How diagnosis with microarrays can help cancer patients

Sir — Alizadeh *et al.*[1] show how the analysis of gene expression using high-density DNA microarrays can improve the diagnostic accuracy of diffuse large B-cell lymphoma. But there are many problems to be overcome before this approach may become generally applicable to cancer diagnosis, as hoped for by Berns in his interesting News and Views article "Gene expression in diagnosis"[2].

Analysis of gene expression using DNA microarrays is unlikely to replace histopathology as the prime indicator of prognosis. In relation to cancer, the histopathologist makes three important judgements: diagnosing the cell of origin (tumour type) of the cancer; how closely the tumour resembles the tissue of origin (tumour grade); and the extent or site to which the cancer has spread (tumour stage). The extent or stage of the cancer is by far the most important judgement in most types of cancer; it dictates treatment and is an accurate predictor of the prognosis.

Tumour grade also correlates strongly with prognosis, but this is a subjective assessment, which limits its reproducibility and clinical value. It is in grading tumours that microarrays are most likely to improve the accuracy of prognosis.

It is not by chance that the first applications of microarrays to the diagnosis of cancer were made on leukaemias and lymphomas[1,3]. These cancers tend to be single cells that can be obtained non-invasively in a blood sample and can be separated to high purity using cell-surface markers. However, 90 per cent of cancers are solid tumours that have to be surgically removed and are extremely difficult to purify. The microarray approach can provide only a crude average of gene expression across all the cells used to prepare the RNA or DNA. Unless the cancer-cell preparation is highly pure, the contribution of the myriad other cells within the cancer (normal cells, supporting stroma, blood vessels, lymphocytes, and so on) can mask the expression pattern on the array. Pure cancer cells can be obtained by laser microdissection of tissue sections or by cell sorting, but these are labour-intensive and time-consuming processes.

Another problem is the variability in invasive potential between cancer cells within the same tumour. For example, prostate cancer is often present in many distinct foci, only one of which may have the potential to be invasive and dictate the outcome for the patient. Must each focus be analysed separately? Within one focus there may only be a few cells with the potential to invade — will their gene-expression pattern be masked by the surrounding, less malignant cells?

There are already a vast number of prognostic markers available for every type of cancer, and many of these are of independent prognostic significance. However, they are of little use to the individual patient because, although statistically significant, they do not provide the quality of information needed to be confident that a major operation, for example radical prostatectomy or cystectomy, is beneficial.

The acid test for DNA microarrays in cancer diagnosis will be whether the information they provide alters the patient's treatment — a likely outcome but yet to be proven. Using pure populations of cancer cells (for example, cancer-cell lines, flow- or magnetically sorted cancer cells, or cells obtained by microdissection), new and more powerful prognostic markers will be identified using microarrays, as demonstrated by Alizadeh *et al.*[1]. It will then be possible to use conventional methods on tissue sections (such as immunohistochemistry and *in situ* hybridization) to apply these new markers to individual cancers.

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1. Alizadeh, A. A. *et al. Nature* **403,** 503–511 (2000).
2. Berns, A. *Nature* **403,** 491–492 (2000).
3. Golub, T. R. *et al. Science* **286,** 531–537 (1999).

Short-sighted move to close the 12-m telescope

Sir — Recent budgetary choices have forced the closure of the US National Radio Astronomy Observatory 12-m telescope in Kitt Peak, Arizona. As this detrimentally affects astronomy in many ways, I am writing to oppose this move.

The 12-m telescope remains one of the most important and vital components of US millimetre astronomy. For graduate students in the United States, it is the only accessible, competitive, peer-reviewed facility capable of both training them as future scientists and providing for internationally recognized research. The 12-m telescope is a vital component to my own PhD thesis and much of my future work is predicated on its existence. Specifically, wide-field mapping and full synthesis imaging will not be possible without it.

Alternatives such as CSO, JCMT, HHT and IRAM are inadequate. None of them except IRAM 30-m has the frequency coverage of the 12-m. For example, deuterium-bearing molecules are often found to have ground-state transitions below 85 GHz, the limiting tuning range of many other receiver systems. The deuterium component of the insterstellar medium (ISM) — as a measure of primordial nucleosynthetic products, chemical evolution in the ISM, and observational limit on abundance predictions from star-formation theories — will no longer be accessible.

The alternative facilities noted above are less accessible to US astronomers than the 12-m telescope, either because the observatories have closed associations with their parent institutions or because they are very expensive to reach. Furthermore, the HHT, though a capable enough system, lacks receivers at 2-mm and 3-mm wavelengths to compensate for the loss of the 12-m telescope.

Two solutions are apparent. The first is to establish a consortium of universities to take over operation of the 12-m. Some emergency funding, even if outside the National Science Foundation's budget, must be obtained in the interim period in order to allow minimal operation of the 12-m. This will also allow NRAO to retain the staff, engineers and scientists whose vast millimetre knowledge will disappear if the closure goes through as planned.

Many of us have written to counteract the impression that the 12-m telescope is no longer a vibrant instrument, or that NRAO has overextended itself. The national observatories maintain widely accessible, strong facilities with flexibility and extensibility. The 12-m telescope remains important until work begins of the construction of the Atacama Large Millimetre Array (ALMA) — 64 antennas located at 5,000 m in Chile's Atacama Desert.

