

ALSO IN THIS SECTION

Illegal seeds overtake India's cotton fields p1333

US NCI launches nanotechnology plan p1335

Kenyan dispute illuminates bioprospecting difficulties p1337

News in brief p1339

News Feature: Biogenetics standoff p1343

Industry wary of NIH consultancy moratorium

Noting that “vulnerabilities” in the agency’s oversight system give him “pause,” the National Institutes of National Health (NIH) Deputy Director Raynard Kington announced on 24 September plans for instituting a one-year moratorium on consulting agreements with industry involving any NIH employee. Unsure of the impact of this proposed moratorium, biotech industry representatives say that the situation should be closely monitored.

Earlier in June, amid a series of sometimes combative hearings, NIH Director Elias Zerhouni promised members of Congress to “revamp the NIH ethics program,” including a similar ban on consulting that was then limited to NIH senior staff (*Nat. Biotechnol.* 22, 796, 2004). However, after Washington, DC’s Office of Government Ethics (OGE) issued a report suggesting that Zerhouni’s recommendations did not go far enough and the House Committee on Oversight and Investigation turned up 100 unreported arrangements between industry and NIH scientists from a survey of 20 companies, the powers that be at the NIH apparently decided to pull the plug on consultancies, at least temporarily (see **Box 1**).

In his September memorandum, Kington states, “we still value interactions between NIH staff and industry.” Other officials at the agency point out that this new measure could affect as many as 60 consulting agreements, but would not affect broader NIH–industry interactions that are based on cooperative R&D agreements (CRADAs). Companies sometimes fund research done by NIH scientists under such CRADAs, whereas the firms typically pay the NIH employees directly under consulting relationships.

Aside from the announcement to halt all consulting with industry, NIH officials are providing little new information about why they plan to impose such a broad, albeit temporary ban. Instead, Kington noted, the moratorium “will give us time to complete our review of specific cases, develop effective information systems to track outside activities, and develop more effective ethics training programs for staff before a final policy is put in place.”



Researchers at the NIH campus in Bethesda, Maryland may be banned from consulting for industry.

This information deficit makes it difficult, if not impossible, to assess the overall impact that these changes could have on industry, according to Carl Feldbaum, outgoing president of the Biotechnology Industry Organization in Washington, DC. “We don’t know the foundation or the seriousness—if it’s real or perceived conflicts of interest, or worse,” he says. “Before gauging this [proposed moratorium], we want to know about the underlying activity and behavior. And we should withhold judgment until we can gauge whether this reaction at NIH fits the behavior. We want to know if Draconian outcomes are warranted.”

However, despite a “generalized concern” about the effects of this moratorium, “no one is calling us to register individual concerns,” Feldbaum says. “Companies have not weighed in with us, and there is probably no way to quantify the impact. As this proceeds, we’ll ask members if this is affecting them, and we’ll track it closely.”

Some clues as to what is moving NIH officials come from those congressional hearings

held in May and June of this year. Director Zerhouni testified that “the tipping point” for him was a situation involving a CRADA between the NIH and Correlologic Systems, a biotech company in Bethesda, Maryland. Correlologic President Peter Levine testified before Congress that a relationship with NCI scientists went from fruitful and informal in 1999 to sour and riddled with suspicions, including dubious statements by senior NCI scientists about proprietary information possibly being transmitted to another biotech company, Predicant Biosciences (formerly Biospect of S. San Francisco, California). Relations between the company and the NCI early this year were “not cricket” and did not represent a “good way to foster good public-private sector relations,” according to Levine.

During the June hearing, Jonathan Heller, a vice president of Predicant, denied wrongdoing and said the company “followed the rules and acted appropriately” when dealing with several of the same NCI scientists as Correlologic.

However the specific charges and counter-

Box 1 Conflicts of interest unfold

1995. NIH head Harold Varmus releases caps on amounts of money an NIH scientist can receive from outside sources.

1998. Title 42 ruling allows senior scientists to keep outside consulting arrangements confidential.

December 2003. *LA Times* publishes investigative report on consulting arrangements between NIH scientists and industry.

