30TH WORLD MOLECULAR ENGINEERING NETWORK CONFERENCE
SAN JOSE DEL CABO ✵ MAY 2 – 5, 2020

December 9, 2019

The CABO organizers are pleased to invite you to attend the *30th Annual World Molecular Engineering Network (WMEN)* Conference, from **Saturday, May 2nd to Tuesday, May 5th, 2020, featuring Professor James A. Wells as a keynote speaker**. The meeting is hosted by Scripps and QBI at the UCSF School of Pharmacy.

Each year, world-class scientists meet for four days in the seclusion of a beach resort in San José del Cabo, Mexico. About 60 scientists from UCSF and Scripps as well as colleagues from other UC campuses and pharmaceutical / biotechnology industries attend the meeting. Science sessions are held on Saturday evening, Sunday-Tuesday mornings and early evenings. Ample time is available for social and scientific interactions in a relaxed setting. Summaries of presentations and impressions of the meeting provided by participants are published in the attached Cabo Report and on our website at http://salilab.org/cabo.

The annual UCSF-Scripps hosted Cabo conference:

- Began in 1990 to encourage academic-industrial collaborations;
- Focuses on the structure and function of bio-molecules and drug discovery;
- Is judged to be among the "very best meetings attended" by participants;
- Provides a unique opportunity to develop academic/industry interactions.

Faculty attendees are asked to invite one first-rate senior postdoctoral or graduate student to attend the meeting. Company attendees usually make presentations, which have been highlights of the conferences. Pharmaceutical & biotech companies have the opportunity to recruit our best students; our colleagues from the Venture Capital industry meet academic entrepreneurs, and law firms meet prospective clients.

In past years, corporate participants have paid a registration fee of $5,000 per company and covered their travel/hotel expenses. Non-attending sponsors have usually contributed $1,500 to help defray conference expenses. All participants are acknowledged and receive a summary of the meeting. Industry participants are requested to make their check payable to "**Regents of the University of California**" and send it to the attention of **Gina Nguyen**, UCSF, Box 2350, 1700 4th Street, BH-308, San Francisco, CA 94158, or pay by credit card through this link: **https://makeagift.ucsf.edu/qbi**

If you or an alternate from your company wish to participate, let us know at your earliest convenience. For additional details, visit our web site at http://salilab.org/cabo or contact Gina Nguyen at ginat.nguyen@ucsf.edu.

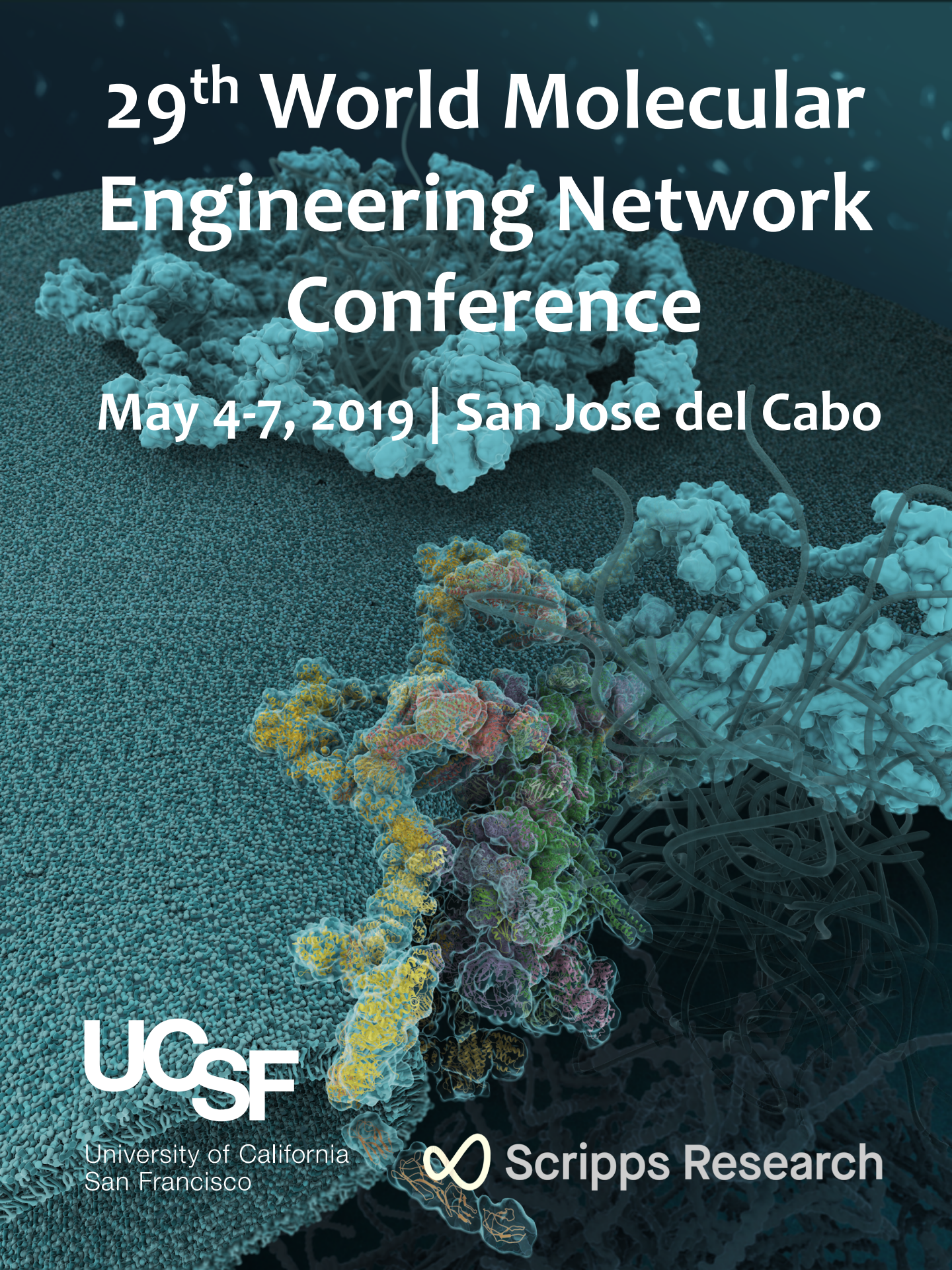
We look forward to hearing from you, and hope you will join us in San José del Cabo.

