



Yale Center for Clinical Investigation

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Photo credit: Terry Dagradi

TRAINING THE NEXT GENERATION OF CLINICAL AND TRANSLATIONAL INVESTIGATORS

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In 2006, Erik Shapiro, PH.D., assistant professor of diagnostic radiology, was conducting studies in rodents using cellular and functional MRI to develop novel strategies for manipulating stem and progenitor cell migration in the brain. He decided to apply to the newly established YCCI Scholars program with a proposal to develop analytical imaging tools for tracking transplanted and endogenous stem and tissue cells in humans, with the goal of speeding up the development of stem cell therapies. Shapiro's project fit perfectly with YCCI's goal of bringing medical advances from lab to patient, and he was among the first round of junior faculty and fellows awarded funding for research and salary support under the Scholar program. Shapiro has since gone on to receive a five-year \$1.5 million New Innovator Award from the NIH. "The Scholar program allowed me to investigate translating something that we only had expectations for in the lab and ask what it would take to bring it into the clinic," he said.

The Scholars program addresses a critical need to jump-start the careers of clinical researchers like Shapiro. According to the Association of American Medical Colleges, there is a national shortage of physician-investigators, with more than half of clinical departments unable to fill openings for junior physician investigators in recent years. "Nurturing and training the next generation of clinical and translational researchers is vital not just to YCCI but to the future of biomedical research at Yale," said Director Robert Sherwin, M.D., C.N.H. Long Professor of Medicine. "Our investment in the Scholars program reflects our commitment to equip young investigators to pursue rewarding careers in clinical and translational research."



Photo credit: Robert A. Lisak

Since its inception, the YCCI Scholar program has nurtured the careers of 39 investigators in departments and schools across the entire medical campus. Training investigators in a variety of disciplines is crucial to developing researchers who can bring knowledge from bench to bedside. Scholars in both nursing and public health, for example, offer expertise in taking clinical science into the community – an area that the School of Medicine is seeking to strengthen. Since receiving their awards, YCCI Scholars have published more than 113 papers (with an additional 31 in press), given conference presentations, and collaborated with colleagues both nationally and internationally. They have been active in obtaining independent funding, competing successfully for numerous federal and

Educational co-directors Eugene Shapiro, M.D., and Judy Cho, M.D., lead the program.

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Director's Corner

Even though YCCI isn't yet four years old, we're constantly evaluating and redesigning our programs and services in an effort to better suit the needs of clinical and translational investigators. There have been many changes along the way as we've learned how to help investigators conduct research more efficiently. But one thing that hasn't changed is our commitment to educating and training the next generation of investigators.

When YCCI was established, I viewed this commitment as perhaps our most important goal, and we're now beginning to reap the fruit of our efforts to educate young clinician researchers. The first two rounds of YCCI Scholars have pursued exciting projects for which they've obtained national recognition as well as millions of dollars in independent funding. As the third and fourth rounds of Scholars pursue their research projects, I have high expectations that they will continue along the same path. I'm particularly pleased with the newly revamped mentorship program, in which senior faculty members have joined forces with their colleagues to offer mentees interdisciplinary perspectives and varying points of view.

As with all of our programs, we're continually looking for ways to improve our efforts in the educational arena. The new Master of Health Science Research degree is one innovation designed to provide research training for Scholars who don't already have an advanced degree. Our efforts are supported by the national CTSA consortium through its development of educational standards and coursework that can be utilized by CTSA sites around the country.

As we continue to develop avenues for training clinical and translational researchers, we look forward to supporting and guiding the careers of Scholars and other investigators who participate in our programs.

