HHS Public Access

Author manuscript

Expert Rev Vaccines. Author manuscript; available in PMC 2019 January 09.

Published in final edited form as:

Expert Rev Vaccines. 2013 October ; 12(10): 1115–1118. doi:10.1586/14760584.2013.836906.

Cancer Vaccines: 21st century approaches to harnessing an ancient modality to fight cancer

Jay A. Berzofsky, **Lauren V. Wood**, and **Masaki Terabe**

Vaccine Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland 20892 USA

Keywords

Cancer vaccines; immunoregulation; NKT cells; prostate cancer; CD8 T cells

The role of the immune system to prevent cancer has been hypothesized and studied for many decades, but has remained controversial until recent evidence has convincingly confirmed that many nascent cancers are eradicated by the immune system before they become clinically evident, and that the cancers we detect are ones that are highly selected to escape the mechanisms of immune surveillance, so called “immunoediting” [1]. At the same time, the field of cancer vaccines has been reinvigorated by the landmark of the first cancer vaccine to be licensed by the FDA in the US, sipuleucel-T, for prostate cancer [2]. Concurrently the first checkpoint blockade agent, Ipilimumab monoclonal antibody to CTLA-4, was also licensed to treat malignant melanoma[3]. However, more basic research is needed before cancer vaccines can become a widespread modality for treating cancer.

Our lab has developed a multistep “push-pull” approach to cancer vaccines [4,5]. We start with the basic skeleton of a vaccine, an antigen used to induce an immune response. In the first step, we improve on the antigen itself by a process called “epitope enhancement” in which we modify the amino acid sequence of epitopes to increase their affinity for MHC molecules that present them to T cells, making them more immunogenic [6]. Although sometimes these modifications can affect what the T cell sees as well, we have shown that in many instances, enhanced epitopes induce T cells that recognize the wild type epitope presented by the cancer (or virus-infected cell). Moreover, Gros et al [7] have shown that epitope enhancement can have an additional benefit, by making more immunogenic the subdominant epitopes that were too weak in the wild type form to lead to negative selection and immune tolerance, whereas T cells specific for the strong tumor antigens may have been tolerized or deleted. We have applied this approach to the TARP prostate cancer vaccine described below.

Secondly, we need to improve the response using defined molecular adjuvants, not only to increase the quantity of the response, but especially to improve its functional quality. For example, we have found that IL-15 as a vaccine adjuvant can increase the avidity of the

Corresponding Author: Jay A. Berzofsky, M.D., Ph.D., Chief, Vaccine Branch, Center for Cancer Research, NCI, NIH, Building 41-Room D702D, 41 Medlars Drive, Bethesda, MD 20892-5062. Tel: 301-496-6874; Fax: 301-480-0681. berzofsj@mail.nih.gov.

$CD8^+$ T cells elicited by the vaccine [8] as well as their longevity [9] and can substitute for $CD4^+$ T cell help to prevent antigen-induced death on re-encounter with antigen [10], which has been described for $CD8^+$ T cells primed without help [11]. Similarly, we have seen that costimulatory molecules can promote a $CD8^+$ T cell response [12] and induce higher avidity T cells [13]. We have also identified a triple combination of ligands for TLR 2/6, 3, and 9, which improves the $CD8^+$ T cell avidity and antiviral efficacy more than any double combination of these ligands, even though the numbers of T cells are not increased beyond what would be induced by the double combination [14]. This result, combined with our original observation that high avidity $CD8^+$ T cells are more effective at clearing virus than lower avidity cells [15], emphasizes that the quality of T cells and their functional capacity may be more important than their quantity in anti-viral or anti-tumor efficacy [5].

Recently, we have discovered another agent that may be useful as a vaccine adjuvant, a novel class of agonists for type I NKT cells. It has long been known that type I or semi-invariant NKT cells (iNKT cells) contribute to protection against cancer [16]. These true T cells, unlike conventional T cells, are defined by their recognition of lipids instead of peptides, presented by a non-classical class I MHC molecule, CD1d. It was shown that their prototype synthetic agonist, alpha-galactosylceramide (α-GalCer) could protect against some cancers in mice and also could serve as a vaccine adjuvant [17] [18]. We found that beta-mannosylceramide (β-ManCer), which was not expected to protect against cancer because of its beta-linkage, could nevertheless protect, but by a different mechanism, requiring TNF-α and nitric oxide synthase (NOS) but not interferon-γ (IFN-γ), whereas protection by α-GalCer was dependent on IFN-γ but not TNF-α or NOS [19]. Thus, this was the first of a novel class of iNKT-cell agonists that protected against cancer by a mechanism different from that of all previously known NKT agonists, and which we found could also synergize with α-GalCer. Despite its promising preclinical effects, α-GalCer has not had significant clinical success to date, perhaps because of natural anti-α-Gal antibodies in humans that are absent in mice, and/or because of its tendency to induce anergy of iNKT cells, precluding multiple dosing. In contrast, β-ManCer is not susceptible to natural anti-α-Gal antibodies because of the use of a different sugar and linkage, and we have recently shown that it also induces only much more transient anergy [20]. These features, together with its novel mechanism of action, may make it a promising candidate for clinical development. In preliminary studies, we have also found it to be a useful vaccine adjuvant in mice and are currently developing it for clinical translation.

