Current status of cancer immunotherapy

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To prove clinical benefits of cancer vaccine is currently difficult, except for one phase III trial has documented improved overall survival with the vaccine, Sipuleucel-T, although induction of anti-tumor immune responses through cancer vaccine is theoretically promising and would be straightforward. In contrast, immune checkpoint blockade with anti-CTLA4 mAb and anti-PD-1 mAb has demonstrated clear evidence of objective responses including improved overall survival and tumor shrinkage, driving renewed enthusiasm for cancer immunotherapy in multiple cancer types. In addition, there is a promising novel cancer immunotherapy, CAR therapy—a personalized treatment that involves genetically modifying a patient's T- cells to make them target tumor cells. We are now facing new era of cancer immunotherapy.

Introduction

Recent approval of Sipuluecel-T, which is a cancer vaccine with an activated antigen presenting cells (APCs) and lymphocyte mixture for hormone refractory prostate cáncer, paved the way to antigen-specific cancer immunotherapy [1]. Moreover, immune checkpoint blockade with therapeutic mAbs such as anti-CTLA4 mAb and anti-PD1 mAb for melanoma implicate a new era of the immunotherapy in the anti-cancer strategy [2,3]. Due to recent advanced technologies in molecular and cellular immunology, it has been reported that several immunogenic tumor-antigens expressed by tumor cells are identified and the characterization of tumor-specific cytotoxic T lymphocytes (CTLs) in cancer patients was successfully performed [4,5]. These observations have attracted the interest of researchers and clinicians in the use of vaccines as one of anti-tumor interventions. Moreover, modern engineering technologies enabled to generate mAbs specific for certain target molecules, and recent breakthrough results from mAbs therapy inhibiting immune checkpoints such a CTLA4 and PD-1 could pave the way to a new field of cancer immunotherapy. In this review, recent advances in cancer immunotherapy are discussed with particular focus on cancer vaccine and immune checkpoint blockade.

Cancer vaccine

A number of investigations have generated in-depth insights into the molecular and cellular mechanisms relating to anti-cancer immune responses. Identification of immunogenic tumor-antigens and the characterization of tumor-specific CTLs in cancer patients[4,5] could attract an enormous interest in translational research, which leads to several clinical trials of cancer vaccine. Recently, a panel of preparations for cancer vaccine has been tested for their ability to elicit tumor-specific immune responses and induce anti-tumor effects *in vivo*. There are a number of possibilities of cancer vaccine preparations[6-9]; (1) synthetic tumor-associate antigens (TAAs), in the form of either short peptides or full-length proteins, which are expected to bind MHC molecules on the surface of antigen-presenting cells (APCs) or relies on the uptake and processing by APCs; (2) whole tumor lysates, containing TAAs alone or complexed with chaperones; (3) TAA-encoding vectors, in the form of naked DNA or RNA; (4) DC-based vaccines, including DCs loaded with TAAs *ex vivo* as well as fusion proteins that allow for the selective delivery of TAAs to DCs *in vivo*.

Among them, only one cell-based vaccine, sipuleucel-T (Provenge®), has been clinically approved for the treatment of patients with metastatic hormone-refractory prostate cancer in 2010[1]. No other vaccines based on synthetic TAAs or DNA-based preparation are currently approved for clinical use for malignant tumors, with exceptions of Cervarix® and Gardasil®, the two multivalent vaccines that have been approved as prophylactic measures against HPV-infection-related cervical cáncer[10,11]. Thus, cancer vaccine has been struggling to show evidence in improvement of patient`s survival. There are several reasons to explain the difficulties in the development of effective cancer vaccines[12,13]; (1) poor antigenicity of tumor antigen; (2) heterogenic expression of tumor antigen; (2) the issues relating vaccine administration schedule and route as well as the presence and type of adjuvants and (3) immunosuppressive networks at both local and systemic levels.

Thus, cancer vaccine has been struggling to show evidence in clinical benefits such as improvement of survival or quality of life. Several clinical trials with different antigens as well as different preparations are on-going (Table 1).

