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Director's Corner by Ronald J. Sokol, MD

I hope you all enjoyed the first issue of CCTSI Connections, the electronic newsletter from the Colorado Clinical and Translational Sciences Institute that debuted last month. This month we are featuring two high impact CCTSI-supported research projects and have important dates that you’ll want to put on your calendar. For example, if you are interested in the CCTSI Pilot Grant awards, the deadline for the Letter of Intent is September 1, 2010. Also, don’t forget that if you are a CCTSI paid staff member, you should plan on attending the CCTSI All-Staff meeting Wednesday, September 15 from 8-11 in Room: P26-3500 Education 1 at the Anschutz Medical Campus. Please read more about these dates in the “Upcoming Events” section of the newsletter.

Lastly, if you have announcements or story ideas you’d like to see in future newsletters, please contact Natascha Palmer at natascha.palmer@ucdenver.edu.

Upcoming Events & Important Dates

Pilot Awards’ Deadlines Coming Soon
The Requests for Applications for the three Colorado Clinical and Translational Sciences Institute (CCTSI) Pilot Grant Programs are currently available with a Letter of Intent deadline of September 1, 2010 and full applications are due October 4, 2010.

The Pilot Grants Program will provide $700,000 of funds for translational research and consists of the 1) CO-Pilot Awards for Clinical and Translational Research, 2) Child and Maternal Health Pilot Awards, and 3) Community Engagement Pilot Awards for encouraging Community-Academic Partnerships.

The RFAs for the three pilot programs can be found on the CCTSI website. Please note that in order to apply for any of the pilot grants, one is now required to register as a member of the CCTSI with the exception of community members for the Community Engagement Pilot Awards. CCTSI membership registration is fast and easy thus allowing you access to training, funding and other resources and tools.

You can obtain more information about CCTSI and these funding opportunities by visiting http://cctsi.ucdenver.edu/Funding. If you have specific questions regarding the three pilot programs please contact the point people listed below. For other questions, feel free to contact the CCTSI office at 720-848-7100.

- For questions regarding the CO-Pilot Awards for Clinical and Translational Research, contact Sarah Stallings at 720-848-5519 or sarah.stallings@ucdenver.edu
- For questions regarding the Child and Maternal Health Pilot Awards, contact Bonnie Savone at 303-724-1602 or bonnie.savone@ucdenver.edu
- For questions regarding the Community Engagement Pilot Awards for encouraging Community-Academic Partnerships, contact Dee Smyth at 303-724-2447 or dee.smyth@ucdenver.edu

If you're having trouble viewing this email, you may see it online.
CCTSI All-Staff Meeting
All CCTSI paid personnel & staff, please mark your calendar and plan on attending the annual CCTSI All-Staff Meeting. The meeting is scheduled for Wednesday, September 15, 2010 from 8-11am in Room: P26-3500 Education 1 at the Anschutz Medical Campus.

Please take a minute to RSVP by Friday, August 27th for this All-Staff Meeting. Breakfast will be provided so plan on arriving early if possible.

CCTSI Informatics Seminar Series
Mark your calendars now and save the Third Thursday at Three-Thirty-Three. The Informatics Seminar Series schedule is as follows:

- September 16, 2010 — The Colorado Telehealth Network
- October 21, 2010 — RedCap Best Practices
- November 18, 2010 — The HMO Research Network and the Virtual Data Warehouse
- December 16, 2010 — i2b2 & Accelerating Translational Research

All seminars will be in Teaching Lab 2 at the Health Sciences Library at the Anschutz Medical Campus. Please be sure to arrive early as refreshments will be served thirty minutes prior to the seminar start. If you are unable to attend in person, please know that all seminars are available via live video stream. For more information on the series or to view archived trainings, visit the Informatics section at cctsi.ucdenver.edu.

