WORLD MOLECULAR ENGINEERING NETWORK

CABO 2015

UCSF University of California, San Francisco
School of Pharmacy

The Scripps Research Institute®

Our History

The WMEN conference has been held for the past 25 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 (TSRI). Drs. Daniel Santi and Ian Wilson started the meetings and created the unique scientific ambience. The meeting style has remained unchanged but, thirteen years ago, the venue moved from Cabo San Lucas to all-inclusive resorts in San Jose del Cabo. The 2015 meeting could not be held this year at the Hyatt Ziva (formerly Barcelo Los Cabos Palace) as in 2014, due to hurricane damage. However, we were able to move location to Secrets Puerto Los Cabos, which turned out to be a great venue with good conference facilities and accommodation. However, we will return to the Hyatt Diva for 2016-7 as they have finished their rather extensive renovation and were keen to have us back. Consequently, we negotiated a good deal for the next two years.

Each year, the meeting attracts approximately 60 academic, industrial, and biotech participants, as well as venture capitalists and patent attorneys. The attendees are composed of Professors, laboratory heads or research directors, but we also encourage participation of the next

generation of scientists through selecting around 20 of the top graduate students and postdoctoral fellows from UCSF, TSRI, UC Berkeley and Stanford. The spirit of scientific research is enhanced and refreshed in this stunning setting in Los Cabos with always a stellar and fun group of participants. We are also grateful to our sponsors whose generous support makes this meeting possible every year.

WMEN CABO XXV, May 3-6, 2015

World Molecular Engineering Network
Twenty-Fifth Annual Meeting on Structural Biology

Sunday Evening, May 3

17:15	**Ian Wilson and Andrej Sali**	**Introduction and Welcome**
17:30	**Sasha Kamb, Amgen**	**Keynote Lecture-** Alzheimer's disease: The confluence of genetics, molecular structure and new medicines
18:15-18:25	**Self-Introductions**	
	Daniel J. Cipriano	Merck Research Labs
	Jakob Loven	Third Rock Ventures
	Jaume Pons	UCSF/Rinat-Pfizer

18:30-20:45 **Short Presentations (5+1 min.) by TSRI and UCSF Graduate Students, Postdocs and Researchers (Chair: Dennis Wolan)**

	Jessica Bruhn	TSRI	Insights into the molecular and structural properties governing RNA virus transcription and replication
	Sandip Chatterjee	TSRI	A comprehensive database and search method for microbiome metaproteomics
	Jonathan Hulce	TSRI	Extended N-hydroxyhydantoin carbamate inhibitors of mammalian lipases
	Jennifer Kefauver	TSRI	Compositional heterogeneity of Swell1, the volume-regulated anion channel
	Bryan Martin	TSRI	The Octamer Repeat motif, a novel molecular architecture involved in splicing regulation
	Charles Murin	TSRI	Structures of protective antibodies reveal sites of vulnerability on Ebola virus
	Erika Olson	TSRI	Structure-guided optimization of a peptide antagonist of EphA4 activation
	Nicole Schirle Oakdale	TSRI	The crystal structure of human argonaute2
	Jessica Sheu-	TSRI	Structural studies of higher-order

	Gruttadauria		miRNA-induced silencing complexes
	Peter Thuy-Boun	TSRI	The development of tools for profiling gut microbial sulfatases
	Yuh Ana Wang	TSRI	Chemical metaproteomics of the human distal gut microbiota
	Break		
	Elena Sablin	UCSF	Regulation of NR5A receptors by PIP3 hormone.
	Courtney French	UCB	Transcriptome analysis reveals thousands of targets of nonsense-mediated mRNA decay that offer clues to the mechanism in different species
	Geoffrey Smith	UCSF	Exploring the kinetics of cell signaling with small molecules: a unique temporal requirement for JAK3 activity in IL-2 signaling
	Alex Vecchio	UCSF	Piece by piece: putting together the tight junction three-dimensional puzzle
	Benjamin Barad	UCSF	Side-chain directed model and map analysis for 3D electron cryomicroscopy
	Peter Cimermancic	UCSF	Finding small-molecule modulators of large macromolecular assemblies
	Marco Lolicato	UCSF	Activation of a human ion channel by physical forces
	Nicolas Strauli	UCSF	Deconvolution of selection pressures in overlapped genes: The story of Tat and Rev
21:00	**Reception**		**Poolside**

Monday Morning, May 4			**Structural Biology (Chair: Kathleen Aertgeerts)**
09:00	**Andrej Sali**	UCSF	Integrative structure determination based on EMAP data
09:20	**John Tainer**	TSRI	Better design of proteins and protein cages by X-ray scattering
09:40	**James Fraser**	UCSF	BBC PUBS: Results from our first year graduate students!
10:00	**Jeff Lengyel**	FEI	Beyond the frontiers of the Cell - unveiling the wonders of Nature at the molecular level
10:20	**Break**		
10:40	**Elizabeth**	TSRI	Switching protein conformations and

	Getzoff		assemblies: light and ligands, redox and radicals
11:00	**Otomo Takanori**	TSRI	Structural insights into the functions of the autophagic ubiquitin-like proteins
11:20	**Ashok Deniz**	TSRI	Biophysics of a disordered protein, from single molecules to droplets
Monday Afternoon, May 4			**Virology and Immunology (Chair: Jim Paulson)**
16:30	**Andrew Ward**	TSRI	High resolution cryoEM of viral glycoproteins
16:50	**Ian Wilson**	TRSI	Recognition of influenza virus by broadly neutralizing antibodies
17:10	**Jim Paulson**	TSRI	Targeting immune cells
17:30	**Pedro Paz**	Bayer Healthcare	Modeling MHCII-peptide-TCR interactions for prediction of immunogenicity
17:50	**Break**		
			Membrane Proteins (Chair: Andrew Ward)
18:10	**Robert Stroud**	UCSF	Membrane transporters in action: how do they work?
18:30	**Dan Minor**	UCSF	How ion channels respond to temperature and pressure
18:50	**Mark Yeager**	UVA	Allosteric enhancers of adenosine receptors for treatment of a disease that has increased 300% in last 20 years
19:10	**Kathleen Aertgeerts**	Dart Neuro-Science	Integrative methods to facilitate structure-based GPCR drug discovery
Tuesday Morning, May 5			
			SPONSORS (Chair: Dan Santi)
9:00	**Daniel Santi**	UCSF/Pro Lynx	A chemical approach to half-life extension of therapeutics
9:20	**Mathias Rickert**	Rinat Laboratories- Pfizer, Inc.	Production of soluble and active microbial transglutaminase for site-specific antibody drug conjugation in *Escherichia coli*

