

Neoantigen: A Long March toward Cancer Immunotherapy

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Somatic mutations in cancer give rise to neoantigens. Technology revolutions in cancer genomics and immunology have made it possible to rapidly identify neoantigens for cancer vaccines. Leisegang and colleagues report that it is

practical to rapidly identify neoantigens for adoptive T-cell therapy in a mouse tumor model. *Clin Cancer Res*; 22(11); 2602–4. ©2016 AACR.

See related article by Leisegang et al., p. 2734

In this issue of *Clinical Cancer Research*, a new development in adoptive T-cell therapy experimental mouse tumor model is reported by Leisegang and colleagues (1).

In retrospect, the 1990s were considered a golden period for tumor immunology when many tumor antigens recognized by T cells were identified. The antigens reported by Boon and colleagues in both murine and human cancers (2, 3) were derived from genes that are overexpressed in cancer and fetal tissues (4). The second class of unmutated antigens recognized by tumor-reactive T cells is tissue-specific antigens that are also found in tumor cells (5). These unmutated tumor antigens were favored for cancer vaccines and cancer therapy because they are present in a high proportion of human cancers. However, the classical study by Prehn and Main (6) has cast a long shadow on the utility of the shared tumor antigen, as their *in vivo* analysis showed that tumor rejection antigens are by and large individually specific. In supporting this notion, Ramarathinam and colleagues reported that, although multiple lineages of murine tumor cells expressed P1A, the first unmutated tumor antigen to be identified, these lineages were not cross-protective (7). Although cancer patients have a high frequency of T cells specific for unmutated antigens, these T cells were unable to control cancer growth (8). Consistent with this notion, the first transgenic mice that expressed unmutated tumor antigen-specific T-cell receptor (TCR) on all T cells were not able to reject tumors that express the antigen, P1A (9). The poor therapeutic effect of these T cells may have been predicated because the host must have developed mechanisms to either eradicate or functionally restrain the T cells that can potentially target self-tissues.

The concept that cancer cells must express neoantigen can be traced back more than 60 years when Prehn and Main demon-

strated that tumor antigens are individually specific (6). Its validation must wait for more than 40 years, when Leisegang and colleagues reported the first identification of tumor antigen that are derived from mutations (1). Although the drawbacks of targeting unmutated tumor antigens have raised the potential significance of targeting neoantigens, the challenge of identifying and targeting individually specific neoantigens must wait for both technology revolution and wider acceptance of their significance in cancer immunotherapy. In this issue, in mouse tumor induced by UV irradiation, Monach and colleagues provided the first and unequivocal evidence that neoantigens can be targeted for cancer immunotherapy (10).

Cancer genomics have revealed a large number of mutations in clinical cancer samples. The technical advances in rapid identifications for personalized cancer treatment have intrigued immunologists into targeting these mutations for cancer immune therapy. Meanwhile, advances in targeting CTLA-4 and PD-1 pathways allowed one to identify high mutation burden as biomarkers for therapeutic responses. Furthermore, recent attempts to mine the mutations in cancer suggest an abundance of neoantigens for immune targeting. One such attempt was reported by Duan and colleagues several years ago, with successful attempts to identify mutations in cancer cell lines that can be used as potential therapeutic vaccines (11).

De novo-identified neoantigens have been explored for cancer vaccines but rarely for adoptive T-cell therapy. As a therapeutic vaccine has never been as successful as a preventive vaccine even in cases of viral infection, the impact of neoantigen-based vaccination is considerably less than that of immunotherapy using T cells that recognize the neoantigens. Obviously, more is needed to develop adoptive T-cell therapy from mutations identified by genomics. The work reported by Leisegang and colleagues (1) marked a major advance toward neoantigen-based immunotherapy.

Leisegang and colleagues (1) used a UV-induced carcinoma to test the notion of immunotherapy (Fig. 1). The authors divided the cancer into 20 fragments to identify antigens that were shared among different fragments. Taking a page from evolutionary biologists, Leisegang and colleagues identified trunk antigens that were shared among all fragments. As expected, a high number of trunk antigens existed in a given tumor, which suggested a rich source of neoantigens. Using a publicly accessible computation