Even with all of these strategies to “push” immune responses, it is still necessary to “pull” the responses by blocking negative regulation by a host of cells and molecules that dampen the immune response to prevent over-reaction. Cancers have evolved mechanisms to exploit these immune control mechanisms to evade the immune response. Antibodies have been developed to block checkpoint molecules like CTLA-4 mentioned above and PD-1 that dampen T cell activation or lead to exhaustion, and blocking the combination may be even more effective [21]. Myeloid-derived suppressor cells [22] and M2 macrophages [23] also play suppressive role in the tumor microenvironment. Our lab discovered that type II NKT cells, which lack the invariant TCR-α chain but still recognize lipids presented by CD1d, are another suppressor of tumor immunity [24–27]. We also found that type I and type II NKT cells, besides having opposite roles in tumor immunity, crossregulate each other, forming a

new immunoregulatory axis, analogous to the Th1/Th2 axis, such that whichever dominates can influence the subsequent adaptive immune response [28]. In some mouse tumor models, Treg cells seemed to be the dominant suppressor, whereas in others, type II NKT cells dominated. Recently, we found that both could suppress the same tumor, and which one dominated depended on a third cell, the type I NKT cell, which could inhibit the type II NKT cells and thus determine the balance between the two regulators, essentially regulating the regulators [29]. In the absence of type I NKT cells, it was necessary to block both type II NKT cells and Treg cells to prevent tumor growth. As cancer patients often have defective type I NKT cell function, it may also be necessary in such patients to block the action of both of these regulators.

We found that TGF-β was a key downstream mediator of NKT cell suppression of tumor immunity [25], and it also plays a critical role for suppressing Th1 responses including induction of Treg cells, so blockade of TGF-β could abrogate activities of both regulatory cells. In some mouse tumor models, we found that blockade of TGF-β was sufficient to prevent tumor growth, without any other treatment [25], whereas in other mouse tumors, anti-TGF-β alone had no effect on tumor growth, but the antibody synergized with a cancer vaccine [30,31]. We therefore translated these findings to test a human anti-TGF-β monoclonal antibody in melanoma patients. In a phase I study of the antibody (GC1008, Genzyme Corp) as a single agent (trial NCT00356460, sponsor, Genzyme Corp.), we found several tumor responses, including one 89% partial response lasting about a year, and several cases of mixed responses and stable disease, without dose-limiting toxicities [32]. Thus, this is a promising agent to test in combination with a cancer vaccine.

We also translated our epitope enhancement approach described above to develop a peptide vaccine against prostate cancer. The T-cell Receptor γ-chain Alternate Reading Frame (TARP) protein is a tumor antigen discovered by Ira Pastan's lab [33] that uses a portion of the TCR-γ chain DNA sequence read in a different open reading frame, and thus bears no resemblance in amino acid sequence. It is expressed in about 95% of prostate cancers of all stages, Gleason types and hormonal status, as well as about 50% of breast cancers. We mapped two HLA-A2 binding epitopes, one high affinity, and one of modest affinity that we enhanced by replacing one anchor residue [34]. These induced human T cells that killed human cancer cells expressing TARP and HLA-A*0201. We then translated these findings into a randomized clinical trial (trial NCT00972309, sponsor, NCI) of TARP vaccination in men with stage D0 prostate cancer who have undergone primary therapy of their tumor but have PSA biochemical evidence of recurrence. In this setting, the slope of the PSA rise (which can also be expressed as PSA doubling time) is a validated measure of tumor growth, so that we could follow growth despite the presence of only minimal residual disease. One arm received the TARP peptides in Montanide ISA51 VG adjuvant along with GM-CSF, and a second arm received the same two peptides pulsed onto autologous dendritic cells (DCs). As there was no significant difference between the arms in the change in the slope log PSA from baseline, the two arms could be combined. In the whole cohort together, 72% showed a decreased slope at 24 weeks and 74% showed a decreased slope at 48 weeks compared to their own pre-treatment values, both highly statistically significant (Wood et al, ms in preparation). Also, estimates of tumor growth rate suggested that the median tumor growth rate constant fell to half the baseline value. About 77% of study subjects developed TARP-

specific $CD8^+$ T cell responses, but these responses did not correlate with decreased slope and slowing in PSA velocity. Despite the lack of an immune correlate of the observed clinical activity so far (work in progress), these promising results on tumor growth have motivated a randomized, placebo-controlled phase II clinical trial that is being developed to validate this result. If anti-tumor activity is confirmed, the TARP vaccine could be tested in earlier, i.e. the neoadjuvant or adjuvant setting, as well as more advanced stages of prostate cancer in addition to breast cancer.

