Resident Memory T Cells as Surrogate Markers of the Efficacy of Cancer Vaccines
Mevyn Nizard1,2, Hélène Roussel1,2, and Eric Tartour1,2,3

Cancer vaccine boost via the cervicovaginal rather than the intramuscular route of immunization appears to be crucial to induce genital CD8+ T cells and tumor regression. This clinical activity is correlated with the ability of the mucosal route to elicit resident memory T cells in the genital tract. Clin Cancer Res; 22(3); 530–2. ©2015 AACR.

In this issue of Clinical Cancer Research, Sun and colleagues provide various clues to improve cancer vaccine (1). Possible control of tumor growth by the immune system is now widely accepted with the clinical breakthrough provided by the blockade of inhibitory pathways (i.e., PD-L1/PD-L1/2, CTLA-4-CD80/CD86). Although cancer vaccines have been tested for more than 20 years, clinical success rates remain modest. Provenge was the only cancer vaccine approved on the basis of its ability to prolong survival of hormone-refractory prostate cancer patients by an average of 4 months (2). Various recent phase III therapeutic cancer vaccine trials (Magrit, telomerase vaccine GV1001, Stimmuvax, Immatics, etc.) failed to achieve their primary objectives (3, 4). Improvement of cancer vaccine design is therefore mandatory for their clinical implementation. Sun and colleagues demonstrate that heterologous prime-boost vaccination elicited stronger specific CD8+ T-cell response than homologous prime-boost immunization using DNA vaccine or recombinant vaccinia-based boost (TA-HPV) encoding HPV16 E6 and E7 proteins (1). Although the mechanisms explaining the efficacy of this heterologous prime-boost regimen have not been fully elucidated, heterologous prime-boost is known to recruit various arms of the immune response and focus the response on the antigens shared between the two vaccine vehicles thereby avoiding the risk of vaccine neutralization especially for immunogenic delivery vectors (virus). The efficacy of the prime-boost strategy demonstrated by Sun and colleagues is in line with various interesting preliminary clinical results obtained in humans with heterologous prime-boost vaccines. Indeed, Le and colleagues showed that heterologous prime-boost with GM-CSF-secreting allogeneic pancreatic tumor cells followed by a Listeria-based vaccine incorporating mesothelin extends the median survival from 3.9 months to 6.1 months in patients with advanced pancreatic cancer (5). The Prostvac vaccine composed of two recombinant viral vectors (vaccinia for priming and fowlpox for boosting), each encoding transgenes for PSA and three costimulatory molecules (CD80, ICAM-1, and LFA-3), increased the median OS by 8.5 months in a phase II randomized trial in metastatic prostatic cancer patients (6).

One striking and original result from the Wu study is that local cervicovaginal administration of the boost with TA-HPV, rather than via the intramuscular route, markedly improved its efficacy in terms of both local anti-E7 CD8+ T-cell response and genital tumor protection. This result was also confirmed when the boost was performed with a vaccine composed of an E7 peptide, but not when the DNA vaccine was used for the boost. However, as suggested by the authors, it is likely that the cervicovaginal route is not appropriate for the DNA format of the vaccine (1). These results could be explained by the imprinting of T cells after their initial activation, as it has been shown that dendritic cell (DC) priming at one specific mucosal site determines the subsequent homing of T cells to specific mucosal sites (Fig. 1). This concept has been validated in various infection models, in which mucosal vaccines induce a better local immune response to pathogens than the systemic route of administration. This better local immune response results in better control of the mucosal pathogens (7). Recently, our group also reported, in an orthotopic head and neck cancer model, a greater infiltration of antitumor CD8+ T cells after tumor graft in mice that had been previously intranasally immunized with a cancer vaccine than in mice vaccinated via the intramuscular route with the same vaccine (8). Interestingly, in the study by Sun and colleagues, cervicovaginal vaccine-induced specific CD8+ T cells expressed the CD103 integrin, which qualified them as memory resident T cells (TRM; ref. 1). These cells have been shown to stably reside in peripheral tissues and do not enter the circulation for prolonged periods of time. TRM rapidly acquire effector functions following secondary antigenic stimulation and are highly protective against subsequent local infections (9). Intravaginal immunization with human papillomavirus vectors (HPV pseudoviruses) that transiently expressed a model antigen in cervicovaginal keratinocytes also induced a greater number of tissue resident CD8+ T-cell responses than the intramuscular route of immunization (10). In human cancer, various recent studies have shown that infiltration of tumors by CD103+CD8+ T cells was correlated with better clinical outcome in patients with lung cancer, ovarian cancer, and bladder cancer (11).
Induction of persistent intraepithelial CD8+ T-cell responses (TRM) may therefore be the key to the development of cancer vaccines. Various approaches have been successfully developed to harness this local tumor immunity and the generation of TRM. We and other authors have shown that the mucosal route of immunization imprints T cells with a mucosal homing program defined by a profile of integrin and chemokine receptors promoting their homing to the site of initial activation. Tumors located at mucosal sites (lung, colorectal, genital, head and neck) are exposed to mucosal immunity, organized within a connecting network called MALT (mucosal-associated lymphoid tissues), which may explain why the intranasal route of immunization may induce a genital immune response via the recirculation of mucosal dendritic cells (12).

In the study by Sun and colleagues, α4β7 and CCR9 induced on T cells are necessary for the homing of antitumor-specific T cells to the cervicovaginal tract (1). The same set of molecules are also required for the homing to the digestive tract, whereas expression of CCR10 and P-and E-selectin ligands on T cells direct the homing of T cells to the skin (7). Sun and colleagues showed that the ability of dendritic cells in the cervicovaginal tract to produce retinoic acid may explain in part the specific integrin program induced after cervicovaginal immunization (1). It extends previous results about the key role of local dendritic cells to imprint a specific program on T cells to favour their homing to the site of their initial activation (8, 13).

After systemic vaccination, a combined mucosal signal delivered via the local administration of TLR ligands or chemokines was also efficient to promote migration of T cells to the mucosal site, resulting in clearance of pathogens or tumor regression (14).

However, other studies have claimed that systemic immunization without mucosal signal delivery can overcome immune compartmentalization. A DNA vaccine targeting HPV proteins...
administered via the intramuscular route induced regression of cervical intraepithelial neoplasia by two thirds in 18.2% of cases compared with a spontaneous regression rate of 30% in the placebo group. This 18.2% difference between the two groups is the first demonstration of the efficacy of a vaccine directed against mucosal tumors (15). However, in this case and in other cases, the respective efficiency of mucosal and systemic immunization regimens has never been compared and the mucosal route of immunization could enhance the modest clinical efficacy already observed.

Overall, two important translational clinical considerations can be drawn from Wu and colleagues’ study: (i) monitoring of cancer vaccines in clinical practice is based on analysis of the immune response in the blood, which does not always reflect the intensity of intratumor immune response (1, 8). This point may explain some of the controversies concerning the clinical value of vaccine-induced immune response to predict cancer vaccine efficacy; (ii) induction of local antitumor immunity and especially resident memory T cells should constitute a new criterion for the successful clinical development of therapeutic cancer vaccines.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: M. Nizard, H. Roussel, E. Tartour
Study supervision: E. Tartour

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