



INDIANACTSI
Clinical and Translational Sciences Institute



Biennial
Progress
Report

Welcome Message from Anantha Shekhar

I would like to introduce you to the Indiana Clinical and Translational Sciences Institute. The Indiana CTSI is a statewide laboratory established in 2008 with a multimillion dollar grant from the National Institutes of Health supplemented by matching funds from our member institutions. It is a model of innovative public and private partnerships whose goal is to speed the transition of discoveries in the lab into new treatments and therapies in the health care system. And as one of 60 regional “homes” for clinical and translational health established by the NIH, we also connect researchers and innovators in Indiana to others with a similar mission across the country.

As the only statewide translational hub in this national program, the Indiana CTSI is led by Indiana University, Purdue University, and the University of Notre Dame. Over the past four years, we’ve made great strides in creating a translational research pipeline that carries discoveries from “bench to bedside,” including distributing \$12.5 million in grants and awards to promising research projects. We currently support over 80 full-time equivalent professional jobs across the state, contributing to its economy in our own small way. This report highlights some of the greatest achievements to arise from this improvement in research infrastructure, including drug development projects targeted at diseases such as autism and osteoporosis, a multi-institute partnership to advance the fight against cancer, and a device development program to assist people with Alzheimer’s disease.

We’ve also developed a new system to connect patients with clinical research and contributed to community health projects that range from downtown Indianapolis to southern Kenya. We also possess a strong commitment to basic research, the foundation for all scientific accomplishment, spotlighted in vignettes throughout this report.

Our mission is to translate new ideas from the lab or the classroom into new health care practices or therapies in the community. Our programs support our five mission goals—to encourage translational research, to train the next generation of translational researchers, to engage with the local community, to provide access to the latest equipment and technologies, and to foster collaboration between colleagues and across institutions.

The Indiana CTSI is working to transform the things we do every day as scholars and researchers—to connect people in order to create new knowledge, new products, and new ideas—and to do it faster and more efficiently.



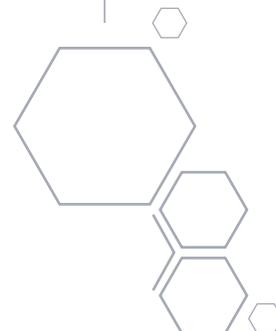
Anantha Shekhar, M.D., Ph.D., director of the Indiana CTSI

Acknowledgments

The Indiana CTSI would like to acknowledge the generous financial, intellectual, and scientific contributions of its institutional partners in helping make its first four years a tremendous success. Institution partners include the Indiana University School of Medicine, Indiana University–Purdue University Indianapolis, Indiana University Bloomington, Purdue University, and the University of Notre Dame.

Our special thanks go to D. Craig Brater, M.D., dean of the IU School of Medicine; Charles R. Bantz, Ph.D., chancellor of IUPUI; Jorge V. José, Ph.D., vice president for research at IU; Richard O. Buckius, Ph.D., vice president for research at Purdue; and Robert J. Bernhard, Ph.D., vice president for research at Notre Dame.

We also wish to thank the many local, state, and national public and private partners whose contributions help the Indiana CTSI accelerate research across Indiana and beyond. The complete list of our affiliated university, business, health care, and community groups can be found at indianactsi.org/about/partners.



Sincerely,

A handwritten signature in black ink that reads "Anantha Shekhar". The signature is fluid and cursive, written in a professional style.

Anantha Shekhar, M.D., Ph.D.
Director, Indiana CTSI

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About the Indiana CTSA: The Indiana Clinical and Translational Sciences Institute is a statewide collaboration between Indiana University, Purdue University, the University of Notre Dame, and public and private partnerships that facilitates the translation of scientific discoveries in the lab into new treatments and therapies in Indiana and beyond. It was established in 2008 with a \$25 million Clinical and Translational Science Award from the National Center for Research Resources of the National Institutes of Health, supplemented by the state, the three member universities, and public and private partnerships. Indiana CTSA is a member of a national network of 60 CTSA-funded organizations across the United States. For more information, visit <http://www.indianactsi.org>.



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Research

The Indiana CTSI is committed to accelerating translational research by funding pilot projects and providing researchers with strategic leadership and mentorship to identify, evaluate, and support innovative research at each step of the translational cycle.

Researchers Receive Grant to Curb Sexually Transmitted Disease

IU researchers are revealing the microorganisms behind many common—but poorly understood—bacterial infections affecting sexually active men in Indiana.

Barbara Van Der Pol, Ph.D., assistant professor of epidemiology in the School of Health, Physical Education, and Recreation at IU Bloomington, and David Nelson, Ph.D., assistant professor of biology at IU Bloomington, are co-investigators on a \$6.1 million grant from the National Institutes of Health Human Microbiome Project. The project is one of just eight nationwide selected to receive funding from this NIH project. J. Dennis Fortenberry, M.D., professor of pediatrics at the IU School of Medicine, serves as the principal investigator.

“This project will play a key step in the NIH’s larger mission to identify and understand all the microbes in the human body,” said Dr. Fortenberry. “Although our bodies contain trillions of these microorganisms, surprisingly little is known about their role in human health and disease, especially as related to men’s sexual health.”

The study combines anonymous patient data from healthy men and patients at an STI/STD clinic in Indianapolis with high-tech molecular analysis, and is uncovering the physical and behavioral causes behind urethral infections in men. Early support for the project was provided by the Indiana CTSI.

“This is actually the main cause of male health care visits to HMOs and other federal care institutions,” says Van Der Pol, citing a 2001 study in which nearly 70 percent of first-time clinical visits by men were related to urethritis, which includes inflammation of the urethra, pain during urination, pain during sex, or burning and itching.

“Less than one in five of the urethritis cases from the 2001 study could be effectively diagnosed and treated,” added Van Der Pol.

Undiagnosed cases, or “idiopathic urethritis,” may be triggered by parasites, viruses, or bacterial infections such as gonorrhea and chlamydia. The least understood infections stem from bacteria that cannot be grown in a lab—making it difficult for scientists to conduct testing.

Van Der Pol works closely with officials at the Bell Flower Clinic, a sexual health clinic operated by the Marion County Department of Public Health STD Control Program, whose patients provide the samples analyzed by Nelson.

The goal? To pinpoint the precise microbial communities behind these “idiopathic” infections. Early findings have been eye-opening, says Van Der Pol; one such finding identifies infected men who lack a bacteria that, in women, serves a protective function. Analysis also reveals some men are carrying a bacteria more commonly associated with women suffering from complications in pregnancy, such as miscarriage, which they may pass on during intercourse. Both findings suggest the study on men may impact women’s health as well.

The study is resulting in new insights into previously unexplored bacteria, and also may help predict behaviors most likely to cause urethritis, including the role of same-versus opposite-sex couplings or the type of sexual activity in which they’re engaged.

Van Der Pol says the next step is using this data to create practical sexual behavior recommendations for at-risk populations—empowering patients to take greater control of their health.

Barbara Van Der Pol, Ph.D., and David Nelson, Ph.D., are co-investigators on a \$6.1 million grant to study male STD/STIs from the Human Microbiome Project of the National Institutes of Health.





