30th Scripps / UCSF Conference

May 7-10, 2022 | San Jose del Cabo

UCSF
University of California
San Francisco

Scripps Research

Our History

The Scripps/UCSF conference has been held for the past 30 years during the month of May in Los Cabos, Mexico. The meetings originated from a grant from the Rockefeller Foundation supporting research collaborations between scientists at UCSF, MRC Cambridge and The Scripps Research Institute (TSRI). Drs. Daniel Santi and Ian Wilson started the meetings and created the unique scientific ambience. The meeting style has remained unchanged but, sixteen years ago, the venue moved from Cabo San Lucas to all-inclusive resorts in San Jose del Cabo. The 2016 meeting returned to the Hyatt Ziva (formerly Barceló Los Cabos Palace) that was completely renovated after Hurricane Odile in 2014.

Each year, the meeting attracts approximately 60 academic, industrial, and biotech participants, as well as venture capitalists and patent attorneys. The attendees are composed of Professors, laboratory heads or research directors, but we also encourage participation of the next generation of scientists through selecting around 20-25 of the top graduate students and postdoctoral fellows from UCSF, TSRI, UC Berkeley and Stanford. The spirit of scientific research is enhanced and refreshed in this stunning setting in Los Cabos with an always stellar and fun group of participants. We are also extremely grateful to our sponsors whose generous support makes this meeting possible every year.

Scripps/UCSF Conference 2022, May 7–10

All sessions in Los Arcos Room (please note this is a new room this year one level below)

Saturday Evening, May 7, 2022			
17:30 – 17:40	**Introduction and Welcome**		Ian Wilson and Andrej Sali
17:40 – 17:45	**Self-Introductions**	Colin Deniston	Novartis
		Anil Gupta	Calibr at TSRI
17:45 – 20:45	**Short Presentations (4 + 1 min.) by TSRI, UCSF, and Stanford Graduate Students and Postdocs (Chair: Mia Huang, TSRI)**		
	Batuujin Burendei	TSRI	Structural determination of otopetrins
	Che Chun Tsui	TSRI	Sensational ion channels: structure and simulation
	Caroline Cuoco	TSRI	A8: At the intersection of stress signaling and lipid metabolism
	Chika Kikuchi	TSRI	Evolution of H3N2 influenza virus for recognition of human airway receptors
	Nina Moore	TSRI	Structural characterization of broad neutralizing antibodies to influenza A
	Hailee Perrett	TSRI	Cryo-EM structures of arenaviral fusion glycoproteins reveal conserved sites of vulnerability
	Tanwee Alkutkar	TSRI	Mapping epitopes for anti-EBOV monoclonal antibodies elicited by vaccination during the ChAOX1 Oxford vaccine trial
	Reem Moskovitz	TSRI	Structural insights into novel epitopes in *Plasmodium falciparum* circumsporozoite protein
	Nelson Wu	TSRI	Structure-based malaria immunogen design
	Payal Pratap	TSRI	Using electron microscopy polyclonal epitope mapping to guide iterative structure-based HIV vaccine design
	Christina Garza	TSRI	Molecular dynamics studies of HIV capsid disassembly
	Michaela Medina	TSRI	Cryo-electron tomography reveals drastic mitochondrial membrane remodeling in response to endoplasmic reticulum stress
	Sarah Mosure	TSRI/UF	Mechanisms of REV-ERB-dependent heme signaling
	Zoe Adams	TSRI	Alkynomycins: Leveraging the Glaser coupling to rigidify peptide macrocycles and develop novel therapeutics
	Short Break		
	Andrew Ambrose	UCSF	Discovery of a specific caspase-6 inhibitor and its use in tauopathy
	Bieke Vanslembrouck	UCSF	Structural differences of chromatin across different cell types
	Daniel Conrad	UCSF	Using lipid-conjugated DNA barcodes for multiplexed single-cell sequencing
	Hyun Jun Yang	UCSF	FLAMES multi-dimensional spectra microscopy enables the quantitative determination of distinct amyloid strains

	Janice Goh (Jia Ni Goh)	UCSF	An integrative framework of preclinical models for novel TB drug regimen development
	Jie Zhou	UCSF	Targeting and blocking proteolytic neo-epitopes
	Laura Keller	Stanford	Chemoproteomics identifies proline-specific serine proteases involved in membrane integrity in gut commensal bacteria
	Nicole Wenzell	UCSF	Defining Sec61 client sensitivity using substrate-selective cotransins
	Sergei Pourmal	UCSF	Structures of multidrug resistance protein MRP4 reveal basis of substrate specificity
	Matthew Hancock	UCSF	Bayesian multi-state modeling from X-ray crystallography
	Berliza Soriano	UCSF	Builders and breakers: Enzymes involved in peptidoglycan homeostasis
	Zhen (Annie) Lin	UCSF	Molecular mechanisms underlying ligand-specific activation of engineered Notch
21:00 – 23:00	**Reception with Buffet**		**Poolside**