January 2004. NIH Director Zerhouni creates Blue Ribbon panel to investigate possible conflict of interest at the NIH.

May 2004. Blue Ribbon panel recommends banning senior officials from earning money from consulting and limiting activities of scientists, with respect to time, and amount and type of compensation.

May–June 2004. Zerhouni presents recommendations to the House Subcommittee on Oversight and Investigations.

July 2004. Government Office on Ethics recommends that NIH adopt tougher standards of conduct.

September 2004. NIH proposes one-year moratorium on all consulting arrangements between NIH scientists and industry, pending approval by the department of Health & Human Services and OGE.

charges become resolved, the situation at its worst made Correllogic look “radioactive,” making it difficult for it to negotiate with

potential collaborators, particularly academics who fear repercussions that could impair their funding, Levine says. Looking back, those dif-

ficulties meant lost time and diverted resources, which was “not beneficial for a small biotech company.”

Meanwhile, the September and June announcements from leaders at NIH are getting mixed reactions from scientists and administrative staff there, and in some cases those reactions are accompanied by confusion. For example, the memo has led some at NIH to doubt the prospects for negotiating other kinds of arrangements with industry, even including innocuous efforts such as arranging jointly sponsored conferences, one official says. “It’s a shot in the head to senior PhDs and MDs, especially those doing clinical research,” says another official. “People feel like they are being watched over, and many of them will leave,” he predicts.

On the other hand, a senior scientist at NIH doing basic research shrugs his shoulders over such prospects and is scornful of past consulting arrangements. They “never should have been allowed,” he says, and no one at NIH “should get a dime” for consulting with industry.

Jeffrey L. Fox, Washington

Illegal seeds overtake India's cotton fields

Indian agricultural minister Sharad Pawar admitted in parliament on August 16 that there is a flourishing illegal market in genetically modified (GM) cotton seeds, strengthening allegations by the industry that more than half of all the GM cotton now growing in the country is from unapproved varieties. Pawar, Indian scientists and seed companies want state governments to take action against the seed producers and traders to protect the industry and to prevent an impending 'biodisaster.'

India's Genetic Engineering Approval Committee (GEAC), the country's main agbiotech regulatory body, opened the door to genetically modified (GM) products in 2002 (*Nat. Biotechnol.* 20, 415, 2002) and now allows the sale of four varieties of insect-resistant GM cotton, all of which carry St. Louis-based Monsanto's proprietary *cry1Ac* gene from *Bacillus thuringiensis* (*Bt*). Now in its third year of use in India, *Bt* cotton—including illegal varieties—is estimated to cover more than three million acres in the country, which is about one-third of the total area of planted cotton.

But, because of poor monitoring by the government, "80% of all *Bt* cotton growing in India are nameless, unlicensed varieties," says Sateesh Kumar, managing director of Prabhat Agri-Biotech in Hyderabad. This year, farmers have planted unapproved GM cotton in more than half-a-million acres in the Gujarat state alone, say industry executives.

The problem started in 2001 when an unlicensed *Bt* cotton hybrid carrying the *cry1Ac* gene was found growing on over 10,000 acres in the western state of Gujarat (*Nat. Biotechnol.* 19, 1090, 2001). Failure by the government to enforce GEAC's order to destroy the crop or to punish Navbharat Seeds, the Ahmedabad-based company that sold the unapproved seeds, emboldened seed producers to covertly multiply and sell them. Two things created the demand for this illegal variety: its demonstrated ability to resist bollworm attack and the relatively low price (Rs.600 (\$13) for 450 grams compared to Rs.1,600 (\$35) for an approved variety marketed by Monsanto licensee Mahyco in Jalna).

