In this issue of Clinical Cancer Research, Moon and colleagues describe a "partially human" tumor treatment model that they use to evaluate a combination of T-cell–adoptive therapy and PD-1 blockade (1). This work appears against a background where our understanding of the molecular basis of the immune response to cancer has been rapidly accelerating in the last decade. In particular, progress in the fields of tumor-associated antigens and the tumor microenvironment has been rapidly translated into effective clinical therapies. New concepts (actually still hypotheses) about why some tumors are immunogenic and what drives or blocks tumor rejection are being widely offered and embraced with enthusiasm. The next major challenge will be to decide which combination therapies (among innumerable candidates) should be applied to individual patients to successfully orchestrate this most personal of "personalized" cancer therapies.

It may be easiest to divide our new knowledge into the forces that promote cancer rejection and those that prevent it. Proven proregression forces consist of a sufficient T-cell repertoire, reactive with safe tumor-associated antigens, and cytokines which can activate and expand these cells. Other modulators of T-cell activation, expansion, and survival, such as costimulatory and prosurvival moieties, can also provide valuable support. Perhaps the earliest example of a curative immunotherapy exploiting this side of the equation was the use of IL-2 in patients with metastatic melanoma and renal cancer (2). Adoptive T-cell transfer, the infusion of large numbers of tumor-reactive T cells activated, expanded, or even receptor-engineered in vitro, has been shown to be a rapid and direct way to put in place a T-cell repertoire capable of supporting tumor rejection. For patients with metastatic melanoma, durable complete responses were achieved with a single such transfer of expanded tumor infiltrating lymphocytes when other immunotherapeutic approaches had failed (3). In just the last few years, we have come to realize that many of the natural T-cell populations resident in tumors recognize epitopes encoded by some of the many tumor-specific mutations present in nearly all cancers (4, 5). This exciting finding opens the possibility of identifying safe and tumor-specific T-cell targets in nearly all types of human cancers. At the same time, it is clear that these native T-cell repertoires alone are insufficient to cause regression of the most common types of human cancer.

The other major advance has been in our understanding of the immunosuppressive tumor microenvironment. An enormous list of cells, cytokines, and inhibitory receptors has been shown to be able to suppress antitumor responses in vitro or in animal models. Many of these prove to be the other side of T-cell receptor engagement—reciprocally stimulated by successful T-cell activation to prevent us from suffering the consequences of unchecked immune responses. One class of inhibitors that has given rise to highly effective clinical interventions has been the agents targeting the immune checkpoints, antibodies preventing the PD-1 and CTLA-4 "off-switches" from being activated and shutting down immune responses. It is both surprising and illuminating that the blockade of PD-1 alone in patients with melanoma can result in objective tumor regressions in up to 40% of patients (6). This speaks volumes about the adequacy of the endogenous antitumor T-cell repertoire in these patients as well as the (in)significance of the multitude of other candidate immune inhibitors in the melanoma microenvironment. The fact that adding anti–CTLA-4 antibody to anti–PD-1 antibody seems to slightly increase the response rates attained illustrates the fact that a small subset of patients seem to have both of these "brakes" on (6). Also illuminating is the fact that patients who have not shown tumor regression with either anti-PD-1 or anti–CTLA-4 antibodies can still respond to adoptive cell therapy (J.C. Yang; unpublished data). This implies that the T-cell repertoire can be limiting in some patients as well. It is clear that the best tumor regression will be achieved when all factors preventing the host from rejecting their tumor are simultaneously addressed. That brings us to the article published in this volume of Clinical Cancer Research (1). Moon and colleagues engineered human lymphocytes with a clinically tested HLA-A0201–restricted T-cell receptor against the tumor-germline antigen NY-ESO-1, previously shown to mediate tumor regression in patients. These were then used in an HLA-A2 transgenic immunodeficient mouse bearing an HLA-A0201+ human lung cancer expressing NY-ESO-1. The question posed was whether the addition of an anti-human PD-1 antibody could augment the efficacy of adoptive cell transfer in this model. Similar work has been done with murine tumors in mice using anti-mouse PD-1 and predicts that benefit would be seen (7). Moon and colleagues showed that the transferred human T cells did migrate to sites of tumor but became hypofunctional while expressing inhibitory receptors, including PD-1. Finally, the addition of anti-human PD-1 to the T-cell transfer showed the greatest...
inhibition of tumor growth despite the antibody showing no independent antitumor activity.

It is compellingly rational that the best tumor rejection will be seen when the antitumor T-cell repertoire is optimized and local immunosuppressive forces in the tumor are blocked. The immediate question is which of these requirements is limiting in most patients with cancer. In patients with melanoma, both the repertoire and the response to available checkpoint inhibitors seem to be superior to most other cancers. One could argue that the repertoire is driving this because effective antigen engagement seems to be the main stimulus for the expression of inhibitory receptors and their ligands (8). A current hypothesis is that the antigens responsible for this endogenous antitumor T-cell response are "neoantigens" encoded by tumor-specific mutations. Due to UV mutagenesis, melanoma is one of the most mutated human cancers (9). Other cancers associated with smoking are also highly mutated and have some of the highest response rates to anti–PD-1 (also higher than the same types of cancers occurring in nonsmokers). Perhaps the most telling observation is that mismatch-repair–deficient tumors, containing a mean of 24-fold more mutations than a group of mismatch-proficient cancers (which had no responses to anti–PD-1), have one of the highest rates of response to anti–PD-1 (10). If this hypothesis proves to be true, then the limiting factor for rejecting most human cancers (and perhaps many of those not responsive to checkpoint inhibitors) is that the T-cell repertoire is insufficient. All tumors have mutations, but not every mutated epitope is processed and presented by the patient’s HLA alleles and not all T-cell responses are potent enough to reject a tumor. It stands to reason that the more candidate mutated epitopes a tumor has, the more likely one will be sufficient to contribute to tumor rejection. Having stated that the repertoire is likely to be limiting for many human cancers, it is equally important that all inhibitory factors be identified and therapeutically blocked. It is very likely that there are other factors that will need to be identified and "drugged" to optimally block the hostile tumor microenvironment. The combination of adoptive T-cell transfer and anti–PD-1 antibody described by Moon and colleagues is just one of many combination immunotherapies to explore. Clinically testing all of the candidate combinations against multiple tumors types is an impossible task, and the validity of surrogate murine models is not yet clear. The new availability of tumor exomic sequencing and RNAseq or nanoscale analysis on an individual patient basis may provide the means to simultaneously analyze the antigenic repertoire of a patient’s cancer and the most important immunosuppressive factors impeding its rejection. And for the first time, we may have the means to use this information in a clinically effective way. Many have spoken about the immune response using an automotive metaphor—"driving" the T-cell response and "taking off the brakes." Now, access to patient-specific molecular tumor analysis may provide us the "roadmap" we will need to reach curative cancer immunotherapies.

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The Immunotherapy Roadmap
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