Cancer Neoantigens: A Promising Source of Immunogens for Cancer Immunotherapy

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Abstract

Recent progress in cancer immunotherapy has been remarkable, especially the clinical development of immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 antibodies. The success of these agents has revealed the importance of anti-tumor immune activities in curing cancers.

Cancer peptide vaccines constitute another approach to eliciting and boosting anti-tumor immune responses. While conventional cancer vaccines have had limited clinical efficacy, targeting mainly tumor-associated self-antigens, a novel approach is now being explored to target tumor-specific antigens generated from gene mutations occurring in tumor cells during neoplastic transformation. Theoretically, immune responses to these so-called “cancer neoantigens” are not attenuated by host central tolerance in the thymus and do not trigger autoimmune reactions. Despite these theoretical considerations, until recently there were major technical difficulties in applying neoantigen-based cancer vaccines to bedside practice, because the mutations in each tumor are so numerous and which one/subset of neoantigens would be immunogenic enough to eliminate the tumor is uncertain. Recent developments in genomics and bioinformatics, including massively parallel sequencing (MPS) and epitope prediction algorithms, have provided a major breakthrough, enabling more comprehensive and efficient identification of target antigens. Although further refinements are needed for actual bedside application, the preclinical and clinical evidence for the effectiveness of targeting cancer neoantigens continues to accumulate.

In this review, we discuss the current status and future challenges of developing neoantigen-based personalized immunotherapy.

Keywords: Cancer immunology; Cancer immunotherapy; Cancer neoantigen; Cancer vaccine; Epitope prediction; Oncogenomics; Somatic mutations; Whole-exome sequencing

Abbreviations

Ab: Antibody; cDNA: complementary DNA; CTL: Cytotoxic T cell; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; ELISPOT: Enzyme-Linked Immunospot Assay; HLA: Human Leukocyte Antigen; MHC: Major Histocompatibility Complex; MPS: Massively Parallel Sequencing; PD-1: Programmed Cell Death-1; TAA: Tumor-Associated Antigen; TIL: Tumor-Infiltrating Lymphocyte; TCR: T-Cell Receptor; TSA: Tumor-Specific Antigen; WES: Whole-Exome Sequencing

Introduction

Recent progress in cancer immunology and the development of cancer immunotherapy has been truly remarkable. One of the most dramatic breakthrouts has been the clinical development of immune checkpoint inhibitors [1-3]. Serial clinical trials have shown their feasibility and efficacy in patients with previously incurable advanced malignancies. Many ongoing studies are actively investigating the potential for synergistic effects by combining immune checkpoint inhibitors with other agents, including other checkpoint inhibitors [4], cytotoxic agents [2], monoclonal antibodies [5], small molecule inhibitors [6], anti-cancer vaccines [1,7], cytokines [8], or radiotherapy [9,10]. The success of these immunomodulators has highlighted the critical importance of anti-tumor immune activities for curing cancers.

Peptide-based cancer vaccine is another attractive approach to evoking these anti-tumor immune activities, especially those of cytotoxic T-lymphocytes (CTL). Despite intensive investigations, however, their clinical effects have been rather disappointing [11,12]. Although there might be many explanations for this, the most critical issue is likely to be target-antigen selection. Conventional cancer vaccines have targeted tumor-associated antigens (TAAs) which would impair anti-tumor T-cell activities, have produced poor
clinical effects. Risks of autoimmune reactions must also be taken into consideration [15,16].

In this regard, it is more reasonable to design cancer vaccines targeting tumor-specific antigens (TSAs), which are theoretically recognized as "non-self" by the host immune system and bypass central tolerance in the thymus. Examples include cancer vaccines targeting pathogen-associated antigens [17], mutated growth factor receptor [18,19], mutated K-ras [20,21], or idiotype-derived antigens [22]. Somatic mutations in tumor genes, which usually accumulate tens to hundreds of fold during neoplastic transformation, could occur in protein-coding regions. Whether missense or frameshift, every mutation has the potential to generate TSAs. These mutant TSAs, also known as "cancer neoantigens", might be an attractive source of targets for vaccine therapy [23-27]. Neoantigen-based cancer vaccine has a potential to induce more robust and specific anti-tumor T-cell responses compared with conventional shared-antigen-targeted vaccines. Furthermore, neoantigens could also be targeted in other cancer immunotherapies, including adoptive T-cell therapy.

