The field of immunotherapy has progressed rapidly, expanding from the use of monoclonal antibodies and interferons, to more innovative approaches now being tested in laboratories and in the clinic. Several challenges still exist in the field, including adverse effects of therapy and the high cost of treatment. As a result, new approaches to immunotherapy are constantly being explored in order to overcome these limitations. While the field is grounded mainly in the domain of biologics, more recently alternative approaches using synthetic molecules as well as natural products have been under investigation. A more unconventional approach, involving the introduction of a parasitic infection in the body is also currently in clinical trials. Moreover, the avenues for the application of immunotherapy have also expanded. While originally aimed at the treatment of cancers, their potential applications have expanded to allergies, neurodegenerative diseases, infections, osteoporosis, and hyperlipidemia. The scope of immunotherapies moving forward will be discussed in this chapter.
11.1 Introduction

Over the past decade, immunotherapies have become increasingly popular in the treatment of several diseases. It has most significantly impacted the treatment received by cancer patients, providing an alternative to conventional chemotherapy, where cytotoxic drugs produce severe side effects. Although we have come a long way in making a range of immunotherapies available to patients, this class of therapies still poses a range of challenges that need to be tackled. With several forms of immunotherapies currently in clinical trials, and even more in the early stages of development, researchers in the field are constantly striving to overcome the current limitations and make better therapies available to patients. This chapter aims to cover some of the new approaches and avenues for immunotherapy.

11.2 Approaches to Immunotherapy

11.2.1 Biologics in Immunotherapy

Biopharmaceuticals form a large proportion of immunotherapeutic options currently available to patients and are therefore the area where most work is being done to overcome existing limitations. Over recent years, significant work has been done on checkpoint inhibitors, oncolytic viruses, therapeutic vaccines, and bispecific antibodies for immunotherapy (Riley et al. 2019). Much of this progress has been a result of the identification of specific biomarkers and antigens found on cancer cells that can be targeted in order to achieve selective responses.

Prophylactic vaccines for infectious diseases were one of the earliest forms of immunotherapy. An area that is rapidly progressing in current times is therapeutic vaccines for cancer. They possess advantage over other forms of immunotherapy due to their ability to generate immunological memory (Lopes et al. 2019). These vaccines could consist of cells, peptides, or genetic material, aimed at eliciting a targeted immune response for the tumor (Lopes et al. 2019). Vaccines containing nucleic acids, for example, aim to deliver DNA or mRNA to antigen presenting cells, such that the desired antigen can be expressed and presented to T cells, in order to trigger an immune response (Riley et al. 2019). DNA vaccines bear advantage over mRNA vaccines in that they are better able to integrate into the cells’ genome, but are limited by the need for intra-nuclear drug delivery. mRNA vaccines, on the other hand, only require intracellular presence which is slightly easier to achieve (Riley et al. 2019). However, for these approaches to see clinical success, the development of specialized delivery systems would be a key tool. So far, no DNA vaccines have
been approved for use by the FDA (Lopes et al. 2019). In situ vaccinations have also drawn a lot of attention. These allow intra-tumor delivery of the therapeutic agents. They offer the advantage of targeted delivery, without the need to identify specific antigens. This allows for optimized delivery, with minimal systemic side effects (Sheen and Fiering 2019).

Another technology exploiting the knowledge of tumor antigens is immune effector cell targeting (Guo et al. 2013). While this can be achieved using CAR-T cells, a specific type of bispecific antibody, bispecific T cell engager (BiTE) is thought to present significant advantages. Originally developed by Amgen, these agents are much smaller than traditional antibodies, and act by forming a bridge between cytotoxic T cells and tumor cells (Guo et al. 2013). This binding activates the T cells to secrete cytotoxic chemicals, activate other components of the immune system, and bring about cell lysis (Huehls et al. 2015). Apart from presenting a high potency and efficacy, they differ from other bispecific antibodies in their ability to produce a response even in the absence of T cell co-stimulation (Guo et al. 2013). In 2018, Blinatumomab, by Amgen, was the first BiTE to gain FDA approval for use in the treatment of lymphoblastic leukemia (Jen et al. 2019). Several others are currently in clinical trials.

### 11.2.2 Small Molecules in Immunotherapy

Immunotherapies rely on the use of biologics to boost immune responses. However more recently, efforts are being directed towards the design and development of small molecules that can target pathways involved in immune responses, with several candidates currently in preclinical and clinical studies.

