

WORLD MOLECULAR ENGINEERING NETWORK



CABO 2016

Our History

The WMEN conference has been held for the past 26 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, fourteen 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 Barcelo 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 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 7-11, 2016

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

Saturday Evening, May 7

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

17:30 **Ian Wilson, TSRI** **Keynote Lecture-**
A perspective on antibody structure and function from 35 years in the field

18:15 **Self-Introductions**
Mira Chaurushiya 5AM Ventures
Jack Kirsh UC Berkeley
Bellos Hadjivassiliou Celgene

18:30-20:45 **Short Presentations (5+1 min.) by TSRI, UCSF, UCB and Stanford Graduate Students, Postdocs, etc. (Chair: Erica Ollmann Saphire)**

	Jessica Bruhn	TSRI	Insights into the molecular and structural properties governing RNA virus transcription and replication
	Alexander Krois	TSRI	Versatility through Flexibility-p53 and intrinsic disorder
	Jennifer Kefauver	TSRI	Structural heterogeneity in SWELL1, the volume-regulated anion channel
	Charles Daniel Murin	TSRI	One gene, two proteins: cryoEM structures of Ebola Virus sGP in complex with protective antibodies
	Erika Olson	TSRI	Structure-guided optimization of a peptide antagonist of EphA4 activation
	Danielle Grotjahn	TSRI	Cryo-electron tomography of the dynein-dynactin complex bound to microtubules
	Sergey Shnitkind	TSRI	Structural ensemble and phosphorylation-dependent regulation of an intrinsically disordered transcription factor
	Shanshan Lang	TSRI	Anti-idiotypic antibody K1-19 for flu vaccination
	Sasha Moola	TSRI	Crystal structures of two related broadly neutralizing antibodies against the N332 supersite in HIV Env
	Break		

	Cristina Arrigoni	UCSF	Structural and functional characterization of a ion channel temperature sensitive domain
	Manasi Bhate	UCSF	Structure and function of bilayer stress-sensing transmembrane domains
	John-Marc Chandonia	UCB	Party like it's 1999: structural novelty has regressed two decades
	Zachary Hill	UCSF	Proximity tagging of small molecule protein targets using an engineered NEDD8 ligase
	Alexander Kintzer	UCSF	Structure, inhibition and regulation of a two-pore channel TPC1
	Daniel Saltzberg	UCSF	Integrative structure modeling based on HDX data
	Christopher Schulze	Stanford	An in vivo multiplexed small molecule screening platform identifies a pro-metastatic factor in pancreatic cancer
	Robyn Kaake	UCSF	Cross-linking mass spectrometry and virus-host protein complexes
21:00	Reception		Poolside

Sunday Morning, May 8			Integrative Structural Biology (Chair: Robert Stroud)
09:00	Andrej Sali	UCSF	Integrative mapping of metabolic pathways
09:20	Ashok Deniz	TSRI	Biophysics of protein disorder at single molecule resolution
09:40	Takanori Otomo	TSRI	Structural insights into autophagosome formation
10:00	Carolyn Larabell	UCSF	Enhancing molecular information with correlated and hybrid methods
10:20	Break		
10:40	Jeff Lengyel	FEI	Recent technological developments in cryoTEM: advancing challenging structural biology research
11:00	Gabriel Lander	TSRI	An ensemble approach for atomic-level structure determination from cryoEM maps
11:20	Andrew Ward	TSRI	Structural studies of viral glycoproteins from HIV to Coronavirus
11:40	Daniel Santi	Prolynx/ UCSF	An ultra-long acting GLP-1 agonist

Sunday Afternoon, May 8			Antibodies. Epitopes and Vaccines (Chair: Jim Paulson)
16:30	Erica Ollmann Saphire	TSRI	Antibodies against Ebola virus: A global collaboration
16:50	Adrian Guthals	Mapp Biopharma	MS/MS sequencing of native human antibodies
17:10	James Wells	UCSF	The Antibiome: recombinant antibodies en mass
17:30	Vijay Reddy	TSRI	Tomato bushy stunt virus (TBSV): a versatile display platform for antigenic epitopes and vaccine design
17:50	Break		
			Membrane Proteins (Chair: Andrew Ward)
18:10	Robert Stroud	UCSF	Electric potential vs. proton driven transport
18:30	Qinghai Zhang	TSRI	Structural flexibility and ligand binding of multidrug ABC transporters
18:50	William DeGrado	UCSF	High resolution view of drug-binding and proton conduction pathway of M2 proton channel from XFELs crystallography
19:10	Daniel Minor Jr	UCSF	How an ion channel domain can control temperature responses
Monday Morning, May 9			
			SPONSORS (Chair: Dan Santi)
9:20	Jody Berry	GRIFOLS	Stereotypical antibody responses: A characteristic of all dominant epitopes?
9:40	Jonathan Moore	Vertex	Biophysical insight in drug discovery
10:00	Hing Sham	GBT	GBT440, a potent allosteric modifier of Hb oxygenation
10:20	Daniel Kirschhofer	Genentech	Neutrophil serine protease 4 is a pro-inflammatory enzyme with a unique active site structure
10:40	Break		
11:00	Pat Walters	Relay Therapeutics	Integrating public data into the drug discovery workflow

11:20	Jonathan Zalevsky	Nektar	Design and engineering of NKTR-214; an IL-2 pathway agonist immunotherapy that replenishes the immune system for the treatment of cancer
11:40	Mary Matyskiela	Celgene	Ligand-dependent recruitment of substrates to the cereblon-CRL4 ubiquitin ligase
12:00	Jaume Pons	UCSF/ Alexo	New ideas about blocking CD47
12:20	Magdalena Dorywalksa	Rinat Pfizer	Molecular basis of valine-citrulline-PABC linker instability in site-specific ADCs and its mitigation by linker design
Monday Afternoon, May 9			Nucleic Acids and Nucleic Acid Binding Proteins and Evolution (Chair: Nevan Krogan)
16:30	David Millar	TSRI	Trafficking and assembly of HIV-1
16:50	James Williamson	TSRI	Structure and dynamics of 50S ribosome assembly intermediates
17:10	Glen Spraggon	GNF	Unnatural DNA aptamers and the potential to general unique macromolecular targeting modalities
17:30	Pedro Serrano-Navarro	TSRI	NMR identifies new functional roles for arginine-serine-rich domains
17:50	Break		
			Chemical Biology Chair : Chair: Floyd Romesberg)
18:10	Dennis Wolan	TSRI	Elucidation of aberrant host and microbial proteins in colitis by large-scale metaproteomics
18:30	Phil Dawson	TSRI	Chemical ligation and bioconjugation, addressing large protein targets.
18:50	Jim Paulson	TSRI	HIV glycosylation
19:10	Matthew Bogyo	Stanford	Selective targeting of the malaria proteasome using structural and functional analysis