Companies are becoming frustrated at the lack of accountability for the illicit behavior. "We spend millions of rupees in research and then wait for years for



A farmer in Andhra Pradesh proudly displays his five-acre farm of illegal *Bt* cotton, which he says provides higher yields than legal varieties.

regulatory clearance," says Foujdar Singh, adviser to Syngenta India Limited in Hyderabad, whose insect-resistant cotton is undergoing field trials. "But here are unauthorized varieties openly sold in

market for the past three years. If this is the situation, why should companies invest in R&D at all?"

Perhaps potentially more harmful for India's cotton industry is a looming

Box 1 GM containment problems around the globe

India is one of several countries to have recent problems with unapproved varieties of GM crops popping up. Whereas in India, greedy traders colluding with unsuspecting farmers are spreading illegal cottonseeds, in other countries the problems are arising for different reasons:

- On 13 September, Thailand, which does not allow the commercial planting of GM crops, ordered a halt to the distribution of papaya seeds from its research station in Khon Kaen three months after Greenpeace campaigners discovered the presence of GM virus-resistant papayas outside the station. The government is investigating whether GM seedlings were sold to the farmers, which seems a more likely scenario than gene flow.
- Organic papaya growers in Hawaii have increasingly found their trees to have transgenes that confer resistance to ringspot virus since GM varieties were introduced in 1998. In this case, the culprit is almost certainly gene flow through pollen blowing in from nearby GM papaya farms.
- The *New Scientist* reported on 20 September that over one million GM insect-resistant poplar trees have been 'lost' in China. The government planted the trees over 8,000 square kilometers in an effort to prevent flash floods and halt the spread of deserts, but now no one knows exactly which trees in the areas are transgenic. China's Ministry of Agriculture has not kept track of them because they are not crops, and the country's State Forestry Bureau does not have a licensing system to properly trace the trees.

KSJ & Aaron Bouchie

environmental disaster if pests develop widespread resistance to the *Bt* crop. Such resistance is typically combated by planting refugia of non-*Bt* cotton, which dilutes the presence of *Bt*-resistant genes in pest populations through gene flow. But farmers planting illegal seeds are not obliged to provide such refugia for resistance management. Syngenta's Singh predicts, "Only when there is a major pest problem farmers will wake up" and stop planting the illegal varieties without refugia.

"The illegal proliferation of GM varieties must cease or else the biosafety regulations will be rendered meaningless," warns a government committee headed by M.S. Swaminathan, a noted agricultural scientist and chairman of his own Research Foundation in Chennai. But it is not going to be easy, because traders masquerading as farmers sell the illegal seeds in unmarked cloth bags, no bills or receipts issued, according to Singh. "Indian laws allow farmer-to-farmer sales,

even of patented varieties, as long as they are not branded," explains Prabhat's Kumar.

"We have been running up and down the government corridors seeking a ban on illegal seeds, but the organized sector cannot do much unless the government is

Industry sources say that illegal seeds produced in about 8,000 acres in Gujarat and 4,000 acres in Andhra Pradesh are enough to plant 2.5 million acres.

firm," says Singh. In response, government officials claim to have registered 18 complaints and to have conducted 40 raids, with arrests in four states and seizures of 62 kilograms of illegal seeds.

But industry officials doubt the sincerity of these efforts. "If the government really wanted to end the illegal trade, it could have raided the seed production centers," says Kumar. Industry sources say that illegal seeds produced in about 8,000 acres in Gujarat and 4,000 acres in Andhra Pradesh are enough to plant 2.5 million acres—about twice the quantity of legal seeds that Mahyco claims to have sold this year.

How long the illegal seeds will rule the Indian *Bt* market is unclear. The fight is expected to intensify in two years when 12 more varieties of *Bt* cotton hybrids developed by Raasi Seeds, Ankur Seeds and Mahyco are expected to reach the market.

