Halted trial renews questions about cancer vaccines

Citing ethics violations and ‘important flaws’ in methodology, Swiss authorities have ended a much-heralded cancer vaccine trial at Zürich University and will allow a second trial in the multicenter program to continue only after the errors have been corrected.

Coordinators of the trials—in Zürich and in five collaborating centers in Germany—are themselves considering whether to end the second trial because patient responses have been below expectations. The trials had been testing dendritic cells designed to carry antigens of melanoma tumors.

The problems once again call into question the viability of dendritic cell cancer vaccines, just months after a paper involving such a vaccine was retracted (Nat. Med. 9, 1221; 2003).

“There’s very few people conducting careful, thoughtful clinical trials [with dendritic cell vaccines],” says Drew Pardoll, professor of oncology at Johns Hopkins University. Nearly all flashy pilot trials have later proven too good to be true, Pardoll points out. “Now, if I see dramatic results, I virtually just don’t believe it.”

Specialized in presenting foreign peptides to the immune system, dendritic cells loaded with antigens can amplify a specific immune response. Many researchers are trying to translate this principle into effective clinical treatments. Although some immunologists doubt the immune system can successfully be deployed against the body’s own tumors, the vaccines have proven successful in animal studies.

Frank Nestle and colleagues were among the first to report major success in human trials: of 16 patients treated with their vaccine, more than 30% showed shrinking tumors, they reported (Nat. Med. 4, 328–332; 1998). Because standard chemotherapy benefits 10–15% of melanoma patients, the announcement created a stir.

Nestle continued his pilot trial in Zürich. In 2000, along with five German hospitals, he also helped launch a randomized, multicenter trial in which 240 patients would receive either dendritic cells or chemotherapy as initial treatment. That trial would have yielded significant results if the response rates had been 30% with the vaccine, says trial coordinator Dirk Schadendorf, head of the dermatology clinic at Mannheim University, one of the German centers.

But in February 2003, internal accusations at Zürich University prompted investigations that revealed details. Statisticians are now busy calculating whether results from the first 107 patients make it likely the multicenter trial can still yield useful outcomes, he says. Depending on the results, the trial could be continued, expanded or terminated, he adds.

Controversy over the Swiss trial will only add to the image of a messy field, says Nina Bhardwaj, who studies dendritic cell vaccines at New York University. The main problem, Bhardwaj says, is the lack of standardized protocols for conducting trials with the vaccines. “People use different preparations, doses, frequencies, antigens and ways of loading them onto dendritic cells—they even use different ways to measure outcomes,” Bhardwaj says. “We need to come together to strategize, or we will shoot ourselves in the foot.”

Eli Gilboa, research director of the Center for Genetic and Cellular Therapies at Duke University, says there is “undue pressure exerted on researchers to engage prematurely in clinical trials and offer hopeful indications of success.” Much more work—most of it unglamorous and unpublishable—will be needed to translate powerful results in animals to useful treatments in humans, Gilboa says.

Still, many in the field remain optimistic, citing a few ongoing trials that could validate the approach.

Dendritic cells are “one of the most promising approaches to stimulate protective immunity against cancer,” says Gilboa. Even Nestle, beleaguered in Zürich, is upbeat. “Science is like the stock market—after excitement comes disillusion,” Nestle says. “But in the long term, the trend is up. Don’t declare this field dead too soon.”

Peter Vermij, Washington, DC
Martina Frei, Zürich, contributed to this report
China’s new AIDS policy faces great wall of skepticism

China has finally announced its decision to act on its impending AIDS crisis, but experts say its strategy is in many ways premature and poorly planned.

Official estimates place the number of HIV-positive people in China at 840,000, which is relatively low for a population of 1.2 billion. Most cases are from high-risk groups such as intravenous drug users, prostitutes, long-distance truck drivers and plasma sellers, often in isolated rural areas. But the numbers are rising dramatically, with a 44% increase between 2001 and 2002, and the epidemic is starting to spread to urban areas. At the current rate, the United Nations (UN) projects 10–20 million cases in China by the year 2010.

Faced with that specter and the shortcomings of its long-neglected health system, made evident by SARS, the Chinese government in early 2003 launched an ambitious plan to train doctors, build 124 new treatment centers, increase awareness and deliver treatment and counseling to patients in 56 of the country’s hardest-hit counties.

