Targeting Neoantigens for Personalised Immunotherapy

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Targeting Neoantigens for Personalised Immunotherapy

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Abstract

This review discusses the rapidly evolving field of immunotherapy research, focusing on the types of cancer antigens that can be recognised by the immune system and potential methods by which neoantigens can be exploited clinically to successfully target and clear tumour cells. Recent studies suggest that the likelihood of successful immunotherapeutic targeting of cancer will be reliant on immune response to neoantigens. This type of cancer specific antigen arises from somatic variants that result in alteration of the expressed protein sequence. Massively parallel sequencing techniques now allow the rapid identification of these genomic mutations and algorithms can be used to predict those that will be processed by the proteasome, bind to the transporter complex and encode peptides that bind strongly to individual MHC molecules. The emerging data from assessment of the immunogenicity of neoantigens suggests that only a minority of mutations will form targetable epitopes and therefore the potential for immunotherapeutic targeting will be greater in cancers with a higher frequency of protein altering somatic variants. It is evident that neoantigens contribute to the success of some immunotherapeutic interventions and that there is significant scope for specific targeting of these antigens to develop new treatment approaches.

Key points:

This review discusses the types of cancer antigens that can be recognised by the immune system and the method by which these antigens are shown to the immune cells.

The focus is then drawn to the neoantigen classification of tumour antigen and methods by which this can be clinically targeted.

This review concludes with the current challenges and future goals of targeting neoantigens in the treatment of cancer.

1 Introduction

Since the hypotheses was put forward by Paul Ehrlich at the start of the 20th century that the immune system can control the development of tumourigenic cells [1], researchers have been striving to understand the nature of this control, how it fails and how to manipulate it to clear tumour cells. Enthusiasm and focus on the immune control of cancer has gone through significant peaks and troughs in the intervening 100 years and is currently undergoing a significant resurgence (for reviews on the history of immunotherapy, references [1-3] are recommended). Thanks to technological advances, researchers are now able to molecularly characterise tumours and responding immune cells. This has

led to breakthroughs including the identification of pharmacologically targetable immune suppression markers and a greater understanding of the immune targets displayed by cancer cells, which is the subject of this review.

The importance of many subsets of cells within the immune system to the surveillance, recognition and removal of cancer cells has been uncovered and significant research has been undertaken to attempt to manipulate these cell types to promote cancer clearance (excellent reviews discussing the interplay of immune cells involved in the "elimination, equilibrium and escape" of tumour cells are: [4-6]). Immune cells that can recognise cancer cells as being different to 'self', include $CD4^+$ and $CD8^+$ T-cells and B-cell subsets. This review will focus on the immune targets displayed by cancer cells to be recognised by T-cells; a recommended review of the role of B cells in tumour recognition and immune suppression is by Yuen et al [7].

1.1 Types of antigens displayed by cancer cells

Broadly, there are four main types of immune targets displayed by cancer cells (known as 'antigens'):

1. Tumour associated antigens: Processed fragments of proteins that are normally expressed at low levels in the cell, but are over expressed in cancer cells, often due to genomic amplification. Examples include ERBB2 in breast cancer [8], CD19 in B-cell malignancies [9] and tyrosinase in melanomas [10].

2. Cancer/Testis (CT) antigens: Derived from proteins usually only expressed by reproductive tissues (e.g. testes, foetal ovaries and placenta) and have limited/no expression in all other adult tissues. As normal reproductive cells do not display antigens [11], CT epitopes are considered to be fairly cancer specific. Examples include MAGE [12] and NY-ESO-1 [13]; a comprehensive list and evaluation of CT antigens are available at http://www.cta.lncc.br/ (Ludwig Institute for Cancer Research).

3. Viral antigens: Some cancers are associated with viral infection, such as the human papilloma virus and cervical or oropharyngeal cancers [14, 15]. The proteins encoded by the viral open reading frames within the cell can be processed and displayed on the cancer cells, making this a cancer specific antigen.

4. Neoantigens/neoepitopes: This classification of antigen is the result of a mutation in a protein coding region that occurs in a non-germline cell after birth, first identified in a murine models [16, 17]. Such somatic mutations accumulate in the cancer cell during the initiation, development and metastasis of the tumour. When the mutated protein product is processed by the cell and the peptide fragment containing this mutation is displayed, it can be recognised as 'non-self' by the immune system, stimulating an anti-tumour response.

Many *in vitro*, *in vivo* and clinical trial studies have been carried out focusing on tumour antigens from the first three classifications to understand their utility as targets for immunotherapy. These approaches work on the assumption that a given tumour type is likely to display certain antigens and targeting them has resulted in tumour regression and/or complete response in some patients. The response rates were, however, consistently low, despite many different methods of raising an immune response to these three types of antigen being investigated [18].

The seminal work of Lennerz et al in 2005 demonstrated a high degree of individuality in the anti-tumour immune response and that the predominant antigen responses uncovered were against mutated neoepitopes [19]. This was followed up by Segal et al, who used early next generation sequencing data from breast and colorectal cancer [20] as the basis for neoantigen prediction, concluding that there was a "gold mine" of potential for targeting immunogenic peptides created from both 'driver' and 'passenger' somatic variants [21]. Prior to the advent of whole genome/exome sequencing, the method to identify neoepitopes was by labour-intensive individual cDNA library screening (e.g. as performed in [19]) and as a result, the number of identified and studied neoantigens was fairly low. Massively parallel sequencing has become a mainstay technique (reviewed in [22]), meaning that tumour specific genetic mutations affecting protein coding regions can be rapidly identified, which has facilitated the prediction of neoepitopes. This has boosted the interest in the use of these neoantigens for personalised immunotherapy.

1.2 MHC protein processing

All vertebrates express MHC (major histocompatibility complex) on the majority of their cells, which sample peptide fragments within, or outside, the cell to alert the immune system to infection by pathogens. This process requires T-cells to distinguish 'self' from 'non-self'; the MHC complexes display peptides from all protein sources and if the T-cells recognise 'self' peptide, there is a risk of autoimmunity. In humans, the proteins are encoded by genes in a cluster on chromosome 6. They are broadly split into two types: MHC-class I and MHC-class II molecules. Humans have three classical MHC-class I genes, called HLA-A, HLA-B and HLA-C and three classical MHC-class II molecules: HLA-DR, HLA-DQ and HLA-DP; non-classical MHC molecules also exist. $CD8^+$ T cells recognise internal protein-derived peptides displayed on MHC-class I molecules, while $CD4^+$ T cells recognise externally derived peptides bound to MHC-class II.

