Fast forward for gene therapy

Last month's approval by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) of three independent proposals to begin limited trials for the severe hereditary lung disease, cystic fibrosis (CF), heralds a new era in gene-therapy research for common hereditary diseases.

Until now, gene therapy has focused largely on expensive *ex vivo* approaches for rare diseases, including certain forms of cancer and immunodeficiency, although the RAC last year also approved ambitious proposals for brain and lung cancer. By contrast, the CF proposals call for the direct administration *in vivo* of the normal CF gene encapsulated within an adenovirus vector. Despite earlier concerns about the safety of such viruses and the efficacy with which they can be prevented from replicating, the RAC passed the three proposals unanimously. Many experts believe that such direct administration is necessary to realize the true potential of gene therapy in a clinical setting.

In the United States, at least 15 clinical gene-therapy trials are in progress, so far with mixed results. Efforts to treat rare genetic disorders such as adenine deaminase (ADA) deficiency in two children and familial hypercholesterolaemia (FH) in an adult woman are proving effective. Indeed, James Wilson of the University of Michigan, whose team is treating the female FH patient with the low-density lipoprotein receptor gene, was recently granted permission by RAC to extend the study to four new patients. By contrast, studies using transformed tumour infiltrating lymphocytes have come under fire (see *Nature* **360**, 399; 1992) and many other trials have not yet yielded conclusive results. Research questions remain about the purification of viruses in large quantities and the targeting of specific populations of cells.

The next twelve months may see European researchers gaining ground. Two prominent European investigators, Dinko Valerio in the Netherlands and Claudio Bordignon in Italy, are already attempting to target stem cells to prolong the effectiveness of the treatment for ADA deficiency. In Germany, a proposal by Roland Mertelsmann to transfect the cytokine interleukin 2 into fibroblasts before using them as a vaccine for cancer patients was recently approved by the state of Baden-Würtenberg (see *Nature* **360**, 702; 1992).

In Britain, however, a proposal by Valerio's collaborators to begin trials for ADA deficiency, as well as a separate strategy for CF therapy from investigators in London, have suffered because the government has not yet set up a formal expert review board. Similar concerns among other European investigators regarding the paucity of approved gene-therapy trials has prompted some to approach the RAC about the possibility of using it to examine European-based proposals.

With anxieties about the safety issues and effectiveness of gene therapy decreasing, 1993 could see a spate of new proposals as investigators turn to new diseases and alternative strategies to deliver healthy genes. Many other proposals are likely to be of the 'gene marketing' variety, in which researchers tag populations of cells such as bone marrow cells with a recombinant marker gene before transplanting them back into the host.

Kevin Davies

Recession grips industrial R&D

This year seems likely to be another gloomy 12 months for industrial research and development (R&D) as the global recession continues to depress spending and force cutbacks in research. One of the few bright spots is the pharmaceutical industry, which is weathering the recession with continued heavy investment in drug development.

Last year, even Japan, which maintained buoyant growth into the 1990s, found it could not escape the tide of recession. Major players in Japan's industrial research, such as the electronics and automobile industries, have been forced to freeze R&D budgets as their profits fell to all-time lows (see *Nature* **356**, 93; 1992). The end of 1992 saw International Business Machines (IBM) announce a cut of $1 billion in its planned outlay on R&D worldwide in 1993, the latest in a string of bad economic news that included last summer's announcement by British Petroleum that it will shed nearly half of its research staff in Britain and the United States (see *Nature* **358**, 528; 1992).

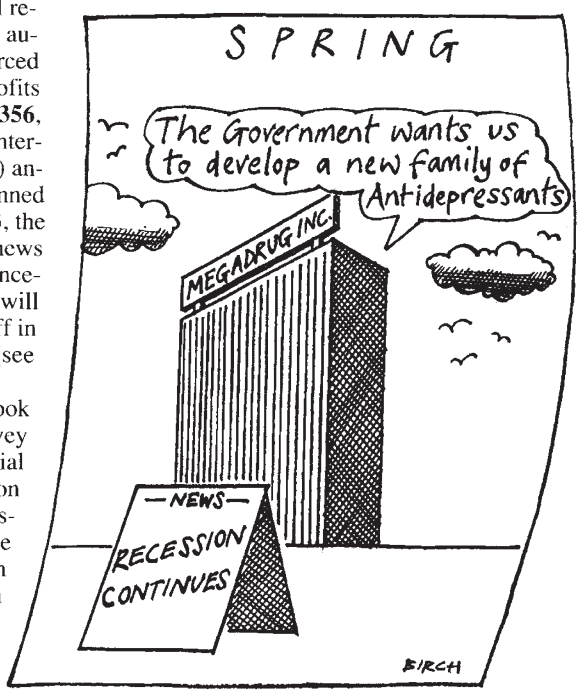
Prospects for the coming year look even grimmer. An end-of-year survey by the Washington-based Industrial Research Institute, an organization representing 260 prominent industrial companies, predicts that the recession will hit R&D spending in the United States even harder in 1993. More than a quarter (28 per cent) of the 141 companies replying to the survey say that they plan to cut their R&D budgets this year and even more (36 per cent) will spend less on equipment and R&D facilities. In Japan, the recession has prompted some bizarre economy measures, including switching off the heating during lunch breaks and eliminating business cards for researchers (see *Nature* **360**, 98; 1992).

