sound waves with single-electron quantum waves moving over a flat surface of copper. The speaker is the STM tip held just above the surface and supplying electrons; the frequency of the sound is the energy (and corresponding wavelength, controlled by the voltage applied to the tip) of the electrons; and the walls and furniture are edges or other defects, such as iron atoms set in a particular pattern. Finally, power output in the acoustic case becomes current flow in the STM. The famous STM images are the power map of the region scanned by the tip.

The analogy goes further still — real walls and furniture can absorb sound, and windows may be open, so some of the outgoing sound energy is either absorbed or escapes, making the returning signal weaker. In a typical room the sound bounces only a couple of times before it is negligible. That happens with electrons too: in the classic 'quantum corral' arrangement of, say, 60 iron atoms in a circle, the iron walls reflect only about 25% of the wave back into the cavity[5].

We can now begin to understand the latest experiments by Eigler's group: Manoharan *et al.*[4] have created a tiny laboratory for remote sensing, in the form of an elliptical quantum corral a few tens of ångströms across. An ellipse is a remarkable geometric object that perfectly focuses either waves or rays starting at one focus onto the other focus (Fig. 1). Manoharan *et al.* put a cobalt atom at one focus and bombarded it with electrons from an STM tip placed at the other focus. Cobalt has what is called a Kondo resonance at low temperatures. This arises because cobalt has a magnetic moment, which at low temperatures causes the 'Fermi sea' of conduction electrons around it (if it is embedded in a metal such as copper) to become oppositely polarized, thereby screening the magnetic moment and producing a many-body singlet state. This Kondo resonance is observed as a rise in resistance at very low temperatures, as the Kondo clouds form, making the magnetic impurities more effective at scattering conduction electrons.

It was Eigler's original dream to see a Kondo resonance up close and personal. The first STM evidence for a Kondo resonance was seen by Madhavan *et al.*[6], a group led by M. F. Crommie, who did the original quantum corral work with Eigler and Lutz. (Li *et al.*[7] saw STM surface Kondo resonances around the same time.) The experiments in an elliptical corral reported by Manoharan *et al.*[4] add a remarkable twist. The Kondo resonance, which manifests itself as a blip in the conductance if the tip is held just above the cobalt atom, has the same (but attenuated) blip if the tip is at the empty focus of the elliptical corral. This raises several fascinating issues. If a Kondo blip is seen at the remote location, does that mean the electronic structure is perturbed there too? Is the electronic structure really being projected to a remote place, as the authors claim? Or, like a light bulb at one focus of a mirrored elliptical room, do we just see a light bulb at the other focus (as would happen), only to find out that it's not really there when we try to touch it?

We may get some insight by returning to the acoustic analogy. Suppose at one focus of an elliptical room there is a drum that resonates near some frequency, simulating a Kondo resonance. With the speaker on top of the drum, we find a blip in power supplied near the resonance frequency. If we then put the speaker at the other focus, what will happen as we sweep through that same frequency? This is left as an exercise for the reader, as are any conclusions to be drawn regarding remote projection. ■

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1. Crommie, M. F., Lutz, C. P. & Eigler, D. M. *Nature* **363,** 524–527 (1993).
2. Crommie, M. F., Lutz, C. P. & Eigler, D. M. *Science* **262,** 218–220 (1993).
3. *Physics Today* November (1993).
4. Manoharan, H. C., Lutz, C. P. & Eigler, D. M. *Nature* **403,** 512–515 (2000).
5. Heller, E. J., Crommie, M. F., Lutz, C. P. & Eigler, D. M. *Nature* **369,** 464–466 (1994).
6. Madhavan, V. *et al. Science* **280,** 567–569 (1998).
7. Li, J., Schneider, W.-D., Berndt, R. & Delley, B. *Phys. Rev. Lett.* **80,** 2893–2896 (1998).
8. Weber, E. H. *Wellenlehre: Auf Experimente Gegrundet oder über die Wellen Tropfbarer Flüssigkeiten mit Anwendung auf die Schall- und Lichtwellen* (Bey Gerhard Fleischer, Leipzig, 1825).

