Dear Editor,

Please find enclosed a modified version of my Microreview manuscript “The Key to Ending Cancer is Not a Cure”. To address the concerns and comments raised by the 3 reviewers, I made the following changes to improve and clarify the manuscript. It is my hope that these changes make the manuscript acceptable for publication in Microreviews in Cell and Molecular Biology.

Sincerely,

Emily Vandenabeele

**Reviewer 1:**

1. Briefly state if you found the comments of Reviewer 1 helpful or not.

 I did not find the comments of Reviewer 1 to be particularly helpful, aside from one comment that was made about my sources. Most of the comments were vague, such as “only a few revisions could strengthen it even more” and consequently did not allow me to find problem areas in my manuscript. I did notice that they referred to an annotated document, but that document was not provided to me.

2. What changes did you make to your manuscript as a result of the comments of Reviewer 1?

Reviewer 1 did state that I should add a primary source to the microreview, so I did include another source that details what is new in the CRISPR/cancer research field.

**Reviewer 2:**

1. Briefly state if you found the comments of Reviewer 2 helpful or not.

 I did find the comments of Reviewer 2 to be extremely helpful in my revision process. Their comments were specific enough for me to understand where my clarity issues were, but they did not seem to be too nitpicky either.

2. What changes did you make to your manuscript as a result of the comments of Reviewer 2?

 I revised my abstract slightly (mainly word edits here and there), as well as added a little more information about the CRISPR system and its relevance specifically to cancer research as a result of Reviewer 2’s comments.

**Reviewer 3:**

1. Briefly state if you found the comments of Reviewer 3 helpful or not.

 I found the comments of Reviewer 3 to be slightly helpful in my revision process. There was not a whole lot that Reviewer 3 asked me to revise, but they gave helpful insight on the inclusion of the full CRISPR and CAS names for the sake of the readers to gain the full scope of what CRISPR-CAS is. Reviewer 3 did mention some left out information on the CRISPR system, though this was done intentionally in the microreview as to not detract from the main topic of the microreview with large chunks of information.

2. What changes did you make to your manuscript as a result of the comments of Reviewer 3?

 I did include the full title of CRISPR-CAS in the introduction as a result of comments by Reviewer 3.

**The Key to Ending Cancer Is Not A Cure**

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**Key Words:**

Cancer, cancer cure, cancer prevention, CRISPR-CAS9

**Cancer is on its way to becoming the number one cause of death worldwide, and the race towards a cure is more akin to an ultramarathon than the five-hundred-meter dash everyone thinks it is. But, perhaps all hope for eradicating cancer from human civilization does not rest on a cure – perhaps cancer prevention can play a larger role than what is currently believed. Cancer prevention has been around for quite some time in a wide variety of methods, such as vaccinations, screenings, and changes in lifestyle choices. New research has pointed to a promising method of cancer prevention: gene editing. Through use of a system called the CRISPR-CAS9, human genetics can be altered to prevent and potentially destroy cancer cells in the body. The CRISPR-CAS9 system is still relatively new in the field of cancer research, and consequently there is more research to be done, but this system could change the very future of cancer in humans.**

**Introduction**

Cancer is predicted to become the leading cause of death worldwide sometime within this century and the mad dash for a cure is hardly quelling this disease’s impact on humans (Drexler 2020). The “cure” that is talked about with such hope is so difficult to create because cancer is not a single disease, but rather a wide variety of diseases with a single commonality: atypical cell production (Seladi-Schulman 2019). Additionally, a “cure” entails far more than the modern-day “treatment”; the cure for cancer would eradicate all cancer from the body and ensure that the cancer does not return for the patient’s lifetime, while a cancer “treatment” can either shrink, stop the progression of, or eliminate cancer in the patient without the guarantee of the patient remaining cancer-free (Mayo Clinic Staff 2020; Seladi-Schulman 2019). Despite the cure for cancer seeming to be impossible to create, perhaps there is still hope for human civilization to be deemed cancer-free. The idea of cancer prevention has been around for as long as humans have been trying to find a cure for cancer, but it appears to be far less spoken about. Recently, however, there has been a surge of research in the field of cancer prevention, with some researchers even claiming that the cure for cancer would not be nearly as impactful on the cancer caseload as would a combination of new and old cancer prevention methods (Drexler 2020). These researchers hold the belief that if all cancer is prevented, then there is no longer a need for a cure (Drexler 2020).

