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A guide to current therapies in immuno-oncology.

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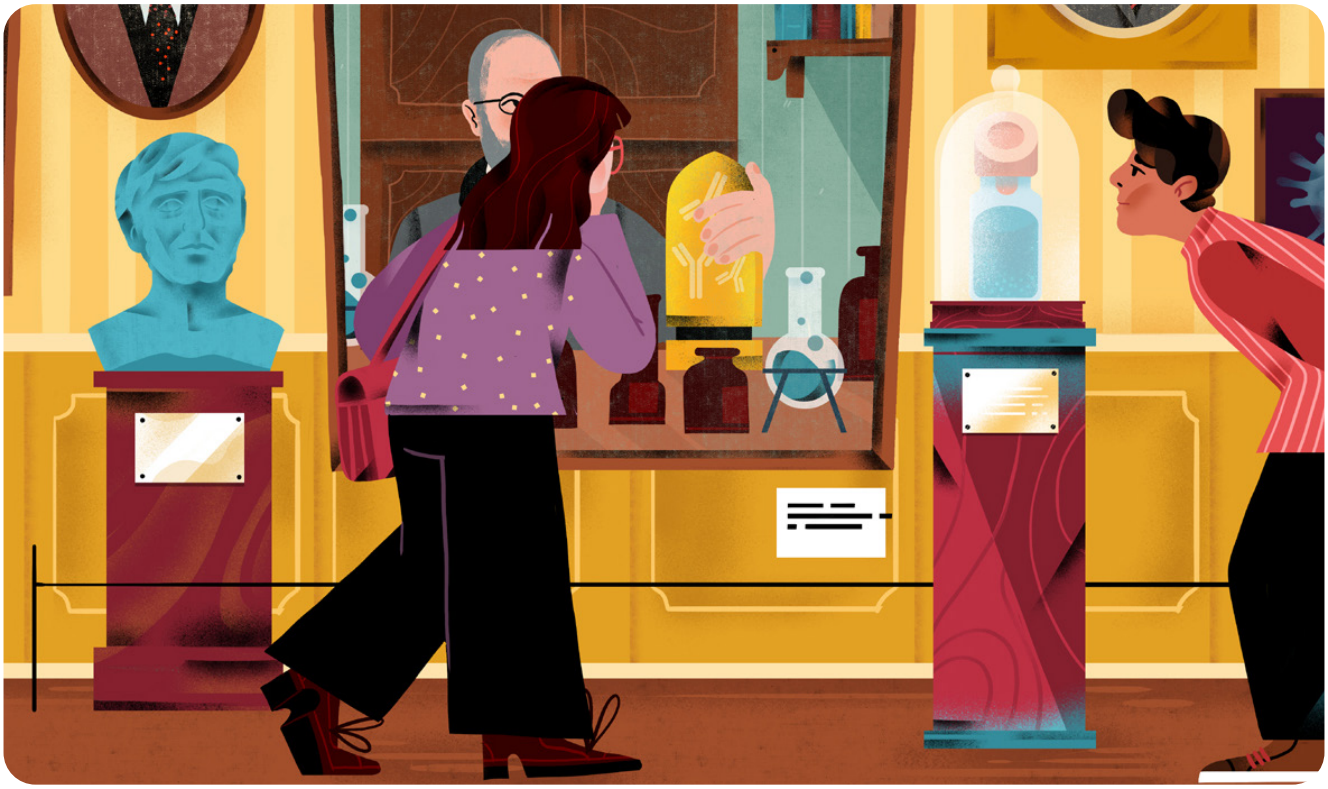


Looking back at immuno-oncology history

It is the year 1868. German surgeon Wilhelm Busch reports that he has shrunken the tumor of a patient through an intentional infection with bacteria for the first time in history[1] – an achievement that marks the birth of modern immuno-oncology.

Busch's research is repeated by Friedrich Fehleisen in 1882[1]. He too observes a regression in tumor size after his patients are infected with erysipelas caused by Streptococcus pyogenes[1].

Nine years later, in 1891, American surgeon William Coley reports long-term regression of sarcoma in patients with inoperable tumors after injection of the heat-inactivated bacteria S. pyogenes and Serratia marcescens, termed "Coley's toxins" at the time[1,2]. The immune stimulation triggered by these injections results in high regression rates and even cures in as many as 1,000 patients[1,2].

While Coley was using immune stimulation to treat cancer patients in America, research on immunity in Europe was reaching a momentum: In 1890, Emil von Behring and Shibasaburo Kitasato took their first tentative steps towards developing vaccines when they observed that the serum of animals immunized against diphtheria could be used to cure infected animals and also protect animals from later infection[3].

In 1901, the German physician Paul Ehrlich proposed the side-chain theory to explain how cells in the body would protect it against pathogens[1,3]. Though this theory would later be proven wrong, Ehrlich also proposed the "magic bullet" theory, which stated that a host body could specifically target, attack and disarm pathogens and prevent them from causing harm. Magic bullets – now called antibodies – formed the basis of modern immunology[3].

