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Patent amplification

To the Editor:

As the inventor of the Kauffman/Ballivet patent, I read with interest your recent commentary (*Nature Biotechnol.* **17**, 2, 1999). I believe I can contribute two important additional pieces of information.

First, the commentary presents a brief chronicle of scientific literature pertinent to the Kauffman/Ballivet patent. The date of filing of the patent is critical in order to evaluate this literature in the context of prior art. The Kauffman/Ballivet patent series claims priority from early 1985.

Second, the final sentence of the piece expresses the hope that the price of licensing the Kauffman/Ballivet patent will not be too high. In fact, we intend to make the patent available on a nonexclusive basis to anyone who needs it. To this end, it is interesting that reference is made in your piece to the Cohen and Boyer patent. We have developed a licensing program in consultation with Niels Reimber who devised the licensing program for the Cohen and Boyer patent.

I hope this information is useful.

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To the editor:

A recent commentary by Harvey Bialy (*Nature Biotechnol.* **17**, 2, 1999) addressed a patent awarded to Stuart Kauffman and Marc Ballivet. Bialy is certainly correct that the patent is "every bit as fundamental…and every bit as important" as that of Stanley Cohen and Herbert Boyer covering recombinant DNA technology. However, I must correct the record with respect to the nine scientific publications that Bialy characterizes as "pertinent to Kauffman's staggeringly broad claims."

The referenced publications do not constitute history against which the patentability of the issued claims is to be judged. The Kauffman–Ballivet patent application was, in fact, filed in 1985, prior to all but one of the references cited in the commentary. Furthermore, Hutchinson et al., which had indeed been previously published, describes only the methods that had become conventional by 1985 for introducing single sequence changes into DNA. It is in fact Kauffman's pioneering technique of producing stochastically generated arrays of polymers that distinguishes his invention from the conventional wisdom of the time and supports the award of proprietary protection.

Bialy further expresses the "hope that the US Patent Office has been rigorous" in its evaluation of Kauffman's application for patent. As an attorney of record of the application, I can assure him and your readers that it has. Numerous references, including scientific articles and published patent documents, were considered by the US Patent Office during the extensive examination determining the patentability of the claimed invention. None was found to anticipate or render obvious the elegant invention of Kauffman and Ballivet.

I would also point out that the patent to which the commentary is directed is but one of five related patents that have thus far issued from the original application; each claims different aspects of the original invention of Kauffman and Ballivet.

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Uncloaking RNases

To the editor:

We would like to comment on the recent paper describing ribonucleases (RNases) engineered to be resistant to the intracellular RNase inhibitor (RI) (Suzuki et al., *Nature Biotechnol.* **17**, 265, 1999) and the accompanying analysis "Smartbombs and cloaking devices" because we feel that the authors of the respective pieces neglected to clearly frame these results in the context of other work in this emerging field.

Several published studies suggest that the role of RI in RNase cytotoxicity is not straightforward; there is not always a positive correlation between RI resistance of engineered RNases and cytotoxicity. In one example, two hybrid rhRNase-onconase proteins were equally cytotoxic to cells, even though one of the hybrids was 100,000 times more sensitive to inhibition by RI[1].

These results suggest that factors other than RI sensitivity affect cytotoxicity. In this regard onconase and RNase A were shown to cause cell death by affecting different points is the cell cycle in NIH/3T3 fibroblasts[2]. Thus, intracellular targets of individual RNases have to be considered as well as RI inhibition.

Misreferencing obscured other important contributions in this field. Deonarain and Epenetos[3] designed, engineered, and expressed an sFv-bovine seminal RNase fusion protein targeted to the placental antigen alkaline phosphatase, and not Zewe et al.[4] Work on a small chimeric anti-transferrin receptor single-chain sFv fused to the human RNase angiogenin by Newton et al.[5] was assigned to Deonarain and Epenetos, while Zewe et al. actually engineered the same sFv with pancreatic rhRNase and rhEDN[4].

All of these fusion proteins engineered with "uncloaked RNases" were potent cytotoxins to their respective target cell lines. Was RI not present in those cell lines or was it in a compartment not accessible to the targeted RNases? To try to resolve these questions, future feats of imaginative engineering should be combined with studies of cellular biology to correlate RNase cytotoxicity with direct measurement of intracellular RI levels, RNase mechanism and intracellular routing.

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1. Boix, E. et al. *J. Mol. Biol.* **257**, 992–1007 (1996).
2. Smith. M. et al. *Exp. Cell Res.* **247**, 220–232 (1999).
3. Deonarain, M. et al. *Br. J. Cancer* **77**, 537–546 (1998).
4. Zewe, M. et al. *Immunotechnology* **3**, 127–136 (1997).
5. Newton, D. et al. *Biochemistry* **35**, 545–553(1996).