9:40	**Craig Muir**	Third Rock Ventures	Cytomx, Global Blood, Myokardia, allostery and FibroCO; innovation, patient focus and assiduosity since 2010
10:00	**Christian Cunningham**	Genentech Inc.	USP30 and Parkin homeostatically regulate atypical ubiquitin chains on mitochondria
10:20	**Break**		
10:40	**Wayne Fairbrother**	Genentech ,Inc.	Targeting Bcl-2-family proteins
11:00	**Ute Hoch**	Nektar Therapeutic	Etirinotecan pegol: Teaching an old dog new tricks
11:20	**Joshua Salafsky**	Biodesy, Inc.	Detecting and distinguishing conformations sensitively by second-harmonic generation (SHG) for drug discovery and basic research
11:40	**Glen Spraggon**	GNF	The structure and design of LDK378 (Ceritinib): A potent anaplastic lymphoma kinase inhibitor
Tuesday Afternoon, May 5			**Nucleic Acids and Nucleic Acid Binding Proteins and Evolution (Chair: John Tainer)**
16:30	**David Millar**	TSRI	Functional coordination during DNA polymerase activity
16:50	**Ian MacRae**	TSRI	Structural mechanisms in RNA silencing
17:10	**Jamie Williamson**	TSRI	Combined EM and MS studies of ribosome assembly
17:30	**Floyd Romesberg**	TSRI	A semi-synthetic organism with an expanded genetic alphabet
17:50	**Break**		
			Chemical Biology Chair : Jack Taunton)
18:10	**Phil Dawson**	TSRI	Chemical ligation and bioconjugation, addressing large protein targets.
18:30	**Dennis Wolan**	TSRI	Chemical-based interrogation of the human gut microbiome
18:50	**Jack Kirsch**	UCB	Can the effect of an arbitrary mutation on the catalytic activity of an enzyme be predicted?
19:10	**Jack Taunton**	UCSF	Substrate-selective modulators of protein secretion

Wednesday Morning, May 6			**Computation, Health and Disease (Chair: Andrej Sali)**
8:50	**Ryan Hernandez**	UCSF	Population genomics of health and disease
9:10	**Steven Brenner**	UC Berkeley	Diagnostic role of exome sequencing in immune deficiency disorders
9:30	**Robert Fletterick**	UCSF	Inhibiting androgen receptor
09:50	**Break**		
10:10	**Gabriel Lander**	TSRI	Investigating the machinery of cellular homeostasis by multiscale imaging
10:30	**Arthur Olson**	TSRI	What's up with docking?
11:00	**Ian Wilson and Andrej Sali**		**Closing Remarks**

In order to protect individual rights and promote discussion, it is a requirement of the Scripps-UCSF Cabo WMEN Annual Meeting on Structural Biology Conference that no information presented is to be used or disclosed without the specific approval of the disclosing party. Each attendee of the Conference agrees that any information presented, whether in a formal talk or discussion, is a private communication from the individual making the contribution and is presented with the restriction that such information is not for public use. Each member of a Conference acknowledges and agrees to these restrictions as a condition of attending the Conference.

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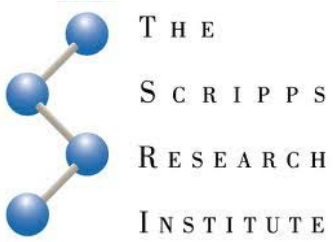
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The following pages are summaries of presentations and comments on the meeting and venue.

WMEN Conference
San Jose del Cabo

For more information, contact:

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Presentation: I presented our work developing novel validation tools for de novo models built using data from high-resolution electron cryomicroscopy. We used side-chain-directed sampling of map values in combination with prior knowledge about the physical constraints on side chain orientations to develop a statistic, called the EMRinger score, which is able to sensitively report on the agreement of backbone positioning between the model and the experimental data.

Impressions: I really enjoyed the meeting. In particular, I appreciated that everyone presented their research. Having the students speak first meant that it was easy to start conversations with everyone at the meeting. I also really appreciated seeing the range of research on display, both from the academic participants and also from the corporate sponsors of the event. The environment was fantastic, both due to the small size of the meeting and the beautiful location.

Name: Steven E. Brenner
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Overview: I am a computational biologist and Professor at the University of California, Berkeley, with an adjunct appointment at UCSF. My research includes exome analyses for diagnoses and disease discovery, sequence and homology analysis for protein function prediction, protein structure analysis, genome-wide splicing studies, and exploring alternative splicing and the regulation of gene expression via splicing and RNA surveillance.
Interpretation of human genome and metagenome variation
In the early 1990s I trained in the world's first genome laboratory, overseen by Walter Gilbert, who proposed that by 2040, one could

envisage newborns' genomes being routinely sequenced. As the sequencing of individual genomes became a reality, I re-entered the field of genome sequence analysis, aiming to understand what was needed to interpret individuals' genetic variation. In particular, I have been analyzing the genomes of newborns with undiagnosed disease, and using the sequencing information to correctly diagnose them sometimes a decade before they would have received correct diagnoses otherwise (if ever). I currently lead the analysis for the NBSeq project to explore whether genome sequencing at birth from dried blood spots can be used as an effective contributor for newborn screening for metabolic disorders. My group has also explored the metagenome, having contributed to the Sorcerer II Global Ocean Sampling project; more recently we focused on implications of the human microbiome for disease.

I co-chair the Critical Assessment of Genome Interpretation (CAGI) (https://genomeintrepretation.org) project, which aims to establish and advance the state-of-the-art in genome interpretation. Our group also has an interest in genetic data sharing and privacy.