We conclude that cancer vaccines can be improved by the multistep push-pull approach described, including epitope enhancement of the vaccine antigens, use of defined molecular adjuvants to improve the functional quality as well as quantity of immune response, and blockade of negative regulatory mechanisms exploited by the tumor to evade immunosurveillance. To successfully tackle a difficult adversary like cancer, that has learned to exploit the weaknesses in the immune system to evade it and escape it, we may need a combination of many such novel strategies in our 21^{st} century armamentarium to effectively harness our most ancient defense modality-- the immune system--to fight and ultimately conquer cancer.

Acknowledgments:

This work was supported by intramural research funding Z01 SC 004020. Some funds for the GC1008 clinical trial NCT00356460 were provided by the Genzyme Corporation. Both clinical trials NCT00356460 and NCT00972309 were ethically approved by the NCI IRB.

References

1. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol, 22, 329–360 (2004). [PubMed: 15032581]
2. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med, 363(5), 411–422 (2010). [PubMed: 20818862]
3. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med, 363(8), 711–723 (2010). [PubMed: 20525992]
4. Berzofsky JA. A push-pull vaccine strategy using Toll-like receptor ligands, IL-15, and blockade of negative regulation to improve the quality and quantity of T cell immune responses. Vaccine, 30(29), 4323–4327 (2011). [PubMed: 22115635]
5. Berzofsky JA, Terabe M, Wood LV. Strategies to use immune modulators in therapeutic vaccines against cancer. Semin Oncol, 39(3), 348–357 (2012). [PubMed: 22595057]
6. Berzofsky JA, Ahlers JD, Belyakov IM. Strategies for designing and optimizing new generation vaccines. Nature Reviews Immunology, 1(3), 209–219 (2001).
7. Gross DA, Graff-Dubois S, Opolon P et al. High vaccination efficiency of low-affinity epitopes in antitumor immunotherapy. J Clin Invest, 113(3), 425–433 (2004). [PubMed: 14755339]
8. Oh S, Perera LP, Burke DS, Waldmann TA, Berzofsky JA. IL-15/IL-15R alpha-mediated avidity maturation of memory $CD8^+$ T cells. Proc Natl Acad Sci U S A, 101(42), 15154–15159 (2004). [PubMed: 15477598]
9. Oh S, Berzofsky JA, Burke DS, Waldmann TA, Perera LP. Coadministration of HIV vaccine vectors with vaccinia viruses expressing IL-15 but not IL-2 induces long-lasting cellular immunity. Proc Natl Acad Sci U S A, 100(6), 3392–3397 (2003). [PubMed: 12626740]
10. Oh S, Perera LP, Terabe M, Ni L, Waldmann TA, Berzofsky JA. IL-15 as a mediator of CD4+ help for CD8+ T cell longevity and avoidance of TRAIL-mediated apoptosis. Proc Natl Acad Sci U S A, 105(13), 5201–5206 (2008). [PubMed: 18362335]

