Yale Center for Clinical Investigation

November 2008

2 Church Street South, Suite 114 | New Haven, Connecticut 06519 | p 203.785.3482 | f 203.737.2480

Core Research Facilities Offer Investigators High-Tech Equipment and Expertise

Some of the most valuable tools at the disposal of YSM investigators in clinical and translational research can be found within the core research facilities, a wide-ranging array of cutting-edge instrumentation and technologies not often found at academic institutions. The services and resources offered by the cores provide investigators with opportunities to utilize sophisticated equipment and expertise in such areas as:

- Biostatistics and bioinformatics
- Drug discovery and development
- Genomics and proteomics
- Human specimen analysis
- Imaging
- Animal resources

The core research facilities reflect the medical school's investment in and commitment to providing researchers with the advanced technology necessary to carry out today's high-tech research. The strategic planning initiative that led to the formation of ycci, however, also revealed the need for a central mechanism for organizing and coordinating the research cores. The Clinical and Translational Science Award (CTSA) granted to YSM in 2006, combined with strategic partnerships with the School of Medicine, the Yale Child Study Center and the Yale Cancer Center, has allowed YCCI to leverage this investment to expand and integrate the core resources to stimulate the growth of clinical and translational research. YCCI supports the cores through strategic investment in equipment, equipment upgrades, pilot funding, and staff and leadership support.

Under the co-direction of Carolyn Slayman, PH.D., Sterling Professor of Genetics and Deputy Dean for Academic and Scientific Affairs, and Kevan Herold, M.D., professor of immunobiology and a member of the Human Translational Immunology program, the core resources have been organized into clusters that enable investigators to easily locate the technologies and services applicable to their projects. A new website was recently launched (http://medicine.yale.edu/cores/) that includes descriptions of core services, contact information, and directions for using the core facilities, including a link to the Yale Resource Scheduler (http://scheduler.yale.edu/). This feature allows researchers to schedule core facilities online (see article on page 6).

Photo by Robert A. Lisak

YCCI funded the purchase of the Waters nanoACQUITY UPLC® System, which provides high resolution chromatography for protein identification and characterization.

Because the research cores encompass a wide range of facilities, their structure and organization are still a work in progress. For example, Drug Development, Cognition & Behavior, and Physiology & Metabolism are under development and will be added in the coming months. Meanwhile, new technologies have been acquired for existing core facilities,

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Inside This Issue

Photo credit: Terry Dagradi

Director's Corner

When YCCI was established, it was with the idea of bringing together all the tools necessary to smooth the way for investigators to carry out clinical and translational research. We were very fortunate in that many of the resources necessary to make that happen already existed on campus—the challenge has been to organize and integrate them so that they are easily accessible to those interested in conducting research, regardless of their level of experience or expertise.

I think the Core Research Facilities are an excellent example of this principle in action. Many of them are well-established facilities that have been offering investigators an incredible choice of state-of-the-art technology for years. What we've tried to do is take that choice to the next level by funding upgrades, recruiting experts and developing services that will make it easy for investigators to find and utilize the variety of technology and skills available at YSM.

The Cores' resources represent an opportunity for us not only to expand clinical research but also to integrate our strengths in basic science with translational research. We would like to bring investigators together in ways they haven't utilized before, and we think the cores are an ideal way to accomplish that. We're especially excited that the West Campus will enable us to expand our resources to develop new technologies and will create opportunities to drive the connections between basic and clinical science. We believe that our long-term success depends on this collaboration and we look forward to working with investigators to make sure it happens.

Robert Sherwin, M.D.
YCCI Director

Featured Events:

Bioinformatics Workshops

Pathway Analysis Programs
November 17, 3:00 p.m.

Automatic Protein Docking
December 10, 3:00 p.m.

see top of Events Calendar on page 2 for details

Core Resources Issue

Written by Jill Max

Events Calendar

Bioinformatics Workshops

November 17, 3:00 p.m. to 4:00 p.m.
Pathway Analysis Programs
presented by Can Bruce, PH.D.,
Associate Director of Bioinformatics Resource, Keck Biotechnology Resources Laboratory
TAC N203, 300 Cedar Street

December 10, 3:00 p.m. to 4:00 p.m.
Automatic Protein Docking
presented by Yong Kong, PH.D.,
Associate Director of Bioinformatics Resource, Keck Biotechnology Resources Laboratory
TAC N303, 300 Cedar Street

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 encourage all faculty and staff to attend.

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

November 11, noon to 1:00 p.m.
The Regulation of Surface Colonization by *Pseudomonas aeruginosa*
presented by Thomas Scott Murray
TAC N203, 300 Cedar Street

November 24, noon to 1:00 p.m.
Faculty Development and Promotion
presented by Linda Bockenstedt
TAC N303, 300 Cedar Street

December 9, noon to 1:00 p.m.
Community-based Research on Childhood Obesity
presented by Margaret Grey
TAC N203, 300 Cedar Street

January 13, noon to 1:00 p.m.
Genetic Testing
presented by Maurice (Jeremiah) Mahoney
TAC N203, 300 Cedar Street

Video Broadcasts on Obesity

CARE will sponsor two video broadcasts of lectures on obesity from the UCONN Center for Health, Intervention, and Prevention. Lunch will be provided. Please RSVP to Alycia Santilli at alycia.santilli@yale.edu or 785-7651.

