Their research pleased the National Institutes of Health (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.”

Dr. Miller and Dr. Steitz collaborated to characterize a related virus that causes Kaposis sarcoma. The grant also supported Dr. DiMaio’s pioneering research in identifying viral oncoproteins, 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 culturing 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 moulded each other’s careers.”

In turn, the partners in this program grant have moulded 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. “It’s 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.”

“Now more than half of our patients are adults,” said Dr. Roberts, “but people still die prematurely—between 45 and 55 in the United States, despite being short of normal life expectancy.”

“Dr. Roberts was recruited to Yale in 2012 after the hospital committed itself to revamping its haematology/bone marrow program to address the needs of young adults. The idea was to open a clinic devoted to sickle cell patients and staffed it with advanced practice professionals like Ms. Cole, who were experienced in caring for patients with SCD and opioid use. To help patients manage their pain and psychological 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 continued to improve. “It’s a typo error,” said Dr. Roberts,” around 85 percent of our adult patients are not admitted to the hospital.”

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 these 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 her team studied how EBV gets activated. They found that EBV encodes a protein called ORF15, which is expressed in the nucleus of infected cells. ORF15 interacts with cellular proteins to initiate the viral transcription process. This interaction allows EBV to hijack the cell’s machinery to synthesize viral RNA and DNA. The viral transcripts are then transported to the cytoplasm, where they can be translated into viral proteins and assembled into complete viral particles.

ORF15 is a viral oncoprotein, and its overexpression in cancer cells can contribute to the development of EBV-associated lymphomas. The discovery of ORF15 and its role in EBV-induced cancer has opened up a new field in the study of viral oncogenesis, with implications for the understanding of other viruses associated with cancer. The grant also supported Dr. Miller’s research on the molecular basis of cancer virus replication and transformation, and its impact on innate defense.

Their research on the molecular basis of cancer virus replication and transformation, and its impact on innate defense, has led to significant advances in the understanding of viral oncogenesis and the development of new therapeutic strategies. The grant's continued support has allowed Dr. Miller and her team to expand their research, leading to new insights and discoveries that are shaping the future of cancer research and treatment.

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 typifies 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 groundbreaking.”

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 pneumococcal disease.

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Phoebe Conley | fall-winter 2021

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These days, if an acute episode sends a patient to the emergency room, the provider can look at the patient record for the recommended dose of opioids, and can reach out to the dedicated SCD providers.

The program cares for about 200 adults and 200 children, seen in side-by-side clinics at Smilow. Dr. Roberts is excited by the arrival of Dr. Calhoun, whose priority is to make sure those patients transition smoothly into adult SCD care.

Taking responsibility for one’s healthcare is challenging for any young adult, noted Dr. Calhoun, but SCD adds the complication of a chronic disease. Young adults with SCD may find the healthcare system intimidating or may avoid the hospital because they feel stigmatized as drug-seekers. They may also be unsure how to navigate insurance or a job or admission into college. Many young SCD patients are fatalistic and expect little in terms of a career or family.

“And it’s just not true,” said Dr. Calhoun. “We need to get them excited about their future while they’re young. They can have a full life. We can’t control things outside of the hospital, but we can reach out and wrap our arms around them to help them through those things at a pivotal time. It’s a life’s work for me.”

The future does hold promise. Opioids remain the best option for acute episodes, but several other drugs, like crizanlizumab, now help patients with SCD manage their pain. And though the only current cure for SCD is a bone marrow transplant from a sibling who is also a complete genetic match, other curative innovations are on the horizon.

Dr. Calhoun and Roberts are excited by the prospect of bringing such trials to Yale. Dr. Calhoun is confident that the personal relationships built between Yale’s SCD providers and patients have formed the trust necessary to enroll participants in trials. She wants to expand that relationship into the community, to educate people about SCD.

“Awareness is such a critical part of making things better,” she said, “especially for young people trying to fit in. As we get new therapies and we learn how to treat sickle cell better, it’s important for them to be able to say, ‘Yeah, I have sickle cell disease and sometimes I have bad pain but I’m still able to do what I want.’ How empowering is that? How empowering is that? It’s not an overnight thing. It takes a consistent and continuous investment, but it has tremendous returns. When you can help people stay alive, what better return is there?”

Dr. Cecelia Calhoun, MD