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Immunotherapy: A Revolutionary Approach to Disease Treatment Harnessing the Body's Own Defense

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Abstract
The body has natural defenses against cancer even before the modern age, as evidenced by a plethora of research and meta-analyses show bing tumors can appear out of the blue, sometimes on their own, sometimes in response to a fever or disease. These days, immunosuppression is associated with a higher risk of cancer, and spontaneous tumor regression of untreated malignant tumors is recognized as an uncommon but real phenomenon. The standard treatment for bladder cancer since its successful demonstration in 1976 has been the intravenous infusion of live, attenuated Bacillus Calmette-Guérin bacteria. Tumor, host, and environment complex interactions are necessary for effective immunization against cancer. Since more people are paying attention to cancer treatment, cancer immunotherapy, which employs a variety of tactics to boost tumor immunity, marks a paradigm shift in the field.

Keywords
Immunotherapy, Cancer Treatment, Tumor Regression, BCG Therapy

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INTRODUCTION
The advances made in cancer biology and pathogenesis during the past two decades have resulted in the emergence of immunotherapeutic strategies that have revolutionized the treatment of malignancies. A move that was once exclusively from relatively non-selective toxic agents to a few targeted therapies has now burgeoned into a multitude of specific, mechanism-based therapies. New knowledge has been translated to creative and daring therapeutic trials, and small discoveries have energized big moves. Most notably, perhaps for the first time in the field of medicine, new and astonishing immunotherapies showed a response evaluation criteria surpassing all previous treatment regimens, even the most toxic ones. Tumors that have repelled the biggest hitters of immunotherapy have predicted an eventual response and, upon cessation of treatment, led to permanent remissions for several years, if not decades, even in very advanced stages of the disease (Naran et al., 2018; Raghani et al., 2024; Kamrani et al., 2023; Sahu & Suryawanshi, 2021).

Despite extensive global efforts directed towards hygiene, vaccination, sanitation, education, and access to drugs, infectious diseases remain a leading cause of morbidity and mortality worldwide. Every year, more than 10 million people die of infectious diseases, second only to cancer. Of these deaths, more than 90% exceed the age of one year and often occur in resource-poor settings. Infectious disease continues to be a rapidly spreading scourge in countries undergoing socio-political upheaval. In addition, increasing antimicrobial resistance is leading to treatment failure, resulting in death. Currently known antivirals, antibacterials, and antifungals, discovered more than 100 years ago, largely target the same molecular entities as their respective prokaryotic or eukaryotic cells, resulting in toxicity in patients. Therefore, there is an urgent, unmet, and enormous need for novel, innovative therapeutics that target the many vulnerabilities of pathogens while sparing their host. (Baker et al., 2022; Frenkel, 2021; Hacker, 2024; Kirtane et al., 2021)

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Since the dawn of humankind, infectious pathogens successfully fashioned a hospitable environment within their host and modulated host metabolic functions to support their nutritional requirements. At the same time, they suppress host defenses by altering regulatory mechanisms and redirecting the appropriate outcome of the immune response. Pathologies characterized by similar mechanisms, further corroborated by onco-microbiology, evolve for cancer. Insight on how pathogens are contained, exported, and reprogrammed has driven advances in targeted therapy. Many insight-exploitative trials are being performed, but very few have made it outside the labs. Perpetual evolution and adjustments of newly acquired or engineered abilities render such strategies invariably frail. Nonetheless, in this somber light, due to their increased understanding, some rationally developed and repurposed immunotherapies have crossed the desert and captured the summit. These similar mechanisms, insights, agents, and approaches to immunotherapy still bear great potential yet to be utilized in the offensive against infections. (Herrera et al., 2022; Li et al., 2023; Majumder et al., 2024; Dey et al., 2024)

HISTORICAL BACKGROUND OF IMMUNOTHERAPY

It has become apocalyptic to speak about a revolution in the development of new strategies for the treatment of human disease. Medicine has made extraordinary progress since the Middle Ages, with infectious diseases that were once a scourge for humanity now being treatable, and surgery techniques that are much advanced. On the other hand, hardly any improvement in the management of cancer has been made, although surgery, radio- and chemotherapy have led to a modest prolongation of life for some patients with certain types of neoplasia. Notwithstanding, the side effects of most of these treatments have heavily prejudiced the quality of life in the surviving patients. Research on cancer in the past few decades has led to the insight that individuum and tumorigenic transformation of cells (neoplasia) would result in a triumph of Darwin's natural selection theory. It has long been accepted that neoplastic cells arise from the translation of an abnormal genetic code from DNA to mRNA sorted to ribosomes in the cytoplasm that resulted in the synthesis of abnormal proteins and/or abnormal glycosylation of normal proteins. To date, it can be concluded that internal selection processes clearly do act in cancer disease (Khan et al., 2021). However, there have been doubts about the capability of the immune system to act as an external selection force. How could a system that is normally only capable of reacting against antigenic molecules (non-self) emanating from a microbe or a painted pathogenic organism distinguish between (normally) non-antigenic molecules produced by neoplastically transformed cells? There is increasing evidence that the immune system can eliminate neoplastic cells, and a new concept of immuno-selection to act against cancer disease has been developed 14. In the early 1960s, evidence was provided that most (if not all) normal cells express different immunogenic molecules than cells that are aberrantly proliferating and forming a tumor. Similarly, findings were described demonstrating that infection with certain viruses and chemical carcinogens can lead to the expression of virus- or chemical-induced MAGE-class immunogenic molecules on the tumor cells but not on the normal cells (the first time direct evidence was obtained that there can be differences in the peptide- and/or glyco-structure of proteins between normal cells and cancer cells imprinted at the genetic level). Finally, attempts were initiated to actively induce immunological rejection of tumors using allogeneic or autologous cell-lines expressing such immunogenic molecules. (Peña-Romero & Orenes-Piñero, 2022; Xia et al., 2021; Elmusrati et al., 2021; Wang et al., 2023)

MECHANISMS OF ACTION

In efforts to bias the immune response towards antitumor immunity, most approaches to treating cancer with immunotherapy focus on the key players in the response, the T cells (Meiliana et al., 2016). Broadly, there are two approaches to manipulating the T cell response: either augment the existing T cells at work within the tumor or events leading to other tissues, or provide new T cells which will be biased towards recognizing the

tumor. For the latter, two major types of manipulation are in use. The first is called T cell receptor (TCR) therapy, in which T cells are given new receptors that specifically recognize a small number of possible antigens displayed in a specific way by the target tumors; usually a peptide bound to the MHC. Unlike CAR therapy, TCR therapy is constrained to use T cells matching the tissues with the target peptides and therefore restricting the number of patients that can benefit. The second approach is chimeric antigen receptor (CAR) therapy. That approach uses viruses that deliver a gene that encodes an artificial protein that can bind to the receptors used by the detecting T cells in a non-typical way, and therefore not needing to match the person's immune type. Instead, with CAR therapy the targeting protein acts as a bridge, delivering the activating signal via the CD3 domain of the T cells' own receptor. This means that almost anyone can donate T cells that can be made into a CAR therapy for a tumor that expresses the corresponding antigen. The underlying premise is that a receptor protein will bind tightly to a particular epitope and make T cells with that receptor specific for the cells displaying its antigen with tight context requirement. Hence TCR- or CAR-based T cell therapy targeting identical antigens will have extremely different populations of starting T cells and therefore different potential outcomes. Provided new T cells are able to gain access to the tumor and proliferate, the two treatments processes are essentially the same. Therefore, many approaches that enhance the resulting T cell response are equally applicable regardless of how the T cells are introduced, and this commonality has led both approaches to be termed adoptive T cell therapy or ACT. One of the principal problems with ACT is the generation of pair varying T cells that have both the appropriate receptor for the tumor-targeting, and are potently efficacious. As ACT therapies begin to enter mainstream clinical usage, an obvious area to develop is to investigate how they can be incorporated with the other classes of cancer immunotherapy. These other treatments often target processes that happen much earlier in the cancer process, before the initial induction of the T cell, and presumably with the right combinations could lead to a stronger starting T cell population. (Want et al., 2023; Oliveira & Wu, 2023; Gong et al., 2021; Tay et al., 2021)

