CANCER RESEARCH INSTITUTE
FY2023 Highlights and Accomplishments

As the leading nonprofit organization committed to revolutionizing cancer treatment by leveraging our immune system's potential since our founding 70 years ago, the Cancer Research Institute (CRI) provides financial support for both laboratory and clinical research in the fields of immunology and tumor immunology, the latter of which CRI’s visionary backing has played a crucial role in pioneering and nurturing. These endeavors continue to deepen our comprehension of the relationship between cancer and the immune system, leading to advancements in cancer therapy and opening new avenues for further research in the field.

As an important indication of this progress, the U.S. Food and Drug Administration (FDA) has issued twelve immunotherapy approvals since July 2022, including the first approval of a checkpoint inhibitor for any type of sarcoma. This year revealed exciting immunotherapy clinical trial results. Most prominently, a phase 2 study heralded the arrival of personalized neoantigen vaccines onto the clinical scene. When combined with checkpoint immunotherapy, these unique, patient-tailored vaccines significantly reduced cancer recurrence after surgery in people with high-risk melanoma.

The Cancer Research Institute, both our scientists and our programs, also celebrated notable achievements this past fiscal year, many reflecting the growing importance of technology in both cancer immunology research and cancer immunotherapy treatments. By empowering scientists utilizing cutting-edge tools like CRISPR, artificial intelligence, bacterial ‘trojan horses’ and more, we hope to push the boundaries of what is possible to help improve how care is administered currently as well as design better immunotherapies for the future. This progress will require technology to unravel the complexity of the tumor-immune microenvironment and cancer ecosystem as a whole, and shed light on the mechanisms that explain why some patients respond to immunotherapy but not others.

One such promising technology involves circulating tumor DNA, or ctDNA. By analyzing ctDNA via a simple blood draw, doctors can gain insights into the genetic alterations and mutations present in tumors and monitor their activity. In a phase 1/2 trial funded through CRI’s Anna-Maria Kellen Clinical Accelerator, researchers demonstrated ctDNA’s superior predictive capabilities compared to conventional radiographic scans as far as detecting responses in lung cancer patients receiving immunotherapy and chemotherapy. In particular, this ctDNA approach detected responses faster and more accurately, and was better at predicting long term outcomes and patient survival.

Recognizing the need to empower physicians seeking to bring novel cancer immunotherapies into the clinic, especially in areas with a high unmet need, we launched a groundbreaking Clinical Innovator program. By seeking mechanistic insights into clinical response and striving to discover predictive biomarkers, these investigator-initiated studies have the potential to revolutionize cancer treatment. To ensure the maximum impact of each clinical trial, our organization collaborates closely with researchers, offering expert advice and assistance in optimizing trial design and translational studies.
This coordinated effort amplifies the potential for groundbreaking discoveries that can shape the future of cancer care.

Furthermore, we bolstered our longstanding postdoctoral program with an Immuno-Informatics Fellowship that addresses the critical need for scientists who possess a deep understanding of both quantitative and biological sciences. The program aims to support talented young researchers from around the world who wish to receive dual training in immunology and data science, including computational biologists seeking to expand their knowledge of immunology, as well as cancer immunologists interested in gaining proficiency in computational biology, data science, and genomics. Under the mentorship of world-renowned scientists in these fields, fellows will engage in cutting-edge research at the interface of cancer immunology and computational biology. By providing comprehensive training and equipping the next generation of scientists with practical tools, we are fostering an environment where novel ideas at the intersection of immunology and computational biology can thrive.

In FY2023, thanks to generous donor support, CRI was able to award $28.7 million in grants, fellowships, and other awards to 73 of the world’s leading immunologists, tumor immunologists, data scientists, and other key contributors in cancer immunotherapy research. This vital funding supports innovative and bold science, trains future generations of scientific leaders, powers open-access bioinformatics and cancer immunotherapy information resource hubs, spurs groundbreaking incubators developing cutting-edge immunotherapies, and connects patients with clinical trials that offer new and promising treatment options. Throughout the 70 years since our founding, CRI has invested more than $515 million in efforts to pioneer and foster the field of tumor immunology, which has provided the foundation for today’s treatments that are saving millions of lives around the world each year and enabling the development of next-generation immunotherapies with the potential to overcome today’s challenges and provide more cures to more patients.