Photo: John Gentry, IUPUI

Craig Erickson, M.D.



common inherited form of developmental disability, with as many as two-thirds of individuals with the disorder displaying evidence of autism spectrum disorders.

“We have been treating small numbers of both adults and children and have observed improvements in eye contact, social interaction, and speech,” says Dr. Erickson. “This is very early work, but it appears promising.”

Acamprosate affects chemicals in the brain by blocking certain receptors associated with mental health. The trial supported by the Indiana CTSI will explore its ability to reduce various autism symptoms, including inattention, hyperactivity, language impairment, irritability, and social deficits in 5- to 17-year-old children with fragile X syndrome.

In addition to partial support for the clinical trial, the Indiana CTSI supports this research through a two-year career development award to Dr. Erickson.

“Dr. Erickson’s research and work in this area is unique,” says Bradley Fravel, Ph.D., M.B.A., a senior technology manager at the IU Research and Technology Corporation. “IURTC has applied for a use patent because—while we are far from definitive knowledge and treatment—early data [suggests] this drug has real potential as a therapy for both children and adults with autism.”

In November 2010, Dr. Erickson and colleagues reported in the *Journal of Autism and Developmental Disorders* on the first trial of acamprosate in adults with fragile X syndrome and autism. The drug was associated with improved linguistic abilities in the three patients studied. During five months of treatment all showed unexpected marked communication improvement.

The preliminary data on acamprosate in individuals with fragile X syndrome seems promising, says Dr. Erickson, who also cautions that larger scale, multicenter clinical trials are needed to reveal the drug’s true potential.

Drug Used to Treat Alcoholism May Help Those with Fragile X and Autism

The Indiana CTSI is supporting a clinical trial to further research that suggests adults and children with autism and fragile X syndrome show improved communication and social behavior when treated with acamprosate, a drug currently approved by the Food and Drug Administration for the treatment of alcoholism in adults.

Craig Erickson, M.D., assistant professor of psychiatry at the IU School of Medicine and clinical director of the Christian Sarkine Autism Treatment Center, is the inventor on a pending utility patent for the use of acamprosate as a therapeutic agent for fragile X syndrome, the most common inherited form of intellectual disability and the most frequent single gene cause of autism. Fragile X syndrome is the most

Computer models to detect early signs of Alzheimer’s

Michael Jones, Ph.D., assistant professor of psychology at IU Bloomington, and Andrew Saykin, Psy.D., Raymond C. Beeler Professor of Radiology and director of the IU Center for Neuroimaging, IU School of Medicine, are exploring advanced computational models to detect Alzheimer’s disease.

Building upon evidence that a “loosening of semantic relationships” is an early warning sign of Alzheimer’s disease, Jones and Saykin are analyzing perceptions about common connections between words to detect early warning signs for the disorder. (Healthy subjects will generally connect “cat” to “dog,” for example; patients

with mild cognitive impairment—a predictor of Alzheimer’s—are more likely to suggest less related pairings, such as “cat” and “pig.”) The contrast between word connections generated by computer models and responses from human subjects asked to recall long lists of related words may accurately identify patients suffering from the earliest effects of the disease.

Early detection is the greatest hope for treating the worst effects of Alzheimer’s disease, says Jones. This project is supported in part by a \$75,000 Collaboration in Translational Research grant from the Indiana CTSI.



Robots That Teach Kids to Combat Autism

According to data published in spring 2012, one out of every 88 children born in the U.S. is diagnosed with an autism spectrum disorder. Treatment for those children requires as much attention as the diagnoses.

Joshua Diehl, Ph.D., assistant professor of psychology at the University of Notre Dame, specializes in developmental disorders, with an emphasis on autism spectrum disorders and dyslexia.

“The signature characteristic for all children with autism is difficulty communicating,” adds Diehl, whose research projects and therapies focus on helping children with autism break through those barriers and communicate more effectively. “Many of the children desire to be social, but comprehension is a barrier.”

In therapy sessions with children with autism, Diehl focuses on breaking down those individual behaviors and teaching communication piece by piece. One method is through the use of “Nao,” a robot programmed to simplify communication behaviors such as gestures and facial expressions, and teach children with autism how to use and understand them.

This sort of intervention takes place on a regular basis in the F.U.N. Lab—the whimsically named Laboratory For Understanding Neurodevelopment—and is supported in part by a \$20,000 grant from the Indiana CTSI Project Development Team at Notre Dame.

“In a simple conversation, there are gestures, facial expressions, words, and voice inflection—all of which come naturally for most people,” Diehl says. “Children with autism don’t always understand social conventions or norms. They can accomplish these behaviors individually, but putting them together is difficult.”

These intuitive behaviors need to be taught. Moreover, Diehl says many children with autism respond more readily to interactions with Nao. As comfort level improves, they grow more comfortable with the transition from robots to people.

“The most important part of social interaction is understanding what’s being said and being able to be understood,” says Diehl. “If we can bridge this social gap,



Photo: Matt Cashore, University of Notre Dame

it will open up so many doors for children with autism and help them in all aspects of their lives.”

As the timeline for autism diagnosis has shrunk over the past few decades, from age 4 to 5 years to 6 to 18 months, Diehl says many pediatric interventions focus on increasingly younger children. Yet the need remains for intervention for older children with autism.

“We need to focus on services and therapies for children beyond the first few years of life,” he says. “What can we do for a child with autism who’s 11, 12, or even 18? These parents are still looking for ways to help their children.”

One study conducted by Diehl geared toward older children and adolescents with high-functioning autism or Asperger syndrome focuses on language comprehension.

“We are trying to understand how children with autism spectrum disorders perform on a range of tasks measuring language comprehension abilities,” he says, “and compare them with typically developing children and adolescents.”

Continuing research is crucial for understanding what works for children with autism as well as how to use that information for effective treatment plans.

“In an ideal scenario,” says Diehl, “children would receive individualized treatment for areas in which they’re struggling and benefit from those tailored treatments throughout their lives.”

Preventing pathogenic bacteria infections

Joshua Shrouf, Ph.D., assistant professor of civil engineering and geological sciences and a member of the Eck Institute for Global Health at the University of Notre Dame, is conducting an investigation into *Pseudomonas aeruginosa*, an opportunistic pathogenic bacterium that commonly affects patients with cystic fibrosis, severe burns, and gastroenteritis—not to mention individuals who fail to properly clean their contact lenses.

With Indiana CTSI support, Shrouf is working to reveal the various ways in which *P. aeruginosa*

spreads, with an eye toward more effectively preventing infections. Among the revelations uncovered by his work has been a strange spreading growth pattern—or “walking” action—witnessed over countless hours of laboratory observation.

The discovery of this ability of the bacteria to “stand up” and move about while vertical—seen specifically in environments with certain wet properties—may provide new insights into infections that affect moist environments, such as the lungs or wet skin.



Advancing the Fight Against HIV in Africa

You often hear that children are the future. In western Kenya, that future depends to a great extent on the health of children infected with HIV.

Rachel Vreeman, M.D., assistant professor of pediatrics at the IU School of Medicine, is doing her part to bring the HIV epidemic in Africa under control by ensuring that children

with the disease get the medicine they need to transform the disease from a fatal illness into a chronic but manageable condition. Her work is supported in part by the Indiana CTSI, from which she received a \$75,000 postdoctoral research fellowship in 2008.