Gene regulation by alternative splicing and nonsense-mediated mRNA decay; transcriptome regulation

Nonsense-mediated mRNA decay (NMD) is a cellular RNA surveillance system that recognizes transcripts with premature termination codons and degrades them. We discovered large numbers of natural alternative splice forms that appear to be targets for NMD, and we have seen that this is a mode of gene regulation. All conserved members of the SR family of splice regulators have an unproductive alternative mRNA isoform targeted for NMD77. Strikingly, the splice pattern for each is conserved in mouse and always associated with an ultraconserved or highly conserved region of perfect identity between human and mouse. Remarkably, this seems to have evolved independently in every one of the genes, suggesting that this is a natural mode of regulation. We have used RNA-Seq to explore the pervasiveness of NMD in numerous species and to understand its behavior, finding that 20% of expressed human genes make isoforms targeted for degradation. We are now detailing the evolution of this gene-expression regulation mechanism, having initially discovered that the oldest known alternative splicing is for regulation, targeting transcripts for degradation.

We have collaborated with many others on RNA regulation analyses. Within the modENCODE consortium, studied comparative transcriptomes115, and we discovered the repertoire of targets for alternative splicing in the fly, as well as unexpected relationships between the development of fly and worm.

Prediction of protein function using Bayesian phylogenetic function prediction

We are awash in proteins discovered through high-throughput sequencing projects. As only a minuscule fraction of these have been experimentally characterized, computational methods are widely used for automated annotation. Unfortunately, these predictions have littered the databases with erroneous information, for a variety of reasons including the propagation of errors and the systematic flaws in BLAST and related methods. In collaboration with Michael Jordan's group, we have developed a statistical approach to predicting protein function that uses a protein family's phylogenetic tree, as the natural structure for representing protein relationships. We overlay on this all known protein functions in the family. We use a model of function evolution to then infer the functions of all other protein functions. SIFTER was recently honored as the best-performing sequence-based method in the Critical Assessment of Function Annotation, performing at in the top few of dozens of competitors in both 2013 and 2015. To provide broader access to this method, we established webserver with predictions on millions of proteins. We are also experimentally validating the function predictions, with a focus on the Nudix family

Protein evolution and structure

I was an original author of the SCOP: Structural Classification of Proteins database, which comprehensively organizes protein domains by their evolutionary and structural relationships7. While the original database has now been retired, I have augmented and continued development of this resource with the ASTRAL and SCOPe databases (http://scop.berkeley.edu). I have used these resources to understand progress in structural biology, and to interpret evolutionary relationships. I have also been engaged in developing new methodologies.

Presentation: I discussed an analysis protocol developed in my lab for individual genome interpretation and used its distinctive features to diagnose numerous clinical cases. We applied the

protocol to exomes from patients with undiagnosed primary immune disorders, with a particular focus on infants with absent or low T cell receptor excision circles (TRECs), a marker for T-cells, at birth. To yield high quality sets of possible causative variants, we used multiple callers with multisample calling and integrated variant annotation, variant filtering, and gene prioritization.

Our first cases involved two unrelated infant girls with low TRECs at birth that were not eligible for a bone marrow transplantation because no abnormalities were found in genes related to severe combined immunodeficiency (SCID). We discovered compound heterozygous variants in the ATM gene for both the infants. After clinical confirmation, this discovery offered a very early diagnosis of Ataxia Telangiectasia (AT), allowing for avoidance of undue irradiation and live vaccinations as well as revealing a new potential role for TREC screening in AT diagnosis.

In another case, the affected siblings had early onset bullous phempigoid, a chronic autoimmune disorder. Our analysis revealed compound heterozygous mutations in ZAP70, a gene associated with profound primary immunodeficiency, the opposite phenotype. Cellular immunological studies indicated that one variant was hypomorphic and the other was hyperactive. These combined to yield a novel presentation, adding to the existing phenotype repertoire of ZAP70 in humans. Our analysis protocol focuses on genomic features that may be overlooked by other methods.

In the case of a female with severe influenza pneumonia, our annotation tool, Varant, flagged variants in PRKDC apparently occurring after the genomically encoded stop codon. This stop codon in the reference genome was correctly identified as premature due to a rare single base deletion. But accounting for the proband being normal at this position, we correctly annotated the proband's two variants as nonsynonymous mutations likely causative for the phenotype.

Our protocol has been similarly revealing in other SCID and CID cases which highlight unique features of the analysis framework that facilitate genetic discovery. These help provide crucial information to offer prompt appropriate treatment, family genetic counseling, and avoidance of diagnostic odyssey.

I also briefly discussed plans for evaluating sequencing in

newborn screening, as well as the importance that structural genomics has had in allowing us to interpret genomic variation

Impressions: The WMEN meeting in Cabo was excellent in terms of size and duration; large enough to have enough strong diversity of science but small enough that there was time to speak with nearly everyone in the group. The attendees and presents were consistently outstanding.

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Presentation: My research focuses on the molecular and structural properties governing the transcription and replication of viral RNA. My projects include understanding the role of the Ebola virus matrix protein (VP40) in controlling transcription and replication, likely through binding to specific Ebola mRNAs. I am also working on a better understanding of the role of the viral polymerase co-factor called the phosphoprotein for Nipah virus and VP35 for Ebola virus. I am using a combination of approaches including x-ray crystallography, biochemistry, minigenome assays, RNA sequencing and quantitative PCR.

Impressions: This was an excellent opportunity for me to meet and interact with scientists in similar field both at Scripps and at other institutes/companies. The location of the conference was very nice and provided ample opportunities for scientific discussions. The talks were all very interesting and thought provoking. I was able to talk about my research and get ideas from my fellow scientists. Thank you so much for this opportunity!

Name: Sandip Chatterjee
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Presentation: A comprehensive database and search method for microbiome metaproteomics.

Impressions: The meeting was very well organized and the talks were excellent in quality, overall. The breadth of presenters' research was nice to see, and added some variety to the meeting. The meeting was just the right size -- small enough to encourage close interactions with other attendees but large enough to offer some diversity of background, research, and experience in various fields.

