralization activity over monovalent Fab.

Impressions: I thought the meeting was great - all the talks by students, faculty, and industry generated scientific discussion and dialogue. I thought the length, number, and diversity of talks were just right. I generally liked the resort

though the staff was rather rigid when it came to dining, e.g. not allowing people to combine tables, which limits the interaction between groups of people.

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Presentation: My research goal is to determine the crystal structure of transhydrogenase, an inner mitochondrial membrane enzyme of respiration that has been shown to involve in type 2 diabetes. We are developing constructs and protocols to express and purify the protein from *Thermus thermophilus* for crystallization.

Impressions: I am very grateful to have the opportunity to participate in this excellent meeting. Not only there were awesome presentations from PIs and sponsors, the interactions with outstanding scientists have been overwhelmingly inspiring. It was truly an eye-opening experience for graduate students.

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Presentation: Single-particle EM reveals large-scale conformational variability of the Ltn1 E3 ligase

Impressions: This meeting is different from any other meetings that I've attended in that it brings together researchers from different scientific, as well as industrial backgrounds. In my opinion, this is a major benefit for attendees. This is particularly beneficial for my field (electron microscopy), as it is often not discussed as a standard technique in structural biology. This particular meeting gives me the opportunity to present my work in oral format, and consequently it provides more exposure to the types of questions that we can address than I would normally have. This is my third time attending this meeting, and also the third time that either I or someone from the lab has come out of it with a concrete collaboration on an interesting problem. I am therefore very satisfied by its organization, format, and outcome.

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Presentation: Replication without H-Bonds: The structure of a DNA polymerase replicating an expanded genetic alphabet

Impressions: Nicely organized meeting in a premium location with outstanding scientists from both academia and industry. Plenty of time for interactions and recreational activity. Very strong scientific program.

Recommendations: Due to the large size of the resort, it was sometimes tough to find a person I wanted to talk to. From this perspective, a smaller location would be better.

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Presentation: Gram-negative bacteria possess an asymmetric outer membrane in which the inner leaflet is composed primarily of phospholipids, while the outer leaflet contains mainly lipopolysaccharide (LPS). LPS forms a structural barrier that protects Gram-negative bacteria from antibiotics and other environmental stressors. LPS is anchored to the outer membrane by lipid A, a unique glucosamine-based saccharolipid. Lipid A biosynthesis is required for bacterial viability and pathogenesis. While most lipid A biosynthetic genes are present in a single copy, one gene, lpxH, encoding a membrane-associated specific UDPdiacylglucosamine hydrolase, is absent in ~30% of Gram-negative bacteria. We hypothesized that a transformational analogue of LpxH must exist in these organisms. We identified this gene, designated lpxI, in *Caulobacter crescentus*, and confirmed its ability to cover for a deficiency of lpxH in *Escherichia coli. Caulobacter crescentus* LpxI (CcLpxI) and it numerous homologues lack similarity to any other known hydrolase. We solved the X-ray crystal structure of this peripheral membrane enzyme using a single-wavelength anomalous dispersion (SAD) dataset collected on Se-Met derivatized protein. The structural data reveal two domains, together comprising a novel fold. Unexpectedly, “apo” CcLpxI copurified and co-crystallized

stoichiometrically with its product, diacylglucosamine-1-phosphate (lipid X), the saccharolipid precursor of lipid A. We then identified and determined the 2.55 Å X-ray crystal structure of an inactive point mutant of CcLpxI,which co-purified in a stoichiometric ratio with its substrate, UDP-2,3-diacyglucosamine. The conformation of substrate-liganded CcLpxI differs significantly from the product-liganded wild-type enzyme. Taken together with analytical unltracentrifugation data, this observation suggests that large-scale domain re-arrangement occurs during LpxI substrate binding and/or catalysis.
These data provide an interesting example of lipid-protein interaction, and set the stage for additional structural and mechanistic work.

Impressions: This meeting was an extraordinary opportunity to follow the latest biochemical and biophysical discoveries made by regional academia and industry. The limited number of attendees afforded postdoctoral researchers the chance to interact with industrial and academic leaders in an informal setting. The seminars provided impetus for fascinating discussions on the sidelines of the meeting, and inspired a variety of potential collaborations.

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Overview: My laboratory is developing and applying single-molecule fluorescence methods for the analysis of biomolecular dynamics. We have three main areas of interest. (1) Structural dynamics of DNA replication enzymes. (2) Function of the HIV-1 Rev protein. (3)

Signaling by G protein coupled receptors. We have developed novel single-molecule approaches to study each of these systems.