Sincerely,

Dan Santi, Andrej Sali, Robert Stroud
UCSF Organizers

29th World Molecular Engineering Network Conference

May 4-7, 2019 | San Jose del Cabo



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Our History

The WMEN conference has been held for the past 29 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, sixteen years ago, the venue moved from Cabo San Lucas to all-inclusive resorts in San Jose del Cabo. The 2016 meeting returned to the Hyatt Ziva (formerly Barceló Los Cabos Palace) that was completely renovated after Hurricane Odile in 2014.

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 20-25 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 an always stellar and fun group of participants. We are also extremely grateful to our sponsors whose generous support makes this meeting possible every year.

World Molecular Engineering Network (WMEN) CABO XXIX, May 4–7, 2019

San Francisco / San Ignacio Rooms

Saturday Evening, May 4, 2019			
16:15 – 16:30	**Introduction and Welcome** Ian Wilson and Andrej Sali		
16:30– 17:30	**Keynote Lecture**		
	Robert Stroud	UCSF	Discovery
17:30 – 17:45	**Self-Introductions**	Jill Chrencik	Merck
		Steven Strutt	Global Blood Therapeutics
17:45– 20:30	**Short Presentations (5 + 1 min.) by TSRI , UCSF, UCB, LBNL and Stanford Graduate Students and Postdocs (Chair: Gabriel Lander)**		
	Mengyu Wu	TSRI CA	Cryo-EM: highs, lows, and pursuing allosteric intermediates
	Christopher Cottrell	TSRI CA	Targeting the HIV fusion peptide
	Rotimi Omorodion	TSRI CA	Structural evolution of anti-HIV broadly neutralizing antibodies
	Karthik Gangavarapu	TSRI CA	Genomic epidemiology of West Nile virus in the United States
	Janice Xu	TSRI CA	Fishing out Pd_dinase, a commensal gut bacterial protease, and homologues from the microbiome
	James Ferguson	TSRI CA	Using ^{19}F-NMR to observe different states of transthyretin mutants
	Ke Yang	TSRI CA	Structure and dynamics of a viral transcription factor HTLV-1 HBZ
	Angelo Solania	TSRI CA	Structural characterization of the prime side of caspases using ketone inhibitors
	Gabriel Brighty	TSRI CA	Discovery of a new PARP1 inhibitor via inverse drug discovery
	Paige Dickson	TSRI CA	Development of chemical tools to probe the 26S proteasome
	Wesley Cochrane	TSRI FL	Activity-based DNA-encoded library screening
	Tim Strutzenberg	TSRI FL	HDX-MS reveals hyperactivation mechanism of RORγ
	Sebastian Jojoa	TSRI CA	Cryo-EM structure of the mechanically activated ion channel OSCA1.2
	Yao Xiao	TSRI CA	Deciphering the distinct enzymatic properties of plant Argonaute protein
	Short Break		
	Joshua Yim	Stanford	Translating optical chemical probes for cancer imaging
	Jessica Spradlin	UC Berkeley	Harnessing the anti-cancer natural product nimbolide for targeted protein degradation
	Jenna Pellegrino	UCSF	Binding and activity of novel streptogramin A analogs
	Garrett Gaskins	UCSF	Automating diagnosis of melanocytic atypia
	Barak Raveh	UCSF	Integrative multiscale modeling of dynamic biological systems
	Meghna Gupta	UCSF	Nutrient sensing and transceptors
	Regina Shin	UC Berkeley	Chemical targeting of the mTORC1 signaling pathway
	Marco Mravic	UCSF	Membrane protein design: biophysical principles and chemical biology tools
20:30 – 22:00	**Reception with Buffet**		**Poolside**

World Molecular Engineering Network (WMEN) CABO XXIX, May 4–7, 2019

Sunday Morning, May 5, 2019			**Structure and Biology of Cellular Processes (Chair: Kathleen Aertgeerts)**
08:30	Andreas Martin	UC Berkeley	Watching a fine-tuned molecular machine at work: Structural and functional studies of the 26S proteasome during ATP-dependent substrate processing
08:50	Gabriel Lander	TSRI CA	Studying mitochondrial protein quality control with cryoEM
09:10	Danielle Grotjahn	TSRI CA	Visualizing mitochondrial fission machinery in situ by cryo-electron tomography
09:30	Carolyn Larabell	UCSF/LBNL	Probing membraneless organelles and phase separated droplets
09:50	Ahmet Yildiz	UC Berkeley	The mechanism and regulation of mammalian dynein-dynactin
10:10	**Break**		
10:30	Lisa Racki	TSRI CA	The cell biology of starvation: polyphosphate granule biogenesis in *Pseudomonas aeruginosa*
10:50	Roberto Zoncu	UC Berkeley	Dissecting and reconstituting lysosome-based nutrient sensing in health and disease
11:10	Takanori Otomo	TSRI CA	A molecular mechanism for autophagosome membrane expansion
11:30	Bill DeGrado	UCSF	Deep mutational scanning of α-synuclein reveals the molecular basis for its toxicity in yeast
11:50	Tina Izard	TSRI FL	Correlation of the tumor-suppressive function and structure of NF2
Sunday Afternoon, May 5, 2019			**Chemical Biology (Chair: Pat Griffin)**
16:00	Dennis Wolan	TSRI CA	New approaches for lead inhibitor optimization
16:20	Phil Dawson	TSRI CA	Non covalently immobilized macromolecules in organic solvent: from protein engineering to DNA encoded libraries
16:40	Matt Bogyo	Stanford	Applications of chemical probes for studies of serine hydrolases in parasite and bacterial pathogens
17:00	Ian Seiple	UCSF	Can we beat nature? Rational design, chemical syntheses, and molecular mechanisms of action of new antibiotics based on old natural products
17:20	Daniel Nomura	UC Berkeley	Reimagining druggability using chemoproteomic platforms
17:40	Chris Parker	TSRI FL	Chemoproteomic ligand and target discovery in cells
18:00	**Break and Photograph**		
			Membrane Proteins (Chair: Claudio Ciferri)
18:20	Andrew Ward	TSRI CA	CryoEM structures of membrane proteins
18:40	Mark Yeager	U. Virginia	Connexin, innexin and pannexin channels are really SWELL
19:00	Dan Minor	UCSF	The importance of selectivity filter gating for ion channel function
19:20	Lou Noodleman	TSRI CA	A branched catalytic reaction cycle for proton transfer and proton pumping in a bacterial cytochrome c oxidase
20:15 – 22:30	*Sponsor Dinner, by invitation only* – Adults Pool		