Name: Peter Cimermancic
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Presentation: My research focuses on finding small-molecule modulators of large cellular macromolecular assemblies. I develop and use computational tools that aid virtual screening against targets, whose structures were determined at lower resolutions, and whose binding sites are flexible and cryptic. At the meeting, I presented our progress in identifying and developing allosteric small-molecule modulators of the proteasome.

Impressions: Excellent meeting! I really liked the quality and lengths of the talks, time for socializing between and after the sessions, and the presence of speakers from industry. No changes needed to the meeting format.

Name: Philip Dawson
Department: Department of Chemistry, TSRI
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Overview: My laboratory focuses on the development of methods for the chemical manipulation of peptides, proteins and other

complex biological macromolecules. Our goal is to mimic structures found in Nature to better understand their structure and function and to enhance the biological and physical properties of proteins through highly chemoselective chemical ligation and bioconjugation reactions. We apply these tools broadly in immunogen design, nanoparticle functionalization, protein medicinal chemistry and an array of biophysical studies on protein structure-function.

Presentation: Starting with a low affinity hit from a peptide phage display library against the ephrin receptor EphA4, we have synthesized a series of macrocyclic peptides that are potent antagonists of the EphA4. Inhibiton of this receptor has been shown to be efficacious in rat models of ALS presumably acting through inhibition of the negative regulation that EphA4 exerts on nerve growth. The structure based optimization of this peptide for affinity and pharmacology was presented.

Impressions: This is an excellent meeting with an exceptional mix of exciting talks that present important questions and results. The setting of the meeting facilitates interactions between the faculty, students and industrial participants in a way that is not mirrored by any conference that I attend. I look forward to participating again.

Name: Ashok Deniz
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Overview: My lab develops and utilizes novel and state-of-the-art single-molecule fluorescence approaches to tackling key questions in protein biophysics. A recent focus has been to use these techniques to understand the structural biophysics of disordered proteins that are important in a wide array of cellular functions, but whose complexity presents challenges for conventional methods.

Presentation: I spoke about our recent studies of a disordered protein, whose cellular function have been linked to its switchable structural state. By using single-molecule fluorescence and complementary techniques, we discovered a complex mechanism

by which this protein transitions between its multiple structural states, with important implications for its regulation and cellular function.

Impressions: The size of the group - optimal
Location of the meeting - excellent
Attendees and presenters - excellent
Length of the meeting - optimal

The size of the group and length and format of the meeting were optimal. Together with the high quality and diverse science of the attendees and nice location, the meeting provided an outstanding venue for exchange of cutting-edge information and ideas, and sparking collaboration.

Name: James Fraser
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Overview: My group uses two complementary approaches to study the relationship between protein conformational ensembles and function. To dissect consequences of mutations on organismal fitness, we use high-throughput systems biology and biophysical methods to analyze large sets of clinically or biophysically interesting mutations. To improve our ability to engineer new protein functions, we investigate changes to the conformational ensemble as new enzymatic and binding functions emerge from directed evolution studies.

Presentation: I described the work of UCSF graduate students in a project-based course called Physical Underpinnings of Biological Systems (PUBS) that is required for all incoming first year iPQB and CCB graduate students at UCSF. The students work in teams developing a project that incorporates deep sequencing-based mutational profiling, automated microscopy, and computational biology to investigate the fitness effects of combinations of mutations and chemical perturbations.

Impressions: This is my favorite meeting and I try to attend every year. It is great to catch up with the Scripps folks and hear about the exciting developments from our industrial colleagues. The contacts that I have made at this meeting are amazing.

Na**me: Courtney French**
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Presentation: Many alternatively spliced isoforms contain a premature termination codon that targets them for degradation by the nonsense-mediated mRNA decay RNA surveillance system (NMD). Some such unproductive splicing events have a regulatory function, whereby alternative splicing and NMD act together to impact protein expression. We have performed RNA-Seq analysis on cells where NMD has been inhibited and found that 20% of the genes expressed in HeLa cells produce alternative isoforms that are degraded by NMD. We found that the 50nt rule is a strong predictor of NMD degradation while 3' UTR length has little global effect. Based on an extensive literature analysis, we have also produced a model of known splice factor regulatory interactions. Protein-RNA interactions are extensive and most tested cases reflect auto- and cross-regulation through splicing and NMD, yielding a robust network. We see little evidence of a hierarchy with master regulators of splicing.

Impressions: I greatly enjoyed the meeting! Many of the topics were a bit outside my area of research and so I learned a lot. I was particularly interested in hearing about the clinical applications of molecular engineering. Overall, I thought the size, location, and organization of the meeting were great and facilitated many interesting discussions.

Name: Ryan Hernandez
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Overview: Another great meeting. Less organized at airport than years passed left many from UCSF scrambling to figure out what to do.

Presentation: They were all great!
Impressions: Overall, great meeting.

Name: Jonathan Hulce
Supervisor: Cravatt
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Presentation: N-hydroxyhydantoin carbamate inhibitors of mammalian serine hydrolases

Impressions: Meeting was great, mostly high impact presentations, short talks may be very difficult to give for non-structural attendees; perhaps would benefit by inviting more faculty/students who are not directly structural biologists but have a strong structural component to their research.

Name: Jennifer Kefauver
Supervisor: Andrew Ward and Ardem Patapoutian
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Presentation: Compositional Heterogeneity in Swell1, the volume-regulated anion channel.

The mammalian volume-regulated anion channel (VRAC) is a ubiquitous chloride channel responsible for releasing chloride ions upon hypo-osmotic stress, preventing the cell from bursting. The five members of the LRRC8 family, renamed Swell1, were recently discovered to be components of VRAC. The landscape of potential VRAC heteromer variety is enormous. My project will utilize molecular biology (e.g. CRISPR knock-out cell lines), biochemistry (e.g. separation by size and isoelectric point), and cryo-EM data processing (e.g. 3D classification) to characterize structural variations that arise from these different potential combinations of Swell1 subunits.

Impressions: This meeting was incredibly valuable and informative. I enjoyed the broad coverage of biological topics and

structural techniques by the presenters. Most of all, the small group size allowed great conversations about science and career, and ideas from the professors in this group have already resulted in phenomenal progress in my project.

