IN brief

Bt brinjal splits Indian cabinet

M. Singh in pacifying mode.

India's prime minister, Manmohan Singh, has intervened in the political wrangle that erupted over a genetically modified (GM) eggplant strain due for commercial release. Approval of the locally developed *Bacillus thuringiensis* (*Bt*) variety appeared imminent, but on

February 9, the minister of environment and forests, Jairam Ramesh, responded to public opposition by declaring an indefinite moratorium on the approval of *Bt* brinjal, as it is known locally, on the grounds of insufficient data to confirm that it is safe to eat. This decision has created a cabinet rift, prompting Singh to hold a consultation with senior government officials. *Bt* brinjal is India's first locally developed GM food crop and was created by Mahyco, a Jalna-based Maharashtra Hybrid Seeds Company in a joint venture with Monsanto, the St. Louis-based seed giant. Last October, the Genetic Engineering Approval Committee (GEAC), India's official regulatory body for registering GM organisms, approved release of the transgenic brinjal, opening the door for commercialization of another dozen or so GM crops in the pipeline. The environment minister's decision to over-rule the GEAC was unexpected. But it followed vociferous feedback from civil societies and advice from scientists, including Monkombu Swaminathan of 'green revolution' fame and Pushpa Bhargava, founder of the Centre for Cellular and Molecular Biology in Hyderabad, that additional safety testing of the GM brinjal was warranted. Chavali Kameswara Rao, secretary of Bangalore-based Foundation for Biotechnology Awareness and Education, believes the environment minister caved in to intense lobbying pressure from activists. He fears the resultant delay of commercialization will promote clandestine cultivation of *Bt* brinjal—similar to what happened previously in India with *Bt* cotton (*Nat. Biotechnol.* **22**, 1333–1334, 2004). On February 24, Singh and senior cabinet members agreed to set up a national biotech regulatory authority to oversee registration of transgenic products and requested that the GEAC resolve outstanding safety concerns relating to *Bt* brinjal. No time frame for these deliberations was set, however. The Department of Biotechnology (DBT), the main funding agency for transgenic research, has stayed out of the controversy. But as Prasantha Kumar Ghosh, DBT's former head of biosafety puts it, "There is no scientific basis for a moratorium." Bhim Sain Bajaj, president of the Hyderabad chapter of All-India Biotech Association, agrees. "It is a big mistake...the time will come when India will have to import rice and vegetables and we will regret [this decision]." *Killugudi Jayaraman*

Administration (FDA) for inflammation of the retina in cytomegalovirus-infected patients. Although a breakthrough experimental therapy, the treatment has not been able to build a substantial commercial market.

The company's current lead antisense product will compete for market share with the statins, a highly successful group of drugs (including Pfizer's blockbuster Lipitor; atorvastatin) that reduce levels of cholesterol, low-density lipoprotein (LDL), apolipoprotein B100 (ApoB), and triglycerides through inhibition of 3-hydroxy-3-methyl glutaryl co-enzyme A (HMG-CoA) reductase. Instead of targeting HMG-CoA reductase, mipomersen acts directly on ApoB, the protein responsible for carrying plaque-thickening LDL cholesterol into the arteries. As a second-generation 2'-O-(2-methoxy) ethyl-modified ribose oligonucleotide, the DNA oligonucleotide exhibits high affinity for ApoB messenger RNA. Binding of the ApoB mRNA by mipomersen then triggers cellular ribonuclease H to hydrolyze RNA phosphodiester bonds, thereby inhibiting translation and suppressing levels of ApoB protein.

On the basis of previous clinical data published last month (*The Lancet* **375**, 998–1006, 2010), mipomersen seems to do a better job than statins at fighting the dramatic cholesterol levels in individuals with FH, a rare genetic disorder. In the severe form of the disease, which affects 10,000 people worldwide, homozygous patients often have LDL levels up to six times normal, making patients susceptible to heart attacks as early as childhood. Phase 3 studies in homozygous patients led to an impressive 25% drop in LDL levels. This success prompted Isis and its partner Genzyme of Cambridge, Massachusetts, to initiate a phase 3 trial in heterozygous patients, with a view to seeking approval in the 1.5 million people who have less severe forms of FH and then extending the therapy to anyone with high cholesterol that is insufficiently controlled by statins (*Nat. Biotechnol.* **26**, 148, 2008).

The trial results announced in February for the heterozygous FH population included 124 individuals with pre-existing coronary artery disease, who were already taking maximum-tolerated doses of statins. After 26 weeks of treatment, mipomersen achieved a 28% reduction in LDL, compared with a 5% increase among controls. Isis stated that 45% dipped below 100 mg/dl—the recognized treatment goal. The study also met three secondary endpoints, with reductions in ApoB, total cholesterol and non-high-density-lipoprotein cholesterol.

The news was not all positive, however. Elevated liver enzymes were observed in 12 of 83 patients; in 5 patients, levels reached three times the upper limit of normal. It was these results, when made public, that prompted the company's shares to plummet by 17%. "Alone, [the liver enzyme increase] is not indicative of liver toxicity, but I think it serves as such a red flag, and investors have been burned so many times, they're not going to mess with this," says Edward Tenthoff, who is a senior research analyst and managing director at Piper Jaffray in Minneapolis.

In the earlier homozygous FH trial, 28 patients on mipomersen experienced a 24.7% decrease in LDL, compared with a 3.3% reduction among the placebo group. Four patients (12%) had increases in concentrations of the liver enzyme alanine aminotransferase (ALT) of at least three times the upper limits of the normal range. Other liver tests, including levels of bilirubin, albumin and prothrombin, showed no signs of liver damage, according to the company.

Importantly for antisense technology as a whole, the spike in enzyme levels is not entirely unexpected; in fact, it is likely to be target specific, given that lipid-lowering drugs are known to be one of the rare examples in which a pharmacodynamic property of the drug class as a whole accounts for liver toxicity. Statins, for example, are associated with a dose-related increase in the incidence of the liver ALT three times greater than the upper limits of the normal (threshold set by regulators); indeed, acute liver failure occurs in about one in a million statin-treated patients. The 124 patients in the mipomersen trial were already on high doses of statins.

For its part, Isis believes that elevated liver enzymes are not an inherent problem of antisense technology. For one thing, individuals who had the steepest drop in LDL and ApoB levels on mipomersen tended to have higher enzyme levels. What's more, ~5,000 people have been treated with oligonucleotides against other targets, with no evidence of ALT increases, according to Geary. "[The elevated enzymes] are more likely an on-target side effect that's related to the mechanism. I don't know that this is necessarily a black mark on antisense," says Brian Abrahams, senior biotech analyst at Oppenheimer & Co in New York.

As yet, the mechanism underlying the increase in liver enzymes in a small number of patients is not well understood. Possible explanations include alterations in the lipid concentrations in hepatocyte membranes, which could cause mild hepatic cell dysfunction, "but as far as I can tell it's uncer-