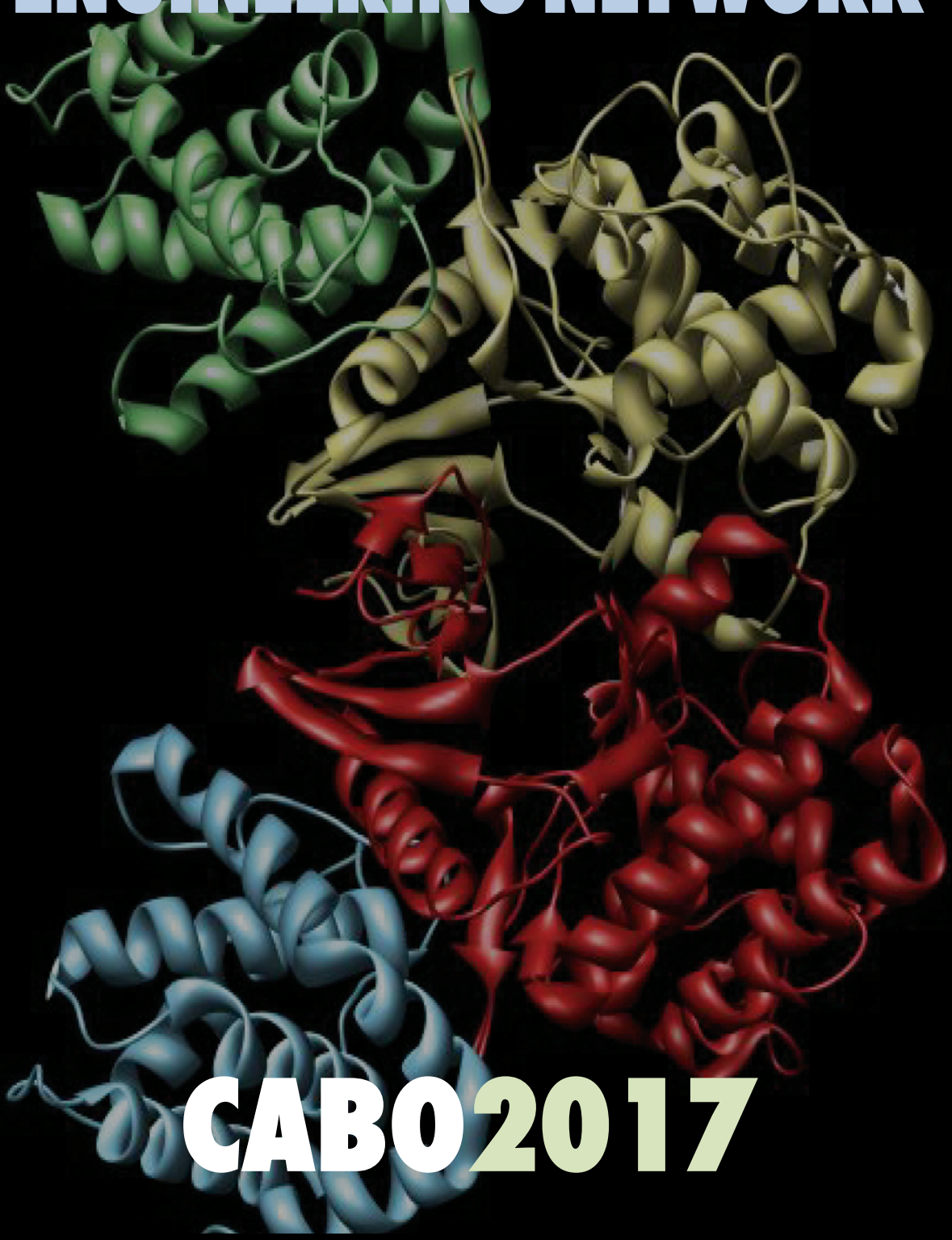
WORLD MOLECULAR ENGINEERING NETWORK



CABO 2017

UCSF University of California, San Francisco
School of Pharmacy

The Scripps Research Institute®

Our History

The WMEN conference has been held for the past 27 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, fifteen years ago, the venue moved from Cabo San Lucas to all-inclusive resorts in San Jose del Cabo. The 2017 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.

WMEN CABO XXVII, May 6-9, 2017

Twenty-Seventh Annual Meeting on Structural Biology

Saturday Evening, May 6

17:00	**Ian Wilson and Andrej Sali**	**Introduction and Welcome**
17:15	**Peter Walter, UCSF**	**Keynote Lecture-** From protein folding to cognition: a serendipitous path of discovery
18:00	**Self-Introductions**	
	Jack Kirsch	UCB
	Jeanne Baker	Merck
	Jacob Cha	Pliant Therapeiutics
	Jonathan Moore	Vertex Pharmaceuticals

18:10-20:45 **Short Presentations (5+1 min.) by TSRI and UCSF Graduate Students, Postdocs, and Other Researchers**
(Chair: Erica Ollmann Saphire)

Cristina Puchades Garcia	TSRI	Mitochondrial inner membrane AAA proteases
Alexander Krois	TSRI	Versatility through flexibility - p53 and intrinsic disorder
Jennifer Kefauver	TSRI	Architecture of the volume-regulated anion channel
Christopher Cottrell	TSRI	Modeling glycans into EM density
Ke Yang	TSRI	Structural basis of cooperativity in a hematopoietic transcription factor: Coactivator ternary complex
Danielle Grotjahn	TSRI	Three-dimensional snapshots of the dynein-dynactin complex
Sergey Shnitkind	TSRI	Regulation of a transcription factor
Emily Roncase	TSRI	Insights into activation and substrate selectivity of a clostripain-like protease from *B. thetaiotaomicron*
Sasha Moola	TSRI	Crystallographic characterization of a novel family of broadly neutralizing anti-HIV antibodies

Break

	Louise Heinrich	UCSF	ORACL 2.0: Casting a Wider Net
	Ruth Huttenhain	UCSF	An approach to spatiotemporally resolve protein interaction networks in living cells
	Chien-Hsiang Hsu	UCSF	Want early retirement? Check your p21
	Matthew Ravalin	UCSF	Linking caspases & proteostasis networks through TPR domains
	Brooke Gardner	UCSF	Molecular motors involved in peroxisome biogenesis
	Natalia Sevillano	UCSF	Identification of inhibitory antibodies for active urokinase plasminogen activator (uPA)
	Bryan Thurtle-Schmidt	UCSF	The elevator mechanism: a model for transport by SLC4 anion exchangers
	Jordan Carelli	UCSF	Anti-cancer cyclic peptides trap distinct conformational states of ribosome-bound elongation factor 1A
	Lina Leon	UCSF	Defining Cas3 recruitment in a minimal system
	Krisna Van Dyke	UCSF	Characterizing the structural basis of bacterial cell wall recognition
	Aditya Anand	UCSF	Structural insights into the activity of a memory-enhancing compound
	Ilan Chemmama	UCSF	Towards modeling multiple states of biomolecules satisfying spatial restraints from single-particle EM
	Jain-Hua Chen	UCSF	Imaging and characterizing the relationship between cell size and nuclear shape
	Allison Roberts	UCB	Utilizing chemoproteomic profiling to discover anti-cancer covalent ligands and druggable hotspots
	Assen Rougev	UCSF	Genetic interactions mapping in mammalian cells using CRISPRi
	Nicholas Polizzi	UCSF	A core principle of ligand-binding protein design
21:00	**Reception**		**Poolside**

