ICTR TTRC Creating New Pathways For Drug Discovery and Development

Translational research for therapeutics is globally challenged by rising research and development costs, limited new chemical entities in the pipeline, longer development time, and lack of efficacy. Due to the so-called “valley of death,” over the last decade only one out of approximately 10,000 newly-discovered molecules makes it to the market, at the cost per successful drug of greater than $1.5 billion for research and development and clinical testing.

Research-intensive universities around the world are also feeling various challenges. As investors and industry become increasingly cost sensitive and risk averse, licensing of university technologies is diminishing, along with a critical revenue stream for many campuses. As a result, there are limited development and commercial pathways for numerous issued patents held by universities.

Countering these trends are new paradigms led by universities. A new UW ICTR drug discovery and development initiative is one such program.

John Kao, PhD, directs the Translational Technologies and Resources Core (TTRC) of the NIH-funded Institute for Clinical and Translational Research (ICTR) at UW-Madison. The goal of the TTRC is collaboration with campus-wide expertise, and with other universities, to offer a mechanism for clinical and translational researchers to move new drugs and potential therapies down the developmental path.

NIH Support through NCATS

Innovative partnerships among academia and the private and public sectors today are meant to address the obvious health, societal, and economic crises due to slowing drug development. In 2011, the NIH established the National Center for Advancing Translational Sciences (NCATS) to catalyze the translation of diagnostics and therapeutics across a wide range of human diseases (see p.3 story).

NCATS supports diagnostics and therapeutics development partly by funding a national network of clinical and translational research institutions through the Clinical and Translational Science Awards (CTSA), of which ICTR at UW-

Continued on page 8

A drug discovery-to-development critical path
UW Madison ICTR Report
By Marc Drezner, MD, ICTR Executive Director
Senior Associate Dean, UW SMPH

The renewal of our NIH Clinical and Translational Science Award in 2012 marked both a celebration of the many things we are doing right at UW ICTR and a re-focusing of our efforts in response to NIH directives. This issue outlines the remarkable efforts of our Translational Technologies and Resources Core (TTRC), under the directorship of John Kao, to expand our technical assistance in the areas of drug discovery and development of new therapeutics. There are many steps in the pathway from basic discovery research to product launch; some would liken it more to a maze than a straight route! The TTRC is working to provide as much assistance along the way as possible. Our hope is that this newsletter becomes a resource for investigators; to that end, the center of this newsletter is designed to be a stand-alone flyer referencing our network of affiliated laboratories and centers.

This issue also announces the incoming students in our Graduate Program in Clinical Investigation (GPCI) and in the TL1 pre-doctoral training program. Four new GPCI students are starting this fall, in addition to seven joining the program earlier in the year. We are particularly proud of those individuals who have earned a MS degree and chosen to continue on in the PhD track. Training the future research workforce is another aspect of the NIH mission that we take very seriously and this group represents the continuing excellence of our students. Welcome!

The Marshfield Report
By Murray Brilliant, PhD, ICTR Asst. Director
Director MCRF Center for Human Genetics

A unique resource of the ICTR Translational Technologies and Resources Core (TTRC) is the Personalized Medicine Research Project (PMRP) of the Marshfield Clinic. PMRP is a population-based biobank with approximately 20,000 adult participants. PMRP was established to foster research to improve health and patient care. Information gathered from studies using this biobank has already contributed to making personalized medicine a reality.

PMRP is used to find associations between biomarkers (DNA, plasma and serum samples) on all 20,000 participants with their virtually complete long-term electronic health records. PMRP has been used to discover complex genetic variants linked to asthma, diabetes, hypertension, glaucoma, cataract, macular degeneration, pharmacogenetics, various cancers, lab values, and many other diseases and medical parameters. Because of the long-term nature of the electronic health records of PMRP participants (nearly 30 years), PMRP is ideal to study disease progression and longitudinal treatment outcomes.

PMRP has been used to study a variety of diseases by investigators at the Marshfield Clinic and at UW-Madison. Examples include the study of Alleles of the FMR1 Gene Associated with Fragile X led by Marsha Mailick, PhD (Waisman Center); Breast Cancer, Genetic Variation and Imaging led by Elizabeth Burnside, MD, PhD (UWSPMH); and Development of a Genetic Test for Age-related Macular Degeneration led by Murray Brilliant, PhD (Marshfield Clinic).

All genotyping data on PMRP subjects are incorporated into the database and so the resource gets more valuable over time, as the variants from one study can be used in the analysis of the next. Indeed, dense genetic data are available on approximately 12,000 subjects. This includes (with some overlap) 5,000 samples with over 500,000 genome-wide single nucleotide polymorphisms and 10,000 samples with over 250,000 exome variants. Imputation expands the number of markers on a single individual to up to 38,000,000.
NIH Encourages Pharma-Academic Partnerships

As federal and private research budgets have become more restricted in recent years, the NIH has promoted new mechanisms to enhance the efficiency of academic and pharmaceutical industry partnerships and advance drug and therapeutic discovery.

Several of those initiatives are led by the NIH National Center for Advancing Translational Sciences (NCATS). NCATS is home to the 61 Clinical and Translational Science Awards (CTSA), one of which is awarded to the UW-Madison Institute for Clinical and Translational Research (ICTR).

Re-engineering the use of existing molecules

As part of an effort to rescue and repurpose existing partially-developed compounds, NIH launched in May 2012 a new drug-centric pilot program to accelerate new treatments for patients, by matching researchers with a selection of proprietary molecular compounds. The Discovering New Therapeutic Uses for Existing Molecules initiative gives investigators access to drugs in the development pipeline that have already passed human safety testing and other key steps.

Five private firms – AbbVie (formerly Abbott), AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, Janssen Research & Development, LLC, Pfizer, and Sanofi – provided 58 compounds for the pilot program.