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Table 1. Recent clinical trials of cancer vaccine with purified TAAs or peptides

Indications	Phase	Antigen preparation	Antigens
Hematological malignancy (AML, CML etc)	I	Fusion proteins	NY-ESO-1
Hematological malignancy (AML, CML etc)	I/II	Fusion proteins	MAGEA10, WT1
Breast	II	Peptides	HER2
CIN	I	Fusion proteins	E7
GBM	I/II II	Peptides HSP-TAA complexes	Multiple Multiple
Melanoma	I I I I/II	Full length TAAs, Peptides HSP-TAA complexes Phosphopeptides Peptides	NY-ESO-1 gp100 BCAR3, IRS2 MAGEA3.A1 NA17.A2
MPM	II	Peptides	WT1
Multiple Myeloma	I	Peptides	Multiple
NSCLC	I/II I/II	Peptides Peptides	MUC1 TERT
Prostate cancer	I/II	Peptides	TERT

Abbreviations: AML, acute myeloid leukemia; CIN, cervical intraepithelial neoplasia; CML, chronic myeloid leukemia; GBM, glioblastoma multiforme; HSP, heat-shock protein; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung carcinoma; TAA , tumor-associated antigen.

Multi-peptide vaccine

Several phase II and III clinical trials have recently demonstrated the promising and the therapeutic potentials of cancer vaccination[1,14-17]. However, most of them are performed with single antigen-based vaccination with several modifications and the clinical benefit seems to be very limited. In order to further improve the clinical responses of cancer vaccination treatment, it is necessary to consider the application of a combination of multiple vaccines derived from the different target molecules, because it may overcome the issue of heterogeneity of tumor cells and also avoid the escape of tumor cells from peptide-specific immune response by loss of antigen expression [18,19]. In general, the preferable characteristic of the target molecules for development of cancer vaccines are: (1) high immunogenicity, (2) very common expression in cancer cells, (3) specific expression in cancer cells and (4) essential molecules for cell survival (to avoid loss of expression).

We have been shown that three novel HLA-A24-restricted immunodominant peptides, which are derived from three different Cancer-Testis antigens, TTK protein kinase (TTK), lymphocyte antigen 6 complex locus K (LY6K), and insulin-like growth factor (IGF)-II mRNA binding protein 3 (IMP-3), are promising targets for cáncer vaccination against esophageal squamous cell carcinoma (ESCC). [15, 20, 21]. This is due to the findings; limited expression in tumor tissue,

highly frequent expression (>95%) of ESCC; homogenous expression within ESCC; and essential molecules for survival and proliferation. Moreover, it has shown that these peptides could stimulate CTL that recognized and killed ESCC cells endogenously expressing these antigens *in vitro*. Therefore, we had performed a phase I clinical cancer vaccination trials with a combination of multiple peptides that were derived from TTK, LY6K, and IMP3 for the *HLA-A*2402* (+) patients with advanced ESCC, and the evidence in the phase I trial supported a recommendation moving forward to the phase II trial[21]. In the following phase II trial, 60 ESCC patients who failed to standard therapy were enrolled[15]. All enrolled patients had received the vaccination without knowing HLA-A type, and the HLA type were key-opened at analysis point and then, the endpoints were evaluated between HLA-A*2402 positive (24(+)) and HLA-A*2402 negative (24(-)) group in sub-group analysis. As a result, the OS in the 24 (+) group (n=35) tended to be better than that in the 24(-) group (n=25, MST 4.6 vs. 2.6 months, respectively, $p = 0.121$). The PFS in the 24(+) group was significantly better than that in the 24(-) group ($p = 0.032$). The patients having URLC10-, TTK-, and KOC1-specific CTL responses revealed the better OS in comparison to those not having CTL responses, respectively. We reported that the phase II clinical trial of cancer vaccination demonstrated the immune-response induced by the vaccination could induce the better prognosis in advanced ESCC. Based on our phase I and II clinical trials, a pharmaceutical company in Japan is preparing

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phase III RCT trial of cancer vaccine against ESCC.

Another promising phase I/II trial of cancer vaccine with multiple antigenic peptides, which consist of HLA class I and II-binding peptides are reported[22]. A total of 96 renal cell cancer patients were treated with multi-peptide vaccine in combination with cyclophosphamide. The trial showed the combination of multi-peptide vaccine with cyclophosphamide could provide clinical survival benefits and better induction rates of antigen-specific T-cell responses. Therefore, a randomized phase III trial is currently ongoing in Germany.