“We’re focusing on helping infected children learn to live a lifetime with medication,” says Dr. Vreeman, co-director of pediatric research for AMPATH, an outgrowth of IU’s collaboration with the Moi University School of Medicine in Eldoret, Kenya. “HIV medications must be taken consistently, otherwise the HIV virus can mutate into a form that is resistant to treatment. Ensuring that children take their medicine correctly can be difficult amidst challenges that range from a lack of adequate nutrition to a culture that often still stigmatizes HIV infections.”

Since 2001, AMPATH’s medical staff have cared for more than 100,000 patients, including 20,000 children. Identifying children with problems taking their medicines, then developing responses to those problems, drives Dr. Vreeman’s research in Kenya.

“Adherence to the HIV medicines may seem like a narrow issue, but it is crucial to our larger work,” she says. “Over the long term, adherence to these medicines is absolutely vital to sustaining what we’ve done to keep people alive.”

And so in a small office in Eldoret, Caroline Watiri Maina, a Kenyan research assistant, talks to a mother who had brought her seven-year-old son, and his medicine, to the AMPATH clinic. As she walked the woman through a questionnaire about her son’s success in taking his medications, Maina removed the cap from a medicine bottle—and plugged it into a laptop.



Photo: Indiana University School of Medicine

Rachel Vreeman, M.D., assistant professor of pediatrics at the IU School of Medicine

Modeling fetal alcohol syndrome with zebrafish

With support from the Indiana CTSI Project Development Team program, Marisol Sepulveda, D.V.M., Ph.D., associate professor of forestry and natural resources at Purdue University, is developing an animal model for fetal alcohol syndrome in zebrafish.

Although they may seem an unlikely candidate, Dr. Sepulveda says zebrafish serve as a good animal model for fetal alcohol syndrome because their genetic code shares many similarities to the human genome. Moreover, they may be exposed to ethanol as embryos more easily than more

traditional mammalian models that gestate inside the body of the mother—and offer significant cost savings compared to more “traditional” animal models due to their ability to reproduce quickly and in large numbers.

This project is being conducted at the Bindley Bioscience Center at Purdue University, a partner institution of the Indiana CTSI.





Photo: Eric Schoch, Indiana University School of Medicine

Caroline Watiri Maina, a Kenyan research assistant, speaks to a mother about her son's HIV medication adherence.



The high-tech bottle cap is a key component of the research project. It contains a computer chip that detects when the bottle is opened. The next time the patient visits the clinic, Maina or another coordinator will transfer the information to the computer, which will display the day and time the bottle was opened. This gives the researchers a picture of exactly when the patients are—or are not—taking their medicine.

“We have to remind them to open it only when they are taking the medicine because that’s the only way we can know what time they are really taking it,” she says.

Maina’s computer says the woman’s son missed medications on three separate days. The mother says she will be more vigilant.

Adherence issues are complicated by social and cultural issues, such as continued stigma about HIV infection. Simply taking medicines regularly can seem “suspicious”

in a community where few people are treated for chronic illnesses, which also include high blood pressure or diabetes.

Moreover, children who are successfully being treated for HIV will appear healthy, which makes their need to take medications regularly seem odd, or unimportant, to those who don’t know their status.

Although Dr. Vreeman and her colleagues perform counseling and referrals, their primary goal is to hone the questionnaire they use to learn why—or why not—children are getting their medicines.

In the next phase, Dr. Vreeman’s team will begin making home visits to ask about compliance—AMPATH’s emphasis on getting out into the community that has helped make the program a success.

“We’re worried we’re missing kids who need help,” she says. “Until we know who is having problems, we can’t help them.”

Improving pediatric cancer treatment in Kenya

Jamie Renbarger, M.D., assistant professor of pediatrics and clinical pharmacology at the IU School of Medicine, is working to quell the negative side effects caused by vincristine, an anti-cancer drug commonly used in children.

Early research suggests children who naturally produce the CYP3A5 enzyme in greater quantities are less likely to experience negative symptoms. Among those largely unaffected were younger children as well as African-American youths, who only suffered adverse effects 4.5 percent of the time, versus 34.8 percent in Caucasians. To further the project, Dr. Renbarger has expanded her work to Kenya, where the IU School of Medicine conducts

an international medical program in partnership with the Moi University School of Medicine. Early results appear to confirm that African children experience fewer negative symptoms from the drug, suggesting they may react positively to higher doses—improving its effectiveness in the fight against cancer both at home and abroad.

The project is supported by about \$3 million in federal research grants, including more than \$383,800 from the Clinical and Translational Sciences Award of the National Institutes of Health. The CTSA grant has been awarded jointly to the Indiana CTSI and CTSA centers at the University of Michigan, Vanderbilt University, and George Washington University.



New Compound May Accelerate Bone Healing, Prevent Osteoporosis

An Indiana CTSI scientist studying human bone growth has received a \$2.6 million grant from the U.S. Department of Defense to study a chemical compound with potential to fight osteoporosis and accelerate broken bone healing.

Hiroki Yokota, Ph.D., professor of biomedical engineering at IUPUI, will investigate the effect of salubrinal—a chemical compound originally developed to encourage insulin production in individuals with diabetes—on human bone strength and growth. Early laboratory research



supported by the Indiana CTSI suggests weakened bones treated with salubrinal experience a statistically significant increase in strength—as well as accelerated healing in bones that have been fractured.

“As a mechanical engineer, I was originally exploring mechanical stimulation—exercise—to strengthen bones,” says Yokota. “But by studying these mechanisms, I came across a molecular pathway that became the beginning of this discovery.”

Acute pelvic and hip fractures account for about 350,000 hospitalizations each year in the United States, with 76 percent of patients being female and annual cases expected to reach 650,000 by 2050. About 25 percent of fracture patients previously living independently require full-time nursing care post-fracture, with only a quarter returning to pre-injury levels of activity and half never fully recovering.

Older populations are increasingly affected by weakened and broken bones because aging cells are no longer able to produce sufficient levels of collagen, the protein from which bones derive their strength. Salubrinal prevents this cellular decline by strengthening the body’s “protein-producing machinery,” which creates collagen and keeps bones strong.

“In preliminary studies, particularly in bone fractures, we’ve seen an effect in as little as a week,” says Yokota, “and the effect is even stronger in two weeks. We’re not ready to cite numbers, but I can say it appears significant.”

He notes that the process by which salubrinal heals fractures may also apply to type 2 diabetes, the disease for which salubrinal was originally developed.

“Salubrinal stimulates a cellular ‘rescue program’ in response to stress,” says Yokota, noting that some diabetes may be caused by the pancreas killing insulin-producing islet cells in response to increased insulin needs—a process similar to the cellular shutdown that can occur in bones overtaxed by collagen production.

“With this drug,” he adds, “the cells just enjoy the body’s rescue response without really experiencing any new negative pressure. Using salubrinal is basically about trying to treat cells a little better.”

Reducing chronic pain with cannabinoids

Ken Mackie, M.D., professor of psychological and brain science at the Gill Center for Biomolecular Science at IU Bloomington, is investigating the treatment of chronic pain with cannabinoids, chemical compounds structurally related to THC, the primary psychoactive component in cannabis.

