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Vaccine Strategy in Melanoma

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SYNOPSIS

The incidence of melanoma continues to increase even as advances in immunotherapy have led to survival benefits in advanced stages. Vaccines are capable of inducing strong, anti-tumor immune responses with limited toxicity. Some vaccines have demonstrated clinical benefit in clinical trials alone; however, others have not despite inducing strong immune responses. Recent advancements have improved vaccine design, while combining vaccines with other immunotherapies offers promise. This review highlights the underlying principles of vaccine development, common components of vaccines, the remaining challenges and future directions of vaccine therapy in melanoma.

Keywords

Melanoma; Vaccine; Tumor-Associated Antigen; Neoantigen; Vaccine Adjuvant; T cell

Introduction

The development of vaccines against cancer has driven significant advancements in the field of tumor immunology, leading to a better understanding of the immune response against cancer. There is new expertise on the nature of tumor-associated antigens, making it possible to even genetically engineer immunogenic antigens for melanoma vaccines. This has been

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Minyoung Kwak, Katie Leick, and Marit Melssen: nothing to disclose

Craig Slingluff, Jr: see chart below

achieved through advances in sequencing and manipulating genomes, development of algorithms to define putative T cell antigens, identification of different immune cell types, and unraveling complexities of the tumor microenvironment.

The promise of cancer vaccines is that vaccines induce targeted, tumor-specific immune responses with long-term memory in cases of recurrence or metastasis, with low risk of toxicity overall. There has been renewed focus on the potential of immunotherapy due to the recent success of checkpoint blockade therapy in advanced melanoma. When patients lack a pre-existing immune response to their cancer, they are unlikely to respond to checkpoint blockade; so, there is renewed interest in vaccines to induce antitumor immune responses that did not arise spontaneously. There is potential value of combining vaccine therapy with other immunotherapies to improve tumor control. Clinical trials implementing these combination therapies are currently underway. In this review, we summarize the current antigen and vaccine adjuvant strategies under investigation, and highlight the progress made with recent melanoma vaccine therapies in clinical trials.

Background on Tumor Antigenicity and Immune Activation

Cancer vaccines contain tumor-associated antigens and vaccine adjuvants to elicit the activation of dendritic cells and antigen-specific T cells. Initiation of the immune response against tumor cells occurs through recognition of tumor-associated antigens that must be processed and presented on MHC complexes by antigen-presenting cells (APCs) (Figure 1). Specific T cells recognize these MHC-antigen complexes leading to their activation and proliferation. Antigen presentation on MHC class I generally activates cytotoxic CD8 T cells (T_{CD8}), whereas presentation on MHC class II activates CD4 helper T cells (T_{CD4}). Elements of both CD8 and CD4 T cells are likely needed to mount an optimal response for tumor control and long-term memory.

Cancer vaccine formulations also incorporate ‘vaccine adjuvants’ to increase T cell stimulation by activating APCs, thereby enhancing antigen presentation and co-stimulation. Many vaccine adjuvants stimulate pattern-recognition receptors (PRRs) on APCs. These PRRs recognize PAMPs (pathogen- associated molecular patterns) or DAMPs (damage-associated molecular patterns), heat shock proteins, or reactive oxygen intermediates[1]. PAMPs include Toll-like receptor (TLR) agonists, such as CpG sequences. Introducing a tumor-associated antigen with vaccine adjuvants allows for an improved antigen-specific immune response to enhance tumor control.

Vaccine Strategies: Antigen

Antigens used in melanoma vaccines may be shared across patients or may be neoantigens that are uniquely expressed. Different types of antigens have been identified in melanoma (Figure 2), and are summarized below. The type of antigen that is selected can determine the tumor-specificity, type, and strength of the ensuing immune response.

Shared melanoma antigens

Melanocytic differentiation antigens—Melanocytic differentiation antigens are expressed by most melanoma tumors and induce T cell responses[2,3]. The shared aspect of

these antigens enables broad application and generalization of shared antigen-targeting vaccines across multiple patients. Tyrosinase, TRP-2, Melan-A/MART-1, and gp-100 are common source proteins that are also expressed on normal melanocytes and on a few other pigmented cells. Thus, successful immune targeting of melanocytic antigens has the potential to induce autoimmunity to melanocytes. Additionally, since these antigens are present in some normal tissues, responses to them may be limited by pre-existing central tolerance[4]. Regardless, some vaccine and adoptive therapies targeting these antigens have been successful[5,6].