Tuesday Morning, May 10			Computation, Health and Disease (Chair: Andrej Sali)
8:50 9:10	Stefano Forli Kathryn DeFea	TSRI UC Riverside	Molecular modeling for drug design Biased targeting of protease-activated- receptor-2: inhibition of β -arrestin- dependent inflammation
9:30	Steven Brenner	UCB	Interpreting newborn genomes
09:50	Break		
10:10	Nevan Krogan	UCSF	Using systems approaches to study disease
10:30	Natalia Jura	UCSF	Mechanistic insights into receptor tyrosine kinase activation
10:50	Mehrdad Moshrefi	Merck	Biologics discovery at Merck Research Laboratories
11:30	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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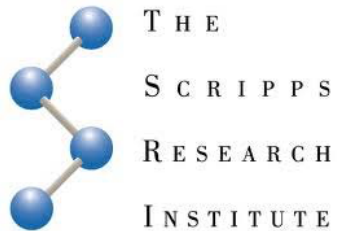
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The following pages are summaries of presentations and comments on the meeting and venue.

WMEN Conference San Jose del Cabo

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Presentation: My work is focused on the understanding of activation mechanisms in ion channels through a number of biophysical approaches, including X-ray crystallography and electrophysiology. In particular, I study the regulation of a cytoplasmic domain in bacterial sodium channels that confers temperature dependence to the activation of the channel through a drastic conformational transition from a folded to an unfolded state.

Impressions: The meeting was really informative, set in a great location and the number of the attendees is ideal for establishing new networks and knowing new people even within the same university.

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Presentation: Structure and function of bilayer stress-sensing transmembrane domains.

The bacterial membrane is an attractive target for new antibiotics. Histidine Kinases (HKs) are highly conserved transmembrane signaling proteins that help bacteria sense and adapt to various stimuli, including the effects of antibiotics. My talk focused on NsaS: a recently identified membrane stress-sensing HK from *S. aureus* that is part of the *S. aureus* response to human innate immunity [1], and is implicated in the development of resistance to antibiotics Nisin, Bacitracin and Brilacidin [2]. Nsas provides a unique opportunity to unravel the mysteries of bacterial membrane-stress at a molecular level, because in addition to being a stress-sensor and an important drug target, it is also a small protein with a simple architecture that makes it highly amenable to high-resolution

structural and biophysical studies in native membranes.

I reported progress towards determining the structure of the physiologically relevant dimeric transmembrane domain from NsaS. Biophysical and structural studies of NsaS in detergent micelles by solution NMR show a tightly packed 4-helix bundle in the membrane with a short ordered loop connecting the transmembrane helices. Site-specific measurements of protein dynamics show regions of structural plasticity at the domain interfaces that might be important for signaling. Disulfide crosslinking and solids NMR in native membranes suggest that membrane active antibiotics induce a structural change in the transmembrane domain of NsaS. Strategies to integrate diverse spectroscopic and biochemical restraints into an integrative structural model will be discussed. Mechanisms by which membrane structure and stress might be read by histidine kinase proteins and transduced into cytoplasmic kinase activity were discussed.

Impressions: This was a fantastic meeting - I learned a lot and made many good friends. The informal vibe allowed for very honest conversations around challenges that the field faces as a whole.

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Overview: The proteasome is an essential enzyme complex found in virtually all cells. It is currently a target for anti-cancer drugs that exploit an increased need for protein turn over in rapidly dividing cells. Furthermore, proteasome inhibitors have been shown to be highly effective at killing malaria parasites in all stages of their infective stages. However, current clinical drugs are far too toxic to use for the treatment of malaria due to their activity against the human enzyme. Therefore, compounds that specifically block the parasite proteasome have the potential be highly valuable new anti-malarial therapeutics.

Presentation: I presented work regarding our efforts to develop inhibitors that are selective to the malaria proteasome. We have used a combination of substrate profiling methods and structural

biology to identify differences in the active sites of the malaria and human proteasome complexes. Specifically, we obtained a cryo-EM structure of the malaria proteasome complex with our inhibitor bound in the active site. We were then able to use all of this information to develop inhibitors that killed parasites without causing toxicity to the host cells. Finally, we found that our malaria-specific proteasome inhibitors show strong synergy with the front-line anti-malarial drug artemisinin. Our results suggest that it should be possible to selectively target the malaria proteasome without excessive toxicity to the host. Furthermore, proteasome inhibitors have the potential to prevent the development of resistance to artemisinin-based drugs.

Impressions: This is an outstanding meeting that I have attended at least 6 times since 1999. I enjoy the format of postdoc and student short talks at the start of the meeting. It is also a great way to set up new collaborations with Scripps and UCSF labs and to meet several people in industry and the VC community. The venue is great and the support from the sponsors is greatly appreciated, as it is more and more difficult to find funds to attend meetings.

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Overview: The Brenner research lab has three key research interests involving computational and experimental genomics.

Individual genome interpretation. We have a longstanding interest in personal genome interpretation (1). In particular, we 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) (2,3). We are currently involved in an effort to explore whether genome sequencing at birth can be used as an effective means for newborn screening. This would supplement or replace the mass spectrometry methods currently used to identify diseases that are not clinically evident but if untreated have led to severe consequences including death. We also organize the Critical Assessment of Genome Interpretation (CAGI) project (4), 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 (5).

