



Bridging the gap for investigators bench to bedside and Back

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**2008 ANNUAL
SYMPOSIUM
March 17, 2008**

From the Director

"It was the best of times, it was the worst of times...it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us..."

These words by Charles Dickens aptly describe the state of research today. In so many ways it is a great time to be doing research: the revolution in 'omics is upon us, incredibly powerful high-throughput and systems-based technologies are at our fingertips, personalized predictive medicine is at our doorstep, and we have a beautiful, new building in which to make our discoveries. But it is also a tough time: federal funding for research is flat, grants have been cut, the line of A2 applications at study section is long, we are losing disenchanted students who seek greener pastures, it seems harder to publish (are reviewers more cranky?) and regulatory hurdles for clinical trials are overwhelming.

Thanks to the CCHMC Board of Trustees, one source of potential help is the Translational Research Trials Office. In this issue, we are pleased to announce the recipients of our most recent grant competition. The competition was stiff, as we had 65 letters of intent. In our version of an "economics stimulation package," we have awarded \$800,000 to a dozen different investigators for their projects that were judged by the review committee to be most meritorious. Two of the projects are new cores, which will benefit numerous other investigators. Thank you to the review committee for their hard work, and congratulations to all the awardees!

We are also pleased to announce several new staff in the TRTO to help investigators conduct clinical-translational research, particularly IND-directed studies. We are confident our expansion will help us serve the CCHMC research community more effectively.

In these difficult times we too are stretched, so we are introducing a new charge-back system (fee-for-service and FTE-based). Remember, when using the TRTO for your clinical trial you also get a variety of subsidized core services such as biostatistics, database management, and monitoring. Benefits also include IND expertise, CRAs with up-to-date training, and cross-coverage. Your dollar goes farther with us than if you go it alone!

We all know that like most things biologic, the challenges that make this not the best of times are circadian, so we must tighten the belt a bit, put our heads down, and get through it. Better times are surely just ahead.

*Tim Cripe, MD, PhD
Director, TRTO*

New TRTO Leadership

Introducing Sheri Uber, MS, MBA Clinical Research Manager, TRTO

Sheri Uber has a strong history of success within regulated healthcare, biomedical and pharmaceutical industries. With a perspective of industry, GMP and Six Sigma process improvement experience, she brings the ability to motivate a productive research team. Sheri completed her MS and MBA at the University of Cincinnati. She is keenly interested in translational work and welcomes the inherent challenges of novel investigator initiated studies.

Sheri continues the change process in TRTO that was initiated by Peggy Kaiser, MSN, former interim manager of TRTO. Peggy is now pursuing her dream: working as a nurse practitioner on the Bone Marrow Transplantation team since late 2007.



Future TRTO staffers of 2025

Welcome to our newest TRTO Employees !

Marianne Brunner, RN

Marianne is a registered nurse, who has been with CCHMC and the TRTO since August, 2007. Prior to coming to Children's, she worked for 11 years at Procter & Gamble in product Research and Development. Her responsibilities included coordinating studies, method development, and system improvements. Marianne and her husband live in Clifton and have 2 sons.

Leslie Korbee, BS, SI (ASCP)

Leslie joined TRTO as a medical writer in late summer of 2007. She has over fifteen years of research experience with expertise in respiratory, orthopedics, and immunology. Leslie enjoys the variety of projects and specialties that TRTO serves. She also is an active volunteer at St. Xavier High School.

Susan Mc Mahan, RN

Susan McMahan brings eighteen years experience as a Special Care Nursery/OB nurse at local hospitals to her new role as a research coordinator in the TRTO. She has also worked as a nurse consultant in research for Procter & Gamble. Susan brings a strong work ethic and a proven ability to coordinate complex activities. In her other role as a mother, Susan coordinates the logistics of everyday life for her seven children who range in age from 16 months to 16 years.

Michael Kulhmann

Michael Kuhlmann, TRTO Data Coordinator, brings a wealth of computer knowledge and experience to this position. He worked in a similar capacity at the University of Cincinnati. Currently, he is pursuing his degree at UC in Electrical Engineering Technology with a concentration in telecommunications. He is looking forward to graduation in June of this year.

Growth for TRTO Staff

Positive changes demanded
new roles and increased teamwork.

