In this article...  
- How immunotherapy functions in the body and a history of its development  
- Using immunotherapies including monoclonal antibodies to treat cancers  
- The role of immunotherapy in treating autoimmune disease and allergy

The lymphatic system 6: the history and function of immunotherapies

Key points

Immunotherapies stimulate or suppress the immune system to prevent or manage disease  

Immunotherapy is used in cancer treatment to detect and attack malignant cells  

Such therapies include monoclonal antibodies, tumour-infiltrating lymphocyte therapy, chimeric antigen receptor T-cell therapy, and oncolytic virus therapy  

Other immunotherapies reduce the body’s aberrant responses in patients with autoimmune disease  

Immunotherapies can also treat allergies by gradually desensitising the patient to the allergen

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Abstract  This article, the final in a six-part series about the lymphatic system, discusses the history and development of immunotherapy. It highlights a number of immunotherapies that are available for different health conditions – including cancer, autoimmune disease and allergy – and explores how they function and interact with the immune system.


This is the final article in a series of six that has examined the structure and function of the lymphatic system, including its role in tissue drainage, its overlap with the immune system, and the nature of both non-specific and specific immune responses. Part 5 of this series focused on antibody-mediated immunity and the nature and role of vaccines, and this final article examines how advances in immunology and molecular biology have allowed the development of advanced immunotherapies that harness elements of the immune system to target and treat a range of diseases (Knight and Nigam, 2021).

What is immunotherapy?  

Immunotherapy can be defined as any therapy that can either stimulate or suppress the immune system to help prevent or manage disease (Thappa and Minu, 2016). Immunotherapies that upregulate the immune system can be very useful in enhancing the system’s ability to recognise and target pathogens or malignant cells. Alternatively, immunotherapies that down-regulate the immune system can help treat allergies or manage chronic inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis.

As we have discussed throughout this series, the immune system is incredibly complex, both in terms of the cells and tissues involved and in the diversity of the chemical modulators of immunity, which include antibodies, complement components and cytokines. This complexity provides multiple targets for potential immunotherapies, many of which have been exploited over the years. The most widespread immunotherapy is vaccination, which, as described in the previous article in this series, primes the immune system by stimulating the production of specific antibodies and memory cells. These then provide protection against the disease for which the vaccine was designed.

Early history of immunotherapy  

Shortly after Edward Jenner was conducting research in the late 18th century that led to the development of the smallpox vaccine (see part 5), early research was being carried out into upregulating the immune system to treat cancer. Throughout history there have been numerous reports of tumour regression...
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following fever or infection. In 1868, the German physician Wilhelm Busch noted tumour shrinkage in a patient he deliberately infected with the bacterium *Streptococcus pyogenes*. This work was developed by the American surgeon William Coley (today known as the father of immunotherapy), who used injected heat-inactivated *Streptococcus pyogenes* to treat many patients with inoperable cancers, including sarcomas, lymphomas and testicular carcinoma. Using this technique, over 1,000 patients were either cured or showed significant tumour regression (Oiseth and Aziz, 2017). Coley wrongly believed toxins associated with the infectious agents were responsible for the observed tumour destruction. Indeed these supposed active agents were universally referred to as “Coley’s toxins” at this time. However, today it is recognised the anti-tumour effects were due to the injected bacteria eliciting an immune response against the tumour (Bucktrout et al, 2018). Despite Coley’s apparent success in using infection to enhance tumour recognition and destruction, this approach was largely abandoned with the emergence of new techniques in treating cancer such as radiotherapy and chemotherapy.

“Anything that can compromise immune function can increase the risk of cancer, such as ageing, stress and certain immunosuppressive medications”

Coley’s approach was revisited in 1959, when it was noted that Bacillus Calmette-Guérin (BCG), which is the same modified bacterium used in the creation of the tuberculosis vaccine, was able to exert anti-tumour effects in mice (Old et al, 1959). BCG was subsequently demonstrated to be effective in humans in the treatment of bladder cancer (Morales et al, 1976) and it is now known that it can upregulate immunity, predominantly by enhancing non-specific immune responses in a phenomenon called trained immunity (Curtis and Sparrow, 2020).

These early studies provided initial evidence that immunotherapy could treat malignancy by harnessing the power of the immune system. Today, with advancing knowledge of the multiple elements involved in both non-specific and specific immune responses, several different forms of immunotherapy have been developed to treat cancer and subsequently a variety of other diseases.

Detection of malignant cells

Cell division (mitosis) is essential to facilitate growth and repair in the body. However, the DNA replication essential to mitosis is susceptible to errors that can lead to mutations and potentially malignancy. Cancers commonly arise in tissues where cell division is rapid, including epithelial tissue, bone marrow and glandular tissue. It has been suggested that malignant cells arise daily and a healthy, finely tuned immune system allows rapid detection and destruction before tumours can arise (Sterle et al, 2014). This may help explain why anything that can compromise immune function can increase the risk of cancer, such as ageing, stress and certain immunosuppressive medications.