Immune System Overview

The word "Immunotherapy" refers to the treatment of a disease through the amplification of the immune system. As early as 1890, the American oncologist William B. Coley was the first to discover that Bacillus Calmette-Guerin, an attenuated mycobacterium, could induce refractory skin sarcomas into regression (Mukherjee et al., 2022). Immunotherapy continues to be an innovative cancer treatment that modifies a patient's immune system to attack cancer cells. It is one type of biological therapy. The benefit of immunotherapy is heightened when it is combined with conventional antitumor therapy or systemically administered with various immune checkpoint inhibitors (ICIs). Cancer Immunotherapy, among other immunotherapies, has radically expanded our toolkit against cancer. The current FDA approval of ICIs like antibodies against CTLA4, PD1, PDL1, as well as several chimeric antigen receptor T cells, bispecific T cell engager therapies, and vaccines, have transformed treatment and prognostication across different cancer types (Hiam-Galvez et al., 2021). Details related to the primary and adoptive cell transfer immune therapy are explicated below.

Most immune cells stem from hematopoietic stem cells (HSCs), which form either common lymphoid progenitors (CLPs) or common myeloid progenitor (CMP) cells in the fetal yolk sac, liver, and bone marrow. Emerging from CLPs are T cells and natural killer (NK) cells, which thrive in the thymus and bone marrow, respectively. CMP primarily produces all other innate immune cells, participating in both humoral and adaptive immunity. Germinal center B cells mature into memory B cells or long-lived plasma cells that migrate to the bone marrow to produce antibodies. M1 macrophages phagocytose and cross-present antigens to naive T cells in combination with costimulatory signals, and secrete pro-inflammatory cytokines, inducing tumor regression. As the tumor develops, macrophages trans-differentiate to M2 instead,

losing their tumor-fighting ability. T helper cells secrete cytokines to polarize B cells. After the presentation of antigens on MHC-1 molecules, cytotoxic T cells kill target cells by secreting perforin and granzymes. Dendritic cells participate in both arms of the adaptive immune response, acting as professional antigen-presenting cells (APCs) and secreting immune-modulating cytokines. (Atkins et al., 2021; Shevyrev et al., 2023; Ni et al., 2024; Soares-da-Silva et al., 2021)

Types of Immune Responses

The immune system is a complex network of molecules and cells that protect the host from infectious microorganisms, parasites, and cancer. It is built to identify and eliminate foreign antigens in a non-self manner. It is clear from observations of immune responses that some cells must be able to recognize foreign antigens and respond to them. Professional antigen presenting cells include Dendritic Cells (DCs), Macrophages, and B-cells. Of these, DCs are the most potent antigen presenters. This is due to their unique phenotype, differential distribution, and function, as well as the signals they can provide to activate T lymphocytes. The aspects of the individual immune response that are most relevant to its clinical application are the characterization of the cognate antigen, the type of immune response, innate immunity, the nature of the protective response, the influence of innate immune responses on vaccine design, and the specificity of immune effectors for regulatory approaches to vaccination (Sisay, 2015).

Active immunotherapies stimulate the body's own immune system to fight the disease. This can be done by either stimulating the immune system to work harder or smarter or giving immune system components, such as man-made immune system proteins that trigger the body's immune system to recognize and respond to cancerous cells. The development of immunotherapy technology is more recent. Passive immunotherapy simply introduces new antibodies into the system to enhance the pre-existing immune response. It uses small molecules to block inhibitory checkpoint pathways in the immune cells, thus enhancing the immune response against diseases. It is expanding rapidly because of successes in the clinic. Monoclonal antibodies can be designed to be more effective or less toxic. Newer platforms can manufacture antibodies much faster and cheaper. Combinations of immunotherapies will be key in using them in suboptimal settings. Treatment of autoimmune diseases will be a more challenging area. (Varadé et al., 2021; Peña-Romero & Orenes-Piñero, 2022; Wu et al., 2021)

TYPES OF IMMUNOTHERAPY

Immunotherapy is a medical treatment that utilizes body's immune system to fight diseases, especially cancer. There are several forms of immunotherapy including monoclonal antibodies, immune checkpoint inhibitors, cancer vaccines, oncolytic viruses, and cell therapy. Monoclonal antibodies are laboratory-made antibodies designed to bind to specific targets called antigens on the lymphoma cell surface. This homing signal triggers the immune system to attack the lymphoma cells (including natural killer cells and complement proteins). Monoclonal antibodies for treatment of lymphoma include rituximab and inotuzumab ozogamicin (Sisay, 2015). Immune checkpoint inhibitors take the brakes off the immune system. They are 'immune checkpoints' that act as regulators, allowing the body's immune system to become reactivated and undergo clonal expansion to attack tumours. This approach to immunotherapy is targeting cancer-specific antigens through vaccines. Cancer vaccines can be used as either therapeutic or preventive vaccines. Therapeutic vaccines treating pre-existing cancer have some disadvantages. Cancer vaccines rely on antigen-specific immune pathways that are context sensitive, i.e., cancer vaccine efficacy is dependent on the properties of the cancer. Oncolytic viruses are engineered to preferentially invade and kill cancer cells with decreased effects on normal cells. Tumour ablation liberates tumour antigens that activate a systemic anti-cancer immune response. It is thought that at least some of the individual genetically modified cells will proliferate and/or survive long enough to bear the burden of treatment.

Monoclonal Antibodies

Monoclonal antibodies, which are artificially produced antibodies, are a highly specific kind of therapeutic antibody. Therapeutic antibodies are proteins produced in cells or organisms such as mice, rats, monkeys, rabbits and humans. A variety of human IgG isotype antibodies are produced for therapeutic purposes, but IgG1 is the most common (Meiliana et al., 2016). Antibodies can interact with a different range of antigens than chemical-based drugs, making them an alternative to small molecule drugs. They are produced through a biologics development pipeline that touts their high specificity and lower toxicity in preclinical stages. monoclonal antibodies (mAbs), or monoclonal immunoglobulins, are antibodies produced by identical immune cells and target a specific epitope. Given the many advantages of antibodies, they are an efficient and effective targeted therapeutics that have been used to develop widely used anti-tumor agents in cancer treatments.

Various strategies have been incorporated for the design of pre-targeted delivery of drugs using mAbs or Fab fragments and radiolabeling agents. The significant advantages of monoclonal antibodies make them a noteworthy area of research for enhancing the utilization of antibody-based strategies. Antidrug antibody or anti-idotypes antibodies were relatively specific and effective IgGs derivatives that were generally used to enhance anticancer efficacy. A serotype involved in the development of monoclonal tumoral immune ineffective responses occurrence and one of the important mAbs mechanisms of action in the tumor-reactive mAbs are the potential induction of adaptive immune responses. Antibody-induced immune responses followed some steps such as antibody internalization and constitutive degradation in endosomes as well as the intracellular route of the antigen to the proteasome. Following digestion into peptide fragments, MHC class II and I lysosome loading events allow presentation of the mAbs/antigen complexes to T cells. Regulatory mechanisms of susceptibility to the enhancement of endogenous anticancer immunity by mAbs occurred at the natural serotype and antigenic specificity-dependent events. Antidrug immunity mode of action for the mechanistic pharmacology of anti-drug antibody in the pre-targeted delivery of monoclonal antibodies can work synergistically with antibody-drug conjugates to ameliorate systemic toxicity.

Checkpoint Inhibitors

The immune checkpoint inhibitors include monoclonal antibodies against the inhibitory receptors CTLA-4, PD-1, and PD-L1. They are currently among the most exciting and fastest expanding treatment options for cancer, and in recent years, there have been significant advances in both basic and applied immunology research that underline this success. Immune checkpoints are normal control pathways in immune cells that are crucial for the maintenance of immune homeostasis and self-tolerance. Cancerous tumors can express immune checkpoints to evade immune control, and their blocking can reinvigorate pre-existing tumor immunity to therapeutic advantage (Makuku et al., 2021).

