our mission is discovery
our goal is to cure cancer

ANNUAL REPORT • 2009–10
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A Message from the Director

The Purdue University Center for Cancer Research is an outstanding cancer research center. We know that. You know that. And guess what? People all over the country are joining forces and understanding the research advances taking place at Purdue. What an amazing time to be a Boilermaker! This annual report provides you with a snapshot of the 2009–10 fiscal year, and you know the saying: A picture is worth a thousand words. So, as you digest the year’s highlights, let your mind explore beyond these few words and captivating images.

Our center is spread across the Purdue campus; we leverage our expertise across six colleges and 17 departments. The collaborative interactions fostered by the Center for Cancer Research focus faculty with mutual interests in cancer research in a way that spawns new ideas for investigating the prevention, diagnosis, and treatment of cancer of all kinds.

This year the Center for Cancer Research has been involved in a special collaborative effort with the Oncological Sciences Center (OSC) on campus. The OSC features the Cancer Culture and Community program. This unique program explores our response to cancer as expressed through the arts and literature. Members of the Purdue and Greater Lafayette communities were invited by OSC to share their cancer stories in anticipation of a visit to Purdue on November 4, 2010, by Joyce Brabner, coauthor of Our Cancer Year, and Frank Stack, the book’s illustrator. The stories were compiled and sent to local volunteer writers and artists who created Lafayette — Our Cancer Year.

“Our” book is dedicated to everyone who has fought cancer — with special thoughts of Brabner’s husband, Harvey Pekar, who died of cancer on July 12, 2010, at age 70. Brabner and Pekar wrote Our Cancer Year in the aftermath of cancer diagnosis and treatment earlier in his life.

Brabner and Strack headline the Cancer Culture and Community Colloquium at 7:30 p.m., November 4, in Stewart Center’s Fowler Hall. The event is free and open to the public. Visit www.purdue.edu/dp/cancerstory for additional information.

In so many ways, it’s been another rewarding year. We thank each of you for your support, dedication, and passion for the Purdue University Center for Cancer Research. Our mission is discovery. Our goal is to cure cancer.

Boiler Up!

Dr. Timothy L. Ratliff
Robert Wallace Miller Director
Purdue University Center for Cancer Research
Metrics

It’s been another incredible year for the Purdue University Center for Cancer Research. The information that follows is a synopsis of highlights.

Publications
Members of the Purdue University Center for Cancer Research produced 468 publications during fiscal year 2009–10.

Honors and Awards
Several Center for Cancer Research faculty members received notable commendations during fiscal year 2009–10.

Dr. Graham Cooks was named a Fellow by the American Association for the Advancement of Science.

Dr. Mark Cushman was named Distinguished Professor of Medicinal Chemistry at Purdue.

Dr. Donna Fekete, Professor of Biological Sciences, was named a Fellow by the American Association for the Advancement of Science.

Dr. Arun Ghosh, Ian P. Rothwell Distinguished Professor of Chemistry and Medicinal Chemistry and Molecular Pharmacology, received the Jeanne D. and James P. Chaney Research and Scholarship Achievement Award, the International Union of Pure and Applied Chemistry Award, the American Chemical Society Award, and the Arthur C. Cope Award for outstanding contributions to organic chemistry.

Dr. Jim Leary, Professor of Basic Medical Sciences and Biomedical Engineering, was named a Columbus Scholar by the Christopher Columbus Foundation.

Dr. David Riese, Associate Professor of Medicinal Chemistry and Molecular Pharmacology, received the Lions Club Cancer Researcher of the Year Award.

Clinical Trials
Currently, faculty from the Center for Cancer Research have 11 drugs in various stages of clinical trials. During fiscal year 2009–10, drugs recently developed by Dr. Mark Cushman and Dr. Philip Low reached the late-developmental phases of clinical trials.

Read more about Dr. Cushman’s and Dr. Low’s clinical trials on pages 14 and 15.
Development Update

As we close the books on an outstanding year for the Purdue University Center for Cancer Research, it is important to recognize the contributions of our many supporters. The success of our researchers in uncovering answers to the mysteries of cancer is tied to providing the resources necessary for them to conduct their research. Running a major research laboratory is an expensive proposition, and without your gifts it would be difficult for our scientists to advance their work.

So, thank you. Thank you for sharing your gifts with us. Thank you for understanding the importance of private giving to bolster our resources. Thank you for sharing our vision.

Your gifts were part of a record year for the center. We received 5,490 gifts in 2009–10, a record. We received 1,014 gifts of $100 or more, also a record. With total private giving at $1,487,849, we surpassed $1 million for the third consecutive year.

