Translation of cancer immunotherapies

To the editor:

In a recently published commentary[1], Pardoll and Allison make several valid points about the barriers to translation of promising immunotherapies from the laboratory to the clinic, and raise further awareness of the issues surrounding increased regulatory burdens for academic investigators. Much of their focus is on the National Cancer Institute (NCI) and US Food and Drug Administration (FDA), federal agencies responsible for funding and regulating immunotherapy drug development. They indicated that the overly complex burden placed by the FDA on university investigators stands in the way of new immunotherapeutic drug development.

The overall mission of the FDA in its regulatory role remains patient safety. It is simply inconceivable that the burden of proof for the safety of a new product or combination, whether developed by academic investigators or by companies, be relaxed. But without diminishing the need for certain regulatory reform, we believe in the old adage that 'good education starts at home' and that the authors perhaps place too large of an onus on the NCI and the FDA to lift barriers to progress in the field on biologics and immunologic therapies. Rather, we believe that difficulties arise when translational, lab-based investigators with preclinical data on promising drugs who are unfamiliar with the complexities of the drug development process and the FDA's investigational new drug (IND) application process wish to pursue the meritorious path of taking their drugs forward to a clinical trial. The FDA must continue to improve upon its special relationship with investigators who will generally be involved in early phase 1 and 2 studies and not the later phases of development.

The undersigned are academic investigators who have filed multiple investigator INDs in the past decade and have found the FDA to be genuinely interested in promoting the development of new and innovative agents, individually or in combination. We have not perceived the FDA to be antagonistic to the development of treatment regimens involving experimental agents in new combinatorial clinical strategies, as claimed by Pardoll and Allison. The complex and often arcane pathways usually known only to a few investigators by which new drugs are developed, including pre-IND meetings, the filing of the investigator IND and the necessity for annual reports and serious adverse event reporting are tedious and could be streamlined. Greater representation by FDA personnel in the proceedings of meetings like those of the American Society of Clinical Oncology, the European Organization for the Research and Treatment of Cancer and the American Association for Cancer Research, their presence at smaller disease-oriented conferences and new initiatives in which young clinical investigators visit the FDA for a regulatory orientation or attend seminars taught by senior FDA officials and learn the ins and outs of the regulatory and approval process are promising. The answer to faster drug development is not less oversight by the FDA; rather, it is greater education about and familiarity with the regulatory and approval process by investigators.

We agree with Pardoll and Allison that the regulatory infrastructure required for translational trials cannot practically be included within current R01 and R21 funding. NCI and other institutes of the US National Institutes of Health (NIH) must augment Cancer Center and other grants to provide a greater level of infrastructural support to assist investigators in navigating the increasingly complex regulatory waters. As an example, the NIH road map has jump-started an initiative to develop regional translational research centers (see the National Center for Complementary and Alternative Medicine website), which could provide important new infrastructure. Universities must invest their NIH overhead dollars to increase infrastructural support and education in clinical regulatory matters. The FDA will also need to do a better job of educating and informing investigators, and seeking a closer partnership with university-based investigators to move immunotherapeutic agents singly or in combination forward to clinical trials.

The most important hurdles to more rapid development of complex combination immunotherapies are issues of intellectual property, product liability and profit. The NCI is not a legislative or judicial body, and however well meaning, cannot enforce its will to induce companies to allow investigators access to their products and proprietary information. An independent effort, possibly linked to an entity like the Immune Tolerance Network, or supported by charitable donations and consortia of universities and companies akin to that achieved by the semiconductor industry might break the log-jam in immunotherapy development by providing legal, administrative and financial resources.

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1. Pardoll, D. & Alison, J. *Nat. Med.* **10**, 887–892 (2004).

Pardoll and Allison reply:

Mulé and Weber correctly point out that, although our commentary focused on the importance of developing enhanced mechanisms for continuing education of the FDA on new developments in biologic and immunologic therapies, an equal if not greater 'regulatory barrier' is failure of education on the part of academic investigators regarding established pathways to therapeutics development. Indeed, few institutions have created any formal internal educational mechanism for regulatory issues, although recognition of this need is increasing as the number of investigator-held INDs grows. A further problem on which all agree is the lack of funding mechanisms to support key regulatory affairs personnel to assist investigators developing more complex combinatorial strategies. In the case of cancer, the NCI-designated Cancer Center Support Grants are an obvi-