CRI Cancer Research Institute™

From Theory to Therapy:

The History of Cancer Immunotherapy

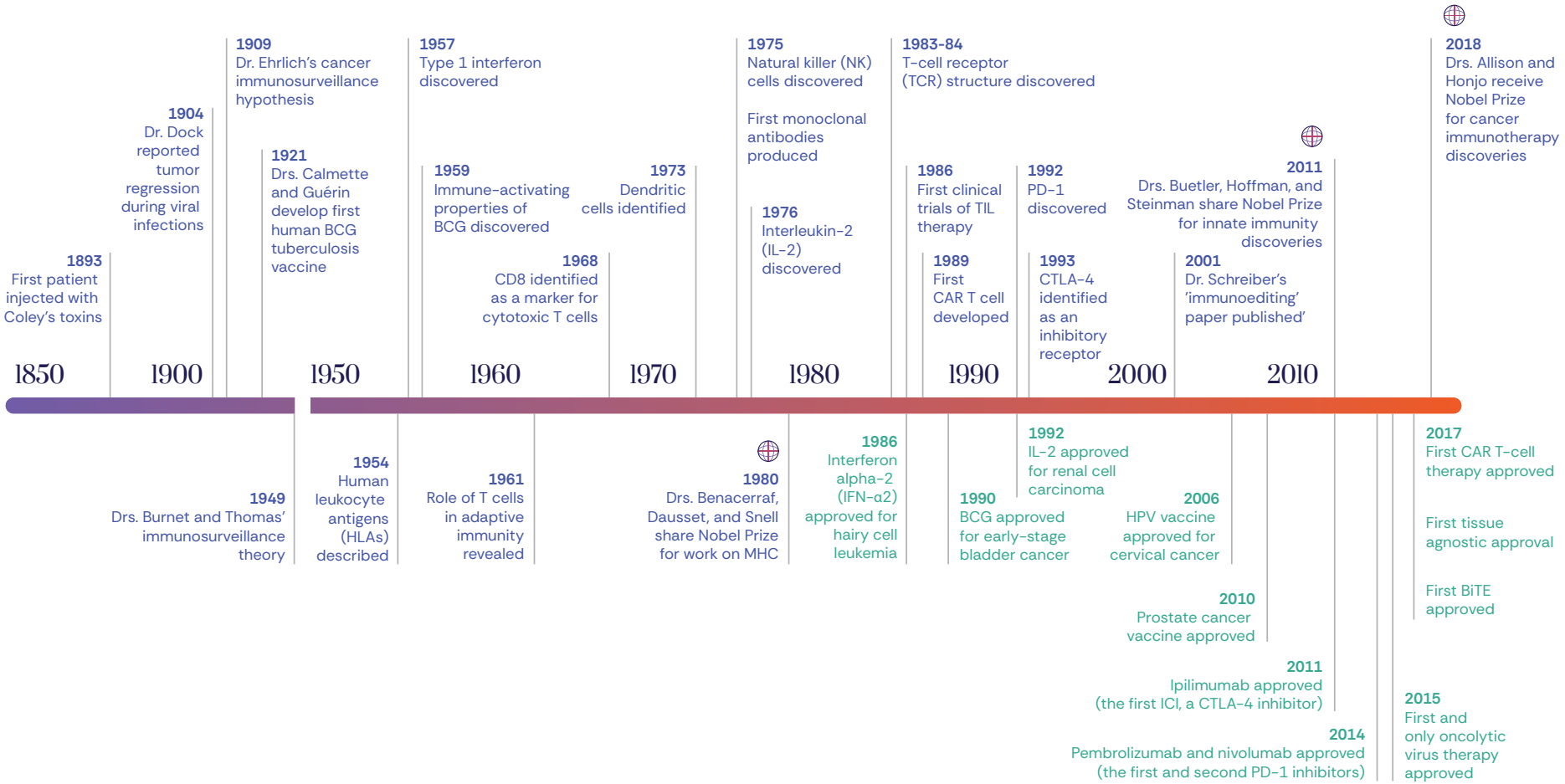
Cancer is one of the leading causes of death worldwide, with an estimated 20 million new cases and nearly 10 million deaths in 2022 alone.[1] Traditional cancer treatments – including surgery, radiation, and chemotherapy – have played critical roles in controlling disease. Surgery is often used to remove localized tumors, radiation targets cancerous tissue with high-energy beams, and chemotherapy attacks rapidly dividing cells. More recently, targeted therapies have been developed to inhibit specific molecular pathways involved in tumor growth. Each of these modalities offers unique benefits, but also comes with certain limitations, such as toxicity, resistance, or limited effectiveness in certain cancer types.