MAGE-A3 vaccine

It is generally believed that MAGRIT trial (the phase III trial of cancer vaccine with MAGE-A3 against non-small cell lung cancer) is a promising clinical trial to show the clinical benefit of cancer vaccine. The reasons are: (1) the trial is performed as an adjuvant setting for patients with curatively resected tumors, (2) MAGE-A3 is a well- characterized tumor antigen and (3) the preceding phase II trial was shown to have a promising result. MAGE-A3 is a well-characterized cancer testis-antigen[23] that is selectively expressed on tumor cells, but not expressed in normal cells except for the testes, where MHC molecules are not expressed. Immunogenicity of MAGE-A3 was extensively evaluated at both antigenic peptide levels and cellular levels *in vivo* as well as *in vitro*. In lung cancer, MAGE-A3 expression increases with tumor stage; the antigen is expressed in approximately 35% of lung tumors[24]. The pharmaceutical company, GlaxoSmithKline (GSK) has been developing a cancer vaccine strategy using MAGE-A3 protein with several combinations of adjuvants, which can stimulate DCs and enhances protein antigen uptake by DCs. In the phase II study of the MAGE-A3 vaccine, 182 patients with curatively resected, MAGE-A3-positive NSCLC tumors (stages IB and II) were randomly assigned to receive MAGE-A3 vaccine ($n = 122$) or placebo ($n = 60$) at 2:1 ratio. Although the primary end point of the trial, disease-free survival, was not significantly different between the two groups (HR 0.74, 95% CI 0.44–1.2, $P = 0.107$), there was a promising tendency of better disease-free survival in the vaccine group (data not published and available in the meeting proceeding). Of interest is, a tumor gene-expression profile was investigated in this phase II clinical trial, and revealed a 43% relative risk reduction for recurrence in the vaccine treated group in patients with a favorable gene-signature profile (HR 0.57, 95% CI 0.25–1.34, $P = 0.99$). These data supported the design and initiation of a large phase III trial, called MAGRIT.

In the MAGRIT trial, 2,270 patients with curatively resected tumors expressing MAGE-A3 were randomly assigned to receive either vaccine or placebo setting as same as the previous phase II trial, but with some modification of adjuvant. Notably, this trial is the largest interventional study of cancer vaccine, attracting a huge interest in immunotherapy all over the world. However, the preliminary results from the MAGRIT trial has just been released (March 2014), where cancer vaccine did not significantly extend the disease-free survival compared to the placebo group (only available in the press release). More detailed analysis relating to the favourable gene-signature profile is awaited.

Immune checkpoint blockade

Immune checkpoint

Genetic and epigenetic alterations that are typical features of

cancers provide a diverse set of antigens, by which the anti-tumor immunity is induced and activated. In an interaction between T-cells and tumor, the grade and quality of the T-cell-responses, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between activating and inhibitory signals, where the inhibitory signals are currently called as immune checkpoints[25-27]. Under normal conditions, immune checkpoints play a crucial role for the prevention of autoimmunity and also to protect tissues from damage when the immune system is responding to pathogenic infection. It is generally accepted that the up-regulation of immune-checkpoint proteins can be induced by tumors and lead to a prominent immune evasion mechanism. The two immune checkpoint receptors that have been actively studied in the context of clinical cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1) — which are both inhibitory receptors (Figure 1).

CTLA4 is expressed exclusively on T-cells where it fundamentally regulates the degree of the early stages of T-cell activation. In principal, CTLA4 counteracts and inhibits the activity of the T-cell co-stimulatory receptor, CD28 and leads to inhibitory signals[28,29]. Once antigen recognition occurs through TCR, CD28 signaling strongly enhances TCR signaling and leads to activating T-cells, while CTLA4 inhibits the activity of CD28. CD28 and CTLA4 share identical ligands: CD80 (also known as B7.1) and CD86 (also known as B7.2)[28,29].
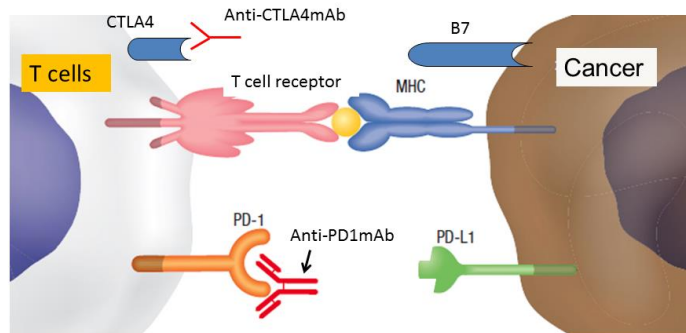