November 13, 12:30 p.m.
Rajiv Kumar and Brad Weinberg, Shape Up Rhode Island
Yale School of Public Health
135 College Street, Room 229

December 4, 12:30 p.m.
Christina Economos
Yale School of Public Health
135 College Street, Room 229

Exploring the Depths of the Genome and Proteome

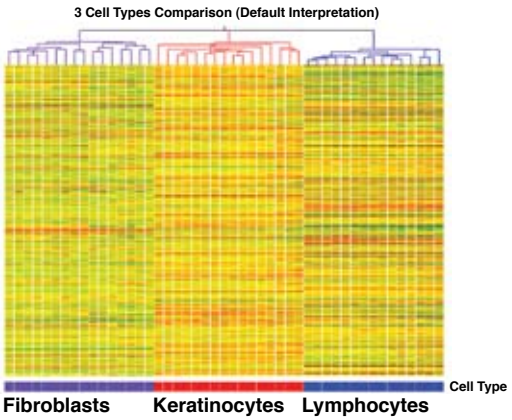
Biomedical research increasingly depends on expensive instrumentation to understand the roles of genes and proteins in disease. Analyzing DNA sequence variations and differential mRNA and protein expression associated with diseases can lead to more accurate diagnosis and prognosis; molecular classification of disease subtypes; deeper understanding of the molecular basis of diseases; new therapeutics; and personalized medicine.

At Yale, the W.M. Keck Foundation Biotechnology Resource Laboratory provides investigators with help in all aspects of genomics and proteomics research. The Keck Lab was founded in 1980 to bring a wide range of biotechnologies within reach of Yale investigators. While Yale requests always have priority, non-Yale requests ensure that when the University's demand is low, Keck can still maintain maximum productivity that benefits all users. With 50 staff and more than 100 instruments, Keck (http://keck.med.yale.edu/) provides more than 175 genomic, proteomic, biophysics, biostatistics, bioinformatics, and high-performance computing services. In 2007, these included 255,559 services to 429 Yale and 564 non-Yale investigators at 280 institutions, with 92 percent of requests coming from Yale. Grant reviews typically point to the high quality of this unit and its contributions to biomedical research with such comments as, "the Keck Lab is the premier biotechnology resource center in the world," and, "the contribution of this lab to biomedical research in the U.S. has been and will continue to be enormous."

As verified by surveys, Keck provides an unusually wide range of biotechnologies. "If Yale investigators take advantage of what Keck offers when they're writing grant applications, I believe they'll have a very large competitive advantage," said Ken Williams, PH.D., director of the Keck Lab.

Keck's instrumentation has been positively leveraged by grants, including four NIH Center grants or contracts awarded since 1998. These grants fund technological and biomedical research and subsidize service charges for many Yale investigators. Since FY03 the Keck Lab has also provided core resources for five other NIH Center grants, while Keck staff members have submitted 15 other successful grants or administrative supplements and have directly supported 11 other successful user grants – usually by providing staff members with expertise in the technologies needed to complete the specific aims of the grant. Keck has also supplied supporting letters, advice and methods, as well as edited sections of many other successful Yale grant applications from which the lab did not derive funding.

Keck genomics technologies include next-generation and conventional DNA sequencing, SNP genotyping, oligonucleotide synthesis, and both Affymetrix and Illumina microarray analysis. Using Affymetrix genotyping, Josephine Hoh, PH.D., associate professor of epidemiology and ophthalmology and visual science, and her group associated an SNP in human complement factor H with the occurrence of age-related macular degeneration.[1] This research was recognized as exceptional by the Faculty of 1000, an organization that highlights important publications in biology; it was also mentioned by the Secretary of Health and Human Services at the American Society for Human Genetics in 2005. In another *Science* publication,[2] Arya Mani, M.D., assistant professor of medicine, identified an LRP6 mutation associated with early coronary disease and metabolic risk factors.



Microarray technology shows how different cell types are distinguished by global gene expression in Bale's study of basal cell carcinoma.

Affymetrix gene expression analyses have been used in a trial of sirolimus, an immunosuppressant drug candidate for treating basal cell carcinoma. Allen Bale, M.D., professor of genetics, studied the drug's effect on a pathway involved in cell differentiation. After applying the drug to the skin of patients genetically predisposed to skin cancer versus controls, Bale and colleagues looked for changes in gene expression. "Our results so far indicate that you can really use molecular instead of clinical endpoints in an early clinical trial," he said.

As personalized medicine advances, patient genotypes or gene expression profiles will aid in optimizing disease treatment. The Keck Lab's next-generation DNA sequencing service will facilitate reaching this goal. Matthew State, M.D., PH.D., Harris Associate Professor of Child Psychiatry in the Child Study Center and Director of the Program in Neurogenetics, is already using this technology to determine expression profiles of human adult and fetal brain regions.

