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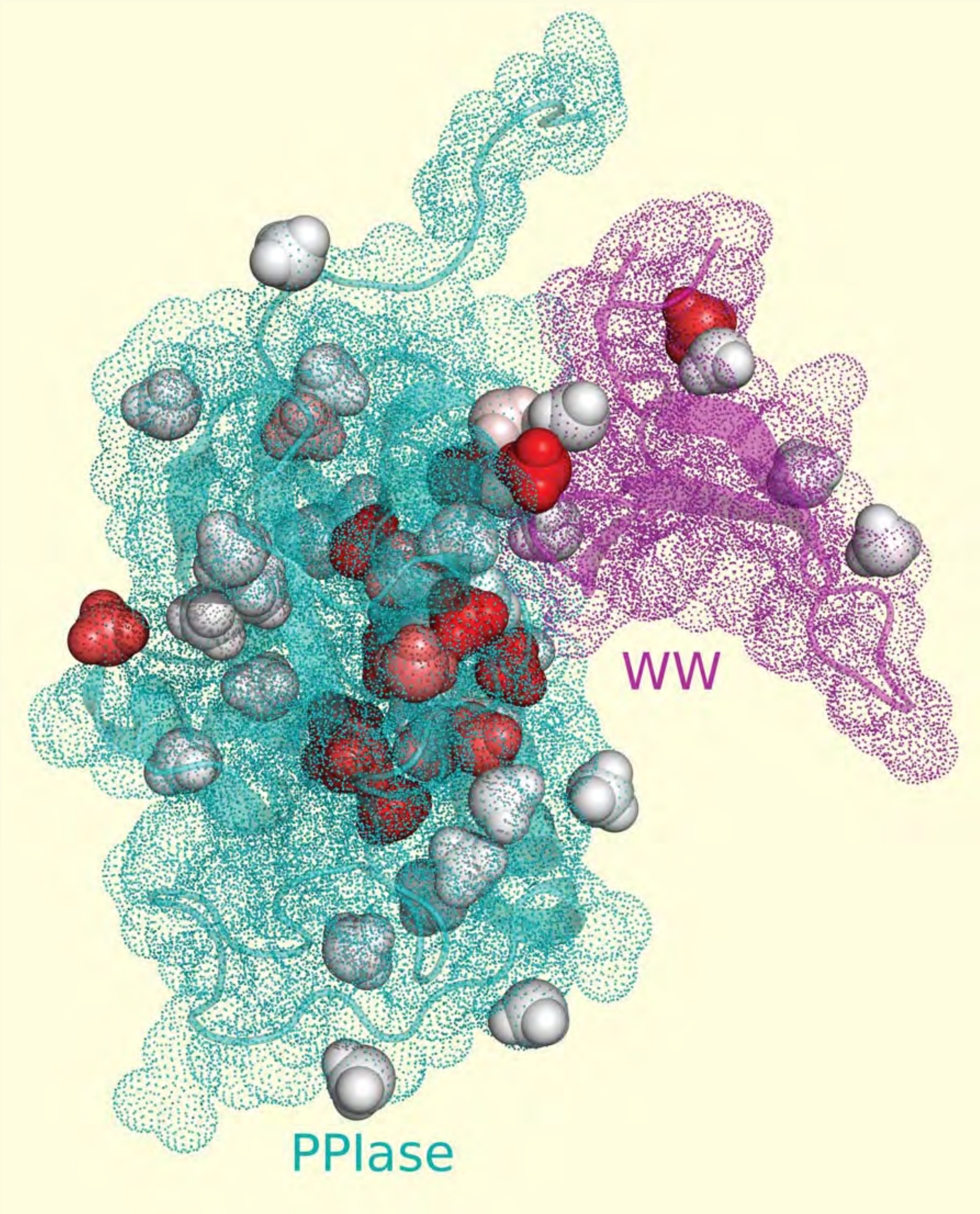
Renaissance

BIOMEDICAL RESEARCH



LETTER FROM THE DEAN

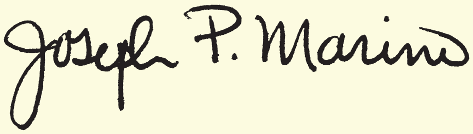
Our previous issue of *Renaissance* highlighted the college's most significant milestone in recent history: the opening of the new Jordan Hall of Science, a $70 million building dedicated to providing our undergraduates with the finest science learning facility in the country. This issue of *Renaissance* focuses on yet another major development that I believe is destined to become an important milestone for the College of Science and for the University as a whole.