William Coley
"Coley's Toxins", 1891

Frank Burnet & Lewis Thomas
Immunosurveillance Theory, 1959

Gerald Edelman & Rodney Porter
Chemical Structure of Antibodies, 1959

Georges Köhler & César Milstein
Hybridoma Technology, 1975

Famous Immuno-Oncology Researchers

Over the next century, the momentum in immunology continued to thrive, soon laying the groundwork for immuno-oncology as we know it today: Danish researcher Niels Jerne formulated the natural selection theory of antibody formulation in 1955[1]; two years later, Alick Isaacs and Jean Lindenmann discovered and described interferon[1]; Gerald Edelman and Rodney Porter first described the chemical structure of antibodies in 1959[1,3]; and in the same year, Lewis Thomas and F. Macfarlane Burnet established the cancer immunosurveillance theory, which states that lymphocytes can recognize and eliminate continuously arising transformed cells[1,7]. Also in 1959, Ruth and John Graham published the first cancer vaccine study[2,5]; And in 1967, Jacques Miller showed that the thymus produces T-cells and that these play an essential role in the immune response, and can fight certain tumors[2,6].

Following in the successful footsteps of the 1950s and 60s, the 1970s also experienced a boom in immuno-oncology-related discoveries. These included the first description of dendritic cells by Ralph Steinmann and Zanvil Cohn[1,2]; the discovery of how killer T-cells recognize virus-infected cells through the virus antigen and the major histocompatibility complex (MHC) by Peter Doherty and Rolf Zinkernagel in 1974[1,2]; as well as the publication of the hybridoma technology for the production of monoclonal antibodies by George Koehler and Cesar Milstein in 1975[1,3]. That same year also saw the discovery of the tumor necrosis factor (TNF) and the first description of natural killer (NK) cells[1,2].

Though research in immuno-oncology has come extremely far, traditional therapies such as surgery, chemotherapy and radiotherapy are still widely applied. However, they can be harmful to the patient by affecting healthy tissues or only treating localized tumors without preventing malignancies[7]. The field of immuno-oncology, on the other hand, uses a patient's own immune system to specifically target and eliminate tumors and malignancies, and reduce adverse events in the process.

Immuno-oncology applies two strategies to fight cancer: passive therapies and active therapies. This white paper will discuss these different strategies in detail.

Therapeutic strategies in immuno-oncology

Passive therapies

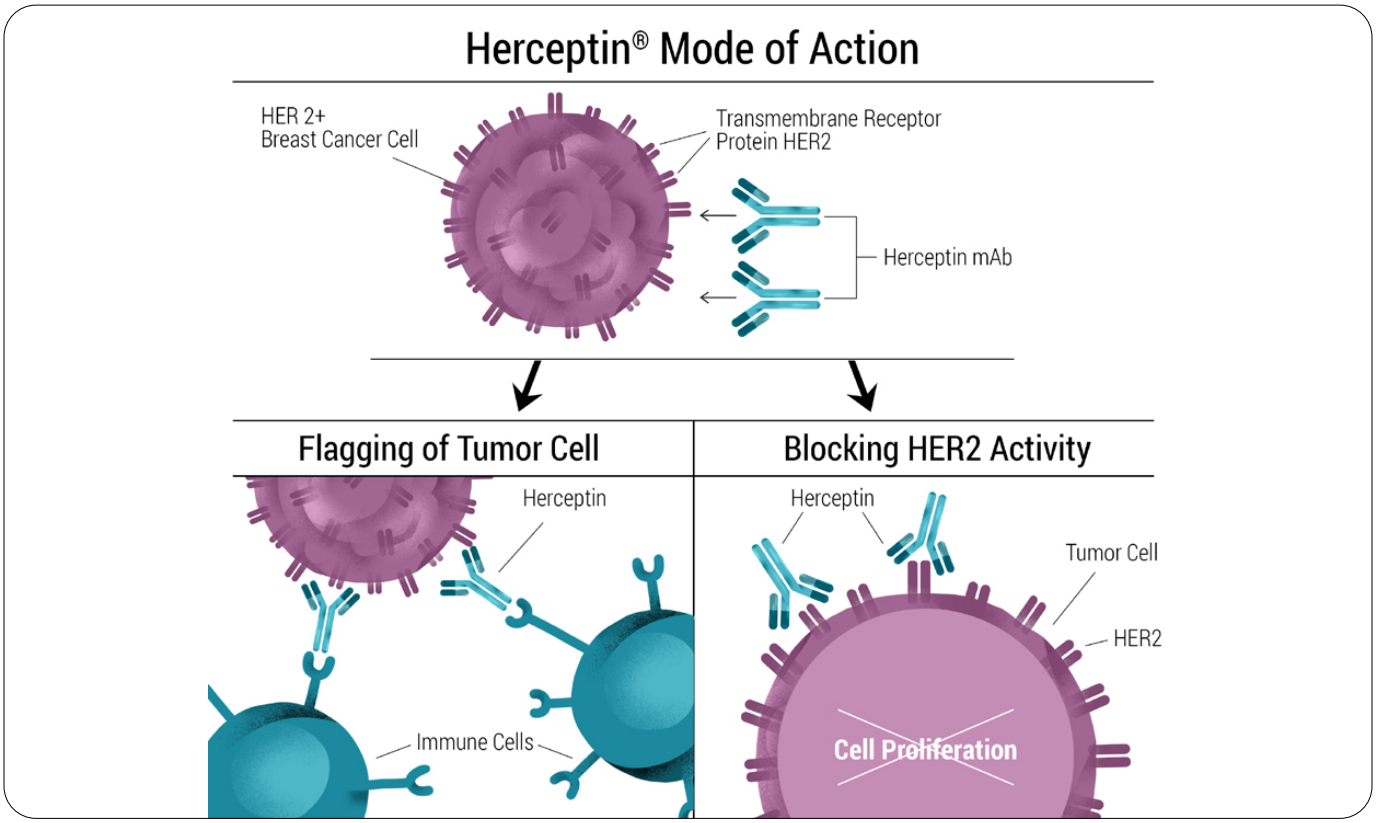
Passive therapies are the oldest immunotherapies and are defined as immunology-based treatments that do not engage the patient's' immune system directly[7]. They include antibodies, oncolytic viruses and cellular therapies, also known as adoptive cell transfer (ACT)[7].

