Society of General Physiologists

eNewsletter Fall, 2019

Welcome to our first e-newsletter. Newsletters will be issued twice a year, following the spring and fall SGP Council meetings. They will contain a summary of Council activity as well as fun and informative info for SGP members.

SGP Mission:

To promote and disseminate knowledge and interest in the subject of general physiology.

What is General Physiology?

General Physiology is a conceptual approach that recognizes the physico-chemical bases of biological processes. It uses quantitative experimental techniques to probe the mechanisms underlying physiological processes.

Read more about the SGP

A Brief History of the Society of General Physiologists
Prosser CL and Buck J, 1997 J Gen Physiol 109(4):vii
http://jgp.rupress.org/content/jgp/109/4/vii.full.pdf

2019 SGP Scholars at the Marine Biological Laboratory

Every summer, the SGP honors students in the summer courses at the Marine Biological Laboratory in Woods Hole as SGP Scholars. The SGP Scholars are students in a Summer course at the Marine Biological Laboratory who are nominated by their course directors, and generally have a strong chemical, physical, or quantitative background. This long-standing tradition was established in the 1970s by the former SGP member Benjamin "Benny" Kaminer. Benny was born in Poland, raised in South Africa, and began conducting research at the MBL with

Albert Szent-Györgyi around 1960. In the 1970s, he became chair of Physiology at Boston University Medical School, as well as councilor and treasurer of the SGP. Benny took charge of SGP's scholarship committee and created the SGP scholars program at the MBL. In 1987, Benny asked Paul De Weer of the University of Pennsylvania to join him in overseeing the MBL scholars program. Paul had just served as the SGP president, and had been conducting research at the MBL since 1966. Following Benny's passing in 2003, Paul continued his service to the MBL scholars program with David Gadsby of Rockefeller University, his decades-long collaborator at MBL, and they continued the tradition until David fell ill in 2017 (see obituary below). In 2018, Clay Armstrong of the University of Pennsylvania joined Paul to congratulate the scholars. They, both octogenarians, decided that the "job" (however pleasant) should be taken over by a younger generation. We look forward to propagating this important tradition that strengthens ties between the SGP and the MBL while introducing promising young scientists to the SGP.

Our social media committee asked the 2019 SGP Scholars a few questions:
1) What are your current research interests?
2) Could you share a little-known personal fun fact?
3) What does receiving this fellowship means to you?

Hannah Arbach
University of Washington
Embryology Course

1) My current research interests are in two areas, first characterizing branched nuclear morphology and second is studying the spatial temporal dynamics of chromatin closure in regeneration.

2) In my spare time I home brew, mostly focusing on Belgian style ales.

3) Being an SGP scholar is an incredible honor. I'm excited to continue the tradition of understanding complex cellular processes at the molecular level.

Sophie Miller
California Institute of Technology
Neurobiology Course

1) My current research interests are related to developing and using new tools to study local translation of mRNA in neurons.

2) When I'm not doing experiments in my lab coat, I can be spotted rowing on

the nearest body of water in the bright pink lycra unisuit from the boat club where I fell in love with the sport in the UK at Cambridge.

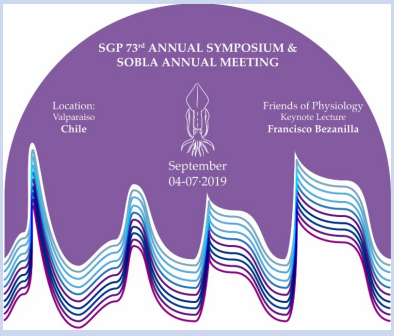
3) I am delighted and honored to receive this award. I am inspired by the the SGP's standards of scientific rigor and their goal of promoting quantitative approaches to studying biological systems.

Audrey M. Williams
University of Chicago
Physiology Course

1) I am broadly curious about spatial organization in biology, especially at the subcellular to tissue-scale. In my current research, I look at how a transmembrane signaling complex transmits information across cell junctions, and at how this directional signal propagates across a cell field.

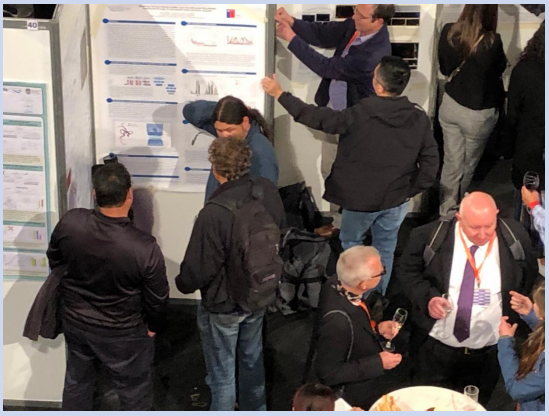
2)Before starting my PhD, I spent a year taking care of miniature donkeys.