Just 15 years ago, Notre Dame's reputation in cancer research rested on just one man, Morris Pollard. Today, after a dynamic period of growth, cancer research at the University has made important contributions in the war on cancer, most notably in the fields of prostate cancer, breast cancer, and colon cancer. The reputation of our researchers has never been higher. With the recent gift of $10 million from Charles "Mike" Harper and matching funds from the state of Indiana, Notre Dame cancer researchers will soon have a centralized home. The new building will be constructed adjacent to the Indiana University School of Medicine–South Bend and will mean yet another leap ahead for both the medical school and our Walther Cancer Research Center faculty.

Significant advances in biomedical research are also being made to stop the spread of infectious diseases, including malaria, lymphatic filariasis, dengue fever, and West Nile encephalitis. Researchers in the Center for Global Health and Infectious Disease have a unique international reputation for their expertise in the management of genomic mapping of the vectors of human pathogens. This issue of *Renaissance* is intended to give you a broad, wide-angle look at the field of biomedical research at the University of Notre Dame. I think you will come away with a much deeper understanding of what has taken place at Notre Dame in recent years.

At the same time that we are elevating our research agendas, we have paid considerable attention to the revision and improvement of our academic curricula for undergraduates. This issue of *Renaissance* highlights the progress to date in course revisions and innovations for chemistry, physics, math, and biological sciences. We are increasing the number of undergraduates doing research. We feel that the combination of curricular improvements and a greater emphasis on undergraduate research will further strengthen the undergraduate experience in science.

Best regards,



Joseph P. Marino
William K. Warren Foundation Dean
College of Science

On the cover:
Human Pin1, an enzyme controlling cell growth and a current therapeutic target by cancer research. The red spheres indicate sites of reduced flexibility on substrate binding, as revealed by the Jeffrey W. Peng lab using Notre Dame's 700 MHz and 800 MHz NMR spectrometers. Reduced flexibility occurs along an internal conduit connecting the inter-domain interface with the catalytic site. *See story on page 20.*

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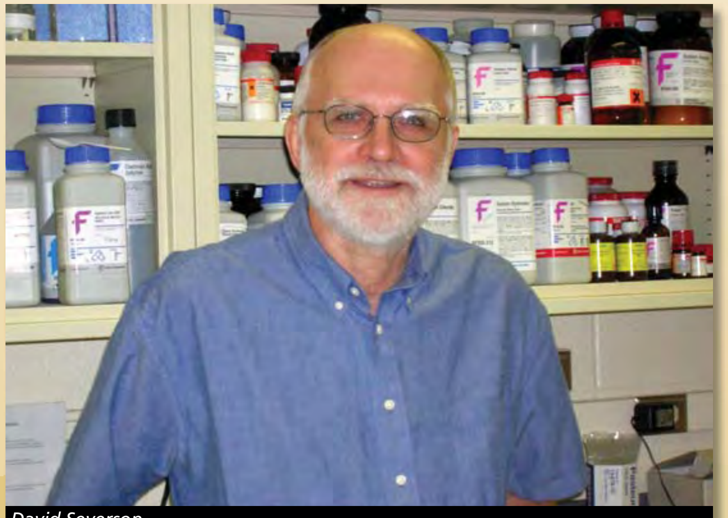
Notre Dame Takes Leading Role in Another Mosquito Gene Map


David Severson

No doubt, the disease-carrying mosquito called *Aedes aegypti* is carrying on as if nothing has changed. In developing countries where it's virtually unchecked, it causes an astounding 50 million cases of dengue fever a year. More than a third of the world's population is at risk of dengue. It also spreads yellow fever, which, despite a vaccine, kills 30,000 people a year in Africa and South America.

But something has changed. Scientists now have a map they hope will show them how to curtail disease transmission by *Aedes aegypti*: the map of its DNA.

Led by University of Notre Dame professor of biological sciences **David W. Severson**, researchers from around the world have sequenced the mosquito's genome and identified its genes.

The major findings of their two-and-a-half-year-long project were announced May 17 in the online journal *Science Express*. The article, coauthored by scientists from 28 institutions, suggests avenues for research aimed at conventional countermeasures, like insecticides and repellents, and new genetic approaches targeting the vector's ability to harbor and transmit pathogens. No one should be surprised if researchers come up with angles not yet considered. "Bright people will look at this and find new things," Severson said.

