

EXPLORATION OF USAGE OF PERSPECTIVES FEATURES OF NOVEL BIOMARKERS IN CANCER THERAPY AND EMERGING ASPECTS

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Abstract

The biomarkers offer the personalized treatment strategies, real-time monitoring, and early detection. In the era of precision medicine, identifying and validating these biomarkers has great potential to transform cancer therapy. The use of non-invasive biomarkers is very important. Some of the biomarkers are being used efficiently for detecting the early stage of cancers or its progression, nonetheless, there prevails a huge gap in identifying biomarkers with high sensitivity and specificity for effective diagnosis and prognosis of cancer. The biomarkers assisted in the regulation of the normal process through differentiation of the cancerous cells. Protein biomarkers are continuously being researched since they are simple to assess and abundant in the serum of the affected body. Reflectance confocal microscopy and optical coherence tomography are non-invasive methods for diagnosing skin cancers like melanoma. CAR-T cell therapy is used for cancer treatment due to their targeting ability of particular antigens such as glycosylated proteins and epitopes that are expressed on surface of cancerous cells. The most effective cancer biomarkers, regardless of their kind, are straightforward, repeatable, reliable, and affordable detection methods that are linked to quantifiable improvements in patient outcomes.

INTRODUCTION

Biomarkers that have been extensively used in the clinical diagnosis. They have a wide range of types comprising of the different targeting nature of the tumour cells. The use of biomarkers in the cancer diagnosis and treatment has grown significantly in recent years. Biomarkers are biological substances

found in the blood, other of the body fluids, or tissues that signal an abnormal process, the condition, or disease [1,2]. Through tracking the drug response, prognosis, and early cancer diagnosis, they might help in the advancing the precision medicine. Finding effective treatment methods and

early detection is a never-ending task in oncology. Despite the fact that tissue biopsies and other traditional techniques have long been the cornerstones of cancer diagnosis and therapy. The emergence of non-invasive biomarkers is fundamentally altering the medical field. Numerous substances and analytes, ranging from exosomes and

circulating tumor DNA to the effective microRNAs and metabolites, are the most considered non-invasive biomarkers. They have broad types of applications in mediating the cancers cell through eliciting the various responses induced in the form of the chemical reactions [1,2,3].

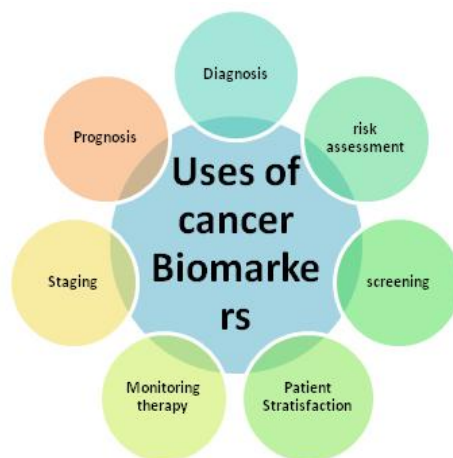


Fig-1: Shows the potential usage of addressing the features of biomarkers and novel design

The main advantage of the using the specific nature of biomarkers for detection of the particular diseases. The biomarkers offer the various kinds personalized treatment strategies, real-time monitoring, and early detection [2,3]. In the era of precision medicine, identifying and validating these biomarkers has great potential to the transform cancer therapy. Clinical research on biomarker-based medications has made great strides. There will be a significant number of clinical trials underway to investigate the efficacy of biomarkers in various cancer types. Positive results from research on biomarkers like Programmed Death-Ligand 1 (PD-L1) and Epidermal Growth Factor Receptor (EGFR) mutations for non-small cell lung cancer (NSCLC) have led to the approval of many targeted medications. Therefore, the specific nature of cancer could be detection through of the controlling the particular diseases [4].

Breast cancer that is the tumour proliferating based and affected the different cells of body through targeting the normal cells. The treatment of breast cancer is mostly determined by BRCA and HER2 mutations, and ongoing research is examining other biomarker targets. Variants of the androgen receptor and gene mutations of its coactivators have been extensively studied for a range of applications [5,6]. The use of non-invasive biomarkers is very important.

Techniques such as liquid biopsies, which look for biomarkers in physiological fluids including blood, urine, and saliva, provide a less invasive alternative to traditional tissue biopsies. This approach provides a dynamic view of the various cancer's progression and is helpful for continuously monitoring the disease's progression and response to treatment. The more of the tumour proliferating, the more of the disease progression that can be controlled in the effective ways by using the biomarkers [6].