Sunday Morning, May 8, 2022			
			Keynote Lecture
08:30	Robert Stroud	UCSF	Introduction
08:45	Jim Wells	UCSF	Plundering biology for new treasure
09:45	**Break**		
			Structure and Biology of Cellular Processes (Chair: Andrew Ward, TSRI)
10:00	Carolyn Larabell	UCSF	Imaging membraneless organelles and aggregates with soft x-ray tomography
10:20	Valentina Loconte	UCSF	Quantitative mapping of cellular structural properties using soft X-ray tomography
10:40	Danielle Grotjahn	TSRI	Structure among the chaos: using cellular tomography to study mitochondrial behavior
11:00	Keren Lasker	TSRI	Structure and function of the bacterial condensate PopZ
11:20	**Break**		
11:40	Ahmet Yildez	UC Berkeley	The regulation of motors by microtubule associated proteins
12:00	Young-Wook Jun	UCSF	Biophysical mechanisms of cis- and trans-activation of endogenous and engineered Notch
12:20	Jacob Brink	JEOL	Workflows with the CRYO ARM
12:40	Cary Bauer	Bruker	The Bruker D8 VENTURE – Advances in biological crystallography

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Sunday Afternoon, May 8, 2022			**Chemical Biology (Chair: Jim Wells, UCSF)**
16:00	Michelle Arkin	UCSF	Site-directed drug discovery for challenging targets
16:20	Michael Erb	TSRI	Chemical modulation of tumorigenic transcriptional control
16:40	Luke Lairson	TSRI	Metabolically stable small molecule STING agonists
17:00	Matthew Bogyo	Stanford	Identification of covalent binding ligands using phage display
17:20	**Group photo**		Main lobby steps to pools
17:40	Christian Cunningham	Genentech	Cracking the code of macrocycle drug discovery
18:00	Chris Parker	TSRI	Proteome-wide ligand and target discovery in cells
18:20	Philip Dawson	TSRI	Stretching peptides: beta-strand mimics and antibiotics
18:40	Dillon Flood	Elsie Biotechnologies	Harnessing the full potential of chemical gene silencing therapeutics through complete exploration of chemical space
19:00	Daniel Santi	ProLynx	PLX038 in the DNA damage response
20:00 – 22:30	*Sponsor Dinner, by invitation only – El Agave*		

Monday Morning, May 9, 2022			**Immunology , Microbial Pathogens, Glycans (Chair: Danielle Grojahn, TSRI)**
08:30	Ian Wilson	TSRI	Immune response to SARS-CoV-2 and variants of concern
08:50	Andrew Ward	TSRI	Sequence from structure
09:10	Mark Yeager	U Miami	CryoEM structures of the human HIV-1 restriction factor SERINC3 and function as a lipid transporter
09:30	Travis Young	Calibr at TSRI	Controllable CAR-T cells: clinical progress
09:50	**Break**		
10:20	James Paulson	TSRI	Exploiting inhibitory Siglecs to suppress unwanted immune responses
10:50	Mia Huang	TSRI	Taming glycoconjugate structure and interactions in development and disease
11:10	Allison Williams	UCSF	Cracking the code for protein-peptidoglycan recognition
11:30	John Gross	UCSF	Order from chaos: how mRNA stability is regulated by an intrinsically disordered protein

12:00 – 13:00	**UCSF COVID Group Testing**	**Location: Sports Bar Terrace**

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Monday Afternoon, May 9, 2022			**Non-ribosomal and ribosomal synthesis (Chair: Carolyn Larabell, UCSF)**
16:00	Robert Stroud	UCSF	Caught in the act! The naked truth
16:20	Raktim Roy	TSRI/UF	Allosteric regulations in non-ribosomal peptide synthetases
16:40	Jamie Williamson	TSRI	Visualizing early events in 50S ribosome assembly
17:00	Katrin Karbstein	TSRI/UF	Quality control in ribosome maturation
17:20	**Break**		
			Membranes and Membrane Proteins (Chair: Robert Stroud, UCSF)
17:40	Daniel Minor Jr	UCSF	A through the looking glass view of ion channel structure
18:00	Jonathan Moore	Rectify Pharma	Targeting ABC transporters in rare disease
18:20	Evan Miller	UC Berkeley	Electrophysiology, unplugged: Molecules to visualize biological membrane potentials

Tuesday Morning, May 10, 2022			**Integrative Computational and Structure Biology etc. (Chair: Keren Lasker, TSRI)**
08:30	Andrej Sali	UCSF	Model integration
08:50	William DeGrado	UCSF	Protein design
09:10	Stefano Forli	TSRI	Proteome-wide covalent virtual screenings: milliseconds to nanomolar
09:30	**Break**		
09:50	David Millar	TSRI	Conformational dynamics of DNA polymerases revealed at the single-molecule level
10:10	Art Olson	TSRI	Building and visualizing the molecular nature of cellular landscape

10:30	**Ian Wilson and Andrej Sali**	**Closing Remarks**

12:00 – 13:00	**Scripps COVID Group Testing**	**Location: Sports Bar Terrace**

In order to protect individual rights and promote discussion, it is a requirement of the Scripps/UCSF CABO Annual Meeting 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 the 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.

