40 YEARS OF CANCER IMMUNOTHERAPY RESEARCH:

Paving the way for breakthrough treatments

Immunotherapy is a form of cancer treatment that harnesses the natural strength of a body's immune system to prevent, control and–in some cases–even eliminate cancer. It has revolutionized the field of oncology and shifted the paradigm of cancer care, delivering significant improvements in survival and side effects for numerous patients across a wide range of cancers.[1]

IMMUNOTHERAPY THROUGH THE YEARS

The idea of unleashing the immune system to battle cancer cells isn't new. It can be traced back more than a century to Dr. William Coley, a renowned New York surgeon who administered the first immune-modulating therapy for cancer in 1891.[2] Some of the most significant advances, however, have occurred in the last 40 years as a result of key discoveries related to how our immune system works that paved the way for translating the concept of immunotherapy into a reality for patients.

These remarkable advances as well as innovations across the cancer field have contributed greatly to the more than 30% drop in cancer mortality since the mid-1990s. In fact, between 2000 and 2016 alone, new cancer medicines were associated with 1.3 million prevented cancer deaths.[3]

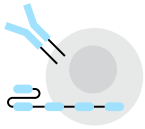
While scientists have made great progress in understanding the ways the immune system can fight cancer, much still remains to be learned about the complex interaction between a patient's immune system and cancer's biology. But what we have learned to date is allowing researchers to push the boundaries of science and is leading to new strategies for delivering more personalized, targeted treatments to patients.

A FLOURISHING FIELD OF TREATMENT OPTIONS

From vaccines that can prevent liver and cervical cancer to the first checkpoint inhibitor proven to significantly extend the lives of individuals with metastatic melanoma, new medicines are improving and extending the lives of cancer patients in ways that have markedly contributed to declines in cancer mortality.[4]

There are currently five different classes of immunotherapies available for patients across 20 cancer types.[5] And between 2017 and 2020 alone, the immuno-oncology pipeline has grown 233%.[6,7] Each class of cancer immunotherapies takes a different approach. Some help the immune system stop or slow cancer cells' growth while others help the immune system destroy cancer cells or stop cancer from spreading to other parts of the body. They can be used alone or combined with other cancer treatments or even targeted to patients with certain genetic markers.

The five classes of cancer immunotherapy include the following:[8]

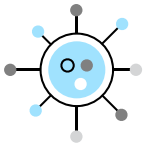


ADOPTIVE CELL THERAPY

Uses the cells of our immune system to eliminate cancer by either directly isolating immune cells and expanding their numbers or programming some immune cells to target cancer cells and enhance their cancer-fighting capabilities (e.g., CAR T-cell therapy, see below)

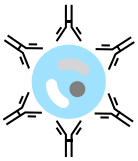
IMMUNOMODULATORS

Manipulate the "gas pedals" and "brakes" of the immune system to fight cancer (e.g., immune checkpoint inhibitors (see below), cytokines, adjuvants)



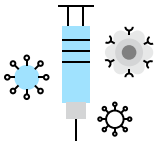
ONCOLYTIC (TUMOR-INFECTING) VIRAL THERAPY

Uses modified viruses that can infect and destroy tumor cells



TARGETED MONOCLONAL ANTIBODIES

Disrupt cancer cell activity and alert the immune system to attack cancer



CANCER VACCINES

Include preventative vaccines, which can protect against cancer, and therapeutic vaccines, which train the immune system to recognize and eliminate cancer cells

CAR T-cell therapy is a form of gene-modified adoptive cell therapy which involves permanently altering a patient's T-cells to recognize, target and kill cancer cells. As of April 2022, there are currently six U.S. Food and Drug Administration (FDA) approved CAR-T therapies, which are widely viewed as transforming cancer treatment today.

