nature biotechnology

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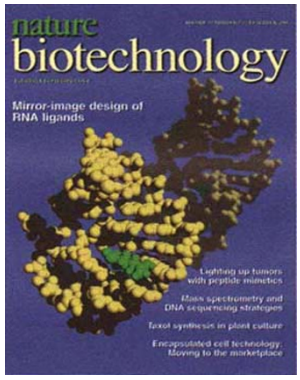
Measuring Taxol production

To the editor:

I have worked on the use of plant cell cultures for the potential production of pharmaceuticals and other high value compounds for over 20 years (including the last six on Taxol® or paclitaxel production). I was pleased to see in your September 1996 issue of *Nature Biotechnology* that both the editorial "Solving the Taxol dilemma" and the analysis "Taxol production in plant cell culture comes of age" have recognized that plant cell culture technology is in a good position to support the commercial production of Taxol (and, in my estimation, several other important compounds).



However, these opinion pieces contain inferences that may be misleading to your readers. Most disturbing is that the level of production quoted in the editorial (300 mg/L in 2 weeks) is not reported in the paper by Yukimune and colleagues. In their paper the highest level of production reported is 110.1 mg/L—measured 14 days after elicitation by methyl jasmonate. There is no source for the 300 mg/L in 2 weeks number, which is the basis for the sixfold improvement in the rate of volumetric productivity used in both the editorial and analysis. Likewise, there is no source in the article for the operation at 200 L, although operation of plant cell culture processes at much higher levels has been known for more than a decade, so such a result is not particularly surprising.

The editorial also included another error in that it claimed that in a soon to be pubished article that the fungus, *Pestalotiopsis microspora*, could produce paclitaxel at 50 mg/L. I presume that the writer was referring to an article by Strobel et al. (*Microbiology* **142**:435–440, 1996). I believe your editorial writer meant 50 μg/L. On page 439 of the Strobel et al. article they write, "The total amount of taxol produced per litre was about 60–70 μg." In a similar vein, I note that on p. 1063 of the same issue of *Nature Biotechnology*, that Taxol overproduction is attributed to "100 mM methyl jasmonate," which must surely be 100 μM.

While reactor scale and volumetric productivity are important economic considerations, other issues, such as growth rate and the ability to establish stable cultures, are at least as important to developing a commercial scale process. These issues were not considered in your editorial or analysis.

Finally, your editorial did not comment on what I believe to be perhaps the most intriguing aspect of the paper by Yukimune et al. They report that methyl jasmonate would selectively enhance paclitaxel production over other taxanes and then provide reasonable speculation on how this observation relates to the biosynthesis of paclitaxel. Since the pathway to paclitaxel is not well understood, experiments with elicitors may provide important tools to probe biosynthesis. Indeed, we have found in our own work with arachidonic acid and a variety of fungal elicitors that we had three classes of response: (1) preferential enhancement of Taxol, (2) preferential enhancement of other taxanes, and (3) equal enhancement of Taxol and other taxanes (see Ciddi et al., *Biotechnol. Lett.* **17**:1343-1346, 1995).

Since many readers may only skim your opinion and analysis sections and not read the original article carefully, it is important that these sections, especially with respect to numbers and units, are checked as carefully as the original articles.

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Taxol supply problem? What problem?

To the editor:

The editorial on page 1055 of the September 1996 issue of *Nature Biotechnology* speaks of solving the "Taxol dilemma." In particular I would comment on the statement: "Obtaining enough of the cancer agent paclitaxel. . . remains a vexing problem." Actually this problem was solved three years ago by the acylation of 10-deacetyl baccatin III, isolated from a plentiful and renewable source of *Taxus* needles.

Thus the supply problem of Taxol, which appeared so formidable in 1988, has now been completely solved by semisynthesis. There is no vexing problem of Taxol supply and no "Taxol dilemma." (cf. R.A. Holton et al., 1995, pp. 97–121 in *Taxol: Science and Applications*, M. Suffness (ed.), CRC Press, Boca Raton, FL.)

The editorial contains another statement that should be questioned, namely that: "According to the NCI, 45% of anticancer drugs approved for commercial use are either natural products or derived from natural products." I have reviewed all of the cancer drugs listed in the *US Physicians Desk Reference* and found a total of 73 out of which nine were from higher plants or based on them (12%), and five were antibiotics or of microbial origin (7%), for a total of 19% (nowhere near 45%). While I am a proponent of the use of natural products as sources of drugs, I do not believe that the cause is advanced by overstating the case.

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Nature Biotechnology replies:

With regard to Dr. Shuler's queries, the Taxol production level (300 mg/L in 2 weeks at 200 L) quoted in our editorial and analysis was originally presented in the last paragraph of the results and discussion section of the paper by Yukimune et al. Because the optimization protocol was not described sufficiently in the paper, however, we chose to remove these data before publication, but neglected to cite them as unpublished data in our editorial and analysis sections. We apologize for any confusion this may have caused to our readers.

According to Gary Strobel (Montana State University, Bozeman), Taxol production of one of the nine fungal isolates described in the *Microbiology* paper has indeed been optimized 1000-fold (i.e., to levels of 50 mg/L) since the publication of that paper.

In response to Dr. Gordon's letter, while we appreciate that semisynthesis currently supplies commercial demand for Taxol, this does not negate the importance of plant cell culture, particularly if production levels become competitive. In plant cell culture, high-yielding variants can be selected easily, supply is consistent in quality and quantity all year round, the product is "cleaner" (with fewer contaminants), and novel derivatives can be generated by manipulating cells and culture conditions.