The Impacts of Immunotherapy on Cancer

Rachel Morris, Shayna N. Scott, Toni Mortimer, Abigail Schekall and Kim L. O'Neill*

Department of Microbiology and Molecular Biology, Brigham Young University, Provo, Utah 84602.

Correspondence:
Kim L. O'Neill, Department of Microbiology and Molecular Biology, Brigham Young University, Room 3145 Life Sciences Building, Provo, UT 84602, Tel: (801)-422-2449.

Received: 29 November 2021; **Accepted:** 22 December 2021

ABSTRACT

Since the start of the 21st century, immunotherapies geared to treating cancer have continued to be refined. After a slow decline in cancer mortality rate during the last few decades, the SARS-CoV-2 pandemic is now expected to possibly increase advanced cancer stage and mortality in the future, due to delayed diagnosis and treatment resulting from recent reorganization in healthcare. Thus, the development of new cancer immunotherapies has never been more urgent. Novel research focusing on MOTO-CARs or CAR-Ms may have particular importance in revolutionizing CAR-T cell therapy. The following mini-review outlines a brief history of immunotherapy discoveries and new treatments against cancer, and reports the recent progress in checkpoint inhibitors, cancer vaccines, CAR-T cell therapies, and other major immunotherapies.

Introduction

The previous decades saw a 1% decline in cancer mortalities during the 1990s, 1.5% during the 2000s, and a 2.3% in the late 2010s. In 2020, slowed diagnosis, treatment, and healthcare setting closures associated with the SARS-CoV-2 pandemic were projected to result in a temporary drop in cancer rates followed by a sharp increase in advanced stage cancer and mortality. Desai et al. revealed that prior to May 2020, about 2% of all COVID-19 patients already had cancer [1] and Siegel et al. predicted that in 2021 there would be approximately 1,898,160 newly diagnosed cancer cases and 608,570 deaths in the United States [2]. Therefore, despite some recent improvements in cancer mortality, it continues to be a worldwide problem during the SARS-CoV-2 pandemic.

COVID-19 disease severity is thought be nearly 76% higher in cancer patients [3]. Thus, cancer patients have a potentially higher risk for need of invasive ventilation and intensive care unit (ICU) compared to non-cancer individuals [4]. Also, traditional chemotherapy or surgery treatments for cancer are associated with increased risk for adverse effects associated with COVID-19 [5,6]. Such risks make the refinement and utilization of new cancer immunotherapies more urgent than ever to allow for more treatment options for cancer patients. As difficulties continue to arise with SARS-CoV-2 waves, immunotherapies will continue to have an increasingly important role in cancer patients' health. In the following mini-review, we give a general history and highlight some of the major immunotherapy developments aimed to improve cancer treatment.

Early Major Events in Immunotherapy

William B. Coley (1862-1936), a bone sarcoma surgeon at New York Memorial Hospital, noticed a relationship between tumor regression of patients with ulcerated tumors that simultaneously developed a streptococcal infection. In an effort to produce these same results in his patients, Coley began injecting this bacterium into the tumors of several patients in 1892. Many patients experienced tumor regression while some died from erysipelas caused by the infection. However, several of the patients that died still experienced some tumor shrinkage [7]. Eventually, Coley developed a heat-killed vaccine containing Gram-positive *Streptococcus pyogenes* and Gram-negative *Serratia marcescens*, later known as "Coley's toxins." Coley began using his toxins and

reported remarkable success, which he eventually published [8]. Despite Coley becoming the "Father of Immunotherapy" with this discovery, his toxins eventually fell out of use due to inconsistencies in his work and harsh criticism that followed [9]. Although Coley's work suggested that the immune system and tumor rejection may be linked, the mechanisms for that relationship were unknown. Later research led to Paul Ehrlich's proposing that the immune system is capable of recognizing and eliminating cancer cells by 1909 [10], which laid the foundation for the immunosurveillance hypothesis to be postulated by Thomas and Burnet [11,12]. Another finding from the early 1950s that helped propel immunology forward was the discovery of the ability to transfer passive immunity to mice by exposing them with lymph node grafts of mice previously inoculated with tumor cells [13,14].