Both MHC-class I and –class II genes have significant population variation, with polymorphisms resulting in amino-acid differences particularly concentrated in the region that binds the processed peptides. This results in different binding strengths to the same peptides being conferred by these individual genotypes. There are now thousands of different HLA alleles identified in the human

population, which results in considerable population variety in the peptides that can bind. The structure that binds the peptide consists of a groove formed by two anti-parallel α-helices overlaying an eight-strand β-sheet. An important difference between MHC-class I and MHC-class II is in the binding groove positioning of the peptide; in MHC-class I, the peptide is confined at both the N- and C-termini, while for MHC-class II the peptides are not restricted by the groove and can overhang. This has important consequences for prediction algorithms for which peptides can bind to molecules of each type. Receptors on the T-cell can recognise and bind the MHC molecule-peptide complex. Comprehensive reviews on the structure of the MHC molecules (e.g. [23]) and recognition by T-cells of the MHC-peptide complex (e.g. [24]) are available, which provide a greater depth of insight into the intricacies of these processes.

The immune recognition by T-cells can be broadly considered as a two-part process where-by: 1) the protein has to be cleaved within the proteasome into the specific peptides [25] capable of binding to the TAP (transporter associated with antigen processing) complex for selective movement of peptides to the endoplasmic reticulum for processing [26] and to the specific HLA molecule (dictated by the MHC polymorphic variations in the population) 2) the T-cell receptor is able to recognise the HLA bound peptide.

1.3 Cancer antigen immune recognition

The key to the recognition of cancer cells by the immune system is distinguishing between 'self' and 'non-self'. Viral antigens and mutated peptide neoantigens are more likely to be sufficiently different to 'self' to stimulate a significant immune response than those antigens derived from over- or restricted- tissue expression. Indeed, the affinity of the T-cell receptor and subsequent strength of the immune response to the former type of epitopes tends to be stronger than those seen for the latter [27, 28]. The viral, over-expression and CT antigens have the advantage over neoantigens that a single epitope is more likely to be shared between individuals with the same HLA allele. The neoepitope approach is dictated by the combination of tumour mutation and HLA restriction and is therefore more likely to be a personalised therapy; although notable exceptions do exist, where the neoepitope is formed from more common mutations important in the tumourigenic process.

1.4 Identification of neoantigens

1.4.1 Types of neoantigen

Neoantigens can arise from any genomic mutation that occurs in the cancer cell that results in an alteration in the sequence of an expressed protein. These can include non-synonymous mutations (e.g. [19, 29]), retained introns (e.g. [30]), post-translational modification that alters amino acid (e.g.[31]), gene fusions (e.g. [32]) and frameshift in/del variants (e.g. [33]). Attempts have been made

to use mass spectrometry methodology to directly identify the peptides bound to the MHC-class I molecules on the membranes of cancer cells, with varying degrees of success; indeed, while thousands of peptides can be identified, neoantigens are only rarely detected [34-42]. Prior to the advent of massively parallel sequencing, the main screening method for finding neoantigens was cDNA expression libraries, which was very labour intensive (e.g. as described in Lennerz et al [19]). Other efforts focused on common driver mutations, to investigate if the combination of mutated peptide/HLA type was immunogenic; this has included BRAF [43, 44], KRAS [45, 46], p53 [47] and NRAS [48].

1.4.2 Prediction of neoantigen in the era of next generation sequencing technology

The ability to rapidly identify tumour specific genetic variants has enabled researchers to attempt to predict the immunogenic epitopes created. Firstly, integration of mRNA expression data to the mutation information, using either whole genome microarrays (e.g. [29]) or RNA-seq (e.g. [49, 50]), is required in order to identify which of the mutated genes are transcribed. The mutations in expressed genes are then taken forward for epitope prediction using algorithms specific for HLA-alleles. This requires the amino acid sequence to be translated from the surrounding genetic sequence. A confounding factor is population polymorphism, which if in phase with the somatic variant may additionally alter amino acids from the reference sequence; working directly from sequencing data allows this to be taken into consideration. Examples of epitope prediction algorithms include SYFPEITHI [51], RANKPEP [52], NetMHCpan [53], NetMHCcons [54], PickPocket [55], MHCflurry (in pre-print, https://doi.org/10.1101/174243), ANN [56] and SMM [57]. The algorithms have been trained using characterised epitope/MHC combinations, which have allowed consensus sequence to be identified and predict likelihood of binding ability of short peptide sequences. These algorithms have differing capabilities of identifying epitopes that bind to HLA-alleles, influenced by the training set. As a result, the less common HLA-alleles tend to have higher binding scores (e.g. as assessed in [29, 34]), which means that using a standard threshold to indicate “strong” binding is currently likely to miss potential neoepitopes binding to rarer HLA-alleles. As more studies identify and functionally examine the peptides binding to HLA-alleles are carried out, the more robust these analyses will become; the current interest in this field is significantly increasing available data. Bioinformatic pipelines have been created that use whole genome/exome sequencing data and integrate the analysis to include HLA allele typing, mRNA expression data, peptide processing prediction and HLA allele binding for the wildtype and mutated peptide. These include pVAC-seq [58], TIminer [59], Cloudneo [60] and MuPeXi [61].Testing of neoantigen immunogenicity

Taking the data from the prediction algorithms, there are a number of methods by which immunoreactive neoepitopes can be identified. These include screening of the predicted peptides

across mixed lymphocyte-tumour culture (MLTC) (e.g. [19, 29]), exposure of tandem mini-genes (e.g. [62-66]) or pMHC multimers (e.g. [50, 67, 68]) to immune cells, and the pulsing of putative peptides with antigen presentation cells (such as dendritic cells or B-cells) and co-culture with T-cells, followed by T-cell exposure to predicted peptide pools (e.g. [69]). These approaches can identify existing memory T-cell immune responses in patients, or reactive naïve T-cells in patients/donors, which have potential clinical utility.

1.5 MHC-class II restricted neoantigens

The role of the T_{H1} subset of $CD4^+$ T-cells in priming, supporting, recruiting and proliferation of $CD8^+$ T-cells is well established; however other $CD4^+$ T-cells subsets (e.g. T_{H2} and T_{reg}) might promote tumour cell survival when activated. [70] Immunoreactive MHC-class II restricted neoantigens recognised by $CD4^+$ T-cells have been described (e.g. [64, 71-73]; reviewed in [70]) and have been shown to elicit a clinically relevant response when immunotherapeutically targeted [62]. In order for MHC-class II restricted neoantigens to be clinically applicable on a large scale, more reliable prediction of the peptides that will bind to MHC-class II and a better understanding of the factors influencing $CD4^+$ subset activation are required.

2 Immunotherapeutic potential of neoantigens

From the recent studies of neoantigens it is clear that only a minority of somatic variants create an immunogenic antigen (e.g. [29, 50, 66, 71, 74-79]). This means that the cancer types with a higher genomic mutation burden are more likely to form neoantigens, as there are more opportunities for one to be produced [71, 74, 78, 80-82]. Additionally, the presence of neoantigen(s) has been shown to contribute to the success of the checkpoint immunotherapies (targeting PD-1/PD-L1/CTLA4) (e.g. [50, 75, 83]) and other forms of immunotherapy, including dendritic cell vaccines (e.g. *unpublished observations* and [29], assessing patients from these clinical trials [84, 85]) and adoptive T-cell transfer (e.g. [86, 87]). Additionally, many studies have assessed the potential influence of neoantigens on overall survival and/or therapeutic success, without performing functional assessment of the immune response, including neoantigen fitness models that predicts tumour response to checkpoint blockade immunotherapy (e.g. [78, 88]) and *in silico* assessment of genomic data predicting neoantigen burden (e.g. [74-76, 80, 89]). Together, these data suggest that the likelihood of successful immunotherapeutic targeting of neoantigens will be greater in cancers with a higher frequency of protein altering somatic variants, but was not sufficient to predict clinical benefit.

