CRI Cancer Research Institute™
For a world immune to cancer.™

Executive Summary

Since our founding in 1953, the Cancer Research Institute (CRI) has been at the forefront of advancing immunotherapy, fundamentally reshaping cancer treatment, and establishing immunotherapy as the fourth pillar of cancer care.

Thanks to CRI's 71 years of dedication, **45 percent of all newly diagnosed cancer patients, or 9 million people,** are eligible for at least one form of immunotherapy today.

At the heart of CRI's approach is our "**People x Biology x Data**" strategy, which emphasizes the integration of bioinformatics, artificial intelligence (AI), and machine learning to advance cancer immunotherapy. By leveraging these cutting-edge technologies, CRI enhances researchers' ability to analyze complex biological data, identify novel biomarkers, and develop personalized treatment strategies. This innovative framework accelerates the pace of discovery and ensures that new insights are translated into effective therapies for patients. CRI supports scientists throughout the entire arc of discovery, from basic and translational research to clinical trials and FDA approval.

In the past year alone, there have been **13 new FDA approvals** for immunotherapy treatments, covering **10 different drugs across 11 types of cancer**. By funding innovative studies, CRI empowers researchers to uncover the fundamental mechanisms of the immune system's interaction with cancer.

CRI-funded clinical trials focus on detailed patient data collection to generate new research questions and continuously refine treatment strategies through thorough analysis of extensive datasets.

In the past year, CRI-funded scientists across our entire range of programs published **381 original research papers and impactful reviews**. By sharing their findings, they have expanded collaboration and accelerated the pace of discovery.

From theory to approval, CRI is there every step of the way for our researchers and clinicians. This comprehensive support system, coupled with our persistent vision, has **positioned CRI as the central force** in integrating immunotherapy into standard cancer care and driving continuous innovations to create a world immune to cancer.

Research Programs — By the Numbers

64 Grants | 42 Institutions | 7 Countries

CRI's robust preclinical and translational research programs bridge laboratory discoveries to clinical trials, ensuring promising therapies reach patients.

In our 2023-24 fiscal year, CRI awarded **$22,765,861** in **64 new grants** to researchers from **42 different institutions** across **seven countries**.

These grants were conferred to leading researchers and postdoctoral fellows worldwide, fostering mechanistic discoveries that fuel next-generation immunotherapies for cancer patients.

Expanding Science — Facilitating Research — Finding Cures

Science is an unending endeavor, and the challenges that researchers face require pivoting and reevaluating strategies. A crucial element of CRI's success is our Scientific Advisory Council's visionary foresight in anticipating trends in cancer therapy and identifying which scientists to fund. In short, **we boldly follow the science without prejudice** to save more lives by fueling the discovery and development of powerful immunotherapies for all cancers.

Years of research and pursuit to find a better cure for cancer have brought immunotherapy to the forefront of cancer treatment, making it the first line of treatment for many metastatic cancers, including non-small cell lung cancer (NSCLC) and melanoma. As previously mentioned, **45 percent** of newly diagnosed cancer patients are now eligible for immunotherapy, a testament to CRI's success in advancing this treatment.

As a new era of cancer therapy emerges, the CRI scientific network continues to challenge the status quo and forge an innovative path. We achieve this by harnessing cutting-edge research, fostering interdisciplinary collaboration, and relentlessly pursuing breakthroughs that push the boundaries of what is possible in cancer treatment.

This year's grants included **five CRI Lloyd J. Old STAR Awards, seven CLIP Awards, three Clinical Innovator Awards, four Clinical Accelerator Awards,** and **five Technology Impact Awards,** all directed towards leading scientists in cancer immunology. Additionally, we awarded **28 CRI Irvington Postdoctoral Fellowships – including three for the Fellowship to Promote Racial Diversity,** and **four Immuno-Informatics Postdoctoral Fellowships** to promising young scientists embarking on their careers in cancer immunology.

These recipients were expertly vetted and selected by CRI's Scientific Advisory Council, through a merit-based open application process, identifying the best and brightest minds in cancer immunology.

Personalizing Immunotherapies

Cancer's complexity requires personalized treatment because each tumor has distinct genetic and molecular characteristics. Tailoring strategies to these unique features is essential for effectively addressing the diverse and evolving nature of cancer.