Robert Sherwin, M.D.
YCCI Director

Featured Event: December 4, 2:30 PM

Registering Clinical Trials, with an emphasis on reporting results and adverse events

Presented by Deborah Zarin, M.D., director of clinicaltrials.gov

see the Events Calendar on page 2 for details

EDUCATION ISSUE

TRAINING THE NEXT GENERATION *cont.*

private sector grants and awards. Nine Scholars have already obtained individual K Career Development Awards and 17 have obtained their own R Awards. As a group, they have received more than \$42 million in independent funding. These Scholars include:

- **Zubin Bhagwagar**, M.D., D. PHIL., was awarded a NARSAD Young Investigator Award to investigate the interaction between serotonin and GABA in depressed patients via tryptophan depletion and proton magnetic resonance spectroscopy (1H MRS).
- **Chiang-shan Li**, M.D., PH.D., received an Ro1 grant for a project that combines fMRI and experimental psychology to examine deficits in cognitive control as a pathogenetic process to cocaine dependence.
- As a result of his research, **Lei Chen**, M.D., was asked by the American College of Emergency Physicians to help draft new national guidelines on the use of ultrasound in pediatric emergency medicine.
- **James McPartland**, PH.D., has received an Ro3 award for his work on visual processing in autism spectrum disorder.
- **Kristina Crothers**, M.D., has received an Ro1 award to conduct longitudinal studies of HIV-associated lung infections and their complications.
- **Karen Dorsey**, M.D., PH.D., received a minority supplement to an Ro1 grant to develop a training program to change obesity-related behavior in children.
- **Arthur Simen**, M.D., PH.D., has received a Beeson Ko8 and an Ro3 award to identify alterations in DNA methylation that may underlie the chronic elevation of risk for drug abuse after stress.
- **Nina Kadan-Lottick**, M.D., M.S.P.H., has received a large grant from the Donaghy Foundation as well as funding from other sources to study childhood cancer.
- **Karen Bearss**, PH.D., developed an exportable parent training manual for preschool-age children with autism and behavioral problems. She is conducting a pilot study of the manual to support grant funding for a large-scale randomized trial.
- **Tené Lewis**, PH.D., received a K Award for a pilot study to identify psychosocial factors associated with the development of cardiovascular disease in African-American women and determine whether these factors are also associated with markers of pre-clinical CVD.

Like their predecessors, the newly appointed 2009 YCCI Scholars (who now also include K Award winners) are a diverse group of investigators immersed in a range of clinical and translational research projects. Some of their studies include: characterizing neurochemical disturbances associated with epileptic seizures in patients with drug-resistant temporal lobe epilepsy; exploring adaptations of brain energy metabolism to hypoglycemia; evaluating coping, parenting, and maternal-child adjustment in type 1 diabetes; identifying the optimal dose of cranberry capsules for prevention of UTIs in nursing home residents; characterizing a gene-environmental interaction in the etiology of autism spectrum disorder; identifying follicle stimulating hormone receptor (FSHR) mutations in women undergoing infertility treatments; developing new statistical methods for predicting clinical outcomes; and developing new methodological approaches to investigating frontal and subcortical glutamate and GABA in obsessive-compulsive disorder.

A key component of Scholars' training is the participation of mentors to guide their work and offer advice. The program was revamped last year to include a Career Oversight Committee to augment each Scholar's primary mentor(s). The Career Oversight Committee is a team of senior faculty members from various departments who provide an unbiased perspective on Scholars' progress and career development. "We're pleased to have such a distinguished group of senior investigators who are willing to devote their time and effort to mentoring promising young scientists," said Eugene Shapiro, M.D., professor of pediatrics, investigative medicine and epidemiology, who co-directs YCCI's educational program with Judy Cho, M.D., associate professor of medicine and genetics. Scholars are enthusiastic about the additional guidance provided by the committees. 2008 YCCI Scholar Leora Horwitz, M.D., M.H.S., assistant professor of medicine, is working with every member of her committee on specific aspects of mentoring that each is uniquely capable of and willing to provide. "I think some big changes in my career will result from their advice," she said.

"When we established YCCI, we set out to provide education and training to investigators who were at the beginning of their careers," said Sherwin. "I think the success of the program can be seen by the caliber of those who have applied and what they've accomplished so far." 🌟

Events Calendar

December 4, 2009, 2:30 PM to 3:30 PM

Deborah Zarin, M.D., director of clinicaltrials.gov, will present an overview of the FDA Amendment Act requiring the registration of clinical trials on clinicaltrials.gov, with an emphasis on the requirements for reporting results and adverse events. There will be ample opportunity for questions and discussion following her presentation. Although Dr. Zarin's presentation is aimed at the faculty investigator, all research staff are invited to participate.

