

## nature biotechnology

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### Plant ferritin and human iron deficiency

To the editor:

The paper by Goto et al.<sup>1</sup> in your March issue highlights overexpression of the iron storage protein ferritin in transgenic plants as an approach for treating iron deficiency in humans. Goto et al. overexpress iron in seeds, achieving a threefold increase in iron content in seeds, levels comparable to experiments in my laboratory in which ferritin was overexpressed in leaves<sup>2</sup>. Another group has shown that oral administration of plant ferritin can alleviate iron deficiency anemia in rats<sup>3</sup>. These findings have promulgated the idea that iron-fortified transgenic plants overexpressing ferritin could be used to mitigate iron deficiency in the human diet<sup>1</sup>.

Iron uptake, however, is not determined only by levels of iron storage proteins. Complex interactions between plant and soil within the rhizosphere also profoundly influence iron content. Solid phases controlling iron solubility in soils, chemical speciation of iron in solution, importance of redox in the solubilization of iron, and the role of synthetic and natural chelates in transport processes that occur near roots are among soil-dependent factors determining iron bioavailability<sup>4</sup>. In addition, plant iron uptake mechanisms are intimately associated with loading processes of other metals, some of them being potentially toxic for humans. Ferritin overaccumulation in transgenic tobacco leaves leads to excessive iron sequestration and the activation of iron transport systems, as revealed by an increase in root ferric reductase activity<sup>2</sup>. Independently, it has been reported that iron-deficiency activation of the IRT1 ferrous iron transporter was most likely responsible for cadmium loading of pea plants<sup>5</sup>. In grasses, iron(III) uptake occurs through phytosiderophores of the mugineic acid family; this transport system, activated under the above conditions, is also capable of transporting metals such as zinc and probably copper<sup>6</sup>.

In the light of these findings, the behavior of transgenic plants overexpressing ferritin with regard to iron and heavy-metal loading under various soil conditions should be addressed in future experiments.

Only after the risks of toxic metal loading have been deemed acceptable can such plants be introduced into the human food chain.

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### Human monoclonal antibodies: The emperor's new clothes?

To the editor:

With the advent of human immunoglobulin transgenic animals, where megabase-sized human DNA has been introduced into the mouse germline, the traditional approach to producing monoclonal antibodies has come into vogue again. The reason is that well-established technologies, developed since the introduction of B cell hybridomas in 1975, can be utilized to generate human monoclonal antibodies. Human monoclonal antibodies have for the last 20 years been the goal of every scientist interested in immunotherapy of humans, since these molecules evoke a minimal immune response, a severe problem associated with the use of mouse monoclonal antibodies in the clinic. However, since the first mouse monoclonal antibodies were introduced, a completely new approach was published in the beginning of the 1990s, namely phage display of human antibodies, where the diversity of the entire humoral immune response could be created in a small test tube. Overnight the monoclonal antibody technology was declared obsolete, since phage display of antibodies was put forward as a much faster and more robust alternative. When the arguments are put forward in favor of today's new kid on the block—the transgenic mouse—history repeats itself but in a reverse manner, i.e., now monoclonal antibodies are the fast track to the clinic<sup>1</sup>. This analysis is being pushed on the scientific community by analysts to investors of the biotech industry, probably not around when the phage antibodies were raised to the skies<sup>2</sup>. What also appears to be forgotten is that no matter how human the immune response of the transgenic mouse is, the problem of selecting a fusion partner to immortalize the B cell repertoire still

remains the same. When “totally” human monoclonal antibodies are produced from human immunoglobulin, transgenic mice myelomas of mouse origin are used as fusion partners<sup>3,4</sup>. The main problem is then the glycosylation pattern the human antibody ends up with, which is far from human and contains the Gal $\beta$ 1-3Gal residue. It is well known that human individuals contain a human anti-Gal $\beta$ 1-3Gal IgG antibody titer of up to 100  $\mu$ g/ml (ref. 5), which immediately will complex an in vivo administered human antibody derived from a transgenic mouse. This concern was published by us in 1993, based on the observation that the serum half-life of mouse monoclonal antibodies was inversely proportional to the antibody content of Gal $\beta$ 1-3Gal residues<sup>6</sup>. It was quite clear that if an antibody contained Gal $\beta$ 1-3Gal residues it would not survive for long in the human circulation. On the other hand, human monoclonal antibodies derived from EBV cell lines showed no evidence of the Gal $\beta$ 1-3Gal residue and did consequently not react with the human anti-Gal $\beta$ 1-3Gal IgG antibodies. Does then the transgenic animal approach offer any advantages over e.g. phage displayed antibodies? The major advantage is not the one put forward by biotech investors but is rather the access to the affinity maturation machinery of the mouse resulting in truly high affinities—albeit a feature also found in highly functional antibody libraries. In summary, the scientific achievement in constructing the human immunoglobulin transgenic mice is on the highest level but the commercial arguments, fueled by the biotech investors, are controversial and ill founded, where one major limiting factor is simply forgotten.

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### Erratum

In the June issue, the Research Analysis article “Nurturing nature: engineering new antibodies” (p. 538) was printed with an incomplete figure. The correct figure is available with the online version of the article.