Antibodies

The commercialization of highly specific, chemically identical monoclonal antibodies began with the publication of Milstein and Koehler's hybridoma technology in 1975[3]. It was a huge step that enabled the unlimited production of monoclonal antibodies and soon resulted in the first approved antibodies for the treatment of transplant rejection, immune disorders, infectious diseases and cancers.

One of the best known monoclonal antibody therapies is Roche's trastuzumab, marketed as Herceptin®. It was approved by the FDA in 1998, closely followed by the EMA in 2000[3,8,9]. Trastuzumab is a recombinant humanized monoclonal antibody used for the treatment of HER2-positive early-stage or metastatic breast cancer, as well as HER2-positive metastatic adenocarcinoma[3,9].

HER2 is a transmembrane receptor protein that belongs to the family of receptor tyrosine kinases[10]. In HER2-positive breast cancers, the HER2 protein is overexpressed, which causes an increase in intracellular signalling resulting in uncontrolled cell proliferation[10]. Trastuzumab inhibits HER2 activity and flags the HER2-receptor so that the immune system can recognize and attack the tumor cells[9,10].



Adapted from Breastcancer.org

In 2004, the FDA granted marketing approval for Avastin® – also known as bevacizumab – for the treatment of a variety of cancers, including non-small-cell lung cancer, and breast, ovarian and colorectal neoplasms, as well as renal cell carcinoma[11,12]. Bevacizumab is a recombinant humanized monoclonal antibody that can recognize and inhibit vascular endothelial growth factor (VEGF)[11,12]. The inhibition of VEGF slows down angiogenesis and reduces the growth of tumor blood vessels, which decreases the blood supply to the tumor and makes it more susceptible to chemotherapy[3,12].

Another well-known anti-tumor monoclonal antibody is cetuximab, marketed as Erbitux®. Cetuximab recognizes and attaches to epidermal growth factor receptor (EGFR) on tumor cells[13]. Cetuximab inhibits EGFR and prevents it from activating RAS genes, which are responsible for tumor cell growth[13]. Cetuximab was approved by the FDA and EMA in 2004, for the treatment of metastatic colorectal cancer and head and neck cancers[13,14].

A different approach to the treatment of cancer is the use of multi-specific antibodies. These are antibodies or proteins that are engineered using different techniques, such as recombinant DNA or cell fusion technologies[15]. As they contain two or more highly-specific antigen-binding sites, multi-specific antibodies come with a variety of advantages[15]. The two binding sites can be used to target different molecules, cells or microorganisms, respectively[15]. For example, one binding site might target a tumor cell, while the other binding site recruits an immune cell. Alternatively, one binding site might be used to carry a cytotoxic payload, while the other binds to a target cell or organism. Multi-specific antibodies can also be used to identify or bind one target cell type with increased specificity[15].

Probably the most advanced multi-specific approach out there is Amgen's Bispecific T-cell Engager (BiTE®) technology[15,16]. The BiTE® technology is made up of two engineered side-chain antibodies, which are flexibly linked and each target different antigens[16]. One antibody binds to a specific surface molecule on targeted tumor cells, while the other antibody binds to CD3, an antigen on the surface of T-cells[15,16]. The binding of CD3 activates the cytotoxic T-cells and leads to tumor cell lysis[15].

Oncolytic viruses

Oncolytic viruses are viruses, such as herpes simplex viruses (HSV), adenoviruses, measles viruses, reoviruses and vaccinia viruses that have been genetically engineered to selectively target and kill tumor cells without affecting the surrounding healthy cells[17].

Amgen's talimogene laherparepvec (Imlygic®) was the first oncolytic viral therapy to be approved in the US[18].

Used for the treatment of unresectable melanoma, talimogene laherparepvec is a genetically modified herpes simplex virus type 1[18]. Though its mode of action is not fully understood, talimogene laherparepvec is thought to infect and replicate in tumors as well as initiate the production of a protein that triggers an immune response, resulting in tumor cell lysis[18].