Shared mutated antigens—Mutated antigens arise from acquired somatic mutations or single-nucleotide polymorphisms (SNPs) in melanoma cells and are often unique to a given patient tumor, although some are present in a fraction of patients. Because mutated antigens arise through tumorigenesis, they are absent in normal cells. BRAF, KIT, and NRAS mutations are common mutated antigens in melanoma. Antigenic BRAF peptides encompassing the V600E driver mutation of melanoma have been reported[7–10], inducing BRAF-specific immune responses in humans[9,10] and tumor control in mice[7,8]. These data support further clinical investigation of these mutated antigens in vaccines.

Cancer germ line antigens—Cancer germ line antigens are expressed in the placenta or testis as immune privileged sites[11], while also being uniquely expressed in some malignant tumors. The immunogenicity and unique expression of these antigens in cancers, rather than in normal cells, provides an opportunity to elicit an antitumor immune response using vaccines. Their restricted expression justifies considering them a form of neoantigen. MAGE-A1, MAGE-A3, BAGE, GAGE, and NY-ESO-1 are a few examples of cancer germ line antigens that have been identified. Adoptive T cell therapy using T cells expressing a T cell receptor (TCR) transduced with NY-ESO-1 induced objective clinical responses in 55% of patients with advanced melanoma[12]. Thus, cancer germ line antigens can be effective tumor regression antigens. On the other hand, a MAGE-A3 vaccine failed to enhance survival in a phase III trial[13]; so, the use of cancer germ line antigens in vaccines remains to be optimized. Although some cancer germ line antigens are solely expressed on tumor cells, a few studies using adoptive T cell therapies have shown cross-reactivity with normal tissues when very high affinity TCRs are used[14]. Interestingly, some cancer germ line antigens may be sequestered and thus not subject to preexisting tolerance, whereas others may not be sequestered[15]. Understanding this phenomenon may improve selection of cancer germ line antigens for cancer vaccines.

Phosphopeptides—Phosphorylation of oncogenic proteins supports malignant transformation; thus, targeting them is a promising strategy. Phosphorylated peptides derived from those proteins can be presented by both MHC class I and II molecules, which induces an immune response to the phosphorylated peptide sequence specifically[16–19]. Identification of tumor-specific phosphopeptide antigens may provide opportunities for personalized immune vaccine therapies[20]. A first-in-humans clinical trial has recently been completed (NCT01846143).

Mutated neoantigens—The term ‘neo-antigen’ refers to newly expressed or acquired antigens, as in genomic mutations found within tumors but not in normal somatic cells. Due to its unique genetic sequence, the transcribed DNA, RNA, or translated peptide fragments can be used as a unique source of tumor-associated antigens. The advantage of these mutated neoantigens in vaccines is that it may avoid pre-existing central tolerance that is expected with shared antigens[4] and should reduce risks of on-target autoimmune reactivity. Data also suggests that therapeutic T cells may respond more strongly to mutated neoantigens than to shared antigens[21,22]. Newer approaches have developed algorithms to predict and select advantageous immunogenic features of the mutanome. These mutated epitopes can be engineered into vaccines using a personalized approach[23]. A disadvantage of this personalized technique is the time required for the synthesis of personalized vaccines. Methods to predict immunogenic neoantigens were applied to patients and successfully showed immunogenicity of predicted neoantigens with promising clinical outcomes in a small number of patients[23–25]. However, much research still needs to be done to expand these preliminary results and to optimize immune responses to neoantigens.

Antigen Type and Adjuvants

Selection of an appropriate antigen type can influence the immune response following treatment. Vaccines may use antigen as whole tumor cells, RNA or DNA, single or multiple peptides, or APCs displaying the target antigen. Both efficacy and toxicity can be related to intrinsic immunologic potency, cross-reactivity of vaccine targets to antigen on normal cells, and associated adjuvants.

Peptide Vaccines—Peptide vaccines can be synthesized as short or long with single- or multi-peptide mixtures. Peptides are weakly immunogenic when naked peptide is used[26,27]; however, their use in combination with vaccine adjuvants or immune therapies induces potent, and frequently durable, T cell responses[28–33].

Short Peptide Vaccines—Short peptide vaccines representing minimal CD8 epitopes (usually 9 amino acids long) thus elicit a cytotoxic T_{CD8} response by binding MHC class I. Their effects on T_{CD8} are advantageous as it activates effector cells directly, thus negating the need for further antigen processing by APCs. Immune response rates may approach 100% in humans, of which 1–5% of the T_{CD8} population are peptide-specific effector T_{CD8}[28,29,31]. Minimal epitope vaccines can induce strong T_{CD8} responses alone[29]. One study designed minimal epitope vaccines based on individual patient mutated neoantigens and generated neoantigen-specific T cell responses in all three patients, affecting 23–89% of the T_{CD8} population; memory T cells were present for up to 4 months[34,24,35]. Short peptide vaccines may be limited by proteolytic degradation[36], tolerance due to suboptimal antigen presentation, and less sustained immune responses[37].