Figure 1: *Immune checkpoint blockade with mAbs*

PD-L1 is an inhibitory B7 family member broadly distributed in various tissues and cell types, and is often expressed after exposure to inflammatory cytokines, especially IFN-γ [25,30]. PD-L1 interacts with PD-1 and can inhibit T-cell activation and CTL-mediated lysis[3,31]. Marked expression of PD-L1 has been reported in various types of human cáncer[26,32]. It has been reported that the inhibition of PD1-PD-L1 interaction with therapeutic mAbs induced significant and durable responses in several types of refractory tumor in clinical trials[2,33,34]. Therefore, PD-L1 expression appears to be one of the key mechanisms for tumors to avoid the host's immune response.

Immune checkpoint blockade with mAbs

In 2010, it was reported that the anti-CTLA4 mAb therapy had extended life in advanced melanoma in a randomized trial and the U.S. FDA approved the anti–CTLA4 mAb for

Table 2 Agents targeting immune-checkpoint

Target	Biological function	Antibody (fusion protein)	Phase	Cancer type
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved Phase II and III	melanoma, multiple cancers
PD1	Inhibitory receptor	MDX-1106 MK3475 CT-011 AMP-224	Phase I/II Phase I Phase I Phase I	melanoma, renal, lung multiple cancers multiple cancers multiple cancers
PDL1	Ligand for PD1	MDX-1105	Phase I	multiple cancers
LAG3	Inhibitory receptor	IMP321	Phase II	breast cancer
B7-H3	Inhibitory ligand	MGA271	Phase I	multiple cancers
B7-H4	Inhibitory ligand			Preclinical
TIM3	Inhibitory receptor			Preclinical

CTLA4, cytotoxic T-lymphocyte-associated antigen 4; FDA, US Food and Drug Administration; LAG3, lymphocyte activation gene 3; PD1, programmed cell death protein 1; PDL, PD1 ligand; TIM3, T-cell membrane protein 3.

metastatic melanoma[35]. In 2012, yet another breakthrough result of immune checkpoint blockade had come up, in which anti–PD-1 mAb therapy resulted in tumor-shrinkage in about half or more in 31% of those with melanoma, 29% with kidney cancer, and 17% with lung cáncer[31,33]. Interestingly, it was reported that combination of anti–CTLA4 mAb with anti–PD-1 mAb led to "deep and rapid tumor regression" in almost a third of melanoma patients[36]. With both anti–CTLA4 and anti–PD-1 mAbs, some patients kept responding even after the treatment had been discontinued, suggesting their immune memory had been established. Some, particularly those with anti–CTLA4 mAb treatment, developed side-effects such as inflammation of the colon or of the pituitary gland.

As described above, these immune checkpoints are only part of the receptors and ligands to inhibit specific types of immune responses at various levels. The next steps for developing immune checkpoint blockade are mainly two challenges as follows. First is the identification of potential biomarkers that can determine which immune checkpoint pathway or pathways dominate in a particular tumor — this will be crucial to guide the choice of inhibitor. For example, in the case of anit-PD1 mAb therapy, the expression of PD-L1 on tumor cells was reported to be the most obvious potential determinants of responsiveness to anti-PD-1 mAb.

The second challenge is the clinical development of combinatorial approaches. Animal and pre-clinical data suggested that there was a strong synergy between tumor vaccines and inhibition of immune checkpoints[37]. Anti-CTLA4 and anti-PD-1 mAbs strongly enhances the amplitude of vaccine-induced anti-tumor responses in many poorly immunogenic tumor models[37,38]. However, there was no synergistic effect between cancer vaccine and anti-CTLA4 mAb in a pivotal RCT, in which combination of gp100-peptide vaccine with anti-CTLA4 mAb did not show any survival benefits compared to the group with anti-CTLA4 mAb alone[35].

CAR therapy

Currently, there is another promising area of immunotherapy. In 2010, Rosenberg *et al*. published encouraging results from so-called chimeric antigen receptor therapy, or CAR therapy—a personalized treatment that involves genetically modifying a patient's T-cells to make them target tumor cells[39,40]. Moreover, it has been reported that there was amazing responses to CAR therapy: patients with advanced stages of leukemia that melted away, in which the T-cell therapy put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed. CAR therapy is now the focus of numerous clinical trials[41]. Although engineered T-cells are still experimental, researchers are extensively working on developing the CAR therapy with great hope.