In June 2013, NIH funded nine projects totaling $12.7 million. These projects paired academic research groups with a selection of pharmaceutical industry compounds to explore new treatments for patients in eight disease areas, including Alzheimer’s, Duchenne muscular dystrophy, and schizophrenia, among others.

More information about the initiative can be found on the NCATS website (www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/agreements.html).

Role for the CTSA sites including UW ICTR

The CTSA program in the NCATS Division of Clinical Innovation has also been charged with advancing the development of new drugs and therapeutics. NCATS challenged all CTSA sites, including UW ICTR, to build better bridges between pre-clinical and clinical science. As outlined in this issue, the Translational Technologies and Resources Core is leading the UW ICTR response to these NCATS goals (ictr.wisc.edu/LaboratoryServices).

Support for private-academic contracts

NCATS has also supported the legal aspects of pharmaceutical industry and academic partnerships. Especially when joint ventures occur at earlier stages in the drug discovery process (www.nature.com/news/2011/110622/full/474433a.html), conflict of interest issues must be resolved.

NCATS has helped to minimize some of the administrative hurdles to new partnerships by providing template agreements to streamline the legal and administrative process for partnering across multiple organizations. The agreements save time and effort as well as provide a roadmap for handling intellectual property used in or developed through the program (www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/agreements.html).

The Marshfield Report... Continued from page 2

The genotyping data will also increase as a result of the recent purchase of an Illumina MiSeq Next Generation DNA Sequencer, robotic sample preparation system, and computer data processing and storage system to enable next-generation DNA sequencing at the Marshfield TTRC. This system will also support new and ongoing research projects and provide capabilities for new areas of research. It is anticipated that this system will complement current sequencing core facilities, and provide additional sequencing capacity beyond that which is currently available to ICTR scientists at UW and Marshfield Clinic Research Foundation (MCRF), and facilitate collaborations between ICTR scientists at UW and MCRF.

ICTR members receive free de-identified aggregated PMRP data for pre-award (feasibility) queries, e.g., patient counts and numbers of samples with genotypes. An i2b2 interface for these queries will shortly be launched and available on-line. PMRP data and samples are available on a fee basis to ICTR members who have secured appropriate scientific merit review, PMRP Oversight Committee and IRB approvals for specific research projects.

For more information, please contact Tonia Carter, PhD, ICTR PMRP coordinator, (715)221-6467.
TTRC Resource Area: Imaging

Imaging modalities play a central role in measuring outcomes for many types of clinical research, including drug discovery and therapeutics. The UW TTRC affiliates include four campus facilities offering a wide range of imaging services, ranging from routine clinical measurements to highly specialized research tests.

SPOTLIGHT on the Wisconsin Institute for Medical Research (WIMR) Imaging Facility:

Based in the UW Department of Radiology, and physically located in WIMR, the WIMR Imaging Facility offers a variety of imaging and image processing services. Imaging modalities include Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron Emission Tomography (PET), Ultrasound (US), Biomagnetism, Angiography, combined PET/CT, and soon, combined MRI/PET.

Faculty working with the WIMR Imaging Facility can also assist in defining specific aims, designing imaging studies, establishing imaging protocols, and interpreting and analyzing results. The facility is equipped with the specialized equipment needed to image both small and large animals, and with the state-of-the-art clinical equipment needed for imaging human subjects for basic science investigations, translational development work, or clinical trials.

TTRC Resource Area: Analysis of Gene and Protein Function

Drug discovery often depends on identification of functional perturbants of key metabolic pathways and processes identified during the course of basic research. Such perturbants can include antibodies, siRNAs, peptides, and other small molecules. Literally 10s of 1000s of molecules may need to be screened to identify potential candidates. While this process is beyond the capacity of many individual investigators, TTRC affiliates include four facilities on campus whose experienced staff can assist in many of the necessary technologies.

SPOTLIGHT on the Small Molecule Screening and Synthesis Facility (SMSSF):

Located in the Wisconsin Institutes for Medical Research, the SMSSF provides high-throughput screening of drug-like chemical libraries and human RNAi libraries; biological profiling assays and mechanism of action assays; synthetic medicinal chemistry and lead optimization; synthetic and natural product compound purification and identification; molecular modeling and virtual screening; and mycoplasma detection in cultured cells. The facility is committed to offering the best possible pricing for ICTR members.

A recent collaboration between the SMSSF and ICTR member, Luigi Puglielli, MD, PhD (UW SMPH Department of Medicine), supported an investigator’s research. First, the Puglielli lab designed a high throughput assay for two brain acetyltransferase enzymes implicated in Alzheimer’s disease. SMSSF used this assay to screen 14,400 different chemical derivatives. One compound caused conformational changes in the target protein that led to reduced activity and in vivo degradation of the unstable form. This work was published in the Journal of Biological Chemistry.

A recent example of collaborations between the WIMR Imaging Core and investigators is the research of Jennifer Rehm, MD (UW SMPH Department of Pediatrics), and Scott Reeder, MD, PhD (UW SMPH Department of Radiology). WIMR MRI technologists managed pediatric and young adult patients for this project, while affiliated faculty helped to develop faster techniques to quantify visceral adipose tissue. The study imaged over 130 girls and young women, correlating ectopic and subcutaneous fat deposition with serum biomarkers of metabolic disease. The novel method was validated as a reliable, rapid, and noninvasive means of quantifying hepatic fat content. This work was published in Obesity.

ICTR members will receive a 30% discount off the standard research imaging rates, following protocol review and approval. The maximum ICTR discount per year per study is $6,000. Also, time is made available on the imaging systems at no charge for gathering pilot data for inclusion in grant applications, or for gathering feasibility data before or after a grant is awarded.