Elva Turner, BSEd, CCRA

Elva has been instrumental in the evolution of the TRTO. Within the past year, Elva developed a quality plan, including implementation of department SOPs, monitoring of investigator-initiated (TRTO) studies and participation in the TRTO process improvement team. Elva is a valuable resource not only for TRTO staff members, but for anyone who has questions with regards to FDA regulations, ICH and institutional guidances and GCP.

Rubina Dosani, MS

This year, Rubina has taken on new responsibilities with protocol development. She continues to manage a complex array of regulatory issues for pre-clinical studies conducted in multiple departments. Her work is respected by investigators as thorough and concise. Rubina's laboratory background serves her well in the pre-clinical arena. She also serves the research community by serving on the education committee for CRP here at CCHMC.

Carol Johnson, Administrative Ass't.

Carol continues to facilitate the everyday work life for so many aspects of daily operations for TRTO. As the staff has grown, Carol has insured that every TRTO staff member has the support services, supplies, and information necessary to excel here at CCHMC. Carol assists with the Translational Research Initiative grant process and the annual TRTO symposium. Her pleasant professional manner is an asset to the department.

Susan Radtke, MSN, CRP

Kudos to Susan Radtke! Her abstract has been accepted for presentation at the 2008 annual meeting of ACRP this April. Her topic is "Filing an Investigator-Initiated IND." Susan also recently completed work on a guide for filing INDs. Susan's role at TRTO has evolved into our IND internal consultant. Her work has enabled a broad span of investigator initiated studies. She also has mentored new TRTO staff with IND regulatory work. Investigators at CCHMC value her expertise in regulatory compliance issues and ethics.

Carrie Stevens, BS

All of the normal donor studies managed by TRTO are Carrie's domain. Donor tissues are integral to the success of many labs at CCHRF. Carrie's outgoing disposition makes her an exceptional donor recruiter. Carrie also serves as database manager for the biological sample tracking system of over 1000 samples. She manages cord blood collection protocols at our neighboring institutions, and the repository for the Rare Lung Disease Consortium. She is best known for her superb work on drums for the popular local rock band "Therapy."

Kimberley Wilson, MS

Our resident "Epi Person" has taken on the role of specialist in data analysis. In this role, Kim is the go to person for data capture design. She has recently completed a data capture system for adverse events based on the CTCAE guidelines. Her system will allow rapid data capture and ease of analysis for annual FDA reports and IRB reports as well. Thanks, Kim!

Megan Mueller, Student Intern

Megan is a UC senior majoring in Business Administration. Always ready with a smile, she assists the department with compilation for training materials and study support documents.

TRTO Annual Symposium

Faculty, clinical trials researchers, and investigators are turning out in droves for this year's TRTO-sponsored symposium entitled:

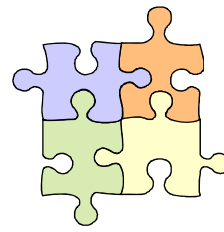
"The Challenges and Rewards of Investigator Initiated Trials."

To date over 80 faculty and investigators have registered for the meeting. Registrations are available until March 7.

Translational and clinical scientists create a vibrant research culture at this institution and keep CCHMC at the leading edge of advances in pediatric health care. To keep investigators current, the symposium will focus on IND trials from FDA, industry and legal perspectives.

Of special interest on the program is "Between a Rock and a Hard Place: Conflicts Between the Role of Investigator and Physician" presented by **John F. Ennever, MD, PhD, Medical Director of the Clinical Trials Office at the Columbia University Medical Center.**

Dr. Ennever is a member of the Division of Gastroenterology, Hepatology and Nutrition in the Department of Pediatrics. In the newly created Irving Institute for Clinical and Translational Research, (an NIH CTSA site) Dr. Ennever chairs the Clinical Research Center Advisory Committee and as director of the Regulatory Knowledge and Support and Ethics core resource.



New Solutions for the research puzzle

We are fortunate to include Patricia Holobaugh, Chief of the Bioresearch Monitoring Branch Food and Drug Administration Center for Biologic Evaluation and Research.

Ms. Holobaugh will present the FDA perspective on different paradigms for submitting Investigator-initiated research IND's to the FDA, and how these choices impact the investigator and the institution. Her case studies of sponsor-investigators will highlight suggestions that will help investigators avoid problems.

The afternoon session will present **DeenDayal B. Reddy, MS., MA., PhD. Sr. Manager: Medical Information Services of DEY, L.P.** [An Affiliate of MYLAN, Inc.] Dr. Reddy will offer the industry perspective on Investigator initiated studies, explaining the process of obtaining support for clinical research.