Extensive work has been done with a modified gp100 peptide (gp100 $_{209–217}$;209–2M) that is a modified form of peptide naturally presented by HLA-A2 to T_{CD8}. Vaccination with gp100 209–2M alone increased peptide-specific T cells in 97% of patients[31]. Addition of gp100 to IL-2 in a clinical trial involving patients with advanced melanoma significantly increased clinical response rates and improved progression-free survival[38,39]. However,

combination of gp100 peptide with checkpoint blockade therapies such as ipilimumab showed no therapeutic benefit compared to ipilimumab alone[40]. Mechanisms underlying this limitation have been explored in mice and suggest the addition of gp100 peptide vaccine in an antigen-depot vaccine with ipilimumab may lead to sequestration and destruction of non-gp100-specific effector T cells, particularly those effector T cells that are induced by ipilimumab[41]. This finding needs to be studied further in patients.

Helper Peptide Vaccines—Helper T_{CD4} are activated by recognition of peptide presented on class II MHC molecules and induce a multifaceted immune response by supporting APC, T_{CD8} effector function, and T cell memory formation. Thus, immune therapies targeting helper T_{CD4} offer promise for tumor control[32]. A peptide vaccine composed of a mixture of 6 melanoma helper peptides (6MHP) that are recognized by T_{CD4} has been used in clinical trials and induces a Th1 T_{CD4} response without increasing the proportion of T_{regs} (regulatory T cells). T_{CD8} responses also occurred via epitope spreading[27]. Sixty-five percent of 6MHP- treated patients with stage IV melanoma developed an immune response, and treatment with vaccine significantly improved overall survival compared to matched controls[27]. Patient survival was associated with antibody response rates and the formation of memory T_{CD4} immune responses[26].

Long Peptide Vaccines—Long peptide vaccines refer to lengths of 20–30 amino acids and carry the potential benefit of activating both T_{CD8} and T_{CD4} responses. Murine work demonstrated more efficient internalization and processing of long peptides by APCs compared to protein, resulting in more sustained T_{CD8} activation[42]. A phase I clinical trial of NY-ESO-1-derived long peptide (30 amino acids) combined with adjuvant induced antigen-specific T cells only when peptide was used in combination with adjuvant, but not with peptide alone[32]. Vaccination with long peptide targeting up to 20 predicted personal neoantigens successfully induced neoantigen-specific T_{CD4} responses to 60% of antigens, while T_{CD8} responses were limited to only 16% of unique neoantigens, suggesting preferential activation of T_{CD4} by long peptides[25]. Additionally, 4 of 6 patients had no recurrence 25 months after vaccination, suggesting the potential for clinical benefits and long-lasting effects of long peptide vaccines[25].

RNA, DNA, and Protein Vaccines—RNA or DNA encoding genes for tumor antigens or immune enhancers can be introduced into APCs or myocytes through bacterial or viral vectors to synthesize peptides and mediate a vaccine effect. Some RNA vaccines involve electroporation of APCs to enable incorporation of mRNA encoding melanoma- associated antigens or immunostimulatory ligands to facilitate antigen-specific T cell responses. In such studies, T_{CD8} responses were detected in 57–80% of patients, but no objective clinical responses were observed[43,44]. Some recent RNA vaccines are designed and personalized based on mutations expressed and identified by RNA sequencing and selected for predicted high affinity binding to MHC class I and II. These are engineered into synthetic RNA and delivered using a vaccine vehicle. The majority of responses induced were T_{CD4} responses[23], comparable to personalized neoepitope vaccines based on mutated peptides[25]. Neoepitope vaccination also resulted in a broadened repertoire of T cells[23]. A phase I clinical trial of DNA vaccine-encoding genes for immunogenic epitopes for gp100 and

TRP2 demonstrated an immune response rate of 84%, comparable to other peptide vaccines using gp100[45,38]. Despite induction of an immune response, DNA vaccines evoke limited objective clinical responses[45].

