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# Cancer Vaccination: Various Platforms and Recent Advances

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## Abstract

Cancer immunotherapy has branched into various categories, and one of the most promising and also frustrating approaches is cancer vaccination. Vaccination has saved a million lives in the world. However, Cancer Vaccine technology has gone a long and challenging way to reach today's place. A lot of failures in this therapy, galvanized scientists to find more efficient methods for better targeting and precise antigen and adjuvant selection. Divergent platforms and various vaccine types have been tested during the last thirty years. Dendritic Cells, Long/Short peptides, whole tumor cell lysate, viral-based, and Genetic-based vaccines are the most common vaccine types. Novel approaches in cancer vaccination are mainly based on personalized vaccination, Nano-carrier usage, and combination therapy. Moving from TAAs to Neoantigens made scientists achieve more immunogenic vaccines and transferring from bare antigen usage into Nano-/micro-vaccine platforms provided scientists with better targeting and localized vaccines. Also, progresses in the biomaterial field pave the way for developing a more functional vaccine. In this review paper, main vaccine types and novel strategies in cancer vaccine production have been briefly discussed.

**Keywords:** Cancer vaccine • Nanovaccine • Personalized vaccination • Combination therapy • Adjuvant

## Introduction

Medicine was revolutionized with the advent of vaccines; a lot of vaccines have been produced to halt infectious diseases by alerting the immune system to fight against pathogens [1]. But the usage of vaccines against cancers has gone a long way to reach its today's place. Historically, in 1957 Dr. Prehn and his co-workers for the first time revealed that immune system could be alerted against a specific cancer. While, they showed that mice immune induction could prevent them from sarcoma for long time, this is a determined protection only for that kind of tumors no other sarcomas [2]. These findings led scientists to the concept of Cancer Immunotherapy. Melanoma was the first cancer which attracted scientists for cancer immunotherapy. One of the early phase-I immunotherapy trials have been done on 22 patients suffering melanoma. The aim of research was to evaluate the toxicity and immunogenicity of cancer immunotherapy approaches on melanoma. Two cell lines of melanoma were lysed mechanically and together with DETOX adjuvant were administrated to patients. Successful immune inductions were achieved in 13 patients and the results were indicative of minimal toxicity [3]. There was a hope to prevent cancer recurrence with creating immune memory [4]. Although, the usages of immunotherapy in fighting against cancers have fascinated scientists for many years, worries about autoimmune reactions and unwanted inflammations slowed its progress [5].

George Klein in 1967 discovered the concept of tumor-specific antigens which later led scientists to the advent of cancer vaccines [6]. During 1995 to 2004, more than 500 vaccines were injected to nearly 440 metastatic cancer patients by NCI Surgery Branch. These vaccines in most cases were on the basis of peptide and viral vaccines demonstrated the efficiency of cancer vaccination [7]. Sipuleucel-T was the first cancer vaccine which is approved by FDA to combat prostate cancer, and the results revealed that the usage of vaccine will effectively prolong the survival rate [8]. Despite all these efforts in vaccine production, only a small number of cancer vaccine and adjuvants have been already licensed. And, this is due to complexities in cancer vaccine production [9]. Other obstacles which slowed the vaccine production including, low immunogenicity of vaccine platforms (antigens are self-derived), tumor suppressive microenvironment, target delivery issues and toxicity of vaccines [6,10]. While the results on therapeutic cancer vaccines were disconcerting, advances in preventing cancer vaccines were acceptable, two preventive cancer vaccines HBV (vaccine against hepatitis B virus) and HPV (vaccine against human papillomavirus) have been proven to be successful [1,11].

Recent clinical trials on Cancer vaccine are indicative of high progress in vaccines usage [12,13]. However, the efficiency of these vaccines is mostly confined to low residual disease and pre-malignancy cancers. Therefore, combination on cancer vaccines with chemotherapy, radiotherapy, Surgery, immune check point blockade and adoptive cell transferring is vital [12,14]. And also, personalized vaccination seems to be one of the most novel approaches in cancer Immunotherapy [15]. In this review article we will first define the most useful concepts in cancer vaccination and then, indicate main and recent approaches in cancer vaccination.

