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5 Cedarbrook Drive
Cranbury, NJ 08512
United States

Phone: (800) 436-9910

(609) 497-0253

Fax: (609) 497-0321

Inquiries: peprotech.info@thermofisher.com

Service: peprotech.customerservice@thermofisher.com

Sales: peprotech.sales@thermofisher.com

thermofisher.com/peprotech

Introduction

The immune system is composed of a complex network of cells, tissues, and organs that function together as the body's defense against infectious organisms, diseases, and other invasive agents. Representing a duality of responsibilities, the immune system initiates the body's quick and efficient response to harmful agents, while also distinguishing these threats from the body's healthy cells and working to avoid autoimmunity, which is an attack against the host.

The immune system is composed of several different cell types that collectively serve to protect the body from bacterial, fungal, and viral infections, as well as from the growth and dispersal of tumor cells. The various cell types have distinct and specialized functions, such as engulfing bacteria, producing antibodies, and killing parasites, tumor cells, and virally infected cells.

Generally, the immune system can be divided into two major layers of defense: innate immune responses and adaptive immune responses. The innate immune response is an organism's immediate reaction to and generic barrier against infections, whereas the adaptive immune response is specific to the invasive agent and can initiate antibody production, cell-mediated responses, and immunological memory. While both innate and adaptive immunity depend upon the actions of leukocytes, the adaptive response relies specifically upon three specialized leukocytes called lymphocytes: B lymphocytes (B cells), T cells, and natural killer (NK) cells. These three types of lymphocytes collectively define the adaptive immune response; however, they each have focused roles and function through distinct types of receptors. Whereas B cells are responsible for the production of antibodies and are referred to as "plasma cells" in their mature form, T cells can develop into effector cells in response to an activating antigen and are responsible for cell-mediated immunity. The functions of effector cells fall into one of three broad classes: killing, activation, and regulation. For example, cytotoxic T cells serve the purpose of killing cells that have been infected with intercellular pathogens, such as viruses. While helper T cells provide essential intercellular signals that influence the behavior and activity of other immune cells (including B cells and macrophages), regulatory T cells mediate the activity of other lymphocytes and help regulate immune responses. During the course of the immune response, a number of those B and T cells that have survived past infections can also serve to differentiate into the long-living lymphocytes, known as memory cells, responsible for immunological memory.

Lymphocytes and other cells from the immune system, such as macrophages and dendritic cells, produce a large array of cell-signaling proteins that are collectively referred to as cytokines, which are responsible for the intercellular communications necessary for the accurate and efficient performance of both innate and adaptive immune responses. Cytokines are proteins produced, usually as the result of an activating stimulus, by various cells of the body and induce signaling by binding to specific cell surface receptors. In general terms, cytokines are responsible for much of the activation and regulation of the body's response to disease and infection, and can directly affect the activity of most immune cells. Playing a crucial role in the functioning of lymphocytes, cytokines can serve to recruit other cells in the body's response to invasion and act to mediate normal cellular processes. Thus, deciphering the action of cytokines is central to understanding various aspects of the immune system.

The body produces several different classes of cytokines, including:

- Colony-stimulating factors: cause proliferation and differentiation of specific target cells
- Growth and differentiation factors: subfamily of TGF-β–like proteins that play an important role during prenatal and postnatal development, and the maintenance of various tissues
- Proinflammatory cytokines: promote systemic and site-specific inflammation
- Chemokines: a group of structurally related cytokines that can induce chemotaxis of specific nearby cells

Our understanding of the immune system has advanced significantly in recent years, and it has become evident that cytokines play a central role in the activation and regulation of the immune response. This booklet describes a diverse number of commercially available cytokine products. By offering this wide array of cytokine reagents, it is the goal of Thermo Fisher Scientific to contribute to the continuing advances of immune system–related research and the overall improvement of worldwide health.

Contents

Cells of the immune system

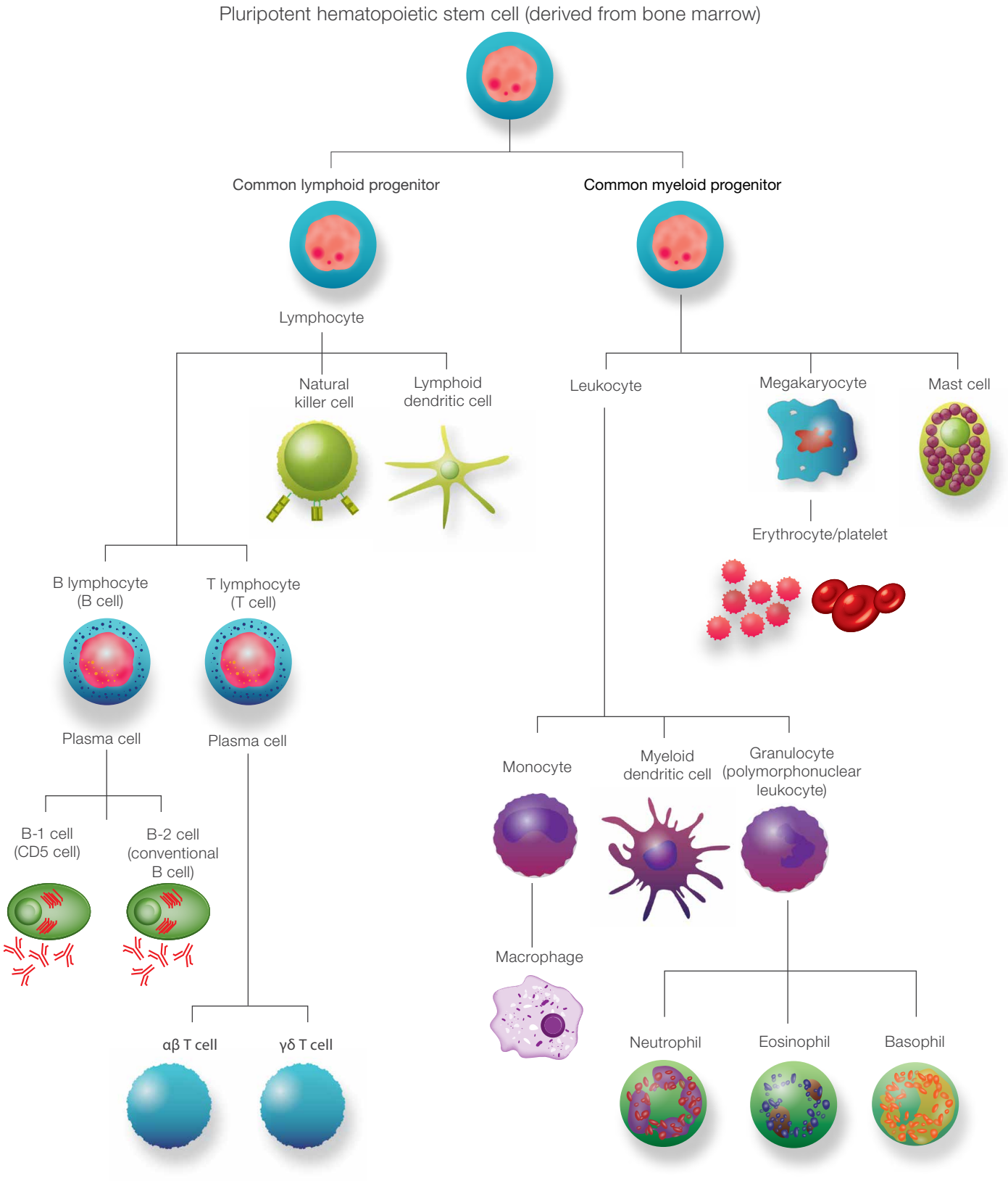
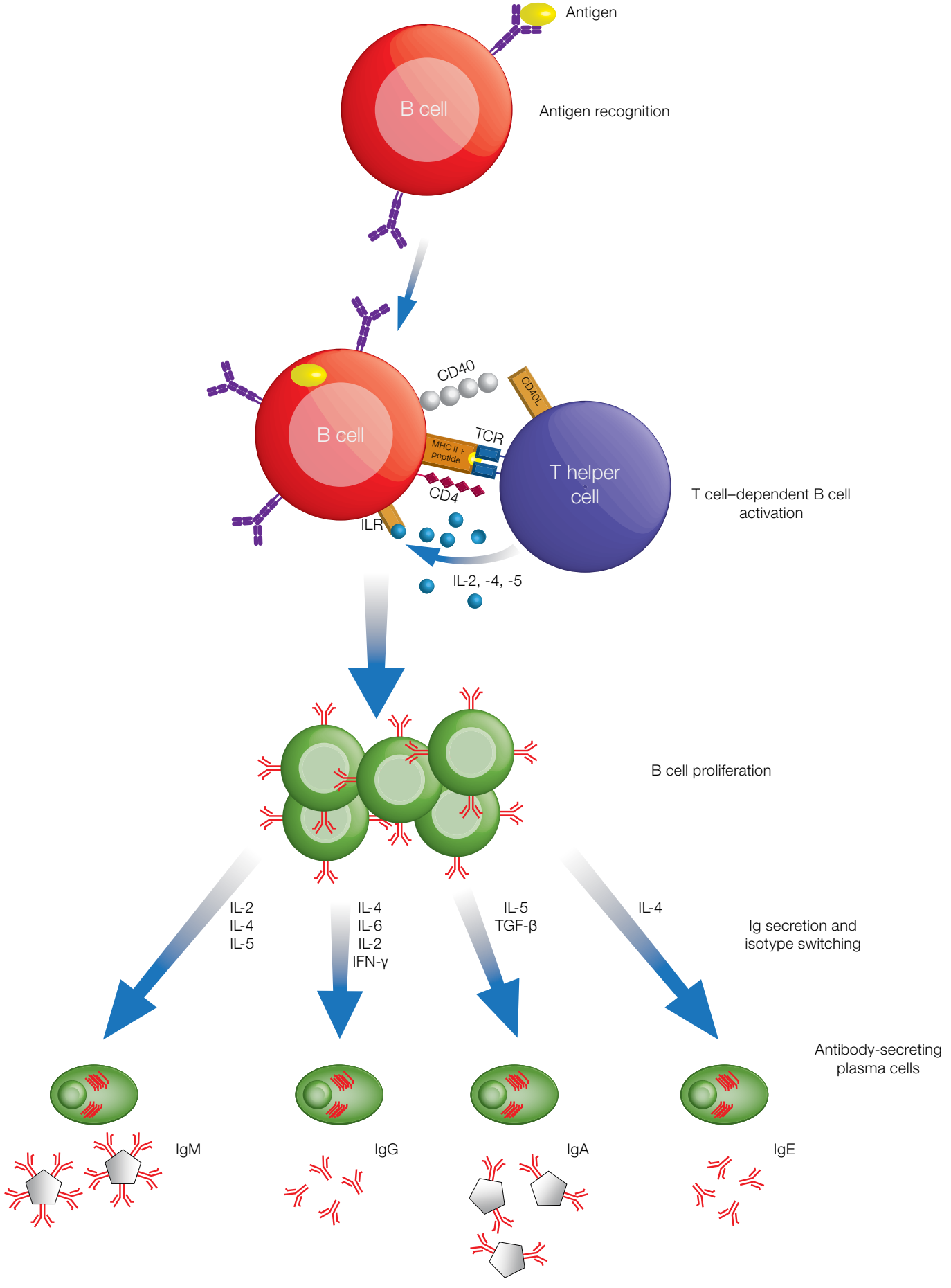


