Review of: "Targeting Cancer Cell Signaling Using Precision Oncology Towards a Holistic Approach to Cancer Therapeutics"

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Potential competing interests: No potential competing interests to declare.

1. Holistic approach to cancer therapeutics must include emerging multi-modal approaches but these approaches have clinical challenges. For example, emerging therapies must effectively shut down multiple enabling characteristics that drive different cancer invasion and progression. These therapies must include the concomitant suppression of growth factor signalling and anti-apoptotic pathways, immune-derived promoters of tumorigenesis, mechanisms of acquired drug resistance, and pro-metastatic signals that facilitate cancer cell migration and successful homing of disseminated tumour cells.Also, the difficulty in diagnosing certain cancers at early stages further contributes to low survival rates. For example, pancreatic cancer (PDAC) is located in the retro-peritoneum of patients who present with non-specific symptoms. PDAC is not diagnosed until it has reached an advanced clinical stage in over 80% of patients, with only a 5% five year survival rate. Furthermore, lack of effective screening and early biomarker detection has prevented clinicians from identifying this cancer in a pre-malignant stage.
2. A multi-Modal approaches to optimizing treatment must (a) suppression of cancer cell metabolism and growth, (b) tumor-associated inflammation and (c) apoptosis-resistant cancer cells. Also, major metabolic pathways in cancer cells may also be exploited. This may include: 1) the disabled/reduced supply of glucose and glutamine to the tumor; 2) interruption of the mechanisms that enable survival in a hypoxic environment; and/or 3) prevention of the cancer cell's ability to digest intracellular organelles for energy. Since aberrant metabolic pathways have become a hallmark of cancer, investigators have identified several key metabolic enzymes to target, including hexokinase, pyruvate kinase, lactate dehydrogenase A (LDHA) and ampicillin-activated proteinkinase (AMPK).
3. Some areas of the manuscript require more in-depth analyses articulating the current clinical challenges.
4. One of the primary challenges in developing effective therapies for malignant tumors is the specific targeting of a **heterogeneous cancer cell population within the tumor**. The cancerous tumor is made up of a variety of distinct cells with specialized receptors and proteins that could potentially be viable targets for drugs. In addition, the diverse signals from the local microenvironment may also contribute to the induction of tumor growth and metastasis. Collectively, these factors must be strategically studied and targeted in order to develop an effective treatment protocol. Targeted multimodal (holistic) approaches need to be strategically studied in order to develop a treatment protocol that is successful in controlling tumor growth and preventing metastatic burden.
5. Genomic testing involves many stakeholders working in a coordinated

fashion to deliver high-quality tissue samples to high-quality laboratories, where appropriate next-generation sequencing (NGS) molecular analysis leads to actionable results. Clinicians should be familiar with the types of genomic variants reported

by the laboratory and the technology used to determine the results, including limitations of current testing methodologies and reports. Interpretation of genomic results is best undertaken with multidisciplinary input to reduce uncertainty in clinical recommendations relating to a documented variant.Due to the development of resistance to targeted therapies, resampling and retesting of tumors, including using liquid biopsy technology after clinical progression, may be important in making treatment decisions. The value of molecular profiling depends on avoiding both under-utilization for well-documented variant target-drug pairs and over-utilization of variant-drug therapy without proven benefit.

6. The manuscript reveals over 800 grammar errors which require attention. Also, there is 19% plagiarism which also require attention before any consideration of publication.
7. Recommedation: Major revisions