which is a further argument that their approach is unlikely to be adopted.

Finally, the dearth of valid clinical data supporting the use of phage therapy must be acknowledged. But the fact remains that phage therapy is still practiced in certain parts of the world, so there should be no bar to actually performing a valid clinical trial testing phage therapy versus small-molecule antibiotics. The statement that "Phage have been administered to countless persons, including children, without evident toxicity," is based—like much of the information in this field—mainly, if not totally, on anecdote. What the field needs is some validated data published in peer-reviewed journals rather than in the popular press.

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Drugs in crops

To the editor:

Your editorial in the February issue (*Nat. Biotechnol.* **22**, 13, 2004) expressed concerns about the use of conventional crops, mainly maize, for the production of biopharmaceuticals. With the current capacity crunch for production of biopharmaceuticals by current-day technologies, and the projected demand for therapeutic proteins (such as antibodies) in the next few years[1,2], it is imperative that the acceptance of plants for molecular farming proceed smoothly.

Throughout the debate on the use of plants as production platforms for pharmaceutical proteins, we have been puzzled by the persistent and exclusive focus on the use of existing crop varieties. This focus has, predictably, triggered and fueled concerns about this exciting new agricultural opportunity from stake-holding industry groups[3,4]. However, those participating in the debate might take note of the fact that existing commercial crop varieties are unlikely to be optimal for plant-manufactured pharmaceutical applications anyway, having been bred and selected entirely for their present-day, traditional uses. This is true of both food (*e.g.*, corn) and non-food (*e.g.*, tobacco) crops that might be used in such applications.

Fortunately, however, it may be quite unnecessary to turn to alternatives, such as undomesticated plants or rarely cultivated crops, which might require new development of appropriate gene expression technology and so on. We contend that modern plant breeding approaches can be used to develop novel and distinctive cultivars of the desired (conventional) crops, which will be optimally suited to biopharmaceutical applications in every respect. Together with appropriate crop-management protocols, the resulting crop system will completely obviate any compromise or contamination of the equivalent traditional crop.

To illustrate this approach with tobacco[5–7], which is the subject of several plant manufactured pharmaceutical platforms, we note that the US tobacco industry has voiced a zero-tolerance standard for genetically modified (GM) contamination of the conventional crop (Dean Wallace, Council for Burley Tobacco, personal communication). Transgene escape can be ameliorated through the use of male sterile varieties[8], although the proximity of fertile, non-GM tobacco nearby could result in the production of some seed and the potential for GM volunteer plants. However, we believe that through an F_1 hybrid strategy, we can take advantage of the many benefits of tobacco as a platform for producing pharmaceuticals while at the same time eliminating its drawbacks. We have found that interspecific crosses between tobacco and certain other species of *Nicotiana* produce vigorous, completely sterile hybrid plants that are morphologically distinct from conventional tobacco (thus achieving identity preservation) and can be planted and grown in a manner similar to conventional tobacco (though at a higher plant density) using existing infrastructure (float beds, machinery, fertilizers, herbicides, *etc.*), yet can be mechanically harvested three or four times during the growing season. For production of pharmaceutical or industrial proteins, the maternal (tobacco) cultivar is transformed with a gene of interest, and homozygous transformants with high-level protein expression are selected and crossed with the other species. It is the resulting F_1 hybrid offspring that are grown in the field, as with hybrid maize. Our present work involves breeding a tobacco cultivar that is optimized for plant-manufactured pharmaceutical applications, and we are in the process of evaluating the performance of our hybrids with the appropriate gene expression systems.

We feel that all parties participating in the debate over biopharmaceutical crops will benefit from consideration of developing plant varieties specifically tailored to plant manufacture of pharmaceuticals, which will permit the use of existing transformation and gene-expression technologies without imposing undue risk to conventional crops or the environment. The hybrid *Nicotiana* approach effectively addresses the main concerns about 'third-generation' GM crops[9] and could very well lead to simplified regulatory requirements in the near future.

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