In collaboration with Michael Vasko, Ph.D., Paul Stark Professor and chair of pharmacology, and professor of anesthesia at the IU School of Medicine, Dr. Mackie is trying to close the gap between research into CB1 and CB2. The first is a well-known cannabinoids receptor in

the brain that reduces pain but also produces undesired psychoactivity; the other is an under-investigated immune- and brain-cell receptor that seems to reduce pain but not produce psychoactivity. The project is supported by \$75,000 from the Indiana CTSI.

“The overall reason for this research is that inadequately treated chronic pain is a major problem in the U.S.,” says Dr. Mackie, noting chronic pain affects about 70 million Americans.



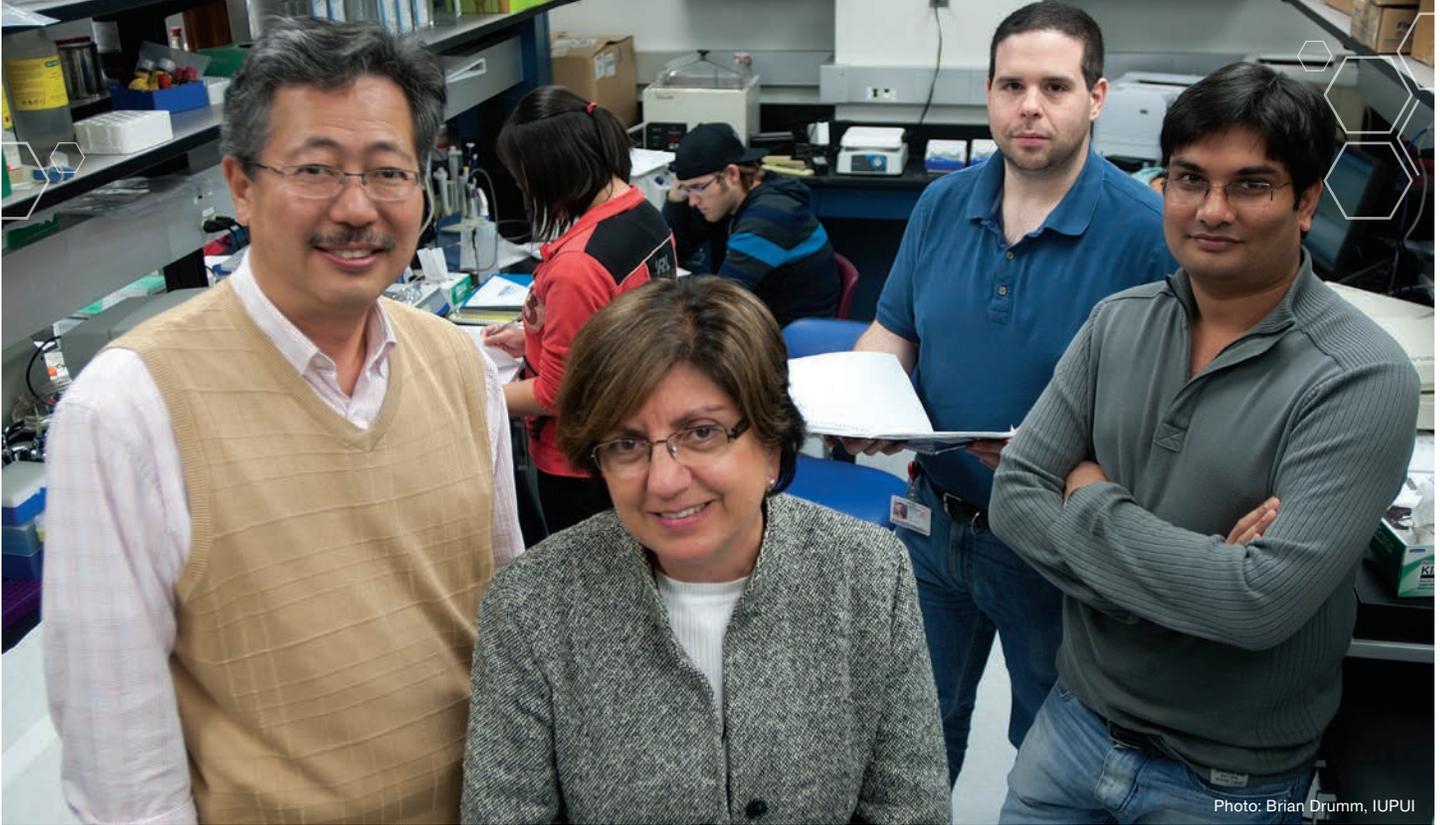


Photo: Brian Drumm, IUPUI

Hiroki Yokota, Ph.D., professor of biomedical engineering, IUPUI, and Teresita Bellido, Ph.D., professor of anatomy and cell biology, IU School of Medicine, with team members Jeffrey Benson (Bellido Lab) and Gaurav Swarnkar, Ph.D. (Yokota Lab).

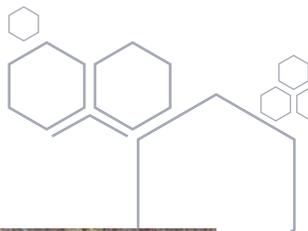
The DOD funds will help support continued research into salubrinal’s effect on broken or weakened bones, and the development of dosing guidelines. In addition, Yokota’s project received key early support from a \$20,000 Research Inventions and Scientific Commercialization Grant. The funds fueled research identifying a chemical partner that combines with the salubrinal to create a safe, nontoxic drug easily absorbable by the human body.

Developing a pill from the compound’s current, injectable

form—which will make it easier to administer as well as increase its potential marketability—is also a priority.

“Our ultimate goal is FDA approval to provide a safe, efficacious, easy-to-use drug therapy that will heal hip fractures in the geriatric population,” says Yokota, who aims to move the drug toward early clinical trials.

Additional support for Yokota’s other projects related to bone strength and growth comes from the National Institutes of Health and NASA.



Building better pancreatic cells for transplantation

Jenna Rickus, Ph.D., associate professor of agricultural and biological engineering at Purdue University, is exploring the biosilicification of pancreatic islets for transplantation, with support from the Indiana CTSI.

Although islet transplantation is a potentially viable therapy for type 1 diabetes, Rickus says patients who encounter good outcomes early on don’t generally go on to long-term success. Soft polymers to protect and support implanted islets from rejection by the patient’s immune system have met limited success, but aren’t able to

overcome long-term immune and inflammation problems or delays to the insulin-glucose control system caused by the barrier these polymers erect between islets and molecular structures in the body.

With Raghu Mirmira, Ph.D., M.D., associate professor of pediatrics at the IU School of Medicine, Rickus is exploring a new approach using biosilicification to create extremely thin encapsulation materials that won’t interfere with the islet’s natural functions but still protect against negative immunoresponse.





Community

The Indiana CTSI fosters robust community engagement by creating novel programs in which participation flows from academia to the community and back again. Support structures include the Indiana Community Health Engagement Program (CHEP) and pilot programs in rural and global health research.



Photo: John Gentry, IUPUI

Sarah Wiehe, M.D., M.P.H., and Gabriel Filippelli, Ph.D., analyzed Indianapolis neighborhoods for lead contamination.