As part of the plan, the government in April launched a pilot to distribute free antiretroviral drugs to 3,000 patients in the impoverished Henan province who had contracted HIV through unsanitary blood-selling practices. But without a system to treat and/or monitor the patients—a senior health minister recently estimated that China has fewer than 100 doctors with experience in treating AIDS—the patients were left to follow the complicated drug regimens on their own.

“The elements are simply not in place yet for such a program,” says Joel Rehnstrom, the UNAIDS coordinator in China.

Not surprisingly, nearly a fifth of the patients in the pilot program have dropped out because they were not counseled about the side effects. Without adequate instruction, patients will use the drugs erratically, which can lead to the rise of drug-resistant HIV strains, says David Ho of the Aaron Diamond AIDS Research Center in New York. Another problem is that China is limited in using locally produced off-patent drugs such as nevirapine, ddI and AZT. “Their options are somewhat limited,” says Ho. “They have the drugs to make one cocktail, and if it doesn’t work, they don’t have a backup.”

Experts say the pilot program may be premature, but are eager to see it get off its feet. In mid-October, the UN Global Fund gave the country a financial boost with a five-year, $98 million grant. The goal is eventually to provide free antiretroviral therapy to all HIV/AIDS patients who cannot afford it.

But even if there are available drugs, notes Jing Jun, professor of sociology and public policy at Tsinghua University in Beijing, only 40,000 of the country’s estimated 1 million cases are officially diagnosed. Until there is greater public confidence in health care and less fear of stigma, Jing says, people will be reluctant to come forward for voluntary testing.

Recent months have seen other political milestones in China’s stance toward AIDS. In late November, state-sanctioned ads promoting condoms for AIDS prevention began appearing on national television. Condom ads appeared briefly in 1999, but were quickly banned for violating obscenity laws. On 10 November, Tsinghua University in Beijing, one of the country’s most prominent schools, hosted a highly publicized summit with prominent participants, including former US president Bill Clinton.

And on 1 December, World AIDS Day, Chinese Premier Wen Jiabao made a televised visit to AIDS patients, marking the first public gesture of acknowledgment from the highest levels of central government.

AIDS activists have praised the government’s increasing efforts to target high-risk groups, but say there is a desperate need to educate the general public. Awareness of AIDS is extremely low, particularly in rural areas, they add, and risk factors such as drug use are increasing.

“We have a window of opportunity for the next two to three years to avoid a catastrophic epidemic,” says Tsinghua’s Jing. “My gut feeling is that key players in the government realize that there is this chance now. If they miss it, we will pay a very high price.”

I-han Chou, Tokyo

AIDS infections, deaths hit record high in 2003

More people became infected with HIV and died from AIDS in 2003 than ever before, according to a new report from the United Nations. A few nations are finally beginning to pay attention and are changing their policies to address the rising numbers.

Approximately 5 million people were infected with HIV in 2003, bringing the total number of people with HIV/AIDS to 40 million worldwide, including about 2.5 million children under 15, according to the report. About 3.1 million people died from AIDS in 2003. The highest numbers were in sub-Saharan Africa, followed by the Asia/Pacific region, primarily India and China.

To combat the epidemic, India says it hopes by April to begin providing free antiretroviral drugs (ARVs) to its patients. By the end of 2004, each of South Africa’s 50 health districts would also have at least one center distributing free ARVs, according to that country’s government. Both announcements mark major shifts in the nations’ AIDS policies.

Meanwhile, the World Health Organization’s ‘3 by 5’ initiative, which promises to deliver ARVs to 3 million people by 2005, called for countries to train 100,000 workers and treat patients with four combinations of ARVs.

Aparna Surendran, New York
Legal battle threatens universities’ use of patented technologies

Duke University researchers have been asked to review their use of patented research technologies and use alternative approaches wherever possible. An ongoing legal battle between the university and a former researcher could trigger similar reviews at other institutions.

For more than 100 years, US scientists have used proprietary reagents, devices and techniques under an ‘experimental exemption’ to patent laws. But this summer, the US Supreme Court declined to review a lower court decision in Madey vs. Duke, which challenged the university’s use of former faculty member John M.J. Madey’s free-electron laser. As a result, it is questionable whether the exemption will protect scientists against patent infringement liability.