Gene regulation by alternative splicing and nonsense-mediated mRNA decay. 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 NMD6. 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 are using RNA-Seq to explore the pervasiveness of NMD in numerous species (7), and to understand its behavior, finding that 20% of expressed human genes make isoforms targeted for degradation. As part of a modENCODE consortium, we discovered the repertoire of targets for alternative splicing in the fly, as well as unexpected relationships between the development of fly and worm (8-12). We are 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 (13).

Prediction of protein function using Bayesian phylogenomics. 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 (14). 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. Even our initial implementations of this method, called SIFTER (Statistical Inference of Function Through Evolutionary Relationships) have performed better than other methods in widespread use. SIFTER was recently

honored as the best-performing sequence-based method in the Critical Assessment of Function Annotation (15). We are also experimentally validating the function predictions, with a focus on the Nudix family¹⁶. We are also involved in maintaining the SCOPe: Structural Classification of Proteins extended database (17), a key resource for understanding protein structure data (18). We analyze structural characterization efforts (19).

Recent selected publications

1. Brenner SE. 2007. Common sense for our genomes. *Nature* 449:783-784.
2. Patel JP, et al. 2015. Nijmegen breakage syndrome detected by newborn screening for T cell receptor excision circles (TRECs). *J Clin Immunol* 35:227-233.
3. Chan AY et al. Novel autoimmune syndrome due to the combined actions of a hypomorphic and an activating mutation of zeta-chain associated protein kinase ZAP-70. *J Exp Med*
4. Callaway E. 2010. Mutation-prediction software rewarded. *Nature*. published online. doi:10.1038/news.2010.679
5. Brenner SE. 2013. Be prepared for the big genome leak. *Nature* 498:139.
6. Lareau LF, Inada M, Green RE, Wengrod JC, Brenner SE. 2007. Unproductive splicing of SR genes associated with highly conserved and ultraconserved DNA elements. *Nature* 446:926-929.
7. Hansen KD, Lareau LF, Blanchette M, Green RE, Meng Q, Rehwinkel J, Gallusser FL, Izaurralde E, Rio DC, Dudoit S, Brenner SE. 2009. Genome-wide identification of alternative splice forms down-regulated by nonsense-mediated mRNA decay in *Drosophila*. *PLoS Genetics* 5:e1000525.
8. Gerstein M, et al. 2014. Comparative analysis of the transcriptome across distant species. *Nature* 512:445-448.
9. Boyle A, et al. 2014. Comparative analysis of regulatory information and circuits across distant species. *Nature* 512:453-456.
10. Li JJ, Huang H, Bickel PJ, Brenner SE. 2014. Comparison of *D. melanogaster* and *C. elegans* developmental stages, tissues, and cells by modENCODE RNA-seq data. *Genome Res* 24:1086-1101.
11. Graveley BR, Brooks AN, Carlson JW, Duff MO, Landolin J, Yang L, et al. 2011. The developmental transcriptome of *Drosophila melanogaster*. *Nature* 471:473-479.
12. Brooks AN, Duff MO, May G, Yang L, Bolisetty M, Landolin J, Wan K, Sandler J, Celniker SE, Graveley BR, Brenner SE. 2015. Regulation of alternative splicing in *Drosophila* by 56 RNA binding proteins. *Genome Res* 25:1771-80.

13. Lareau LF, Brenner SE. 2015. Regulation of splicing factors by alternative splicing and NMD is conserved between kingdoms yet evolutionarily flexible. *Mol Biol Evol* 32:1072-1079.
14. Engelhardt BE, Jordan MI, Srouji JR, Brenner SE. 2011. Genome-scale phylogenetic function annotation of large and diverse protein families. *Genome Res* 21:1969-1980
15. Radivojac P, et al. 2013. A large-scale evaluation of computational protein function prediction. *Nature Meth* 10:221-227.
16. Xu A, Desai AM, Brenner SE, Kirsch JF. 2013. A continuous fluorescence assay for the characterization of Nudix hydrolases. *Anal Biochem* 437:178-184.
17. Fox NK, Brenner SE, Chandonia JM. 2013. SCOPe: Structural Classification of Proteins extended, integrating SCOP and ASTRAL data and classification of new structures. *Nucl Acids Res* 42:D304-9.
18. Fox NK, Brenner SE, Chandonia JM. 2015. The value of protein structure classification information surveying the scientific literature. *Proteins* 83:2025-38.
19. Chandonia JM, Brenner SE. 2006. The impact of structural genomics: expectations and outcomes. *Science* 311:347-351. \

Presentation: Diagnostic Role of Exome Sequencing in Immune Deficiency Disorders and the Critical Assessment of Genome Interpretation

This presentation covered three projects in interpretation of human genomic variation. We have developed an analysis protocol whose distinctive features enabled solving clinical cases. Applied to exomes from newborn patients with undiagnosed primary immune disorders, it helped guide appropriate treatment, family genetic counseling, and avoidance of diagnostic odyssey.

Preliminary findings will be shared from NBSeq, a project that explores the feasibility of sequencing to augment or supersede mass spectrometry for public health newborn screening. The Critical Assessment of Genome Interpretation (CAGI) is a community experiment to objectively assess computational methods for predicting the phenotypic impacts of genomic variation. The fourth international CAGI concluded in March 2016 and new results were presented.

Impressions: I was delighted to be able to participate again in this meeting. The meeting has a well-honed design to which I would not suggest major changes. The conference has outstanding

researchers giving extremely current and exciting work. It is always a great opportunity for me to learn of state-of-the-art research and make new connections. The location is close enough to avoid undue travel, but provides a congenial atmosphere conducive to interaction. I enjoy the student/postdoc talks on the first night.

Some suggestions: have the program include the name of trainees/advisor/mentor, to better relate them to their work. The venue this year was not quite as nice as last year, but still delightful. Also, consider having one afternoon with a longer break to allow people to explore the Cabo area without missing sessions. The meeting is outstanding in every way.

