



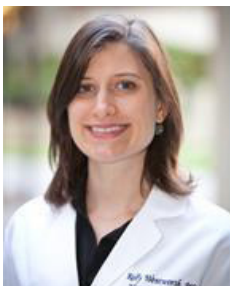
UCSF Department of Medicine ZUCKERBERG SAN FRANCISCO GENERAL

EMPOWERING PHYSICIAN SCIENTISTS AT ZSFG

Physician-scientists have a foot in two worlds: they conduct research inspired by unsolved problems facing their patients, then help translate lab discoveries back to the clinic. Their deep understanding of these different realms gives them unique perspectives on identifying important research questions and applying exciting lab discoveries to patient care. The ZSFG Department is fortunate to have a number of these highly talented faculty and a new research building, PRIDE Hall. This issue features three of our physician-scientists.

Clues from Bone Clinic Prompting Discovery

“Looking for the outliers and studying what has gone wrong allows us to make more general observations about disease processes,” said Kelly Wentworth, MD, Assistant Professor of Medicine in the ZSFG Division of Endocrinology.



Kelly Wentworth, MD

She cares for clinic and hospitalized patients with skeletal diseases such as osteoporosis, as well as a range of less common ones. As a translational scientist, she focuses on two extremely rare diseases: fibrous dysplasia (FD), in which normal bone

is replaced by fibrotic tissue that makes the bones weak and vulnerable to fracture, and fibrodysplasia ossificans progressiva (FOP), in which a genetic mutation activates bone formation in muscles, tendons and other places it shouldn't be.

“I try to understand the underlying signaling pathways in the skeleton and bone as a model for



Dr. Kelly Wentworth in the lab.

what's going on in the bone environment,” she said. “What we learn from these rare diseases can be applied to more common bone diseases.” For example, identifying the genetic pathways underlying FD could shed light on why some people have delayed healing of bone fractures. Although FD and FOP are very rare, because of her specialized expertise Dr. Wentworth sees many of these patients at ZSFG and UCSF. Developing trusting relationships with them not only allows her to provide excellent clinical care, but also helps her uncover clues about what causes their diseases.

For example, Dr. Wentworth's colleagues saw a young soccer player and gymnast in clinic with FOP who experienced her first disease flare-up at age 17; most FOP patients develop abnormal bone formation in their muscles before age 10, often after minor sports injuries. “Even though this patient had the same genetic disease, she had a relatively mild phenotype,” she said. “Without seeing the patient in clinic and hearing about all her

daily activities, we probably wouldn't have picked up on that.” That spurred the team to analyze that patient's DNA. Dr. Wentworth and her colleagues identified a few genetic mutations that might have a protective effect, delaying the onset of FOP.

Building those relationships with patients also helps accelerate research. “One of my research studies uses bone that normally gets thrown away after surgery,” said Dr. Wentworth. “By explaining to patients what we do in the lab, most of them say, ‘I really want to donate my sample, because it's important to advance research.’”

Dr. Wentworth's journey to becoming a physician-scientist was serendipitous. Although she had done some lab research during medical training, she was mainly pursuing a clinical career as a hospitalist at the University of Washington Medical Center when she worked with some endocrinologists. “I thought, ‘Gosh, what you do is really cool. You're able to see patients, but then go back to the



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lab and exercise that part of your brain to take care of patients,” she recalled.

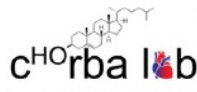
Her physician-scientist colleagues encouraged her to pursue this new direction, so in 2014 she came to UCSF for a fellowship in endocrinology, metabolism and diabetes, working in the lab of Edward Hsiao, MD, PhD, Associate Professor in the UCSF Division of Endocrinology and Metabolism. “Even though you might be going down one path, reassessing and figuring out what you enjoy is really important,” said Dr. Wentworth. “Seeing people model this career path was inspirational. At UCSF and San Francisco General in particular, there’s a culture of encouragement for being not just a physician but also a scientist.” She is currently working to establish her own lab.

She appreciates the nurturing ecosystem for physician-scientists at UCSF. “On a national level, the NIH Career Development Grant is very supportive of physician-scientists and has been instrumental,” said Dr. Wentworth. “Here, the Division of Endocrinology values our work and tries very hard



to give us enough time and resources to do both research and clinical care.” She is also active in the UCSF Women Physician-Scientists Supergroup, founded in 2020 by Carolyn Sangokoya, MD, PhD, Instructor in the Departments of Pathology and Laboratory Medicine. The group hosts a speaker series, writing group, and networking and mentoring opportunities, and administers small grants to support research and career advancement.