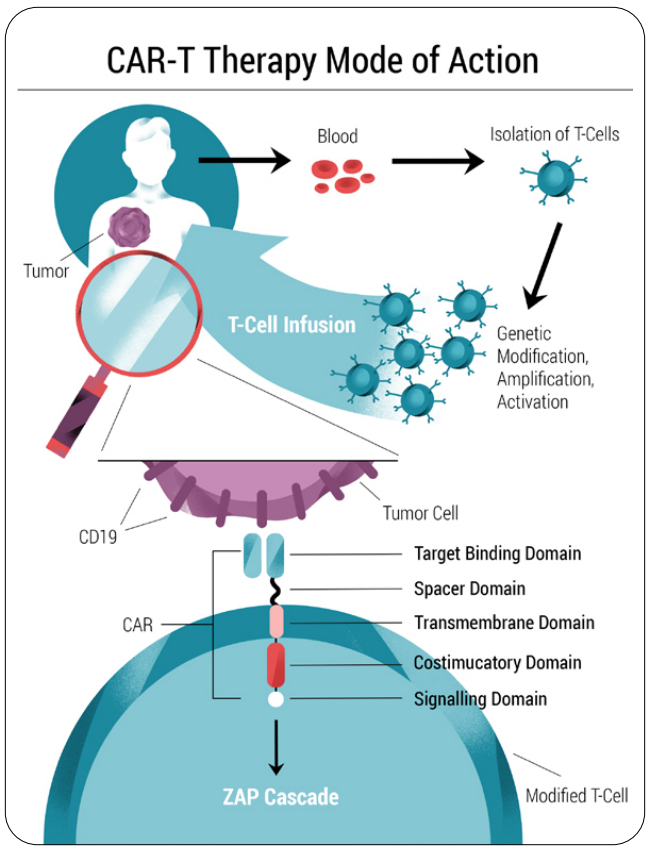
Cellular therapies

With the first two therapies approved in the US in 2017 and in Europe in 2018, last year's science news was bursting with it: Chimeric Antigen Receptor T-cell (CAR-T) therapy.

In CAR-T therapy, a patient's own T-cells are engineered to express a Chimeric Antigen Receptor (CAR) on their membrane [7,19]. The extracellular fragment is a highly specific monoclonal antibody that can recognize the antigen on the patient's tumor[7]. The intracellular fragment is responsible for activating the T-cell through the T-cell receptor (TCR) pathway when the CAR binds to its target antigen[7,19]. Once activated, the Zeta-chainassociated protein kinase (ZAP) cascade is triggered, which results in cytokine release and ultimately, cell death[7].

During CAR-T therapy, T-cells are extracted from the patient's blood and isolated. The isolated T-cells are modified to express the CAR, activated and amplified, and then re-introduced into the patient[7,19]. CAR-T therapy is a personalized therapy and highly specific to each patient's particular tumor[7,19].

Although CAR-T clinical trials have shown remission rates of up to 94% in patients whose tumors failed to react to other therapies, CAR-T therapy has also been associated with severe adverse events, including neurotoxicity and cytokine storms[19,20].



Adapted from Revvity & Labiotech.eu

The first ever CAR-T therapy to be approved by the FDA was Novartis' tisagenlecleucel (Kymriah®) in August 2017. Kymriah® is used for the treatment of relapsing B-cell acute lymphoblastic leukemia (ALL) in children and adolescents[21]. In the case of this CAR-T therapy, the CAR is designed to target the CD19 antigen that is found on malignant B-cells[21]. Kymriah® was approved by the EMA in August 2018[22].

However, with a one-time infusion cost of $475,000, Kymriah® is also the most expensive immuno-oncology therapy on the market today[21].

Two months after Kymriah® was approved, the FDA authorized the use of Gilead's Yescarta® (axicabtagene ciloleucel) for the treatment of an aggressive type of B-cell non-Hodgkin lymphoma[23]. The EMA approved the therapy in August 2018[22]. Yescarta® also targets the CD19 antigen found on tumor cells. A one-time infusion of Yescarta® costs $373,000[23].

There might only be two products on the market today, but the potential for CAR-T therapy is huge. Researchers are currently working on finding more antigens other than CD19 that can be targeted with CAR-T therapy[24], such as B-cell Maturation Antigen (BCMA). So far, targeting CD19 has been effective in fighting blood cancers, but the issue of finding other target antigens to treat solid tumor indications remains[24]. Unlike liquid tumors, however, CAR-T cells are prevented from reaching solid tumors, as they are usually found in an inhibitory immunosuppressive microenvironment[24]. Companies Juno Therapeutics and Novartis currently have products in preclinical development that address these issues, and are designed to boost CAR-T cell activity within the hostile microenvironment of solid tumors[24].

Other cellular immuno-oncology therapies include genetically engineered T-cell receptors (TCRs) and Tumor Infiltrating Lymphocytes (TILs).

Similar to CAR-T therapy, genetically modified TCRs are engineered to improve the ability of T-cell receptors to recognize and fight specific antigens[7,25]. Unlike CARs, however, they do not carry an antibody on the extracellular fragment, which remains similar to naturally occuring T-cell receptors and is engineered to provide higher specificity to a tumor marker[7]. The intracellular component of the modified TCR also remains similar to the naturally occurring T-cell receptor, and activates the TCR pathway when the extracellular domain of the TCR binds to the tumor antigen, causing cell death[7].

During TCR therapy, T-cells are isolated from the patient's blood and tested on the patient's tumor. T-cells with the best response to the tumor are selected and genetically modified to exhibit even higher specificity[7]. These cells are then amplified, activated and reintroduced into the patient[7].

Like CAR-T therapy, TCR therapy allows for a highly personalized approach. Although a number of companiesare working on the promising therapy, there have beenmajor setbacks along the way, with cytokine releasesyndrome observed in some patients, raising doubt about the safety of TCR therapy[26].

Another cellular immuno-oncology therapy comprises the use of Tumor Infiltrating Lymphocytes, or TILs. TILs include T-cells, B-cells and Natural Killer (NK) cells, which are found in the tumor microenvironment or have already infiltrated the tumor[7].

Contrary to CAR-T or TCR therapy, TIL therapy does not use cell engineering technology. However, like in the other cell therapies, the TILs are extracted from the patient – in this case the patient's tumor[7]. Once harvested from the tumor, the TILs are cultured and amplified[7]. In order to make them react stronger to the tumor, the TILs are also overactivated with the help of interleukin-2 (IL2), a cytokine that has a strong effect on the immune system and promotes growth of T-cells and NK cells[27]. The activated and amplified TILs are then re-injected into the patient.

