UC DAVIS CLINICAL AND TRANSLATIONAL SCIENCE CENTER

CTSConnections

Building research teams of the future to improve human health • 2015 • Volume 5, Issue 1

TRANSLATIONAL PROFILE

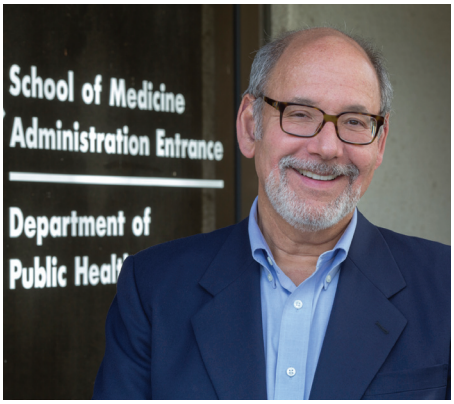
An offer he could not refuse: prominent epidemiologist Brad Pollock returns to UC

THE OPPORTUNITY TO BUILD CONNECTIONS within the UC System proved too difficult to resist for Brad H. Pollock, Ph.D., M.P.H., recently appointed chair of the Department of Public Health Sciences.

As the founding chair of the Department of Epidemiology and Biostatistics at the University of Texas Health Science Center in San Antonio, where he directed two core programs at the CTSA-funded Institute for Integration of Medicine and Science (IIMS), Pollock was well entrenched in a professionally satisfying career. Specializing in pediatric cancer epidemiology, he had developed nationwide prominence conducting and participating in multi-institutional studies in oncology, diabetes, HIV, and obesity. When he received a cold call from a recruiter, he was not in the market for a new position. But after reflecting upon the possibilities that UC Davis would offer, he changed his mind.

Pollock found himself drawn to Sacramento by the reputation of the UC Davis Department of Public Health Sciences and the strength of its three cores – epidemiology, biostatistics, and environmental and occupational health. His prior collaborations with UC Davis faculty members through CTSA committee work made the position even more attractive.

Notable among them is CTSC Director Lars Berglund, with whom Pollock had become acquainted by virtue of Berglund's participation on the external advisory board of the IIMS in San Antonio. To Pollock, the opportunity to strengthen his collaborations through another CTSA center was magnetic. The work at UC Davis' NCI-designated Comprehensive Cancer Center greatly impressed



Brad H. Pollock, Ph.D., M.P.H.

Pollock, a native Southern Californian who obtained his bachelor's degree at UC Irvine and earned his master's and doctoral degrees at UCLA, and whose family members remain in California. The personal reasons for him to join UC Davis outweighed any advantages of remaining in Texas.

Pollock would not have come to UC Davis, though, if it were not for UC Davis Health System's institutional investment and commitment to biomedical informatics, and if the Department of Public Health Sciences was not as highly regarded as it is. With his department's stellar reputation and complement of faculty expertise,

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DIRECTOR'S MESSAGE

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

COLLABORATION AND ENGAGEMENT are two key words linked with today's research enterprise. The CTSC has always had a focus on promotion of team science, especially within our Pilot Award program. We also encourage research teams to tap into our Community Engagement services, which are designed to foster collaboration with community stakeholders, especially those who represent underserved populations.

In this edition of the CTSC Connections newsletter, we focus on Patient-Centered Outcome Research (PCOR) – research that includes individual input by members of UC Davis research faculty and staff. PCOR is a new way to conduct research with a focus on input from key stakeholders before a project starts. An ongoing project involving this type of research is pSCANNER (Patient-centered SCAlable National Network for Effectiveness Research). This project encompasses 24 researchers, 9 data sites, and over 24 million patients. Funded by the Patient-Centered Outcomes Research Institute (PCORI), this project is one of 11 national clinical data research

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PILOT PROFILE

CTSC Pilot project leads to increased funding for Charles Stephensen's research team

PUBLIC HEALTH OFFICIALS have been frustrated that the oral polio vaccine is not as effective for infants and young children in equatorial Third-World countries as it is for children in Western nations. Infants and young children respond better to immunization when they have sufficient levels of vitamin A and high levels of intestinal *Bifidobacterium* bacteria, which are specially adapted to grow in the intestine of infants consuming breast milk. Common in developing nations, vitamin A deficiency is associated with reduced immunity and increased susceptibility to life-threatening infections. Could vitamin A supplementation work together with *Bifidobacterium* in the intestinal tracts of children who have insufficient levels of desirable intestinal microbiota to improve vaccine responses?