Following the Supreme Court decision, Duke Medical Center Dean R. Sanders Williams sent a memo to researchers advising them to purchase reagents, devices and kits from commercial suppliers who have acquired the appropriate licenses. The memo was meant to inform researchers how the ongoing legal battle may affect them, Williams says.

“At this point, we have not used central authority to mandate any sweeping changes,” says Williams. “We have not asked them to undo any experimental programs that are in progress.”

Outside Duke, most universities are taking a wait-and-see approach as the case continues to move through the courts, but some are extremely worried about liability, says Peter Ludwig, a New York City patent lawyer who has been following the case.

“I can’t help but come away with the deer-in-the-headlights analogy,” says Ludwig. “This hit them like a ton of bricks. It’s a difficult problem to wrestle with and they don’t know which way to go.”

Others say the ruling came as no surprise. “From everything I had ever read on the research exemption, that exemption was very, very narrow—and we never relied on it,” says Lita Nelson, director of the Massachusetts Institute of Technology’s technology licensing office. “The ruling did not change our understanding of the law.”

Ludwig says it’s possible industry will back away from the legal battles and the bad blood that would come with demanding licensing fees from universities.

“Maybe it will just blow over and go away,” he says. “[But] I think it’s only a question of time before someone is going to make a claim against an institution and say, ‘You’ve been using our technology and we want you to pay us.’”

Tinker Ready, Boston

The refrain in Spain is that Barbacid is to blame

Oncologist Mariano Barbacid is having his worst year since he returned home in 1998. After repeatedly clashing with health officials over funding for the Spanish National Cancer Center (CNIO)—of which he is director—he is facing the resignation of two prominent CNIO researchers.

In an e-mail sent on 7 November to CNIO staff, Luis Serrano resigned as head of the CNIO’s structural and computational biology program, complaining of Barbacid’s “abuses of authority,” “excessive hierarchization” and “narrow scientific vision.”

Serrano, who heads a similar program at the Heidelberg-based European Molecular Biology Laboratory, devoted 25% of his time to the CNIO full time in September 2004. Barbacid may be a good scientist, Serrano admits. But he says Serrano is “immature” and that his “virulent” letter was prompted by his ambition to be the next director of the CNIO.

During his time at the US National Cancer Institute, Barbacid established a research group that was one of three in 1982 to isolate a human oncogene. Fifteen years later, as vice president of Oncology Drug Discovery at Bristol-Myers Squibb, Barbacid was approached by the Spanish health ministry to lead the CNIO.

Barbacid’s personality has led to several clashes with both policy makers and scientists in Spain. His complaints in the national press about money for the CNIO have annoyed government officials who, he says, have blacklisted him for research grants. Health ministry officials declined to comment. Still, the CNIO has in the last four years obtained several grants from the science ministry and the European Commission. Several people at the CNIO, who asked not to be named, agree with Serrano’s criticisms. But Pere Puigdomenech, director of the Barcelona-based Institute of Molecular Biology, backs Barbacid. “It’s normal that CNIO’s quality output is still scarce since it’s not been [much]
The global effort to eradicate tuberculosis (TB) may soon gain the tools to succeed. New TB vaccine candidates—the first in more than 80 years—are now in phase 1 clinical trials.

The available bacillus Calmette-Guérin (BCG) vaccine is safe and has been used worldwide for decades. But while it offers children some protection, many adults remain susceptible to pulmonary infection. TB incidence has been exacerbated in recent years by the HIV epidemic and by the rise of drug-resistant strains of Mycobacterium tuberculosis. According to the World Health Organization (WHO), about one-third of the world's population is infected with TB, with 8 million new cases and as many as 3 million deaths each year.

Leading the new effort are two candidates based on the current vaccine. Marcus Horwitz, a microbiologist at the University of California in Los Angeles, has modified BCG to overexpress the 30-kDa protein A85b, a major secretory protein of M. tuberculosis. In guinea pig models, the recombinant vaccine is more protective than BCG.

