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2. H. Shimojo, *Bibl. Haematol.* (no. 40) (1975), p. 771; A. Oya, *ibid.*, p. 775.
3. *Safety in Healthcare Laboratories* (World Health Organization, Geneva, 1997), p. 16.

Patenting Genomic Technologies

The review article "Can patents deter innovation? The anticommons in biomedical research" by Michael A. Heller and Rebecca S. Eisenberg (*Science*'s Compass, 1 May, p. 698) has errors of fact and some erroneous assumptions as it relates to Cre-loxP patents owned and administered by the DuPont Pharmaceuticals Company.

Heller and Eisenberg misstate a purported DuPont "right to participate in future negotiations to develop commercial products that fall outside the scope of their patent claims" and our purported ability and intent "to leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development." We reserve neither right in our license agreements with academic and other not-for-profit institutions.

Cre-loxP is a highly regarded recombinase system that has demonstrated ability to efficiently and selectively introduce or delete DNA segments into the genome, even in quiescent postmitotic cells. DuPont has put this valuable technology into the academic domain at no cost and with a few necessary and limited restrictions. It is our sincere desire to broadly disseminate this valuable technology. To date, hundreds of academic research licenses have been granted, enabling scientists to push ahead with critical research. In such academic agreements, DuPont reserves the right to "pay a reasonable royalty or other financial consideration" and "will negotiate in good faith" to obtain nonexclusive, grant-back rights to improvements in the technology, a de minimum recognition that DuPont provides the technology at no charge to academics. If academic institutions desire to transfer technology using Cre-loxP to other nonprofit institutions, DuPont allows such transfer, providing that the recipient institution has signed a free research license. In keeping with DuPont's mission to make Cre-loxP widely available to the research community, all such transfers are favorably considered.

Academic research licenses are intended to allow unfettered intellectual pursuit, but *not* to allow free transfer of valuable intellectual property from the not-for-profit sector to the commercial realm. If academic institutions develop novel uses for Cre-loxP that they wish to commercially license or transfer to a for-profit entity, DuPont reserves the right to negotiate, along with others, with the institution in question for possible use of that new commercial product. Any transfer of Cre-loxP–based technology from the nonprofit to the commercial setting involves a "good faith negotiation of an arrangement, in either cash or non-cash consideration, and consistent with the contribution made by the Licensed Patents." In essence, if an academic institution deviates from its free research license and uses Cre-loxP technology in pursuit of commercially applicable research, there is a "transfer tax" imposed to move this from the academic to the commercial universe. No reasonable person could expect DuPont to enable academic researchers to commercialize inventions using our patented processes, obtained at no cost, without recognizing the contribution of this enabling technology.

DuPont has paid, and continues to obligate itself to pay, millions of dollars to universities and government institutions for access to patented technologies. DuPont believes that it is appropriate to pay for enabling and proprietary technology, so long as there are no stacking downstream obligations for nonpivotal technologies. Hundreds of scientists with a primary interest in advancing scientific knowledge have benefited and continue to benefit from free access to Cre-loxP technology. DuPont is proud to have contributed such an exciting technology into common use and is pleased by its rapid adoption.

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Response

In our review, we cited DuPont's Non-Commercial Research License Agreements for Cre-loxP as one example of a reach through license agreement (RTLA) that provides access to upstream biomedical research tools in exchange for rights in future discoveries. Our concern is that as RTLAs proliferate, upstream owners will stack competing, inconsistent claims on top of future commercial products. The greater the number of owners who need to reach agreement, the greater the risk that bargaining will fail. The result may be a "tragedy of the anticommons," in which more upstream patent rights paradoxically lead to fewer downstream products.

The letter by Block and Curran contains ambiguities that leave us uncertain as to their meaning. They concede that, at least for "Cre-loxP–based technology," the agreements reserve a place at the bargaining table for DuPont in future "good faith negotiation." Perhaps, then, the error in our characterization was that further negotiations with DuPont would not be necessary for the transfer of discoveries that fall outside the scope of DuPont's patents. But elsewhere their letter suggests that users of Cre-loxP might be expected to pay a "transfer tax" to DuPont before pursuing commercial development of discoveries that were "enabled" by the use of Cre-loxP.

The language of DuPont's Non-Commercial Research License Agreement echoes these ambiguities. We have seen different versions of this agreement, some signed and others negotiated to impasse over certain key provisions. The agreements confer a license to use Cre-loxP technology "for Research Purposes only" and require the licensee to apply to DuPont for an additional license before using the technology for "Commercial Purposes." Two specific examples of "research for Commercial Purposes" are set forth, neither of which seems likely to involve ongoing use of Cre-loxP technology: (i) "research and development of therapeutic products towards filing of an IND [investigational new drug]," or (ii) "research, development and clinical trials towards commercialization of products resulting from such efforts." DuPont retains a veto right over all activities falling within its definition of use for "Commercial Purposes" by specifying that "[s]uch license, if any, is to be granted at the sole discretion of DuPont."

If, contrary to our characterizations, these agreements do not give DuPont "the right to participate in future negotiations to develop commercial products that fall outside the scope of their patent claims" and do not permit DuPont "to leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development," then what exactly do these provisions mean?

Suppose that an academic scientist uses Cre-loxP to create research animals in order to study the function of a particular gene. In the course of these studies, the scientist observes that the gene appears to

play a role in a particular disease. As the scientist continues to study the disease pathway, perhaps in collaboration with colleagues at other institutions, the research eventually yields a molecule that might serve as a drug target and may have commercial value. Further use of Cre-loxP is not necessary for drug screening, but arguably it was "directly or indirectly" through prior use of Cre-loxP, under the terms of DuPont's Non-Commercial Research License Agreement, that the target and its function were identified. May the university enter into licenses with commercial firms without having to negotiate further with DuPont? Or must the university seek a commercial license "at the sole discretion of DuPont"?

If DuPont's rights under the agreement reach through to subsequent discoveries that do not make ongoing use of Cre-loxP, we stand by our initial characterizations. If the university has no further obligations to DuPont, DuPont could spare itself and its licensees the burden of costly and time-consuming negotiations by specifying in its agreements that "nothing in this agreement gives DuPont any rights to any future invention made possible through prior use of Cre-loxP technology, except to the extent that use of the invention involves ongoing infringement of DuPont's patents."

Piercing the fog of any single RTLA is exhausting. As more such agreements are proposed, more time is consumed reviewing and renegotiating their terms. As more such agreements are signed, their provisions will inevitably come into conflict, requiring future negotiations over rights to future products. Each agreement increases the threat that promising biomedical discoveries will be forgone in a tragedy of the anticommons.

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CORRECTIONS AND CLARIFICATIONS

In the 16 October letters by Michael D. Green and George W. Pearsall published under the title "Standards for engineer witnesses" (*Science*'s Compass, pp. 415 and 416, respectively), the name of the company Merrell Dow Pharmaceuticals, Inc. was misspelled. The name was also misspelled in the News of the Week article "Should engineers meet same standards as scientists?" by Jocelyn Kaiser (11 Sept., p. 1578).

Figure 5 (p. 703) in the Research Article "The transcriptional program of sporulation in budding yeast" by S. Chu *et al.*, 23 Oct., p. 699) was printed incorrectly. The correct figure appears at right.