Immune checkpoint inhibitors are immunomodulators that help take the brakes off the immune system to attack cancer cells. In recent years, immune checkpoint inhibitors became available to patients, targeting various checkpoints such as PD-1, PD-L1 and CTLA-4. The first checkpoint inhibitor was approved to treat melanoma in 2011, and subsequently this class of medicines has proven effective across a wide range of cancers–such as lung, liver, kidney, colon, bladder, gastric, esophageal, breast and endometrial cancers and many more. In fact, the first checkpoint inhibitor was also later approved to treat patients whose tumors expressed certain genetic features regardless of the tissue in which the cancer originated.

40 YEARS OF ADVANCES IN IMMUNO-ONCOLOGY

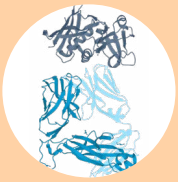
1980s – Foundational Research Begins

Early 1980s

Scientists begin to research new ways to use T-cells and monoclonal antibodies to treat cancer.[9] During the same period, the role of the T-cell receptor (TCR), a type of immune cell that recognizes and binds to foreign substances, is determined.[10]

Monoclonal antibodies (mAbs) are synthetic versions of the body's antibodies, which the immune system relies on to detect and destroy harmful pathogens. They are produced in a laboratory and designed to restore, mimic, inhibit or enhance immune system functions. Though used for many years across a range of diseases, mAbs have emerged as an effective approach in immunotherapy as they can target and defeat tricks that tumors use to evade the immune system.[11]

Determining the role of the T-cell receptor (TCR) was a pivotal moment for immunotherapy, **laying the groundwork for important discoveries in the fields of immune checkpoint inhibition, adoptive cell therapy and therapeutic cancer vaccines.**



Mid 1980s

The first immune checkpoint molecule, cytotoxic T-lymphocyte antigen number 4 (CTLA-4), is discovered.[12]

Found on the surface of T-cells, CTLA-4 acts as a brake on the immune system. Its discovery **laid the foundation for future checkpoint inhibitors.**

Late 1980s

First human testing and use of genetically engineered T-cells that can recognize and kill cancer cells.[13, 14]

The T-cells were removed from tumors, modified in a laboratory and returned to patients to help the immune system identify and destroy cancer cells. **This success paved the way for future advances in adoptive cell therapy, including CAR T-cell therapy.**

1990s – Foundational Research Continues, Early Therapeutic Successes and Setbacks

Early 1990s

First tumor-specific antigen, the melanoma antigen gene (MAGE), discovered by melanoma researchers in Belgium in 1991, opens up new ways to use tumor antigens to stimulate the immune system to better fight cancer cells. A second immune checkpoint protein, programmed cell death-1 (PD-1), is discovered by researchers at Kyoto University in Japan (1992).[15, 16]

Mid 1990s

The concept of modifying Chimeric antigen T-cells (CAR T-cells) is introduced but fails in initial clinical studies due to technical intricacies and knowledge gaps.[17]

Antigens are toxins or other foreign substances which induce an immune response in the body, especially the production of antibodies.

This research **laid the groundwork for future CAR T-cell therapies**, a type of treatment in which a patient's T-cells are changed in the laboratory so they will bind to cancer cells and kill them.

Late 1990s

The first mAbs for cancer—rituximab for non-Hodgkin's lymphoma (1997) and trastuzumab for HER2 positive breast cancer (1998)—are approved by the FDA, and the first evidence that gene-expression profiling can distinguish between cancer types is published (1999).[18]

A **gene expression profile** is a laboratory method that may be used to analyze the activity or "expression" of a number of different genes within an individual's cancer cells to characterize a specific tumor and help doctors determine how to select the best treatment for this individual patient.[19]

2000s - New Targets Identified and Medicines Developed

2000

Clinical trials launched to test the first immune checkpoint inhibitor drug containing a mAb targeted against CTLA-4 (ipilimumab for melanoma).[20]

2001

Two separate in-vivo studies show that certain tumor cells are destroyed by natural killer (NK) cells—a type of white blood cell that has small particles with enzymes that can kill tumor cells or cells infected with a virus—establishing a new mechanism for how NK cells recognize tumor cells and laying the groundwork for them to become key components of multipronged therapeutic strategies for cancer.[21, 22, 23]