Conclusion and future prospective

To prove clinical benefits of cancer vaccine is currently difficult, except for one phase III trial has documented improved overall survival with the vaccine, Sipuleucel-T, although induction of anti-tumor immune responses through cancer vaccine is theoretically promising and would be straightforward. In contrast, immune checkpoint blockade with anti-CTLA4 mAb and anti-PD-1 mAb has demonstrated clear evidence of objective responses, driving renewed enthusiasm for cancer immunotherapy in multiple cancer types. In addition, there is a promising novel cancer immunotherapy, CAR therapy—a personalized treatment that involves genetically modifying a patient's T-cells to make them target tumor cells. We are now facing new era of cancer immunotherapy.

References

1. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363(5):411-22.
2. Bachy E, Coiffier B. Anti-PD1 antibody: a new approach to treatment of lymphomas. Lancet Oncol. 2014; 15(1):7-8.
3. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000; 192(7):1027-34.
4. Huppa JB, Davis MM. T-cell-antigen recognition and the immunological synapse. Nat Rev Immunol. 2003; 3(12):973-83.
5. Masopust D, Schenkel JM. The integration of T-cell migration, differentiation and function. Nat Rev Immunol. 2013; 13(5):309-20.
6. 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.
7. Bonifaz LC, Bonnyay DP, Charalambous A, Darguste DI, Fujii S, Soares H, Brimnes MK, Moltedo B, Moran TM, Steinman RM. *In vivo* targeting of antigens to maturing dendritic cells via the DEC-205 receptor improves T-cell vaccination. J Exp Med. 2004; 199(6):815-24.
8. Aranda F, Vacchelli E, Eggermont A, Galon J, Sautes-Fridman C, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: Peptide vaccines in cancer therapy. Oncoimmunology. 2013; 2(12):e26621.
9. Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nat Rev Clin Oncol.2014; 11(1):24-37.
10. Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries--key challenges and issues. N Engl J Med 2007; 356(19):1908-10.
11. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009; 374(9686):301-14.
12. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008; 26:677-704.
13. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol. 2006; 90:51-81.
14. Schwartzentruber DJ, Lawson DH, Richards JM, Conry RM, Miller DM, Treisman J, Gailani F, Riley L, Conlon K, Pockaj B, Kendra KL, White RL, Gonzalez R, Kuzel TM, Curti B, Leming PD, Whitman ED, Balkissoon J, Reintgen DS, Kaufman H, Marincola FM, Merino MJ, Rosenberg SA, Choyke P, Vena D, Hwu P. gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med. 2011; 364(22):2119-27.
15. Kono K, Iinuma H, Akutsu Y, Tanaka H, Hayashi N, Uchikado Y, Noguchi T, Fujii H, Okinaka K, Fukushima R, Matsubara H, Ohira M, Baba H, Natsugoe S, Kitano S, Takeda K, Yoshida K, Tsunoda T, Nakamura Y. Multicenter, phase II clinical trial of cancer vaccination for advanced esophageal cancer with three peptides derived from novel cancer-testis antigens. J Transl Med. 2012; 10:141.
16. Okada H, Kalinski P, Ueda R, Hoji A, Kohanbash G, Donegan TE, Mintz AH, Engh JA, Bartlett DL, Brown CK, Zeh H, Holtzman MP, Reinhart TA, Whiteside TL, Butterfield LH, Hamilton RL, Potter DM, Pollack IF, Salazar AM, Lieberman FS. Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with {alpha}-type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. J Clin Oncol. 2011; 29(3):330-6.
17. Slingluff CL, Jr., Petroni GR, Chianese-Bullock KA, Smolkin ME, Ross MI, Haas NB, von Mehren M, Grosh WW. Randomized multicenter trial of the effects of melanoma-associated helper peptides and cyclophosphamide on the immunogenicity of a multipeptide melanoma vaccine. J Clin Oncol. 2011; 29(21):2924-32.
18. Cecco S, Muraro E, Giacomin E, Martorelli D, Lazzarini R, Baldo P, Dolcetti R. Cancer vaccines in phase II/III clinical trials: state of the art and future perspectives. Curr Cancer Drug Targets. 2011; 11(1):85-102.
19. Lesterhuis WJ, Haanen JB, Punt CJ. Cancer immunotherapy--revisited. Nat Rev Drug Discov. 2011; 10(8):591-600.
20. Mizukami Y, Kono K, Daigo Y, Takano A, Tsunoda T, Kawaguchi Y, Nakamura Y, Fujii H. Detection of novel cancer-testis antigen-specific T-cell responses in TIL, regional lymph nodes, and PBL in patients with esophageal squamous cell carcinoma. Cancer Sci 2008; 99(7):1448-54.
21. Kono K, Mizukami Y, Daigo Y, Takano A, Masuda K, Yoshida K, Tsunoda T, Kawaguchi Y, Nakamura Y, Fujii H. Vaccination with multiple peptides derived from novel cancer-testis antigens can induce specific T-cell responses and clinical responses in advanced esophageal cancer. Cancer Sci. 2009; 100(8):1502-9.
22. Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylik C, Staehler M, Brugger W, Dietrich PY, Mendrzyk R, Hilf N, Schoor O, Fritsche J, Mahr A, Maurer D, Vass V, Trautwein C, Lewandrowski P, Flohr C, Pohla H, Stanczak JJ, Bronte V, Mandruzzato S, Biedermann T, Pawelec G, Derhovanessian E, Yamagishi H, Miki T, Hongo F, Takaha N, Hirakawa K, Tanaka H, Stevanovic S, Frisch J, Mayer-Mokler A, Kirner A, Rammensee HG, Reinhardt C, Singh-Jasuja H. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med. 2012; 18(8):1254-61.
23. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nat Rev Cancer. 2005; 5(8):615-25.
24. Brichard VG, Lejeune D. GSK's antigen-specific cancer immunotherapy programme: pilot results leading to Phase III clinical development. Vaccine. 2007; 27: 25 Suppl 2:B61-71.
25. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005; 23:515-48.
26. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008; 8(6):467-77.
27. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12(4):252-64.
28. Schwartz RH. Costimulation of T lymphocytes: the role of CD28, CTLA-4, and B7/BB1 in interleukin-2 production and immunotherapy. Cell. 1992; 71(7):1065-8.
29. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T-cell costimulation. Annu Rev Immunol. 1996; 14:233-58.
30. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005; 5(5):375-86.
31. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002; 8(8):793-800.