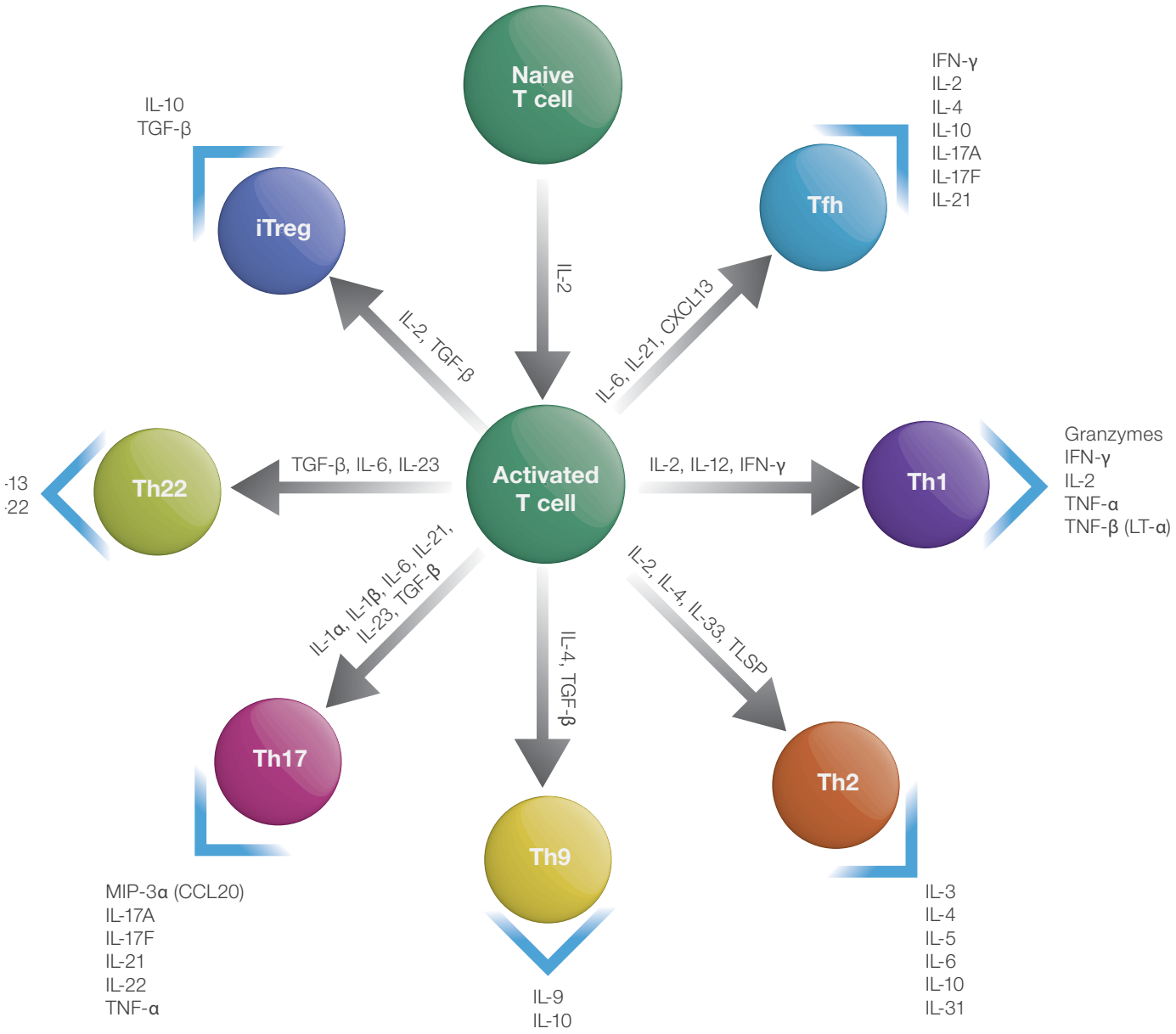
Figure contains some content modified from Janeway CA et al. (2005) *Immunobiology: the immune system in health and disease*. 6th ed. New York: Garland Science.

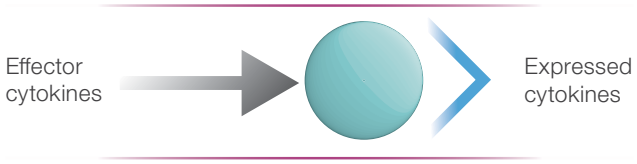
B cells


Antigen
B cell
Antigen recognition
B cell
CD40
CD40L
TCR
MHC II + peptide
CD4
ILR
T helper cell
T cell–dependent B cell activation
IL-2, -4, -5
B cell proliferation
IL-2
IL-4
IL-5
IL-4
IL-6
IL-2
IFN-γ
IL-5
TGF-β
IL-4
Ig secretion and isotype switching
Antibody-secreting plasma cells
IgM
IgG
IgA
IgE

T helper cells

Key effector cytokines, expressed cytokines, and other proteins related to T helper cells





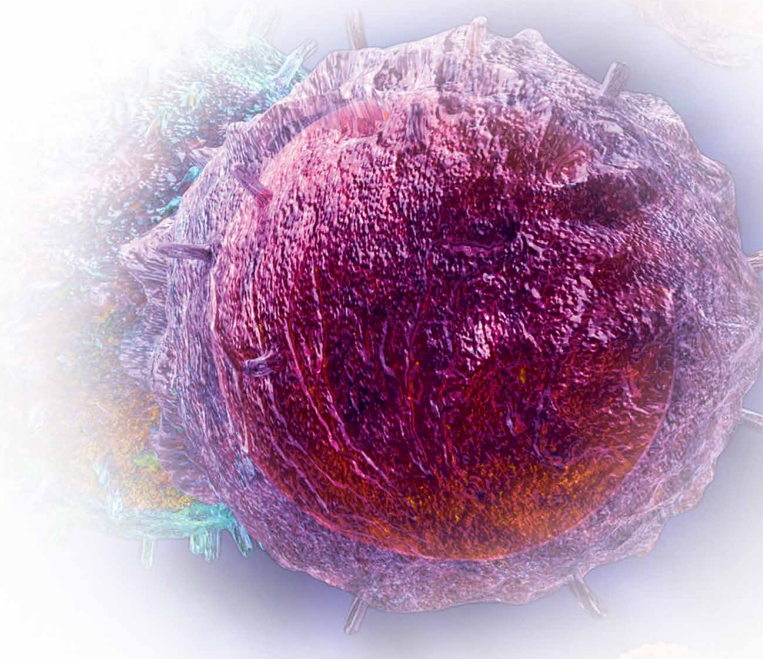
T helper type 1 (Th1) cells

Cytokines, factors, and other proteins associated with Th1 cells

Granzyme B	IL-12
IFN-γ	IL-18
IL-2	IL-27
IL-10	TNF-α, -β

Disease/disorder association

- Inflammatory bowel disease
- Multiple sclerosis
- Rheumatoid arthritis
- Type I diabetes



T helper type 2 (Th2) cells

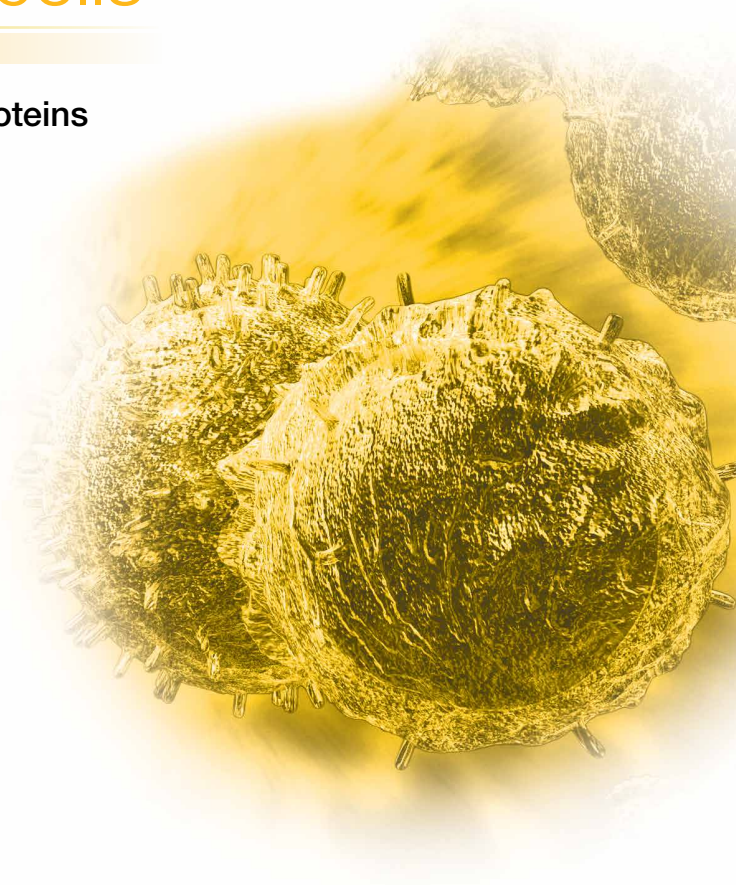
Cytokines, factors, and other proteins associated with Th2 cells

IFN-γ	IL-13
IL-2	IL-21
IL-4	IL-25
IL-4 receptor α	IL-31
IL-5	IL-33
IL-6	TSLP
IL-9	