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Presentation: Insights into the structural assemblies governing RNA virus transcription and genomic replication

Mononegaviruses are non-segmented, single-stranded RNA viruses with negative-sense genomes. The limited size of the genomes of these viruses means that each protein encoded has multiple functions, with oligomerization being critical to determining which function is achieved. Oligomerization and its functional consequences have been analyzed here for a key component of the viral replication complex and for the viral matrix.

Mononegaviruses must encode their own viral RNA-dependent RNA polymerase (RdRp) in order to transcribe mRNA and replicate their genome. This RdRp is comprised of two proteins: the large protein, L, which contains all of the catalytic activity of this enzyme and the phosphoprotein, P, which acts as a co-factor and tethers L to the viral genome. For filoviruses, VP35 is the P homolog. These polymerase co-factors, P and VP35, must homo-oligomerize in order to function; and, in the case of paramyxoviruses and filoviruses, this oligomerization is engendered by a long, coiled-coil domain. Here, I illustrated that the Nipah P multimerization domain is a long, parallel, tetrameric, coiled coil, which a central basic patch

essential for polymerase function. Studies on the Marburg virus VP35 oligomerization domain indicate that it is also a long, parallel, coiled coil, but that it is trimeric instead of tetrameric. Trimerization was unexpected as VP35 of the related filovirus Ebola virus is tetrameric. However, these distinct oligomeric states may give rise to the observed differences in the RNA replication strategies and potency of immune evasion by these two related viruses.

Impressions: As always, this conference is one of the best places to hear about new and interesting science, and have important scientific discussions. As a young scientist trying to build my network both within academia and industry, I was very thankful to have this opportunity. I love that this conference has no poster session and was thankful for all of the opportunities to speak with the other attendees. I am excited to try some new techniques that I heard about at this conference and look forward to collaborating with others at this meeting.

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Presentation: The rate at which new protein structures are solved has steadily increased, and now averages over 800 structures per month. However, only 17 of these structures per month (i.e. 2%) represent the first solved structure from a Pfam protein family. The first structure from a protein family enables inference of the fold and of ancient relationships to other proteins. Seventeen families per month is the lowest rate at which families have been structurally characterized in nearly 20 years, despite vastly more efficient technology, and is less than half the rate at which families were solved during the heyday of Structural Genomics, between 2003 and 2007. This decline in structural novelty has made interpretation of human genetic variation more challenging than would otherwise be the case: while ~60% of the residues in the human proteome are homologous to a known structure, this fraction might be 80% had structural characterization of new protein families continued at the 2007 pace.

Impressions: The size and length of the meeting were perfect. I appreciated the time people took to craft a presentation specifically for this meeting. I had many great discussions with other attendees, which I expect will lead to productive new collaborations. The location was also excellent.

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Overview: My lab's research focuses on single-molecule biophysical studies of protein disorder. Intrinsically disordered proteins are ubiquitous and functionally important in cell biology, but are hard to study by conventional methods due to their conformational heterogeneity. Our work mainly uses single-molecule methods, which avoid ensemble averaging and therefore permit more detailed studies of such dynamic structural complexity.

Presentation: I presented our ongoing work using single-molecule FRET and complementary ensemble methods to study multiple structural states in intrinsically disordered proteins. One focus is understanding how these structural landscapes can be modulated by binding to partners. In addition, I discussed initial studies using these methods to study IDP structural features in phase separated protein droplets, of relevance to the biology of membraneless cellular granules.

Impressions: The excellent quality of presenters/attendees, compact size of the meeting, high-quality location, and structure of the meeting (intense presentation sessions with plenty of time in between for interactions), combined to encourage detailed discussions of a diverse array of key and cutting-edge topics related to structural biology. Overall, this was an outstanding meeting.

Name: Stefano Forli

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Overview: The meeting has been a terrific experience. I liked the selection of talks and the variety of presenter background. For young investigators such as myself, this is a perfect chance to showcase my research and start new collaborations. Indeed, the relaxed and informal environment facilitates dramatically interactions.

Presentation: A very strong point of the meeting for me has been the variety of subjects and disciplines from talented scientists. Presentations covered a wide range of subjects, from basic to applied research, including some drug design presentations, which I particularly appreciated.

Impressions: Overall, the meeting is a perfect occasion for interacting with many skilled scientists, discovering new interesting targets and approaches, and establishing new connections and collaborations.

I am definitely looking forward to the next opportunity to participate.

**Name: Danielle Grotjahn
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Presentation: My research project uses cryo-electron tomography to examine the three dimensional (3D) ultrastructure of the dynein-dynactin motor protein complex. In our preliminary 3D analysis, we elucidated several key features regarding the arrangement of the complex that were missing from previous two-dimensional (2D) structural characterization. We hope that by directly visualizing the 3D organization of the dynein-dynactin complex, we will shed light on mechanisms that allow for the activation and directed movement of the motor complex along microtubules in cells.

Impressions: I thought this was one of the best meetings I've ever attended! I think one of the aspects that make this meeting different from others is that nearly everyone (with few exceptions) that attends the meeting is required to present. From my experience, this leads to more interaction and networking opportunities among the attendees, both during and after the organized meeting sessions. As a graduate student, I also benefitted from presenting my research and receiving feedback and comments on my project. I would recommend no changes to the meeting, as I think it is already well organized and structured.

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Presentation: My postdoctoral work has focused on the development and application of an engineered protein ligase based on the NEDD8-E2 conjugating enzyme, which we have named the NEDDylator. By conjugating the NEDDylator to bait proteins, we previously showed that we could uniquely tag prey proteins with a biotinylated NEDD8 tag and then use this tag to identify the prey proteins. I have focused on applying this technology to identifying the protein targets of small molecules. In my presentation, I described our use of the kinase inhibitor dasatinib as a test system. I showed that we were able to label and identify known targets of dasatinib in cellular lysates using the NEDDylator and a SILAC-based quantitative proteomics workflow.