Horwitz’s research is backed by the US-based Aeras Global Tuberculosis Vaccine Foundation, which will in January begin a phase 1 trial of the vaccine. The foundation has already established a trial site in Cape Town, South Africa, where it is conducting a phase 4 trial of BCG’s Tokyo strain to evaluate routes of administration. “We are building the capacity to do large community-based trials,” says Larry Geiter, a principal investigator of the trial.

Oxford University researcher Helen McShane is completing safety and immunogenicity trials of a TB subunit vaccine in the Gambia. The MVA85-A vaccine is built from a smallpox virus that is engineered to overexpress the secretory protein 85A. “The strategy is to boost BCG, rather than replace it,” says McShane.

Other groups are using strategies to return the BCG vaccine to its original virulence. In 1999, Marcel Behr, a researcher at McGill University, reported that BCG had lost several genes since its creation in the 1920s (Science 284, 1520–1523; 1999). Behr is now selectively adding back the lost genes in an attempt to prove that the genetic lesions are not just cosmetic, but functional. “We are figuring out where the wounds are and trying to patch them,” Behr says. “It is a BCG Band-Aid.”

Stewart Cole and his colleagues at the Pasteur Institute—which developed the first TB vaccine—recently reported successfully restoring several lost BCG genes. When the researchers added back the RD-1 locus of 11 genes into the vaccine, immunized mice and guinea pigs showed better protection against infection.

A critical element in the fight against TB is coinfection with HIV. Ford von Reyn, professor of medicine at Dartmouth, and his colleagues have developed a TB booster that is safe in HIV-positive patients. The multidose, killed vaccine doesn’t adversely affect viral load or CD4 count, and increases cellular immune response and production of interferon-γ, says von Reyn.

Responding to “worrying trends” in antimicrobial resistance in Europe, the European Union has announced two new projects, totaling $16 million, to study how resistance arises.

There is increasing incidence of Escherichia coli strains resistant to third-generation cephalosporins, a consistent rise in fluoroquinolone resistance, and resistance rates of more than 50% to ampicillin, according to a new report from the European Antimicrobial Resistance Surveillance System (EARSS), an infectious disease network of 28 countries.

Resistance to third-generation cephalosporins has remained lower than 6% in most countries. But higher rates in some eastern European countries are associated with the spread of strains producing β-lactamases, enzymes that can destroy aminopenicillins such as ampicillin. The EARSS also reports a “consistent and marked” rise in fluoroquinolone-resistant E. coli in many European countries. Rates of resistance are currently about 10%, but eight countries experienced a 1.5-fold increase in just two years.

Resistance in E. coli to traditional antibiotics such as aminopenicillins is now common in Europe, with only Finland and Sweden reporting rates of less than 30%. Among the 25 countries surveyed, resistance rates varied from 25% to 64%. More than half of all strains isolated from bloodstream infections harbor plasmids that encode β-lactamases. The report is based on routinely generated antimicrobial susceptibility data from 700 laboratories and an estimated sample population of 100 million.

EARSS monitors resistance in several other major pathogens, including Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis and E. faecium, but it singles out E. coli resistance as showing the most worrying trends. Multiresistant bacteria pose a “potentially serious impediment” to transplant surgery, cancer therapy and treatment of infections, warns Hajo Grundmann, project leader for the EARSS.

Tony Sheldon, Utrecht
List of ‘prurient’ research stirs fear, anger among US scientists

A ‘hit list’ of more than 150 National Institutes of Health (NIH)-funded scientists conducting behavioral research on HIV/AIDS transmission, homosexuality and drug abuse is stirring anger and fear in the scientific community.

The Traditional Values Coalition, which says it represents more than 43,000 US churches, compiled a list of what it calls “smarmy,” “prurient” and “provocative” research and is demanding that the NIH justify funding the projects. In response, the NIH has asked some of the researchers to write summaries defending their work.

“The list is a source of concern for researchers on two levels,” says Ken Mayer, director of Brown University’s AIDS program. “It is making scientists anxious about whether their research will be targeted, and it is creating disincentives to developing effective HIV-prevention programs.”

To prevent the spread of AIDS, it is important to understand triggers and cultural influences on behavior, Mayer says. “Two decades of carefully done research of what works and not in HIV prevention tells us it must be culturally specific,” he says. The coalition is allowing ideology to get in the way of data-driven science, he adds.