Hope Memorial Building, Room 110,
315 Cedar Street

Please RSVP to Alicia Lakomski at
alicia.lakomski@yale.edu or 785-3482.

Joint YCCI/Investigative Medicine Program Scholars Research-in-Progress Meetings

This is an opportunity to learn about the scholars and the work they're doing. We would like to encourage all faculty and staff to attend.

Meetings will feature presentations from individual scholars. Lunch will be provided.

December 8, NOON to 1:00 PM

Can Dermal Fibroblasts Recapitulate Forebrain Development?

presented by Anita Huttner
and

Survival of Hepatitis C in Syringes

presented by Elijah Paintsil
Giarman Room, 5HM B-201, 333 Cedar Street

January 12, 2010, NOON to 1:00 PM

Imaging Dopamine D2/3 Receptors with [11C] PHNO PET

Presentation by Kelly Cosgrove
Giarman Room, 5HM B-201, 333 Cedar Street

January 25, 2010, NOON to 1:00 PM

Biostatistics in Clinical and Translational Research

presented by Hongyu Zhao, PH.D., director of the Keck Laboratory Biostatistics Resource and director of the Yale Center for Statistical Genomics and Proteomics; and James Dziura, PH.D., M.P.H., manager of YCCI's Biostatistical Support Unit

TAC N203, 300 Cedar Street

2009 YCCI SCHOLARS

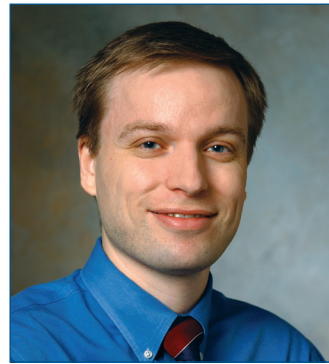
Jerry Domian, Yale Academic Media and Technology



KELLY COSGROVE, PH.D.
 Assistant Professor of Psychiatry
Test-Retest Reproducibility of $\{^{11}C\}$ PHNO PET Using the Constant Infusion Paradigm



KAVITA DHODAPKAR, M.D.
 Assistant Professor of Pediatrics
Regulating Fcγ Receptor Balance in Autoimmunity



TORE EID, M.D., PH.D.
 Associate Research Scientist, Laboratory Medicine
Characterizing the Metabolome of Epileptic Seizures

Jerry Domian, Yale Academic Media and Technology



RAIMUND HERZOG, M.D.
 Lecturer, Molecular Biophysics and Biochemistry (Internal Medicine)
Adaptations of Brain Energy Metabolism to Hypoglycemia



SARAH JASER, PH.D.
 Associate Research Scientist, Nursing
Coping, Parenting & Maternal-Child Adjustment in Type 1 Diabetes



MANISHA JUTHANI-MEHTA, M.D.
 Assistant Professor of Medicine (Infectious Diseases)
Cranberry Capsules for the Prevention of UTI in Nursing Home Residents



YOUNG-SHIN KIM, M.D., PH.D., M.S., M.P.H.
 Assistant Professor, Child Study Center
A Gene Environment Interaction in the Etiology of Autism Spectrum Disorder



MARIA LALIOTI, PH.D.
 Assistant Professor, of Obstetrics, Gynecology and Reproductive Sciences
Identification and Functional Characterization of Follicle Stimulating Hormone Receptor Variants



ANNETTE MOLINARO, PH.D.
 Assistant Professor of Epidemiology and Public Health
Novel Statistical Methods for Predicting Clinical Outcomes and Assessing Variable Importance in the Presence of Competing Risks



