ABSTRACT
In the dynamic landscape of cancer treatment, discovery-based research in T cell biology has proven transformative, ushering in revolutionary immunotherapies. This paper navigates the impact of fundamental research on cancer therapy, tracing its evolution from 19th-century trailblazers Wilhelm Busch and Friedrich Fehleisen to recent breakthroughs by James P. Allison. By understanding T cells, the immune system’s superheroes, we can illuminate the pivotal role of selectively targeting and eliminating cancer cells with unprecedented precision. Advances such as checkpoint blockade antibodies have freed tumor-infiltrating T cells from inhibition, allowing them to kill tumor cells effectively. This was a revolutionary breakthrough. Historical insights, such as the discovery of immunocompetent recirculating lymphocytes and the function of the thymus, laid the groundwork for these advances. This ongoing dialogue on resource allocation recognizes foundational research as the cornerstone for innovative therapies, ensuring a sustainable pipeline of discoveries that shape the future of T cell cancer treatment.

KEY WORDS: immunotherapy, T cell biology, checkpoint blockade, thymus, foundational research, CAR T cell therapy, spontaneous tumour regression

1 | INTRODUCTION
In 1906, the Flexner report recommended that medical schools integrate the study of natural sciences into medical teaching and practice, following the model set by the recently established Johns Hopkins School of Medicine. Connecting physiology with clinical medicine eventually laid the groundwork for what we now refer to as “translational medicine” from discovery-based research (Pardoll, 2012). The pivotal role of discovery-based research in cancer treatments, especially in T lymphocyte (T cell) biology, is strikingly evident. Immunotherapies mark a shift in cancer treatment and instill newfound optimism among patients and families facing formidable challenges. Capitalizing on foundational insights, cancer therapies can target and eliminate cells selectively and precisely with the body’s own immune defenses. The role of discovery-based research in expanding the comprehension of fundamental biological processes has fostered breakthroughs with implications in medical science and patient care. The past five decades have seen activity in immunological research of T cell biology which has shown remarkable achievements from laboratory discoveries being translated into tangible clinical successes (Waldman et al., 2020).

The curiosity-driven pursuit of advancing immunotherapies formed the foundation of scientific progress, leading researchers to unexpected findings and novel insights (Rasheed & Koyyala, 2021). The evolution of studying T cell biology in the context of cancer treatment highlights the critical need for sustained funding in this realm. Financial support is crucial for advancing the understanding of immune responses, paving the way for innovative breakthroughs that promise to reshape the landscape of medical science and provide effective solutions to the challenges posed by cancer. This review aims to explore the historical and contemporary contributions of discovery-based research to the advancements in T cell biology and its impact on cancer immunotherapy.
DISCUSSION

2.1 Early Days of Immunotherapy

The work of Busch and Fehleisen in the nineteenth century provides insights into the impact of discovery-based research in the immune system’s role in combating neoplastic diseases (Rasheed & Koyyala, 2021). At the time, they were independently investigating ways to culture *Streptococcus pyogenes*, a pathogen with a long history as the causative agent of erysipelas - an infection that has rapid-onset, surface-level skin infection often affects elderly and immunocompromised individuals, newborns and young children, typically following bacterial entry through a breach in the skin (Celestin et al., 2007). In their work to culture the bacteria, Busch and Fehleisen observed that tumor regression occurred in tissues following bacterial inoculation and disease development. This phenomenon is known as spontaneous tumor regression.

Scientists have documented and been puzzled by spontaneous tumor regression for centuries. It is sometimes called the St. Peregrine tumor (Jessy, 2011). St. Peregrine Laziosi, a priest who lived from 1265 to 1345, suffered from cancer of the tibia; St. Peregrine needed his leg amputated due to a severe infection caused by the tumor, which had broken through the skin, possibly due to bacterial infection. Remarkably, when the scheduled operation approached, his physician was astounded to find no trace of the tumor. According to stories, after a night of intense prayer, St. Peregrine’s illness disappeared, which some attribute to divine intervention (Figure 1). Astonishingly, St. Peregrine never suffered a recurrence of his tumor. Still to this day, St. Peregrine is known as the Patron Saint of Cancer Patients.