Small molecules present several advantages over biologics, and moving forward, the field would definitely benefit from further exploring the potential role of small molecules in immunotherapies. Their advantages include:

- Greater oral bioavailability (Kerr and Chisholm 2019)
- Better tumor penetration (Kerr and Chisholm 2019)
- Greater control over bioavailability, allowing for more control over potential adverse effects (Kerr and Chisholm 2019)
- Ability to target pathways involved in immune responses that biologics are not able to alter (Chen et al. 2019)
- Potential to access a wider range of target, including nuclear receptors, as a result of their membrane permeability (Chen et al. 2019)
- Better therapeutic index (Chen et al. 2019)
- Lower cost of production (Kerr and Chisholm 2019)

The most popular pathways that have been investigated in this area are the STING pathway, involved in activation of inflammatory genes, PD-1/PD-L1, which interferes with T cell response in tumor environments, and indoleamine 2,3-dioxygenase 1(IDO1), which is also involved in allowing cancer cells to evade
immune responses (Chen et al. 2019). Several molecules interfering with these pathways are in various stages of preclinical and clinical development. Epacadostat, an IDO1 inhibitor, that rapidly progressed through clinical trials, failed in phase 3 (Chen et al. 2019). ADU-S100 and MK-1454 are agonists of the STING pathway, and are currently in Phase I clinical trials. The main drawback of these, like most other forms of immunotherapy, is that they can potentially trigger unsolicited immune responses in patients (Kerr and Chisholm 2019). PD-L1 antagonists are currently in the earlier stages of development. BMS-1001 and BMS-1116 are still in the preclinical stages (Kerr and Chisholm 2019).

Another approach to the use of small molecules in immunotherapy is the application of cytokines. These are endogenous molecules that are able to transmit pro-inflammatory and anti-inflammatory signals to cells (Berraondo et al. 2019). These could potentially be used alone, as well as in conjunction with other forms of immunotherapy, in order to enhance the activity seen. The main challenges that must be overcome are the systemic inflammatory effects produced and the difficulties in localizing them to the site of the tumor (Berraondo et al. 2019).

These small molecule-based approaches have the potential to make affordable and convenient forms of immunotherapy easily available to patients. These pharmaceuticals could readily be developed into suitable dosage forms that can conveniently be administered to patients.

11.2.3 Parasite Immunotherapy

A slightly unconventional approach that has been in research in recent years is based on the hypothesis that a negative correlation exists between parasitic infections and cancer. This form of cancer immunotherapy would involve introducing a parasitic infection in a patient, in order to evoke an immune response, which is predicted to have an anti-angiogenic effect (Darani and Yousefi 2012). This theory is based on the finding that certain mucins, uniquely expressed by cancer cells, are also found in parasitic antigens. Therefore, parasites that possess mucin-type O-glycans on their surface are thought to be able to induce a joint immune response towards cancer cells expressing similar antigens (Darani and Yousefi 2012). The Tk antigen, for example, which is found in human colorectal cancer, is also expressed by Taenia crassiceps, T. hydatigena, and Mesocestoides vogae. Both adaptive and innate immune responses are thought to be triggered, which can act against tumor cells (Berraondo et al. 2019).

There has been significant preclinical data supporting this. When a solid lymphoma was introduced into Trypanosoma cruzi-infected mice, growth of the tumor was found to be inhibited (Chen et al. 2019). Multiple studies have also been conducted using Toxoplasma-infected mice. When compared with mice infected with the formalin-fixed pathogen, a reduction in tumor size was observed. In another study, Toxoplasma was also found to delay tumor formation (Darani and Yousefi 2012).
The effect of infection of Lewis lung cancer mice with *Plasmodium yodii* was also investigated (Chen et al. 2011). A strong adaptive as well as innate immune response was observed. An increase in the levels of interferon-γ and tumor necrosis factor-α was recorded. Proliferation of natural killer cells as well as tumor-specific T cells was also observed. The immune response generated in this manner is thought to be longer lasting than by other means. The study showed an increase in the proportion of apoptotic cancer cells, and a reduction in proliferative cells in the mice. Two antigens are thought to be responsible for initiating this immune response: the glycosylphospholipid inositol on the cell surface, and the hemozoin, which is a by-product of the parasite’s metabolism (Chen et al. 2011). This concept has now gained permission for translation to human trials. This will involve infection of cancer patients with *Plasmodium vivax*, with blood levels of the parasite being maintained at a low level using artesunate for several weeks. The treatment will be terminated by administration of a course of chloroquine or artesiminin (U.S. National Library of Medicine 2020a). However, the studies in animal models did present some challenges, which mean that the results may not be directly reproducible in humans. In mice, *Plasmodium* infection does not cause fever, and the course of infection is much shorter than in humans (Darani and Yousefi 2012). Therefore, the outcomes of this clinical study can be expected to produce interesting outcomes.

The biggest challenge with this type of treatment is the possibility of it progressing to a high intensity infection, which could have damaging effects on the patient. While a low intensity infection can have beneficial effects, its progression could be fatal. The choice of parasite is also crucial. Not only should the pathogen possess glycosylated antigens, it must also be sufficiently safe to use in humans (Darani and Yousefi 2012). So while this unique approach to immunotherapy has recently progressed to clinical testing, it is one that should be considered with great caution.