Since the earlier work of Lennerz et al [19], the identification of neoantigens eliciting dominant immune responses capable of initiating tumour clearance has continued, which has encouraged

researchers to target them therapeutically. The approaches used to date will be outlined in the following sections.

2.1 CAR-modified T cells

Chimeric antigen receptors (CAR) are synthetic molecules designed to direct T cells to recognise specific antigens. CAR-modified T-cells are an autologous method of overcoming tolerance and have been successfully used in the treatment of B cell malignancies, with the cells directed to the over-expressed CD19 molecule [90-92]. It is extremely important for CAR-modified T-cells to only be directed towards surface antigens confined to the cancer cell, to avoid serious off-target effects and toxicities (e.g. [93, 94]) and is a significant limitation of this approach. The direction of CAR-modified T-cells against neoepitopes has been examined. An example of this is the cancer specific epidermal growth factor variant III (EGFRvIII), which is caused by an in-frame deletion of exons 2-7, resulting in constitutively activation of EGFR signalling [95]. Cancers with this variant present include glioblastomas and head and neck squamous cell carcinoma [96, 97]. CAR-modified T-cell therapies against this neoepitope [98] are currently in clinical trial (e.g. NCT01454596 and NCT02209376), for which the results are eagerly anticipated. The advantage of targeting EGFRvIII is that it is a common 'driver' mutation in certain solid cancers and therefore the production of these CAR-modified T-cells can be applied to a high proportion of patients.

Individually engineered CAR-modified T-cells against neoantigens is plausible if the T-cell receptor recognising the HLA-bound peptide is known or can be predicted (the possibility is further discussed in the reviews: [99, 100]). The potential of unpredictable off-target effects due to cross-reactivity, where the engineered T-cell receptor recognises other displayed antigens, cannot currently be anticipated [101]. Together with the additional intensive manufacturing that would be required for each patient's personalised therapy means it is unlikely this approach will be used routinely in the near future, but pose intriguing research subjects of investigation.

2.2 Adoptive T-cell transfer

Adoptive T-cell transfer in the treatment of cancer involves the *in vitro* selection and expansion of tumour reactive lymphoctyes, which are grown under conditions aimed to overcome the tolerisation that exists *in vivo*. As the selection and expansion occurs *in vitro*, it is possible to modify the host immune setting and/or the reactive cells before cell transfer back into the patient. Examples of this approach being clinically implemented are the isolation, expansion and transfer of HLA-DPB1*04:01 restricted NY-ESO-1 reactive $CD4^+$ T-cells, derived from the peripheral blood of a melanoma patient, which resulted in prolonged clinical remission [102] and the isolation and expansion of autologous tumour infiltrating lymphocytes (TIL) from melanoma patients, which were reinfused back into

patients who had undergone lymphodepletion, in the presence of interleukin 2 (IL-2), resulting in ~20% complete durable response [103-105].

Adoptive T-cell transfer is also highly amenable to focus on neoepitope reactive T-cells. Indeed, adoptive T-cell transfer of neoantigen reactive cells has been trialled in the clinical setting. This includes the identification of polyclonal $CD8^+$ T-cells reactive against a neoepitope restricted through HLA-C*08:02 derived from the KRAS mutation p.G12D in TIL from a patient with colorectal cancer, which was expanded and transferred back into the patient, resulting in tumour regression [86]. In this patient, a metastatic deposit stopped responding and upon analysis, the mechanism of resistance was identified as the loss of the HLA-C*08:02 allele [86]. Another example was the screening of TIL from lung metastasis in a patient with cholangiocarcinoma, using a mini-gene construct that encoded each of the 26 non-synonymous tumour specific mutations, which identified reactivity to a p.E805G mutation in ERBB2IP, restricted through HLA-DQB1*06:01 and recognised by $CD4^+$ T_{H1} cells. Following expansion of these cells, adoptive transfer in the presence of IL-2 resulted in a halt of tumour progression and disease stabilisation. A lung metastasis stopped responding and the process was repeated with TIL from the progressing tumour, focusing on polyfunctional (IFNγ, TNF-α and IL-2 producing) neoepitope reactive cells, which again resulted in tumour regression and stabilisation [62].

The identification of autologous reactive T-cells is not always possible using the currently available methods. Therefore, research has also investigated the possibility of using donor T-cells that recognise patient specific neoepitopes for adoptive T-cell transfer. A feasibility study found reactivity to 11 predicted neoepitopes from two HLA-A*02:01 stage IV melanoma in donor blood cells, using monocyte derived dendritic cells transfected with candidate epitopes in a mini-gene, followed by analysis with pMHC multimers. Results from a third melanoma patient did not yield any reactive cells from donor blood for the chosen predicted neoepitopes [67]. These results therefore indicate there is scope to use non-autologous T-cells for targeting individual neoantigens in future therapies for some patients.

2.3 Other potential avenues for immunotherapeutic treatments with neoantigens

Other possible approaches to target cancer antigens either attempt to reinvigorate an identifiable existing but supressed immune response, or try to initiate naïve reactivities to potentially displayed neoepitope(s). These include therapeutic vaccination with recombinant viral vectors encoding tumour specific antigen (e.g. as reviewed in [106]), vaccination with recombinant proteins/peptides, with adjuvants (e.g. [107] and as reviewed in [108, 109]), dendritic cell vaccines, primed with specific antigens (e.g. [42] and as reviewed in [110]) and RNA based poly-epitope vaccines [111]. While these approaches have been significantly explored for CT and over-expression antigens, there still remains

significant scope to explore these options targeting neoantigens. A major lesson from these previous trials is that these approaches are generally well tolerated, providing scope for combinations of treatments to attempt to overcome resistance mechanisms. A search of currently registered clinical trials revealed a significant number (at the time of writing n=~40) that include a neoantigen component. This includes the combination of personalised neoepitope DNA vaccine with anti-PD-1 checkpoint inhibition (e.g. NCT03199040, triple negative breast cancer; NCT02950766, renal cell carcinoma), dendritic cell vaccine raised against defined neoepitopes (e.g. NCT03300843, melanoma, gastrointestinal, breast, ovarian and pancreatic cancers) and adjuvant personalised neoantigen peptide vaccine, with the immunostimulant poly-ICLC (e.g. NCT02510950, glioblastoma and astrocytoma and NCT01970358, melanoma). The immunotherapy field has been moving rapidly in recent years and these clinical trials will continue pushing the field forwards.