Whole Cell Vaccines—Whole cancer cells can be integrated into vaccines and serve as a source of antigen for APC presentation. They contain numerous mutated neoantigens that are inherent to the tumor, which does not mandate that they be identified prior to designing and manufacturing the vaccine. Whole cells can be modified to express particular tumor antigens or immune enhancers to further potentiate immune responses. This type of vaccine is typically more proficient at inducing expansion of T_{CD4} than T_{CD8}, resulting in an attenuated antitumor immune response. Despite whole cell vaccines showing initial promise to prolong survival with high clinical response rates, a large randomized phase III clinical trial showed no significant clinical benefit[46]. There is currently a phase 3 clinical trial underway (NCT01546571) using a cell-based vaccine derived from cell line supernatants containing antigens shed by tumor cells, which significantly improved disease-free survival in vaccine-treated patients in a prior phase 2 trial[47].

Vaccine Strategies: Vaccine Adjuvants

Vaccine adjuvants are aimed at producing more robust immune responses by increasing antigen uptake and presentation, recruiting other immune cells, and/or forming a depot effect for sustained release of antigen[48,49].

Incomplete Freund's Adjuvant (IFA)

A common adjuvant used in peptide vaccines for melanoma is Montanide ISA 51 (Seppic, Inc), a form of Incomplete Freund's Adjuvant (IFA). This is an oil-based agent where droplets of aqueous peptide are contained within a surrounding oil phase. This facilitates a depot effect at the vaccine site, allowing for continued antigen exposure in a stabilized oil emulsion[48]. In humans, immune responses to peptides in IFA were greater than peptides pulsed on APCs[50,51]. In mice, the depot effect of IFA may also lead to vaccine-site sequestration of activated T cells against antigen[52] that may prevent T cell homing to tumor. There are data suggesting the added immunologic benefit of other adjuvants such as CD40 stimulating antibody and TLR agonists instead of IFA to avoid these concerns. Human studies have not yet been done to determine whether CD40 antibody plus TLR agonists can induce a much stronger T cell response than IFA alone; however, our studies continue to support the addition of IFA to TLR agonists in melanoma vaccines with short peptides[53].

Dendritic Cell Vaccines

Dendritic cell (DC) vaccines use autologous DC to present antigen and to stimulate immune cells by releasing pro-inflammatory cytokines. In preparation for vaccine synthesis, DCs are isolated from peripheral blood. The vaccine can then be packaged using various adjuvants to induce DC activation, or autologous DCs can be pulsed with antigen ex-vivo and administered in the same patient. Vaccination route may determine the tissue site where the DCs will migrate[54]. A randomized phase II trial using autologous DC vaccines with GM-CSF in patients with advanced melanoma showed longer survival compared to a tumor cell

vaccine, with 70% reduction in risk of death[55]. However, this trial had low patient numbers and unequal prognostic factors. Other trials demonstrated lower T cell responses with DC vaccines when compared to peptide vaccines with adjuvant[50,51].

Another potential method of further stimulating DCs in murine models is an in-vivo method using viral vectors and CD40 stimulating antibodies. CD40 is a co-stimulatory receptor on DCs that adds to DC maturation and T_{CD8} activation[56,57]. The addition of CD40 antibody to a combination of TLR3 agonists and a neoantigen vaccine against colon adenocarcinoma in mice showed improved survival compared to either agonist alone, with expansion of neoantigen-specific T cells in both the periphery and in the tumor microenvironment[58]. These preclinical results show promise in the strength of CD40 for DC activation but still need to be evaluated in humans.

Toll-like Receptor (TLR) Agonists—TLR agonists stimulate PRRs on DCs to promote antigen processing and presentation to T cells. A common TLR agonist used in melanoma vaccine adjuvants is the TLR3 agonist poly-ICLC (polyinosine-polycytidylic acid). This agonist matures DCs to generate T_{CD8} and NK cells with higher cytotoxic capacity[59,60]. The combination of IFA and poly-ICLC with long NY-ESO-1 peptides showed that both adjuvants had different but beneficial effects on antigen-specific activation of T_{CD4}: emulsification of the antigen in IFA increased antigen-specific T_{CD4}, while poly-ICLC induced a Th1 phenotype, leading to increased cell-mediated immunity and inflammatory response[61].

CpG is an oligodeoxynucleotide fragment rich in cytosine and guanine, similar to bacterial DNA that is an agonist for TLR9 and induces DC maturation[62,63]. With DC maturation, CpG has also been shown to increase co-stimulatory surface marker expression with increases in proinflammatory cytokines needed for cytotoxic T_{CD8} co-stimulation[62,63], and possibly B cell stimulation[64]. Addition of CpG to IFA has dramatically enhanced T cell responses to a short peptide vaccine[62]. Despite its effectiveness in T_{CD8} promotion, a mouse model suggests it may require decreased levels of immunosuppressive T_{regs} and multiple booster vaccinations to maximize its effect[65]. On the other hand, resiquimod (R848) is an agonist for TLR7 and TLR8 that has been found to decrease the immunosuppressive function of T_{regs}[66] and myeloid-derived suppressor cells (MDSC)[67], supporting increased T cell proliferation.