Presentation: I described our recent discovery of an innate fidelity checkpoint in DNA polymerase I (Pol I). Like all polymerases, Pol I must select the correct nucleotide substrate (complementary to the template base) and actively reject the three incorrect substrates during each cycle of nucleotide incorporation. The mechanism of nucleotide substrate selection is thought to involve conformational changes within a flexible fingers subdomain of the polymerase. We developed a FRET method to monitor conformational changes within the fingers as individual Pol I molecules performed nucleotide substrate selection. We discovered that the fingers sample through three distinct conformations, "open", "closed" and a previously unrecognized intermediate "ajar" conformation. Our results demonstrate that the ajar conformation serves as a kinetic checkpoint to reject incorrect nucleotide substrates before the enzyme encloses the nascent base pair and catalyzes phosphoryl transfer.

Impressions: I felt that the meeting was stronger than ever, even after more than 20 years (I have attended all previous meetings). The new venue is a significant improvement on the El Presidente. The meeting room is excellent and the bedrooms are comfortable and modern. The corporate feel of Barcelo detracts somewhat (for me), but this is a better venue overall.

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Overview: My laboratory studies the structures and functions of ion channels. In addition to structural biophysics, my laboratory has a program on developing new compounds to study ion channel pharmacology and in vivo function.

Presentation: I presented our latest work on the dissection of voltage-gated sodium channels into pore-only proteins that can be used to study the basic properties of sodium and calcium ion permeation and as the basis for the development of new sensor proteins for controlling cell excitation. I also presented a brand new story regarding the structure and mechanism of a voltage-sensitive lipid phosphatase.

Impressions: This was again an excellent meeting. There was a good balance of industrial and academic talks. In general, presentations were focused on the most latest and exciting developments from the presenters. The atmosphere was open and encouraged great discussion among the attendees.

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Presentation: I am studying transcriptional multi-component assemblies by focusing on the essential transcription factors Steroidogenic factor 1 (SF-1) and Liver Receptor Homolog 1 (LRH-1) and their co-regulators, which are critical to embryonic stem (ES) cells and to induced pluripotent stem (iPS) cells. We use biochemical techniques to evaluate the possibility to achieve stable transcriptional

protein assemblies in vitro in the presence of appropriate DNA molecules. Stabilized protein assemblies are screened for novel binding partners including proteins and RNAs and are used in crystallographic studies.

The introduction of posttranslational modifications (PTMs) into SF-1 and LRH-1 is very critical and can further increase protein stability and might help to identify novel protein binding partners. I use expressed protein ligation to generate homogeneously modified proteins that allow crystallographic studies.

Impressions: The conference was fantastic. I was impressed by the high quality of the presentations. It was great to meet and interact with so many interesting scientists from academy and industry.

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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. We also have a significant effort on the role of receptors of human and avian influenza viruses, and the role of receptor specificity as a barrier for transmission of avian viruses in human populations.

Presentation: Glycosyltransferases and receptor specificity of avian and human Influenza.
The talk covered two high profile vignettes representing high profile 'side projects' in our group. 1) Remarkably there are few inhibitors of glycosyltransferases identified to date suitable for probing the roles of glycans by regulation of their biosynthesis. The talk covered our recent development of metabolic inhibitors that comprise sugar analogs that are taken up by the cell and incorporated into nucleotide donor sugars that are transition state inhibitors of whole classes of enzymes. Two inhibitors, 3F-NeuAc and 2F-Fuc, when fed to cells shut down the addition of terminal sialic acids and fucose, respectively, onto glycans of cell surface glycoproteins. While these inhibitors dramatically remodel the glycome of the cell, there is no apparent toxicity. Together they add to the armamentarium of tools available to probe the functions of the glycome. 2) In collaboration with the groups of Ian Wilson at TSRI and Ruben Donis at the CDC, we have worked on understanding what it would take for the H5N1 influenza virus to acquire human virus type receptor specificity, now considered a key barrier for transmission in the human population. Through rational design and 'in vitro' evolution strategies, 3 mutations were discovered that were capable of a complete switch from recognition of the avian type receptor (NeuAcα2-3Gal) to the human type receptor (NeuAcα2-6Gal). By reverse engineering, mutations put back into a reassortant virus were demonstrated to provide weak aerosol transmission in ferrets, an animal model of human influenza. The work shows that the H5 hemagglutinin can acquire mutations in nature that provide for binding to human type receptors, but this by itself is not sufficient for efficient transmission in mammals.