In the second half of the 20th century, greater efforts were made to investigate the role of T cells in the antitumor response. This early work laid the foundation for the use of autologous immune cells. In the 1980s, Rosenberg et al. identified lymphokine-activated killer cells (LAK) that could be activated by IL-2 and used to treat patients [15]. Dr. Steven Rosenberg and his team administered these T lymphocytes simultaneously with doses of IL-2 to 25 patients with metastatic cancer, with results indicating that 11 patients had over 50% tumor volume regression [16]. Later, this therapy was improved by using tumor-infiltrating lymphocytes (TILs), which expanded more readily with IL-2 exposure and showed enhanced therapeutic potency [17]. These results suggested that adoptive cell transfer is an effective strategy to treat advanced cancers.

Checkpoint Inhibitors

An immune response is regulated by a series of checkpoints that control the innate and adaptive immune system [18]. Immune checkpoints consist of immunoregulatory pathways that prevent autoimmunity and maintain homeostasis [18,19]. Tumor cells hijack these checkpoints to block the antitumor response and promote immune evasion. Checkpoint inhibitor therapies disrupt the interaction between an immunological checkpoint and its corresponding inhibitory ligand, thus releasing the brakes to induce an antitumor response [20,21]. Within the last decade, cancer's ability to utilize inhibitory checkpoints in immune evasion was investigated further. In 2018, Dr. James P. Allison and Dr. Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their research of checkpoint inhibitors and development of novel immunotherapies that inhibit negative immune regulation. Dr. Allison studied cytotoxic T-lymphocyte antigen 4 (CTLA-4), and Dr. Honjo helped discover programmed cell death protein 1 (PD-1) [22]. The CTLA-4 pathway is thought to operate during the initiation of an immune response, halting potentially autoreactive T cells during naïve T cell activation, whereas the PD-1 pathway participates in the regulation of previously activated T cells during later stages of an immune response [23]. CTLA-4 outcompetes co-stimulatory receptor CD28 by binding CD80 and CD86 with a higher affinity, thus mediating immunosuppression by decreasing signaling [24,25]. Homologous to CD28, PD-1 is also involved in mediating immunosuppression and results in reduced cell cycle progression and cytokine production [24].

Since 2018, several therapies targeting these proteins have undergone clinical trial. One therapeutic strategy uses Ipilimumab, a humanized monoclonal antibody designed to inhibit CTLA-4, an immunoinhibitory receptor displayed on T cells [26]. Tumor regression was observed in patients during phase I and II trials [27]. Over 20% of patients treated with Ipilimumab demonstrated improved long-term survival. Such patients survived over 4 years while others survived at least 10 years [28]. Ipilimumab was first approved by the Food and Drug Administration in 2011. Additional encouraging results were observed during clinical trials for therapies targeting PD-L1, a receptor that is often overexpressed on tumors and interacts with PD-1 on T cells to promote inhibitory functions. Examples of drugs that target PD-1/PD-L1 are Atezolizumab, Nivolumab, and Pembrolizumab [20,27,29]. Clinical reports of phase I trial for combination therapy of antibodies targeting both CTLA-4 and PD-1 demonstrated tumor regression of 80% or higher in approximately 50% of patients [27]. Due to their lower risk for high-grade toxicities compared to standard therapies, as well as their curative potential, checkpoint inhibitor therapies are revolutionary to immunotherapy and cancer treatment.

Cancer Vaccines, Cytokine Therapy, & Oncolytic Viral Therapy

Vaccination is one immune strategy that has become increasingly important to target cancer. Therapeutic vaccines can be used for prophylaxis or administered to patients with an existing malignancy or that has gone into remission [30]. Generally, traditional vaccines are used to target foreign pathogens such as bacteria and viruses. However, there are some cancer-preventative vaccines that follow this pattern, such as vaccines against human papillomavirus (HPV) and hepatitis B virus (HBV). Since 1982, the HBV vaccine has prevented new HBV infections and decreased rates of chronic liver disease and hepatocellular carcinoma. The HPV vaccine targets oncogenic HPVs 16 and 18 which are linked to 70% of all cervical cancers [31]. Kaposi's Sarcoma-associated herpesvirus (KSHV), also called Human Herpes Virus-8 (HHV-8), is known to cause Kaposi sarcoma (KS), a neoplasm that commonly appears in Acquired Immune Deficiency Syndrome (AIDS) patients. Currently, there are no specific antiviral therapies to treat HHV or approved vaccines. However, such vaccines are under development. For example, Chauhan et al. designed a multi-epitope vaccine that targets KSHV glycoproteins that facilitate viral entry. The vaccine had binding affinity with Toll-like receptor 9 (TLR-9), which is mainly displayed on B cells and plasmacytoid dendritic cells (pDCs). Also, the vaccine contains a CD8, CD4, and Interferon-gamma (IFN-γ) epitope, thus the vaccine is designed to induce a humoral and adaptive immune response [32]. Mulama et al. tested a KSHV envelope glycoprotein-targeting subunit vaccine in rabbits. This vaccine was developed by purifying the glycoproteins required for entry (gB, gpK8.1, and gH/gL). The vaccine-induced strong antibody responses and immunoglobulins isolated from immunized rabbits successfully neutralized KSHV infection in tested cell lines (B