Busch and Fehleisen’s unexpected discovery of the link between *Streptococcus pyogenes* infection and tumor regression illuminated a previously unnoticed connection between concurrent infections and tumor resolution, catalyzing a profound impact on scientific inquiry. Their findings not only unveiled a novel aspect of immunology but also instigated a surge of interest in exploring the intricate interplay between the immune system and cancer. Their work acted as a catalyst for further investigation, prompting researchers to delve deeper into the mechanisms underlying spontaneous tumor regression and the immune system’s role in cancer defense. As Isaac Newton famously remarked, “If I have seen further, it is by standing on the shoulders of giants.” In much the same way, the pivotal discoveries made by Busch and Fehleisen provided a solid foundation upon which subsequent scientists could build, propelling the field of cancer immunology forward into new realms of understanding and discovery.

Expanding upon the legacy established by Busch and Fehleisen, this newfound comprehension served as a springboard for the endeavors of William B. Coley, who was widely acknowledged in the realm of immunology (Figure 2). Coley, in his capacity as a young surgeon, embarked on a path of innovative research that would leave an indelible mark on the field (Řihová & Šťastný, 2015). Coley expanded the literature by observing that sarcoma patients who developed superficial erysipelas after surgery did better than those who did not. Coley went on to treat his cancer patients with erysipelas injections, known as Coley toxins. Despite showing promise, these toxins were high-risk, and there was an understandable aversion to exposing patients to live streptococci (Zacharski & Sukhatme, 2005). Coley himself reported success rates ranging from around 10% to 20% in certain cases, particularly with sarcomas and some other forms of cancer (McCarthy, 2006). While some patients experienced significant remissions or even apparent cures, others did not respond to the treatment, and some experienced severe side effects, such as infection, which led to mortality. (Řihová & Šťastný, 2015). This method would be abandoned when innovations in radiotherapy and chemotherapy were introduced at the beginning of the 20th century. Immunotherapies would see no significant expansion until the 1960s with the discovery of T cells and the elucidation of the thymus.

2.2 Thymus Revisited and Discovering T Cells

T cells derive their name from their association with the thymus gland, where they undergo maturation after
production in the bone marrow. When fully matured, these white blood cells circulate throughout the body, patrolling for signs of infection or abnormalities (Cleveland Clinic medical professional, 2021). Playing an indispensable role in the immune system, T cells constitute a vital component of adaptive immunity, orchestrating targeted responses against pathogens, including viruses, bacteria, and abnormal or cancerous cells (Zhang & Zhang, 2020). The absence of T cells would elevate the risk of every encounter with pathogens to a life-threatening level. T cells play a pivotal role in eliminating infected or cancerous cells and contribute actively to the immune response by collaborating with B lymphocytes (B cells) to eradicate invading pathogens (Vogelzang et al., 2008). Their multifaceted functions emphasize the critical nature of T cells in preserving immune surveillance and in responding effectively to various threats within the body.

With the discovery of T cells in the 1960s and 1970s, researchers were engaged in critical questions surrounding the immune system (Kaufmann, 2019). It was James Gowans, who conducted research in immunology during the late 1950s and early 1960s, that would help pave the way to advancing understanding of how lymphocytes, including T cells, migrate within the body (Gowans et al., 1962; Kaufmann, 2019). Initially, Gowans and his team experimented on mice to understand how the immune system initiates responses to foreign antigens and pathogens and how graft-versus-host reactions would occur within thoracic duct cells (Gowans et al., 1962). In this process, they sought to explore the role of small lymphocytes, or B and T cells, critical players in the immune system. The researchers used radioisotope labeling to enable identification and characterize of specific subsets of immune cells. By selectively labeling certain cell types, scientists could distinguish between different populations of lymphocytes and other immune cells, shedding light on their roles in immune responses.

Gowans’s use of radioisotopes established the methodologies in immunology research that enabled scientists to study immune cell behavior, migration, and interactions, contributing to a more comprehensive understanding of the immune system’s intricacies (Zhang & Zhang, 2020). By utilizing radioisotopes to track the movement of lymphocytes, Gowans’s research uncovered a previously hidden world of cellular migration within the body (Gowans et al., 1962). He observed that after injecting labeled lymphocytes into an animal, these cells would leave the bloodstream, enter lymphoid tissues such as lymph nodes, and later return to the blood. This movement was unexpected, as the prevailing view until then was that lymphocytes were largely stationary. His findings not only revealed the continuous circulation of lymphocytes, including T cells, through the bloodstream and lymphoid tissues, but also provided a crucial foundation for deciphering the migratory patterns of these immune cells (Johnson, 2021; Wallersteiner, 2020). This newfound comprehension opened a gateway to understanding the orchestration of immune responses, igniting curiosity about the journeys immune cells embark upon in their surveillance and defense roles. Gowans’s studies laid the groundwork for subsequent investigations into the thymus’s role and the eventual discovery and characterization of T cells as a distinct population of lymphocytes, showcasing scientific inquiry’s iterative and collaborative nature (Kaufmann, 2019; Wallersteiner, 2020).