World Molecular Engineering Network (WMEN) CABO XXIX, May 4–7, 2019

Monday Morning, May 6, 2019			**Sponsors (Chair: Daniel Santi)**
09:00	Michael Ruf	Bruker	D8 VENTURE - Advances in biological crystallography
09:20	Claudio Ciferri	Genentech	Building cryo-EM at Genentech to enable research and drug discovery
09:40	Elena Menichelli	GNF	Unraveling the structural plasticity of the theophylline aptamer RNA
10:00	Kathleen Aertgeerts	Vertex Pharmaceuticals	Structural insights into allosteric sites will bring integral membrane protein SBDD to the next level
10:20	**Break**		
10:40	Damon Hamel	Nektar	NKTR-255: Enhancing the immunotherapeutic potential of IL-15
11:00	Vyas Ramanan	Third Rock Ventures	Company creation at Third Rock Ventures: The story of Maze Therapeutics
11:20	Norman Oppenheimer	UCSF	Thermal stabilization of NAD by GAPDH and the implications for evolution and metabolism
Monday Afternoon, May 6, 2019			**Ribosome & Nuclear Receptors (Chair: Lisa Racki)**
16:00	Jamie Williamson	TSRI CA	Single molecule studies of ribosome assembly
16:20	Pat Griffin	TSRI FL	Selective modulation of nuclear receptors
16:40	Doug Kojetin	TSRI FL	Structural basis of PPARγ transcriptional repression
17:00	Kendall Nettles	TSRI FL	Structure-based design for targeting ERalpha in tamoxifen-resistant breast cancer
17:20	**Break**		
			Glycobiology and Microbial Pathogens (Chair: Bill DeGrado)
17:40	Ian Wilson	TSRI CA	Antibody-inspired design of influenza virus therapeutics
18:00	Jim Paulson	TSRI CA	Airway receptors of human influenza virus
18:20	Mia Huang	TRSI FL	Elucidating global glycan-protein interactions in native cellular environments
18:40	David Millar	TSRI CA	Dynamics of HIV-1 Gag assembly
Tuesday Morning, May 7, 2019			**Computation, Systems Biology and the Cell (Chair: Carolyn Larabell)**
08:30	Andrej Sali	UCSF	Meta-modeling of the cell
08:50	Graham Johnson	Allen Institute	Prototyping multiscale whole-cell visual analysis & modeling techniques
09:10	Arthur Olson	TSRI CA	Building the molecular cell
09:30	**Break**		
09:50	William Balch	TSRI CA	Variation Spatial Profiling (VSP): A machine learning paradigm to bridge sequence-to-function-to-structure for individualized medicine
10.10	Michel Sanner	TSRI CA	Advances in peptide docking
10:30	Stefano Forli	TSRI CA	Charting hydrogen bonds
10:50	**Ian Wilson and Andrej Sali**		**Closing Remarks**

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

WMEN Conference
San Jose del Cabo

For more information, contact:

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Name: Kathleen Aertgeerts
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Overview: Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. We discovered and developed the first medicines to treat the underlying cause of cystic fibrosis (CF), a rare, life-threatening genetic disease. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Presentation: Human GPR40 receptor (hGPR40), also known as free fatty-acid receptor 1 (FFAR1), is a G-protein-coupled receptor that binds long-chain free fatty acids to enhance glucose-dependent insulin secretion. Novel treatments for type-2 diabetes mellitus are therefore possible by targeting hGPR40 with partial or full agonists. The first crystal structure of hGPR40 was solved in the presence of TAK-875, an orally available, potent and selective partial agonist of the receptor. The co-complex structure reveals a unique binding mode of TAK-875 and suggests that entry to the non-canonical binding pocket most probably occurs via the lipid bilayer. The hGPR40-TAK-875 structure also uncovered a second and allosteric binding site facing the lipid bilayer. Small molecules that occupy this site display full agonist activity of hGPR40 and can provide additional efficacy to partial agonists. This work was performed by my previous team at Takeda and can be found in the public domain (Srivastava et al., Nature (2014) 170, 483-91).

Impressions: Location: Excellent
Number of participants: Excellent
Length of meeting: Just right
Great scientific meeting. I particularly enjoyed the integrative approaches used to relate in vitro/in vivo biology results to structure as well as novel chemical biology approaches to modulate proteins.

Name: Matthew Bogyo
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Impressions: This is a great meeting that I enjoy attending. I have attended since 2000. I think the format is great and particularly like the shorter talks for faculty and the speed talks for postdocs. It is great that everyone gets to present so you get to know all the attendees by the end of the meeting.

