

Research Article



An Evidence-based Medical Research on the Comparative Quantification of TGFβ and Telomerase Experimentations, with their Molecular Pharmacological Analyses as Targets of Oncoimmunotherapeutic Vaccines

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ABSTRACT

The basic oncotherapeutic vaccines used are cell based vaccines including whole cell vaccines, genetically modified tumour cell vaccines and dendritic cell vaccines, anti-idiotypic antibody based vaccines, protein or peptide based vaccines, heat shock protein-based vaccines, viral, bacterial or yeast vectors based vaccines, mRNA or DNA nucleic acid based vaccines, vaccines based on tumour associated antigens like overexpressed proteins, differentiation antigens, cancer-testis antigens and oncofoetal antigens, and tumour specific antigens including oncogenic viral antigens, antigen presenting cells or molecular neoantigens based vaccines with specific CD8+ T cells and, CD4+ T cells, and nanoparticles vectors based vaccines. The objective of this evidence-based medical research was the comparative quantification of TGFβ and telomerase experimentations, with their molecular pharmacological analyses as targets of oncoimmunotherapeutic vaccines. A molecular pharmacological multi-variate, qualitative, analytical study of the retrieved literature derived through a thorough literature review from various available literature databases, was performed, to record, review, thoroughly analyse and delineate the molecular pharmacological basis of oncoimmunotherapeutic vaccines from a wide-ranged study literature containing molecular pharmacological researches, reviews, case presentations and varied databases about the pharmaco-oncoimmunotherapeutic rationale of the clinical use of vaccines in the treatment of cancer patients, with a specific emphasis on telomerase and TGFβ, as molecular pharmacological targets of oncoimmunotherapeutic vaccines. After that, a multi-variate evidence-based medical research study of comparative quantification and analysis of the global heterogeneous multidisciplinary experimentations and study literature on telomerase and TGFβ, as molecular pharmacological targets of pharmaco-onco-immuno-therapeutic vaccines, affecting global malignant and borderline malignant patients. This study was conducted, by recording, calculating and statistically deriving the percentages of analyses of telomerase and TGFβ, retrieved from the study literature database, along with graphical representation of the deduced study results. In this study, the percentage of analyses conducted on telomerase was 61%, whereas the percentage of analyses conducted on TGFβ was 39%. Both telomerase and TGFβ, were elaborated in details, as molecular pharmacological targets of oncoimmunotherapeutic vaccines. Telomerase is more widely analysed than TGFβ, and both were elaborated in details, as sufficiently efficacious molecular pharmacological targets for oncoimmunotherapeutic vaccines.

Keywords: Pharmaco-onco-immuno-therapeutic vaccines, TGFβ, Telomerase, Comparative analytical quantification, Molecular Pharmacology.

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INTRODUCTION

Anti-cancer pharmaco-onco-immuno-therapeutics have always remained the treatment modalities for an ever-significant iatrical indication of

malignancies or borderline malignancies, within the usual therapeutic scenario of common or rare diseases. Never redundant, and never archaic, anti-cancer pharmaco-onco-immuno-therapeutics have been incessantly reducing and relieving the immense suffering and pain of many, throughout all strata of life. Such indispensable remains its necessity, in the perennially pertinent chronicles of disease and treatment.

The prevailing types of cancer immunotherapy are : (i) monoclonal antibodies against specific antigens, (ii) immune checkpoint blockade (ICB) to release the "breaks" of T cells, (iii) chimeric antigen receptor (CAR) T cell therapy, using a patient's autologous cells, (iv) oncolytic



viruses that selectively kill cancer cells and (v) cancer vaccines. Presently, among the most evident available immunotherapeutic treatments, few include anti-CTLA4, anti-PD1 and anti-PD-L1, CAR T cells against acute lymphoblastic leukemia and B-cell lymphoma. Although expensive and associated with immunological adverse effects, the therapeutic success of cancer immunotherapy has reinforced their anti-cancer therapeutic use. Tumour antigens are the proteins overexpressed in the tumour tissue, causing tumor initiation, progression and metastasis, against which the anti-cancer vaccines induce a specific and long-lasting immune response.¹

