Yale Center for Clinical Investigation

Fall 2012

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Photo by Terry Dagradi

West Campus Update

The West Campus is home to several School of Medicine research cores, where cutting-edge science opens the way to medical advances. Here we highlight two cores that are upgrading facilities and expanding services to help investigators bring discoveries from bench to bedside.

Yale Center for Molecular Discovery Combines Biology and Chemistry to Advance Research

Offering small-molecule compounds, siRNA collections, and high-throughput assay design and execution, the Yale Center for Molecular Discovery (YCMD) provides a service-oriented, results-driven approach to advance the scientific work of Yale investigators. The newly formed center, created in early 2012 by merging the Yale Small Molecule Discovery Center and the Yale Center for High Throughput Cell Biology, is poised to both expedite basic science discoveries and advance such breakthroughs to make them more attractive to industry.

The model for developing the next generation of drugs has changed completely during the last decade; pharmaceutical companies have abandoned the early-stage work they had historically undertaken, leaving it to academic centers to evaluate basic biology discoveries for potential drug development. "There's a 'valley of death' and we're trying to bridge that by pushing the discoveries at Yale further toward compounds that would be more attractive to pharma or maybe even a venture capitalist," said **Craig Crews,** PH.D., the center's executive director.

The PerkinElmer Opera microscope allows investigators to automatically capture hundreds of thousands of images in a few hours.

Working closely with Yale's Office of Cooperative Research and supporting that center's mission of educating investigators and moving discoveries through the pipeline, YCMD also supports the goal of the National Center for Advancing Translational Sciences (NCATS) to speed the process of translating scientific discoveries into new therapies.

The Center, located on the West Campus, has recently become a core of the Yale Cancer Center and has expanded its staff—many of whom come from pharmaceutical companies—to include experts in computational and medicinal chemistry. YCMD focuses on small molecules, the precursors of what could become drugs; or small interfering RNA (siRNA), which allows researchers to knock out any gene in the genome, scaling assays and experiments into 384-well plates. This approach allows researchers to interrogate whatever they're investigating with thousands of samples, but can also produce variable results.

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Inside This Issue

Director's Corner

This issue of the YCCI newsletter features the School of Medicine's Core Research Facilities, which offer a wide range of world-class technologies to facilitate translational research.

These days, it's impossible to have discoveries without such technologies, but YSM goes beyond sophisticated instrumentation. We have dedicated scholars who push science to its limits and faculty leaders who are there to help them do it. Our core directors not only conduct their own groundbreaking research, they are also superb collaborators who work with other senior scientists while at the same time pursuing the mission of training junior investigators.

Last year, the Clinical and Translational Science Awards shifted to oversight by the National Center for Advancing Translational Sciences (NCATS), whose mission is to catalyze the generation of innovative methods and technologies that will lead to the development of new diagnostics and therapeutics. The move to NCATS dovetails perfectly with Yale's strengths in basic scientific research and discovery, which are supported by the cores. At the same time, the cores help support NCATS as it seeks to facilitate the translation of basic biological discoveries into clinical applications.

The fact is that translation would be impossible without the Core Research Facilities. That's why we want to ensure that Yale investigators are aware of the science taking place thanks to these resources; how to utilize them; and the ways in which it's possible to collaborate with faculty and staff. The breadth of these facilities is too vast to cover in one issue of our newsletter, but we hope that you find this update on the latest developments to be both useful and inspiring.

Robert Sherwin, M.D.
YCCI Director

Acknowledging Core Resources

When you utilize Core resources, don't forget to acknowledge the resources in your publications, and forward the publications to the appropriate cores. These publications are very useful when applying for instrumentation and other grants that benefit Yale's research community.

CORES SPECIAL ISSUE

Written by Jill Max

Events Calendar

Coffee and Conversation

8:00 a.m., Cohen Auditorium
(Coffee at 7:30 a.m.)

- ***January 16***

EPIC TRAINING
Presented by Sharlene Seidman

- ***February 20***

ROLE OF OFFICE OF RESEARCH ADMINISTRATION
Presented by Andrew Rudczynski

Lunch and Learn Series

12:00 p.m.; lunch will be provided.

- ***January 10***

RECRUITMENT AND BRANDING
Presented by Jackie Leutze, Mason, Inc.
Park Street Auditorium

- ***February 14***

SCIENTIFIC MISCONDUCT
Presented by Sarah Rockwell
300 George Street, IFR Auditorium

To register, visit http://www.yale.edu/training; browse courses by course owner, select CTSA/YCCI, then select Clinical Trials.

For more information, contact LaToya Howard at latoya.howard@yale.edu or call 737-3661.

Research-in-Progress Meetings

These meetings feature presentations from YCCI Scholars and Investigative Medicine Program students, as well as trainees from the Medical Research Scholars Program (MSRP). We encourage all faculty and staff to attend. All meetings listed below will take place at noon in TAC N203; lunch is provided.

- ***January 14 and 28***
- ***February 11 and 25***

Please visit our website at http://ycci.yale.edu/education/lectures/schedule/index.aspx to find the list of presenters and projects.

Second Annual YCCI Scholar Day Retreat (see page 9)

- ***March 1***

West Campus Update: YCMD Combines Biology and Chemistry to Advance Research *continued from page 1*

"Part of what we do is create the robustness that allows us to have reproducibility," said **Michael Kinch,** PH.D., director of YCMD. Besides the experience of its staff, YCMD offers state-of-the-art instrumentation, including a new microscope capable of high-content, high-throughput imaging of multiwell plates. The PerkinElmer Opera is one of fewer than a dozen such microscopes being used by academic centers; it allows investigators to capture hundreds of thousands of images automatically in a few hours. YCMD also prides itself on identifying novel uses for its instrumentation, much of which came from Bayer when Yale acquired the West Campus. "We've been pushing it in directions maybe that it hasn't been intended to go," said Kinch.