Realizing this need, CRI is breaking new grounds in personalized immunotherapy by funding a plethora of research initiatives.

CRI-funded researchers are addressing cancer's complexity by identifying new targets such as tumor-specific neo-antigens, creating advanced genome-editing tools, and developing personalized cancer vaccines and cellular therapies. These efforts aim to unravel cancer's diverse nature and create customized treatments that align with each patient's unique cancer profile.

Our researchers are especially dedicated to exploring the potential of cutting-edge, personalized cancer vaccines across various cancer types. By advancing breakthroughs in multiple cancers and utilizing sophisticated technologies to analyze data, they are developing tailored vaccines aimed at targeting individual tumors with unparalleled precision.

CRI Lloyd J. Old STAR **Gavin Peter Dunn, MD, PhD**, from the Washington University School of Medicine, is advancing personalized vaccines against glioblastoma (GBM) to improve immune response against these malignant brain cancers. In a recent publication, Dr. Dunn reported results from a clinical trial that tested the safety and efficacy of the personalized peptide vaccine, NeoVax, in GBM patients. The preliminary findings show the vaccine was effective in boosting immune response in these trial participants. Dr. Dunn is expanding his trial to include a larger pool of patients, further testing the efficacy of the NeoVax cancer vaccine to improve patient response.

Fellow CRI Lloyd J. Old STAR **Joshua D. Brody, MD**, from the Icahn School of Medicine at Mount Sinai, is investigating a therapeutic cancer vaccine approach, known as *in situ* vaccination (ISV), that induces anti-tumor immunity at the tumor site and can cause regression of tumors throughout the body. In his

recent publication, Dr. Brody's ISV research investigates the use of viral and bacterial pathogen components in vaccines to activate dendritic cells, offering a more effective method than synthetic alternatives. This personalized method enhances tumor antigen-specific T cell responses and promotes tumor regressions. Such tailored immune stimulants could pave the way for new FDA-approved, clinical-grade treatments in early-phase cancer trials.

CRI-CLIP recipient **Christopher Klebanoff, MD,** at Memorial Sloan Kettering Cancer Center (MSKCC), is pioneering the identification of tumor antigens to develop strategies that will boost the efficiency of chimeric antigen receptor (CAR) T cells against various types of cancer including hard-to-treat-solid-tumor cancers like breast, ovarian, colon, and pancreatic cancer. In Dr. Klebanoff's lab, CRI Irvington postdoctoral fellows **Lauren B. Banks, PhD,** and **Inaki Etxeberria, PhD,** are making strides in this mission. Dr. Banks is focusing on neo-antigens in sarcoma to guide T cell therapy, while Dr. Etxeberria targets mutated NRAS genes in melanoma to develop cutting-edge CAR T cells that target these mutations. These efforts are expanding CAR T therapy by developing precision-based CAR T cells that target specific mutations present in tumors.

Beyond neo-antigen and cancer vaccines, CRI scientists are engaged in developing new strategies to identify the unique properties of tumors that can be exploited to develop personalized immunotherapies.

CRISPR-based gene editing is a groundbreaking technique providing scientists worldwide with unparalleled control over reprogramming genetic code to improve patient outcomes. Leveraging the full potential of CRISPR tools, CRI scientists are enhancing the design of adoptive T cell therapies, such as CAR T cell therapy, making them more robust and effective.

CRI Lloyd J. Old STAR, **Alexander Marson, MD, PhD,** at the University of California, San Francisco (UCSF) and the Gladstone-UCSF Institute of Genomic Immunology, is at the forefront of using CRISPR-based gene editing to develop robust and durable CAR T therapies. By using high-throughput CRISPR screening, Dr. Marson is exploring protein-coding and non-coding genetic mechanisms that regulate specialized T cell functions.

CRI postdoctoral fellow **Mirat Sojitra, PhD**, at Stanford University, is investigating glycosylation on cancer cells through CRISPR-based screening to develop personalized therapy strategies for cancer patients. In a recent publication, Dr. Sojitra described a method for creating various types of genetically coded glycosylation using chemical and enzymatic reactions. This glycosylation library was then used to study how these modifications affect immune reactions, with the goal of developing more effective immunotherapies.