Impressions: Over the years, I have come to look forward to the format of the meeting with intense scientific content presented by faculty, students and sponsors in a relaxed

setting that encourages social interactions and networking. This year the meeting was particularly exciting, benefiting from both long time regular participants, returning occasional participants, and new faculty, students and sponsors. The new venue also added a sense of 'new life' to the meeting. From everyone I talked to, the combination of good science and pleasant venue evaporated doubts about sustainability. Word of mouth reports will surely generate enthusiasm for the meeting next year.

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Presentation: My research uses ribozymes to model evolution in vitro to better understand the factors that determine evolutionary trajectories. Recent work suggests that variations in mutability ñ the susceptibility of individual sequences to mutation ñ may play a significant role in shaping evolutionary outcomes. Using high-throughput sequencing, we determined the mutation frequency at every nucleotide position of a short ribozyme genome during a single copying cycle. This mutation rate was surprisingly variable from position to position, and likely depends on local genetic context. This variation implies that certain evolutionary paths may be more or less accessible based solely on mutability, irrespective of fitness.

Impressions: Overall, this meeting was fantastic. The presentations were interesting and educational, and I am grateful for the opportunity to attend, to present, and to interact with so many scientists. The location was beautiful,

but the grounds may have been too large to encourage as much spontaneous discussion as possible, as it was a bit difficult to track people down during free time and for meals. Nonetheless, this was the best conference I have attended during graduate school.

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Presentation: Student/Postdoctoral presentations: This was a very interesting opportunity to gain exposure to a wide variety of research endeavors by both UCSF and TSRI students and postdocs. The only fault with this portion of the meeting was the limited time available to each presenter. In many cases, 5 minutes was not enough time to fully grasp scope of many of the research projects and, from the presenter's perspective, this limited time presented a very daunting challenge. That being said it is realized that this short time limit is unavoidable unless student number is sacrificed for increased time, which would be a great disservice to both the students who have the opportunity to attend such a unique meeting and the other attendees who would miss out on great research. All in all, I was very pleased with this portion of the meeting and feel that it should continue to be an integral part of all future WMEN meetings.

PI and Industry Rep Presentations: I thought that these presentations where very informative and also provided a

unique opportunity for exposure to a wide variety of research fields, many of which were outside my own. The time allotment of 20 minutes also seemed adequate to relay a complete story. As a burgeoning young scientist I found this exposure to both academic and commercial research particularly beneficial.

Impressions: Overall the meeting was great. The wide variety of talks and the opportunity to interact with other presenters and industry representatives was a unique and wonderful opportunity. The hotel was very nice, the food was good, and the beer was plenty. Also kudos to Hilary and the others behind the scenes for making the meeting a great success.

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Presentation: My research has focused on ALS (Lou Gehrig's disease), and particularly how the large number of mutations (>150) in the gene encoding Cu,Zn-Superoxide dismutase can lead to protein misfolding and aggregation. These mutations are spread throughout the protein, leading to the same phenotype, but highly differential kinetics. Having developed a small-angle X-ray scattering (SAXS) based assay to monitor aggregate formation in vitro, I investigated the G93 mutational hotspot, and found that at this site, aberrant copper incorporation via the copper chaperone for SOD is directly correlated to aggregation tendency. We are now using Cu2+ EPR to better understand how the copper environment may be relevant to

pathogenesis in these mutants. Lastly, we are using our assay as a foundation for screening for small molecule stabilizers of the dimeric protein fold. ALS at present is fatal with no useful treatments.

Impressions: Having attended 1 prior meeting at the previous venue, my impressions of the new site are mixed but positive overall. There was a small amount of confusion the first day with the welcome agent, but after that resort staff were helpful and courteous. The meeting size was just perfect, although the resort is somewhat spread out. People wanting to get together at night typically found each other at one of the lobby bars, and that seemed to work fine, They were strict about making us vacate up to our rooms promptly at 2am, but that is probably appropriate. The food at the new venue was delicious - a big improvement. The length of the meeting and the talk lengths is perfect and the overall format is very enjoyable. I hope to attend another Cabo meeting in the future!

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Overview: The 20 min talks are great, just enough time to understand what everyone is doing, and short enough to have a large number. Great combination of focus on structure, dynamics, and drug development.