Cancer immunotherapy represents a revolutionary paradigm in cancer care, harnessing the body's own immune defenses to combat malignancies with unprecedented precision and often fewer long-term side effects. Today there are immunotherapy options available for more than 30 kinds of solid tumors and hematological malignancies, with often durable response rates in patients with advanced or otherwise hard-to-treat cancers.

This report explores the history of cancer immunotherapy over the last 100+ years, from early observations to modern breakthroughs, and highlights its transformative ability in the fight against cancer **(Figure 1).**

FIGURE 1 A Timeline of Select Key Events in the Field of Cancer Immunotherapy

● Scientific advancements and recognitions ● Regulatory approvals



Cancer: A Formidable Foe

Cancer encompasses a diverse group of diseases that arise from the breakdown of normal cellular control mechanisms, leading to uncontrolled cell growth with invasion and destruction of adjacent or distant tissues.[2] Genetic mutations and epigenetic changes in cancer cells help them to evade growth suppression, resist cell death, and proliferate unchecked.

Metastasis is a process wherein cancer cells spread to distant organs.[3] Malignant cells that metastasize may form invasive solid tumors or proliferate diffusely within the bloodstream, lymphatic system, and bone marrow.

Foundational Concepts of Immunotherapy

The roots of immunotherapy can be traced to the late 19th century, when Dr. William B. Coley observed that patients who experienced bacterial infections sometimes had subsequent regression of their tumors.[4] He decided to inject tumors with bacteria, and later mixtures of bacterial toxins, in the hopes of rallying the body's natural defenses to treat the cancer. Results early on were mixed, but he observed long-lasting tumor regression in many cases, at the expense of causing some severe infections.[4] Around the same time, the concept of viral infection therapy emerged when Dr. George Dock noted remission in a patient with leukemia post-influenza in 1904,[5] hinting at viruses' potential to trigger anti-tumor immunity.

While Coley and Dock never fully elucidated the underlying mechanisms of action – that they had observed anti-cancer activities from the body's immune system – Dr. Paul Ehrlich began to make these connections. In 1909, he postulated that cancer develops spontaneously and that the immune system could detect and attack emerging cancer cells.[6] In 1949, Drs. Frank Burnet and Lewis Thomas independently elaborated on this "cancer immunosurveillance hypothesis", suggesting that immune cells learn to distinguish the body's tissues from foreign threats and can activate an immune response in the presence of such a threat.[6] Evidence to support this would soon emerge with the discoveries of natural killer (NK) cells and T-cell function as well as the existence of tumor-specific antigens.

In 1959, Dr. Lloyd J. Old, working with Drs. Baruj Benacerraf and Donald A. Clark, reported that mice rejected tumors after their immune systems were activated with injection of Bacillus Calmette-Guérin (BCG), a bacterium used as a vaccine against tuberculosis.[7] Based on this, investigators like Dr. Georges Mathé in France and Dr. Donald Morton in California conducted preclinical work with BCG, treating patients with leukemia and melanoma, respectively, but with little success.

