

CTSCconnections

Building research teams of the future to improve human health • 2016 • Volume 6, Issue 1

TRANSLATIONAL PROFILE

James Kovach – interpreter across fields

IT IS PROBABLY SAFE TO SAY that Jim Kovach has had a career path like no other. He attended medical school during off seasons while playing as a linebacker with the New Orleans Saints, and after obtaining his medical degree played another season with the San Francisco 49ers. He then retired from the National Football League, and a few years later, obtained a law degree from Stanford University.

After working as an attorney for several years, he has filled leadership roles in innovative institutes and start-up enterprises in the medical technology and professional sports arenas.



James Kovach, M.D., J.D., Director of Translational Entrepreneurship and Industry Research Alliances

In 2011, Kovach helped launch CrowdOptic, a San Francisco-based software company that streams Google Glass videos in real time to enhance teaching, collaboration, and emergency response. The technology is used by universities and medical centers, as well as sports franchises, to enhance the audience experience.

Kovach also served as the Chief Operating Officer (COO) for eight years at Athersys, a publicly traded, clinical-stage biotech company in Cleveland, where he identified and acquired stem cell and other technologies to accelerate drug

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DIRECTOR'S MESSAGE

Lars Berglund, M.D., Ph.D.

LAST SUMMER, A GROUP OF EXPERIENCED INVESTIGATORS and grant writers convened to prepare the third Clinical and Translational Science Award (CTSA) application. In 2006, UC Davis received one of the first 12 of such awards and a renewal was funded for a subsequent 5 years in 2011. The new grant will provide another 5 years of CTSC support. With this award and the generous ongoing support from the School of Medicine, the CTSC continues to offer a wide and evolving array of services to support biomedical and translational research. The grant application outlines the organizational structure that is now required by the NIH National Center for Advancing Translational Sciences (NCATS), the NIH institute that supports the CTSA program.

Some features of the new award include infrastructure to facilitate involvement in multi-center clinical trials, expanded efforts to involve patients across the lifespan and with rare diseases, and formal relationships with the Betty Irene Moore School of Nursing, Center for Health and Technology, and the School of Veterinary Medicine. Together with the existing resources that include clinical research ethics, biomedical informatics, biostatistics, community engagement, a pilot award program, regulatory support, a research clinic, and robust scholar programs, the CTSC is well positioned to continue to expand its ability to serve the UC Davis biomedical research community in a variety of innovative ways.

The new award further weaves the CTSC into the institutional fabric of the UC Davis research enterprise. From its inception, the CTSC served as an incubator to

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discovery efforts. He next spent five years as president and COO of the Buck Institute for Research on Aging, an independent research organization in Novato, CA that utilizes cutting-edge technologies dedicated to extending optimum health throughout life.

Kovach's extensive experience in the medical, technology, business, and legal worlds led him to UC Davis, where he has served as a consultant since 2013 and is now the director of Translational Entrepreneurship and Industry Research Alliances.

"The constant in my career has been an interest in different perspectives of how ideas are conceived and implemented," said Kovach. "I am always looking at the intersection of basic science, translational research, and entrepreneurial activities."

Promoting innovation

Kovach serves as a liaison at UC Davis between the many players inherent in medical innovation with the goal of more efficiently bringing advances to market. He advises students, faculty, and fellows on the full spectrum of activities that lie between basic research and the use of new products in healthcare. At the same time, he meets with potential partners in industry who can sponsor research at the university.

"I see myself as an interpreter across the different facets of translational medicine," Kovach said. "I have been in the trenches throughout my career with basic scientists, engineers, clinicians, industry, and regulatory folks, so feel I am in a unique position to help all of them understand each other's positions and needs."