PD-1, programmed cell death protein 1, also known as CD279, PDCD1, and SLEB2, is an immunoglobulin superfamily member and an important immune checkpoint. It is considered a marker for T-cell exhaustion and is expressed on activated, exhausted, and dysfunctional T cells, B cells, macrophages, regulatory T cells, and natural killer (NK) cells. PD-1 is known to have two ligands: PD-L1 and PD-L2, which belong to the B7 family and bind the receptor with comparable affinities. PD-L1 is the most studied ligand, and it is often upregulated in tumors (along with its cognate receptor, PD-1) under inflammatory conditions in a range of cancers, including melanoma, lung cancer, breast cancer, and some hematological malignancies 34. PD-1 has been used as a target for monoclonal antibodies leading to the rapid development of PD-1 blocking therapies. Monoclonal antibodies are currently approved or under clinical investigation with PD-1 as the target. PD-1 is believed to represent a key component of a series of negative feedback loops in the immune system to control T-cell activity. PD-L1 and PD-L2 can suppress T-cell activity and induce T-cell tolerance, which may possibly lead to T-cell memory impairment and poor immune response. PD-1/L1 induces the suppression of

proliferation in both CD4 and CD8 T cells. Inhibition of this pathway may enhance antitumor effects and reinvigorate T cells in various states of dysfunction.

Cytokine Therapy

Cytokine therapy describes the use of cytokine drugs such as tumor necrosis factor alpha (TNF-α) or interleukin 2 (IL-2) which are potent cancer therapeutics (Runbeck et al., 2021). However, poor pharmacokinetics and off-target toxicities remain their greatest problems lead to systemic side effects. Consequently, the combinations of antibody-cytokine fusion proteins, termed immunocytokines, are designed to directly deliver the pro-inflammatory environment to the malignant tissues. Hence, selectively activating the anti-tumor immune response and preventing unwanted peripheral toxicity. Immunocytokines exploit the distribution profile of mAbs leading to build-up at the tumor site maximizing the efficacy of the infused cytokine moiety. To date, a great number of immunocytokines have been engineered and tested in preclinical tumor-bearing models as well as several being introduced into clinical trials showing promising clinical responses.

The doses of mAbs used to eradicate residual disseminated disease are often well above those safely achievable in humans, hence immunotoxins have been sometimes only partially successful in ongoing trials. Interestingly, immunotoxins comprised of a mAb conjugated to either an enzymatic toxin or a cytotoxic drug were both shown to be potent for late-stage solid tumors which remain refractive to traditional therapies, demonstrating the potential for current mAbs to be applied in an immunotoxicology context. Hence, immune-modulatory ab-drug conjugates combining an anti-PD1 or anti-PD-L1 mAb with a cytotoxic alkylating agent are being developed to normalize the tumor vasculature and restrain the remodeling of macrophages in the tumor microenvironment. These strategies should ultimately lead to enhanced combination outcomes of both ab-drug conjugates with additional early-phase therapies such as anti-CTLA4 mAbs and oncolytic virus. These immunobiologics are thought to jointly maximize the immune startup response and maintain it.

Cancer Vaccines

The term vaccine refers to a preparation of immunogenic agent(s) which is administered to induce protective immunity against a disease. Cancer vaccines can be classified broadly into two categories: preventive vaccines and therapeutic vaccines. Preventive cancer vaccines are administered to individuals who have not yet developed the disease. They induce T and B cell memory responses to tumor associated antigens (TAAs) or infectious agents such as viruses, parasites, or bacteria that are responsible for the development of cancers. Therapeutic vaccines are administered to patients who have already developed the disease. They induce immune responses capable of eliminating established tumors (Slingluff & Speiser, 2005).

Preventive cancer vaccines have drastically reduced the incidence of cervical cancer in young women. Cancer preventive vaccines are limited to 15–20% of cancers caused by infectious agents, and limited individual target selection diversity. In contrast, therapeutic cancer vaccines have virtually no limits in patient population selection diversity or antigen selection diversity. Advances in high-throughput genomics and bioinformatics technologies have facilitated the precision identification of non-synonymous somatic mutation (or neoantigen) derived peptides exclusively found in tumor cells and not in normal tissues.

Melanoma has been intensely studied with the identification of the first neoantigen, which is mutant BRAF V600E peptide. The robust and durable immune responses induced by neoantigen vaccines have been demonstrated in a large variety of advanced solid tumors like non-small cell lung cancer (Li et al., 2023). Although neoantigen-based therapeutic cancer vaccines are not approved as standard treatment of cancer, early clinical trials show encouraging outcomes of neoantigen vaccines as monotherapy or in combination with checkpoint inhibitors. Advances in understanding the biology of neoantigens and

precision identification of neoantigens by high-throughput sequencing and bioinformatics have transformed neoadjuvancy into a real and powerful tool to eliminate tumors and prevent recurrences through the design and personalization of effective neoantigen-based therapeutic vaccines tailored for each cancer patient.

Adoptive Cell Transfer

Adoptive cell transfer (ACT) is an emerging technology that allows the isolation and engineering of potent, patient-specific T cells for infusion back into patients. To date, ACTs have typically involved the infusion of expanded T-cell populations obtained from tumor-infiltrating lymphocytes (TILs) directed against an individual patient's tumor. A second treatment strategy, the introduction of T cells that have been engineered to express a tumor-specific T cell receptor (TCR) or a chimeric antigen receptor (CAR), is increasingly under investigation (Perica et al., 2015). Clinical responses to ACT have been seen when the transferred T-cell populations recognize either tumor-specific antigens or a broad class of antigens, including shared mutant forms of common cellular protein.

Despite a frequency of potential targets on the order of 100 million shared mutant-deletion or neoantigens per patient, ACT targeting of these antigens remains largely unexplored. This is due in part to a shortage of preclinical models and methodologies. Identification of appropriate surface-display technology and forms for pMHC or pMHC/peptide/antibody reagents for this purpose is needed, and evaluation of these reagents will require assessment of their performance in the context of various T-cell input populations. For technical reasons or historical precedent, the most frequent assays employed in present use rely upon the use of monomorphic class I MHC tetramers or monomers, CD8 T cells and the A2.1 or A3.1 (human) MHC. Presentation of antigens on MHC-PE multimers or pMHC disc-shaped display, in the context of CD4 T cells and human HLA-4 (or polymorphism-matched) MHC 39. Why the former screening methodology has been so widely adopted is not entirely clear.

It is evident, however, that there are significant limitations associated with this approach. Caverna-based foldable pMHC constructs promise to greatly expand the range of antigens that can be presented for functional analysis. Nonetheless, questions surrounding labeling and display density have yet to be resolved and, in the context of most laboratories, it is likely that there will still be limitations to access and use of pMHC probes for some time to come. Nevertheless, labels that can characterize the biophysics of affinity will extend the range of experiments that probe the physiology of T-cells and ultimately their responses to both resistance and therapeutic targeting.

APPLICATIONS OF IMMUNOTHERAPY

The advances in cancer biology and pathogenesis have brought about immunotherapeutic strategies that have revolutionized the treatment of malignancies since the late 1990s. Increasing evidence of discrepancies in immune responses in identical individuals, coupled with an increased understanding of the intricacies of immune responses in physiology and disease, has led to the identification and classification of key immune elements that drive effector and regulatory responses against tumors. Substantial efforts have been devoted to the characterization of immune responses in cancer pathogenesis, even suggesting that there may be an unfolding co-evolution of immune responses against malignancies. Nevertheless, malignancies have devised multiple defence mechanisms to subvert host anti-tumor surveillance at virtually every step of the immune response to tumors. These advances in cancer biology and understanding of cancer pathogenesis have led to numerous immunotherapeutic strategies to reactivate anti-tumor immunity with varying degrees of success. The population of cancer antigen-specific cytotoxic T cells is necessary to mount a protective immune response against tumors, existing as part of a small na?ve T cell pool in secondary lymphoid organs. Once activated, T cells proliferate and differentiate, mobilizing effector functions to eradicate tumors. T cells are also endowed with powerful ability to

retract immune responses, to maintain tolerance and homeostasis, to limit collateral damage to host tissues. There are other types of T cell activation, in which peripheral na?ve T cells differentiate into T cell effector memory cells and T cell central memory cells. These are different from the earlier-described subsets for which an anergic state is reached. Following recognition of the cognate antigens alongside the requisite co-stimulation for naive T cell activation, antigen-irrelevant fast-acting co-inhibitory receptors such as PD-1 and Lag3 are upregulated.

