Yale Center for Clinical Investigation

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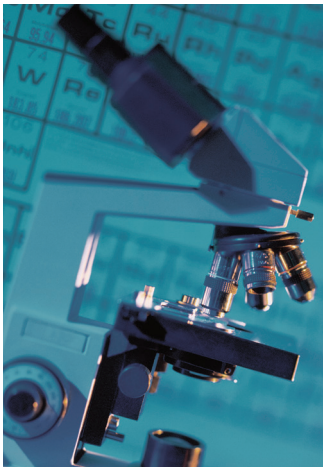
Education and Training Programs Offer Wide Array of Opportunities

Inside This Issue

When William Tamborlane, MD, professor of pediatrics at the School of Medicine and deputy director of YCCI, was a young physician in the 1970s, he never took a course in statistics and knew very little about study design. He had neither the skills nor the training to conduct clinical research and was left largely to his own devices to figure out how it was carried out. But today, 30 years later, the environment in which clinical research is conducted is too competitive and complicated for investigators to fend for themselves as Tamborlane once did. Young scientists need training and guidance in order to design and carry out clinical trials. That's why YCCI's educational component is fundamental not only to the program but also to the future of clinical research at Yale.

Even before YCCI opened its doors in January 2006, Robert J. Alpern, MD, dean of the medical school and Ensign Professor of Medicine, initiated a strategic planning process to evaluate and bolster clinical and translational research at Yale. Establishing a home for the training of the next generation of clinical and translational scientists emerged as a major goal of that initiative and became one of YCCI's missions. It also dovetailed perfectly with the National Institutes of Health (NIH) Roadmap for Medical Research, an ambitious effort to streamline medical research in order to bring the results more quickly to patients, and played a key role in the five-year, $57.3 million Clinical and Translational Science Award (CTSA) that Yale received in October 2006.

Training investigators in patient-oriented research is critical because there is a national shortage of physician investigators, according to a recent survey by the Association of American Medical Colleges. The survey found that between 2002 and 2004, more than half of clinical departments with openings for junior physician investigators were not able to fill their positions. This brings some urgency to the training of young scientists, a task that YCCI is poised to carry out. "The development of bright, qualified, enthusiastic clinical and translational investigators is one of the keystones of the CTSA program, as well as what we envision as the key role of better coordination of clinical research at Yale under YCCI," said Tamborlane. "We want to identify young investigators of high potential, and we want to make sure that they are given every opportunity to take the steps forward to begin to realize that potential." The idea is to imbue investigators with a spirit of discovery, train them in the use of state-of-the-art research tools, give them the skills to work within complex research teams and support their professional development while at Yale and beyond.



Next Issue

- YCCI's Services: Learn about the support we offer to help plan, design and carry out clinical trials

YCCI's educational programs expand and build upon the exceptionally strong foundation of Yale's network of existing programs and span the entire medical campus. They include the Investigative Medicine Program (IMP), which awards a PhD in investigative medicine to physicians, the K program for postdoctoral

continued on page 6

Photo by Terry Dagradi

Director's Corner

Recently the PIs from the 24 institutions that received CTSA grants had an opportunity to meet with NIH Director Elias A. Zerhouni, MD, and ask him what he considered to be the most important aspect of furthering medical research.

I couldn't agree more with his answer: training the next generation of scientists. When we put together the CTSA grant, we spent a lot of time and effort devising ways to expand YCCI's educational programs, because I believe that of all the different areas the CTSA is helping to fund, developing young scientists' careers is critical. I think that if we're going to have an impact on clinical research, we need to provide the setting necessary to foster the development of skilled and knowledgeable clinical and translational researchers.

We've tried to do this by offering educational opportunities to students in medicine, nursing and public health, as well as faculty members who have already embarked upon their careers. By creating programs that give researchers access to funding, experienced mentors and courses designed to further their expertise in clinical and translational sciences, we hope to give them the tools to enable them to succeed in today's complex and competitive research environment.

This special issue of the newsletter is intended to give you an overview of YCCI's educational programs and maybe even spark your interest in applying for an award, becoming a mentor, attending a lecture or enrolling in a course. We hope you'll take advantage of all that YCCI has to offer.

Robert Sherwin, MD
YCCI Director

YCCI to Launch Recruitment Campaign for Research Studies

See *New Campaign Designed to Increase Participation in Yale Clinical Trials,* **page 2.**

Special Expanded Issue

Written by Jill Max

Events Calendar

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

These meetings are 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.