Systemic Cytokines

Other types of vaccine adjuvants involve the use of immune cell cytokines. GM-CSF (granulocyte- macrophage colony-stimulating factor) is used to attract and activate DCs to further promote peptide antigen-specific responses[68,69]. GM-CSF enhanced immunogenicity of a cell-based vaccine in mice[68], and combined with a peptide vaccine, increased T cell responses when compared to DCs pulsed with the same peptide antigen[51]. However, in a large randomized clinical trial, the addition of GM-CSF to a peptide vaccine significantly decreased responses in both T_{CD8} and T_{CD4} compared to peptide vaccine alone[70]. Also, another large randomized clinical trial revealed that adding GM-CSF to a melanoma cell

vaccine resulted in worse survival and early melanoma-related death[71]. The use of GM-CSF as a vaccine adjuvant is cautionary and requires further investigation.

Systemic IL-2 infusions have also been used as a vaccine adjuvant in melanoma due to its overall stimulatory effect on T cells, and its clinical activity as high-dose monotherapy. When I L-2 was combined with the peptide vaccine gp-100, clinical responses were significantly higher than with I L-2 alone, with associated longer progression-free survival[72]. Peptide-specific immunogenicity occurred in 19% of patients who received both gp100 and I L-2, but this antigen specificity did not correlate with clinical response. Other studies have failed to show immunologic or clinical benefit of I L-2, GM-CSF, or interferon-alpha in combination with melanoma vaccines[73,74].

Current Melanoma Vaccine Trials

There are many ongoing clinical trials studying the impacts of various antigen formats and adjuvants on immune responses and clinical outcomes (Figure 3A). Among these, DC and peptide vaccines predominate. Peptide vaccines use a variety of adjuvants, the most common of which is IFA (Figure 3B). DC vaccines, as an adjuvant on their own, do not frequently utilize additional adjuvants (Figure 3C). Combination therapy with vaccines provides an opportunity to target the immune system through another mechanism to augment anti-tumor effects and potentiate clinical benefits. The most common combination therapy for peptide vaccines is checkpoint blockade, while IL-2 is most common among combination therapies used with DC vaccines, though DC vaccines utilize more combination therapies overall (Figure 3B, C).

Novel approaches

Prophylactic melanoma vaccine

With the success of the generation of a prophylactic vaccine for virus-induced cervical cancer, the idea of prophylactic vaccines against melanoma regains interest. Preclinical in vivo studies have shown potential of this approach, regardless of whether a DC-, RNA-, whole cell- or peptide-based antigen vehicle was used[75–78].

Stem cell-based vaccines

Induced pluripotent stem cells (Ipsc's) are immunogenic pluripotent stem-like cells that can be generated from a patient's cells. Their gene expression is similar to embryonic stem cells and includes expression of many tumor antigens. In preclinical models of melanoma and other solid tumors, immunization and therapeutic vaccination of iPSC's induced robust T_{CD4} and T_{CD8} responses, as well as a reduction in tumor burden[79]. Though these studies are still in the preclinical phase, they show potential for generating effective, personalized vaccines.

Conclusions

Melanoma vaccine research has shown the potential for vaccines to elicit antigen-specific T cells as well as provide some tumor control. Understanding the importance of specific immunologic effects of antigen vehicle and adjuvant is vital to the progression of vaccine

strategy. As our knowledge base expands through preclinical studies and results from recent clinical trials are finalized, we will be able to better optimize our approach for sustained tumor control.

Current therapies that involve vaccines alone have limitations due to discordance between antigen-specific T cell expansion and tumor control. Despite cancer vaccines showing lasting immune response rates up to 100%[28,31], vaccines alone have led to clinical response rates below 10% in most studies[80]. This low clinical response may be due to insufficient T cell priming, poor homing to tumor, dysfunction of T cells in the tumor microenvironment, or progressive loss of function. Some of these may be due to defects in antigen presentation, or immunosuppressive changes in the tumor microenvironment that could lead to anergic T cells or interference with T cell homing to tumor[81]. The advancement of neoantigen technology, along with newer adjuvant strategies, are all promising additions to increase clinical response. There are other preclinical methods of inhibiting immunosuppressive effects currently under investigation, as well. Therefore, the combination of vaccines with other immunotherapies has clear theoretical advantages as we await results of ongoing clinical trials.