Unlike other cell therapies, TIL therapy is thought to be transferable between patients[7]. Though no TIL therapy has been approved by the authorities to date, numerous clinical studies are underway and are testing the treatment on patients with a variety of cancers[28].

Active therapies

In active immuno-oncology, the patient's own immune system is stimulated with the use of an antigen presenting cell (APC). The immune system recognizes the APC as an invader and attacks[29]. Active therapies include cytokine treatments, therapeutic vaccines, immune checkpoint activators and inhibitors, and small molecules.

Cytokine treatments

As small glycoproteins, cytokines bind to the surface receptors of immune cells and regulate their survival, development and function. Cytokine treatment is the oldest active immuno-oncology therapy and is based on the infusion of cytokines to activate the patient's own immune system[7,27]. IL-2, which is also used in the passive TIL therapy, was discovered as the T-cell growth factor in 1976 and was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma, and for metastatic melanoma in 1998[27]. Though originally approved as a monotherapy, IL-2 is now being tested in combination with other cytokines like GM-CSF, cellbased immunotherapies, chemotherapeutic agents, peptide vaccines and immune checkpoint inhibitors[27].

The only other FDA approved cytokine treatment to date is interferon-alpha (IFN-α), which activates NK cells, causing tumor cell death[7]

Therapeutic vaccines

The idea for the development of therapeutic vaccines came with the discovery that lymphocytes can selectively target antigens on tumor cell membranes and attack the tumor cells[17]. Unlike traditional vaccines, therapeutic vaccines are not preventive, but have a therapeutic effect by strengthening a patient's immune response[7]. A variety of therapeutic vaccines is currently being studied. They are classified on the basis of the antigen they present and include: dendritic cell vaccines, whole-cell tumor vaccines, DNA or RNAbased vaccines, protein or peptide vaccines, and viralbased vaccines[17].

To date, dendritic cell vaccines have been the most successful, as the only therapeutic vaccine currently on the market is Dendreon Corporation's sipuleucel-T (PROVENGE®), a dendritic cell vaccine that was approved by the FDA in 2010 and by the EMA in 2013 for the treatment of prostate cancer[7,17,30].

In the body, dendritic cells are autologous antigen presenting cells (APCs) that present the antigens of incorporated foreign molecules on their surface membrane to T-cells[17]. For the production of a dendritic cell vaccine, dendritic cells are isolated from the patient, genetically modified to express highly specific neoantigens, and then re-introduced into the patient where they activate T-cells and result in tumor cell death[7,17].

Immune checkpoint inhibitors

In order to prevent being attacked by the immune system's T-cells, other cells in the human body express co-receptors called immune checkpoints on their extracellular membrane. When a T-cell binds to a checkpoint, it recognizes the cell as harmless and does not elicit an immune response[7,32]. However, some cancer cells also express these same checkpoints, which allows them to go "unnoticed" by the body's T-cells and avoid an immune response[7,31,32]. Agents that either activate or deactivate these immune checkpoints are very promising as cancer therapies[31,32].

For instance, programmed cell death protein 1 (PD1) is an immune checkpoint receptor found on the surface of T-cells and B-cells. When PD1 binds to programmed death-ligand 1 (PD-L1) on the surface of other cells, it suppresses an immune response and the T-cell remains deactivated[7,32,33].

Unfortunately, many cancers also express PD-L1 on their surface so they remain unharmed by T-cells. When a drug blocks either PD1 or PD-L1, the T-cell can finally recognize the tumor cell, is activated and an immune response triggered, resulting in tumor cell death[7,32].

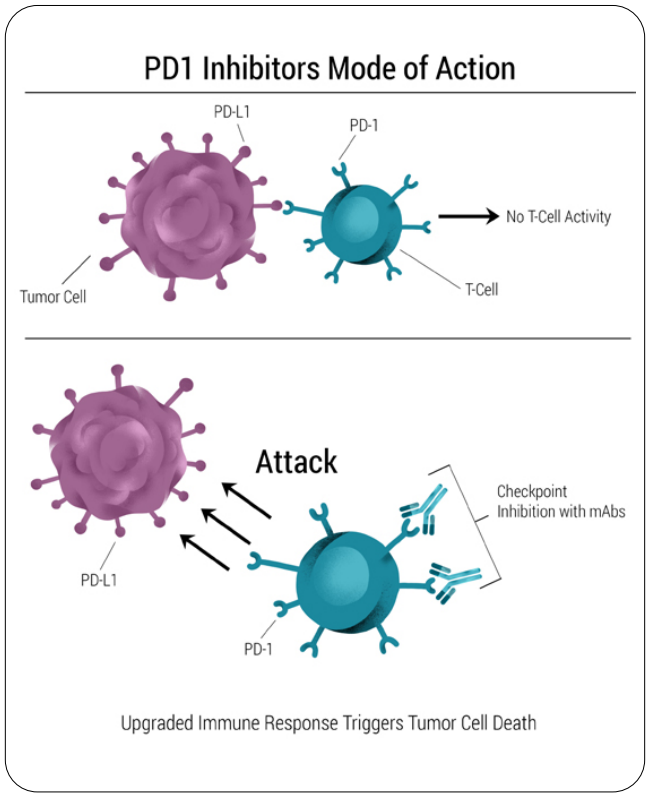
In 2011, ipilimumab (YERVOY®) became the first immune checkpoint inhibitor to be approved by the FDA[17,33]. The active ingredient of YERVOY® is a monoclonal antibody that binds to and blocks the activity of cytotoxic T-lymphocyte-associated protein 4 (CTLA- 4), an immune checkpoint protein that is expressed on the surface of T-cells[17,34]. Binding by YERVOY®, activates T-cells and triggers an immune response causing tumor cell lysis[17,34]. YERVOY® is used for the treatment of advanced melanoma[34].