- ***March 31, noon to 1:30 pm***
  Brady Auditorium, 310 Cedar Street
  The YCCI External Scientific Advisory Board will be joining us for this meeting during its annual site visit. *Physiologic Mediators of Physical Activity and Obesity in Children*, presented by Karen Dorsey, and *From Mice to Men: Magnetic Resonance Imaging of Cellular Migration*, presented by Erik Shapiro
- ***April 15, noon to 1:30 pm***
  TAC N203, 300 Cedar Street
  Estrogen Receptor-Mediated Rapid Signaling in Endothelial Progenitor Cell Contributions to Ischemia, presented by Katie Moriarty, and *Toll-like Receptor 7, B Cells, and Plasmacytoid Dendritic Cells at a Nexus in Systemic Autoimmunity*, presented by Abraham Tzou
- ***April 28, noon to 1:30 pm***
  TAC N303, 300 Cedar Street
  Angiopoietin-2 in Severe Sepsis and Septic Shock, presented by Jonathan Siner
- ***May 6, noon to 1:30 pm***
  TAC N203, 300 Cedar Street
  Psychosocial Factors and Cardiovascular Disease in African-American Women: Developing a Program of Clinical and Translational Research, presented by Tené Lewis, and *Genetic Studies of Major Depressive Disorder*, presented by Arthur Simen
- ***May 19, noon to 1:30 pm***
  TAC N303, 300 Cedar Street
  Submitting Your Grant to NIH: Questions and Answers, presented by Eugene Shapiro

Yale/Rockefeller Scholar Event

May 22
New Haven Lawn Club , 193 Whitney Avenue
Featuring posters from both Yale and Rockefeller CTSA scholars, panel discussions and a special keynote address by Richard Lifton

Milestones in Public Health Grand Rounds, Winslow Auditorium, 60 College Street

March 26, noon to 1:00 pm
Health Disparities in Asthma: Environmental & Social Contributions

April 9, noon to 1:00 pm
Black-White Differences in Risk Factors for Cognitive Decline and Alzheimer's Disease

New Campaign Designed to Increase Participation in Yale Clinical Trials

One of the challenges researchers face in conducting clinical trials is recruiting appropriate volunteers who are willing to participate in research studies. YCCI is about to tackle this problem with a new recruitment campaign aimed at potential volunteers.

"A lot of researchers have been talking to us about how difficult it is to recruit patients to their studies," said YCCI chief operating officer Tesheia Johnson. "We've been wanting to address their concerns, and now we're able to dedicate the effort and resources to find the best ways of reaching potential volunteers."

A series of focus groups was held in February to determine how to effectively recruit volunteers. Participants ranging in age from 25 to 70 were asked about their familiarity with clinical trials, including their understanding of how drug development and treatments go from the laboratory to the patient. They were also asked what would motivate them to participate in a clinical trial, what they would want to know before taking part and whether they were aware that Yale conducts such studies. In addition, participants were asked to respond to different types of media and to possible ads, including several currently placed by Yale.

"The focus groups gave us a lot of ideas about how to stimulate enrollment," said Johnson. "People seem to be hungry for information, but they're looking for honesty and they want us to provide it in a format and venue that are applicable to their situation."

The new campaign, which will be launched during National Volunteer Week at the end of April, will include some combination of radio, TV, public service newspaper, direct mail, billboard and Internet ads. YCCI is also considering assembling research teams to go out into the community to interact with different patient populations.

Plans also include revamping the current website to make it easier for volunteers to navigate. The website will include a new clinical trials database that will interface with clinicaltrials.gov to track all trials at Yale. Patients will be able to easily find the trials best suited to their needs, which will be described in public-friendly text. By clicking further into the site, they will also be able to find more detailed clinical and scientific information about the studies. Other features include links to the Web pages of investigators conducting trials and to a healthy-volunteers database that will enable individuals to identify current trials for which they may be eligible or future research studies about which they would like to learn more.

Since the idea behind the campaign is to bolster recruitment for all clinical trials at Yale, researchers seeking participants are asked to contact Tracy Yale at 785-7467 (tracey.yale@yale.edu) or Kelly Burton at 785-2519 (kelly.burton@yale.edu) with trial, disease and contact information. YCCI's goal is to compile a list of researchers and their study teams by specialty so that volunteers can be immediately directed to the appropriate contact person when they call.

These ads are examples of the new campaign to recruit participants for clinical trials.

Career Development for Young Clinicians: YCCI and K Scholars

Two of YCCI's programs, led by educational co-directors Judy Cho, MD, and Eugene Shapiro, MD, afford young clinicians at the beginning of their careers an opportunity to pursue research projects, take courses specially designed for clinical researchers and benefit from the guidance of experienced mentors.

