Dear Editor,

 Please find enclosed a modified version of my Microreview, “Recent Progress in Cancer Immunotherapy.” To address the concerns and comments raised by the three reviewers, I made the following changes to improve and clarify the manuscript. It is my hope that these changes will make this Microreview acceptable for publication in Microreviews in Cell and Molecular Biology.

Sincerely,

Taytum Crockett

**Reviewer 1:**

I found the comments from Reviewer 1 to be helpful. This reviewer stated that I provided factual data that is correctly cited, as well as stating that I had no grammatical errors. This allowed me to focus on the content that other reviewers provided comments on, as well as helped ensure that my manuscript is correctly cited.

As Reviewer 1 did not provide any comments on changing my manuscript, I made no changes based on this review.

**Reviewer 2:**

I found the comments from Reviewer 2 to be very helpful. I did agree that the use of “Gorbet and Ranjan” is repetitive in my paper.

 With the comments provided from Reviewer 2, I rephrased “Gorbet and Ranjan” in multiple places to “researchers” to help strengthen my manuscript.

**Reviewer 3:**

 While I did not agree with the comments left by Reviewer 3, I still took them into consideration when revising my manuscript. This reviewer stated that the manuscript felt fragmented and rushed.

 I revised my manuscript and tried to find a way to make my manuscript flow better, but I decided not to change any part of the text. I felt that my transitions were appropriate and there was not really any way to restructure my manuscript.

**Recent Progress in Cancer Immunotherapy**

**Key Words:**Cancer, advancements, vaccines, nanoparticles, checkpoint inhibitors, imaging

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**Abstract**

Cancer immunotherapy has been an ever-changing area in the field of medicine. Researchers have developed many different therapies and are continuing to make more advancements. Along with more research on radiation therapy, there has been progress towards other therapies such as vaccinations, nanoparticles, checkpoint inhibitors, and immune cell imaging. There are certain limitations that researchers are facing that include virus replication, varying levels of immunotoxicity, and changes in immune cell function during treatment.

**Introduction**

Cancer immunotherapy is a method of cancer treatment that assists the immune system’s own ability to fight off disease. This type of treatment takes a body’s natural defenses and gives those defenses a boost in order to help the body treat itself. In their article, Gorbet and Ranjan discuss numerous advancements in the field of oncology, as well as the limitations to each. This article primarily focuses on immunoadjuvants, nanoparticles, checkpoint inhibitors, and noninvasive imaging.

**Recent Progress**

Gorbet and Ranjan first discuss immunoadjuvants, specifically vaccines that work with the immune system in order to assist in fighting off cancer. These vaccines are similar to modern vaccines, but a tumor is used as an antigen source in order to obtain a specific immune response in the patient [1]. There have been recent discoveries that in situ vaccinations (ISVs) have the possibility to reduce treatment cost on a per patient basis due to the “simplicity of treatment,” [1]. The use of oncolytic viruses has also been another recent approach, such as adenoviruses, poxviruses, herpes simplex virus, and coxsackieviruses [1]. According to the National Cancer Institute, these oncolytic viruses trigger an immune response against cancer [2]. After the virus has infected the target tumor cell, the virus is replicated inside the cell until it bursts and releases antigens that allow the cancer to be recognized by the immune system [2]. There has also been recent interest in using dendritic cells for possible therapy for solid tumors, but the researchers wanted to aim their focus on the in situ vaccines.

The article continues to discuss both inorganic and organic nanoparticles as a means to treat cancer. Benefits of nanoparticles include a high surface area to volume ratio, which allows them to carry antigens, antibodies, and other small molecules throughout the body [1]. It is discussed that these particles have the ability to be tailored in order to increase exposure to tumors. Inorganic nanoparticles (INPs) are helpful with image contrasting due to their high optical, magnetic, and thermal properties [1]. Nanoparticles allow certain medications to be delivered directly to the target tumor. This aids in maintaining healthy tissue while targeting tumor tissue [3].

Gorbet and Ranjan also discuss the recent testing of checkpoint inhibitors for use in cancer treatment. Checkpoint inhibitors work by blocking the proteins that keep the immune system from attacking cancer cells [4]. The checkpoint inhibitors specifically discussed in this article include anti PD-1and anti CTLA-4. The anti PD-1 antibody blocks PD1 and PDL1 interactions [5]. The recent developments in the use of anti PD-1 are due to the blockage of the cascade reaction of immunosuppression to activate T cell function and the killing of tumor cells [1]. The anti CTLA-4 antibody blocks the CTLA-4 interactions, which regulates T-cell activation. This has the possibility to enhance immune responses [5]. Recent progress of this therapy shows that the use of anti CTLA-4 drugs can be used because specific cancer cell lines can inhibit both immune activation and cytotoxic killing [1].

Noninvasive imaging is another recent discovery discussed in the article. Most recently, there was a development of using Cerenkov luminescence (CL) imaging to track T cells, as well as both in vivo and ex vivo models of radioluminescence imaging in tumors [1]. There are also numerous reports of characterization of immune cell phenotypes by CT images, genomic data, and histopathological features of tumor biopsies [1]. Two photon microscopy and macrophage imaging have also been recent advancements in noninvasive imaging [1].

**Discussion**

 With new discoveries and advancements in the field of medicine, there are certain limitations and issues that researchers come across. For the immunoadjuvants, there is a common issue in which the treatment has to cross the blood-brain barrier [1]. This barrier is a very important feature to the immune system, as it protects the brain’s environment. Gorbet and Ranjan discuss potential ways to remedy this, such as injecting the treatment directly into the central nervous system or using smaller vaccines [1]. However, it was pointed out that the use of these vaccines has not had well-studied long term effects, which could pose to be a big issue.

 For the use of nanoparticles, there have been varying levels of immunotoxicity to both inorganic and organic nanoparticles. According to the researchers, the inhalation of these nanoparticles has been proven to have high levels of toxicity [1]. It was stated that, the smaller the particle the more toxic it is. Their proposal to solve this issue is using combination therapy, in which nanoparticles would be used in combination with other treatments such as checkpoint inhibitors [1].

 Gorbet and Ranjan also discuss the limitations of using checkpoint inhibitors, most notably the varying side effects that are most experienced [1]. The side effects that were stated include imbalances in hormones for most patients, insufficient cortisol levels, inflamed respiratory and kidney tissues, and a large amount of unresponsiveness to this therapy [1].

 Noninvasive imaging also has its drawbacks, which includes an accidental change in function of immune cells [1]. According to the researchers, the agents that are being imaged have the ability to bind to T cells or macrophages and change their function. It was stated that this limitation may be overcome if there is a way to completely control the imaging process [1].

**References**

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