3 Challenges and future opportunities

There are several important challenges to overcome and key basic immunological questions that require answering before neoantigens are exploited to their full potential. One of the obstacles is the 'personalised' nature of the therapy, which requires each tumour to be sequenced and results analysed for each individuals HLA genotypes; the therapy of choice is then manufactured specifically for each patient. Work is being carried out to automate this process further, however, with patients urgently awaiting treatment upon diagnosis, the time to perform analysis and manufacture compared to 'off the shelf' options are still of considerable consideration. Tumour heterogeneity is also an important factor to overcome. As previously reviewed [18], immunotherapy targeting multiple antigens have a higher objective response rate than those focused on a single epitope. When a single target is the focus of a therapy, resistance is also more likely, an example of which was previously discussed, where the restricting HLA-C allele of the epitope target was selectively deleted in a metastatic deposit [86].

In order to fully exploit neoepitopes, a better understanding is required of: a) the reason why certain sequences are more likely to be processed and displayed on MHC-class I or MHC-class II molecules and b) what factors control mutated proteins are processed and shuttled to the lymph nodes for interrogation by antigen presenting cells stimulate $CD8^+$ and/or $CD4^+$ T-cells. The increased identification of immunoreactive neoantigens and the characterisation of the tumour context in which they occur will begin to address these fundamental questions. Additionally, the binding prediction algorithms for MHC-class II are still considered to be relatively imprecise, which given the success of recent clinical studies specifically targeting the neoantigen specific $CD4^+$ immune response in patients [43, 62, 71, 102], is a significant area requiring improvement.

Finally, mechanisms of resistance to immunotherapies include loss of MHC alleles from the gene cluster on chromosome 6, loss of expression of HLA support molecules (such as β_2-microglobulin and CIITA), loss of expression of the antigen target(s) and a hostile tumour microenvironment (the recent review by Sharma et al [112] explores these mechanisms in detail). In order for immunotherapies to produce a durable complete response, it is important that the molecular mechanisms driving resistance methods are characterised, to identify strategies that prevent or circumnavigate them. It is highly likely that future treatment regimens will involve combination of therapy types and further research into synergistic drug combinations is a current research priority.

4 Concluding remarks

The immunotherapy field is currently undergoing a significant resurgence in popularity due to the identification of antibodies that can target the immune checkpoint markers PD-1 and CTLA4 on T_{reg} cells and PD-L1 on cancer cells. The blocking of suppressive immune cells allows a reinvigorated anti-cancer immune response, which seems to be largely targeting neoepitopes. This classification of antigen can be independently predicted and confirmed, allowing a combination of immunotherapeutic approaches to be trialled in order to improve survival time and overall durability of the response. While there are still many avenues to explore in this field, the pace at which research is being performed and translated into clinical trials is remarkable and are leading to ever improving outcomes for patients.

Acknowledgements

This review brings together a large amount of work in a rapidly developing area in order to provide an overall picture of the current state of the field. As a result, there are recommendations throughout to review papers that focus in on a specific area, which will provide further details on those topics. I apologise to colleagues who may feel their work is inadequately cited, or that further details should have been provided, but for space and clarity this review could only use selected specific examples.

Compliance with Ethical Standards

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References

1. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nature reviews Cancer. 2008;8(6):473-80. Epub 2008/05/13. doi: 10.1038/nrc2394. PubMed PMID: 18469827.
2. Decker WK, da Silva RF, Sanabria MH, Angelo LS, Guimaraes F, Burt BM, et al. Cancer Immunotherapy: Historical Perspective of a Clinical Revolution and Emerging Preclinical Animal Models. Front Immunol. 2017;8:829. Epub 2017/08/22. doi: 10.3389/fimmu.2017.00829. PubMed PMID: 28824608; PubMed Central PMCID: PMCPMC5539135.
3. Kirkwood JM, Butterfield LH, Tarhini AA, Zarour H, Kalinski P, Ferrone S. Immunotherapy of cancer in 2012. CA Cancer J Clin. 2012;62(5):309-35. Epub 2012/05/12. doi: 10.3322/caac.20132. PubMed PMID: 22576456; PubMed Central PMCID: PMCPMC3445708.
4. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol. 2011;29:235-71. doi: 10.1146/annurev-immunol-031210-101324. PubMed PMID: 21219185.
5. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565-70. doi: 10.1126/science.1203486. PubMed PMID: 21436444.
6. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014;27:16-25. Epub 2014/02/18. doi: 10.1016/j.coi.2014.01.004. PubMed PMID: 24531241; PubMed Central PMCID: PMCPMC4388310.
7. Yuen GJ, Demissie E, Pillai S. B lymphocytes and cancer: a love-hate relationship. Trends in cancer. 2016;2(12):747-57. doi: 10.1016/j.trecan.2016.10.010. PubMed PMID: 28626801; PubMed Central PMCID: PMC5472356.
8. Ellsworth RE, Ellsworth DL, Patney HL, Deyarmin B, Love B, Hooke JA, et al. Amplification of HER2 is a marker for global genomic instability. BMC cancer. 2008;8:297. doi: 10.1186/1471-2407-8-297. PubMed PMID: 18854030; PubMed Central PMCID: PMC2571108.
9. Wang K, Wei G, Liu D. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Experimental hematology & oncology. 2012;1(1):36. doi: 10.1186/2162-3619-1-36. PubMed PMID: 23210908; PubMed Central PMCID: PMC3520838.
10. Brichard V, Van Pel A, Wolfel T, Wolfel C, De Plaen E, Lethe B, et al. The tyrosinase gene codes for an antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. The Journal of experimental medicine. 1993;178(2):489-95. PubMed PMID: 8340755; PubMed Central PMCID: PMC2191123.
11. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nature reviews Cancer. 2005;5(8):615-25. doi: 10.1038/nrc1669. PubMed PMID: 16034368.
12. Chomez P, De Backer O, Bertrand M, De Plaen E, Boon T, Lucas S. An overview of the MAGE gene family with the identification of all human members of the family. Cancer research. 2001;61(14):5544-51. PubMed PMID: 11454705.
13. Gnjatic S, Nishikawa H, Jungbluth AA, Gure AO, Ritter G, Jager E, et al. NY-ESO-1: review of an immunogenic tumor antigen. Advances in cancer research. 2006;95:1-30. doi: 10.1016/S0065-230X(06)95001-5. PubMed PMID: 16860654.
14. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of pathology. 1999;189(1):12-9. doi: 10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F. PubMed PMID: 10451482.
15. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. Journal of the National Cancer Institute. 2000;92(9):709-20. PubMed PMID: 10793107.