Figure 2: From left to right; Wilhelm Busch (1826–1881) observed that injecting erysipelas infection into a patient’s tumor caused it to vanish (Waldman et al., 2020). Friedrich Fehleisen (1854–1924) identified Streptococcus pyogenes as the causative agent of erysipelas (Waldman et al., 2020). William Coley (1862–1936) created what would be known as Coley’s Toxins (Rihová & Šťastný, 2015). Photo credits: Wikipedia
Inspired by Gowans's revelations, subsequent researchers, such as Jacques Miller, took this understanding to explore the thymus's mysteries and unveil its central role in nurturing T cells. “I was always thrilled by the brilliant lectures given in London by Peter Medawar and Jim Gowans. They were towering figures, both physically (over 6 ft tall) and in their impact on immunology. Their enthusiasm was infectious, and I began to wish that I had chosen to work on lymphocytes and immunological tolerance rather than on mouse leukemia!” (Miller, 2004). Gowans's curiosity-driven insights thus initiated Miller’s journey into the intricate dynamics of immune cell migration, fueling a cascade of discovery-based research in immunology.

At the time of the discovery of the T cell, researchers were interested in understanding the function of various organs in the immune system. Miller’s initial research objective was not specifically to study the thymus; instead, he aimed to explore the immune system's overall function through experiments on mice lymphocytic leukemia (Miller, 2011). It was known that lymphocytic leukemia in mice, whether occurring spontaneously or triggered by irradiation or chemical agents, involved the thymus and that removing the thymus in adult mice prevented disease development. However, researchers had not investigated the role of the thymus in virus-induced leukemia (Miller, 2011). In the early 20th century, the significance of the thymus eluded doctors, who often mistook its enlarged state in infancy as abnormal since, after autopsies following illnesses, the thymus diminished in size which was deemed typical. In instances of infant mortality under anesthesia for unrelated conditions, blame was wrongly attributed to the thymus for allegedly obstructing breathing rather than to the anesthetic itself. Some physicians even proposed irradiation as a means to reduce the organ's size (Miller, 2004).

In early experiments, Miller and his colleagues conducted thymectomy procedures on mice, surgically removing their thymus glands (Miller & Sadelain, 2015). These efforts aimed to understand the role of the thymus in leukemia. They found that it was crucial to administer leukemic extracts at birth to induce leukemia. Mice that were inoculated with leukemia at birth and underwent a thymectomy at 4-5 weeks old did not develop the disease unless they were later grafted with syngeneic thymus tissue from newborn donors. Remarkably, even grafting the thymus six months after thymectomy allowed for leukemic transformation, indicating that the virus remained latent in the mice (Miller, 2004).

The most groundbreaking observation came when Miller noticed severe immunodeficiencies in the mice without a thymus, which became highly susceptible to infections, especially from antigens (Miller & Sadelain, 2015). Histological examinations revealed a significant deficiency of lymphocytes in the blood and lymphoid tissues, as well as liver lesions suggestive of hepatitis virus infection. These results reveal that the thymus is essential in developing and maintaining the immune system. Miller’s work demonstrated that the thymus was critical for producing immunologically competent lymphocytes during the neonatal period.

Testing their immune response capacity, Miller grafted mice that underwent a thymectomy with skin from allogeneic mice and rats, observing that they accepted the grafts (Miller & Sadelain, 2015). This supported the hypothesis that the thymus produces essential lymphocytes for immune responses. These results shifted Miller’s research focus from leukemogenesis to immunogenesis, revealing the thymus’s vital role in T cell maturation. Despite initial hesitation due to skepticism from the immunological community, Miller’s work revealed the thymus’s critical role in producing immunologically competent T cells, marking a significant breakthrough in understanding immune system function (Miller & Sadelain, 2015).