Name: Jack Kirsch
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Overview: I love this meeting. It is the only one that I am sure to attend each year. The talks are well prepared, and the discussions informative. I attend all sessions. This year's venue was the best yet. The food and accommodations were superb, and made up for the relative isolation from the town.

Presentation: I presented computational work with UCB undergraduates showing that the effect of an arbitrary mutant introduced anywhere in an enzyme on the catalytic activity could be predicted with a high degree of confidence. The effect of distance from the active site decreases generally as the cube.

Impressions: See overview

Name: Gabriel Lander
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Overview: Our group is interested in determining the structural mechanisms that are involved in neuronal homeostasis, which includes cargo transport within neurons, and role of the ubiquitin-proteasome pathway in mitophagy. We utilize cryo-electron microscopy and image processing methodologies to determine the structures of the complexes involved in these systems, in order to better understand their molecular mechanisms.

Presentation: I briefly presented the structural organization of the dynein-dynactin microtubule motor complex that was solved using

a combination of 2D and 3D analyses. These data show the structural constraints that dynactin imposes on dynein in order to induce a unidirectional processive motor. I also presented a recent high resolution structure of the 26S proteasome lid complex, which shows the mechanism of auto-inhibition of the deubiquitinase during assembly of this complex.

Impressions: As usual, I enjoyed the format of the meeting and I think that the size is appropriate and setting is conducive to discussion.

Name: Marco Lolicato
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Presentation: Activation of a human ion channel by physical forces.
I'm interested in the K2P potassium channel family. K2P channels operate as background leak channels; they are open at rest, so that under physiological conditions, a potassium gradient across the cell membrane causes an efflux of potassium ions, setting the resting potential of the cell at a negative value.
K2P channels are sensitive to many physical forces (such as temperature, pH and stretch), but the mechanism of their modulation is till unclear.
With structural and biophysical approaches I am trying to address this fundamental question.

Impressions: Great meeting: great talks and perfect location.

Name: Ian MacRae
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Overview: My research focuses on understanding and harnessing gene-silencing processes in humans. We are taking a structural approach towards understand mechanisms of gene-silencing mediated by small RNAs (microRNAs, siRNAs and piRNAs), with the goal of illuminating novel approaches for the treatment of human disease.

Presentation: We determined high-resolution crystal structures of the protein Argonaute2, the core protein subunit of RNA Induced Silencing Complexes (RISC) found abundantly in human cells. Analysis of these structures revealed how Argonaute binds to miRNAs and uses the encoded sequence information to identify and silence target messenger RNAs. The application of these insights towards the development of miRNA inhibitors and chemical modifications that improve siRNA delivery will be presented at the next Cabo meeting.

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

The small size of the meeting, intimate setting, and the high quality of presentations provided an outstanding environment for establishing new connections between the participants. This meeting provides a unique and valuable avenue for creating new ideas and forging unanticipated collaborations.

Name: Bryan Martin
Supervisor: Kurt Wüthrich
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Presentation: My research presentation focused on the structure determination of the Octamer Repeat (OCRE) of RBM10 by solution state NMR. The structure of the tyrosine-rich domain involved in the spliceosome was found to have a novel fold composed of a six-stranded anti-parallel β-sheet. We propose that the fold is stabilized by four evolutionary conserved "lock" residues (two tyrosines, a tryptophan and a proline), which are involved in hydrophobic and aromatic-aromatic interactions. Further, the high frequency of tyrosine in the sequence results in many phenol

groups exposed to the solvent, which may be important for mediating protein-protein interactions.

Impressions: I enjoyed the meeting very much and found the ratio of students/postdocs to PIs made it very open for conversations to happen across all levels. I was interested in the sponsor presentations more than I had anticipated and enjoyed talking with some of the representatives at the meeting as well. Overall, I thoroughly enjoyed the experience and see no issues to be addressed in the future.

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Overview: My laboratory is engaged in the development and application of single-molecule fluorescence spectroscopy for studies of bimolecular dynamics. Current projects include (i) mechanisms of GPCR activation, (ii) trafficking of HIV-1 RNA, and (iii) functional coordination during DNA polymerase activity.

Presentation: I described how the three distinct enzymatic activities of bacterial DNA polymerase I are physically coordinated to achieve accurate and efficient DNA replication. Specifically, I described a single-molecule FRET assay to monitor the physical movement of the DNA substrate between the spatially distinct pol and 3'-5' exo sites during the transition from polymerization to proofreading activity, revealing that the enzyme and DNA remain associated during this transition. I also described a smFRET assay that monitors the location of the flexibly tethered 5' nuclease domain during each mode of enzymatic activity. Overall, the results reveal the global rearrangements of the enzyme-DNA complex that mediate the conversion from one mode of activity to another.

Impressions: This meeting gets better and better each year and is still vibrant after 25 years. I continue to attend this meeting for the high quality of the science and the informal atmosphere that encourages discussion. While the meeting room facilities were

good, I was disappointed by Hotel Secrets. The location is too isolated. I prefer the hotels closer to San Jose del Cabo.

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Overview: The WMEN meeting is generally one of the most enjoyable and informative meetings that I attend. This year's meeting met such expectations. I appreciate the broad molecular focus of the meeting and the diversity of participants from both academic and industrial labs. The 5-minute presentations are particularly notable. They set the tone for the meeting and facilitate follow up conversations with the postdocs and students.

Presentation: The origins of mechanical and thermal detection in the nervous system remain unclear. I presented recent studies from my laboratory on a prototype mechano- and themo-sensitive ion channel family (the TREK family of K2P potassium channels). These included the development of a novel TREK-1 agonist small molecule and structural studies that reveal the deformations of the protein that are associated with activation by both pressure and temperature.

Impressions: It was a fantastic meeting. The relaxed setting is perfect for helping to foster discussions with the participants. The organizers really do a terrific job putting together this meeting.

Name: Arthur Olson
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Overview: My laboratory focuses on computational structural biology. We develop and apply software for molecular modeling, docking, and visualization. Our main software development is in the area of molecular docking, virtual screening and building

models of molecular environments. Our current main application area is in modeling and analysis of molecular interactions in HIV and the evolution of drug resistance.