Sunday Morning, May 7

Integrative Structural Biology (Chair: Robert Stroud)

08:40	**Andrej Sali**	UCSF	Integrative structural biology
09:00	**Jeff Lengyel**	FEI	In situ structural biology - Advances in cryo-electron tomography
09:20	**Gabriel Lander**	TSRI	Electron microscopy of molecular motors in motion
09:40	**Mark Yeagar**	TSRI	MicroED structure of a CTD-SP1

			construct of HIV-1 Gag with maturation inhibitor Bevirimat
10:00	**Bo Huang**	UCSF	Watching the inner life of a cell: CRISPR, GFP and Imagenomics
10:20	**Break**		
10:40	**Kendall Nettles**	TSRI	Super-resolution X-ray crystallography for deciphering ligand-induced allostery
11:00	**Peter Wright**	TSRI	Allosteric regulation of the hypoxic response by an intrinsically disordered protein switch
11:20	**Jane Dyson**	TSRI	Intrinsically disordered viral proteins and cancer
11:40	**Patrick Griffin**	TSRI	Chemical biology and differential HDX to probe ligand mediated receptor signaling
12:00	**Takanori Otomo**	TSRI	Structural insight into the membrane associations required for autophagosome biogenesis

Sunday Afternoon, May 7

Antibodies, Epitopes and Vaccines (Chair: Ian Wilson)

16:00	**Dennis Burton**	TSRI	Evaluating HIV vaccine immunogens
16:20	**Andrew Ward**	TSRI	Structure-guided immunogen design
16:40	**Andy Deng**	BMS	V gene germline encoded binding
17:00	**Charly Craik**	UCSF	Targeting dynamic protein targets with antibodies for structural and functional insight
17:20	**Jack Johnson**	TSRI	Archeal virus structure
17:40	**Break**		

Membrane Proteins (Chair: Andrew Ward)

18:00	**Dan Minor**	UCSF	Insights into ion channel mechanism and structure
18:20	**Dennis Wolan**	TSRI	Inhibitors of bacterial lipoprotein signal peptidase as novel antibiotics
18:40	**Robert Stroud**	UCSF	Integrating cell health into endolysosomal targeting and delivery, QED!!
19:00	**David Millar**	TSRI	Conformational dynamics of GPCRs
19:20	**Matthew Francis**	UCB	Targeting the N-terminus for site-selective protein bioconjugation

Monday Morning, May 8

SPONSORS
(Chair: Andrej Sali)

9:00	**Steve Doberstein**	Nektar	NKTR-181: Separating analgesia from abuse liability of opioids
9:20	**Jeremy Murray**	Genentech	Breaking down barriers: Structural biology of lipoprotein biosynthesis in bacteria
9:35	**Paola Di Lello**	Genentech	Discovery and characterization of small molecule fragments that bind and inhibit the USP7
9:50	**Jeff Finer/ Jeff Tong**	3rd Rock Ventures	Third Rock Ventures: Company building strategy and examples of current projects
10:20	**Glen Spraggon**	GNF	Proteasome inhibitors for the treatment of Leishmaniasis, Chagas Disease and Sleeping Sickness
10:40	**Paul Marinec**	Reflexion	Development of a potent D-protein Inhibitor of VEGF-A with reduced immunogenicity and a longer half-life
11:00	**James Partridge**	GBT	Structures of full-length plasma kallikrein bound to highly specific inhibitors illustrate a new mode of targeted inhibition
11:20	**Break**		
11:40	**Cornelia Bellamacina**	Novartis	Discovery of chemical biology probes inhibiting activation of SGK3 kinase in cancer cells
12:00	**James Love**	Atum	Optimization of protein production in human cells
12:20	**Kathleen Aertgeerts**	DART Neuro-science	Rapid optimization of recombinant GPCR protein expression and stability using virus-like particles

Monday Afternoon, May 8

Nucleic Acids and Nucleic Acid Binding Proteins and Evolution
(Chair: David Millar)

16:00	**Jamie Williamson**	TSRI	Quantitative analysis of ribosomal RNA modifications in human cells
16:20	**Carolyn Larabell**	UCSF	Chromatin structure, from stem cell to tumor cell

16:40	**Floyd Romesberg**	TSRI	A semi-synthetic organism that stores and retrieves increased genetic information
17:00	**Larry Gerace**	TSRI	Signaling control at the nuclear periphery
17:20	**Libby Getzoff**	TSRI	Deciphering functional insights from related protein structures and sequences
17:40	**Break**		

Chemical Biology (Chair: Kathleen Aertgeerts)

18:00	**Jack Taunton**	UCSF	How to be selectively promiscuous
18:20	**Qinghai Zhang**	TSRI	Novel amphiphiles for membrane protein studies
18:40	**Daniel Nomura**	UCB	Mapping disease-relevant druggable hotspots using chemoproteomic platforms
19:00	**Jason Gestwicki**	UCSF	Control of tau homeostasis by chaperone networks
19:20	**Lani Wu**	UCSF	The prophesies of ORACLs

Tuesday Morning, May 9

Computation, Health and Disease (Chair: Carolyn Larabell)

8:30	**William DeGrado**	UCSF	Structure and function of amyloid- and prion-forming proteins
8:50	**Steven Altschuler**	UCSF	GSK3 - The center of the universe
9:10	**Stefano Forli**	TSRI	Design of virtual large focused libraries of HIV-1 Integrase inhibitors
9:30	**Nevan Krogan**	UCSF	Using systems approaches to studying disease
09:50	**Ahmet Yildiz**	UCB	The mechanism of dynein motility
10:10	**Joseph Bondy-Denomy**	UCSF	Bacterial viruses thwart CRISPR-Cas bacterial immune systems
10:30	**Seemay Chou**	UCSF	From bacteria to ticks: lessons in antimicrobial defense
10:50	**Arthur Olson**	TSRI	Envisioning the molecular cell
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 suc information is not for public use. Each member of a Conference acknowledges and agrees to these restrictions as a condition of attending the Conference.

Thank you to our sponsors!

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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Ian Wilson
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JoAnne Williams
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Name: Steven Altschuler
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Overview: We seek to understand design principles of biological systems and diseases. We combine intravital imaging, novel organoid systems, computer vision and mathematical modeling to understand how tissues pattern and maintain homeostasis. Two ongoing projects are: neural circuit wiring in the fly and morphogenic signaling in intestinal epithelium.

Presentation: I presented our current work on developing 2D gut organoids. We are using these to direct morphogenic signaling control of tissue patterning. We are also using them as a high-throughput platform for performing single and combination drug perturbations.

Impressions: The meeting was a fantastic opportunity to hear cutting edge science. It was also a first chance for me to meet our colleagues at Scripps and UCB. During the meeting, I initiated several research collaborations.

Name: Cornelia Bellamacina
Department: Novartis Institutes for Biomedical Research
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Overview: I work in the Structural and Biophysical Chemistry group at NIBR Emeryville. The Emeryville site focuses on infectious diseases. Our group performs iterative SBDD on local ID targets as well as fragment hit finding and mechanism of action studies on early stage projects. In addition we support biological projects and non-local disease areas at other NIBR sites such as Oncology and Autoimminity and Transplantation.

