The $802 million fallacy

To the editor:

The articles by DeFrancesco in the June issue (*Nat. Biotechnol.* **22**, 663–664,2004) and Miller in the August issue (*Nat. Biotechnol.* **22**, 944, 2004) discuss Merrill Goozner's book entitled *The $800 Million Pill: The Truth Behind the Cost of New Drugs.* At every partnering or financing meeting, at least a dozen biotech presentations or conversations will refer to the Tufts Center for the Study of Drug Development figure for the average cost of developing a new drug. The latest Tufts study, dating back to November 2001, puts this figure at $802 million. With subsequent inflation and the natural tendency of biotech executives to round upward, this usually comes out as "just under a billion dollars." Shareholders should remove, with immediate effect, any CEO of a biotech company that is working on a drug that costs that much to develop.

The $802 million figure applies to the kinds of drugs that were surveyed in the Tufts Center study. That study looked at 68 randomly selected new drugs from ten companies. Few biotech companies could muster an average of over six drugs each, so we conclude that the numbers did not come from typical biotech companies.

Most of the money that goes to make this average figure is spent running long or large late-stage clinical trials. The billion-dollar drugs will either be 'me-too' compounds, where a large patient cohort is required to reveal the marginal advantage of the compound over the current market incumbent, or they will be novel drugs for chronic conditions where long-term trials across a broad section of the population are required to show prolonged safety and efficacy.

For pharma companies, it is a valid commercial strategy—if not an entirely commendable one—to develop 'me-too' compounds to defend their franchises in particular indications. Pharma companies can also afford to commit huge resources in search of treatments for chronic conditions.

This is not for biotech companies, however. Investors will never give them enough money to allow them properly to leverage the value of compounds that require extended trials. Instead, biotech companies ought to concentrate on drugs that are both differentiated from current market offering and address acute medical needs.

The good news is that most biotech companies recognize this. They do focus on novel compounds, and they do work in indications like cancer and infectious disease. They often work in niche indications where the medical needs are more pronounced. Any longer term projects, such as therapies for metabolic and autoimmune disease, are out-licensed early in development.

Consequently, the drug development cost for biotech companies would be much lower than the Tuft estimate, perhaps by almost an order of magnitude. But this doesn't seem to stop biotech CEOs quoting the $802 million figure.

John Hodgson

Critical I Ltd., The Colin Sanders Innovation Centre, Mewburn Road, Banbury, OX16 9PA, UK. Hodgson is also Editor at Large, Nature Biotechnology. e-mail: john.hodgson@criticali.net

'Informative' horizontal gene transfer

To the editor:

The Perspective of Nielsen and Townsend on p. 1110 presents an interesting analysis of current studies on horizontal gene transfer from transgenic plants into microbial ecosystems. With respect to their analysis of our work on gene transfer from transgenic plants into human intestinal microbes (*Nat. Biotechnol.* **22**, 204–209, 2004), we would like to clarify some of the issues raised.

Nielsen and Townsend comment on the limitations imposed by the multiple rounds of subculturing, indicating that our analysis is "uninformative." It was not the intention of our work to quantify the frequency of bacterial transformants in the intestinal microflora, but to seek evidence of their existence. We believe, therefore, that the identification of these microbes using an enrichment and PCR strategy is highly informative.

We also wish to point out that as the small intestinal bacterial population numbers are relatively low (10^6 organisms/g), and our PCR methodology will analyze 10^6 genomes per reaction, we have interrogated a significant proportion of the bacterial population. We also believe that as the level of the PCR product did not significantly vary throughout the seven subcultures, our media did not specifically select (positively or negatively) the transgene-containing bacteria.

We think that maybe the crucial point made by Nielsen and Townsend is that one can never be sure that gene transfer events have not occurred as it could take a protracted time for the transformant(s) to be sufficiently abundant within a bacterial population to be detected. Thus, the authors are correct in suggesting that although we did not find evidence for additional gene transfer events subsequent to consumption of the GM meal, current methodology may not have detected the transformants if transfer were an extremely rare event.

In their concluding remarks, Nielsen and Townsend identify the importance of more focus on the bacterial genetic composition and environmental conditions that facilitate positive selection of bacterial transformants. Although substantial manipulation of the environmental conditions of the human small intestine is clearly impractical, we agree that analysis of the genomes of the bacterial transformants, both with respect to identifying the organisms and the site and mechanism of transgene integration, is likely to advance understanding of the risks associated with gene transfer from transgenic plants to the human intestinal flora. Indeed, we intend to characterize the genomic context of transgenic plant-derived recombinant genes in the bacterial transformants. This will provide insight into both the identity of these organisms and the mechanism of transgene chromosomal (or episomal) integration.

Harry J Gilbert[1], Anthony G O'Donnell[2] & John C Mathers[3,4]

[1]Schools of Cell and Molecular Biosciences, [2]Biology, [3]Clinical Medical Sciences and [4]The Human Nutrition Research Centre, University of Newcastle upon Tyne, ME1 7RU, UK. e-mail: h.j.gilbert@Newcastle.ac.uk