16. De Plaen E, Lurquin C, Van Pel A, Mariame B, Szikora JP, Wolfel T, et al. Immunogenic (tum-) variants of mouse tumor P815: cloning of the gene of tum- antigen P91A and identification of the tum- mutation. Proc Natl Acad Sci U S A. 1988;85(7):2274-8. Epub 1988/04/01. PubMed PMID: 3127830; PubMed Central PMCID: PMCPMC279973.
17. Monach PA, Meredith SC, Siegel CT, Schreiber H. A unique tumor antigen produced by a single amino acid substitution. Immunity. 1995;2(1):45-59. Epub 1995/01/01. PubMed PMID: 7600302.
18. Neller MA, Lopez JA, Schmidt CW. Antigens for cancer immunotherapy. Semin Immunol. 2008;20(5):286-95. Epub 2008/10/28. doi: 10.1016/j.smim.2008.09.006. PubMed PMID: 18951039.
19. Lennerz V, Fatho M, Gentilini C, Frye RA, Lifke A, Ferel D, et al. The response of autologous T cells to a human melanoma is dominated by mutated neoantigens. Proc Natl Acad Sci U S A. 2005;102(44):16013-8. doi: 10.1073/pnas.0500090102. PubMed PMID: 16247014; PubMed Central PMCID: PMC1266037.
20. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, et al. The consensus coding sequences of human breast and colorectal cancers. Science. 2006;314(5797):268-74. Epub 2006/09/09. doi: 10.1126/science.1133427. PubMed PMID: 16959974.
21. Segal NH, Parsons DW, Peggs KS, Velculescu V, Kinzler KW, Vogelstein B, et al. Epitope landscape in breast and colorectal cancer. Cancer Res. 2008;68(3):889-92. Epub 2008/02/05. doi: 10.1158/0008-5472.CAN-07-3095. PubMed PMID: 18245491.
22. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. Nat Rev Genet. 2016;17(6):333-51. Epub 2016/05/18. doi: 10.1038/nrg.2016.49. PubMed PMID: 27184599.
23. Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. Annual review of immunology. 2013;31:443-73. doi: 10.1146/annurev-immunol-032712-095910. PubMed PMID: 23298205; PubMed Central PMCID: PMC4026165.
24. Wucherpfennig KW, Gagnon E, Call MJ, Huseby ES, Call ME. Structural biology of the T-cell receptor: insights into receptor assembly, ligand recognition, and initiation of signaling. Cold Spring Harbor perspectives in biology. 2010;2(4):a005140. doi: 10.1101/cshperspect.a005140. PubMed PMID: 20452950; PubMed Central PMCID: PMC2845206.
25. Uebel S, Tampe R. Specificity of the proteasome and the TAP transporter. Curr Opin Immunol. 1999;11(2):203-8. Epub 1999/05/14. PubMed PMID: 10322157.
26. Lehnert E, Tampe R. Structure and Dynamics of Antigenic Peptides in Complex with TAP. Front Immunol. 2017;8:10. Epub 2017/02/15. doi: 10.3389/fimmu.2017.00010. PubMed PMID: 28194151; PubMed Central PMCID: PMCPMC5277011.
27. Aleksic M, Liddy N, Molloy PE, Pumphrey N, Vuidepot A, Chang KM, et al. Different affinity windows for virus and cancer-specific T-cell receptors: implications for therapeutic strategies. European journal of immunology. 2012;42(12):3174-9. Epub 2012/09/06. doi: 10.1002/eji.201242606. PubMed PMID: 22949370; PubMed Central PMCID: PMCPMC3776049.
28. Tan MP, Gerry AB, Brewer JE, Melchiori L, Bridgeman JS, Bennett AD, et al. T cell receptor binding affinity governs the functional profile of cancer-specific CD8+ T cells. Clin Exp Immunol. 2015;180(2):255-70. Epub 2014/12/17. doi: 10.1111/cei.12570. PubMed PMID: 25496365; PubMed Central PMCID: PMCPMC4408161.
29. Pritchard AL, Burel JG, Neller MA, Hayward NK, Lopez JA, Fatho M, et al. Exome Sequencing to Predict Neoantigens in Melanoma. Cancer immunology research. 2015;3(9):992-8. doi: 10.1158/2326-6066.CIR-15-0088. PubMed PMID: 26048577.
30. Lupetti R, Pisarra P, Verrecchia A, Farina C, Nicolini G, Anichini A, et al. Translation of a retained intron in tyrosinase-related protein (TRP) 2 mRNA generates a new cytotoxic T lymphocyte (CTL)-defined and shared human melanoma antigen not expressed in normal cells of the melanocytic lineage. J Exp Med. 1998;188(6):1005-16. PubMed PMID: 9743519; PubMed Central PMCID: PMC2212536.
31. Skipper JC, Hendrickson RC, Gulden PH, Brichard V, Van Pel A, Chen Y, et al. An HLA-A2-restricted tyrosinase antigen on melanoma cells results from posttranslational modification and

suggests a novel pathway for processing of membrane proteins. J Exp Med. 1996;183(2):527-34. PubMed PMID: 8627164; PubMed Central PMCID: PMC2192446.
32. Chang TC, Carter RA, Li Y, Li Y, Wang H, Edmonson MN, et al. The neoepitope landscape in pediatric cancers. Genome medicine. 2017;9(1):78. doi: 10.1186/s13073-017-0468-3. PubMed PMID: 28854978; PubMed Central PMCID: PMC5577668.
33. Linnebacher M, Gebert J, Rudy W, Woerner S, Yuan YP, Bork P, et al. Frameshift peptide-derived T-cell epitopes: a source of novel tumor-specific antigens. Int J Cancer. 2001;93(1):6-11. Epub 2001/06/08. doi: 10.1002/ijc.1298 [pii]. PubMed PMID: 11391614.
34. Pritchard AL, Hastie ML, Neller M, Gorman JJ, Schmidt CW, Hayward NK. Exploration of peptides bound to MHC class I molecules in melanoma. Pigment Cell Melanoma Res. 2015;28(3):281-94. doi: 10.1111/pcmr.12357. PubMed PMID: 25645385.
35. Bassani-Sternberg M, Braunlein E, Klar R, Engleitner T, Sinitcyn P, Audehm S, et al. Direct identification of clinically relevant neoepitopes presented on native human melanoma tissue by mass spectrometry. Nature communications. 2016;7:13404. doi: 10.1038/ncomms13404. PubMed PMID: 27869121; PubMed Central PMCID: PMC5121339.
36. Abelin JG, Keskin DB, Sarkizova S, Hartigan CR, Zhang W, Sidney J, et al. Mass Spectrometry Profiling of HLA-Associated Peptidomes in Mono-allelic Cells Enables More Accurate Epitope Prediction. Immunity. 2017;46(2):315-26. doi: 10.1016/j.immuni.2017.02.007. PubMed PMID: 28228285; PubMed Central PMCID: PMC5405381.
37. Gloger A, Ritz D, Fugmann T, Neri D. Mass spectrometric analysis of the HLA class I peptidome of melanoma cell lines as a promising tool for the identification of putative tumor-associated HLA epitopes. Cancer immunology, immunotherapy : CII. 2016;65(11):1377-93. doi: 10.1007/s00262-016-1897-3. PubMed PMID: 27600516; PubMed Central PMCID: PMC5509013.
38. Jarmalavicius S, Welte Y, Walden P. High immunogenicity of the human leukocyte antigen peptidomes of melanoma tumor cells. J Biol Chem. 2012;287(40):33401-11. doi: 10.1074/jbc.M112.358903. PubMed PMID: 22869377; PubMed Central PMCID: PMC3460442.
39. Yadav M, Jhunjhunwala S, Phung QT, Lupardus P, Tanguay J, Bumbaca S, et al. Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. Nature. 2014;515(7528):572-6. doi: 10.1038/nature14001. PubMed PMID: 25428506.
40. Hogan KT, Eisinger DP, Cupp SB, 3rd, Lekstrom KJ, Deacon DD, Shabanowitz J, et al. The peptide recognized by HLA-A68.2-restricted, squamous cell carcinoma of the lung-specific cytotoxic T lymphocytes is derived from a mutated elongation factor 2 gene. Cancer Res. 1998;58(22):5144-50. Epub 1998/11/21. PubMed PMID: 9823325.
41. Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature. 2014;515(7528):577-81. Epub 2014/11/28. doi: 10.1038/nature13988. PubMed PMID: 25428507; PubMed Central PMCID: PMCPMC4279952.
42. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348(6236):803-8. Epub 2015/04/04. doi: 10.1126/science.aaa3828. PubMed PMID: 25837513; PubMed Central PMCID: PMCPMC4549796.
43. Sharkey MS, Lizee G, Gonzales MI, Patel S, Topalian SL. CD4(+) T-cell recognition of mutated B-RAF in melanoma patients harboring the V599E mutation. Cancer research. 2004;64(5):1595-9. PubMed PMID: 14996715.
44. Somasundaram R, Swoboda R, Caputo L, Otvos L, Weber B, Volpe P, et al. Human leukocyte antigen-A2-restricted CTL responses to mutated BRAF peptides in melanoma patients. Cancer research. 2006;66(6):3287-93. doi: 10.1158/0008-5472.CAN-05-1932. PubMed PMID: 16540682.
45. Bergmann-Leitner ES, Kantor JA, Shupert WL, Schlom J, Abrams SI. Identification of a human CD8+ T lymphocyte neo-epitope created by a ras codon 12 mutation which is restricted by the HLA-A2 allele. Cellular immunology. 1998;187(2):103-16. doi: 10.1006/cimm.1998.1325. PubMed PMID: 9732698.