Disease/disorder association

- Asthma
- Chronic allergic inflammation

T helper type 9 (Th9) cells



Cytokines, factors, and other proteins associated with Th9 cells

IL-4

IL-4 receptor α

IL-9

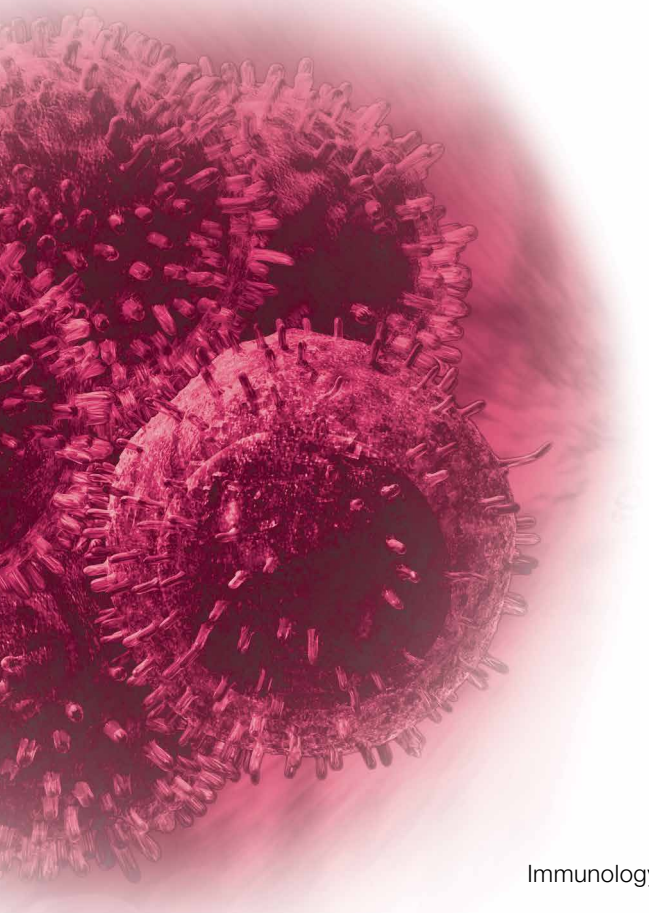
IL-10

TGF-β1, -β2, -β3

Disease/disorder association

- Airway remodeling autoimmune disease
- Chronic allergic inflammation

T helper type 17 (Th17) cells



Cytokines, factors, and other proteins associated with Th17 cells

IL-1β

IL-6

IL-6 receptor α

IL-17E

IL-17F

IL-21

IL-22

IL-23

IL-26

MIP-3α (CCL20)

TNF-α

Disease/disorder association

- Inflammatory bowel disease
- Multiple sclerosis
- Rheumatoid arthritis

T follicular helper (Tfh) cells

Cytokines, factors, and other proteins associated with Tfh cells

CD40 ligand

BCA-1 (CXCL13)

IFN-γ

IL-2

IL-4

IL-6

IL-6 receptor α

IL-10

IL-12

IL-21

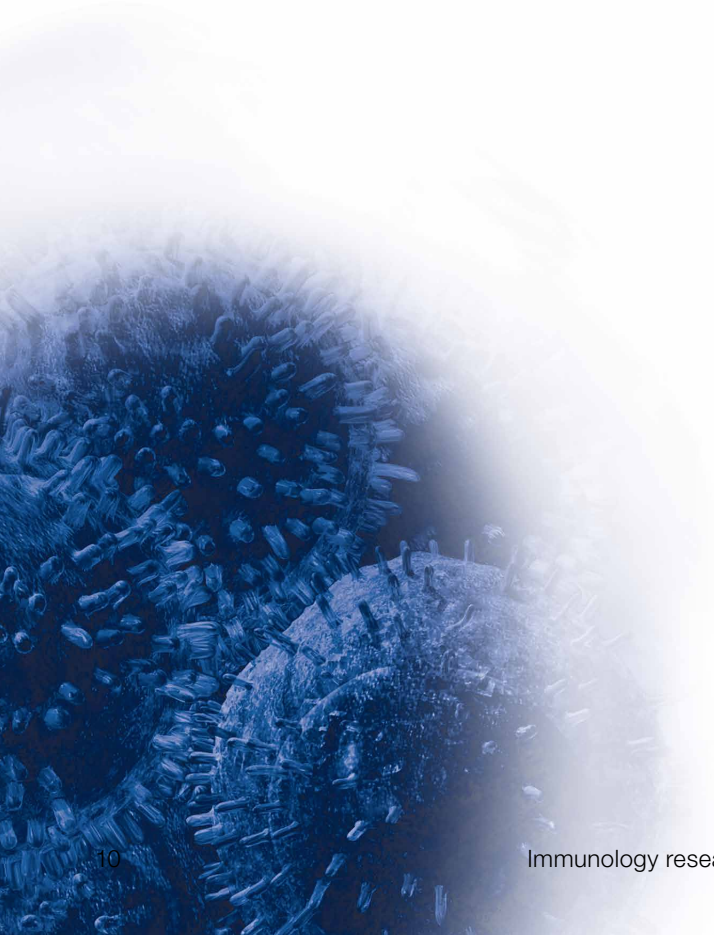
IL-17A

IL-17F

Disease/disorder association

- Autoimmune disorders
- Cancers

Regulatory T (Treg) cells



Cytokines, factors, and other proteins associated with Treg cells

AITRL

Galectin-1

IL-2

IL-10

IL-12

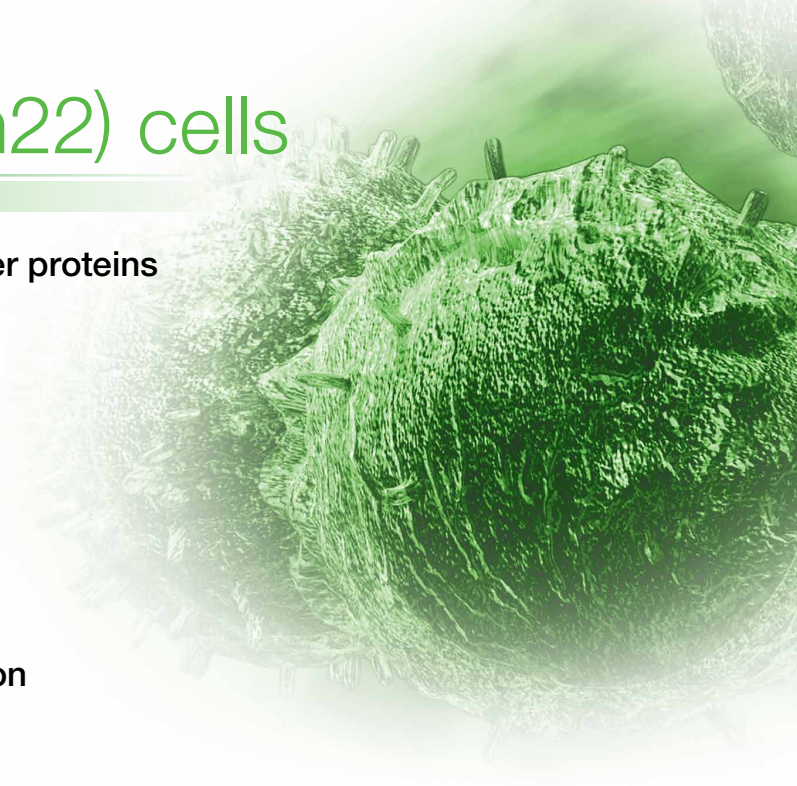
IL-35

TGF-β1, -β2, -β3

Disease/disorder association

- Autoimmune disorders
- Inflammatory disorders

T helper type 22 (Th22) cells

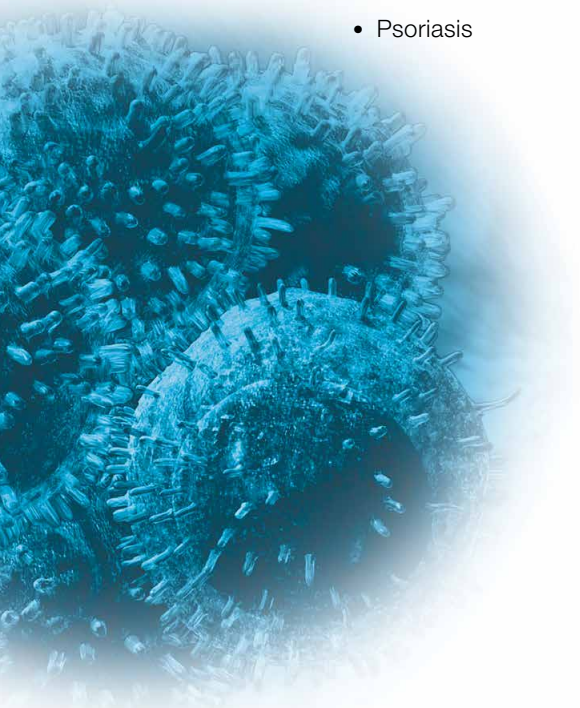


Cytokines, factors, and other proteins associated with Th22 cells

IL-6	IL-22
IL-6 receptor α	IL-26
IL-10	TGF-β1, -β2, -β3
IL-13	TNF-α
IL-21	

Disease/disorder association

- Allergic contact dermatitis
- Atopic eczema
- Psoriasis



Natural killer T (NKT) cells

Cytokines, factors, and other proteins associated with NKT cells

GM-CSF	IL-13
IFN-γ	TNF-α
IL-10	

Disease/disorder association

- Asthma
- Atherosclerosis
- Cancers

Cytotoxic T lymphocytes (CTLs)

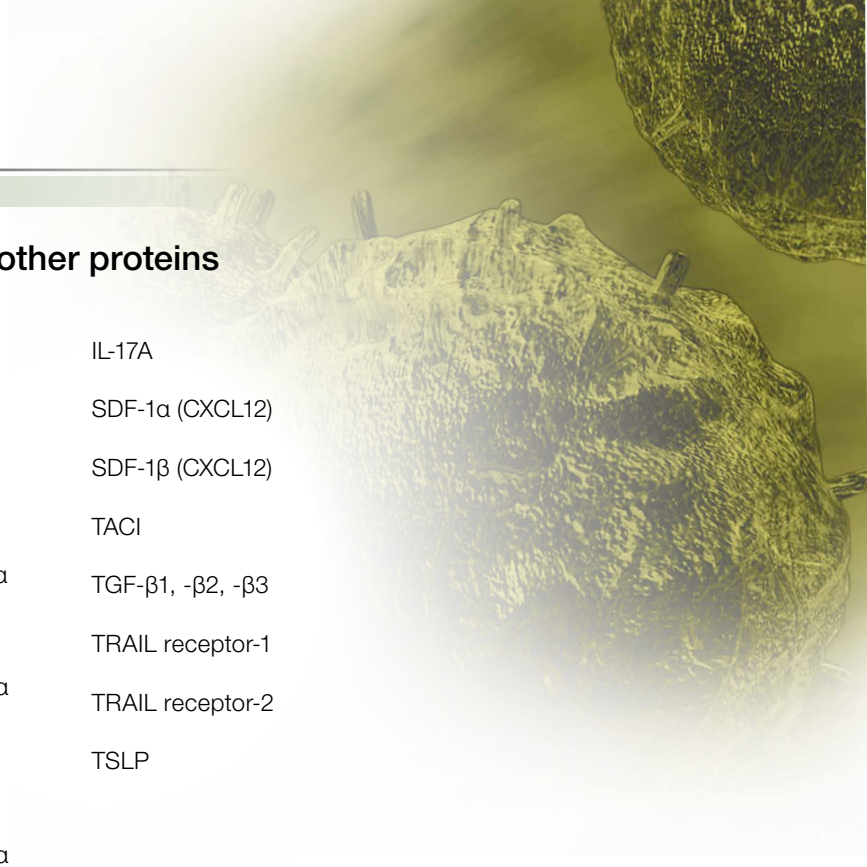
Cytokines, factors, and other proteins associated with CTLs

Fas ligand	IFN-γ
Granzyme B	TNF-α, -β

Disease/disorder association

- Arthritis
- Liver injury due to HBV (hepatitis B virus)