cells, fibroblast, epithelial, and endothelial) [33]. Other cancer-related vaccines are neoantigen vaccines, which consist of one or more tumor-specific antigens combined with an adjuvant to elicit a tumor-specific immune response. So far, personalized neoantigen vaccines have proven a viable and safe treatment strategy for some patients with melanoma and glioblastoma. Results from studies targeting glioblastoma are especially encouraging due to glioblastomas being characterized as "cold" tumors with low mutational burden [34]. For example, Keskin et al. observed that neoantigen-specific T cells can migrate into an intracranial glioblastoma tumor [35]. In 2010, Sipuleucel-T became the first approved therapeutic cancer vaccine. Sipuleucel-T elicits the production of T cells that target prostatic acid phosphatase (PAP) on prostate cancer cells. Increased overall survival in patients with castrate-resistant prostate adenocarcinoma has been demonstrated [36]. Cancer vaccines will continue to undergo investigation to identify unique antigens and improve vaccine delivery platforms to ensure an effective treatment [34].

Before its debut as an immunotherapy, cytokines were recognized as systematic soluble factors that can regulate lymphocyte function and inflammatory responses [30]. Generally, these therapies aim to promote an antitumor response by stimulating the proliferation, activation, and differentiation of immune cells, including T and natural killer (NK) cells. In the past 25 years, cytokines have transformed into vital diagnostic, prognostic, and therapeutic tools in cancer treatment. Some of the most renowned cytokine and cytokine-related therapies include interleukins and interferons (IFN) [37]. Currently, interleukin-2 (IL-2) is approved for treating metastatic renal cell carcinoma and metastatic melanoma [38]. IL-2 is known to induce pleiotropic effects on immune cells. The α chain on the αβγ trimeric complex of the IL-2 receptor is thought to bind IL-2 and induce a conformational change that allows IL-2 to bind to the rest of the complex [39]. Several signaling pathways are activated to elicit the recruitment of JAK kinases, or Janus family tyrosine kinases, to the cytoplasmic domains of the αβγ trimeric complex. Other phosphorylation and activating events occur to initiate the STAT signaling pathway and mitogen-activated protein kinase (MAPK) signaling pathway, which further promotes immune cell survival, differentiation, and activation [40,41]. Generally, interferons are used to treat some leukemias, lymphomas, melanomas, and metastatic renal cancer. However, cytokine therapies lack efficacy and display toxicity when given as a monotherapy. As a result, interferon therapies combined with other therapies, such as checkpoint inhibitors, are undergoing investigation [42]. One recent study tested IFN-α in combination with PD-1 blockade in treating stage III/IV melanoma. Results indicated that patients that had previously received pegylated IFN-α (PEG-IFN-α) had lower recurrence rates after receiving PD-1 blockade therapy [43]. Typically, IFN-α is administered subcutaneously and the most common side effects are flu-like symptoms (fever, myalgia, headache, etc.) [44]. More research will be necessary to find the best ways to utilize cytokines for treating cancer.

Another cancer therapy strategy uses oncolytic viruses. In 1948, Alice Moore discovered that injecting Russian Far East encephalitis virus into rodent models could selectively identify and destroy cancer cells [45]. Oncolytic viruses preferentially infect and kill tumor cells instead of normal tissue due to the overexpression of viral receptors that facilitate viral entry [30]. One approved oncolytic virus therapy is talimogene laherparepvec (TVEC), also termed Imlygic, which is a genetically-modified herpes simplex virus used to treat unresectable metastatic melanoma [15]. The TVEC mechanism of action includes using surface cellular adhesion molecules, termed nectins, to enter tumor cells and replicate. Oncogenic and anti-viral pathways, such as protein kinase R (PKR) and type I interferon (IFN) pathways, are disrupted [46]. The PKR pathway regulates cell proliferation, antiviral responses, and inhibits protein synthesis when activated. Type 1 IFN has antitumor and antiviral activity and is somewhat mediated by PKR activation. Some malignant cell types, such as melanoma and bladder cancer, may prevent a proper antiviral response by downregulating type I IFN receptor expression [47,48]. Because these pathways may already be suppressed within cancer cells, TVEC replication and lysis of cells tend to be selective to cancer cells [49]. Advances in genetic engineering and virus transformation technology continue to make oncolytic virus therapy development a reality [15].