Launched in 2006, the YCCI Scholar program, an integral part of the CTSA program, is focused on furthering the training of junior faculty members or fellows who are ready to transition to faculty and are strongly committed to careers in clinical or translational research.

In the first year of the program, YCCI asked the departmental chairs and the deans of the schools of nursing and public health for nominations of promising candidates. The response was impressive: 62 nominations were received, and 15 awards for salary and research support were granted for a period of two years. Last year, an additional five scholars received awards, bringing the total funding to over $2.5 million. Scholars must conduct patient-oriented research in one of the following categories: clinical research, translational research and outreach.

The scholars (see pages 6 and 7) come from diverse backgrounds in areas of medicine such as pediatrics, psychiatry, internal medicine and radiology, as well as nursing and public health. Training investigators in a variety of disciplines is crucial to developing researchers who are able to bring knowledge from the bench to the bedside. Scholars in nursing and public health, for example, offer expertise in moving clinical science to the community, an area that the School of Medicine is seeking to strengthen. "I think it's critical for us here in New Haven, but it's also critical for science," said Margaret Grey, DrPH, RN, dean of the School of Nursing.

For those a bit further along in their careers, YCCI has expanded the K training program, for postdoctoral fellows and junior faculty in the first three years of their appointments. The goal of this program is to develop a cadre of outstanding researchers in patient-oriented research and to prepare them to assume leadership roles in academia. Currently there are five scholars (see page 7) from the departments of internal medicine (pulmonary and critical care), pediatrics (hematology/oncology) and psychiatry. Educational programs are individualized, and the CTSA grant has also allowed YCCI to create an intensive curriculum on clinical research ethics that focuses on the responsible conduct of research for all scholars, including those in the Investigative Medicine Program (see article on page 4).

Mentoring is an important aspect of both programs, which were once separate but have now been combined under one umbrella. It is an area that Eugene Shapiro, MD, co-director for education for YCCI and director of the K training program, wants to bolster. All scholars have their own mentors, but Shapiro wants to set up committees to nurture their progress. "It may be helpful to have people a little farther away to monitor if they're on the right track," he said. Mentoring committees will be composed of scientists from diverse disciplines with established track records of training clinical investigators.

Through twice-monthly research-in-progress meetings, YCCI scholars have an opportunity to learn about each other's research, which hopefully will encourage collaborations. In May, the scholars will meet with their colleagues from The Rockefeller University, also a recipient of a CTSA grant.

Events Calendar *continued*

Good Clinical Practice Training
Hope Building, Room 103, 315 Cedar Street

May 8, 9:00 am to 4:30 pm
Part I: *The Fundamentals of Good Clinical Practice*

June 19, 9:00 am to 4:30 pm
Part II: *Advanced Good Clinical Practice Training*

GCP training is being offered to all clinical research professionals to provide an understanding of GCP concepts, including what is required and why. The second session is a follow-up that examines GCP components in greater detail and discusses the regulatory ramifications of noncompliance. Both programs are led by Brian P. Bennett, who has 15 years of experience in clinical training and development. Courses are limited to 50 participants. To register, visit http://www.yale.edu/training and select YCCI Clinical Trials Education & Training Program.

Childhood Obesity Summit

May 22, 8:00 am to 4:30 pm
Yale Center for Excellence, 300 George Street

Eugene D. Shapiro, MD

YCCI Co-Director for Education

Deputy Director, Investigative Medicine Program

Director, K Program

Professor of Pediatrics and Epidemiology

Judy H. Cho, MD

YCCI Co-Director for Education

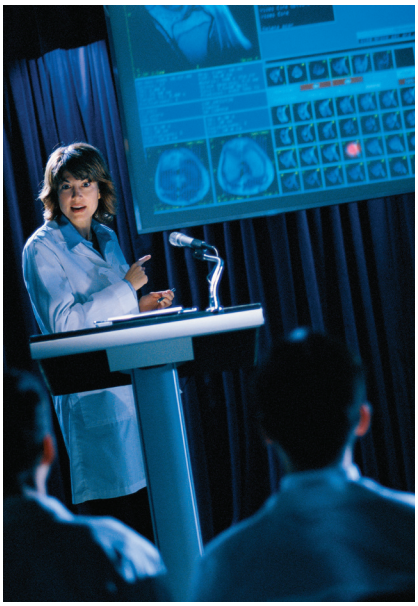
Associate Professor of Medicine (digestive diseases) and Genetics

Investigative Medicine Program Offers Unique Clinical Training

Joseph Craft, MD
Associate Director for Education
Director, Investigative Medicine Program
Professor of Medicine (rheumatology) and Immunobiology

The Investigative Medicine Program (IMP) is a unique interdisciplinary training program for physicians that leads to a PhD in Investigative Medicine from the Graduate School of Arts and Sciences. "These are physicians interested in clinical investigation, so it's an opportunity for them to get high-quality research training yet take that back to the clinic," said Joseph Craft, MD, associate director for education and IMP director.

