New German government muddies the biotech waters

Germany's newly elected coalition government, comprising the left-of-center Social Democrat Party (SPD) and the Green Party, has announced its policies. "Science and education politics will play an important role for the new government," claims Edelgard Bulmahn (SPD), the new minister for science and education. However, some observers worry that US perception of the Greens as antibiotechnology, combined with the coalition's hazy announcements regarding biotechnology will damage overseas investor confidence in an industrial sector that the previous German government endeavored to nurture and stimulate over the past few years.

The new agreement between the two partners in the coalition took nearly a month to reach after the German election in September. The agreement clearly states that "education and science are our answers to the challenges of the next century." And during its election campaign, the SPD made it clear it would continue with the biotechnology policies formulated by the outgoing Christian Democratic Party (CDU) and carry on funding such CDU biotechnology research programs as the human and plant genome projects. Bulmahn, keen to continue with competitions as a way of promoting biotechnology growth, also says she wants more contests like the 1996 BioRegio (*Nat. Biotechnol.* **15:**943, 1997), pioneered by Jürgen Rüttgers, the former CDU Minister of Science.

However, some fear that the SPD's Green coalition partners could be detrimental to both Bulmahn's position and Germany's nascent biotechnology industry. "US investors and companies have recently shown some hesitation toward investing in German biotechnology," says Rüdiger Hermann, a lawyer at Gaedertz (a law firm in Frankfurt am Main), and a consultant to a number of German and US biotechnology firms. "The Green Party is often seen by American investors as an environmental organization that boycotts biotechnology and therefore appears to be an unreliable political partner."

Predictably, it is the food and agriculture biotechnology sector, already generally less accepted by the German public than medical biotechnology, that looks as if it will be most affected by the coalition agreement. The new government, which has made a clear distinction between the medical and agricultural applications of biotechnology, has announced that it will increase risk assessments for new biotechnology developments in food and agriculture. "We have to place new emphasis on long-term monitoring of possible risks posed by the introduction of genetically modified crops and foods," says Wolf-Michael Catenhusen, the new parliamentary state secretary at the Ministry of Education and Science (Bulmahn's deputy).

Catenhusen, who was also the chairman of the parliamentary committee that dealt with this issue from 1987 to 1994, does not think increased risk assessments will discourage foreign investors, saying that similar precautions are being taken in other European countries. "Great Britain has just set up a new commission to deal with these risk-assessment issues," he points out.

However, it is not clear how the new assessments in Germany will work, who will be most affected, or whether the standards will be in line with similar USDA regulations. Although he acknowledges that "this kind of research is a task for academia," Catenhusen says that industry cooperation is necessary, but that "we do not want to burden small start-up biotech companies."

Although critical of the ambiguity of the coalition announcement, Hermann thinks that if increased risk assessments become too burdensome, companies will simply conduct biotechnology trials in other countries such as Switzerland, which he says is far more biotechnology-business friendly.

The issue of labeling of genetically modified organisms (GMOs) is also somewhat murky. The previous German government passed a new law in the summer allowing labeling of foods that are GMO-free and not made with the aid of modern biotechnology (*Nat. Biotechnol.* **16:**712, 1998). Although companies question aspects of the regulation, such as contamination thresholds, the new government seems intent on implementing the new law as quickly as possible. "We have to take the sensibilities of consumers into account," says Catenhusen. "We do not want to stop GMOs in food, but we do want to provide more scientific information [about them]." However, he is unable to say who will be responsible for providing this information, saying only that "[It] cannot be done by industry alone."

Another fuzzy area is the new government's desire to place more emphasis on ethical issues concerning biotechnology. In June, the CDU government decided to establish a reference center for bioethics in Bonn, similar to the Kennedy Institute in Washington, DC. Although Catenhusen says he favors further research in bioethics, he hesitates in answering questions regarding government funding for this field. "We have to have more discussions with different groups such as the churches or consumer organizations and associations for the disabled," he says evasively.

Hermann thinks this lack of clarity in the new government's policies will concern investors. "If the new government does not want to make potential investors uncertain," he says, "it will need to take a clear stand soon and come up with some hard facts."

Ellen Peerenboom

Ellen Peerenboom is a freelance writer working in Cologne, Germany.

Naked DNA vaccines come of age

A "naked DNA" vaccine for malaria has promoted an immune response in healthy volunteers (*Science* **282:**476, 1998), challenging skepticism that DNA alone injected into muscle can mobilize cytotoxic T (CD8+) lymphocytes (CTLs) to kill such intracellular parasites as *Plasmodium falciparum*, the cause of malaria. As well as serving as a proof of principle for "naked DNA," the results are an important step in the fight against malaria, for which there is no vaccine.

The purpose of the study—a collaborative effort between Vical (San Diego, CA), the Naval Medical Research Center (NMRC, Bethesda, MD), and Pasteur Mérieux Connaught (Swiftwater, PA)—was to determine if immunization with DNA alone was safe, well-tolerated, and immunogenic in normal humans, says lead investigator Stephen Hoffman, director of the NMRC malaria program.