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Presentation: Protein-protein interactions are integral to many different biological challenges but lack the deep and well-defined binding pockets classically targeted with small molecule drugs. Current strategies for designing competent ligands for these types of sites focus on introducing artificial elements to stabilize the desired conformation, but often disrupt interactions that are crucial for binding, such as the backbone of the ligand. At this conference, I presented a strategy for enforcing an extended structure of a peptide-based small molecule using a macrocycle consisting of two nearby side chains, thereby stretching the peptide backbone while leaving backbone proton donors and acceptors intact. This macrocycle is completed with a diyne rod accessible by Glaser bracing. I showed data on the synthetic optimization of this class of compounds, as well as a small library of compounds varying in ring size and stereochemistry that explore the effects of the Glaser brace on backbone structure.

Impressions: This meeting was a robust opportunity to both present and discuss the work I've done in my PhD as well as gain inspiration and learn about techniques that could help me push the work further. The group was a perfect size for being able to have repeat interactions with attendees, establishing strong contacts. The location was both extremely pleasant and amenable to developing new connections. There was diversity in the science presented from both UCSF and Scripps researchers which made for both a lot of new learning and new insights into fields I was already more familiar with. The conference was the perfect length, with both sufficient time to get through a significant number of different topics (I was a huge fan of the fact that every single person at the conference presented, meaning that we got a full introduction to each attendees research) and down time to rejuvenate the brain/focus before another session started. The length of the conference was also not very disruptive of work going on in lab as I didn't even lose a full week of lab work but learned a lot. Overall, it was clear to me that the details of this conference have been carefully honed over the years and it runs very smoothly with a reason behind every detail of the plan.

Name: Andrew Ambrose
Supervisor: Michelle Arkin
Department: Pharm Chem UCSF
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Presentation: Flash talk about discovery of a selective caspase-6 inhibitor and its affect in cellular models of Alzheimer's Disease and tau cleavage.

Impressions: I thought it was a great meeting. Everyone was very accessible, and the talks were great. It could potentially benefit with some more structured activities in the afternoons, but I think that might be pretty challenging to set up.

Name: Matthew Bogyo
Department: Pathology, Stanford University
Mailing address: 300 Pasteur Dr., Edwards R 343, Stanford, CA 94305-5324
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Phone number: 650-725-4132

Presentation: Identification of covalent binding ligands using phage display.

Impressions: This was another great meeting. I like the student speed talks and the faculty presentations were also really good. Maybe shorten the PI talks slightly to force them to be more focused on making their points. that would give a bit more time for group interactions. Maybe have a group event at one of the afternoon off times. Or you could also do an evening hang out at one of the bars so that the group comes together for interactions outside the meeting room.

Name: Batuujin Burendei
Supervisor: Andrew Ward, Stefano Forli
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Presentation: Title: Small molecule inhibitor design for a family of proton channels
My work involves molecular docking based virtual screening and cryo-electron microscopy to find small molecule inhibitors for the Otopetrin family of proton channels. Otopetrins currently have no specific inhibitor molecules, thus searching available compound libraries for inhibitors could yield a toolkit small molecule that is useful for electrophysiological and structural studies of Otopetrins.

Impressions: For the symposium venue, I thought the number of people attending was appropriate, the seats were almost fully filled for all talk sessions.
Can't complain at all about the location of the conference, Hyatt Ziva was very enjoyable. I even got to see some of the town too. It was very nice to see graduate students from UCSF this year, because I think previously only postdocs from UCSF right? I think the student body between the two institutes got along well too. I would very much like to meet more grad students from UCSF, or other institutes from San Francisco. The length of the symposium was fine for me. Any longer would've been a bit too long. It was nice to have one free afternoon / evening for the last day as well. For other comments, we had heard of Ian taking the students out for a snorkling trip, which I think a lot of people were looking forward to. It would've been awesome if that had happened this year. Overall, it was a very enjoyable symposium. Thank you.

Name: Danny Conrad
Supervisor: Zev Gartner
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Presentation: "Using lipid-conjugated DNA barcodes for multiplexed single-cell sequencing"

Impressions: I had a great time and loved meeting all of the students from Scripps, and those from UCSF I didn't know previously. I think we would have benefited from having a planned group outing or activity other than the reception on the first night. Many people were too tired or shy on the first night, and so besides that the only time to chat with PIs was if you caught them right before/after/between talks.

Name: Michael Erb
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Overview: My group is principally focused on using small-molecule tools to drug and study transcriptional regulatory programs in human cancer cells. We develop drug-like chemical probes and apply them in translational model systems to study dysregulated gene expression programs. We aim to nominate new targets for therapeutic intervention and uncover basic mechanisms of transcriptional regulation in physiological and pathophysiological systems.

Presentation: We identified a previously unrecognized synthetic lethality between histone deacetylase 1 (HDAC1) and HDAC2 that results from recurrent hemizygous deletions of HDAC1 in neuroblastoma and HDAC2 in lymphoid malignancies. We engineered neuroblastoma cells to express tagged alleles of HDAC2 that are responsive to chemically induced degradation. We discovered that acute degradation of HDAC2 in neuroblastoma cells with hemizygous HDAC1 deletions results in the destabilization of the HDAC1/2-containing NuRD chromatin remodeler complex, ultimately leading to the degradation of several neuroblastoma-specific vulnerabilities. Future efforts will be oriented to identify direct-acting small molecules that can induce the degradation of HDAC1 or 2 selectively, without the need for genetic engineering approaches.