### 11.2.4 Natural Products

Compounds isolated from natural product have also been shown to exhibit immunostimulatory effects. While not currently in use, if developed to enhance their potency and pharmacokinetics, they could potentially be used in conjunction with cytotoxic chemotherapeutic agents in order to reverse their immunosuppressive effects. Tylophora alkaloids, for example, showed immune regulation in conjunction with cytotoxic agents (Bach and Lee 2019). Interestingly, however, similar to parasite immunotherapy, a large number of natural products found to produce an anti-tumor immune-stimulatory response were polysaccharides in nature. A soluble polysaccharide fraction extracted from red wine was found to reduce tumor weight and volume in an animal model, by boosting the production of lymphocytes and tumor necrosis factor-α (TNF-α) (Stipp et al. 2017). Similarly, when a polysaccharide fraction from *Artemisia argyi* was tested in a Sarcoma-180 tumor-bearing mouse model, the immune response suppressed by the tumor was found to be
restored. Levels of T-lymphocytes, TNF-α, and interleukins (IL) 2, 6, and 12 were found to be increased (Bao et al. 2013). However, while an extract from *Grifola frondosa* exhibited immune-stimulatory activity in preclinical studies, it gave mixed results when taken to Phase I/II clinical trials. Its administration was associated with the production of both immune-stimulatory (IL2) and suppressive (IL10) cytokines (Deng et al. 2009). Therefore, while several animal studies have shown promising results, translation of these therapies to humans may prove to be more challenging.

### 11.3 Avenues for Immunotherapy

Up till quite recently, the applications of immunotherapy have majorly been grounded in the treatment of cancers, and to an extent, for autoimmune diseases. As the treatment option becomes better established, and its benefits become more evident, scientists have begun exploring its applications to other disease areas.

#### 11.3.1 Neurodegenerative Diseases

The most prominent area where the applications of immunotherapy are being explored is in the treatment of neurological disorders. There has been significant research done on the applications of immunotherapy for treatment of Alzheimer’s disease, for which there is currently no cure available. It is thought that humoral and cellular immunity could be involved in clearing amyloid-β (Weiner and Frenkel 2006), which is a component of the plaques responsible for disease progression. Several approaches have been investigated to achieve this, including the activation of T-helper cells, and stimulation of microglial cells, to initiate an innate immune response (Weiner and Frenkel 2006). Active immunization approaches have also been investigated, testing the use of synthetic amyloid-β or its fragments conjugated to a carrier protein, as a vaccine (Deng et al. 2009). While intact amyloid-β42 progressed to phase II clinical trials, it was found to cause meningeal encephalitis in a number of patients (Schenk 2002). Alternatively, passive immunity approaches are also possible. The anti-amyloid-β antibody, bapineuzumab, was the first in the class to progress to phase III trials. However, its efficacy is uncertain, and was found to cause vasogenic edema (Kerchner and Boxer 2010). An alternative hypothesis for disease progression in Alzheimer’s involves the role of tau protein. Many believe that tau lesions are a better indicator of disease than amyloid plaque deposition (Pedersen and Sigurdsson 2015). Based on this hypothesis, anti-tau monoclonal antibodies and vaccines containing tau protein or its fragments have been investigated (Pedersen and Sigurdsson 2015).

Following the progression of Alzheimer’s immunotherapies to clinical trials, the approach has also been investigated in Parkinson’s disease. Patients of Parkinson’s disease as well as Multiple System Atrophy (MSA) are known to show neuronal accumulation of α-synuclein, resulting in nerve damage (Brudek et al. 2017). A study showed that these patients exhibit lower plasma levels of anti-α-synuclein
auto-antibodies than healthy subjects (Brudek et al. 2017). On this basis, immuno-
therapy approaches such as vaccination with α-synuclein fragments, or the adminis-
tration of monoclonal antibodies would be warranted (Brudek et al. 2017). It,
however, appears that targeting innate immunity would be more promising than
adaptive immunity by systemic immune blockade. Genomic analysis has shown
correlation of neuroinflammatory genes in these diseases. The key though is
identifying specific pathways for intervention that target non-neuronal cell reactions
in neurodegenerative disease (Sims et al. 2017).

In addition to these, applications of immunotherapy in multiple sclerosis
(MS) and amyotrophic lateral sclerosis (ALS) are also under investigation
(Villoslada et al. 2008). This is particularly important, since effective therapies are
not yet available for most neurodegenerative diseases. One of the major challenges is
understanding the role of immune modulation in preventing progression of disease
Another obstacle is the delivery of these treatments to the brain, across the blood–
brain barrier. Therefore, it is equally important to undertake research into delivery
systems to facilitate the administration of these therapies.

11.3.2 Infectious Diseases

In addition to vaccines and interferon based therapies that are common for the
treatment of infectious diseases, other forms of immunotherapy have also been
investigated for the treatment of infectious diseases. In spite of the availability of
efficacious antiviral drugs for its treatment, T cell based immunotherapies are being
investigated for the treatment of hepatitis C (Fuller et al. 2013). T cell
immunotherapies are also in clinical trials for the treatment of hepatitis B
(U.S. National Library of Medicine 2020b). INO-9112, a DNA plasmid coding for
the transcription of interleukin-12, delivered by electroporation, is in phase II clinical
trials for the treatment of hepatitis B (U.S. National Library of Medicine 2020b). A
granulocyte macrophage colony stimulating factor has also gained approval for the
treatment of this infection, and phase IV studies are currently underway for its
assessment (U.S. National Library of Medicine 2020b).