Cancer

Gene expression in diagnosis

Anton Berns

With advances in high-density DNA microarray technology, it has become possible to screen large numbers of genes to see whether or not they are active under various conditions. This is gene-expression profiling, and there has been an expectation that it will revolutionize cancer diagnosis (Box 1)[1,2]. The thinking is that tumour behaviour is dictated by the expression of thousands of genes, and that micro-array analysis should allow that behaviour and the clinical consequences to be predic-ted. This rationale is sound enough, but until now it has not been substantiated by experiment.

On page 503 of this issue[3], Alizadeh *et al.* deliver such substantiation. The particular cancer they have looked at is diffuse large B-cell lymphoma (DLBCL), a disease that takes in a clinically and morphologically varied group of tumours that affect the lymph system and blood. The authors carried out gene-expression profiling with a 'Lymphochip', a microarray carrying 18,000 clones of complementary DNA designed to monitor genes involved in normal and abnormal lymphocyte development.

Using clustering analysis, Alizadeh *et al.* could separate DLBCL into two categories, which had marked differences in overall survival of the patients concerned. The gene-expression signatures of these subgroups corresponded to distinct stages in the differentiation of B cells, the type of lymphocyte that makes antibodies.

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin's lymphoma. With current treatments, long-term survival can be achieved in only 40% of patients. There are no reliable indicators — morphological, clinical, immunohistochemical or genetic — that can be used to recognize subclasses of DLBCL and point to a differential therapeutic approach to patients[4].

Expression profiling has already shown its usefulness in identifying genes with high

Box 1: Gene-expression profiling with microarrays

Imagine a 1-cm^2 chessboard. Instead of 64 squares, it has thousands, each containing DNA from a specific gene. This is a DNA microarray. The activity of each gene on the microarray can be compared in two populations of cells (A and B).

When a gene is expressed it makes a transcript, and the whole population of these products from a cell can be tagged with a fluorescent dye (say, red for the A cells, green for the B cells). The microarray is bathed in a mixture of the red and green transcripts. Those that originate from a specific gene will bind to that gene on the microarray, turning red, green or somewhere in between, depending on the relative numbers of transcripts in the two cell types.

So the microarray provides a snapshot of gene activity for thousands of genes. Data from many experiments can be compared and genes that have consistent patterns of activity can be grouped or clustered. In this way, genes that characterize a particular cell state, such as malignancy, can be identified — so providing new information about the biology of the cell state.

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or low expression levels in specific cell types under defined conditions — for instance, when being stimulated with growth factors or treated with drugs, or when the cell's degree of attachment to the extracellular matrix varies (this last characteristic may determine tumour spread)[2,5–7]. More recently, reports on tumour classification have also begun to emerge. Acute leukaemias can effectively be divided into the lymphoblastic and myeloblastic forms by expression profiling[8]. But in these studies, no multigene-expression signature was found that correlated with a new leukaemia subgroup, or with clinical outcome, in the relatively small group of tumours examined.

In the case of Alizadeh and colleagues' analysis[3] of DLBCL, the situation is different. Hierarchical clustering of the gene-expression data divided DLBCLs into two groups: one had the signature of B cells from the germinal centres (the B-cell factories in lymph nodes); the other had the signature of activated B cells. The outlook for patients who had tumours with the activated-B-like signature was much worse — 16 out of 21 died, compared with 6 out of 19 patients with the germinal-centre B-cell signature. Importantly, the predictive value was independent of the standard clinical parameters of prognosis, the International Prognostic Indicator.

That is far from the end of the story, of course. As the authors point out, most of the patients in the 'favourable prognosis' group that die do so within the first two years of diagnosis, whereas some of the patients in the 'poor prognosis' group were still alive after five years. The question is whether there is a 'hidden signature' that, if found, would enable early identification of these subgroups. For the moment, we just cannot say. Testing of more tumours, and using larger or different DNA microarrays, might be needed to resolve this question. In addition, some prognostic indicators might escape detection by expression profiling as they are qualitative, rather than quantitative. That is, genetic (allelic) differences might mean that some genes escape expression screening. They could encode proteins with a different activity or stability that affects tumour progression or response to treatment. In this respect, monitoring of single-nucleotide polymorphisms (SNPs — individual differences at a single base pair that mark a particular genetic variation in the population) would constitute an appealing complementary approach to screening[9].