The Challenge, with the participation of nearly 1,600 runners and walkers in April, raised more than $50,000 for cancer research. We are proud to partner with Purdue Intercollegiate Athletics and Coach Danny Hope to present this community event. A festival atmosphere adds to the cause, thanks to the efforts of Beth Steurer, Paulette Moody, and a contingent of volunteers.

The third Jordan-Rieger Fund Dinner was hosted in Indianapolis in November 2009 and raised $25,000 for pancreatic cancer research. Jenny Jordan Pickett and Robin Rieger Walsh established the event, which spotlights the center in Indianapolis. Please plan to join us for this year’s event on Saturday, November 13.

During the year, we hosted presentations in Naples, Florida; Chicago; Indianapolis; Cincinnati; and other cities. We will continue to take our message to our supporters. It is gratifying to receive your gifts and to learn of your motivations for supporting cancer research. These very personal stories inspire our faculty and staff.

Thank you for every gift you make toward curing cancer. You are a part of our success at the Purdue University Center for Cancer Research!
The Challenge

Success definitely builds on success at the Purdue University Center for Cancer Research. The Challenge: 5K Run/Walk and resulting funds raised for research is one such example. A record number of nearly 1,600 participants in the third annual Challenge held on April 17, 2010, resulted in record proceeds of more than $50,000 to fund cancer research at the center.

“The Challenge started as a way to bring the community, cancer survivors, and loved ones together for a great cause,” says Beth Steurer, Director of Donor Relations at the Purdue University Center for Cancer Research and the Race Director. “Our goals for dollars raised and participants have climbed each year, and we continue to surpass our goals,” Steurer says. “In three years, we have raised more than $130,000 for cancer research here at Purdue.”

Dr. Sophie Lelièvre, Associate Professor of Basic Medical Sciences and leader of the center’s Breast Cancer Discovery Group, received the second Challenge Research Award for $30,000. She will be exploring how the most aggressive forms of breast cancer evolve from early lesions.

“We will make use of a unique cell line that mimics noninvasive stages of triple negative forms of breast cancer,” Lelièvre says. “These cells have the capabilities of evolving into invasive forms. Using a tissue culture system that we helped develop, we will test a novel concept that we are proposing on how less aggressive parts of the cancerous lesions formed by this type of breast cancer cells can help push the more aggressive cells toward an invasive behavior, which is usually accompanied with a higher risk of metastasis.”

Sisters for Life

“Cancer can invoke fear, but it also can inspire action. When far-flung sorority sisters agreed to participate in The Purdue Challenge in honor of two sisters battling cancer, no one imagined the impact it would have on all of us. Our gathering not only brought us together as sisters, but also presented an opportunity to help Purdue researchers. One of our two honorees joined us just days after a chemotherapy treatment. To say she inspired us is an understatement! She walked, rode in a wheelchair, and walked some more. Her determination and strength throughout the very long day seemed endless. She was appreciative of the time spent with her supporters. We relived some great times and made new memories. All in all, we were overjoyed to suspend the ‘battle’ against cancer for a while and, instead, to just spend time as friends on a beautiful springtime walk.”

Lorraine Hubert, Organizer of Sisters for Life

Jama Hottenstein, a 1976 Purdue graduate, passed away July 6.
Cell Growth and Differentiation

At first glance, yeast, fruit flies, zebra fish, chickens, and mice might not appear to have much in common. But these organisms are all being used as model systems by cancer researchers in the Cell Growth and Differentiation signature area, and they may hold the key to understanding what goes wrong inside cancerous cells.

Model systems are just that — systems to model humans. They allow researchers to gather knowledge more quickly and inexpensively than studying human cells and, in some cases, enable them to perform experiments that would be impossible or unethical on humans.

Dr. Scott Briggs is using yeast to study protein factors that control how certain genes are expressed — genes that if mutated or altered in humans can lead to cancers such as breast, prostate, and leukemia. The insights he's uncovering should allow researchers to develop compounds that can be used for new cancer therapies.

“Understanding how something functions is the best way to solve a problem,” Briggs says. “For a mechanic to fix a car engine, he has to understand how the engine is built and how it operates normally. The same is true for cancer researchers. We need to understand how a cell functions before we can understand what may go wrong and how to fix it.”

Another ideal model system for studying cancer is Drosophila. The fruit fly, as it is more commonly known, is inexpensive to study, easy to maintain, and open to manipulation. Dr. Henry Chang is using Drosophila to study Notch, a membrane protein with a direct link to leukemia.