Proteomics has become increasingly important in recent years because there is often poor agreement between mRNA and protein expression data. Furthermore, genomic technologies

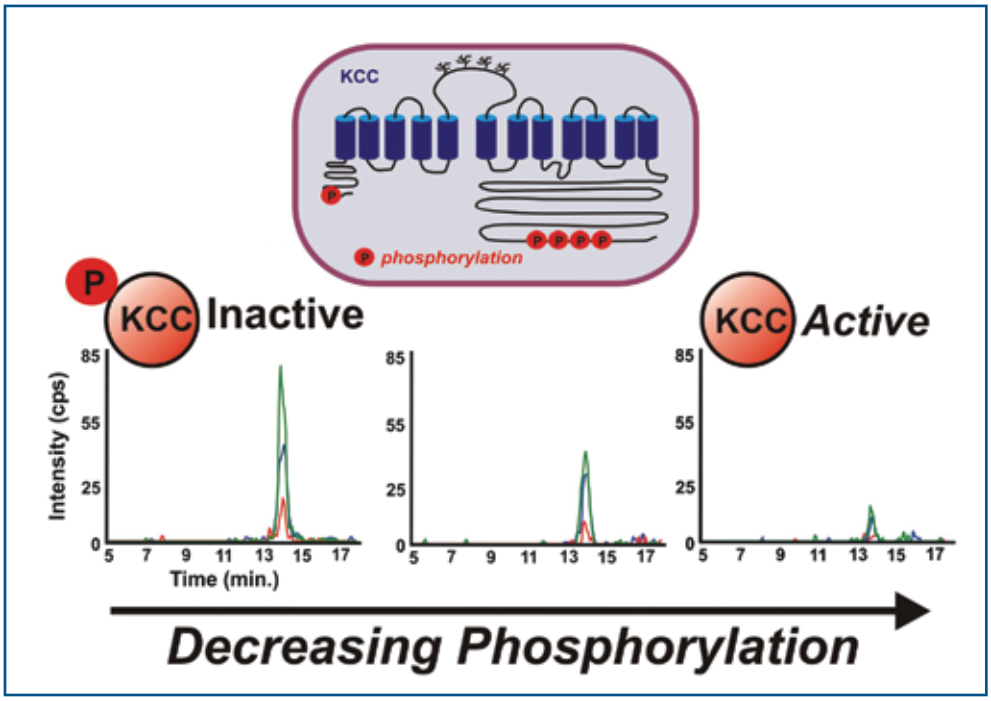
are unable to predict the occurrence and extent of such protein post-translational modifications (PTM) as phosphorylation, which occurs on more than 30 percent of human proteins and often modulates protein function. Proteomic challenges are well illustrated in plasma. Each of the ~500 plasma proteins is estimated to have ~100 variants due to splicing, processing and ptms. Added to these 50,000 variants are ~21,000 other proteins in the human proteome that may leak into plasma. Each of these proteins in turn may have ~50 variants, thus adding ~1,000,000 potential proteins that are mixed with perhaps ~10 million immunoglobulin sequences. Compounding this challenge is the ~10^{10} range in plasma protein concentrations. Even when the maximum amount of plasma that can be accommodated by a given technology is analyzed, many proteins are still present in such low concentrations that they cannot be detected by current technologies. Researchers are, however, finding ways to increase the power of proteomics technologies. For example, iTRAQ™ (multiplexed isobaric tagging technology) quantifies ~500 proteins per sample. Its capabilities can be further enhanced by prior immunological depletion of abundant proteins; by chromatographic or other fractionation; and by enriching for proteins with specific PTMS, thus enabling analyses to reach deeper into proteomes.

Richard Lifton, M.D., PH.D., Sterling Professor of Genetics, and his colleagues use genomics to understand the genetic basis of hypertension. One member of the Lifton laboratory, associate research scientist Jesse Rinehart, PH.D., has recently complemented these approaches with cutting-edge proteomics. Rinehart is studying a potassium chloride cotransporter (KCC) that is dysfunctional in sickle cell anemia. He and his colleagues have discovered that KCC phosphorylation regulates cell volume, a finding that sheds light on the disease process and on the ways in which blood cells work. "The resources of the Keck Lab have helped us obtain fantastic insight into the disease process," said Rinehart.

Rinehart has used Keck resources to help visualize, process, analyze and interpret massive data sets. He utilized Keck's Bioinformatics and High Performance Computing Resources to help develop a strategy to identify protein phosphorylation sites in large data sets.

The Bioinformatics and Biostatistics Resources provide users with access to open source, commercial and in-house software. "A high-density microarray can generate millions of features—too many to look at or to process visually," said Hongyu Zhao, PH.D., director of the biostatistics resource and co-director, together with Mark Gerstein, PH.D., of the bioinformatics resource. "We help people make better sense of their data." Zhao, Gerstein and colleagues develop statistical tools to interpret genome-wide association studies, improve algorithms to identify disease biomarkers, and integrate different types of data to analyze transcription and signaling networks to ascertain events at the physiological level. They encourage investigators to contact them with questions during the grant preparation or study design phases to take advantage of their expertise in these resources.

"We've tried to set up everything we can possibly think of to help clinical investigators who may not have experience with state-of-the-art genomics and proteomics technology to give them as much support as we can so they'll succeed," said Williams.



The phosphorylation sites of the K-Cl cotransporters (KCC) are shown in the context of a topology diagram of the protein (top). KCCs transport potassium and chloride out of the cell and are activated by dephosphorylation. MRM experiments (bottom) show for the first time which residues are dephosphorylated to activate the protein. These results from studies by Lifton, Rinehart and their colleagues reveal the details of a widespread cellular process, as well as suggest a possible mechanism for KCC dysfunction in such diseases as sickle cell anemia.