To put this novel neoantigen-based approach to bedside practice, one of major bottleneck is how to select immunogenically potent antigens rapidly. Oncogenomics have revealed that mutational frequency varies across tumor classes and among patients [28,29], and that recurrent tumorigenic mutations are rather rare, while most of the enormous number of mutations present are specific to each patient [30-33]. Until recently, there were technical obstacles to preparing immunogenically potent epitopes. However, recent developments in genomics and bioinformatics have enabled more high-throughput surveys to be performed.

Preclinical Considerations

Since the groundbreaking study by Mandelboim et al., which demonstrated the anti-tumor effect of peptide therapy derived from tumor gene mutations in murine lung carcinoma [38], a series of murine and human studies have shown that mutated cancer neoantigens are recognized by CTLs and induce anti-tumor responses by immunization with synthetic peptides in prophylactic and/or therapeutic settings [39-46].

Lennerz et al. attempted to identify immunogenic neoantigens in patient-derived melanoma tissue [39]. They screened the cDNA library with MLTCs (mixed lymphocyte-tumor cell cultures) and employed the IFN-γ ELISPOT (enzyme-linked immunospot) assay. They identified five neoantigens generated from somatic point mutations. Immune monitoring of T-cell responses suggested somatic mutation-derived cancer neoantigens to be capable of inducing more robust and enduring anti-tumor responses than tumor-associated self-antigens.

Although missense mutations generally account for a large majority (about 85%) of somatic mutations occurring in tumor cells, frame shift mutations derived from nucleotide deletions or insertions have also been shown to yield potent and specific immunogens, referred to as novel open reading frames or "neoORFs" [40,41].

Novel "reverse immunology" approach for discovering immunogenic cancer neoantigens

While conventional studies have had technical limitations and screening relatively small numbers of peptides or cDNA library pools derived from tumor tissue has been both costly and time-consuming, recent technical progress in genomics and bioinformatics has enabled more high-throughput surveys to be performed.

Figure 1 shows an example of the processes applied to identify cancer neoantigens, which consist of three steps: screening, selection, and validation of the candidate immunogen. The left flowchart shows the process of identifying cancer neoantigens for target of immunotherapy, consisting of three steps: screening, selection, and validation of the candidate immunogen. The right hierarchy chart* shows the process of narrowing candidate antigens through each step. First, the whole genome/exome sequence profile is comprehensively screened to identify tumor-specific somatic mutations (cancer neoantigens) by massive parallel sequencing of tumor and normal tissues, respectively. Second, computational algorithms are used for predicting the affinity of the mutation-derived peptides with the patient's own HLA and/or TCR. Third, synthetic mutated peptides and wild-type peptides are used to validate the immunogenicity and specificity of the identified antigens by in vitro T-cell assay or in vivo immunization. Validated antigens could be applied to immunotherapy as either biomarkers of responses to immunotherapy, or as targets of cancer immunotherapy, including cancer vaccines and adoptive T-cell therapy. Each area does not necessarily illustrate a precise proportion.
experimental validation of cancer neoantigens. Although prediction and validation are not limited in the ways discussed above and are continuously being improved, this neoantigen-discovery process is referred to as the “reverse immunology (or vaccinology)” approach [47-49]. Some examples of alternative way of epitope selection are mentioned below, including “minigene” library screening and utilizing mass spectrometry analysis. Each way has advantages and disadvantages and it needs to wait for further data accumulation to obviously determine which way is superior to others.

Castle et al. performed MPS and used the NetMHC algorithm to identify target neoantigens for designing a cancer vaccine against B16F10 murine melanoma [42]. They identified 962 nonsynonymous somatic point mutations, 563 of which were actually expressed in tumor genes. They then selected 50 mutations for in vivo validation of immunogenicity and specificity, by administering either mutated or wild-type synthetic long peptides to the experimental mice. Approximately one third (16/50) showed the induction of a T-cell response, two of which were confirmed to have antitumor effects in both prophylactic and therapeutic settings.