K.S. Jayaraman, Hyderabad, India

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US NCI launches nanotechnology plan

The US National Cancer Institute (NCI) on 13 September formally unveiled its Alliance for Nanotechnology in Cancer, a 5-year, \$144.3 million initiative to fund the development of nanotechnology-based cancer products, as well as the standards for such products. The alliance aims to join together private and public sector researchers, who have high hopes for the NCI's goal of jump-starting efforts to get more cancer products into the hands of clinicians more quickly.

The alliance has established the Nanotechnology Characterization Laboratory (NCL), whose primary mission will be to facilitate the regulatory review of nanotechnology-based cancer products, such as targeted drug delivery vehicles, imaging contrast agents and *in vivo* diagnostic agents. Based at the NCI's Frederick, Maryland, research campus, this national laboratory will work closely with both the National Institute of Standards and Technology (NIST) and the US Food and Drug Administration (FDA) to develop standards for both the characterization of nanoscale materials and for preclinical testing of products that use such materials.

"The goal is to establish a set of standards and assays that companies can use in preparation for regulatory filings to characterize nanoparticles in terms of their size and composition, their behavior in the body and their safety," explains NCL Director Scott

McNeil. "Ideally, this will create a standard data package that will make the FDA's job easier and expedite its review of an Investigational New Drug application." Janet Woodcock, FDA's acting deputy commissioner for operations, seconds this: "We expect the NCL to facilitate the development of therapeutics and diagnostics using nan-

"We expect the NCL to facilitate the development of therapeutics and diagnostics using nanotechnology by developing the [scientific standards] needed to inform our regulatory decisions," says Janet Woodcock.

otechnology by developing the [scientific standards] needed to inform our regulatory decisions."

That link between the FDA, NIST and the NCL will provide a boost to the developing field of cancer nanotechnology. "If the FDA says that going through [the NCL and NIST] or using the assay cascade [to be] developed by the NCL gives you a fast track to start clinical trials, then this would be very important," says James Baker, director of the

University of Michigan's Center for Biologic Nanotechnology.

With an initial budget of over \$4 million and a complement of six scientists, the NCL will begin accepting materials for testing this November. The NIST will immediately handle all physical characterization work and the NCL will begin running its set of preclinical assays (such as absorption, distribution, metabolism and excretion assays, and toxicology screens) in January. The NCL's McNeil anticipates that it will take between 12 and 18 months to yield a full package of preclinical data for any given material. A technical advisory board, whose members will be drawn from private and public sectors, will help prioritize material review should the NCL be inundated with material submissions.

The bulk of the alliance's cash will use a contract-based mechanism to fund up to five centers for excellence in nanotechnology, at a total of \$90.8 million over 5 years. More similar to European initiatives (see **Box 1**) than to the NIH's Nanomedicine Roadmap Initiative, which focuses on fundamental research, the mission of the centers is to develop specific diagnostic, imaging and therapeutic products using nanotechnology. Envisioned as a consortia of three to five institutions, each center will need to meet product development milestones and will be strongly encouraged to recruit biotech and

Box 1 Europe dives into nanobiotech

Several new European Commission (EC)-funded initiatives that are aimed at integrating academic research with the needs of industry point to a centralized strategy for bolstering the convergence of the nanotechnology and biotechnology sectors, with government funding for nanomedicine-related projects totaling €90 (\$110) million for the period between 2002 and 2006. "One of the things Europe is very good at is building networks," says Tim Harper, CEO of Cientifica, a Madrid-based consultancy for nanotechnology firms.

February saw the birth of Nano2Life, Europe's first Network of Excellence in nanobiotechnology. Consisting of 23 public research institutes in 12 countries, the program receives €8.8 (\$10.8) million from the EC; the partners will commit an additional €6 (\$7.4) million. So far this year, the network has seeded 20 initial research projects and has embarked on a roadmap initiative, slated for completion in mid-2005, to analyze ongoing R&D, to survey industry needs and to prioritize the field's commercial needs. Ultimately, the goal is to create a virtual European institute for nanobiotechnology, says program coordinator Patrick Boisseau of the Atomic Energy Commission in Grenoble.