## Mechanism of Tumor Cell Detection by Immune System

Normally, tumor cells are identified by CD8+ T lymphocytes. Firstly, Antigen Presenting Cells (APCs) recognize tumor antigens. Then, naive CD8+ T cells differentiated and activated into cytotoxic T lymphocytes (CTLs). CTLs move into tumor cite and by recognition of MHC class I-antigen complex on the surface of the neoplastic cells, CTLs induce tumor cells lysis. However, there are many situations that avoid immune system to kill cancerous cells. Such as: a) immune suppressive microenvironment which is caused by solid malignancies, in this situation tumor cells express

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factors which may kill T cells or prevent the infiltration of T cells. b) T cell exhaustion as a result of endurance antigen expression, this condition is also known as T cell dysfunction. c) In adequate number of CTLs which is mostly caused by problems in the presentation of tumor antigens [13]. The immunosuppressive act of tumor cells is happening via these pathways: a group of cancerous cells loss the MHC expression which disables APCs to recognize them. Another group of cancerous cells secrete cytokines that suppress immune system. These cancers make physical barriers from collagen; fibrin and etc. thus become unreachable to immune cells [16]. Some tumors also have the ability to induce immune-tolerance by up-regulating the inhibitory factors. There is an approach in cancer immunology that suggesting the down-regulation of immune checkpoints e.g. PD1 and CTLA4 to increase the immune system anti-tumor reaction [16]. From the aforementioned mechanism, it is clear that the purpose of a cancer vaccine is its ability in promoting immune system, especially the CD8+ T cells to fight against tumor cells [14] (Figure 1).

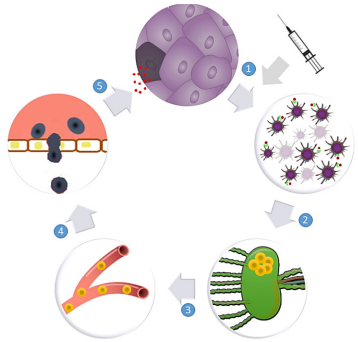

**Figure 1.** The schematic mechanism of vaccine function or release of tumor antigens in the ECM after tumor death. 1) Administrated vaccine or released tumor antigens are initiate immune responses 2) Tumor antigens are recognized by APCs (mainly Dendritic Cells) 3) APCs migrate into Lymph node and trigger T cell differentiation and proliferation (naïve T cells differentiate into mature T cells) 4,5) Matures T cells infiltrate via blood vessels in to tumor site and CTLs induce tumor cell apoptosis.

## Tumor Antigens

Tumor antigens were discovered in 1991, when the first melanoma antigen MAGE was found. Since then, a lots of tumor antigens were recognized. Furthermore, by the advent of T cells capability in tumor suppression, the usages of immunotherapy in fighting against cancers have developed a lot. Cancerous tissues are mainly overexpress normal or express mutated antigens. TAs are mostly proteins which are overexpressed in tumor cells and boast a crucial impact on cancer cells initiation, progression and metastases. It is demanding to categorize tumor antigens into two various groups: mutated antigens (tumor specific antigens) and shared (associated) antigens [17,18]. Between 1990s and 2000s the cancer vaccines investigations mainly focused on tumor associated antigens because these antigens were common in patients with the same cancers. On the other hand, mutated antigens were unique in each patient. Challenges in production of TAA based cancer vaccines during the last two decades consisted of inadequate foreignness along with lack of experience in vaccine production which led many researches into disconcerting results [19]. However, TSAs (Tumor Specific Antigens) were generated from protein sequence alteration causing them to bind MHC alleles and as a result to be identified by T cells as a foreigner. These antigens are similar to neoepitopes and the immune system has never been faced them before [19]. It would be true to say that antigen selection is the most important stage in cancer vaccination. Ideally, selected antigen should be highly immunogenic, express in all the tumor cells and also be tumor-specific. However, only a few of antigens or sometimes none of the antigens are shown all the aforementioned criteria [11].