11. Janssen EM, Droin NM, Lemmens EE et al. CD4+ T-cell help controls CD8+ T-cell memory via TRAIL-mediated activation-induced cell death. Nature, 434(7029), 88–93 (2005). [PubMed: 15744305]
12. Ahlers JD, Belyakov IM, Terabe M et al. A push-pull approach to maximize vaccine efficacy: abrogating suppression with an IL-13 inhibitor while augmenting help with GM-CSF and CD40L. Proc Natl Acad Sci U S A, 99(20), 13020–13025 (2002). [PubMed: 12232042]
13. Oh S, Hodge JW, Ahlers JD, Burke DS, Schlom J, Berzofsky JA. Selective induction of high avidity CTL by altering the balance of signals from antigen presenting cells. J Immunol, 170, 2523–2530 (2003). [PubMed: 12594278]
14. Zhu Q, Egelston C, Gagnon S et al. Using 3 TLR ligands as a combination adjuvant induces qualitative changes in T cell responses needed for antiviral protection in mice. J Clin Invest, 120(2), 607–616 (2010). [PubMed: 20101095]
15. Alexander-Miller MA, Leggatt GR, Berzofsky JA. Selective expansion of high or low avidity cytotoxic T lymphocytes and efficacy for adoptive immunotherapy. Proc.Natl.Acad.Sci.U.S.A, 93, 4102–4107 (1996). [PubMed: 8633023]
16. Swann JB, Coquet JM, Smyth MJ, Godfrey DI. CD1-restricted T cells and tumor immunity. Curr Top Microbiol Immunol, 314, 293–323 (2007). [PubMed: 17593666]
17. Taniguchi M, Harada M, Kojo S, Nakayama T, Wakao H. The regulatory role of Valpha14 NKT cells in innate and acquired immune response. Annu Rev Immunol, 21, 483–513 (2003). [PubMed: 12543936]
18. Gonzalez-Aseguinolaza G, Van Kaer L, Bergmann CC et al. Natural killer T cell ligand alpha-galactosylceramide enhances protective immunity induced by malaria vaccines. J Exp Med, 195(5), 617–624 (2002). [PubMed: 11877484]
19. O'Konek JJ, Illarionov P, Khursigara DS et al. Mouse and human iNKT cell agonist beta-mannosylceramide reveals a distinct mechanism of tumor immunity. J Clin Invest, 121, 683–694 (2011). [PubMed: 21245578]
20. O'Konek JJ, Kato S, Takao S et al. beta-mannosylceramide activates type I natural killer T cells to induce tumor immunity without inducing long-term functional anergy. Clin Cancer Res, (2013), in press.
21. Wolchok JD, Kluger H, Callahan MK et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med, (2013).
22. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol, 9(3), 162–174 (2009). [PubMed: 19197294]
23. Sinha P, Clements VK, Ostrand-Rosenberg S. Interleukin-13-regulated M2 macrophages in combination with myeloid suppressor cells block immune surveillance against metastasis. Cancer Res, 65(24), 11743–11751 (2005). [PubMed: 16357187]
24. Terabe M, Matsui S, Noben-Trauth N et al. NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. Nature Immunology, 1(6), 515–520 (2000). [PubMed: 11101874]
25. Terabe M, Matsui S, Park J-M et al. Transforming Growth Factor-β production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block Cytotoxic T Lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. J Exp Med, 198(11), 1741–1752 (2003). [PubMed: 14657224]
26. Terabe M, Swann J, Ambrosino E et al. A nonclassical non-Va14Ja18 CD1d-restricted (type II) NKT cell is sufficient for down-regulation of tumor immunosurveillance. J Exp Med, 202(12), 1627–1633 (2005). [PubMed: 16365146]
27. Park JM, Terabe M, van den Broeke LT, Donaldson DD, Berzofsky JA. Unmasking immunosurveillance against a syngeneic colon cancer by elimination of CD4+ NKT regulatory cells and IL-13. International J. of Cancer, 114(1), 80–87 (2004).
28. Ambrosino E, Terabe M, Halder RC et al. Cross-regulation between type I and type II NKT cells in regulating tumor immunity: A new immunoregulatory axis. J Immunol, 179, 5126–5136 (2007). [PubMed: 17911598]
29. Izhak L, Ambrosino E, Kato S et al. Delicate balance among three types of T cells in concurrent regulation of tumor immunity. Cancer Res, 73(5), 1514–1523 (2013). [PubMed: 23319803]

30. Terabe M, Ambrosino E, Takaku S et al. Synergistic enhancement of CD8+ T cell-mediated tumor vaccine efficacy by an anti-transforming growth factor-beta monoclonal antibody. Clin Cancer Res, 15(21), 6560–6569 (2009). [PubMed: 19861451]

31. Takaku S, Terabe M, Ambrosino E et al. Blockade of TGF-beta enhances tumor vaccine efficacy mediated by CD8(+) T cells. Int J Cancer, 126(7), 1666–1674 (2009 (2010)). [PubMed: 19830696]

32. Morris JC, Shapiro GI, Tan AR et al. Phase I/II Study of GC1008: A human anti-transforming growth factor-beta (TGFb) monoclonal antibody (MAb) in patients with advanced malignant melanoma (MM) or renal cell carcinoma (RCC). J. Clin. Oncol., 26(15S (Part I of II)) (2008).

33. Wolfgang CD, Essand M, Vincent JJ, Lee B, Pastan I. TARP: a nuclear protein expressed in prostate and breast cancer cells derived from an alternate reading frame of the T cell receptor gamma chain locus. Proc Natl Acad Sci U S A, 97(17), 9437–9442 (2000). [PubMed: 10931945]

34. Oh S, Terabe M, Pendleton CD et al. Human CTL to wild type and enhanced epitopes of a novel prostate and breast tumor-associated protein, TARP, lyse human breast cancer cells. Cancer Research, 64, 2610–2618 (2004). [PubMed: 15059918]