Quest Journals
Journal of Medical and Dental Science Research
Volume 9~ Issue 2 (2022) pp: 46-50
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Neoantigens based molecules as clinical tools for cancer immunotherapy: conception and translational attributes

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Abstract
Cancer neoantigens are cancer specific abnormal proteins produced as direct consequence of non-synchronous somatic mutations on the surface of individual cancer cells, and are not part of central tolerance. They are target for cancer cell cycle checkpoint blockade and can specifically activate the body's immune system.
When neoantigens are incorporated in a vaccine construct, they can be designed to specifically induce the immune system to generate T-cells that recognize tumour cells, causing these tumour neoantigens to be recognized by neoantigen-specific T-cell receptors (TCRs). As a clinical tool being studied for engagement against cancer, some published data indicate need to be further studied to screen for its potential clinical use.
The challenges have been in areas of working out the precise nature of inoculation, difficult method for identification and detection of neoantigens, fear of autoimmunity to normal tissues, dynamic variation of neoantigen landscape, and maintenance of high T cell titer-post vaccination.
This short communication aims at highlighting the conceptual birth of neoantigens and its attributes, for possibilities of being used for bio-molecule based immunotherapy.
Key words*: Neoantigen, T-cell, personalized therapy, mutant, immunotherapy, tumour, vaccine, clinical trials.*

R*eceived 09 Feb, 2022;* ***R****evised 20 Feb, 2022;* ***A****ccepted 23 Feb, 2022 © The author(s) 2022.*
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I. Introduction

Cancer is a generic term for a large group of diseases that can affect any part of the body and are characterized by cell growth that is out-of-control. This adds to the importance of efforts directed against this health problem that humans are faced with. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2010 while the most common types with highest incidences are breast cancer (2.26 million cases), lung cancer, colon and rectum, prostrate and skin (non-melanoma). Among these, lung cancer is the most common cause of death (1.8 million in 2020) (WHO, 2022). In some countries, it is not the leading cause. For instance, in the United States, cancer is the second leading cause of death (CDC, 2022).

Many of the cases of cancer are preventable and treatable when detected early (Lingwood et al, 2008; CDC, 2022; Gine et al, 2022). As such, the scientific community searches for new leads of new treatment options to booster the clinical tool base for tackling cancer. Immunotherapy has been an option for treatment, with some successes recorded through the use of various types of antibodies designs to treat cancer (Herbst rs et al, 2016; Ozurumba-Dwight et al, 2021; Gine et al, 2022). One of the new treatment options through immunotherapy has been neoantigens based therapeutic designs constructs.

For instance, in the area of immumological links to cancer and quest to dive more into these concepts and contribute to pool of findings, it was reported that the acquisition of a protective vertebrate immune system hinges on the efficient generation of a diverse but self-tolerant repertoire of T cells by the thymus (Adoro et al 2017). Celik and Dokur (2020) highlighted the emergence and development of immunotherapy in cancer

treatment, adding that cancer immunotherapy is a rapidly developing and changing sub-specialty in the realm of oncology.

Cancer neoantigens, also known as Tumor specific antigens (TSAs) are cancer specific abnormal proteins produced as direct consequence of non-synchronous somatic mutations on the surface of individual cancer cells, and practically exempted from central tolerance. They are a repertoire of peptides that display on the tumor cell surface and could be specifically recognized by neoantigen-specific T cell receptors (TCRs) (Jiang et al, 2019; Schumacher et al, 2019). They can technically serve as and can specifically activate the body's immune system to prepare related antigens based vaccines (Yi et al, 2018; Peng et al, 2019). For instance, Tumour-specific target for cancer cell cycle checkpoint blockade antigens (TSA) as targets for anti-tumour therapies has accelerated within the past decade. The most commonly studied class of TSA is those derived from non-synonymous single nucleotide variants (SNVs), or SNV-neoantigens (Smith et al, 2019).