TTRC Imaging Affiliated Laboratories
- UW Atherosclerosis Imaging Research Program
- UW Cardiovascular Physiology Core Facility
- UW Translational Research Initiatives in Pathology Lab
- Wisconsin Institute for Medical Research (WIMR) Imaging Facility

For more information: ictr.wisc.edu/Imaging

TTRC Gene and Protein Function Affiliated Laboratories
- Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics (3PLab) (UWCCC)
- Marshfield Clinic Research Foundation Core Laboratory
- Small Molecule Screening and Synthesis Facility (UWCCC)
- UW Biotechnology Center

For more information: ictr.wisc.edu/GeneExp
TTRC Resource Area: Gene Expression Profiling, Genotyping, and Genomic Analysis

DNA sequence analysis and gene expression studies are at the cutting edge of genomics research and an increasingly important part of clinical translational research. There are several complementary facilities at UW capable of performing these studies in collaboration with ICTR investigators. TTRC affiliates include six well-equipped centers offering services specialized for clinical and translational research. In addition, the ICTR Biomedical Informatics core offers data management and security service consultations necessary in the era of “Big Data.” (Volume 6 No. 2 (2013) issue of UW ICTR Today.)

SPOTLIGHT on the UWHC Molecular Diagnostics Laboratory:

The UW Hospital and Clinics (UWHC) genomics effort is centered in the UWHC Molecular Diagnostic Laboratory led by director William Rehrauer, PhD. Accredited by the College of American Pathologists, this facility offers molecular-based profiling of tumors and various genetic assays applicable to personalized medicine strategies, in addition to standard clinical screens. The cancer genetics panel will take advantage of a newly-acquired Ion Torrent Next Generation Sequencing platform. An important aspect of all the testing is the Clinical Laboratory Improvement Amendments (CLIA) certification of the laboratory.

TTRC Resource Area: Animal Models

Animal models play a key role for biomedical researchers both in basic science and in the transition from pre-clinical to clinical testing of new therapeutics. TTRC affiliates include four campus facilities with expertise in generation of animal and tumor xenograft models; testing the effect of perturbants and/or genetic changes in behavioral, disease, and pharmacological models; and preclinical pharmacokinetics and dosing.

SPOTLIGHT on the UW Cardiovascular Physiology Core Facility:

At the UW Cardiovascular Physiology Core Facility, surgeon scientists specialize in studies that focus on aneurysm, stroke, drug toxicology, heart failure, and arrhythmias, as well as gene, drug, and cell therapy. Their services encompass a wide range of small and large animal models.

Recent collaborative studies with campus groups include 1) echocardiography of transgenic mice to determine whether overexpression of key metabolic enzymes have increased resistance to acute and chronic oxidative or ischemic stress, 2) testing of myocardial injection catheters for delivery of stem cells to infarcted swine hearts, and 3) small and large animal model testing of stem cell therapy for ischemic myocardial damage. The facility can also provide a mouse model to test other novel treatments for myocardial infarction.

ICTR members receive discounted rates on services at the Cardiovascular Physiology Core Facility and can acquire preliminary data for grants at or below cost.

TTRC Gene Expression Profiling, Genotyping and Genomic Analysis Affiliated Laboratories

- ICTR-WNPRC Assay Laboratory
- Marshfield Clinic Research Foundation Core Laboratory
- UW Biotechnology Center
- UW Translational Research Initiatives in Pathology Lab
- UWHC Clinical Labs (Molecular Diagnostics Laboratory)
- Wisconsin State Laboratory of Hygiene

For more information: ictr.wisc.edu/GeneExpAnalysis

Perspective from UW-Madison Provost and Vice Chancellor for Academic Affairs:

Paul DeLuca, PhD

"Increasingly the focus of modern biomedical research is at the interface between discovery and application in the treatment of diseases and diagnosis of the same. This step in the process is an extraordinarily complex issue and a significant part of the UW ICTR mission. TTRC is dedicated precisely to that role. We can anticipate that TTRC positions the institution very broadly to seek and apply new knowledge to the greater public good. This is certainly part of the Wisconsin Idea.”

TTRC Animal Model Affiliated Laboratories

- Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics (3P Lab) (UWCCC)
- ICTR-WNPRC Assay Laboratory
- UW Biotechnology Center (Transgenic Animal Facility)
- UW Cardiovascular Physiology Core Facility

For more information: ictr.wisc.edu/AnimalModels
TTRC Resource Area: Assay Services

Assisting clinical investigators and basic scientists in accessing campus expertise in assay development and performance was one of the original goals of the ICTR TTRC when the institute was first founded in 2007. As this issue outlines, the mission of the TTRC has grown to include drug and novel therapeutic activities, yet assay service providers remain key members of the TTRC network. Nine major centers are committed to helping researchers at all points on the spectrum of clinical and translational research.

SPOTLIGHT on the ICTR-WNPRC Assay Laboratory:

The ICTR-WNPRC Assay Laboratory provides determinations of steroids, proteins, vitamins, neurotransmitters, immune- and bio-markers, drugs, and other biologically active compounds in a wide variety of samples. Recent developments include high throughput assays for Vitamin D and multiplex determination of steroids using triple quadrupole mass spectrometry.

To illustrate, assay services staff worked with ICTR member Ashleigh Theberge, PhD (UW Departments of Biomedical Engineering and Urology, UWCCC), to develop a specialized technique to measure glucocorticoids from extracts of cell cultures. Similarly, ICTR members in the UW School of Veterinary Medicine Department of Comparative Biosciences took advantage of ICTR-WNPRC expertise to measure multiple steroids from cell cultures due to steroidogenesis in human prostate cancer cells. Both projects utilized triple quadrupole mass spectrometry.

The ICTR-WNPRC Assay Laboratory offers consultations on appropriate methods and provides discounts for ICTR members. They specialize in developing new methodologies and in adapting their methods to measure analytes in all biological fluids, for primates and other species.