Several forms of immunotherapy are under assessment for the treatment of
persistent fungal infections. Antibody therapies have been tested clinically. Cell-
based therapies that have been studied include the use of T cells, dendritic cells, and
neutrophils. The use of pentraxins has also shown potential, with PTX3 showing
in vitro efficacy against Aspergillus. Thymosin-α1 has been shown to trigger the
maturation of dendritic cells when exposed to Aspergillus, as well as enhancing the
production of interleukin-12 (Armstrong-James and Harrison 2012).

Immunotherapies, therefore, have great potential as inhibitors of fungal growth,
however, the major hurdle lies in their inability to compete with the low cost of
standard antifungal therapy. The real value of these therapies would only really exist
in immunocompromised patients, in whom standard antifungal drugs prove to be
ineffective, in case of persistent infections.
Immunotherapies have also been proposed as a potential treatment option for viral infections such as SARS-CoV and MERS-CoV. Both active and passive immunity approaches are being proposed to tackle the 2019–2020 coronavirus pandemic. Potential passive immunization approaches involve the administration of antibodies, either by means of plasma translation, from a person who has already recovered from the disease, or through the administration of externally manufactured monoclonal antibodies (Shanmugaraj et al. 2020). In the case of viral infections that spread rapidly and are likely to undergo frequent mutations, a combination of monoclonal antibodies, targeting various epitopes on the virus is thought to be able to provide a more robust treatment option (U.S. National Library of Medicine 2020b). In the case of active immunization, vaccines containing the whole virus as well as DNA fragments are being clinically tested, but so far, none have gained FDA approval (Amin Jafari and Ghasemi 2020). Other approaches that have been proposed include administration of polypeptide hormones to induce maturation of T cells and ACE2 immunoadhesion (Amin Jafari and Ghasemi 2020). Unfortunately, so far, none have seen clinical success.

11.3.3 Autoimmune Diseases

The applications of immunotherapies for the treatment of autoimmune diseases have become common knowledge. Immune checkpoint blockade, anti-T cell therapy, anti-B-cell therapy are in clinical practice and some of the applications are in various stages of clinical trials. Immunotherapy has the unique capability to balance and reinstate immune system. The therapy has shown promising results in potentially treating diabetes mellitus, psoriasis, and rheumatoid arthritis.

11.3.4 Other Applications

There is an increasing interest in the potential of immunotherapy for dealing with common allergies. Multiple clinical trials are underway, exploring the prospect of using immunotherapeutic agents to curb autoimmune responses responsible for peanut allergies, cows’ milk allergies, other food allergies, as well as allergic rhinitis (U.S. National Library of Medicine 2020b). These are being investigated in both children and adults, and could become common treatment options in the coming years.

Potential for the application of immunotherapies also exists in the treatment of myositis, a group of inflammatory myopathies characterized by muscle weakness and endomysial inflammation. Symptomatic relief is generally provided to patients through the administration of steroids. The development of immunotherapies would allow for reduced doses of steroids, which are known to produce significant adverse effects. Researchers are attempting to develop monoclonal antibodies and fusion proteins to treat the disease, but the major challenge lies in the systematic testing of muscle strength to assess their efficacy (Dalakas 2010).
The monoclonal antibody stamulumab was tested for its ability to treat Duchenne muscular dystrophy. It acted by inhibiting myostatin, which has a growth-limiting effect on muscle tissue (Wagner et al. 2008). The drug is no longer being developed, however, other forms of immunotherapy could have applications in this disease area.

Another avenue that holds great potential is the treatment of osteoporosis, both in men and in post-menopausal women. Eli Lilly and Company developed a monoclonal antibody, named Blosozumab, to inhibit the SOST gene, and in effect increase osteoblast activity (McColm et al. 2014). This agent has completed phase II trials, in which it exhibited good efficacy and tolerance. The potential effects on breast cancer, and presence of anti-drug antibodies is still being investigated (Recker et al. 2015). Therapies such as this could become the standard of care for osteoporosis in the years to come.

An interesting agent to gain FDA approval was the monoclonal antibody Alirocumab. While it was approved in 2015, as a cholesterol lowering drug, it is not considered cost-effective in comparison to the statins that are readily available (Kazi et al. 2016). This continues to be a challenge for the development of immunotherapies, especially those that are biologics in nature. While they may be able to produce desirable clinical outcomes, it is difficult to bring down the prices to compete with the small molecules that form the standard of care in many disease areas.

Many novel strategies are emerging to strengthen and widen the reach of immunotherapy. These include bypassing endogenous immunity with cellular therapies, altering microenvironment, and modulating metabolic pathways to augment the immune response. For example—reprogramming of myeloid cells abundant in the tumor environment had been utilized to prime T cell response, delivery of cytokines, stimulation of toll-like receptor (TLR) ligands.(Cubillos-Ruiz et al. 2015; Kerkar et al. 2011)

Hypoxia and hypoxia induced vascular endothelial growth factor (VEGF) is suppressive of certain myeloid cells. The combination of antiVEGF and checkpoint blockade was found to be effective in preclinical and clinical settings. (Hodi et al. 2014)

The causal effect relationship between microbiome and response to checkpoint blockade has been shown in cancer patients.(Routy et al. 2018)