Unlike SNV-neoantigens, which are largely patient specific in expression, some classes of alternative TSAs are shared among the population (such as splice variant antigens, gene fusion antigens, and hERV antigens), making them ideal for off-the-shelf therapies ((Smith et al, 2019). Groups of scientist have been emerging and have broadened the screens for other alternative TSAs derived from self and non-self-antigens. These alternative TSAs include antigens derived from mutational frame-shifts, splice variants, and gene fusions.

The major types of tumor antigens are Tumor associated antigens (TAAs), Cancer germline antigens (CGAs) and neoantigens or tumor specific antigens (TSAs) (Vigneron , 2015; Feola et al, 2020; Valilou and Rezaei, 2019 *)*.

TAAs and CGAs can be found expressed on tumor cell surface and on healthy or immune privileged tissues which have low levels of its expression, especially reproductive tissues. TAAs like carcino-embryonic antigen and melanoma associated antigen are present in and shared by a subgroup of patients and a variety of clinical studies examined the efficacy of different TAA-derived peptide vaccines (Wagner et al 2018).

Justification for this article

The entry of neoantigens in cancer immunotherapy, has come through engagement in form of personalized vaccines (Clinicaltrials.gov, 2021). Neoantigens have been found to be cancer specific and can be predicted from patients' genomic data **(Jiang et al 2020; Ying et al 2020)**.

The practical concept of genetic instability of tumor cells which often lead to a large number of mutations and expression of non-synchronous mutations can lead to formation of "tumor specific antigens" called "neoantigens". As such, the description by **Han et al, (2020)** that neoantigens are direct consequences of somatic mutations presenting on the surface of individual cancer cells is in line with its foremost synopsis on neoantigens.

Since neoantigens are expressed in normal tissues, neoantigen-specific T-cells are not subject to central and peripheral tolerance, while also lacking ability to induce normal tissue destruction. This has made neoantigens prospects as targets for T-cell based cancer immunotherapy. The works of **Lu et al (2019) and Han (2020)** opined that this has supported research into neoantigens as targets for T-cell-based cancer immunotherapy.

Considering the fact that the immune system does not tolerate neoantigens, they are harmful to the body. As such, they can be targeted by immunotherapeutic science to block then from functioning as blockers of normal human checkpoints.

They have been clearly found to be fully associated with cancer cells. Tumor neoantigens are foreign protein and absent from normal organs and tissues.

The major objectives of this insight oriented review are to highlight the conceptual birth of neoantigens and its bio-molecular attributes, for possibilities of translational usage in cancer immunotherapy.

Historical lane and conceptual birth

In the early twentieth century, many findings revealed that the immune system can recognize and eliminate tumor cells, but the type of non-self molecules that can offer this patterned immune challenge against tumor cells was not definitive at this period, until the first of such non-self bio-molecules was found to be recognized by T-cells in 1998 **(**Oiseth and Aziz, 2017**;** Abbas AK, et al 2017; Brodin and Davis, 2017**)**.

It is on record that **De Plaen et al (1988)** discovered this mutant antigen of the first neoantigen while working on mouse tumor model using cDNA library sequencing of the gene they screened. A mutant gene should attain a certain quantitative threshold and must be of a specific characterized type before qualifying as a neoantigen bio-molecule.

The challenges

The huddles for neoantigen breakthrough as therapeutic clinical tool against cancer include: determination of the precise nature of inoculation to be engaged, fear of autoimmunity to normal tissues, the difficult method of identification and detection of neoantigens, dynamic variation of neoantigen landscape, identification of potential neoantigen, maintenance of high T cell titer post vaccination (Oiseth and Aziz, 2017; Hutchinson and Pritchard, 2018; Yi et al, 2018 ; Schumacher et al 2019).

Therapeutic vaccines based on the TAAs or CGAs have obtained dismal results mainly due to the central and peripheral tolerance mechanisms. Actually, cancer vaccines were first employed to target TAAs, which are over-expressed in tumors but also expressed in normal tissues.