As it discussed before, although the potential of vaccination in cancer immunotherapy is clear, clinical trial results were not appealing. One of the major obstacles would be antigen finding and choosing. For many decades, scientists have focused on a single antigen. While, usage of multiple neoepitopes (tumor antigens) are more capable to alert the immune system. Hence, usage of whole tumor lysate seems to be fulfilling [20].

### Tumor Associated Antigens (TAAs)

In the early stages of cancer vaccines, scientists focused on Tumor Associated Antigens (TAAs). TAAs express in both normal and tumor cells but they overexpress in neoplastic cells [21]. To give an example, cancer testis antigens are express in both natural and cancerous cells, but they only express in germline cells in normal people [22]. Some of the most common TAAs are MUC1, HER2, MAGE, tyrosinase and etc. These vaccines were produced to promote T cells against self-proteins. Scientists long strive on this vaccines based on TAAs failed to show promising results [21].

### Adaptive tumor immunity

Tumor-associated antigens are considered as the initiator in T cell antitumor immunity activation. TAAs are represented to T cells via MHC class I and II molecules with the help of antigen presenting cells. Co-stimulatory molecules like chemokines and cytokines activate T cells and other immune cells from innate immune system. T helper cells, have an impact on tumor cells via various pathways, they secrete cytokines and chemokines which trigger anti-tumor immunity. TH1 and TH2 CD4 T cells regulate cellular and humoral immunity respectively. TH1 by activating CD8 T cells and TH2 by B cells activation. CTLs are triggered directly by APCs or indirectly via complement system [16].

### Tumor-specific antigen or mutated antigens

Usage of TSA-based vaccines are promising since their expression only confined to tumor cells and could be identified as neo-antigen by immune system and thus, encourage anti-tumor immunity [23]. Hence, unlike TAAs these antigens may not cause systemic toxicity or tolerance problems. However, establishing successful immunogenic vaccine system is challenging due to the dynamic and changeable behavior of neoantigens. In addition, only specific peptide antigens have the ability to be recognized by MHCs [19]. Various mutations my cause neoantigens. This is to say that, neoepitopes could be developed from complicated DNA alterations, such as, insertion or deletion, duplication or fusion, hence this alteration may influence gene reading frame and thus, resulting in multiple neoepitopes at the same time. The important challenge is the ability to map and select efficient somatic mutanome which is recognizable by MHCs and produce the vaccine based on these antigens [19,24].

## Various Types of Cancer Vaccines

There exist various platforms for cancer vaccine production. Whole tumor cell, Viral-based, recombinant vectors, peptide-based, dendritic cell, DNA-based and RNA-based vaccine are the most used platforms [25]. And recently, Nano vaccines platforms attracted too much attention. Here in the table an overview of various vaccine pros and cons have been represented.

### Whole tumor cell vaccine

One of the promising methods in cancer vaccination is the usage of whole tumor antigens providing vaccine with whole needed antigens without any further selection. These vaccines are a source of epitopes which could bind to both MHC class I and II and as a result make better anti-tumor immunity. Moreover, this method will decrease the chance of tumor escape because of multi-epitope targeting mechanism. In this method the tumor cells could be either autologous or allogeneic [26]. Producing autologous tumor antigen vaccines is costly and allogenic vaccines are less immunogenic [6]. Furthermore, although the usage of whole tumor lysates will provide complete source of tumor antigens and as a result induce both CTL and CD4+ T helpers, these platforms are unstable, it has been shown that the DCs antigen uptake via this method is low and also the antigen cross-presentation is insufficient [27]. Furthermore, procedures needed before vaccination, the tumors should lyse due to possible hazards of live tumor vaccination (Table 1) [28,48].