Vaccination represents the first form of host-directed immunotherapy and includes various categories. Most vaccines work by introducing a non-infectious version of a disease-causing microbe. The non-infectious version can be a whole microbe that is either killed or unable to grow within the host as a live attenuated or engineered microbe. It can also be a protective or immunogenic component of a microbe such as a protein, polysaccharide, or nucleic acid that successfully elicits, amplifies, and maintains long-lasting effector and/or memory T cell responses against the entire or part of the disease-causing or pathologic microbe and/or its products once the non-infectious version of the pathogen has been delivered to the host. Vaccination has eradicated some diseases such as smallpox, and attenuated the burden of infections such as polio and hepatitis B. Despite these successes, vaccines have not performed as well in eradicating or mitigating cancers or chronic diseases. Vaccine therapy against cancer comprises the administration of some vaccine types on their own and in combination with other types of immune-based therapies, such as immune checkpoints, to improve efficacy (Naran et al., 2018).

Cancer Treatment

Among various diseases, immune systems and immune responses play some role in the behaviours that distinguish self from non-self otherwise considered as foreign. Cancer, among other infectious diseases and self-diseases, is also one of the targets for immune system. However, evasion mechanisms that can potentially span the entire spectrum of immune responses and bypass their recognition and also mechanisms for poor immunogenicity of tumours have evolved in malignant cells. Immunotherapy is a type of treatment that helps the immune system fight cancer. It teaches the immune system to recognize what is foreign, such as a cancer cell. This can be achieved by identifying specific unique markers of the tumour cells, usually proteins expressed either on the surface of a cell or within the cell itself ((Abel, 2019)). Early on, immunotherapy researchers used a specific kind of immune cell called dendritic cells that play a role in cancer recognition. They mixed these cells, taken from the patient, with tumour cells so that the dendritic cell would a viral vector to insert a DNA sequence into the genome of this immune cell. This system has proven successful in the treatment of some forms of blood cancer, which express a single, identifiable and cancer-specific target called CD19. However, problems start to appear when we try to translate that approach towards other cancers, such as solid tumours.

In these diseases, the tumour is very often heterogeneous which means that the markers we are looking for are present in some areas of the tumour but not in others. That means that the immune cells that have been armed to seek out and destroy the targeted tumour may not find their target. Another problem is that even if we could overcome the heterogeneity hurdle, antibodies, or immunotoxins often do not penetrate far into the solid tumours, nor do the T cells that are redirected with these antibodies (Laskowski & Rezvani, 2020). These T cells may often enter solid tumours only in small numbers or do not persist there long enough to mediate any effective anti-tumour response. In addition, the cytotoxic T lymphocytes produced against a distinct foreign target in their induced expression of their T-cell receptor, often encounter many ways to be turned off by the abundant natural immune suppressors of the local microenvironment. Angiogenesis means the creation of new blood vessels. One of the defining properties of a malignant cancer is the ability for it to spread to other parts of the affected organ, as well as to other sites in the body. To do this the tumour creates its own network of blood vessels to sustain itself on its travels.

Autoimmune Diseases

Autoimmune diseases are hypothesized to arise from an unbalanced immune response, resulting in the coactivation of pro-inflammatory processes and self-reactivity against autoantigens, as well as a lack of regulatory T-cell (Treg) activity. Clinical manifestations can be specific organ damage or systemic alterations. They share similar immune and environmental pathophysiologies, and their clinical signs have proved useful for common therapeutic approaches. Standard treatments rely mainly on immunosuppression, using agents such as glucocorticoids, non-steroidal anti-inflammatory drugs, cytotoxic molecules, and biological agents targeting co-stimulatory pathways, cytokines or their receptors or cytotoxic T-lymphocyte-associated protein 4. These are lamentably predominantly symptomatic ones, with a failure to adequately address the root cause of diseases, resulting in psychological and financial stress for patients, as well as multi-organ failures and mortality in more severe cases (Carballido et al., 2020).

In particular, monoclonal antibodies against cytokines or T-cell signal transduction pathways have shown efficacy in antinuclear antibody production, progression of nephritis and mortality in lupus mouse models. Immunotherapies are being developed, based on mabs, cytokines, anti-idiotypes, liposomes or small molecules, as more specific and safer alternatives to small molecules with broad immunosuppressive activities, but they still do not distinguish between disease-causing and protective cell targets. Such a combinatorial attack on several cellular targets results in non-responsiveness and no long-term functional recovery. In addition, this presents a risk of serious severe congenital immunodeficiencies. Antigen-specific approaches inducing immune tolerance represent an emerging trend carrying the potential to be curative without inducing broad immunosuppression. These types of therapies are based on antigenic epitopes derived from the same proteins that are targeted by the autoreactive T and B cells. These antigenic epitopes are administered to patients to induce regulatory responses capable of restoring homeostasis. The safety and efficacy of tolerance-inducing therapies is critically dependent on how "ritualistic" intervention regimens are used, such as the need to use concatenated antigens, narrow application windows of treatment, and a compelling rationale to reconsider this approach.

Infectious Diseases

While the historical attention on immunotherapy has revolved around cancer, the development of similar therapeutic approaches for infectious diseases is now being extensively examined. Despite extensive global efforts, infectious diseases remain a leading cause of morbidity and mortality worldwide. As proof, tuberculosis (TB), which kills 1.6 million individuals each year, is now the leading cause of death from an infectious agent, surpassing human immunodeficiency virus (HIV). Consequently, infectious diseases need urgent attention. Current approaches rely extensively on small-molecule antimicrobials. However, these drugs are increasingly harder to develop and experience extensive preclinical and clinical attrition, leading to a dearth of new compounds despite intense investment. There are growing anxieties that, should these decades-long trends continue, the world may soon enter a "post-antibiotic" era whereby routine surgeries and other procedures once thought redundant simply will not be possible (Naran et al., 2018). Therefore, a need for novel, innovative therapeutics that address the current challenges of increasing antimicrobial resistance and a shrinking pipeline of new classes of drugs is needed. Infectious pathogens fashion a hospitable environment within the host wherein multi-faceted survival strategies are unleashed. In this context, the exploitation of multiple host metabolic and trophic functions, coupled to immune evasion and suppression, are amongst the broader principles that guide the establishment of chronicity. These parallels, and the advances made in targeted therapy in cancer, may inform the rational development of therapeutic interventions for infectious diseases. This novel approach complements traditional anti-infective strategies and represents the second arm of anti-infective treatment. This review accentuates the evolving role of key targeted immune interventions that are approved, as well as those in development, for various cancers and

infectious diseases. The general features of adoptive therapies, those that enhance T cell effector function, and ligand-based therapies, that neutralize or eliminate diseased cells, are discussed in the context of specific diseases that, to date, lack appropriate remedial treatment; cancer, HIV, TB, and drug-resistant bacterial and fungal infections. The remarkable diversity and versatility that distinguishes immunotherapy is emphasized, establishing this approach within the armory of curative therapeutics across diseases.