Some of these challenges have been practically worked on to uplift the quality and potency of neoantigens based vaccines. For instance, in the area of identification of neoantigens which play a key role in screens for immunogenicity and its improvements, Typically emerged means of identification of quality neoantigens include: detecting neoantigens from biopsies obtained from tumor and normal cells, sequencing to identify mutant antigens and abnormal proteins, use of computer models to predict promising mutants , supportive use of mass spectrometry-based immunoproteomics or proteogenomics to cross-check and validate , and the use of *in-vivo* and *in-vitro* immunological analysis to again cross-check and confirm if it's a neoantigen (**Li et al 2017;** Garcia-Garijo et al 2019; Gopanenko et al 2020; Stephens et al 2021).

In addition, immunogenicity of neoantigens has occasionally raised concern. To tackle this, techniques have been developed, one of which is the use of DNA to deliver multiple neopeptide epitopes incorporating cytokines as adjuvant, which hindered tumor growth (Jiang et al 2020).

Translational applications of neoantigens based drugs as therapeutic tools against cancer

Neoantigens can be incorporated in a vaccine construct, they can be designed to specifically induce the immune system to generate T-cells that recognize tumor cells in a unique clinically personalized vaccine tool (Aurisicchio et al, 2018), causing these tumor neoantigens to be recognized by neoantigen-specific T-cell receptors (TCRs) via the major histocompatibility complex (MHC) molecules (**Jiang et al, (2019)**. As a result, immunotherapy can target the presence of neoantigens during cancer cell proliferation and its disease progression when neoantigens can be found at significantly high levels, At this period, they are associated with immune escape, immunoediting and sensitivity to immune checkpoint inhibitors.

Stemming from the basic principle of its mode of action in personalized immunotherapy, neoantigens specifically stimulate the immune system through highly targeted antigenic peptides which improves the inherent ability of immune cells to recognize and attack tumour cells.

As an emerging novel clinical tool against cancer, a number of published data point in the direction of its being beneficially curative against a broad spectrum of cancer such as recurrent, advanced and refractory cancer (Chen et al, 2019; Ott et al, 2022), while therapeutic personalized vaccines and adoptive T cell transfer are two major immunotherapeutic ways in which neoantigens have been out to use in cancer therapy.

Unlike neoantigens, two other common types of tumor antigens, named tumor-associated antigens (TAAs) and cancer-germline antigens (CGAs), are not only expressed on the tumor cell surface, they would also be found on healthy or immune-privileged tissues (especially reproductive tissues including testes, fetal ovaries, and trophoblasts) with low levels of expression (Jiang et al, 2019).

Peptide-based cancer vaccines typically consist of a sequence of amino acids derived from tumour-specific or tumour-associated antigens (TSA/TAA), the difference being whether the antigen is specific to cancer cells (TSA) or whether it can be found both on healthy and cancer cells, but at elevated levels in cancer (TAA) (Stephens et al 2021).

Peptide-based cancer vaccines are amongst a pool of therapeutic strategies for cancer treatment, of which included DNA/RNA vaccines and adoptive cell transfer (ACT). DNA and RNA-based vaccines are inexpensive to produce, and have the advantage of not being HLA-specific, as observed with peptide-based cancer vaccines, (Walters et al 2017).

Neoantigens come with a very minute sizes but intricate in nature, whose details and capabilities are yet to fully unfold. However, the numerous advantages of which includes likelihood of higher and dynamic immunogenicity, its multi-target nature from polyclonality, broad spectrum of usage, personalized attributes in vaccine design per patient, are been presented and worked upon against the challenges.

At the moment, neoantigen based personalized therapeutic vaccines and adaptive T-cell transfers are among the few major methods through which neoantigens have been studied for engagement in immunotherapeutic clinical tools (Stephens et al 2021).

Exploring widely for meoantigen usage and other areas of applications, combinational therapies have showed some support in cancer therapy. For instance, neoantigen-based vaccine and adoptive cell transfers (ACT) treatment have shown promising results in preliminary investigations (Sahin and Tureci, 2018; Chen et al, 2019).