| Vaccine Type | Advantages | Disadvantages | Reference |
|---|---|---|---|
| Whole Tumor | -Multi-epitope Targeting | -Unstable | [6,26,27,28] |
| Cell Lysate vaccine | -High anti-tumor immunity | -Low uptake by APCs | |
| | -Induction of Both CTL & CD4+ T helper | -Hard Production | |
| | -Good in combination of nanovaccines | -Expensive in autologous production | |
| | | -Risk of autoimmune reaction | |
| Dendritic Cell Vaccine | -Cross-antigen presentation | -Costly | [29-34] |
| | -Natural Adjuvant | -Intradermal injection of vaccine may cause low DC movement to lymph nodes | |
| | -Link innate and adaptive immune system | -Low amount of DCs in blood | |
| | -Safe | -Most functional in individualized vaccination | |
| | -Most powerful APCs | | |
| | -T cell reaction initiator | | |
| | -Good for combination therapy | | |
| Peptide Vaccine (TAA-based) | -High Safety | -Low amino-acids peptides are not highly immunogenic | [1,6,22,35,36] |
| | -Large scale production | -Short peptide vaccines could not be target specific (off-target delivery) | |
| | -Easy and quick to produce | -Short peptide could not induce CD4+ T cells | |
| | -Poly-epitope and long peptide vaccines are more immunogenic | -Cause central tolerance with low immunogenicity | |
| | | -Autoimmune worries | |
| Peptide Vaccine (Neoantigen-based) | -Low risk of immune tolerance and autoimmunity | -Tumor alteration by the time | [21,22,28,37] |
| | -Stable & low toxic | -Expensive approaches (Novel methods will decrease the cost) | |
| | -Shared tumor-specific antigen vaccines are good for commercial usages | -Hard production method (Need bioinformatics methods for neoantigen finding) | |
| | -Good immunogenicity | | |
| | -Good in combination therapy | | |
| Live-organism based vaccine | -High immunogenicity | -Produce more anti-viral immunity compared with anti-tumor immunity | [38-43] |
| | -Natural adjuvant | -Could be infective ( Usage of Virus like particles solve the problem | |
| | -Modifiable vectors: able to be armed with TAAs or TSAs (antigens and peptides) | -Toxicity worries | |
| | -Selective migration to tumor cite | | |
| | -Present tumor antigens to APCs easily | | |
| | -They can directly lyse tumors | | |
| RNA-based Vaccine | -Safer | -Instability (Solved by novel delivery approaches: liposomes and nanoparticles) | [36,44,45-47] |
| | -Low cost and good for commercial usage | -Delivery obstacles | |
| | -Naked nucleic acids are unstable | -Degrade easily (Modification needed) | |
| | -mRNA vaccine are transfect easier, safer, more potent, can better select tumor antigens and more accurate delivery compared with DNA vaccine | | |
| | -mRNA vaccine are not mutagenic | | |
| DNA-based vaccine | -Biocompatible | -Worries on genomic integration with normal somatic or germ cells. | [17,21,48] |
| | -low cost & scalable production | -Low positive results in human clinical trials (mainly due to minimal genome integration- novel methods like EP will be demanding) | |
| | -Safe | -Are not able to overcome tumor immunosuppressive environment (combination therapy solve the problem) | |
| | -Stable | | |
| | -Multiple antigen delivery capability | | |

**Table 1.** Investigation of various vaccine types weaks and strengths.

Active tumors may cause new tumors and also they may secrete immune suppressive cytokines and make the vaccination useless. Freeze-thaw and irradiation are two of most common methods for cell lysis [6].

Recent advances in tumor cell lysate vaccination mainly focused on usage of biomaterials for sufficient and specific delivery of tumor antigens into the target DCs [27]. Another novel approach is combination of whole tumor lysate with either dendritic cells or polymeric matrixes [49].