TTRC Assay Services Affiliated Laboratories

- Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics (3P Lab) (UWCCC)
- Flow Cytometry Lab (UWCCC)
- ICTR-WNPRC Assay Laboratory
- Marshfield Clinic Research Foundation Core Laboratory
- Small Molecule Screening and Synthesis Facility (UWCCC)
- UW Translational Research Initiatives in Pathology Laboratory
- UWHC Clinical Laboratories
- Wisconsin State Laboratory of Hygiene

For more information: ictr.wisc.edu/assayserv

TTRC Resource Area: Therapeutic Discovery & Development

The drug discovery and development arm of the TTRC has become a major component of the cross-campus facilities network. Six centers are available to UW ICTR members, offering access and expertise in drug action, formulation, delivery, pharmacokinetics, clinical pharmacology, regulations, and human research. All have signed agreements with ICTR and are committed to offering the best possible pricing for ICTR members.

SPOTLIGHT on the Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics (3P Lab):

The 3P Lab provides bioanalytical assay development, validation, and performance for clinical studies – with services encompassing complex sample acquisition, sophisticated pharmacokinetic assays in all biological fluids, and preclinical therapeutic studies. GLP and CLIA level performance is available.

Recent successful projects include research led by Howard Bailey, MD (Department of Medicine), in which 3P Lab services developed and validated a triple quadrupole mass spectrometry assay for the first in human trial of a novel retinoid being tested as a chemoprevention agent and therapeutic agent for breast cancer. The primary endpoint was to determine bioavailability, dose proportionality, and in vivo metabolism and half-life of the agent. 3P Lab also collected and processed the samples.

The 3P Lab offers free initial consultations for new projects, in addition to assisting investigators with grants, letters of intent, and preparation of reports and manuscripts.

TTRC Therapeutic Discovery & Development Affiliated Laboratories

- Analytical Instrumentation Laboratory for Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics (3P Lab) (UWCCC)
- Small Molecule Screening and Synthesis Facility (UWCCC)
- UW Biotechnology Center
- UW Cardiovascular Physiology Core Facility
- Waisman Biomanufacturing Facility
- Zeeh Pharmaceutical Experiment Station, School of Pharmacy

For more information: ictr.wisc.edu/Therapeutic
The ICTR Translational Technologies & Resources Core (TTRC) offers investigators a wide range of research resources – in a collaborative arrangement with many current UW and Marshfield Clinic facilities.

Resource areas are: 1) analysis of gene/protein function; 2) assay services; 3) animal models; 4) gene expression profiling, genotyping, and genomic analysis; 5) imaging; and 6) therapeutic discovery and development.

TTRC-affiliated laboratories strive to offer ICTR investigators services "at cost" or with discounted rates.