Numerous advanced technologies that have broad range of applications could be used for targeting the cancers cells and thus helpful in controlling the various infectious diseases. Genomic technologies are promising to provide better understanding, detection and treatment of cancer. It characterizes and unfolds tumours at the molecular level [2,3]. Although characterization is difficult, current and emerging molecular biomarkers as a guiding tool in diagnosis and prognosis hold significant importance in effective cancer management. Some of the biomarkers are being used efficiently for detecting the early stage of cancers or its progression, nonetheless, there prevails a huge gap in identifying the biomarkers with high sensitivity and specificity for effective diagnosis and prognosis of cancer. In addition, the several clinical studies have advocated

the use of molecular marker information in drug designing to achieve a targeted therapy. The immune based therapy is the valuable for targeting the cancerous cells and inhibiting the infectious diseases [7].

The number of variations affected the individuals also some variations leads the abnormality and defects for the incoming and proliferating cells. Nonetheless, early cancer detection can be achieved using non-invasive or minimally invasive diagnostics, and it is crucial to develop such methods for clinical use. The specific to a tumour, such as protein overexpression and mutations in oncogene and tumour suppressor genes [7]. These fundamental precision medicine techniques are used in routine molecular pathology to identify biomarkers for diagnosis and prognosis in response to specific targeted therapy. Methods have lately replaced traditional approaches more and more because they enable the simultaneous study of a variety of genomic alterations, including as mutations, copy number variations, and fusion of multiple genes. The abnormal cells lead the poor growth and inconsistent to the development process and affected the overall cells of the body [7,8].

Advanced techniques in the detection of the cancer-causing cells could be diagnosed and inhibited through the various applications of the novel antibodies and also the growth bind to the inhibitors. Moreover, tissue microarray is an effective technique for high throughput molecular analysis of sick tissue samples in order to find prognostic and diagnostic biomarkers [9]. However, the potential expression of biomarker heterogeneity is not clearly represented in samples with small volumes. Therefore, it is also recommended to collect a large number of punches from different tumour regions in the array that have larger biopsy sizes. Liquid biopsy assesses molecular biomarkers mostly in blood for cancer diagnosis and prognosis. Molecular RNA levels are commonly also measured using the gold standard, the highly sensitive real-time polymerase chain reaction. RT-PCR necessitates the expensive equipment and carries a significant risk of contaminating genomic DNA. The novel antibodies have diverse nature and show the interactions to the other kinds and through the applications of the novel inhibitors with proteins based targeting affinity [9,10].

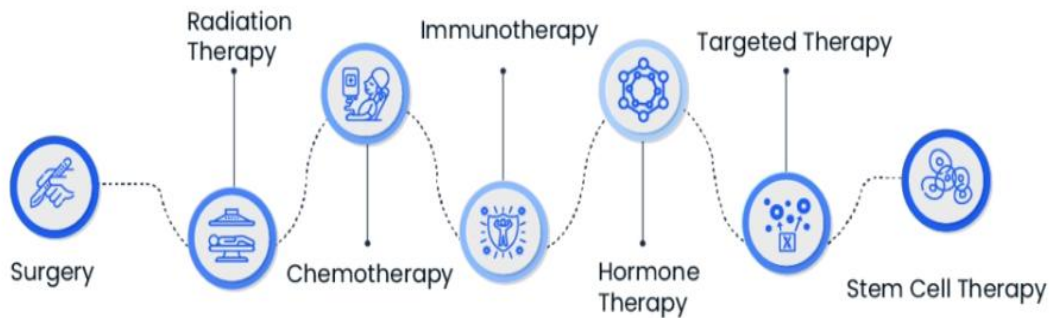


Fig-2: Shows the numerous types of treatments undergoing the biomedical therapy

Innovative prospects

Some mutational effects lead the poor growth and improper development of the various cells that assisted in the regulation of the normal process. Mutations and gene abnormalities are important cancer biomarkers that can reveal the important information about the underlying genetic alterations that cause cancer to develop and spread [11]. These are a few examples of gene mutations and changes that serve as cancer biomarkers. Targeted therapy selection is aided by the genetic mutation, which

increases cell proliferation in melanoma patients [11]. EGFR inhibitors are more likely to work in the patients with non-small-cell lung cancer who have EGFR mutations. In colorectal cancer, KRAS mutations trigger the signaling pathways that affect how well a treatment works. BRCA1/BRCA2 mutations increase the risk of ovarian and breast cancer and affect treatment decisions. MammaPrint is an assay that looks at the activity of around 18 genes in breast cancer using gene expression. Mutations in tumour suppressor genes, oncogene alterations, and mismatch-repair gene mutations are

the examples of the DNA biomarkers. Mutations in the suppressor gene and the KRAS oncogene are signs of metastasis. The tumour-based cells and sometimes mismatching the process of the abnormal

development could lead the effects. The biomarkers in regulation of the normal process through differentiation of cancerous cells [11,12].