32. Song M, Chen D, Lu B, Wang C, Zhang J, Huang L, Wang X, Timmons CL, Hu J, Liu B, Wu X, Wang L, Wang J, Liu H. PTEN loss increases PD-L1 protein expression and affects the correlation between PD-L1 expression and clinical parameters in colorectal cancer. PLoS One. [Research Support, Non-U.S. Gov't]. 2013; 8(6):e65821.

33. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Elassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumeh PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013; 369(2):134-44.

34. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, Xu H, Yao S, Pons A, Chen L, Pardoll DM, Brahmer JR, Topalian SL. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res. 2013; 19(2):462-8.

35. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363(8):711-23.

36. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K,   Burke M M,   Caldwell A,   Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013; 369(2):122-33.

37. van Elsas A, Hurwitz AA, Allison JP. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. J Exp Med. 1999; 190(3):355-66.

38. Li B, VanRoey M, Wang C, Chen TH, Korman A, Jooss K. Anti-programmed death-1 synergizes with granulocyte macrophage colony-stimulating factor--secreting tumor cell immunotherapy providing therapeutic benefit to mice with established tumors. Clin Cancer Res 2009; 15(5):1623-34.

39. Burns WR, Zhao Y, Frankel TL, Hinrichs CS, Zheng Z, Xu H, Feldman SA, Ferrone S, Rosenberg SA, Morgan RA. A high molecular weight melanoma-associated antigen-specific chimeric antigen receptor redirects lymphocytes to target human melanomas. Cancer Res. 2010; 70(8):3027-33.

40. Kochenderfer JN, Yu Z, Frasheri D, Restifo NP, Rosenberg SA. Adoptive transfer of syngeneic T-cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood. 2010; 116(19):3875-86.

41. Brenner MK. CAR T-cells for acute myeloid leukemia: the LeY of the land. Mol Ther. 2013; 21(11):1983-4

Potential Conflicts of Interests:

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Abbreviations:

APCs: Antigen Presenting Cells
PD1:   Programmed Cell Death Protein 1
TAAs: Tumor-associate Antigens
CTLA4:   Cytotoxic T Lymphocyte-associated Antigen 4
CTLS: Cytotoxic T Lymphocytes
CAR: Chimeric Antigen Receptor

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