Elucidation of the genetic code of the insect and overseeing a journal article with 96 coauthors proved to be an enormous task, "a long slog involving what felt like a cast of thousands," as Severson put it.

Severson, whose lab in the Galvin Life Sciences Building supplied mosquito DNA and RNA for sequencing, said the group's most surprising finding came in the first year of work. The project began in February 2004 with funding approval from the National Institute of Allergy and Infectious Disease.

A preliminary assembly of DNA base pair sequences, accomplished by the Institute for Genomic Research (TIGR) in Rockville, Md., and the Broad Institute of MIT and Harvard, revealed that the mosquito's genome was unexpectedly large. In fact, at 1.38 billion base pairs, the

Scientists now have a map they hope will show them how to curtail disease transmission by* Aedes aegypti*: the map of its DNA.

genome was not only 40 percent larger than estimated but a startling five times as large as that of the malaria vector, *Anopheles gambiae,* which was the first mosquito to be sequenced.

The difference is not in the number of chromosomes or genes, as both mosquitoes have three chromosomes and about 16,000 genes. Instead, in the 150 million years since the insects diverged on the evolutionary tree, the *Aedes aegypti* genome has become cluttered with a vast amount of repetitive DNA sequences known as transposable elements. These elements make up almost half of its genome, and cause its genes to be four to five times as long as those of the *Anopheles gambiae*, according to the paper.

Both the reasons for the difference in genome size and their effect on the organism are unclear, Severson said. It's a matter for further research and discovery.

After the sequencing was completed in October 2005, the second phase of annotation (identifying individual genes across the genome) was carried out independently by groups at TIGR and at Notre Dame's VectorBase, a Web-based bioinformatics resource headed by University of Notre Dame professor of biological sciences Frank Collins. "The two groups hashed out huge differences in their annotations and agreed on a final version," Severson said, "which was posted to GenBank in June 2006."

At that point, an initial draft of the dengue vector's genetic blueprint had been posted on the Internet for use by researchers. But, it would be almost a year before Severson and his coauthors could pull together the journal article and arrange for its publication with the editors of *Science*.

Now that the genome has been completed and announced to the world in a prestigious scientific journal, Severson expects that researchers from around the world will be irresistibly drawn to it like newspaper readers to the daily Soduko puzzle. After all, it holds the secrets to how this highly evolved, blood-feeding insect finds its prey, survives pesticides, acquires viruses, and passes them on to millions of people.

"It brings people into the research community," he said. "People who were doing other work can now ask some detailed questions." ⊕

BSL Level 3 Facility

In his best-selling book *The Hot Zone* author Richard Preston led his readers into a place few people would dare venture into—a Biosafety Laboratory (BSL) Level 4 facility.

Preston's chilling account of the 1989 outbreak of the deadly *Ebola* virus in a monkey-holding facility in Reston, Va., introduced readers to the world of ultra-secure laboratories where scientists in "moon-suits" work with dangerous agents under strict protocols.

Notre Dame now has its own BSL facility, which opened in May 2007. Fortunately, you will not find anything like the *Ebola* virus in Notre Dame's new BSL Level 3 facility in Galvin Life Science Building. "We wouldn't even want to bring those kind of diseases here," said biologist **David Severson**, who recently directed an international team that sequenced the genome of a mosquito that carries the dengue fever virus. "Our BSL Level 3 facility is unique. It is built around the whole idea of pathogen-infected arthropods," Severson said. "Even though it is small, it is a modern, contemporary facility that was built with a lot of thought behind it. Our scientists can study mosquitoes infected with a malaria pathogen—*Plasmodium falciparum*—or the dengue fever virus, or sand flies infected with the leishmaniasis pathogen."