Cancer vaccines are usually derived from the patient's tumour cells or the antigens found on their surface, which may help the immune system to identify and kill these malignant cells. The currently designed vaccines intends to trigger the immune system to attack cancer cells in a more effective, reliable and safe manner.^{2,3}

Pharmaco-Immuno-Therapeutic Anti-Cancer Vaccines

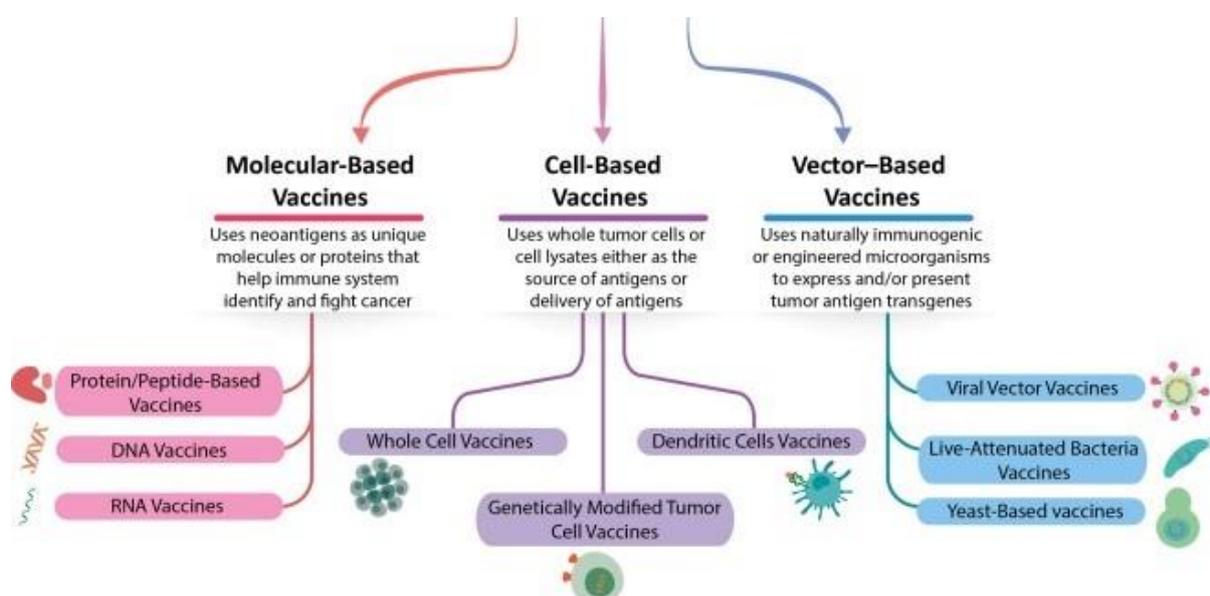


Figure 1: Pharmaco-immuno-therapeutic anti-cancer vaccines.²

Modern biotechnological techniques involving drug carriers, like hydrogels, modified polymers, emulsions, liposomes, virosomes, nanodiscs, cell membranes, self-assembled proteins, virus-like particles, and nucleic acids, are used to deliver and develop biomaterial-based vaccines, used for personalised oncoimmunotherapy. The development of anticancer immunotherapy also includes the appropriate monotherapy or combination therapy with cellular vaccines, tumour-associated antigens, neoantigens and chimeric antigen receptor T cells (CAR-T).^{3,4}

Pharmaco-immuno-therapeutic anti-cancer vaccines are attractive systemic immunotherapies that activate and expand antigen specific CD8+ and CD4+ T cells to enhance anti-tumour immunity.³ In cancer vaccines clinical trials, the major factors to reflect on would include the engineering of antigen-presenting cells, potential toxicity of antigenic areas, pharmacokinetics and pharmacodynamics of vaccines, and monitoring of the patients' immune response.