Urban Health Project Protects Against Pediatric Lead Infection

They once made the city a center for industry, but the old factories of Indianapolis also left behind a harmful environmental legacy. Now research by two IUPUI faculty could help Hoosiers protect against the worst health effects of this toxic inheritance.

Gabriel Filippelli, Ph.D., professor and chair of earth sciences at IUPUI and previously an oceanographer in California, says a desire to explore local issues prompted him to “dig into” urban soil contamination after relocating to the Midwest.

Using data from a graduate student thesis, he performed a preliminary investigation that suggested a connection between soil lead levels and childhood lead poisoning. But more precise medical data was needed to confirm the theory.

Together with Sarah Wiehe, M.D., M.P.H., assistant professor of pediatrics at the IU School of Medicine, Filippelli applied for assistance from the Indiana CTSI Project Development Team program, which brings together subject experts from across Indiana University, Purdue University, and the University of Notre Dame to provide investigators access to expert project planning advice. The group also may offer discretionary grants to promising research projects.

With \$18,000 from the Indiana CTSI, Filippelli obtained more than 16,000 data points from local children tested for lead poisoning from 1999 to 2008, including not only their test results but also information on race, sex, age, socio-economic status, and—most important—addresses. Data mining services and database access also were provided by the Regenstrief Institute, an Indiana CTSI partner.

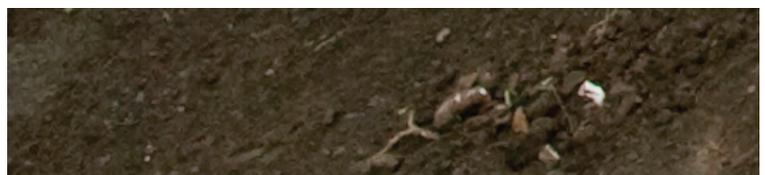
Using geolocation methods to correlate this data against a map of the city, Filippelli was able to successfully confirm that low-income children in residences near the city’s formerly industrial center were also those who experienced significantly higher blood lead poisoning rates. Causes range from the fact that children in low-income neighborhoods are more likely to play outside to the observation that yards in richer households generally provide a thicker layer of protective topsoil. The age of the paints and other building materials used in poorer homes may also increase the risk of lead exposure in children.

The ability to confirm a connection between lead levels in the soil and the blood is the first step in reducing exposures, says Filippelli. The results reveal multiple pathways by which lead may go from the soil to children, including not just former industrial emissions but also the legacy left by the use of leaded gasoline and lead-based paints.

Based in part on the strength of this study, Filippelli and colleagues successfully received \$300,000 from the IUPUI Signature Center Initiative Program to establish the IUPUI Center for Urban Health.

The center will focus on environment, community, and health. The goal is to enhance health and sustainability for urban populations, with an eye toward both environmental legacies and emerging threats.

Daniel Johnson, Ph.D., assistant professor of geography at IUPUI, and Terrell Zollinger, Dr.P.H., professor of public health at the IU School of Medicine, are also among the center’s founders.



Pioneering Patients Advance Medicine with Online Registry

When Fred Kocher walked into his doctor's office 10 years ago, he expected a routine checkup. He walked out diagnosed with multiple myeloma—a form of cancer that affects white blood cells—and a frightful prognosis.

“At that time the expectation was my lifespan would be about two to four years from the date of diagnosis,” says Kocher. “Now my condition is basically stable—very little has changed since my original diagnosis in 2001.”

Kocher credits his longevity to his physician, Rafat Abonour, M.D., an oncologist at the IU Melvin and Bren Simon Cancer Center and a leader in clinical trials recruitment with Indiana CTSI. Dr. Abonour encouraged Kocher to participate in three clinical trials that provided early access to life-saving medications, including Revlimid, a cancer drug approved for widespread use by the FDA in 2006.

“I've benefitted from a combination of approved drugs as well as rapid improvements in clinical research for myeloma,” says Kocher. “For me, clinical trials have been very effective.”

Dr. Abonour says pioneering patients—as well as healthy volunteers—willing to participate in research studies are key to transforming discoveries from the laboratory into new treatments in the community. Too many promising research projects fail in the early to mid stages due to lack of study participants, with patients failing to benefit from the results.

A powerful online tool developed by the Indiana CTSI offers those interested in contributing to research a way to discover studies in which they may be eligible to participate. INresearch.org is an online volunteer registry that streamlines and accelerates the process by which medical discoveries reach patients in the health care system.

Individuals who sign up at INresearch.org create and manage an online health profile. Volunteers may then be invited to join a study when their health information matches the criteria of a specific research project.

Participation may include answering a survey, taking part in interviews, undergoing a physical exam, or trying a new treatment or medication.

“I think the registry will provide two tiers of benefit,” says Dr. Abonour, who is also a professor of pathology and laboratory medicine at the IU School of Medicine. “As healthy volunteers and patients with certain conditions sign up and indicate their willingness to participate—or to be approached about discussing certain treatment options that may be available to them—we will gain information about



many new people available for research studies. The registry is also searchable by patients interested in open studies that may improve their outcomes.”

“I'm grateful to anyone who's ever participated in a research study,” says Anantha Shekhar, M.D., Ph.D., who is the director of the Indiana CTSI as well as a practicing psychiatrist. “After a career of working with patients with chronic disabling mental conditions—where we don't fully understand the causes and for which we have few successful treatments—I understand the urgency for more research.”

Participating in a research study “offers hope to patients through the invaluable information it provides to doctors and scientists working to transform promising new medical discoveries into a wider reality,” he adds.

Kocher, the multiple myeloma patient, agrees.

“I feel like I'm part of the advancement of medical science—as well as a true beneficiary of all the great work that's come before me.”

Rafat Abonour, M.D., meets with Fred Kocher, a multiple myeloma patient and clinical trial volunteer.