The normal immune response to malignant cells is multifaceted and still poorly understood. It centres around continual immunosurveillance by a variety of different cell types that detects changes to the surface proteins (antigens) expressed on cells that have become malignant. These surface antigens that arise in cancer are referred to as tumour-associated antigens (TAAs) and can be used by the immune system to target malignant cells for destruction.

Two major groups of specialised lymphocytes are primarily involved in detecting malignant cells. T-cytotoxic cells (also known as CD8+ cells) have a receptor called the T-cell receptor (TCR), which can recognise unique proteins called major histocompatibility complex class 1 (MHC class 1) proteins. These ‘self-proteins’ are present on most human cells (with the major exception of erythrocytes), where they act to identify cells as belonging in that individual’s body. The TCR usually interacts with and recognises MHC class 1 proteins when presented together with other surface antigens expressed by the cell. If these surface antigens have undergone structural changes and are recognised as TAAs indicative of a malignant cell, the T-cytotoxic cell can be activated.

Activated T-cytotoxic cells produce a variety of lytic enzymes and a glycoprotein called perforin, which can tear holes in the cell membranes of malignant cells quickly, resulting in lysis (bursting) and cellular death (Martinez-Lostao et al, 2015). T-cytotoxic cells are so sensitive that they can recognise a single amino acid change on a surface antigen that could be indicative of a malignant change within the cell (Rosenberg and Huang, 2018).

A second group of lymphocytes, called natural killer (NK) cells, work in tandem with the T-cytotoxic cells. Like their counterparts these cells circulate in a dormant state, but when they detect TAAs on malignant cells they undergo activation and release granules containing enzymes that initiate lysis and destruction of the target cells (Eissmann, 2020). Unlike T-cytotoxic cells, NK cells do not have a dominant receptor that is comparable to the TCR. However, they are adept in detecting changes in MHC class 1 proteins, which are often either absent or expressed at lower concentrations in malignant cells. NK cells can also release a variety of chemicals, including tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), which further enhance the killing of malignant cells either directly or by recruiting other cell types to amplify the immune response (Wang et al, 2012).

Although there have been major advances in the treatment of cancer recently – including more effective and targeted forms of surgery, radiotherapy and chemotherapy – each year there are still around 17 million new cases of cancer and approximately 9.5 million cancer-related deaths worldwide (American Cancer Society, 2020). Recently, vaccines have been developed against viruses such as the human papilloma virus (HPV), which are expected to significantly reduce the number of women diagnosed with cervical cancer and the number of people with other HPV-induced malignancies (for example certain forms of prostate and throat cancer). Over the last 10 years, as understanding of cancer biology and immunity has advanced, research into the use of immunotherapy to treat malignant disease has significantly increased, with several novel forms of treatment being developed and introduced into clinical practice.

Monoclonal antibodies

As discussed throughout this series, antibodies are immunoglobulins that can bind to antigens with a high degree of specificity. This can be visualised as a key (the antigen) fitting into a lock (the antigen-binding sites of the antibody molecule). Antibodies typically lock onto foreign material, such as bacteria and viruses, effectively marking them out for destruction in a process called opsonisation. This is discussed in more detail in the third and fifth articles in this series.

Because antibody molecules are so specific, they provide useful tools for marking and targeting cells and individual
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This drug consists of a monoclonal antibody conjugated to the radioisotope iodine ¹³¹. Once administered, the drug circulates and binds specifically to malignant cells. It delivers the iodine ¹³¹, which, due to its radioactivity, begins to kill the target cells (Coulson et al, 2014).

Immune checkpoint inhibitors
Throughout this series we have highlighted the complexity of the immune system and the overlap between the non-specific immune responses that protect against a diverse variety of potential threats and specific immune responses that target single antigens.

To ensure immune pathways are well coordinated and proportionate and do not unduly damage healthy tissue, there are checkpoints that monitor and decelerate immune responses and to eventually bring them to an end when the threat has been dealt with. One of the mechanisms by which malignant cells evade detection is by acting on immune checkpoints to arrest tumour-specific responses. Ipilimumab is a type of monoclonal antibody known as an immune checkpoint inhibitor and binds to a receptor called CTLA-4. This receptor is recognised as an important downregulatory immune checkpoint and is important for stopping autoimmune reactions that could lead to damage to healthy tissues. However, when the CTLA-4 receptor is activated in the locality of a tumour, it results in inhibition of immune responses.

Molecules. Indeed, early on in their use, antibodies were often referred to as ‘magic bullets’. Today scientists can produce monoclonal antibodies that bind to TAAs that are specific to particular types of cancer cells.