B cells



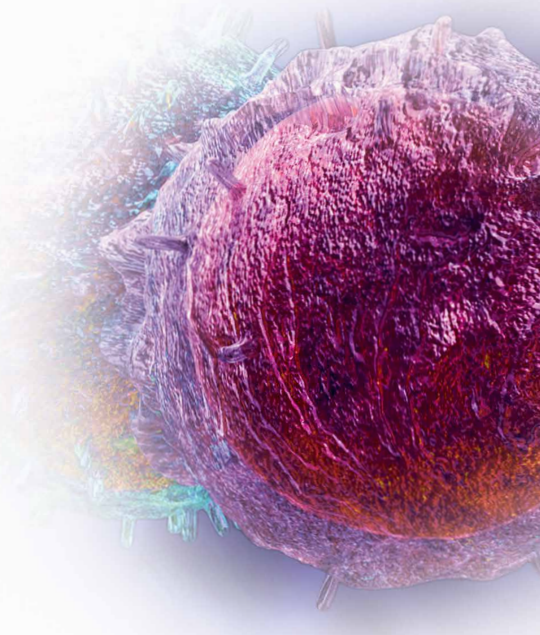
Cytokines, factors, and other proteins associated with B cells

4-1BB ligand
4-1BB receptor
BAFF
BAFF receptor
BCA-1 (CXCL13)
BCMA
CD23
CD27 ligand
CD30 ligand
CD40 ligand
Exodus-2 (CCL21)
HVEM
ICAM-1
IFN-α, -γ
IL-2
IL-2 receptor α
IL-4
IL-4 receptor α
IL-5
IL-6
IL-6 receptor α
IL-10
IL-17A
SDF-1α (CXCL12)
SDF-1β (CXCL12)
TACI
TGF-β1, -β2, -β3
TRAIL receptor-1
TRAIL receptor-2
TSLP

Disease/disorder association

- Autoimmune disorders
- Cancers
- Diabetes
- Graves' disease
- Immunodeficiencies
- Inflammatory bowel disease

Dendritic cells (DCs)



Cytokines, factors, and other proteins associated with DCs

AITRL
CD40 ligand
Eotaxin (CCL11)
Eotaxin-2 (CCL24)
Eotaxin-3 (CCL26)
Exodus-2 (CCL21)
Flt3 ligand
Fractalkine (CX3CL1)
GM-CSF
I-309 (CCL1)
ICAM-1
IFN-γ
IFN-β
IFN-γ
IL-2
IL-3
IL-4
IL-6
IL-8 (CXCL8)
IL-12
IL-13
IL-15
IL-21
IL-27
IP-10 (CXCL10)
I-TAC (CXCL11)
MCPs
MDC (CCL22)
MIG (CXCL9)
MIP-1α (CCL3)
MIP-1β (CCL4)
MIP-3α (CCL20)
MIP-3β (CCL19)
RANTES (CCL5)
SDF-1 (CXCL12)
TLR3
TNF-α
TSLP

Disease/disorder association

- Allergies
- HIV infection
- Inflammatory bowel disease

Natural killer (NK) cells

Cytokines, factors, and other proteins associated with NK cells

CD27 ligand
CD30 ligand
Fas ligand
Fas receptor
Granzyme B
IFN-γ
IL-2
IL-7
IL-10
IL-12
IL-15
TRAIL

Disease/disorder association

- Cancers
- HIV infection

Macrophages

Cytokines, factors, and other proteins associated with macrophages

CD40	IL-10	MIF
CD40 ligand	IL-12	MIG (CXCL9)
G-CSF	IL-18	MIP-1α (CCL3)
GM-CSF	IL-27	MIP-1β (CCL2)
IFNs	IP-10 (CXCL10)	MIP-2 (CXCL2)
IL-1β	I-TAC (CXCL11)	Oncostatin M
IL-1RA	LIF	RANTES (CCL5)
IL-3	MCP-1 (CCL2)	TGF-β1, -β2, -β3
IL-4	MCP-2 (CCL8)	TNF-α
IL-6	MCP-3 (CCL7)	
IL-8 (CXCL8)	M-CSF	

Disease/disorder association

- Cancers
- Chikungunya
- Heart diseases
- HIV infection
- Leishmaniasis
- Obesity
- Tuberculosis

Monocytes

Cytokines, factors, and other proteins associated with monocytes

4-1BB ligand	IL-24	MIP-3α (CCL19)
BRAK (CXCL14)	LAG-1 (CCL4L1)	MIP-3β (CCL20)
C10 (CCL6)	LD78β (CCL3L1)	MIP-5 (CCL15)
CD27 ligand	LEC (CCL16)	OX40 ligand
Fractalkine (CX3CL1)	LIGHT	RANTES (CCL5)
HCC-1 (CCL14)	MCPs	SDF-1α (CXCL12)
IL-4	M-CSF	SDF-1β (CXCL12)
IL-19	MIP-1α (CCL3)	TNF-α
IL-20	MIP-1β (CCL2)	

Disease/disorder association

- Cancers
- Chronic inflammation
- Hyperadrenocorticism
- Immune-related diseases
- Pyogenic granuloma
- Red cell regeneration
- Sarcoidosis
- Viral fever

Neutrophils

Cytokines, factors, and other proteins associated with neutrophils

ENA-78 (CXCL5)
GCP-2 (CXCL6)
GROα/MGSA (CXCL1)
GROβ (CXCL2)
GROγ (CXCL3)
IL-8 (CXCL8)
Lungkine (CXCL15)
MIP-3α (CCL19)
MIP-3β (CCL20)
MIP-5 (CXCL15)
NAP-2 (CXCL7)
SDF-1α (CXCL12)
SDF-1β (CXCL12)

Disease/disorder association

- Aplastic anemia
- Inflammation
- Leukemia
- Pulmonary emphysema

Eosinophils

Cytokines, factors, and other proteins associated with eosinophils

Eotaxin (CCL11)
Eoxtain-2 (CCL24)
Eotaxin-3 (CCL26)
HCC-1 (CCL14)
MCP-3 (CCL7)
MCP-4 (CCL13)
MIP-1α (CCL3)
MIP-5 (CCL15)
RANTES (CCL5)

Disease/disorder association

- Addison's disease
- Eosinophilic esophagitis
- Hodgkin's disease
- Reflux esophagitis
- Rheumatoid arthritis
- Skin diseases

Basophils

Cytokines, factors, and other proteins associated with basophils

Eotaxin (CCL11)
Eotaxin-2 (CCL24)
Eotaxin-3 (CCL26)
MCPs
RANTES (CCL5)

Disease/disorder association

- Cancers
- Inflammation, allergies

Immunotherapy awakens the immune system to fight disease

Over the last few decades, there have been numerous advancements in cancer treatments and technologies. Historically, cancer has been treated using three modalities:

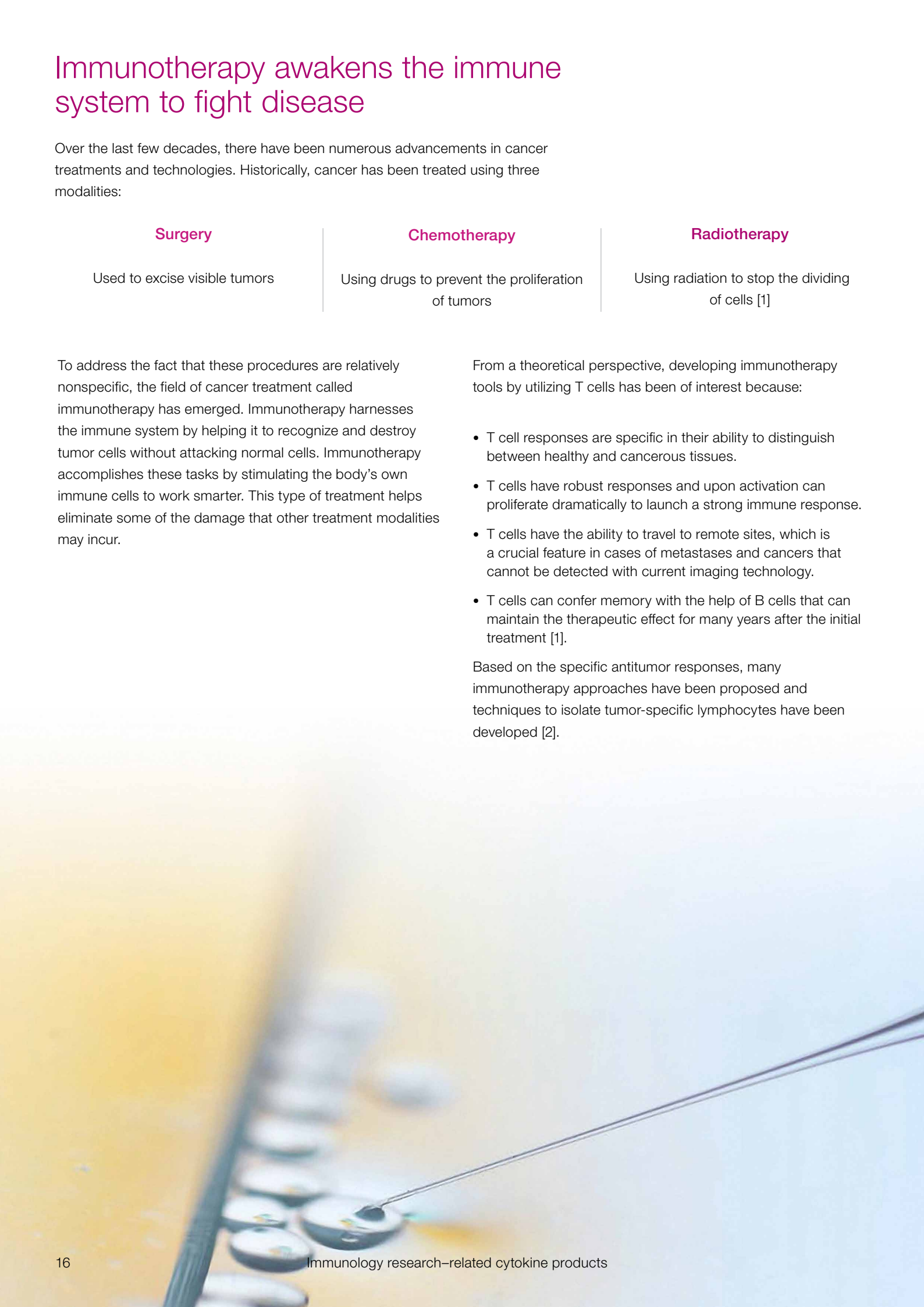
Surgery	Chemotherapy	Radiotherapy
Used to excise visible tumors	Using drugs to prevent the proliferation of tumors	Using radiation to stop the dividing of cells [1]

To address the fact that these procedures are relatively nonspecific, the field of cancer treatment called immunotherapy has emerged. Immunotherapy harnesses the immune system by helping it to recognize and destroy tumor cells without attacking normal cells. Immunotherapy accomplishes these tasks by stimulating the body's own immune cells to work smarter. This type of treatment helps eliminate some of the damage that other treatment modalities may incur.