In 1975, in collaboration with Dr. Elizabeth Carswell and other colleagues, Old combined BCG vaccination and stimulation with one of Coley's bacterial toxins to activate the immune system in mice. From the blood of these animals, the investigators purified a cytokine they named "tumor necrosis factor" or TNF.[8]

Administration of TNF caused tumors in mice and humans to undergo rapid death by choking off the tumors' blood supply – further evidence of the power of the immune system to fight cancer –, but TNF ultimately proved to be too toxic to enter the clinic.[8] In the years that followed, Old and colleagues discovered that different types of immune cells could be distinguished by distinct markers on their cell surface and that T cells can be trained to recognize, target, and attack an established tumor.

These foundational concepts and discoveries shaped the development of today's most advanced immunotherapies, including immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapy.

Mobilizing Immunity: Pioneering Cytokine Therapies

The discovery of interferon in 1957 and its ability to activate immune responses against tumors[9] was the first of many in a new class of "immunomodulators" that would eventually become FDA-approved immunotherapies to treat patients with cancer. Interferon alpha-2 (IFN-α2) was one of the first FDA-approved immunotherapies in 1986 for patients with hairy cell leukemia.[10] Prior to that, in 1976, Dr. Robert Gallo and his colleagues identified interleukin-2 (IL-2) as a T-cell growth factor, enabling long-term T-cell cultures and revolutionizing immunology research.[10] Less than 10 years later, Dr. Steven A. Rosenberg and colleagues reported the first medically-induced complete remissions in patients with metastatic melanoma by administering high-dose recombinant IL-2, demonstrating the immune system's potential to eradicate advanced cancers.[10] IL-2 gained FDA approval for treatment of patients with renal cell carcinoma and melanoma in 1992 and 1998, respectively.[11] However, like TNF, IL-2's success in the clinic was limited by severe toxicity and treatment often required hospitalization. Despite its challenges, IL-2 therapy paved the way for the development of new immunotherapy strategies such as expanding tumor-infiltrating lymphocytes (TILs) and engineering CAR T cells.[12]