### 11.4 Challenges and Limitations of Immunotherapies

During the last decades, our understanding of underlying mechanisms and pathways that drive and regulate immune cell activity in health and disease state has developed significantly. In spite of these advances in the field of immunotherapies, certain hurdles are along the implementation way. The major obstacles include unpredictable efficacy and patients response, need for more target-specific, clinically significant biomarkers, approaches to tackle heterogeneity of disease and associated toxicity, concrete, strategic study design to improve efficacy, delivery methods of immunotherapy, and cost.
One of the biggest challenges posed by the existing immunotherapeutic options, particularly those targeting the adaptive immune system, is that the treatment tends to be effective only in a select group of patients. In the case of cancer patients, there tends to be vast variability in the genotypes of tumor antigens found on malignant cells, in the cancer type, and the expression of biomarkers. This makes it difficult to design therapies that not only selectively kill cancer cells but are also effective in a large majority of patients (Ventola 2017a). This can also present a challenge in the design of clinical trials. Since many immunotherapies are targeted to certain tumor specific antigens, screening for the corresponding biomarkers in clinical trial subjects becomes essential. This often leads to small cohorts of patients qualifying for the trials, and false negative results if biomarkers are not used as a criterion for shortlisting (Ventola 2017a).

The pharmacokinetics, safety, and toxicity of immunotherapeutic approaches have also been an area of concern. In order to optimize the application of immunotherapeutics, thorough knowledge of the pharmacokinetics (PK), exposure–effect relationship, and toxicity profile of these drugs must be studied further. This can help in effectively mitigating immune related adverse events. Apart from this monoclonal antibodies have proved to be amongst the most popular forms of immunotherapy, with the first one being approved by the FDA in 2002. These, like other drugs, present challenges of adverse reactions, most commonly allergic responses (Mahmuda et al. 2017). Additionally, several monoclonal antibody therapies have been reported to cause immunodeficiency in patients, making them increasingly prone to infectious diseases. Certain monoclonal antibodies, including infliximab and rituximab have also been shown to cause immune thrombocytopenia in patients (Hansel et al. 2010).

Chimeric antigen receptor T cell (CAR-T cell) immunotherapy drugs have also been approved by the FDA for the treatment of lymphomas and leukemia. The major challenge that these forms of therapy present is that they trigger an excessive release of cytokines into the bloodstream (Xia et al. 2019). This cytokine release syndrome is also observed as a side effect of infusion of certain monoclonal antibodies, as well as cytokine immunotherapy using interleukin 2. This is physiologically exhibited as fever, malaise, cardiac effects, and hepatic and renal dysfunction, which must critically be controlled clinically. This is often done by means of immunsuppression, which in turn presents a range of side effects of its own. Furthermore, neurological toxicity, allergic reactions, and off-target binding have also been observed during CAR-T cell therapy (Bonifant et al. 2016).

Another approach to immunotherapy that has been applied is adoptive immunotherapy, wherein cells of the immune system, most commonly T cells or Natural Killer (NK) cells, are directly administered to the patient. These may come from the patient and be expanded ex vivo, or be obtained from a donor. Ex vivo expansion is a slow process, and a large number of cells must be administered in order to observe a response (Childs and Carlsten 2015). Adoptive immunotherapy has led to the concept of personalized immunotherapy especially to treat cancer. In case of personalized medication, it is essential to thoroughly understand the tendency and pattern of anti-tumor immune responses which can vary from patient to patient.
Accurate identification of neoantigens, patient-specific immunosuppressive mechanisms, and precise application of genomic information can help in improving the efficacy of personalized therapy (Kakimi et al. 2017).

The significance of biomarkers that have been identified is also, at times, questionable. Human epidermal growth factor (HER2) levels, for example, have been found to be elevated in approximately 20% of gastric cancer patients. While the monoclonal antibody trastuzumab is thought to be effective in patients expressing this factor, the therapy is found to be beneficial in only 40–50% of the patients (Ventola 2017a). So while there is a need for the identification of new biomarkers indicative of tumors, it should be noted that many of those already identified are not always predictive, and significant validation is required to confirm their role in disease. The diversity of mutations occurring in malignant cells makes this particularly challenging (Ventola 2017a). Such mutations also give rise to the problem of tumor heterogeneity. Variation amongst cells within the tumor means that frequent biopsies are necessary to identify the antigens presented on the cells. It also results in monotherapies with targeted agents being ineffective; combination therapy is essential to achieve desired effects (Ventola 2017a).

Such mutations in target antigens give rise to variations in efficacy of the treatment amongst patients. Many immunotherapeutic approaches target a specific antigen, and since the proportion of cells within the tumor expressing that antigen can vary, the efficacy of response also tends to be variable (Sambi and Bagheri 2019). Unpredictability of the efficacy can also be attributed to variations in the tumor microenvironment, amongst individuals, as well as on the basis of tumor location (Kakimi et al. 2017). Moreover, an individual’s ability to produce an immune response impacts the efficacy of therapy, especially when the treatment relies on active immunity (Sambi and Bagheri 2019). For example, in geriatric patients, immunosenescence is observed, as well as the presence of auto-antibodies. This can significantly impact the individual’s response to treatment with immune checkpoint blockers (Ventola 2017b). Similarly, patients who have previously received chemotherapy tend to have a compromised immune system and are therefore unable to elicit an effective immune response when administered immunotherapy (Sambi and Bagheri 2019). An additional cause of variability when using non-human monoclonal antibodies is that the body’s immune system may recognize them as “foreign,” and elicit an immune response against them, thus reducing efficacy of the treatment (Ventola 2017b).