Genomics and Proteomics Databases Speed Data Analysis

The Keck Lab and the Center for Medical Informatics, directed by Perry Miller, M.D., PH.D., developed the Yale Microarray Database, which archives microarray data and provides tools for retrieval and analysis; and the Yale Protein Expression Database, which archives, manages and quantifies protein expression data. Instead of sifting through hundreds of text pages, researchers now access their proteomics data via the Internet in a layered format that begins with an overview and allows them to click on proteins about which they wish to learn more.

1. Klein, R., Zeiss, C., Chew, E., Tsai, J., Sackler, R., Chad, H., Henning, A., SanGiovanni, J., Mane, S., Mayne, S., Bracken, M., Ferris, F., Ott, J., Barnstable, C., Hoh, J. (2005) Complement factor H polymorphism in age-related macular degeneration. *Science* 308: 309-452.

2. Mani, A., Radhakrishnan, J., Wang, H., Mani, A., Mani, M., Nelson-Williams, C., Carew, K., Mane, S., Najmabadi, H., Wu, D., Lifton, R. (2007) LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science* 315:1278-82.

Calling All Neuroscientists

Thanks to a Microarray Center Grant in Neuroscience (PI: shrikant.mane@yale.edu), the Microarray Resource offers service charge discounts for neuroscience projects. Discounts are also available for neuroproteomics research that falls within the mission (http://info.med.yale.edu/nida-proteomics/mission.htm) of the NIDA Neuroproteomics Center (PI: kenneth.williams@yale.edu, co-PI: angus.nairn@yale.edu).

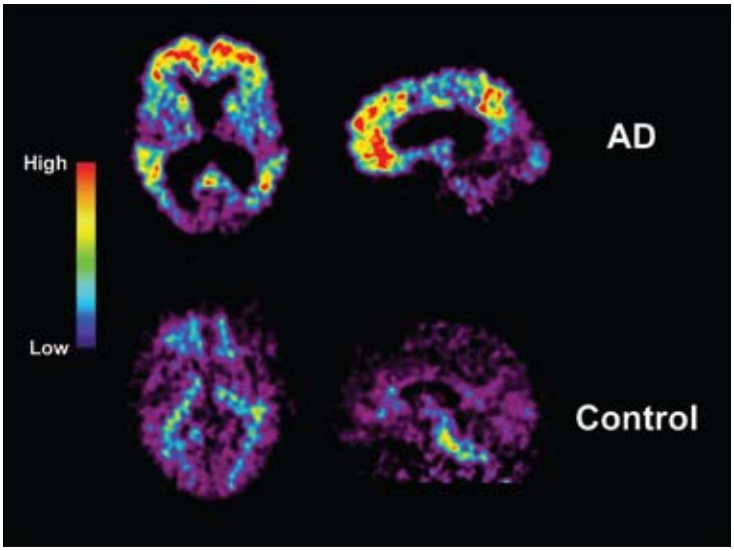
Using Imaging Technology to Track and Visualize the Body's Inner Workings

Yale's imaging core facilities are being used to explore virtually every organ system in the body as well as to develop a variety of therapeutic approaches through interdepartmental and interdisciplinary collaborations.

The Positron Emission Tomography (PET) Research Center, which opened last year in a new facility on Howard Avenue, has been primarily busy with brain studies that allow researchers to track a variety of physiological and pharmacological systems. PET technology is sensitive as well as broad—able to measure even very small concentrations of receptors, antibodies and proteins while at the same time allowing researchers to look at blood flow, metabolism and synthesis. "This is a Swiss army knife tool in that we can image many small systems all using the same technology," said Richard Carson, PH.D., professor of diagnostic radiology and biomedical engineering and director of the PET Center. Equipped with one of only 18 PET scanners in the world that can image the human brain at a resolution of 2.5 millimeters and track head movements 20 times per second, the PET Center also houses a whole-body scanner; a cyclotron and radiochemistry lab to produce short-lived radioactive isotopes; and image processing and analyzing technology to help researchers interpret data. "We have a team of scientists who are interested in looking at new applications and developing novel radiopharmaceuticals to image unique biochemical or pharmacological pathways," said Carson. Visit http://petcenter.yale.edu/ for more information.

Christopher van Dyck, M.D., associate professor of psychiatry and neurobiology and director of the Alzheimer's Disease Research Unit, has used PET Center facilities to image the brains of middle-aged relatives of Alzheimer's patients. He is looking for differences in amyloid deposits in the brains of those who have the *ApoE4* gene, the major genetic risk factor for Alzheimer's disease, compared to those in relatives who don't carry the gene to see whether signs of the disease can be detected before symptoms appear. Van Dyck is also involved in multicenter trials of a number of anti-amyloid therapies, including intravenous immunoglobin (IVIG), in the hope of slowing down the progression of the disease and even of being able to prevent it in the future. "Not only are we assessing these individuals cognitively in their daily functioning, but we can do a PET scan before and after treatment and see exactly what's happening with amyloid deposition," he said.