From a theoretical perspective, developing immunotherapy tools by utilizing T cells has been of interest because:

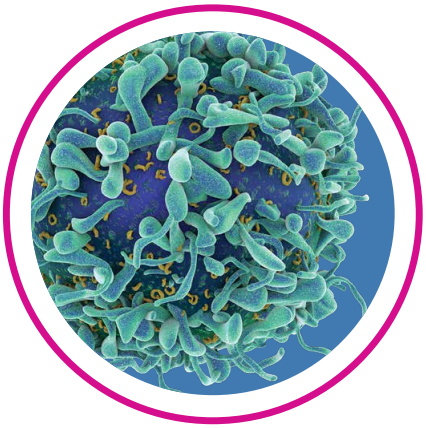
- T cell responses are specific in their ability to distinguish between healthy and cancerous tissues.
- T cells have robust responses and upon activation can proliferate dramatically to launch a strong immune response.
- T cells have the ability to travel to remote sites, which is a crucial feature in cases of metastases and cancers that cannot be detected with current imaging technology.
- T cells can confer memory with the help of B cells that can maintain the therapeutic effect for many years after the initial treatment [1].

Based on the specific antitumor responses, many immunotherapy approaches have been proposed and techniques to isolate tumor-specific lymphocytes have been developed [2].



Adoptive cell therapy (ACT)

ACT is an immunotherapy approach in which antitumor lymphocytes (most of which are T cells) are harvested from the cancer patient, expanded *in vitro*, and then reinfused back into the patient. This procedure is often performed in conjunction with vaccines, growth factors that can enhance the *in vivo* impact of the transferred cells, and lymphodepleting chemotherapy in order to ensure that the body tolerates the tumor-targeting cells [3]. Since adoptive therapies physically separate the emerging antitumor cells from their host, it is possible to manipulate the cells and their response mechanisms in ways that are clinically relevant [1].



In order for T cells to mount a specific response to tumor cells, they need to be able to recognize and target antigens on the tumor that are nonexistent or poorly expressed in healthy tissue. Tumor-associated antigens (TAAs) were identified in the 1990s and provided definitive proof that immune cells can distinguish between cancerous and noncancerous tissue [1,4].

There are several main cell sources that are able to recognize these tumor-specific antigens or exhibit antitumor activity that can be used for adoptive immunotherapy:

- **Tumor-infiltrating lymphocytes (TILs):** Naturally occurring T cells located within the tumors, TILs can be isolated and grown *in vitro* to be reinfused into the patient after sufficient growth.
- **T cells expressing physiological T cell receptors (TCRs) and synthetic receptors called chimeric antigen receptors (CARs):** TCRs and CARs are two types of receptors that are used to redirect T cells. In a patient who lacks culturable TILs, or in which growing TILs is difficult, one can genetically engineer T cells that can perform the same antitumor function by introducing tumor-targeting receptors or other attributes that can help the cells to efficiently eliminate cancerous cells. Since this process occurs *in vitro*, it is possible to engineer qualities that do not occur naturally in these cells.
- **Dendritic cells (DCs):** These cells exhibit an extremely potent ability to present antigens to T cells. DCs have been used as a potential therapy via a vaccine, as they can independently mount a robust immune response.
- **Natural killer (NK) cells:** These cells have recently advanced as a model for immunotherapy because of their ability to induce antibody-dependent cellular cytotoxicity (ADCC), manipulate receptor-mediated activation, and function as a form of an adoptive immunotherapy with CAR modifications.
- **Cytokine-induced killer cells:** A subset of the population of NK cells, cytokine-induced killer cells have been discovered and targeted as a potential immunotherapy method, because the cells can be readily grown *in vitro* and show major histocompatibility complex (MHC)-unrestricted activity against tumors.

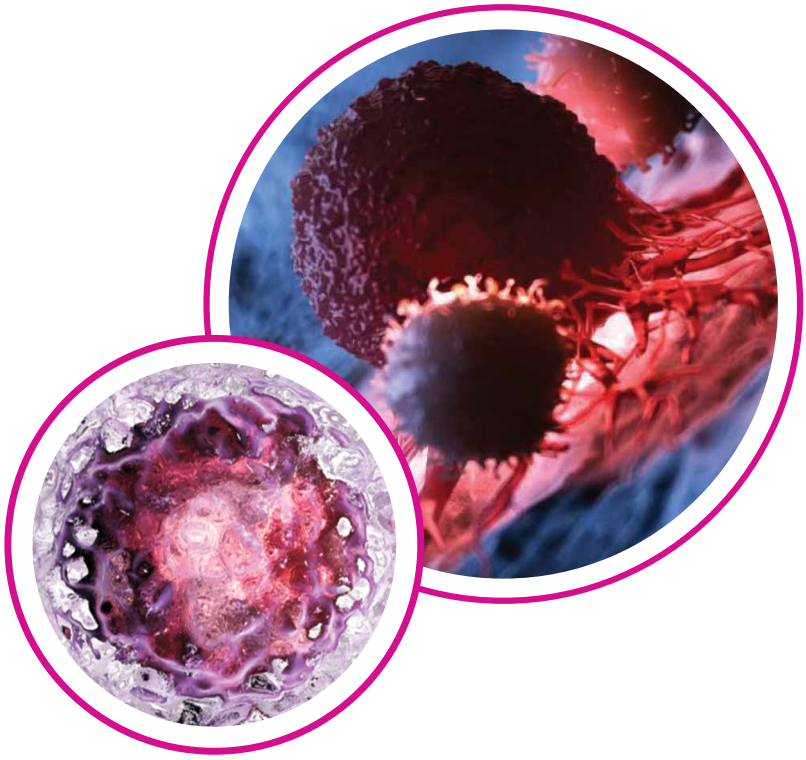
Tumor-infiltrating lymphocytes (TILs)

TILs are the most natural source of cells that can provide the desired immune response for cancer therapies. These cells were among the first cells utilized for ACT in the 1980s, at which point it was demonstrated that TILs, cultured with IL-2, a lymphotropic cytokine, exhibited cytotoxic activity against cancer cells *in vitro* [5,6]. Since these cells were originally located within tumors, they were found to be more potent than other lymphocytes in the body.

The technologies used to isolate and manipulate TILs are mostly geared toward preparing the patient's own TILs, growing them, and reintroducing them into the patient to kill cancer cells [7]. The adoptive cell transfer of autologous TILs has been shown to effectively mediate tumor regression in the majority of patients with metastatic melanoma, for example, and thus shows promise in terms of being able to achieve complete regression, which has been observed in a subset of patients with epithelial tumors [8,9].

In order to produce therapeutic TILs, resected tumor tissue is cultured in medium containing IL-2 for approximately 4–6 weeks. Once enough TILs are grown from these cultures, they undergo rapid expansion during a period of 2–4 weeks with the aid of feeder cells, a higher concentration of IL-2, and soluble CD3 antibody [10]. Next, these TILs are incubated with an autologous tumor to select for the ones that react to the tumor. Once this is done, the levels of IFN-γ secreted into the medium can be measured using an IFN-γ enzyme-linked immunosorbent assay (ELISA) [11].

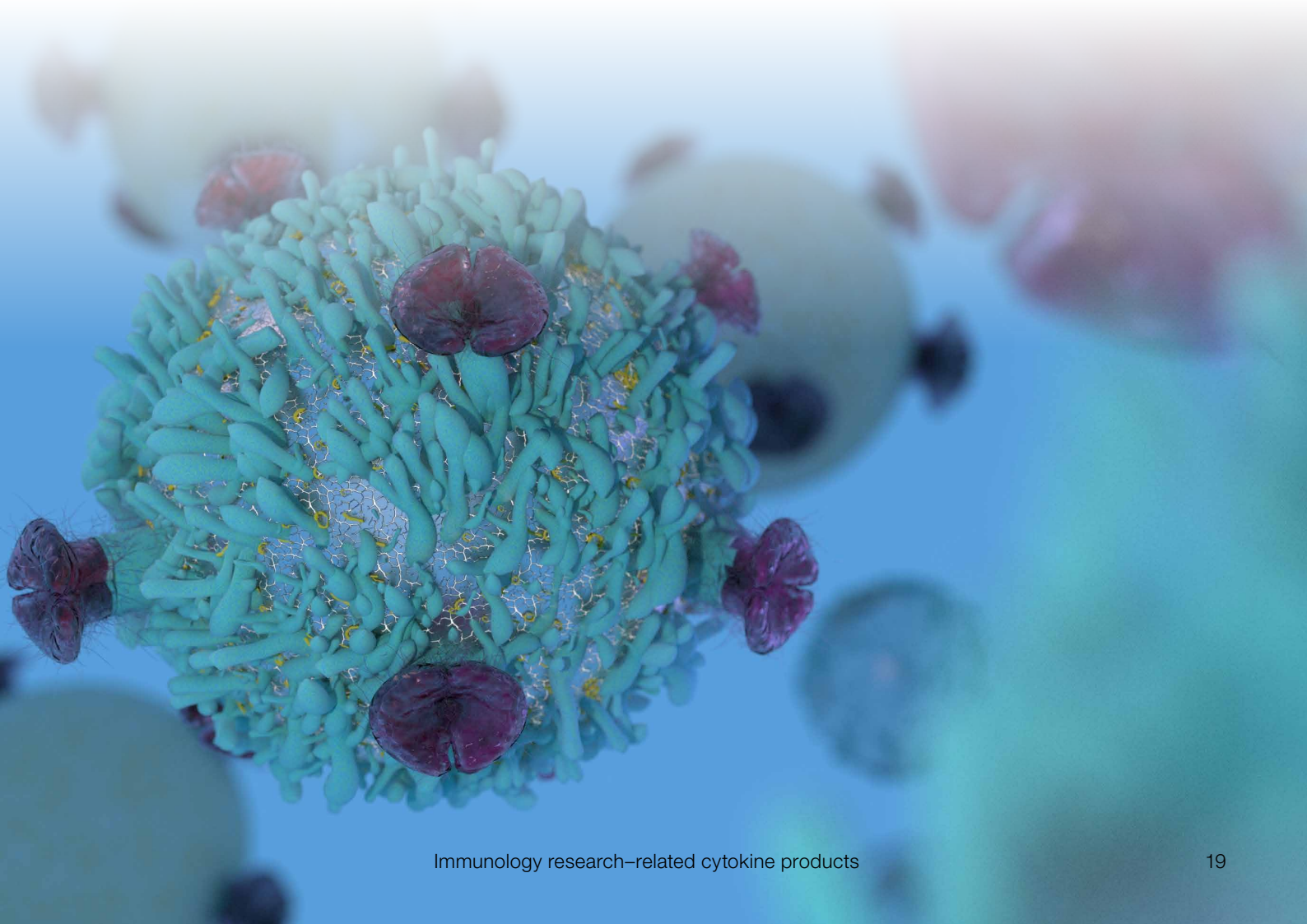
Sometimes the autologous tumor is unavailable or difficult to grow in culture, posing a problem in the selection process. To mitigate this issue, researchers have developed new methods that utilize deep-sequencing technology to identify neoantigens that are presented by the tumor, which can then be synthesized as short peptides and used to identify tumor-reactive TILs [12].