Understanding Tumor Microenvironment

Tumors thrive within a supportive tumor microenvironment (TME) that aids their growth and survival. CRI scientists are leading efforts to understand and manipulate the TME, explore tumor-immune interactions, and shed mechanistic insights into T cell exhaustion. Using advanced imaging and computational methods, CRI scientists aim to develop innovative strategies to understand the inner workings of the TME and its impact on immune cell function. By leveraging these insights, they seek to enhance T cell activity and create more effective and targeted cancer therapies.

CRI Lloyd J. Old STAR **Andrea Schietinger, PhD,** at MSKCC, is revolutionizing our understanding of tumor-immune interactions within the TME. Her latest publication characterized unique immune

structures called 'immune triads' in the TME, which play a crucial role in effectively eliminating tumor cells.

Cancer cells have a ravenous appetite that drains the TME of essential nutrients like glucose and oxygen. This resource-deprived TME impedes the ability of our immune system to fight and eliminate cancer cells. By addressing the tumor-induced metabolic changes that hinder T cell effectiveness, CRI scientists are developing strategies to restore and amplify the immune system's ability to combat cancer.

CRI Lloyd J. Old STAR **Guoliang Cui, PhD,** from the Hefei Comprehensive National Science Center in China, is studying different factors that regulate T cell exhaustion and influence the efficiency of immunotherapy. His recent publication showed how the availability of certain metabolites, like serine, influences the differentiation of regulatory T cells and suppresses the immune system to aid tumor growth.

Understanding metabolism is crucial for optimizing CAR T cell therapy, as the metabolic state of T cells can significantly influence their effectiveness and persistence within the tumor environment. By exploring how metabolism impacts CAR T cell function, researchers can refine these therapies to improve their performance and outcomes in cancer treatment.

Exploring the role of metabolism in CAR T cell activity, CRI Lloyd J. Old STAR **Yvonne Chen, PhD,** from the University of California, Los Angeles (UCLA), is developing next-generation engineering approaches to enhance the efficiency of T cell therapy. In a recent publication, Dr. Chen described how different CAR molecules guide metabolism in CAR T cells to impact their functional activity and ability to fight tumors.

Cancer cells rely on specific metabolites for growth, metastasis and immune evasion. Understanding this metabolic dependency can reveal new opportunities for targeting and disrupting cancer cell function and help in boosting anti-tumor immunotherapy responses.

CRI Clinical Innovator grant recipient **Marina Baretti, MD,** from the Johns Hopkins University School of Medicine, is investigating how targeting the metabolic dependence of tumor cells on glutamine can improve immunotherapy for fibrolamellar carcinoma (FLC). She is conducting a clinical trial to test if combining the drug DRP-104, which targets glutamine, with the immune checkpoint inhibitor durvalumab, can improve treatment for patients with fibrolamellar carcinoma (FLC).

By integrating basic and clinical research with tumor immunology, CRI scientists are identifying novel targets and mechanisms that drive immune evasion and tumor progression, ultimately enabling the design of treatments that are finely tuned to the unique metabolic and microenvironmental landscapes of individual tumors. By combining innovative approaches with a deep understanding of tumor immune system, our scientists are developing new strategies to overcome existing challenges and enhance the efficacy of immunotherapies.

Technological advancements in genomics and high-throughput microscopic imaging are significantly boosting our understanding of cancer. These tools allow scientists to delve deeper into the genetic mutations and molecular alterations within cancer cells and provide a full view of cellular interactions and dynamics within the TME.

CRI Technology Impact award recipient, **Ido Amit, PhD,** from the Weizmann Institute of Science in Israel, is developing and employing high-resolution techniques including spatial transcriptomics to decipher molecular crosstalk between cells in the TME. Dr. Amit's research will identify novel pathways

and signaling molecules involved in processes such as tumor escape, immune cell exhaustion, and suppression, ultimately gaining insights into the fundamentals of the response or resistance to immunotherapy treatments. CRI Immuno-Informatics Fellow **Kai Kun Xie, PhD,** working in Dr. Amit's lab at the Weizmann Institute of Science, is using bioinformatics to analyze this spatial imaging data to improve our understanding of tumor immune responses and develop strong immunotherapies.

As we continue to unravel the complexities of the TME, CRI-supported research is paving the way for transformative advancements in cancer treatment. CRI scientists are generating a treasure trove of imaging and genomic screening data that is being used to develop next-generation immunotherapies.