Possible role of neoantigen-specific immune activities in cancer immunooediting

Matsushita et al. used chemically induced sarcoma (d42m1) in immunodeficient mice to create a spontaneous tumor model [43]. They employed MPS and the MHC class epitope prediction algorithm (IEDB algorithm), and identified mutant spectrin-β2 as a potential tumor rejection antigen, that is a target of tumor-eradicating CTL response. They validated the strong immunogenicity of spectrin-β2 for immunodeficient mice, especially when the T-cell epitopes were expressed or presentation of the immunogen during their expression or presentation of the immunogen during their progression. This immune escape was not observed in immunodeficient mice, and genetic reintroduction of the same immunogen resulted in a reversal of this process, thereby restoring the immunogen.

These studies suggest neoantigen-specific T-cell recognition to play an essential role in immunosurveillance and immunooediting.

Following these landmark studies, the significance of cancer neoantigen-specific immune responses was more recently investigated in other settings [45,46].

Gubin et al. used similar genomics and bioinformatics approaches to search for cancer neoantigens in mice harboring chemically-induced sarcoma (d42m-T3) treated with anti-PD-1 and/or anti-CTLA-4 Ab [45]. They used three HLA-binding prediction algorithms (SMM, ANN, and NetMHCpan) and identified mAlg8 and mLama4 as tumor-specific HLA-class epitopes in the experimental mice after immune checkpoint blockade. They detected functional cognate CTL clones in vitro, which showed treatment-specific transcriptional profiles (anti-PD-1 vs. anti-CTLA-4 vs. both). The investigators then synthesized long peptides incorporating mAlg8 (21-mer) and mLAMA (28-mer) and vaccinated tumor-harboring mice in combination with poly(I:C). They showed anti-tumor effects of the vaccination comparable to those of immune checkpoint inhibitors in therapeutic settings.

Yadav et al. employed another approach to identifying immunogenic neoantigens in two tumor cell lines of MC-38 and TRAMP-C1 [46]. They used mass spectrometry analysis combined with whole-exosome/transcriptome sequencing. Of 1290 and 67 mutations expressed in MC-38 and TRAMP-C1, respectively, 170 and 6 were predicted to bind MHC-class II molecule by the NETMHC-3.4 algorithm. On the other hand, only 7 and 0, respectively, were shown to be present on the MHC-class II molecule by mass spectrometry. Two of the 7 antigens were structurally predicted to be immunogenic, and both actually showed strong anti-tumor responses in vitro. Their study suggested that utilizing mass spectrometry as another filter is one of the ways to reduce the burden of validation assays, which are extremely laborious, thereby simplifying the neoantigen discovery process.

Clinical Application

Based on the preclinical models, promising evidence has been accumulating in support of the significance of tumor neoantigen-specific immune responses in tumor rejection and the effectiveness of targeting these neoantigens in next generation immunotherapies [50-61].

Adoptive tumor-infiltrating lymphocyte (TIL) transfer therapy

Although recent clinical studies have shown the effectiveness of adoptive TIL transfer therapy for human cancers, especially melanoma, the target antigens recognized by dominant TIL clones remain elusive. Serial studies have shown neoantigen-specific TIL clones in the infusion products and peripheral blood of patients who experienced clinical benefit from such therapy [50-53].

Robbins et al. used MPS and the NetMHCpan2.4 HLA-binding prediction algorithm to identify mutated epitopes recognized by TILs, in three melanoma patients who had tumor regression after adoptive TIL therapy [52]. They identified seven mutated neoantigens as targets of therapeutic TIL products.

Recently Lu et al. applied a novel approach to discover target antigens of clinically effective TILs, in two melanoma patients who had experienced long-term remission after adoptive TIL therapy [53]. Instead of using epitope prediction algorithms, which are sometimes inaccurate because of insufficient validation or low frequencies of HLA alleles with scarce epitope data, the investigators screened minigene library pools and made comparisons with conventional cDNA screening. Minigene is a gene fragment that includes an exon and it’s control region. The epitope encoded by a minigene is processed and presented on HLA molecules of the minigene-transfected target cell. They synthesized tandem minigene constructs that encode multiple candidate epitopes identified by MPS for efficient screening. While several previously described or undescribed nonmutated antigens were identified by the cDNA approach, only the novel minigene approach revealed two mutated neoantigens (KIF2C and POLA2, both of which play important roles in cell proliferation) as TIL targets. These results suggested that minigene screening might facilitate the higher-throughput discovery of target antigens for next generation immunotherapy, including more specific adoptive TIL therapy with purification of effective clones. Whether this minigene approach is
Other types of malignancy besides melanoma