Presentation: Successful expansion of the genetic alphabet

Impressions: As always, great meeting. It is regularly one of the best I attend. New venue was probably better than previously.

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Overview: Synergenics, LLC., a consortium of companies owned and strategically managed centrally, was established in order to achieve enhanced efficiency in the development of innovative products through the more effective management of human, financial, and technical resources. The general idea is that profitability/liquidity can provide resources, which can be strategically reinvested in the most value-enhancing projects. Projects can be initiated, and terminated efficiently. and changes in development and business plans can be adapted to new conditions can be accommodated.

The overall focus of Synergenics is to develop products for the "whole world", and can be sold at a profit in 80% of the world. This requires stringent controls of costs, while maintaining high quality standards.

Presentation: Several Synergenics companies were presented as examples:

VENTRIA BIOSYSTEMS has developed a proprietary system for the production of up to metic tons of HUMAN proteins in rice. Currently, Ventria produces Lactoferrin, Lysozyme, and serum albumin...each of these products has both a human therapeutic, and other commercial uses in the biotech/food industry. One of these products (Ven100) has

been approved for registration trials by the FDA for antibiotic associated diarrhea, as a first indication.

HUMABS has a proprietary system for interrogating the human memory Bcell, and plasma cell repertoire, with automated screening for uniquely potent antibodies whose gens can then be used to produce the antibody in standard commercial systems for therapeutics/vaccines/and diagnostic uses. Humabs has licensed a product for cytomegalovirus, pan-influenza A, which neutralizes all 16 subtypes of flu hemagglutinins, and is in the early stage of developing a potent antibody with neutralizes BOTH RSV and MPV viruses.

BIOENERGENICS, is developing a small molecule which specifically inhibits a proprietary kinase which in turn act as a transcription factor controlling the synthesis of the enzymes associated with the synthesis of fatty acids and their associated lipids. Contro of this system also effect insulin sensitivity, and other activities associated with the metabolic syndrome. A highly active small molecule and backup have been developed by the Synergenics Biopharma group and are preparing for FDA approval for phase I clinical trial in hyperlipidemia

PATHOLOGICA is developing products to control macrophage functions in inflammatory disease. One of these addresses acute pain, the fist product PA300 displays the efficacy of dexamethasone, without the side effects, much more potent than other Nsaids, without causing bleeding or kidney side effects. This orally available product has a wide safety margin, and the dossier is being prepared for presentation to the FDA for initiation of phase I clinical trials this year.

The second project concerns a role of this compound in controlling macrophage induced inflammation associated with dementia in HIV disease. Studies in macaques and in

human macrophages in vitro indicate a powerful effect of PA300 in controlling macrophage infiltration, associated inflammatory markers, and elimination of HIV from human macrophages, at least in part via selective killing of infected cells. This approach has the potential of eliminating the macrophage reservoir in AIDS patients,which seems to persist even in the presence of HAART drugs.

Impressions: I thought this was spectacular meeting--essentially presenting the state of the art in molecular analysis via physical methods (diffraction, NMR, electron microscopy), as well as the development of small molecule inhibitors/activators of specific systems. The diverse audience were ALL represented in the talks, and the organization in general was superb. The talks by the sponsors were both instructive and well-delivered. I think overall it was one of the most effective, and enjoyable meetings I have ever attended. The organization led by Dan Santi and Ian Wilson and also by Hilary Mahon was superb.

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Overview: I presented an overview of ProLynx, start-up company I recently co-founded. The company develops technology for half-life extension of drugs.

Presentation: Conjugation to macromolecular carriers is a proven strategy for improving the pharmacokinetics of drugs, with many stable polyethylene glycol conjugates having reached the market. Stable conjugates suffer several limitations: loss of drug potency due to conjugation, confining the drug to the extracellular space, and the requirement for a