Monoclonal antibodies are produced by injecting the desired target antigen (for example, a TAA protein on the surface of a breast cancer cell) into an experimental animal, such as a mouse or rabbit. Antibody-forming B-cells are then removed from the animal and fused with malignant myeloma cells to form a hybridoma cell line. This cell line is immortal and will continually divide and generate large amounts of specific antibody that can bind to and recognise the original antigen, which is expressed on the target cancer cells (Fig 1). These antibody molecules are described as monoclonal because they are produced from this single hybridoma cell line.

In around 20% of breast cancers, a protein called human epidermal growth factor receptor 2 (HER2) is expressed in large quantities on the surface of the malignant cells. In such patients, human epidermal growth factors bind to this receptor and stimulate cell division, promoting tumour growth. Trastuzumab, is probably the best-known monoclonal antibody cancer immunotherapy drug currently in use. This drug has been designed to bind to and physically block the HER2 receptor, thereby preventing human epidermal growth factors from binding and eliciting tumour growth (Fig 2). Additionally, because antibody molecules mark out material via the process opsonisation, the malignant cells of the tumour mass can now be targeted and effectively destroyed by the immune system (NHS, 2019).

In addition to trastuzumab, several other monoclonal antibodies have been developed to target a variety of cancers, including Hodgkin and non-Hodgkin lymphomas, leukaemias, colorectal cancer, squamous cell carcinoma, lung carcinoma, renal carcinoma and malignant melanoma. Because many forms of cancer metastasise, in addition to targeting primary tumours, monoclonal antibodies have also been developed to target general metastatic spread. For example, the drug denosumab targets bony metastases, which are frequently seen in common malignancies, such as breast and prostate cancer (Kimiz-Gebologlu et al, 2018).

In line with the original vision of monoclonal antibodies acting as ‘magic bullets’, they can be modified by being conjugated to therapeutic agents, such as radioactive isotopes or chemotherapeutic agents. Conjugated antibodies provide an effective way of delivering therapeutic agents directly and specifically to the target cells and, therefore, usually have fewer side-effects than standard radiotherapy or chemotherapy. A good example of a conjugated monoclonal antibody is the drug tositumomab, which is used in the treatment of relapsed non-Hodgkin lymphoma.
against malignant cells. By binding to CTLA-4, ipilimumab acts as a physical block, preventing activation of the receptor and the subsequent downregulation of tumour-specific immune responses. The end result is enhanced tumour recognition and killing. Ipilimumab has been shown to be effective in treating advanced metastatic malignant melanoma, renal carcinoma and some forms of prostate cancer (Tarhini et al, 2010).

**Other immunotherapies to treat cancer**

**Tumour-infiltrating lymphocyte therapy**

Malignant tumours are usually detected and frequently infiltrated by T-cytotoxic cells and NK cells. Tumour-infiltrating lymphocyte (TIL) therapy involves surgically removing an existing tumour mass, harvesting these infiltrating cells and culturing them in vitro (Fig 3). The addition of cytokines, such as interleukin 2, to the culture medium allows lymphocytes that have recognised the tumour to be cultured in high numbers before eventually being reintroduced into the patient. This amplified population of specific lymphocytes circulates through the body before infiltrating any resident tumour masses and killing the malignant cells. TIL therapy has been used successfully to treat multiple forms of aggressive cancers, including malignant melanoma, non-small cell lung cancer and gastric, colorectal, pancreatic and hepatic carcinoma (Hendry et al, 2017).

**Chimeric antigen receptor T-cell therapy**

TIL therapy relies on the patient’s immune system having detected the malignant cells and started the process of tumour infiltration. However, not everyone with cancer has an immune system that has recognised the presence of malignant cells. This could be for a variety of reasons:

- An ageing immune system;
- Long-term use of immunosuppressive drugs;
Oncolytic virus therapy

Certain viruses have long been known to have the ability to trigger malignancy. These oncoviruses include:
- Certain strains of HPV, which are known to elicit premalignant changes that can result in cervical cancer;
- Hepatitis B and C, which can both elicit primary liver cancer.

However, there are also multiple reports of viral infections being associated with tumour shrinkage and cancer regression. A report published in 1904 described a woman with myeloid leukaemia who went into remission following infection with the influenza virus (Dock, 1904). It appears that viruses can inhibit cancers, either by infecting the malignant cells and directly causing their death or by upregulating the immune system and increasing the chances of malignant cells being detected.

Viruses that lead to the death of malignant cells are referred to as oncoviruses and provide a valuable new tool for treating cancer (Zheng et al, 2019).

Multiple viruses are currently being explored for oncolytic activity and potential therapeutic use, including measles, reovirus, coxsackie virus, parvovirus and adenovirus. However, the most attention has been focused on modified strains of the herpes virus that have been attenuated to prevent healthy tissue damage and genetically modified to enhance their ability to recognise and target malignant cells (Raja et al, 2018).