Impressions: Only my first time attending this meeting, but I enjoyed every minute of it. Had the opportunity to meet many influential people in my field for the first time, share our science with a new audience, and receive key feedback from respected colleagues. Size and location made it very easy to connect with new colleagues.

Name: Janice Goh
Supervisor: Rada Savic
Department: BTS, UCSF
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Presentation: How do novel in vitro assays values compare against MIC targets in designing dose regimens for TB?

Impressions: The meeting was very welcoming and inclusive. The laid-back atmosphere made it very conducive to network with trainees from other institutions and talk about science in a non-threatening environment.

Name: John Gross
Department: UCSF Pharm Chem
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Presentation: Structural insights into the molecular arms race between HIV Vif and human APOBEC3G

Impressions: Great atmosphere for informal interactions; a broad array of science from structural and chemical biology to biophysics and structure of ribosome quality control. I enjoyed meeting new colleagues and catching up with ones I've met before.

Name: Danielle Grotjahn
Department: Integrative structural and computational biology, Scripps Research
Mailing address: 10550 North Torrey Pines Road, Hazen 112, La Jolla, CA 92037
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Overview: A primary focus of the Grotjahn Lab research program is to understand how mitochondrial networks change shape, and thus function, in response to cellular stress. We define the structural and functional interactions that mediate these stress-induced modulations to mitochondria using the cellular tomography workflow, which combines multiple imaging modalities such as correlative light and electron microscopy (CLEM), cryo-focused ion beam (cryo-FIB) milling, and cryo-electron tomography (cryo-ET). Through our high-resolution cellular imaging efforts, we generate three-dimensional snapshots of mitochondria with all endogenous molecular interactions pristinely preserved and shine new light the pathogenic mechanisms that contribute to mitochondrial dysfunction.

Presentation: Cellular stress associated with the accumulation of misfolded proteins in the endoplasmic reticulum (ER stress) is signaled to mitochondria through the activation of the PERK arm of the unfolded protein response (UPR) and leads to pathogenic mitochondrial dysfunction. However, the mechanisms mediating the connection between ER stress and

mitochondrial dysfunction in these diseases remains a mystery. To address this, we developed a semi-automatic correlative light and electron microscopy (CLEM) workflow to correlate ER stress-induced changes in mitochondrial network morphology to ultrastructural changes in membrane ultrastructure. To complement this workflow, we developed a suite of tools to perform “3D morphometrics” to analyze complex membrane geometries (i.e. membrane curvature, intra- and inter-membrane distance, surface area, etc.) across millions of square microns of cellular membranes. We aggregated quantifications of membrane ultrastructures across dozens of tomograms per experimental condition, and thus begin to shed light on the mechanistic underpinnings that regulate membrane remodeling in response to cellular stress conditions.

Impressions: This continues to be my favorite meeting! I really appreciate that every participant presents their work, which helps foster conversations and interactions throughout the meeting. The location and accommodations are excellent, and so is the science. I felt that there were adequate precautions for the COVID-19 pandemic, and overall had a great experience. Can't wait to go back again!

Name: Matthew Hancock
Supervisor: Andrej Sali
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Presentation: Bayesian multi-state modeling from X-ray crystallography.

Proteins often realize biological function through their ability to translate between multiple low-energy states. Explicitly modeling heterogeneity from X-ray diffraction data will uncover biologically relevant alternative states in high-resolution detail. We demonstrate how the challenges of a highly parameterized multi-state model may be overcome by integrating diverse input information through the Bayesian modeling framework.

Impressions: All aspects of the meeting exceeded expectations. One aspect that stood out was the intimacy afforded by the number of attendees. The group size was balanced such that it reflected a broad array of scientific disciplines yet allowed for all attendees to present their work. As a result, I was able to build meaningful connections with other trainees and faculty.

Name: Mia Huang
Department: TSRI Molecular Medicine
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Presentation: My group focuses on chemical glycobiology and is involved in the development and application of tools that facilitate the study of how glycans regulate biological functions. I presented our findings related to the integrated use of proximity tagging technology and high resolution mass spectrometry to capture and identify the glycoprotein interactions of disease-related proteins, a feat that has not been easily achieved using standard approaches. We found some interesting glycopeptide differences related to isogenic mutations of cancer cell lines, which we will follow-up and present on in coming years.

Impressions: As always, the format allows for in-depth conversations and discussions amongst PIs and students. As a junior PI, this meeting has been tremendous in helping me build my network. Location and length of the meeting are excellent. The first night having all students present flash talks was slightly overwhelming, but the good thing is, it facilitated discussions with students.

Name: Young-wook Jun
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Presentation: Biophysical mechanisms of Notch signaling at cellular interface.

I presented a talk on our recent unpublished results describing biophysical mechanisms that regulate Notch signaling at cellular interface.

Impressions: The Scripps/UCSF conference was extremely interesting. The conference covered top-notch science in various topics of molecular and structural biology, as well as new cutting-edge tools. It was super helpful for me and was an excellent meeting to exchange novel scientific findings between scientists from both institutes.

Name: Katrin Karbstein
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Presentation: Ribosome remodeling and repair.

Impressions: Terrific science; I enjoyed the fact that many institutions were represented.