circulating conjugate. Current research is directed toward overcoming such limitations through releasable conjugates in which the drug is covalently linked to the carrier through a cleavable linker. Satisfactory linkers that provide predictable cleavage rates tunable over a wide time range that are useful for both circulating and non-circulating conjugates are not yet available. We describe such conjugation linkers on the basis of a nonenzymatic β-elimination reaction with preprogrammed, highly tunable cleavage rates. A set of modular linkers is described that bears a succinimidyl carbonate group for attachment to an amine-containing drug or prodrug, an azido group for conjugation to the carrier, and a tunable modulator that controls the rate of β-eliminative cleavage. The linkers provide predictable, tunable release rates of ligands from macromolecular conjugates both in vitro and in vivo, with half-lives spanning from a range of hours to >1 y at physiological pH. A circulating PEG conjugate achieved a 56-fold half-life extension of the 39-aa peptide exenatide in rats, and a noncirculating s.c. hydrogel conjugate achieved a 150- fold extension. Using slow-cleaving linkers, the hydrogel format provides a generic format for once-a-month dosage forms of potent drugs. The hydrogel format has been further developed to contain very slow-cleaving β-eliminative linkers that allow controllable degradation rates. The releasable linkers provide additional benefits that include lowering Cmax and pharmacokinetic coordination of drug combinations.

Impressions: I attended with my spouse Leah and my 10 year-old son, Angelo. The meeting was probably the best I have attended yet. The talks were crisp, and the science was terrific. There was plenty of time to interact, and the hotel and food very good. The attendees and talks from Industry were particularly impressive.

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Presentation: I gave a short talk about the structure, function, and evolution of Solute Carrier (SLC) Transporters. Particularly, we use comparative modeling, virtual screening, and experimental validation to describe specificity determinants in biomedically important membrane transporters.

Impressions: The meeting was excellent. The talks were very interesting and covered diverse topics that are related to drug discovery. As a computational structural biologist it was especially interesting to learn new experimental techniques that I am usually not exposed to. Almost all speakers were approachable, which provided a great opportunity to network and make new friends.

The place was very nice. As a postdoc I had to share a room, but because the rooms were more like suites, each one of us had his own room, which was really convenient. The organization was outstanding and everything ran smoothly. Whenever we needed something Hilary was always there to help.

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Impressions: The meeting was very good this year. Enjoyed the change of venue, excellent rooms and the food

was significantly improved. The talks were very good with adequate time to interact with fellow attendees.

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Presentation: Talk Title: Voltage-gated sodium channel protein dissection creates a set of functional 'pore-only' proteins.

My research focuses on the understanding the mechanism of sodium ion conduction through bacterial sodium channels. Using molecular biology I have created the pore proteins expressing solely the ion permeation module of a set of bacterial sodium channels. These constructs display superior over-expression and stability as compared to the full length protein expressed in bacteria. Using an array of biochemical and biophysical techniques I have showed that the pore proteins are highly helical, monodisperse tetramers in solution. Using electrophysiology we showed that the pore proteins are sodium selective channels that are blocked by the known channel inhibitor mibefradil. A three amino acid replacement in the selectivity filter of the channels turns the channel into a calcium permeable ion channel. We propose the pore protein to be an excellent model for high resolution structural studies understanding sodium vs. calcium selectivity binding and permeability through ion channels.

Impressions: This meeting was outstanding! The presentations by the PI's conducting leading research in all fields were very interesting and informative. The sponsor's

presentations were impressive. The overall atmosphere was very casual and friendly which created a great opportunity to communicate and learn. I am grateful to have had the opportunity to attend the meeting and would recommend no changes in the meeting.

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Overview: Structural Genomics of the Human GPCR Superfamily

Presentation: GPCRs constitute one of the largest protein families in the human genome and play essential roles in normal cell processes, most notably in cell signaling. The human GPCR family contains more than 800 members and recognizes thousands of different ligands and activates a number of signaling pathways through interactions with a small number of binding partners. GPCRs have also been implicated in numerous human diseases, and represent more than 40% of drug targets. Delivering GPCR structures in close collaboration with experts on specific receptor systems is of immense value to the basic science community interested in cell signaling and molecular recognition, as well as the applied science community interested in drug discovery. This work is being followed up with additional biophysical characterization including NMR spectroscopy and community wide assessments with computational biology groups throughout the world. Crystal structures are now available for rhodopsin, adrenergic, and adenosine receptors in both inactive and activated forms, as well as for chemokine, dopamine, histamine, S1P1 and opioid receptors in inactive conformations. A review of the common structural

features seen in these receptors and the scope of structural diversity of GPCRs at different levels of homology provides insight into our growing understanding of the biology of GPCR action and their impact on drug discovery. Given the current set of GPCR structural data, a distinct modularity is now being observed between the extracellular (ligand-binding) and intracellular (signaling) regions. The rapidly expanding repertoire of GPCR structures provides a solid framework for experimental and molecular modeling studies, and helps to chart a roadmap for comprehensive structural coverage of the whole superfamily and an understanding of GPCR biological and therapeutic mechanisms.