Presentation: I presented work on an early stage oncology project, SGK3. The work focused on how we used profile QSAR and other computational approaches to quickly and efficiently obtain tool molecules for biological validation with limited resources. The computational approaches afforded the team with plenty of active-site yet novel compounds, abrogating a need for traditional HTS,

instead the HTS effort was tooled towards finding allosteric inhibitors. Expert knowledge and straightforward chemistry facilitated the work and led to a quick No-Go decision for the project

Impressions: Great meeting, great format. I appreciate that everyone gets to talk. Great venue, facilitating plenty of interactions. As a suggestion, since it is all inclusive, ask the graduate students if they would like to dine as small groups with a sponsor. I recall as a post-doc wanting to soak up knowledge from all sources so that I could choose the right career path. I as a sponsor would be willing to host such a meal. I'll even pick up the dinner tab!

Name: Joseph Bondy-Denomy
Department: Microbiology and Immunology
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Phone number: 415-519-9433

Overview: The meeting provided a great forum for young investigators such as myself to get to know the Scripps/UCSF community in the structural biology area. This was particularly important for interactions with UCSF faculty who I do not normally interact with.

The non-science aspects of the meeting were also top notch. Great venue, support staff, food, social interactions, etc.

Presentation: Presentations were first rate, elite, cutting edge science. A fantastic exposure for all, especially the trainees that this meeting is catered to frankly. The format of having everyone give a talk is unusual but great, in my opinion. My student really enjoyed presenting her work and I received a lot of positive feedback about mine.

Also a great spot for someone like myself who is not a structural biologist to see the latest state of the art and get feedback from future potential collaborators.

Impressions: Very positive. Please see above.

Name: Jordan Carelli
Supervisor: Jack Taunton
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Presentation: Ternatin is a cyclic peptide natural product that was originally studied for potent antiadipogenic activity, but had no known target or mechanism of action. In previous work, we described the synthesis and target elucidation of ternatins, showing that they inhibit cancer cell growth by binding to the translation elongation factor 1A (eEF1A) ternary complex with aa-tRNA and GTP. With biophysicist collaborators, we have recently used cryo-EM and single-molecule fluorescence imaging experiments to determine that ternatins trap eEF1A on elongating ribosomes. Currently, I am investigating the fate of ternatin-trapped eEF1A, which I recently discovered is specifically targeted for proteasomal degradation.

Impressions: The meeting was excellent. I enjoyed getting broad exposure to fascinating work from scientists at UCSF, Scripps, and Berkeley. I particularly enjoyed getting to hear from everyone at the meeting, a feature enabled by the size of the conference. The setting was perfect for both hearing formal talks and getting to know new colleagues.

Name: Ilan E. Chemmama
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Phone number: 786-262-6090

Presentation: Proteins and their complexes can exist in multiple conformational and compositional states. Accurate modeling of these multiple states is key to understanding and modulating their functions. We describe an integrative method for computing a model of multiple states of a biomolecular system, based primarily on particle images from electron microscopy (EM). Our Bayesian approach leverages prior knowledge about the stereochemistry of

molecules, image noise, and potentially other sources of information (e.g., atomic structures of complex subunits and chemical cross-links). We tested the accuracy of the method by using a synthetic benchmark relying on the γ-secretase structure.

Impressions: The meeting was excellent, in term of the number of attendees, the presentations, the science presented and discussed during the meeting, and obviously the location. I most enjoyed the presentations from the invited companies; a minor comment would to have them integrated with academics across the meeting schedule rather than all in one session.

Name: Jian-Hua Chen
Supervisor: Carolyn Larabell
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Presentation: Regulation of the spatial organization of cells and organelles remains poorly understood. One course of action required to elucidate this process is to visualize and quantify all organelles in the cell in three dimensions and, to account for cell heterogeneity, to examine a large number of cells. We are doing this using soft x-ray tomography, a high-resolution (better than 50 nm), quantitative imaging technology that generates high-contrast views of organelles in intact cells in the near-native state. Image contrast is generated by the absorption of x-rays by cellular constituents, and absorption is linear with thickness and concentration of organic molecules in each voxel. Therefore, each voxel contains a value, the linear absorption coefficient (LAC), that reveals the concentration of bio-organic molecules in that voxel (3D pixel). We can use these values to identify and segment individual organelles. For example, mitochondria can be identified by histogram using their LAC values (between 0.31-0.35 μm^{-1}) and computationally segmented, making identification rapid and more objective.

Impressions: I've been hearing to this prestigious meeting for a while from my PI. It's such a good opportunity that I could join this superb meeting to interact with scientists and get inspired. I would recommend no change to this meeting.

Name: Seemay Chou
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Overview: Structural basis of the bacterial cell wall by antibacterial enzymes

Presentation: Evolutionary and structural/biochemical characterization of a superfamily of bacterial competition toxins

Impressions: I really enjoyed the meeting and found it incredibly useful for getting to know fellow structural biologist from diverse perspectives at UCSF and Scripps. Particularly as a new junior investigator, the more low-key setting and requirement that all investigators and their trainees give short talks was very amenable to this. One observation I would like to offer is that there seemed to be an unusually low proportion of female faculty members represented. I think it would be great for myself and the trainees if this aspect could be addressed at future meetings. All in all, this was one of my favorite meetings this year!

Name: Christopher Cottrell
Supervisor: Andrew Ward
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Presentation: My research focuses on using insights derived from structural biology to design novel HIV immunogens to elicit broadly neutralizing antibodies. My presentation described ways to build and refine N-linked glycans into electron density maps generated from high-resolution cryo electron microscopy.

Impressions: The meeting was excellent. I had numerous opportunities to discuss my research with many investigators from different fields. I learned a great deal from the PI presentations including some novel approaches that could be applied to my

research. The Sponsor talks were also good and provided a unique perspective. I would recommend no changes to the meeting.

Name: Charles S. Craik
Department: Pharmaceutical Chemistry/UCSF
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Overview: The research interests of the Craik lab focus on defining the roles and mechanisms of enzymes and challenging membrane proteins in complex biological processes and on developing technologies to facilitate these studies. Information on the lab can be found at the following website: http://www.craiklab.ucsf.edu/. The primary emphasis of our work has been on enzymes, and more recently on membrane transporters, with a particular emphasis on macromolecular recognition. Our original protein engineering studies have evolved to encompass various proteases as well as their endogenous inhibitors and membrane-bound receptors. We have developed a powerful new technology to detect and profile post-translational modifying enzymes, including proteases and kinases, using a multiplexed peptide library and mass spectrometry. This technology is being used to determine the proteolytic signatures associated with pancreatic and breast cancer as well as infectious diseases and takes advantage of the 30 years of experience that the Craik lab has in biochemistry, molecular oncology and virology. In addition, we have been developing functional imaging probes for breast, colon and prostate cancer using novel approaches that in particular use recombinant antibody technologies to identify informative conformational states of proteins. Our cancer work leverages clinical collaborations with the Kirkwood, Esserman, Small, Fong, and Munster labs at UCSF. Our infectious disease work is strengthened by our collaborations with the Johnson, Madhani, Krogan, Gross and Koshla labs at UCSF and Stanford and our structural work combines forces with the labs of the Fletterick, Stroud and Cheng labs. The work has the potential to impact the field of molecular oncology and virology by helping speed structure determinations and target validation of challenging targets and provide valuable data and reagents to both the research and clinical communities for validating new biomarkers, prognostics, imaging agents and cell biology tools for challenging proteins associated with disease.