Appendix

Name of commercial interest	What I received	My role	When	Support provided to:	Scientific/research area	Relevant
Celldex	Research funding	research support (to UVA)	ongoing	University of Virginia	Cancer immunotherapy	Yes
Celldex	Consulting fee/honorarium	Scientific Advisory Board honorarium	6/6/16	Self	Cancer immunotherapy	Yes
CureVac	Consulting fee	Scientific Advisory Board member	Ongoing	Self	Cancer vaccines, using peptides	Yes
Polynoma	Consulting fee	Principal Investigator, for phase III trial of POL-103A	Ongoing	University of Virginia	Cancer vaccines, melanoma	Yes
Glaxo Smith Kline (GSK)	Research funding	Funding for clinical trial of MAGE-A3 vaccine trial Mel55 (NCT01425749)	Ongoing	University of Virginia	Cancer vaccines, vaccine adjuvants	Yes
Castle Biosciences	Honorarium - consulting fee	Scientific advisory board meeting fall 2014	Past	Self	Melanoma clinical care	No
Merck	PD-1 antibody for use in investigator- initiated trial	Principal investigator of Mel64 trial	Ongoing	University of Virginia	Melanoma immune therapy	Yes
Merck	Research funding and PD-1 Ab for use in investigator- initiated trial	Sponsor-investigator for PD-101 trial	Ongoing	University of Virginia	Pancreatic cancer immune therapy	Yes
Merck	Research funding	Biomarker study. Clinical trial in pancreatic CA	Ongoing	University of Virginia	Immune therapy	Yes
3M	Resiquimod for use in Mel60 clinical trial of melanoma vaccine, with long peptides	Principal investigator of Mel60 trial (funded by Melanoma Research Alliance)	Ongoing	University of Virginia	Cancer vaccines	Yes
Theraclion	Staff and equipment support for AM003 trial	Research Support	Ongoing	University of Virginia	Focused ultrasound	No
UVA Licensing and Ventures Group	Royalties	Co-inventor on peptides for use in cancer vaccines, some licensed to GSK	Ongoing	Self	Peptide vaccines for cancer	Yes
Immatics	Consulting Fee	Scientific Advisory Board member	Ongoing, but ending 2018–19	University of Virginia	Peptide vaccines for cancer	Yes

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KEY POINTS

- Cancer vaccines are formulated with tumor-associated antigens and vaccine adjuvants to elicit a targeted immune response for tumor control.
- The elicited T cell response to tumor-associated antigens may be discordant with tumor control; current strategies of vaccine antigens and adjuvants are under investigation to improve clinical response rates.
- Many clinical trials are currently underway to determine the optimal combinations for the different types of tumor-associated antigens, vaccine adjuvants, and other immunotherapies such as checkpoint blockade therapy.