“Many cancers are caused by mutations in genes, and to understand how disruptions of these genes lead to uncontrolled cell growth, we need to understand their normal functions,” Chang says. “The perception is that a fruit fly is very different from a human, but most human cancer-causing genes have counterparts in fruit flies.”
Mice are the animals most commonly used to model human cancer, and Dr. James Fleet is studying them in his quest to find a link between dietary factors and the progression of colon cancer. Fleet has developed a genetically modified mouse model that limits cancer-causing gene changes to the large intestine and induces mutations only in a subset of the colon cells. That makes his model more similar to the common sporadic colon cancer that affects most people.

“We sometimes develop drugs to treat cancer with many blind spots in our understanding of biology,” Fleet says. “That limits our success. Fundamental biology research gives us the best chance of developing ways to prevent, diagnose, and treat cancer.”

Dr. Donna Fekete agrees. Her research isn't directly cancer-related, but the model systems she uses to study inner ear development — chicken, zebra fish, and mice embryos — could soon be put to use by cancer researchers. Zebra fish embryos, for example, are virtually transparent, making them a potentially useful tool for drug screening.

“We can gain an understanding of how things go wrong in cancer cells by studying how things go right to make a fish’s ear or a fly’s wing,” Fekete says. “Just a small change in a gene that normally controls when cells stop dividing to make a body part could cause those cells to form a tumor.”
Brain cancer is a leading cause of cancer-related deaths in the United States and, unfortunately, among the most difficult illnesses to treat. The biggest obstacle is a network of blood capillaries — called the “blood-brain barrier” — that restricts the passage of anti-cancer drugs into the brain. Drs. Jean Chmielewski and Christine Hrycyna are working to break through that barrier, developing new agents to promote effective delivery of treatment.

“What we’re trying to do is to get anti-cancer drugs through this barrier by blocking the protein pumps that remove drugs before they can enter the brain,” Chmielewski says.

The major protein pump that limits penetration of therapies into the brain is called P-glycoprotein (P-gp). This protein first was discovered in drug-resistant cancer cells and more recently was identified as a key factor in the blood-brain barrier. Researchers believe it serves a protective role, stopping the accumulation of toxic agents in the brain by discharging the compounds back into the blood stream. This function is important for human health, but Chmielewski and Hrycyna, who are teamed within the Chemical and Structural Biology signature area, hope to circumvent the pump temporarily to allow anti-cancer compounds access to the brain.

“You can think of P-gp as a molecular vacuum cleaner, removing chemotherapeutic drugs before they can enter the brain,” Hrycyna says. “By clogging it, we can temporarily stop it from working.”
The team has taken advantage of multiple drug-binding sites in the pump portion of P-gp to develop these blocking agents or inhibitors.

“By chemically connecting two molecules that weakly bind to P-gp, we have made highly potent and tightly binding inhibitors of the pump,” Chmielewski says. “We have shown that these inhibitors allow anti-cancer drugs like Paclitaxel to easily enter drug-resistant cancer cells.”

The two researchers are now moving toward specific brain applications such as a brain capillary model and an in vivo brain penetration assay with collaborators at the National Institutes of Health.

“We’re very excited that our inhibitors work in isolated brain capillaries, and we’re now taking these compounds to the next level with animal studies,” Hrycyna says. “Our ultimate goal is that these reversing agents would have clinical use in assisting the treatment of patients with brain tumors.”

Hrycyna and Chmielewski have worked together for five years to develop inhibitors of P-gp, sharing students and authoring joint publications. They attribute much of their success to the synergy of their research expertise in biochemistry and chemical biology.
Drug Delivery and Molecular Sensing

They may be a thousand times smaller than the diameter of a human hair, but the medical probes developed by Dr. Joseph Irudayaraj and his team within the Drug Delivery and Molecular Sensing signature area soon could make a big difference helping doctors track down and treat cancer. These nanoscale, multifunctional probes with antibodies on board can help pinpoint the location of tumors within the human body and may one day be used to attack cancer cells directly — while mitigating damage to nearby healthy cells and lessening the side effects of chemotherapy.

“These probes have the ability to latch onto a tumor cell, carrying drugs to target and treat as well as reveal cancer cells,” Irudayaraj says.