This work was supported by NIGMS PSI:Biology for GPCR structure processing (U54GM094618) and the NIH Roadmap Initiative (JCIMPT) for technology development (GM073197).

Impressions: Great meeting, best of the year and I really liked the new hotel! I would like to see a return of the panels as I think these discussions help to expand the interactions.

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Overview: The Pfizer, La Jolla Structural Biology Group focuses on small molecule structure based drug design of oncology therapeutic area targets.

Presentation: The presentation gave illustrative examples of challenges and considerations in small molecule targeting of protein-protein interactions and clinical resistance in receptor tyrosine kinases.

Impressions: The depth, breadth and quality of all the talks were excellent and as well as very interesting.

I found the meeting atmosphere to be very collegial and excellent in fostering post-presentation discussions and idea sharing.

An excellent meeting and venue.

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Overview: We use X-ray crystallography to study the structure and function of the membrane bound mitochondrial enzymes, transhydrogenase and cytochrome oxidase; understand the mechanism of the vitamin D metabolizing mitochondrial cytochrome P450, CYP24A1; define substrate specificity in microsomal, drug-metabolizing cytochrome P450s; and enable drug design against HIV protease in order to develop allosteric inhibitors to counteract resistance.

Presentation: My presentation summarized progress toward structure determination of energy-linked nicotinamide nucleotide transhydrogenase (TH), an inner mitochondrial membrane enzyme that couples the proton motive force (pmf) generated by respiration to formation of NADPH. Current experiments are focused on the three-component TH from *Thermus thermophilus*. Crystal structures of the soluble domains, alone and in complex, have been determined. The membrane component can be separately expressed and purified via association with a His-tagged

soluble domain, which is removed following purification, to enable crystallization in the lipidic cubic phase.

Impressions: The Cabo meeting is unique for the high quality of science presented and the breadth of important problems addressed in structural biology and drug discovery. The talks from biotech industry scientists add valuable perspective. The new venue for this year's meeting was excellent in all regards. The size of the meeting is ideal for allowing all attendees to give talks and interact informally.

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Overview: My research focuses on dynamic macromolecular interactions that control pathways in cells with implications for cancer and infectious disease. We are developing and applying x-ray scattering and diffraction methods to define conformations and complexes for biological prediction and disease interventions. This conference provides key ideas and data for my funded research.

Presentation: We are developing and providing others with methods for small angle x-ray scattering (SAXS) combined with crystallography. I presented methods and results regarding combined x-ray methods to define accurate conformations and complexes in solution under physiological conditions. The results presented are relevant to the design of novel interventions for cancer and other human diseases.

Impressions: This meeting provided key emerging and novel methods and results that generated much discussion

and impact on ongoing efforts. This small and high impact meeting is cost effective in providing methods, data, and ideas for advanced research efforts relevant to human disease.

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Presentation: The development and characterization of a cathepsin S-directed, quenched activity-based probe - BMV083 - was presented. This probe makes use of an optimized nonpeptidic scaffold leading to enhanced in vivo properties relative to previously reported peptide-based probes. In a syngeneic breast cancer model, BMV083 provides high tumor-specific fluorescence that can be visualized using noninvasive optical imaging methods. Furthermore, analysis of probe-labeled cells demonstrates that the probe primarily targets macrophages with an M2 phenotype. Thus, BMV083 is a potential valuable in vivo reporter for tumor-associated macrophages that could greatly facilitate the future studies of macrophage function in the process of tumorigenesis.

Impressions: This was a great, well-organized meeting held at a fantastic location. The size of the meeting invites for great interaction between students, postdocs, PIs and the representatives from industry. The high quality presentations

spanning a range of topics were very inspirational. Keep up the good work.

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Overview: Very enjoyable as usual. Great mix of academic and industrial science, although it seemed that industry was over-represented compared to previous years. Great new venue.

Presentation: Many speakers presented unpublished data, which is great. 15/5min format was perfect. No A/V issues which was nice.

Impressions: Left with new collaborations and excitement about science**.**

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Overview: This was probably the most scientifically interesting meeting of the last 5 or so Cabo meetings. There

was a good diversity of new investigators, and new industry sponsors to keep things fresh. The quality of the presentations and the discussions were excellent. This is a great mix of Scripps UCSF and company scientists.