Some studies observed that some patients do not respond to checkpoint inhibitors when given alone as therapy (Ott et al 2016, Helwick 2016). As such, combining checkpoint inhibitors such as (programmed cell death-1 inhibitor (PD-1) with neoantigen based vaccine formulations has been another option in carefully crafted combinatorial therapy. A typical instance has engaged nanocarriers such as liposomes to deliver black phosphorus quantum co-encapsulation of a neoantigen peptide "Adpg", as assessed by Jinxie et al (2020) to disperse it in F127 gel. This led to release of granulocyte-macrophage colony-stimulating factor (GM-CSF) that in turn recruited antigen presenting cells (APC) cells which primed native T-cells. The resultant effect was increase in tumor infiltrating CD8+ T-cells and hindering tumor progression, in what is termed photothermal therapy. As such, combining neoantigens with other cancer therapeutic strategies may provide new dimensions for antitumor therapeutic effects.

Jiang et al (2019) added that both neoantigen-based vaccine and ACT treatments show very promising antitumor effect when used together, with high specificity and safety in preliminary studies.

How do ACTs function, we may ask? ACTs function by taking a patient's cells, expanding, and engineering them *ex vivo*, before transplanting them back into the body. CAR-T (Chimeric antigen receptor therapy- a type of tetment in which a patient's Tcell are changed in the laboratory so they will bind to cancer cells and kill them) and TIL (Tumour infiltrating lymphocytes - a type of therapy in which TIL are removed from a patient's tumour and grown in large numbers in the laboratory) therapies are examples of this, and have proven to have anti-tumour therapeutic effects with a strong and highly personalized immunogenic profile (Rosenburg et al, 2015).

Typical neoantigens based drugs on clinical trials are:

1) TSA-CLT (Tumour specific antigen-induced cytotoxic T lymphocytes undergoing Phase 1 clinical trials - ClinicalTrials gov identifier NCT02959905 (ClinicalTrials.gov, 2022)

2) Personalized neoantigen peptide combined with Targeted drugs in the treatment of non-small cell lung cancer– ClinicalTrils.gov identifier NCT04487093 (ClinicalTrials.gov, 2022).

3) Personalized cancer antigen targeting shared neoantigens – ClinicalTrials.gov identifier NCT03953235 (ClinicalTrials.gov, 2022). This candidate neoantigen based therapeutic vaccine design in combination with immune checkpoint blockade, is on trials in patients with advanced or metastatic non-small cell lung cancer microsatellite stable collateral cancer, pancreatic cancer and shared neoantigen positive tumours. Its Phase 1 clinical trials has evaluated for dose, safety, immunogenicity and early clinical activity of GRT-C903 and GRT-R904 based neoantigen vaccines and has stepped on to Phase 2 clinical trials.

4) Personalized neoantigen therapy plus Anti-PD-1 in patients with advanced melanoma, non-small cell lung cancer or bladder cancer. Results from clinical trials indicated that its dosage was safe with no treatment related serious adverse events. De novo neoantigen– specific CD4+ and CD8+ T cell responses were observed post vaccination in all of the 82 patients – ClinicalTrials.gov NCT02897765 (Clinical Trials.gov, 2022; Ott et al, 2020).

Given the forgoing synopsis, the discovery of neoantigen mutant bio-molecules in tumor cells and channeling them into carefully crafted vaccines for immunotherapy has been entry options in the pool of clinical tools for treating cancer and fighting the burden of cancer. Exploring the combinatorial therapeutic attributes of neoantigens based drug designs with other therapeutic methods is a coupled option in this regards. Cancer has inputted tears and untimely death in homes across the globe, for cancer knows no bounds. It's been a tough task. The scientific community battle on with ne/emerging therapeutic options to mine, explore potentials, attempt molecular reconstructions where necessary and harness, for which neoantigens based therapy is one.

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ACKNOWLEDGEMENT: Gratitude to key build-up instructional Senior Professors at specific Universities in Manchester, Lyngby, London, and North Carolina at Chapel Hill. Appreciation to partners in Ontario and Saudi Arabia for logistic support.