Name: Gabriel Brighty
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Presentation: At WMEN, I spoke about how the process of Inverse Drug Discovery lead to the discovery of an irreversible PARP1 inhibitor. This process begins with the synthesis of organic compounds of moderate structural complexity, each harboring a weakly electrophilic moiety and terminal alkyne. Cell culture (or cell lysate) is then incubated with these compounds for 4-16 hr, then proteins that react with these compounds are identified by affinity purification followed by proteomic mass spectrometry. These more structurally simple compounds can then be optimized to bind tighter and react faster with a particular protein (identified by mass spectrometry). To date, I have examined the proteomic reactivity of compounds containing fluorosulfates, sulfuramidimidoyl fluorides, and mono fluoro-s-triazines.

Impressions: Overall I had a great time at the WMEN conference. I believe the optimal size of the group was exactly as it was this year, but could be a little bigger even. The location was fantastic; no complaints about location. I was content with most of the speakers' presentations and believe the duration of each talk was more or less optimal. I was very pleased to have met and chatted with such highly-regarded scientists, most of whom I would probably not have otherwise met. I do believe the conference could include more members, which would increase the amount of talks, which would increase the duration...I could live with that.

Name: Jill Chrencik
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Overview: Overall, the meeting was excellent, well timed, great talks, good discussion, and fantastic location.

Presentation: Presentations were thought inspiring, forward looking, and of genuine interest, particularly to the structural biology community. The short PhD talks are interesting to all and a good venue to present current data.

Impressions: Excellent meeting of west coast institutions engaged in similar functional areas. Was able to network quite a bit and found the meeting enjoyable. Location is clearly amazing!

Name: Sebastian Jojoa Cruz
Supervisor: Andrew Ward
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Presentation: My research focuses in solving the structure of members of the OSCA/Tmem63 family of mechanosensitive ion channels to identify conserved features to elucidate the molecular mechanisms of mechanosensation used by these proteins. In this meeting, I presented the first structure of OSCA1.2 and a model of how it might sense membrane tension.

Impressions: The meeting was great. I learned a lot from the PIs talk and got a lot of ideas for new experiments from interacting with other attendees.

Name: Philip Dawson
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Overview: We study the chemical manipulation of macromolecules to facilitate their analysis by diverse biophysical techniques and to customize their function for cellular or pharmaceutical evaluation. Using chemical ligation approaches, we can synthesize proteins with site selective probes and post translational modifications that are impossible to generate through biosynthesis.

Presentation: The structural diversity of DNA Encoded Libraries has been limited since the hydrophilic, unprotected nature of the DNA tag severely limits the repertoire of compatible chemical reactions. Rather than pursuing the optimization of individual synthetic organic reactions for water compatibility, we reasoned that a general strategy for transferring DNA-substrates into organic solvents could significantly expand the structural diversity explored by DEL. Reversible absorption of macromolecules to a solid support (RASS) has facilitated peptide and protein modification, enabling the use of anhydrous solvents and multistep synthetic procedures. This RASS strategy was adapted for DEL through a polystyrene based, quaternary ammonium resin. Adsorption of DNA headpiece substrates to this resin was found to facilitate transfer to organic solvents such as DMA, THF, and CH2Cl2. This RASS approach for DEL has enabled the development of Ni mediated carbon-carbon (C(sp2)-C(sp3)) and carbon-heteroatom (C-N, C-S, C-P) cross couplings with broad substrate scope and with excellent DNA compatibility. The immobilization of the DNA has also facilitated the use of electrochemical transformations. This expanded scope of reaction conditions compatible with DEL library generation has the promise to contribute to the generation of conformationally diverse scaffolds with drug-like properties.

Impressions: The meeting was inspiring and well organized. The format of every participant presenting is excellent and each speaker has sufficient time to provide a deep and focused presentation of an exciting new project in the lab. The location is well suited to foster social interactions and further scientific discussion over meals and afternoon free time. The mix of academic and industrial researchers from diverse career levels is a strong component of the meeting. A great meeting that I return to regularly.

Name: Paige Dickson
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Presentation: My work focuses on validating the proteasomal ubiquitin receptor Rpn13 as a high-priority cancer target. I have characterized the mechanism of action of a peptoid KDT-11, identified in the Kodadek lab through a high-throughput Rpn13-binding screen, revealing that a cancer-cell selective G1/S cell cycle arrest occurs upon treatment. The cell cycle arrest profile and subsequent apoptosis-mediated cell death is not observed in non-diseased cells, suggesting an improved

therapeutic window for targeting this protein. However, current efforts to link this phenotype to Rpn13 target engagement suggest that this effect is mediated through an alternate target.

Impressions: This meeting was an incredible opportunity to network with academics and industry professionals alike, and hear the incredible research that is going on across Scripps campuses and other institutions. The meeting size was perfect -- all talks were reasonable in length and there was ample opportunity to meet with any conference attendees we wished. The meeting length was reasonable and the format was excellent. What a great location to share incredible science. Thank you for this opportunity!

Name: James Ferguson
Supervisor: Peter Wright
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Presentation: Using 19F-NMR to observe different states of Transthyretin

Impressions: Excellent meeting in a good location.

Name: Stefano Forli
Department: Integrative Structural and Computational Biology, TSRI
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Overview: My lab is interested in the development and application of computational methods for structure-based drug design. Our work is often in collaboration with other experimental labs that provide us with applications for the methods we develop, as well as new challenges that require innovative and original solutions.

Presentation: We have used QM calculations to explore the HB properties of a large dataset of molecular fragments (+100), analyzing both strength and directionality. In particular, to quantify directionality, we defined a directionality index (D_i) that allowed us to compare this property in different molecules. As a result, we found that strength and directionality are not correlated, as previously thought. We discussed the implications of these findings in thermodynamics, force field development, and drug design.

Impressions: The size of the group is excellent, with what looks like an optimal balance between the number of talks and attendees, the subjects covered.