Despite a supplementary budget of more than ¥10,000 billion (US$80 billion) introduced by the Japanese government a few months ago to boost the economy, the recession in Japan is expected to continue well into this year, and many observers predict that companies will be forced to slash their R&D budgets during the 1993 fiscal year, which begins on 1 April.

The recession is also affecting Japanese government research spending. Nevertheless, industry, including some non-Japanese companies, is turning to Japan's Ministry of International Trade and Industry (MITI) for support of long-term precompetitive research.

The situation is particularly severe in Europe because of the costs of reunifying Germany. In western Germany, 1,500 research positions will be shed in national research institutes and Germany has cut its funding to large-scale European projects, such as the European Space Agency and CERN (the European Laboratory for Particle Physics) (see *Nature* **360**, 701; 1992). The development of a strong research base in Spain through increased government spending has also been delayed by the recession (see *Nature* **360**, 502; 1992). And the leading government organization for applied research in the Netherlands, the TNO, has been told to find more money from industry because of cutbacks in government support (see *Nature* **360**, 402; 1992).

The only bright spot in all the gloom is the drug industry. As one of the directors of Japan's Takeda Pharmaceutical company puts it, "people have to continue buying drugs even in a recession". Glaxo, the British-based pharmaceutical group and one of the largest companies in the world, plans to boost its R&D spending from £600 million



(US$900 million) to £720 million in 1993 to try to maintain its success in developing such popular drugs as its anti-ulcer medicine Zantac. And while most of Japanese industry has held down R&D spending, Japan's drug industry increased its spending on R&D in 1992 by 6 per cent, a rate well above inflation. Similarly, in the United States and Switzerland drug companies are maintaining heavy investment in drug development, exceeding 10 per cent of sales.

Another glimmer of hope is offered by the election of Bill Clinton as US president. Many observers expect Clinton to strengthen government support of industrial research, much as the Ministry of International Trade and Industry does in Japan. But any such policies are unlikely to have much effect on spending during 1993.

David Swinbanks

Agricultural biotech moves into spotlight

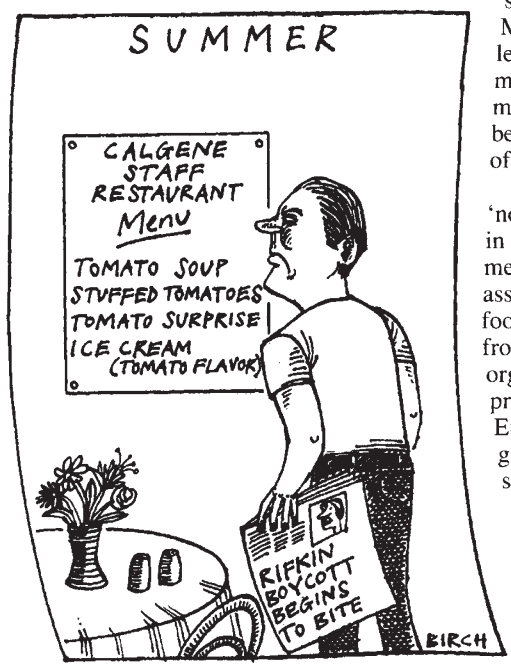
The year is likely to be the most critical yet for the agricultural biotechnology industry. This summer, all eyes will be on Calgene, Inc. of Davis, California, as it introduces its rot-resistant Flavr Savr tomato into the $3.5-billion annual US market. A successful launch will also pave the way for the next wave of genetically engineered foods and make it easier for agricultural biotechnology companies to raise capital.