**TTRC VOUCHER AWARD PROGRAM**
- Lead Applicants must document an urgent need for services based upon recent extramural grant review, or milestones for therapeutic development, e.g., formulation, analytical development, animal toxicology/pharmacokinetics. Applicants must also certify non-supplanting of funds for requested activities.
- Requested awards typically range from $1,000 to $5,000, redeemable for services at one of the ICTR affiliated laboratories. All funds are provided directly to the TTRC affiliate facility and must be used within six months of the award.
- Please visit: [ictr.wisc.edu/FundingOpportunities](http://ictr.wisc.edu/FundingOpportunities) for a current list of providers and future application deadlines for the voucher program and for other funding opportunities.
<table>
<thead>
<tr>
<th>Laboratory Name</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P Analytical Instrumentation Laboratory (UWCCC)</td>
<td>Provides: Sample Acquisition, Pharmacokinetic Analytical Assays, Pharmacogenetic Assays, Pharmacodynamic Assays, and Preclinical Analytic Services. Contact — Joanne Kolesar, PharmD, (608) 262-5549, <a href="mailto:mkolesar@pharmacy.wisc.edu">mkolesar@pharmacy.wisc.edu</a></td>
</tr>
<tr>
<td>Flow Cytometry Lab (UWCCC), Wisconsin Institutes for</td>
<td>Access to cutting-edge instruments, technical expertise &amp; training in flow cytometry. Single &amp; live cell sorting. High parameter flow cytometry essay and protocol development for immunophenotyping, immunomonitoring, functional and developmental assays plus sample processing, data acquisition &amp; analysis. Contact — Dagna Sheerar, <a href="mailto:dsheerar@wisc.edu">dsheerar@wisc.edu</a></td>
</tr>
<tr>
<td>Medical Research, Room 7016, 1111 Highland Ave, Madison, WI 53705</td>
<td></td>
</tr>
<tr>
<td>ICTR-WNPRC Assay Laboratory, 1220 Capitol Court, Madison, WI 53715</td>
<td>The Wisconsin National Primate Research Center provides a wide range of services to the broader scientific community, including: Assay Services, Genetics Services, Virology Services, Immunology Services, ELISA Controller Resource, Aging Resource, Primate Tissue Resource and Scientific Protocol Implementation. Contact — Toni Ziegler, PhD, (608) 263-3507 or <a href="mailto:ziegler@primate.wisc.edu">ziegler@primate.wisc.edu</a></td>
</tr>
<tr>
<td>Marshfield Clinic Research Foundation Core Laboratory, 1000 N. Oak Ave, Marshfield, WI 54449</td>
<td>Provides: Proficiencies in microbiology, virology, cell culture, molecular biology, DNA sequencing, genotyping, and can assist with new assay development. Also provides biological specimen banking services for individual Personalized Medicine Research Project cohort. Full service veterinary lab with same services as clinical lab. Contact — Jen Meece, PhD, 715-221-6465 or Toll-free:1-800-782-8581, ext. 16465 or <a href="mailto:Meece.Jennifer@mcrf.mfldclin.edu">Meece.Jennifer@mcrf.mfldclin.edu</a></td>
</tr>
<tr>
<td>Small Molecule Screening and Synthesis Facility (UWCCC), Wisconsin Institutes for Medical Research, Room 6003, 1111 Highland Ave, Madison, WI 53705</td>
<td>Provides: High-throughput screening of drug-like chemical libraries and human RNAi libraries; Biological profiling assays and mechanism of action assays; Synthetic medicinal chemistry and lead optimization; Synthetic and natural product compound purification and identification; Molecular modeling and virtual screening. Contact — Michael Hoffmann, PhD, (608) 265-8687 or <a href="mailto:fmhoffma@wisc.edu">fmhoffma@wisc.edu</a></td>
</tr>
<tr>
<td>UW Atherosclerosis Imaging Research Program, Clinical Science Center H6/377, 600 Highland Ave, Madison, WI 53705</td>
<td>Provides: Serves as a core ultrasound reading and training laboratory for studies that use ultrasound-based research tools as surrogates for atherosclerosis and cardiovascular disease risk; and 2) in addition to clinical services. Contact — Claudia E. Korczak, DVM, RDCS, <a href="mailto:ck4@medicine.wisc.edu">ck4@medicine.wisc.edu</a>, (608) 265-9947</td>
</tr>
<tr>
<td>UW Biotechnology Center, 425 Henry Mall, Madison, WI 53706</td>
<td>DNA synthesis and sequencing, peptide synthesis, peptide sequencing and mass spectrometry of phosphopeptides and small metabolites, production of transgenic/knockout mice and rats, bioinformatics, and education programs. Contact — Charles Konstizke, (608) 262-8607 or <a href="mailto:cmkonzstzke@biotech.wisc.edu">cmkonzstzke@biotech.wisc.edu</a></td>
</tr>
<tr>
<td>UW Cardiovascular Physiology Core Facility, 1671 Medical Science Center, 1300 University Ave, Madison, WI 53706</td>
<td>This special animal physiology facility offers laboratory services for creating and studying animal models of disease, including animal surgeries, imaging (ultrasound) and physiologic measurements on animals ranging from primates to mice. Contact — Timothy Hacker, PhD, Director, (608) 263-1539 or <a href="mailto:th2@medicine.wisc.edu">th2@medicine.wisc.edu</a></td>
</tr>
<tr>
<td>UW Translational Research Initiatives in Pathology (TRIP) Lab, Clinical Science Center K4/442-8550, 600 Highland Ave, Madison, WI 53705</td>
<td>Provides: High-quality histological, molecular/morphometric analyses and consultative services such as tissue arrays, laser dissection microscopy, quantitative morphometric analyses via imaging, and IHC/ISH on a fee for service basis. Contact — Sally Ann Drew, BS, MT, <a href="mailto:trip@pathology.wisc.edu">trip@pathology.wisc.edu</a></td>
</tr>
<tr>
<td>UW Health Clinical Laboratories, UW Hospital and Clinics, 600 Highland Ave, Madison, WI 53792</td>
<td>Provides: Vast number of common clinical assays and measures. Accreditation under CLIA, CAP, JCAHO, AABB, ASHI, FACT, and FDA. Contact — Jane Maney, (608) 262-5803 or <a href="mailto:jmaney@uwhealth.org">jmaney@uwhealth.org</a></td>
</tr>
<tr>
<td>Waisman Biomanufacturing Facility, Waisman Center, 1500 Highland Ave, Madison, WI 53705-2280</td>
<td>Manufactures clinical-grade biological pharmaceuticals for early stage (Phase I and II) human clinical trials. Plasmid DNA and viral vectors for gene therapy, processing cell therapeutics, aseptic filling of parenteral therapeutics, producing recombinant proteins expressed in bacterial or mammalian systems. Contact — Kari Thostenson, (608) 890-4704 or <a href="mailto:kthostenson@waisman.wisc.edu">kthostenson@waisman.wisc.edu</a></td>
</tr>
<tr>
<td>WIMR Imaging Facility, Wisconsin Institutes for Medical Research, 1111 Highland Ave, Madison, WI 53705</td>
<td>This ICTR imaging services component provides ICTR members access to multi-modality diagnostic imaging technologies and expertise in image acquisition and analysis. With ICTR membership, investigators will receive a 30% discount (max $6,000 per year) off the standard research imaging rates. Contact — Frank Korosec, PhD, (608) 265-5588 or <a href="mailto:FkKorosec@wisc.edu">FkKorosec@wisc.edu</a></td>
</tr>
<tr>
<td>Wisconsin State Laboratory of Hygiene, 465 Henry Mall, Madison, WI 53706</td>
<td>Provides: Clinical, environmental, and occupational laboratory services; numerous diagnostic testing options (real time PCR, pyrosequencing, FISH, PFGE, MS, oCGH, serology, cytogenetics, BSL-3 laboratories). Contact — <a href="mailto:research@slh.wisc.edu">research@slh.wisc.edu</a> or (608) 890-1093</td>
</tr>
<tr>
<td>Zeeh Pharmaceutical Experiment Station, Rennebohm Hall, 777 Highland Ave, Madison, WI 53705</td>
<td>Covers a range of pharmaceutical development activities including customized R &amp; D for traditional and non-traditional pharmaceutical-related opportunities. Services include physicochemical testing, dosage form design and development, and pre-GLP (and GMP) manufacturing of test articles for animal and human studies. Contact — Edmund Elder, Jr., PhD, RPh, (608) 890-1198 or <a href="mailto:elder@pharmacy.wisc.edu">elder@pharmacy.wisc.edu</a></td>
</tr>
</tbody>
</table>

ictr.wisc.edu/LaboratoryServices
ICTR Voucher Awardees Summer 2013

Five awards were made for the first round competition for TTRC service vouchers from ICTR. Examples of the way awardees will use their service vouchers are shown at the right.

- Ian Bird, PhD (SMPH, ObGyn):
  High throughput screening of CLA isoforms as a novel therapy for preeclampsia
  Facility: Small Molecule Screening and Synthesis Facility (SMSSF)

- Wei Xu, PhD (SMPH, Oncology):
  Cell-based HTS for chemical modulators of the CARM1 arginine methyltransferase
  Facility: SMSSF

- David Lynn, PhD (COE, Chemical & Biological Engineering):
  Transfer of DNA to arteries using film-coated catheter balloons
  Facility: Cardiovascular Physiology Facility

- Albee Messing, SVM, PhD (SVM, Comparative Biosciences):
  Pharmacological suppressors of GFAP expression for Alexander Disease
  Facility: 3P Analytical Instrumentation Laboratory

- Mark Burkard, MD, PhD (SMPH, Medicine):
  Modification of polyol-specific chemicals for target identification
  Facility: SMSSF

Contact Marwa Bassiouni, TTRC administrator, for additional information about the voucher program and upcoming application deadlines, msbassio@wisc.edu, (608)265-6234, or check on-line, www.ictr.wisc.edu/FundingOpportunities.