One new area of emphasis is the collection of novel organisms, which springs out of work done by Yale investigators. For example, Yale has a rich collection of natural compounds culled from rainforests and other sources that researchers are encouraged to deposit in YCMD's library. The scientists hope that screens run against these compounds will lead to the discovery of new drugs. "Because we are screening to industrial standards in an industrial setting with ex-industry staff, this isn't just an academic exercise," said Crews. "We have the capabilities and the expertise to bring to bear real-world pharmaceutical help to academic researchers."

Crews' own successful research contributed to the creation of YCMD. His lab found that epoxomicin, a compound produced naturally by a microbial organism, could function as a highly potent selective inhibitor of the proteasome. This finding led to the development of Kyprolis (carfilzomib), a drug that was recently approved by the FDA for the treatment of multiple myeloma. Crews, who is the Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology and professor of chemistry and of pharmacology, set up YCMD's infrastructure. He has been active in the Center's efforts to buy chemical libraries; help investigators design assays to discover which compounds are active; and work with them to develop these compounds further.

Richard Lifton, M.D.,PH.D., right, with Craig Crews, PH.D., center, and Michael Simons, M.D., director of the Yale Cardiovascular Research Center, left

Several years ago, **Ronald Breaker,** PH.D., the Henry Ford II Professor and chair of the Department of Molecular, Cellular and Developmental Biology, was the first researcher to successfully complete a high-throughput screen using Yale's chemical screening facility. His lab's early work on bacterial riboswitches—portions of messenger RNA that control gene expression—recently led to the discovery of a new riboswitch that responds to fluoride. Fluoride is known to be toxic to bacteria, which may account for its role in preventing dental cavities, but until recently scientists did not know how bacteria counteract fluoride toxicity. Breaker and his colleagues discovered two protein channels that flush fluoride out of cells. They have spent the last year or so conducting high-throughput screens to identify compounds that plug those channels, thereby increasing fluoride's toxicity to bacteria, including pathogens. The ultimate goal is to develop new and powerful antimicrobial agents. "Don't ever think that you won't do something like this in your scientific program, because there may come a time when you'll have the ideal idea for a high-throughput screen," said Breaker. "You don't have to be an expert to successfully run one of these screens. The core is staffed with people who do this on a daily basis and are very good at it."

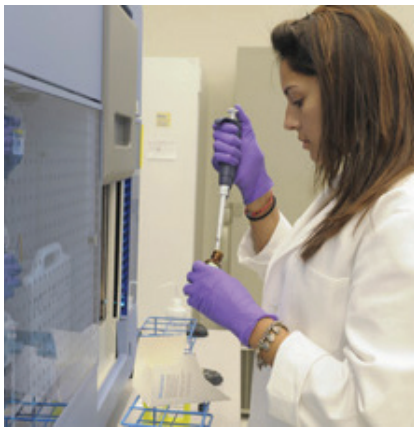
One unique aspect of working with YCMD is that each investigator is paired with a staff member. "That way we can transfer from the lab the deep knowledge of the system and introduce the practicalities," said Kinch. Last year, YCMD completed more than 80 projects, underwriting about $3 for every $1 contributed by investigators. The majority of projects undertaken by YCMD come from a request for proposals, such as a pilot program with Johnson & Johnson for projects aimed at target discovery and/or early proof-of-concept to identify molecules that alter key biological behaviors. The center also supports between 20 and 30 grant applications each year, writing sections and guiding investigators.

YCMD collaborates with researchers from anywhere within the University on a wide range of projects and is reaching out to other universities to establish strategic partnerships in which Yale investigators can exchange expertise with their counterparts in other institutions. "We want to make sure we're a good citizen in a bigger community," said Kinch.

West Campus Update: YCGA Provides World-Class DNA Sequence Analyses

From its beginnings in 2008 as a small next-generation DNA sequencing operation in the Microarray Resource of Yale's Keck Foundation Biotechnology Resource Lab, the Yale Center for Genome Analysis (YCGA) has grown into a state-of-the-art facility that provides more than 40 different analyses to study genetic events. The introduction of new platforms, a substantial Mendelian Center grant from the National Institutes of Health (NIH), and the expertise of the center's 23 staff members provide unparalleled opportunities for Yale investigators to collaborate on sequencing projects that have led to notable discoveries.

Located in a newly renovated building on Yale's West Campus, the center boasts 10 Illumina HiSeq sequencing systems, each of which analyzes between 400 and 500 billion bases per week. While first- and second-generation sequencing technologies utilize amplification, YCGA now offers platforms capable of single-molecule sequencing in real time and rapid turnaround of data. The PacBio platform, one of three newly acquired third-generation sequencers, can sequence up to 10,000-base-long fragments at a time—a vast improvement over earlier technologies.



DNA sequencing can provide a deeper understanding of DNA and RNA than any other technology. While microarray technology revolutionized biomedical research, it has several limitations that DNA sequencing can overcome. The cost of sequencing, once prohibitive, is rapidly decreasing, so that performing sequencing at the genome level is becoming more affordable. YCGA will soon acquire four Ion Proton sequencers—powerful machines that have the potential to analyze the entire human genome in 24 hours for about $1,000.

Exome analysis makes it possible to sequence protein-coding genes, which constitute one percent of the human genome but harbor 85 percent of disease-causing mutations. Whole-exome sequencing is significantly cheaper than whole-genome sequencing, and the price is declining; over the past year, the cost of sequencing a single human exome decreased from $2,500 to less than $600.

YCGA recently received $11.2 million from the NIH to establish the Center for Mendelian Genomics at Yale, one of three national centers that will study the genetic basis of rare disorders which afflict some 25 million Americans. The centers are expected to shed light on common diseases as well. For researchers, this is an unprecedented opportunity. "This work is carried out on a collaborative basis and at no cost to investigators for qualified samples," said **Shrikant Mane,** PH.D., director of YCGA. "We do the sequencing and analysis and give them the results." YCGA is also performing the genomics for a multiyear collaboration with Gilead Sciences to accelerate the development of drugs against new cancer targets. DNA sequencing results will be used to define new driver genes, and map out pathways and mechanisms in tumors related to cell proliferation, inhibition of cell death, metastasis, and drug resistance.