To date, most of our knowledge of cancer neoantigens has been obtained mainly from malignant melanoma, which is known among human malignancies to have an especially high mutational load. Several studies have, however, extended such findings to other tumors [51,56-59].

Tran et al. studied a metastatic chemo-refractory cholangiocarcinoma patient who showed a clinical response to autologous adoptive TIL therapy [51]. They performed WES and identified mutant erbb2 interacting protein (ERBB2IP) on tumor cells. ERBB2IP-specific CD4+ helper T cells were dominant in the TIL-derived infusion product, as well as being detectable in the patient’s peripheral blood for months after treatment. When the disease recurred, the patient was re-treated with adoptive TIL and again experienced tumor regression. This study showed that mutation-specific helper T cells can mediate anti-cancer effects in epithelial tumors, which account for the majority (80%) of human malignancies.

Rajasagi et al. used previously identified somatic mutation data from 91 patients with chronic lymphocytic leukemia (CLL) and the NetMHCpan algorithm [56]. Identified neoantigens were classified according to predicted HLA-binding affinities: IC50 <150 nM indicated strong binders; 150<IC50<500 nM intermediate to weak binders; IC50>500 nM non-binders. The immunogenicity and specificity of candidate antigens were validated by IFNγ-ELISPOT assay and CD107a staining as a marker of CTL degranulation by flow cytometry. Of 1838 nonsynonymous mutations, 90% were missense mutations. In 31 patients whose HLA information was available, a median of 22 peptides per case was predicted to bind HLA (10 were strong and 12 were intermediate to weak). Approximately 55% of candidate epitopes were validated by an in vitro experiment using synthesized peptides. The investigators then focused on the two patients who underwent allogeneic-hematopoietic stem cell transplantation and experienced long-term disease-free survival. Specific CTL responses to patient-specific immunogenic neoantigens (ALMS1, C6ORF89, and FNDC3B) were detected.

Immune checkpoint blockade therapy

The significance of neoantigen-specific T-cell responses has been suggested in patients treated with immune checkpoint inhibitors [45,54,55]. These observations may provide the rationale for combining immunomodulators with cancer vaccines.

Rooji et al. reported a melanoma patient who experienced a clinical response to anti-CTLA-4 Ab therapy [54]. They used MPS and MHC-binding prediction algorithms (NetChop Cterm3.0 and NetMHC3.2 algorithms), and identified two immunogenic neoantigens expressed on tumor cells. The dominant CTL clone recognized one of them, encoded by the ATR (ataxia telangiectasia and Rad3 related) gene. Monitoring of the patient’s CTLs in peripheral blood revealed that CTLA-4 blockade induced a dramatic expansion of neoantigen-specific CTLs.

Snyder and colleagues followed a similar approach, using whole-exome sequencing (WES) and epitope prediction algorithms in melanoma patients treated with anti-CTLA-4 Ab [55]. They identified several immunogenic neoantigens, and compared the mutational load or signature between the patient groups with or without clinical benefit. While mutational load alone was not sufficient to predict a patient’s outcome, the neoantigen signature in each patient was strongly associated with the clinical response to anti-CTLA-4 Ab therapy.

Neoantigen-specific CD4+ helper T cells

Several studies have suggested that, as observed in CD8+ T cells, cancer neoantigen-specific CD4+ helper T cells play an important role in anti-tumor immune activities [51,60].

Linnetemann et al. studied five patients with melanoma [60]. They synthesized neoantigen peptides containing a candidate mutation identified by tumor exome sequencing, and validated them in vitro. CD4+ T cells from tumor tissue were incubated with immortalized autologous B cells from peripheral blood as an antigen presenting cell (APC), and cytokine production was then measured. In the five tumors studied, their immunogenicities of approximately 0.5% (0-1.5%) for candidate neoantigens were validated, suggesting the detection frequency of spontaneous neoantigen recognition by CD4+ T-cell clones to be as low as that of CD8+ T cells, as observed in other studies. The neoantigen-specific CD4+ T cells were detectable for months in the blood of patients who had a clinical response to autologous adoptive T-cell therapy.