Awardee Spotlight: Wei Xu and SMSSF Services

The Xu lab works on a protein arginine methyltransferase named CARM1 that activates transcription of a number of cancer-relevant transcription factors. As CARM1 regulates breast cancer cell proliferation and metastasis, identification of small molecule modulators of CARM1 via HTS assays would enable more facile and rigorous approaches to understanding the roles of CARM1 activity in cancer cells, as well as provide leads for anti-cancer drugs with a novel mechanism of action.

Using a newly established assay to identify chemical modulators of CARM1 activity, SMSSF will screen large compound libraries to identify candidate compounds with the drug-like properties amendable for lead optimization by medical chemistry. SMSSF will provide compound libraries, perform primary large scale screening using robotic liquid handling system, and facilitate compound optimization by medical chemists, thus generating important proof of concept data for future competitive funding applications.

Awardee Spotlight: David Lynn and UW Cardiovascular Physiology Core Facility

A key objective of research in the Lynn lab is to develop approaches to the immobilization and release of DNA from surfaces and advance the design of coatings that can be used to promote ‘contact-mediated’ transfer of DNA to cells, such as from the surface of an implantable medical device. They have developed approaches to the design of ultrathin, polymer-based coatings, called ‘polyelectrolyte multilayers,’ that can be used to promote the short-duration, localized transfer of plasmid DNA to vascular tissue using inflatable catheter balloons, and have demonstrated functional transfer of DNA in a rat model of arterial injury.

A collaboration with Timothy Hacker, PhD, at the UW Cardiovascular Physiology Core Facility will confirm and extend results from the rodent model using a large animal model that more accurately mimics human vasculature. Demonstrating the local, non-viral transfer of DNA to the vascular wall in pigs will provide key preliminary data for both the underlying science and the potential for clinical translation of this approach, and will considerably strengthen an upcoming competitive proposal to the NIH.

Perspective from the Wisconsin Alumni Research Foundation: Mark Stoveken, Pharmaceutical Licensing Manager

“One of the best ways WARF can help ICTR members to translate the fruits of their research into meaningful new therapies is to help researchers who are interested in advancing their research toward application in the clinic, to really understand the translation and commercialization pathway. Many members of our patenting and licensing staff have previous industry experience and they can offer helpful insights into the development and commercialization process, including how to move early research into the commercialization track and how to assemble quality patent applications.”
Madison is one of 61. The ICTR TTRC objective is to optimize the campus environment by coordinating infrastructures to facilitate basic discovery research and development and to generate critical data.

**Major First Steps**

First, to answer the NIH/NCATS challenge, TTRC Director Kao reorganized and augmented the translational technologies core into a nimble network of affiliated resource facilities on- and off-campus to address the research needs of ICTR members – adding new facilities specifically to address the drug discovery and development challenges.

Kao notes, “Our TTRC affiliates collaborate and assist on experimental activities and outcomes characterized by clear milestones. By generating critical data, TTRC collaborating labs add “translation” value to existing basic science discoveries.”

This issue of the newsletter features profiles of many of the TTRC-affiliated labs and their massive capabilities in a wide range of areas. In addition, a two-sided flyer outlining all cooperating groups is included in this newsletter for easy reference. The drug discovery to development graphic on page 1 illustrates some of the critical steps in moving basic discovery research to the product launch stage.

Second, TTRC launched a service voucher program to address investigator’s urgent research needs for pilot data. The voucher program is specifically aimed at unfunded, competitively-scored grant applications that need additional data for resubmission. The first voucher awards are profiled in this issue and on the web. A new voucher competition is coming November 1, 2013.

Third, UW ICTR is negotiating a collaboration with the University of Minnesota (UMN) – and potentially other CTSA sites – through the Midwest Consortium on Drug Discovery (MDCD). MDCD encourages the NCATS consortium of CTSA institutions to pool their complementary expertise and resources to develop new therapeutic technologies.

Bruce Blazar, MD, director of the UMN Clinical and Translational Science Institute, comments, “MC3D will provide UW and UMN investigators with unique, complementary expertise for drug development and translation, beginning with target identification, medicinal chemistry, pharmacokinetics, small and large animal models for proof of concept and toxicology studies, and unparalleled GMP manufacturing.”

Fourth, the long-standing partnership of UW ICTR with the Marshfield Clinic Research Foundation (MCRF) extends to the TTRC. MCRF offers ICTR members a wealth of expertise in its unique bioinformatics, gene sequencing, and small and large animal models for reference. The Marshfield Report column).

UW Campus Collaborations

In addition, ICTR Executive Director Marc Drezner, MD, and TTRC Director Kao are working with campus stakeholders to establish an integrated resource to attract interests and investments from the public and private sector, including multinational pharmaceutical companies. Among the groups included in this ICTR TTRC initiative are the Wisconsin Alumni Research Foundation (WARF), the UW-Madison Provost’s Office, and the UW Office of Corporate Relations.