The program, which began admitting students in 2000, serves as the administrative home for the educational component of YCCI. According to Eugene Shapiro, MD, co-director for education for YCCI and IMP deputy director, there have been both an increasing recognition of the importance of training in clinical research and an increasing demand for the program and the courses it offers, which are open not only to students seeking a PhD but also to those in the schools of medicine, nursing and public health. In fact, the program provides short-term research training for over 100 medical students, residents, interns, fellows and junior faculty who aren't IMP scholars. There are also plans to develop a master's program in health science research for those who wish to further their education in clinical research but don't want to pursue a PhD.



A total of 25 trainees have matriculated since the IMP began admitting students. Their specialties include general surgery, internal medicine, laboratory medicine, obstetrics & gynecology, pathology, pediatrics and psychiatry. Trainees must complete at least two years of postgraduate clinical training before entering the program and typically enter after completing their residency or the clinical portion of their subspecialty training. Most students complete the program in three to four years.

A core group of courses, unique to the IMP and organized around the themes of patient-oriented and disease-focused research, is the centerpiece of the program. Other offerings include courses on translation research and molecular tools, ethical and practical issues in clinical investigation, grants, NIH and manuscripts, and additional courses tailored to both laboratory- and clinically based patient-oriented research. Students are occupied with full-time coursework for the first 12 months of the program. After that they must pass a comprehensive qualifying exam and submit their thesis proposal. They meet with their thesis committee every six months to discuss their projects, which may encompass a variety of disciplines, including the following:

- Evaluating risk factors and interventions for disease using modern concepts in quantitative methods and clinical study design
- Exploring the molecular basis for a disease from the laboratory standpoint
- Investigating the biochemical, physiologic and genetic bases for disease in a clinical research setting

To date, 11 students have graduated from the program, and eight more will graduate this year. Alumni have gone on to academic positions at Yale, Memorial Sloan-Kettering Cancer Center, the University of Pittsburgh, the University of Texas Health Science Center at San Antonio, the University of Pennsylvania School of Medicine, the Cleveland Clinic Foundation and the Hadassah Hebrew University School of Medicine.

IMP Scholars

Christopher Hoimes, DO
Cancer Center, Clinical Fellow
Thesis TBD

Anita Huttner, MD
Neurobiology, Staff Affiliate
Role of palladin in neocortical development

Roger Jou, MD
Psychiatry, Resident
Characterization of abnormal neural connectivity in autism spectrum disorders using diffusion tensor magnetic resonance imaging

Agnes Kim, MD
Internal Medicine (cardiology), Postdoctoral Fellow
Mechanisms of AMPK regulation in the heart

Nancy Kim, MD
Internal Medicine, Postdoctoral Fellow
Persistence with oral hypoglycemic therapy one year after initiation

Vishal Mehra, MD
Internal Medicine (cardiology), Postdoctoral Fellow
The effect of free fatty acids on VEGF-induced angiogenic responses

Edward Miller, MD
Internal Medicine (cardiology), Clinical Fellow
The cardioprotective effects of AMP-activated protein kinase

Katie Moriarty, MD
Internal Medicine (cardiology), Postdoctoral Fellow
Estrogen receptor-mediated rapid signaling in endothelial progenitor cell contributions to ischemia

Justin Paglino, MD
Laboratory Medicine, Postdoctoral Fellow
Understanding and enhancing the oncoselectivity of minute virus of mice

Karin Provost, DO
Internal Medicine (pulmonology and critical care), Postdoctoral Fellow
Regulation of the airway epithelial responses in asthma

Jennifer Sherr, MD
Pediatrics, Postdoctoral Fellow
Thesis TBD

Paul Tang, MD
Surgery, Resident
Role of innate immunity in flow-mediated vascular remodeling

Abraham Tzou, MD
Laboratory Medicine, Postdoctoral Fellow
Toll-like receptor 7, B cells, and plasmacytoid dendritic cells at a nexus in systemic autoimmunity

Alexander Westphal, MD
Psychiatry, Postdoctoral Fellow
Influences of action on perception in people with autism spectrum disorders

Predoctoral Program has Opportunities for Students at Every Level

In October 2005, under the NIH Roadmap initiative, Yale was one of 10 medical schools to receive T32 funding for clinical research training among medical, nursing and biomedical engineering students. The goal of this novel program, which has been expanded under the CTSA grant, is to train the next generation of clinical researchers by equipping them with strong methodological skills, an understanding of how to work within multidisciplinary teams and a vision that will advance efforts to improve health and patient care.