The parameters affecting vaccine efficacy and requiring optimization are : size, surface properties, shape, surface change, and sustained release of antigen or nanovaccine.³

The basic oncotherapeutic vaccines used are cell based vaccines including whole cell vaccines, genetically modified tumour cell vaccines and dendritic cell vaccines, anti-idiotypic antibody based vaccines, protein or peptide based vaccines, heat shock protein-based vaccines, viral, bacterial or yeast vectors based vaccines, mRNA or DNA nucleic acid based vaccines, vaccines based on tumour associated antigens like overexpressed proteins, differentiation antigens, cancer-testis antigens and oncofoetal antigens, and tumour specific antigens including oncogenic viral antigens, antigen presenting cells or molecular neoantigens based vaccines with specific CD8+ T cells and, CD4+ T cells, and nanoparticles vectors based vaccines (Figure 1).

The necessity to overcome immunosuppression mechanisms or immune tolerance would be a very crucial step for developing therapeutic cancer vaccines. A better understanding of neoantigens, tumor immune surveillance escape mechanisms and host-tumor interactions would give rise to more effective and safer cancer vaccines.^{2,5}

Oncotherapeutic vaccines are used either as a substitute oncotherapy in the treatment of chemoresistant or chemorefractory, and radioresistant or radiorefractory malignancies; or are used as a combination oncotherapy, along with chemotherapy, radiotherapy, targeted therapy, and surgical therapy.

The combination therapies of vaccines based on peptides, proteins, viruses, DNA, prime boost, dendritic cells, tumour lysates and tumour cells, along with various other treatment modalities, like, (i) standard of care : ablation, chemotherapy, radiation, small molecules; (ii) checkpoint

blockade : CTLA-4, PD-1, PDL-1; (iii) immunotherapy : cytokines (IL-2, IFN- α , GM-CSF), co-stimulation, adaptive transfer of effectors, and (iv) suppression reduction : lymphodepletion, Tregs, MDSC reduction or inhibition are also usual, in recent times.⁶

The monotherapeutic potential of pharmaco-immunotherapeutic anti-cancer vaccines is still in the investigative stages.

Such modalities of oncoimmunotherapy always increase the comprehensive oncotherapeutic efficacy, while reducing the occurrence of frequent adverse effects, caused by any oncotherapeutic regimen, otherwise.

Objectives

The objective of this evidence-based medical research was the comparative quantification of TGF β and telomerase experimentations, with their molecular pharmacological analyses as targets of oncoimmunotherapeutic vaccines.

MATERIALS AND METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the global regulatory requirements. Informed consent was obtained from the participants or organisations concerned with this study, and the confidentiality of related medical databases and study literature was maintained, as per global standards. This study involved no risk to any patient, and was conducted with lofty ethical values.

Study Design

The study design was a multi-variate, multi-centre, retrospective, quantitative research study, and a molecular pharmacological multi-variate, qualitative, analytical study.

Study Population

The study population was global patients, suffering from various stages of malignancies or borderline malignancies. The study population database was a global heterogenous multi-disciplinary experimentations and study literature on pharmaco-onco-immuno-therapeutic vaccines.

Study Period

The study period was 1 year, from January, 1999 to February, 1999; January, 2002 to June, 2002; June, 2015; April, 2016 to June, 2016; May, 2017; and October, 2021 to December, 2021.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular

Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Clinical Pathology, Molecular Diagnostics, Zoology, and Molecular Medicine, at Dr. B. R. Ambedkar Medical College and Hospitals, J. J. M. Medical College and Hospitals, Presidency College, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Dr. Moumita Hazra's World Enterprises, Hazra Nursing Home, K.D. Medical College Hospital and Research Center, Gouri Devi Institute of Medical Sciences and Hospital, and Mamata Medical College and Hospitals.

Study Procedure

A qualitative multivariate analysis of the retrieved literature derived from a thorough literature review from various available literature databases was performed, to record, review, thoroughly analyse and delineate the molecular pharmacological basis of oncoimmunotherapeutic vaccines from a wide-ranged study literature containing molecular pharmacological researches, reviews, case presentations and varied databases about the pharmacoconcoimmunotherapeutic rationale of the clinical use of vaccines in the treatment of cancer patients. Subsequently, a specific emphasis was placed on the thorough qualitative review and analysis of the retrieved literature derived from various available literature databases about telomerase and TGF β , as molecular pharmacological targets of oncoimmunotherapeutic vaccines.

