

Reply to 'Poor trial design leaves gene therapy death a mystery'

To the editor:

We were heartened to see that *Nature Medicine* chose to cover the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC)'s review of the death of Jolee Mohr, which occurred while she was enrolled in a gene therapy trial¹, but we are concerned that the article did not reflect the panel's discussion and conclusions.

The RAC committee members were mindful of the dangers of drawing definitive conclusions on the basis of limited information and did not declare a cause of death in the case. Still, the data they were presented with clearly showed that the amount of gene therapy product outside the knee—where it was injected and where it was designed to remain—was negligible. Instead, the panel was presented with extensive evidence that systemic antiarthritis immunosuppressants, which Mohr was also taking, have been definitively linked to opportunistic infections such as the histoplasmosis that contributed to her death.

Yet the article, in quoting a witness who was neither a member of the blue-ribbon NIH committee nor an immunologist or rheumatologist, gave the impression that the gene therapy Mohr received remains a prime candidate for a cause of death, a supposition that was not borne out by the evidence shown at the meeting.

We are also concerned that the headline, "Poor trial design leaves gene therapy death a mystery," suggests that the phase 1/2 trial of our therapy for rheumatoid arthritis was not designed according to current good

practices because patients were permitted to use other arthritis drugs. Yet continuance of maintenance therapy has been a mainstay of trial design in this or any field. This protocol underwent a most rigorous screening process and was evaluated not only by leading rheumatologists and the institutions that performed the research, but also by the NIH itself. Indeed, the assertion that the trial design was flawed was never made by any member of the RAC during the meeting, so the claim that this was an official outcome of the meeting is troublesome.

Mohr's death was a tragedy. We at Targeted Genetics have made every effort to assist the doctors, pathologists, researchers and regulatory bodies who are seeking to better understand why she died. We respect the conclusions of the NIH's expert panel, which reviewed all the available information and cast no aspersions on the gene therapy product, and we hope that their measured assessment will receive more prominent mention in the future.

H Stewart Parker

President and CEO, Targeted Genetics Corporation, 1100 Olive Way, Ste. 100, Seattle, Washington 98101, USA.
e-mail: Stewart.Parker@targen.com

COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturemedicine/>.

1. Wadman, M. *Nat. Med.* **13**, 1124 (2007).

Microarrays: retracing steps

To the editor:

Recently, Potti *et al.*¹ published an article in *Nature Medicine* reporting an approach predicting whether a tumor will respond to chemotherapy. Using publicly available data, they derived signatures from microarray profiles of the NCI-60 human cancer cell lines with known *in vitro* sensitivity or resistance to a particular drug. They used these profiles to predict *in vivo* chemotherapeutic response to seven different drugs. In order to help investigators at our institution use similar approaches, we tried to reproduce their results. We used the same published data and additional information generously supplied by the authors regarding methods, lists of cell lines called sensitive or resistant, and the software used to perform their analysis.

We report here our inability to reproduce their findings. Details of our methods and results are described in the supplementary information (**Supplementary Reports 0–9**) and are summarized here.

1. We cannot reproduce their selection of cell lines. The most sensitive and resistant lines should be used to focus on drug effects. However, the GI₅₀ (the concentration needed to reduce the growth of treated cells to half that of untreated cells) concentrations for their sensitive and resistant lines overlap (**Supplementary Report 3**). Our analyses used both their cell lines and ones we selected independently.

2. The lists of genes initially reported in the supplementary information on the *Nature Medicine* website¹ are wrong because of an 'off-

by-one' indexing error (**Supplementary Report 9**): for example, probe set 1881_at was reported instead of probe set 1882_at. These lists were revised but are still incorrect.

3. Using their software and lists of cell lines, we reproduced their published heatmaps for six out of seven drugs. (We could not reproduce the heatmap for cytoxin.) However, after correcting for the off-by-one error, we matched the reported gene lists exactly for only three out of seven drugs (**Supplementary Report 9**). The other lists contain outliers.

4. For docetaxel, their software yields only 31 of their 50 reported genes. Of the remaining 19 (**Supplementary Report 9**), Chang *et al.*² name 14 as useful discriminators in the paper that described the test set used by Potti *et al.*¹. We do not know how these 19 can be obtained from the training data, and we suspect that they were included by mistake. The model may more easily predict test classes with these genes.

5. Their software does not maintain the independence of training and test sets, and the test data alter the model. Specifically, their software uses 'metagenes': weighted combinations of individual genes. Weights are assigned through a singular value decomposition (SVD). Their software applies SVD to the training and test data simultaneously, yielding different weights than when SVD is applied only to the training data (**Supplementary Report 9**). Even using this more extensive model, however, we could not reproduce the reported results.

6. The interaction between point 4 (accidentally including genes from Chang *et al.*² whose expression levels separate the test set responders from