As with many researchers who use imaging studies in their work, van Dyck's studies involve multiple imaging modalities. He uses technology at the Magnetic Resonance Research Center (MRRC) to conduct MRI scans to aid in PET scan analysis, identify the region of the brain he's looking at and compare rates of brain atrophy with active treatment versus placebo. The MRRC has several state-of-the-art imaging systems of differing strengths for MRI; it also offers magnetic resonance spectroscopy (MRS), which gives information about chemical reactions occurring in different organs and changes in metabolism in a variety of disease states. Among these resources are a new state-of-the-art 7T human head scanner—one of the highest field systems for human studies in the world; an ultra-high-field 11.7T system for rodent studies; and a 3T functional magnetic resonance imaging (fMRI) system that is being upgraded to state-of-the-art multi-receiver capabilities. These resources are available to both Yale investigators and investigators from other institutions.



In the top two slides from van Dyck's study (upper left is horizontal or transaxial; upper right is mid-sagittal) the yellow and red colors correspond to the greatest binding of the tracer to amyloid deposits. High uptake levels appear in those areas known to have amyloid plaques and to be most important for cognitive function (the so-called association cortices: frontal, parietal, etc.), with relative sparing of the primary motor and sensory cortices as well as the cerebellum. The healthy control shows only minimal uptake in the white matter and brain stem.

Many of the projects done at the center involve functional imaging studies that examine such features as the amount of neuronal activity in the brain. MMRC co-director Todd Constable, PH.D., director of MRI research and professor of diagnostic radiology and biomedical engineering, works with van Dyck and other investigators who are using anatomical and functional MRI to study the brain. "If investigators have a problem where imaging might play a role, they should contact us about doing some type of collaborative work," said MRRC director Douglas Rothman, PH.D., professor of diagnostic radiology and biomedical engineering, and MRS research director. "We're very open to that, including in areas where we don't currently have research going on." In addition to Constable and Rothman, the MRRC has seven faculty members who specialize in different areas of MRI, ranging from molecular imaging and cell tracking to the development of novel MRI technology.

Figure 1

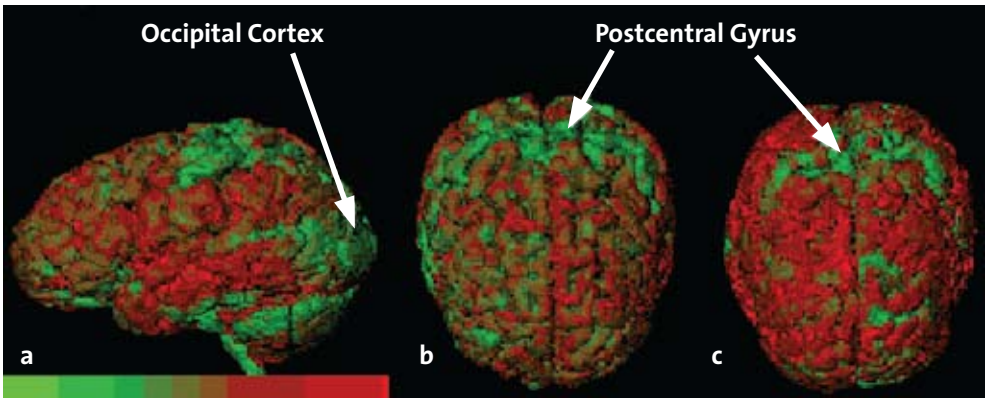


FIGURE 1: A mathematical strategy based on two coupled differential equations developed by Duncan's group is used to locate automatically the bounding surfaces between i) the gray and white matter and ii) the gray matter and cerebrospinal fluid (CSF) from a three-dimensional magnetic resonance image of a human subject. The thickness of the gray matter in the cortex is color coded as a range between 1mm (brightest green) to 4mm (red).

One example of work being carried out in a field that hasn't traditionally used bioimaging is a project by Alan Dardik, M.D., PH.D., assistant professor of vascular surgery, who has worked with Constable and MRRC engineers to develop implantable coils for blood vessels. Dardik is using the coils for ultra-high-resolution measurements of flow turbulence in models of arterial stenosis. Another innovative use of MRI and MRS technology has been part of a collaborative project between James Duncan, PH.D., Ebenezer K. Hunt Professor of Biomedical Engineering and professor of diagnostic radiology, and Dennis Spencer, M.D., Harvey and Kate Cushing Professor of Neurosurgery. The project involves the development of image-guided neurosurgical techniques for use in treating severe epilepsy. Duncan is also working with Constable, Rothman, Hoby Hetherington, PH.D., professor of neurosurgery and diagnostic radiology, and Robin de Graaf, PH.D., associate professor of diagnostic radiology, to develop methods of integrating state-of-the-art anatomical, functional and chemical imaging. Spencer is able to overlay these images in the operating room to help locate epileptogenic regions in the brain and avoid brain regions associated with motor and language function. This multi-stage invasive surgery can cause such brain changes as swelling, so the team members have also developed image processing and modeling software that updates the images throughout the surgical process. Their hope is to refine the imaging technology and software to the point where surgeons like Spencer might be able to locate and target epileptogenic regions precisely without having to undertake open-brain surgery.

Duncan heads the Image Processing and Analysis Group, which uses software and other tools to help investigators make the most of YSM's imaging technology. The BioImage Suite, for example, which is a processing package unique to Yale but available also to non-Yale scientists, was developed by Xenophon Papademetris, PH.D., assistant professor of diagnostic radiology and biomedical engineering. This software has extensive capabilities in both neuro/cardiac and abdominal image analysis; it is able to focus automatically on selected features (for example, fat distribution in diabetes), so that investigators don't have to painstakingly analyze every slice. The BioImage Suite can also be integrated with other biomedical image processing software. (Visit http://www.bioimagesuite.org/ for more information).