Impressions: I believe the size of the group was appropriate. I had many great interactions, both in small groups and one-on-one. The location of the meeting was very nice. The resort was clean and upscale. The quality of the talks was very high, and the diversity of topics was nice. I enjoyed the vast majority of talks. Speakers were also very respectful of their time slots, so sessions did not drag on. That was appreciated. The length of the meeting in terms of days was fine. I felt like the sessions went kind of late every day. It was nice to have the afternoon off, but having sessions during supertime meant that we ended up eating pretty late every night.

Name: Jennifer Kefauver

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Presentation: I presented my research on the structural heterogeneity of the Volume Regulated Anion Channel. This ubiquitous vertebrate channel that senses hypo-osmotic stress was recently shown to be composed of the five members of the LRRC8 family of transmembrane proteins. Each subunit is differentially expressed in various cell types and the presence of different LRRC8 subunits affects single-channel properties. However, this compositional heterogeneity makes structural studies difficult. We use CRISPR/Cas9 to knock out each subunit, then over-express tagged constructs to produce a maximally homogenous sample for structural studies.

Impressions: I really enjoyed every aspect of this meeting. The small group size and the opportunity to hear each person speak about their research make this conference unique. Speaking to professors and postdocs has given me fantastic insights into my own work and my career.

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Email address: afkintzer@msg.ucsf.edu
Phone number: 4154763937

Presentation: Structure of a Two-pore channel TPC1

Impressions: Wonderful small group of brilliant scientists from top institutions and companies. The balance between cutting-edge academic and industrial research was a rare treat. While humbling on one hand, this meeting brought a wide perspective to important areas in biomedical research.

Name: Jack Kirsch
Department: QB3 Institute, UC Berkeley
Mailing address: 572 Stanley Hall

UC Berkeley, CA 94720
Email address: jfkrisch@berkeley.edu
Phone number: (510) 642-6368

Overview: Inspiring and informative as it has been for the last 20 years. I learned from all of the talks, and continue to be impressed by the attendees' accomplishments. Those from industry were particularly good this year.

Presentation: I am retired, so I did not present this year (:

Impressions: The site was well chosen, as there were many opportunities for informal talks. The rooms were comfortable and the food excellent. My only regret was that I didn't have a chance to go to the pool or even to leave the hotel, because I was so engaged with speaking with colleagues and students.

Name: Alexander Krois
Supervisor: Peter Wright
Department: The Scripps Research Institute (DISCO Bio)
Mailing address: 3435 Lebon Drive, Apt 1131
San Diego, CA, 92122
Email address: akrois@scripps.edu
Phone number: (919)624-1589

Presentation: "Versatility through flexibility, p53, intrinsic disorder, and inteins"

My work seeks to characterize long-range interactions involving the intrinsically disordered domains of p53. Prior NMR work on full-length p53 has been limited by the size of the protein (~180kDa), and by substantial resonance overlaps in the NMR spectra. Using trans-intein splicing, I have generated segmentally labeled p53 proteins in which only select regions are isotopically enriched and thus visible by NMR. These construct are now being used to probe how the disordered domains of p53 behave in the context of the full-length protein, and how they relate to p53 function.

Impressions: This was a very enjoyable meeting. I feel I learned a great deal and met a large number of new people. I was very pleased with the site of the conference, and how everything was organized.

Name: Gabriel Lander
Department: TSRI
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HZ 102L
La Jolla, CA 92037
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Overview: An inspiring conference that prompts new ideas for existing and new projects in lab. Held at an excellent setting & venue for one-on-one scientific discussions and conducive to setting up new collaborations.

Presentation: I discussed a new validation criterion for assessing the quality of atomic models generated from cryoEM reconstruction. An ensemble of structures are generated, and RMSDs based on the convergence of the models are used to pinpoint well-structured or poorly defined areas of density.

Impressions: The best meeting I attend all year. I'm exposed to more interesting and applicable science in Cabo than in most other conferences.

Name: Carolyn Larabell
Department: University of California, San Francisco
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94143-2722
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Overview: My research focuses on developing new imaging tools, most recently soft x-ray tomography. This imaging technique is similar to medical CT scans, but images cellular structures at about 30-50 nm resolution. We are also developing methods for correlated fluorescence and x-ray tomography to reveal the location of molecules with respect to cell structures.

Presentation: I briefly described the principles of soft x-ray tomography (SXT) and its quantitative imaging abilities, and then showed examples. We used SXT to image and quantify the increase in chromatin compaction and its concomitant spatial reorganization during the processes of neurogenesis and hematopoiesis. I also showed correlated fluorescence and x-ray

tomography of the inactive X chromosome and its structural organization in the intact interphase cell.

Impressions: Excellent meeting! Just the right size and environment to encourage interactions and collaborations.

Name: David Millar

Department: Integrative Structural & Computational Biology,
The Scripps Research Institute

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La Jolla CA 92037

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Phone number: (858) 784 9870

Overview: My lab is engaged in the development and application of single-molecule fluorescence methods for the study of protein conformational dynamics and protein-nucleic acid interactions. Our specific areas of interest are: (1) activation mechanisms and signaling by G protein-coupled receptors, (2) functional coordination in DNA polymerases and (3) trafficking and assembly of HIV-1.

Presentation: I presented our recent studies of the role of the HIV-1 Rev protein and the host protein DDX1 during nuclear export of viral mRNA. Rev is the essential viral protein required for viral RNA export from the nucleus to the cytoplasm of an infected cell, but its activity is significantly enhanced by the host protein DDX1, a member of the DEAD-box family. We have developed single-molecule assays to investigate how DDX1 promotes Rev function. Our results show that DDX1 promotes oligomerization of Rev on its cognate RNA, the Rev-response element (RRE). DDX1 achieves this effect by conformational remodeling of the RRE. I also described a new project in which we are using single-molecule methods to visualize the oligomerization of the HIV-1 Gag protein during HIV-1 assembly.

Impressions: This is one of the best scientific meetings that I attend each year and I have been to all 26 meetings. The quality of the science is always outstanding and I enjoy the opportunity to learn about equally exciting developments in the biotech and pharma sectors.