Charles Stephensen

That is the question that prompted Charles Stephensen, Ph.D. to initiate an international study in 2010. Stephensen, a U.S. Department of Agriculture research scientist with an appointment as a UC Davis adjunct professor of nutrition, teamed with pediatrician Mark Underwood, M.D., and established a new collaboration with microbiologist David Mills, Ph.D. of the Department of Viticulture and Enology to answer this question. Other collaborators included Rubhana Raqib and Shaikh Ahmad from the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) in Dhaka, along with trainee Nazmul Huda, an icddr,b lab scientist from Bangladesh who is pursuing his Ph.D. through the UC Davis Nutritional Biology Graduate Group. Stephensen submitted a proposal to the CTSC and received a pilot project award to study the relationship between vitamin A and immunization efficacy.

Stephensen and his colleagues collaborated with a study group in which infants in a Bangladesh maternity hospital were given high doses of vitamin A shortly after birth. Under the pilot award, Stephensen's team used a new molecular technique called 16S rDNA pyrosequencing in combination with real-time PCR to analyze changes over time in the intestinal microbiota of the infants participating in the study. This work is forming the basis of Huda's Ph.D. thesis.

"We confirmed, as expected, that the gut microbiota composition was

(Continued on page 8)

Brad Pollock *Continued from page 1*

Pollock intends to build upon that foundation and broaden public health cores by developing two new structures: a division of health services research and a division of health informatics.

"Elements of medical informatics are scattered throughout the School of Medicine and the UC Davis Health System, but we lack a single academic department to concentrate its base. This new division of health informatics will help establish essential linkages that will support conducting multidisciplinary clinical and population-based research," said Pollock, whose energy and enthusiasm appear inexhaustible. "The CTSC is the home for doing this trans-disciplinary work, which is now the way you have to approach most of our health problems."

He plans to expand and fortify the research infrastructure by integrating clinical epidemiology, biostatistics, health IT, and medical informatics. Doing so will enable the CTSC to accommodate and coordinate studies of increasing complexity. He sees opportunity for cross-pollination among the UC Davis schools of medicine, nursing, veterinary medicine, and the graduate school of management, and the colleges of engineering, biological sciences, and agricultural and environmental sciences.

As a strong proponent of integral and continuing education, Pollock also plans to borrow a strategy from the playbook of executive MBA programs to enable working health professionals to more easily obtain training in public health in an expanded master's in public health (MPH) degree program. He favors class scheduling adjustments and some online components to make the MPH program more accessible to clinical professionals. "We have the technology to offer distance learning using two-way interactive video class sessions," Pollock said. He also wants to develop a joint MD-MPH option for our medical students.

"The educational mission of the CTSC is just as important as its research functions. How do we train the next generation of people to do state-of-the-art health research? The CTSC is now one of the major drivers nationally of training a whole cadre of people to be able to understand this cross-disciplinary approach to doing health research," Pollock said. "In our department, we are very much involved in training more junior faculty who want to develop clinical research careers. Now in modern epidemiology, we need to have resources like the CTSC to be able to do the work that we do. That's really the connector."

Turning the tables on clinical research

Practice makes perfect…however, over time, there is the potential for repeated activity to become mechanized. Research is about answering questions and solving problems, but novelty offers unique opportunities for new discoveries, insights, and potential solutions.

Historically, researchers developed a question and designed a study to address their hypothesis, often with grant funding. Upon gaining regulatory and human subjects protection approval, a study would ensue with patients recruited and tested, data gathered and analyzed, and a report written to summarize the outcomes.

