Purdue News

Anatomy of a master: Michael Rossmann

Like many famous masters responsible for history-making achievements, Michael Rossmann, who is best known for solving crucial mysteries about viruses, had his skeptics early on.

Download Photo Here
Photo caption below

A puzzle-solver from his boyhood in England, Rossmann himself concedes that as a young research scientist he was more interested in satisfying his own curiosities in molecular biology than in pursuing high profile research -- the work others considered more important.

Rossmann's own mentor, the late Max Perutz, of the Medical Research Council Laboratory for Molecular Biology at Cambridge, England, was an early skeptic. He nevertheless gave free reign to

Rossmann, allowing him to develop ideas and tools that would later prove critically important to the new science of structural biology. Rossmann worked with Perutz for eight years before coming to Purdue in 1964.

Having made numerous basic biological discoveries that have earned him universally coveted accolades, the 72-year-old Rossmann is in his 39th year at Purdue and in his 25th year as Purdue's Hanley Distinguished Professor of Biological Sciences.

His early unwillingness to acquiesce to others' definitions of "significant research" and his unwavering determination to solve nature's most complex puzzles may be at the heart of his mastery.

Enormous puzzles

Fitting together a molecular jigsaw puzzle made of a million pieces, in 1970, Rossmann and his team of research associates used five years of research data to build an intracellular enzyme, the protein lactate dehydrongenase, or LDH, which is vital to metabolism.

Dr. William McElroy, then-director of the National Science Foundation and former

Download Photo Here
Photo caption below

Johns Hopkins University biology department chair, called the achievement "a fine example of basic research that may well have a future positive impact in the field of medicine."

At the time, LDH, whose presence in the blood in large amounts is correlated to cancerous tumors, was the most complicated enzyme ever to be pieced together.

This complex molecular jigsaw puzzle came together courtesy of X-ray diffraction, a means by which scientists study biological molecule structures.

The technique allows scientists, who grow crystals of the molecule they want to study, to shine X-rays on the crystal to see exactly where atoms are positioned inside the molecule.

Rossmann is widely recognized for developing X-ray crystallography techniques to study particularly small molecular structures, such as viruses.

As his colleagues worldwide took note of his outstanding contributions to science, Rossmann was named a fellow of the American Academy of Arts and Sciences in 1978.

From tiny to tinier

In 1979, Rossmann and his associates became the second group in the world to map a virus when they constructed a three-dimensional model of the Southern Bean Mosaic Virus.

Download Photo Here
Photo caption below

Then, not long after his election to the National Academy of Sciences in 1984, Rossmann accomplished what still is hailed as one of his crowning achievements -- mapping a common cold virus.

In 1985, he became the first scientist to build a model of human rhinovirus-14, HRV-14, one of about 100 known cold virus strains.

At the time, Rossmann explained that this was not a cure for the common cold, but that it had opened the scientific gate to new avenues leading to the development of antiviral drugs.

"The juxtaposition of different atoms provides the chemical basis for biological and chemical activity," Rossmann said in September 1985. Rossman added that the results provided insight into how a virus works and suggested ways for developing anti-rhinovirus compounds as well drugs to fight other viral pathogens.

The breakthrough had made it possible to study surface features and interactions of a virus at atomic resolution. Once those features and interactions could be understood, they could potentially be manipulated by drugs to neutralize the virus.

In addition to that promising potential, Rossmann's common cold analysis, which used novel and powerful techniques, provided the means by which structures of many other viruses now are being studied.

Renown and support

Exactly one year after the Sept. 12, 1985 announcement that Rossmann and his team of scientists had built a cold virus, he and his colleagues announced they had discovered how antiviral agents bind to the virus to prevent it from reproducing.

The discovery, another crucial step toward a vaccine or cure for the common cold, was covered by the distinguished journal Science.

The research tested compounds that rendered the virus helpless by preventing it from opening to release its infectious material and it provided the first glimpse of how antiviral agents work within the structure of a virus.

In tracing the path used by the compounds to enter the virus, Rossmann's group used techniques it pioneered in its work on HRV-14.

Two months after the Science article, Rossmann was among scientists given the MERIT Award or Method to Extend Research in Time Award, from the National Institutes of Health.

Download Photo Here
Photo caption below

The NIH gives the awards, which extend up to 10 years of support, to scientists "whose research competence and productivity are distinctly superior and who are highly likely to continue to perform in an outstanding manner."

Then in 1988 came the announcement of a $6.5 million grant from the Lucille P. Markey Charitable Trust to support Rossmann and to expand structural biology at Purdue.