3) I'm so glad to be participating in the MBL Physiology course- I've used many new technologies, had a ton of interesting discussions, designed a research project, and it's only week two!



73rd Annual SGP Symposium and SOBLA Annual Meeting
"Structural Basis of Electrical Signaling in the Nervous System and Heart"
Valparaíso, Chile
September 4-7, 2019

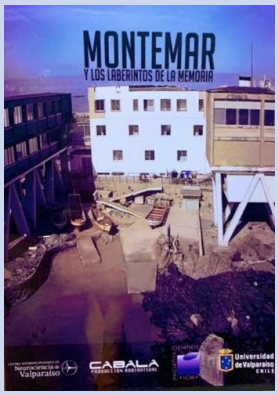
The 73rd annual symposium of the SGP was a uniquely wonderful event. For the first time, the symposium was not held at the Marine Biological Laboratory in Woods Hole. Instead we relocated to Valparaíso, Chile, where the squid with the largest giant axons swim.



The symposium was jointly sponsored with the Latin American Society of Biophysics, SOBLA (Sociedad de Biofísicos Latinoamericanos). SOBLA is a scientific society aimed toward strengthening biophysical research among Hispanic investigators in the US and Latin America. The SGP/SOBLA 2019 symposium brought together experts in key areas from structure to physiology, who by combining multidisciplinary approaches have elucidated molecular, cellular, and integrative physiology of channels/transporters in a variety of animal models that are relevant to physiology and disease.

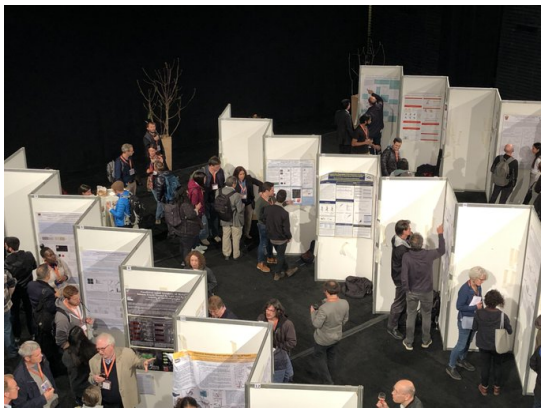
The symposium was an important platform fostering new scientific collaboration between scientists from the USA and Latin America. Scientists and trainees from both US and Latin America exchanged professional and cultural experiences that help us to create a better and trusted global scientific community. A special highlight of this meeting was a successful SGP fundraising campaign that supported fellowships for Latin American students

and postdocs to attend the meeting. All of this was enabled by years of dreaming and planning by the organizers, *Jorge Contreras, Miguel Holmgren, Ramon Latorre, and Brad Rothberg* who worked steadfastly to pull off this extraordinary event. Three cheers for the organizers! Information about the meeting can be found at https://sobla2019.com.



Check out the inspiring video that chronicles the history of Chilean biophysics at the laboratory at Montemar:
Montemar y los Laberintos de la Memoria.

Mark your Calendar!
Upcoming SGP Events



74th Annual SGP Symposium

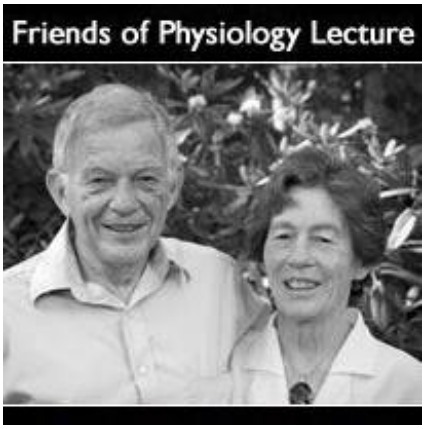
Ion channels and Transporters in Immunity, Inflammation, and Antitumor Immunity

September 9-13, 2020
Marine Biological Laboratory,
Woods Hole, MA
Organizers: Stefan Feske, MD, Bimal Desai, PhD

75th Annual SGP Symposium

Membrane Proteins in Context: Structure and function in native cells and macromolecular complexes

September 2-6, 2021
Marine Biological Laboratory, Woods Hole, MA
Organizers: Matt Trudeau, PhD; Cathy Proenza, PhD



2020 SGP-JGP Mixer

"All the people who matter and free beer!"

Sunday February 15, 2020
Biophysical Society Meeting
San Diego, CA

Watch your email for details and registration

in early 2020

Toiling in between channels and transporters

In Memoriam

David C. Gadsby, Ph.D.