Checkpoint Blockade to Cellular Engineering: The Modern Immunotherapy Era

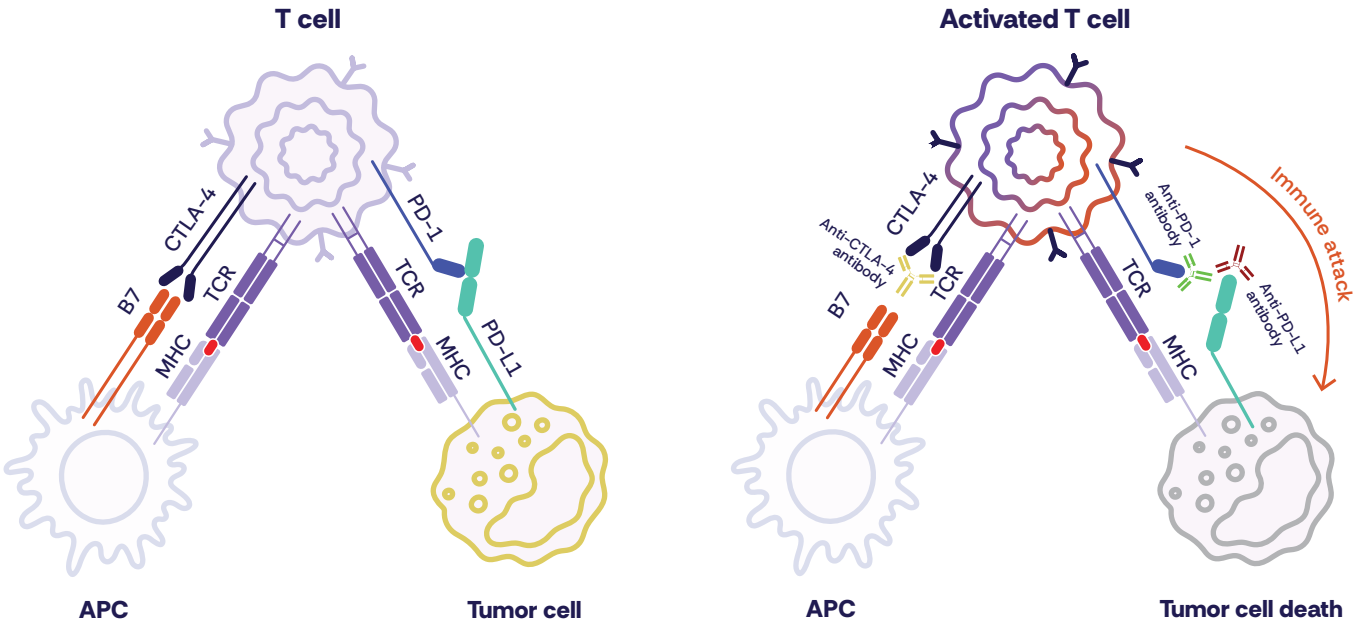
Immune Checkpoint Inhibitors

The advent of ICIs marked a paradigm shift in cancer treatment, beginning in the 1990s with the identification and characterization of two key immune regulators that act as "brakes"on T-cell activity: CTLA-4 (cytotoxic T lymphocyte antigen 4) and PD-1 (programmed cell death protein 1)[13,14] **(Figure 2).**

While many scientists studied the role of CTLA-4 in autoimmune disease, Dr. James P. Allison decided to investigate if an antibody against this cell-surface receptor could disengage the T-cell brake and unleash the immune system to attack cancer cells. His group's seminal experiments in the mid-1990s had astounding results, eradicating tumors in mice and proving the concept of immune checkpoint inhibition.[13,14]

FIGURE 2 **A Schematic Representation of CTLA-4 and PD-1 Signaling in Immunotherapy**

APC, antigen-presenting cell. MHC, major histocompatibility complex. TCR, T-cell receptor.



This work culminated in the development of ipilimumab (Yervoy®), which doubled survival rates in patients with refractory cases of metastatic melanoma.[15] In 2011, ipilimumab became the first ICI approved by the FDA to treat cancer.

Meanwhile, in 1992, Dr. Tasuku Honjo had discovered another protein expressed on the surface of T cells called PD-1 that prevents T cells from killing other cells, including cancer cells.[16] Subsequent clinical studies blocking PD-1 activity with pembrolizumab (Keytruda®) proved effective in patients with unresectable or metastatic melanoma,[17] leading to FDA approval in 2014 as the second FDA-approved ICI.

The impact of CTLA-4 and PD-1 on immunotherapy, and more broadly, immuno-oncology, were so groundbreaking that Allison and Honjo were jointly awarded the 2018 Nobel Prize in Physiology or Medicine, "for their discovery of cancer therapy by inhibition of negative immune regulation."[18] These discoveries also established a blueprint for next-generation therapies targeting novel checkpoints, like LAG-3 and TIM-3. As of 2024, a total of 12 ICIs have been approved by the FDA for more than 20 cancer types, redefining oncology by achieving durable remissions in patients with many previously untreatable cancers.

Combination Therapies and Bispecific Antibodies

The success of ICIs spurred a flurry of combination strategies and biomarker-driven approaches, shaping a new era of precision immunotherapy. Combining ICIs like ipilimumab and nivolumab (Opdivo®) enhances anti-tumor immunity by targeting different stages of T-cell activation and preventing T-cell exhaustion.[4]

Fine-Tuning the Brakes: Keeping T Cells in Check

T cells rely on a finely tuned balance between activating and inhibitory signals – like accelerators and brakes – to regulate immune responses. Inhibitory checkpoint proteins expressed on the surface of T cells, such as CTLA-4 and PD-1, act as critical brakes, preventing excessive activation that could damage healthy tissues. While essential for maintaining self-tolerance, these checkpoint pathways can be exploited by cancer cells to suppress T-cell activity and evade immune detection.