Shrikant Mane, PH.D., director of YCGA

In 2009, YCGA was the first center to use exome sequencing to make a clinical diagnosis. In a matter of days, investigators led by **Richard Lifton,** M.D., PH.D., used whole-exome sequencing to identify a mutation in both copies of the gene associated with congenital chloride diarrhea in an infant. The center is now CLIA-certified for exome analysis, qualifying it to perform diagnostic testing.

Utilized by 120 PIs from 38 departments, YCGA's sequencing platforms have helped unravel genes and pathways involved in such disorders as brain malformations, hypertension, Gaucher disease, and squamous-cell carcinoma. In the past year, research conducted in collaboration with the center has led to the following breakthroughs:

- A team led by **Ruth Halaban,** PH.D., discovered a mutation in the RAC1 gene that plays a role in melanoma and is the third most frequent mutation, occurring in about nine percent of melanomas caused by UV exposure. The newly discovered pathway could be a potential target for the development of new therapies *(Nature Genetics)*.

- Using whole-exome sequencing, **Matthew State,** M.D., PH.D., uncovered three genes that almost certainly contribute to autism, with the likelihood of discovering additional genes as sequencing efforts continue *(Nature)*.

- Whole-exome sequencing was also used by Lifton's group to identify mutations in two genes that play a role in hypertension and electrolyte homeostasis *(Nature)*.

"There is a very strong collaboration between Yale researchers and the Center, and that is why we are so successful," said Mane. Technological advancements and increased capability will hopefully lead not only to continued discoveries in basic biology and the genetics of disease, but ultimately to new and better treatments.

Keck Biotechnology Resource Lab Offers Wide Range of Technologies

Biomedical research is increasingly dependent on highly sophisticated instrumentation. For Yale investigators, the Keck Biotechnology Resource Laboratory provides access to one of the largest academic biotech laboratories of its kind. Keck's 150 technologies are organized into three genomic, three proteomic, and three multidisciplinary resources, providing a wide range of syntheses and analyses that includes gene expression and SNP genotyping using microarray and bead technologies; oligonucleotide and peptide synthesis; DNA and protein sequencing; biophysical analysis of proteins and other biopolymers; biostatistical and bioinformatics analyses; mass spectrometry; protein profiling; and high-performance computing.

Keck At a Glance

RESOURCE	DIRECTOR	MAJOR SERVICES
Genomics	Shrikant Mane, PH.D	
DNA sequencing	Nancy daSilva, PH.D	Individual tube sequencing, high-volume plate sequencing, PCR purification, fragment analysis, ready-to-run service
Microarray	Guilin Wang, PH.D	Expression, genotyping, methylation, miRNA, gene expression, CGH
Oligonucleotide synthesis	Joe DeLuca	Wide variety of complex specialty syntheses
Proteomics	Erol Gulcicek, PH.D	
Biophysics	Ewa Folta-Stogniew, PH.D	Resources to study the oligomeric state of biomolecular assemblies and the thermodynamics and kinetics of macromolecular interactions
MS/Proteomics	Chris Colangelo, PH.D (protein profiling) TuKiet Lam, PH.D (FTICR/MS)	Protein profiling
Protein Chemistry		
Amino acid analysis	Myron Crawford	Amino acid composition of peptides and proteins
Protein/peptide sequencing	Myron Crawford	Amino-terminal sequencing
Small-scale peptide synthesis	Janet Crawford	Fmoc peptide synthesis (25-100 µmol)
Large-scale peptide synthesis	James I. Elliott, PH.D	*t*-BOC peptide synthesis (0.5 mmol)
High-performance Computing		
Bioinformatics	Mark Gerstein, PH.D and Hongyu Zhao, PH.D	Support of software provided by core; consultation on DNA/protein sequence, microarray, protein structure, pathway analysis; collaboration on bioinformatics projects
Biostatistics	Hongyu Zhao, PH.D	Statistical and computational analysis of such various types of data as gene expression, genotyping, mass spectrometry, next-generation sequencing, and many others
High-performance computing	Robert Bjornson, PH.D and Nicholas Carriero, PH.D	Analysis and interpretation of data resulting from Keck technologies

Advantages of Working with Keck

"One of the ways by which Keck seeks to achieve its goal of maximizing its contribution to biomedical research is by balancing services with grant support," said Williams. This approach enables the lab to provide better and more analytical services at lower cost. NIH-funded and other centers closely associated with Keck carry out research that results in new and improved technologies, which are then made available to the more than 1,000 investigators from 300 institutions who use Keck's services each year. For example, Keck's NIDA Neuroproteomics Center Grant enables the 26 investigators in the Neuroproteomics Center to utilize MS/proteomics technologies at no charge while at the same time allowing Keck to offer a range of proteome analyses on a service-charge basis to other investigators.

Keck's bioinformatics and biostatistics resources stand ready to help users interpret the often huge amounts of data that result from the high-throughput analyses it provides. In close collaboration with the Center for Medical Informatics, Keck has built the Yale Protein Expression Database (YPED), an integrated Web-accessible software system that addresses the storage, retrieval, and integrated analysis of high-throughput proteomic and small-molecule analyses. The YPED interface supports sample submission, project management, sample tracking, data import, sample administration, and user billing. It also contains a repository for public access to protein identification experimental data and serves as a peptide spectral library for all of Keck's protein database search identification results. "We believe that few if any other academic core labs provide their users with similar databases to help fully leverage their analyses," said Williams.

The Keck Lab is one of the oldest academic core labs built on a service-charge model. While Keck's facilities are open to both Yale

Keck offers a number of technologies not often found in academic core labs. Its proteomics capabilities include amino acid analysis; peptide/protein sequencing using the Edman degradation; large-scale peptide synthesis using *t*-BOC chemistry to synthesize and purify custom synthetic peptides; and biophysics facilities. Keck's Basic Protein Identification service has been streamlined to offer investigators lower prices and a quick turnaround. Samples are digested with trypsin and analyzed by LC-MS/MS on a Thermo Scientific LTQ Orbitrap, then searched against the NCBInr or UniProtKB/Swiss-Prot databases.