Bonnie Halpern-Felsher, a researcher at the University of California in San Francisco, says an NIH program officer told her that her current grant was not under question, but she might have to be concerned about future grants. She studies adolescent risk judgment and HIV infection.

Even those scientists who don’t agree with all the research projects say the list questions the peer-review process. “The peer-review process needs to prevail,” says Halpern-Felsher.

The list is only the latest in a series of efforts by conservative religious organizations to censor science that they find distasteful or morally repugnant, says Judith Auerbach, vice president of public policy at the American Foundation for AIDS Research.

In July 2003, the House of Representatives narrowly missed pulling funding from five research grants on sexual behavior. At a Congressional hearing in early October, NIH director Elias Zerhouni was asked to provide a written explanation for a number of grants, after which he was given the longer ‘hit list’, says Auerbach. The upcoming NIH reauthorization hearings can also be used to strengthen, add to, or define the outer limits of funding for certain research areas, Auerbach notes.

“We are concerned with the larger context in which the list is appearing,” she says. “Where is this all going?”

Vicki Brower, New York

Fatal flaw in baby formula sparks reform in Israeli ministry

A German baby formula that caused severe vitamin deficiency in 13 Israeli infants and killed 2 has led to a radical revamp of Israel’s regulatory framework for infant formula, making the requirements more stringent than for pharmaceuticals.

In early November, several Israeli babies were hospitalized with the neurologic and cardiac symptoms of beriberi, a severe deficiency in thiamine, or vitamin B1. Thiamine has essential roles in converting carbohydrates to energy and in the synthesis of the neurotransmitter acetylcholine.

The infants had all been fed Remedia Super Soya 1, a kosher infant formula manufactured exclusively for Israel by the German company Humana. The affair prompted a police investigation in both Israel and Germany. Subsequent testing revealed that, contrary to product labels, the formula almost entirely lacked thiamine. The product has since been withdrawn from the market.

Humana, the oldest and one of the largest baby food companies in Germany, admitted to a series of blunders and fired four workers. According to a company spokesman, a Humana employee failed to add thiamine to the product because the vitamin naturally occurs in soybeans. The soy was treated with heat, however, which destroyed the thiamine.

Because follow-up quality testing didn’t pick up on the deficiency, the scandal raised questions about the adequacy of the Israeli Health Ministry’s supervision. In response, the Ministry changed its regulations for baby formulas. Previously, manufacturers had to submit laboratory test results for a formula’s ingredients, after which the Ministry performed random testing of selected ingredients. Under the new regulations, the Ministry will test all batches of locally produced or imported formulas.

In effect, the Ministry will be duplicating the quality assurance process of the manufacturer—a practice unheard of anywhere else in the world, says Dorit Nitzan-Kaluski, director of the Ministry’s Food and Nutrition Administration. “It’s a catastrophe for the country because it’s a huge expense and a huge mess, but there’s no choice,” says Nitzan-Kaluski. “We’ve lost our credibility.”

In the US, manufacturers submit lab tests for each new infant formula to the Food and Drug Administration, but the agency doesn’t retest the formulas before they go to market. It does, however, perform annual inspections of manufacturing plants and collect samples for nutrient analyses.

Beriberi is rare in the US and in Europe because most foods there are vitamin-enriched, and is seen primarily in chronic alcoholics or in people on dialysis. It is more common in parts of East Asia, where milled or polished rice is a dietary staple, but its incidence there has also dropped sharply as economic conditions have improved.

Luba Vikhanski, Tel Aviv

Hope and hype for cancer drugs
The year 2003 saw no shortage of cancer headlines—from the approval of several new cancer drugs to the increasing application of genomic and proteomic technologies to classify and predict cancer. But recent successes have not been unequivocal, and emphasize the need for tempered optimism.

The anti angiogenesis drug Avastin, in combination with other therapies, showed promise in extending survival of patients with advanced colorectal cancer, but a second, smaller trial did not corroborate the results. The US Food and Drug Administration (FDA) approved Velcade—a proteasome inhibitor—for multiple myeloma, and the tyrosine-kinase inhibitor Iressa for advanced non-small cell lung cancer, but neither drug’s clinical potential has yet been adequately confirmed. Still, the Swiss equivalent of the FDA has approved Erbitux, a monoclonal antibody to the epidermal growth factor receptor—one of the tyrosine kinases targeted by Iressa—for drug-resistant colorectal cancer.