ICIs disrupt these interactions – anti-CTLA-4 enhances early T-cell priming in lymphoid organs, while anti-PD-1 restores effector function in the tumor microenvironment – allowing T cells to mount a more effective response against tumors **(Figure 2).** Once the threat is cleared, the immune system re-engages the brakes to prevent prolonged inflammation and limit collateral tissue damage.

This has improved response rates in patients with cancers such as melanoma, but it can increase immune-related side effects as well. Coupling ICIs with radiation and/or chemotherapy can boostimmune responses by increasing tumor antigen release and antigen presentation. Targeted therapies, such as vascular endothelial growth factor (VEGF) inhibitors, are also being combined with ICIs to modulate the tumor microenvironment and improve T-cell infiltration.[19] Additionally, multi-agent regimens that combine ICIs with cancer vaccines, adoptive cell therapies, or cytokines are actively being explored to leverage complementary immune pathways. Clinical trials continue to evaluate these and other combination strategies to enhance efficacy while limiting toxicity.

Bispecific T-cell engagers (BiTEs) offer another approach. These engineered antibodies work by simultaneously binding to a T cell via CD3 and a tumor cell via a cancer-associated marker like CD19. This physical linkage activates the T cell, triggering it to release cytotoxic molecules that kill the cancer cell, even if the T cell would not have recognized the tumor on its own. Blinatumomab (Blincyto®), the first BiTE demonstrating the power of this approach, was approved by the FDA for B-cell leukemia in 2017.[20] Today there are eight FDA-approved bispecific antibodies to treat leukemia, melanoma, multiple myeloma, non-Hodgkin lymphoma, and small cell lung cancer. New multispecific formats and combinations of BiTEs with ICIs are being developed and tested to improve efficacy and reduce side effects.

Cancer Vaccinces

The evolution of cancer vaccines spans over a century, marked by incremental breakthroughs progressing from broad immune activation to precision-targeted therapies. In 1990, the BCG vaccine became the first immunotherapy of any type to be approved by the FDA, and it is still used today for the treatment of patients with early-stage bladder cancer.[21] As noted, BCG's ability to restrict tumor growth was first revealed by Old and Benacerraf over 30 years earlier.

The first FDA-approved therapeutic vaccine developed specifically for cancer was sipuleucel-T (Provenge®) in 2010.[22] As a dendritic cell-based vaccine, sipuleucel-T generated much excitement but ultimately showed limited clinical benefit for patients with prostate cancer.[14]

Unfortunately, many cancer vaccine strategies have not come to therapeutic fruition. For example, peptide vaccines targeting tumor-associated antigens (e.g., MUC1, NY-ESO-1) have only shown modest efficacy in clinical trials;[23] this was partly due to the weak immune activation and poor antigen presentation.

Excitingly, lipid-coated mRNA, a new player on the vaccine scene, may provide a way to overcome these limitations. The mRNA vaccine revolution began in the 2010s, leveraging advances in lipid nanoparticle delivery and nucleoside modifications to stabilize RNA. The power and impact of mRNA vaccines was unforgettably demonstrated during the recent coronavirus disease 2019 (COVID-19) pandemic, preventing an estimated 14.4 million deaths in 2021 alone.[24]

Treating Cancer: A Historical Perspective

The challenge of treating cancer has persisted throughout human history.