Community-Based Research Conference
This all-day conference titled "Reconciling Regulations with Realities" on Friday, September 17, 2010 at AMC in Research Building 2, Trivisible Room, aims to discuss institutional review of community-based participatory research projects. By bringing together people from academic institutions, community organizations and institutional review boards, attendees will be able to identify challenges and generate solutions to gain a better understanding and improve how the IRB, scholars and community-based organizations protect those with whom research is conducted. For more information, contact Jean Scandlyn at Jean.Scandlyn@ucdenver.edu.

Conference on Clinical Research for Rare Diseases (CCRRD)
The Rare Diseases Clinical Research Network (RDCRN) and the Clinical and Translational Science Awards (CTSA) program of the NIH are sponsoring the 2nd Conference on Clinical Research for Rare Diseases (CCRRD) on Tuesday September 21, 2010 in Bethesda, Maryland. This unique conference will focus on research methodology for rare diseases and should be of particular interest to trainees and junior faculty engaged in research in rare diseases. For more information about the conference, including details about the program, applying for travel awards, and conference logistics and registration, visit the conference website: https://rarediseasesnetwork.epi.usf.edu/conference/index.htm

Funding Opportunity 2011 NIH Director’s Transformative Research Projects Program
Announcing a funding opportunity for the NIH Director’s Transformative Research Projects (T-R01) Program:

- Exceptionally innovative, high risk, original and/or unconventional research
- Clinical, basic, and/or behavioral/social science research projects
- Up to $25 million total costs per year for a single project
- One-third of total funding budget geared to projects with more than $1 Million in direct costs.

The deadline for submitting Transformative Research Project applications is October 27, 2010 with Letters of Intent due by September 27, 2010. See the instructions in the RFA (RFA-RM-10-010). Additional information, including Frequently Asked Questions about the Transformative Research Projects Program is available at: http://commonfund.nih.gov/T-R01. Send questions to T_R01@mail.nih.gov.

The NIH Common Fund (formerly the NIH Roadmap) encourages collaboration and supports a series of exceptionally high impact, trans-NIH programs. These programs are supported by the Common Fund, and managed by the NIH Office of the Director in partnership with the various NIH Institutes, Centers and Offices.

Research Features

![Graph showing blood loss in c.c.s](image)
CipherSensor

Investigators in the Departments of Surgery and Computer Science at the University of Colorado have developed a high speed software technology that utilizes state-of-the-art feature extraction, machine learning techniques and advanced statistical methods to analyze real-time physiological waveform data. The technology that underlies their research was originally developed for an image-based robot navigation system under the DARPA-sponsored Learning Applied to Ground Robots (LAGR) program. In 2008 the investigators applied their software-based technology to the analysis of physiological data gathered from human lower body negative pressure (LBNP) studies of acute blood loss at the U.S. Army Institute of Surgical Research (USAIRS). This led to the discovery of several, previously hidden hemodynamic relationships that are predictive of acute blood loss and risk for hemodynamic decompensation.

In the example above, human noninvasive blood pressure waveform data alone is used to continuously estimate how much blood loss (LBNP) an experimental subject is experiencing in real-time (Figure, red dots). The method also continuously predicts the amount of blood loss (LBNP) at which a subject will decompensate (Figure, blue dots). Hemodynamic decompensation occurs when the red and blue tracings converge (Figure). Importantly, the method also provides real-time information on the effectiveness of IV fluid resuscitation efforts. When the red and blue tracings are diverging, IV fluid resuscitation efforts are effectively restoring intravascular volume. This work has led to the development of an entirely new type of predictive, non-invasive medical device called CipherSensor and a startup company called Flashback Technologies, LLC which has licensed the technology from CU.

Figure Description. Live, real-time, noninvasive estimation of LBNP (blood loss) with concurrent, noninvasive prediction of the LBNP level at which the subject will experience hemodynamic decompensation. This work was supported by NIH/NCCR Colorado CTBS Grant Number UL1 RR025783. The work is ongoing and continues to be supported by the Department of Defense SBIR/STTR award W81XWH-09-C-0160 and BAA award W81XWH-09-1-0750, among others.