After that, a multi-variate evidence-based medical research study was conducted, involving the comparative quantification and analysis of the global heterogenous multi-disciplinary experimentations and study literature on telomerase and TGF β , as molecular pharmacological targets of pharmaco-onco-immuno-therapeutic vaccines, affecting malignant and borderline malignant patients. This study was conducted, by recording, calculating and statistically deriving the percentage of analyses retrieved from the study literature database, each about telomerase and TGF β , along with graphical representation of the deduced study results.

RESULTS

The thorough qualitative analysis of the retrieved literature recorded from different types of medical experimentations and medical databases about telomerase and TGF β , as molecular pharmacological targets of oncoimmunotherapeutic vaccines, elaborated the following molecular pharmacological findings: ¹⁻³⁶

Telomerase as a molecular pharmacological target of oncoimmunotherapeutic vaccines:

This qualitative analysis has shown that telomerase activation is a major cell immortalization mechanism; which forms an essential step in the process of carcinogenesis. Loss of telomerase and telomere attrition resulted in genome instability and human cells' replicative senescence,



and chromosomal aberrations at end replicative life span. Through telomerase activation, cancer cells acquire the ability of unlimited proliferation. Expression of telomerase is sufficient for cell escape from M1 and M2 proliferative barriers and for cell immortalization.²⁷

Telomerase activity is also linked to epithelial-to-mesenchymal transition and cancer stemness, which provides the cancer cells their metastatic potential. Telomerase is expressed in most tumour types of varying cell lineages, across all stages of development; and hence, is an appropriate target for therapeutic vaccination.

When cells are approaching the Hayflick Limit in cell cultures, the time to senescence is extended by the inactivation of tumour suppressor proteins TP53 and Retinoblastoma protein (pRb). These cells would undergo an event termed “crisis”, when majority of cells in the culture die. The telomeres are lost and the integrity of chromosome declines with every subsequent cell division. The exposed chromosome ends, called double stranded breaks in DNA, and such damage is repaired by reattaching (religating) the broken ends together, due to which the ends of different chromosomes fuses. During the anaphase of cell division, the fused chromosomes randomly ripped apart, causes mutations and chromosomal abnormalities, making the cell’s genome unstable. Either apoptosis or an additional mutation causes the activation of telomerase, wherein some types of cells and their offsprings become immortal, and their chromosomes will not become unstable, bypassing the Hayflick Limit, thus avoiding cell death. The cancer cells are considered “immortal”, because telomerase activity allows them to divide forever, forming tumours. The example of cancer cells’ immortality, is observed within the HeLa cells.

The following alterations are required for the formation of tumorigenic cells :

- a) activation of TERT
- b) loss of p53 pathway function
- c) loss of pRb pathway function
- d) activation of Ras or myc protooncogenes
- e) aberration of PP2A protein phosphatase

The alternative lengthening of telomeres involves the recombination mediated DNA replication and the current ALT models, wherein, there are :

- a) roll – spread replication or recombination mechanism using circular telomeric DNA generated by homologous recombination
- b) extension of a telomere end using a sister telomere as a template
- c) extension of 3’ end of telomere in T-loop configuration

In lymphoma:

Telomerase activity is down-regulated by anti-neoplastic radiation and chemotherapeutic agents in malignant

lymphoma cells. The expression of hTERT may not be correlated with telomerase activity. P27/ Kip1 may be involved in the G2/M growth arrest induced by anti-neoplastic agents.¹⁷

In thyroid cytology and cytology of other disorders:

Telomerase activity has been demonstrated in 85-90% of frozen tumours mainly in those with endocrine differentiation, such as neoplasms of breast, prostate, thyroid, parathyroid and adrenal gland and neuroblastomas. Telomerase activity can be detected in pleural fluid, bronchial washings, urine washings and breast FNA.¹¹

Telomerase, as a target for pharmaco-onco-immunotherapeutic drugs and vaccines :

- Telomerase is a significant drug target, because telomerase is required for the immortality of cancer cells.
- If a drug turns off telomerase in the cancer cells, telomere shortening would resume, for which the telomere length would be lost. As the cells continue to divide, mutations will occur and cell stability will decrease.