The second immune checkpoint inhibitor to be marketed was nivolumab (Opdivo®), approved by the FDA in 2014 and the EMA in 2015[33,35]. It can be used to treat melanoma, non-small cell lung cancer, advanced renal cell carcinoma, Hodgkin lymphoma, squamous cell cancer of the head and neck, and urothelial cancer[35].

It's active substance, nivolumab, is a monoclonal antibody that binds to PD1. This prevents tumor cells from deactivating T-cells and increases the immune response[32,35].

Other PD1 inhibitors include pembrolizumab (Keytruda®), approved by the FDA in 2014, and cemiplimab (Libtayo®), FDA approved in 2018[32].

In May 2017, the FDA granted accelerated approval to the PD-L1 inhibitor durvalumab (Imfinzi®) for the treatment of advanced or metastatic urothelial carcinoma[36]. Other approved PD-L1 inhibitors include atezolizumab (Tecentriq®), approved in 2016, and avelumab (Bavencio®), approved in 2017[32]



Adapted from Angelousi, A. et al. 2018, Neuroendocrinology, 106:89–100

Nobel Prize Winners 2018

For their work on immune checkpoint inhibitors, James P. Allison – discoverer of CTLA-4 – and Tasuku Honjo – discoverer of PD1 – received the Nobel Prize in Physiology or Medicine in 2018[37].

Currently, there are numerous other checkpoint inhibitors and activators in clinical development.

Small molecules

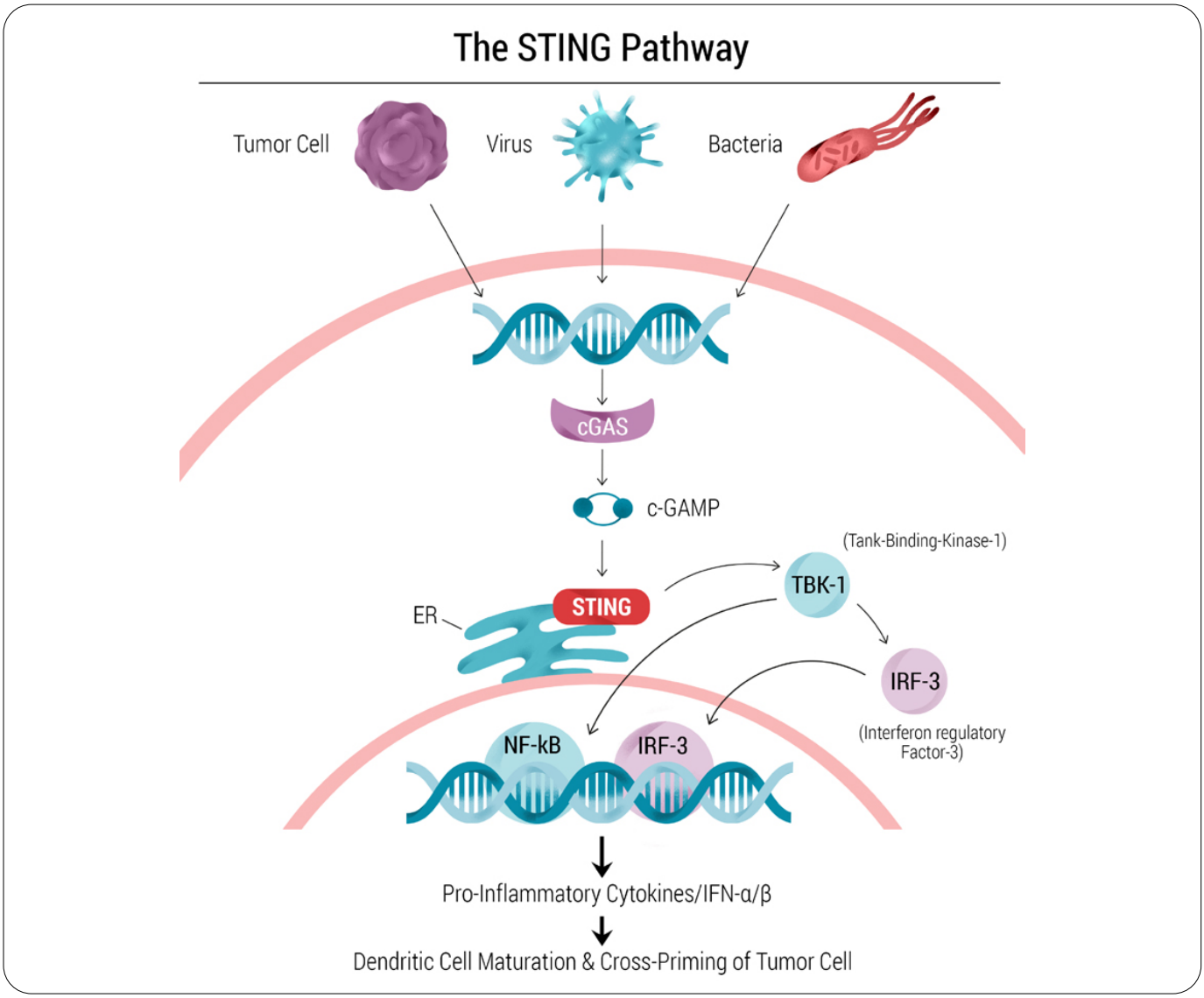
Small molecules have many advantages over other immuno-oncology therapies: a variety of them have already been studied and characterized, they have the ability to access environments and cross physiological barriers that large proteins cannot, and they are usually administered orally, which makes it more comfortable for patients[17]. Though there are a wide variety of small molecule therapies in immuno-oncology, this section will focus on Toll-like receptors and the STING pathway.