This research addresses the military and civilian need for physiology-based decision support algorithms, which utilize noninvasive sensor technologies to provide real-time insight into the early compensatory changes that are triggered by injury. On the battlefield and in civilian trauma settings, medics must quickly determine injury severity, initiate IV fluid therapy, establish a triage order and transport potential survivors. The physiology of an injured patient is constantly changing, however, and triage should be a continuous process and not a point in time; casualties should move from one category of injury severity to another, based on their response to therapy. This is difficult to determine, because every patient experiences hemodynamic decompensation at a unique volume and duration of acute blood loss. The early identification of trauma patients who are more likely to experience hemodynamic decompensation with less blood loss could prove critical to early intervention, establishing a triage order and better outcomes. For more information regarding this project contact, Steve Moulton, MD, Director of Pediatric Trauma and Burn Services at The Children’s Hospital, Professor of Surgery at the University of Colorado, School of Medicine and Co-founder, Flashback Technologies, LLC at Moulton.Steven@tchden.org.

Tetrahydrobiopterin (BH4) Deficiency, Inflammation and Large Artery Stiffening in Estrogen-Deficient Postmenopausal Women (or BLAST study)

As women get older and go through menopause, estradiol levels decrease to low levels. Also with aging and menopause, vascular health deteriorates (e.g., arteries stiffen, cells that line the arteries become impaired) which can lead to the development of heart disease. In this study we wanted to understand what causes vascular health to deteriorate in postmenopausal women who have low estradiol levels. Specifically, we wanted to see if the impairment in vascular function in postmenopausal women compared to premenopausal women is because of changes in natural substances in the body that cause the arteries to expand (called tetrahydrobiopterin or BH4) and those that are involved in fighting off infections (i.e., inflammatory cytokines). We believed that arteries are stiffer in postmenopausal women because of a decrease in the BH4 substance and due to an increase in inflammation in the artery wall. Also, we wanted to find out if a short-term increase in estrogen levels caused the arteries to become healthier and if this was due to increasing BH4 and decreasing inflammation.

Thirty-three healthy women participated in this study: 9 premenopausal who were on average 34 years of age and 24 postmenopausal women who were on average 58 years of age and not taking any form of hormone therapy. Two measures of vascular function were assessed before and 3 hours after the oral ingestion of BH4 and before and 2 days after the injection of a medication that lowers inflammation called Enbrel. One measure called brachial artery flow-mediated dilation (FMD) evaluates how healthy the cells that line the inside of the artery wall called endothelial cells. These cells help to prevent the development of cardiovascular disease through the release of protective substances. One such substance called nitric oxide (NO) causes the artery to dilate. Thus, by measuring the amount of dilation of the brachial artery allows us to assess how much nitric oxide is being released from the cells that line the arteries. The second measure of vascular function called carotid artery compliance evaluates the flexibility (i.e., stiffness) of the arteries that are located around the heart.