Allergy Treatment

About 30% of the world population suffers from allergic diseases. Allergen immunotherapy is also a form of specific immunotherapy, which is the only treatment to achieve the expansion of the allergen-specific tolerance compartment and the conversion of an allergic patient into a tolerogenic state, classical long-term therapies for hypertension, dyslipidemia, and chronic inflammatory diseases. Nowadays, AIT is still neglected in most countries, especially in Asia, and a one-time cost-effective treatment providing long-lasting immunologic and clinical tolerance would be more ideal. There are two forms of AIT available today: subcutaneous immunotherapy and sublingual immunotherapy. Three basic forms of SCIT can be applied in AIT: injection of whole allergen extracts, injection of modified allergen extracts, and administration of recombinant engineered allergy vaccines. Thus far, recombinant engineered allergy vaccines have synergies, including: standardization and stability, the potential to tailor a specific therapy for individual patients, and safe delivery by administration routes other than injection. However, whole extract AIT still has ways to better provide safer, faster, and more effective long-term treatments wishful for those burdened by allergies. Several strategies have been evaluated: new extract preparations with reduced epitope exposure; alternative delivery routes; and co-administration of immune-modifying compounds. Amongst AITs approved in various regions, some are available as SCIT, and others as SLIT. Only extract-based AITs have been available for food proteins so far due to low serum IgE levels and low sensitization prevalence in comparison with other allergen types. All four food substances directed at substantial IgE-mediated allergies have shown surprisingly food substance-specific increases in safety and efficacy. Another milestone rendering AITs available to the pediatric population is a specific modality. A strong focus should be placed on the development of non-injectable allergy vaccine platforms for regions where certain allergens incur multiple positions of high epidemiologic hazard.

CURRENT RESEARCH AND DEVELOPMENTS

The last decade has witnessed a surge of enthusiasm and hope for immunotherapy as it has bravely entered the clinic and delivered unprecedented responses to patients with severe cancer indications and poor prognosis. For most of the last century, immunotherapy has taken a back seat to traditional cancer treatments that harnessed chemicals and irradiation. Nevertheless, in the past decade, cell-based immunotherapies have gained momentum and emerged as powerful players that vastly expand treatment possibilities from the solid tumors to hematologic malignancies (Laskowski & Rezvani, 2020). Now, with the advent of next generation sequencing and single-cell profiling technologies, it is becoming possible to explore the immune system in unprecedented depth, opening the way for new discoveries and potential breakthroughs. At the same time, the advancements in gene editing techniques for targeting and modifying the genome with high precision are translating this knowledge into a new generation of custom-designed therapies. These innovations will change the way we think of and treat patients suffering from life-threatening cancers.

In May 2020, the first convincing clinical data establishing the feasibility, safety, and efficacy of CB-derived CAR-NK cells as a viable off-the-shelf strategy for the treatment of acute myeloid leukemia (AML) and advanced B cell malignancies were reported (Naran et al., 2018). To date, this is one of the first fully commercialized cell-based therapies for sale to patients worldwide, and a multitude of related approaches are currently being explored. Combinations of NK cells with

small molecules or co-stimulatory compounds are being studied to empower their function. Engineered, off-the-shelf NK-92 cells with induced expression of cytokines or costimulatory receptors are being manufactured. Protocols have been established for the manufacture of induced pluripotent stem cell derived NK cells. These are complex cells produced on a scale that is, by nature, prone to variations that are difficult to detect, making on-demand manufacturing possibly overly complicated and time consuming. In addition, the NK cell field is still young as only a few integrative engineered cell therapies have entered clinical trials.

Clinical Trials

Immunotherapy is a treatment approach that utilizes the body's immune system to fight disease. It works by either stimulating the immune system to kill cancer cells or using synthetic immune system components. Immunotherapy has shown responses in multiple cancers and is now a standard therapy for some subtypes of malignancy. It is generally well-tolerated, has a favorable side-effect profile, and can provide long-lasting responses. However, immunotherapies often fail to produce a response in the majority of patients, and the mechanisms by which they work are still being elucidated. Clinical trials allow researchers to match a treatment to a population that stands to benefit from it, amassing evidence of safety and efficacy; however, there are additional factors that determine the success or failure of the trial as a whole.

To expand into broader patient populations, clinical trials focus on understanding the predictors of response to immunotherapy. “Molecular signatures” that differentiate non-responding from responding tumors are being investigated aggressively. Once identified, these signatures could be used to refine eligibility for specific immunotherapies, as well as to develop companion diagnostics that optimize treatment. In cases where the signature is not tumor-intrinsic or if the response mechanism is not well understood, the goal is to sensitize the ‘cold’ tumors. To this end, combination studies massively outnumber monotherapy studies in the clinical trial arena. Many of these combinations make sense biologically, while many more are what might be called ‘high-risk bets.’ High-risk combination treatments seek to leverage known responders further, as well as to combine modalities that are thought unlikely to promote synergy. A broad spectrum of combinations of existing drugs existing in the clinic or in development are analyzed together with correlates of minimal response that guide patient selection.

Immune checkpoint inhibition (ICI) blocks the pathways used by both the tumor and the tumor microenvironment to evade the immune system. It can be manipulated systemically or locally (i.e., injecting directly into the tumor). Monotherapies like anti-PD-1 nivolumab and anti-PD-L1 pembrolizumab have already received FDA approval for use with melanoma and squamous cell carcinoma of the head and neck. ICI also has the potential to sensitize tumors to treatment with chemotherapy (or radiation) by inducing an adaptive immune response to tumor neoantigens and immune co-stimulation through Upregulation of CD80/CD86 44. Maximizing the therapeutic index of ICI is of paramount importance as costs increase. Several agents such as the anti-CTLA-4 ipilimumab are being assessed in the adjuvant setting given promising results. In patients with localized squamous cell carcinoma of the mouth and throat, randomized ICI in the adjuvant setting has significantly improved overall survival. Here, adjuvant ICI has emerged as a newly standard treatment option.

Emerging Therapies

Advances in understanding of the immune system’s potent and diverse functions in combating infection and malignancy have led to the successful development of immunotherapeutic strategies that harness its full potential for the treatment of disease. The versatility of immunotherapeutic strategies is described with a focus on two distinct classes of therapies that both result in enhanced T cell effector function and target either a T cell immune receptor or ligand-based mechanism of action that neutralizes or eliminates diseased cells (Naran et al., 2018). The paradigm shift in immunotherapy has largely centered on the development of

monoclonal antibodies as checkpoint inhibitors against solid and hematological diseases. Similarly, engineered antibodies that redirect T cell-mediated killing of target cells have garnered excitement in cancer therapy with recent promising results in infectious disease. Advances in the engineering of antibody-conjugates against malignancy are paving the way to the exploration of these types of strategies in infectious disease, particularly targeting HIV and various bacterial and fungal infections. The high cost associated with the development of these agents will necessitate comprehensive evaluations of economic sustainability in regards to broad rollout in low- and middle-income countries where the burden of disease, particularly of HIV and TB, remains significant. While use of these T cell-based therapies has revolutionized treatment of hematological cancers, they have been met with complications during patient care. Common adverse effects associated with the use of these agents include neurotoxicity that requires high dose steroid administration often leading to severe side effects in patients as well as CRS. There remains a small population of patients that do not respond to immunotherapy, some attributed to the presence of various resistance mechanisms. A prominent current focus in the field is on combinatorial strategies that address these issues such as promoting an immunogenic tumor microenvironment by introducing an existing arsenal of chemotherapeutic agents with immune checkpoint inhibitors. While immunotherapies have revolutionized cancer treatment, exciting and new strategies still need to be tested in clinical trials against infectious disease, where the consequences of chronic antigen exposure and dysfunctional immunity remain a challenge.