The use of medical probes to target, track, and treat diseased cells simultaneously isn’t new. But most existing probes contain either magnetic particles, which show up easily on magnetic resonance imaging (MRI) scans, or luminescent particles such as gold, which emit light visible via optical microscopy. Both options have strengths and limitations. MRI scans can penetrate deep into tissue, but sometimes lack precision. Optical microscopy is a more sensitive and precise technique, but can only track cells close to the surface of the body.

Irudayaraj’s nanoprobes are the first to contain both gold and magnetic particles, so they can be tracked easily and accurately with different imaging devices as they target cancerous tissue, regardless of its location within the body.

“Better tracking of the nanoprobes should allow doctors to pinpoint the location of known tumors and better treat the cancer,” Irudayaraj says.

In laboratory tests, Irudayaraj and his team inserted nanoprobes coated with Herceptin — a drug used to treat metastatic breast cancer — into live human tumor cells. The probes reached the cells’ endosomes, which perform a sorting function to deliver drugs and other substances to the appropriate locations. The team also has designed probes...
to target the nucleus. That’s important because it enables the researchers to track exactly how a drug is distributed to different parts of a cell. With that knowledge, they can more accurately estimate how much of a drug is needed to treat a particular cancer cell.

“Cancer treatments often use high drug concentrations that end up damaging healthy cells near a tumor,” Irudayaraj says. “Targeting only tumor cells with nanoprobes should require fewer drugs and mitigate the side effects of cancer chemotherapy treatment. Each nanoprobe would act like a deliverer of a mail package — a dose of the drug — directly to the appropriate location.”

While the team’s initial research has focused on breast cancer cells, Irudayaraj says the nanoprobes can be used to target any type of cancer. And their broad application has attracted the interest of a number of pharmaceutical companies and other cancer researchers, who are looking for new and proven methods to improve drug uptake.

“We’re all interested in discovering more effective ways to detect cancer and administer therapy,” Irudayaraj says. “High-end scientific tools like nanoprobes can help us reach that goal.”
Medicinal Chemistry

Using molecules to unravel the biological puzzle of cancer is the goal of medicinal chemistry, and new technologies are helping researchers better understand current treatments and discover new therapies.

Dr. Tony Hazbun is using systems biology — a holistic look at complex interactions in biological systems — and robotics to study cancer cells treated with certain drugs. The systems approach allows Hazbun to map complicated relationships within a cell. Automation enables him to conduct and repeat experiments quickly and cost effectively.

In his work with pancreatic cancer, Hazbun simulates the over-expression of the protein *Aurora kinase* in yeast cells, then identifies what genes are essential for cellular growth when this protein is overproduced. Documenting these relationships helps him understand how cancer cells regulate and monitor growth.

“*The typical way to attack cancer is to identify the bad protein and target it,*” Hazbun says. “We’re looking at ways to target the accessory proteins that help the bad protein. That could allow us to develop treatments that target just cancer cells and reduce the effects of chemotherapy.”

Dr. Laurie Parker uses mass spectrometry, an analytical technique to determine a molecule’s composition, to quantify the response of leukemia cells and patients to the drug Gleevec. While successful in the clinic, Gleevec doesn’t work for everyone and has long-term side effects. Both issues are related to selectivity — how the drug affects other proteins beyond the cancer-causing one it’s designed to inhibit. To study its effects, Parker designs molecules to travel inside cells and report on whether the specific leukemia-related protein is activated or inhibited and determine potential drug resistance.

Parker hopes her work will advance personalized medicine — detecting cancer cells in a patient, determining whether prescribed drugs are working, and developing and choosing new drugs to treat the unique characteristics of an individual’s cancer.
“Our lab is developing tools that could be used to monitor the effects of drugs more closely,” Parker says. “This should enable doctors to see if drugs are working much earlier so they can try something else before it’s too late.”

Dr. Vincent Jo Davisson’s team is using an approach called “molecular cytomics” to provide a new basis for screening cervical cancers. Current clinical protocols suffer from false negatives and positives, but by applying additional molecular features to the cancer screenings, oncologists will be able to detect serious cases early, evaluate the risk for disease progression, avoid unnecessary procedures, and provide a prognosis at the time of diagnosis.

Dr. Davisson’s team also uses targeted discovery approaches to design new molecular therapeutics — agents with a high degree of specificity for pathways and processes associated with an individual cancer. They’re currently working to target DNA repair processes in specific breast tumors.

“Cancer genomes undergo constant challenges from environmental agents, causing damage to DNA and resulting in replication errors. Tumor cells are able to resist certain DNA targeting drugs and radiation therapy,” Davisson says. “However, tumors get addicted to certain types of DNA repair pathways or lack others making them particularly sensitive. We can target our discovery of new drugs to these areas.”
Research Highlight

The journey literally took decades, but Drs. Mark Cushman and Philip Low have finally reached the promised land. Each has invested his career in developing cancer treatments now undergoing human clinical trials.