Neoantigen as a biomarker predicting patient outcomes

Immunogenic cancer neoantigens have the potential to be utilized as biomarkers predicting clinical responses to immunotherapy and outcomes, as well as serving as targets for immunotherapy [55,61].

Brown et al. sought to identify cancer neoantigens as prognostic biomarkers, using RNA-sequence data from 515 patients with six types of malignancies from The Cancer Genome Atlas [61]. The predicted immunogenic mutation load was associated with better survival. The tumors with high somatic mutations had higher CTL contents (inferred from CD8A gene expression) and expressions of the so-called exhaustion markers PDCD1 and CTLA-4 than those with fewer mutations, suggesting CTL-dependent immunoediting.

As mentioned above, another recent study by Snyder et al. also highlighted the significance of the neoantigen signature as a prognostic biomarker in patients harboring unresectable melanomas treated with CTLA-4 blockade [55].

Utility of computational epitope prediction

Accumulating evidence suggests the utility of in silico epitope prediction [35-37].

In a recent retrospective analysis, Fritsch et al. applied computational prediction with the NetMHCpanv2.4 algorithm to previously reported data on neoantigens identified by ex vivo CD8+ T-cell reactivity and associated with clinical benefit, to elucidate whether there is consistency between functional T-cell screening and the computational algorithm prediction [26]. In total, 26 of the 31 (87%) neoantigens were predicted to bind patient-specific MHC: 20 were classified as strong binders (IC50<50 nM); 3 as moderate binders (50<IC50<150 nM); 4 as weak binders (150<IC50<500 nM). Furthermore, importantly, the majority, 26 of the 35 (74%) neoantigens, had comparable affinity to cognate MHC with unmutated native peptides.
Discussion

Mounting evidence indicates that neoantigen-specific anti-tumor immune responses occur spontaneously in cancer patients and have the potential to be employed in the next generation of immunotherapeutic modalities. One of the possibly significant features of cancer neoantigens is their utility as response/prognostic biomarkers, which allows patients who could reasonably expect clinical benefit from cancer immunotherapy to be selected. Another characteristic is the possibility of serving as target antigens for immunotherapy. These approaches may lead to neoantigen-based personalized cancer vaccines, adoptive T-cell therapy, and so on.

How can we efficiently and reliably select potent neoantigens for cancer immunotherapy?

Many obstacles remain to be overcome before the concept of neoantigen-incorporated immunotherapy can be applied to routine bedside practice. Most importantly, methods of rapidly selecting the epitope which is optimal for each patient must be devised. The "reverse immunology" approach, which employs computational epitope prediction and in vitro validation of candidate epitopes, has enabled us to efficiently select immunogenically potent neoantigens from the enormous number of somatic mutations in an individual tumor. However, there are still limitations and further refinement is necessary in actually selecting immunogenic antigens in vivo that are sufficient to achieve tumor eradication.

Massively parallel sequencing: One of the conceptual limitations of MPS is that the genetic information must be obtained from a limited amount of patient tumor tissue. It may be difficult in some cases, especially if repetitive biopsy is impossible for technical or ethical reasons, and when a given immunogenically robust antigen is not abundantly expressed on the tumor cells. Furthermore, increasing gene expression heterogeneity during the course of tumor progression also poses a problem when sampling tumor tissue from one site if there are multiple lesions.

Epitope prediction algorithms: At present, which one/set of algorithms we should use remains elusive. Many types of algorithms are available, and these can predict either MHC-peptide or MHC-peptide-complex-TCR bindings. Although continuously being developed and refined, to date, only a few of these algorithms have been well-validated, as in the case of the NetMHC algorithm for peptide-HLA-II bindings [37]. They also have unavoidable limitations due to the low frequency of HLA alleles with scarce binding data. In addition, as suggested by Fritsch et al. [26], the immunogenic potency of neoantigens does not always depend on the peptide-MHC binding intensity.