When more expression signatures of larger tumour sets become available, it will become clear how this approach will improve monitoring of the stages in which tumours grow and spread, and therefore prognosis. The expectations are high. Furthermore, the better definition of patient groups, made possible by expression profiling, is of obvious importance for assessing the efficacy of various treatments. Patients will benefit directly from the tailoring of therapies to specific subclasses of tumours.

Finally, gene-expression profiling can be used to identify the genes and pathways that really matter for the tumorigenic process, thereby revealing new targets for therapy. The studies discussed here, and others, show that it is indeed feasible to identify such pathways. For example, high expression of the homeobox gene *HOXA9*, previously identified as a potent oncogene, was correlated with the failure to induce remission in a small group of patients suffering from acute myeloblastic leukaemia[8]. The DLBCL study revealed the increased expression of a series of genes involved in the inhibition of apoptosis (programmed cell death); this, too, might be a therapeutic avenue to explore.

A word of caution. Prognoses based on gene-expression signatures, and — in the future — SNP analysis, are likely to have their limitations. These methods will probably provide quite reliable predictions of the patient responses to initial therapies. The question then is how much 'noise' will remain as a result of tumour heterogeneity and genetic instability. Both are hallmarks of most malignancies and can lead to recurrent disease, as cancer specialists and their patients know only too well. Time will tell.

For the moment we are witnessing spectacular developments in tumour diagnosis. These developments are going hand in hand with new treatments targeted to defined regulatory pathways that are frequently deregulated in cancer. So although caution is in order, so too is optimism. ■

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1. Alizadeh, A. A. *et al. J. Clin. Immunol.* **18,** 373–379 (1998).
2. Perou, C. M. *et al. Proc. Natl Acad. Sci. USA* **96,** 9212–9217 (1999).
3. Alizadeh, A. A. *et al. Nature* **403,** 503–511 (2000).
4. Harris, N. L. *et al. J. Clin. Oncol.* **17,** 3835–3849 (1999).
5. Iyer, V. R. *et al. Science* **283,** 83–87 (1999).
6. Marton, M. J. *et al. Nature Med.* **4,** 1293–1301 (1998).
7. Alon, U. *et al. Proc. Natl Acad. Sci. USA* **96,** 6745–6750 (1999).
8. Golub, T. R. *et al. Science* **286,** 531–537 (1999).
9. Cargill, M. *et al. Nature Genet.* **22,** 231–238 (1999).

Plant ecology

Alien invaders

Peter D. Moore

There are plenty of examples of the ecological mayhem that can result from the human introduction of species into new areas. Stories of goats on Pacific islands, rabbits in Australia and rats in New Zealand are all familiar, as are the world's plant pests, from the aquatic weeds of tropical waterways to the nitrogen-fixing shrubs of Hawaii. The ecological repercussions of plant invasions are often far-reaching, and a fuller understanding of the complexities of ecosystem relationships may provide methods for the control of invasive species. These principles are illustrated by papers in the journals *Conservation Biology* and *Journal of Applied Ecology*. The first deals with the impact of invasive shrubs on songbird breeding success in North America[1]; the second with the potential control of unwanted grasses on golf courses in Britain[2].

Studies of invasive plants often concentrate on the effects of the newcomer on the existing plant community, but its influence may be felt throughout the ecosystem. Schmidt and Whelan[1] have analysed the consequences of the invasion of native North American woodlands by exotic shrubs — a honeysuckle, *Lonicera maackii*, and buckthorn, *Rhamnus catharticus*. Their particular concern was whether these shrubs are used for nesting by woodland songbirds and, if so, whether nest predation in these species differs from that found in native shrubs and trees. Both of these invasive shrubs are now common in the eastern part of North America, and both proved to be suitable for and attractive to nesting American robins (*Turdus migratorius*; Fig. 1)

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Figure 1 **The American robin (*Turdus migratorius*), painted by J. J. Audubon. Schmidt and Whelan[1] found that the robins' nests were more vulnerable to predation when sited in the invading honeysuckle *Lonicera maackii* than in native trees and shrubs.**