CAR-T Cell Therapy
Researchers have long attempted to genetically engineer immune cells to enhance the antitumor response. The first official engineered chimeric antigen receptor (CAR) T cell was developed in 1989 by an Israeli group at the Weizmann Institute of Science [50]. This CAR-T was designed to overcome the need for MHC antigen presentation while retaining antibody-like specificity [50]. In 1993, CAR-T cells targeting HER2, a cell surface antigen that is often overexpressed in adenocarcinomas, was engineered by the same Israeli group [51]. This first design presented several limitations, one of which being difficulty in T cell activation without the presentation of costimulatory molecules from tumor cells. Since then, CAR-T designs have been modified to increase specificity, efficacy, and persistence [10]. Dr. Carl June's use of CD-19 directed CAR-T cells in targeting malignant CD19+ B cells to treat patients with advanced chronic lymphocytic leukemia (CLL) was a major breakthrough [52,53]. One clinical trial resulted in complete remission in 10 of 14 patients with follicular lymphoma and 6 of 14 patients with diffuse B-cell lymphoma [54]. In 2017, the US Food and Drug Administration (FDA) also approved anti-CD19 CAR-T cell therapy to treat B cell malignancies [55]. However, targeting biomarkers such as CD19 and CD20 in solid tumors has not experienced the same clinical success observed in liquid tumors [10,56]. As a result, exploring new potential biomarkers to enhance treatment in both solid and liquid tumors is an ongoing process [56].

There are limitations that prevent CAR-T cell distribution and access. One concern is the risk for off-target effects and killing of normal cells, which may be overcome by careful selection and

discovery of new biomarkers unique to tumors [57]. However, more research will be required to identify novel biomarkers that are tumor specific. Another limitation is that the CAR-T cells may be inhibited by the tumor microenvironment (TME) due to the Warburg effect [53], which promotes a nutrient-depleted and toxic environment that inhibits CAR-T cell ability to function and survive [58,59]. CAR-T cells also confront the obstacle of successfully trafficking to and staying active in the TME because the tumor does not secret TNF-α, a proinflammatory cytokine [60]. Strategies to overcome obstacles associated with the TME are currently under investigation [61,62]. Another concern is relapse associated with antigen escape. CAR-T cells are engineered to target one particle antigen of the tumor cells, but are rendered ineffective when the tumor cells manipulate their phenotype or surface antigens to evade targeting [59]. However, expansion of current biomarkers will address this issue [56,63,64]. An additional challenge is risk for cytokine release syndrome (CRS), which is frequently observed in patients that undergo CAR-T cell therapy [10,57]. CRS is a systemic inflammatory response that results from the binding of the CAR-T cell to its target, which induces activation of surrounding immune cells. Although the mechanism is not fully understood, CRS is potentially fatal and, therefore, poses a considerable risk [65].

As mentioned earlier, T cells have difficulty trafficking to solid tumors, and, when CAR-T cells do arrive at the tumor site, they are often immunosuppressed by the TME. In fact, tumor-associated macrophages (TAMs), which are macrophages that reside in advanced or growing tumors and promote tumor growth, are known to inhibit T cell activity against tumors [66]. However, when the TAMs are properly stimulated by inhibiting certain signals, such as TGF-β, interacting with TLR ligands or stimulation from type 1 IFN, the TAMs can interact with T cells to enhance the antitumor response [66]. Due to the death signals secreted by tumors, and sometimes the cells surrounding the tumors, macrophages are actively recruited to the tumor site, and often make up half of the total tumor mass [67,68]. Thus, genetically engineered macrophages with CARs, termed MOTO-CARs or CAR-Ms, are a potential alternative to CAR-T cell therapy to add to the immunotherapy toolbox because they may potentially overcome several limitations present in CAR-T cell therapy.