Drug delivery in immunotherapy also presents several challenges. Large biological molecules such as proteins are not only prone to degradation but also present problems with solubility and permeability. Antigens used in immunotherapy tend to be sensitive to the varying environments in the body (Yang et al. 2019). Moreover, many agents, such as agonists of stimulator of the interferon genes (STING) receptor, require intra-tumor drug delivery (Ramanjulu et al. 2018).

Nanoparticles have been under investigation for their potential as a delivery system for immunotherapies. They are able to protect sensitive molecules and increase the half-life. However, they have been found to give rise to toxicity issues, and show uncontrollable drug release profiles. The interactions between
nanoparticles and the biological agent incorporated in them have also not been fully investigated (Yang et al. 2019).

Another approach that has been explored in recent years is use of microfluidic squeezing to achieve intracellular delivery. While this technology has great potential and an array of applications, it still presents several challenges that need to be addressed. When used for the administration of large macromolecules, the system uses forceful mechano-poration, which has been found to cause destruction of cells. The large molecules also run the risk of clogging the delivery device. Moreover, the technology uses a large external pressure system to achieve this, which makes it inconvenient to use (Szeto et al. 2015).

Cancer and viral diseases having immunocompromised status and treated with adoptive immunotherapy had shown great promises, and it is an emerging technology. The prerequisite for the implementation of adoptive technology is a clinical-grade ex vivo expansion of T cells that needs human or fetal bovine serum. The use of serum poses a threat of infectious agents, and hence the strategy of a xeno-free serum replacement (SR) Cell Therapy System (CTS) had been investigated. The SR based immune cell manufacturing platform demonstrated comparable results with traditional method and would serve as a promising therapeutic approach for the patients. (Rasmussen et al. 2010)

Finally, the most significant drawback seen with all the commonly used forms of immunotherapy is the cost involved. These are expensive treatment options, and are proving to be a significant burden on healthcare and insurance providers. The cost of these treatment options means that people in many parts of the world are unlikely to have access to them (Ventola 2017a). This is a significant challenge that must be overcome in the coming years, so that all the patients likely to benefit from immunotherapy have access to the option.

11.5 Translation of Immunotherapies: From Bench to Bed

Like most drugs and therapies, the translation of immunotherapies from the lab to the clinic can be a tedious process, with a high attrition rate. One of the most significant factors contributing to this is the relevance of animal models used in preclinical studies. Mice have most commonly been used to assess the safety and efficacy of many medicinal products. In the case of most diseases, mice have been proven to express disease patterns and therapeutic responses that translate well into humans (Mestas and Hughes 2004). They are also relatively easy to genetically modify using technologies such as CRISPR (Mestas and Hughes 2004; Tao and Reese 2017). Additionally, human and mouse immune systems share a structure that is overall quite similar (Mestas and Hughes 2004).

However, certain differences in the composition of the immune system can lead to significant differences in how the results of preclinical studies translate to humans. For example, human blood is found to have higher ratio of neutrophils to lymphocytes, while mice have a higher proportion of lymphocytes in their blood (Mestas and Hughes 2004). Differences are also observed in toll-like receptors and
in defensins (Kazi et al. 2016). With more target-specific immunotherapies currently being investigated, subtle differences such as these can majorly affect how accurately animal models are able to predict clinical results (Mestas and Hughes 2004). Another aspect that must be accounted for when looking at diseases and therapies impacting the immune system is the basal immune response observed in species and individuals (Tao and Reese 2017). This is largely influenced by the individual’s microbiome, as well as environmental exposure to pathogens. Experimental mice are generally housed in extremely hygienic conditions, while humans are constantly exposed to antigens in the environment. This can influence the aggressiveness of the immune response elicited. By-stander infections can also affect the response. As a result, many immunotherapies that appear promising in mice often do not translate well into humans (Tao and Reese 2017). Selecting animal models that most accurately resemble human disease and responses is always a challenge, and even more so in immunotherapy. This is an obstacle that must be overcome in order to be able to bring more immunotherapeutic options to the clinic.

The regulatory framework laid down for immune therapies has been harmonized and is following a structured pattern for approval. Post approval regulatory mandates also require setting up of a robust pharmacovigilance system and submissions of several data and checklists.

