# Seven Scientists with Novel Approaches to Fighting Cancer

The Damon Runyon Cancer Research Foundation awards $2.8 million to innovative early career scientists.

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The Damon Runyon Cancer Research Foundation announced that seven scientists with novel approaches to fighting cancer have been named 2021 recipients of the Damon Runyon-Rachleff Innovation Award. Five initial grants of $400,000 over two years were awarded to early career scientists whose projects have the potential to significantly impact the prevention, diagnosis and treatment of cancer. Each project will have the opportunity for up to two additional years of funding (four years total for $800,000). This year, “Stage 2” continuation support was granted to two awardees who demonstrated significant progress on their proposed research during the first two years of the award.

The Damon Runyon-Rachleff Innovation Award funds cancer research by exceptionally creative thinkers with “high-risk/high-reward” ideas who lack sufficient preliminary data to obtain traditional funding. The awardees are selected through a highly competitive and rigorous process by a scientific committee comprised of leading cancer researchers who are innovators themselves. Only those scientists with a clear vision and passion for curing cancer are selected to receive the prestigious award.

Examples of past success stories from Damon Runyon-Rachleff Innovators include development of the gene editing technology CRISPR and single-cell sequencing techniques that are revolutionizing not just cancer research, but biomedical sciences globally.

This program was established thanks to the generosity of Andy and Debbie Rachleff.

**New 2021 Damon Runyon-Rachleff Innovators:**

Luisa F. Escobar-Hoyos, PhD

Yale University

“Understanding RNA splicing in tumor cell adaptation and anti-tumor immunity”

Current pancreatic cancer chemotherapies are not effective, and targeted therapies are only

applicable in about 5% of cases. Furthermore, pancreatic cancers cause immune cell stress, limiting the success of immunotherapies in this disease. Using mouse models and tumor samples from pancreatic cancer patients, Dr. Escobar-Hoyos has identified that changes in RNA splicing, a process that controls protein diversity in cells, are crucial for pancreatic cancer development, therapy resistance, and disruption of anti-tumor immunity. The proposed project will dissect the molecular role of RNA splicing in pancreatic cancer, which likely drives the disease's lethality. She seeks to develop a novel anti-RNA splicing therapy with dual action—a targeted therapy against tumor cells coupled with an immunotherapy to restore immune cell anti-tumor activity—to more effectively treat pancreatic cancer patients.

Danielle Grotjahn, PhD

The Scripps Research Institute

"Uncovering structural mechanisms of mitochondrial fragmentation in cancer by cellular cryo-electron tomography"

A unifying hallmark of several types of cancer is the uncontrolled fragmentation of mitochondria, the microscopic compartments that generate energy for the cell. Although many key players have been implicated in this process, the manner in which these factors assemble to modify the mitochondrial architecture and induce the unrestricted fragmentation associated with cancer is unknown. Dr. Grotjahn uses cutting-edge instrumentation, powerful electron microscopes, and pioneering image processing approaches to visualize this process inside cancer cells. Her work has the potential to identify new targets to block mitochondrial fragmentation as a future therapeutic strategy to prevent cancerous cell proliferation and tumor growth.

Mandar D. Muzumdar, MD

Yale University School of Medicine

"Targeting endocrine-exocrine signaling in pancreatic ductal adenocarcinoma progression"

Obesity is a major risk factor for over a dozen cancer types, including pancreatic cancer, the third leading cause of cancer-related death in the United States. Despite the rising prevalence of obesity worldwide, surprisingly little is known about how it promotes cancer development. Using animal models that closely mimic human pancreatic cancer, Dr. Muzumdar showed that obesity could provoke abnormal signals sent by the hormone-producing cells of the pancreas to their neighboring tumor-forming cells. In this project, he seeks to understand how these hormones are induced and act to drive cancer formation in obesity. Targeting pancreatic hormone signaling could provide a new approach for the prevention and treatment of pancreatic cancer and other obesity-associated cancers.

Sabrina L. Spencer, PhD

University of Colorado, Boulder

“Causes and consequences of rapid cancer cell adaptation to MAPK pathway inhibitors”

Until recently, basic research in oncology has primarily focused on mutations that drive cancer drug resistance. While the contribution of mutations to cancer drug resistance is undeniable, how cells adapt to drugs on short time scales, long before genetic mutations arise, is very poorly understood. Dr. Spencer will use multi-day time-lapse microscopy to study how individual cancer cells adapt to drugs targeting cell proliferation during the first few days of drug treatment. She will identify the molecular events that allow individual rogue cells to escape from drug action. These early drug “escapees” could represent a seed population enabling development of permanent (genetic) drug resistance and, if understood, could be therapeutically eliminated to reduce tumor relapse. Dr. Spencer is co-funded with the Mark Foundation for Cancer Research.

Joshua A. Weinstein, PhD

The University of Chicago

“A novel DNA microscopy platform for rapid discovery of immunogenic tumor neoantigens”

The human adaptive immune system continuously surveils for proteins and protein fragments that do not belong. Mutated protein fragments in tumor cells, called neoantigens, form a basis by which the adaptive immune system discriminates between cancer and healthy cells. Delivered therapeutically, neoantigens specific to a tumor can similarly serve as anti-tumor vaccines. Dr. Weinstein has developed a new imaging modality that simultaneously identifies new genetic mutations and physically maps interactions between the cells that possess them. He is working to apply this technology to the identification of tumor-specific therapeutic neoantigens most capable of eliciting immune response.

**2021 Stage 2 Damon Runyon-Rachleff Innovators:**

Xiaochun Li, PhD

University of Texas Southwestern Medical Center

“Investigation of Hedgehog and Wnt signaling mechanisms”

Hedgehog (Hh) and Wnt are signaling pathways required for proper development during the formation of an embryo. These pathways can also be activated abnormally in adult tissue and have been implicated in multiple cancers. Several small molecule inhibitors and antibodies targeting Hh or Wnt signaling are being tested in clinical trials but a detailed understanding of these processes is lacking. Dr. Li will apply cell and structural biology approaches to dissect the signaling mechanisms at an atomic level. These mechanistic details will help identify potential targets for therapeutic intervention and provide valuable information regarding antibody and compound design.

Alexandra-Chloé Villani, PhD

Massachusetts General Hospital

“Deciphering the Achilles’ heel of cancer immunotherapy”

Immune checkpoint inhibitors unleash the immune system to attack tumors; they have revolutionized the treatment of solid cancers by changing the prognosis for many patients, improving their quality of life and offering long-lasting remission. However, these immunotherapies can also spur assaults on healthy organs called “immune-related adverse events” (irAEs), ranging from minor rashes and fevers to severe gastrointestinal complications and deadly heart inflammation. Dr. Villani is analyzing patient samples using state-of-the-art genomic technologies and integrative immunological approaches to understand why and how these irAEs occur in cancer patients. Ultimately, she aims to identify therapeutic solutions to prevent or clinically manage irAEs without reducing the lifesaving potential of immunotherapy.

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