Presentation: My talk this year was entitled "Envisioning the Visible Molecular Cell." In it I described the current work in my lab, in collaboration with that of Graham Johnson at UCSF, in advancing the capabilities of the cellPACK software suite, and its application to modeling the mature and immature HIV virion.

Impressions: As usual, a great scientific meeting with excellent talks, and sufficient time for informal discussion. The new hotel surpassed all previous venues with regard to hotel amenities. However its location was more isolated than previous venues -- which had both good and bad aspects.

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Presentation: My research focuses on developing a peptide antagonist for the transmembrane tyrosine kinase receptor EphA4. EphA4 activation causes neuronal cell death and has been identified as a therapeutic target in neurodegenerative diseases such as ALS as well as brain and spinal cord traumatic injury. We aim to iteratively improve the therapeutic properties of a peptide antagonist preliminary hit from phage display using all the chemical diversity available through solid-phase peptide total synthesis. We have to date achieved low nanomolar inhibitory potency and high stability in serum.

Impressions: The meeting was wonderful and extremely educational. The faculty talk length was appropriate and the breadth of fields covered was quite impressive. I though the size of the meeting was excellent for getting to meet a majority of the other presenters. I really enjoyed interacting with the attendees from industry as well as the academic PIs in an informal setting. And, of course, the location was simply phenomenal! I thought the meeting was very well organized; the only minor suggestion I

thought of was that the talks might benefit from a green/yellow/red signal from the moderators. Overall, I had a fantastic time and learned quite a lot!

Name: Takanori Otomo
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Overview: Research in my group aims at understanding the structural and biochemical mechanisms of autophagy and its underlying regulation. We are particularly interested in the protein complexes that directly mediate the formation of the double-membraned vesicles called autophagosomes. We combine X-ray crystallography, NMR spectroscopy, and electron microscopy to determine the structure of these proteins and their complexes. Our goal is to provide sufficient details at atomic resolution to help explain how the concerted action of autophagy-related proteins generates the vesicles as well as how autophagosomes sequester selective cargo for degradation. We hope our finding will have direct impact on rational development of therapeutics targeting autophagy for cure of human diseases, such as cancer and neurodegeneration.

Presentation: I presented our crystal structure of the human ATG12-ATG5-ATG16 complex, which functions as the E3 factor for the lipidation of the ubiquitin-like protein ATG8. Our results explain how this E3 factor is built to exhibit its function, solving a long-sought mystery of the role of the conjugation between ATG12 and ATG5. We have also characterized how the E3 interacts with the E2 enzyme ATG3, highlighting the structural uniqueness of this E2-E3 pair. Our next goal is to understand how the E3 stimulate the transfer of ATG8 to phosphatidylethanolamine.

Impressions: The meeting provided a great opportunity to learn more about both institutions as well as some others. There were also opportunities to interact with various people who we normally do not meet. Overall this was a fantastic meeting.

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Overview: Our group investigates biological roles of glycans as information containing molecules, in particular glycans that serve as receptors for human pathogens such as influenza virus, and as ligands for immune cell receptors that recognize glycans on cell surface glycoproteins of other cells as a means of detecting self to modulate immune cell function.

Presentation: This year I presented our progress in designing nanoparticles decorated with glycan ligands of the Siglec family of immune cell receptors for in vivo targeting of immune cells that express the corresponding siglec. To date, we have been successful to develop specific ligands for 11 of 23 human and murine siglecs. Examples of in vivo targeting nanoparticles to macrophages, lymphoma cells and normal B cells were used to illustrate the power of exploiting this platform to elucidate the roles of siglecs in modulating immune cell signaling, and to exploit their functions to control immune responses.

Impressions: The unique balance of student, principle investigator and biotech/pharma attendees was stimulating as always. The science was outstanding, and the social interactions facilitated by the relaxed setting were terrific. One of my favorite events of the year.

Name: Floyd Romesberg
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Overview: My lab works on various aspects of understanding and manipulating evolution. About 1/4 of my group is focused on developing novel approaches to antibiotic discover. About 1/4 works on understanding the biophysical consequences of the mutations that are introduced into proteins during their evolution.

About 1/4 works on evolving DNA polymerases top recognize modified substrates. And about 1/4 works on developing an unnatural base pair that can be replicated, transcribed, and translated in living cells, which is what I presented at the most recent meeting.

Presentation: My presentation was titled "A semi-synthetic organism with an expanded genetic alphabet." We have recently developed an organism that stably replicates DNA with three base pairs (the natural two plus a third unnatural base pair that we have developed in my lab) and which transcribes it into RNA.

Impressions: This is the best meeting that I go to every year. The format with short talks allows a lot of topics to be covered and a nice overview of what all of my colleagues are working on. Its great to see year-to-year big picture progress without getting bogged down in details. Details are great for a handful of talks, but this meeting is unique in that it allows you to get an overview of what everyone is doing. The science is also spectacular. The numbers were fine.

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Presentation: The focus of my research is structural and functional analyses of mechanisms of regulation of nuclear receptors SF-1 and LRH-1 (NR5As). Our recent work revealed that signaling lipids PIP2 and PIP3 bind NR5As and regulate their activity. The crystal structure of PIP3-SF-1 complex defined a new regulatory surface organized by the bound PIP3 hormone. This surface harbors a cluster of human SF-1 mutations that lead to endocrine disorders. Our work explains how these puzzling mutations cripple SF-1 activity. We propose that the newly defined regulatory surface acts as a PIP3-mediated interface between NR5As and their co-regulatory binding partners.

Impressions: The size and the format of the meeting could not be better!

The PI's talks were both informative and thought provoking, and the sponsor's presentations felt truly inspirational.
I would recommend no changes in the meeting.

Name: Andrej Sali
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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: To understand the cell, we need to know the structures of its macromolecular assemblies. Determining these structures generally requires pure samples of the studied assemblies. Here, we describe how to compute spatial restraints on macromolecular assemblies from genetic interaction data determined by cellular assays and how to use these restraints for integrative structure determination of macromolecular assemblies. Benchmarks indicate that genetic interactions can be comparable in their utility to a sparse set of chemical cross-linking data.