The discovery-based research on the role of the thymus, a once-dismissed vestigial organ, has since emerged as a crucial regulator of immune functions. These revelations not only elucidated the intricacies of T cell maturation but also laid the foundation for a cascade of subsequent research. Miller’s contributions fueled a deeper understanding of the dynamic interplay between the thymus and the broader immune system, setting the stage for several advancements in

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**Figure 3.** The interaction among blood circulation, the lymphatic system, and the composition of immune cells in both incoming (afferent) and outgoing (efferent) lymphatic vessels. The flow of lymph fluid is depicted by blue arrows. Image provided by Johnson, 2021.
immunology (Miller & Sadelain, 2015). His pioneering work not only defined the thymus’s role but also inspired a new era of curiosity-driven investigations, ultimately influencing the development of immunotherapies that harness the power of T cells for targeted cancer treatment.

The work performed by Gowans and his methodologies with radioisotope-based imaging modalities would go on to be adapted for monitoring treatment responses and personalizing immunotherapy approaches, allowing for tailored interventions based on individual patient immune profiles. It also set the stage for the work of Jacques Miller, which showcased the thymus as a central hub for T cell maturation (Miller, 2004). The synergy between Gowans’s exploration of lymphocyte migration and Miller’s investigations into T cell development highlights the collaborative nature of research. This work has become instrumental in contemporary immunotherapy. The knowledge from their collective efforts has played a pivotal role in pioneering the advancement of immune-based cancer therapies, leveraging insights into immune cell behavior and T cell maturation to develop innovative treatments that harness the body’s immune system to combat cancer effectively. This emphasizes the profound and interconnected impact of historical and contemporary curiosity-driven research on shaping the trajectory of cancer treatment.

2.3 T Cells and Cancer Treatment

In his lecture at the Parker Institute for Cancer Immunotherapy, James P Allison, 2018 Nobel Prize winner, describes his amazement at the extraordinary ability of T cells to “decide” on how to attack foreign entities. “I remained fascinated by the complexity of the T cell response, which involved moving through the body to sample different antigens and then making decisions about when to proliferate in order to amass an army of cells that would eradicate any foreign entity. The superhero of our immune system! But, how did T cells make such complicated decisions? What were the signals that regulated T cell responses?”

Initially, Allison’s cancer immunotherapy work focused on activating T cells through approaches including cytokines and antigenic vaccines (Allison, 2018). However, a limited understanding of T cells prompted a shift towards fundamental research on the molecular mechanisms of T cells, revealing intricate inhibitory pathways that could be manipulated for potent T cell responses against tumors. This paved the way for developing an immune checkpoint blockade, a transformative cancer therapy. Through a series of experiments, Allison sought to identify the T cell receptor (TCR), a task considered the “holy grail” of immunology (Mitra et al., 2023; Allison, 2018). The discovery of a clonally-specific antigen on T cells, later confirmed by others, led to the proposal that this protein was the elusive TCR. Despite initial skepticism, functional data from other laboratories corroborated the findings, culminating in the intense race to clone TCR genes, which other researchers ultimately achieved (Allison, 2018).

The complexity of T cell activation became evident, revealing that TCR engagement alone was insufficient to activate these cells. The unexpected discovery of cytotoxic lymphocyte antigen-4 (CTLA-4) introduced a pilgrim shift by opposing Cluster of Differentiation 28 (CD28)-mediated costimulation (Mitra et al., 2023). CD28 is a co-stimulatory molecule located on the surface of T cells. Upon encountering an antigen-presenting cell (APC) presenting a matching antigen, CD28 engages with a ligand on the APC, delivering a crucial secondary signal that triggers T cell activation, proliferation, and functional responses; however, with the discovery of CTLA-4, which emerged as the first immune checkpoint capable of negatively modulating T cell activation, significant advancements were made in understanding immune regulation (Waldman et al., 2020). CTLA-4 operates by counteracting the co-stimulatory effects mediated by CD28, thus dampening T cell responses, and would play a
crucial role in maintaining immune system homeostasis (Hudson et al., 2023). Allison’s experiments showcased that blocking CTLA-4 with an antibody would lead to anti-tumour immune responses, marking a pivotal moment bridging the historical and contemporary aspects of T cell research (Waldman, Fritz, & Lenardo, 2020). From fundamental discoveries to recognizing immune checkpoints, this path illustrates how understanding T cell intricacies informs the development of novel immunotherapies (Allison, 2018). The interplay between T cell signals, costimulation, and immune checkpoints, enriched by the cumulative efforts of researchers spanning decades, not only elucidates the inner workings of the immune system but also unveils novel avenues for treating cancer by harnessing the potency of T cells with proven success.