Name: Daniel L Minor

Department: Cardiovascular Research Institute/ UCSF

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Overview: My laboratory studies the fundamental mechanisms of ion channel action. We use a combination of structural and functional measurements to understand the means by which channels sense and respond to inputs. We are also deeply vested in the development of new chemical biological approaches that can control channel function.

Presentation: I presented our recent studies on the origins of thermal sensing by ion channels. This has been a topic of great interest having considerable debates in the field regarding whether thermal sensing in channels happens via the action of a dedicated 'temperature sensor' domain, akin to how voltage or ligands may be sensed, vs. having an origin in a more distributed property of the molecule. Our studies of the large family of bacterial voltage-gated sodium channels (BacNavs) identified the first bona fide temperature sensor domain in an ion channel. Our combined X-ray crystallographic, electron paramagnetic resonance spectroscopy, and electrophysiological studies demonstrate that a domain termed the 'neck' that is located just under the cytoplasmic side of the channel pore undergoes a temperature-dependent unfolding reaction that endows the channel with the ability to sense and respond to temperature changes. This architecture is found throughout the voltage-gated ion channel family, most notably in channels involved in pain sensing. Hence, our findings uncover a general mechanism for ion channel modulation.

Impressions: The meeting was terrific. The talks were uniformly of exceptional quality. The balance between lectures and interaction time was perfect and allowed for many discussions with both academic and industrial colleagues.

Name: Sasha Moola
Supervisor: Prof Ian A. Wilson
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Phone number: 8148269015

Presentation: My research focuses on using X-ray crystallography to understand the evolution of broadly neutralizing antibodies against HIV during natural infection - in particular, the evolution of antibodies directed against the glycan-centered N332 supersite of vulnerability in a donor from the longitudinal Protocol C cohort. I presented 4 crystal structures of antibodies from this lineage, which reveal two distinct sublineages descended from the same B-cell and occurring concurrently within this individual. Each sublineage contains a distinct insertion in the heavy chain CDRH1, and the structures suggest that their mechanisms of action may differ substantially. Further structures will provide insight into these mechanisms and how they were elicited via antibody-antigen interactions over the course of natural infection.

Impressions: The meeting provided a wonderful opportunity to engage with a variety of structural research outside of my immediate field, and was a very suitable size to allow interaction with other attendees. The setting was fantastic and the talks were very interesting, and of a quantity and length that allowed the meeting to be informative and intensive without being overwhelming.

Name: Daniel Murin

Supervisor: Andrew Ward

Department: Department of Integrative Structural and Computational Biology

Mailing address: 10550 North Torrey Pines Rd, La Jolla, CA, 92037

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Presentation: One Gene, Two Proteins: Cryo EM Structures of Ebola Virus sGP

Impressions: I was happy to be back at the Hyatt Ziva. I thought everything ran very smoothly and we were very comfortable the entire time. I wouldn't change a thing and hope I get invited again to go in the future!

Name: Takanori Otomo

Department: Integrative Structural and Computational Biology/TSRI

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Overview: Research in the Otomo lab aims at elucidating the molecular mechanisms underlying and regulating autophagy. We are particularly interested in understanding the function of the protein complexes that directly mediate the formation of the double-membraned vesicles called autophagosomes. We use all major structural tools, such as X-ray crystallography, NMR spectroscopy, and electron microscopy (EM in collaboration with the Lander group), to gain structural information on autophagy-related proteins. Hypotheses generated from structural studies are tested using biochemical and cellular autophagy assays. Our goal is to provide sufficient details at atomic resolution to help explain how the concerted action of autophagy-related proteins generates autophagosomes as well as how cargos are sequestered into autophagosomes for selective degradation. We hope our findings will have direct impacts on rational developments of therapeutics targeting autophagy for cure of human diseases, such as cancer and neurodegeneration.

Presentation: I presented our unpublished crystal structure of Atg23, a yeast protein required for early step of autophagy. Although the precise function of this protein had not been identified, Atg23 was known to be required for generating small vesicles carrying the autophagic integral membrane protein Atg9 from Golgi. The helix-rich structure of Atg23 appears to be new and mediates dimerization in the crystal. The dimerization generates a curved, elongated architecture with negatively charged amino acids in the concave side. This structure led us to hypothesize that Atg23 may function as the membrane-sculpting protein. Our biochemical data support this hypothesis, providing the basis of the formation of Atg9 vesicles. Thus our structural biology approach has allowed us to identify the biochemical function of Atg23, highlighting the power of structural biology for mechanistic studies.

Impressions: The meeting provided a great opportunity to learn more about structural studies carried out in TSRI and UCSF. There were also opportunities to interact with various people who we

normally do not meet. Overall this was a fantastic meeting.

Name: Vijay Reddy

Department: Integrative Structural and Computational Biology

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The Scripps Research Institute,

La Jolla, 92037

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Overview: My group's research involves structure-based approaches in virology: 1) Structural virology, 2) Structural bioinformatics and 3) Customized vaccine design. We employ structural and molecular biology approaches to understand the molecular basis for virus lifecycle. We also maintain a virus structure database (<http://viperdbscripps.edu>), where the coordinates of the structures of spherical viruses are stored in a single icosahedral convention and computationally analyzed in terms of protein-protein interactions and surface properties. Additionally, we use simple virus capsids as the polyvalent platforms for displaying foreign epitopes of interest and use them as customized vaccines.

Presentation: I presented the work on using Tomato Bushy Stunt Virus (TBSV), a plant virus, as the versatile vaccine display platform. We displayed 180 copies of epitopes from the ricin toxin on the surface of TBSV. Using this reagent, we were able raise antibodies in mice that detected full-length ricin toxin in western blots. Further studies are underway to display Dengue virus T-cell epitopes on the surface of TBSV. Additionally, I briefly introduced and described VIPERdb, the virus structural database.

Impressions: Location: Excellent

Number of participants: Ideal

Length of the meeting: Perfect

The presentations were excellent and stimulated a lot of discussions. Overall, the Cabo meeting provided a great avenue for sprouting new ideas, fostering healthy discussions and future collaborations.