Impressions: Informative and enjoyable!

Name: Daniel Santi
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Overview: I presented an overview of ProLynx, a biotech company I co-founded. The company develops technology for half-life extension of drugs-small molecules, peptides and proteins.

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.

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: 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: The crystal structure of human Argonaute2

Impressions: Loved it! Really liked that we got to interact with the sponsors, and that the sponsors all gave research talks.

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Supervisor: Ian MacRae
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Presentation: "Structural studies of higher-order miRNA-induced silencing complexes"

MicroRNAs (miRNAs) are small regulatory RNAs that function in a wide array of mammalian processes that underlie cardiovascular health and pathology. miRNAs function from within large ribonucleoprotein complexes that coordinate the repression and degradation of targeted message RNAs (mRNA). At their core, these silencing complexes contain the proteins Argonaute (Ago) and a member of the TNRC6 family of proteins. TNRC6 binds to Ago and recruits mRNA degradation factors to targeted messages. Despite the important role of miRNAs in human biology, the assembly and structure of the large silencing complexes in which they function are poorly understood. Previously, it has been shown that tryptophan residues located in the TNRC6 Ago Binding Domain (ABD) are necessary for binding to Ago. Current work has revealed that three tryptophan-binding pockets located within the PIWI domain of Ago mediate the recognition of these tryptophan residues on TNRC6. We have characterized these pockets and will determine their relative contributions to TNRC6 recruitment, as well as their role in miRNA silencing. The multivalent nature of the Ago-TNRC6 interaction likely contributes to the formation of diverse higher-order silencing complexes, whose structural and mechanistic characteristics are topic for future work.

Impressions: The meeting was a great forum to interact with leaders, students, and post-docs alike in both similar and diverse disciplines. The smaller size provided an excellent space to

pursue active scientific dialogue in a one-on-one, highly interactive environment. I found it to be an excellent experience. The venue was more than adequate, though the resort was very isolated from the town. It may be nice to be closer to other activities in the future.

Name: Glen Spraggon
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Overview: As part of the Novartis Institute of Biomedical Research (NIBR), the Genomics Institute of the Novartis Research Foundation (GNF) focuses on the discovery of new molecules and technologies to address unmet medical needs.

My group is focused on the design of novel small molecule and protein based therapeutics using structure and computation to guide the innovation. The projects that take place within the group range from the optimization of protein properties guided by structure, via protein engineering, to the development of bioactive organic molecules by structure-aided drug design. These activities are closely coupled with the adoption and development of new technologies to further enable these endeavors.

Presentation: Anaplastic Lymphoma Kinase (ALK) is an oncogenic receptor tyrosine kinase associated with various cancers via somatic and germline mutations which induce a constitutively active protein. Utilizing structure, high throughput screening and medicinal chemistry expertize, it was possible to design a specific and potent ALK inhibitor, LDK378, which inhibits the enzymatic mechanism of ALK. The molecule has been effective in provided a treatment for victims of ALK mediated non-small cell lung cancer. Cancer is an evolving disease where point mutations at various residues within the ALK kinase domain can induce resistance to drugs. High-resolution structures of inhibitors with ALK provide insight into the mechanisms of this resistance and afford the potential to personally tailor small molecule treatment to the evolution of the cancer.

Impressions: The WMEN conference was an ideal venue for scientific discussion, the size of the meeting and the format was

extremely conducive to the exchange of information and the cross-fertilization of ideas across the many scientific disciplines represented by the participants.

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Presentation: Deconvolution of selection pressures in overlapped genes: The story of Tat and Rev

Impressions: I thought the meeting was great. I talked to many interesting people, and learned a great deal about the various scientific projects going on. I would have liked to have seen a more inter-disciplinary meeting in terms of the type of science that is being presented. This year seemed a little overly heavy on the structural biology side. All-in-all, it was great.

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Overview: The project I described was titled 'The mechanism of transmembrane secondary Transporters as therapeutic targets for small molecule and antibody therapeutics'. The work from my laboratory discussed the mechanisms that determine correct targeting of membrane proteins and receptors, highlighted by the structural determinations of membrane protein structures at high resolution by X-ray crystallography. Particularly, I discussed the the Calcium proton antiporter, a eukaryotic phosphate transporter, and a glucose transporter GLUT1 bound to drug leads, and to ctyochalasin B**.**

Presentation: The mechanism of transporters was described in reference to a high-resolution structure of the eukaryotic transporters VCX, PiPT and GLUT1. The structure of these, were

presented and revealed a partially opened pore that enables substrate binding and release. These structures lead to a mechanism by which secondary transporters work, and shows that we can inhibit their activity and so block, for example glucose uptake by cancer cells that are highly dependent on glucose. The general mechanisms require conformational changes and thus antibody therapeutics we have shown to block their action.

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Presentation: My project deals with the development of small molecule activity based probes for profiling gut microbial proteins. In particular, we're interested in identifying bacterial proteins capable of degrading the human mucosal lining that physically separates hosts from their microbiota. We hypothesize that in patients with inflammatory GI disorders, there will be key alterations in the proteomic repertoire of mucus degrading proteins that plays an important role in infiltration and ultimately progression from a healthy to a diseased state. We are currently synthesizing and validating small molecule sulfatase inhibitors and non-hydrolyzable sialic acid mimetics.

Impressions: Though structural at its core, I found that the expansion of subject matter to other areas enlightening. For example, even though I had trouble fully following the bioinformatic presentations, they opened my eyes to all the new tools available to non-specialized audiences. There were also interesting novel works that I would probably not have found on my own. Personally, I thought Libby Getzoff's UV sensing protein was particularly interesting especially in light of all the radical chemistry I have been delving into. The setting for the meeting was similar to the previous year. The only thing that was different was the absence of an outside reception on the first night that might have helped to facilitate more interaction due to high winds. Overall, it was a great meeting!