The first oncolytic virus that has been licensed for use is a modified herpes simplex virus (the same virus responsible for cold sores) called talimogene laherparepvec, which is currently recommended for the treatment of late-stage malignant melanoma. It is injected into the tumour site, where it exerts a dual effect. First, it directly infects malignant cells, killing them and initiating lysis; second it upregulates immune responses both local to the tumour and systemically, which enhances immune recognition of malignant cells and subsequent immune-mediated killing (Conry et al, 2018).

Use of immunotherapies outside cancer treatment

Although most current research is focused on developing immunotherapies for treating different cancer types, the ability to modulate immune responses is valuable in the treatment of a multitude of non-malignant diseases.

Immunotherapies to treat autoimmune disease

Autoimmune diseases usually involve an upregulated immune system mistakenly targeting the body’s own cells and tissues. Because most of the major autoimmune diseases involve varying degrees of inflammation, many are treated initially with anti-inflammatory drugs. For example, the symptoms of rheumatoid arthritis are often initially managed by combinations of non-steroidal anti-inflammatory drugs, corticosteroids and a variety of disease-modifying anti-rheumatic drugs.

Similarly, the management of other autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis and autoimmune psoriasis, is primarily centred around anti-inflammatory medications. Although many patients can control their symptoms well by following such regimes, because these medications promote general immunosuppression, they can significantly increase the risk of infection and cause gastrointestinal symptoms, skin thinning, hepatotoxicity and fatigue (Hirsch and Ponda, 2014).

Because autoimmune diseases are, by definition, associated with abnormal immune responses, immunotherapies that can reduce these aberrant responses have been developed. A key immunotherapy in the treatment of rheumatoid arthritis is the monoclonal antibody infliximab. This binds to the inflammatory mediator called tumour necrosis factor alpha (TNF-α), thereby preventing it from binding to its cellular receptors (Fig 4).

TNF-α is responsible for helping perpetuate pain and inflammation in rheumatoid arthritis patients’ joints and infliximab significantly reduces these symptoms (Farrugia and Baron, 2016). Because infliximab blocks the activity of a common inflammatory mediator, it is also useful in treating a variety of other chronic inflammatory conditions, including...
Ulcerative colitis, Crohn’s disease, psoriatic arthritis and ankylosing spondylitis.

**Immunotherapies to treat allergy**
The fourth article in this series explored the nature of allergy, highlighting that some individuals are atopic and at increased risk of developing allergic responses against harmless environmental materials. In a small proportion of these people the allergic responses can become severe and potentially develop into life-threatening anaphylaxis.

Most immunotherapies that treat allergy are based on the principle of gradually desensitising the patient to the allergen that triggers the response. This is achieved by progressively exposing them to greater and greater concentrations of the allergen. This approach can potentially desensitise patients to any allergen; in specialised allergy clinics, patients are routinely desensitised to a diverse variety of food allergens, pollens and insect or animal venoms.

There are two major mechanisms of introducing the allergen (such as a specific pollen or pollen mixture to treat hayfever) into the patient:

- **Subcutaneous immunotherapy (SCIT)** involves injecting increasing concentrations of the allergen into the subcutaneous fatty layer (hypodermis) under the skin;
- **Sublingual immunotherapy (SLIT)** involves placing increasing concentrations of the allergen underneath the tongue.

Both methods have advantages; SCIT is generally regarded as more effective than SLIT, while SLIT has the benefit of being non-invasive. Gradual exposure to increasing doses of either subcutaneous or sublingual allergens promotes desensitisation by inducing progressive immune tolerance of the allergen within the body. As a result, when exposed to the allergen, fewer inflammatory mediators are released and the allergic response is less pronounced. The benefits of three years of either SCIT or SLIT immunotherapy appear to be long-lasting, with reductions usually associated with pollen and house dust mites—a much greater precautions must be taken when attempting to desensitise patients to allergens that can trigger anaphylaxis, such as animal venoms and peanut or shellfish proteins. A new immunotherapy has recently been developed that is based on peanut proteins. This drug has been named AR101 and its use in treating peanut allergies in children is currently being explored with promising initial results (Vickery et al, 2018).

**Conclusion**
Throughout this series of six articles we have highlighted the importance of the lymphatic system to human health and focused heavily on its overlap with the immune system. For over one and a half centuries the powers of the immune system have been harnessed through the use of vaccines, which have saved the lives of millions of people from infectious disease. As our technology and understanding of immunity have improved, the use of various immunotherapies to bolster or modify immune responses has gradually been introduced. Although the use of immunotherapy is still in its infancy, it clearly has the potential to provide targeted therapies that will revolutionise the treatment of a multitude of diseases. **NT**

**Quick Fact**
17 million New cases of cancer each year worldwide

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