There are a wide variety of currently employed methods of cancer prevention, ranging from vaccinations like the HPV vaccine that can prevent cancer caused by HPV such as cervical cancer, to eating healthier and exercising often to prevent obesity and tangentially prevent linked cancers such as breast and colorectal cancers (Center for Disease Control and Prevention 2020). While cancer prevention is not at the forefront of most researchers minds, there has been some progress made on creating new and more advanced methods. The most promising of which is a combination of early cancer screening/targeting patient who are at higher risk of developing cancer genetically speaking and gene editing (Pancholi 2020).

**Recent Progress**

There is a lot of talk about utilizing gene editing, specifically gene editing through the use of the Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated protein 9 (also known as CRISPR-CAS9) system, to cure cancer (Pancholi 2020). While this system does seem rather promising for cancer treatment, it can also prove to be rather useful in the field of cancer prevention when paired with early cancer screening and/or targeting individuals at high risk for developing cancer (Pancholi 2020; Drexler 2020). The CRISPR-CAS9 system is highly complex and still undergoing great research, but it shows such immense potential that researchers believe it may be the key to eradicating the cancer problem (NIC Staff 2020).

CRISPR-CAS9 has the capability to alter human DNA very precisely and, apparently, very easily (NCI Staff). This system of gene editing was discovered in 2013, but has made leaps and bound in term of applicability since then (NCI Staff 2020). The CRISPR-CAS9 system utilizes an RNA targeting device, often called the “guide RNA”, to lead a DNA-cutting enzyme (in the case of the CAS9 system, this would be the CAS9 enzyme) to a previously specified section of DNA to ‘delete’ or digest, thereby eliminating the problem gene (Pancholi 2020). In some cases, the enzyme will edit the gene to correct a mistake rather than eliminating it (Pancholi 2020).

In the field of cancer research, CRISPR-CAS9 has the potential to target specific cancer-causing genes in patients deemed to be high-risk, be they mutated or natural, and edit or eradicate them, thus preventing cancer in the patient (Pancholi 2020). If patients who are deemed high-risk for developing cancer undergo a CRISPR-CAS9 treatment, the system has the potential to completely eradicate the risk for cancer (Pancholi 2020). The CRISPR-CAS9 system has also been utilized in the cancer cure research field, as it has the potential to target cancerous cells are prevent them from replicating, or even target and modify T-cells (immune cells) to allow for the patient’s own blood cells to fight off the cancer (Pancholi 2020).

Recently, the CRISPR-CAS9 has gotten more advanced. A new RNA guide, deemed “proGuide” has been developed by a team of researchers in Chicago (Clarke et al. 2021). This RNA guide will allow gene editing to occur sequentially as opposed to all at once, which is currently the method employed (Clarke et al. 2021). This development is crucial to cancer research, as it accounts for how diseases progress over a period of time (Clarke et al. 2021).

**Discussion**

It is quite possible that gene editing holds the key to preventing cancer in future generations and thus making the treatment of cancer a thing of the past. CRISPR-CAS9 is a relatively new system, but it takes into account, or could take into account, a wide variety of factors that affect cancer treatment: time, genetic mutations, and cell replication. CRISPR-CAS9 may very well be the most sophisticated method for preventing cancer thus far. However, much more research needs to be done on the matter. As stated before, gene editing holds promise for cancer prevention, but the current research does leave much to be desired. One of the largest unknowns in the use of gene editing revolves around how the system will account for all one hundred plus varieties of cancer, some of which are caused purely by environmental factors rather than genetic factors (Center for Disease Control and Prevention 2020). Another major issue that people are confronted with when utilizing gene editing, specifically the CRISPR-CAS9 system, is the potential for the system to “cut” untargeted DNA, which could potentially cause life-threatening problems for the patient, including cancer (NCI Staff 2020). The idea of the system utilized to prevent cancer causing cancer can be quite off-putting for potential patients and is thus a pitfall that must be thoroughly researched and eliminated to allow for the CRISPR-CAS9 system to become trusted by patients and medical professionals alike. It is also believed by many that there is not going to be a single solution to the problem that is cancer and consequently, it should not just be gene editing that is employed to prevent cancer (Drexler 2020; Seladi-Schulman 2019). Both current and undiscovered methods of prevention, alongside treatment, are going to be necessary if humans are truly to be cancer-free one day.

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