Name: Laura Keller
Supervisor: Matthew Bogyo
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Presentation: Serine hydrolases are a diverse class of enzymes that play important roles in cell signaling and human metabolism. Little is known about the functions of these enzymes in gut commensal bacteria. Using bioinformatics and activity-based probes, we identified 27 active serine hydrolases in the gut symbiont Bacteroides thetaiotaomicron. Two are highly specific to the Bacteroidetes phylumm and are predicted homologs of the human protease dipeptidyl peptidase 4 (hDPP4), a key enzyme that regulates hormone and insulin signaling. Functional studies revealed that one is a true homolog of hDPP4, BT4193, while the other is a misannotated proline-specific triaminopeptidase. We demonstrate that BT4193 is important for envelope integrity and is inhibited by FDA-approved, hDPP4-targeting drugs for treatment of

type 2 diabetes. Taken together, our findings suggest that serine hydrolases contribute to gut microbiota dynamics and may be potential off-targets for existing drugs that could result in unintended alterations of the microbiota

Impressions: The meeting was incredibly well-run and organized. I really enjoyed having all of the trainees present the first evening, as it helped introduce the trainees from all of the institutions early on and helped contextualize the later professor talks. Giving the speed talk was immensely useful, as it required me to synthesize my research into the key highlights. The size of group was perfect for getting to learn about the latest research and network with great scientists.

Name: Chika Kikuchi
Supervisor: James C. Paulson
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Presentation: My research focuses on the interaction between human airway glycome and recent H3N2 influenza viruses. H3 hemagglutinin has narrowed its receptor specificity toward only extended sialoglycans in the last two decades. However, whether or not these glycans exist on human airway epithelial cells has not been shown before. We have analyzed human airway epithelium glycome by MALDI-TOF-MS glycomics to confirm the existence of extended glycans. Immunofluorescence microscopy showed that these extended glycans serve as functional receptors for recent H3N2 influenza viruses on the human airway epithelium.

Impressions: This meeting exceeded my expectations, and I feel very fortunate to have been there! The setting (group size, number of presenters, duration) was optimal - I learned a broad range of research topics, and still, I had enough time and opportunity to discuss further with presenters during the conference since it had a lot of time that allowed attendees to interact. The setting that everyone including sponsors gave a talk effectively encouraged interactions during the meeting. It might help trainee presenters to have another minute or two per person, but I would rather have a short presentation than have a smaller group/fewer attendees.

Name: Luke Lairson
Department: Chemistry, Scripps
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Presentation: Our laboratory uses chemical biology-based approaches to elucidate novel biological mechanisms associated with human disease and to identify starting points for the development of therapeutic agents. Three major focuses in the lab involve studying remyelination and oligodendrocyte biology, identifying mechanisms for targeting cancers a cell type selective manner and characterizing cGAS-STING signaling-related mechanisms.

My talked described how we used a pathway-targeted phenotypic screening approach to identify a small molecule STING agonist with in vivo anti-tumor immunity-promoting activity and focused on a potential structural basis for observed differential downstream signaling activities of different classes of STING agonists.

Impressions: This was one of the best meetings I have attended. The format and scientific content were outstanding. It was a privilege to have had the opportunity to attend.

Name: Keren Lasker
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Presentation: Intracellular phase separation is emerging as a universal principle for organizing biochemical reactions in time and space. The conserved intrinsically disordered protein PopZ forms condensates at the poles of the bacterium *Caulobacter crescentus*, which in turn orchestrate cell-cycle regulating signaling cascades. I presented data showing that the material properties of these condensates are determined by a balance between attractive and repulsive forces mediated by a helical oligomerization domain and an expanded disordered region, respectively. A series of PopZ mutants disrupting this balance results in condensates that span the material properties spectrum, from liquid to solid. A narrow range of condensate material properties supports proper cell division, linking emergent properties to organismal fitness. Finally, I showed how we use these insights to repurpose PopZ as a modular platform for generating tunable synthetic condensates in human cells.

Impressions: I found the meeting to be highly stimulating. The speakers presented cutting-edge science, and there was a good balance between academia and industry, scientists at different career stages, including short talks by students and postdocs. The meeting format and venue promoted interactions between all participants. Overall, excellent meeting in all aspects.

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Presentation: Synthetic Notch receptors (synNotch) have exhibited promising therapeutic applications toward targeted cancer treatment with enhanced selectivity and specificity. Recently, murine Notch1 based synNotch was re-engineered to develop a new class of fully humanized receptors called SNIPRs (SyNthetic Intramembrane Proteolysis Receptors) (Zhu and Roybal et al., 2021). Surprisingly, the full deletion of the negative regulatory region (NRR), the signal switching domain of endogenous Notch, in minimal SNIPRs resulted in robust and ligand-specific activation. This suggests that SNIPRs use an operating mechanism distinct from the traditional sequential cleavages (i.e., S2 and S3 proteolysis). We interrogated how ligand-receptor interaction triggers SNIPR activation by employing protein engineering, artificial cell-cell junctional models, spatial imaging, and DNA nanotechnology. We found that SNIPR ligand-receptor interactions form unique interfacial membrane microdomains that enrich cholesterol-rich lipids and y-secretase, wherein SNIPR releases its intracellular domain (ICD). We show that size-based protein membrane reconstruction is critical for establishing the membrane microdomain with high proteolytic activity for SNIPR activation. Our study revealed the

mechanism underlying NRR-independent engineered Notch activation, which promises for designing novel synthetic receptors with improved performance.