Presentation: The presentation at the XXVII WMEN symposium in Cabo San Lucas, Mexico was on Targeting Challenging Protein Targets with Conformationally Selective Recombinant Fabs. We currently lack tools and reagents required to study proteins with high conformational entropy and large hetero-oligomeric complexes. Identifying conformation- and composition-specific fragments of antibodies (Fabs) against these targets can help elucidate detailed structure and mechanism by acting as fiducial markers for cryo-electron microscopy (EM) and as labels for biochemical assays. These Fabs can also enable the study of dynamic complex assembly with functional probes that focus on activity. Antibodies are ubiquitous reagents for biological and biochemical research endeavors, including quantifying proteins, identifying the temporal and spatial pattern of expression in cells and tissues, identifying post-translational modifications, locating interacting partners, facilitating protein crystallization for structure determination, and exploring the role of specific proteins in disease pathogenesis. Such studies require recombinant antibodies of high specificity and potency. Rapid identification of Fabs that recognize native protein structure makes phage display a valuable method to obtain subnanometer resolution 3D structures of proteins and complexes using single particle cryoEM. Antibody binding to the target membrane protein can yield a homogenous population of the protein. Antibody interactions can also form stable and rigid complexes and the Fab provides a defined feature for accurate image alignment. In addition, the Fabs enable functional assays of particular states of the target protein. The generation of widely available, renewable, validated, and standardized sets of recombinant Abs against dynamic and challenging targets are accelerating studies of protein function and their validation as bona fide therapeutic targets. Methods that speed the reliable characterization of phage display selected antibody fragments were discussed in my presentation. Examples where recombinant Fabs provided unique insight in steps in the assembly of virus-host factor complexes, conformational states of complex membrane proteins such as ABC transporters and probes of functional states of enzymes involved in signaling pathways by stabilizing otherwise transient intermediate states were presented and discussed.

Impressions: Exceptional presentations in a relaxed setting that greatly facilitated discussion and possible collaborations. The size made the short presentations a bit challenging to adsorb in one setting but it was great to see all of the students and postdocs participate.

Name: William DeGrado
Department: UCSF
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Phone number: 415-476-9679

Overview: We focus on molecular design as an approach to understand mechanisms in biology and chemistry.

Presentation: De novo protein design, in which one designs proteins beginning from first principles, provides an approach that critically tests our understanding of protein folding and function, while also laying the groundwork for the design of novel proteins and biomimetic polymers. The de novo design of proteins has proven to be a useful approach for understanding the features in a protein sequence that allow them to fold into their unique three-dimensional structures, as well as how their structures achieve complex functions from molecular recognition to catalysis. This presentation focused on the design of water-soluble and membrane proteins with predetermined structures and functions, including binding of metal ion cofactors, small molecule ligands, and the transmembrane domains of natural proteins.

Impressions: This was an outstanding meeting, with excellent interactions between investigators in industry and academics. The site was well selected, and conducive to many informal discussions.

Name: Andy Deng
Department: Protein Engineering
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Phone number: 650-260-9930

Overview: Protein engineering to support various oncology efforts at BMS

Presentation: Story about human antibody germline genes with innate ability to bind pathogenic bacterial antigens. These germline antibodies are functionally blocking and has significant affinity against IsdB, a protein that is apart of the iron acquisition pathway for Staph A.

Impressions: I was impressed by the science presented, and was very interested in many of the topics. Overall it was a great

experience. I do wish there was a little more down time, as the day ran long with the sheer number of talks.

Name: Jane Dyson
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Overview: We are interested in the role of dynamics and intrinsic disorder in the functions of proteins. One major topic is related to the interactions of client proteins with molecular chaperones such as Hsp90. Another focus is on the interplay of disorder and partial order in the complexes involved in NFkappaB signaling. We use NMR and a number of other biophysical techniques to characterize these large, dynamic systems.

Presentation: Viruses utilize disordered proteins to disrupt and subvert cellular processes. An important way that these viral proteins work is by competing with cellular proteins (also disordered) for binding to targets. We were interested in the mechanism by which certain strains of human papilloma viruses cause cancer (particularly cervical cancer), while other, closely-related strains have only a low probability of causing cancer. Our studies showed that the difference is likely related to the affinity of one viral protein, HPVE7. The E7 protein from high-risk HPV strains has a higher affinity for the TAZ2 domain of the general transcriptional coactivator CBP, stabilizing a ternary complex with the retinoblastoma protein pRb, which normally blocks the cell cycle at the G1-S checkpoint. Formation of a stable E7-pRb-CBP complex potentiates the degradation of pRb, allowing premature entry into S phase and leading to uncontrolled cellular proliferation.

Impressions: Very well organized. The meeting venue is very pleasant. The lecture hall was perennially a bit too cold. I felt that there were rather too many lectures for me to take everything in - fewer, higher quality, perhaps slightly longer lectures highlighting particular themes might be more congenial.

Name: Stefano Forli
Department: Dept. of Integrative Structural and Computation,TSRI
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Overview: The main focus of my research is the application of computational methods for modeling interactions between small molecules and biological macromolecules, with a strong emphasis on drug design. For that we develop software and and innovative protocols to study the different physics components involved in the modulation of macromolecule structure and function, and to identify new molecular leads for drug design.

Presentation: We presented the application of an in-silico protocol designed to explore the chemical space of a series of derivatives of HIV-1 integrase inhibitors. The protocol was based on the synthetic pathway used by our collaborators, and allowed us to enumerate a very large number of derivatives and test them. The goal was to identify the most promising derivatives able to improve binding interactions, prioritizing their synthesis using molecular docking.

Impressions: Group size: there was a good balance between variety and diversity of topics and the number of participants. A smaller group would have probably facilitated close interactions between attendees, but at the price of the number of topics covered.

Location: Confirmed as an excellent location, like the previous year.

Length of the meeting: Perfect

Attendees and presenters: I liked the large coverage span provided by the speakers, and I believe one of the strongest qualities of the WMEN conference is the perspective provided by having such a number of different topics.

Name: Brooke Gardner
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Presentation: I work on the AAA-ATPase motors Pex1 and Pex6 that are involved in the maintenance of peroxisomes and commonly mutated in peroxisome biogenesis disorders in humans. We found that Pex1 and Pex6 form a heterohexameric motor with alternating subunits. Together they bind and unfold a partner protein, Pex15, by threading it through the central pore using the hydrophobic pore loop residues.

Impressions: I enjoyed the talks at this meeting, particularly the focus on mechanistic understanding of channels, viruses, and motors. The sponsors talks were very informative as to how this mechanistic understanding can lead to drug discovery. I would have felt more comfortable, however, if more female PIs were invited to the conference.

Name: Larry Gerace
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Overview: Our laboratory studies the organization and functions of the nuclear envelope and endoplasmic reticulum. Our experimental approaches involve the analysis of protein constituents of these organelles using biochemical and structural approaches, combined with structure/function studies in cultured cells and mouse models. A particular focus involves proteins of the nuclear lamina, a functional scaffold underlying the nuclear envelope.