To find out more about core technologies for human, animal and cell imaging, visit http://medicine.yale.edu/cores/imaging.aspx.

Figure 2

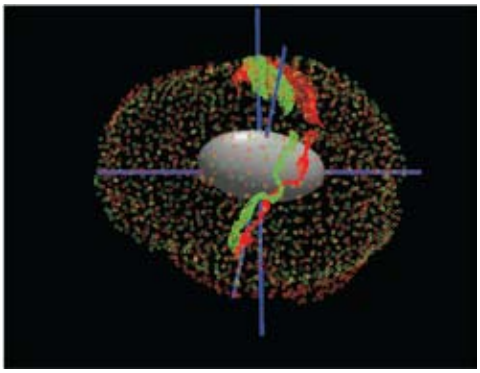


Figure 3

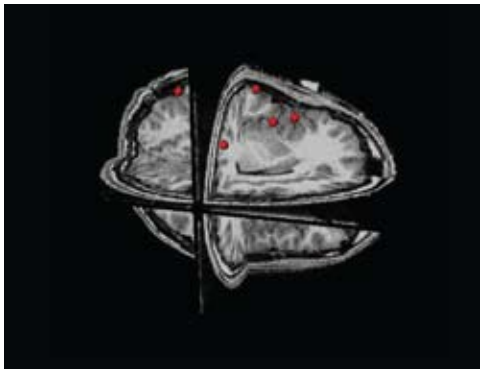
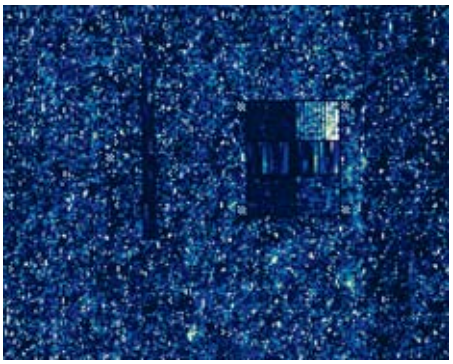


FIGURE 2: Taking the segmented cortical surface results from Figure 1, another algorithm is used to locate 3D "ribbons" representing the central sulci in the human brain. Cortical surface points and the points on the central sulci are used together to warp image data from one subject into nonrigid correspondence with that of another subject in order to compare quantitative measurements across subjects.

FIGURE 3: Part of Duncan and Spencer's image-guided epilepsy surgery project, the locations of a set of anatomical landmarks are shown in red on top of the subject's underlying anatomical MRI scan. These landmarks were used to validate an approach that uses brain surface information and an elastic model of brain deformation to compensate for brain shift that occurs during surgery (which can cause inaccuracies in the surgeon's reference frame used as a roadmap during the procedure).

Core Research Facilities *continued from page 1*



This image shows raw data from an Affymetrix gene expression array. The signal intensity of each tile corresponds to the level of expression of individual genes in the sample. Dark areas represent little or no expression, whereas white areas indicate strong expression.

such as a triple quad mass spectrometer capable of quantifying levels of multiple proteins (Genomics & Proteomics) and equipment to establish a state-of-the-art immune monitoring facility for use in immunomodulatory translational clinical trials (Human Specimen Analysis). "We've invested heavily in cores so that researchers with wide ranges of interest can find the expertise they need," said Slayman.

Developing new research tools and methods is often hampered by the lack of necessary start-up funds, so part of YCCI's pilot award program is aimed at the development of novel clinical and translational research methods. Last year, grants were awarded for research in internal medicine/endocrinology, pathology, nephrology and bioinformatics. The projects that received funding involved utilizing four-angle saturation transfer (FAST)-MRS to investigate mitochondrial function in human muscle; evaluating the effects of the extracellular enzyme ATX as a molecular target for chemotherapy; determining the ability of two urine biomarkers to aid in the differential diagnosis of renal dysfunction; and characterizing pathway functions in leukemia using gene expression data from a large number of studies. In the upcoming year, proposals for pilot projects will be considered on a rolling basis; several projects are currently under review.

The Dean's Workshops, designed to address new developments in biomedical research methodologies and applications, offer an excellent opportunity for investigators to learn more about the application of core services to their research. Two workshops held this fall were devoted to resources available at the Keck Laboratory. A September workshop examined the ways in which such recent developments in genomics as microarrays and high-throughput DNA sequencing are driving new developments in biomedical research and reshaping our understanding of the human genome. The session held in October focused on the ways in which mass-spectrometry tools used in proteomics can shed light on the human proteome. In addition to highlighting the work of individual investigators, the workshops offered opportunities for researchers to meet the directors of the cores.

YCCI plans to improve the utilization of core technologies by organizing a core mentoring committee to be headed by Jordan Pober, M.D., PH.D., professor of immunobiology, pathology and dermatology. The committee will serve as a referral resource to link investigators to the leaders of the appropriate research cores as they develop study protocols. This resource will enable core directors to work with investigators in selecting the experimental approaches best suited to their projects and facilitate interdisciplinary collaboration. It will also provide an opportunity for the committee to identify innovative projects that would benefit from additional funding and resources.