The development of two robust LC-MRM assays for human red blood cell membrane and mouse post-synaptic density fractions now enables Keck to quantify 57 and 119 proteins respectively. The resource is also performing small-molecule quantitation, in particular looking at creatinine levels in urine using mass spectrometry, which allows for increased accuracy compared to older methods.

One example of an innovative project involving Keck's resources is the work being done in collaboration with **Chirag Parikh,** M.D., PH.D., and **Lloyd Cantley,** M.D., on a targeted proteome assay for urine to identify biomarkers of polycystic kidney disease and acute kidney injury (AKI). "The current traditional methods of diagnosis are outdated, not accurate, and delayed," said Parikh, associate professor of medicine (nephrology). Until now, most work in this area has been done in animal models. Parikh and his colleagues have taken it to the next level, enrolling 2,000 subjects from 11 institutions to obtain random human samples of individuals with and without AKI. Instead of testing one protein at a time, technology at the Keck lab has allowed Parikh and Cantley to test multiple proteins at the same time; they currently have a list of 200 proteins they're targeting. Parikh, who had not worked with Keck previously, said that the experience has been rewarding. "It's a new technology and the Keck people have been very supportive," he said. "Identifying that magic protein that will help us with either recovery, early diagnosis, or prognosis would be a home run, but the journey so far looks very productive."

Keck's genomics technologies include Sanger sequencing, microarray, and oligonucleotide synthesis. Microarray, now located at the Yale Center for Genome Analysis, is winding down as investigators turn to sequencing for identifying genes associated with disease. The oligo synthesis resource provides rapid turnaround and a wide variety of high-quality and complex specialty syntheses.

Keck's high-performance computing (HPC) resource has about 275 active users from 60 Yale laboratories and is accessible at no cost, thanks to two NIH Shared Instrumentation Grants. HPC is supported by staff with appointments in computer science and an extremely high level of expertise. A number of faculty have purchased their own nodes and/or storage; and new queuing software is expected to allow "common" sharing of idle computing nodes by hundreds of users when these owners are not using them. "You can do high computing," said **Kenneth Williams,** PH.D., co-director of Keck, pointing out that HPC creates almost 200 accounts for new users each year.

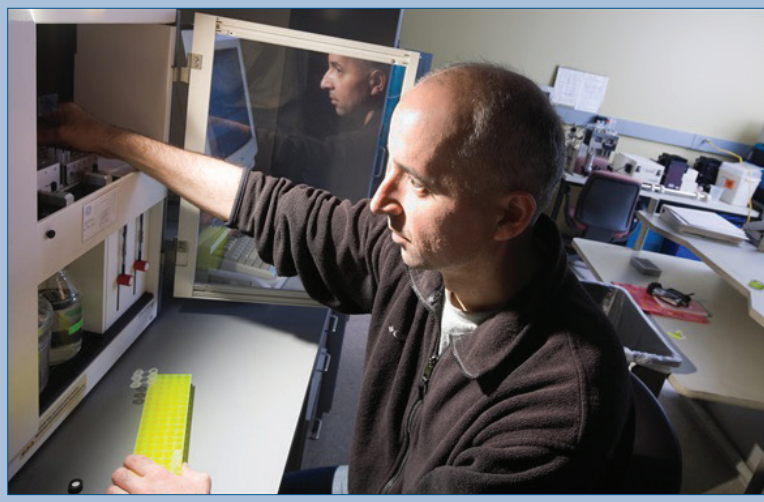
How to Charge the Cost of Analyses and Syntheses to Grants

- For $10,000 or less in services annually, it is usually best to request funding in the "Other Expenses" category. Services should be clearly delineated (number of samples, cost per sample) and well justified in terms of achieving the proposed specific aims.
- For $20,000 or more in services annually, the best approach is to request funding for the actual Keck staff effort, supplies, and instrument maintenance/repair rather than on a service charge basis.
- For annual services in the $10,000 to $20,000 range, either approach may be used.

Letters of support in all three cases are usually not required but are available on request.

and non-Yale users, Yale investigators receive priority and benefit from lower rates. Most analyses and syntheses are provided on a full-service basis. The backlog of non-Yale requests helps maintain high productivity and low service charges when Yale demand is below capacity. The backlog also increases the ability of the Keck lab to compete for grants. For example, Keck has been awarded 25 NIH Shared Instrumentation Grants (SIGs); the current NIH SIG provided $600K for Keck's LTQ Orbitrap Elite Mass Spectrometer and was supported by 52 faculty members at 10 universities across the country. Keck's ability to attract requests from approximately 600 investigators and more than 300 institutions each year is a testament to the high quality of the services it offers.

Sample submission forms, drop-off hours and locations can found online at http://medicine.yale.edu/keck/index.aspx; or call 203-737-2206 for more information.



Boosting Resolution and Efficiency at the MR Research Center

Yale's Magnetic Resonance Research Center (MRRC) houses cutting-edge MR equipment, infrastructure and expertise to support the more than 60 investigators who utilize its services.

Among its five human magnets is a 7T human head system—one of a limited number throughout the world—that provides excellent resolution in terms of MR spectroscopy for looking at specific metabolites. "It potentially has the ability to do very-high-resolution functional and structural imaging of the brain," said **Todd Constable**, PH.D., co-director of MRI research and professor of diagnostic radiology, of biomedical engineering, and of neurosurgery. He expects to see a dramatic increase in use of the system over the next couple of years as investigators become aware of its capabilities.

Along with Douglas Rothman, PH.D., Todd Constable, PH.D., co-directs the Yale Magnetic Resonance Research Center (MRRC) and oversees MRI research.

With the addition of a second 3T magnet and the upgrade of its existing 3T magnet, the MRRC now has two state-of-the-art 3T systems that are primarily dedicated to functional imaging but also support cardiac and vascular research as well as drug testing and other patient studies. The School of Medicine has recruited several imaging faculty, particularly in neurology and psychiatry with others on the way, who are expected to make use of this resource.