Attorney Lisa Murtha, JD, CHC, Managing Director of the Huron Consulting Group, will offer the legal perspective of investigator-initiated studies. Her presentation will offer an overview of the rules of research related billing. She will share tips to protect sponsor/investigators and offer a discussion of informed consent.

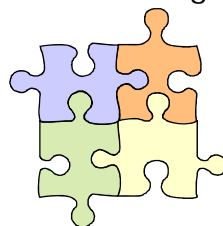
2008 TRI Grants Awarded

This is the seventh year for the TRI awards program. The review team received a record 65 letters of intent. As investigators from across multiple disciplines at CCHMC become involved in translational work, the volume of requests for support continues to grow.

The annual Translational Research Initiative (TRI) grant review process has just concluded. We sincerely thank the members of the review committee:

Applications for scientific retreats focusing on translational ideas are taken throughout the year.

This highly successful awards program provided opportunities for 15 CCHMC researchers in 2007. The compelling projects of these researchers keep CCHMC at the leading edge of translational work.



TRI Grants

Solving the \$\$\$ puzzle for new translational work

Bruce Aronow	Timothy Crombleholme	Lorah Dorn	James Heubi	Nancy Sawtell	Sander Vinks
Mitchell Cohen	Stella Davies	Tracy Glauser	Chris Karp	Kurt Schibler	Nicole Robinson (CTC)
Bob Colbert	Ted Denson	Lee Grimes	Daniel Lovell	Patrick Tso	Mi-ok Kim (Biostats)
Tim Cripe	Prasad Devarajan	Gurjit Hershey	Ardythe Morrow	Bruce Trapnell	

This year, we are pleased to announce that the TRI has funded 11 projects.

PI	Division	Title	Award amount
Aliberti, Julio	Molecular Immunology, Pulmonary Medicine	Adjuvant Use of IDO Inhibition to Treat Chronic Infection	\$45,000
Colbert, Robert	Rheumatology	Activation of the IL-23/IL-17 Axis in Spondyloarthritis	\$45,458
Devarajan, Prasad	Nephrology & Hypertension	A Novel Urinary Biomarker Panel For Lupus Nephritis	\$61,933
Kercsmar, Carolyn	Pulmonary Medicine	CORE: Airway Diseases Research Testing and Diagnostic Core	\$50,000
McAuliffe, John	Anesthesia	Improving Acute Pediatric Pain Management Using Neurogenomics	\$76,400
Molkentin, Jeffrey	Molecular Cardio Biology	Mitochondrial-directed Necrosis Underlies Muscular Dystrophy: A New Clinical Vantage Point	\$99,939
Morrow, Ardythe	Epidemiology & Biostatistics	Novel Salivary Biomarkers for Risk of Necrotizing Enterocolitis and Death in Premature Infants	\$100,000
Saldana, Shannon	Pediatric Pharmacology	CYP2D6 Pharmacogenetics in Risperidone-Treated Children	\$75,669
Vinks, Alexander	Pediatric Pharmacology	Pharmacogenetics of IMPDH in Kidney Transplant Patients	\$100,000
Ware, Stephanie	Mol Cardiovascular Biology & Human Genetics	Novel Diagnostics for Familial & Metabolic Cardiomyopathy	\$93,250
Wells, James	Developmental Biology	CORE: Human Embryonic Stem Cell Core	\$50,000

TRTO STUDY MONITORING SERVICES

Study monitoring services are offered by the TRTO to ensure compliance with federal regulations. Our investigators who conduct IND studies are required by the FDA to provide monitoring review. The TRTO study monitors actively collaborate with study staff to develop a successful study operational plan. Collaboration from the outset improves the outcome by providing an ounce of prevention, rather than a pound of painful clean up and time delays. New research coordinators are mentored by our TRTO monitors in the nuts and bolts of strong study start up. Using the skill set of an experienced quality assurance and compliance staff member to create data collection systems (source and CRF) at the front end of a study is a giant translational step taken by the TRTO to minimize study operational missteps.

Study sponsors and investigators at CCHMC have also learned that a good study monitor and a well designed data collection plan is the institution's best friend in protecting them from FDA "love letters" otherwise known as 483's. [This month's Trial Tip](#) comes from Elva Turner, BSEd, CCRC, TRTO's Clinical Quality Coordinator. As a clinical quality coordinator, Elva provides monitoring services to any trial supported by the TRTO. In her day to day work she designs and implements monitoring plans and reviews study records. She also serves as the department's guru for regulatory issues.