Other groups of investigators have attempted other approaches rather than computational prediction, and some results have suggested superior utility [46,53]. Although T-cell assays can be more accurate than in silico predictions, this approach also has theoretical limitations in that the spectrum of candidate epitopes might be significantly influenced by the patient's existing T-cell repertoire. Because there can be no treatment delay in most patients with advanced tumors, further refinement is needed to simplify the epitope discovery process for routine bedside practice.

In vitro T-cell assays for epitope validation: The in vitro T-cell assays for validating candidate epitopes, as applied in many cases using ELISPOT or intracellular cytokine staining by flowcytometric assay, have limitations. One is low sensitivity, especially in cases where a given T-cell clone recognizing the identified neoantigen is extremely rare in the patient's T-cell repertoire. In fact, in many studies, the proportion of the validated neoantigens in total identified in silico is low (0.5-1.0%). Given that about one third of the candidate neoantigens were immunogenic in a murine model [42], these studies may underestimate the actual number. This might be attributable, at least in part, to the low sensitivity of the T-cell assay.

Other problems surrounding neoantigen-based immunotherapy

How many neoantigens should be targeted simultaneously?: Several important issues, besides epitope selection, remain to be resolved. One involves how many neoantigens should be included. A number of outstanding studies have suggested that T-cell recognition of TSAs could play a role in tumor immune escape or immunoediting as well as tumor rejection, and that tumors with multiple neoantigens tend not to recur [42-44]. It is thus reasonable to target multiple epitopes simultaneously, thereby possibly generating more potent immune reactions, and/or preventing immune escape. To date, absolute numbers of epitopes to be included have not been established. While there is a notion that we should incorporate as many neoantigens as we can identify, taking into account current manufacturing limitations and cost-effectiveness, incorporating 10-20 epitopes would appear to be practical.

Who actually benefits from neoantigen-based immunotherapy?: Another problem involves patient selection. As yet, only a small fraction of patients have experienced long-term survival after cancer immunotherapy, which carries risks of severe immune-related adverse events, especially immune checkpoint inhibitors or CAR (chimeric antigen receptor)-T cell therapy. As yet we have no established "baseline (or pretreatment)" biomarkers for selecting patients who would benefit from immunotherapy. In the context of immune checkpoint blockade therapies, several potential predictive/prognostic biomarkers have been suggested [55,62-67]. For further identification of potent biomarkers, there is an urgent need to establish a standardized immunologic monitoring system after cancer immunotherapy.

Combination therapy for synergistic efficacy: In the future, combination therapy with a neoantigen-based vaccine and other immunotherapy might be possible. Accumulating evidence suggests that a synergistic effect can be obtained by combining immune checkpoint blockade and/or adoptive T-cell therapy. As for cancer vaccines, challenges, including optimization of the mode of delivery, adjuvant formulations, and administration schedules, remain. The potential synergistic anti-tumor effect that might be obtained by combining vaccines with other immunotherapies, especially immunomodulators, is also intriguing.

All of these approaches should be evaluated in the context of clinical trials. Recently, the Dana-Farber group has been conducting a phase clinical trial to evaluate the safety and feasibility of a personalized neoantigen cancer vaccine in patients with advanced melanoma (NCT01970358). They employ WES and an epitope prediction algorithm to identify target neoantigens. The patients are administered 1.2 mg of peptide with poly-ICLC according to the schedule. The plan is to monitor the immune responses to this vaccination and the results are eagerly awaited.
Conclusion

Conventional immunotherapy targeting shared TAAs has shown insufficient efficacy. This is partially attributable to the host’s immune tolerance, which would attenuate anti-tumor immune activities. The concept of cancer neoantigen-based immunotherapy, which targets patient-specific somatic mutations occurring during neoplastic transformation, may shed light on the major problem of target selection. As an example, a neoantigen-incorporated peptide vaccine might merit further investigation. Before we can apply this concept to actual bedside practice, many problems must be overcome. More preclinical and clinical investigations are needed.