Excellent location, service, and structures.

The meeting is a great opportunity to showcase innovative approaches and results to an audience with a very diverse backgrounds, which provides always very useful insight.

The length of the meeting is optimal.

Name: Karthik G
Supervisor: Kristian Andersen and Andrew Su
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Presentation: Genomic epidemiology of West Nile virus in the Unites States

Impressions: The talks were very interesting especially given the broad range of topics discussed. It was very interesting to me, personally, to see the application of computational methods in structural biology. While I use many of these methods in my direct research I wasn't aware of their application outside of my field. All in all, very scientifically fulfilling!

Name: Danielle Grotjahn
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Overview: My research focuses on using cutting-edge techniques in cellular cryo-electron tomography imaging to study the functional and structural interactions that mediate the mitochondrial division (fission) process. We are in the process of using a combination of genetic and pharmacological approaches to examine the precise role of the actin cytoskeleton network involved in mitochondria outer membrane constriction.

Presentation: We developed an experimental approach to capture ultrastructural snapshots of the mitochondrial fission process using a combination of cryo-focused ion beam (cryo-FIB) milling and cellular cryo-electron tomography (cryo-ET) imaging. Contrary to previously proposed models, our preliminary data analyses suggests the actin cytoskeleton assembles into long, unbranched filaments that emanate from nearby endoplasmic reticulum to constrict mitochondria outer membranes during fission. We also observed other filamentous structures associated with mitochondrial constrictions that do not resemble actin filaments nor microtubules structures. We hypothesize that these 10 nanometer filaments are septin intermediate filaments. We are in the process of using a combination of structural and genetic approaches to validate the identity of these filaments in the next year, and we hope to present this progress at the next Cabo meeting.

Impressions: This meeting is one my favorite to attend. I really enjoy the style of the meeting, in that each attendee is required to present. I think the presenters did a much better job this year at sticking to their allotted time, which I appreciated very much.

Name: Gabriel Lander
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Overview: This is an excellent meeting that assembles world-renowned scientists and emerging leaders in the field in a relaxing and beautiful resort environment that encourages one-on-one scientific discussions. The small size of the meeting, the informal nature of the talks, the free time in the afternoons, are all conducive to, and often lead to, successful and prolific collaborations. The attendees are mainly structural biologists, and I enjoy learning about the newest developments in structure determination methodologies and interpretation, as the diversity in approaches and techniques that are presented always prompts new ideas for the ongoing projects in my lab. There are also numerous exceptional non-structural researchers who attend this meeting, which broadens the scope of the lectures and further encourages multidisciplinary discussion and collaboration.

Presentation: Mitochondrial AAA+ quality control proteases regulate diverse aspects of mitochondrial biology through specialized protein degradation, but the underlying molecular mechanisms that define the diverse activities of these enzymes remain mysterious. Two different mitochondrial AAA+ proteases reside in the inner mitochondrial membrane but expose enzymatic domains to the intermembrane space and matrix. Using cryo-EM, we show that these hexameric complexes use a hand-over-hand mechanism of substrate translocation through a sequential ATP hydrolysis cycle. The basic translocation mechanism we describe is likely to be evolutionarily conserved from bacteria to humans. Our results provide a molecular basis for neurological phenotypes associated with different mutations and establish a structural framework to understand how different members of the AAA+ superfamily achieve specialized, diverse biological functions. While a hand-over-hand translocation is emerging as the conserved mechanism by which ATP hydrolysis drives substrate translocation within the classical clade of AAA+ proteins, the operating principles of the distantly related HCLR clade, which includes the important quality control protease Lon, is also of great interest. We determined a cryo-electron microscopy structure of *Y. pestis* Lon, revealing that although sequential ATP hydrolysis and hand-over-hand substrate translocation are conserved in this AAA+ protease, Lon processes substrates through a distinct molecular mechanism involving structural features unique to the HCLR clade. We define a previously unobserved translocation mechanism that is likely conserved across HCLR proteins and reveal how distinct structural configurations of distantly-related AAA+ enzymes can power hand-over-hand substrate translocation.

Impressions: Every year this meeting seems to get better, and this meeting was no exception. I say without reservation that this is the best meeting I attend all year. I'm exposed to more interesting and applicable science in Cabo than in most other conferences, and I always return to lab energized and enthusiastic, eager to push my lab members to branch aspects of their projects in new directions.

Name: David Millar
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Overview: The major focus of my laboratory is the development and application of single-molecule fluorescence methods for biophysical studies of macromolecular dynamics and assembly processes. Our three current projects are: (1) Conformational dynamics of G protein-coupled receptors, (2) functional coordination in DNA polymerases, and (3) protein-protein and protein-RNA assembly processes in the HIV-1 system.

Presentation: This year I described studies of Gag assembly. The Gag polyprotein is the major structural protein of HIV-1. Multiple Gag molecules coalesce to surround the viral genomic RNA and to build the immature viral capsid. While the majority of this assembly occurs on the plasma membrane, less is known about where Gag first encounters the genomic RNA and the extent to which Gag multimerizes in the cytoplasm. To address these questions, we are developing a single-molecule system to visualize the early stages of Gag assembly around viral RNA. Various RNA constructs derived from the HIV-1 5, UTR were immobilized on a quartz surface and a small Alexa Fluor 555 fluorophore was incorporated in Gag at a site between the MA and CA domains. Single-molecule TIRF microscopy was used to visualize Gag molecules as they assembled, one by one, around the RNA. For RNA constructs containing the Psi packaging signal, we observed dynamic assembly of multiple Gag monomers, whereas non-Psi RNAs only showed a single Gag binding event. Dwell time analysis of single-molecule trajectories showed that the nucleation step was rate limiting and that subsequent Gag monomers bind more rapidly to the Psi RNA. As a complement to these in vitro studies, we are also using single-molecule fluorescence methods to investigate Gag assembly in cells. In collaboration with the Williamson lab at TSRI, we transfect mammalian cells with Gag-GFP and then separate Gag-containing complexes from cell lysates by sucrose gradient fractionation. We find that Gag-GFP is contained in a series of discrete complexes of increasing size. Individual complexes are captured on a surface with anti-GFP antibody and single-molecule photobleaching is used to count the number of Gag monomers within each complex. We find that 10S, 40S and 80S complexes each contain only one or two Gag monomers, despite their vastly different sizes. These observations are at odds with Gag assembly models that assign 40S and 80S complexes to intermediates in a sequential assembly pathway. We also find that 150S and 800S complexes contain many Gag monomers, suggesting that these reflect bona fide assembly intermediates.