## DC vaccine

Dendritic cells are able to control the activity of both T and B cells, and they could initiate immune responses via cytokine secretion or by migration into lymph node and inducing T cell proliferation [50]. DCs as the most vital APCs for CD4+ and/or CD8+ T cell induction [32,33], by cross-presentation of foreign antigens to MHC class I, has attracted scientists interests in immunotherapy. And also, DCs usage as natural adjuvants make them interesting candidate for cancer immunotherapy. Hence, many vaccines have been prepared based on various DC subsets during the last 2 decades [32,34]. Moreover, DCs could link adaptive and innate immune system [30]. However, DC vaccine are considered to be expensive in comparison with other vaccination methods and this problem can be solved with the usage of natural DCs and precise protocol for DCs isolation and culturing will decline the procedure to 48 hours after cell freezing [31]. In a study in 2019 Wculek and her team, developed a dendritic cell vaccine. They isolated cDC1s of mouse spleen and loaded with antigens which were driven from whole tumor cell lysis. Finally, they tested the vaccine efficiency in combination with anti-PD-1 treatment and they compared their result with anti-PD-1 treatment alone. The combination therapy prevented the tumor growth by activating both CD8+ and CD4+ T cell responses. And more importantly, the tumors which were resistant to anti-PD-1 treatment have shown positive results in combination therapy [34].

## Peptide vaccine

Peptide vaccines are consisted of immunogenic peptides with adjuvant. These vaccines are produced to bind with MHC class I or class II and become recognizable to APCs. So, a comprehensive knowledge of MHC class I and class II binding mechanism is needed. Initial peptide vaccines were consisted of single short peptides (less than 15 amino acids). Although, these vaccines were safe (low toxicity), beneficial for large scale production and target specific, due to low amount amino acids, these vaccine were not able to produce high immunogenicity and as the nature of tumors are heterogeneous, these vaccines were not able to target the tumors well because of tumor antigen alteration in different cancer stages [1,22,35]. Additionally, short peptide vaccines could not trigger CD4 T cells whose efficiency in CTL induction is proved [1].

In order to boost the immunogenicity and functionality of peptide vaccine many divergent platforms have been emerged. Amphiphilic peptides and usage of Toll-like receptor agonists, precise selection of adjuvants and combination therapy are the most common modification in peptide vaccine production [1]. In addition, usage of poly-epitopes versus single epitope have shown to increase the efficiency of the vaccine in both murine and human models [1,51]. Multiple peptide vaccination will increase the immune system anti-tumor activity by induction of various T-cells and also they are able to conquer problems like tumor antigen change or epitope loss [22].

Recent studies revealed that some of the natural epitopes could not activate the immune system. Accordingly, the usage of modified peptide vaccines with more immunogenic features may raise anti-tumor immunity [14]. In a study scientists found that amphiphilic vaccines are more capable of immunogenicity in combination with poly-IC. And also, systemic administration would be more effective than local administration in CD8 T cell activation [52].

Peptide vaccine could be produced based on TAAs or neoantigens. Most of the produced peptide vaccines were based on TAAs (non-mutated antigens). As, these antigens were self-derived antigens they led to central tolerance as well as inadequate immune response. Moreover, there exist worries about autoimmune reactions in the usage of TAA peptide vaccines [22]. Peptide vaccine based on neoantigens only existed in tumor cells, and prepared as a result of DNA mutations, hence the risk of autoimmune reactions and immune tolerance are low [22,28]. There are two groups of neoantigens, personalized and shared. Shared neoantigens are those mutated antigens which are common in patients with the same cancer and they are useful for commercial approaches. Personalized neoantigen vaccines provide scientists with more accurate responses and higher rate of survival, but these vaccines are costly with low public usage [22].

## Live organism-based vaccines

Viruses are normally immune activating resulted from their natural adjuvants [39] and it is possible to transfer tumor antigens via engineered viruses. Recombinant viruses can easily infect APCs, especially DCs, and present tumor antigens as a pathogen to the APCs which indeed, induce T cell anti-cancer immunity [53]. Oncolytic viruses are designed to infect and replicate only in tumor cells and leave normal cells undamaged [39,54]. By killing the cancerous cells, the tumor antigens are released in ECM and thus induce CTL anti-tumor immunity. Although, this process seems to be effective, usage of bare OV may mostly induce anti-viral immunity rather than anti-tumor immunity. Hence, one of the novel approaches is that covering OV by the peptides which are chosen from TAAs. Selecting the suitable peptides to bind on the surface of OV is of a great concern [39]. Vaccinia virus (VV) is belong to poxvirus family and it has been shown to be effective cancer vaccine in combination with other common therapies and clinical trials have only declared its positive effect in combination therapy not alone. The main advantages of recombinant VV vaccines in tumor immunotherapy would be: their vectors are modifiable to change them into more immunogenic vaccine and secondly they could be armed with TAAs, TSAs or immune-stimulatory molecules to become more immunogenic [41].

