By means of well-characterized autoimmunity models, we comparatively probed the "selfness" of malignant cells and their normal counterparts. We found that tumors activate self-tolerance mechanisms much more efficiently than normal tissues, reflecting a status of immunoprivileged "self." Our findings indicate that potent autoimmune responses can eradicate established malignancies, yet the collateral destruction of healthy tissues may prove difficult to circumvent.

Recent clinical trials testing immunotherapeutic anticancer regimens have generated exciting results. The ultimate success of such interventions, however, will likely depend on the immunological identity of tumors. Adaptive immunity is characterized by fine specificities, owing to a lymphocyte repertoire that is capable of discriminating the "self" from "non-self" tissues. Tumors represent a dilemma to this dichotomy. Cancer cells originate indeed from the malignant transformation of healthy cells, i.e., they have a self origin. However, neoplastic cells are also characterized by genomic instability and hence presumably generates an array of new antigens (neoantigens) that may not be perceived as self by the immune system. A long-standing premise of tumors as "altered self" entities posits that malignant cells can be perceived as self by the immune system. Of note, a large body of evidence from experimental tumor models indicates that cancer-specific immunity can be readily achieved, and that antitumor immune responses can eradicate neoplasms, e.g., melanoma.

By means of well-characterized autoimmunity models, we comparatively probed the "selfness" of malignant cells and their normal counterparts. We found that tumors activate self-tolerance mechanisms much more efficiently than normal tissues, reflecting a status of immunoprivileged "self." Our findings indicate that potent autoimmune responses can eradicate established malignancies, yet the collateral destruction of healthy tissues may prove difficult to circumvent.
Figure 1. Tumor as an “altered self” or “immunoprivileged self” entity. The hypothesis that self epitopes are abundant in the antigenic repertoire of tumor cells is based on the facts that tumor-specific antigens (TSAs) are difficult to identify and that antitumor immune responses often target self antigens. Blue dashes depict the immunosuppressive microenvironment that is often associated with tumors. Oval areas reflect overall tumor burdens and do not necessarily represent individual tumor sites. Ab, antibody; TIC, tumor-initiating cell.

oncogenesis. Thus, the study was not a direct refutation of the “altered self” view or the immunosurveillance hypothesis.5 Likely, both a situation of “altered self” and one of “immunoprivileged self” could be represented in the natural history of spontaneous tumors.

Nevertheless, the premises of tumor as an “altered self” or an “immunoprivileged self” entity have distinct implications for antitumor immunity and immunotherapy (Fig. 1). On one hand, according to the “altered self” view, genetic changes in tumor-initiating cells (TICs) generate an array of neoantigenic epitopes.
Tumors evade the attack of the immune system by establishing a microenvironment constituted by immunosuppressive cells and factors. Targeting tumor-specific antigens while blocking immunosuppressive factors can reduce the tumor burden and eventually eradicate neoplastic lesions. On the other hand, according to the “immunoprivileged self” view, despite substantial genetic and epigenetic changes, neoantigens would account for a minimal fraction of the antigenic repertoire of TICs as compared with self antigens. Thus, established tumors are largely “self” in their immunological identity. Furthermore, immunosuppressive elements orchestrated by self-antigen-specific Treg cells form a local microenvironment that can inhibit even potent autoimmune responses. In this setting, neoantigen-specific antitumor immunity edits the antigenic identity of neoplasms to limited extents, leaving untouched the tumor immune privileges.

Is cancer an immunological problem or an oncological one? 1 The “immunoprivileged self” hypothesis would suggest that cancer is an immunological problem at its root, yet the eradication of this problem would be beyond the reach of immunology in the absence of oncological interventions. “But the worst enemy you can meet will always be yourself…,” as the nineteenth century German philosopher Friedrich Nietzsche wrote in Thus Spoke Zarathustra, which also stated, “You must be ready to burn yourself in your own flame…” Tumor as an “immunoprivileged self” entity may constitute the worst possible challenge for the immune system. Autoimmune inflammatory reactions could be effective as the body’s own “flame” but only if “burns” are not life-threatening. Therefore, the impact of immunotherapy by itself may be limited, unless the tumor antigenic repertoire is substantially altered or its immunoprivilege eliminated by physical interventions such as surgical removal, radiation therapy or chemotherapeutic agents.

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

References
1. Hodi FS, O’Day SJ, McDermott DE, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711-23; PMID:20525992; http://dx.doi.org/10.1056/NEJMoa1003466
2. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DE, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366:2443-54; PMID:22658127; http://dx.doi.org/10.1056/NEJMoa1200690
3. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366:2455-65; PMID:22658128; http://dx.doi.org/10.1056/NEJMoa1200694
4. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 1971; 68:820-3; PMID:5279523; http://dx.doi.org/10.1073/pnas.68.4.820
5. Burner FM. The concept of immunological surveillance. Prog Exp Tumor Res 1970; 15:1-27; PMID:4921480
6. Caspi RR. Immunotherapy of autoimmunity and cancer: the penalty for success. Nat Rev Immunol 2008; 8:970-6; PMID:19088897; http://dx.doi.org/10.1038/nri2438
7. Misu J, Bai E, Devarajan P, Chen Z. Autoimmunity-mediated antitumor immunity: tumor as an immunoprivileged self. Eur J Immunol 2012; 42:2584-96; PMID:22777737; http://dx.doi.org/10.1002/eji.201242590
8. Benhar I, London A, Schwartz M. The privileged immunity of immune privileged organs: the case of the eye. Front Immunol 2012; 3:296; PMID:23049533; http://dx.doi.org/10.3389/fimmu.2012.00296
9. Gilboa E. The risk of autoimmunity associated with tumor immunotherapy. Nat Immunol 2001; 2:789-92; PMID:11526387; http://dx.doi.org/10.1038/ni0901-789
10. Zitvogel L, Kroemer G. OncoImmunology: a new journal at the frontier between oncology and immunology. Oncoimmunology 2012; 1:1-2; PMID:22720206; http://dx.doi.org/10.4161/onci.1.1.17645