Impressions: This meeting continues to be one of the highlights of the scientific year for me. The quality of the presentations and the range of topics are truly impressive. I think the number of attendees and the length of the meeting are just right. The Hyatt Ziva provides a pleasant and effective venue for the meeting.

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Overview: My laboratory studies molecules involved in electrical signaling in the brain, heart, and nerves. We focus on understanding the structural mechanisms that govern the opening and closing of ion channel proteins and seek to understand how they interact with drugs and toxins.

Presentation: I presented an overview of our work on developing small molecule modulators for a class of potassium channels (K2P channels) that are important for pain responses. I also presented new, unpublished work on the mechanisms by which organisms can resist environmental neurotoxins.

Impressions: The meeting was excellent having a terrific mixture of academic and industrial scientists as well as participants at various career stages (from student to well-established

professors). The informal and collegial atmosphere of the meeting allowed ample time for scientific discussions and the opportunity to establish new contacts.

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Overview: Our lab is focused on applications of quantum chemistry, electrostatics, and molecular dynamics to calculating and analyzing structures and energetics of reaction pathways in redox active metalloenzymes. We use Density Functional Theory methods (DFT) for our calculations, and make extensive use of a variety of spectroscopies, comparing calculated and experimental spectroscopic parameters to understand states and pathways beyond considerations of energies alone. We also perform experimental work using X-ray crystallography utilizing synchrotron light sources and X-ray free electron lasers (XFELS). Currently, our main area of study involves the reaction mechanism of cytochrome c oxidase. This enzyme is the final electron acceptor in the electron transport chain in the mitochondrial inner membrane, and in the periplasmic membrane of various aerobic bacteria. The linkage between electron and proton transfer to molecular oxygen by the active site heme iron-copper complex yielding water, and proton pumping across the membrane contains many important and unresolved problems. In a separate area, we have a longstanding interest and efforts directed toward understanding the mechanisms and functions of enzymes containing iron-sulfur clusters, both in normal metabolic networks, and in the metabolic pathways of pathogenic organisms. In pathogens, understanding the distinctive features of their essential reaction pathways utilizing iron-sulfur enzymes may lead to strategies for developing effective inhibitors.

Presentation: After presenting an overview of the catalytic reaction cycle of cytochrome c oxidase(s)(CcOs), I showed based on our DFT calculations how in the oxidative part of the pathway after O-O bond cleavage, a combination of electron and proton transfers can be used to drive proton pumping in a bacterial cytochrome c oxidase. There are still many fundamental unresolved issues in calculating and analyzing the relevant reaction pathways in different types of bacterial CcOs, and in larger and more complex mitochondrial CcOs. We are continuing to refine our analysis of different parts of the reaction cycle, connecting the catalytic reaction pathway in the dinuclear iron-copper complex to the proton input and proton output pathways through the protein-water network, and examining the rate and control of the electron transfer pathways as well.

Impressions: I was very favorably impressed by the very broad scope of this meeting, and the quality of the presentations, including both the very short presentations by the graduate students, and the more extensive presentations of investigators from industry and academics. I thought also that the thematic organization of the different sessions was excellent. The Conference site at the Hyatt resort in Cabo was very beautiful and relaxing, and encouraged interactions within the group.

Name: Art Olson
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Overview: As usual, the meeting brought together a great group of structural biologists to discuss their latest work. The meeting has evolved over the years to follow the trends in structural and computational molecular biology. Larger molecular systems were presented with a significant amount of cryo electron microscopy and cell biology.

Presentation: I present the latest developments on our work in developing and utilizing tools for building, visualizing and analyzing mesoscale models of cellular environments. I talked about progress in representing fibrous molecules and applications of our CellPACK program to understand HIV maturation and the insulin secretory granule in Pancreatic Beta Cells.

Impressions: Still ranks as one of the best meetings that I attend each year. Everyone presents, and lots of time to talk one-on-one. The venue is excellent.

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Presentation: Structural evolution of anti-HIV broadly neutralizing antibodies
My research uses X-ray crystallography to investigate structural co-evolution of the HIV envelope glycoprotein (Env) and broadly neutralizing antibodies in naturally infected humans. Donor PC76 is one such individual from the Protocol C longitudinal study, antibodies from whom target the N332-glycan supersite epitope on Env. By obtaining crystal structures of these antibodies, we have elucidated structural features of these antibodies correlating with broadly neutralizing activity.

Impressions: I found the meeting to be rather informative, and I enjoyed the diversity in scientific questions and techniques that were discussed. I appreciated the industry perspectives as well. For future editions, I see the meeting benefiting from having slightly more attendees.

Name: Christopher Parker
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Overview: Our research integrates chemical synthesis with mass spectrometry and cell/molecular biology to (1) study how small molecules might regulate, or be designed to regulate complex biological processes, such as immune responses and metabolism, and (2) help illuminate molecular mechanisms that contribute to diseases, such as cancer. Key to our program is our continuous development of various technologies tools that enable us to map small molecule-protein interactions in living cells.