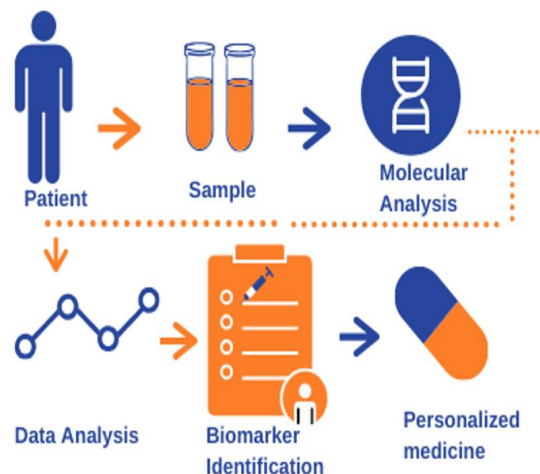


Fig-3: Shows the technological and emerging designing the biomarkers for the advancing aspects

The detection of the emerging cancerous cells through the advanced technologies become important through advances in the clinical sciences. During the early stages of the outbreak, the first and subsequent annual lung cancer test to avoid exposing the general population to COVID-19 [13]. When the percentage of people with lung nodules suggestive of malignancy once screening resumed climbed from 8% institution baseline levels to 29%, referrals to thoracic surgery or interventional pulmonology suddenly jumped. Even with the challenges presented by the COVID-19 epidemic, telemedicine services gained the popularity because they made the collaborative decision-making required for lung cancer screening more convenient. One area of advancement is the application of artificial intelligence in LDCT for the early diagnosis of lung cancer. The contrasted AI with human systems, many of which were carried out over a decade ago, found that AI algorithms were either on par with or marginally worse than their human counterparts. However, the false-positive rate was higher for the AI algorithms. The artificial intelligence-based protocols targeting the cancerous cells through advanced technologies could be a gateway in discovering the novel kinds of the biomarkers with high efficacy for the particular diseases [13,th14].

The metals-based detection of some proliferating cells that could be compared to the normal cells for controlling the different types of diseases [2,3]. The gold standard for identifying the surgical excision, even though a non-invasive approach is preferable. The three most popular techniques for doing PWI are dynamic contrast enhanced, dynamic susceptibility contrast, and arterial spin labelling. It uses the blood as an endogenous artery tracer, whereas require the use of an exogenous contrast agent. Each technique demonstrated the most exceptional diagnostic with accuracy, according to a recent meta-analysis of their diagnostic capabilities regarding the differentiation. While on the other hand, some proliferating cells that could be compared to the normal cells through discovering the novel therapies [15,16].

The biochemical reactions that could be happened in the biosensors-based detection are also helpful for the detection of the cancerous cells. Since each of the several techniques has solid evidence in the scientific literature, it is still up for debate which is also superior than the old studies [1,3]. Since imaging provides information on the glioma's metabolic status, it is thought to be a also helpful alternate method for distinguishing TP from TRA. Although radio-active labelled glucose is widely used in nuclear medicine, its clinical application for

imaging is limited because to the strong physiological absorption of glucose in the cerebral and cerebellar cortex, which results in a low tumour-to-background ratio. Some types of other with biosensors-based detection for the cancerous cells are also in validating of the specific disease [16,17].

Some cells that undergo the heavy stress and leads the production of abnormal cells through free radicals. Tumours contrast more with the background because normal brain tissue has a limited physiological uptake of amino acids compared to glucose [18]. However, to support rapid proliferation, glioma cells have a notably greater dietary requirement for amino acids. Therefore, positron-emitting nuclide-labelled amino acids are interesting probes for the imaging of gliomas before to and during treatment [15]. A recent overview of the diagnostic potential of each method has been released [16,17]. It has been evident that employing either PET allows for a more precise separation between TRA and TP, notwithstanding disagreements over the relative advantages of each technique or the complementary information they offer. Therefore, more research is necessary to ascertain the optimal use. The production of the abnormal cells could be detected through biomarkers [4,18].