Many research-intensive universities are asking the same hard question, “should we and are we prepared to do what it takes to de-risk promising medical technologies so we can bring them to the public faster, cheaper, and more efficiently?” The answer at UW-Madison is “yes” and the ICTR TTRC is playing a leading role, thus fulfilling both its NIH-mandated mission and the values of the “Wisconsin Idea,” an historic commitment to have academic research applied to solving problems that are important to all the citizens of the state.
Save the Date

**Development of Robust Experimental Assay Methods (aDREAM) Conference**

Theme: “Assay Reproducibility, Replicability and Robustness”

**Date:** Thursday and Friday, October 17-18, 2013

Location: Promega BioPharmaceutical Technology Center, Madison, WI

Online Registration: [www.formstack.com/forms/promega-adream_conference_2013](http://www.formstack.com/forms/promega-adream_conference_2013)

For more information, contact Michael Hoffmann, hoffmann@oncology.wisc.edu. The UWCCC Small Molecule Screening and Synthesis Facility, a TTRC-affiliated laboratory, is one of the sponsors of the conference.

---

**How to Acknowledge ICTR Support**

Publications arising from UW ICTR supported research should acknowledge support by stating “Supported by grant UL1TR000427 from the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences, NIH.”

**Don’t Forget PubMed Central Submissions**

Investigators holding an NIH grant, or receiving services through an organization like the NIH-funded ICTR, must submit publications arising from such support to the NIH PubMed Central Public Access site (publicaccess.nih.gov). Failure to comply can lead to sanctions from NIH, including withdrawal of grant support. Many campus resources are available to assist investigators with the process (ebling.library.wisc.edu/help/nih.php), and individual assistance can be obtained by contacting Julie Schneider, nihpolicy@library.wisc.edu, (608)263-5755.

**Did You Miss an ICTR Event?**

Many ICTR presentations are streamed and are also available live on the web, [live.videos.med.wisc.edu/](http://live.videos.med.wisc.edu/) and will also be available in the SMPH video library, [videos.med.wisc.edu/events/77](http://videos.med.wisc.edu/events/77).

---

**Did You Know?**

**Clinical Research Unit Wins UWHC Top Awards**

The ICTR Clinical Research Unit (CRU), located on D6/6 in UW Hospital and Clinics, again received two first-place inpatient awards in the hospital’s 2013 Nursing Excellence Awards. The CRU is supported by the NIH Clinical and Translational Science Award, and provides free research space and nursing support for non-industry research studies approved by the unit review committee.

One CRU award was for outstanding achievement in the category of Inpatient Staff Engagement for Performance Excellence, while the second was for Patient Satisfaction with Nursing. The CRU also took two of the top three awards in the 2012 competition.

**Human Subjects Research Vs. Quality Improvement Vs. Program Evaluation?**

As IRB oversight is limited to human subjects research, it is important to be able to make the distinction among different types of activities and identify those that either require or are exempt from regulatory oversight. Frequently, investigators also need formal IRB determinations of project status for journals, conferences, and funding sources, among others.

The UW Health Sciences (HS) IRBs Office has updated previous guidance to assist study teams in determining whether a project requires submission to the HS IRB as a human research project. In addition, the HS IRBs Office has developed an online Research Decision Tool that can provide certification that the project does not require IRB review and oversight. The new guidance materials are available on the HS IRBs Office website at: [kb.wisc.edu/hsirbs/page.php?id=33386](http://kb.wisc.edu/hsirbs/page.php?id=33386)

If you have any questions regarding the guidance materials or use of the Research Decision Tool, please contact the HS IRBs Office at 263-2362 for assistance.
**Grant Writing I**

Topics include:
- Anatomy of an NIH Grant: Writing with the Reviewer in Mind
- Identifying and Tracking Sources of Support
- Thinking Like a PI: Getting from Idea to Submission
- Career Development Awards

**Grant Writing II**

Topics include:
- NIH Peer Review Process and Criteria
- Effective Peer Review
- Mock Grant Review
- Submitting Your Grant Successfully: Institutional Support
- Responding to “Pink Sheets”

**Manuscript Writing I**

Topics include:
- Integrating Writing and Research
- Targeting Journals
- Negotiating Authorship
- Creating Effective Tables and Figures
- Telling a Story with Your Science

**Manuscript Writing II**

Topics include:
- Setting Up for Acceptance and/or Handling Rejection
- From the Editors’ POV
- Writing an Appropriate Cover Letter
- Providing Effective Peer Feedback

Participants in this workshop should actively be working on a manuscript to be shared for group critique and feedback.

For more information about these workshops, please contact Karin Silet, silet@wisc.edu, (608)262-3903.
Marshfield Clinic Research Foundation Summer Research Interns

Marshfield Clinic Research Foundation (MCRF) continues a 40-plus-year tradition of the Summer Student Research Internship Program with the 2013 group of 10 interns. The summer program is for undergraduate and graduate students pursing degrees in biomedical sciences, epidemiology/public health, and biomedical informatics.

Directed by Huong McLean, PhD, and Bobbi Bradley, MPH, the summer internship provides a 12-week research experience tailored to the student’s skill level and is related to ongoing research at the Marshfield Clinic. The program enables students to put their education into practice as they work side-by-side with scientists who are experts in their fields.

The Summer Research Internship Program is supported entirely through philanthropy. Thanks to the generosity of many community partners, clinic employees, foundations, businesses, and a major sponsorship by The Boldt Company, the program had the financial resources this year to expand from eight to 10 students for the first time in its 50-year history. Marshfield Clinic and its Research Foundation is a partner of the UW ICTR, and each year ICTR has representation on the Summer Student Intern Research Program selection committee.