Their work will likely get a boost in the next few years from two patents filed by Constable and his team aimed at reducing the time needed to perform MR studies. For the last 40 years, MRI has utilized technology using linear magnetic field gradients to perform spatial encoding. Constable's group has introduced combinations of receiver coils and non-linear magnetic field gradients for encoding that allow more efficient data collection, potentially reducing the time required for MRI by a factor of 2 or more. "Even a factor of 2 would have a huge impact on the cost of MRI, access to MRI and patient comfort," said Constable. "Typically a clinical study is on the order of an hour; this could reduce that to half an hour or even less." The technique could be applied to almost any MRI imaging pulse sequence. Siemens Medical has licensed the patents and has provided almost $1 million worth of hardware to support efforts to bring this new approach to clinical settings.

Under the leadership of **John Krystal,** M.D., the department of psychiatry has made ample use of the MRRC in its translational research efforts to unravel the mechanisms underlying conditions such as schizophrenia. **Alan Anticevic,** PH.D., associate research scientist in psychiatry, is part of a group of researchers who use pharmacological neuroimaging and computational modeling to examine large-scale brain functioning. Their approach, reported online ahead of print in the *Proceedings of the National Academy of Sciences*, showed that disruption of a molecular signaling mechanism within larger neural systems may contribute to the symptoms of schizophrenia.

Anticevic recently received a prestigious $1.8 million NIH Director's Early Independence Award to continue this line of inquiry in a project that combines three complementary approaches—clinical neuroimaging of patients; pharmacological neuroimaging; and a mathematical model developed on the level of single neurons—to understand the mechanism underlying the cognitive disturbances in schizophrenia. "Cognitive disturbances are poorly treated, not well understood, and a source of functional impairment; and yet we don't really know what causes them," he said. "If we can understand the mechanisms behind this problem, then we can begin to understand how to develop better treatments in a truly mechanistically derived fashion," he said.

The MRRC will be a key site for Anticevic's research, a prospect that he looks forward to. "The entire center continues to be a fantastic resource, all the way from the MR technicians to the leadership," he noted. "The scanners are cutting-edge, which really allows investigators to push the envelope, and I can readily interface with the technology and receive technical support when I need it."

The center offers regular seminars in bioimaging, fMRI and neuromolecular imaging for those who would like to learn more about imaging applications for research. The schedule can be found online at http://mrrc.yale.edu/home/seminars/index.aspx. Information about getting started with research ideas or protocols can be found at http://mrrc.yale.edu/users/index.aspx.

Yale Center for Analytical Sciences Offers a Wealth of Collaborative Opportunities

When the Yale Center for Analytical Sciences (YCAS) was established in 2010, the vision was to create a center that would incorporate a high level of both academic excellence and leadership as well as a range of professionals who could facilitate and implement translational research. Since then, YCAS has been serving the needs of the medical campus by expanding both services and staff. Last year, consultations with the center—about 400 of which were first-time discussions with investigators—led to 90 grant applications and about 90 publications. "We're excited because we're seeing both junior and senior investigators who are getting funded after working with us," said **Peter Peduzzi**, PH.D., professor of public health (biostatistics) and director of YCAS.

"For us to support investigators and have adequate staff we have to understand what the needs are and have a little bit of lead time, so we geared up very quickly to accommodate that demand," said **Paul Cleary**, PH.D., dean of the School of Public Health, which supports YCAS along with YCCI and the Cancer Center. "I think it's been a tremendous success."

YCAS has grown rapidly and is still expanding; there are now 18 full-time staff members and over 30 people affiliated with the center, including scientists who offer specialized expertise. For example, **Hongyu Zhao**, PH.D., chair of biostatistics in the School of Public Health, who is affiliated with YCAS, analyzes genomic or proteomic data sets requested through the Center when the need arises. "Peter has done a great job of tying things together," he said.

When it comes to working with YCAS, the earlier the better. As research budgets get tighter, there is pressure on investigators to be more efficient with their funding dollars. At the same time, journals and grant review boards are increasingly demanding careful statistical review. "For proposals to be of the highest quality, have the highest probability of success, and yield the best data, a statistician can often provide invaluable consultation very early," said Cleary. Peduzzi urges investigators to contact YCAS when they're writing the grant to help with study design and make provisions for statistical analysis so that support will be available when the grant comes through.

Peter Peduzzi, PH.D. and James Dziura, PH.D., director and deputy director of YCAS

Peduzzi also cautions against underestimating the time it takes to perform statistical analyses. "There are very few analyses we do that are simple," said **James Dziura**, PH.D., deputy director of YCAS. "A lot of our analyses have to deal with complex issues like missing data, which usually means we're using multiple imputation techniques to establish how robust our conclusions are."

There are a number of ways to collaborate with the center, and its leadership has made an effort to make it accessible to investigators without their having to pay for services before there's been any contact. YCAS's weekly research and design and analytic clinics, which impose no obligation and are free to investigators, offer opportunities to collaborate with the center's statisticians on research and study design questions, or to seek help in making sense of data that have been collected. There are spots for four research and design and two analytic clinics each week; to date, they have rarely been fully booked. "The clinics have grown significantly in popularity," comments William **Casey King**, PH.D., executive director of YCAS. "We started with one research and design clinic and one analytic clinic, and have since doubled each in response to the tremendous demand for our services. We are always looking for new ways to better meet the needs of the research community." The center also has office hours by appointment, offering investigators the opportunity of working with a biostatistician whose expertise matches their needs. The YCAS website has a list of available hours and expertise so that researchers can find the right person to suit their statistical needs.

"YCAS can give statistical input from the very get-go, which is the way it needs to be done to work well," said **Roy Herbst**, M.D., PH.D., chief of medical oncology and associate director of translational research for the Yale Cancer Center and professor of medicine (medical oncology) and of pharmacology, who has worked with the center on grants both large and small.