Cushman began working to synthesize natural anti-cancer compounds in the 1970s. Early on, he published a paper about a known compound and submitted his work to the National Cancer Institute (NCI). The response? “Quit wasting the taxpayers’ money and send us something we don’t already have.”

So Cushman took another look at a different compound, an indenoisoquinoline created through an unexpected chemical reaction. The compound proved to be an inhibitor to topoisomerase I, an enzyme involved in DNA replication. He sent it to the NCI, and then he waited — for nearly two decades.

“Eighteen years later, the compound woke up,” says Cushman, Distinguished Professor of Medicinal Chemistry. “The Institute called to say they’d developed a computer algorithm that predicted it might be a useful anti-cancer agent in humans.”

That led to another decade of work, as Cushman and his team — along with collaborators from NCI — designed, synthesized, and evaluated more than 400 indenoisoquinolines. In the end, two were deemed most promising and are now in Phase 1 clinical trials, being tested for human use. Both compounds damage the DNA in cancer cells, resulting in cell death. Cushman hopes they’ll be useful in treating cancers that haven’t responded well to standard therapies like surgery and radiation.

“These compounds could potentially inhibit many different types of cancer,” Cushman says. “Exactly which cancers is a question that will be answered through clinical trials. We also hope to learn the best combination of these compounds with other drugs to treat cancer most effectively.”

So far, Cushman’s compounds have proven to be superior to similar drugs on the market. In animal models, they’re less toxic, more stable, more efficacious, and less susceptible to drug resistance.
Low’s research also extends back more than two decades, when he discovered that many cancer cells have an appetite for folic acid, known in its naturally occurring form as folate. Cancer cells with folate receptors eat up chemotherapy drugs linked to folate in large quantities and, in the process, poison themselves. Low’s team has developed a number of targeted drugs that exploit this tendency.

“The vast majority of chemotherapy drugs today distribute systematically to all tissues of the body. We’ve all seen the results of that. People get sick. Their hair falls out. They’re subject to infections,” says Low, the Ralph C. Corley Distinguished Professor of Chemistry. “By targeting the malignant cells, we can avoid the toxicity and maximize the potency — in other words, kill the cancer cells more quickly while eliminating side effects.”

Low and his colleagues at Endocyte, a biopharmaceutical company, currently have one imaging agent (used to determine if a patient’s cancer has a folate receptor) and five drugs in Phase 1 and 2 clinical trials. If approved, they’ll be used to treat breast, colorectal, endometrial, kidney, lung, ovarian, and prostate cancers, as well as a number of other diseases.

While both Cushman and Low are thrilled about the progress of their research, they’re also realistic about their drugs’ chances for success. Each drug must make it through three phases of clinical trials before it can be approved by the Food & Drug Administration. Only about 10 percent of drugs that reach clinical trials ultimately become commercially available treatments for cancer.

If any of the drugs is approved, the next step is commercial development. The Purdue Research Foundation has licensed Cushman’s compounds to a start-up company, which he says would most likely develop the drugs to a certain stage and then sell them to a larger pharmaceutical company. Endocyte would manage the commercialization process for Low.

Both researchers credit the Purdue University Center for Cancer Research for providing the funding, technology, and camaraderie essential to their research.

“Being around a community of scientists interested in the same problem facilitates an exchange of information you can use to accelerate your own work,” Low says.
PURDUE UNIVERSITY CENTER FOR CANCER RESEARCH

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Chemical and Structural Biology
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Program Co-Leader: David Thompson, Ph.D. (Chemistry)

Drug Delivery and Molecular Sensing
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2009–10 Honor Roll of Donors

Faculty researchers at the Purdue University Center for Cancer Research continue to expand our knowledge of the basic cancer cell and its remaining secrets. Your generous gifts support our multi-faceted exploration of novel ideas, new treatment techniques, and prevention methods. Thank you for believing in us. Your partnership with us has primed our research, and with each research breakthrough we are one step closer to a cancer-free world.

In an effort to trim our printing costs and paper usage, we are providing an online donor honor roll, where we salute each individual, corporation, and foundation that contributed to our fight against cancer during fiscal year 2009–10. Please visit www.cancerresearch.purdue.edu/links/communications to view the Donor Honor Roll, or call (765) 494-1109 to request a printed version.
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