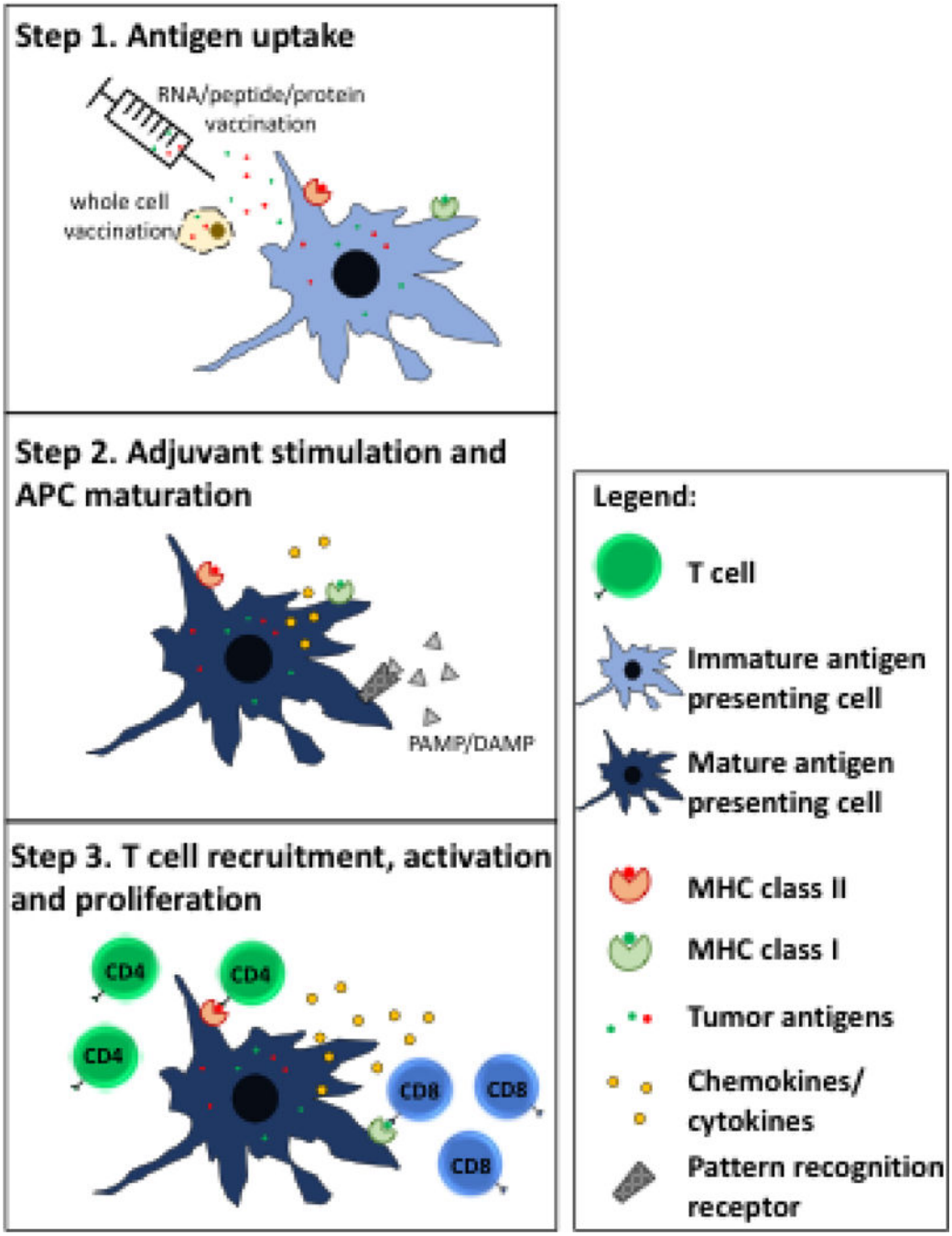

Figure 1: Mechanism of immune response induction following vaccination.

Step 1. Vaccination allows tumor antigen to be taken up by antigen-presenting cells (APCs). Step 2. Adjuvant stimulation supports activation and maturation of APCs. Step 3. APCs present antigen to CD8 T cells via MHC class I and to CD4 T cells through MHC class II, resulting in their activation and proliferation and thereby launching an antitumor immune response.