The acquisition of the West Campus, formerly the Bayer HealthCare complex located in Orange/West Haven, will allow for the expansion of biomedical research conducted at Yale and will undoubtedly play a role in the future expansion of the core facilities. Cores already slated for development include siRNA screening, small-molecule screening, and next-generation DNA sequencing.

Researchers are encouraged to contact core directors to find out how core services can benefit their projects, either on a fee-for-service basis or through collaborative arrangements. In addition, most cores are able to support a limited number of free pilot studies intended to collect preliminary data for grant applications. "We want to urge investigators to use the resources offered by cores at any stage of their projects, but contacting resource directors at the earliest stages of planning will help investigators make the best use of what we have to offer," said Slayman.

Resource Scheduler

Faculty and staff can quickly and easily reserve resources, including core facilities, via the Yale Resource Scheduler. YCCI contributed to the development of the scheduler in an attempt to modernize the processes and ease the administrative burden involved in clinical trials. The scheduler can be used to help manage large center grants and simplify reporting via such features as the ability to validate a PTAEO and generate a monthly usage report to bill against or run through financial software. It requires only a minute or two to answer a few questions when scheduling resources in order to centralize reporting and ensure that time is allocated to the appropriate grant.

YSM and YCCI are excited to be able to offer this time-saving tool to investigators. To get started, go to the Resource Scheduler page at http://scheduler.yale.edu/ and click on Request a Resource Account.

Core Resources Contact Information (area code 203)

Biomedical Informatics Core			
Perry Miller, Director of Biomedical Informatics	737-2903	perry.miller@yale.edu	300 George St., Suite 501
Pradeep Mutalik, Associate Research Scientist, Medical Informatics	737-5266	pradeep.mutalik@yale.edu	300 George St., Suite 501
Michael Krauthammer, Assistant Professor Pathology	737-1233	michael.krauthammer@yale.edu	TAC 309
Cynthia Brandt, Associate Professor Anesthesiology (Medical Informatics)	737-5762	cynthia.brandt@yale.edu	300 George St., Suite 501
Biostatistical Support of YCCI			
James Dziura, Manager of Biostatistical Support Unit	737-4468	james.dziura@yale.edu	2 Church St., Suite 112
Center for Chemical Genomics			
Janie Merkel, Director, Center for Chemical Genomics	432-5930	janie.merkel@yale.edu	219 Prospect KBT 736
Michael Salcius, Biotechnology Associate	432-5581	michael.salcius@yale.edu	219 Prospect KBT 736
Center for Cell & Molecular Imaging			
Michael H. Nathanson, Section of Digestive Diseases and Cell Biology	785-7312	michael.nathanson@yale.edu	TAC S241D
Al Mennone, Research Associate, Section of Digestive Diseases	785-3154	al.mennone@yale.edu	TAC S230
Core Laboratory			
Li Wen, Director of Core Laboratory Services	785-7186	li.wen@yale.edu	TAC S141C
Ralph Jacob, Manager of Core Laboratory Services	785-4422	ralph.jacob@yale.edu	Hunter 5
Electron Microscopy Facility, Center for Cell and Molecular Imaging (CCMI)			
Christoph Rahner, Director of Electron Microscopy Core Facility	785-4322	christoph.rahner@yale.edu	SHM, IE16/26
Flow Cytometry Facility			
Mark Shlomchik, Professor of Laboratory Medicine and Immunobiology	737-2089	mark.shlomchik@yale.edu	TAC S541A
Geoff Lyon, Biotechnology Assoc. II	785-2299	geoff.lyon@yale.edu	Amistad S-416
Ewa Menet, Training and Analysis Specialist	785-7958/49	ewa.menet@yale.edu	TAC S613
Immune Monitoring			
Lesley Devine, Science Director	785-2031	lesley.devine@yale.edu	LCI 600
Keck Lab			
Ken Williams, Director of Keck Facility	737-2206	kenneth.williams@yale.edu	300 George G005
Shrikant Mane, Associate Director	737-2229	shrikant.mane@yale.edu	300 George 2119
Psychiatry SPECT Imaging			
Julie K Staley-Gottschalk, Assistant Professor of Psychiatry	932-5711 x3324	julie.staley@yale.edu	950 Campbell Ave.
The CINEMA Laboratory			
Derek Toomre, Assistant Professor of Cell Biology	785-7371	derek.toomre@yale.edu	SHM C-229
Yale MR Research Center			
Douglas Rothman, Director of Magnetic Resonance	785-6202	douglas.rothman@yale.edu	TAC N138
R. Todd Constable, Professor of Diagnostic Radiology and Neurosurgery	737-2768	todd.constable@yale.edu	TAC N132
Yale Pathology Tissue Services (YPTS)			
David Rimm, Director of Yale Pathology Tissue Services	737-4204	david.rimm@yale.edu	BML 116
Yale PET Center			
Richard E. Carson, Director of PET Center	737-2814	richard.e.carson@yale.edu	LMP 89A
Yu-Shin Ding, Director of PET Radiochemistry	785-4297	yu-shin.ding@yale.edu	LMP 89B
Henry Huang, Co-Director of PET Radiochemistry	785-3193	henry.huang@yale.edu	MRC-PET 137A
Robert Fulbright, Interim Medical Director	785-6145	robert.fulbright@yale.edu	TAC N137
Mindy McQueen, PET scheduler/Administrative Assistant	785-2978	melinda.mcqueen@yale.edu	MRC-PET 136
Tara Zalatimo, Administrative Coordinator	737-9738	tara.zalatimo@yale.edu	LMP 89C
General PET Inquiries		pet.center@yale.edu	