TRTO TRIAL TIP

The following tip provided by Elva Turner helps define the distinction between quality control and quality assurance activity, and between auditing and monitoring. During an FDA inspection, monitoring records will be reviewed; audit records are not of interest.

"Quality control" (QC) is the steps taken during the generation of a product or service to ensure product/service quality. For a clinical trial, "quality control" encompasses steps taken during the clinical trial (e.g., investigator supervision and [study monitoring](#)) to ensure that the trial meets protocol and procedural requirements and is reproducible.

"Quality assurance" (QA) refers to a systematic process to determine whether the quality control system is working and effective. Most often, [quality assurance](#) in clinical trials is implemented through independent [auditing](#) of quality control activities and, where applicable, by regulatory authorities through inspection of quality control systems and activities. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

"The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements." (ICH E6, Section 5.19)

"Quality improvement" refers to a systematic process for taking the knowledge gained through quality assurance audits and activities and using this knowledge to make changes in systems and activities in order to increase the ability to fulfill quality requirements then and for the future.

TRTO TRIAL TIP CONTINUED

What is the difference between monitoring, auditing, and inspecting?

Monitoring is “[t]he act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).” (ICH E6, 1.38; see also ICH E6, 5.18, generally, for detailed guidance on study monitoring.)

Monitoring is part of the clinical trial.

Investigators who initiate a study under an IND are responsible for selecting qualified monitors and for ensuring this quality control activity occurs during the trial.

Upon inspection, the FDA will review QC activity, which may include:

1. how the sponsor selects qualified monitor(s)
2. Comparison of source documents against CRF to determine if data is verified
3. Determination of how the sponsor (a) assures that IRB approval is obtained prior to enrollment (b) assures informed consent is obtained from all subjects in the study (c) handles SAEs (d) makes corrects to CRFs.

The investigator who initiates an IND study is responsible for study monitoring per the FDA: 21 CFR 312 subpart D: Responsibilities of Sponsors and Investigators.

Auditing is an independent review to determine sponsor/study compliance with SOPs and regulations, which may occur at any point during or after the clinical trial. The FDA won't routinely review audit reports, but they will:

1. Determine if QA audits are performed
2. Determine how the Quality Assurance Unit (e.g. ORCRA) is organized and operates
3. Obtain a copy of procedures (SOPs and Guidelines) for QA audits
4. Describe the separation of functions between the Quality Assurance Unit and monitoring of clinical trials.

An inspection is “[t]he act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities or at other establishments deemed appropriate by the regulatory authority(ies).” (ICH E6, 1.29) The purpose of such inspection is to determine whether research was conducted in compliance with national/local laws and regulations for the conduct of research and the protection of human subjects.



VOLUNTEERS NEEDED!!

Peripheral Blood Stem Cell Mobilization and Donation Study

- Purpose:** To collect blood cells from normal donors. These cells will be evaluated for expansion, freezing and gene therapy expansion. The cells may also be used by other investigators who have an Institutional Review Board approved protocol.
- Investigator:** Punam Malik, MD
- To qualify you must:**
- ◆ be between the ages of 18 and 40
 - ◆ be in generally good health
 - ◆ have normal blood counts
 - ◆ be willing to take growth factor injections for 4 days
 - ◆ be willing to undergo white blood cell collection
 - ◆ not be pregnant or nursing
 - ◆ not have donated blood, platelets, or bone marrow within 6 weeks or never received G-CSF
 - ◆ not have sickle cell disease or sickle cell trait
 - ◆ not be taking certain medications
 - ◆ not be allergic to E-coli
 - ◆ sign informed consent
- Length/Duration:** Prescreening visit, 2 outpatient visits, 4 days of G-CSF injections, and 1 day of stem cell collection
- Location:** CCHMC and Hoxworth Blood Center
- Benefits:** You will not receive any medical benefit from taking part in the study. However, information obtained from this study may help in the treatment of blood cell disorders and cancer
- Compensation:** You will be paid \$400 upon completion of the stem cell collection or \$125 if you withdraw before the stem cell collection, but after the growth factor administration. (Some donors are needed who will not be required to receive G-CSF but still must meet the above qualification criteria. These donors will be paid \$200.)
- Contact:** Translational Research Trials Office, CCHMC, 513-636-4553