To advance the innovation process at UC Davis, he and School of Medicine colleagues Nam Tran and Benjamin Keller have brought a course called "Bioinnovation" to the Sacramento campus. Meeting over one quarter, the course creates teams among students across degree programs and disciplines, including engineering, business, and medicine. Providing a background in such topics as patent law, Food and Drug Administration (FDA) regulations, and intellectual property, students are concurrently "parachuted" into a clinical problem, said Kovach, such as improving the care and recovery of burn patients. Kovach helps the students brainstorm, develop prototypes of new therapies or

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DIRECTOR'S MESSAGE *continued from page 1*

transform and catalyze translational research. In 2016, the CTSC now offers a fully-fledged array of tools to engage and support the workforce and provide a wealth of services. Over the last 10 years, the ranking for NIH funding for the UC Davis



Lars Berglund, M.D., Ph.D.

School of Medicine increased from 51st in the U.S. to 30th. The CTSC played a significant role in the current ranking by providing: scholars with the training necessary to become principal investigators, pilot funding to launch research critical to grant applications, and resources to investigators at all career stages to ensure their success in implementation of research projects.

Over the past 10 years, the CTSC awarded 157 pilot projects that included 376 trainees, and resulted in a 30-fold return on investment. To date, we have trained 72 T and 27 K scholars. Thirteen (13) of our K scholars, to date, have received NIH funding, published 989 papers (H index of 13.5), were granted 3 patents, and several have achieved leadership roles at NIH, academic institutions, state agencies, professional societies,

and positions on scientific advisory boards. Overall, investigators that have used the CTSC in some capacity published more than 1,300 papers in over 500 journals which have been cited 34,000 times (2.7 times the global average). Through collaborations among the other four UC medical centers, the CTSC provides access to 14 million patient records to facilitate research.

There are many examples of the positive impact the CTSC has had on the research enterprise at UC Davis. But one thing is clear... Investigators who rely upon the CTSC benefit from their experiences and success begets success. As requests for our services increase, we remain dedicated to our mission of *building research teams of the future to improve human health.* §

devices, and learn the nuts and bolts of eventually bringing their ideas and new products to market.

“Innovation and product development are not part of a traditional medical education,” said Kovach. “But I firmly believe that these are processes that can be taught.”

Maximizing success

Surprisingly, Kovach says that he wants to see ideas fail – early in the development process, that is. He notes that the most time-consuming and costly phases of developing a new device or drug are the last stages – especially large clinical trials, where well over half of novel drug candidates fail in Phase III clinical testing, the last stage prior to FDA approval. He notes that the average drug costs approximately \$3 billion in a research and development process that can take decades. Kovach strives to increase the proportion of ultimately beneficial products in the pipeline and bring down the costs of research and development in order to maximize efficiency.

“If a new therapy is going to fail, it should fail quickly,” said Kovach. “We need to design products smarter – using tools such as informatics, artificial intelligence, and chemical design – so that they go into the process with a high expectation for success.”

Kovach believes the resources that UC Davis offers provide an optimal environment to maximize new product success. He cites the strong academic and clinical resources of the medical school, veterinary school, college of engineering, genome center, and programs in biomedical informatics and biostatistics. In addition, the culture of collaboration across disciplines at UC Davis provides the perfect incubator for successfully creating new therapies. He notes that

national recognition of the importance of the CTSC's efforts to support and facilitate outstanding translational science – starting with basic research to find unexpected results and translating to new diagnostics and therapies for patients – is reflected by the support from the National Institutes of Health,

other funding agencies, and private foundations.

“The CTSC – the hub of all the factors needed for successful innovation – is at the forefront of new discoveries,” said Kovach. “I see my role as smoothing the path to bring great new ideas to fruition.” §

CLH 298 Biolnnovation, Spring 2017 (2 units)

Do you have a medical background and the desire to become an innovator? Have an idea for a new therapy or device you want to bring to market? Interested in improving the practice and delivery of medicine through new technologies? If your answer is “yes,” consider taking this course on Biolnnovation from the Clinical Research Graduate Group.