Personalized Immunotherapy

The efficacy of cancer immunotherapy is through immunization using peptide-based TAAs or genetically modified whole tumor cells. However, there are still some challenges with respect to a limited scope of immune response. Highly personalized treatment would be an ideal solution, taking heterogeneity of tumors and their microenvironments into consideration. Recent advanced technologies, such as high-throughput sequencing-based whole-exome sequencing and machine learning algorithms, enable a rapid decomposition of tumor-specific mutations in an individual patient, which makes feasible a precision medicine in the immunotherapy field. Peptide mixtures containing MHC class I- and class II-binding neoantigens are subcutaneously co-inoculated with an adjuvant in naive mice at the inoculation sites. Since one personalized neoantigen vaccine was designed, it was applied to many checkpoints, such as immune microenvironment characterization, efficacy and safety evaluation, and administration scheduling adjustment. Subsequently, the personalized neoantigen vaccines were administrated to the individual patients in the clinic. Neoantigen (NA) specific proliferation, cytotoxicity, and recruitment were evaluated based on the second batch of PBMC. After comprehensive evaluation of the safety and efficacy of the personalized cancer vaccines, anti-cancer efficacy was analyzed. With a few modifications of the classical protocol, this platform can greatly assist the preclinical development and evaluation of personalized neoantigen vaccines (Li et al., 2023).

To exploit the groundbreaking potential of personalized peptide-based cancer immunotherapy, an easily adaptable epitope discovery platform was developed, integrated with high-definition mass spectrometry and bioinformatics tools. In conjunction with an adaptation of a strategy for diagnosis of HLA loss, the mass spectrometry platform permitted the identification of frequent mutations in a low-purity sample of a patient with melanoma. This study highlights the potential of an agnostic, rapid, and precise method for exploitation of tumor mutation burden (TMB) in the era of pan-cancer immunotherapies (Silverio & Patel, 2017). In order to facilitate the in-depth understanding of current critical findings regarding NA discovery methods, neoantigen identification chemistries, production systems, and administration routes, in addition to preclinical and clinical studies, a comprehensive review is provided aimed at providing insights into future directions for promoting the successful clinical translation of personalized neoantigen-targeted therapies.

CHALLENGES AND LIMITATIONS

After decades of extensive study, immunotherapies are now recognised as an essential tool for treating cancer. Immunotherapies significantly prevent aggressive solid tumours and/or lymphomas in some patients who do not respond to chemotherapy, providing substantial improvements in patient endurance and sense of fulfilment. Certain tumours are more favourable targets for immunotherapy than others 46. In addition to their retaliatory immunity, autoimmune ailments and germs can be aided to raise tolerance and new strategies to dismiss aberrant immunity. The effective implementation of genetic alteration and tissue regeneration might increase the host's capacity to re-build recognition of a degenerating microbe and the effectiveness of CD4+ helper T-cell subtypes in coordinating host reputation and reactivity. Numerous methods are being developed for synthetic subunit vaccines and pre-made immunity cell activatory adjuvants. But despite the untapped potential of diagnostics, insights, preventative applications, and broad vaccine development strategies, vaccination has limitations. Immunological persecution might be hidden elimination, regulating the closeness of recognition by karyotype variation, restructuration of the genomic region, or replacement of antigen encoding. Alternatively, an advantageous microenvironment might create a favourable niche for emergence of stability, and sieving of antigen escape. Soundness signals present in the target tissue might inhibit the rejection of mutated cells.

The past decade has demonstrated tremendous promise for the use of immune-based drug treatments to treat melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and more recently, bladder, kidney, breast, and prostate tumours (D'Errico et al., 2017). On the downside, immune treatment is not without its faults. Not all tumours are created equal, and there aren't many warning signs of toxicity yet. It becomes increasingly important to determine the best case for treatment as approval for additional indications is granted. Immuno-oncology is still in its relative infancy and faces many challenges and roadblocks that must yet be overcome. The traditional methods used to evaluate drug choices during the age of chemotherapy and specific treatments certainly wouldn't be appropriate for the new immunotherapies. Historically, evidence of total response rates has sufficed to make the change from phase I to phase III trials. In contrast, for immunotherapy agents, the bar was merely raised, shifting the need for evidence well into phase III studies. Herein lies the conundrum: it is becoming increasingly challenging to extend the viability of combination treatments established in clinical practice. Little evidence exists to persuade investigators to deviate from simply using these drugs for standard monotherapy. Expanding the use of such agents may facilitate drug sales, but the viability of these combinations to improve patients' lives is far from certain. At the other end of the spectrum, PIBORs have simply not yet shown impressive efficacy in ongoing clinical preliminary studies. Their security profiles need to be upgraded. The response percentage keeps varying for indefinite reasons after being tested from many viewpoints, with variable antigen particularity and expression levels, and very recently, the function through the gut microbiota. A contemporary slide shows evidence suggesting that the major impact of these drugs may have little to do with cancer immunity but other elements. Various microbiological, virological, and magnetic resonance imaging mentions have been put forward as possible screening strategies to demonstrate a non-cancer-dependency impact.

Adverse Effects

Immunotherapy has improved outcomes for treatment of various malignancies; broader access to treatment, patient education, clinical research, and the continuing evolution of different immunotherapeutic techniques and medications should all be prioritized in the future. Oncologists are now confronted with the new challenges of managing a novel range of adverse events unique to immunotherapy, given the potentially life-threatening severity and uncontrollable nature of such adverse events (Rahman et al., 2022). Immune-related adverse effects in patients undergoing immunotherapy typically differ from non-specific adverse reactions involving damage to normal tissue and generally present as an

exaggerated inflammatory response, primarily involving autoimmune processes, with a relatively long lag before onset of damage and prolonged effector cell presence after cessation of therapy (Dahiya et al., 2020). These observations suggest that early supervision is crucial and that proactive detection techniques should be developed not only for on-target autoimmune-type reactions but also for off-target damages, in consideration of how cell relocation, proliferation, and effector function occur in parallel, thereby leading to therapies that are potentially more effective and less damaging.

It is important to explore the main immune-related adverse effects linked with immunotherapy and the underlying biological mechanisms of their occurrence. Severe adverse effects driven by the immune system hitting healthy normal tissue would necessitate careful early monitoring, making it necessary to investigate pathways resulting in clinical grades ≥ 3 immune-related adverse events for possible early detection. Understanding the mechanisms behind well-studied adverse effects would not only clarify their relationship with treatment but, more importantly, would also help in consideration of which patients may be at risk. As clinical stage risk factors cannot yet be accurately defined for most autoimmune skin diseases and there are other mechanisms of action for cancer treatment methods, there is a special need to delve deeper into early monitoring of patient-specific high-risk strategies to rule out undesired effects in patients.

Cost and Accessibility

The advent of immunotherapy is the most profound paradigm shift in the Cancer Therapy landscape since the introduction of Chemotherapy over 70 years ago. Anti-PD-1/PD-L1 immune checkpoint inhibitors are the most successful class of Cancer ImmunoTherapeutics, as evidenced by their unprecedented clinical success and approval for use in >25 different cancers. The broader impact of Immuno-Oncology has been fueling the explosive growth of novel investments towards the R&D of additional varieties of immuno-oncology drugs/applications against an ever-expanding range of cancers. Fueled by some of the most high-profile collaborations and acquisitions across pharmaceutical, biotechnology, diagnostic, and other closely allied sectors, this monumental growth trajectory has glaringly revealed vulnerabilities across multiple sectors along the Immuno-Oncology industry road map.

Given the breath-taking breadth of the Immuno-Oncology success story, it would be intuitive to expect that ample solutions and successful defense strategies exist to counter these economic vulnerabilities. However, the odds are stacked against everyone involved in supporting the booming Immuno-Oncology industry: Patients are becoming increasingly aware of the potential of these novel drugs/applications on their condition, and in turn, they are becoming ever more demanding of Health Care Providers (HCP) and Legislators to ensure their fair and equitable access. Pharmaceutical companies have invested billions of dollars into the discovery and development of Novel Anti-PD-1/-L1 Antibodies, Conventional Chemo-radiotherapies, and CAR-T immune therapies (Au, 2017). The clinical success and multi-billion dollar revenue generated by these drugs have invigorated the furious chase for new mice models and novel uses of Ab-mediated drug combinations against an increasing number of cancers. Botched clinical trials and late-stage failures have nevertheless French-kissed both large and small immuno-oncology drug and vaccine companies and consortia, many of whom are now barren of monetizing drugs/applications. Publicly traded companies involved in the AAV platform space analysis have charting curves like that of ICAR cars going off track; it will take incredible ingenuity and untold treasure to get back on track and avoid disaster. Genotypic/person genomic neo-antigen discovery and patient selection analysis companies are similarly scrambling for solutions and losses at this point; adoption of their technologies and solutions must overcome the draconian level of hurdles facing such a transformative potential. Lesions radiomics is also becoming the pagoda among Health Care Providers, as symbolized by the exclamation point question posed, “Is it always targeted/sequencing

biopsy, not detection on CT-PET!?" (Adunlin et al., 2019).