Like viral vaccines, bacteria are also used for cancer vaccination. They can selectively migrate to tumor cites, inhibit tumor growth and increase the rate of survival [40]. One of the most common bacteria is Listeria which could be modified to introduce neoantigens to patients. Advaxis is one of the most active companies which are working on Listeria bacterium; they succeeded to produce multiple bacterial platforms for every patient. Each bacterium has the ability to carry fifty neoantigens [55].

## Genetic-based vaccines

It was in 1990 when scientists for the first time, transferred RNA and DNA into mouse skeletal muscle and detected the nucleic acid production. They administrated the DNA and RNA vectors without any special delivery system [56]. Three year later, the concept of immunization with the help of DNAs is generated in 1993, when Yankauckas and his team, developed a plasmid DNA system against influenza. The plasmid DNA system were loaded with the influenza nucleoprotein gene and injected to mice. The results have shown one year immunity by activating CTL responses [57].

Cancer Vaccines on the basis of DNAs are considered to be one of the most promising approaches in cancer vaccination. These findings are resulted from several clinical studies. It is said that DNA vaccines can efficiently boost immune responses with minor side effects [58]. Plasmid DNAs are consisted of unmethylated and repeated Cytosine-guanine cites and thus, they are immunogenic and these platforms are both use as antigen and adjuvant [6,59]. Although, Plasmid DNA vaccines have shown desirable safety and acceptable responses in both specific and shared tumor antigens, tumor immunosuppressive environment have diminished their efficiency and caused DNA vaccines low therapeutic responses in clinical trials [17]. To tackle this problem, two different approaches have tested. Firstly, choosing suitable antigens and installing them in the plasmid system in order to, activating more immune responses and better targeting. Second method would be combination therapy so as to, decrease the tumor immunosuppressive environment or galvanize the immune system responses [17]. To boost the DNA transfection, considering the best delivery

method is crucial. Electroporation is one of the best methods for plasmid DNA vaccine transfection. This method is based on electric pulses which increase the membrane of the cells more permeable and enhance plasmid DNAs internalization [60].

Mentioning the benefits of mRNA vaccines over viral and DNA based vaccines, it is vital declaring that these vaccines are safe. mRNA vaccines are neither mutagenic nor prone to infect patients. Moreover, these vaccines degraded easily through cellular mechanisms. And also, advances in mRNA production make them stable and easily translatable. Lastly, these vaccines are considered to be potent for commercial usage because they are reproducible, low cost and scalable [46]. Moreover, production of mRNA vaccines is easier with less steps compared with DNA vaccines [47].

To better compare mRNA vaccines with DNA vaccines it is good to mention their internalization ability. As it is clear, functional nucleic acid based vaccines are able to internalize to nucleus or cytoplasm of the APC cells, especially, dendritic cells. This procedure may be in vivo or ex vivo. In in vivo method vaccine directly administrate to the tissue. But, in ex vivo approach nucleic acids are transfected with isolated APCs (mainly DCs) prior to administration. This ex vivo transfection is expensive procedure and more common in mRNA vaccines [47].

One of the most crucial factors in mRNA vaccine development is the mRNA penetration ability over cell membrane in order to reach the cytoplasm and being translated. Two different methods are developed to deliver the mRNA vaccines [46]. One method would be modifying the DCs by mRNAs and then administrating the modified DC vaccine [61]. However, this approach is costly because it is a cell therapy method. The second delivery method is usage of mRNAs without any carrier. This approach is financially effective and rapid, but there is no control over target cell delivery [46].