11.6 Conclusion

Immunotherapy is the blockbuster therapeutic option invented in the current decade, unraveling the multiple facets of the human immune system and its interplay in disease. Immunotherapy based drugs are now being approved for the treatment of wide plethora of diseases. Its scope is not confined to the oncology area, but widens beyond oncology, ranging from autoimmune disorder to infectious diseases. The therapy has shown promising results but nevertheless cost to benefit ratio is required to be taken into consideration in order to advocate and promote the therapy. Immunotherapy has emerged as viable alternative to existing measures. Taking note of vast research and preclinical, clinical investigation carried out in this area in the last decade, we need to further define key challenges and roadblocks to clinical progress of immunotherapy. Extensive research is required to be done so that it gains acceptance worldwide. Efforts to understand the molecular and cellular interplay between different immune cells, identification, and evaluation of clinical biomarkers, cost-effective and robust, accurate, reliable, reproducible biomarkers along with drug discovery and development, customized safety and efficacy testing designs are some of few challenges that need to be focused and addressed. The collaborative efforts of academics and industry are required to address these key challenges and to develop an improved therapeutic option for patients. It is essential that all the concerned stakeholders must be brought on the same page to appreciate all these “facets” of immunotherapies to make it a successful and go-to healthcare therapy for many diseases in the future that will benefit mankind.
References

Amin Jafari A, Ghasemi S (2020) The possible of immunotherapy for COVID-19: a systematic review. Int Immunopharmacol 2:106455

Armstrong-James D, Harrison TS (2012) Immunotherapy for fungal infections. Curr Opin Microbiol 15(4):434–439

Bach DH, Lee SK (2019) The potential impacts of tylophora alkaloids and their derivatives in modulating inflammation, viral infections, and cancer. Curr Med Chem 26(25):4709–4725

Bao X, Yuan H, Wang C, Liu JLM (2013) Antitumor and immunomodulatory activities of a polysaccharide from Artemisia argyi. Carbohydr Polym 98(1):1236–1243

Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, Rodríguez-Ruiz ME, Ponz-Sarvise M, Castañón E, Melero I (2019) Cytokines in clinical cancer immunotherapy. Br J Cancer 120(1):6–15

Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ (2016) Toxicity and management in CAR T-cell therapy. Mol Ther 3:16011

Brudek T, Winge K, Folke J, Christensen S, Fog K, Pakkenberg B, Pedersen LO (2017) Autoimmune antibody decline in Parkinson’s disease and multiple system atrophy: a step towards immunotherapeutic strategies. Mol Neurodegener 12(1):44

Chen L, He Z, Qin L, Li Q, Shi X, Zhao S, Chen L, Zhong N, Chen X (2011) Antitumor effect of malaria parasite infection in a murine Lewis lung cancer model through induction of innate and adaptive immunity. PLoS One 6(9):e24407

Chen S, Song Z, Zhang A (2019) Small-molecule immuno-oncology therapy: advances, challenges and new directions. Curr Top Med Chem 19(3):180–185

Childs RW, Carlsten M (2015) Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: the force awakens. Nat Rev Drug Discov 14(7):487–498

Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A et al (2015) ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell 161:1527–1538

Dalakas MC (2010) Immunotherapy of myositis: issues, concerns and future prospects. Nat Rev Rheumatol 6(3):129

Darani HY, Yousefi M (2012) Parasites and cancers: parasite antigens as possible targets for cancer immunotherapy. Future Oncol 8(12):1529–1535

Deng G, Lin H, Seidman A, Fornier M, D’Andrea G, Wesa K, Yeung S, Cunningham-Rundles S, Vickers AJ, Cassileth B (2009) A phase I/II trial of a polysaccharide extract from Grifola frondosa (Maitake mushroom) in breast cancer patients: immunological effects. J Cancer Res Clin Oncol 135(9):1215–1221

Fuller MJ, Callendret B, Zhu B, Freeman GJ, Hasselschwert DL, Satterfield W, Sharpe AH, Dustin LB, Rice CM, Grakoui A, Ahmed R (2013) Immunotherapy of chronic hepatitis C virus infection with antibodies against programmed cell death-1 (PD-1). Proc Natl Acad Sci 110(37):15001–15006

Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY (2013) Therapeutic cancer vaccines: past, present, and future. In: In advances in cancer research, vol 119. Academy Press, New York, pp 421–475

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ (2010) The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 9(4):325–338

Hodi FS, Lawrence D, Lezcano C, Wu X, Zhou J et al (2014) Bevacizumab plus ipilimumab in patients with metastatic melanoma. Cancer Immunol Res 2:632–642

Huehls AM, Coupet TA, Sentman CL (2015) Bispecific T-cell engagers for cancer immunotherapy. Immunol Cell Biol 93(3):290–296