Macrophages are a part of the innate immune system and, thus, are able to target cells without antigen specificity [67]. Therefore, flexible targeting by MOTO-CARs may be utilized against multiple different biomarkers and prevent the tumor's ability to undergo antigen escape. This is in stark contrast to the CAR-Ts' restriction to one specific biomarker [68]. Also, this characteristic of MOTO-CAR therapy may reduce toxic effects, as anti-CD19 CAR-T cells have been observed to target normal CD19+ B cells [69]. Therefore, MOTO-CARs may be less likely to target normal cells because they are not restricted to one antigen [67]. Another challenge is that, upon activation, T cells play a dominant role in immune cellular response. As a result, the T cells' reaction can be overly aggressive and induce CRS, thus making them difficult

to control while increasing the risk for adverse side effects in the patients [57]. Such effects may be especially damaging considering the long period of time that T cells may persist in the body, even after the tumor has been eliminated. In contrast, MOTO-CARs are more easily controlled because they possess a shorter life span. Lastly, MOTO-CAR therapy also has the potential to be more cost-effective than CAR-T cell therapy with CAR-T cell production taking approximately 8-10 weeks, while MOTO-CAR production only requires approximately 3 days [68]. Also, one dose of CAR-T cells that is administered to the patient costs approximately $400,000 and, therefore, prevents individuals from fully participating in CAR-T cell therapy [70]. Overall, CAR-T cell therapies are a breakthrough in immunotherapy that will evolve into stronger treatment options as further research is conducted investigating novel biomarkers and the CAR design is further refined to overcome limitations.

Conclusion

Over time, research has produced several innovative treatment strategies to add to the immunotherapy toolbox. The most notable developments mentioned being checkpoint inhibitors, cancer vaccines, cytokine therapies, viral oncolytic therapies, and CAR-T cell therapies. The development of MOTO-CARs is especially interesting with the refinement of CAR-T cell therapies. Although these strategies continue to experience challenges and undergo further improvements, the future of cancer immunotherapy has never been more critical due to the potential repercussions of the SARS-CoV-2 pandemic on cancer cases. The expansion of immunotherapy observed, especially within the past few decades, will be important to provide cancer patients with improved treatments.

References

1. Desai A, Sachdeva S, Parekh T, et al. COVID-19 and Cancer Lessons From a Pooled Meta-Analysis. JCO Glob Oncol. 2020; 6: 557-559.
2. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics 2021. CA Cancer J Clin. 2021; 71: 7-33.
3. Ofori-Asenso R, Ogundipe O, Agyeman AA, et al. Cancer is associated with severe disease in COVID-19 patients a systematic review and meta-analysis. E cancer medical science. 2020; 14.
4. Bora VR, Patel BM. The Deadly Duo of COVID-19 and Cancer. Front Mol Biosci. 2021; 0: 196.
5. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection a nationwide analysis in China. Lancet Oncol. 2020; 21: 335-337.
6. Lee AJX, Purshouse K. COVID-19 and cancer registries learning from the first peak of the SARS-CoV-2 pandemic. Br J Cancer. 2021; 124: 1777-1784.
7. McCarthy EF. The Toxins of William B. Coley and the Treatment of Bone and Soft-Tissue Sarcomas. Iowa Orthop J. 2006; 26: 154.
8. Coley WB. The Treatment of Inoperable Sarcoma by Bacterial Toxins the Mixed Toxins of the Streptococcus erysipelas and

the Bacillus prodigiosus. Proc R Soc Med. 1910; 3: 1.

9. Hoption Cann SA, Van Netten JP, Van Netten C, et al. Spontaneous regression a hidden treasure buried in time. Med Hypotheses. 2002; 58: 115-119.

10. Carlson RD, Flickinger JC, Snook AE. Talkin Toxins from Coley's to Modern Cancer Immunotherapy. Toxins Basel. 2020; 12.

11. Thomas L. On immunosurveillance in human cancer. Yale J Biol Med. 1982; 55: 329.

12. Burnet FM. The Concept of Immunological Surveillance. Prog Exp tumor Res Fortschritte der Exp Tumorforschung Prog la Rech Exp des tumeurs. 1970; 13: 1-27.

13. Mitchison NA. Studies on the Immunological Response to Foreign Tumor Transplants in the Mouse I. The Role of Lymph Node Cells in Conferring Immunity by Adoptive Transfer. J Exp Med. 1955; 102: 157.