The most challenging aspect of her work is navigating between the distinct spheres of the lab and clinic. Although she is always available to respond



to patient emergencies, on lab days she tries to schedule specific blocks of time to follow up on routine patient care emails so she can focus on research the rest of the time. She also plans ahead. “If I’m in clinic on Monday and Thursday, I’d need to postpone a three-day experiment until the following week,” she said.

“I love the variety in what I do,” said Dr. Wentworth. “I really value the time I spend with patients, talking about their concerns and treatment options. I also really enjoy being in the lab, interpreting data, and writing grants and papers. It’s exciting to be able to see patients, and also answer critically important biological questions in the lab. As physician-scientists we can only exist within a system that values what we do, and a place like San Francisco General goes out of their way to support us.”

Bridging Cardiovascular Disease Care and Chemical Biology

“I like to bring my clinical experience to identify a research question I think will be important, then let the science take me where it’s going to go,” said John Chorba, MD, Assistant Professor in the ZSFG Division of Cardiology. In addition to reading cardiac echocardiograms and caring for hospitalized patients on the cardiology service and in intensive care, he also spends about three-quarters of his time on research. He established his independent lab in 2021 after working as a postdoctoral fellow and assistant professor in the lab of Kevan Shokat, PhD, Professor in the Department of Cellular and Molecular Pharmacology.

Many of Dr. Chorba’s patients struggle with high cholesterol, and his research focuses on cardio-

vascular disease and lipid metabolism. “I have a background in chemical biology, which is like molecular carpentry,” he said. “You’re building molecules from the ground up.”

Much of his recent work has centered around PCSK9, a protein that contributes to high cholesterol levels. Although injectable forms of PCSK9 inhibitors were approved by the U.S. Food and Drug Administration (FDA) in the last decade, they are expensive and often not covered by public health insurance.

“The problem is there is no cheap oral pill you can take,” said Dr. Chorba. “It’s frustrating being on service and thinking, ‘I could give someone this therapy, but I can’t because they’re poor.’”



John Chorba, MD

He spent years as a UCSF cardiology fellow and postdoctoral scholar trying to solve this problem, making important discoveries that he and his collaborators are trying to translate into an affordable pill version of a PCSK9 inhibitor. “I love the science behind it – that’s what got me fascinated,” said Dr. Chorba. “But I also wanted to do something that would make an impact.”

As a physician-scientist, Dr. Chorba leverages his clinical observations and close working relationships with the medical team to identify promising avenues for investigation, as well as practical ways to pursue them. For example, he wanted to find out if heparin, a blood thinner commonly used to prevent clots during medical procedures such as



cardiac catheterizations, affected how PCSK9 is brought into the liver.

“Because I’ve experienced life in the hospital, I know that people get heparin all the time,” said Dr. Chorba. “I purchased a cooler off Amazon, and asked the Cardiac Catheterization Laboratory nurses to put patient blood samples [from

cardiologists. Dr. Chorba is excited about this tool’s potential to help identify patients with heart murmurs who should receive timely referrals to a cardiologist. “The beauty of this approach is that everybody uses a stethoscope, including medical assistants,” he said. “If we make it user-friendly and leverage this technology that’s already widely implemented, we have the infrastructure to get

said Dr. Chorba. “Being in the hospital and seeing patients keeps me connected and helps me ask certain questions that are important. . . . Science is incredibly fun. Whether you are the principal investigator or a summer intern, anyone can make a really interesting observation that can become transformational. The biggest advances in science are from people making connections that weren’t obvious.”



before and after they received heparin] in the cooler rather than in the trash.” By analyzing these samples from patient volunteers, his team learned more about the biology of PCSK9. “If something is already happening in normal clinical care, sometimes you can take advantage of that to conduct frugal science,” he said.

Besides his wet lab research, Dr. Chorba has also partnered with Eko, a Berkeley-based company that uses machine learning to analyze heart sounds to improve diagnosis of cardiovascular disease. “I’m not a machine learning expert, but I do understand what pieces of information would actually be helpful for a clinician,” he said.

He originally served as a mentor for the UC Berkeley engineering undergraduates who founded Eko, which has developed digital stethoscopes and FDA-approved machine learning algorithms to detect heart murmurs on par with expert

more information from the tests we’re already doing.”

Dr. Chorba helped lead the initial study for this AI-enhanced approach at ZSFG, collecting de-identified electronic stethoscope recordings and echocardiography results from study volunteers. The study sites later expanded to several other locations nationally. “It’s been fun to combine my research and clinical background with [company members’] data science background,” he said. “They are also scientists at heart, so we get to geek out and also move towards something that will be translatable to the clinic. That degree of rapidity from conception all the way to clinical care is pretty cool.” Now he is working with another ZSFG colleague to develop new algorithms for other types of heart disease.

“As a physician-scientist you exist in two different realms, and can help bridge these different worlds,”

Caring for HIV While Exploring Human Immunology

As a physician-scientist, Rachel Rutishauser, MD, PhD, Associate Professor of Medicine in the ZSFG Division of Experimental Medicine, is adept at navigating steep learning curves in two distinct domains.