Presentation: Our work on Lem2, a transmembrane protein associated with the nuclear lamina, demonstrates its involvement in the inactivation of MAP kinase signals in the nucleus. MAP kinase signaling is a key effector of intercelluar communication that regulates patterns of gene expression. Loss of Lem2 leads to hyperactivation of MAP kinases, which causes prenatal lethality in embryos, and metabolic disorders and muscular dystrophy in adults.

Impressions: This is one of the best meetings I have attended. All of the presentations were outstanding, and covered a wide range of emerging technologies and fascinating biological questions. The relatively small size of the meeting, in the context of the excellent

meeting venue, promoted a high level level of free and open discussion and interaction among the participants. The length of the meeting was ideal.

Name: Jason E Gestwicki
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Phone number: 415-502-7121

Overview: The Gestwicki group explores questions in protein folding, molecular chaperones and protein misfolding disease. Our approach is to assemble drug-like small molecules that target protein-protein interactions in the chaperone network to reveal the logic of protein homeostasis and to develop therapeutics to re-balance diseased systems. Our goals are to understand how chaperones identify misfolded proteins, how they make triage decisions and why this process becomes broken. We have active projects across a number of different chaperone systems, in therapeutics areas of neurodegeneration (e.g. tauopathy, polyglutamine disorders) and cancer (e,g. prostate, breast).

Presentation: At the 2017 WMEN meeting, we presented the discovery of specific chaperones that suppress prion formation of microtubule-associated protein tau (MAPT/tau). Using a large-scale mapping approach, we identified the binding site of 30 different chaperones on tau and then used a series of secondary assays to reveal which of these direct protein-protein interactions are most important in tau misfolding.

Impressions: Fantastic mix of methods, models and systems. There are few meetings these days that can claim the scope of WMEN. Also a great chance to form new alliances with UCSF/TSRI faculty (I started a great new collaboration this year).

Name: Elizabeth Getzoff
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Overview: My research aims to characterize functionally important protein conformational states and intermolecular interactions by coupling X-ray crystallography with other complementary biophysical techniques, molecular biology, computational analyses and, more recently, genomic, proteomic and post-translational modification data. We apply the resulting knowledge to protein and inhibitor design, and to understanding synergistic protein/cofactor, protein-protein and protein-DNA interactions for key biological processes.

Presentation: My presentation highlighted two projects from my lab in which proteins with related structures and sequences suggest functional insights. We determined the structure, dimeric assembly and tryptophan pyramid light sensor of the plant photoreceptor UVR8 (UV Resistance Locus B), which shares intriguing sequence and structural features with mammalian RCC1 (Regulator of Chromosome Condensation 1), a guanine nucleotide exchange factor for Ran GTPase. Both proteins regulate transcription and are reported to bind chromatin. My lab also determined the first structure of a cryptochrome and has extensively studied the structure and function of many members of the photolyase and cryptochrome family. Photolyases repair UV-damaged DNA, whereas cryptochromes are transcriptional repressors of the circadian clock. Photolyases and cryptochromes share a protein fold that binds FAD in an unusual U-shaped conformation, but the molecular mechanisms for cryptochrome function and regulation remain cryptic.

Impressions: As always, the Cabo meeting provided a great forum for interactive discussions on innovative research. The scale of the meeting and the informal environment promote collegial interactions, making it easy to meet young scientists as well as reconnect with established colleagues. I particularly enjoyed opportunities to be exposed to new areas of cutting edge research, explore cross-disciplinary insights and extend collaborations.

Name: Danielle Grotjahn
Supervisor: Gabriel Lander
Department: ISCB/TSRI
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Presentation: Three-dimensional snapshots of the microtubule-bound dynein-dynactin complex

Impressions: One of my favorite conferences! I think its great that everyone at the conference presents their research. One of the major issues this year was that some of the presenters did not keep to their allotted time, and most went over. I realize this is hard to regulate, perhaps a visual cue (light timer) would be helpful for the speakers. Overall, the location, science and discussions were great!

Name: Chien-Hsiang Hsu
Supervisor: Drs. Steve Altschuler and Lani Wu
Department: Pharmaceutical Chemistry
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Phone number: 214-680-1361

Presentation: My research focuses on cellular decision during the process of drug-induced senescence in cancer. p21 has been shown to be an important effector that promotes senescence during this process. However, using live-cell time-lapse microscopy and single-cell tracking, we found two different p21 dynamics with fast and delayed expression leading to proliferation and senescence, respectively. Currently, we are investigating why fast p21 expression helps cells stay proliferative and the cause of fast and delayed p21 expression.

Impressions: This meeting was great. I especially like the design that every participant has a chance to present his/her work. Also, starting with postdoc and student presentation is a nice idea since it serves as a primer for me when their mentors present.

Name: Jennifer Kefauver
Supervisor: Andrew Ward and Ardem Patapoutian
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Phone number: 858-784-7170

Presentation: I presented my structural studies on the Volume-Regulated Anion Channel using cryoEM. This volume-sensing ion channel is expressed in nearly all vertebrate cell types and acts as an emergency release valve during hypotonic stress through the

release of chloride ions and organic osmolytes. My studies focus on understanding the heterogeneous composition of the channel by five contributing LRRC8 subunits, and on methods to limit that heterogeneity so as to improve the resolution achievable by single-particle 3D reconstruction.

Impressions: The location and length of the meeting were wonderful, and the presentations were informative. I especially appreciate the presenters who choose to highlight a small/unique story from their lab that might be orthogonal to the majority of the lab's focus and those who present about new/developing methods in structural or computational biology. The size of the group this year was a bit overwhelming, in terms of number of talks, and opportunity to network with professors, but I still very much appreciate that every person at the meeting gives a talk.

Name: Jack Kirsch
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Overview: I have attended 20 of the 27 past CABO meetings, and have always benefitted from the high density of valuable information communicated by the presenters. I think that this year, there may have been a few too many talks, and would suggest some mechanism to reduce the number by 5%.

Presentation: I am retired, and did not present this year. I did, however, invite 4 PIs from Berkeley, who, I believed acquitted themselves well, and broadened the overall perspective.

Impressions: At this juncture, excellence is expected, and it was delivered. The venue is superb, the food good, and there was adequate time for one on one interactions. Perhaps a few less talks (see above) might have allowed time for more socialization.

Name: Gabriel Lander
Department: Dept of Integrative Structural & Computational Biology, The Scripps Research Institute
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Phone number: 858-784-8793

Overview: This is an excellent meeting that assembles both world renown scientists with emerging leaders in the field in a setting that encourages one-on-one scientific discussions that are conducive to, and often lead to, successful and prolific collaborations. The attendees are mainly structural biologists, although the diversity in approaches and techniques that are presented always prompts new ideas for the ongoing projects in my lab.

Presentation: I presented two of the ongoing projects in my lab. The first is our work using the 200keV Talos Arctica to solve structures at better than 3 ≈ resolution. The second part of the presentation focused on our work on the dynein-dynactin motor complex, which is the sole anterograde transporter of all cargo in cells. We used cryo-EM tomography to determine the first 3D structure of this complex, revealing how the dynactin cofactor recruits 2 dynein homodimers, assembling 4 dynein motors for fast and processive movement along microtubules.