March 26, 1947 - March 10, 2019

by László Csanády

David C. Gadsby, Ph.D. passed away in New York City on March 10, 2019. Dr. Gadsby was a Professor Emeritus at Rockefeller University, and had been Associate Editor of the Journal of General Physiology for 24 years, from 1984 to 2008, as well as president of the Society of General Physiologists between 1999 and 2000. He was the 1995 recipient of the K. S. Cole Award of the Biophysical Society, and a member of the Royal Society since 2005.

Following completion of his PhD at University College London, Dr. Gadsby joined Paul Cranefield's laboratory at the Rockefeller University, New York, in 1975. Studying electrical properties of cardiac Purkinje fibers, he developed methods to selectively measure the small currents carried by the electrogenic transport cycle of the Na^+/K^+ pump. Becoming quickly independent, he continued his research on the pump's transport mechanism, pioneering the application of the patch-clamp technique for studying currents of a transporter. Using systematic quantitative analysis he showed that the Na^+/K^+ pump reaction cycle includes only a single voltage-dependent step which, however, does not limit the rate of either the forward or the reverse transport cycle. He later identified K^+ translocation as the rate-limiting step, and measured rate constants for all the individual steps of the pump cycle.

In 1989, David Gadsby, Robert Rakowski, and Paul De Weer developed a revolutionary system which allowed simultaneous measurement of Na^+/K^+ pump

current and ion flux from a controlled membrane area of a squid giant axon perfused both internally and externally. This started a two-decade long annual adventure of the trio, later joined by Francisco Bezanilla and Miguel Holmgren, at the Woods Hole Marine Biological Laboratory in Massachusetts, exploiting the squid season for advancing the fundamental understanding of Na^+/K^+ pump function. Using this system the team identified that the release of external Na^+ (or its rebinding in reverse-mode operation) is the predominant charge-moving step in the pump's cycle, suggesting that extracellular Na^+ ions must reach their binding sites deep in the pump molecule through a high-field access channel. This finding implied that part of the pump molecule is functionally analogous to an ion channel. Using high-speed voltage jump experiments they were later able to clearly show that during normal-mode cycling of the pump the three transported Na^+ ions are de-occluded and released to the extracellular solution one at a time, in a strict order.

Consistent with idea that the extracellular parts of the pump may form an ion-channel-like structure, the marine toxin palytoxin was found to convert Na^+/K^+ pumps into nonselective cation channels by disrupting the normal strict coupling between opening of one access pathway and closing of the other. Studying regulation of gating of single palytoxin-bound Na^+/K^+ pump-channels by the physiological ligands ATP, Na^+, and K^+, Gadsby's lab was first to demonstrate that, despite the bound palytoxin, partial reactions of the normal pump cycle persist. This affirmed the alternating access model of ion pumps, and allowed the study of ion occlusion and deocclusion steps at the microscopic level, in single Na^+/K^+ pump molecules. Using cysteine scanning of the anticipated ion permeation pathway in palytoxin-bound Na^+/K^+ pump-channels, their studies discovered not only a wide but deep outer vestibule which leads to a narrow charge-selectivity filter formed by acidic residues that allow the approach of cations but exclude anions, but also a single unbroken cation pathway that traverses palytoxin-bound Na^+/K^+ pump-channels from one side of the membrane to the other. In recent years, the lab's work identified inward proton transport through the actively cycling Na^+/K^+ pump, classifying it among hybrid channel-transporters. The potential pathological relevance of pump-mediated proton influx during extracellular acidification remains to be explored.

In 1989, the year the gene cftr, loss-of-function mutations of which cause cystic fibrosis, was cloned, Dr. Gadsby discovered a cAMP-dependent chloride current in cardiac myocytes. Investigating its regulation via G proteins, as well as its single-channel properties, he later concluded that this cardiac chloride current is carried by the Cystic Fibrosis Transmembrane conductance Regulator (CFTR), an epithelial chloride ion channel known to be activated through phosphorylation by cAMP-dependent protein kinase, and gated by binding and hydrolysis of cytosolic ATP. That discovery started off a second line of decades-long research in his lab, focused on understanding structure and function of CFTR, the only channel