Impressions: It was a fascinating opportunity for me to meet other students/postdocs as well as influential PIs in the field. I really enjoyed learning about people's research and getting to know them on a more personal level.

Name: David Millar
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Presentation: My lab develops and applies new single-molecule fluorescence methods for the analysis of protein dynamics and protein-nucleic acid interactions. This year I described our recent studies of DNA polymerase I, a model polymerase that coordinates three separate enzymatic activities during lagging strand DNA replication. Using site-specific fluorophore labeling and single-molecule FRET, we resolved distinct subpopulations of Pol I bound to model DNA substrates, corresponding to separate enzymatic activities, and we showed that the different complexes could freely interconvert between individual encounters between Pol I and DNA. These observations help to explain how the different enzymatic activities of Pol I are physically coordinated.

Impressions: This meeting continues to be one of the highlights of the scientific year for me. The repeated attendance of many attendees (I have attended every meeting) attests to the high quality of the science and the excellent opportunities for interactions with Scripps, UCSF and other participants. The Hyatt Ziva provides a convenient venue and the group size and duration of the meeting are just right.

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Presentation: I presented my lab's work on the development of fluorescent indicators to monitor change in membrane potential. Our lab has been investigating the use of photoinduced electron transfer (PeT) within a donor / molecular wire / acceptor framework to achieve optical voltage sensing with rapid kinetics (sub-millisecond) and high sensitivity (>25% $\Delta F/F$ per 100 mV change). Most of our applications have focused on detecting changes in the plasma membrane potential of electrically excitable cells like neurons and cardiomyocytes. To achieve this, we intentionally design our voltage-sensitive fluorophores (VoltageFluors) with charged, ionic substituents to keep them anchored in the plasma membrane. Without the ionic groups, the VoltageFluors stain internal membranes. More recently, we invented a method to re-direct VoltageFluors to the endoplasmic reticulum (ER). In this talk, I showed how tetrazine-substituted rhodamine voltage reporters (RhoVRs) can become actived when paired with a ceramide-

labeled transcyclooctene to enable voltage imaging in the ER. The ER is presumed to be electrically neutral, but measuring voltage changes in intact ER is difficult. I showed data describing how we used RhoVRs to measure membrane potential dynamics of the ER and plasma membrane during whole-cell voltage clamp of HeLa cells. The ER and plasma membrane potentials move in concert and the ER displays rectifying behavior at plasma membrane potentials above 0 mV. Although these data were unpublished at the time of presentation, the study has recently been accepted in the Journal of the American Chemical Society (2022, 142, 12138-46).

Impressions: Overall, I thought the meeting was fantastic. This was my first time attending the Scripps/UCSF conference. I'd be delighted to attend again!
(a) I thought the size was appropriate – larger and it may have been difficult to meet people; smaller and the range of topics explored would have been less diverse.
(b) The location was great. The Los Cabos resort was amazing.
(c) Attendees and presenters was well-balanced. I liked hearing from all of the trainees at the beginning.
(d) Length of meeting. I thought this was appropriate…perhaps could have been a ½ day longer?
(e) Other: As a first-time attendee, it would have been great to have a list of attendees (not a schedule) in advance of the meeting, just to know how to tailor the talk to the audience.

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Overview: My laboratory studies the structure, function, and chemical biology of ion channels. We also study mechanisms by which poisonous organisms avoid auto-intoxication. Both studies are focused on developing deep molecular insights into the function and misfunction of the human brain, heart, and nervous system.

Presentation: I presented recent findings from my laboratory regarding the discovery of a core, independently folded unit common to all voltage-gated ion channel pore domains. This context independent structural robustness, supported by molecular dynamics simulations, indicates that VGIC PD tertiary structure is independent of quaternary interactions. This fold occurs throughout the VGIC superfamily and in diverse transmembrane and soluble proteins. Strikingly, characterization of PD subunit-binding Fabs indicates that non canonical quaternary PD conformations can occur in full-length VGICs. Together, our data demonstrate that the VGIC PD is an autonomously folded unit. This property has implications for VGIC biogenesis, understanding functional states, de novo channel design, and VGIC structural origins.

Impressions: The meeting has a fantastic mixture of academic and industrial scientists who share common interests in molecular mechanisms of biological function. It provides an outstanding, friendly, and relaxed venue that facilitates communication and encourages informal interactions. After >2 years of no in person meetings, we all appreciate that the most important part of science exchange is the informal interactions that occur at meetings such as this one. There is no other way to meet new people and generate new ideas and directions of research collaboration. The quality of the participants and level of discussion at this meeting is at the highest level. It is a real treasure.

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Presentation: Structural Insights into Novel Epitopes in Plasmodium falciparum Circumsporozoite Protein

Impressions: Meeting was very well organized, and all talks given were very interesting. The 5-minute limit on student talks was challenging and I believe some speakers could've benefitted from additional Time. However, the brief nature of the presentation is a great communication skills exercise.