T cell receptors (TCRs)

Since not all tumors yield readily available TILs, the use of TCRs that exhibit tumor antigen–recognizing properties has emerged as an important strategy for adoptive T cell therapies. Most of the clinical efforts in this realm to date have focused on self-peptides that are upregulated in some cancers, such as the WT1 antigen; differentiation antigens, such as gp100 and MART-1; and cancer-testis antigens, such as NY-ESO and MAGE-A3 [13]. Most of these human "tumor-associated" antigens that are targeted by TCR-engineered T cell therapy are also expressed in normal tissues, albeit at a lower density than on the surface of cancer cells. Therefore, it is challenging to determine what TCR affinity is necessary to confer therapeutic activity without posing a threat to normal or unrelated tissues, which is hard to anticipate. Many investigational efforts are focused on developing methods to capture neoantigen-reactive TCR genes from the patient's peripheral blood or other samples.

Though this particular approach allows for the generation of tumor-specific T cells without the need to isolate TILs from tumors, it has a few limitations. The major drawback of this approach is HLA restriction, where a given T cell will only recognize and respond to an antigen when it is bound to a particular MHC molecule [14]. Another issue is the competition for pairing with endogenous TCR chains, which can lead to lower levels of tumor-specific TCRs or possible off-target reactivities of mispaired TCRs that can result in graft-versus-host reactions. To combat mispairing, scientists have started to use cysteines in exogenous TCR-constant domains that promote preferential pairing, or gene editing strategies that limit the expression of endogenous TCR chains. Though this concern exists in theory, there have been no reported adverse events related to mispaired TCR formation in clinical trials [14].



Chimeric antigen receptors (CARs)

One alternative to obtaining T cells with antitumor reactivity while avoiding the complications that can arise from HLA restriction is to genetically engineer T cells to express chimeric antigen receptors (CARs). CARs are receptors that have been engineered to give T cells the ability to target a specific protein by combining antigen-binding and T cell–activating functions into a single receptor [15]. More specifically, CARs are hybrid receptors formed by the fusion of an extracellular tumor antigen–binding domain, typically a single-chain variable fragment (scFv) of an antibody, with intracellular T cell signaling and costimulatory domains.

CARs were originally generated by Zelig Eshhar and colleagues in the late 1980s in order to study TCR signaling [16]. Because of their chimeric construction, CARs can provide non–MHC restricted recognition of cancer cell antigens, which ultimately results in targeted T cell activation. By incorporating chimeric molecules that recognize tumor antigens as well as actively promoting a cascade of signals that could induce further damage to tumor cells, CAR therapy can give patients an alternative that breaks the acquired tolerance of immune cells and bypasses the restrictions of HLA-mediated antigen recognition that are present with TLR-based therapies [17].

Typically, in order to generate CAR T cells, activated leukocytes are first removed from the patient and then processed to isolate the autologous peripheral blood mononuclear cells (PBMCs) [18]. In order to activate T cells that can effectively fight against cancer, the cells are incubated with IL-2, anti-CD3, and anti-CD28 [19,20]. Subsequently, the T cells are transfected with CAR genes through integration of a gamma retrovirus or lentiviral vectors and expanded using cytokines such as IL-7, IL-15, and IL-21 [19]. Since these CAR T cells are further divided into $CD4^+$ and $CD8^+$ subsets, these markers can be used to select these cells; the optimal ratio of $CD4^+$ to $CD8^+$ CAR T cells is of interest for maximum efficacy of this line of treatment [21]. Prior to the introduction of the engineered T cells, the patient often undergoes lymphodepletion chemotherapy. Lymphodepletion is the depletion of endogenous T cells, including Tregs, which promotes the expansion and survival of the CAR T cells once they have been reinfused [19].

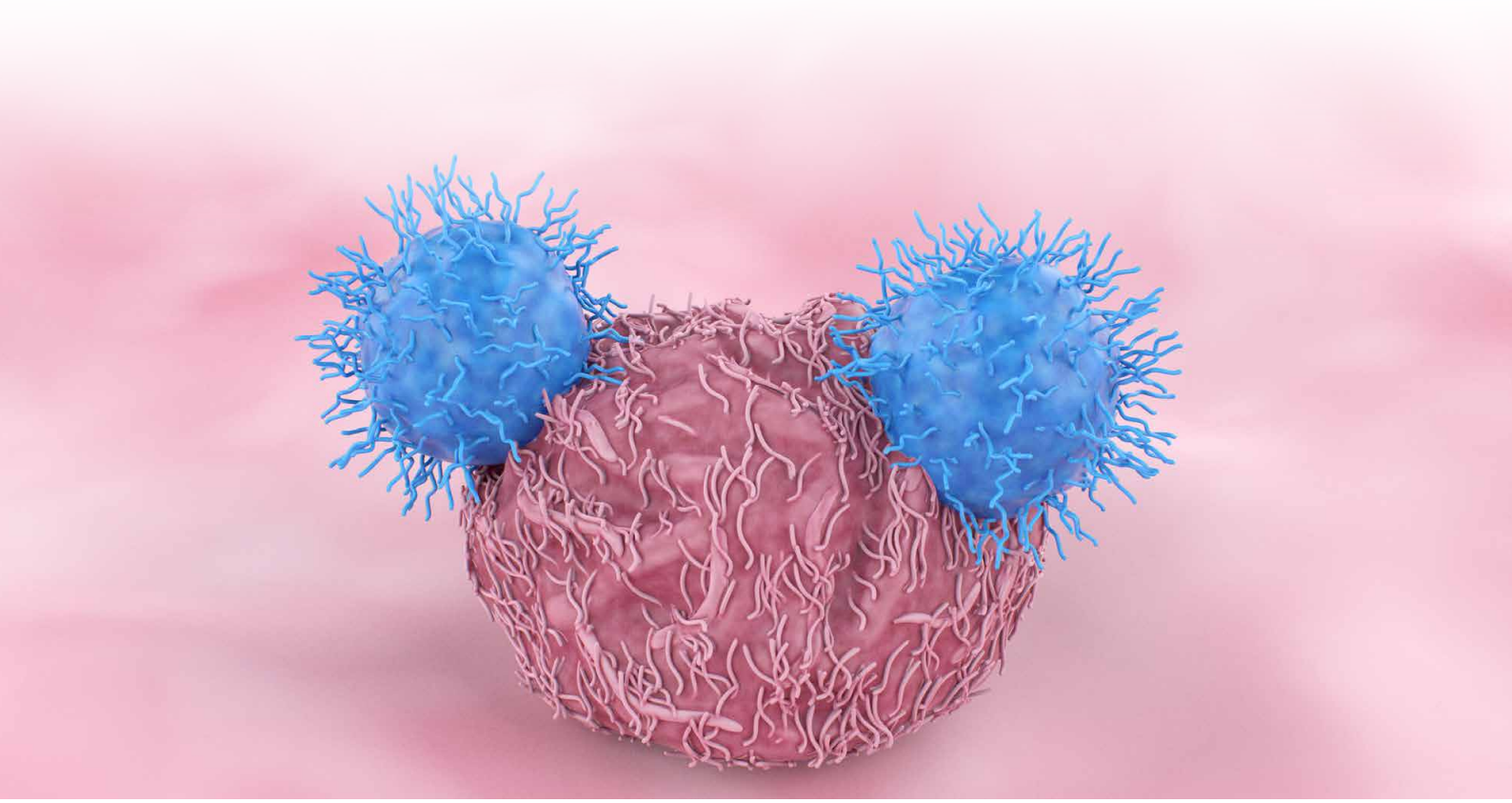
Because of the success of CAR T cells targeted at CD19 in patients with B cell hematologic malignancies, the U.S. Food and Drug Administration approved two CAR T cell therapies. Tisagenlecleucel (KYMRIAH® immunotherapy by Novartis) is indicated for the treatment of advanced leukemia in children and young adults up to 25 years of age who have large B cell acute precursor lymphoblastic leukemia (ALL) that has either relapsed or failed to respond to previous conventional treatment. The other, axicabtagene ciloleucel (YESCARTA® immunotherapy by Kite Pharma), is approved for treating adults who have either relapsed or refractory cancer that has not responded to previous conventional treatment(s). It is also approved for high-grade lymphoma, diffuse large B cell lymphoma (DLBCL), or DLBCL resulting from follicular lymphoma.

Despite these breakthroughs in the treatment of hematological malignancies, it has been difficult to use CAR T cell therapy against solid tumors. The poor specificity and efficacy of CAR T cell therapy against these tumors can be at least partially attributed to the lack of specific targetable antigens [17]. In addition, it is difficult for CAR T cells to navigate in the hostile microenvironment of solid tumors, so future efforts are focused on alleviating these problems so that solid tumors can be better treated with this form of immunotherapy [17].

Researchers have utilized the same CAR technology to equip other immune cells, such as NK cells and even macrophages, to recognize tumors [22]. Although these cells are probably not going to replace CAR T cell therapy, these alternative approaches to fighting cancer could add to the arsenal of therapies that are currently being developed. NK cells, which belong to the innate immune system, act as a first line of defense against cancer cells, scanning the other cells in the body and destroying those that are defective or infected, such as tumor cells [22].

Preliminary studies conducted on chimeric antigen receptor natural killer cells (CAR NK cells) have shown that they perform as well as CAR T cells against ovarian tumors and substantially better than unaltered NK cells [23]. In addition, CAR NK cells have shown less toxicity compared to CAR T cells, which is a significant benefit for this therapy [23].

Additionally, scientists have observed that NK cells harvested from a donor, engineered with CARs, and then administered to patients do not appear to cause the fatal immune complication of graft-versus-host disease [23]. This phenomenon opens up the possibility to eliminate some of the expenses associated with therapies that rely on the extraction of immune cells from the patient's blood in favor of approaches that can harvest these cells from umbilical cord blood donations, for example [23]. Thus, one batch of human NK cells derived from induced pluripotent stem cells (iPSCs) could potentially be used to treat thousands of patients, without the need to create a new product for each patient [23].



Dendritic cell vaccinations

Dendritic cells (DCs) are leukocytes that are uniquely potent in their ability to present antigens to T cells, serving as a bridge between the innate and adaptive immune systems [19]. Because of this property, dendritic cells have been selected as a potential target for therapeutic cancer vaccines [24].

Dendritic cells were originally described in the 1970s by Steinman and Cohn, and they are often referred to as “nature’s adjuvant” because they are the most potent antigen-presenting cells (APCs) and are capable of activating both naive and memory immune responses [25,26]. Since DCs are able to independently mount a comprehensive immune response, they are of particular interest in the formation of vaccines.