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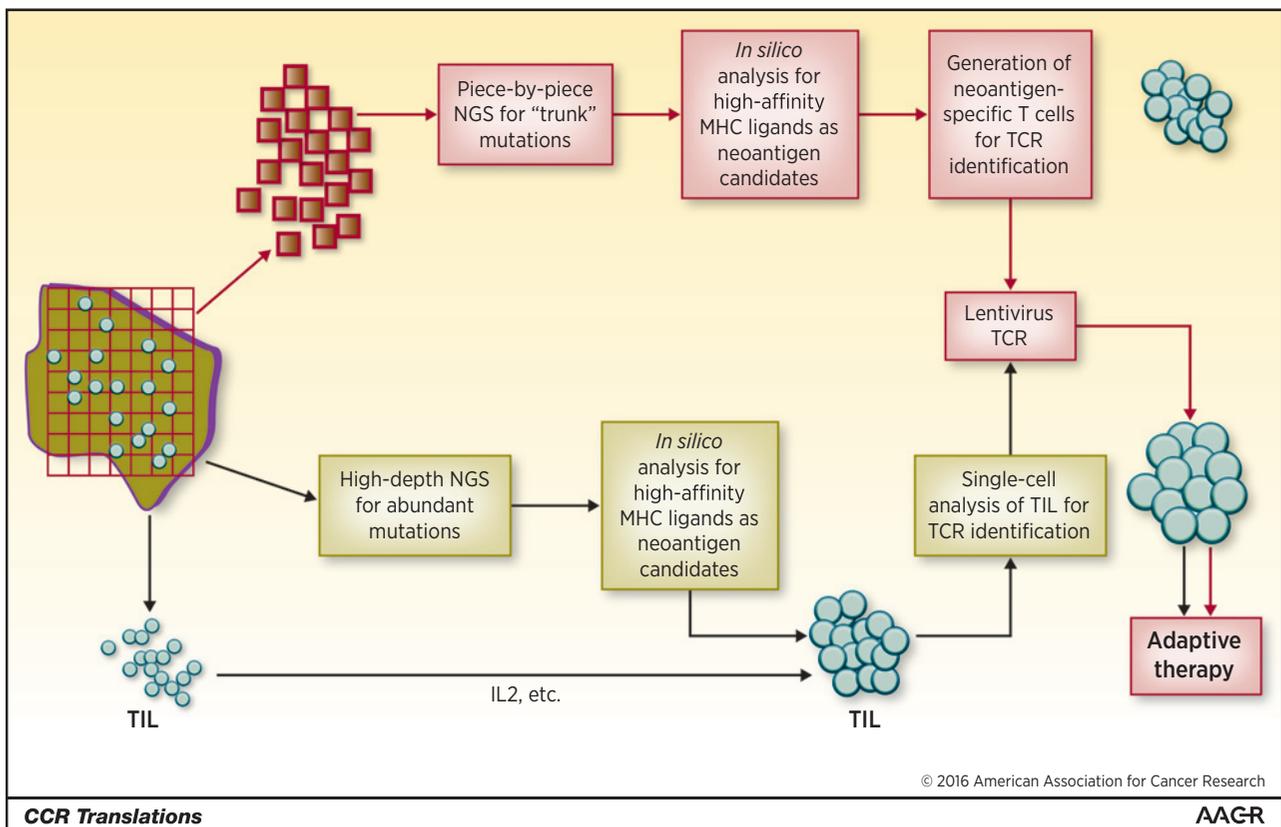


Figure 1.

Neoantigen-specific adoptive T-cell therapy. Top, the approach used by Leisegang and colleagues (1); bottom, possible modifications for a practical adaptation for clinical translation. NGS, next-generation sequencing; TIL, tumor-infiltrating lymphocytes.

program, the authors sought for mutations that can yield high affinity epitope in the mouse MHC class I and chose one with the highest prevalence for the production of antigen-specific T cells. Surprisingly, the antigen chosen by the unbiased approach turned out to be the same as the neoantigen identified nearly 20 years ago (12). The historical coincidence speaks volumes for the significance of this antigen in cancer biology and suggests that although neoantigen is cancer specific, it does not have to be individually specific for each cancer. As such, a personalized T-cell therapy may not have to be as personal as one might have predicted from the classical studies of Prehn and Main (6).

Leisegang and colleagues (1) then identified the TCR from an antigen-specific T-cell line and transduced the TCR into polyclonal T cells. The transduced T cells were found highly efficient in lysing tumor cells expressing the antigen and induced a significant therapeutic response in mice bearing large tumors from which the neoantigen had been identified in the first place. The therapeutic response is much improved if the antigen was overexpressed or if the adoptive therapy was combined with irradiation, where complete rejection without recurrence was observed in a high proportion of mice with large tumor burden.

The extent of antigen loss in tumor cells is comparable between this study and earlier studies using transgenic T cells specific for unmutated tumor antigen P1A (13). The similarity suggests that immune evasion is an obstacle not only for therapy based on unmutated tumor antigens but also for neoantigens. How might such a barrier be overcome?

Leisegang and colleagues (1) have demonstrated that such evasion can be avoided to a large extent by combination with irradiation therapy. Irradiation has been shown to enhance immune response through the induction of type I IFN. By reducing tumor burden, irradiation may reduce the number of tumor cells with preexisting clones with either deletion or loss of expression of the tumor antigen. Consistent with this notion, Leisegang and colleagues showed that the recurrent tumors consist of those with deletion and those without deletion but lack gene expression.

Development of a therapy-resistant clone is nothing new in cancer and infectious diseases. Traditionally, such mutations are best dealt with through the use of drug cocktails. Fortunately, given the large number of neoantigenic epitope identified, immunologists are richly endowed with targets for combination therapy. As approaches for all antigens are substantially the same, combination therapy with multiple TCRs is clearly feasible.

The most important aspect of this study is that with some minor modification based on existing technology, the concept can be translated into clinical trials targeting neoantigens in human cancer. Such modification may include identification of TCR from tumor-infiltrating cells rather than from T cells generated from peptide immunization (Fig. 1). As the identification of TCR from tumor-infiltrating cells has been successful, it is anticipated that one would be able to identify the missing link between these T cells and their antigens and use the TCR for adoptive cancer therapy.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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