The following are the telomerase inhibition related potential telomerase vaccines :

- a) Adenovirus or plasmid based vaccine,
- b) Autologous dendritic cell based vaccine, which showed significant PSA doubling times as well as T-cell response,
- c) Embryonic stem cell derived dendritic cell vaccine.

These vaccines would adapt the human immune system to attack cancer cells expressing telomerase.

Geron’s telomerase inhibitor drug stops cancer cell proliferation by inhibiting telomerase, by the mutation of RNA template of telomerase; and thus, unable to grant replicative immortality to cancer, disallow glycolysis to be initiated, and does not upregulate Blackburn’s 70 cancer bad genes.

The tumour types with increased telomerase expression combined with an immune permissive tumour microenvironment increases the therapeutic potential of telomerase targeting oncological vaccines.

TGFβ as a molecular pharmacological target of oncoimmunotherapeutic vaccines:

The uniqueness of TGFβ is associated with the display of its paradoxical activity, as it inhibits cellular transformation and prevents cancer progression in the early stages of tumorigenesis, but in the later stages, it promotes tumour progression through facilitating epithelial to mesenchymal transition, stimulating angiogenesis and inducing immunosuppression.

Due to this sort of a correlated balanced synchronization of stepwise chronologically contrasting tumour promoting and tumour suppressive abilities, TGFβ and its pathway has represented potential opportunities for drug development;



and several therapies, including oncovaccines, targeting TGF β pathway, have been identified.

Blockade of only TGF β 1 and 2 is sufficient to enhance the efficacy of oncovaccines, which is further increased by PD-1 checkpoint blockade immunotherapy.

Vaccine-based strategies with TGF β as oncotherapeutic vaccine targets:

Two types of vaccines combined with TGF- β antisense have been developed, namely belagenpumatucel-L, and gemogenovatucl-T. Belagenpumatucel-L, a nonviral gene-based allogeneic tumor cell vaccine targeting TGF- β 2, with acceptable safety profile and increased survival rate, is the first vaccine accessing the phase III trial, in non-small cell lung cancer patients. Combinational therapies with radiotherapy, chemotherapy or immunotherapy, are also in investigative phases. Previous clinical studies have shown that the treatment in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) and TGF- β 2 ASO promotes the immune response and further suppress tumor growth. They constructed a TAG plasmid co-expressing GM-CSF and TGF- β 2 ASO, and the plasmid was incorporated into an autologous whole-cell vaccine. There were selective immune responses to the autologous TAG vaccine with >10-fold increase in IFN- γ expression over baseline. Gemogenovatucl-T, is a combination of GM-CSF expression with a novel bifunctional short hairpin RNAi targeting furin convertase, involved in TGF- β 1 and β 2 precursor. In the phase I trial, there were no adverse events, and the vaccine increased the immune response as reported in a previous study. A phase II study was also conducted to evaluate its combination with nivolumab, a PD-1 inhibitor, in metastatic NSCLC. A phase II with favorable 1-year survival in metastatic Ewing's sarcoma supports the justification of further testing and moving to the phase III trial. In an ongoing phase II trial, the maintenance of gemogenovatucl-T is investigated in women with high-risk stage ovarian cancer (IIIb–IV) following surgery and primary chemotherapy. There was high rate of induction in T-cell activation and improvement in median relapse-free survival. Considering the broad expression and roles of TGF- β 1 and TGF- β 2 in malignancy, further exploration of gemogenovatucl-T vaccine is required.

The comparative quantification of the variegated experimentations conducted on telomerase and TGF β , as molecular pharmacological targets of oncoimmunotherapeutic vaccines, delineated the following study results:

Figure 2 depicts that the percentage of analyses conducted on telomerase is 61%, whereas the percentage of analyses conducted on TGF β is 39%, thus showing telomerase to be more widely analysed than TGF β ; and both were elaborated in details, as sufficiently efficacious molecular pharmacological targets for oncoimmunotherapeutic vaccines.