Today, the federal government is encouraging involvement of stakeholder input from the outset – before a study is designed. This methodology is called PCOR (Patient-Centered Outcomes Research) and it is a relatively new concept in the traditional research arena. Instead of unilaterally deciding what to study, researchers consult with a variety of stakeholders – including patients – to develop the research question and to craft and implement the study.

What is PCORI?

The Patient-Centered Outcomes Research Institute (PCORI) is a nonprofit, nongovernmental organization located in Washington, DC. Congress authorized the establishment of PCORI in the Patient Protection and Affordable Care Act of 2010.

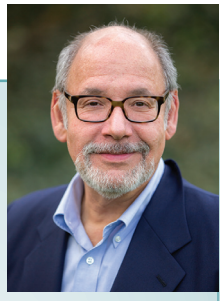
Mandate

To improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers and policy makers make informed health decisions by funding work that will improve the methods used to conduct such studies.

Mission

PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers and the broader healthcare community. They call this "research done differently."

Text borrowed with permission from the PCORI website: pcori.org/about-us



Brad Pollock, M.P.H., Ph.D.

- Professor and Rolkin Chair
- Department of Public Health Sciences
- Methods Core Director for a PCORnet CDRN
- Co-Chair, PCORnet Clinical Trials Task Force
- Member, PCORnet ADAPTABLE aspirin clinical trial protocol design committee

PCORI Role: Award Recipient (Co-PI)

- Title of proposal: Greater Plains Collaborative Clinical Data Research Network (CDRN) (University of Texas San Antonio)
- Funding dates: March 1, 2014 – September 31, 2015
- Amount of award: $700,000 (part of a $7,000,000 CDRN)

Advice

1. Patient/subject engagement must be integrated into every aspect of a project.
2. To be competitive, investigators need to leverage PCORI-sponsored infrastructure (e.g., PCORnet).
3. Impact must be measurable using high-quality outcome assessment methodologies; the significance of a potential PCORI-funded project is given more weight than with many NIH proposals.

Final thoughts

PCORI funds research that directly addresses patient/subject issues with patient/subject engagement using high-quality methodological approaches. PCORnet was established to leverage existing electronic health record technology for direct use in clinical and translational research.

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Heather M. Young, Ph.D., R.N., F.A.A.N.

- Associate Vice Chancellor for Nursing
- Dean and Professor
- Betty Irene Moore School of Nursing

PCORI Role: Award Recipient (PI)

- Title of Proposal: Patient and Provider Engagement and Empowerment Through Technology (P2E2T2) Program to Improve Health in Diabetes
- Funding dates: September 2014 – August 2017
- Amount of award: $2,098,246

Advice

1. Establish a patient advisory board early and engage your stakeholders in identifying the research question and advising on design.
2. Propose a formal plan for patient engagement throughout the project, with strong consideration for compensating patient stakeholders in an equitable manner.
3. Focus on the outcomes from a patient perspective – how the research will advance positive health outcomes as defined by the target population.

Final thoughts

A focus on patients is at the center of every aspect of the research, from design to outcomes. PCORI enacts its mission in tangible ways and it is clear that the expected overall outcome is improved health care and better health, deeply informed by the target population.

The PCORI grant management team includes a program officer, a patient engagement officer and a contract administrator, who all oversee the project with quarterly telephone calls, assuring robust patient engagement and implementation according to detailed milestones, as well as providing advice and problem solving assistance.

"PCORI turns grant writing upside down. It is all about the patient and other stakeholders – PCORI forces you to see their point of view in a most intense way – and then to write your grant and do the research with that as your focus."

—Nathan Kuppermann, M.D., Ph.D.

Joshua Fenton, M.D., M.P.H.