In order to form these vaccines, immature DCs are generated from immune cells that are removed from the patient’s blood, using IL-4 and GM-CSF, loaded with tumor antigen *ex vivo*, and matured [27]. Once the dendritic cells are grown, the loaded DCs are then reinfused into the patient to induce a protective and therapeutic antitumor response by allowing the vaccine DCs to present to T cells in the body [28].

Pilot clinical trials for patients with non-Hodgkin’s lymphoma and melanoma have shown an induction of antitumor immune responses and subsequent tumor regression [28]. In addition, it has been shown that preconditioning the vaccine site with a potent recall antigen, such as tetanus/diphtheria toxoid, can significantly improve the efficacy of DC vaccines [29].

Thus, by utilizing the antigen-presenting mechanism of DCs, there are several opportunities to develop effective cancer immunotherapies. In fact, sipuleucel-T (PROVENGE™ immunotherapy), developed by Dendreon Corporation, was the first DC-based cancer vaccine approved by the U.S. Food and Drug Administration in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer [29].

Although this vaccine has been shown to be effective, as it improves median survival by 4.1 months, it is still an expensive mode of treatment due to its personalized nature. Additionally, none of the phase III clinical trials found a significant difference in the time to disease progression. These circumstances indicate the need for a significant improvement of this mode of cancer immunotherapy to become widespread [29]. There are indications that in order to be more efficacious, DC vaccination should be used in combination with other immunotherapies, such as immune checkpoint inhibitor therapy [30].

Natural killer (NK) cell immunotherapy

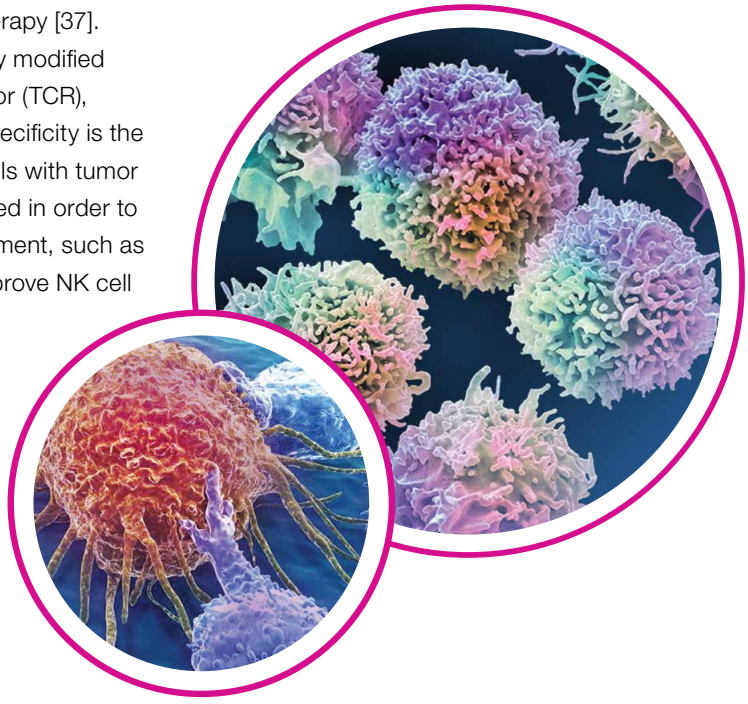
NK cells are a part of the innate immune system and are characterized by their lack of CD3/TCR molecules and by the surface expression of CD16 and CD56 [31]. As such, they have the distinct ability to mediate cytotoxicity in response to stimulation by a target cell. In addition, NK cells interact with other cells of the immune system in several ways. For example, by producing cytokines, such as tumor necrosis factor (TNF)-α and interferon (IFN)-γ, they mediate downstream adaptive immune responses by influencing the magnitude of T cell responses [31]. On the other hand, NK cells themselves are regulated by cytokines, such as IL-2, IL-12, IL-15, IL-18, and IL-21, and by interactions with other cells, such as dendritic cells and macrophages [32].

Initially, studies of adoptive NK cell therapy were oriented toward enhancing the antitumor activity of the NK cells. Doing so involved using $CD56^+$ beads to select for NK cells and infusing the autologous $CD56^+$ cells into patients, followed by the administration of cytokines IL-2 or IL-15 to encourage additional *in vivo* stimulation and support their expansion, but this method was found to be ineffective [33].

NK cell–based immunotherapy can potentially be used as a therapeutic option for solid tumors, which are more difficult to treat using other immunotherapies; however, challenges exist such as trafficking to sites of tumors and penetrating the tumor capsule in order to exert their function [34]. A strategy to mitigate these setbacks is to target regulatory T cells in order to target the immunosuppressive tumor microenvironments, which could potentially help to treat solid tumors [34].

NK cells can be isolated from a patient and treated with a number of cytokines, including IL-2, IL-12, IL-15, and IL-18 [35]. Once these NK cells have been expanded and activated *ex vivo*, they are infused into the patient. Studies in experimental models have shown that these cytokine-induced, memory-like (CIML) NK cells have significant activity against tumors once they are infused [35]. Expansion of NK cells isolated from PBMCs generally includes using feeder cells in order to provide the NK cells with a stimulatory signal; however, it was also shown that NK cells isolated from cord blood could be efficiently expanded by a feeder-free system [36].

Various strategies are being explored to increase NK cell effectivity and overcome problems associated with this mode of immunotherapy [37]. In order to improve NK cell specificity, NK cells are genetically modified to express a chimeric antigen receptor (CAR) or T cell receptor (TCR), specific for the tumor antigen. Another method to improve specificity is the use of NK cells with antibody engagers that cross-link NK cells with tumor cells. Diverse genetic modifications of NK cells are also studied in order to overcome suppression of NK cells in the tumor microenvironment, such as disruption of immune checkpoints, as well as methods to improve NK cell migration to tumors. As for other immunotherapy modalities, combination therapy might improve NK cell efficacy. Despite the great advances of NK cell immunotherapy, important issues should be addressed, such as NK cell potency and persistence, and dealing with potential safety risks.



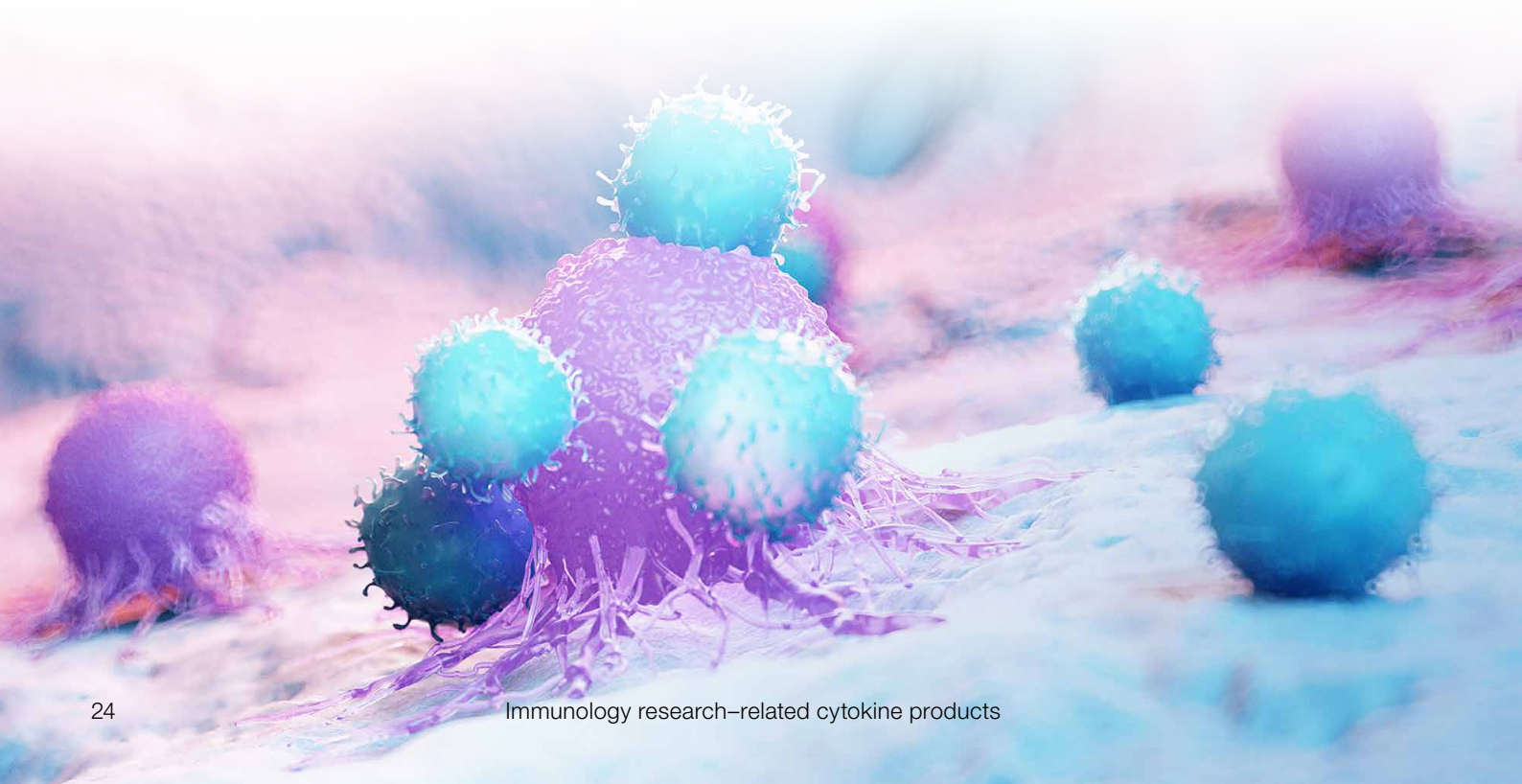
Cytokine-induced killer (CIK) cells

Cytokine-induced killer (CIK) cells are a heterogeneous population of effector $CD3^+$ $CD56^+$ NK cells that can be used in a similar fashion to other immunotherapy methods, because they can be easily expanded *in vitro* from PBMCs [38]. They are an ideal candidate for immunotherapy approaches since they exhibit MHC-unrestricted antitumor activity that is both safe and effective [38].

CIK cells were first developed in 1991 by growing PBMCs in the presence of IFN-γ, a CD3 monoclonal antibody, and IL-2 [39]. Subsequent studies showed that besides using IL-2, CIK cells could also be generated by using exogenous IL-7 or IL-12 [40]. Studies in which DCs were co-cultured with CIK cells showed that they interact with one another, which resulted in changes to the surface molecule expression of both cell types and led to an increase in IL-12 expression [41]. From a therapy perspective, combining DCs and CIK cells can be more effective than either one alone [41].

In order to generate CIK cells, PBMCs are first separated from the blood by centrifugation and then treated with IFN-γ to activate macrophages. This step promotes the IL-12– and CD58/LFA-3–mediated signaling, both of which enhance the cytotoxicity of CIK cells. After one day, the CD3 antibody and IL-2 are added to the cells. Every 2 days, fresh IL-2 is added to the medium; after three to four weeks of culture, the generated CIK cells can be infused back into the patient [38].