As it is concluded so far, Tumor cell vaccines, dendritic cell vaccines, nucleic acid-based vaccines and long synthesized peptides are the main strategies in neoantigen targeting [37].

## Nano-Vaccines

The usage of biomaterials in cancer vaccination have gained much attention recently, this is due to the fact that biomaterials encapsulated antigens could enhance the immunogenicity by improving the delivery and better presentation to APCs. Biomaterials have the ability to protect the antigens degradation and hence make a stable vaccine platform during administration and delivery, and also they improve the controlled release of antigens. In addition, there are lots of methods for surface modification of biomaterials in order to specify the targeting manner of vaccine. It is needless mentioning that, nano-/ micro-vaccine are able to encapsulate both adjuvant and antigens and this co-delivery will definitely improve the immunogenicity of vaccines. Finally, NPs are easily phagocytosed by APCs, so they easily penetrate inside the antigen presenting cells [4,27,62].

Recently, cancer vaccination technology, have been focused on co-delivery of both antigens and adjuvants with the help of nanovaccines [63]. Thus, this platform which is consisted of nano-carrier, adjuvant and antigen will activate DC responses better. In a study in 2020, the combination of nanomedicine and nanovaccine administrated to patients suffering highly malignant breast cancer after surgery. The nanomedicine increased the tumor immunogenicity and triggered Immunogenic Cell Death (ICD) of residual tumor cells and nanovaccine raised the DCs maturation. Hence, the combination of various immunotherapy methods will cause a synergetic effect on immune induction [64].

Nanovaccines are defined into two groups: synthetic and natural nanovaccines. Synthetic nanovaccines could be organic or inorganic. Gold nanoparticles are one of the famous platforms in inorganic vaccines. Regarding, Orgainc synthetic nanovaccines, ther are many platforms based on polymers and lipids have been produced so far. The most common form of nano-vaccines are natural vaccines. Natural nanovaccines are more biocompatible in comparison with synthetic ones [62]. In a study in 2017, a nanovaccine has produced which were contained antigens and Nano-particles of PC7A polymer. Ovalbumin (OVA) is used as model antigen. 10 μg of OVA together with 30 μg of various polymer nano-particles were produced to investigate the OVA-specific responses of each platform. The results have shown that PC7A nano-particles have shown better or at least comparable results in comparison with many commonly used adjuvants. This system could promote the response of two groups of T cells, CTL and Th (Th1 and Th2) [63].

## Personalized Vaccines

During these years of cancer immunotherapy studies, scientists faced major problems which mentioned before, but there exist a major obstacle in the way of individualized immunotherapy which was tumor-specific antigens uniqueness in every individual and the first step would be identifying these mutnome and for many years this procedure was really challenging [23]. To distinguish the process of personalized vaccination there are 5 steps. At first, patient's blood and neoplasm samples should be taken for DNA and RNA extraction. Then, by comparing normal and cancerous DNA sequences, scientists will find the mutations. Both, RNA analysis which will give some information about amount of neoepitope expression and MHC binding prediction will directing scientists toward choosing the most sufficient neoepitopes. In the last stage, prioritized antigens are produced and injected to the patient [19].To analyze whether a neoantigen have the ability to bind MHC class I alleles or not, there exist some common tools like NetMHC and IEDB consensus tools. It is hard to predict MHC class II binding affinity due to, their open binding pockets. However, MHC class I consisted of defined amino acids with specific anchor position [19].

In 2015, scientists surprised by their new findings. They understood that the huge amounts of mutated antigens are immunogenic and they were recognized via CD4+ T cells not CD8+ T cells. Hence, the team established a system that prioritized mutations by bioinformatic mechanism. This system selected the best mutations by the capability to bind with MHC Class II and the neo-antigen rate of expression. Then they revealed that these mRNA vaccines which are based on multiple neo-epitopes are able to control tumor growth and also reshape the tumor microenvironment into the immunogenic environment which could attract CTLs [23].