She finished her PhD in immunobiology at Yale University in 2010 and came to UCSF for her internal medicine residency and fellowship, where she focused on developing her clinical skills. “During those five years away from the lab, all of cancer immunology happened, many new tools to assess the human immune system emerged, and CRISPR editing became more mainstream,” said Dr. Rutishauser. “At the time I thought, ‘All this crazy stuff is happening in the field, but it’s going to be different a year from now. When I get back to my postdoc, I’ll figure it out and take the time to do the deep dive.’”



Rachel Rutishauser, MD, PhD

After five years as an infectious disease fellow and postdoctoral scholar in the ZSFG Division of Experimental Medicine, working in the labs of Mike McCune, MD, PhD, Professor of Medicine, and Peter Hunt, MD, Professor of Medicine, Dr. Rutishauser established her own lab in 2020.

Those research and clinical threads now intertwine in her current work. She sees patients in Ward 86, ZSFG’s world-renowned HIV clinic, and cares for hospitalized patients a few weeks a year. “I love my patients and the complexities of medicine,” said Dr. Rutishauser. Many of her patients have chosen to participate in research, contributing their time



The Rutishauser Lab (left to right clockwise): Gina Borgo, Demi Sandel, Lily Zemelko, Rafael Tibúrcio, Rachel Rutishauser, Shayleen Singh, Kaiti Schwartz, Wendy Hung, and Julia Wagner

“These are the killer cells that are capable of finding infected cells and killing them,” she said. “We focus on situations where that doesn’t happen as well, such as HIV?”

Her group also studies how CD8+ T cells fight viral infections in infants, whose immune systems function differently while in utero in order to tolerate their mothers’ immune systems. Dr. Rutishauser’s lab also investigates systems immunology, trying to better understand how different cell types interact with each other to produce an effective immune response.

Dr. Rutishauser currently leads research on using chimeric antigen receptor (CAR) T cell therapies to improve immune response against HIV. Similar to the use of CAR T cells in cancer immunotherapy, her group’s pioneering clinical trials take T cells out of patients with

HIV, engineer them to boost their efficacy against the HIV virus, and reinfuse them into patients. Her lab studies how the CAR T cells interact with HIV over time, and what are the long-term clinical outcomes. Because CAR T cells are a potent therapy with potentially significant side effects, participants are closely monitored, including receiving bloodwork three times a week early on. “We appreciate the dedication of our study participants so much,” she said. “They’re very friendly and say, ‘I’m here again to get some blood drawn.’ It’s very special.”

Dr. Rutishauser loves teaching, both in the lab and clinic, and is passionate about mentoring other physician-scientists. She founded a support group for early-career physician-scientists applying for a K award, a mentored scientist grant which is key for launching one’s career. In response to her advocacy, the UCSF Departments of Medicine, Neurology and Pediatrics partnered to create the

Physician-Scientist Career Development Program, which provides support and resources to help people successfully write K award applications.

“It took institutional commitment to fund this office and give administrative support and resources to this program, and it’s made a very material difference in training physician-scientists,” said Dr. Rutishauser. “It’s so great to be able to point people to that resource, and it makes a big difference to the people I’m mentoring.”

She tells her mentees that every physician-scientist’s path is different. “Everybody has different opportunities, so don’t compare yourself to others,” said Dr. Rutishauser. “Talk to as many people as you can to understand what those opportunities are. You have a lot of flexibility, and aren’t tied down to just research or medicine. Listen to yourself and what you’re passionate about.”

She appreciates her colleagues in the Division of Experimental Medicine. “This division is so special,” said Dr. Rutishauser. “We have a really collegial environment of people who do HIV, TB and malaria research, and we all learn from each other. We have the most amazing admin team, grants people, lab manager, and people on the legal side. That supportive infrastructure allows us to do these clinical studies as physician-scientists.... This path is really hard, but it’s incredibly rewarding. It provides opportunities in both medicine and research that you couldn’t imagine if you were in one alone. Doing research that has direct patient impact is the most meaningful thing to me.”

Elizabeth Chur

Editors: Neil Powe, Laurae Pearson, Kevin Weil

SPOTLIGHT

Larissa Thomas, MD, Division of General Internal Medicine, and Leigh Kimberg, MD, Division of General Internal Medicine, were both recipients of an educational grant from the Haile T. Debas Academy of Medical Educations.

Lisa Winston, MD, Division of HIV, ID, and Global Medicine, has been named the Associate Medical Director for ZSFG Med/Surg effective July 1, 2023.

Beth Harleman, MD, Division of Hospital Medicine was named a 2023 Master Clinician in the Department of Medicine.