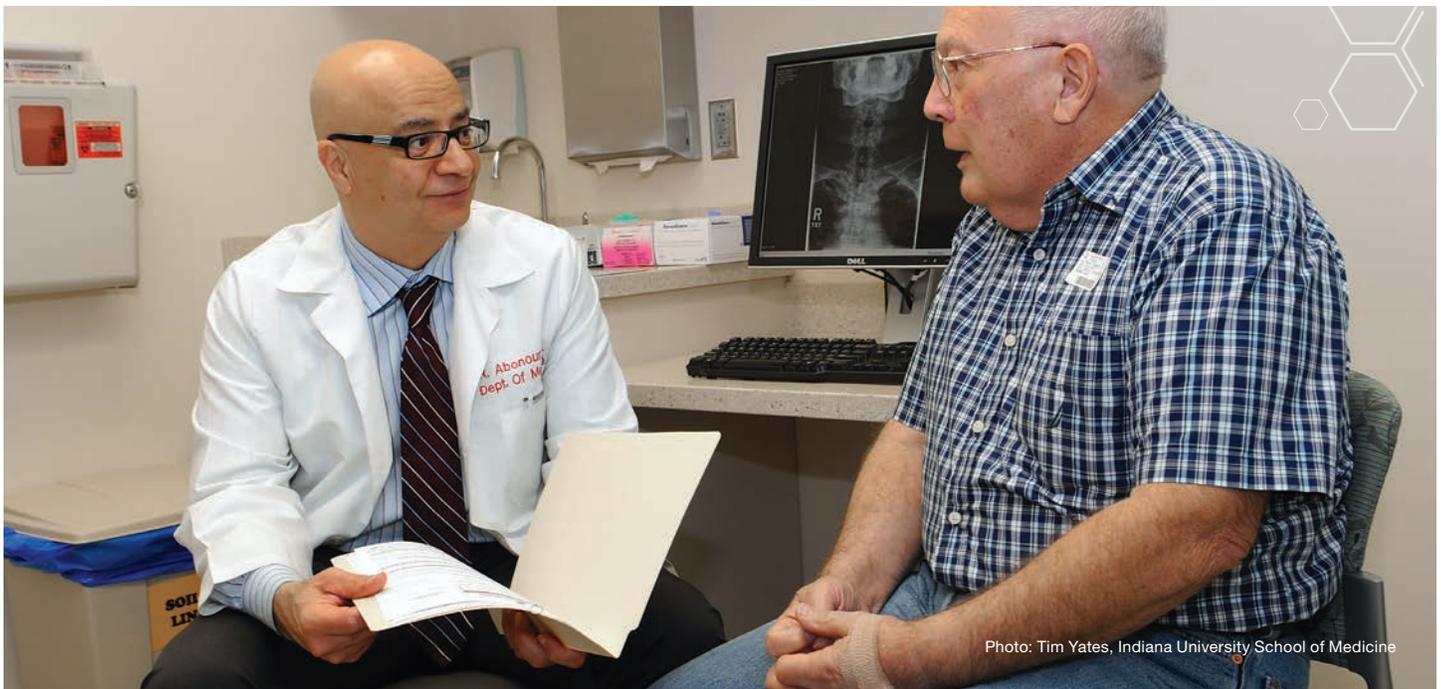


Photo: Tim Yates, Indiana University School of Medicine

Pearl Grlz Project Merges Art and Science to Protect Urban Teens Against Neighborhood Risks

It's hard to imagine a greater gulf than the gap between the language of scientific research and teenage girls, but Sarah Wiehe, M.D., M.P.H., associate professor of pediatrics at the IU School of Medicine, says that's exactly the span she had to bridge to implement an innovative research project on health risks in adolescent girls supported by the Indiana CTSI.

The "Pearl Grlz" project—so named for the eponymous Blackberry Pearl cell phone model and a texting abbreviation for "girls" popular among teens—uses GPS data from cell phones to correlate risk factors among girls age 14 to 17 with their physical environment. The participation of 50 teens from the west side of Indianapolis has grown the project into a true success story—thanks to a unique effort to merge art and science between Dr. Wiehe and Helen Yuko Sanematsu, M.F.A., assistant professor of visual communication design at the Herron School of Art and Design at IUPUI.

"Helen really brought an entirely different perspective to the table," says Dr. Wiehe, who met Sanematsu at a neighborhood association meeting in Indianapolis. "She really gets how to engage the community in research with visual communication."

At first no one was eager to support the study due to concern that participants wouldn't consent to being monitored by their cell phones, says Wiehe. But they failed to grasp the extent to which ideas about privacy have been altered among today's teens by the forces of technology—especially social networking—not to mention the allure of a top-shelf cell phone with unlimited text messaging.

After earning strong adolescent participation in a pilot study funded by IU Health and the IU School of Medicine's General Clinical Research Center—later a part of the Indiana CTSI—Pearl Grlz garnered \$300,000 from the Robert Wood Johnson Foundation (RWJF) Physician Faculty Scholars Program to expand the project. The pilot study received \$20,000 from the Indiana CTSI.

Yet recruitment for the RWJF-funded study grew challenging. Unlike the pilot project, in which the girls were personally recruited by a research specialist at a local health clinic, the new study meant going into the community.

The key to successful engagement required turning recruitment materials over to teens—to learn what messages spoke to their generation. With assistance from a key research team member, Bwana LaToy Brooks, Dr. Wiehe and Sanematsu began to run "focus groups" to learn the language of teenage girls—and also to get a sense of their "visual landscape."

Helen Yuko Sanematsu, M.F.A.



Dr. Wiehe even bicycled around the girls' neighborhood to solicit opinions on new poster designs created by Sanematsu.

"We got teen girls involved in developing the message," says Sanematsu. "We started talking the language of the target population, not the language of the Ivory Tower."

The new posters sported appealing graphic design and information about the cell phone being used in the study. Teens were unconcerned about the information disclosure required by the study, says Dr. Wiehe; they simply wanted practical information about the phone.

Yet the girls also seemed eager to talk about deeper topics and volunteered information about the risky situations they encounter away from home, such as places they met pressure to have sex, to drink, or to use drugs. "Adolescents spend half or more of their life not at home," says Wiehe. "If we can track where they spend that time, we might be able to tailor interventions using cell phones as a platform. If we know girls are more likely to engage in risky behaviors in a crime-ridden area or far from home, then we could target their phones in real-time with text messages suggesting they use protection or consider an alternate activity."

Now, Dr. Wiehe and Sanematsu are collaborating on a new project using blogs to learn about the lives of Latino teens supported by a \$20,000 grant from the Indiana CTSI Pediatric Project Development Team.

The insights from the Communicating Life in Our Community (CLIC) project will support recruitment for the next phase of Pearl Grlz, which will track 20 teens for 18 months—the longest study yet.

"We want to achieve equal representation among white, African-American, and Latina girls in this phase," says Dr. Wiehe. "We want to reach out to everyone in the community."





e-education

The Indiana CTSI is training the next generation of translational researchers by strengthening existing programs, and creating new ones, to educate trainees and engage faculty in the translational sciences.



Photo: Australian National University

The John Curtin School of Medical Research at Australian National University

Australia Visit Advances International Exchange Program

Through a groundbreaking partnership with Australian National University (ANU), the Indiana CTSI will spread expertise in translational medicine from America's heartland to across the globe.

The project to establish an exchange program in translational medicine between ANU and the Indiana CTSI grew from a relationship that began after Anantha Shekhar, M.D., Ph.D., director of the Indiana CTSI, attended the First International Conference on Translational Medicine at ANU in fall 2010.

"This exchange program will provide the opportunity to look at translational research through a more global scope," says Dr. Shekhar. "It will not only create opportunities for international partnerships but also increase the quality of research supported by the Indiana CTSI."

Participants in the exchange program will be selected from among students at the three partner institutions of the Indiana CTSI—Indiana University, Purdue University, and the University of Notre Dame. The program will provide participants vital training in translational research methods as well as connections to mentors at the collaborative institution who have complementary interests.

Julio Licinio, M.D., director of the ANU John Curtin School of Medical Research (JCSMR), which last year

established a new department of translational medicine, says the university is "delighted" by the opportunity to collaborate with the Indiana CTSI.

"Indiana's strengths will provide our institute much-needed scientific partnerships across the full spectrum of translational science in the U.S.," he says. "Likewise, Indiana will have access to a broad base of research resources and a vast academic network in the Asia-Pacific region."

