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Cloudy horizon for Australian synchrotron
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All at sea
Mixed outlook for battered cod stocks across the Atlantic
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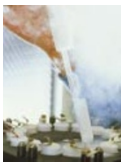

Cool response
Most frozen embryos can't be used for stem-cell research
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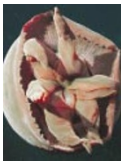

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Giant jellyfish makes a splash in the species stakes
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Biologists take tentative steps towards bespoke cancer drugs

David Cyranoski, Tokyo

Japanese biologists are vying with each other to identify patients who are likely to develop side-effects from a highly promising cancer therapy.

Their pioneering efforts to screen for side-effect susceptibility will help to shape future drug development and clinical trials, as expectations grow for prescriptions that are better tailored to an individual's genetic make-up or physiological condition.

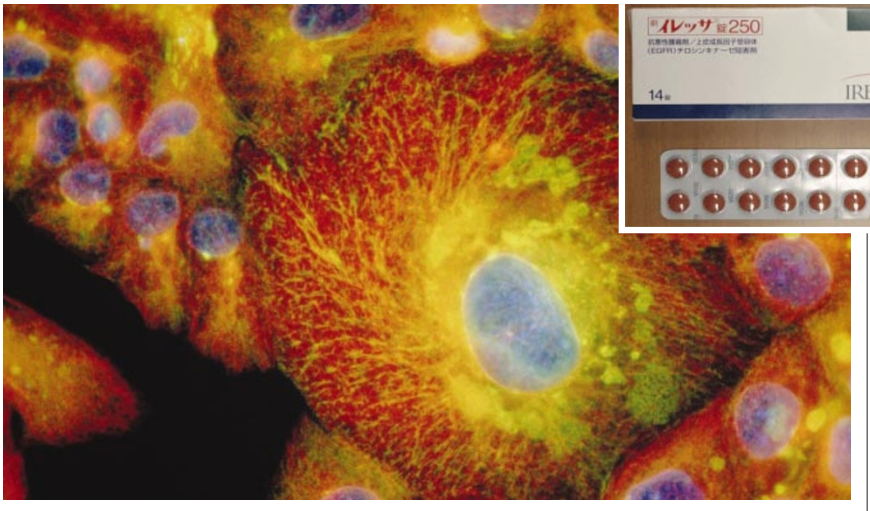
The studies are focused on the anticancer drug Iressa. Last July, Japan became the first country to approve the therapy, after it sped through the country's new fast-track drug-approval system. Despite the 246 deaths so far ascribed to its side-effects, 28,000 Japanese lung-cancer patients are using Iressa, and the United States and Australia this month approved the drug.

Produced by Anglo–Swedish company AstraZeneca, Iressa is one of a revolutionary new generation of therapies based on an understanding of the specific gene mutations that cause individual cancers (see *Nature* **416,** 470–474; 2002). The drug is a tyrosine-kinase inhibitor, which blocks specific growth-factor receptors — proteins on the cell membrane that pass on signals commanding the cell to grow and are overactivated in cancer.

Despite hopes that this type of drug would cause side-effects in very few patients, 616 people receiving Iressa in Japan have developed severe reactions — mostly a pneumonia-like illness called interstitial lung disease (ILD). Nonetheless, health officials say that the drug works too well for it to be recalled given the lack of other options for treating the disease. The health ministry says that various hospitals throughout the country have reported reductions in tumour size in between one-sixth and one-third of cases.

The two studies, which will begin shortly, are collaborations between universities and AstraZeneca. One will track the levels of certain blood proteins in different patients, and the other will examine the genetic differences between individuals called single-nucleotide polymorphisms (SNPs).

The SNPs project, led by Yusuke Nakamura of the University of Tokyo, will scour some 4,000 SNPs in 200 genes to look for patterns that correlate with a tendency to experience side-effects. If they cannot find a pattern in this limited study, they will expand the range genome-wide to some 200,000 SNPs.



N. KEDERSHA/SPL; KYODO (INSET)

On target: Iressa (inset) inhibits proteins that control the growth of lung cancer cells.

The second study will be led by Yoshiji Fujita, head of Tokyo Medical University's new Clinical Proteome Center. Fujita's team will take blood samples from 500 patients before and after they first take Iressa, and again after two months, by which time any side-effects should have developed. The group will look for any change in protein levels that correlates with later development of ILD. If all goes well, Fujita hopes that by next summer he will have a protein chip under development that will be able to tell patients within 12 hours of them starting the therapy whether they should stop taking Iressa or adjust its dosage .

But questions remain about both approaches. SRL in Tokyo, Japan's largest clinical-testing company, recently decided to devote its entire science programme to gene and protein expression, foregoing SNPs. "There are just too many SNPs, and finding the target is too difficult," says chief technology officer Kazumasa Hikiji. "Expression studies are more accurate and more cost-effective."

And sceptics argue that SNPs may not provide a definitive marker when side-effects turn out to be caused by non-genetic factors, such as the intake of other drugs. Even Nakamura accepts that there is no guarantee it will work. "If many genes are involved, and each has a very limited effect, it may be difficult to get a positive result," he concedes.

The protein studies "make good sense", according to Charles Sawyers of the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles. However, "the question is whether the pattern is strong enough to be seen", he says. "I think there is a risk that both approaches could fail, as the clinical application here is new. But the scientific rationale behind both is quite strong."

For AstraZeneca, any news about what is going on will be good news. "Ideally the tests will say: 'the genetic factors are like this and the protein expression is like this', and in that gap, we will be able to figure out how Iressa is involved," says Michio Tanaka, team leader for the company's oncology and therapy research division in Osaka.

The repercussions could be far-reaching, according to Fujita. "If we succeed, patients and drug-approval agencies will begin to expect studies on early detection of side-effects from pharmaceutical companies that are doing clinical trials," he says. ■