46. Shono Y, Tanimura H, Iwahashi M, Tsunoda T, Tani M, Tanaka H, et al. Specific T-cell immunity against Ki-ras peptides in patients with pancreatic and colorectal cancers. British journal of cancer. 2003;88(4):530-6. doi: 10.1038/sj.bjc.6600697. PubMed PMID: 12592366; PubMed Central PMCID: PMC2377177.
47. Ichiki Y, Takenoyama M, Mizukami M, So T, Sugaya M, Yasuda M, et al. Simultaneous cellular and humoral immune response against mutated p53 in a patient with lung cancer. Journal of immunology. 2004;172(8):4844-50. PubMed PMID: 15067062.
48. Linard B, Bezieau S, Benlalam H, Labarriere N, Guilloux Y, Diez E, et al. A ras-mutated peptide targeted by CTL infiltrating a human melanoma lesion. Journal of immunology. 2002;168(9):4802-8. PubMed PMID: 11971032.
49. Karasaki T, Nagayama K, Kuwano H, Nitadori JI, Sato M, Anraku M, et al. Prediction and prioritization of neoantigens: integration of RNA sequencing data with whole-exome sequencing. Cancer science. 2017;108(2):170-7. doi: 10.1111/cas.13131. PubMed PMID: 27960040; PubMed Central PMCID: PMC5329159.
50. van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol. 2013;31(32):e439-42. doi: 10.1200/JCO.2012.47.7521. PubMed PMID: 24043743; PubMed Central PMCID: PMC3836220.
51. Schuler MM, Nastke MD, Stevanovikc S. SYFPEITHI: database for searching and T-cell epitope prediction. Methods in molecular biology. 2007;409:75-93. PubMed PMID: 18449993.
52. Reche PA, Glutting JP, Reinherz EL. Prediction of MHC class I binding peptides using profile motifs. Human immunology. 2002;63(9):701-9. PubMed PMID: 12175724.
53. Jurtz V, Paul S, Andreatta M, Marcatili P, Peters B, Nielsen M. NetMHCpan-4.0: Improved Peptide-MHC Class I Interaction Predictions Integrating Eluted Ligand and Peptide Binding Affinity Data. Journal of immunology. 2017;199(9):3360-8. doi: 10.4049/jimmunol.1700893. PubMed PMID: 28978689.
54. Karosiene E, Lundegaard C, Lund O, Nielsen M. NetMHCcons: a consensus method for the major histocompatibility complex class I predictions. Immunogenetics. 2012;64(3):177-86. doi: 10.1007/s00251-011-0579-8. PubMed PMID: 22009319.
55. Zhang H, Lund O, Nielsen M. The PickPocket method for predicting binding specificities for receptors based on receptor pocket similarities: application to MHC-peptide binding. Bioinformatics. 2009;25(10):1293-9. doi: 10.1093/bioinformatics/btp137. PubMed PMID: 19297351; PubMed Central PMCID: PMC2732311.
56. Singh SP, Mishra BN. Prediction of MHC binding peptide using Gibbs motif sampler, weight matrix and artificial neural network. Bioinformation. 2008;3(4):150-5. PubMed PMID: 19238237; PubMed Central PMCID: PMC2639663.
57. Peters B, Sette A. Generating quantitative models describing the sequence specificity of biological processes with the stabilized matrix method. BMC bioinformatics. 2005;6:132. doi: 10.1186/1471-2105-6-132. PubMed PMID: 15927070; PubMed Central PMCID: PMC1173087.
58. Hundal J, Carreno BM, Petti AA, Linette GP, Griffith OL, Mardis ER, et al. pVAC-Seq: A genome-guided in silico approach to identifying tumor neoantigens. Genome Med. 2016;8(1):11. Epub 2016/01/31. doi: 10.1186/s13073-016-0264-5. PubMed PMID: 26825632; PubMed Central PMCID: PMCPMC4733280.
59. Tappeiner E, Finotello F, Charoentong P, Mayer C, Rieder D, Trajanoski Z. TIminer: NGS data mining pipeline for cancer immunology and immunotherapy. Bioinformatics. 2017;33(19):3140-1. Epub 2017/06/22. doi: 10.1093/bioinformatics/btx377. PubMed PMID: 28633385.
60. Bais P, Namburi S, Gatti DM, Zhang X, Chuang JH. CloudNeo: a cloud pipeline for identifying patient-specific tumor neoantigens. Bioinformatics. 2017;33(19):3110-2. Epub 2017/06/13. doi: 10.1093/bioinformatics/btx375. PubMed PMID: 28605406.