Toll-like receptors (TLRs) can be found on the surface membranes of APCs, leukocytes, and tissue cells[17]. They can detect pathogenic antigens of bacterial, viral or fungal origin, and bind to them[17]. Upon antigen binding, the TLRs trigger a cytokine-mediated immune response using dendritic cells and NK cells[17]. TLRs are therefore used and studied as active immuno-oncology therapies, as well as therapies for infectious and inflammatory diseases.

Small molecules are designed to activate the ten different TLRs in the human body and trigger an immune response. They can be derived from viruses or bacteria, and include double-stranded RNA, which binds to TLR3, lipopolysaccharides that bind to TLR4, and a distinct class of oligodeoxynucleotides that bind to TLR9[38].

The first TLR agonist to be approved by the FDA in 1997, was a topical treatment for genital warts called imiquimod (Zyclara®)[17,38]. It was approved for the treatment of basal cell carcinoma in 2004[38]. Imiquimod is an agonist of TLR7 and TLR8[38].

In 2016, the EMA granted orphan drug designation to resiquimod (R848) for the treatment of cutaneous T-cell lymphoma[39]. Resiquimod is applied to the skin where it is thought to bind to TLR7 and TLR8 and trigger an immune response[39].



Adapted from Nimbus Therapeutics & InvivoGen

Although numerous other TLR agonists are being studied, there have been many setbacks[38]. There are several reasons for this: Many of the ligands have difficult molecular properties, including high polarity, poor stability, and a lack of lipophilic binding sites, which makes it hard to create orally available drugs[38]. Also, researchers have had difficulties in cloning and expressing TLR proteins in cell lines used in recombinant protein production, as well as problems with the development of reliable high-throughput binding assays[38].

Another target that can be used for the treatment of cancer with small molecules, is **STING** (STimulator of INterferon Genes), a protein that was discovered in 2008[40]. The discovery of STING made researchers recall the story of "Coley's toxins" – the shrinkage of large tumors after infection with pathogens.

STING is a part of the innate immune system and is activated during an infection with pathogens. On a molecular level, STING is activated by dinucleotides of bacterial such as cyclic diguanylate (diGMP) or cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), as well as mammalian non-canonical cyclic di-nucleotide, 2′-3′ cGAMP. cGAMP is a cyclic dinucleotide (CDN), which is mobilized by the enzyme GMP-AMP synthase (cGAS)[38,40,41]. Upon activation, the usually symmetrical STING dimer proteins shift and form a closed conformation[38].

Activation of STING triggers a signaling cascade that leads to the production of the cytokines IFN-α/β, which promote the maturation of dendritic cells and the cross-priming of tumor specific cytotoxic T-cells[38,40].

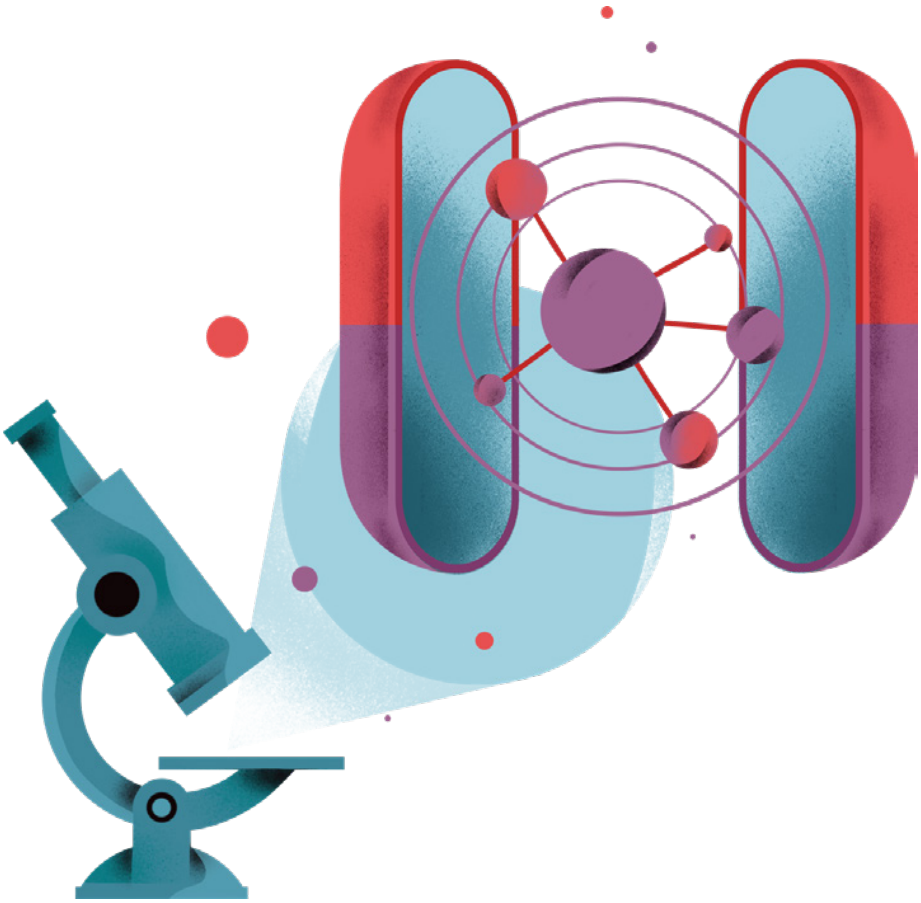
In 2010, a promising phase III clinical trial testing the tumor-vascular disrupting agent DMXAA (Vadimezan) by Novartis flatlined[38]. Though it had looked promising as a STING agonist in preclinical trials, it failed to show the expected results in phase III[38]. In 2013, a team at Harvard Medical School discovered that DMXAA had failed in later clinical trials, because it is a selective agonist of mouse STING protein and cannot activate human STING[38,42].