Leveraging Data to Expand Immunotherapy

Spatial imaging technologies, molecular screening, and gene sequencing are not just reserved for scientists conducting research related to the TME. These technologies generate vast amounts of computable data, paving the way for discovering new immunotherapies across various research areas.

Recognizing the pivotal role of data science and computational biology in revolutionizing immunotherapy, CRI is strategically advancing the integration of cutting-edge biological and bioinformatics breakthroughs. Our funding is accelerating the development of innovative therapies, bringing us closer to more targeted and effective cures for cancer patients.

CRI Immuno-Informatics Fellow **Chi-Yun Wu, PhD**, from the J. David Gladstone Institutes, is leading the development of computational methods to decipher how different cancer cell variants affect disease progression and treatment response. In a recent publication, she described a new method of analyzing spatial transcriptomic data in various parts of a tumor to find genes that are important for specific types of cells. Her work improves on earlier methods that looked at gene expression changes across entire tumors but didn't account for how local cell-cell interactions affect gene expression.

Dr. Wu's innovative approach emphasizes the importance of understanding localized gene expression changes within tumors, setting the stage for further research into how cancer cells communicate and evade immune responses.

CRI Postdoctoral Fellow **Chiara Falcomatà**, **PhD**, from the Icahn School of Medicine at Mount Sinai, is using cell-selective proteomics in her research on pancreatic cancer. She intends to identify how signals from the cancer cells help pancreatic cancer evade immune response. In her latest study, she characterized pancreatic cancer subtypes based on extracellular proteins present in tumors and circulation, providing insights to accelerate the discovery of diagnostic markers and therapeutic targets. **This type of cell-specific proteomics analysis would not be possible without bioinformatics and computation tools.**

Spatial imaging, molecular screening, and gene sequencing are reshaping our understanding of tumor biology and generating invaluable data that drives the discovery of new immunotherapies.

CRI's commitment to integrating these cutting-edge biological and computational advancements is fully aligned with our **"People x Biology x Data"** strategy.

This transformative research not only accelerates the development of targeted treatments but also brings us closer to achieving more effective and individualized cures for cancer patients.

Supporting Scientists — Building Careers

At CRI, we proudly lead the way in immunotherapy research, exemplifying our unwavering commitment to scientific excellence. We champion exemplary scientists in immunotherapy, supporting their groundbreaking research. CRI takes immense pride in our scientists, whose pioneering work continues to advance the field of cancer immunology forward and demonstrates a tangible impact on improving patient outcomes and advancing cancer treatment.

Beyond supporting exceptional research, CRI funding provides training and career advancement opportunities, ensuring our scientists become world leaders in cancer immunotherapy. Many early-career scientists funded by CRI return later in their career to seek advanced funding opportunities, a testament to CRI's instrumental role in nurturing talent and fostering long-term scientific progress.

Ansuman Satpathy, MD, PhD, from Stanford University, is a prime example. CRI supported Dr. Satpatahy's postdoctoral research as a CRI postdoctoral fellow. Following a highly successful completion of his fellowship, he was awarded a CRI Technology Impact grant for his research on genetic regulation of T cell immunotherapy resistance in tumors. Dr. Satpathy is currently a CRI Lloyd J. Old STAR, trail-blazing the study of genetic control of tumor immunity at the single-cell level.

In Dr. Satpathy's own words, "*CRI was the first to fund my postdoctoral work, several years before it was apparent that genome technologies would become useful for understanding the immune response to cancer. I am very grateful once again that they have funded my independent laboratory to go after the next hurdle.* "

Yifat Merbl, PhD, from the Weizmann Institute of Science, is another example. Dr. Merbl received her CRI CLIP award in 2022 and with the help of CRI funding advanced her research in protein degradation and anti-tumor immunity. After prolifically authoring numerous publications over the past two years and a rigorous, merit-based review process, Dr. Merbl was selected as incoming CRI Lloyd J. Old STAR for 2024. With CRI's support, Dr. Merbl will continue her innovative work using mass spectrometry analysis of proteasome-cleaved peptides (MAPP).