Target students:

- Schools of Medicine, Veterinary Medicine, and Nursing
 - Scholars, fellows, graduate students, postdoctoral fellows, junior faculty
- College of Engineering
 - Graduate students and postdoctoral fellows
- School of Law and Graduate School of Management
 - Law and M.B.A. students

Description: The goal of this course is to provide students with a basic understanding of the elements of innovation and how to translate these principles into the biomedical design process. The course takes a systematic approach to needs finding, invention, and the implementation of new biomedical technologies.

Immersive learning opportunity: Class members are divided into teams whose members have complementary educational backgrounds. Each team is given access to a clinical environment, where they will identify bottlenecks and clinical needs. Teams then select a clinical need and develop a medical device to address that need.

Example projects from 2015-2016 class:

- Sequential compression integrated with TENS (Transcutaneous Electrical Nerve Stimulation)
- Integrating visual cues to prevent burns

Instructors: Nam Tran, Ph.D., Jim Kovach, M.D., J.D., Benjamin Keller, M.D.

Contact: Connie Koog – cdkoog@ucdavis.edu – 916-703-9132

Next offering: Spring 2017

CTSC investigators conduct game-changing research on critical medical tests

INNOVATIVE NEW THERAPIES tend to get the most attention in translational research, while *in vitro* diagnostic (IVD) testing often receives less press. Medical tests are less highly regulated by the U.S. Food and Drug Administration (FDA) compared to their drug counterparts, and clinicians often take for granted that diagnostic tests are accurate.

Two former CTSC scholars questioned such assumptions and found some surprising results with wide-reaching implications for public health.

Christopher Polage – All positive *C. difficile* test results are not equal

What happens when the introduction of a new clinical test causes the number of people diagnosed with a disease to double? That's what occurred in 2009 when the FDA approved a new polymerase chain reaction (PCR) test for identifying *Clostridium difficile* infection, the leading cause of infectious diarrhea, colitis, and death in hospitals worldwide. The PCR test detects the bacteria's DNA, indicating the presence of the organism in the sample, while the conventional test targeted only the extracellular toxin that mediates disease.

The question of "Which test is better – the old one or the new one?" intrigued Christopher Polage, associate professor in the Department of Pathology and Laboratory Medicine at UC Davis.

"Knowing which test is most accurate clinically is critical," said Polage, who is also director of the UC Davis Health System Microbiology Laboratory. "The answer has tremendous implications if we are unnecessarily diagnosing and treating large numbers of patients with antibiotics."

Polage, who arrived at UC Davis in 2007 and subsequently completed the CTSC Mentored Clinical Research Training Program, received support through the CTSC KL2 ("K12") Program to study the issue. His resulting paper, "Overdiagnosis of *Clostridium difficile* infection in the molecular test era," published in *JAMA Internal Medicine* in November 2015, sent shock waves throughout the infectious disease and diagnostic



Christopher Polage, M.D., Associate Professor, Pathology and Laboratory Medicine

testing communities, and earned him a Distinguished Clinical Research Achievement Award from the Clinical Research Forum. Polage's paper was selected by the Forum as one of the top three studies in the nation that have the potential to change lives and patient outcomes worldwide.

Polage's research found that hospitalized patients with suspected *C. difficile* infection who tested positive by the PCR method but negative by the toxin test had the same clinical outcomes as patients who tested negative with both tests. This finding indicated that these patients do not

need specific treatment for *C. difficile* infection and probably are colonized with the bacteria rather than infected. According to Polage, separate evidence suggests that antibiotic treatment may actually precipitate active disease in asymptomatic patients who are colonized with the organism, making the potential consequences of overtreatment even more serious.

Polage credits his experiences as a CTSC scholar with providing him with the capability of undertaking top-notch translational research. From the contacts he made to identify mentors and collaborators to the support in specific areas such as grant facilitation, biostatistics, and bioinformatics, he received an ideal grounding in the translational research that is critical to his field of laboratory medicine and infectious disease.

Polage was recently awarded a \$2.4 million grant from the Gordon and Betty Moore Foundation to reduce the transmission of *C. difficile* among hospitalized patients. He is also continuing his scrutiny of diagnostic tests – which he views as "unexplored territory" in research – including those for central nervous system and respiratory infections.