The earliest documented cancer treatments date back to 3000 B.C. and involved surgical removal using cauterization. For centuries, surgery remained the only viable option, a practice limited by crude techniques and high risk of complications. Even with later advancements – including the introduction of general anesthesia in the 19th century and the discovery of antibiotics in the 20th century that drastically improved the safety of surgical procedures – surgery tends to be most effective when the cancer is localized and has not yet spread.[25]

The discovery of X-rays in 1896 revolutionized cancer care by introducing radiation therapy. Radiation works by damaging DNA in cells and tissue and can be used to target cancer cells. Within a few years, radiation was used to shrink tumors, and as technology advanced, it became a mainstay treatment option for many cancers. However, radiation therapy, like surgery, is most effective for localized cancer and can damage surrounding healthy tissue.[25]

Chemotherapy emerged in the aftermath of World War II, when nitrogen mustard was found to suppress lymphoma. This breakthrough led to the development of numerous chemotherapy drugs, offering new hope for patients with advanced or metastatic disease. However, these drugs, now called "cytotoxic chemotherapy", target all rapidly dividing cells – cancer and healthy alike – and can cause significant side effects.[25] Today, some chemotherapy drugs can target specific proteins responsible for tumor growth, but tumors often become drug-resistant and then resume their growth.

Meanwhile, personalized neoantigen vaccines, which encode tumor-specific mutations, entered trials in 2017,[26] showing durable responses in patients with melanoma when combined with ICIs. Today, several mRNA and peptide vaccines are in early-stage clinical trials with promising therapeutic results.

Oncolytic Viruses

While certain viruses can contribute to cancer development, other viruses are being harnessed to treat tumors directly. These therapeutic viruses, known as oncolytic viruses, exploit the fact that many cancer cells have weakened antiviral defenses, making them especially vulnerable to infection. Clinical experimentation with wild-type oncolytic viruses began in the 1950s and 1960s, but it wasn't until the 1990s that genetically-engineered viruses enabled researchers to target tumor cells specifically and address common safety concerns.[27]

Since 2004, four oncolytic viruses have been approved worldwide for melanoma, head and neck cancer, and malignant glioma, but only one in the U.S.: talimogene laherparepvec (T-VEC) was approved by the FDA in 2015 for melanoma, based on data from clinical trials led by Dr. Howard Kaufman.[28] T-VEC uses a genetically-modified herpes simplex virus engineered to replicate in melanoma cells, directly lysing tumors and releasing tumor antigens to prime systemic immunity. Several other types of viruses are being explored in clinical trials, including adenovirus, measles virus, and reovirus, but to be broadly applicable in care, delivery strategies will need to optimize tumor targeting, viral clearance, and patient side effects.[29]

When Viruses Lead to Cancer

While most cancers stem from a mix of genetic and environmental factors, 10-20% of cancers worldwide are caused by viral infections.[30] In these cases, vaccines offer a powerful form of cancer prevention by stopping the infection before it can trigger disease.

Here are some examples where immunization has changed the landscape of cancer prevention:

- Infection by high-risk strains of the human papillomavirus (HPV) causes cervical cancer and several head and neck cancers.[31] In 2006, Gardasil® received FDA approval for the prevention of cancers caused by HPV infection. Targeting four HPV strains, Gardasil® protects against cervical cancer by preventing viral infection, showcasing the power of antigen-specific immunity.

  In 2014, the Gardasil® vaccine was expanded to include nine strains of high-risk HPV, resulting in the Gardasil-9® vaccine which is the version commonly administered today.

- Hepatitis B and C viruses are major risk factors for liver cancer. Chronic infections with these viruses can lead to inflammation and cirrhosis (scarring of the liver), which over time can increase the risk of developing liver cancer. Vaccination against Hepatitis B and C, as part of a broader prevention strategy, can reduce a person's risk of liver cancer.[32]

Adoptive Cell Therapies

Often called "living drugs", adoptive cell therapies like TILs, T-cell receptor (TCR) T cells, and CAR T cells harness the power of immune cells to make more potent cancer-targeting cells. In adoptive cell therapies, immune cells from patients or healthy donors are collected, sometimes genetically modified, expanded, and infused back into patients to treat their cancer.