Name: Sarah Mosure
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Presentation: My research focuses on heme regulation of the REV-ERB nuclear receptors, which are a type of ligand-regulated transcription factor. Previous biochemical and structural data conflicted with cell-based models for how heme influences REV-ERB activity. After identifying a heme-dependent assay artifact in fluorescence-based biochemical assays, I used isothermal titration calorimetry, NMR spectroscopy, and X-ray crystallography to identify the structural basis for heme-dependent REV-ERB activity. My results using these fluorescence-independent approaches support a cohesive model with cell-based data.

Impressions: The meeting was fantastic! It was an excellent opportunity to meet scientists from other institutes and industry. I was impressed by the research presentations from PIs and students alike. I thought the formal sit-down dinners the first night (all attendees) and last night (Scripps only) were especially helpful for getting to know my colleagues.

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Presentation: The presentation described our recent work on exploiting the inhibitory Siglec co-receptors for suppressing unwanted immune responses. Antibodies that target activating receptors on immune cells, such as anti-IgD/IgM on B cells or anti-FcεRI on mast cells, activate the cells. We have found that conjugating high affinity glycan ligands of a Siglec found on these

cells results in profound suppression of activation as a result of the recruitment of the respective inhibitory Siglec to the activating receptor. In the context of suppressing activation of mast cells, the anti-FcεRI conjugated with a high affinity ligand of CD33 (Siglec-3) results not only in suppression of mast cell degranulation and anaphylaxis, but also in desensitizing the cell to subsequent activation. The results suggest a potential strategy to exploiting inhibitory Siglecs to suppress unwanted immune responses.

Impressions: It was so good that we were able to resume this annual meeting in CABO. As usual the diversity and quality of the science was outstanding. The quality of the in-person networking is facilitated by the fact that everyone gives a talk, including the students and post-docs on the first day. This plus the informal atmosphere breaks down barriers for a high level of personal interactions among all attendees, and the inevitable collaborations that ensue from the stimulating environment. It was clearly a highlight of the year for me.

Name: Hailee Perrett
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Presentation: My flash talk was based on my dissertation research, which uses single particle cryo-EM and other biophysical techniques to develop and evaluate immunogens for pathogenic Old World arenaviruses including those that cause Lassa fever.

Impressions: Overall, the meeting was great! The talks from faculty members were inspiring and helped me re-frame some of the approaches to my work. It would be nice to have more opportunities for trainees and faculty members to interact. It seemed like the two groups would often segregate themselves (which is understandable and bound to happen), but the interactions I had with faculty from other institutions or other buildings at Scripps was the most valuable part of this experience to me.

Thank you so much for all your work in planning and executing the conference! It has been such a highlight of my graduate experience, and I feel lucky to have had the opportunity to attend!

Name: Andrej Sali
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Presentation: Integrative modeling is an increasingly important tool in structural biology, providing structures by combining data from varied experimental methods and prior information. As a result, molecular architectures of large, heterogeneous, and dynamic systems, such as the ~52 MDa Nuclear Pore Complex, can be mapped with useful accuracy, precision, and completeness. Key challenges in improving integrative modeling include expanding model representations, increasing the variety of input data and prior information, quantifying a match between input information and a model in a Bayesian fashion, inventing more efficient structural sampling, as well as developing better model validation, analysis, and visualization. In addition, two community-level challenges in integrative modeling are being addressed under the auspices

of the Worldwide Protein Data Bank (wwPDB). First, the impact of integrative structures is maximized by PDB-Dev, a prototype wwPDB repository for archiving, validating, visualizing, and disseminating integrative structures. Second, the scope of structural biology is expanded by linking the wwPDB resource for integrative structures with archives of data that have not been generally used for structure determination but are increasingly important for computing integrative structures, such as data from various types of mass spectrometry, spectroscopy, optical microscopy, proteomics, and genetics. To address the largest of modeling problems, a type of integrative modeling called metamodeling is being developed; metamodeling combines different types of input models as opposed to different types of data to compute an output model. Collectively, these developments will facilitate the structural biology mindset in cell biology and underpin spatiotemporal mapping of the entire cell.

Impressions: Could not be more inspiring!

Name: Berliza Marie Soriano
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Presentation: Builders and Breakers: Enzymes Involved in Peptidoglycan Homeostasis

Impressions: This was my first time attending the meeting and my first meeting overall in graduate school. I thought it was a great meeting, while a little bit overwhelming given the fast-paced nature this also help to keep me engaged in each one of the talks. I had such a great time meeting and getting to know other graduate students even from my own school that I haven't interacted with before, it was overall great!

Name: Alex Tsui
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Presentation: Mechanosensor in Venus flytrap – Structure & simulation

Impressions: The meeting was very well organized and took place in a very pleasant venue. As a student we got the chance to presenting lightning (5-minute talks) which we thought were great. It may be great to spread out these presentations on various dates so that it wasn't that much to take in in one go. There are plenty of time to interact with faculty, especially with those from UCSF in a very relaxed setting. I especially enjoyed the talk by Jim Wells.

Name: Bieke Vanslembrouck
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Presentation: Structural differences of chromatin across different cell types.

Impressions: Good meeting, nice people, easy to connect and chat with other attendees. Good for networking.