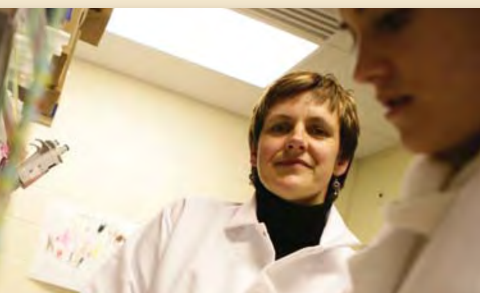
David Severson

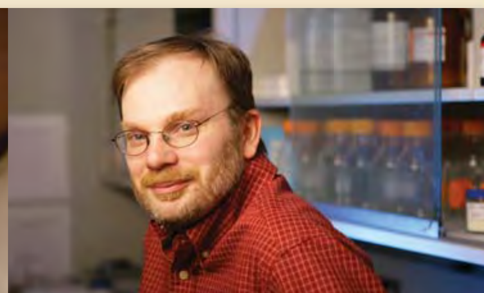
At present, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) require that the type of research conducted by biologists with Notre Dame's Center for Global Health and Infectious Disease be performed in a Level 2 facility. "But there have been a lot of questions within the research community as to whether putting pathogens into

Takes Biologists to the Next Level

these invertebrates is really a Level 2 threat, whether the research we do at Notre Dame is actually closer to the rules for having Level 3," Severson said. According to the CDC and the NIH, a Level 3 facility is required if the research is done with indigenous or exotic agents that may cause serious or potentially lethal disease as a result of exposure by the inhalation route.

Mary Ann McDowell, whose work on sand flies and leishmaniasis is funded in part by the US Army, explained: "We feel that when it comes to infected flying mosquitoes or sand flies, that these insects are no different than an aerosol containing an infectious virus," she said. "So, we felt it was necessary to take more precautions than what is currently required by law. It makes common sense. And down the road, the standards may change, so we will be ahead of the curve."


Mary Ann Mc Dowell


Jeffrey Schorey

Therefore, everyone who goes into the Level 3 facility must follow a rigorous set of rules. For instance, members of the center work with infected insects inside biological safety cabinets. They wear protective clothing and equipment. The Level 3 laboratory is built with a sealed double-door access zone with negative air pressure so that in the unlikely event an infected insect escapes containment, it cannot pass into the hallways of Galvin Life Science Building. Everything leaving the facility must be sterilized. For this, a special autoclave was built into the wall between the BSL 3 Lab and a third-floor hallway in Galvin. No one in the hallway can accidentally open the autoclave. The sterilization process must be completed before somebody on the outside can take anything out.

There are seven rooms inside the laboratory that will allow biologists to work concurrently on multiple research projects.

In another part of Galvin, a smaller Level 3 facility was built for biologist **Jeffrey Schorey**, whose work on tuberculosis also meets Level 3 requirements. Schorey's laboratory became operational in April of 2006, and it could not have come too soon. At the time, Schorey and his graduate students were well into an experiment in which it was necessary to use live TB mycobacterium. "So we were very anxious to have the laboratory up and running," Schorey said. Their work has since been published in the *American Journal of Hematology*.

"Up until now, we couldn't work with virulent strains of mycobacteria tuberculosis," Schorey said. "So we were working on other kinds of mycobacteria that requires Level 2 containment, and we were making inferences about how our findings might relate to TB. But we just couldn't test those hypotheses."

The Notre Dame Center for Global Health and Infectious Diseases has a unique international reputation for its strength in the area of arthropod vectors of human pathogens. The BSL Level 3 facility will have six insectaries to handle multiple ongoing projects being carried out by center members.

Mary Ann McDowell will be using the laboratory to continue her study on how exposure to the saliva from the bite of a mosquito uninfected with the malaria parasite may prompt an immune response in humans. She previously demonstrated such a link between the saliva of the sand fly and its connection with resistance to leishmaniasis, a skin disease that can cause disfigurement and even death.

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UNDERGRADUATE RESEARCH AT THE UNIVERSITY OF NOTRE DAME

Forty-two undergraduate science students from the University of Notre Dame, Saint Mary's College, and Indiana University, South Bend presented the results of their scientific research at the first annual College of Science undergraduate research presentation day in the Jordan Hall of Science on May 4, 2007. The most outstanding students received awards. Read about the event on page 33.

Honors students **Patricia Engle** '06 and **Julian Bigi** '07, who are pictured above, were both extensively involved in research as undergraduates. Engle, a physics major and a Goldwater Scholarship recipient, performed research under nuclear physicist Philippe Collon. She is now earning a PhD in physical oceanography at MIT and is conducting research in the Philippine waters. Bigi, a biochemistry major and 2007 Dean's Award recipient, performed research under chemist Seth Brown since his freshman year. His projects investigated the details of how metals mediate, forming and breaking bonds to oxygen and carbon. Bigi will be pursuing a PhD at the University of California at Berkeley in the fall.

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