2004

More mAb treatments (including cetuximab and avastin for metastatic colorectal cancer) are approved by the FDA.[24]

2008

First PD-1 targeted immune checkpoint inhibitor enters Phase I trials.[25]

2010s - Novel Immunotherapies Reach Patients

2010 FDA approves first therapeutic cancer vaccine, sipuleucel-T, for prostate cancer.[26]

2011 FDA approves first checkpoint inhibitor targeting the CTLA-4 protein, ipilimumab, for metastatic melanoma. It is the first drug of any kind ever shown to extend survival in metastatic melanoma.[27]

2014 FDA approves two more immune checkpoint inhibitors, pembrolizumab and nivolumab, both of which target the PD-1 pathway.

Following initial FDA approval, additional clinical research has found that immunotherapies are often effective in treating different forms of cancer and can show greater efficacy when administered earlier in disease progression or in combination with other treatments. For example, ipilimumab went on to be approved for use in nine additional types of cancer and was expanded for use in combination with additional checkpoint inhibitors.[28, 29] Pembrolizumab went on to be approved for 18 different types of cancer and nivolumab for 10 different cancers. And both of these checkpoint inhibitors moved to first-line treatment for several of those cancers after demonstrating improved survival benefit.[30, 31]

2015 FDA approves first oncolytic virus therapy, a new class of immunotherapies. Talimogene laherparepvec is approved for metastatic melanoma. It is a genetically engineered virus that has been tweaked to preferentially kill cancer cells.[32]

2016 FDA approves fourth checkpoint inhibitor, atezolizumab, for bladder cancer. It targets the PD-1 pathway and is later approved for use in a total of six different cancers.[33]

2017 FDA approves first CAR T-cell therapy, tisagenlecleucel, to treat adults with certain types of large B-cell lymphoma. FDA approves the fifth and sixth checkpoint inhibitors, which target the PD-1 pathway: avelumab, for Merkel cell carcinoma, and durvalumab, for bladder cancer, both of which are later approved for use in several additional cancers.[34, 35, 36, 37]

Tisagenlecleucel's approval for B-cell acute lymphoblastic leukemia came just over a month after the treatment was found to have an 83% overall remission rate in clinical trials, meaning 83% of the patients experienced a complete response that eliminated all signs of their disease.[38]

2018

FDA approves second CAR T-cell therapy, axicabtagene ciloleucel, for the treatment of adult patients with several types of large B-cell lymphoma, and a seventh checkpoint inhibitor, which targets the PD-1 pathway, cemiplimab, for cutaneous squamous cell carcinoma.[39, 40]

The approval of axicabtagene ciloleucel was based on clinical trials demonstrating a **complete remission** rate of 51%.[41]

2020s - Treatment Options Expand, Research Flourishes

2020

FDA approves the third CAR T-cell therapy, brexucabtagene autoleucel, for the treatment of patients with mantle cell lymphoma.[42, 43]

2021

FDA approves two more CAR T-cell therapies, lisocabtagene maraleucel, for large B-cell lymphoma, and idecabtagene vicleucel, for multiple myeloma.[44, 45]

FDA approves the eighth checkpoint inhibitor, dostarlimab, targeting PD-1, for patients with certain types of endometrial cancer.[46, 47]

2022

FDA approves the sixth CAR T-cell therapy, ciltacabtagene autoleucel, for multiple myeloma.[48, 49]

Significant advances continue to be made in the field of immunotherapy, revolutionizing care for certain tumor types and showing promising signs of benefit for hard-to-treat and rare cancers. However, these advancements did not occur overnight and without many setbacks along the way. The more researchers discover about the hundreds of diseases that we now know make up cancer, the more complexity and challenges are uncovered. Behind every medicine that makes it to patients, there are many more investigational medicines that, more often than not, fail. In fact, one analysis examining nine different types of cancer found over the past 20 years, there have been a total of 1,366 unsuccessful investigational drugs and only 115 FDA-approved medicines.[50] Despite these incredible odds, biopharmaceutical researchers remain committed to bringing new treatments for the millions of patients and families facing a cancer diagnosis.

