



Daniel DiMaio, MD, PhD

Joan Steitz, PhD

I. George Miller, MD

A 45 Year Legacy

OF RESEARCH AND COLLABORATION

Steve Kemper writer Peter Baker photographer

The first year that the National Institutes of Health (NIH) funded a group of Yale scientists to explore links between viruses and cancer, U.S. troops evacuated Vietnam, Gerald Ford was president, and the movie *Jaws* broke box office records. The scientists wrote their 400-page proposal on typewriters and made 20 paper copies on Xerox machines. They put it all into a big box and sent it through the U.S. mail. It was 1975.

Their research pleased the NIH so much that the agency renewed the grant—eight times over 45 years. Entitled

“Molecular Basis of Cancer Virus Replication, Transformation, and Innate Defense,” it became the longest-running program project grant at Yale, and the third longest at the NIH. It brought more than \$50 million to Yale labs and resulted in nearly 500 publications, many of them groundbreaking. The grant helped launch the careers of hundreds of scientists who trained under its leadership, including several on the Yale faculty.

Three of the grant’s principals are still at Yale: Daniel DiMaio, MD, PhD, Waldemar Von Zedtwitz Professor

of Genetics, Professor of Therapeutic Radiology, Professor of Molecular Biophysics and Biochemistry, and Deputy Director of Yale Cancer Center; Joan Steitz, PhD, Sterling Professor of Molecular Biophysics and Biochemistry; and I. George Miller, Jr., MD, John F. Enders Professor of Pediatrics and Professor of Epidemiology and of Molecular Biophysics and Biochemistry.

“The grant has had a major impact on how we study viruses,” said Dr. DiMaio, the principal investigator for the last 25 years. “Otherwise, it wouldn’t have lasted

so long. There’s lots of competition out there. Every five years the NIH looked at us closely to see if we were still productive and still a good investment. For many cycles of renewal, they decided that we were.”

After 45 years, he added, the grant’s three leaders decided not to reapply. “We’re sun-setting it. It’s time to let a new generation take over.” It is also time to applaud some of the grant’s research highlights.

The human genome was sequenced about 20 years ago, but the first genome

ever sequenced was funded by this NIH grant almost 25 years earlier, when Sherman Weissman, MD, Sterling Professor of Genetics and the grant’s first principal investigator described the genetic make-up of a virus named SV40. “He developed some of the earliest techniques for sequencing nucleic acids,” said Dr. DiMaio. “That had a profound impact on medicine, and it came from studying tumor viruses.”

Before his death in 2020, another biochemist on the grant, Charles M. Redding, MD, Professor of Genetics,

showed how DNA molecules can recombine to alter genes and proteins, which in turn can cause cancer—a crucial discovery. A former member of the program, David C. Ward, PhD, used the program funding to develop a technology called fluorescence in situ hybridization (FISH). It allows researchers to map chromosomes by locating specific DNA sequences and this technology is a standard diagnostic and research tool in labs worldwide.

Dr. Steitz is a founding member of the grant program, which helped fund

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her landmark discovery of small noncoding RNAs made by viruses. “It turns out that RNAs aren’t just messengers,” she said, “but are also regulatory elements inside cells, and are important to be able to make an oncogenic virus. We’ve discovered a lot of noncoding RNAs, and each new discovery brings all sorts of insights into how viruses are able to successfully infect cells.”

“Joan didn’t just discover them,” added Dr. DiMaio. “She figured out how they work and discovered a lot of new chemistry and structural biology. It opened up a new field.”

Dr. Steitz identified some of those RNAs in collaboration with Dr. I. George Miller, another founding member of the program grant. At the time, scientists knew that viruses caused cancer in animals, noted Dr. Miller, “but nobody believed cancers in people were caused by viruses.” Dr. Miller showed that Epstein-Barr Virus (EBV), a human virus, caused lymphomas in monkeys. This was the first time a human virus had been shown to cause cancer in a primate, providing definitive evidence of its cancer-causing activity. Researchers now know that about 15 percent of all human cancers are caused by viruses. The grant also supported Dr. Miller’s groundbreaking discovery about how EBV gets activated.

Dr. Miller and Dr. Steitz collaborated to characterize a related virus that causes Kaposi sarcoma.

The grant also supported Dr. DiMaio’s pioneering research into identifying viral oncogenes, and how turning them off stops cancer cells from growing. More recently, the grant funded his studies about how viruses get into cells. “It sounds simple,” he said, “but virus entry is a complicated process with hundreds of cellular proteins involved. We’ve discovered some cellular proteins that are important for infection, determined how they work to support infection, and learned some new cell biology.”

These breakthroughs stemmed from the basic science supported by the grant. “Viruses educate us about every aspect of molecular biology and cell biology and immunology,” said Dr. Miller. “We keep on learning things from viruses that are applicable to cancer and to many other problems. If you want to make vaccines, for instance, you have to understand what the virus is doing.”

The grant brought together people from many departments. “We all look at virology from different perspectives,” said Dr. Steitz. Dr. DiMaio is primarily a geneticist, Dr. Steitz a biochemist, and Dr. Miller a pediatrician. “When we get together,” continued Dr. Steitz, “we have

people coming in from many different disciplines and it’s great.”

Their collaborations introduced each other to different approaches and techniques that influenced the direction of their research. Dr. Steitz started with bacterial viruses, then moved into animal viruses after conversations with Dr. Miller. Dr. Steitz helped Dr. Miller understand the advantages of using modern molecular techniques instead of cultivating viruses.

“We’ve really transferred knowledge back and forth,” said Dr. DiMaio. “That’s something very special about this grant. We’re not working in isolation; we helped each other and molded each other’s careers.”

In turn, the partners in this program grant have molded the careers of several hundred grad students and post-docs who were trained under them and are now making their own contributions to the field and paying it forward with their own students. “It’s a long legacy,” said Dr. DiMaio, “like a huge extended family.”

“You can see evidence of that legacy in what’s happening now with COVID-19,” said Dr. Steitz, whose career helped us understand how RNA works. “A lot of work on the immunology of this disease was done here, and the most effective COVID-19 vaccines are RNA-based vaccines.” 🔄