"In stark contrast to the normal evaluation process for medications, clinical outcome studies of diagnostic tests are almost never performed before FDA clearance and clinical implementation," said Polage. "Our study on *C. difficile* is a cautionary tale of what can happen when new diagnostic tests are adopted without systematic investigation of their clinical significance."

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Nam Tran – Are blood glucose meters accurate?

When Nam Tran, assistant clinical professor in the UC Davis Department of Pathology and Laboratory Medicine, began the CTSC Mentored Clinical Research Training Program in 2011, he undertook a very small project.

In a study of just 12 burn-care patients, Tran evaluated the accuracy of a couple of commonly used point-of-care glucose monitoring devices against laboratory plasma glucose measurements. He suspected that certain factors commonly found in burn patients – such as medications (e.g., acetaminophen and vitamin C) in the blood and abnormal hematocrit levels – might influence the accuracy of the readings.

The study found that the state-of-the-art glucose meter tested was accurate due to the ability to automatically correct against medication and hematocrit interferences. However, the existing device used at UC Davis Medical Center led to results that differed from the standard by a mean of 5.7 mg/dL. Such variation was found to significantly alter insulin dosing enough to increase patient risk for hypoglycemia (dangerously low blood glucose levels), according to Tran.

“Insulin is one of the most dangerous drugs we give to patients,” said Tran, who also serves as the Director of Clinical Chemistry and Point-of-Care Testing. “Patients are harmed if doctors bring their blood sugar down too low.” In fact, glucose meters are the most frequently cited IVD device resulting in adverse events according to the FDA. The majority of adverse events are due to inaccurate measurements resulting in hypoglycemia.

The results of this small pilot study had repercussions far beyond the burn

unit where it was conducted. It helped put into motion new restrictions by the Centers for Medicare & Medicaid Services (CMS) and the FDA to ensure that bedside blood glucose measuring devices used for hospitalized patients are first validated for the intended populations. These data were credited with representing the sickest patient population that was submitted to the FDA to illustrate the clinical impact of accurate measurements in the critically ill.

Recent studies conducted by Tran *et al.* revealed even more compelling data. A study involving 122 severely



Nam Tran, Ph.D., M.S., Assistant Clinical Professor, Pathology and Laboratory Medicine

burned children at Shriners Hospital for Children of Northern California revealed patients receiving insulin based on the new autocorrecting glucose meter significantly improved glycemic control compared to prior devices. Tran also found patients receiving insulin therapy using the older non-correcting glucose meters experienced significantly higher glycemic variability and hypoglycemia, which resulted in increased mortality. These data ultimately illustrate accuracy *does matter* and point-of-care glucose meters are not trivial IVD

devices. Through Tran's studies, UC Davis and UC Irvine have changed their glucose meters over to the new autocorrecting devices which two years later remain the only systems cleared by the FDA for the critically ill.

Tran's work in burn patients also involved rapid pathogen detection in sepsis. While participating in the CTSC Mentored Clinical Research Training Program, he was a recipient of a nearly \$1.86 million grant from the U.S. Department of Defense to conduct a larger study in multiple burn centers on a PCR test to detect the presence of *Staphylococcus aureus* within hours rather than up to four days with conventional laboratory testing. That degree of improvement in laboratory turnaround time can be extremely important for a burn patient who needs rapid treatment for sepsis.

Becoming the principal investigator of a large randomized controlled trial involving 5 burn centers was daunting to him at first, but he feels that the program and mentorship provided him with the necessary skills, and just as importantly – a network of support – to succeed. A background in biomedical engineering education is also a big bonus.

“I come at problems from a multidisciplinary perspective, and that can be an advantage,” he said. “I believe that true innovation is derived at the interface(s) between different disciplines.”