Roger Salquist, Calgene's chairman and chief executive officer, has become the industry's standard bearer in building consumer confidence in genetically engineered foods and doing battle with critics. A frequent foe is Jeremy Rifkin of the Washington-based Foundation on Economic Trends, who agrees that this year will also be critical for the foundation. He has promised to step up his 'Pure Food Campaign', and to lead a boycott of each new genetically engineered food until regulators implement pre-market testing and labelling of the foods.

All Calgene has actually done with its Flavr Savr tomato is to isolate the gene that codes for the polygalacturonase enzyme and reintroduce it into selected tomato varieties in the reverse or 'antisense' orientation. That change blocks the action of the enzyme, which causes softening of the fruit, by as much as 99 per cent, producing a better-tasting, longer-lasting tomato that can be harvested from the vine when ripe instead of ripening artificially. If Calgene's tomato is rejected by consumers, predicts Louis Da Gama, executive director of the UK BioIndustry Association (BIA), the idea of introducing novel genes into crop plants "will be dead in the water".

The Flavr Savr tomato is expected to be followed within a year by crops able to tolerate herbicide treatments, and within two to three years by crops resistant to insect attack. Eventually, companies hope to develop families of genetically modified oils and fatty acids for use as foodstuffs and in industrial applications as biodegradable lubricants and hydraulic fluids.

At the same time, there is little reason for optimism among those working on novel animal technologies. Genetically engineered bovine somatotropin (BST), when injected into lactating dairy cows, can boost milk yields by 10 per cent or more but offers no benefit to consumers. Despite a clean bill of health from several review panels, the drug has become a prime target for consumer lobbyists who have raised questions about its safety and who say that it will put small farmers out of business.



Some expect a smoother regulatory ride in the United States for genetically engineered porcine somatotropin, which when given to pigs produces leaner meat. Philip Paxman, chairman of the European Trade Association for Advanced Animal Breeding, points out that a more efficient, more profitable animal is not enough. "There also has to be a social benefit", he says, such as the use of animals to produce human therapeutics or as model systems to study human disease.

Early this year, the European Commission (EC) is expected to start a significant research initiative in agricultural biotechnology involving more than 50 research laboratories. Managed jointly by the John Innes Centre in Norwich, England, and the Max Planck Institute for Breeding Research in Cologne, Germany, and funded initially for three years, the programme is intended to strengthen the European science base and make it a stronger international competitor. Richard Flavell, director of the John Innes Centre, says that the programme will try "to create a platform of research right across Europe that is seamless and that will give rise to discoveries, trained people and information that will be particularly useful to European industry". It is expected to cover research into plant development, with emphasis on hormones and related growth substances, in addition to environmentally friendly agricultural research, research to improve the quality of harvested products and the use of beneficial microorganisms.

Despite positive news last year for the agricultural biotechnology industry in the United States, a patchwork of regulations still exists in Europe. The Council of Ministers' directive on the deliberate release into the environment of genetically modified organisms, due to be adopted by member states in October 1991, has yet to be implemented by six of the 12 countries of the European Communities.

There is some progress expected on the 'novel foods' regulation, under discussion in the Council and in the European Parliament. The regulation sets out a means of assessing the safety of all novel foods and food ingredients, including those produced from or containing genetically modified organisms. The BIA opposes the current proposal, believing that it would place European industry at a disadvantage by going beyond international standards on safety, efficacy and quality.

Legislation is also under discussion in the EC for the labelling of foods produced by genetic modification. Last May, the US Food and Drug Administration gave preliminary approval to eliminating pre-market review and labelling of foods derived from biotechnology except in circumstances where levels of a naturally occurring toxicant have been increased, when an allergen not usually found in a plant has been introduced and where levels of important nutrients have been changed (see *Nature* **357**, 352; 1992).

Diane Gershon

Magnetic fusion proceeds with no end in sight

The inauguration of the Tokamak Fusion Test Reactor (TFTR) at Princeton University on Christmas Eve 1982 was described by the world media as the dawn of the era of fusion energy. Almost exactly a decade later — and 35 years after Sir John Cockcroft said (mistakenly) that he was "99 per cent certain" fusion had been demonstrated at Britain's Harwell laboratory — clean, commercially available energy remains a long-term dream.

This year, for reasons both scientific and political, fusion is again likely to make headlines. On the experimental front, two events stand out: the Joint European Torus (JET) at Culham, England, is expected to reopen in October after being closed for