The Frontiers European Network of Excellence, launched at the Mesa+ Research Institute of the University of Twente, the

Netherlands, in August, funds a network infrastructure for 12 nanotechnology institutes to collaborate and develop instrumentation for life sciences applications. Despite Europe's strong nanotechnology research base, many projects have succumbed to "European Disease"—doing good R&D but not using it," explains Kees Eijkel, technical commercial director of Mesa+. A crucial part of the network, which receives €5 (\$6.1) million in EC funding over 4 years, is the science-to-industry chain, coordinated by Muenster-based tech transfer company CeNTech.

Meanwhile, CellPROM (cell programming by nanoscale devices), the largest EC nanobiotechnology-related Integrated Project, aims to build a prototype of cell manipulation technology to be used for regenerative medicine. The 4-yr, €25 (\$30.1) million initiative, commenced in March, "is one of the first [nanotechnology initiatives] to go beyond more straightforward projects," says Rols Guenther, CSO of Evotec Technologies, a key player in the project.

No one is expecting quick results. "We won't see the large mass market for several years," predicts Boisseau. "But the commitment of large companies to [nanotechnology-based] drug delivery and diagnostics will be crucial."

Alla Katsnelson, New York



Scott McNeil is the director of the NCI's new Nanotechnology Characterization Laboratory, which is expected to speed the translation of nanotechnology research discoveries into clinically useful cancer therapeutics and diagnostics.

pharmaceutical company researchers as equal participants.

Among the products envisioned are new imaging contrast agents, targeted nanoparticles capable of delivering multiple therapeutic agents simultaneously, and a new class of *in vivo* diagnostic agents called "reporters of efficacy," which are designed to determine if a cancer drug is having its intended effect. Center proposals are due in March, and the NCI plans to issue its first contracts by summer 2005. The NCI will hold a meeting for interested research groups in December.

The NCI's cancer nanotechnology plan will also provide \$15.5 million

over 3 years to fund approximately 30 new training grants aimed at providing the multidisciplinary experience needed to merge nanotechnology and cancer biology. An additional \$38 million over 5 years will fund approximately 18 new investigator-initiated grants focused on applying nanotechnology to cancer-related R&D problems. All of these grants are open to any qualified researcher, including those from companies.

Ultimately, says NCI Director Andrew von Eschenbach, this is not just a plan for the NCI, "but a call to action for the cancer research community. It emphasizes the process of building partnerships between the private and public sector with the goal of creating teams best equipped to translate today's knowledge about cancer biology and nanotechnology into clinically useful products."

Joe Alper, Louisville, Colorado

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Kenyan dispute illuminates bioprospecting difficulties

Sensitivities surrounding the politically charged issue of bioprospecting were thrown into stark relief during September by reports that the Kenya Wildlife Service (KWS) planned to launch a multi-million dollar legal claim against Genencor and Procter & Gamble, alleging that a microbial cellulase enzyme illegally obtained from a soda lake in the country was used as an ingredient in the latter company's Tide laundry detergent. Media reports of the controversy played out a familiar narrative: piratical multinational corporations stealing biological resources from an impoverished developing country. As *Nature Biotechnology* went to press, however, negotiations between Genencor and the KWS had opened, and an amicable resolution appeared to be in the offing.

Genencor, of Cambridge, Massachusetts, has never hidden the fact that it markets two industrial cellulases, IndiAge Neutra and Puradax, which were obtained from Kenyan extremophile isolates that can withstand harsh alkaline environments. But their combined sales are modest, amounting to less than \$5 million annually, according to Jack Huttner, Genencor's vice president of communications and public affairs. He categorically denies that Cincinnati, Ohio-based Procter & Gamble uses either product.