Name: Andrew Ward
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Presentation: The main topics that I covered were the use of cryoEM to inform structure-based vaccine design and monoclonal antibody therapeutics. I demonstrated the recent extension of our polyclonal epitope mapping method to high resolution cryoEM. This approach enables a highly parallelized method for analyzing the molecular features of epitope-paratope interactions. Further, our highest resolution maps, when combined with antibody repertoire next generation sequencing, enables identification of monoclonal antibodies directly from cryoEM maps.

Impressions: It was great to be back in Cabo! The size of the meeting was just right with plenty of opportunity to interact with colleagues. Jim Wells gave a great keynote speech, and the majority of the other talks were also of high quality. No need to change anything, just do it again next year.

Name: Nicole Wenzell
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Presentation: Defining Sec61 client sensitivity using substrate-selective cotransins.

Impressions: The meeting was great! As a chemical biologist, I appreciated that the meeting was diversified in terms of types of talks. There was a great opportunity to connect with other trainees at both UCSF and Scripps. I think the conference could have benefited from designated networking time across trainee and PI levels - this is an opportunity I would have enjoyed.

Name: James Williamson
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Presentation: Presented a cryo-EM study on the earliest intermediates in 50S ribosome assembly, and a new assembly map including both RNA and protein components.

Impressions: This was a particularly strong meeting, with new attendees bringing fresh perspectives. The range of topics was very engaging, from structural biology, to drug design, to chemical biology, computational biology and biophysics. There is no comparable meeting with such a range of topics. The opportunity to interact with colleagues from Scripps, UCSF and other institutions, as well as industrial partners, makes for a terrific experience. As always, I came home with new ideas.

Name: Ian A. Wilson
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Presentation: Immune response to SARS-CoV-2 and variants of concern. I presented our work on structural basis of the antibody response to SARS-CoV-2 and the emerging variants. The sites (epitopes) targeted by neutralizing antibodies have been visualized as well as the effect of escape mutations. This information can aid in next-generation SARS-CoV-2 vaccines and therapeutics as well as more universal vaccines against coronaviruses.

Impressions: Another terrific meeting and an inspiring keynote talk from Jim Wells. The meetings somehow seem to just keep getting better and better if that is possible.

Name: Nelson Wu
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Presentation: My research focuses on development of a novel vaccine design for malaria P. falciparum. We focus on the C-terminal domain of the circumsporozoite protein. This domain has two major epitopes, a strain-specific face and a conserved face. Using computational design, we eliminated the binding of strain-specific antibodies without impacting the binding of broad antibodies. These immunogens are being tested in a mice model.

Impressions: The meeting was well-organized to balance time in talks and time enjoying the venue. The graduate attendee size was conducive to networking outside of presentations. It was hard to meet any new professors you did not already know. Perhaps a couple more organized meals like the first night would help.

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Presentation: EMBER multi-dimensional spectral microscopy enables the quantitative determination of distinct amyloid strains.

Each amyloidogenic protein is capable of adopting a number of different amyloid structures, each with molecular distinct repeating structures, known as the conformational strains. Our goal is to in situ recognize these strain differences and fingerprint distinct strains across neurodegenerative diseases. EMBER takes the advantage that even subtle conformational strain differences in amyloids can lead to a significant shift in the excitation and emission. Strain sensing ability in a given dye is first quantified with PCA and UMAP analysis against in vitro fibrils then the best sensing dyes are taken to ex vivo human brain samples for their ability to discriminate Aβ plaques and tau tangles across neurodegenerative diseases. Following this pipeline, we have identified one dye that can discriminate Aβ plaques from sporadic and familial AD, and Down syndrome, and tau tangles from Pick's disease, sporadic and familial AD, and Down syndrome.

Impressions: (a) the optimal size of the group: The size of the group was optimal.
(b) location of the meeting: The location of the meeting was superb.
(c) attendees and presenters: The attendees and presenters from various field grasped the leading-edge sciences.
(d) length of the meeting: The length of the meeting was good.
(e) any other comments: I appreciate the opportunity to go and learn what the professors of UCSF and Scripps are actively studying. Meeting them in-person was superb as I only read their papers.

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Presentation: My lab studies how motor proteins that transport intracellular cargos along microtubules are regulated by proteins that decorate the microtubule surface. It has been proposed that microtubule associated proteins (MAPs) serve as the signals that are encoded onto the MT tracks in order to control the intracellular traffick of motor proteins. We use structural biology and biophysical experiments to understand how MAP7 facilitates kinesin-1 driven transport while blocking the transport driven by other motors. We surprisingly found that MAP7 competes with kinesin for the same tubulin binding site, but kinesin-map7 interaction away from the microtubule surface tehres kinesin to microtubule and enable to motor to walk on map7 decorated microtubules. Our results indicate that specific interactions between a MAP and a motor could regulate which motors can transport a cargo on microtubules decorated by that MAP.

Impressions: This is one of my favorite meetings because of the quality of the talks, the breadth of the research topics both within and outside my field (chemical biology, structural biology, virology, MD simulations), and its excellent venue.

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Presentation: Targeting proteolytic neoepitope in cancer

Impressions: Fantastic science, great organization, great place!

Scripps/UCSF Conference
2022 Keynote Speaker

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

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