- Associate Professor
- Family and Community Medicine

PCORI Role: Award Recipient

- Title of proposal: Promoting Patient-Centered Counseling to Reduce Inappropriate Diagnostic Tests
- Funding dates: 1/1/12 – 12/31/14
- Amount of award: $689,000

Advice

1. Be really clear that PCORI only funds work with "patient-centered" outcomes, that is, outcomes that matter to patients. Studies with biological surrogate outcomes, process outcomes, or costs outcomes will not fly at PCORI.
2. PCORI is very devoted to stakeholder engagement from the inception of the research question all the way through. So investigators need to have a detailed, convincing plan for engaging stakeholders.
3. Although decision aids seem very patient-centered, PCORI is currently holding off on funding decision aids, until it is clearer how to get them into practice.

Final thoughts

PCORI seems more willing than the NIH to take risks. PCORI has funded many large grants that lacked extensive preliminary data.

Nick Anderson, Ph.D.

- Cardiff Professor of Informatics
- Director of Informatics Research

PCORI Role: Award Recipient (Co-PI)

- Title of proposal: CENA – Community Engaged Network for All
- Funding dates: August 2014 – December 2015
- Amount of award: $1,000,000

Advice

1. Develop a comprehensive engagement and outreach plan. PCORI is seeking active and credible inclusion of community input and guidance on all programs.
2. Read the patient engagement rubric. This contains very good evaluation frameworks and sample metrics.
3. Write very clear and measurable milestones, as these will be closely monitored.

Final thoughts

This is a very fast and potentially disruptive way of doing large scale clinical science that forces research programs to have comprehensive and bi-directional engagement with patients. These grants are going to be highly visible throughout their development, and any outcomes resulting from this research is expected to be shared and otherwise made public on a much faster time scale than traditional NIH work. There is a much higher degree of evaluation and engagement by senior PCORI program officers throughout the awards, and a significant emphasis on awards being managed as contracts with very clear deliverables.

Patrick S. Romano, M.D., M.P.H., F.A.C.P., F.A.A.P.

- Co-Editor in Chief, Health Services Research
- Professor of Medicine and Pediatrics
- Center for Healthcare Policy and Research

PCORI Role: Funding proposal reviewer and advisor

Advice

1. Community and stakeholder engagement is essential, and must not be an afterthought. Unfortunately, current IRB policies and procedures sometimes make this engagement more difficult than necessary.
2. Consider whether more "patient-centered outcomes" should be collected, in addition to traditional outcomes such as mortality and disease-free survival. It is not sufficient to take an unsuccessful NIH proposal "off the shelf" and tweak it for submission to PCORI.
3. Carefully read all application instructions and guidelines.

Final thoughts

PCORI provides a dedicated, fee-based funding stream for health services research, not susceptible to the vicissitudes of the annual Congressional appropriation process (which has limited AHRQ's ability to support investigator-initiated research).

Linda Ziegahn, Ph.D.

- Community Engagement and Research Program Manager
- Clinical and Translational Science Center

PCORI Role: Community Engagement consultant

Advice

1. Engage communities – through focus groups, educational activities, advisory boards – while you are writing your proposal. You may find that research questions developed without community or patient input are not the ones that have greatest potential for making a difference in population health.
2. Allow enough time to assemble appropriate community audiences, and work through information-gathering, partnership formation processes. Community and/or patient groups do not necessarily conform to researcher schedules.
3. Maintain regular contact and report results to the group(s) periodically, so they learn about the research process and develop trust in researchers to bring back results of research.

Final thoughts

It takes patients and communities seriously, and provides web-based guidance as to how to actually bring non-scientists into the research process, as partners.

The art of team science advances scientific discovery

MULTIDISCIPLINARY RESEARCH and collaboration are core values of translational science. A well-honed, multidisciplinary team can advance scientific discovery beyond what is usually possible by a single investigator working in a silo.

But creating an effective team takes more than simply identifying a group of potential collaborators. Tina Palmieri, the assistant chief of burns at Shriners Hospital for Children – Northern California and the director of the UC Davis Regional Burn Center, embraced the value of collaborative research to a good end. Her success was recognized by Fred Meyers, vice dean of the UC Davis School of Medicine, who lauded, "Palmieri has become the national leader for conducting multicenter clinical trials in burns." Palmieri attributes much of this success to creating a team environment that works.