61. Bjerregaard AM, Nielsen M, Hadrup SR, Szallasi Z, Eklund AC. MuPeXI: prediction of neo-epitopes from tumor sequencing data. Cancer Immunol Immunother. 2017;66(9):1123-30. Epub 2017/04/22. doi: 10.1007/s00262-017-2001-3. PubMed PMID: 28429069.
62. Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science. 2014;344(6184):641-5. doi: 10.1126/science.1251102. PubMed PMID: 24812403.
63. Lu YC, Yao X, Crystal JS, Li YF, El-Gamil M, Gross C, et al. Efficient identification of mutated cancer antigens recognized by T cells associated with durable tumor regressions. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014;20(13):3401-10. doi: 10.1158/1078-0432.CCR-14-0433. PubMed PMID: 24987109; PubMed Central PMCID: PMC4083471.
64. Tran E, Ahmadzadeh M, Lu YC, Gros A, Turcotte S, Robbins PF, et al. Immunogenicity of somatic mutations in human gastrointestinal cancers. Science. 2015;350(6266):1387-90. doi: 10.1126/science.aad1253. PubMed PMID: 26516200.
65. Mennonna D, Maccalli C, Romano MC, Garavaglia C, Capocefalo F, Bordoni R, et al. T cell neoepitope discovery in colorectal cancer by high throughput profiling of somatic mutations in expressed genes. Gut. 2017;66(3):454-63. doi: 10.1136/gutjnl-2015-309453. PubMed PMID: 26681737; PubMed Central PMCID: PMC5534766.
66. Gros A, Parkhurst MR, Tran E, Pasetto A, Robbins PF, Ilyas S, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22(4):433-8. doi: 10.1038/nm.4051. PubMed PMID: 26901407.
67. Stronen E, Toebes M, Kelderman S, van Buuren MM, Yang W, van Rooij N, et al. Targeting of cancer neoantigens with donor-derived T cell receptor repertoires. Science. 2016;352(6291):1337-41. doi: 10.1126/science.aaf2288. PubMed PMID: 27198675.
68. Cohen CJ, Gartner JJ, Horovitz-Fried M, Shamalov K, Trebska-McGowan K, Bliskovsky VV, et al. Isolation of neoantigen-specific T cells from tumor and peripheral lymphocytes. J Clin Invest. 2015;125(10):3981-91. doi: 10.1172/JCI82416. PubMed PMID: 26389673; PubMed Central PMCID: PMCPMC4607110.
69. Rajasagi M, Shukla SA, Fritsch EF, Keskin DB, DeLuca D, Carmona E, et al. Systematic identification of personal tumor-specific neoantigens in chronic lymphocytic leukemia. Blood. 2014;124(3):453-62. doi: 10.1182/blood-2014-04-567933. PubMed PMID: 24891321; PubMed Central PMCID: PMC4102716.
70. Sun Z, Chen F, Meng F, Wei J, Liu B. MHC class II restricted neoantigen: A promising target in tumor immunotherapy. Cancer Lett. 2017;392:17-25. Epub 2017/01/21. doi: 10.1016/j.canlet.2016.12.039. PubMed PMID: 28104443.
71. Linnemann C, van Buuren MM, Bies L, Verdegaal EM, Schotte R, Calis JJ, et al. High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4+ T cells in human melanoma. Nat Med. 2015;21(1):81-5. doi: 10.1038/nm.3773. PubMed PMID: 25531942.
72. Pieper R, Christian RE, Gonzales MI, Nishimura MI, Gupta G, Settlage RE, et al. Biochemical identification of a mutated human melanoma antigen recognized by CD4(+) T cells. J Exp Med. 1999;189(5):757-66. Epub 1999/03/02. PubMed PMID: 10049939; PubMed Central PMCID: PMCPMC2192954.
73. Wang RF, Wang X, Atwood AC, Topalian SL, Rosenberg SA. Cloning genes encoding MHC class II-restricted antigens: mutated CDC27 as a tumor antigen. Science. 1999;284(5418):1351-4. Epub 1999/05/21. PubMed PMID: 10334988.
74. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124-8. doi: 10.1126/science.aaa1348. PubMed PMID: 25765070; PubMed Central PMCID: PMC4993154.

75. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014;371(23):2189-99. doi: 10.1056/NEJMoa1406498. PubMed PMID: 25409260; PubMed Central PMCID: PMC4315319.
76. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015;350(6257):207-11. doi: 10.1126/science.aad0095. PubMed PMID: 26359337; PubMed Central PMCID: PMC5054517.
77. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016;351(6280):1463-9. doi: 10.1126/science.aaf1490. PubMed PMID: 26940869; PubMed Central PMCID: PMC4984254.
78. Ock CY, Hwang JE, Keam B, Kim SB, Shim JJ, Jang HJ, et al. Genomic landscape associated with potential response to anti-CTLA-4 treatment in cancers. Nature communications. 2017;8(1):1050. doi: 10.1038/s41467-017-01018-0. PubMed PMID: 29051489; PubMed Central PMCID: PMC5648801.
79. Robbins PF, Lu YC, El-Gamil M, Li YF, Gross C, Gartner J, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med. 2013;19(6):747-52. doi: 10.1038/nm.3161. PubMed PMID: 23644516; PubMed Central PMCID: PMC3757932.
80. Brown SD, Warren RL, Gibb EA, Martin SD, Spinelli JJ, Nelson BH, et al. Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival. Genome Res. 2014;24(5):743-50. doi: 10.1101/gr.165985.113. PubMed PMID: 24782321; PubMed Central PMCID: PMC4009604.
81. Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012;482(7385):400-4. doi: 10.1038/nature10755. PubMed PMID: 22318521; PubMed Central PMCID: PMC3874809.
82. Hodges TR, Ott M, Xiu J, Gatalica Z, Swensen J, Zhou S, et al. Mutational burden, immune checkpoint expression, and mismatch repair in glioma: implications for immune checkpoint immunotherapy. Neuro-oncology. 2017;19(8):1047-57. doi: 10.1093/neuonc/nox026. PubMed PMID: 28371827; PubMed Central PMCID: PMC5570198.
83. Balachandran VP, Luksza M, Zhao JN, Makarov V, Moral JA, Remark R, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017;551(7681):512-6. Epub 2017/11/14. doi: 10.1038/nature24462. PubMed PMID: 29132146.
84. O'Rourke MG, Johnson M, Lanagan C, See J, Yang J, Bell JR, et al. Durable complete clinical responses in a phase I/II trial using an autologous melanoma cell/dendritic cell vaccine. Cancer Immunol Immunother. 2003;52(6):387-95. Epub 2003/04/19. doi: 10.1007/s00262-003-0375-x. PubMed PMID: 12682787.
85. O'Rourke MG, Johnson MK, Lanagan CM, See JL, O'Connor LE, Slater GJ, et al. Dendritic cell immunotherapy for stage IV melanoma. Melanoma Res. 2007;17(5):316-22. Epub 2007/09/22. doi: 10.1097/CMR.0b013e3282c3a73b. PubMed PMID: 17885587.
86. Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, et al. T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer. The New England journal of medicine. 2016;375(23):2255-62. doi: 10.1056/NEJMoa1609279. PubMed PMID: 27959684; PubMed Central PMCID: PMC5178827.
87. Verdegaal EM, de Miranda NF, Visser M, Harryvan T, van Buuren MM, Andersen RS, et al. Neoantigen landscape dynamics during human melanoma-T cell interactions. Nature. 2016;536(7614):91-5. Epub 2016/06/29. doi: 10.1038/nature18945. PubMed PMID: 27350335.
88. Luksza M, Riaz N, Makarov V, Balachandran VP, Hellmann MD, Solovyov A, et al. A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy. Nature. 2017;551(7681):517-20. Epub 2017/11/14. doi: 10.1038/nature24473. PubMed PMID: 29132144.
89. Lauss M, Donia M, Harbst K, Andersen R, Mitra S, Rosengren F, et al. Mutational and putative neoantigen load predict clinical benefit of adoptive T cell therapy in melanoma. Nat Commun.

