Response to review.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you for giving me the opportunity to review this manuscript. Immunotherapy is a hot topic in the field of cancer therapy. This is a very meaningful but complex topic. pMMR/MSS mCRC does not respond well to immunotherapy. It is important to explore immunotherapies that can benefit such subtype of patients. 1. Structurally, this manuscript is more like a review. 2. The language of the manuscript should be improved.

Author's Response: Thank you for your comments. As you know, an editorial is an argument that is published in a newspaper or journal. Criticize, praise, or comment on the existing theory, focusing on scientific and clinical facts. It can also be encouraged they believe are beneficial to society and express strong positions. Here, I have intended to highlight organ-specific tumor immunity, especially in colorectal cancer, as a key concern among the multiple issues involved in the resistance to immunotherapies. To do so, it is inevitable to be accompanied by descriptions based on various existing facts. Additionally, this editorial has been edited by a professional English correctional institution.

Reviewer #2:

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The topic chosen falls short of portraying the complexity of the issue handled. The subject "immunotherapy of CRC management" is current hot topic and kindles the readers' enthusiasm. Immunotherapy resistance is complex and multifaceted, not only depended on tumor factors but also on the dynamic intensively explored tumor micro environment. The authors review this in Colorectal cancer and describes immunotherapy resistance by cold, immune-desert, tumor. The tumour factors contributing to resistance is only tip of the iceberg, and an attempt has been made to refer to multiple studies to portray the current level of understanding, though more than 2000 trails are currently in progress on PD -1 & Anti PD -L1 targeted drug itself. The concept of dividing the strategies to clinical and non clinical strategies targeting cold tumors is complex to comprehend. To conclusion drawn viz. "immunotherapies' failure is due to non immunogenic characteristics of cold CRC" oversimplifies the immensely complex perplexing problem. The write up is too long for an ediorial.

Author's Response: Thank you for the valuable comments. Here, I have intended to highlight organ-specific tumor immunity, especially in colorectal cancer, as a key concern among the multiple issues involved in the resistance to immunotherapies. Therefore, from the validity of the concept and immunity score of cold tumors established in cold CRC, the relative prognostic value compared to the pathological stage, lymphatic invasion, tumor differentiation, and microsatellite status is introduced. In addition, this editorial covers a wide range of molecular biological features, such as MSI/dMMR molecular characteristics, suppression of expression of MHC components related to loss of β-2-microglobulin heterozygosity, activation of STAT3 and Wnt/β-catenin signaling, expression of MAPK, VEGF, and IL-8, etc. Tables 1, 2, and 3 summarize all the highlights of this editorial. To date, the major strategies to overcome cold CRC can be divided into methods to increase specific T-cells and T-cell priming, and to promote T-cell trafficking and infiltration. Adoptive cell therapy (CAR-T and CAR-NK), adjuvant immunotherapy, epigenetic modification inhibitors, cancer vaccine, oncolytic viruses, and conventional therapies combinations are performed for T-cells priming. And to promote T-cell trafficking and infiltration, there are methods to utilize TGF-β suppression, oncogenic pathway inhibitors, angiogenesis inhibitors, CXCR4 inhibitors, and immune cytokines. This editorial investigated the clinical and non-clinical studies of the case and actively encourages these attempts, regardless of success or failure.

Of course, as the reviewer comments, more diverse research is being tried in non-clinical settings, but I hope you understand that this editorial focuses on realistic methods that have been tried clinically or are currently being tried. Please see Tables 1-3. Thank you.

Reviewer #3:

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Cold colorectal cancer is currently a challenge in the field of CRC treatment, especially in the field of immunotherapy. How to solve these problems has become a hot topic of basic and clinical research, including the transformation of cold cancer into hot cancer, and the stimulation of T-cell killing. In this article, the author introduced the concept of cold colorectal cancer (CRC) and various strategies across non-clinical and clinical for enhancing immunotherapeutic efficacy and further encourages the journey to an advanced level of immunotherapies targeting cold CRC. This article provided a detailed and systematic review of the latest research and clinical implementation progress in the field of cold colorectal cancer, giving us a comprehensive understanding and inspiration to help the direction of research clinical translation to find.

Author's Response: Thank you for the positive comments. Through this editorial, I would like to share experiences of successes and failures of the attempts for cold CRC counteracts and recommend these attempts continue to be made.

Response to review.

Revision reviewer:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I note that no revision has been done to the article. The editorial focuses mainly on converting cold into hot tumor, by molecular and therapeutic strategies, but fails to impress whether it is for early-stage CRC or metastatic disease. The conclusion lacks punch and fails to synopsize the strategies to compassing to hot tumour. It withers direction to optimal model to human immune system. Use of gut microbiome, role of nano technology in CRC immune modulation are not alluded to. So also, it fails to insinuate the possible biomarkers that may be reckoned with. Nor it warns about immunotherapy related harm to the patient.

Author's Response: Thank you for the valuable comments. Here, I have intended to highlight organ-specific tumor immunity, especially in colorectal cancer, as a key concern among the multiple issues involved in the resistance to immunotherapies. Therefore, from the validity of the concept and immunity score of cold tumors established in cold CRC, the relative prognostic value compared to the pathological stage, lymphatic invasion, tumor differentiation, and microsatellite status is introduced. In addition, this editorial covers a wide range of molecular biological features, such as MSI/dMMR molecular characteristics, suppression of expression of MHC components related to loss of β-2-microglobulin heterozygosity, activation of STAT3 and Wnt/β-catenin signaling, expression of MAPK, VEGF, and IL-8, etc. Tables 1, 2, and 3 summarize all the highlights of this editorial. To date, the major strategies to overcome cold CRC can be divided into methods to increase specific T-cells and T-cell priming, and to promote T-cell trafficking and infiltration. Adoptive cell therapy (CAR-T and CAR-NK), adjuvant immunotherapy, epigenetic modification inhibitors, cancer vaccine, oncolytic viruses, and conventional therapies combinations are performed for T-cells priming. And to promote T-cell trafficking and infiltration, there are methods to utilize TGF-β suppression, oncogenic pathway inhibitors, angiogenesis inhibitors, CXCR4 inhibitors, and immune cytokines. This editorial investigated the clinical and non-clinical studies of the case and actively encourages these attempts, regardless of success or failure.

Of course, as the reviewer comments, more diverse research is being tried in non-clinical settings, but I hope you understand that this editorial focuses on realistic methods that have been tried clinically or are currently being tried. Please see Tables 1-3. Thank you.