"Naked DNA" is, in essence, a plasmid loop that contains the relevant coding and control regions to allow the expression of a pathogen gene inside human cells. The DNA is also "naked" in the sense that it is delivered without the aid of vehicles such as liposomes or virus vectors. Direct intramuscular injection of naked DNA evoked a dose-dependent CTL response in 11 of 17 healthy human volunteers. As required by the US Food and Drug Administration (Rockville, MD), the vaccine incorporated only one gene from the malaria pathogen, which is not sufficient to confer full immunity in disease-naïve individuals but is adequate to test whether it could induce antigen-specific CD8+ T-cell responses.

There are at least seven other malaria vaccines in development, but this is the first example of the use of naked DNA for this disease. Many vaccine experts, including David Weiner of the University of Pennsylvania (Philadelphia) and Stephen Johnston of the University of Texas Southwest Medical Center (Dallas), believe that naked DNA is the best approach to use with the malaria parasite as well as other infectious agents because it can mobilize CTLs. "With an extremely complex life cycle, and the 6,000 genes of the malaria parasite, there is no other technology as well suited to dealing with malaria," asserts Hoffman, who is part of the multicenter team that recently determined the sequence of chromosome 2 of *P. falciparum* (*Science* **282:**1126, 1998).

Many consider DNA vaccines to be conceptually third-generation technology, says Shaefer Price, CEO of PowderJect Vaccines (Madison, WI). PowderJect signed a $321 million deal in March with Glaxo Wellcome (London) for gene-gun DNA vaccine development (*Nat. Biotechnol.* **16:**316, 1998), initially for hepatitis B virus infections. The first-generation vaccines were attenuated live pathogens. They could mobilize CTLs but carried a risk of infection, says Price. The second-generation vaccines are much safer and based on killed pathogens or their purified polymeric components. However, such vaccines usually are not effective in producing cellular immunity (they produce only antibodies), and patients need multiple doses. The third-generation vaccines consist of a pathogen's isolated DNA that functions as part of the intracellular production machinery encoding particular antigens presented to the immune system via the major histocompatibility class I pathway, which produces CTLs.

"DNA vaccines are particularly well-suited to deal with viral diseases where other live vaccines have failed or cannot be constructed due to fear of infection," says Richard Ciccarelli, vice president of vaccines at Wyeth-Lederle's (Radnor, PA, part of American Home Products). Wyeth-Lederle has invested much in DNA vaccines, especially for the treatment of sexually transmitted diseases, says Ciccarelli. To that end, in April 1998, Wyeth-Lederle acquired Apollon (Malvern, PA) for an undisclosed sum, gaining three vaccines, now in phase I/II development, against HIV, herpes simplex, and human papillomavirus. The company is also investigating the use of viral and nonviral vectors to improve the vaccines' effect.

Margaret Liu, vice president of gene therapy and vaccine research at Chiron (Emeryville, CA), once called the ability to generate CTLs without using a live vector "the immunologist's grail." Until recently, she says, vaccine investigators measured only antibody response because they believed that it was impossible to mobilize CTLs in any significant quantity. Since HIV, scientists have come to understand the importance of the cellular response, and have begun moving away from an "all or nothing" approach to treating infections with vaccines, she adds.

DNA vaccines have other potential advantages, too: They can stimulate long-lived immune responses; they can address several diseases in one vaccine; they are cheap and easy to produce; and they are extremely stable and have no special cold storage requirement. Furthermore, candidate vaccines can be purified from diseased tissue. In addition, both Weiner and Johnston see value in the technology as a research tool to select and test antigens.

However, critics claim (and even some supporters admit) that naked DNA vaccines require too much genetic material, and that the vaccines could be more effective if combined with adjuvants, lipids, or polymers. Consequently, most companies and academic teams working with DNA vaccines—including Vical and Apollon—are also experimenting with a variety of vectors to boost the effect of the DNA and reduce the amount needed.

The next step for NMRC "will be to construct a five-gene vaccine with Vical based on an irradiated sporozoite model we know works, but which is impractical to produce as a vaccine," says Hoffman. The group will begin next summer to vaccinate healthy volunteers with the new vaccine, and then will challenge them with a strain of malaria that is treatable. The Vical/Navy group has worked with Epimune (San Diego, CA) to determine peptides that would make the best T-cell epitopes, says Navy staff scientist William Rogers. The third phase will be the construction of a 15-gene vaccine containing 10 antigens from the blood-stage of malaria infection, and five from the liver-stage. If effective, this could address the anticipated need to develop two distinct vaccines, one for uninfected people such as travelers and military personnel, and another for those from areas of endemic infection, Hoffman says. (The UN and World Bank announced in October Operation Roll Back Malaria, an effort to encourage research by companies, which have largely perceived this area as lacking profit.)

Chiron is working only with HIV and hepatitis C to compare refinements of DNA technology, says Liu. Her group is working on second-generation gene vaccines using alpha (RNA) viruses to improve delivery because "they don't replicate to cause disease like viruses do, but make many copies of themselves and target the follicular dendritic cells in lymph nodes." Chiron has also developed "lipitoids"—polymers, more potent than cationic lipids, that improve delivery and reduce the DNA load needed, she says.

Vicki Brower