14. Chem, Ponsford AP, Smedley-Mclean I, et al. Passive transfer of transplantation immunity. Proc R Soc London Ser B - Biol Sci. 1954; 142: 72-87.

15. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020; 17: 807-821.

16. Rosenberg SA, Lotze MT, Muul LM, et al. Observations on the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer. N Engl J Med. 1985; 313: 1485-1492.

17. Rosenberg SA, Spiess P, Lafreniere R. A New Approach to the Adoptive Immunotherapy of Cancer with Tumor-Infiltrating Lymphocytes. Science. 1986; 233: 1318-1321.

18. Sharpe AH. Introduction to checkpoint inhibitors and cancer immunotherapy. Immunol Rev. 2017; 276: 5-8.

19. Marin-Acevedo JA, Dholaria B, Soyano AE, et al. Next generation of immune checkpoint therapy in cancer new developments and challenges. J Hematol Oncol. 2018; 11: 1-20.

20. Iwai Y, Hamanishi J, Chamoto K, et al. Cancer immunotherapies targeting the PD-1 signaling pathway. J Biomed Sci. 2017; 24: 1-11.

21. Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol. 2017; 18: 91-104.

22. James P. Allison, Tasuku Honjo. The 2018 Nobel Prize in Physiology or Medicine Press release. 2018.

23. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways Similarities Differences and Implications of Their Inhibition. Am J Clin Oncol. 2016; 39: 98.

24. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer Mechanisms of Action Efficacy and Limitations. Front Oncol. 2018; 8: 86.

25. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med. 1995; 182: 459.

26. Kittai A, Meshikhes M, Aragon-Ching JB. Ipilimumab A potential immunologic agent in the treatment of metastatic castration-resistant prostate cancer. Cancer Biol Ther. 2014; 15: 1299.

27. Sharma P, Allison JP. Immune Checkpoint Targeting in Cancer Therapy toward Combination Strategies with Curative Potential. Cell. 2015; 161: 205-214.

28. Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. 2015; 33: 1889-1894.

29. Dine J, Gordon R, Shames Y, et al. Immune Checkpoint Inhibitors An Innovation in Immunotherapy for the Treatment and Management of Patients with Cancer. Asia-Pacific J Oncol Nurs. 2017; 4: 127.

30. Carlson RD, Flickinger JC, Snook AE. Talkin Toxins from Coley's to Modern Cancer Immunotherapy. Toxins Basel. 2020; 12.

31. Stanley M. Tumour virus vaccines hepatitis B virus and human papillomavirus. Philos Trans R Soc B Biol Sci. 2017; 372.

32. Chauhan V, Rungta T, Goyal K, et al. Designing a multi-epitope based vaccine to combat Kaposi Sarcoma utilizing immunoinformatics approach. Sci Reports. 2019; 9: 1-15.

33. Mulama DH, Mutsvunguma LZ, Totonchy J, et al. A multivalent Kaposi sarcoma-associated herpesvirus-like particle vaccine capable of eliciting high titers of neutralizing antibodies in immunized rabbits. Vaccine. 2019; 37: 4184.

34. Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol. 2021; 18: 215-229.

35. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. Nat. 2018; 565: 234-239.

36. Cheever MA, Higano CS. PROVENGE Sipuleucel-T in Prostate Cancer The First FDA-Approved Therapeutic Cancer Vaccine. Clin Cancer Res. 2011; 17: 3520-3526.

37. Dinarello CA. Historical Review of Cytokines. Eur J Immunol. 2007; 37: S34.

38. Jiang T, Zhou C, Ren S. Role of IL-2 in cancer immunotherapy. Onco immunology 2016; 5.

39. Wang X, Lupardus P, LaPorte SL, et al. Structural Biology of Shared Cytokine Receptors. Annu Rev Immunol. 2009; 27: 29.

40. Malek TR. The biology of interleukin-2. Annu Rev Immunol. 2008; 26: 453-479.

41. Choudhry H, Helmi N, Abdulaal WH, et al. Prospects of IL-2 in Cancer Immunotherapy. Biomed Res Int. 2018; 2018.

42. Waldmann TA. Cytokines in Cancer Immunotherapy. Cold Spring Harb Perspect Biol. 2018; 10.

43. Jia DD, Niu Y, Zhu H, et al. Prior Therapy with Pegylated-Interferon Alfa-2b Improves the Efficacy of Adjuvant Pembrolizumab in Resectable Advanced Melanoma. Front Oncol. 2021; 11.