Name: Andrej Sali

Department: Bioengineering and Therapeutic Sciences

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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 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

Department: UCSF/ProLynx

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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 C_{max} 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.

Name: Chris Schulze

Supervisor: Matthew Bogyo

Department: Stanford

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Phone number: 732-598-2858

Presentation: An in vivo multiplexed small molecule screening platform identifies a pro-metastatic factor in pancreatic cancer.

Impressions: Great, enjoyed having the students going first so that we all know what everyone is working on from the beginning. Makes the interactions between students/postdocs easier. Liked the venue. Would have like a free afternoon/evening without talks afterwards to appreciate the area outside of the hotel.

Name: Pedro Serrano

**Department: Integrative Structural and Computational Biology,
TSRI**

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MBB-28

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Overview: We use Nuclear Magnetic Resonance (NMR) spectroscopy for the functional and structural characterization of proteins and their interactions with other biomolecules. We are especially interested in investigating how flexibly disordered elements govern protein recruitment and nucleic acid recognition. To this end, we are developing new high-dimensional NMR experiments to obtain complete resonance assignments of unstructured proteins and strategies to produce stable proteins samples for studies in solution. These approaches overcome two important limitations and are being used to study arginine-serine-rich domains in splicing factors, inhibitors of the oncoprotein Myc and p62, which is a central player in mTORC1 activation and cancer.

Presentation: Arginine-serine-rich domain (RS) are flexibly disordered polypeptides present in multiple splicing factors that govern protein recruitment, nuclear localization and RNA recognition. We have shown that, in the splicing factor SFRS1, the RS domain interacts with a RNA recognition motif (RRM) and identified the binding interface. This novel interaction has important functional implications. For example, our biochemical and cell biology assays with mutants disrupting RS-RRM contacts revealed that these are required for nuclear localization and SFRS1 storage in speckles. Binding to RRM also controls the directionality of RS phosphorylation by the kinase SRPK1 and is responsible of the poor solubility observed for RS domains. These initial studies provide a foundation for studying the multiple roles of RS domains during spliceosome complex assembly and catalysis.

Impressions: The meeting was very enjoyable. The quality of the work presented and the speakers was very high. I especially liked the diversity of topics and the opportunity given to graduate students to share their results. The venue and the organization were splendid. Questions or concerns were addresses promptly and very efficiently. The casual setting was especially helpful to establish new collaborations and facilitated scientific discussions.

Name: Shanshan Lang
Supervisor: Ian A. Wilson
Department: TSRI
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Presentation: Anti-idiotypic antibodies K1-18 to engage the VH1-69 germline for flu vaccination

Impressions: Great meeting.

Name: Sergey Shnitkind
Supervisor: Peter Wright
Department: TSRI, Department of Integrative Structural and Computational Biology
Mailing address: 10550 North Torrey Pines Road, MB204, La Jolla, CA 92037
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Phone number: 858-784-2122

Presentation: I work on a ubiquitously expressed transcription factor that is involved in several regulatory networks. This protein contains large regions of intrinsic disorder that contribute to its function and regulation. My research project aims at elucidating how changes in the structural ensemble of this transcription factor, in response to post-translational modifications and binding events, can result in its functional regulation. I use a variety of biophysical techniques including NMR and fluorescence measurements.

Impressions: The meeting provided a great opportunity to meet and network with top scientists. The presentations from both academia and industry scientists were outstanding and very informative. The size of the group and location were ideal for networking after the talks and throughout the day.

Name: Glen Spraggon
Department: GNF
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La Jolla, CA 92121
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Phone number: 858 812 1567

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 protein based biotherapeutics and small molecules 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, 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: Unnatural DNA aptamers, evolved to bind to proteins via Systematic Evolution of Ligands by Exponential Enrichment (SELEX) technology are an alternative to Antibodies and can be used as probes for the understanding of extracellular biology. A small number of Slow Off-Rate Modified Aptamers (SOMAmer) structures exist in complex with Protein targets. The incorporation of unnatural hydrophobic bases into these DNA aptamers, allows the DNA to access a large range of folds and bind to targets in a similar way to proteins. In collaboration with Somalogics Inc. we have extended this structural repertoire by solving the X-ray structure of a SOMAmer in complex with an extracellular protein. The structure illustrates a binding mode that is novel and would be extremely difficult to achieve via a protein based probing technique.

Impressions: The WMEN conference was a wide mixture of novel techniques and molecular engineering topics, covering everywhere from small molecule chemistry and drug discovery to the development of novel biotherapeutics and vaccines. The format and location of the meeting was pleasant and sociable and provided an outstanding setting for education, collaboration and active discussion with scientific leaders in their respective fields. Multi-disciplinary sciences represented at the conference.

Name: Robert M. Stroud

Department: Department of Biochemistry & Biophysics, UCSF

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Overview: The main project in my laboratory discussed concerned the structural determinations of an ion channel TPC1 and two 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 VGLUTs, vesicular glutamate transporters of key importance for the nervous system.

Presentation: The mechanism was defined in structures that show how the channel and transporters work and are sensitive to voltage, and to transported nutrients. Protein crystal structure has a key role in the understanding of an essential process in cell biology. New channels and transporters from human disease connections and from human brain are basis for drug design.

Impressions: Impressions of the Meeting:

Location: Excellent.

Number of participants: Good size

Convenient for access from California, and sufficiently remote to concentrate people's time and attention. Cabo San Lucas is excellent after refinement of location over the years.

Number of participants: A comfortable size for the meeting is about 40 people, with 20 speakers. Attendees and presenters were excellently chosen from the superb groups in structural biology at Scripps and at UCSF.

Length of meeting: The meeting of 3 days length is quite adequate and more would probably be too much.

The science presented was absolutely first rate with many important new breakthroughs in the fields of immunology, drug design, chemical basis for inhibition, chemical basis for understanding enzyme mechanisms and cell surface receptor interactions.