Clinical trials have not only solidified the promise of T cell immunotherapies but have also persuaded even the most skeptical individuals (Sanders, 2018). These innovative cancer treatment methods harness and enhance the body’s immune system to recognize and target cancer cells more effectively (Kaur, 2020). One such success is the Chimeric antigen receptor (CAR) T cell immunotherapy (Mohanty et al., 2019). CAR T cell therapy involves genetically modifying a patient’s T cells in the laboratory to target and kill cancer cells (Figure 4; Huang et al., 2023). The process begins isolating peripheral blood from the patient. Apheresis, a procedure using a specialized machine to collect blood components, is commonly used for this purpose (Mohanty et al., 2019). T cells are then isolated from the peripheral blood sample through leukapheresis, a procedure that removes white blood cells. Next, the cells are transduced with a vector containing the CAR gene, followed by the expansion of CAR T cells in vitro. Finally, the modified T cells are returned to the patient to combat cancer (Huang et al., 2023). This therapy has extended lives such as that of a woman who had a tumor the size of a grapefruit in her lung from melanoma, who is still alive and healthy 13 years later; the 6-year-old who was close to death from leukemia, now in third grade and in remission; and the man with metastatic kidney cancer whose illness continued to diminish even after treatment was halted (Sanders, 2018).

The foundational research that has led to approaches that harness the power of the body’s immune system to target and destroy cancer cells is offering new hope to patients who once faced grim prognosis. A meta-analysis conducted by the National Cancer Database in the United States focused on survival rates among patients with stage four lung cancer. Historically characterized by dismal outcomes, these aggressive forms of cancer have posed significant challenges to clinicians and researchers alike (Foster et al., 2019). However, the analysis revealed optimism: patients treated with immunotherapy exhibited a median survival of 17.3 months, surpassing the 14.4 months observed in those receiving conventional chemotherapy. This is because standard cancer chemotherapy promotes tumor immunity in two significant ways: inducing immunogenic cell death, where tumor cells release antigens and danger signals that activate the immune system, and by disrupting immune evasion strategies employed by tumors (Emens & Middleton, 2015). This process involves the activation of various receptors and signaling pathways. While standard cancer chemotherapy can enhance tumor immunity, it may also cause adverse effects on the body, such as suppressing the immune system and increasing susceptibility to infections, fatigue, and other side effects. On the other hand, T cell immunotherapies such as CAR T cell therapy differ from standard chemotherapy because they involve genetically modifying a patient’s T cells to specifically target and kill cancer cells, offering a more targeted and personalized approach to cancer treatment (Huang et al., 2023). These findings highlight the pivotal role of basic research in driving progress and innovation in cancer therapeutics, paving the way for more effective and personalized treatment strategies that offer renewed hope to patients battling this formidable disease.

3 | CONCLUSIONS

The depth of knowledge from foundational studies shows the complexities of T cell functions and forms the bedrock for developing targeted and personalized cancer therapies. The ability to decipher the nuances of T cell behavior enables scientists to design interventions that precisely harness the body’s natural defenses and tailor them. Rooted in pure research, it minimizes side effects and maximizes therapeutic efficacy, propelling the field toward novel and effective treatments.

Embracing the influence of T cell research on cancer therapy, it becomes apparent that equitable funding is not merely an investment in scientific exploration but a commitment to transformative advancements with enduring implications for human health. It is crucial to acknowledge the pivotal role of foundational research. Such research is the cornerstone for advancing innovative therapies, ensuring a sustainable pipeline of discoveries that will continue to shape the future of cancer treatment and human curiosity. The discovery and advancements that can be made by allowing humans to explore new areas of T cell and immune research serve as a poignant reminder that sometimes, the most
profound discoveries arise not from pursuing answers to existing questions but from recognizing questions that had never been asked.

**CONFLICTS OF INTEREST**

The author declares no conflict of interest.

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