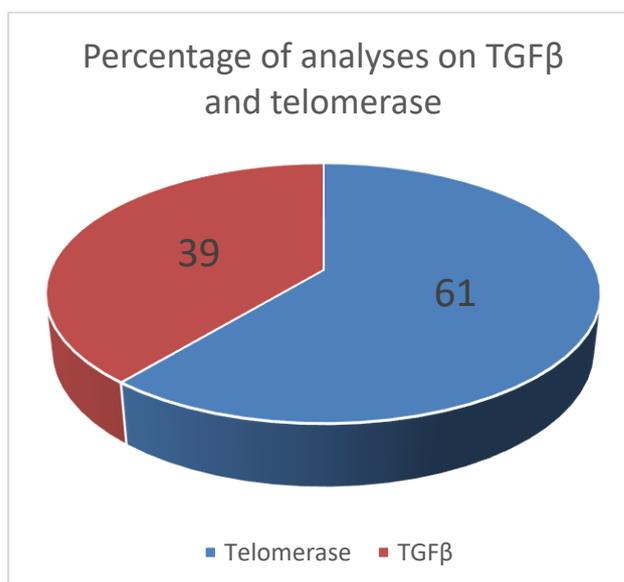


Figure 2: The percentage of analyses conducted on Telomerase and TGF β , as molecular pharmacological targets of oncoimmunotherapeutic vaccines

DISCUSSION

From time immemorial, vaccines have been used to adapt the immune system to recognize pathogens, and prevent and treat diseases, such as cancer.²

The past decade has witnessed a resurgence in the discovery and applications of pharmacotherapeutic cancer vaccines. Better analytical interpretations of tumour-associated antigens, the native immune response and development of novel antigen delivery technologies have improvised the vaccine design. The goals of therapeutic cancer vaccines are to induce tumour regression, eradicate minimal residual disease, establish lasting anti-tumour memory and reduce non-specific or adverse reactions. Tumour-induced immunosuppression and immunoresistance is very necessary to be kept in consideration, during the achievement of these goals. In a study, the methods to improve and expand the antigen repertoire for vaccines, developments in vaccine platforms and explorations of antigen-agnostic *in situ* vaccines, were analysed further, while also focusing on the various strategies for combining suitable vaccine platforms with novel immunomodulatory approaches and standard-of-care treatments for overcoming tumour resistance and enhancing clinical efficacy.³⁷

Vaccination with intranodal injection of neoantigen peptide-loaded dendritic cells (DC) may have clinical and immunological impacts on cancer treatment. Neoantigens represent promising targets for personalized cancer immunotherapy in chemorefractory ovarian cancer. Neoantigens, which are produced in tumor cells as a result of non-synonymous, splicing, or frameshift mutations, have pivotal roles in the effectiveness of immune checkpoint inhibitors.¹ A DC-based vaccine generated by differentiation of autologous Mo-DC pulsed with HOCl oxidized autologous tumor cell lysate (OC-DC vaccine) was tested in platinum-

treated, immunotherapy-naïve, recurrent ovarian cancer patients in a single-center, multi-cohort, non-randomized phase I trial. In this study, the DC-based vaccine was administered either alone, in combination with bevacizumab or in combination with bevacizumab and low-dose intravenous cyclophosphamide until disease progression or vaccine exhaustion. This OC-DC vaccine induced T cell responses (increased in IFN- γ production) to autologous tumor antigens, which were detected in some patients on week 12. Moreover, this antitumour immune response was associated with significantly prolonged survival with increased neo-antigen specific T cells responses, both previously recognized and non-recognized neo-epitopes.^{38, 39}

To enhance the vaccine-induced immune response and the treatment efficacy, therapeutic DNA vaccines could be improved by using two different strategies : (i) by increasing their immunogenicity by selecting and optimizing the best antigen(s) to be inserted into the plasmid DNA; (ii) by combining DNA vaccines with other complementary therapies that could improve their activity by attenuating immunosuppression in the tumor microenvironment or by increasing the activity or number of immune cells.¹

Therapeutic cancer vaccines aim to generate potent immune responses by presentation of antigens to dendritic cells that travel through the lymphatics and present cancer antigens to naive T cells. Activated cytotoxic T lymphocytes proliferate, multiply, and travel throughout the body, with the potential to provide long-lasting immunologic memory. Therapeutic cancer vaccines and combination immunotherapy impact on specific components of the cancer immunity cycle. T cell activation, effector function, and immunological memory specific to therapeutic cancer vaccine therapy (Chen, Mellman, Song *et al*).^{3, 37}

In this evidence-based medical research on the comparative quantification of TGF β and telomerase experimentations, it was found that the percentage of analyses conducted on telomerase was 61%, whereas the percentage of analyses conducted on TGF β was 39%, thus showing telomerase to be more widely analysed than TGF β , with the detailed elaborations of both telomerase and TGF β , as molecular pharmacological targets of oncoimmunotherapeutic vaccines.