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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San Francisco, CA 94143-2722
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Phone number: 415-514-0423

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: James Love
Department: ATUM
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Email address: jlove@atum.bio

Overview: A great meeting in a great location. Well worth while attending and sponsoring.
Presentation: I was very impressed by the high standard of the science from all attendees - from the most junior to senior levels. I learnt a lot.

Impressions: The location and closed nature of the meeting was great. Really good interactions as people didn't wander off. The attendance at all the talks was very high, which was nice.

Name: David Millar
Department: TSRI/Dept of Integrative Structural & Computational Biology
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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 it's 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 it's 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 Minor
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Overview: My laboratory focuses on defining the structural mechanisms by which various classes of ion channels function and on the development of new pharmacological agents that can be used to probe and control channel action. We have particular interest in voltage-gated cation channels and channels from the two-pore, K2P, potassium channel family.

Presentation: My presentation focused on our work on K2P potassium channels. These channels are key players in controlling neuronal excitability, respond to lipids, temperature, and mechanical stretch, and influence pain, temperature perception, and anesthetic responses. These dimeric voltage-gated ion channel (VGIC) superfamily members have a unique topology comprising two pore forming regions per subunit. Contrasting other potassium channels, K2Ps use a selectivity filter ate as the principal gating site. Similar to many ion channels, K2Ps suffer from a poor pharmacologic profile limiting mechanistic and biological studies.

I presented our research efforts that have defined the C-type selectivity filter gate as the central actor in K2P channel function. My talk also showed or discovery and characterization of a new set of K2P activators that directly affect C-type gate function. These new small molecule K2P activators bind to a novel, cryptic binding site behind the selectivity filter and define a new, druggable site for K2P channel modulator development.

Impressions: The meeting was fantastic as usual. The group size was perfect and had the right mix of academic and industrial

scientists. It was also a great size for making new connections with scientists from Scripps, and UCB and for reinforcing interactions with my colleagues from UCSF. The presentations were all of exceptionally high quality. The meeting length was just right and the location was terrific. There is just the right mix of science and 'networking' time. It is truly an exceptional meeting. It is a great privilege to have the opportunity to participate in this event.

Name: Sasha Moola
Supervisor: Ian Wilson
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Phone number: 858-784-9866

Presentation: My research focuses on the evolution of broadly neutralizing antibodies against HIV, and their binding to their target protein, the HIV Envelope glycoprotein (Env). I presented structures of a family of related antibodies from an HIV infected individuals, where HIV-antibody coevolution led to a range of independent insertions in antibodies derived from the same ancestor. These insertions lead to very different antibody conformations and like affect how the antibodies engage with the antigen.

Impressions: The meeting was extremely interesting, facilitating interactions with a wide range of people without the group being so large as to become unwieldy. The attendees and presenters came from a variety of fields and contributed to a interdisciplinary atmosphere. The location of the meeting is wonderful, but the number of presentations means that plenty of time is spent on the science, despite the relatively short meeting.

Name: Kendall Nettles
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Overview: The Nettles lab uses structural and computational approaches to understand how nuclear receptors function as

allosteric signaling molecules. Using a structural systems biology approach, we have discovered how estrogen and glucocorticoid ligands can alter receptor structure to control the recruitment of ligand-selective histone modifying enzymes, and in doing so produce ligands-selective transcriptional outcomes.

Presentation: The first part of the presentation showed how looking at dozens of crystal structures, bound to different ligands, enables super-resolution x-ray crystallography. Using a set of closely related ligands with a wide variance in biological activities, we showed that sub-angtrom perturbations of the receptor can drive biology. The second part of the talk was about using a chemical systems biology approach to discover that it is possible to develop glucocorticoids with differing effects on glucose disposal and protein balance in skeletal muscle, and reveal the cellular circuits underlying these effects.

Impressions: The meeting was outstanding. The talks were all amazing. The meeting size was perfect to enable good discussion and for everyone to participate.

Name: Takanori Otomo
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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: James Partridge
Department: GBT
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Phone number: 650-741-7738

Overview: The research group at global blood works on a variety of projects focused on benign blood related diseases. All projects are structural biology enabled and we are focused on finding small molecule inhibitors.

Presentation: My talk was focused on an early project that we've already terminated and started publishing. I discussed the use of a few small molecule tool compounds with high affinity and varying specificity. X-ray crystallography enabled us to understand why these compounds are so potent and have variable specificity.

Impressions: I think the meeting was of a good size. I feel that the short student presentations should be mixed in with the longer talks. It was difficult to focus on so many short talks presented in

succession. The location of the meeting is fantastic. The quality of talks, and in the overall the whole meeting, was extremely high quality. It's one of the best meetings I've been to and I think it's because the quality of presentations was so high. It's also nice that everyone is required to speak. I'd suggest that the industry talks are not grouped together but rather scheduled into sessions similar in topic.

Name: Nicholas Polizzi
Supervisor: Bill DeGrado
Department: Pharm Chem
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Presentation: De novo design of small-molecule-binding proteins. My work involves identifying the criteria by which proteins bind their cognate ligands with high affinity and specificity, and designing proteins from scratch to critically test these principles.

Impressions: (a) The group size was optimal I think. (b) The location was wonderful. The resort did a good job with food and drinks. (c) The talks between Scripps and UCSF and Berkeley researchers were a good mix. Perhaps Berkeley could have more attendees. (d) Length was good.

Name: Cristina Puchades
Supervisor: Gabriel C. Lander
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Presentation: substrate translocation mechanism of mitochondrial AAA-protease YME1

Impressions: As a grad student, I found this to be a great opportunity to practice presentation skills in front of a larger structure-centered audience

It's also a good opportunity to get to know other structural biologists in California and what they are working on. Its great to establish

connections and functions partially as a DISCOBIO retreat, which I really enjoyed.

Name: Allison Roberts
Supervisor: Dan Nomura
Department: UC Berkeley Chemistry
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Presentation: My talk, Utilizing Chemoproteomic Profiling to Discover Anti-Cancer Covalent Ligands and Draggable Hotspots, focused on my research utilizing chemical genetics coupled with chemoproteomics to identify novel anti-cancer covalent ligands and their targets. Specifically, I discussed my work on pancreatic cancer, where I identified a novel anti-cancer agent and its ability to target UBA5. Overall, my work in the Nomura lab focuses on utilizing the approach discussed above to identify novel anti-cancer covalent ligands/targets, all with the goal of expanding upon what is considered to be the "druggable" proteome in cancer. My future work will focus on using medicinal chemistry to improve the potency and selectivity of the lead compounds I identify.

Impressions: I really enjoyed this meeting! The venue was great and the talks were wonderful. I liked that students/post docs were able to speak, and I also liked the way the sessions were organized. In the future, I think finding room with windows or more natural light would be nice. I was honored that UC Berkeley was included, and would be really excited if more UC Berkeley PIs/students could attend next year!

Name: Assen Roguev
Supervisor: Nevan Krogan
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Phone number: 4157347495

Presentation: Mapping geneVc interacVons with CRISPRi
Impressions: Great! Very well organized. Nice selection of speakers and a good mix between academia and industry.