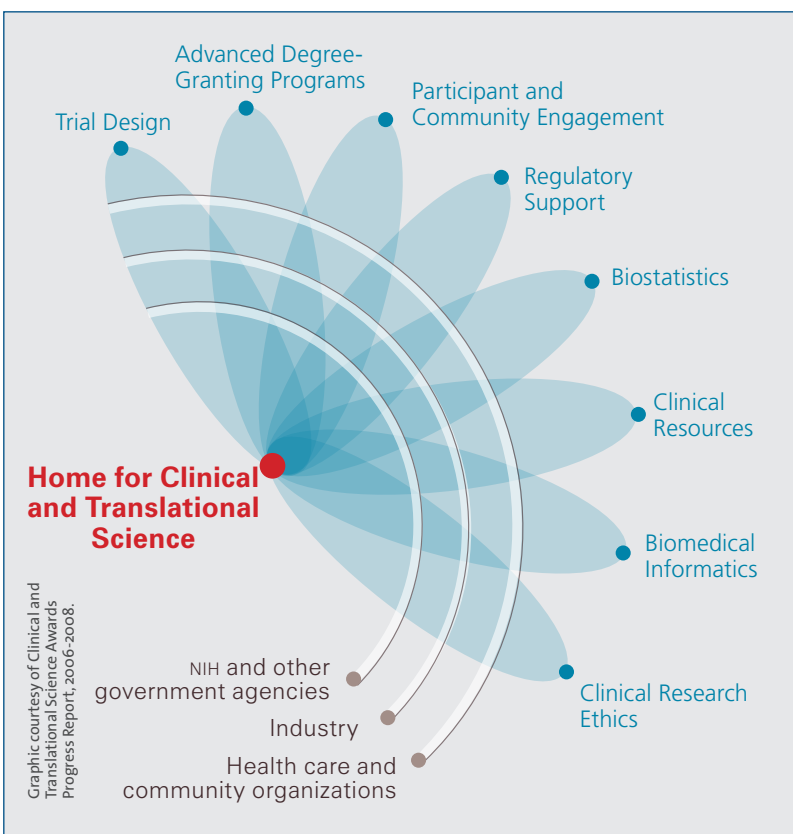
CHRISTOPHER PITTENGER, M.D., PH.D.
 Assistant Professor of Psychiatry
Glutamate Dysregulation in OCD: an MRS Study

Photo credit: Robert A. Lisak



Erik Shapiro presents his work on using cellular and functional MRI to track stem and progenitor cell migration in the brain at a Research-in-Progress meeting.

TRAINING AND CAREER DEVELOPMENT ARE PRIORITIES FOR NATIONAL CTSA CONSORTIUM



Each CTSA institution has created a home for clinical and translational science. Components of the CTSA homes support such specialized areas of research expertise as biostatistics, clinical trial design, and community engagement. Input from NIH and other federal agencies, industry, and private and community organizations helps inform the work of each CTSA institution.

The National CTSA Consortium, comprised of the 46 CTSA-funded institutions and overseen by the National Center for Research Resources (NCRR), shares with YCCI a vision of training investigators in order to improve the quality of clinical and translational research. In fact, training and career development was one of five strategic goals outlined by the consortium at its strategic planning meeting last year.

Five committees were formed to coordinate the consortium's efforts to meet these goals. The Strategic Goal Committee on Training and Career Development of Clinical/Translational Scientists (SGC 2) is working in the following areas to promote training efforts at CTSA sites:

- Establishing a core curriculum aligned with core competencies developed by the Education and Career Development Key Function Committee (KFC).
- Providing open access to training resources across the CTSA consortium.
- Implementing a consortium-wide mentor training program.
- Ensuring that institutions recognize clinical and translational investigation as a valuable enterprise with distinctive metrics and criteria for success.

Key Function Committees (KFCs) contribute to overall SGC goals and best practices. One of the first tasks of the Education and Career Development KFC has been to develop core competencies in 14 thematic areas that define the skills and knowledge needed for

master's degree candidates in clinical and translational research. "In defining the discipline of clinical and translational research you're integrating several disciplines, so it was necessary to have a roadmap of what is most important about training junior investigators," said Carol Merchant, M.D., M.P.H., who serves as NIH coordinator of SGC 2 and program director of Roadmap Career Development Programs at the NCRR. Although each CTSA site develops its own educational programs, the core competencies serve as a guide for subjects that could be included in their educational programs.

During the past year, SGC 2 has laid the groundwork for a national CTSA Educational Resource Program. Led by the University of Rochester, the committee is developing a virtual learning portal to house CTSA and NIH course offerings in areas where particular institutions have strengths as well as course offerings in core competencies. The resource will feature online coursework as well as opportunities for lecturers and scholars to participate in programs at other institutions. SGC 2 also oversees a mentor development working group that is outlining standards for training mentors as well as resources and courses on effective mentoring. The resources will be available on the virtual learning portal.