Experts agree we're on the cusp of even more game-changing discoveries, but in order to maintain this momentum and bring new treatments across the finish line to patients, a supportive policy and regulatory environment are needed that foster continued innovation and progress in cancer.

Treatment advances included here are not exhaustive. Approvals and indications are based on approved FDA labeling and are current as of March 1, 2022.

SOURCES

1 https://www.cancerresearch.org/immunotherapy/what-is-immunotherapy

2 https://www.cancerresearch.org/en-us/join-the-cause/cancer-immunotherapy-month/30-facts/02

3 JP MacEwan et al, "Changes in mortality associated with cancer drug approvals in the United States from 2000 to 2016, J of Med Econ, Nov 2020

4 https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21654 https://www.nejm.org/doi/10.1056/NEJMoa1916623

5 https://www.cancerresearch.org/join-the-cause/cancer-immunotherapy-month/30-facts/04

6 https://www.cancerresearch.org/immunotherapy/treatment-types

7 https://www.cancerresearch.org/scientists/immuno-oncology-landscape

8 https://www.cancerresearch.org/join-the-cause/cancer-immunotherapy-month/30-facts/04

9 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

10 https://www.mdanderson.org/newsroom/nobel-prize/jim-allison-bio.html

11 https://innovation.org/diseases/infectious/coronavirus/How-Monoclonal-Antibodies-Work

12 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

13 https://www.whatisbiotechnology.org/index.php/science/summary/gene-therapy/gene-therapy-modifes-a-patients-genes-to-treat-disease

14 https://www.nature.com/articles/s41577-020-0306-5

15 https://www.ludwigcancerresearch.org/success-story/putting-power-into-cancer-vaccines/

16 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC556898/

17 https://www.whatisbiotechnology.org/index.php/science/summary/gene-therapy/gene-therapy-modifes-a-patients-genes-to-treat-disease

18 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

19 https://www.cancer.gov/publications/dictionaries/cancer-terms/def/gene-expression-profile

20 https://www.whatisbiotechnology.org/index.php/science/summary/cancer-immunotherapy

21 https://www.cancer.gov/publications/dictionaries/cancer-terms/def/natural-killer-cell

22 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

23 https://www.nature.com/articles/s41573-019-0052-1

24 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

25 https://www.whatisbiotechnology.org/index.php/science/summary/cancer-immunotherapy

26 https://www.cancerresearch.org/immunotherapy/timeline-of-progress

27 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s115lbl.pdf

28 https://www.cancer.gov/about-cancer/treatment/drugs/ipilimumab

29 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s115lbl.pdf

30 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s085lbl.pdf

31 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s089lbl.pdf

32 https://www.cancerresearch.org/blog/october-2015/fda-approves-first-in-new-class-of-immunotherapies

33 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761034s029lbl.pdf

34 https://www.novartis.com/news/media-releases/kymriah-tisagenlecleucel-first-class-car-t-therapy-from-novartis-receives-second-fda-approval-treat-appropriate-rr-patients-large-b-cell-lymphoma

35 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s009lbl.pdf

36 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761069s020lbl.pdf

37 https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---KYMRIAH.pdf

38 https://www.cancerresearch.org/blog/august-2017/fda-approves-first-car-t-cell-immunotherapy

39 https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma

40 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761097s005lbl.pdf

41 https://www.fda.gov/media/108377/download

42 https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-relapsed-or-refractory-mcl

43 https://www.fda.gov/media/140409/download

44 https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-large-b-cell-lymphoma

45 https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-multiple-myeloma

46 https://www.fda.gov/news-events/press-announcements/fda-approves-immunotherapy-endometrial-cancer-specific-biomarker

47 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761223s000lbl.pdf

48 https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma

49 https://www.fda.gov/media/156560/download

50 PhRMA. Researching Cancer Medicines: Setbacks and Stepping Stones. June 2020.