This access could include China's Beijing Genomics Institute, another institution through which ANU has established a joint research program.

The exchange program also will contribute to the Indiana CTSI's goal of advancing career development, with participants benefitting from the advantages that experience in international scholarship brings to the highly competitive scientific job market.

"Global partnerships also often result in stronger clinical research and higher impact research papers," adds Dr. Shekhar, noting significant funding opportunities are opened up by grant applications with international partners as co-PIs.

The first cohort of international exchange students to participate in the program will travel to Indiana and Australia in summer 2012.

Training the next generation of translational scientists

While most high school students spent their summer vacation out in the sun or at a summer job, Rachel Hawn contributed to laboratory research on targeted gene therapy for colorectal and cervical cancer.

An Indianapolis high school student, Hawn serves as a lab intern through a project between the Indiana CTSI and Project SEED, an organization that pairs scientifically minded high school students with local researchers.

The program is a rare opportunity for pre-college students to participate in research. Previous participants have even had their names included in published research papers—a remarkable "extracurricular" on a college application.

"Never in my life, not even in college, did I think I would be working with cancer cells," says Hawn, joking that whenever her family hears about what she's working on, they say she's a genius.

The program matches approximately 20 high school students, 8 undergraduate students, and 26 medical students each year with faculty engaged in clinical or translational research.

Additional project partners include the IUPUI Center for Research and Learning and the IU School of Medicine Student Research Program in Academic Medicine.



t echnology

The Indiana CTSI provides comprehensive and versatile research resources and technologies by transforming the existing research infrastructure, as well as establishing new resources, to facilitate projects that bring discoveries out of the lab and into the health care system.

Helping Patients Regain Their Voices

Mary Yeaman, who participates in a special balance and strength program for patients with Parkinson's disease called Rock Steady Boxing, says the first sign that her voice had begun to fade came during a day at the gym. Her surprise was not from an unexpected right jab, but that a louder voice had stolen her conversation partner's attention.

For many people with Parkinson's disease, hypophonia, or "soft voice," is a serious but overlooked problem. Physicians tend to focus on quelling physical ailments, such as tremors, while missing less obvious symptoms like loss of voice—even as those symptoms can make patients feel as though they're disappearing in plain sight. Now a device developed by Jessica Huber, Ph.D., associate professor of speech, language, and hearing sciences at Purdue University, is helping patients like Yeaman raise their voice.

"Sometimes I would start crying, I would get so frustrated being left out of conversations," says Yeaman, whose voice nearly doubled in volume after four weeks on Huber's treatment. Now when people try to interrupt, she pipes up.

"I'll say 'I'm talking now, and you can all be quiet,'" she laughs. "People look at me—and they stop talking! Before, they spoke right over me; I felt like I didn't even exist."

In addition to social gatherings, Yeaman wears the device while running errands and working as a ticket taker at the Conseco Fieldhouse.

The device works by piping background noise into patients' ears when they speak—similar to the low murmur at a crowded cocktail party—prompting an unconscious psychological reaction known as the "Lombard Effect" that causes people to speak louder.

More than 30 patients have used the device, with the average user raising their intensity by about 5 decibels—a significant increase.

Developed by the Indiana CTSI Biomedical Engineering and Bionanotechnology Program at Purdue University, Huber's device is a small plastic tube that sits inside the ear and a wire that affixes to the neck via a small adhesive patch, which ensures the noise only activates when a patient is speaking. The hardware is housed in a small gray box worn around the neck on a lanyard or clipped on the belt.

The device development was supported by more than \$2 million from the National Institutes of Health, including nearly a quarter million from the American Recovery and Reinvestment Act. Additional contributions to the project include \$10,000 from the Indiana CTSI and \$18,900 from the Regenstrief Institute, to investigate potential integration into the health care system.

Recently, Huber received an additional investment of \$350,000 from the Alfred E. Mann Institute for Biomedical Development at Purdue University, Inc., a nonprofit institute located within Discovery Park at Purdue University. The funds will support creating a smaller, more sophisticated—and more marketable—version that fits entirely behind the ear and eliminates the need for a neckpiece.

"Getting to know the patients was a big change in my research direction," says Huber, whose focus has shifted from lab bench to bedside. "What I really want to do is find new ways to help."

The greatest priority is making the device available to a wider patient population, she adds. With support from the Indiana CTSI and Mann Institute, she is well on her way to that goal.

Jessica Huber, Ph.D., shows Mary Yeaman, a patient with Parkinson's Disease, how to use a device to teach her to speak louder.





Partnership

The Indiana CTSI leverages the resources of the greater Indiana community by connecting to a broad array of resources from multiple partner institutions throughout the state of Indiana. The Indiana CTSI has not only begun to connect the translational research activities within our partner institutions, but also enables connections between other institutions funded by the Clinical and Translational Science Award of the National Institutes of Health.

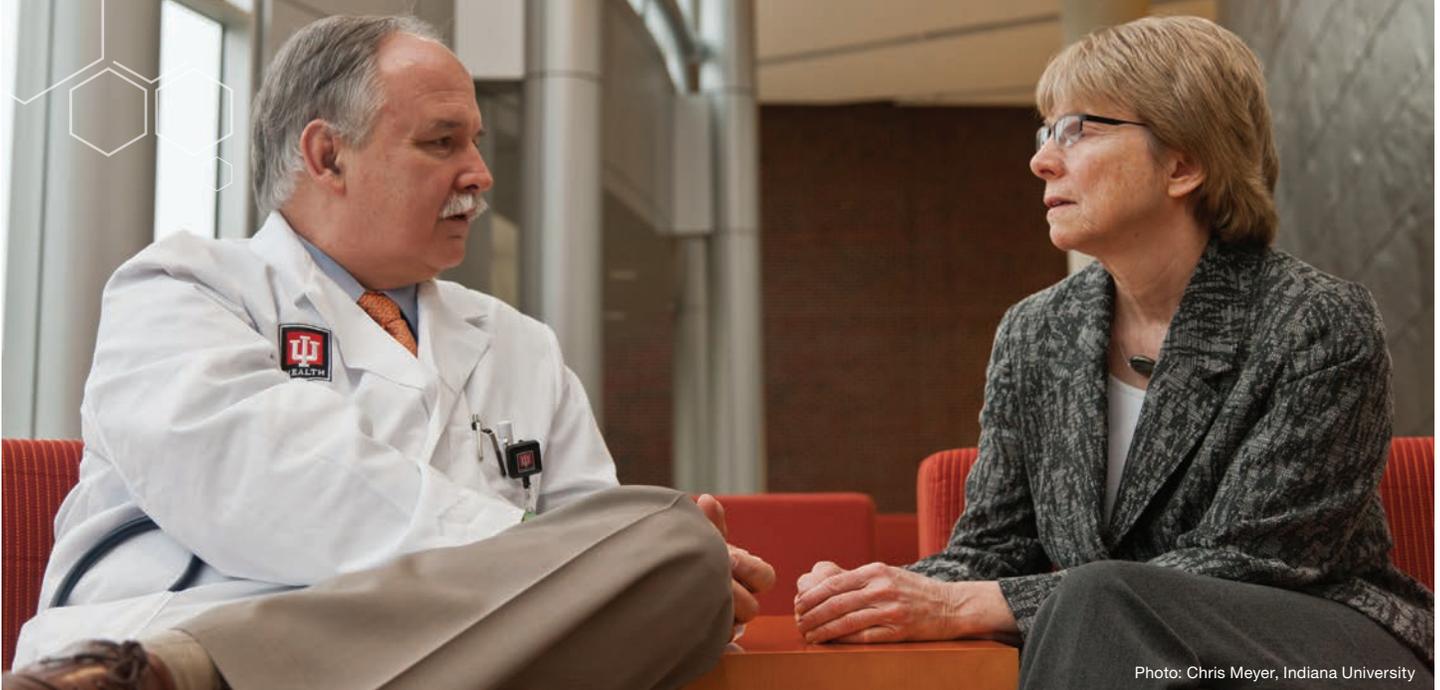


Photo: Chris Meyer, Indiana University

Patrick Loehrer, M.D., left, and Marietta Harrison, Ph.D.