Tran thrives on the excitement generated by combining different fields. He is instructor-of-record of a 1-quarter Bioinnovation course that brings together students obtaining medical, engineering, or business degrees to form teams with the goal of designing a marketable new clinical device or therapy. In 2008, he also developed the first undergraduate biomedical

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Some of the best things in life are free Grant team helps secure funding for investigators

IT IS DUE IN NO SMALL PART to the skill of a three-person team of grant experts that the UC Davis SOM has increased NIH funding over the last 10 years. Operated at no cost to investigators through the SOM Office of Research, this team has a mission to:

- Clarify all stages of the grant process
- Strengthen grant applications to make them more competitive for funding
- Advise in developing and maintaining funding for research careers at all levels
- Review and advise on responding to grant critiques and summary statements
- Monitor new calls for applications, evolving requirements, and policy changes so that investigators are updated with this knowledge in a timely manner
- Make manuscripts more competitive for publication

Drs. Jeffrey Elias, Erica Chedin, and Betty Guo are the three scientists-turned-grant-facilitators who comprise the Grants Facilitation Unit in the UC Davis SOM. Elias, director of the unit, has a wide range of experience as a researcher, department administrator, research mentor, NIH/NSF grantee, study section reviewer, and is the current editor for a journal focused on aging. Prior to arrival at the UC Davis SOM in 2007, Elias served as the Scientific Review Administrator for the study section APDA and was chief of an extramural program for the Behavioral Science Research Division at the National Institute on Aging.

Chedin completed her Ph.D. training at UC Davis (a recipient of the Molecular and Cell Biology T32 graduate



Erica Chedin, Ph.D., Betty Guo, Ph.D., and Jeffrey Elias, Ph.D.

training award) and went on to post-doctoral training at the University of Southern California (a recipient of another T32 then her own NRSA) before returning to UC Davis. After redirecting her career to grant writing support, Chedin gained important expertise in assisting with multi-disciplinary, multi-investigator center grant applications.

Guo has been a grantee, manuscript reviewer, biotechnology consultant, laboratory co-leader, and is trained in PCORI reviewer guidelines. After over a decade as a bench scientist, including a postdoctoral fellowship at Harvard Medical School, Guo's success helping co-workers rewrite manuscripts and respond to critiques expanded into grant writing support. With 10 years of experience as an editor, Dr. Guo has become especially proficient at developing individual research grants, career development awards, and training program proposals. In addition to helping with specific grants, the Grants Facilitation Unit provides training in a larger format, including an annual symposium and two quarters of instruction on grant writing to institutionally-supported training

scholars.

In May of 2016, this team received the UC Davis Health System's Employee Excellence Award for Teamwork and Collaboration. Dr. Ted Wandzilak, Director of Medical Sponsored Programs and Assistant Dean for Research, was extremely pleased at this well-deserved recognition of the team under his leadership. "The grant team is a highly recognized and respected team whose services are in constant demand. The skills, talent, and demonstrated excellence of the Grants Facilitation

SOM Grant Facilitation Team

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Unit have had a significant role in the success and national recognition of the SOM research mission,” he said.

The Grants Facilitation Unit also earned high praise and heart-felt gratitude from Lars Berglund, director of the Clinical and Translational Science Center (CTSC), for its work on what turned out to be a nearly 1900 page grant application for a new CTSA award that had a short, two-month turnaround time.

“Quite honestly,” said Berglund, “I don’t know how we could have completed our proposal without the help of the SOM Grant Facilitation Unit and the Interdisciplinary Research Support team on the Davis campus. The Grants Facilitation Unit worked with us for nearly two years of planning prior to the funding opportunity announcement, and then spent an intense two months working side-by-side with the CTSC team to create a successful application.”