Presentation: We developed a powerful chemical proteomic platform to broadly map the interactions of drug-like small molecules with proteins directly in living cells. With this method, we identified thousands of reversible small molecule-protein interactions, many of which can be site-specifically

determined and involve proteins that fall outside of traditional druggable classes. Such studies expand our understanding of the druggable proteome and aide in chemical probe development.

Impressions: This was my first WMEN meeting and it was certainly one of the top meetings that I have ever attended. All of the science presented was fantastic, with very complementary approaches to interrogate biomolecule function and structure. The size, setting and duration of the meeting was terrific, as it allowed much interaction and discussion.

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Overview: Our lab is interested in biology mediated by protein recognition of glycans as ligands. Major projects include influenza virus recognition of sialic acid containing glycans as receptors on host cells, and elucidating the roles of a family of immune cell receptors called Siglecs, which recognize sialic acid containing ligands on other cells, and serve as checkpoint inhibitors in preventing/regulating unwanted immune responses.

Presentation: This year I talked about evolution of H3N2 influenza virus for recognition sialic acid containing glycans on airway epithelial cells. This virus entered the human population in 1968, and under immune selection it has evolved restricted specificity for a subset of glycans on airway epithelial cells while maintaining fitness for transmission in the human population. We seek to understand how these mutations have evolved in the face of immune selective pressure balanced against the selective pressure to retain binding to and release from host cell receptors to maintain virulence and transmission.

Impressions: This continues to be one of the most stimulating meetings I attend each year. Diverse and extremely high quality science is presented by all attendees including students, post-docs, faculty and industry participants. The work presented this year gave a cutting edge glimpse into the advances in structural and computational biology that will be published over the next couple of years. The interactions between faculty, students and sponsors in the relaxed and elegant environment are truly a special aspect of this unique meeting.

Name: Barak Raveh
Supervisor: Andrej Sali
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Presentation: Integrative modeling of spatiotemporal cellular systems and processes

Impressions: The meeting was exciting in terms of both the formal and informal scientific discussion, covering a wide range of topics, from protein engineering at the atomic level to whole-cell modeling. It also provided an excellent venue for informal discussions in between talks. I enjoyed it whole heartedly.

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, I described how we obtained the structure of the Nup82 subcomplex of the nuclear pore complex, using integrative structure determination based on electron microscopy, chemical crosslinking, and assorted other data.

Impressions: Informative and enjoyable!

Name: Ian Seiple
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Overview: Our group focuses on using chemical synthesis to address biological challenges. One of our main interests is in developing new antibiotics based on old natural products that overcome prevalent resistance mechanisms. We have numerous projects aimed at developing new inhibitors of bacterial protein synthesis by means of modular, scalable chemical synthesis. We also have projects aimed at developing new therapeutic modalities, such as binding-induced dimerizing drugs and trojan horse antibiotics.

Presentation: My presentation focused on overcoming resistance to streptogramin antibiotics mediated by acetyltransferases. Using a modular, fully synthetic route to streptogramins, we were able to design new drugs that completely avoided this resistance mechanism while simultaneously increasing in potency.

Impressions: I thought the meeting was fantastic. The first day did not have enough breaks, however. People were wary from traveling, and at least one more break (e.g., before student talks) would have been appreciated. The location is fantastic, and I love that everybody gave talks. The meeting length was good. Travel was easy.

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Presentation: Autophagy is a lysosomal degradation pathway that eliminates aggregated proteins and damaged organelles to maintain cellular homeostasis. A major route for activating autophagy involves inhibition of the mTORC1 kinase, but selective and complete mTORC1 inhibition remains beyond the reach of current mTORC1-targeting compounds. Here, we have coupled screening of a covalent ligand library with activity-based protein profiling to discover EN6, a small-molecule in vivo activator of autophagy that covalently and selectively targets a cysteine residue in the ATP6V1A subunit of the lysosomal v-ATPase, which mediates mTORC1 activation at the lysosome.

Impressions: Broad interest from chemical biology to structural biology. Very welcoming and cheerful. I would love to come back next year!

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Presentation: I presented my work on structurally characterizing the prime side of caspases using ketomethylene inhibitors. We'll be using this technology to develop and improve the selectivity of tools used to study caspases.

Impressions: The meeting was very informative. I really appreciate the diverse scope of the meeting. This year I found Matthew Bogyo's presentation using turn-on probes to facilitate the excising of cancerous tissue extremely interesting.

On another note, I personally really like the formatting of the talks, but one possible solution would be not have a dedicated sponsor section, but to spread them into appropriate sections through the entire meeting. I do realize certain sponsors will be hard to categorize, but could be accommodated.

Name: Robert Stroud
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Overview: The main projects in my laboratory discussed concerned the structural determinations of an ion channel TPC1 and transmembrane transporters. One was a glucose transporter GLUT1 with various drugs bound as potential anticancer therapeutics. This was a first for transporters of this class. The second was a structure of a homolog of the first neurotransmitter packaging transporter a vesicular glutamate transporter of key importance for the nervous system.

Presentation: I used structures determined by cryoEM to suggest their mechanisms of regulation and transport. Protein structure has a key role in the understanding of essential process in cell biology and designing ways of modulating them using chemical ligands as drug validation of principle.

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

The conference room is generally dialed too cold! Otherwise Cabo San Lucas, and the hotel is excellent after refinement over the years. A record number of participants shows the popularity of this high-quality meeting. Attendees and presenters were excellently chosen from the superb groups in structural biology at Scripps and at UCSF and included a good crop of new investigators. The science presented was absolutely first rate with many important new breakthroughs in the fields of immunology, drug design, chemical basis for inhibition, chemical basis for understanding enzyme mechanisms and cell surface receptor interactions.

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Presentation: Integrating Structural Proteomics into Lead Optimization and Chemical Probe Design: Insights to RORγ Structure and Function

Impressions: My impression of the meeting was very positive. The quality of the talks was excellent and the environment of the meeting was relaxed. As a graduate student, I greatly appreciated the opportunity to prepare a talk in this environment and to participate in this meeting. The contributions of the industrial sponsors was appreciated for helping put on the conference and valuable for making professional connections. I have never been to a conference with the format of the WMEN and afterwards I wish all conferences included an interlude.