Scholar News

YCCI Scholar **Erik Shapiro** was awarded a five-year $1.5 million *New Innovator Award* from the NIH. Launched in 2007, the award helps early-career investigators pursue innovative approaches in transforming biomedical and behavioral science. One of 31 researchers to receive the prestigious award this year, Shapiro will use cellular and functional magnetic resonance imaging to aid in the development of novel strategies for manipulating stem and progenitor cell migration in the brain, particularly in response to injury and disease.

Other Scholars to receive funding awards include:

Sumita Bhaduri-McIntosh, Hood Foundation, *The Role of Regulatory T cells in Controlling EBV-Mediated Outgrowth of B Lymphoma Cells*, $150,000, 2 years

Marsha Guess, 2008 Robert Wood Johnson Foundation, *Harold Amos Medical Faculty Development Program Scholars Award*, $416,558, 4 years

Jonas Hannestad, Society for Nuclear Medicine, *Neuroinflammation and Depression During Interferon-Alpha Treatment of Hepatitis C: A SPECT Study*, $100,000, 2 years; Department of Defense, *Validation of the SPECT Ligand CLINDE as a Marker of Microglial Activation in Baboons*, $150,000, 18 months

Roger Jou, *American Academy of Child & Adolescent Psychiatry and Eli Lilly & Company Pilot Research Award*, $15,000; American Psychiatric Association, *Program for Minority Research Training in Psychiatry, $46,992;* APIRE/Lilly *Psychiatric Research Fellowship*, $45,000

Nina Kadan-Lottick, St. Baldrick's Foundation, $110,000, 3 years

Richard Kibbey, NIH/NIDDK (K08), *Characterization of Mitochondrial GTP as an Intramitochondrial Metabolic Signal*, $671,625

Patty Lee, NIH/NHLBI (R01), *Innate Immune Mechanisms in Emphysema*, $2,074,063, 5 years

Thomas Murray, Yale Child Health Research Center, $200,000, 2 years

Marcella Nunez-Smith, 2008 AAMC *Herbert W. Nickens Faculty Fellowship* for research on discrimination within health care organizations, $15,000, 2 years

Alexander Panda, Preeclampsia Foundation *2008 Vision Grant*, for research on the role of toll-like receptors in preeclampsia, $25,000

Saif Rathore, American Heart Association, *Quality of Care and Outcomes in Cardiovascular Disease and Stroke Young Investigator Award*, $1,000

Clinical Research Compliance

FDA Amendment Act Now Requires Results Reporting

A new deadline connected to the law requiring the registration of clinical trials on clinicaltrials.gov recently passed: Starting on September 27, 2008, the basic results of clinical trials must also be reported.

The government-sponsored registry was established in 2000. At that time, however, it required only the registration of trials of drugs for serious or life-threatening conditions. Requirements changed, however, with the FDA Amendment Act of 2007, which expanded the clinical trials registry to include most trials of drugs, biologics and devices under FDA jurisdiction. Investigators who wanted to publish their results in peer-reviewed journals were required to register them in a public database anyway, thanks to a 2004 policy by the International Committee of Medical Journal Editors (ICJME), which was revised last year to include Phase I trials and pharmacokinetics studies as well. About 13,000 trials were registered when the ICJME policy was announced in 2004; as of late 2008 there are more than 60,000 ongoing and completed trials registered on clinicaltrials.gov, the only registry that presently meets the organization's criteria.

For trials that began after September 27, 2007, the "basic results" provision requires investigators to post the following information within one year after the trial is completed. The details of the requirements are still under discussion; however, they do include the following areas:

- Demographic and baseline characteristics
- Table of values, overall and for each arm
- Number of patients dropped out or excluded from the analysis
- Primary and secondary outcomes
- Table of values for each primary and secondary outcome measure by arm
- Scientifically appropriate tests of statistical significance
- Point of contact for scientific information about the trial
- Agreements that place restrictions on the PI to discuss or publish results after the trial completion date

As with the earlier expanded registration requirements, there are penalties for failing to comply after receiving notice of noncompliance: Fines of up to $10,000 per day and the withholding of grant funds for federally funded trials.

Many researchers are concerned that publishing results could threaten academic and commercial privacy or that such information could ultimately be confusing to the public. This concern will become an even hotter topic of debate with the requirement to register adverse events beginning on September 27, 2009. Although the elements of this additional requirement have not yet been finalized, they could include serious adverse events and other adverse events above a yet-to-be specified frequency threshold, along with other information regarding the adverse events.

YCCI has invited Deborah Zarin, M.D., director of clinicaltrials.gov, to lead an information session on the new requirements in December. Keep an eye on the YCCI website for information about this event. In the meantime, for more information on registering clinical trials, including the draft requirements for registering results, visit http://prsinfo.clinicaltrials.gov. To view an example of a posted record, go to http://clinicaltrials.gov/ct2/show/results/NCT00440011?rslt=With.