Early in her career path, Palmieri recognized that building an optimal team meant bringing together people from diverse disciplines with different areas of expertise and communication styles. She chose to specialize in burn care in part because it epitomizes team medicine – every person who cares for a burn patient is essential. Likewise, when considering research opportunities, Palmieri believed that a team science approach would facilitate discovery, understanding and translation.

To broaden her training, Palmieri enrolled in the UC Davis Mentored Clinical Research Training Program (MCRTP), which focuses on team science. During her time in the program, Palmieri learned not only the mechanics of science, but also the philosophy of team science. This training provided a solid foundation for her future multicenter clinical trial work.

When she became a founding member of the American Burn Association Multicenter Trials Group (MCTG), Palmieri found the perfect arena to build and organize collaborative research teams among burn centers. Writing the group's first paper on toxic epidermal necrolysis, Palmieri secured the cooperation and participation of 20 burn centers from across the U.S. and Canada. This article demonstrated the value of a team approach to multicenter clinical trials, supporting Palmieri's conviction that projects of this magnitude require the energy and expertise of a wide variety of individuals – each of whom contribute in a distinct way. To date, the MCTG has garnered more than $25 million to conduct projects, including multicenter randomized clinical trials involving many national and international burn centers.

Augmenting the expertise of her research team with the help of an alliance of agencies and institutions has proven to be a valuable method of extending the team's reach. The American Burn Association provides administrative help; the CTSC offers informatics, biostatistics, and regulatory support; and the Department of Defense has contributed funding and topic expertise (e.g., the injured soldier) that enhances the group's ability to conduct medical research on burn injuries.

At the heart of the MCTG, however, is the UC Davis Department of Surgery Data Coordinating Center – and the belief that results are only as good as the data upon which they are based. Obtaining high-quality data in an analyzable format is of the highest priority. To this end, a multidisciplinary team consisting of clinicians, biomedical informaticists and biostatisticians was assembled. These disciplines provide expertise from creation of data collection instruments in a secure environment, through data input to analysis.

Members of the clinical, biostatistics and informatics cores of the UC Davis Department of Surgery Data Coordinating Center.

From the beginning, the research team worked together to design data collection tools that met the needs of each discipline interacting with the data.

Director of Research Operations MaryBeth Lawless, R.N., a key leader in the development and coordination of the team as well as a liaison to researchers, ensured that the data collection tools captured what was envisioned by the principal investigator.

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Team Science *Continued from page 6*

Research nurses and coordinators provided input on the design of data collection instruments for accurate data collection and verified the accuracy of data entered into the database.

Sandra Taylor Ph.D., lead biostatistician, developed data analysis plans and contributed to data collection from the perspective of facilitating interim and final data analyses. Prior to each project, Taylor examined the study protocol to identify and address any potential design flaws prior to implementation.

A team of biomedical informaticists (Deborah Lee, M.B.A. and Brian Chan, Ph.D.) developed secure electronic databases that optimized data capture and accuracy, as well as enabled efficient interim and final data analyses.

Members of each discipline play a critical role in producing the high-quality data necessary for transformative research. Collaboration among team members and the principal investigator ensures fidelity with the protocol throughout the process.

Thus far, the group has conducted seven multicenter studies involving 1,080 patients in 23 different states and three countries; two national registry studies involving more than 6 million records.

A group of subject matter experts, each committed to excellence and achieving the bigger goal, underlies the success of this story. "Each person on the data team provides valuable input on the project. Each is empowered to express their viewpoint, and we address concerns together as a team. The success of the project depends on it," said Palmieri.

Keys to building a successful research data team:

- Identify ALL the disciplines and individuals needed to conduct the trial, including physicians and nurses, biostatisticians, biomedical informaticists, and research coordinators.
- Unite the team to identify goals and priorities for the group. Quality of data collection and analysis should be the priority.
- Develop rules for communication and set up regular meetings. Give everyone a voice at the table.
- Periodically reassess study progress, identify areas of deficiency, and work together to resolve issues.
- Bring the team together to celebrate successes. Success is contagious.