In 2017 one clinical trial have shown promising results, in this clinical trial 6 patients with stage III and IV melanoma cancer were investigated by neoepitopes vaccination. In order to produce the personalized vaccine for each patient, normal DNA and mutated DNA are extracted, and then by RNA investigation the mutated peptides which were suitable to bind HLA-A and HLA-B were chosen. A long chain of amino acids were synthesized (20 neoepitopes are targeted for each patients). Finally these neoepitopes together with Toll-like receptor 3 were administrated subcutaneously to patients after 18 weeks of surgery. The vaccination is done in five initial vaccination and two times vaccination for boosting the results. 4 of 6 patients did not see any recurrence. In two of them which had lung metastases, disease recurrence is happened after vaccination. These patients were further treated with PD-1 antibody therapy and the results were optimistic. In general, this research revealed the safety and efficiency of personalized neoantigen vaccination [65].

In another study in 2020, a personalized DC vaccine has produced to fight against ovarian cancer. In this study, both autologus dendritic cells and oxidized autologus whole tumore lysate were administrated to patient suffering from recurrent ovarian cancer. All 392 doses of vaccination have shown to be safe without severe side-effects. The T cell activation increased survival rate significantly. In this study a group of patients were vaccinated by only whole tumore lysate DC vaccine and the other groups are vaccinated with afore mentioned vaccine in combination with cyclo-phosphamide and bevacizumab, VEGF-A blocking antibody. And, it is good mentioning that this clinical therapy either alone or in combination

with cyclo-phosphamide and bevacizumab was safe, efficient and improved immune system antitumor activity [20].

To sum up, these vaccines could trigger both CD8+ and CD4+ T cells. Moreover, although the number of patients who have been treated with neoantigen personalized therapy is low, the results are totally promising [19].

### Recognition and establishment of individualized mutational vaccine

To choose a proper neoepitopes besides the MHC binding prediction, there are some other demanding factors: a nominated neoantigen is better to be expressed in whole tumor colon not a fraction of colony, because, this may extend the checkpoint blockade efficiency. Moreover, it is crucial considering the fact that, tumors are highly heterogenic resulted from a gamut of accumulated mutations, and also their compositions are changing over time [19]. Hence, it is important to find the best neoantigens and injecting time. Mutations are identified by comparing them with normal tissue nucleic acid sequence. This process is usually uses blood cells as a source of normal cells and biopsy of tumor as a source of mutational cells. The neoplastic antigens could drive from fresh, freezed, paraffin-embedded or formalin-fixed tissues. After getting the NGS data of both cancerous and normal cells, statistical analyses enable scientists to select the best antigen candidates [24].

## Combination Therapy

Combination of cancer vaccine therapy with other common cancer treatments such as chemotherapy and radiotherapy, and also novel immunotherapy approaches, especially immune checkpoint antibodies would efficiently boost the vaccine functionality [37]. In a recent review paper, scientists reported the recent advances in usage of radiation as an in situ vaccine [66]. In a study in 2016, ali and his team demonstrated that material-based vaccine together with checkpoint antibodies are capable of CTL induction in humans. They produced a PLG (poly(lactide-co-glycolide) vaccine with anti-PD-1 or anti-CTLA-4 to increase the vaccine efficiency and results have shown up to 50 mm2 reduction in tumor size and 75% rate of survive [37].

## Conclusion

From our best of knowledge, we can conclude that, although previous trials on cancer vaccination were disconcerting and the advances in other immunotherapy methods like immune checkpoint blockade shadowed the usage of cancer vaccination, recent advances in Bioinformatic and Drug Delivery will ignite hope in the field of cancer vaccination. Novel bioinformatic methods improved the prediction and selection of the most immunogenic antigens and their MHC binding ability. Also, in order to survive cancer vaccination, there is a demand for advanced drug delivery platforms which are able to prolong the antigen release which acquire a simultaneous antigen presentation and also localize the vaccine delivery [67]. Nanovaccine platforms, Advances in personalized vaccination and combination therapy are the most novel approaches in cancer vaccination.

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## Conflict of Interest

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