Through our steadfast dedication to fundamental research on the immune system, CRI continues to advance our understanding of cancer’s tricks and vulnerabilities, as well as pursue initiatives with the potential to improve patient outcomes through therapeutic interventions grounded in immunological principles. Moreover, these efforts also drive progress in overcoming not only cancer but also autoimmune, inflammatory, and infectious diseases.

**FY2023 New Awards**

The Cancer Research Institute awarded $28.7 million in research grants and fellowships in the 2023 fiscal year ending June 30, 2023. In total, CRI made 73 awards that will advance cancer immunology research at 41 institutions in 10 countries. CRI grants were awarded to support projects involving a variety of immune-based approaches as well as the development of novel technologies that may help pave the way for the next generation of immunotherapies.

- 30 new CRI Irvington Postdoctoral Fellowships supporting the training and research of young scientists improving our understanding of fundamental cancer and immune biology, including three awardees of our Postdoctoral Fellowship to Promote Racial Diversity. Among the many research avenues they’re investigating are nature-inspired immune cell engineering strategies, the nervous system’s ability to influence tumor immunity and metastasis, methods to harness
beneficial viruses for cancer immunotherapy, as well as how a wide variety of factors—from dietary habits to cigarette smoke to age—affect our immune system and cancer protection.

- 6 inaugural Immuno-Informatics Fellows focusing on deciphering the patterns of immune architecture within breast cancer tumors, understanding how aging affects T cell dysfunction and immunotherapy's effectiveness, developing a single-cell platform to define the global factors regulating immune cell states, and learning the nuances of the IFNγ, a central node in human immunity.

- 12 new Clinic and Laboratory Integration (CLIP) Grants funding efforts to target platelets to improve immunotherapy, generate personalized T cell therapies, map the cellular landscape of chordoma, define the factors of immunotherapy response and resistance in gastroesophageal cancer, develop B cell therapies for brain tumors, and modulate the gut bacteria to improve immunotherapy for multiple myeloma.

- 4 new Technology Impact Awards to explore targeting cancer metabolism via the Warburg effect, improving vaccine design by leveraging computational modelling, improving researchers’ ability to analyze and extract valuable information from preserved tissue, and developing a new discovery platform to identify promising innate immune targets.

- 5 new Lloyd J. Old STAR Awards (Scientists TAKing Risks) of $1.25 million over five years to outstanding tenure-track scientists conducting high-risk, high-reward cancer immunology research with the potential to produce transformative leaps forward in tumor immunology. The latest cohort of STARs is exploring the importance of stem-like T cells in cancer immunity, novel ways of reprogramming tumor-targeting T cells, the impact of DNA repair gene mutations, next generation genome engineering strategies, and CAR T cell therapy approaches for solid cancers in children.

- 3 inaugural Clinical Innovators pursuing promising strategies in the clinic that include a novel cytokine-targeting immunotherapy to treat lung cancer prior to surgery, targeting glutamine metabolism to treat a rare form of liver cancer, and fecal microbiota transplantation in the management of IO associated colitis.

- The CRI-Anna-Maria Kellen Clinical Accelerator’s expansion of circulating tumor DNA (ctDNA) trial is moving forward into phase 2 study after promising initial results indicated that molecular response based on ctDNA levels can be used as a prognostic marker on which clinical decisions can be based, potentially changing medical practice in non-small cell lung cancer (NSCLC).
FY2023 CRI Publications

CRI funded scientists had 300 publications of news-worthy research in top-tier, peer-reviewed academic journals this fiscal year. The highlights include:

**Lloyd J. Old STAR Program (Scientists Taking Risks)**

- CRI Arash Ferdowsi Lloyd J. Old STAR **Peter E. Fecci, MD, PhD** (Duke University), who is exploring how the special properties of brain tumors block effective immune responses against them, had a particularly prolific year. Since July 2022, Dr. Fecci published 15 papers, with 7 as senior author. Dr. Fecci’s two important contributions involve work in *Nature Communications* and *Nature Cancer*, which discovered, respectively, how the CaMKK2 enzyme drives immunotherapy resistance in glioblastoma, and a fascinating new way in which “killer” T cells can eliminate cancer cells without relying on MHC-antigen complexes. Overall, Dr. Fecci’s work is unraveling the immune mysteries of the brain—long considered an “immune privileged” organ—and advancing approaches to shift the balance and improve immunotherapy for brain cancer patients.

- CRI STAR **Amanda Lund, PhD** (NYU Langone Health) is exploring how the lymphatic system influences immune responses against cancer. This past year, Dr. Lund led work published in *Nature Immunology* that revealed how lymphatic vessels use cytokines to make cancer-targeting T cells exit tumors prematurely, thus impeding their ability to eliminate cancer cells. Blocking this process allowed for more T cells to remain within tumors and improved cancer cell elimination in mice with melanoma. Moving forward, strategies targeting lymphatic vessels could complement checkpoint inhibitor and CAR T cell immunotherapies that rely on T cells for clearing out cancer cells. Additionally, Dr. Lund contributed to a study that used single cell sequencing to characterize how chemotherapy impacts the cellular milieu within pancreatic tumors, finding certain changes that may promote immunotherapy resistance.

- CRI STAR **Tal Danino, PhD** (Columbia University) is using synthetic biology to harness bacteria and their unique abilities to improve cancer treatment. Bacteria are ideal delivery vehicles for anti-cancer drugs, including immunotherapies, because they can infiltrate into tumors and deliver payloads locally, thus sparing healthy tissues of potential side effects. This past year, Dr. Danino, as highlighted in *Scientific Reports*, created a screening and evaluation pipeline to characterize bacterial therapies for lung cancer. After identifying theta toxin as a promising anti-cancer molecule produced by bacteria found in human tumors, he showed that toxin-producing bacteria helped control lung tumors in mice, both alone and in combination with chemotherapy, without systemic toxicity. Moving forward, Dr. Danino envisions these bacteria-based approaches, which offer nearly limitless potential, could become a new paradigm of cancer care.
Technology Impact Award

- CRI Technology Impact Award Investigator Yun Wu, PhD (University of Buffalo) led work published in *Cancer Communications* that highlighted the potential value of Axl-LP-VD-CTA09, a novel liposomal nanodrug designed to overcome treatment resistance in lung cancer. In mice, the drug demonstrated the ability to home to tumors in the lungs and prevent cancer cells from assuming a form that promotes metastasis, ultimately improving the effectiveness of standard therapy.

- CRI Technology Impact Award Investigator Adam Mor, MD, PhD (Columbia University) led work published in *Cell Reports Medicine* revealing links between certain immune cells and immunotherapy side effects. His discoveries—that imbalances in certain T cell subsets were associated with arthritis, pneumonitis, and thyroiditis—suggest that measuring immune cell populations prior to treatment could supply important predictive biomarkers for improving care in the clinic.

- CRI Technology Impact Award Investigator Stephanie K. Dougan, PhD (Dana-Farber Cancer Institute and Harvard Medical School) created a new mouse model that is capable of capturing an incredibly important phenomenon known as tumor-immune equilibrium. As published in *Cell Reports*, Dr. Dougan used this model to characterize the central and indispensable roles of IFNγ in immune equilibrium, during which a cancer is seemingly in remission or otherwise stable but may be in the process of mounting a potential relapse. In the future, Dr. Dougan hopes to uncover additional insights into the factors that promote cancer relapse and develop better preventive strategies.