2017;8(1):1738. Epub 2017/11/25. doi: 10.1038/s41467-017-01460-0. PubMed PMID: 29170503; PubMed Central PMCID: PMCPMC5701046.
90. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. The New England journal of medicine. 2011;365(8):725-33. doi: 10.1056/NEJMoa1103849. PubMed PMID: 21830940; PubMed Central PMCID: PMC3387277.
91. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. The New England journal of medicine. 2013;368(16):1509-18. doi: 10.1056/NEJMoa1215134. PubMed PMID: 23527958; PubMed Central PMCID: PMC4058440.
92. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England journal of medicine. 2014;371(16):1507-17. doi: 10.1056/NEJMoa1407222. PubMed PMID: 25317870; PubMed Central PMCID: PMC4267531.
93. Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Molecular therapy : the journal of the American Society of Gene Therapy. 2010;18(4):843-51. doi: 10.1038/mt.2010.24. PubMed PMID: 20179677; PubMed Central PMCID: PMC2862534.
94. Morgan RA, Chinnasamy N, Abate-Daga D, Gros A, Robbins PF, Zheng Z, et al. Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. Journal of immunotherapy. 2013;36(2):133-51. doi: 10.1097/CJI.0b013e3182829903. PubMed PMID: 23377668; PubMed Central PMCID: PMC3581823.
95. Chu CT, Everiss KD, Wikstrand CJ, Batra SK, Kung HJ, Bigner DD. Receptor dimerization is not a factor in the signalling activity of a transforming variant epidermal growth factor receptor (EGFRvIII). The Biochemical journal. 1997;324 (Pt 3):855-61. PubMed PMID: 9210410; PubMed Central PMCID: PMC1218502.
96. Wong AJ, Ruppert JM, Bigner SH, Grzeschik CH, Humphrey PA, Bigner DS, et al. Structural alterations of the epidermal growth factor receptor gene in human gliomas. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(7):2965-9. PubMed PMID: 1557402; PubMed Central PMCID: PMC48784.
97. Sok JC, Coppelli FM, Thomas SM, Lango MN, Xi S, Hunt JL, et al. Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. Clinical cancer research : an official journal of the American Association for Cancer Research. 2006;12(17):5064-73. doi: 10.1158/1078-0432.CCR-06-0913. PubMed PMID: 16951222.
98. Morgan RA, Johnson LA, Davis JL, Zheng Z, Woolard KD, Reap EA, et al. Recognition of glioma stem cells by genetically modified T cells targeting EGFRvIII and development of adoptive cell therapy for glioma. Human gene therapy. 2012;23(10):1043-53. doi: 10.1089/hum.2012.041. PubMed PMID: 22780919; PubMed Central PMCID: PMC3472555.
99. Bethune MT, Joglekar AV. Personalized T cell-mediated cancer immunotherapy: progress and challenges. Curr Opin Biotechnol. 2017;48:142-52. Epub 2017/05/12. doi: 10.1016/j.copbio.2017.03.024. PubMed PMID: 28494274.
100. Lim WA, June CH. The Principles of Engineering Immune Cells to Treat Cancer. Cell. 2017;168(4):724-40. Epub 2017/02/12. doi: 10.1016/j.cell.2017.01.016. PubMed PMID: 28187291; PubMed Central PMCID: PMCPMC5553442.
101. Burrows SR, Miles JJ. Immune parameters to consider when choosing T-cell receptors for therapy. Front Immunol. 2013;4:229. Epub 2013/08/13. doi: 10.3389/fimmu.2013.00229. PubMed PMID: 23935599; PubMed Central PMCID: PMCPMC3733007.
102. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. The New England journal of medicine. 2008;358(25):2698-703. doi: 10.1056/NEJMoa0800251. PubMed PMID: 18565862; PubMed Central PMCID: PMC3277288.

103. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2011;17(13):4550-7. doi: 10.1158/1078-0432.CCR-11-0116. PubMed PMID: 21498393; PubMed Central PMCID: PMC3131487.
104. Dudley ME, Wunderlich JR, Robbins PF, Yang JC, Hwu P, Schwartzentruber DJ, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science. 2002;298(5594):850-4. doi: 10.1126/science.1076514. PubMed PMID: 12242449; PubMed Central PMCID: PMCPMC1764179.
105. Dudley ME, Yang JC, Sherry R, Hughes MS, Royal R, Kammula U, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol. 2008;26(32):5233-9. doi: 10.1200/JCO.2008.16.5449. PubMed PMID: 18809613; PubMed Central PMCID: PMC2652090.
106. Harrop R, John J, Carroll MW. Recombinant viral vectors: cancer vaccines. Advanced drug delivery reviews. 2006;58(8):931-47. doi: 10.1016/j.addr.2006.05.005. PubMed PMID: 17030074.
107. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217-21. Epub 2017/07/06. doi: 10.1038/nature22991. PubMed PMID: 28678778; PubMed Central PMCID: PMCPMC5577644.
108. Tsukahara T, Hirohashi Y, Kanaseki T, Nakatsugawa M, Kubo T, Sato N, et al. Peptide vaccination therapy: Towards the next generation. Pathology international. 2016;66(10):547-53. doi: 10.1111/pin.12438. PubMed PMID: 27435148.
109. Hirayama M, Nishimura Y. The present status and future prospects of peptide-based cancer vaccines. International immunology. 2016;28(7):319-28. doi: 10.1093/intimm/dxw027. PubMed PMID: 27235694.
110. Tacken PJ, de Vries IJ, Torensma R, Figdor CG. Dendritic-cell immunotherapy: from ex vivo loading to in vivo targeting. Nat Rev Immunol. 2007;7(10):790-802. Epub 2007/09/15. doi: nri2173 [pii]10.1038/nri2173. PubMed PMID: 17853902.
111. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Lower M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222-6. doi: 10.1038/nature23003. PubMed PMID: 28678784.
112. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017;168(4):707-23. doi: 10.1016/j.cell.2017.01.017. PubMed PMID: 28187290; PubMed Central PMCID: PMC5391692.