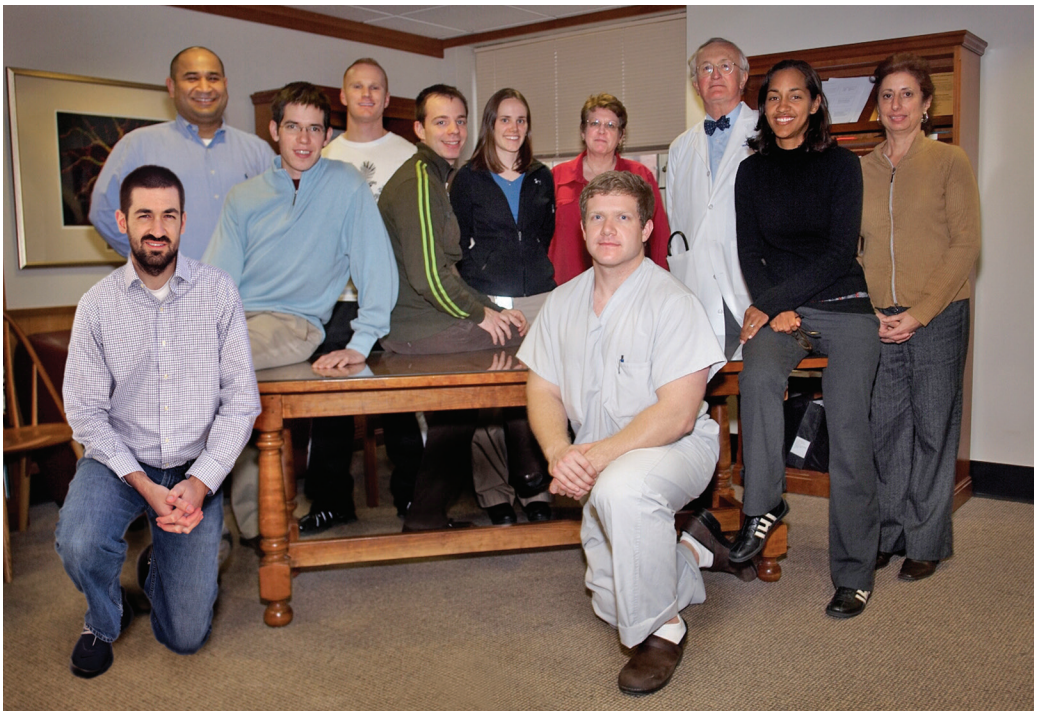
The T32 award supports one-year clinical research projects for six medical students, two MD/PhD students, one PhD nursing student and one student in biomedical engineering. It is particularly well-suited to Yale, where 50 percent of medical students extend their training to a fifth year devoted entirely or in part to research. The grant also supports eight medical students doing short-term clinical research projects that generally last about three months.

"The concept was to add training in clinical research at every level of student interest, from those graduating in four years to students electing a fifth year devoted to a clinical research project and pursuing the new MD/MHS joint degree," said John Forrest Jr., MD, T32 program director, who has been directing the office of student research for the past 25 years.

Students doing one-year projects follow an intensive training core that includes an expanded curriculum made possible under the CTSA. "Leadership and Organization" is one unique offering that helps students develop leadership skills they can draw upon throughout their careers. It's designed to prepare them for the organizational challenges that physician investigators increasingly face while directing complex biomedical research programs. There are also courses on conducting clinical research, biostatistics and statistical data analysis. All T32 scholars complete a detailed proposal of their project that includes background, hypothesis, specific aims, methods and a proposed plan of study.

Student research is already an important part of the School of Medicine curriculum; all Yale medical students do a thesis based on original laboratory or clinical research. Thanks to the CTSA and the T32 program, first-year students working on a clinical research project – approximately 60 percent of each class – now take six two-hour sessions with tutors who provide them with an overview of the objectives, research strategies and methods of patient-oriented research. "We developed this because they're often well-motivated but aren't sure how to go about planning a study," said Forrest.