Antisense approaches such as Genasense, which is directed against the tumor cell survival gene \(BCL2\), continue to disappoint. Despite these setbacks, the FDA has pledged to accelerate approval of cancer drugs and, along with the US National Cancer Institute, to double the number of phase 3 clinical trials for those drugs.

Stem cell research took a new turn in April 2003, when two independent studies suggested that bone marrow cells are not as versatile as previously believed. Rather than differentiating into liver cells, bone marrow stem cells can fuse with host liver cells, groups led by Markus Grompe and David Russell reported (Nature 422, 897–901; 2003 and Nature 422, 901–904; 2003). The news followed reports from 2002 of fusion events in cell culture.

The new data shifts the emphasis in therapeutic applications away from inducing differentiation, which posed a daunting challenge given the number of target cell types. Promoting cell fusion—by harnessing viral genes that promote fusion, for instance—has instead risen to the top of the agenda. Although the shift in emphasis might simplify stem cell therapies, the mangled karyotypes resulting from fusion raise the specter of cancer. Predicts Grompe, “I think that what we are going to see in 2004 is that fusion can be an important tumor progression event.”

Infectious diseases: beyond the usual suspects
2003 kicked off a new threat to public health—severe acute respiratory syndrome (SARS). Emerging from Guangdong, China, in November 2002, the mystery virus quickly became a global threat by April 2003 (Nat. Med. 9, 487; 2003). At record rates, researchers identified the culprit—a new coronavirus—and its receptor, angiotensin-converting enzyme-2. The virus may strike again, so the hunt is on for effective treatments (Nat. Med. 9, 806; 2003) and for a vaccine (see News, page 9).

SARS created an epidemic of nervousness, but the death toll was modest: it killed fewer than 800 people. What did 2003 mean for the bigger killers? Few seemed surprised by the failure of VaxGen’s HIV vaccine (Nat. Med. 9, 376; 2003). On the brighter side, the US Food and Drug Administration approved a new class of HIV drug—a fusion inhibitor called enfuvirtide. Two phase 3 clinical trials showed that enfuvirtide, in combination with other antiretrovirals, can suppress HIV replication in people who no longer respond to available therapy.

The year also saw nations around the world begin publicly addressing their HIV crises. In August, the South African government agreed to provide antiretrovirals to its citizens. More recently, India and China have followed suit. Good news also came for other infectious diseases: the Bill and Melinda Gates Foundation donated $168 million to fuel a renewed effort to fight malaria, which affects more than 300 million in the developing world.

Hormone replacement takes another hit
The debate on hormone replacement therapy (HRT) for postmenopausal women precipitated in the summer of 2003 when results from long-term trials indicated that, contrary to prevailing hypotheses, combination hormone replacement doubles the risk of dementia, including Alzheimer disease.

The Women’s Health Initiative (WHI) was launched in 1998 to evaluate the effects of different HRT treatments. One arm of the trial—testing a combination of estrogen and progestin, the most commonly used form of HRT—was abruptly cut short in 2002 when preliminary results indicated an increased risk of breast cancer.

Various reports published throughout 2003 also indicated higher risks of heart disease, stroke and ovarian cancer, which may outweigh the known benefits of this form of HRT. What is not yet clear is how these results extrapolate to other forms of HRT. It will be crucial to compare the current data with results from the ongoing estrogen-only arm of the WHI to weed out the potential effects of progestin.

‘Bubble boy’ trial delivers blow to gene therapy
The gene therapy field suffered a setback in 2003 when researchers unraveled the mechanism underlying serious complications in a clinical trial once hailed as a landmark success. Alain Fischer’s group at the Necker Hospital for Sick Children in Paris used a retroviral vector to treat X-linked severe combined immunodeficiency—the so-called ‘bubble boy’ disease. But after 2.5 years of success with the therapy, two of ten patients developed a T-cell leukemia–like disease, later shown to be a result of the retrovirus inserting itself near the \(LMO2\) proto-oncogene (Science 302, 415–419; 2003).