YCAS collaborates with a number of such other centers as the Center for Interdisciplinary Research on AIDS, the Yale Liver Center, and the Diabetes Research Center. It has built cores for the Cancer Center Support Grant; the recent renewal of the $11.5 million Yale SPORE in Skin Cancer grant; and a large SPORE in Lung Cancer grant that was recently submitted. "YCAS is an extraordinary resource that allows us to get the statistical support we need for projects in oncology," said Herbst. "We needed to have three different statisticians involved in the program and they were all coordinated through YCAS. I've been very impressed by how well that's worked."

"We're constantly revisiting the model, rethinking what services we should provide, and how to provide them," said Cleary. "We encourage people from all departments to give us their ideas and feedback because scientists in different areas have different needs and perspectives. We try to accommodate those."

YCAS prides itself on the intellectual contribution it makes to Yale research projects. "We're really excited about the scientific collaborations we're part of," said Peduzzi. "Our mission is to create a world-class center full of collaborative possibilities between statistical scientists and researchers so we can really change the way science is done on the Yale campus."

"Our mission is to create a world-class center full of collaborative possibilities between statistical scientists and researchers so we can really change the way science is done on the Yale campus."

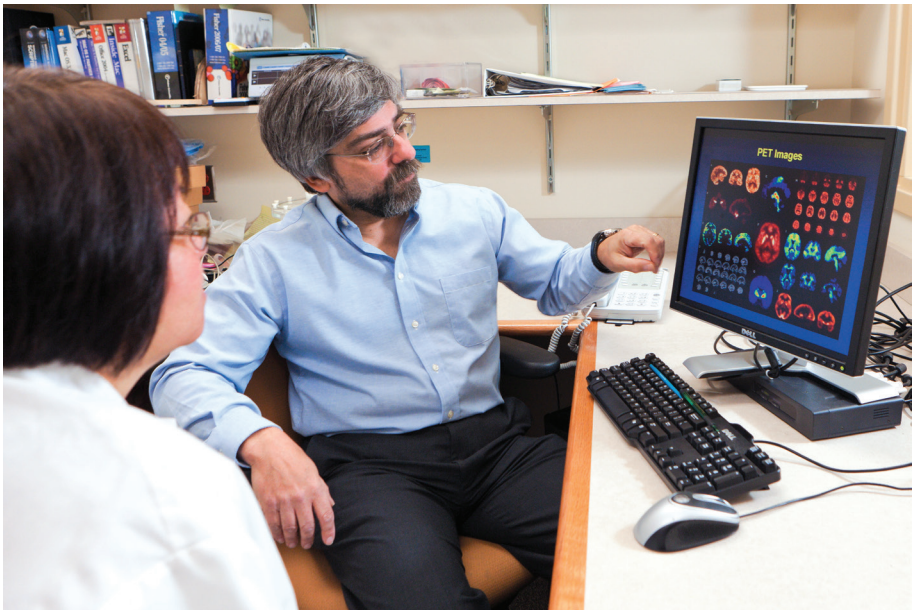
How to Work with YCAS

Research and design clinics are held every Monday and Wednesday from 12–2 p.m. at 300 George Street, Suite 555. To schedule an appointment, contact the center at ycas@yale.edu.

To schedule office hours or an analytic clinic, visit http://publichealth.yale.edu/ycas/officehours/index.aspx. You can choose a biostatistician based on area of expertise, and book appointments online.

PET Research Center Moves beyond the Brain

Since it opened in 2007, Yale's state-of-the-art Positron Emission Tomography (PET) Research Center has been the site of many brain imaging studies to understand the mechanisms underlying neuropsychiatric illness. PET uses novel radioactive drugs (radiotracers) given in trace doses to measure quantitatively a wide range of physiological and pharmacological functions in human beings and research animals. Investigators are now making use of the center for studies in cancer and diabetes, illustrating the versatility of this resource as well as its faculty and staff.