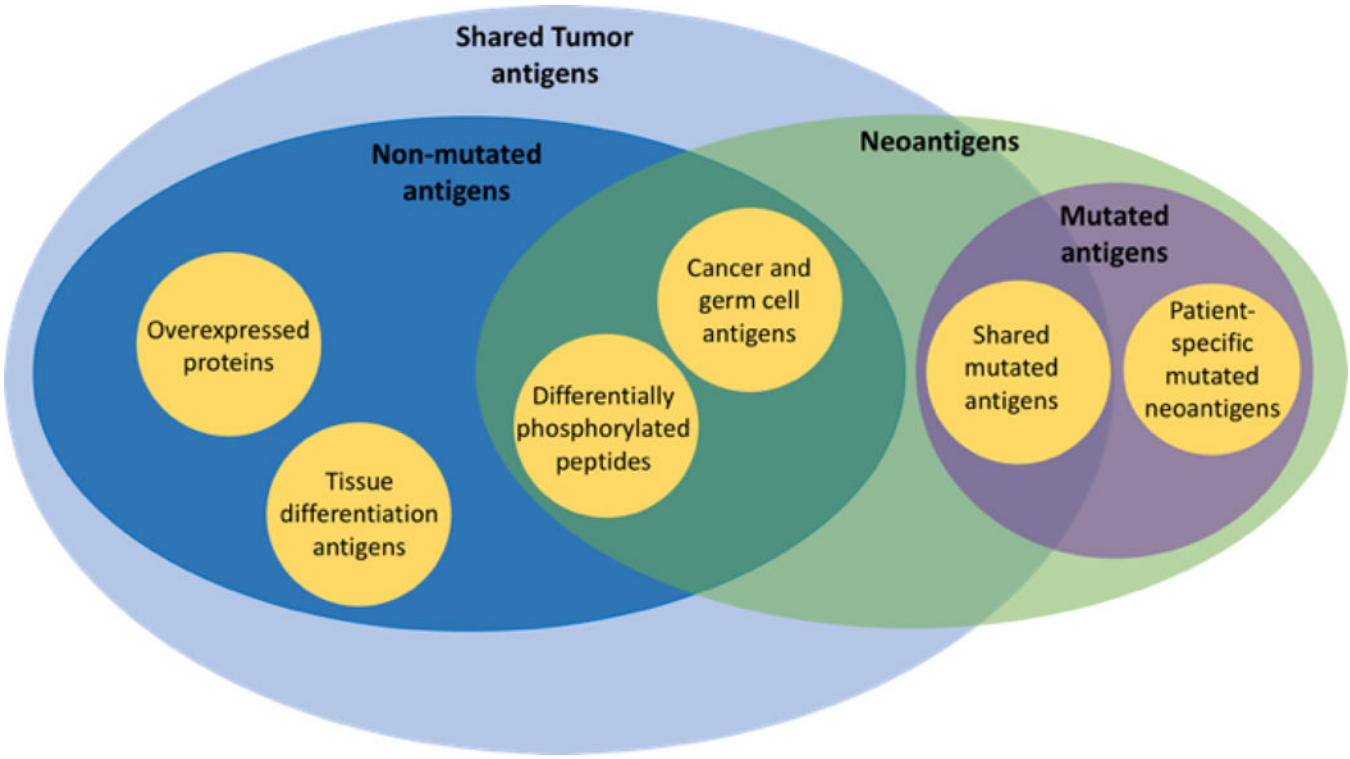

Figure 2:
Different types of tumor-associated antigens in melanoma

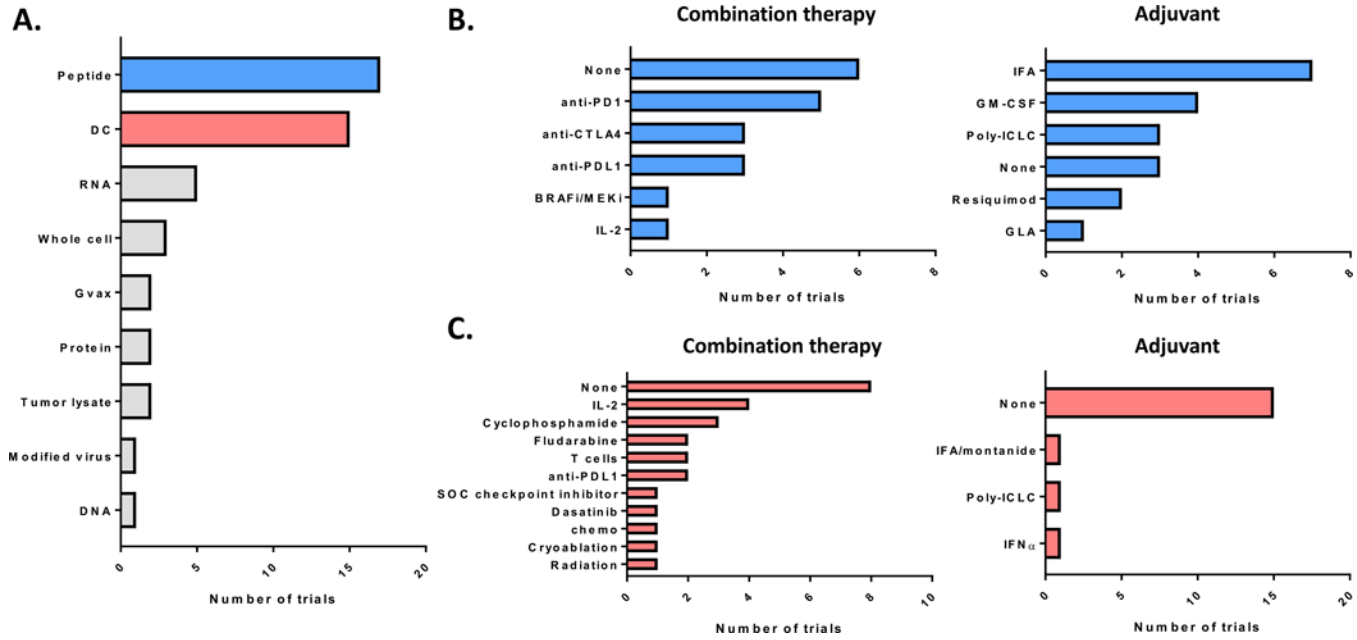

Figure 3: Current vaccine trials in melanoma.

The number of active clinical trials for each melanoma vaccine vehicle as of July 2018 on ClinicalTrials.gov are shown in **A.** Number of active trials using combination therapies and adjuvants are quantified for peptide vaccines in **B** and dendritic cell vaccines in **C.**