Collaborative Project to Support Colon Cancer Research in Rural Indiana

Support from the Indiana CTSI is expanding a project to fight colorectal cancer across the state, from Indianapolis to rural and suburban communities in north central Indiana.

Supported by \$500,000 from the National Institutes of Health, the Indiana CTSI will grow technical and human resources to strengthen cancer research at IU Health Arnett Hospital in Lafayette. The project is a collaborative research effort between the IU Melvin and Bren Simon Cancer Center and the Oncological Sciences Center at Purdue University, and will focus initially on curbing colorectal cancer.

“As a partnership between the state’s three largest research universities, with strong ties to the state’s most comprehensive health system, Indiana University Health, I consider the Indiana CTSI uniquely positioned to support this sort of large-scale, collaborative project,” says Anantha Shekhar, M.D., Ph.D., director of the Indiana CTSI and associate dean for translational research at the IU School of Medicine. “Our technical expertise, patient recruitment knowledge, and sample storage capabilities all align with the

resources needed to bring this already successful project to the next level.”

The Indiana CTSI’s support will fuel two goals: expanding research technology and raising awareness about colorectal cancer research. Mary Lou Smith and Elda Railey, co-founders of the Research Advocacy Network (RAN), a nonprofit organization that brings together patients and researchers, will lead the community education project. RAN will recruit 30 to 50 community representatives to educate their neighbors about the disease and encourage positive actions in the fight against it. Participants will learn about the medical research system, clinical trials, and engage in “hands-on” learning in a medical laboratory.

“There are not nearly as many advocates for research in colorectal cancer as there are for other cancers, like breast cancer,” says Railey. “No one really wants to talk about it because it’s seen as an uncomfortable topic. The colorectal cancer community has very different needs.”

Technical support from the Indiana CTSI will enhance

Economic development mission to India bears fruit

In early 2011, Anantha Shekhar, M.D., Ph.D., director of the Indiana CTSI, joined Mitch Roob, former director of the Indiana Economic Development Corporation, and 13 leaders from Indiana’s life sciences sector for Indiana’s first economic development mission to India.

Following the trip, Indiana CTSI and GVK Biosciences, Asia’s leading contract research organization, forged a partnership to provide access across Indiana to GVK BIO’s Clinical Biomarker Database, a comprehensive collection of biomarkers reported in global clinical trials and in clinical and preclinical studies.

“This trip was a wonderful opportunity to strengthen our biomedical, informatics, and life sciences research resources in the global economy,” says Dr. Shekhar. “I was delighted to be asked to join Secretary Roob to highlight the strengths of IU, IU School of Medicine, and the Indiana CTSI’s academic and private partner institutions to our counterparts in India.”

Trip participants from Indiana CTSI partner institutions included Victor Lechtenberg, Ph.D., interim provost at Purdue University, and Robert J. Bernhard, Ph.D., vice president for research at the University of Notre Dame.





Photo: Brian Drumm, IUPUI

The IU Melvin and Bren Simon Cancer Center (above) and Oncological Sciences Center at Purdue University are partnering with the Indiana CTSI to expand the fight against colorectal and other cancers to rural and suburban communities in north central Indiana.

research infrastructure at the IU Simon Cancer Center and Purdue University. The integration of these institutions' electronic collaboration environments with a separate system used by the Indiana CTSI will accelerate research by providing a single, secure online location in which scientists may share, store, analyze, and annotate their data.

The original partnership between IU and Purdue was created to pioneer a new way to use tissue analysis in the fight against cancer. Scientists at the IU School of Medicine, IU Bloomington, Purdue, Notre Dame, and the University of Texas MD Anderson Cancer Center will subject clinical samples to multiple high tech tests, with the results deposited

into a single "cyberenvironment" accessible to researchers working on the project.

"There's so much information out there now it's difficult for researchers to navigate," says Patrick Loehrer, M.D., director of IUSCC and associate dean for cancer research at the IU School of Medicine. "The key to the future isn't generating more and more studies focusing on very small sample populations or a single form of analysis—it's performing all the key analyses on many samples and using computer models to predict individual risk factors or treatment benefits."

Nearly 300 tissue samples have already undergone analysis, with plans to collect 500 more from patient volunteers at IU Health Arnett. The samples will be stored in the Indiana Biobank, a high-tech sample storage facility managed by the Indiana CTSI.

Marietta Harrison, Ph.D., director of the OSC and associate vice president for research at Purdue, says the project is about growing collaboration, accelerating research, and building capacity.

"Everything we're trying to accomplish with this project matches perfectly with the mission of the Indiana CTSI, IU, and Purdue University," she says.



Photo: Chris Meyer, Indiana University

Marietta Harrison, Ph.D., left, and Patrick Loehrer, M.D.

Teaming up across state lines to fight childhood disease

A pediatric research grant program between CTSA centers at five major Midwestern universities is helping pediatric researchers in Indiana, Ohio, and Kentucky collaborate across state lines to advance research on childhood disease.

The Pediatric Regional Collaborative Grant program, supported in part by the Indiana CTSI, funds research between pediatric scientists across the region, including IU Health Riley Hospital for Children; Cincinnati Children's Hospital Medical Center; Nationwide Children's Hospital in Columbus, Ohio; Rainbow Babies and Children's Hospital in Cleveland; and the

University of Kentucky Department of Pediatrics.

"Unlike those for adult patients, comprehensive child health services are focused in a small number of children's hospitals across the United States," said Wade Clapp, M.D., chair and Richard L. Schreiner Professor of Pediatrics at the IU School of Medicine. "Advancing research into children's diseases is often best served by collaboration among children's hospitals."

This type of cross-institutional collaboration has helped transform the treatment of certain childhood diseases, such as cancers, over the past 30 years.



Get involved with the Indiana CTSI!



To learn more about the Indiana CTSI, please visit our website at www.indianactsi.org. Contact us at info@indianactsi.org, or call 317-278-CTSI (2874).

Join the Indiana CTSI in its efforts to accelerate research and to improve the health of the people of Indiana.



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Anantha Shekhar, M.D., Ph.D., director of the Indiana CTSI (right) and William Tierney, M.D., CEO of the Regenstrief Institute (left), with Francis Collins, M.D., Ph.D., director of the NIH (center), during a visit to the Indiana CTSI in 2010.





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