In the last few years, treatment prospects for CIK cells have improved, and a number of therapies have been developed in order to increase cytolytic activity and safety [34]. Numerous CIK clinical trials are ongoing or completed, and overall the results of these studies seem promising. CIKs can be combined with additional cytokines such as IL-6 and IL-7, DCs, immune checkpoint inhibitors such as CTLA-4 and PD-1, antibodies such as anti-CD20 or anti-CD30, and CARs, which can all improve the efficiency of CIK therapy [38]. However, there are still many avenues of CIK therapy, especially in conjunction with other technologies, that need to be explored.



Immune checkpoint inhibitors

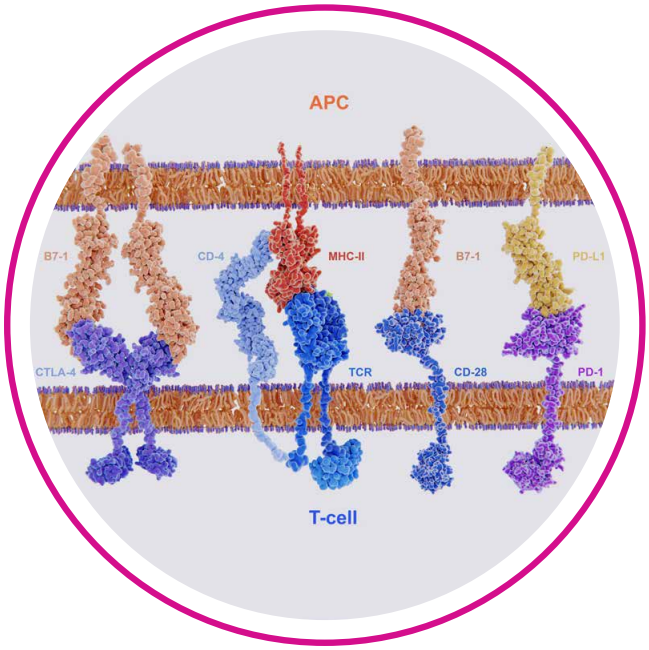
Inherently, the immune system has a system of inhibitory and stimulatory pathways that adjust their response to inflict the most damage on pathogenic targets, while preventing collateral tissue damage and autoimmunity. Immune checkpoints are often manipulated by tumors in order to escape the protective immune response [42]. Since many of these checkpoint molecules are mediated through ligand–receptor interactions, they can be easily targeted by antibodies or recombinant proteins. By inhibiting the inhibitory checkpoint, one can amplify antigen-specific T cell responses, which ultimately generates a more robust immune response [43].

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two of the many inhibitory receptors that have been used for clinical benefit. CTLA-4, which counteracts CD28 activity, was the first receptor of this nature to be targeted for clinical use [44]. CD28 and CTLA-4 share identical ligands CD80 and CD86, but have opposite effects; when CTLA-4 is present, it competes with CD28 to bind to these ligands, thus dampening T cell activation, which is detrimental to the immune response. Therefore, it seems reasonable that blocking CTLA-4 could result in an increased immune response [43].

Preliminary studies with CTLA-4 antibodies showed that mice with partially immunogenic tumors demonstrated significant antitumor responses when treated with CTLA-4, and eventually led to the production of clinical agents [45]. Out of several CTLA-4 antibodies tested in clinical trials, ipilimumab was the first therapy to demonstrate a survival benefit for patients, especially with regards to long-term survival with metastatic melanoma and was approved by the U.S. Food and Drug Administration in 2010 [43].

As an immune-checkpoint receptor, PD-1 is another promising target for immune checkpoint therapy. PD-1 limits the activity of T cells in peripheral tissues during inflammatory responses to infection [46]. This particular mechanism is exploited by many tumors that express the ligand PD-L1, in order to evade an effective immune response by binding the PD-1 that is expressed on TILs from many cancers.

Thus, therapies targeting checkpoint molecules are promising. More than 2,000 clinical trials were underway in 2018 for therapies that block this pathway or combine it with some of the other aforementioned therapies [47].



Immunotherapy against other diseases

Although the majority of articles discuss immunotherapy approaches against cancer, it is important to note that a wide variety of other diseases can be addressed with immunotherapy. Immunotherapy offers the potential to treat numerous conditions in addition to cancer, because many diseases invoke immune responses and can manifest in many ways, such as through inflammation. For example, HIV-1 peptide–loaded DCs have been shown to be safe and to induce immunogenicity in individuals with HIV-1 [48].

Regarding diseases caused by heightened inflammatory responses to otherwise harmless allergens, such as asthma and allergies, allergen immunotherapy has proven effective in controlling symptoms [49]. By repeatedly exposing an individual to the relevant allergen, one can suppress and sometimes resolve the inflammatory response to the offending allergens [50]. Through similar mechanisms to those discussed, the tau protein implicated in Alzheimer's disease can be targeted and eliminated through the use of antibodies and may therefore potentially improve cognition in those who exhibit signs of dementia [51]. All in all, there are numerous applications of immunotherapy that build on the same principles that have driven the development of immunotherapy with regard to cancer.

Conclusion

Immunotherapy harnesses the immune system to help fight a variety of diseases by suppression or activation of the immune response. The ubiquity of cancer has made the disease a target for innovations in this field, including the development of vaccines and unique therapies that harness the exceptional abilities of immune cells.

Not only can immunotherapy treat cancers, but it can also address several chronic diseases, autoimmune disorders, and allergies [23,52]. Such therapies generally provide long-term protection, have fewer side effects, and are more targeted than conventional therapies.

However, several challenges still exist for employing immunotherapy treatments. Major challenges include safety issues, developing personalized combination therapies, dose refinement, cost reduction, target specificity, treatment duration, and disease management. Further research and advances may overcome many of these challenges, and the future seems to be very bright for the field of immunotherapy [23,53].

Immunotherapy reagents

Cytokines

		Cat. No.		
Cytokine	**Species**	**RUO**	**Animal-free RUO**	**PeproGMP product**
EGF	Human		AF-100-15	GMP100-15
	Mouse	315-09	AF-315-09	
	Rat	400-25	AF-400-25	
FGF-basic (FGF-2)	Human	100-18B	AF-100-18B	GMP100-18B
	Mouse	450-33	AF-450-33	
	Rat	400-29		
Flt3 ligand	Human	300-19	AF-300-19	GMP300-19
	Mouse	250-31L		
G-CSF	Human	300-23	AF-300-23	
	Mouse	250-05	AF-250-05	
	Rat	400-37		
GM-CSF	Human	300-03	AF-300-03	
	Mouse	315-03	AF-315-03	
	Rat	400-23	AF-400-23	
IL-1β	Human	200-01B	AF-200-01B	
	Mouse	211-11B	AF-211-11B	
	Rat	400-01B		
IL-2	Human	200-02	AF-200-02	GMP200-02
	Mouse	212-12	AF-212-12	
	Rat	400-02	AF-400-02	
IL-3 (IL-3β for rat)	Human	200-03	AF-200-03	GMP200-03
	Mouse	213-13	AF-213-13	
	Rat	400-03		
IL-4	Human	200-04	AF-200-04	
	Mouse	214-14	AF-214-14	
	Rat	400-04		
IL-6	Human	200-06	AF-200-06	GMP200-06
	Mouse	216-16	AF-216-16	
	Rat	400-06		
IL-7	Human	200-07	AF-200-07	GMP200-07
	Mouse	217-17		
	Rat	400-07		
IL-12	Human	200-12		
	Human	200-12H		
	Mouse	210-12		
IL-13	Human	200-13	AF-200-13	
	Mouse	210-13		
	Rat	400-16		

Cytokine	Species	Cat. No.		
		RUO	Animal-free RUO	PeproGMP product
IL-15	Human	200-15	AF-200-15	GMP200-15
	Mouse	210-15		
	Rat	400-24		
IL-21	Human	200-21	AF-200-21	GMP200-21
	Mouse	210-21	AF-210-21	
	Rat	400-41		
IFN-γ	Human	300-02	AF-300-02	
	Mouse	315-05	AF-315-05	
	Rat	400-20		
SCF	Human	300-07	AF-300-07	GMP300-07
	Mouse	250-03	AF-250-03	
	Rat	400-22	AF-400-22	
TGF-β1	Human	100-21		
	Human	100-21C	AF-100-21C	
TNF-α	Human	300-01A	AF-300-01A	
	Mouse	315-01A	AF-315-01A	
	Rat	400-14		
TPO	Human	300-18	AF-300-18	GMP300-18
	Mouse	315-14	AF-315-14	
	Rat	400-34	AF-400-34	

Immune costimulatory proteins

Ligand	Receptor
CD80 (B7-1)	CD28
CD86 (B7-2)	CD28
OX40L (CD252)	OX40 (CD134)
4-1BBL	4-1BB (CD137)
CD70	CD27
ICOSL (B7-H2, CD275)	ICOS (CD278)
GITRL (AITRL)	GITR (CD357)
CD153 (CD30L)	CD30
CD154	CD40
B7-H7	CD28H
HVEML (LIGHT, CD258)	HVEM (CD270)

Immune checkpoint proteins

Ligand	Receptor
PD-L1 (B7-H1, CD274)	PD1 (CD279)
PD-L2 (B7-DC, CD273)	PD1 (CD279)
CD80 (B7-1)	CTLA4 (CD152)
CD86 (B7-2)	CTLA4 (CD152)
GAL9	TIM3 (CD366)
BTLA (CD272)	HVEM (CD270)
CD160	HVEM (CD270)
MHC-I	KIR
MHC-II	LAG3 (CD223)

ELISA kits

Cytokine	Species	Cat. No.	
		Standard ABTS EDK	Standard TMB EDK
IL-1α	Human	900-K11	900-T11
	Murine	900-K82	
	Rat	900-K204	
IL-1β	Human	900-K95	900-T95
	Murine	900-K47	
	Rat	900-K91	
IL-2	Human	900-K12	900-T12
	Murine	900-K108	900-T108
	Rat	900-K205	
IL-4	Human	900-K14	900-T14
	Murine	900-K49	900-T49
IL-6	Human	900-K16	900-T16
	Murine	900-K50	900-T50
	Rat	900-K86	
IL-10	Human	900-K21	
	Murine	900-K53	900-T53

Cytokine	Species	Cat. No.	
		Standard ABTS EDK	Standard TMB EDK
IL-17A	Human	900-K84	
	Murine	900-K392	
GM-CSF	Human	900-K30	
	Murine	900-K55	
IFN-γ	Human	900-K27	900-T27
	Murine	900-K98	900-T98
	Rat	900-K109	
MCP-1 (CCL2)	Human	900-K31	900-T31
	Murine	900-K126	
	Rat	900-K59	
MIP-1α (CCL3)	Human	900-K35	
	Murine	900-K125	
	Rat	900-K75	
TNF-α	Human	900-K25	900-T25
	Murine	900-K54	900-T54
	Rat	900-K73	900-T73

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