Name: Floyd Romesberg
Department: The Scripps Research Institute
Mailing address: 10550 North Torrey Pines Road, La Jolla, CA
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Phone number: 858-784-7290

Overview: Research in my lab is focused on synthetic biology, biophysics, and medicinal chemistry. The medicinal chemistry is focused on antibiotic development, where we explore targeting protein secretion. The biophysics is focused on efforts to understand how protein dynamics are evolved for function. This involves both IR spectroscopy where we develop new tools to study protein vibrations and ultrafast UV/Vis spectroscopy to understand how antibodies are evolved for molecular recognition. The synthetic biology is directed toward evolving DNA polymerases that accept modified substrates and the creation of semi-synthetic organisms that store and retrieve increased information by virtue of an unnatural base pair.

Presentation: My talk focused on the semi-synthetic organisms, and I described our recent success in getting them to translate proteins with unnatural amino acids.

Impressions: The size of the meeting is just about perfect. There are a lot of participants, which is made possible by the short talks. This allows for a lot of science, and this is the meeting real strength, and what makes it different from other meetings. Its Cabo, need I say more. The meeting is rather focused to TSRI and UCSD, and maybe a little broadening into UB Berkeley, Stanford, and Cal Tech might be nice. The length of the meeting is typical, and perfect. As you might guess from my comments, this is BY FAR, my favorite meeting that I attend.

Name: Emily Roncase
Supervisor: Dennis Wolan
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Presentation: Title: Insights into the activation and substrate selectivity of two clostripain-like proteases from *B. thetaiotaomicron*.

My research focuses on understanding the role gut bacteria play in promoting intestinal inflammation through the secretion of active cysteine proteases. I have determined the structure of two such proteases from the gut commensal /Bacteroides thetaiotaomicron/ that belong to the clostripain-like peptidase family: BT1308 and BT0727. Furthermore, I have determined these proteases self-activate *in trans* and cleave selectively after arginine residues, with preference for small negatively charged side chains in the P2 position.

Impressions: I thoroughly enjoyed this meeting! It goes without saying that the location was superb, and I was very grateful to have gotten the chance to meet so many exceptional scientists in industry and academia. I thought it was a great mix of people, and the size of the group was pretty optimal in my opinion. All-in-all a great meeting, and I wouldn't change a thing!

Name: Andrej Sali
Department: Bioengineering and Therapeutic Sciences
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Phone number: 415 514 4227
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 cross-linking, and assorted other data.

Impressions: Informative and enjoyable!

Name: Daniel Santi
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Overview: Current research is directed toward overcoming such limitations through releasable conjugates in which the drug is covalently linked to the carrier through a cleavable linker. Satisfactory linkers that provide predictable cleavage rates tunable over a wide time range that are useful for both circulating and non-circulating conjugates are not yet available. We describe such conjugation linkers on the basis of a nonenzymatic β-elimination reaction with preprogrammed, highly tunable cleavage rates. A set of modular linkers is described that bears a succinimidyl carbonate group for attachment to an amine-containing drug or prodrug, an azido group for conjugation to the carrier, and a tunable modulator that controls the rate of β-eliminative cleavage. The linkers provide predictable, tunable release rates of ligands from macromolecular conjugates both in vitro and in vivo, with half-lives spanning from a range of hours to >1 y at physiological pH.

Using slow cleaving linkers, the hydrogel format provides a generic format for once-a-month dosage forms of potent drugs. The hydrogel format has been further developed to contain very slow-cleaving β-eliminative linkers that allow controllable degradation rates. The releasable linkers provide additional benefits that include lowering Cmax and pharmacokinetic coordination of drug combinations.

Impressions: The meeting was probably the best I have attended yet. The talks were crisp, and the science was terrific. There was plenty of time to interact, and the hotel and food very good. The attendees and talks from Industry were particularly impressive.

Name: Sergey Shnitkind
Supervisor: Peter Wright
Department: Integrative Structural and Computational Biology, TSRI
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Presentation: I work on a ubiquitously expressed transcription factor that is involved in several regulatory networks. This protein contains large regions of intrinsic disorder and undergoes multiple post-translational modifications. During my presentation I showed how multiple phosphorylation events act as a regulatory rheostat that gradually regulate protein function.

Impressions: The meeting was excellent and very valuable. I had an opportunity to converse with scientists outside my immediate field and discuss new advances in structural and computational biology. The size of the group was good and the location allowed attendees to have productive discussions within the conference center. Talks were informative and had good variety.

Name: Natalia Sevillano
Supervisor: Charles S. Craik
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Presentation:
Proteases are involved in all stages of cancer and represent functional biomarkers that can be targeted to distinguish aggressive disease. Over-expression of the plasminogen activation system (PAS) has been documented in a number of primary and metastatic cancers. The expression of the PAS directly correlates with cancers that are phenotypically aggressive, result in poor clinical prognosis, and quickly acquire drug resistance to first line therapies. Active uPA is a functional biomarker of aggressive cancer that can be selectively targeted for preclinical imaging using an antagonistic molecular approach. Here, we report the identification of a new human antibody (Fab U33) that selectively inhibits the active form of uPA. This antibody targets and internalizes the active form of uPA via a receptor-mediated mechanism by mimicking the action of the

endogenous inhibitor of uPA, PAI-1. We have used U33 labeled with fluorophores or radionuclides to non-invasively detect active uPA in vivo in prostate cancer xenografts and in experimental metastasis models. We affinity-matured U33 by constructing a library of phage-displayed U33 Fabs mutants with randomization of the CDRH2 and CRDRL3 loops. The derived antibodies show at least 20-fold increased affinity to human uPA compared with U33.

Impressions: I really liked the meeting, the location and the organization was perfect.
One of the things I liked most is to hear talks about many different topics and also including talks from academia and industry.

Name: Glen Spraggon
Department: Structural Biology/GNF
Mailing address: Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA
Email address: gspraggon@gnf.org
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 (SOMAmerÆ) 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 extra-cellular 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: Bryan Thurtle-Schmidt
Supervisor: Robert Stroud
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Presentation: My research is on the mechanism of substrate translocation by membrane transporters. In my talk, I presented the structure of a transporter called Bor1, and how structural comparisons between it and other published structures support an "elevator" mechanism of transport.

Impressions: The meeting was at a wonderful facility, and the length of the meeting was great. My only notable comment is that because everyone present speaks, the schedule ended up being fairly packed. That might suggest a potential benefit to either (a) making the number of attendees a bit smaller, or (b) not having everyone speak. But it's a modest suggestion; overall it was quite good as is.

Name: Robert M. Stroud
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Fax number: 415 476 1902

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
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Phone number: 858-784-7320

Overview: Another great gathering in San Jose del Cabo. A wide variety of topics were presented. Student talks were very good as usual

Presentation: I presented our cryoEM work of betacoronavirus S envelope glycoproteins that we are using for rational vaccine design. In particular, I presented structures of HKU1, MERS, and SARS, including a complex with a neutralizing antibody.

Impressions: Great meeting. Maybe too many speakers, especially from industry. Maybe break up the industry talks. Otherwise, the location and format are perfect.

Name: Jamie Williamson
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Overview: The Cabo meeting continues to be a highlight of the scientific calendar, bringing together scientists from san diego and the bay area, as well as industrial sponsors. It is a unique meeting, and the energy and quality of the presentations continues to improve from an excellent baseline.

Presentation: The meeting is enjoying a large subscription of attendees, and the previous tradition of having everyone talk needs to be carefully examined. The student and postdoc talks are a highlight, but with the number of attendees, it has become a forced march. For the PIs, it may be time to allow attendees and participants without requiring that each talk. Also, I think it would be a good idea to disburse the sponsors through the program, rather than concentrate them in a single session. It does them a disservice.