Upon receiving her CRI-Lloyd J Old STAR award, Dr. Merbl remarked *"This grant will help us translate our scientific findings into innovative treatments, potentially offering new hope to cancer patients."*

CRI is continuing to pave the way for more effective and tailored cancer therapies by investing in evolving research techniques and technologies. In a world driven by big data, CRI is committed to providing the best possible training and support to CRI postdoctoral scientists.

To this end, CRI created a unique bioinformatics bootcamp for our postdoctoral fellows. This inaugural teaching session took place April 27, 2024-May 2, 2024, at the Hilton Bonnett Creek in Orlando, FL.

CRI postdoctoral fellow **John A. Frank, PhD,** from Yale University, and CRI-Fibrolamellar Cancer Foundation Fellow **Lindsay K. Dickerson, MD**, with the University of Washington, were just two of the nearly 50 postdoctoral fellows to attend the bootcamp.

"This course has convinced me of the organization's potential to function as a uniquely powerful force in the service of fundamental tumor immunology research and science as a whole", said Dr. Frank in reflecting on his experience with the bootcamp.

The bootcamp provided hands-on bioinformatics and computational training for scientists, providing them with a much-needed training and skill development opportunity to tackle the big data problems they will undoubtedly face in their research.

Dr. Dickerson added, *"This bootcamp honestly was a fantastic experience. It really boosted my training and my career and is probably the best investment that CRI could put into future scientists, especially wet lab and bench scientists."*

By offering hands-on, in-person training, CRI empowers scientists like Dr. Dickerson and Dr. Frank to push the boundaries of cancer research and therapy. This commitment ensures that CRI's fellows are at the forefront of technological advancements, driving the development of more effective and tailored cancer treatments.

Taking Discoveries to the Clinic

Even as we enter a new era of cancer treatment with the power of immunotherapy, many solid cancers remain formidable adversaries owing to their resistance to existing therapies. Building on CRI's cutting-edge research in cancer immunotherapy, our clinical trials are advancing the fight against hard-to-treat cancers and pushing the boundaries to improve standard of care for patients.

To accelerate our path to finding cures, CRI Clinical Accelerator is conducting multi-institution platform clinical trials that combine the expertise of world's leading clinicians and researchers. CRI is currently funding two trials, aimed at testing novel immunotherapy combinations to improve patient outcomes and deepen our understanding of the biology of ovarian and pancreatic cancers, two of the most challenging and devastating cancers.

The IPROC and REVOLUTION clinical trials, that target highly malignant ovarian and pancreatic cancers, respectively, leverage innovative and adaptive trial designs that allow testing safety and efficacy of immunotherapy combinations that have never been tried before. These clinical trials embed state-of-the-art technologies to analyze precious patient samples to identify biomarkers of response and understand resistance mechanisms. More importantly, these studies are designed such that both clinical and translational data can be collectively utilized to iterate onto more effective immunotherapy regimens.

Complementing our Clinical Accelerator is the CRI Clinical Innovator Program that nurtures groundbreaking research by providing seed funding and resources to early-stage ideas. These single-institution clinical trials are ushering in innovative immunotherapy treatment strategies to address various other cancer types. We are currently supporting six separate clinical trials under the Clinical Innovator Program which mirror CRI's ethos of focusing on areas of high unmet need and seek mechanistic insights into clinical response and potentials for biomarker discovery. CRI Clinical Innovator-supported investigators are tackling diseases such as liver cancer, prostate cancer, and glioblastoma.

Through our integrated approach, CRI combines cutting-edge research with rigorous clinical testing to push the boundaries of cancer treatment, particularly for hard-to-treat cancers. By funding and supporting innovative trials across multiple platforms, CRI is driving forward new therapies and advancing our understanding of cancer immunology to ultimately improve patient outcomes and accelerate the path to cures.

Conclusion

CRI's unwavering support for pioneering researchers and their groundbreaking work is revolutionizing cancer care and propelling scientific careers forward. By tackling the intricate challenges of tumor dynamics and immune interactions, CRI is surmounting significant barriers in cancer research.

Our steadfast commitment to these issues accelerates the development of targeted immune based therapies and significantly improves patient outcomes.

Through our dedicated efforts, we are not only spearheading advancements towards more personalized and precise cancer treatments but also fostering the growth of trailblazing scientists who continue to make crucial contributions to the field. This dual impact cements CRI's position as the leading force in the fight against cancer, offering hope and enhancing care for patients worldwide.