Richard Carson, PH.D., director of the Yale PET center

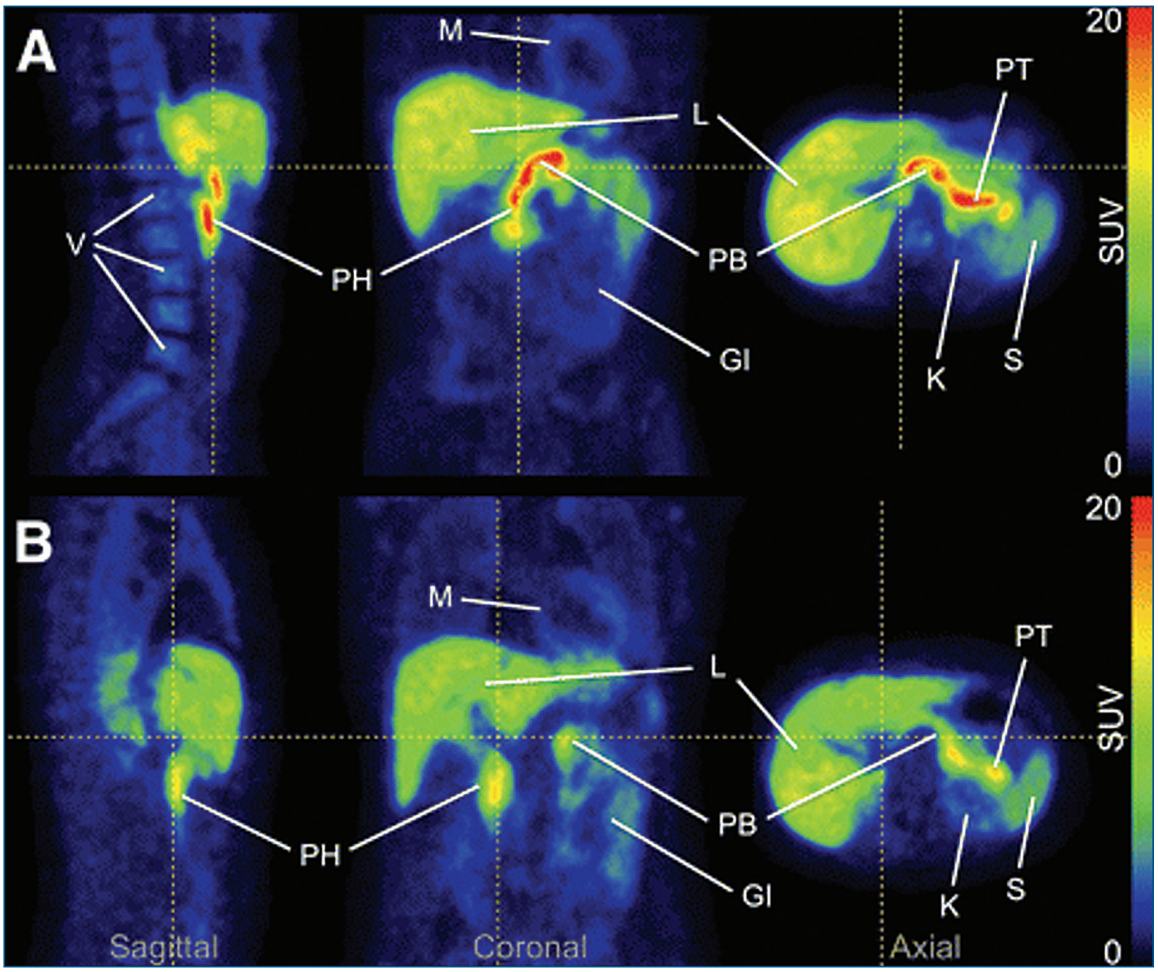
The recent acquisition of two additional scanners, one for use in human subjects and another for small animals—bringing the total to five scanners—has been critical in allowing the center to expand into cancer research. PET is often used in clinical settings to detect and monitor cancer, but there has been a shortage of novel radiotracers used in cancer research. The center is working with investigators from therapeutic radiology to develop tracers that measure hypoxia in tumors in both humans and rodents. Fluoromisonidazole, a tracer that is sensitive to the oxygen content in tissue, will be used in multiple scans to determine the effect of radiation therapy on the hypoxic status of tumors. "We use quantitative imaging to tell us about the cellular and molecular physiology and how that changes with treatment or when comparing patient populations to controls. We do this very well in the brain, and our vision is to do this just as well in cancer," said **Richard Carson,** PH.D., director of the Yale PET Center.

Cancer presents different challenges than brain disorders because tumors occur all over the body. In the case of lung cancer, for example, breathing causes the tumor to move, blurring its image. The center's approach to this problem involves adapting some of the technology used for brain imaging—such as tracking head motion—and applying it to the lungs. **Chi Liu,** PH.D., 2011 YCCI Scholar, and assistant professor of diagnostic radiology and of biomedical engineering, recently joined the center to further these efforts, bringing expertise in correction and modeling for thoracic motion. "We view some of our imaging data as six-dimensional," said Carson. "There are three spatial dimensions; the time dimension for the tracer kinetics; and respiratory and cardiac motion [which] each add a new dimension to the problem."

Diabetes is another area in which PET imaging has been successfully applied. Insulin-producing beta cells are dispersed in islets throughout the pancreas, which makes quantifying them a challenge. **Gary Cline,** PH.D., associate professor of medicine (endocrinology), **Kitt Falk Petersen,** M.D., associate professor of medicine (endocrinology), and their colleagues were recently able to measure the loss of pancreatic islet cells in diabetic patients, which may help in the development of drugs to stop or slow the death of these cells. The team studied healthy patients and those with type 1 diabetes using a radiotracer targeted for the vesicular monoamine transporter type 2 (VMAT2), which is co-expressed with insulin in beta cells. PET scans were used to measure the binding of VMAT2, showing that it was 40 percent lower in diabetic patients than in healthy controls. The study appeared in the June 2012 issue of the *Journal of Nuclear Medicine*. Cline is currently collaborating with **Kevan Herold,** M.D., professor of immunobiology and YCCI's deputy director for translational science, in evaluating different immunotherapies to halt the loss of beta cells in early-onset diabetes. He is also extending his work to type 2 diabetes.

Before working with the PET Center, Cline had used NMR or MRI to conduct clinical research. "Working with the PET Center was kind of a shift in thinking in terms of radioactive isotopes, which for these purposes is much more sensitive for detecting receptor-targeted imaging approaches," said Cline, adding that the center's staff can help with all the steps along the way when conducting research at the facility. "The PET Center's staff and infrastructure is remarkable," he said. "For a person like me who was completely new to PET, the constant input from Rich Carson, the medical staff and the PET researchers really made this research possible."

The PET Research Center conducts ongoing work to develop new tracers, which can be a time-consuming process that involves the interplay between chemistry, biology, pharmacology, and pharmacokinetics. **Yiyun Henry Huang,** PH.D., associate professor of diagnostic radiology and director of chemistry for the PET Center, focuses on developing novel radiotracers for the center; he has developed two unique tracers for kappa-opiate receptors that are being used to study depression and other diseases. One tracer acts as an antagonist while the other acts as an agonist. Many receptor proteins can exist in two states: high affinity, the active state, in which an agonist will bind; or low affinity, in which it won't bind. The new tracers allow researchers to measure the total number of receptors as well as the number in the active state. "We believe this could be a powerful tool, since some diseases are not just reflected in changes in the number of receptors, but also how many of them are in the active state and how that changes with time," said Carson.



PET images from Cline and Petersen's study showing (A) high uptake of a tracer targeting VMAT2 in the pancreas and (B) reduced uptake in a type 1 diabetes patient.

In addition to the two new scanners, the center has added four new hot cells, making it more efficient to develop and produce new radiotracers. It expects to add an additional PET CT scanner dedicated to rodents in the spring. For those who would like to learn more about the PET Research Center's applications, the center sponsors a monthly series called PET Talks. Information is available at http://petcenter.yale.edu/research/pettalks.aspx. Investigators who would like to initiate a human PET research protocol should visit http://petcenter.yale.edu/InformationforInvestigators/index.aspx, which offers a guide and lists the main steps involved.