**From left to right, front row:** Amy Callear, Erica Swenson, Emily Olson, Anna Gajewski, and Megan Vesel. **Back row:** Patrick Lau, Christopher Campbell, Andrew Kuhn, and Adam Sorenson. **Not pictured:** Stephanie Omage

---

**Amy Callear**

*Project Title:* Prognostic Utility of Single-Nucleotide Polymorphisms in Inflammatory Arthritis  
*Mentor:* Steven Schrodi, PhD (Center for Human Genetics)  
*Education:* Current: University of Pittsburgh (Biological Sciences with minors in Chemistry, Neuroscience, and Spanish)

**Christopher Campbell**

*Project Title:* Geospatial Factors for Lyme Disease Risk in Wisconsin  
*Mentor:* Anna Schotthoefer, PhD (Marshfield Clinic Research Foundation Core Lab)  
*Education:* Current: University of Minnesota-Twin Cities (MPH, Epidemiology); University of Minnesota-Twin Cities (Biology and a minor in Statistics)

**Anna Gajewski**

*Project Title:* Influenza and Productivity Loss in the Marshfield Epidemiologic Study Area  
*Mentor:* Jeffrey VanWormer, PhD (Epidemiology Research Center)  
*Education:* Current: Emory University (MPH); Macalester College in St. Paul, MN (Biology and Community and Global Health)

**Andy Kuhn**

*Project Title:* Efficient Management and Retrieval of Large-Scale Next-Generation Sequencing (NGS) Data  
*Mentor:* Dr. Max He (Biomedical Informatics Research Center and Center for Human Genetics)  
*Education:* UW-Stout (Applied Math and Computer Science with a concentration in Bioinformatics)

**Patrick Lau**

*Project Title:* A Longitudinal Study of Adverse Drug Effects in Patients with Fibromyalgia  
*Mentor:* Steven Yale, MD (Clinical Research Center)  
*Education:* Current: The Johns Hopkins University (Public Health Studies)

**Emily Olson**

*Project Title:* Analysis of the Relationship between Obstructive Sleep Apnea and Venothromboembolic Events  
*Mentor:* James Burmester, PhD (Clinical Research Center)  
*Education:* Current: St. Olaf College, Northfield, MN (Mathematics and Biology)

**Stephanie Omage**

*Project Title:* Usability Evaluation of Predictive Text Keyboards in Healthcare Settings  
*Mentors:* Simon Lin, MD, and Andrea Mahne (Biomedical Informatics Research Center)  
*Education:* University of Texas Health Science Center at Houston (MPH, Community Health Practice with a concentration in Maternal & Child Health); University of Houston-Downtown (Biology with minors in Psychology and Chemistry)

**Adam Sorenson**

*Project Title:* Usability Evaluation of a Touch-Based Dental Tooth Charting Application  
*Mentors:* Amit Acharya, BDS, MS, PhD, and Kelsey Schwei, MS (Biomedical Informatics Research Center)  
*Education:* Current: UW-La Crosse (Biochemistry)

**Erica Swenson**

*Project Title:* Radiographic Evaluation of Stillbirth: What Does it Contribute?  
*Mentor:* Elizabeth McPherson, MD (Center for Human Genetics)  
*Education:* Current: UW-Madison School of Medicine and Public Health  
*UW-Stevens Point (Biochemistry with a Music minor)*

**Megan Vesel**

*Project Title:* Developing a Cross-Reference Mapping between Different Dental Diagnostic Terminologies  
*Mentors:* Amit Acharya, BDS, MS, PhD, and Neel Shimpi, BDS, MM (Biomedical Informatics Research Center)  
*Education:* Northern Michigan University (Biology/Physiology with minors in Chemistry and Spanish)
Graduate Program in Clinical Investigation
Welcomes New Students in Fall 2013

Four new students have joined seven earlier 2013 enrollees in the ICTR Graduate Program in Clinical Investigation (GPCI). GPCI now has 31 students currently seeking an MS, PhD, or PhD minor degree. The 11 students new in 2013 represent the UW SMPH Departments of Medicine (Hematology/Oncology and Emergency Medical Services), Ophthalmology and Visual Sciences, Pediatrics (Neonatology and Newborn Medicine), Population Health Sciences, Psychiatry, and Surgery; the UW School of Pharmacy; and the Waisman Center.

Two students who earned the MS degree in Clinical Investigation in May are continuing in the PhD program; a third also plans that step. Michael Repplinger, MD, a clinical assistant professor of Medicine (Emergency Medicine) and Kimberly Shoenbill, MD, a research assistant in the Department of Biostatistics & Medical Informatics, are seeking the PhD in Clinical Investigation (see p 6, Vol. 6 No. 3, 2013, UW ICTR Today).

Chris Sorkness, PharmD, ICTR senior associate executive director, comments, “These incoming PhD and MS students are well positioned to become innovative, interdisciplinary, clinical and translational researchers.” She continues, “Their impressive backgrounds make them a good fit for the GPCI program’s growing reputation for training solutions-oriented academicians and health-care professionals.”

ICTR Pre-Doctoral Training Program Welcomes Two Trainees

Two students have joined four current TL1 trainees for a total of six students in the NIH-funded training program administered by UW ICTR. The goal of the ICTR pre-doctoral TL1 program is to train future clinical and translational leaders and to expose all UW health-care professionals and engineering students to the scientific foundation of this discipline.

In addition to receiving financial assistance including stipend, tuition, fees, and a travel allowance, TL1 trainees participate in a year-long writing workshop and monthly career development seminars, and benefit from structured biannual research mentor meetings. For more information, please check the ICTR web portal (ictr.wisc.edu/TL1Program). All six trainees are currently enrolled as either PhD or PhD minor students in the Graduate Program in Clinical Investigation, a TL1 program requirement.

The next RFA for the TL1 program will be released December 1, 2013, with an anticipated February 1, 2014, deadline.

| Incoming TL1 Trainees and Their Mentors |
|-----------------|------------------|
| Trainee         | Mentor (s)       |
| Kate Sprecher, MS | Ruth Benca, MD, PhD |
| Brittany Young, BS | Vivek Prabhakaran, MD/PhD |
|                 | Professor, Psychiatry, SMPH |
|                 | Assistant Professor, Radiology, SMPH |
|                 | Justin Williams, PhD |
|                 | Associate Professor, Biomedical Engineering, College of Engineering |

How to Apply
The application deadline for fall 2014 entry into GPCI is February 1, 2014. For further information, visit the Graduate Program web pages on the ICTR website (ictr.wisc.edu/GraduateProgram) or contact Sally Wedde, education programs administrator, rec-education@hslc.wisc.edu.