The circulating cells that improperly divides and also leads the production of abnormal cells. Circulating cell-free DNA is extracellular DNA that is released from tumour cells via metabolic secretion, apoptosis, or necrosis [19]. It works similarly to a carrier of genetic or epigenetic modifications unique to the formation of the tumours, DNA methylation, gene variations, etc. Using ctDNA taken from the patient's blood, identified genetic and epigenetic changes associated with the certain cancer types and their metastatic status. The accurate and non-invasive of the continuous monitoring of tumour genomes can benefit from these discoveries and examined microsatellite alterations, including chromosomal deletions. The one of the most common hotspots is the Ser-249 protein 53 mutation. Some mutations could be detection through interaction to the chip-based biomarkers with high specificity [4,19].

Characterizing features

The protein-based biomarkers also showed the various kinds of the specific affinity and interaction to the different types of the cells. Protein biomarkers are continuously being researched since they are simple to assess and abundant in the serum of the affected body. Protein glycosylation is frequently altered during malignant transformation, even in liver cancer [8,11]. Current biomarker research needs more external validation before being employed in clinical settings. Proteomics developments have revealed a wide range of possible protein biomarker alternatives. Several biomarkers that are now being researched for the application in clinical practice are included. The specific interaction to the different types of the cancerous cells through proteomics development could be made in future perspectives [20].

The effective type of immunotherapy could be helpful for controlling the number of diseases. A non-invasive method of seeing and identifying morphologic changes in cutaneous tissue is provided by digital dermoscopy, also known as surface microscopy or luminescence microscopy. The ability to differentiate lentigo maligna, the most common histologic melanoma subtype, using dermoscopy based on its annular granular pattern, angulated lines, and confluence of the various perifollicular pigment [21] demonstrates the value of this diagnostic technique. DD uses luminescence light microscopy to magnify the skin lesions and investigate the dermo-epidermal linkages. These technologies might be helpful for controlling the infectious diseases [21].

Some technologies are also used for detection and in the various kinds of the clinical diagnosis. Reflectance confocal microscopy is also used in the cell detection from the varying skin types. Reflectance confocal microscopy and optical coherence tomography are non-invasive methods for diagnosing skin cancers like melanoma. Despite having a lower resolution than RCM, OCT may provide vertical images at the mid-to-deep dermis level because of its greater depth penetration. Tumour thickness and tissue structural patterns may be assessed using these images [22,23]. This makes it easier to diagnose melanoma early. RCM's capacity to estimate tissue form and produce images in the

horizontal plane facilitates the detection of atypical cells, evaluation of the pigmented lesions, and differentiation of the benign from malignant features. The cell detection of the skin could be made through novel biomarkers [3, 22,23].

Current challenges and innovative strategies

Different types of the pathways with specific nature of the genes could be controlled through interaction to the different biomarkers. Targeting the ROS1 can effectively suppress tumour growth and yield clinical benefits. It also provide the wide summary of the understanding of ROS1 rearrangements, including their oncogenic origins, prevalence, detection the biological methods, molecular features, current therapies, and drug resistance mechanisms [24,25]. A key element in cancer is abnormal translation regulation, which is mediated by the RNA helicase eukaryotic translation initiation factor 4A1. It is regulated by long non-coding RNAs and microRNAs and impacts the development and dissemination of tumour cells. The eIF4A1 may promote precision medicine and focused therapy by serving as a biomarker for tumour diagnosis, staging, and outcome prediction and clinical treatments. The small molecule inhibitors that boost the therapeutic potential of eIF4A1 and show the promise in the clinical practice. Therefore, different types of the pathways might be regulated through gene controlling the various gene factors [22,24].

In the ever-changing area of gene and cell therapies, safety remains the primary priority. Therapy-induced carcinogenesis is one such danger, which occurs when therapeutic gene insertions. Despite these problems, interferons remain an important element of the cancer immunotherapy toolkit, and their effectiveness is being investigated in conjunction with other immunotherapeutic drugs [26,27]. The effectiveness of several immunotherapies is influenced by the expression on tumor cells. Potential antigens in all cancers will be found through the sequencing of tumor genomes, which also brings new prospects and problems for ACT. It gives a summary of the most recent findings and clinical studies in CAR-T cell therapy, along with an explanation of the treatment's theory and uses. [28, 29,30].