Many of the projects undertaken by SGC 2 are conducted on an ongoing basis. For instance, SGC 2 members are working with other strategic and key function committees to develop core competencies in informatics, community engagement, and translational research. Young investigators at Yale and other CTSA institutions will benefit as these efforts are refined and the results disseminated. 🌐

New Society for Clinical and Translational Science Aims to Advance Research and Education

The NIH's creation of the CTSA has heightened awareness of clinical and translational science and highlighted the need to define the identity of this emerging discipline; assist trainees; and encourage the formation of multidisciplinary research teams.

A new professional organization, the Society for Clinical and Translational Science (SCTS), has been founded to address these needs with the ultimate goal of improving human health. "Clinical and translational research is increasingly becoming a complex global endeavor that comes under close public scrutiny," said Robert Sherwin, M.D., director of YCCI and a founding member of the society. "The Society for Clinical and Translational Science provides an avenue for scientists engaged in this type of research to pool resources and expertise to support one another and advance this important discipline."

One of the features of the new society will be an annual meeting in cooperation with the Association for Clinical Research Training (ACRT) to provide a forum to disseminate new developments in the design and conduct of clinical and translational research and facilitate scientific collaboration and networking. The society's first meeting will take place April 5-7, 2010, in Washington, D.C., and will feature a keynote address by Francis Collins, M.D., Ph.D.

Membership dues are initially included in the institutional fee paid by Yale. All scholars, mentors, and faculty associated with YCCI will be enrolled in the society automatically. A subscription to the journal *Clinical and Translational Science*, which will be designated a journal of the SCTS, will be provided free to all members.

NEW PROGRAM OFFERS MASTER OF HEALTH SCIENCE RESEARCH DEGREE TO YCCI SCHOLARS

YCCI is now offering a Master of Health Science Research degree in addition to its PH.D. program in Investigative Medicine.

Unlike its counterparts at many other CTSA sites, YCCI's Investigative Medicine Program was already in place at Yale when the grant was awarded. The new master's program supplements YCCI's educational offerings through courses in epidemiology, biostatistics, informatics, practical and ethical issues in clinical and translational research, and topics in human investigation and grant writing as well as other elective courses. Students are guided by a committee comprised of their primary mentor along with two senior faculty members approved or recommended by the co-directors of education – Eugene Shapiro, M.D., professor of pediatrics, investigative medicine and epidemiology, and Judy Cho, M.D., associate professor of medicine and genetics. Students are required to write a paper suitable for publication in a peer-reviewed journal that must be approved by the committee instead of a thesis.

“The important thing isn't the degree, it's the training,” said Shapiro. “The master's program fills a need to provide training for young investigators in areas that are critical for successfully conducting clinical and translational research.”

The School of Medicine has offered a Master in Health Science Research degree to fifth-year medical students conducting research and to Robert Wood Johnson Clinical Scholars since 2006. The new master's program is specifically designed for YCCI Scholars, who are junior faculty members or fellows. Two students are currently enrolled in the program: 2007 Scholar Lei Chen, M.D., assistant professor of pediatrics (emergency medicine), and

2009 Scholar Raimund Herzog, M.D., instructor in endocrinology. “Besides giving me some background and foundation to further my career as a clinical investigator, the program also lends me credibility in applying for career development grants and extramural support,” said Chen, who is applying for a K Award and expects to receive his degree in May.

One potential benefit of the program is the opportunity it affords researchers to return to the classroom with a fresh outlook after a few years on the job. “I seem to value and treasure the opportunities a little bit more because I have a different perspective,” said Chen. 🌐



Photo credit: Robert A. Lisak

Judy Cho, M.D., YCCI co-director for education pictured second from left, with new YCCI scholars, l to r, Raimund Herzog, M.D., Tore Eid, M.D., PH.D., Kelly Cosgrove, PH.D., Sarah Jaser, PH.D., and Annette Molinaro, PH.D.