Name: Andrew Ward

Department: Integrative Structural and Computational Biology

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La Jolla, CA 92037

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Overview: Another great year of science presented by TSRI, UCSF, industry, and invited guests. There was lot of excitement

about advances in membrane protein structural biology and encouraging data on emerging technologies such as cryoEM. There were also some great talks about early drug discovery. Ian Wilson presented the Keynote lecture that was a history of antibodies and antibody structure that was an impressive compendium of work.

Presentation: I presented high-resolution cryoEM studies of HIV-1 envelope glycoprotein and coronavirus S protein structures. We are using this structural information for vaccine design and development of immunotherapeutics. My talk also included some cautionary notes on not over interpreting cryoEM data.

Impressions: As expected, I had a great time and enjoyed the balance of science and casual discussions with colleagues during the free time. The resort and food were very nice.

Name: Jim Wells
Department: Pharm Chem
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Phone number: 6503435656

Overview: Excellent talks and interactions
Presentation: Presentations were too short. I'd recommend extending each talk by 5 min.

Impressions: Much better venue than the one I was at 4 yrs ago. Good organization and fun interactions. It would be good if each evening there was a designated "party" space with drinks for the group.

Name: James Williamson
Department: DISCOBIO
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MB-33
TSRI
La Jolla, CA 92037
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Phone number: 858-784-8740

Overview: This meeting was one of the more excellent of the recent meetings due to the overall quality of the novel science presented, and the broad range of interactive speakers. Again, the

students and postdoc talks were a highlight, and the industrial talks were much more engaging than in some years.

Presentation:

Impressions: A very unique meeting, bringing together structural biologists at the interface of drug discovery, with a blend of academia and industry. The Scripps/UCSF focus of the meeting is complemented with a range of sponsors and invited guests from great institutions. The venue is excellent. Comfortable rooms and good food, and the meeting room is quite comfortable. The talks are about the right length, and there was generally adequate discussion at the end. The sessions were organized thematically as well as possible

Name: Ian A. Wilson

Department: The Scripps Research Institute

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Phone number: 858-784-9706

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 have directed 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: This year I gave the Keynote lecture entitled "A perspective on antibody structure and function from 35 years in the field' where I discussed the history of antibodies from the first structures by Poljak and Davies back in the early 1970's to present day. In my lab, we have determined over 250 antibody structures and complexes with a wide assortment of antigens including peptides, small molecules, proteins and glycans. We have investigated antibodies from mouse, rabbit, hamster, shark, cow and human where, although they have the same overall immunoglobulin fold, they have specific features that differ from species to species. Cow antibodies, for example, have super-long CDR H3s of more than 60 residues which fold up into a separate domain consisting of a globular, disulfide-rich knob and an elongated beta-strand stalk. Human antibodies can also have long

CDR H3's up to 40 residues that enable them to get into recessed sites of vulnerability on viral antigens and also penetrate the glycan shield on the HIV-1 envelope protein. Analyses of these structures have allowed common features to be recognized even in the CDRs. For example, the canonical structures for the CDRs from Lesk and Chothia in the late 1980's have greatly helped in prediction and design of antibody structures. I concluded with recent examples of how broadly neutralizing antibodies isolated from humans can provide valuable information on how to combat viruses such as HIV and influenza and how this information can be used for design of novel vaccines.

Impressions: Nice to be back at the completely renovated Hyatt Ziva Los Cabos. Excellent meeting as always with an exceptional mix of academia and industry. The formal program was very stimulating as well as the discussions and plentiful opportunities to interact with the diverse and interesting set of participants. The students and postdocs excelled as always in their short and action-packed presentations. It is hard to believe the meeting can keep getting better and better - - but that is what it seems.

Name: Dennis Wolan

Department: Molecular and Exp. Medicine, TSRI

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Overview: Our work focuses on the development, validation, and use of small molecule probes to directly identify and quantitate microbial enzymes from the distal gut microbiome. We use this chemical biology methodology in combination with mass spectrometry-based proteomics and biophysics to find aberrant protein functions associated with human ulcerative colitis.

Presentation: Elucidation of aberrant host and microbial proteins in colitis by large-scale metaproteomics

Impressions: This meeting was exceptional. The quality of cutting-edge research presented by the students, postdocs, and faculty was outstanding. The overall schedule is great, as it allows UCSF and TSRI colleagues to intermingle and discuss potential collaborations.

Name: Qinghai Zhang

Department: Department of Integrative Structural and computational Biology; The Scripps Research Institute

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Overview: We develop chemical tools including membrane simulation reagents and small molecule ligands for structural and functional studies of membrane-bound proteins with biological and biomedical significance. A current focus is to study the polyspecific drug interaction and drug transport mechanism of ATP-binding cassette transporters.

Presentation: We have designed and characterized cyclic peptides as potent inhibitors and stimulators of P-glycoprotein, which is a primary ABC transporter causing multidrug resistance in cancer. I presented new co-crystal structures and structure-activity-relation studies revealing the flexible drug binding sites and conformations of this transporter protein.

Impressions: This is a fantastic meeting with a balanced group of young and senior faculties, graduate students, and representatives from biotech industry. The meeting site is nice and relaxing. The format and schedule of this meeting allows good opportunities for all participants to socialize and interact with each other.

2017 WMEN Keynote Speaker



Peter Walter is a Distinguished Professor of Biochemistry and Biophysics at UCSF and an HHMI Investigator. He graduated from the Free University of Berlin in 1976, and received

his Masters of Science in Organic Chemistry from Vanderbilt University in 1977. In 1981 he obtained his PhD in Biochemistry at The Rockefeller University. In 1983, Peter joined the faculty of the Department of Biochemistry and Biophysics at the University of California at San Francisco, and served as Department Chair from 2001 until 2008. He is the 2016 President of the American Society of Cell Biology. Peter's awards include the Eli Lilly Award, the Passano Award, the Wiley Prize, the Stein & Moore Award, the Gairdner Award, the E.B. Wilson Medal, the Otto Warburg Medal, the Jung Prize, the 2012 Ehrlich and Darmstaedter Prize, the 2014 Shaw Prize, the 2014 Lasker Award and the 2015 Vilcek Prize.

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