44. https://www.ncbi.nlm.nih.gov/books/NBK555932/

45. Kelly E, Russell SJ. History of Oncolytic Viruses Genesis to Genetic Engineering. Mol Ther. 2007; 15: 651-659.

46. Kohlhapp FJ, Kaufman HL. Molecular Pathways Mechanism

of Action for Talimogene Laherparepvec a New Oncolytic Virus Immunotherapy. Clin Cancer Res. 2016; 22: 1048-1054.

47. Pansky A, Hildebrand P, Fasler-Kan E, et al. Defective JAK-STAT Signal Transduction Pathway in Melanoma Cells Resistant to Growth Inhibition by Interferon. Int J Cancer. 2000; 85: 720-725.

48. Zhang K, Matsui Y, Hadaschik BA, et al. Down-regulation of type I interferon receptor sensitizes bladder cancer cells to vesicular stomatitis virus-induced cell death. Int J Cancer. 2010; 127: 830-838.

49. Conry RM, Westbrook B, McKee S, et al. Talimogene laherparepvec First in class oncolytic virotherapy. Hum Vaccin Immunother. 2018; 14: 839.

50. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci USA. 1989; 86: 10024.

51. Stancovski I, Schindler DG, Waks T, et al. Targeting of T lymphocytes to Neu/HER2-expressing cells using chimeric single chain Fv receptors. J Immunol. 1993; 151.

52. Porter DL, Levine BL, Kalos M, et al. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. N Engl J Med. 2011; 365: 725.

53. Kalos M, Levine BL, Porter DL, et al. T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia. Sci Transl Med. 2011; 3: 95ra73.

54. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med. 2017; 377: 2545.

55. Sterner RC, Sterner RM. CAR-T cell therapy current limitations and potential strategies. Blood Cancer J. 2021; 11: 1-11.

56. Townsend MH, Shrestha G, Robison RA, et al. The expansion of targetable biomarkers for CAR T cell therapy. J Exp Clin Cancer Res. 2018; 37.

57. Huang R, Li X, He Y, et al. Recent advances in CAR-T cell engineering. J Hematol Oncol. 2020; 13.

58. Xu X, Gnanaprakasam JNR, Sherman J, et al. A Metabolism Toolbox for CAR T Therapy. Front Oncol. 2019; 9: 322.

59. Hay KA, Turtle CJ. Chimeric Antigen Receptor CAR T cells Lessons Learned from Targeting of CD19 in B cell malignancies. Drugs. 2017; 77: 237.

60. Josephs SF, Ichim TE, Prince SM, et al. Unleashing endogenous TNF-alpha as a cancer immunotherapeutic. J Transl Med. 2018; 16: 1-8.

61. Cherkassky L, Morello A, Villena-Vargas J, et al. Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. J Clin Invest. 2016; 126: 3130.

62. Gargett T, Yu W, Dotti G, et al. GD2-specific CAR T Cells Undergo Potent Activation and Deletion Following Antigen Encounter but can be Protected from Activation-induced Cell Death by PD-1 Blockade. Mol Ther. 2016; 24: 1135.

63. Haso W, Lee DW, Shah NN, et al. Anti-CD22-chimeric antigen receptors targeting B-cell precursor acute lymphoblastic leukemia. Blood. 2013; 121: 1165.

64. Zah E, Lin MY, Silva-Benedict A, et al. T cells expressing CD19/CD20 bi-specific chimeric antigen receptors prevent antigen escape by malignant B cells. Cancer Immunol Res. 2016; 4: 498.

65. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018; 6.

66. Bercovici N, Guérin MV, Trautmann A, et al. The remarkable plasticity of macrophages a chance to fight cancer. Front Immunol. 2019; 10: 1-9.

67. Duan Z, Luo Y. Targeting macrophages in cancer immunotherapy. Signal Transduct Target Ther. 2021; 6: 1-21.

68. Townsend MH, Skidmore JR, Ewell ZD, et al. Macrophage Toll-Like Receptor Chimeric Antigen Receptor MOTO-CAR TM Shows Potent Activation and Killing of Triple Negative Breast Cancer Cells. 2020.

69. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells recognition and management. Blood. 2016; 127: 3321-3330.

70. Hernandez I, Prasad V, Gellad WF. Total Costs of Chimeric Antigen Receptor T-Cell Immunotherapy. JAMA Oncol. 2018; 4: 994-996.