Scholar Day Retreat

YCCI will host the second annual Yale Center for Clinical Investigation Scholar Day Retreat on Friday, March 1, 2013. Our speaker this year is Ray Dolan, Mary Kinross Professor of Neuro-psychiatry at University College London (UCL) and Director of the Wellcome Trust Centre for Neuroimaging at UCL. Professor Dolan is the author of 400 original papers and one of the most cited scientists in the world in the field of neuroscience and behavior. He will be speaking on "Tips for Constructing a Successful Application and Careers in Academia."

Open to all trainees in the Schools of Medicine, Nursing and Public Health, this half-day event starts at noon in the foyer of The Anlyan Center. It will also feature poster presentations and short oral presentations from a number of scholars and trainees. Additional details, including instructions for submitting abstracts, are available at http://ycci.yale.edu/news/2ndscholardayretreat/index.aspx.

New Training Initiative for Research Staff and Faculty

YCCI is pleased to announce that our popular monthly Lunch and Learn sessions will expand to include a monthly Coffee and Conversation series. These series will address a broad range of topics related to clinical trials management and are open to all clinical research faculty and staff.

To view the schedule, visit http://ycci.yale.edu/education/index.aspx. For more information, contact LaToya Howard at latoya.howard@yale.edu or call 737-3661.

Biospecimen Management Coming Soon

OnCore's biospecimen management capability will soon begin to roll out, with the Yale Cancer Center Core lab the first to implement the new platform.

The new module will be integrated with the clinical trial management system, enabling the tracking of fully bar-coded specimens and allowing for data capture of collection, processing, storage, and shipment information. The module also connects the regulatory aspects of sample management with the actual specimens, enabling investigators to ascertain how the samples may be used.

The new functionality is expected to facilitate the launch of a sample repository of healthy volunteers and to help manage large animal specimens. Its flexibility means it can be used not only for large multicenter studies but also for smaller individual studies. Its capabilities include:

- Inventory management
- Requisition and distribution management
- Correlative study sample management
- Flexible reporting capabilities

Enterprise-wide implementation is expected to take over a year because each of Yale's labs has its own samples and data that must be imported into the new system. "We've been wanting to have biospecimen management capability for some time, but it made sense to integrate it with our clinical trials management system and the process required careful planning," said Kevan Herold, M.D., YCCI's deputy director for translational science. "It will be an enormous resource for investigators."

New Associate Director of Research Administration Brings Scientific Expertise to YCCI

YCCI welcomes research scientist **Helen Seow**, PH.D., as associate director of research administration as of September 10, 2012. Seow, who has been a member of Yale's research faculty since 2006, brings expertise in oncology, pharmacology, drug discovery, and preclinical investigation to her new role. In her previous position, she led and managed several research projects to evaluate new anticancer agents. Under her leadership, the compound KS119 was identified as a potential anticancer agent for the treatment of solid tumors. She also supported research efforts to determine the mechanism of action of the anticancer drug laromustine, which was evaluated in a phase III clinical trial for use in patients with acute myelogenous leukemia. Seow has collaborated on the design and development of novel cell-based assays for targeting clinically identified drug-resistant phenotypes. She is also associate editor of *Oncology Research*.

In her new position, Seow will oversee YCCI's scientific operational and research administration, evaluating current programs to determine how they can be improved from the scientific perspective. She will be also be involved in developing and implementing programs that link clinical and translational research with basic science research, and will oversee the biospecimen repository that is being developed in conjunction with OnCore. "I'm looking forward to becoming more involved in the clinical world and moving discoveries from the bench to the bedside," she said.

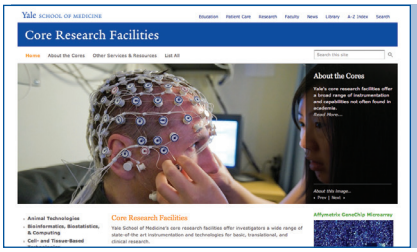
New Associate Director of Clinical Trial Resources Will Provide Additional Support for Researchers

As part of a reorganization of YCCI's administrative structure to better meet the demands of Yale's clinical and translational research enterprise, Kelly Anastasio joined the center as associate director of clinical trial resources in September.

Anastasio has spent the last six years as clinical research and reimbursement manager in the department of orthopaedics, where she was responsible for managing clinical trial activity including budget development, contract negotiations, clinical trials matrix, and operational flow. Her outstanding contributions have had a positive impact on the department's performance, contributing to record levels of accomplishment and she was awarded the Leadership in Research Billing Compliance Award by Yale Medial Group Compliance in 2009. Anastasio is a certified Professional Medical Coding Curriculum instructor whose previous experience includes teaching for the Medical Coding Academy in Branford, CT for the past six years and at The Coding Center of Connecticut prior to that. Her organizational and managerial skills will be an asset to YCCI as it seeks to broaden its ability to provide these critical services to investigators across the health campus.

YCCI offers a wide array of services and resources to support all aspects of clinical and translational research. YCCI staff members help Yale investigators navigate the complex research landscape, lessening administrative burdens and ensuring that studies are conducted safely and efficiently. In her new role, Anastasio will help to pinpoint resources for investigators and develop tools that allow them to transform research ideas into completed studies. She will apply her expertise not only to getting studies up and running, but to sustaining them as well. She will also play a major role in the implementation of OnCore, Yale's clinical trials management system, helping to ensure a smooth and compliant transition across departments in the School of Medicine and YNHH.

"Kelly's broad knowledge and skillful experience in managing all aspects of clinical trials will be a critical asset to YCCI and Yale Medical School overall," said **Steven Gentile**, associate chair of finance and administration for cardiovascular medicine in the Department of Internal Medicine. "Her drive and passion for clinical research is unmatched; and I expect she will be instrumental in helping the Center reach a new level of expertise and achievement."



How to Find Core Resources

To view the wide range of instrumentation and technology available to Yale investigators, visit http://medicine.yale.edu/cores/index.aspx. This website contains a list of resources organized into clusters that make it easy to locate technologies and services. It also contains a handy online tool for scheduling resources.

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