According to another study, the advantages and disadvantages of the different strategies that are reviewed for vaccine applications are :

Strategy No. 1:

Polymeric hydrogels

Advantages :

- Sustained release of NPs or antigens
- Mechanical properties can be controlled to suit method of administration
- Can form stimuli-responsive vaccines for targeted release of antigens

- Adjuvants can be bound and released over time, similar to antigen release

Disadvantages :

- Synthesis process involves many steps
- Crosslinking may involve hazardous triggers
- Scale-up of hydrogel vaccines is difficult
- Can involve slow degradation times depending on polymer used
- Higher cost

Strategy No. 2:

Biologically modified polymers

Advantages :

- Sustained release of antigens
- Form NPs the size of which can be adjusted
- Can encapsulate adjuvants
- Several polymers have adjuvanting properties
- Can be conjugated to immunogenic/targeting molecules through physical or chemical modifications

Disadvantages :

- Physical and chemical conjugation steps increase complexity of synthesis
- Can be difficult to identify and localize species, such as neoantigens
- Chemical characterization of polymers can be difficult
- Batch-to-batch reproducibility can be limited when using certain polymers

Strategy No. 3:

Virus like particles

Advantages :

- Resembles natural pathogens in antigen presentation, but is devoid of the genetic material which makes the pathogen infectious
- Particulate shape and size, similar to pathogens, results in high efficacy
- Can be modified to express adjuvants
- Can be synthesized in numerous cellular systems (yeast, bacteria, mammalian, and insect cells)

Disadvantages :

- Storage of VLPs is difficult and must be done at sub-zero temperatures
- Longevity/storage life can be short, even in ideal temperatures
- Pre-existing immunity against VLP nanocarrier may exist



- Cost of production may be high

Strategy No. 4:

Self-assembled proteins

Advantages :

- Stable structure in vivo
- High immunogenicity due to repetitive antigen display
- Can be manipulated to express both antigens and adjuvants

- Easy production process in bacterial systems

Disadvantages :

- Proteins can be susceptible to enzymatic degradation
- Storage often requires sub-zero temperatures
- Storage and transportation issues because of probable aggregation

Strategy No. 5:

Cell membranes

Advantages :

- Presence of surface proteins and receptors that prevent phagocytic clearance and increase

circulation time

- Interacts with numerous biological molecules in body
- Receptors that are biomarkers for disease/infection serve as antigens and adjuvants

Disadvantages :

- Difficult production and scale-up
- Requires several optimization and characterization steps
- Storage and handling are difficult
- May induce allergic or autoimmune responses
- Batch-to-batch reproducibility can be difficult

Strategy No. 6:

Nucleic acids

Advantages :

- Production of antigens in vitro, mimicking infection by pathogen
- High immunogenicity
- Can be delivered without an adjuvant, usually encodes adjuvant along with antigen
- Relatively easy development and production

Disadvantages :

- Limited to encoding protein antigens
- May require use of delivery system

- May elicit immune response against nucleic acid itself
- Insertion of nucleic acid into host cell genome may affect normal function
- May need multiple boosters of vaccine to maintain immunity
- Low storage temperatures³

CONCLUSIONS

The comparative quantification of TGF β and telomerase experimentations showed that telomerase is more widely analysed than TGF β , and both were elaborated in details, as sufficiently efficacious molecular pharmacological targets for oncoimmunotherapeutic vaccines. Therefore, anti-cancer vaccines are the extraordinarily effective systemic immunotherapies, that systematically enhance the life-long anti-neoplastic prophylactic immunity and produce a very long-lived anti-malignant therapeutic triumph.

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