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Presentation: I gave a brief overview of the biological subject (tight junctions) and problem I am trying to help solve (determining its 3D structure). Epithelia are cells that define body compartments and organs in vertebrates, helping tissues seal and adhere. Tight junctions, a branched multi-protein complex representing the closest cell-cell contacts known to nature, govern both the barrier and adhesive functions of epithelia. The major facilitators of tight junction formation are a family of integral membrane proteins called claudins, which self-associate in both cis and trans, helping to simultaneously tether neighboring epithelial cells while forming sealing barriers between their paracellular spaces. The goal of my research is to determine the 3D architecture of tight junctions by iteratively elucidating the structures of all of the proteins that comprise them, starting with the claudins and working my way along the tight junction strand.

Impressions: It was a privilege to be able to participate in this year's WMEN Conference. The caliber of researchers, universities, and corporations were unparalleled for such a small meeting. The venue was beautiful, the participants ideally numbered, and overall, the conference was a perfect balance of professionalism and informality. Thanks.

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Presentation: Chemical metaproteomics of the human distal gut microbiota

Impressions: Good content overall. New location was great as well.

Name: Andrew Ward
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Overview: Highly productive meeting with plenty of time for interactions with attendees, including faculty, students, and industry. The presentations were generally high quality with a decent amount of unpublished data. Casual environment was conducive to open discussion.

Presentation: I presented my labs' high resolution cryoEM studies of HIV-1 envelope glycoprotein (Env) in complex with neutralizing antibodies that included several structures in the ~4.5 Angstrom range. I focused on resolvable features including complex glycans, a new frontier in cryoEM. One of these structures was of the transmembrane containing Env, an important missing piece of Env biology.

Impressions: The venue was nice but a bit large, making it difficult to find people in the rather extensive resort after everyone disbursed from the meeting. The meeting was appropriate size. Quality was great and I am looking forward to next year.

Name: James Williamson
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Overview: This was a particularly excellent and exciting meeting, and the quality of the talks continues to improve. This is an excellent mix of structural biology and drug discovery, and

everything in between. There is a good balance between institutions, outside guests, and industry sponsors.

Presentation: The new venue was excellent, the meeting room facilities were as good/better than our previous venue. The accommodations were a step up.

The nucleic acids section was particularly strong this year. In particular, the presentation from Romesberg on the expanded genetic code was a highlight.

Impressions: The quality of the short presentations from the students and postdocs is superb, and is a great way to start off the meeting. The students/postdocs are easily recognized, and it enables them to participate more fully in the meeting.

The meeting continues to thrive!

Name: Ian A. Wilson
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Overview: My lab is focused on recognition of microbial pathogens by the immune system, particularly HIV-1, HCV, and influenza virus. We have determined many antibody structures and complexes and are using many of these for structure-assisted vaccine design for flu, HCV and HIV-1. I also direct one of the NIH PSI high throughput structural biology centers that have developed methods and technologies that are being used to advance structure determination by X-ray and NMR.

Presentation: The major surface antigen, the hemagglutinin (HA), of influenza virus is the main target of neutralizing antibodies. However, most antibodies are strain-specific and protect only against highly related strains within the same subtype. Recently, a number of antibodies have been found that are much broader and neutralize across subtypes and groups of influenza A, as well as influenza B, viruses through binding to functionally conserved sites. We have determined x-ray structures of broadly neutralizing antibodies with the HA and have identified highly conserved sites in the HA fusion (stem) in influenza A and B. We have also structurally characterized

antibodies that bind to the conserved receptor binding site and protect against different strains and subtypes. The identification and characterization of these exciting new antibodies provide new opportunities for structure-assisted vaccine design as well as potential therapeutics that afford greater protection against influenza viruses.

Impressions: Excellent as always with an exceptional mix of academia and industry. A terrific overall program with great opportunities to meet and interact with a diverse set of participants. The students and postdocs excelled in their short presentations and the keynote speaker Sasha Kamb was a highlight. The temporary new location for this year worked well, and the rooms and conference center were excellent.

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Overview: The overall goal of our research is to elucidate the roles that commensal microbiome bacterial proteins play in human health and disease, and apply this knowledge towards development of innovative antimicrobial chemical and biological therapies. My laboratory employs an array of biochemical, cellular, biophysical, and high throughput screening methodologies in the identification of the diverse assortment and types of bacterial proteins that are produced within normal and diseased human distal gut microbiomes, in the development of small molecules as probes to elucidate essential commensal bacterial proteins, and as novel therapeutics to modulate the activity of important enzymes in microbiome-related pathogenesis.

Presentation: My talk entitled "Chemical-based interrogation of the human gut microbiome" was an overview of the chemical biological, proteomics, and bioinformatic approaches we are developing and applying to survey and quantitate specific bacterial enzymatic functions within the human distal gut. I introduced chemical probes we have designed and used to isolate bacterial proteins with highly reactive active site cysteine residues and the

bioinformatic process of identifying the parental proteins and bacterial species that produce the labeled proteins. I ended the talk by presenting an approach whereby we perform classical biochemical and structural biological methodologies to understand a protease from a known bacterial species found in the commensal microbiome and how we apply new probes based on this biochemical information to interrogate the microbiome components for additional conserved proteins.

Impressions: This was a fantastic meeting as always and I enjoyed having the conference at the new location. There was a great breadth of research topics covered by the talks and is an excellent environment to develop collaborations.

“It was a privilege to be able to participate in this year's WMEN Conference. The caliber of researchers, universities, and corporations were unparalleled for such a small meeting.”
-Alex Vecchio, Ph.D.

> “The meeting was a great forum to interact with leaders, students, and post-docs alike in both similar and diverse disciplines. “
> - Jessica Sheu-Gruttadauria, Graduate Student

“This meeting gets better and better each year and is still vibrant after 25 years. I continue to attend this meeting for the high quality of the science and the informal atmosphere that encourages discussion.”
-David Millar, Ph.D.

> “This meeting was incredibly valuable and informative. I enjoyed the broad coverage of biological topics and structural techniques by the presenters. Most of all, the small group size allowed great conversations about science and career, and ideas from the professors in this group have already resulted in phenomenal progress in my project.”
> - Jennifer Kefauver, Graduate Student

“Excellent meeting! I really liked the quality and lengths of the talks, time for socializing between and after the sessions, and the presence of speakers from industry.”
- Peter Cimermancic, Ph.D.