Jen EY, Xu Q, Schetter A, Przepiorka D, Shen YL, Roscoe D, Sridhara R, Deissleroth A, Philip R, Farrell AT, Pazdur R (2019) FDA approval: Blinatumomab for patients with B-cell precursor acute lymphoblastic leukemia in morphologic remission with minimal residual disease. Clin Cancer Res 25(2):473–477
Kakimi K, Karasaki T, Matsushita H, Sugie T (2017) Advances in personalized cancer immuno-therapy. Breast Cancer 24(1):16–24
Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K (2016) Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA 316(7):743–753
Kerchner GA, Boxer AL (2010) Bapineuzumab. Expert Opin Biol Ther 10(7):1121–1130
Kerkar SP, Goldszmid RS, Muranski P, Chinnasamy D, Yu Z et al (2011) IL-12 triggers a programmatic change in dysfunctional myeloid-derived cells within mouse tumors. J Clin Investig 121:4746–4757
Kerr WG, Chisholm JD (2019) The next generation of immunotherapy for cancer: small molecules could make big waves. J Immunol 202(1):11–19
Lopes A, Vandermeulen G, Préat V (2019) Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. J Exp Clin Cancer Res 38(1):146
Mahmuda A, Bande F, Al-Zihiry KJ, Abdullaleem N, Majid RA, Hamat RA, Abdullah WO, Unyah Z (2017) Monoclonal antibodies: a review of therapeutic applications and future prospects. Trop J Pharm Res 16(3):713–722
McColm J, Hu L, Womack T, Tang CC, Chiang AY (2014) Single-and multiple-dose randomized studies of blosozumab, a monoclonal antibody against sclerostin, in healthy postmenopausal women. J Bone Miner Res 29(4):935–943
Mestas J, Hughes CC (2004) Of mice and not men: differences between mouse and human immunology. J Immunol 172(5):2731–2738
Pedersen JT, Sigurdsson EM (2015) Tau immunotherapy for Alzheimer’s disease. Trends Mol Med 21(6):394–402
Ramanjulu JM, Pesiridis GS, Yang J, Concha N, Singhaus R, Zhang SY, Tran JL, Moore P, Lehmann S, Eberl HC, Muelbaier M (2018) Design of amidobenzimidazole STING receptor agonists with systemic activity. Nature 564(7736):439–443
Rasmussen AM, Borelli G, Hoel HJ, Listerud K, Gaudernack G, Kvalheim GAT (2010) Ex vivo expansion protocol for human tumor specific T cells for adoptive T cell therapy. J Immunol Methods 355(1–2):52–60
Recker RR, Benson CT, Matsumoto T, Bolognese MA, Robins DA, Alam J, Chiang AY, Hu L, Krege JH, Sowa H, Mittak BH (2015) A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. J Bone Miner Res 30(2):216–224
Riley RS, June CH, Langer R, Mitchell MJ (2019) Delivery technologies for cancer immunother-apy. Nature reviews drug discovery. Nat Rev Drug Discov 18(3):175–196
Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT et al (2018) Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science (80- ) 359:91–97
Samb M, Bagheri LSM (2019) Current challenges in cancer immunotherapy: multimodal approaches to improve efficacy and patient response rates. J Oncol 2019:4508794
Schenk D (2002) Amyloid-β immunotherapy for Alzheimer’s disease: the end of the beginning. Nat Rev Neurosci 3(10):824–828
Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W (2020) Perspectives on monoclonal antibody therapy as potential therapeutic intervention for coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol 38(1):10–18
Sheen MR, Fiering S (2019) In situ vaccination: harvesting low hanging fruit on the cancer immunotherapy tree. Wiley Interdiscip Rev Nanomed Nanobiotechnol 11(1):e1524
Sims R et al (2017) Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer’s disease. Nat Genet 49(9):1373–1384
Stipp MC, de Lacerda Bezerra I, Corso CR, dos Reis Livero FA, Lomba LA, Caillot AR, Zampronio AR, Queiroz-Telles JE, Klassen G, Ramos EA, Sassaki GL (2017) Necroptosis mediates the antineoplastic effects of the soluble fraction of polysaccharide from red wine in Walker-256 tumor-bearing rats. Carbohydr Polym 160:123–133
Szeto GL, Van Egeren D, Worku H, Sharei A, Alejandro B, Park C, Frew K, Brefo M, Mao S, Heimann M, Langer R (2015) Microfluidic squeezing for intracellular antigen loading in polyclonal B-cells as cellular vaccines. Sci Rep 5:10276

Tao L, Reese TA (2017) Making mouse models that reflect human immune responses. Trends Immunol 38(3):181–193

U.S. National Library of Medicine (2020a). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=plasmodium+immunotherapy&cntry=&state=&city=&dist=. Accessed 29 Apr 2020

U.S. National Library of Medicine (2020b). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/results?term=immunotherapy&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&Search=Apply#. Accessed 29 Apr 2020

Ventola CL (2017a) Cancer immunotherapy, part 3: challenges and future trends. Pharm Ther 42(8):514

Ventola CL (2017b) Cancer immunotherapy, part 2: efficacy, safety, and other clinical considerations. Pharm Ther 42(7):452

Villoslada P, Moreno B, Melero I, Pablos JL, Martino G, Uccelli A, Montalban X, Avila J, Rivest S, Acarin L, Appel S (2008) Immunotherapy for neurological diseases. Clin Immunol 128(3):294–305

Wagner KR, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M (2008) A phase I/II trial of MYO-029 in adult subjects with muscular dystrophy. Ann Neurol 63(5):561–571

Weiner HL, Frenkel D (2006) Immunology and immunotherapy of Alzheimer’s disease. Nat Rev Immunol 6(5):404–416

Xia AL, Xu Y, Lu XJ (2019) Cancer immunotherapy: challenges and clinical applications. J Med Genet 56(1):1–3

Yang Z, Ma Y, Zhao H, Yuan Y, Kim BY (2019) Nanotechnology platforms for cancer immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2019:e1590