DIRECTOR'S MESSAGE *continued from page 1*

networks that comprise PCORnet. This program utilizes a distributed architecture to integrate data from existing networks to expand research opportunities.

Another national effort, the 21st Century Cures Initiative, is underway as well. After nearly a year of listening to patients, innovators, researchers, providers, consumers, and regulators, a bipartisan Congressional committee released a document marking continued progress in this undertaking. The goal of this effort is legislation that would include provisions to streamline, modernize, and foster research to accelerate the movement of treatments to the marketplace. The report emphasizes Discovery, Development, and Delivery.

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

The CTSC has been involved in a number of collaborative projects consistent with the recommendations outlined in the 21st Century Cures Initiative. Examples currently in progress across the consortium of UC medical campuses (known as UC Biomedical Research Acceleration, Integration, and Development or "UC BRAID") are programs such as Drug and Device Discovery and Development ("D4"), UC Research Exchange ("UC Rex"), IRB Reliance, and the development of master research contracts with sponsors.

As an institution, UC Davis has embarked upon several new research programs for personalized medicine and the NIH Brain Research through Advancing Innovative Neurotechnologies ("BRAIN") initiative.

All of these efforts align with the goals of the Clinical and Translational Science Awards, our funding mechanism. Although challenges still exist, biomedical research is valued, necessary, and continuing to undergo transformation in order to become more resilient and responsive to the needs of the community. As an institutional resource, the CTSC is poised to support investigators by providing infrastructure and expertise. Our mission is to build research teams of the future to improve human health. With that in mind, and in the spirit of collaboration and engagement. How can we help you?

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2921 Stockton Blvd., Suite 1400
Sacramento, CA 95817

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Charles Stephensen *Continued from page 2*

strongly correlated with the response to early childhood immunization with vaccines delivered orally," Stephensen said. But the study also yielded an unanticipated result. "It was already known that kids living in tropical settings with the potential for poor environmental hygiene have a lower response to oral vaccine than do kids living in Europe or the U.S.," Stephensen said. "What we were not expecting is that they also had better response to injected TB and tetanus toxoid vaccines. This suggests that the intestinal microbiota not only affect the response to an oral vaccine but also affect the systemic immune system. That was a surprise and a novel finding."

Those initial revelations supported by the CTSC Pilot Award enabled the team to secure a three-year, $352,000 grant in January 2014 from the Thrasher Research Fund to expand on the study. "In the pilot project, we studied 48 infants between birth and 15 weeks of age. The new grant allows us to study 250 more infants at those ages, and we will reassess a total of 300 infants when they are about 2 years of age to see if the gut colonization with *Bifidobacterium* at 15 weeks of age also results in better vaccine responses later in infancy," Stephensen said.

He also credits the CTSC and its access to the REDCap (Research Electronic Data Capture) online, web-based clinical research data capture portal for overcoming data management hurdles with colleagues halfway around the globe. "To prepare for the pilot project, we worked with the CTSC to set up a REDCap database online. Thus, data from the clinical assessments in Bangladesh and the laboratory results in Davis were united into a single source for analysis." The REDCap data portal also enabled access by the program manager, who coordinated the data safety monitoring board at the World Health Organization (WHO) headquarters in Geneva.

"The CTSC Pilot Award enabled participation among the four research groups – Bangladesh, USDA, UC Davis, and Geneva," Stephensen added. "The pilot project award was the only way we were able to get this project going, and it certainly took our laboratory in a new direction."

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The UC Davis CTSC is a member of the national CTSA consortium and supported by award TR000002 from the National Institutes of Health's National Center for Advancing Translational Sciences.

CTSC Connections is published twice a year by the UC Davis Health System. To add your name to the mailing list, send an e-mail to CTSCMail@ucdmc.ucdavis.edu.

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

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