Impressions: Overall, most excellent.

Name: Ian A. Wilson
Department: Integrative Structural and Computational Biology - 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.

Presentation: This year I opted not to give a talk as the schedule was too jam-packed.

Impressions:. Excellent meeting as always with an exceptional mix of academia and industry, although ths program was a little too full this year with talks but that said it is great that so many people want to attend. The students and postdocs excelled as always in their short, action-packed presentations. The meeting keeps getting better and always cutting edge

Name: Dennis Wolan
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Overview: New antibiotics are desperately needed to combat the relentless escalation in multidrug-resistant bacterial pathogens. Our goal is to identify and characterize novel inhibitors of a transmembrane protease, lipoprotein signal peptidase, that is required by all bacteria to insert key proteins into their membrane surface. We employ innovative chemical biology, biophysics, proteomic, and cellular techniques with iterations of chemical synthesis to optimize lipoprotein signal peptidase inhibitors and to validate this unique protease as a highly desirable target for design of new antimicrobial agents.

Presentation: Lipoprotein signal peptidase (Lsp) is in the lipoprotein maturation pathway that is involved in attaching a lipid tail onto selected secreted bacterial proteins to facilitate anchoring of these proteins, or lipoproteins, to the cell membrane. Importantly, lipoproteins have a diverse array of essential roles including nutrient uptake, small molecule export, signal transduction, cell wall stability, adhesion, virulence, and antibiotic resistance. Prevention of lipoprotein maturation via Lsp inhibition eliminates viability in Gram- bacteria and infectivity in Gram+ bacteria. We have developed the first FRET-based substrate and assay system to measure Lsp activity in vitro from any bacterial strain of interest and have employed and miniaturized our Lsp assay to perform the first in vitro

bacterial IMP HTS against 646K compounds at our TSRI FL Screening Facility. We have specific Lsp inhibitors that importantly work to kill bacteria.

Impressions: The meeting was full of innovative talks that spanned a wide range of biomedically relevant topics using biophysical, biochemical, chemical, and cell biology techniques. It provides a fantastic opportunity to be updated on the cutting-edge research performed by colleagues at TSRI and UCSF. My laboratory is now involved in several collaborations with groups at UCSF primarily because of the interactions at the Cabo meeting.

Name: Lani Wu
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Overview: We seek to develop rapid, scalable and effective ways to identify drugs. Current areas of investigation include:

1) Machine learning. We develop computational strategies to predict small molecule function from diverse data sources, including high-throughput microscopy and genomics information.

2) Drug discovery. We combine systems-biology and high-throughput approaches for discovering early drug leads for cancer and neurodegeneration.

Presentation: I presented our recent work on identifying optimal reporter cell lines for annotating compound libraries across diverse drug classes.

Impressions: This was a fantastic meeting to learn more about diverse research areas relevant for drug discovery.

Name: Ke Yang
Supervisor: Dr. Peter E. Wright
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Presentation: Structural basis of cooperativity in a hematopoietic transcription factor:coactivator ternary complex.

The KIX domain of the CREB binding protein (CBP) is a primary multi-site interaction domain for a number of intrinsically disordered transcription factors involved in hematopoietic differentiation and disease. I briefly described the structure of a ternary complex formed by KIX and two transcription factors. The structure provides insight to understanding the direct and cooperative mediation of the interactions between multiple transcription factors simultaneously.

Impressions: I enjoyed every aspect of the conference! As a graduate student, I was very thankful to the opportunity to give a brief talk and receive feedback on my work. The diversity of research, wonderful interactions with other attendees from both academia and industry, and the great location make the meeting a very special experience for me.

Name: Ahmet Yildiz
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Overview: My lab develops single molecule imaging methods to study the mechanism of macromolecular enzymes. Specifically, we work on microtubule motor dynein, RNA-guidable endonuclease Cas9 and telomere-associated reverse transcriptase telomerase. We also develop new tools for tracking single molecules in living cells and target specific chromatin region using catalytically-inactive Cas9.

Presentation: My talk summarized our recent findings that present a detailed picture of how a molecular motor dynein moves towards the microtubule minus-end, how its motility is regulated by dynein-associated proteins and how it generates forces for a wide variety of cellular tasks.

Impressions: IT was a fantastic meeting. The quality of the talks well exceeded my expectations. I have learned quite a lot about advances in structural biology biotechnology and their applications to various biological systems. The conference venue and

organization were also spectacular. I would certainly like to attend this again.

Name: Qinghai Zhang
Department: Department of Integrative Structural and Computational Biology / The Scripps Research Institute
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Overview: We develop chemical tools for the structural and functional characterizations of membrane proteins. We are also interested in the development and discovery of small molecule therapeutics targeting membrane proteins of great biological and biomedical significance including transporters, GPCRs and channels. Towards this end, we have devoted efforts to solve membrane protein structures for drug binding and mechanistic studies.

Presentation: I presented MsbA structural studies using novel amphiphiles. MsbA is an ABC transporter-class lipid A flippase and a novel target for antibiotics. Testing novel detergents, especially a class of steroid-based facial amphiphiles, has led us to grow MsbA crystals that diffracted below 3 ≈. I discussed a new MsbA structure determined in complex with lipid A substrate in the context of a dynamic conformational landscape.

Impressions: This is one of the best meetings that I have attended. The location and the length of this meeting is excellent. The meeting maintains a good balance of senior and young investigators as well as postdocs and graduate students. The meeting format is unique in that every attendee speaks, which allows good opportunities for participants to interact with each other and exchange ideas.

2018 WMEN Keynote Speaker
Peter G. Schultz, PhD
President and CEO of the Scripps Research Institute

Peter G. Schultz did his undergraduate and graduate work at the California Institute of Technology. His thesis work with Peter Dervan resulted in the first synthetic molecules (polypyrrole amides) that sequence-selectively cleave DNA. In 1985, after postdoctoral studies at the Massachusetts Institute of Technology with Chris Walsh, he joined the faculty of the University of California at Berkeley, where he was Professor of Chemistry, Principal Investigator at Lawrence Berkeley National Laboratory and an Investigator of the Howard Hughes Medical Institute. Schultz joined the faculty of Scripps in 1999 where he is currently the Scripps Family Professor of Chemistry. He founded and was the Institute Director of the Genomics Institute of the Novartis Research Foundation (GNF) in San Diego, CA from 1999 to 2010 and more recently (2012) the California Institute for Biomedical Research (CALIBR), a not-for-profit institute focused on early stage translational research. In addition, Schultz is a founder of Affymax Research Institute, Syrrx, Kalypsys, Phenomix, Symyx Therapeutics, Ilypsa, Ambrx, Ardelyx, and Wildcat Technologies, pioneers in the application of diversity based approaches to problems in chemistry, materials science and medicine. His awards include the Waterman Award of the National Science Foundation, membership in the National Academy of Sciences and National Institute of Medicine, the Wolf Prize in Chemistry, the Paul Ehrlich Prize, the Arthur C. Cope Award of the American Chemical Society, and the Solvay Prize. He has coauthored 500 scientific publications and trained over 300+ graduate students and postdoctoral fellows, many of whom are on the faculties of major research institutions around the world.