Similar to other studies, we found a significant impairment in the ability of the endothelial cells to release NO and cause dilation of the brachial artery as well as a significant reduction in the flexibility of the carotid artery (i.e, arterial stiffening) in the postmenopausal women compared to the premenopausal women. BH4 ingestion significantly improved the dilation of the endothelial cells and elasticity of the carotid artery in the postmenopausal women but not in the premenopausal women. The lack of improvement in the premenopausal women is probably because they have adequate BH4 levels and preserved vascular function. Next, the postmenopausal women were randomized to either take estrogen (transdermal estradiol patch; 12 women) or placebo patch; 12 women) for two days and were evaluated again before and after oral BH4. Vascular function was improved in the postmenopausal women taking estrogen but remained unchanged in the placebo group. Moreover, there was no further improvement in vascular function with oral ingestion of BH4 in the postmenopausal women taking estrogen. Vascular function also improved with the Enbrel injection in the postmenopausal women in the placebo group but was not further improved in the postmenopausal women in the estrogen group or the premenopausal women. The lack of improvement in the postmenopausal women estrogen group and the LBNP group is possibly related to the anti-inflammatory effects of estrogen. These preliminary data support the idea that the deterioration in vascular health with aging and the loss of estrogen in postmenopausal women is partly related to decreased BH4 levels and vascular inflammation in the artery wall. The findings of this research will help us to understand why vascular health declines with aging in women and how the loss of estrogen with menopause contributes to this decline. Importantly, identifying how this happens may help to develop therapies to prevent heart disease in women.
This project was supported by the UC Denver Center for Women’s Health Research and the Office of Interdisciplinary Research in Women’s Health, CCTSI, and the National Institutes of Health/National Institute on Aging. Collaborators included Dr. Wendy Kohrt, Dr. Amie Meditz and Dr. Kevin Deane. For more information regarding this study contact Kerrie Moreau, PhD, principal investigator, at Kerrie.Moreau@ucdenver.edu.

CCTSI Program Spotlight

Giving Research Teams an Easy Way to do the Right Thing for Their Data Collection Needs

REDCap is a HIPAA-compliant, web-based application developed specifically for human health research data collection. REDCap was developed at Vanderbilt University, which continues oversight of implementation of new features. The REDCap Consortium is comprised of over 130 institutions worldwide currently supporting more than 3,000 studies and 10,000 end users.

REDCap is easy to learn and use yet also provides sophisticated functionality such as: seamless data export to common statistical packages; ability to import data from external sources; advanced features such as branching logic (skip patterns), calculated fields and data validation checks. In addition, REDCap allows the investigator to store PHI and non-PHI in one database, and automatically remove PHI when exporting data to create a de-identified dataset for analysis.

REDCap is supported by the CCTSI in collaboration with the Development & Informatics Service Center (DISC) in the School of Public Health and is fully subsidized for use by CCTSI members whose studies have COMIRB approval. To learn more about REDCap and view the tutorial schedule and location information, go to redcapinfo.ucdenver.edu or email the REDCap Team at REDCap@ucdenver.edu.

Bulletin News

Ultrasound Services
The Adult CTRC located on the 3rd floor of the Leprino Building offers cardiac ultrasound services at "NO COST" for Adult SARC approved protocols and investigator initiated studies. Services include echocardiograms, brachial artery imaging (FMD) and carotid imaging (CIMT). For more information please contact Stephen Belcher at 720-848-6686 or stephen.belcher@uch.edu.

KL2 (K12) Research Scholar Awardees
The CCTSI is pleased to announce the KL2 (K12) Research Scholar awardees. Awardees will receive up to three years of Mentored Career Development funding in clinical translational research. These positions are funded by the NIH/NCRR grant to the CCTSI and two additional positions are funded by The Children’s Hospital (denoted with an *).

2009-2010 KL2 (K12) Research Scholar Awards

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<td>David Nichols, MD</td>
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<td>Testing Redox Regulation as Anti-Inflammatory Therapy in Cystic Fibrosis Lung Disease</td>
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CTSA National Consortium Update

Now in its fourth year, the CTSA consortium has generated resources that transform the research and training environment to enhance the efficiency and quality of clinical and translational research. Examples include a Web-based national recruitment registry that connects researchers with volunteers interested in participating in clinical studies (ResearchMatch.org), and a portal that connects researchers with potential investigational drugs (ctsapharmaportal.org) that may be useful in new ways.
The CTSA Consortium was expanded to **55 sites** in July 2010, as announced by NCRR/NIH. New areas including New Mexico, Virginia and the District of Columbia were added growing the consortium to 55 member institutions. For a complete list of the nine new institutions please visit [ncrr.nih.gov/ctsa2010](http://ncrr.nih.gov/ctsa2010). The ultimate goal of NIH is for the Consortium to reach a maximum of 60 member institutions.