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Anti-Gal antibodies—where's the beef?

To the editor:

In your July issue¹, Carl Borrebaeck avers that murine glycosylation patterns on murine antibodies, and on human antibodies produced in murine cells, will target them for rapid clearance by natural anti-Gal antibodies in humans. But the data defy him.

First there is no evidence for reactivity in vivo. The detection of weakly reactive antibodies in an ELISA assay¹ is not the most appropriate model for what happens in vivo. Many polyreactive antibodies of low affinity exist in serum², but at concentrations is generally well below their K_D ; little of the antigen will be bound in complex. Moreover, use of purified preparations for these assays is known to overstate significantly the effective immunotargeting of polyreactivities in serum³. If anti-Gal antibody were a real phenomenon affecting survival of murine or murine-produced antibodies, it would routinely reveal itself as high levels of HAMAs (or HAHAs) in baseline serum assays in patients, but this is not the case.

Second, there is no physical evidence of such complexes in vivo. We have examined dozens of samples of tracer- or therapeutically radiolabeled mouse and human(ized) antibodies on HPLC sizing columns, either drawn from patients after infusion or by spiking labeled antibody into sera. All show a homogeneous peak in human sera, which is not displaced relative to the same antibody incubated in saline⁴. Yet soluble antigen-antibody complexes are readily detectable in individuals with high antigen levels⁴⁻⁷, in a relation^{4,5,7} that is not to be confused with the postulated anti-Gal antibody-antibody complexes. If there is an immune recognition of significance against Gal-containing mouse or human antibodies, it should be routinely detectable as complexes in vivo at baseline, but this is not the case.

Finally, an abbreviated half-life due to anti-Gal reactivity is simply not true. The humanized anti-Tac antibody, Zenapax, is grown in mouse cells with murine glycosylation patterns. In 92 patients treated, Zenapax had an average survival time of 20 days¹⁰, essentially indistinguishable from "human-grown" human IgGs (23 ± 4 days)¹¹. Similarly for Synnapsis¹² and ABX-IL8¹³. Thus of three humanized or human antibodies grown in mouse cells for which clinical data are avail-

able, none exhibits an accelerated clearance in humans.

There is no evidence for a baseline anti-antibody-mediated clearance, by anti-Gal or any other humoral activity. Accordingly, any further debate should be accompanied by new, clinical data that directly addresses the hypothesis, which has so far been lacking.

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1. Borrebaeck, C. *Nat. Biotechnol.* **17**, 621 (1999).
2. Casali, P. et al. *Immunol. Today* **10**, 364-368 (1989).
3. Moulton, L. J. *Immunol.* **154**, 5769-5778 (1995).
4. Hagg, D.S. et al. *J. Immunol. Methods* **219**, 7-21 (1998).
5. Sharkey, R.M. et al. *Cancer Res.* **50**, 2823-2831 (1990).
6. Junghans, R.P. et al. *J. Biol. Chem.* **271**, 10453-10460 (1996).
7. Junghans, R.P. et al. *Proc. Natl. Acad. Sci. USA* **95**, 1752-1757 (1998).
8. Pimm, M.V. J. *Nucl. Med.* **26**, 1011-1023 (1985).
9. Reynolds, J.C. et al. *Int. J. Rad. Appl. Instrum. [B]* **16**, 121-125 (1989).
10. Vincenti, F. et al. *N. Engl. J. Med.* **338**, 161-165 (1998).
11. Waldmann T. et al. *Prog. Allergy* **13**, 1-110 (1969).
12. The Impact-RSV Study Group. *Pediatrics* **102**, 531-537 (1998).
13. Krueger, J. et al. Presentation, XXII Annual Hawaii Dermatology Seminar (February 1999).

Public and private plant breeding

To the editors:

A survey conducted by Ken Frey at Iowa State University shows that plant breeding research and development in the public sector has decreased 2.5 scientist-years per year from 1990 to 1994¹. During the same period private industry was found to have an annual net growth of 32 scientist-years. The availability of Plant Variety Certificates, plant patents, and the extension of utility patents to cover new varieties as well as plant tissues and genes has contributed to industrial interest in the area. Indeed, technical advances being made by industry may equal or exceed those being made by the public sector. Thus, it may be necessary for all public programs to contain some level of genetically engineered material from industry.

I sent the following survey to 187 public plant breeders; it was subsequently sent to others. The final number who actually received it is unknown.

I have spoken with several plant breeders who have told me that difficulties associated with obtaining "protected genetic stocks" from companies has harmed plant breeding in the public sector. I'm trying to determine how widespread this is.

1. Are you having difficulties obtaining genetic stocks from companies?
2. If yes, has this interfered with your plant breeding research?
3. If yes, has this interfered with your ability to release new varieties?
4. If yes, has this interfered with training of graduate students?

I received 86 responses, representing 25 US universities and 41 crops. Forty-eight percent indicated that they had experienced difficulty in obtaining genetic stocks from private companies; 45% indicated that this

had interfered with their research; 28% felt that it had interfered with their ability to release new varieties, and a shocking 23% reported that it had interfered with the training of graduate students.

This informal survey raises a number of questions:

(1) What is role of public breeding? Is it in the public interest to have future varietal releases done predominantly by industry, especially in light of the industry consolidations, with a concomitant potential decrease in genetic variability? (2) Should more public money be used to maintain a critical mass of public plant breeders? (3) Should industry be content to train plant breeders? If the numbers of plant breeders are decreasing, what does this mean for the future supply of plant breeders for industry?

Many of these problems trace back to "material transfer agreements" (MTAs). Negotiating these will continue to be difficult until the public and private sectors agree on a common culture. This will probably include an acknowledgment that: (1) Title to inventions and/or varieties made will reside with universities; this is mandated by most universities' policy, culture, and federal law. (2) Universities will be required to grant exclusive licenses to industry. (3) Industry will be required to pay royalties for licenses (whether exclusive or nonexclusive) to plant materials developed by universities.

Individuals at the highest levels in industry and academia must meet to discuss these issues. If every MTA starts with each side putting its most onerous terms forward, then negotiations will continue to be slow and the public sector breeders will be hurt in the near term; in the long run, companies may be hurt by a decrease in trained plant breeders. Finally, the public may be hurt by decreased genetic diversity resulting in fewer varietal choices.

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1. Iowa State Univ, *National plant breeding study*. (1996).

Erratum

In the August Business and Regulatory News (*Nature Biotechnology* **17**, 744-745, 1999), the article states that Japan will create a repository of 70,000 cDNA clones obtained from the Japanese population.

The figure should have read 30,000 cDNA clones. The article was also incorrect in stating that a database of SNP map data will be created using SNPs within protein-coding sequences by analyzing full-length human cDNA. The database will comprise SNPs in the promoter region, coding sequences, and the adjacent introns, using genomic DNA from 50 individuals.