The program also includes a Leadership in Biomedicine lecture series in which students hear from distinguished Yale physician-scientists about their perspectives on biomedical research and about personal issues involved in choosing a career pathway in academic medicine.



T32 Awardees

Front row: Shane Lloyd, Jesse Bible

Back row: Saif Rathore, Jonathan Romanyshyn, William Greene, Leon Boudourakis, Laura Dichtel, Mae Geter, John Forrest Jr., Sara Whetstone, Donna Carranzo

Not pictured: Catherine Sumpio, Cheryl Maier

Education and Training Programs *continued from page 1*

fellows and junior faculty and the T32 program for predoctoral students conducting clinical research. YCCI has also established the Scholar program, which provides salary and research support to fellows and junior faculty members who are just starting their careers (see accompanying articles). It's important to note that these programs are not just for PhDs; they are open to students and junior faculty in medicine, nursing, public health and biomedical engineering. Even those not enrolled in one of the programs have the opportunity to take courses such as grant writing or principles of clinical research, both of which are offered through the IMP program. In fact, fellowship accreditation programs are now requiring such coursework, and there is an increasing demand, especially from those in subspecialties that have no educational programs of their own.

The education program is run by co-directors Judy Cho, MD, and Eugene Shapiro, MD, who took over in October and have been busy meeting with the scholars to find out how their research is progressing and what they need. In an effort to promote interdisciplinary collaboration, they have instituted twice-monthly research-in-progress meetings in which scholars present their work to their colleagues. "Hopefully it will help cross-fertilize so people not only will learn what other people are doing, but also will see that it relates to their work and maybe collaborate," said Shapiro. They also have plans to develop a master's program in health science research and to establish mentoring committees to help monitor and guide scholars' progress. "We're trying to provide leadership in helping young people get the tools, the education, the research experience and the mentoring they need to become cutting-edge leaders in clinical and translational research for the future," said Shapiro. "You don't have to be a PhD candidate to get some benefit."

2006 YCCI Scholars

Photo Unavailable

Sumita Bhaduri-McIntosh, MBBS, PhD
Assistant Professor of Pediatrics (infectious diseases)
Early cellular immune responses to Epstein-Barr virus

Zubin Bhagwagar, MD, PhD, MRCPsych
Assistant Professor of Psychiatry
GABA and serotonin interactions in major depressive disorder

Jeptha Curtis, MD
Assistant Professor of Medicine (cardiology)
Drug-eluting stents

Karen Dorsey, MD, PhD
Instructor in Pediatrics
Physiologic mediators of physical activity and obesity in children

Marsha Guess, MD
Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences
Vaginal smooth muscle function in pelvic organ prolapse

Richard Kibbey, MD, PhD
Instructor in Medicine (endocrinology)
Pancreatic beta-cell dysfunction and recovery in type-2 diabetes

Chiang-shan Li, MD, PhD
Assistant Professor of Psychiatry
Neural imaging of cocaine dependence

Tené Lewis, PhD
School of Public Health
Assistant Professor of Epidemiology (chronic diseases)
Psychosocial factors and cardiovascular disease in African-American women

James McPartland, PhD
Associate Research Scientist, Child Study Center
Neural correlates of perceptual expertise in autism

Marcella Nunez-Smith, MD, MHS
Assistant Professor of Medicine
Development of an instrument to measure discrimination in health care systems

2006 YCCI Scholars *continued*

Varman Samuel, MD, PhD

Assistant Professor of Medicine (endocrinology)

Hepatic gluconeogenis in type 2 diabetes

Erik Shapiro, PhD

Assistant Professor of Diagnostic Radiology

From mice to men: magnetic resonance imaging of cellular migration

Juliette Shellman, APRN-BC, PhD

School of Nursing

Assistant Professor of Nursing

Peer to peer reminiscence intervention for older African-Americans

Jonathan Siner, MD

Instructor in Medicine (pulmonary and critical care)

Angiopoietin-2 in severe sepsis and septic shock

Tamar Taddei, MD

Assistant Professor of Medicine (digestive diseases)

Pathophysiologic mechanisms of Gaucher diseases

2007 YCCI Scholars

Karen Bearss, PhD

School of Nursing

Associate Research Scientist, Nursing and Child Study Center

Structured parent training for young children with autism

Lei Chen, MD

Assistant Professor of Pediatrics (emergency medicine)

Bedside ultrasound in children with dehydration from gastroenteritis

Yasuko Iwakiri, PhD

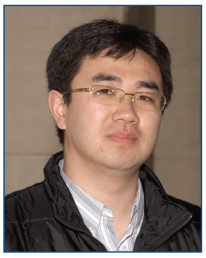
Assistant Professor of Medicine (digestive diseases)