Clinic and Laboratory Integration Program (CLIP)

- CRI CLIP Investigator Elodie Segura, PhD (Institut Curie, Paris) led work published in the *Journal of Experimental Medicine* that gained insights into specialized subsets of macrophages. In the tonsils alone, Dr. Segura identified three distinct types of human macrophages defined by their expression of CD36, which governed their behavior, how long they lived, and what other immune cells they activated. Learning how to better manipulate these important immune cells, which are found throughout our entire body, could lead to better preventive and therapeutic approaches for cancer.

- CRI CLIP Investigator Vincenzo Bronte, MD (Università di Verona, Italy) led work published in *Science Translational Medicine* that uncovered a mechanism through which neutrophils can protect pancreatic tumors. The production of neutrophil extracellular traps, Dr. Bronte found, activates an enzyme that degrades an important immune nutrient, thereby suppressing the proliferation of T cells. Blocking this enzyme's activity restored T cell function and enabled them to better respond to immunotherapy.

- CRI CLIP Investigator Rajan Kulkarni, MD, PhD (Oregon Health & Science University) led work published in *Cancers* that identified possible mechanisms behind skin-related side effects after
In patients whose skin experienced adverse reactions after immunotherapy, Dr. Kulkarni analyzed their blood and observed increases in immune cells called macrophages as well as harmful reactive oxygen species, suggesting strategies to address their impact might be able to help prevent skin-related side effects of immunotherapy.

Postdoctoral Fellowship Program

- CRI Fellow Katie M. Campbell, PhD (University of California, Los Angeles) led work published in Cancer Cell that dissected the factors controlling how likely someone is to respond to immunotherapy. By analyzing samples from more than 500 patients with advanced melanoma who were treated with checkpoint immunotherapy, Dr. Campbell found that prior treatment with CTLA-4 immunotherapy modified the tumor microenvironment and immune cell signatures in ways that impacted patients' responsiveness to PD-1 therapy. Overall, her findings have important implications in the clinic as far as helping doctors determine the optimal treatments for individuals based on their individual cancer and treatment history.

- CRI Fellow Jorge Luis Galeano Niño, PhD (Fred Hutchinson Cancer Research Center) led work published in Nature that highlighted the way bacteria populate tumors within highly organized micro niches. Importantly, cancer cells infected with bacteria were more invasive and recruited myeloid cells that suppress immunity. Dr. Galeano Niño also identified integral cell-bacteria interactions that influence inflammation, metastasis, and cancer progression, illustrating the relevance of bacterial factors when it comes to clinical decision making and optimizing our chances of curing patients.

- CRI Fellow Anghesom Ghebremedhin, PhD (University of California, San Diego) led work published on bioRxiv that demonstrated that targeting immune cells called macrophages might help alleviate fibrosis associated with several diseases of the lungs. In mice, targeting the CD206 receptor on macrophages decreased fibrosis as well as markers of inflammation, and matched up well when compared to fibrosis drugs currently approved by the FDA to treat fibrosis. Overall, the data suggest this macrophage-targeting approach may have potential value for a variety of lung diseases in which fibrosis plays a role.

CRI-Anna-Maria Kellen Clinical Accelerator Team

- Our CRI-Anna-Maria Kellen Clinical Accelerator Team produced 3 new publications in Nature Reviews Drug Discovery, providing comprehensive analyses on immunotherapy clinical trials, the cell therapy landscape, and population diversity in clinical trials.
Summary

Now in our 70th year, CRI is committed to pioneering the next frontiers in tumor immunology, biotechnology, and cancer treatment, investing in the best minds whose contributions to science range from fundamental to transformative. As a testament to our commitment and your support, CRI enabled considerable progress this year in terms of scientific advances, notable clinical discoveries, and new program development. Cancer immunology is advancing at incredible rates thanks to new technologies that allow for rapid learning and productive collaborations among brilliant scientists who benefit from CRI support at critical career inflection points, from the newest and highly promising research scientists to distinguished, highly influential experts and mentors.

Again, we thank you, because the work we do is possible only through your generous contributions, enabling us to realize these achievements. With your continued support, we can create a world immune to cancer.