Regulatory Hurdles

Adverse effects that limit the interpretation of data following this routine include hypersensitivity reactions and fevers that appear in approximately 40% of vaccinated patients. Clarifying the types of patients that should be treated with these active therapies and those who should not, will require further research. These studies could entail the exercise of international multisite protocols, multicenter studies and their simultaneous development. Although this paradigm can result in a more equal distribution of resources, it could bring about slower results since sometimes it takes a long period to get research results ready.

Another strategy could involve commercializing gentler combined therapies. The entire body of scientific research is growing, particularly in the field of genetic engineering and gene therapy, including those based on complemented anti-idiotype or "natural" antigenic approaches that are closer to the mechanisms of human immunity. Even the most irrefutable organized evidence can be denied by too many authorities that build walls or bureaucratic roadblocks to stall the solutions (Fox et al., 2011).

Nevertheless, some impediments could have an even more competitive edge. This pertains to the warped control of information, particularly in the field of genetic engineering. Genetic monoclonal antibodies have been subjected to enforced secrecy. Similar efforts to blacklist less well-known individuals or "other" vaccines are also observed. Hence, a real "magna carta" for this field and the establishment of even independent civil rights committees are needed. In developed countries, an intelligentsia whose leaders seem to be infallible figures should be encouraged.

FUTURE PERSPECTIVES

The 20th century brought about a steady stream of new drugs directed at targeting some of the most pernicious changes in cancer cell biology. For the most part, these agents had their roots in the pharmacopoeia of non-specific anti-cancer agents and efforts to target a specific oncogene now including small molecules, but a wide range of approaches have been pursued. Some of the recent suggestions have highlighted the inappropriateness of trying to prescribe a new drug on rational experimental data alone and called instead for opportunities to match needs to what is available. Pools of more than 100,000 compounds plus connectors exist to disseminate this information. While this intrinsic variation from life itself may present a hurdle for large clinical trials and a sustainable cargo, the extraordinary number of heterogeneous samples or fusions available may finally shift a desire to understand to actually helping the one on the community. Of note in this regard, next generation sequencing has already revolutionized not only how drug targets are selected, but whose drugs are developed 53. Coincidentally, arguably the most "anti-cancer" therapeutic arrived at the decade's start in the form of anti-idiotype antibodies in conjunction with an immune stimulating multifunctional carrier for adjuvant therapy and distant site/visceral metastases; clearly here was the opportunity to really turn back the clock on aberrant neo-antigen expression and immune evasion. What was immediately obvious was that without a massive sandbagging of contemporary technologies investing thought at the scheduling level, it would likely be decades before the intimate connectome of the immune microenvironment could be accessed by conventional means. Fortunately, many groups have stepped into the void as emerging progress in high-dimensional analysis not dissimilar in flavor to network analysis became widely available in biology. High-parameter imaging and mass-cytometry based technologies, unilateral gating, and density-based clustering amongst others, have been operationalized into a broad suite of tools suitable for all but the rarest experimental situations. Notably, as well as revealing critical but unenvisaged new biology, many circuits suggested from previous knowledge, including absolutely fundamental ideas such as the existence of a sentinel-activated T cell that jitters not just prior to secretion but dynamically imparts spatial coherence and elongation to opening channels, have been

validated (Naran et al., 2018). Progress is also inevitably being made clinically aided by parading the new perfusion and molecularly targeted agents on this horse carousel. Combined with the new mouse each of which is too small to detect drift in periphery or manipulate remotely, it is suddenly possible to tighten up embryonic growth in lieu of germline kill loops. Further empirical work in centrifugal growth-motif systems may soon shed light on how the control of metastasis emerges from within.

Innovations in Treatment

Over the past couple of decades, advances in cancer biology and pathogenesis have resulted in immunotherapeutic strategies that have revolutionized the treatment of malignancies. The treatment of cancers transitioned from relatively non-selective toxic agents such as surgery, radiotherapy and chemotherapy, all of which resulted in untold morbidity, to specific, mechanism-based therapies including targeted small molecules and monoclonal antibodies (Naran et al., 2018). Unfortunately, despite educating the immune system to eliminate transformed cells, mechanisms of immune tolerance and immune evasion have emerged. Various strategies to reverse these mechanisms are under investigation; the type and balance of immune responses dictate treatment outcomes.

Infectious diseases remain a leading cause of morbidity and mortality worldwide, necessitating novel, innovative therapeutics that address the growing problem of increasing antimicrobial resistance. The advances made in targeted therapy in cancer, coupled with the general principles and mechanisms of immunity, may inform their rational development in the context of therapeutic intervention of infectious diseases. The evolving role of key targeted immune interventions currently approved and in development for various cancers and infectious diseases, including AIDS, tuberculosis (TB) disease, and drug-resistant infections are accentuated.

The general features of two specific classes of treatments are discussed: i) adoptive therapies, including those that specifically enhance T cell effector function, including the transfer of T cell receptor (TCR)- or chimeric antigen receptor (CAR)-engineered T cells; T cell checkpoint inhibitors; and vaccines, which provide a better stimulus for the activation of disease-specific T cells and the development of immunological memory, to preneoplastic tissues and viral infection or reactivation; ii) ligand-based therapies that neutralize or eliminate diseased cells, including antibodies targeting tumor and infected cell surface-associated ligands, enzymes, or receptors, as well as antibody-drug conjugates. Specific diseases that lack an appropriate remedial treatment and those for which imminent selective intervention against the disease are anticipated, namely cancer, HIV/AIDS, TB disease, and drug-resistant infections, are discussed. Numerous host factors which constitute the immune system influence treatment outcomes and are accountable for disease progression or regression.

Potential for Combination Therapies

The early successes of immune checkpoint inhibitors in melanoma and lung cancer have driven an explosion of interest in immunotherapy as a treatment for cancer. Tumor-directed biological agents, other immune-stimulating agents, and combination strategies to both activate the immune system and deactivate immunosuppressive circuits are being explored for all major tumor sites. While the field is nascent and ongoing research holds both great promise and significant challenges, recent breakthroughs support the hypothesis that cancers can be treated with the immune system (Sanghera & Sanghera, 2019).

There is now substantial preclinical and clinical data supporting the potential benefit of combination approaches to cancer immunotherapy. In particular, strategies designed to increase the amplitude and durability of the immune response, either by using combination therapies or by the concurrent use of separate therapies given at different times, are the most attractive approaches with regards to immunotherapy. However, the potential for adverse effects should be carefully considered.

Several new immune-related adverse events (irAEs) have emerged with the use of immune checkpoint inhibitors, leading to severe autoimmunity in different tissues. The combination of therapies targeting both CTLA-4 and PD-1 leads to a striking increase in the incidence, number, and severity of irAEs and warrants further study.

Curve 1 depicts the proposed disease-disease model as well as the disease-therapies paradigm. The studies showing that pre-existing immunity can suppress initial disease initiation and growth are very important to the presenting models in RasE and RafA mice. These studies rationalize sequential combination vaccines targeting both HSP- and HCAs against growing cancers. Some conclusions can be made on the immunogenicity of HSP-based cancer vaccines by considering several relevant mechanisms underlying presentation to CD4 and CD8 T cells. Strategies to personalize immunotherapy according to the individual patient by designing neoantigens and predictive biomarkers should be explored for improving efficacy and minimizing toxicity. Given the multi-faceted and heterogeneous nature of tumors and the mounting evidence pointing towards the existence of several distinct immunosuppressive circuits, including Tregs, MDSCs, cooperative immune checkpoint inhibition, and tumor hybridity, it seems that different strategies should be explored simultaneously and synergistically to strengthen the full potential of immunotherapy in cancer treatment.