Conclusion

The use of cancer biomarkers in oncology has revolutionized cancer treatment and led to significant advancements in cancer treatments and patient outcomes. Personalized medicine represents a the paradigm change and a turning point in the treatment of cancer since biomarkers enable oncologists to tailor the biomedical treatments according to the unique molecular profile of each patient's tumour. The most effective cancer biomarkers, regardless of their kind, are straightforward, repeatable, reliable, and the affordable detection methods that are linked to quantifiable improvements in patient outcomes. It will look at the current use and possible future advances of cancer biomarkers, taking into consideration both advancements in testing techniques and a better comprehension of tumour biology.

The use of cancer biomarkers in oncology has revolutionized cancer treatment and led to significant advancements in cancer treatments and patient outcomes. Personalized medicine represents a paradigm change and a turning point in the treatment of cancer since biomarkers enable oncologists to tailor treatments according to the unique molecular profile of each patient's tumor. The primary reasons of cancer's poor survival rates, which constitute a substantial global health burden, are a lack of early detection and limited access to timely and traditional therapy. Significant progress has been made in recent years in creating precise, economical, and effective cancer diagnostics. It explains several innovative research that replace traditional screening methods with a multidisciplinary approach to cancer detection.

REFERENCES

1. Rotimi SO, Rotimi OA, Sahlia B. A review of cancer genetics and genomics studies in Africa. *Front Oncol.* (2021) 10:606400.
2. Lianidou ES, Strati A, Markou A. Circulating tumor cells as promising novel biomarkers in solid cancers. *Crit Rev Clin Lab Sci.* (2014) 51:160-71
3. Marrugo-Ramírez J, Mir M, Samitier J. Blood-based cancer biomarkers in liquid biopsy: A

- promising non-invasive alternative to tissue biopsy. *Int J Mol Sci.* (2018) 19:2877.
4. Bashar M, Begam N. Breast cancer surpasses lung cancer as the most commonly diagnosed cancer worldwide. *Indian J Cancer.* (2022) 59:438.
 5. Lopez-Gonzalez L, Sanchez Cendra A, Sanchez Cendra C, Roberts Cervantes ED, Espinosa JC, Pekarek T, et al. Exploring biomarkers in breast cancer: hallmarks of diagnosis, treatment, and follow-up in clinical practice. *Medicina.* (2024) 60:168
 6. Wu M, Wen L, Zhou Y, Wu W. Role of lncRNA AGAP2-AS1 in breast cancer cell resistance to apoptosis by the regulation of MTA1 promoter activity. *Technol Cancer Res Treat.* (2022) 21:153303382210853.
 7. F. Behling, J. Schittenhelm Tissue microarrays - translational biomarker research in the fast lane *Expert Rev. Mol. Diagn.,* 18 (10) (2018), pp. 833-835
 8. Serrati Simona, Simona De Summa, Brunella Pilato, Daniela Petriella, Rosanna Lacalamita, Stefania Tommasi, Rosamaria Pinto Next-generation sequencing: advances and applications in cancer diagnosis *Oncotargets Ther.,* 9 (2016), pp. 7355-7365
 9. Sunali Mehta, Andrew Shelling, Anita Muthukaruppan, Annette Lasham, Cherie Blenkiron, George Laking, Cristin Print Predictive and prognostic molecular markers for cancer medicine *Ther. Adv. Med Oncol.,* 2 (2) (2010), pp. 125-148
 10. V. Ruiz-Valdepenas Montiel, E. Povedano, E. Vargas, R.M. Torrente-Rodríguez, M. Pedrero, A.J. Reviejo, S. Campuzano, J.M. Pingarrón Comparison of Different Strategies for the Development of Highly Sensitive Electrochemical Nucleic Acid Biosensors Using Neither Nanomaterials nor Nucleic Acid Amplification *ACS Sens.,* 3 (1) (2018), pp. 211-221
 11. Tangella, L.P.; Clark, M.E.; Gray, E.S. Resistance mechanisms to targeted therapy in BRAF-mutant melanoma-A mini review. *Biochim. Biophys. Acta (BBA)-Gen. Subj.* 2021, 1865, 129736
 12. Ma, R.; de Pennington, N.; Hofer, M.; Blesing, C.; Stacey, R. Diagnostic and prognostic markers in gliomas-An update. *Br. J. Neurosurg.* 2013, 27, 311-315
 13. Mazzone, P.J.; Gould, M.K.; Arenberg, D.A.; Chen, A.C.; Choi, H.K.; Detterbeck, F.C.; Farjah, F.; Fong, K.M.; Iaccarino, J.M.; Janes, S.M.; et al. Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report. *Radiol. Imaging Cancer* 2020, 2, e204013.
 14. Klein, E.A.; Richards, D.; Cohn, A.; Tummala, M.; Lapham, R.; Cosgrove, D.; Chung, G.; Clement, J.; Gao, J.; Hunkapiller, N.; et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann. Oncol.* 2021, 32, 1167-1177.
 15. Essig, M.; Shiroishi, M.S.; Nguyen, T.B.; Saake, M.; Provenzale, J.M.; Enterline, D.; Anzalone, N.; Dorfler, A.; Rovira, A.; Wintermark, M.; et al. Perfusion MRI: The five most frequently asked technical questions. *AJR Am. J. Roentgenol.* 2013, 200, 24-34
 16. Wang, L.; Wei, L.; Wang, J.; Li, N.; Gao, Y.; Ma, H.; Qu, X.; Zhang, M. Evaluation of perfusion MRI value for tumor progression assessment after glioma radiotherapy: A systematic review and meta-analysis. *Medicine* 2020, 99, e23766.
 17. Shin, K.E.; Ahn, K.J.; Choi, H.S.; Jung, S.L.; Kim, B.S.; Jeon, S.S.; Hong, Y.G. DCE and DSC MR perfusion imaging in the differentiation of recurrent tumour from treatment-related changes in patients with glioma. *Clin. Radiol.* 2014, 69, e264-e272
 18. Sun, A.; Liu, X.; Tang, G. Carbon-11 and Fluorine-18 Labeled Amino Acid Tracers for Positron Emission Tomography Imaging of Tumors. *Front. Chem.* 2017, 5, 124
 19. Kirk GD, Camus-Randon AM, Mendy M et al (2000) Ser-249 p53 mutations in plasma DNA of patients with hepatocellular carcinoma from The Gambia. *J Natl Cancer Inst* 92:148-153