SCHOLARS EXCHANGE IDEAS AT SECOND ANNUAL SCHOLAR EVENT

As part of their mission to educate the next generation of clinical and translational researchers, YCCI and other CTSA sites have created opportunities for Scholars to learn from experienced researchers at other institutions as well as from one another.

YCCI hosted the first Yale/Rockefeller Scholar Event in May 2008, featuring poster presentations from CTSA scholars at both institutions as well as panel discussions on such topics as balancing home and work life, developing clinical and translational scientific careers, and balancing clinical practice and protected time for research. The day also included a keynote lecture from Richard Lifton, M.D., PH.D., Chair of Genetics, who is a Howard Hughes Medical Institute investigator and Sterling Professor at Yale School of Medicine. The event was so successful that it now takes place annually at each site on alternate years. Yale Scholars visited Rockefeller University in July 2009 for Research Collaboration Day. The event featured a keynote model inflammatory disease presentation by James G. Krueger, M.D., PH.D., director of the Milstein Medical Research Program at Rockefeller University and D. Martin Carter Professor in Clinical Investigation. The day also included time for collaboration development and a discussion panel on managing data density. 🌐

NIH-SUPPORTED INVESTIGATORS MUST SUBMIT MANUSCRIPTS TO PUBMED


A new public policy law requires investigators to submit final peer-reviewed journal manuscripts from NIH-supported studies to the National Library of Medicine's digital archive, PubMed Central <http://www.ncbi.nlm.nih.gov/pmc/>. Manuscripts must be submitted on acceptance for publication.

The purpose of the policy is to ensure public access to the published results of NIH-funded research. Manuscripts accepted for publication on or after April 7, 2008 must be accessible on PubMed Central no later than 12 months after publication.

Investigators who receive YCCI/CTSA support from the variety of services, awards and programs that are offered should note that resulting publications are a significant factor in the assessment of Yale's CTSA and thus are very important to the upcoming grant renewal. Publications based on research supported by the YCCI/CTSA should cite the CTSA grant (per the reference below) and must be registered in PubMed Central because only these publications can be provided as evidence of the grant's success.

For information on submission methods, visit http://publicaccess.nih.gov/submit_process.htm. If you need assistance in submitting a manuscript to PubMed Central, please contact Tracy Yale at tracy.yale@yale.edu.

Please use the following reference formula for CTSA-supported research:

"This publication was made possible by CTSA Grant Number UL1 RR024139 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH." 

CLINICAL RESEARCH COMPLIANCE

REPORTING ADVERSE EVENTS UNDER FDA AMENDMENT ACT

By now investigators should be aware of the FDA Amendment Act of 2007 requiring the registration and reporting of results on clinicaltrials.gov for clinical trials of drugs, biologics, and devices under FDA jurisdiction. A new deadline has passed as of September 27, 2009: A summary of adverse events must be included when reporting study results.

Adverse events are divided into two categories: serious adverse events and frequent nonserious adverse events. For both types, reporting must include:

- A table of anticipated and unanticipated adverse events
- Grouping of events by organ system
- The number and frequency of events in each trial arm

All serious adverse events must be reported; nonserious adverse events must be reported if they exceed a frequency of 5 percent within any trial arm. The FDA also requires relevant information about adverse event collection, including details about the method of systematic assessment used.

Failure to register clinical trials or report results can carry fines of up to \$10,000 per day and the withholding of grant funds for federally funded trials. Requirements to register clinical trials and report results and adverse events are a response to public demand for transparency in research studies. For example, allegations that pharmaceutical executives concealed clinical study results showing that antidepressants are not effective in children and might even pose risks led to fraud charges against Forest Laboratories. More recently, a report published in *The New England Journal of Medicine* in November and widely publicized in the media concluded that Pfizer had altered the primary outcome measures of studies involving gabapentin.

YCCI has invited Deborah Zarin, M.D., director of clinicaltrials.gov, National Library of Medicine, to present an overview of the new law with particular focus on the reporting of adverse events and results on December 4. See the Events Calendar on page 2 for details.

For more information on registering clinical trials and reporting results and adverse events, visit <http://prsinfo.clinicaltrials.gov/fdaaa.html>. For additional information, including the procedure for registering a Yale study, visit http://ycci.yale.edu/researchers/register_ctg.html. 