That amount, and more that has followed, supports what's now know as the Purdue structural biology group, a group of Purdue scientists - many of whom were enticed to come to Purdue because of Rossmann's exceptional accomplishments and enthusiasm.

"He's an inspiration to people in the structural biology field because he is extremely enthusiastic about his science and that enthusiasm is infectious," says structural biology group member Janet

Smith, professor of biological sciences.

Fellow group member, Richard Kuhn, who worked with Rossmann to map the first flavivirus, the lethal dengue virus carried by mosquitoes, says Rossmann's intensity and sheer fondness for his work are constant positive influences on the scientists around him.

"When the guy on top works so hard and enjoys what he does so much, that's got to rub off -- and it rubs off in the training of graduates and post-docs as well," Kuhn says.

Current members of the structural biology research group in Purdue's Department of Biological Sciences, including Rossmann, are:

- Timothy Baker
- Jeff Bolin
- Jue Chen
- William Cramer
- Alan Friedman
- Barbara Golden
- Miriam Hasson
- Richard Kuhn
- Amy McGough
- Carol Post
- David Sanders
- Janet Smith
- Cynthia Stauffacher

In the spring of 1998, Michael Rossmann's group announced that it had analyzed in atomic detail the part of the cell's receptor that binds to a cold virus. This finding led to a greater understanding of how cold viruses (rhinoviruses) enter cells -- understanding that was key in the later development of a drug called pleconaril.

Pulmonary Reviews, a monthly news magazine for physicians who specialize in pulmonary and/or critical care medicine, reported on pleconaril in its February 2002 issue, after pleconaril had gone through three phases of human trials.

"The antiviral agent pleconaril both attenuated rhinoviral symptoms and shortened the duration of those symptoms by approximately one day," the magazine reported. "With no reported severe adverse reactions, the oral medication could potentially alleviate the suffering of many cold victims and may also lessen their likelihood of transmitting rhinoviruses to others."

In its report, copyrighted in 2000, ABC News referred to pleconaril as a drug that could disable the cold-causing rhinovirus, but also neutralize the second most common human virus, the enterovirus, which causes a broad range of illnesses including viral meningitis, childhood fevers, inflammation of the heart, polio and infections that kill newborns.

Rossmann's work continues

Through the years, Rossmann's studies also have included coxsackie-, polio-, cardio-, and the enveloped togaviruses, and several double-stranded DNA retroviruses, such as HIV, which causes AIDS.

In 1999, Rossmann and his group of structural and molecular virologists at Purdue received a $6 million grant from the National Institutes of Health to study a family of viruses that includes the West Nile virus. The studies led to the mapping of the dengue virus, a virus in the same family of flaviviruses as West Nile. The ongoing studies have implications for other diseases including yellow fever and hepatitis C virus, and the rubella virus, which causes German measles.

"We have a constant need to improve and upgrade the technological procedures," Rossmann says. "A significant component of our work has been the development of new techniques that can help us and other scientists."

Recently, Rossmann has worked with other structural biologists Purdue to develop ways to combine X-ray crystallography studies with cry-electron microscopy and three-dimensional image reconstruction. The techniques, which use hundreds of two-dimensional images to develop a three-dimensional view of a virus, allow researchers to determine the overall shape of virus particles and see the symmetrical arrangement of their components.

During his career, Rossmann has published more than 375 articles in scientific journals. In addition to other memberships, he is a foreign member of the British Royal Society. He won the Ewald Prize from the International Union of Crystallography in 1996, and in 1999, he was named a Fellow of the American Association of the Advancement of Science. He also was one of 39 scientists named to the first class of Fellows of the Biophysical Society.

Rossmann's work at Purdue is supported by the National Science Foundation and the National Institutes of Allergy and Infectious Diseases.

His body of work, once faulted as too low-profile, has taken on historic significance yet to be realized.

Story by Amy Raley and Susan Gaidos
Photographs by David Umberger

PHOTO CAPTIONS:
Michael Rossmann talks with intensity inside his office in the basement of Lilly Hall of Life Sciences about his antiviral research. His hope is that Purdue will add to and upgrade its structural biology facilities so research efforts can remain at the forefront of the field.

Before computers revolutionized structural biology, Rossmann (shown in 1971) used three-dimensional models to build complex structures such as this enzyme, the protein lactate dehydrongenase, or LDH.

This computer-simulated model of rhinovirus-14, the first cold-causing virus in history to be fully decoded, was created by Michael Rossmann and his research team.

This computer model shows a common cold virus (in blue) interacting with a human antibody (in red). Rhinovirus molecules that are adapting to resist the antibody are in yellow.