Genencor obtained the isolates in 1995, when it purchased the industrial enzymes business of Gist-brocades, now part of DSM, of Heerlen, the Netherlands. They were taken from two Kenyan lakes, Bogoria and Nakuru, during a 1992 bioprospecting expedition led by William Grant of British Leicester University and hosted by Kenyatta University of Nairobi. Huttner says the expedition obtained the necessary permits from Kenya's National Council for Science and Technology, and Kenyatta University received training and laboratory equipment and supplies as part of the original agreement.

However, the KWS, which has jurisdiction over protected areas in the country, claims that additional permits were required because the territory involved was covered by its remit, says Peter Munyi, a Nairobi-based lawyer advising the agency on the case. Munyi declined to comment on what reparations the KWS is now seeking, because negotiations with Genencor are still at an early stage. Genencor's Huttner says the initial correspondence it received from the KWS—after media reports had surfaced in Kenya and in the UK—sought merely to establish the facts of the case.

Regardless of its eventual outcome, the dispute highlights the legal and ethical minefield that biotech companies must negotiate if they want to engage in this kind of research. The UN Convention on Biological Diversity (CBD), ratified by more than 175 countries since being adopted by the 1992 Earth Summit in Rio de Janeiro, is the principal international legal instrument that governs bioprospecting. Its provisions on “fair and equitable sharing of the benefits [e.g., royalties from resulting commercial products; knowledge transfer; support for training initiatives] arising out of the utilization of genetic resources” form the basis of agreements between research organizations and the countries in which they conduct work.

But the whole area is still dogged by controversy. According to Calestous Juma, former executive secretary of the CBD and current professor of the practice of international development at Harvard University, there are problems on both sides—industry needs to define and sign up to best practice, whereas developing countries need to develop coherent biotech policies based on their long-term interests and needs. “A lot of this is a failure not of legal systems, but a failure of finding ways in which developing countries can be genuine partners in biotechnology development,” says Juma.

“No one has problems with sharing the benefits through the contractual agreements as long as there is transparency,” says Lila Feisee, director of intellectual property at the Washington, DC-based Biotechnology Industry Organization, which is currently drawing up guidelines on bioprospecting for its members. Up to now, she says, there has been a lack of clarity and lack of uniformity in



Pink flamingos gather near a hot spring along the shores of Lake Bogoria, Kenya.

implementing the CBD that makes it difficult for companies to decide whether they want to do business in a particular country (see Box 1).

“Part of the problem is you have an unimaginable imbalance of experience and power” between developing countries with poorly resourced regulatory agencies and large multinational corporations, says Michael Gollin, chairman of Washington, DC-based Public Interest Intellectual Property Advisors, a non-profit organization that links developing countries with attorneys who are willing to work on a *pro bono* basis in intellectual property disputes. Many developing countries lack the scientific or legal capacity to enable equal participation in bioprospecting projects, he says.

Although Juma, who is Kenyan, says there are some positive signs that developing countries can use bioprospecting agreements to bolster their own scientific capacity, there are also outstanding cases that could lead to further disputes. “There are several Kenyan cases I am aware of that could come up,” he warns.

Cormac Sheridan, Dublin

Box 1 Sweden tries to shore up CBD responsibilities

In early September, the Swedish Foreign Ministry and the National Board of Trade proposed linking the country's patent system to its obligations under the CBD, by requiring patent applicants to make additional disclosures on the origin of biological materials in cases where they were obtained from developing countries. This would provide stakeholders from developing countries a degree of leverage in any disputes that would flow from bioprospecting agreements drawn up under the auspices of the convention. But SwedenBio, a Stockholm-based biotech industry lobby, has objected, saying that the patent system is not designed to facilitate the kind of benefit-sharing arrangements envisaged by the CBD.

“These provisions should be developed and set down in rules, but it should be done outside the patent system,” says SwedenBio project leader Mats Berggren. “From the point of view of the patent system, the patent has to go to the person who made the inventive contribution,” says Niklas Mattsson, of Malmo, Sweden-based IP consultants Awapatent, who contributed to a SwedenBio position paper on the issue.

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