Hyperdynamic circulatory syndrome in liver disease

Elijah Paintsil, MD

Associate Research Scientist, Pediatrics (infectious diseases) and Pharmacology

Viability of HVC in syringes



Shuangge Ma, PhD

School of Public Health

Assistant Professor of Epidemiology and Public Health

Neoplastic transformation and progression

K Scholars

Kristina Crothers, MD

Assistant Professor of Medicine (pulmonary and critical care)

Characterization of COPD in HIV positive compared to HIV negative patients

Nancy Kim, MD

Postdoctoral Fellow, Internal Medicine

Persistence with oral hypoglycemic therapy one year after initiation

Nina Kadan-Lottick, MD, MSPH

Assistant Professor of Pediatrics (hematology and oncology)

Psychosocial outcomes among children with leukemia

Peter Morgan, MD, PhD

Assistant Professor of Psychiatry

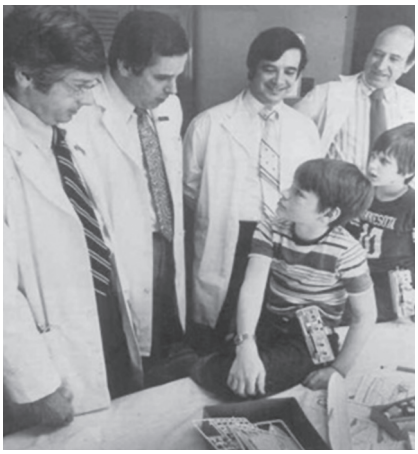
Sleep and cognition in cocaine dependence

Arthur Simen, MD, PhD

Assistant Professor of Psychiatry

Genetic studies of major depressive disorder

Recruitment Campaign Will Include Yale Discoveries



From left: Phillip Felig, MD, Robert Sherwin, MD, William Tamborlane, MD and Myron Genel, MD conducted the landmark study on using an insulin pump to treat diabetes.

Plans for YCCI's new recruitment campaign include transforming the website into a tool patients can use to find information about clinical trials. But the website is also an opportunity to inspire patients to volunteer for studies. One way to do that is to share stories of Yale's past successes. Below is an example of one such story–the development of the first insulin pump to treat diabetes. Investigators who have a similar story to submit are urged to contact Kelly Burton at 785-2519 or kelly.burton@yale.edu.

Like many discoveries, the development of the first insulin pump was a combination of ingenuity and teamwork. In 1979, a group of Yale doctors was conducting studies to figure out the best way to deliver insulin to children who suffer from diabetes. They discovered that giving small amounts continuously, with larger doses at meals, worked better than giving one large dose, because this more closely resembles the way the pancreas produces insulin. Unfortunately, there was no easy way to accomplish this. Around the same time, another Yale doctor was using a portable pump to help solve a different problem: delivering medicine to children who had a dangerous buildup of iron due to frequent blood transfusions. Dr. William Tamborlane, Dr. Robert Sherwin and their colleagues realized that this pump would be ideal for applying what they had learned about insulin delivery to their patients. The insulin pump was first tested in seven children with diabetes and the results were spectacular. Dr. Tamborlane remembers staying overnight in the hospital so that he could monitor the results. When he began to see that blood sugar levels remained stable in his young patients, he knew that he and the other Yale doctors had hit upon a novel and effective treatment for diabetes. The insulin pump, which today has evolved into a device the size of a beeper, continues to gain momentum; last year 350,000 diabetic patients used it, and its popularity continues to grow. Without volunteers like the children and their families who were willing to take a chance on an exciting new treatment, this groundbreaking discovery would not have been possible.

Clinical Research Compliance

Clinical Research Compliance newsletter now Part of Yale Center for Clinical Investigation newsletter

Clinical Research Compliance
Rules and Standards Affecting Human Subjects Research
Published by the Yale Medical Group
December 2007 Issue 21

Off-label use of drugs for anti-cancer treatment

In November the Centers for Medicare & Medicaid Services (CMS) came out with a policy change that will help ensure that patient care involving off-label medications will be guided by objective, evidence-based drug information. This move was championed by the American Society of Health-System Pharmacists (ASHP). According to the ASHP:

"CMS's changes to the list of compendia used to determine medically accepted off-label uses of drugs and biologicals in chemotherapy regimens will place a high priority on whether a publication's evidence evaluation process is transparent and free from conflicts of interest."

