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.

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. “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 yalecancercenter.org | centerpoint magazine
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. Stetz identified some of those RNAs in collaboration with Dr. 1. 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, is caused by viruses. “Viruses educate us about every aspect of modern molecular techniques instead of modern molecular techniques and it’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 working their own contributions to the field and paying it forward with their own students. “It’s a long legacy,” said Dr. DiMaio. “That’s something very special about this grant.”

The grant brought together people from many departments. “We all look at virology from different perspectives,” said Dr. Stetz. Dr. DiMaio is primarily a geneticist, Dr. Stetz a biochemist, and Dr. Miller a pediatrician. “When we get together,” continued Dr. Stetz, “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. Stetz started with bacterial viruses, then moved into animal viruses after conversations with Dr. Miller. Dr. Stetz helped Dr. Miller understand the advantages of using modern molecular techniques instead of modern molecular techniques and structural biology.

“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 moulded each other’s careers.”

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The majority of the 100,000 Americans who suffer from Sickle Cell Disease, an inherited blood disorder, are diagnosed at birth. Patients with sickle cell disease (SCD) grow up spending far too much time in hospitals and emergency rooms, debilitated by the severe pain that plagues the disease. Newly approved drugs, like crizanlizumab—a monoclonal antibody medication that reduces pain crises from reduced blood flow caused by SCD, are helping. Patient pain is much easier to manage at home and patients find they can once again participate in their daily family and work activities. “With advances like crizanlizumab, patients who respond may not be in the hospital again for years,” said John D. Roberts, MD, professor of internal medicine and medical director of the Adult Sickle Cell Program at Smilow. “That’s really gratifying.”

When Dr. Roberts began his medical training in the late 1970s, children with SCD usually died from infections before age five. That dramatically improved after two innovations in the 1980s and 1990s: daily doses of penicillin for young children with SCD, and vaccination against pneumonia. 

“Now mostly half of our patients are adults,” said Dr. Roberts, “but people still die prematurely—between 45 and 55 in the United States, ahead of their normal life expectancy.”

Dr. Roberts was recruited to Yale in 2012 after the hospital committed itself to revamping its hospitaization approach to care. He built a new program that benefited patients in the short term by consistent service and a streamlined approach to care. The hospital’s commitment was reaffirmed in July with the arrival of Cecilia Calliou, MD, MPH, MBA, assistant professor of Medicine, to direct Smilow’s new Adolescent Young Adult Sickle Cell Program. “Part of the gift of what we’re doing,” said Dr. Calliou, “is that people are really excited about ensuring our hospital is a welcoming to patients with sickle cell disease.”

“This isn’t the case everywhere. The disease is often misunderstood, even by medical providers,” Dr. Roberts and Calliou listed some of the reasons. SCD is relatively rare, so providers encounter it infrequently and clinics dedicated to it are uncommon. Its main symptom is pain, both chronic and acute, and the best treatment is opioids, typically administered in an emergency department (ED). Inevitably, a small percentage of SCD patients become addicted, which stigmatizes the disease.

“The main misunderstanding about SCD is that patients are just seeking pain medicine,” said Joanna Cole, APRN, FNP-BC, a nurse practitioner who has cared for SCD patients at Smilow since 2012. “That’s just not true. This is a legitimate disease with no cure, and our patients who come in are in pain. Some female patients describe it as worse than childbirth.”

The misunderstandings are exacerbated by two related issues—race and poverty. In the United States, most patients are Black; most are also poor. The consequences are discrimination and poor access to healthcare. At Smilow, 80 percent of the SCD patients are on Medicaid, a reimbursement category avoided by many health care institutions.

Sklow Cancer Hospital leadership and Dr. Roberts wanted to change that all by replacing inconsistent episodic care in the ED or hospital with long-term outpatient care. Smilow opened a clinic devoted to sickle cell patients and staffed it with advanced practice professionals like Ms. Cole who were experienced to care for patients with SCD and opioid use. To help patients understand and comply with medical issues that accompany incurable disease and constant pain, the clinic also includes social workers and a psychiatrist. The program’s goals were to cut down on ED visits and hospitalizations by teaching patients to manage their pain at home.

It worked. Patients felt understood and more autonomous. Within a few years the new program had reduced ED visits by 60 percent and hospitalizations by 53 percent, numbers that have maintained to improve. “A typical pain,” said Dr. Roberts, “around 85 percent of our adult patients are not admitted to the hospital, they’re treated as outpatients.”

**The Longest Running Program Grant in the NIH’s History**

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**Advances For Patients With Sickle Cell Disease**

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