20. Chen VL, Sharma P (2020) Role of biomarkers and biopsy in hepatocellular carcinoma. *Clin Liver Dis* 24:577-590.
21. Singh, N.; Gupta, S.K. Recent advancement in the early detection of melanoma using computerized tools: An image analysis perspective. *Skin Res. Technol.* 2019, 25, 129-141.
22. Holmes, J.; von Braunmuhl, T.; Berking, C.; Sattler, E.; Ulrich, M.; Reinhold, U.; Kurzen, H.; Dirschka, T.; Kellner, C.; Schuh, S.; et al. Optical coherence tomography of basal cell carcinoma: Influence of location, subtype, observer variability and image quality on diagnostic performance. *Br. J. Dermatol.* 2018, 178, 1102-1110.
23. Dinnes, J.; Deeks, J.J.; Saleh, D.; Chuchu, N.; Bayliss, S.E.; Patel, L.; Davenport, C.; Takwoingi, Y.; Godfrey, K.; Matin, R.N.; et al. Reflectance confocal microscopy for diagnosing cutaneous melanoma in adults. *Cochrane Database Syst. Rev.* 2018, 12, CD01319
24. Kimiz-Gebologlu, I., S. Gulce-Iz, and C. Biray-Avci, Monoclonal antibodies in cancer immunotherapy. *Molecular biology reports*, 2018. 45: p. 2935-2940.
25. Safarzadeh Kozani, P., P. Safarzadeh Kozani, and F. Rahbarizadeh, CAR-T cell therapy in T-cell malignancies: Is success a low-hanging fruit? *Stem cell research & therapy*, 2021. 12(1): p. 1-17.
26. Feins, S., et al., An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. *American journal of hematology*, 2019. 94(S1): p. S3-S9.
27. Wang, Y., et al., Immune checkpoint modulators in cancer immunotherapy: Recent advances and emerging concepts. *Journal of Hematology & Oncology*, 2022. 15(1): p. 1-53.
28. Mohanty, R., et al., CAR T cell therapy: A new era for cancer treatment. *Oncology reports*, 2019. 42(6): p. 2183-2195.
29. Priceman, S.J., et al., Co-stimulatory signaling determines tumor antigen sensitivity and persistence of CAR T cells targeting PSCA+ metastatic prostate cancer. *Oncoimmunology*, 2018. 7(2): p. e1380764.
30. Blackadar CB. Historical review of the causes of cancer. *World journal of clinical oncology*. 2016 Feb 10;7(1):54.