

More views on Imanishi-Kari

Professor Mark Ptashne describes evidence to explain the disputed *Cell* paper, Dr Herman N Eisen (who conducted the MIT inquiry in 1986) concurs, Dr John Cairns (in letter to an unidentified official of the US National Academy) says the affair is the equivalent of Watergate and a former co-worker offers a testimonial to Imanishi-Kari.

From Mark Ptashne (Harvard)

In his account in *Nature*¹ of the MIT inquiry into the "Baltimore affair", Dr Herman Eisen raises one scientific point, and that point deserves some comment.

The central claim of Weaver *et al.*² is as follows: introduction into a mouse of a rearranged gene encoding an immunoglobulin heavy chain with a specific idiotype elicits production of antibody heavy chains that bear the transgene idiotype; remarkably, many of these chains are encoded entirely by endogenous genes. Why might one find such a result important? In the authors' words, the result "...suggests that a rearranged gene introduced into the germ line can activate powerful cellular regulatory influences." According to one interpretation, the result could be a manifestation of the workings of an "idiotype network"; the idiotype network idea, suggested several years ago, has not received strong experimental support.

Two papers published in 1989^{3,4} address the question of whether the central claim might be generally correct. Both of these papers report the use of a mouse to which has been added a rearranged heavy-chain immunoglobulin gene — the idiotype encoded by this gene is different from the one studied by Weaver *et al.*² As in Weaver *et al.*, however, the transgene in these new experiments encodes a heavy chain of type μ^a , whereas the endogenous μ gene is of type μ^b . The paper of Rath *et al.*⁴ shows that these transgenic mice do express antibodies with idiotype of the transgene (called AD8-reactive), but "...all detectable AD8 reactivity was associated with molecules expressing the μ^a allotype and none was detected in association with molecules lacking μ^a ." (Note, for example, that the idiotype was found neither on endogenous γ nor on endogenous μ chains.) Moreover, these idiotype-bearing μ^a chains were found in association with μ^b heavy chains in chimaeric molecules, an additional finding relevant to the controversy over Weaver *et al.*² as I explain below.

The paper of Durdick *et al.*³ finds that following immunization of these transgenic mice with the antigen that interacts with the

transgene product, idiotype can be found associated with γ heavy chains. Molecular analysis reveals, however, that the heavy chains of these antibodies are encoded by recombinants formed between the variable region of the transgene and an endogenous γ gene. These two papers thus fail to replicate, in an experiment involving a different idiotype, the central claim of Weaver *et al.*².

Dr Eisen, in his statement I alluded to at the beginning of this letter, says of Dr M. O'Toole, "But I did not agree with several of her arguments. For example, her assertion that some of the results could be explained by heterodimer formation, which I take to mean μ - γ chimaeric molecules is highly implausible". But O'Toole was referring not to μ - γ chimaeras but to μ - μ chimaeras: her memo to Eisen dated 6 June 1986, states "In sum-

mary, the data on transgenic sera in figures 1 and 2 can be explained...by heterodimer formation." In fact, Fig. 1 of Weaver *et al.*² involves testing only for μ chains, and Fig. 2 does not involve any isotyping. O'Toole's explanation, according to Rath *et al.*⁴, is eminently reasonable and readily testable.

I thank Herman Eisen for graciously reviewing this matter with me (see below). □

From Herman N. Eisen (MIT)

SIR — In my response¹ to Dr O'Toole's previous comments² I referred to her earlier suggestion (in a June 6, 1986 memo) that "heterodimer" formation could account for some of the reactivity in sera from the transgenic mice studied in the disputed paper in *Cell*. I took the term heterodimer to mean a mixed μ - γ (or μ - α) dimer involving one μ ▶

To an officer of the National Academy of Sciences, 28 June 1991

AFTER our conversation, I thought I should produce a list of what I believe are the most important components of the so-called Baltimore affair.

(1) It seems that O'Toole was right in saying that the paper should be withdrawn (as eventually it was), right in thinking that there may have been misconduct (as the Secret Service now claim to have demonstrated) and right in her alternative interpretation for the central section of the paper (see the letter from Mark Ptashne).

(2) Nothing now is likely to stop the affair from progressing to its final disastrous conclusion, and I do not see how the authors of the paper can escape public censure, at the very least. About the only question remaining is whether anyone will actually go to jail.

(3) The whole affair seems to be turning into a kind of scientific Watergate and, like Watergate, is surely destined to be dissected and analysed for years to come.

(4) Some of the blame falls on the scientific community — on those who arranged and conducted the initial, perfunctory inquiries — on the National Academy for not demanding a proper investigation — and on the many scientists who did not look at the evidence and, instead, construed the whole business as a Congressional manoeuvre to attack the scientific establishment. (I remember that originally I too felt that the row was probably a political stunt.)

(5) Because the establishment has played such an undistinguished role, we may find it increasingly difficult to maintain the idea

that science is a genuine search for truth and that scientists are generally honourable and deserving members of society. Simply at the mundane level of money, I could imagine fund-raising for the Academy becoming much harder if Congress is left with the image of the Academy as the organization that sided with Baltimore right or wrong, through thick and thin, to the bitter end.

(6) So I believe that, although it now too late to do much good, the Academy should be issuing a statement (a) reaffirming the aims of science and (b) pointing out that if the rules and principles of science had been observed we wouldn't now be in this mess. For most scientists, science is the pursuit of a truth that is external to our wishes. This truth is quite unlike the verdict of a court of law because it does not depend on advocacy. Instead, each of us has to be responsible for the accuracy of our own statements; we cannot simply count on others to correct our mistakes. Each of us knows more about our own experimnts than anyone else, and when something goes wrong we have to speak up. If the Academy does not say something like that, American scientists may end up with the same kind of public image as many of the country's lawyers and politicians — which would do a great disservice to all young scientists.

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1. Eisen, H. *Nature* **351**, 343 (1991).
2. Weaver, D., Reis, M. H., Albarese, C., Costantini, F., Baltimore, D. & Imanishi Kari, F. *Cell* **45**, 247-259 (1986).
3. Durdick, J. *et al. Proc. natn. Acad. Sci. U.S.A.* **86**, 2346-2350 (1989).
4. Rath, S., Durdick, J., Gerstein, R. M., Selsing, E. & Nisonoff, A. *J. Immun.* **113**, 2074-2080 (1989).
5. O'Toole, M. *Nature* **351**, 180-183 (1991).