The best advice the team has for investigators seeking funding is to plan early. Strategize well in advance by identifying potential collaborators, including biostatisticians; sketch out your Specific Aims; and be prepared

to re-write several iterations of your proposal until you have the best final version. If you would like their assistance, contact them as soon as you begin searching for funding or become aware of a potential funding source. §

Grant Facilitation Unit Services

- Prepare, develop, edit, and review grant applications. Assist with all mechanisms from NIH and other funding agencies, federal and private. Areas of expertise include multi-investigator center grant applications, training grant applications, R-series awards, and NIH Mentored Career Development (K) awards.
- Provide support for collaborative efforts in grant development and symposia.
- Assist investigators with NIH website navigation and identifying key NIH personnel for strategic communications.
- Notify investigators of program announcements and new funding policies/requirements and offer strategic interpretations.
- Provide grant writing educational opportunities, including graduate- and post-graduate level courses, yearly workshops, and just-in-time seminars.
- Review and edit manuscripts.
- Review post-submission summary statements and grant resubmissions.
- Offer guidance for review appeals when applicable.

RESEARCH ETHICS

Bioethicist Yarborough fosters trustworthy research

CAREER PATHS BEGIN IN MANY WAYS, and sometimes it is a simple encounter that alters one’s direction. Mark Yarborough had an experience like this while he was a senior in college. He knew he wasn’t interested in a business career, but what might he do with a degree in philosophy? Then, a brochure from the University of Tennessee about a graduate program in medical ethics – a brand new field at the time – caught his attention. The prospect of being able to focus the special insights and skills of philosophy on a set of pressing issues in real world settings attracted him. And the rest is history.

Yarborough, now Dean’s Professor of Bioethics, recalls how that brochure led him to many different places during his career, including UC Davis. He

considers it good fortune to be able to work almost exclusively on the issues and questions that captured his attention in graduate school – the



Mark Yarborough, Ph.D., Director of CTSC Research Ethics Program

ethical dimensions of biomedical research. Directing the CTSC Research Ethics Consultation Service affords him a unique perspective on the range of issues that researchers find challenging. Engaging CTSC scholars in discussions about research ethics helps him appreciate how early stage researchers integrate a robust sense of professional responsibility into their developing research careers. He also enjoys the challenge of working with a team of basic and clinical investigators hoping to study a new stem cell gene therapy for Huntington’s disease. Seeing firsthand the incredible dedication of research participants, as well as the extraordinary passion and commitment

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Diagnostic Testing *Continued from page 5*

engineering course aimed at helping students understand clinical applications before working with physicians and nurses. Tran especially enjoys introducing engineering students to the medical culture, and conversely, medical students to an engineering mindset. Through building these bridges with biomedical engineering to foster innovation, Tran's engineering students have produced several publications, devices, and inventions during the last eight years.

Engineers may see devices as just clever pieces of technology, he said, but when talking to physicians, they realize how complex and important their effects can be. We also see clinicians quickly understanding the importance of laboratory test accuracy, he added. Outcomes can be improved not only by new therapies, but with therapies guided by better technology.

"Given over 70% of medical decisions are based on some form of laboratory test, I don't underestimate the importance of seemingly simple tests," Tran said. "They can make the difference between life and death." §

Yarborough *Continued from page 7*

of the research team, engages him in a myriad of complicated clinical research questions.

While a career in the field of bioethics offers many rewards, it can also present troubling challenges. While Yarborough was working at a previous institution, the Food and Drug Administration shut down the clinical research enterprise because of problems involving the IRB. This incident led Yarborough to face the most enduring question of his career: How do research institutions know whether or not they deserve the trust that they continuously solicit and enjoy?

This question has kept Yarborough coming to work every day for years. It is a fundamental question, yet it seems to gain little attention. It is Yarborough's hope that research institutions find a way to focus more effort on the challenge of creating a research environment worthy of the public's trust, as opposed to simply looking for better ways to recruit more people to their research. And until that day arrives, Yarborough will be at work every day, exploring the question of institutional trust-worthiness and helping to create an environment that supports it. §

Contact Mark Yarborough at mayarborough@ucdavis.edu to schedule a consultation with the CTSC Research Ethics Consultation Service.



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<http://www.ucdmc.ucdavis.edu/ctsc/>

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