Global Impact of Immunotherapy

Novel trials in immunotherapies represent the health care cutting-edge with expectations of helping diseases with an unmet need of treatment, for which only conservative care options are present, leading to a collection of results to be evaluated (Ascierto et al., 2018). These exciting findings are expected to lead to the generation of new therapeutics for patients with need and correspondingly to additional sanctions for the working companies by the local health authorities. A recently presented result, for the new monoclonal antibody (mAb) for the treatment of immune-mediated inflammatory diseases, was in line with the expectations. Conversely, a result showing no better outcome or disproportionate sequelae between groups was a notable disappointment. However, queries concerning the design of the trial and/or the drug choice will likely lead to subsequent efforts. A new trial for change of indication, formulation, or dosing regimen may well be filed for review seeking sanction considering, for example, how the presented drug may remedy diseases not yet addressed by the already present pharmacotherapy. The greatest interest, however, is directed toward trials aimed at results with the potential to transform treatment paradigms in previously untreatable diseases. Such results will likely be prepared and scrutinized for a long time prior to running the trial 56. Therefore, it is anticipated that the absence of a posting of a result is on account of this level of scrutiny of a trial rather than a failure to reach an anticipated milestone. Nevertheless, it is a prerequisite that such information be collected and disseminated to avoid the presentation later triggering unanticipated adverse impacts.

Large drug companies sponsor several trials and may present scores of trial results across many diseases. Such companies operating in many therapeutic areas typically focus their input on topics of a scope broader than the drug focuses on, generally opting not to present additional results. Over the last few years, the treatment of cancer has undergone a revolution with the generation of checkpoint inhibitors and CAR T-cells. Currently, clinical trials with drugs designed to stimulate effector immune cells and/or deprive tumors of immune suppressive signals comprise a continuing wave of disclosing results. The rapid pace of this research and the public interest accompanying disclosures mean that new concepts and protocols may classify tumors differently as research leads to finding new targets or combinations of targets. A few decades earlier, patients were informed as they entered into a trial, attending an information session and undergoing injector question and answer sessions. With the rapid rush of new drugs, however, the pace of initial approval has now outpaced this type of diligence, and news of potential treatment opportunities reaches patients via social media.

ETHICAL CONSIDERATIONS

Advancements in healthcare and technology pose ethical dilemmas for researchers. Immunotherapy applies this technology to the immune system in combating diseases such as cancer and infectious diseases. Vaccine development is an important aspect of preventative immunotherapy, despite therapeutic immunotherapy representing the majority of clinically available treatments. How preventive vaccines are designed and assessed for their potential to induce beneficial immunity is an ethical issue that companies engaging in vaccine development should consider. The principles of vaccine immunogenicity call for an understanding of key immune signals underlying vaccine-induced humoral and cell-mediated immunity. Such understanding should also include how signals can be manipulated to enhance vaccine-induced immunity, the relevance of analyzing immune parameters in the context of human vaccine studies, and how safety concerns associated with the use of novel technologies may be surpassed by their potential benefits (Naran et al., 2018).

Informed Consent

Informed consent is imperative in the treatment of cancer immunotherapy. This applies to the cancer patient and the patient's family is certainly informed of the process, the benefit and the side effects (Meiliana et al., 2016). In general, based on the patient selection criteria, the physician informs the patient. If needed, a discussion and consultation with related specialists can happen. The aim consultation includes the type of information about the patient's condition, the purpose of the therapy, the expected benefits, the side effects, the chances of recovery, and so on. After the consultation and there is agreement about the role, the doctor writes an explanatory letter, and then the doctor, the patient and the patient's family sign the document. In the case of cancer immunotherapy, the patient will receive an educational video about the dangers of not conducting immunotherapy if the patient is a patient candidate. The life experience of immunity patients and the understanding of the immunotherapy process, before and during, and the possibility of side effects will be explained in that educational video. The treatment will be explained detail using pictures and diagrams regarding the patient's immunotherapy process in the hospital or related laboratories by trained personnel. When the patient is hospitalized for treatment, blood and its derivatives will be taken depending on the source of the immune cells needed for treatment, after the results of laboratory inspection that are needed to prepare the patient for treatment are obtained. The action plan during the patient's treatment period will be presented and explained. Safety against COVID 19 will also be given to health workers, artificial intelligence, physical distancing, and so forth. All the positive things that can increase expectations in the hope of being cured will be informed compared to the behavior of other centers that overlooked the patient, said that immunotherapy was not suitable for them.

Equity in Treatment Access

Administrative barriers posed by health authorities slow down the process of access to immunotherapy. Accessibility of immunotherapy agents is otherwise quite limited for healthcare workers working in the private sector too, especially for mid-level providers and low-income countries. Emergent access for checkpoint inhibitors is feasible through sales and donations, given a good understanding of the drug details and throughput of patients with proper public relations.

Currently, much less than a quarter of cancer patients worldwide receive a proper diagnosis and even less as a direct consequence receive appropriate therapy for the disease. To halt and subsequently control this burgeoning epidemic, a roughly fourfold increase on current spending levels is required, unless current funding surfaces from a different mechanism where immunotherapy might benefit from initial trials aided by government-backed supply of the known best agents available to confront the battle (Naran et al., 2018).

Other interesting factors which were recently shown to affect ethnicity and religion showed no statistically significant correlation in continuing

therapy with checkpoint inhibitors. Interest in establishing a variable on seeking alternate treatment or using unproven agents is recommended. Further comparison of second (and third) line therapy in post immunotherapy patients between the two groups is warranted (Patil et al., 2022). As none of the patients in this study had been on cemiplimab or dostarlimab; outcomes in these patients can only be revealed in a later analysis.

CONCLUSION

Immunotherapy is revolutionizing the treatment of cancer by delivering unprecedented responses in patients with poor prognoses. In this treatment modality, the immune system is harnessed to fight malignant cells. Cell-based immunotherapies are a subset of immunotherapies that utilize live cells to expand treatment possibilities. They start with the isolation of patients' or donors' immune cells, which are then engineered or stimulated ex vivo in order to elicit a potent response against overt or nascent diseases before finally being reintroduced back into the patient, similar to "living drugs" (Laskowski & Rezvani, 2020).

Therapies utilizing chimeric antigen receptor (CAR) engineered T cells have transformed the treatment of hematologic malignancies. Recent successes with CAR-Ts have revived interest in NK cell-based therapies as an off-the-shelf strategy. Multiple preclinical studies and early-phase clinical trials have been launched to evaluate the safety and efficacy of CAR-NK cells based on cells derived from peripheral blood, bone marrow, or umbilical cord blood. These approaches generally rely on K562 feeder cells transduced with multiple genes to support NK cell growth and transduction. Newer, CHO-based technologies with a mesenchymal stem cell-like platform have shown potential as clinically compatible next-generation cell sources.

Adoptive cell therapy (ACT) utilizes immune cells generated ex vivo in order to treat cancer. While ACT can be performed with T cells, there are also FDA-approved NK cell therapies. The principles, players, and limitations of ACT were largely drawn from the rapidly growing clinical applications of T cell-based immunotherapies. Characterization of T and NK cell therapies has exhibited interesting differences that shape clinical choices. Transcriptional studies rely on targeted multiplex panels to quantify RNA species of interest, while the development of droplet-based platforms has enabled the analysis of thousands of RNA species with a single drop of blood. The adaptive immune response manifests over multiple days or weeks, and efforts to quantify it have typically focused on the so-called establishment phase of the interaction between T cells and tumor ROS that has been pioneered by the kinetic proofreading model.

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