To determine medically accepted indications for drugs and biologicals used in anti-cancer treatment, CMS will accept literature from the following list of compendia:

- American Journal of Medicine
- Annals of Internal Medicine
- The Journal of the American Medical Association
- Journal of Clinical Oncology
- Blood
- Journal of the National Cancer Institute
- The New England Journal of Medicine
- British Journal of Cancer
- British Journal of Hematology
- British Medical Journal
- Cancer
- Drugs
- European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology)
- Lancet
- Leukemia
- Annals of Oncology
- Biology of Blood and Marrow Transplantation
- Bone Marrow Transplantation
- Gynecologic Oncology
- Clinical Cancer Research
- International Journal of Radiation, Oncology, Biology, and Physics
- Journal of the National Comprehensive Cancer Network (NCCN)
- Radiation Oncology
- Annals of Surgical Oncology
- Journal of Urology
- Lancet Oncology

Physicians may request that an off-label drug be approved for payment

Physicians may request that an off-label drug be approved for payment by Medicare by submitting a request in writing and including the data supporting its use. The data must include:

(1) A use supported by clinical research that appears in at least two Phase III clinical trials that definitively demonstrate safety and effectiveness; or,

(2) If no Phase III trial evidence is available, at least two Phase II clinical trials with reasonably large patient samples showing consistent results of safety and efficacy may be considered in certain instances such as use in rare diseases in which a Phase III study might be difficult to complete in a reasonable period of time after completion of the Phase II studies, or when overwhelmingly good evidence of safety and effectiveness is noted in the Phase II studies. The Phase III or Phase II trials must come from different centers and be published in national or international peer-reviewed (editorial committee is comprised of physicians) journals. Peer reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).

(3) A use that is an accepted standard of medical practice. Any then published recommendations from specialty societies or in other authoritative evidence-based guidelines' It should be noted that acceptance by individual health care practitioners, or even a limited group of health care practitioners normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with potential financial conflict of interest in the outcome, are not sufficient

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OIG's focus in research

Annually, the Office of the Inspector General publishes their work plan. For 2008, the OIG will review:

1) the FDA's oversight and review of allowable off-label drug promotion and enforcement,

2) the FDA's adverse-event-reporting system for medical devices,

3) the FDA's oversight of research misconduct by clinical investigators,

4) clinical investigators disclosures to the FDA of financial interests. Financial disclosure is required for any studies involving drugs, device, and biologic applications. The OIG will determine the nature of financial interests disclosed by clinical investigators, the extent to which applicants monitor their clinical investigators for financial interests, and the extent to which FDA oversees the process.

5) NIH's monitoring of extramural grantees for potential conflicts of interest.

6) the extent to which the National Cancer Institute (NCI) monitors its research project grants.

7) and determine how and to what extent the NIH is ensuring that grantees comply with NIH policy for Data Safety Monitoring Boards in multi-site clinical trials.

The OIG Work Plan can be found in its' entirety at http://www.oig.hhs.gov/publications/docs/workplan/2008/Work_Plan_FY_2008.pdf

Since November 2002, the Yale Medical Group (YMG) Compliance Department has produced 21 issues of the newsletter *Clinical Research Compliance* (*CRC*). Now that YCCI is producing its own newsletter, YMG felt it made sense to partner with YCCI and become a contributor to the YCCI newsletter. This move will also eliminate the need for faculty and staff to read two separate newsletters. All 21 issues of *CRC* will remain available on the Compliance website at http://www.yalemedicalgroup.org/comply (accessible only from within the Yale system).

New Modifiers for Research

Since 2002, modifier QV has been used for billing routine care services in a Medicare-qualifying clinical research study. Modifier QV has been replaced with modifier Q1. In addition, the modifiers for billing for preapproved devices (QA) and implantable cardiac defibrillators (QR) have been replaced by modifier Q0. The definitions for these new modifiers are as follows:

Q0 – Investigational clinical service provided in a clinical research study that is in an approved clinical research study

Q1 – Routine clinical service provided in a clinical research study that is in an approved clinical research study

Clinical departments should update their encounter forms or other billing documents as appropriate.

NLM Clinical Trial Number

As of April 1, 2008, the Center for Medicare and Medicaid Services (CMS) has announced a new, voluntary reporting for placing a clinical trial number on claims for items and services provided in clinical trials that meet Medicare's qualifying criteria for coverage. The clinical trial number that the CMS is requesting to be voluntarily reported is the number assigned by the National Library of Medicine (NLM) Clinical Trials Data Bank when a new study is registered by a sponsor or investigator.

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