member in the ABC transporter family, whose failure causes cystic fibrosis. Using non-hydrolyzable ATP analogs, vanadate, or Mg^{2+} removal to disrupt the ATP hydrolysis cycle at CFTR's two cytosolic nucleotide binding domains (NBDs) he identified strong coupling between ATP hydrolysis and channel closure, and started to dissect how incremental phosphorylation of its unique cytosolic regulatory domain affects the mechanism of channel gating. To address how structural manipulations affect CFTR channel function, research in the Gadsby lab switched from cardiac myocytes to the frog oocyte heterologous expression system. Exploiting split CFTR channel constructs, obtained by coexpression of its two homologous halves, their studies could demonstrate strong functional asymmetry between the two ATP binding sites. Whereas binding of ATP at NBD2 leads to channel opening and its hydrolysis there prompts channel closing, at NBD1 ATP remains tightly bound and unhydrolyzed for periods that are very long compared to the channel's gating cycle. Emerging structural information on related ABC proteins, together with sequence comparisons across the entire ABC family, allowed identification of key residue interactions that change in a gating-state dependent manner. Using thermodynamic mutant cycles work in the Gadsby lab showed that opening of the CFTR channel pore is coupled to the formation of a stable intramolecular NBD1-NBD2 heterodimer following ATP binding, and that pore closure is coupled to disruption of that dimer, triggered by ATP hydrolysis. These key observations, later confirmed by state-dependent cross-linking of pairs of engineered cysteines, allowed him to explain how the conserved mechanism of the ABC-family active transport cycle is exploited in CFTR to drive opening and closure of the ion channel pore, and suggested that CFTR evolved by degeneration of the intracellular ABC transporter gate. Atomic structures of CFTR obtained a decade later have largely confirmed those predictions.

In addition to his outstanding scientific accomplishments, Dr. Gadsby has trained a large number of young scientists who continue to carry on his work on both channels and pumps. As a mentor, he was committed to passing on to the younger generation his depth and clarity of thinking, his uncompromising rigor in experimentation as well as data interpretation, and his insatiable curiosity towards deeper understanding of natural phenomena. At the same time, he granted great freedom to young scientists, allowing them to delve into problems that attracted their attention, and encouraged them to fully enjoy the excitement of scientific discovery. He showed exceptional patience and understanding, and was not only respected but truly loved by his trainees. Outside the workplace, Dr. Gadsby and his wife Patricia Gadsby cherished friendship with both scientists and non-scientists around the globe. He enjoyed traveling, and was a keen fisherman, often seen cruising the seas around Woods Hole in his boat. All of us who have had the chance to know him feel extremely grateful for this privilege.

SGP Council News

Officers
President: Merritt Maduke, 2018-2019
President-Elect: Crina Nimigean, 2018-2019
Secretary: Andrew Harris, 2017-2019
Treasurer: Frank Horrigan, 2019-2021

Councilors
Alessio Accardi, Councilor, 2019-2021
Anabel Fernandez-Mariño, Postdoc Councilor, 2019-2021
Theanne Griffith, Postdoc Councilor, 2018-2020
Andrea Meredith, Councilor, 2017-2019
Cathy Proenza, Councilor, 2018-2020
Janice L. Robertson, Councilor, 2019-2021
Brad Rothberg, Councilor, 2017-2019
Jon Sack, Councilor, 2018-2020

Highlights of the Fall 2019 SGP Council Meeting

The SGP now has an inclusion policy for society activities, it can be found at https://www.sgpweb.org/governance

The SGP has joined the Societies Consortium on Sexual Harassment in STEMM http://educationcounsel.com/societiesconsortium/

Upcoming election of new Councillors. Watch your email for ballots in October to elect new SGP Council members.

SGP Image Contest

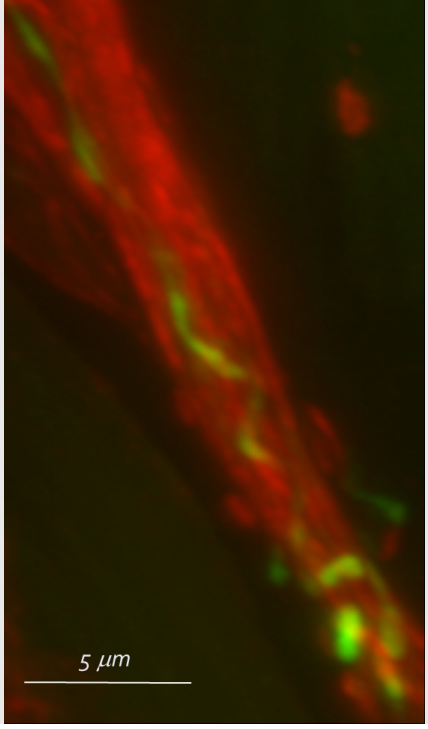
Show off the beauty of your work!

The SGP website would like to promote your research.

Entries can be scientific images, displays of data, published figures, pictures of researchers, places of research, or other creative images that reflect the mission of the SGP

Winners will have their images accredited and integrated into the SGP website.

Upload image entries to:
www.sgpweb.org/imagecontest



Innervation of sinoatrial node myocytes (red, HCN4) by sympathetic neurons (green, tyrosine hydroxylase). Cathy Proenza

---

SGP Newsletter by Cathy Proenza and Jon Sack
SGP Social Media Committee is Anabel Fernandez-Mariño and Theanne Griffith

Click here to join SGP or Renew your Membership

Society of General Physiologists |Website

Follow SGP on your favorite social media platform!