Presentation: The change in venue to Barcelo was a big plus. The facilities are more modern, and the food was significantly improved. I strongly prefer the San Jose area to Cabo San Lucas.

Impressions: Overall, this meeting remains a highlight of the 20 meetings per year that I attend. Scientific impact, coupled with locale, make this a fantastic opportunity to meet with colleagues in structural biology and drug discovery.

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Overview: My lab is focused on recognition of microbial pathogens by the immune system, particularly HIV-1 and influenza virus. We have determined many antibody structures and complexes (over 130) and are using many of these for structure-assisted vaccine design for flu and HIV-1. I also direct one of the NIH PSI high throughput structural biology center that develops methods and technologies that are being used to advance structure determination by X-ray and NMR. We have great collaborations with the Fletterick group at UCSF on stem cells and the Williamson/ Salomon group at TSRI on T cells under PSI:Biology.

Presentation: I did not give one this year as the program was quite full and it was essential to have as many slots as

possible for other participants as I have presented at this meeting for the previous 21 years!!

Impressions: Another really successful meeting- the change in venue worked out well and the meeting room was excellent and well-equipped. The resort is larger than the previous one, but it was still possible to find everyone after the meeting sessions were over. A terrific overall program with great opportunities to meet and interact with a diverse set of participants from academia and industry. The students and postdocs excelled in their short presentation.

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Overview: The ultimate goal of our research is to elucidate the diverse roles that proteins from commensal bacteria of the human gut microbiome have in human health and disease, and apply this information towards the discovery of novel therapies against inflammatory bowel diseases (IBD), obesity, diabetes, and cancer. We develop and use multidisciplinary methodologies in biology and chemistry for resolving key questions in complex biological systems. Our laboratory employs functional proteomic technologies in the identification of the diverse assortment and types of bacterial proteins that are produced within normal and diseased human distal gut microbiomes and uses an array of biochemical, cellular, and biophysical methods towards the characterization of protein functions that are important for the maintenance of host:microbiome symbiosis as well as those proteins that are compromised in disease. We incorporate

this vital information into the development of in vitro and cellular high throughput discovery methods to identify small molecules that specifically regulate the biological function of target bacterial proteins. These small molecules are further employed as chemical probes to elucidate and validate essential commensal bacterial proteins and potential therapeutic targets, respectively, as tools to map the complex host:microbiome proteome network, and as platforms in the development of novel therapeutics for microbiome-related pathogenesis.

Presentation: Negotiating the complexity of the gut microbiome is an enormous challenge. To simplify the microbial proteome, we develop and use small molecule activity-based protein probes (ABPP) and tandem mass spectrometry to covalently label, isolate, identify and compare individual bacterial protein families. Initially, we are focusing our method development on the identification and quantitative distribution of secreted bacterial proteases within murine models of microbiome-related diseases obesity and IBD. Several criteria establish this protein class as an ideal initial system for study: 1) targeting of secreted proteins allows direct assessment of microbial content; 2) secreted proteases are essential for bacterial viability, host colonization and attachment, and modification of host epithelial cells; 3) ABPP probes have been established for all protease subclasses; and 4) secreted proteases represent excellent, untapped targets for drug discovery. Our proteomic methods and analyses towards bacterially-secreted proteases constitute the first major attempt to target a specific class of protein function within microbiota that can be extrapolated and applied to other functional families within the assortment of human microbiomes present on the skin and in other body cavities.

Impressions: This was a fantastic meeting as has been the last 12 that I have attended. The diversity of research subjects presented by the faculty was exceptional as always.

Jack Kirsch best summarized the importance of the meeting by saying the group of attendees represents an important group of scientists and that very few meetings currently exist where one can see such great science. I enjoyed the new location as well.

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Overview: Studies of protein structure and dynamics, primarily by NMR. Specific areas include:

- Characterization of intrinsically disordered proteins.
- Protein folding and misfolding.
- Structural basis for transcriptional regulation by CBP/p300, p53, and viral oncoproteins.
- Role of dynamics in enzyme catalysis.

Presentation: Exploring protein energy landscapes by NMR relaxation
The talk covered applications of NMR relaxation methods, especially relaxation dispersion, to study protein dynamics and identify higher energy conformational substrates relevant to protein function. Applications of these methods to DHFR catalysis and protein folding and misfolding were presented.

Impressions: A very good meeting, excellent opportunities for discussion. Talk quality was a bit variable. The venue was excellent.

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

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

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

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

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

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

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