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Genetic modification and the meat market

Sir — Jonathan Latham[1] in Correspondence states that famine is a problem of global food distribution and arable efficiency rather than of food quantity, and that hence there is no need for genetically modified (GM) crops. Although this argument may in theory apply today, it will not in practice apply tomorrow.

Of course there are scientific questions that still need to be answered about GM technology, but we already know that by

the middle of the twenty-first century the world is going to face a food crisis, and that agriculture will consequently put increased pressure on wildlife habitats.

In 1998, the UK Institute of Biology and six affiliated societies (whose specialist interests range from agricultural production to ecological conservation) produced a report on the social and ethical aspects of GM crops[2]. We cited half a dozen indicators of the forthcoming shortfall in global food supply, including the following. Forty per cent of terrestrial primary productivity is already managed by humanity. The trend for the past 15 years has been a reduction in grain production per capita. Global sea-fish catches have been in steady decline since 1990 because of over-fishing. World carry-over stocks of grain are declining from one year to the next. The grain harvest area per person has been declining since the late 1970s, owing to increasing population, growth in industry and desertification.

The increasing consumption of meat in the rich nations has put more pressure on the poor, although reversing this trend alone (even if it were realistic) would not counter the pressures caused by a population increase of 40 to 80 per cent over the next four decades. The world shows no sign of turning vegetarian. Although I am sympathetic to Latham's conclusion that "what is missing is the 'purchasing power' of the poor", the evidence is that when the poor become a little richer they eat more meat.

Given that agricultural inefficiencies and global inequalities are bound, sadly, to continue, it is likely that genetic modification where appropriate will make a significant contribution to human well-being — and to that of other species.

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1. *Nature* **404,** 222 (2000).
2. *GM Crops: The Social and Ethical Issues* (Institute of Biology, 1998). www.iob.org/gmocrops.html

Distinguished scientists back Germany's DFG…

Sir — Your recent News report "German research agency stifles creativity" (*Nature* **404,** 217; 2000) gives a negative and incorrect impression of the Deutsche Forschungsgemeinschaft (DFG).

Nature claims that DFG's inability to assess novel research areas and interdisciplinary research areas threatens career opportunities, especially for young researchers. The cases mentioned in the *Nature* report, however, are neither representative nor described in an unbiased manner.

Typically, the reviewing process of the DFG takes less than six months and involves a large number of scientists from foreign and German institutions and from senior as well as junior ranks. Every attempt is made to support the best and the most innovative scientific proposals. In fact, time and again high-risk proposals are funded that, for example, would have no better chance of support from the US National Institutes of Health.

Of course, no system is free of errors, and occasional undeserved negative judgements may be made. However, continual efforts are made to improve the system. Overall, we are impressed by the flexibility of the DFG, its unbiased support for creative, high-quality research and its programmes for young scientists and interdisciplinary research even at times when its budget is tight.

At this juncture, our most urgent concern is to convince politicians to increase funding to the DFG significantly. This is particularly important for the support of young scientists. We are very proud of the DFG as a self-governing body of the German scientific community and we believe it to be, by any standards, one of the best scientific funding agencies.

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Kai Simons *Max-Planck-Institut für molekulare Zellbiologie und Genetik, Dresden*
Eberhart Zrenner *Universität Tübingen*
Signed on behalf of 1,164 other biomedical scientists. The full list of names is available from R. J.

…but young researchers feel disillusioned

Sir — Your recent News report "German research agency stifles creativity" (*Nature* **404,** 217; 2000) gives a negative impression of the Deutsche Forschungsgemeinschaft (DFG) — but one that is, in our experience at least, correct.

Nature claims that the process threatens young researchers' career opportunities in particular. Our last four applications for grants in the area of environmental toxicology (mechanisms of microcystin toxicity in the aquatic environment) were rejected, after an average delay of 10–12 months, as "irrelevant" or "dealing with non-existent problems". We did, fortunately, receive support for a similar grant from the European Union; the results of these studies have been or will be published this year, and they form the basis of an EU patent application.

The referees of our unsuccessful DFG applications did not seem, to us, to be up-to-date in their knowledge of the topic, or they had little understanding of environmental toxicology. Indeed, the comments we received from the DFG made us wonder whether the referees had even read the grant. They were so contradictory of each other as to provide us with no constructive advice on how to improve the application. The upshot was that, while we were able to demonstrate that our proposed research could be done, and was publishable in peer-reviewed journals, it was not considered fundable by the DFG. This kind of outcome may not seem devastating to seasoned scientists with established careers. But it impedes the careers of young researchers dependent on DFG funding within Germany, and is demotivating.

A better approach would be for grants to be sent out for review internationally; for referees' comments to be sent to the applicants in their original form, not rewritten by DFG to maintain anonymity (we are happy for peer-review to remain anonymous, but the rewriting leads to incomprehensible comments); and, as proposed in the *Nature* report, for applicants to be able to attend referees' meetings to answer questions and defend their grants.

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***Nature* replies — The *Nature* report states explicitly that the DFG reviewing process averages five to six months. The complaints discussed in the article concern the outliers to this average — applications in new, interdisciplinary, not traditional, areas of research.** ■