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Overview: Excellent meeting that covered a diverse array of topics, and lots of new or unpublished data.

Presentation: I presented the structures of the pH-dependent proton channel, Otopetrin, which is a new class of proton channels that play roles in sour taste reception and digestion. These channels are only the second known eukaryotic proton channel (the other is Hv1) and they adopt a homodimeric assembly with each subunit a completely novel fold. Using cryoEM we obtained 3 and

3.3 Å resolution structures and delineated multiple potential ion permeation pathways. Molecular dynamics simulations resulted in insights about the behavior of water and cholesterol, which was tightly bound to the channel at the dimer interface.

Impressions: The length of the meeting is just right but there were too many talks packed into the schedule. The first night was especially long. Otherwise a fantastic meeting that I look forward to next year.

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Overview: Record number of attendees and talks, making for a very dynamic meeting. Broad representation of new topics was welcome, as was inclusion of new junior faculty members. Great opportunity for interactions, and I witnessed the start of many new collaborations.

Presentation: Talks were (for the most part) excellent. The students/postdoc talks were all very good, and it is helpful to see them all the first night. Excellent discussion after the talks, and in the informal gatherings.
Great energy remains in the Cabo meeting.

Impressions: Great meeting at the forefront of structural biology, biophysics and drug discovery.

Name: Ian A. Wilson
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Overview: My lab works on the structural basis of the immune response to microbial pathogens, especially HIV-1, influenza virus, hepatitis C virus, and *Plasmodium falciparum.*

Presentation: **Antibody-inspired design of influenza virus therapeutics**. I have worked in the influenza field for over 40 years, but there is still so much to be discovered. Currently, we are investigating how human broadly neutralizing antibodies (bnAbs) recognize influenza virus. The hemagglutinin (HA) surface glycoprotein is the main target of the immune response. We have determined many crystal structures of bNabs with different subtypes of influenza virus HA to understand their broad specificity in order to design better vaccines. An added bonus has been that we have learned from these antibodies how to utilize the information on the mode of recognition to design novel therapeutics. No drugs specifically target the HA and such a compound would be effective in preventing the first stage of viral infection – that of cell entry. We have worked with collaborators, including Dennis Wolan at Scripps, David Baker at U. Washington, and Janssen/J&J to design multi-domain llama antibodies, small proteins, peptides and small molecules to the conserved regions of the HA head and stem (receptor binding site and fusion domain.

Impressions: Another great meeting , filled with fascinating science and great interactions with all of the participants. It is hard to believe that this meeting continues to get better and better after almost 30 years. The return attendees both academic and from industry provide a strong endorsement to the meeting's success and standing. A healthy new group of participants from year to year also keeps the meeting fresh and exciting. The venue is still terrific and highly conducive to interaction among participants.

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Overview: In small-molecule drug and probe discovery, medicinal chemistry/lead optimization is a lengthy and challenging process that requires tremendous resources. Ultimately, the lack of automation and reliance on skilled medicinal chemists makes lead compound optimization difficult and time consuming in both the academic and industrial settings. Here, we developed and employed an high-throughput hit-to-lead optimization platform based on the biocompatible SuFEx click chemistry. Our method consists of a one-pot nano- to picomole scale synthesis of analogs in biocompatible conditions that permits the direct measurement of reaction products in a range of in vitro and cell-based biological assays. We applied the platform to the bacterial cysteine protease SpeB and improved inhibitors with 300-fold higher potency from lead compounds. We anticipate our methodology will accelerate the development of drug candidates and robust biological probes in both academia and pharmaceutical arenas.

Presentation: New approaches for lead inhibitor optimization

Impressions: The meeting was fantastic as always with a broad range of presentations on cutting-edge and innovative research in structural biology and chemical biology. Our lab forged several new collaborations that we are actively pursuing as a result of the meeting.

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Presentation: Deciphering the distinct enzymatic properties of plant Argonaute

Impressions: The meeting is great and well-organized, the place is fantastic. It's a good chance for me to know what everyone else is studying and focusing on. I'm really glad to hear so many great and interesting talks.

Name: Janice Xu
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Presentation: My research focuses on the characterization of the gut bacterial protease Pd_dinase. Pd_dinase has a Gly specificity at the P2 position but no specificity at the P1 position. Based on this, the clickable probe, Gly-PropargylGly-AOMK was synthesized. This probe will be used to enrich for Pd_dinase in healthy and diseased fecal samples to evaluate its role in health.

Impressions: It was really fun! The size of the group was bigger than I was expecting but it gave the meeting a very diverse set of talks. The location of the meeting was a great choice. The length of the meeting was just right.

WMEN Conference
2020 Keynote Speaker

James A. Wells, Ph.D. Professor
Department of Pharmaceutical Chemistry, UCSF

Wells' group pioneered the engineering of proteins, antibodies, and small molecules that target catalytic, allosteric, and protein-protein interaction sites; and technologies including protein phage display, alanine-scanning, engineered proteases for improved hydrolysis, bioconjugations, N-terminomics, disulfide "tethering" (a novel site-directed fragment based approach for drug discovery), and more recently an industrialized recombinant antibody production pipeline for the proteome. These lead to important new insights into protease mechanisms, growth factor signaling, hot-spots in protein-protein interfaces, role of caspases in biology, and more recently determining how cell surfaces change in health and disease. His team was integral to several protein products including Somavert for acromegaly, Avastin for cancer, Lifitegrast for dry eye disease, and engineered proteases sold by Pfizer, Genentech, Shire and Genencor, respectively. He is an elected member of the US National Academy of Science, American Association of Arts and Science, and the National Academy of Inventors.