Learning from their mistakes, researchers are now focusing on earlier molecule characterization and have also identified the structure of human dimeric STING[38]. Together with California-based Aduro Biotech, Novartis is currently working on the STING agonist ADU-S100/MIW815. ADU-S100 is a synthetic CDN that is currently being evaluated in phase I clinical trials for the treatment of cutaneously-accessible tumors, such as melanoma, lymphoma, and breast, renal cell, and head-and-neck cancers[38,44].

Merck too is working on a STING agonist called MK-1454, for the treatment of patients with advanced solid tumors or lymphomas. In October 2018, the company published the first results of its phase I clinical trial[45]. The trial tested MK-1454 in combination with its PD1 inhibitor Keytruda®, and as a monotherapy. Whereas no results were observed in the monotherapy arm of the trial, the combination arm of the trial showed that average tumor sizes shrank by 83%[45].

Recently, a study by researchers at GlaxoSmithKline published in Nature in 2018, revealed the potential of a new class of immunotherapy drugs (diABZI) that activate the STING pathway[46]. The small molecule described, effectively binds to STING, triggering a strong anti-tumor response with a lasting regression of tumors[46].

The use of small molecules to trigger immune responses looks promising in the field of immuno-oncology. Especially in combination with other immunotherapies, small molecules can be used to elicit the initial immune response, activating T-cells and the release of cytokines to boost the activity of other therapies and increase their ability to kill tumor cells.



The future of immuno-oncology

...is looking extremely exciting. Between September 2017 and September 2018, the immuno-oncology pipeline saw a 67% increase in the number of active agents, for instance[47]. These 3,394 active agents are based on a variety of mechanisms of action, all of which have been discussed above. They include: immunomodulators – T-cell targeted or other; cancer vaccines, cell therapies, oncolytic viruses, and bispecific antibodies[47].

The field of cell therapies experienced the greatest growth with a 113% increase in the number of active agents[47]. Notably, it seems as though the focus is lying not on clinical research, but rather on basic and preclinical research, where most active agents are positioned at the moment[47]. Globally, more and more companies are getting involved in immuno-oncology research – a fact that reflects the importance and potential of the field[47].

In the last ten years, cancer immunotherapy has experienced an almighty boost. And although we still have a long way to go, it has become a global pillar of cancer therapy enabling the treatment of aggressive cancers and bringing long-lasting survival benefits to patients whose tumors seemed untreatable only a few years ago.

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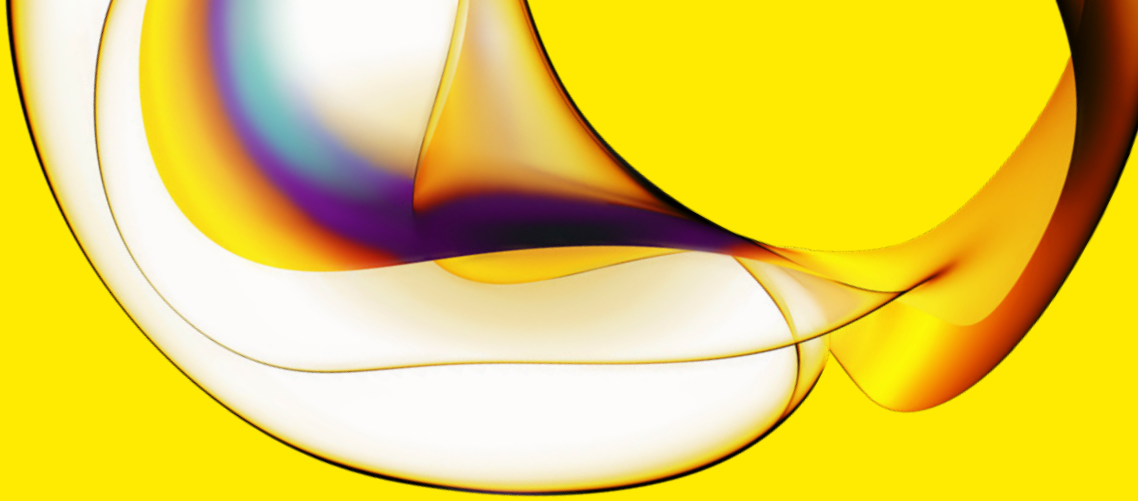

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