Researchers started exploring adoptive cell therapy as early as the 1980s. A pivotal moment came in 1986, when Rosenberg launched a clinical trial using TILs.[33] By harvesting TILs from patients, expanding them in the lab, and reinfusing them, his group demonstrated regression of melanoma – proving that T cells could be harnessed to control cancer. This was the first approach to explore cell-based immunotherapy for cancer treatment. Meanwhile, in 1984, Drs. Tak W. Mak and Mark Davis independently cloned the TCR, identifying its genetic structure and laying the groundwork for genetically-engineered TCR-based therapies.[34]

The emergence of CAR T cells unlocked another transformative facet of adoptive cell therapy. First conceptualized in the 1980s and engineered by Dr. Zelig Eshhar in 1993, early CAR T-cell therapies struggled with short-lived responses.[35] However, the addition of co-stimulatory domains like CD28 and 4-1BB in the late 1990s and 2000s improved CAR T-cell persistence and anti-tumor activity.

A major breakthrough came in 2010[35] when research led by Dr. Carl June resulted in CAR T cells that achieved remission in patients with refractory leukemia, paving the way for the FDA approvals of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) in 2017.

Taken together, these personalized therapies mark a new era by reprogramming the immune system, representing the cutting edge of precision oncology and offering transformative potential for cancers that were once considered incurable.

Looking Ahead: Building a Future Immune to Cancer

Cancer immunotherapy has come a long way – from bacterial extracts and cytokines to ICIs, bispecific antibodies, cancer vaccines, and adoptive cell therapies. The next chapter is even more ambitious, as scientists integrate breakthroughs in synthetic biology, genomics, and data science to design smarter, more adaptable therapies.

Newer cell therapies are being optimized with tools like CRISPR and synthetic signaling domains to better tackle the types of solid tumors that have long been difficult to treat.

These next-generation therapies are built to persist longer in patients, target multiple cancer antigens, and enhance activity within the tumor microenvironment. In parallel, *in vivo* cell therapy approaches – wherein immune cells are engineered directly inside the patient's body – are being explored as a way to simplify manufacturing and improve accessibility. Together with innovative strategies involving bispecific antibodies and innate immune cell activators, these orthogonal approaches are expanding and diversifying the immune toolkit, recruiting multiple arms of the immune system to strengthen the fight against cancer.

Advances in mRNA vaccine platforms and personalized neoantigen prediction are enabling vaccine strategies tailored to each patient's tumor. Oncolytic viruses are being programmed not just to kill cancer cells directly, but to turn tumors into their own vaccine factories.

And researchers are uncovering surprising influences on the response to immunotherapy, from gut bacteria to circadian rhythms, pointing to a more holistic view of cancer–immune interactions.

The future of cancer care is not just about more cures – it's about better ones: therapies that have low toxicity, are accessible off the shelf, and are tuned to each patient's biology. As we continue to dismantle the barriers between data, discovery, and delivery, we inch closer to a world where the immune system doesn't just respond to cancer, but heads it off.

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About CRI

The Cancer Research Institute (CRI) is a nonprofit organization dedicated to advancing the field of cancer immunotherapy through rigorous scientific research and global collaboration. Since 1953, CRI has been instrumental in uncovering the fundamental biology of the immune system and its application to cancer treatment, laying the groundwork for breakthroughs such as checkpoint blockade, cancer vaccines, and engineered cell therapies.

CRI's mission is to create a world immune to cancer by driving scientific discovery, accelerating collaboration, and turning breakthroughs into life-saving treatments. Our work bridges the gap between discovery and patient impact, ensuring that scientific innovation translates into real-world treatments.

To date, CRI has committed over $560 million to research impacting more than 30 cancer types. Our funding strategy is built on the framework of People × Biology × Data: supporting world-class scientists, deepening understanding of tumor–immune system interactions, and harnessing data to guide discovery and translation. By uniting these elements, CRI catalyzes innovation through our global research ecosystem to drive the next generation of discoveries forward.

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