COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Zitvogel and Kroemer reply:

Using various transplantable mouse tumor models and methylcholanthrene-induced sarcomas, our group pioneered the concept that the immune system contributes to the therapeutic efficacy of chemotherapy, provided that three factors are considered.

First, the cytotoxic agent matters. Anthracyclines, oxaliplatin, cyclophosphamide and ionizing irradiation are particularly effective in eliciting tumor-specific T helper 1 (T_H1) and/or T cytotoxic 1 (T_c1) cell responses, but many other anticancer agents are ineffective in this regard[1].

Second, the tumor type matters. Only tumor cells that are able to expose calreticulin[1] (as a result of an endoplasmic reticulum (ER) stress response) and release both ATP (as a result of autophagy)[2,3] and high mobility group box 1 (HMGB1) (as a result of late apoptosis)[4] in response to chemotherapy stimulate an anticancer immune response. Thus, the drug-induced tumor-cell stress must trigger an ER stress response[1], autophagy[3] and late apoptosis[4] to induce the intratumoral accumulation of dendritic cells, γδ T cells (producing interleukin-17) and $CD8^+$ T lymphocytes (producing interferon-γ), which contribute to the anticancer effects of anthracyclines and oxaliplatin[3].

Third, the host matters. Individuals with tumors that are severely immunodeficient or unable to sense the aforementioned danger signals (by Toll-like receptor 4 (TLR4), myeloid differentiation primary response gene 88 (Myd88) or purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7)) do not respond to chemotherapy)[2,4].

These experimental findings are in concordance with several clinical reports describing the relevance of immunogenic cell death to vaccine-elicited immune responses in humans[5], as well as the predictive role of tumor-infiltrating lymphocytes[6] or major histocompatibility complex (MHC) class I expression[7] in the response to neoadjuvant anthracycline-based chemotherapy in breast cancer. Considered together, the available evidence suggests that chemotherapy is more effective if it stimulates an active anticancer immune response[8].

In sharp contrast, de Visser *et al.*[9] provide evidence that adaptive immune responses are dispensable for both therapy with anthracyclines and platinum-based therapies to efficiently delay the manifestation of two distinct oncogene-driven mammary tumor models. We propose two explanations for these results. First, oncogene-driven tumorigenesis might subvert MHC class I expression, ER stress and/or the autophagy machineries[10]. Second, oncogene-driven cancers might not elicit (or might actively subvert) immunosurveillance mechanisms[10], as suggested by the fact that ablation of the immune system does not alter the incidence and manifestation of neoplasia in either of the two breast cancer models examined in de Visser *et al.*[9] Indeed, it remains elusive whether conventional cytotoxic drugs trigger *de novo* priming of a novel T cell repertoire or merely help reactivate a pool of memory effector cells that was previously primed during early oncogenesis. If this latter possibility were the case, the absence of a preexisting anticancer immune response (that is, occurring before therapy) might explain the negative data reported by de Visser *et al.*[9]. The fact that T cells infiltrating the tumor at diagnosis can predict the efficacy of neoadjuvant chemotherapy in patients with breast cancer[6,8] may favor the existence of a pre-therapeutic immunosurveillance mechanism that is reactivated by chemotherapy.

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HIV-1 Env antibodies: are we in a bind or going blind?

To the Editor:

In his *Nature Medicine* 'Bedside to Bench' paper, Tom Hope makes interesting points about the possible roles of neutralizing and non-neutralizing antibodies (NAbs and non-NAbs, respectively) in protection against HIV-1 infection in the RV144 vaccine trial[1]. The efficacy in that trial ranged from a significant 31.2% to a non-significant 26.2%, depending on the statistical method used; when volunteers who became infected with HIV-1 before receiving the full vaccine regimen were excluded, the vaccine had no significant efficacy[2,3]. Opinions, therefore, vary on how much this trial should influence the future direction of vaccine research.

Hypotheses about any protection seen in the RV144 trial generally involve antibodies. Most RV144 participants developed very low titers of gp120-binding antibodies and had only marginal NAb responses. The average titer for antibodies to gp120 in RV144 participants was about 10% of that seen in the AIDSVAX trial of the same gp120s,