References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723.
2. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, et al. (2011) Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364: 2517-2526.
3. Robert C, Long GV, Brady B, Dutriaux C, Maio M, et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372: 320-330.
4. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, et al. (2013) Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369: 122-133.
5. Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, et al. (2014) Safety and patient-specific somatic mutations occurring during neoplastic transformation, may shed light on the major problem of target selection. As an example, a neoantigen-incorporated peptide vaccine might merit further investigation. Before we can apply this concept to actual bedside practice, many problems must be overcome. More preclinical and clinical investigations are needed.

16. Morgana R, Chinnasamy N, Abate-Daga D, Gros A, Robbins PF, et al. (2013) Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. J Immunother 36: 133-151.
17. Kenter GG, Welters MJ, Valentijn AR, Lowik MJ, Berends-van der Meer DM, et al. (2009) Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med 361: 1838-1847.
18. Sampson JH, Heimberger AB, Archer GE, Aldape KD, Friedman AH, et al. (2010) Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. J Clin Oncol 28: 4722-4729.
19. Nedergaard MK, Hedegaard CJ, Poulsen HS (2012) Targeting the epidermal growth factor receptor in solid tumor malignancies. BioDrugs 26: 83-99.
20. Carbone DP, Ciernik IF, Kelley MJ, Smith MC, Nadaf S, et al. (2005) Immunization with mutant p53- and K-ras-derived peptides in cancer patients: immune response and clinical outcome. J Clin Oncol 23: 5099-5107.
21. Weden S, Klemp M, Gladhaug IP, Moller M, Eriksen SA, et al. (2011) Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. Int J Cancer 128: 1120-1128.
22. Baskar S, Kobrin CB, Kwak LW (2004) Autologous lymphoma vaccines induce human T cell responses against multiple, unique epitopes. J Clin Invest 113: 1498-1510.
23. Hacothen N, Fritsch EF, Carter TA, Lander ES, Wu CJ (2013) Getting personal with neoantigen-based therapeutic cancer vaccines. Cancer Immunol Res 1: 11-15.
24. Vononderheide RH, Nathanson KL (2013) Immunotherapy at large: the road to personalized cancer vaccines. Nat Med 19: 1098-1100.
25. Fritsch EF, Hacothen N, Wu CJ (2014) Personal neoantigen cancer vaccines: The momentum builds. Oncoimmunology 3: e29311.
26. Fritsch EF, Rajasagi M, Ott PA, Brusic V, Hacothen N, et al. (2014) HLA-binding properties of tumor neoepitopes in humans. Cancer Immunol Res 2: 522-529.
27. Trajanoski Z, Maccalli C, Menonnona D, Casorati G, Parmiani G, et al. (2015) Somatically mutated tumor antigens in the quest for a more efficacious patient-oriented immunotherapy of cancer. Cancer Immunol Immunother 64: 99-104.
28. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, et al. (2013) Signatures of mutational processes in human cancer. Nature 500: 415-421.
29. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, et al. (2013) Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 499: 214-218.
30. Wood LD, Parsons DW, Jones S, Lin J, Sjobloem T, et al. (2007) The genomic landscapes of human breast and colorectal cancers. Science 318: 1108-1113.
31. Segal NH, Parsons DW, Peggs KS, Velculescu V, Kinzler KW, et al. (2008) Epitope landscape in breast and colorectal cancer. Cancer Res 68: 889-892.
32. Garraway LA, Lander ES (2013) Lessons from the cancer genome. Cell 153: 17-37.
33. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, et al. (2013) Cancer genome landscapes. Science 339: 1546-1558.
34. Thomas BK, Baker AC, Debiasi RM, Winckler W, Laframboise T, et al. (2007) High-throughput oncogene mutation profiling in human cancer. Nat Genet 39: 347-351.
35. Lin HH, Ray S, Tongchusak S, Reinherz EL, Brusic V (2008) Evaluation of MHC class I peptide binding prediction servers: applications for vaccine research. BMC Immunol 9: 8.
36. Zhang GL, Ansari HR, Bradley P, Cawley GC, Hertz T, et al. (2011) Machine learning competition in immunology - Prediction of HLA class I binding peptides. J Immunol Methods 374: 1-4.
37. Snyder A, Chan TA (2015) Immunogenic peptide discovery in cancer genomes. Curr Opin Genet Dev 30C: 7-16.