Although scientists had long been concerned about the risk of insertional mutations, studies in animal models had not supported their fears. Results from the French trial dealt another blow to an already-chastened field (Nat. Med. 9, 977; 2003). Regulatory agencies in the US and UK have since allowed related trials to proceed with extra caution, and researchers are designing safer vectors and protocols for future trials.

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SARS vaccines on the fast track

Just a few months after the virus causing severe acute respiratory syndrome (SARS) was identified, scientists have developed vaccines that they hope to test in humans in the near future.

Researchers at Sinovac Biotech in Beijing have created a vaccine using the inactivated SARS virus, and have already received approval for clinical tests from the Chinese National Institute for the Control of Pharmaceutical and Biological Products. Human trials are expected to begin by the end of December 2003.

Meanwhile, Canada’s multicenter SARS Accelerated Vaccine Initiative is testing three types of inoculations to develop a vaccine that could be ready as early as next fall, and US scientists have engineered a SARS vaccine that triggers the production of protective antibodies in rhesus macaque monkeys. Both groups are planning further animal tests and human clinical trials. It is unlikely that either vaccine will be available if the virus, which infected 8,000 people worldwide last year, returns this winter.

Getting the vaccines ready for public consumption may be hindered by the manufacturing process, which requires level 3 biohazard facilities available in only a few cities worldwide. Some scientists warn that the research is moving ahead before long-term effects of the vaccines can be evaluated.

US to test pediatric drugs

President Bush on 3 December signed the Pediatric Research Equity Act of 2003, which grants the US Food and Drug Administration (FDA) the authority to require drug companies to test adult medicines in children.

Only a quarter of the drugs on the market are specifically tested and labeled for use in children. Doctors often have to estimate the appropriate doses based on adult indications, which can lead to under- or overmedication in children. The new act aims to eliminate that guesswork by making it mandatory for drug companies to conduct pediatric trials of drugs that are to be used in children, even if the companies lack the financial resources to do so voluntarily.

The new law became necessary after the federal court last year struck down the FDA’s ‘pediatric rule’, under which the agency granted itself the authority to require child drug testing (Nat. Med. 9, 631; 2003).

Europe to back some stem cell research

The European Commission will consider funding proposals on human embryonic stem cell research on a case-by-case basis, even though the European Union (EU) could not agree on comprehensive ethical guidelines at a meeting held 3 December.

Funding for stem cell research in Europe was frozen until the end of 2003 while the Commission proposed ethical guidelines in July. Those guidelines passed in Parliament, but the Competitiveness Council, which decides on such proposed EU legislation, was split on the guidelines. Germany, Austria and Italy opposed spending money on embryonic research, whereas Britain, Sweden and the Netherlands supported the work.

Ireland will take on the EU presidency for six months, beginning January 2004. It is possible that Ireland could ask the Council ministers to revisit a vote on the guidelines, but Irish Deputy Prime Minister Mary Harney has said she could not see the issue being resolved under Irish leadership.

Meanwhile, the United Nations General Assembly in December upheld its earlier decision (Nat. Med. 9, 1440; 2003) to postpone a vote on human cloning. The organization’s legal committee had initially voted to postpone the vote for two years but after a bloc of 40 countries led by the US and Costa Rica reintroduced the issue, it has agreed to review the decision after one year.

China approves world’s first gene therapy drug

China’s State Food and Drug Administration has approved the world’s first commercial gene therapy drug for cancer. The drug, Gendicine, is manufactured by ShiBioGeneTech and will hit the market in January.

Some researchers say it may be too early to commercialize gene therapy. But the regulatory system in China—where the technology has not been dogged by controversy as it has in the West—may be more open to its benefits. There are at least six other biotechnology firms worldwide with phase 2 or later trials of gene therapy products for cancer.

Gendicine contains an adenovirus expressing the p53 oncogene, known to trigger apoptosis. Many cancers result from mutant or inactive p53. ShiBio tested the therapy in patients with late-stage head and neck squamous-cell carcinoma, which comprises 10% of all new cancer cases in China. Mutant p53 is found in more than 60% of those tumors.

In the largest trial, 64% of patients showed complete regression of tumors after eight weeks of radiotherapy and weekly Gendicine injections. The patients were monitored for up to five years after the trial. The rate of complete regression in the radiotherapy-only patients was three times lower; 32% of patients who received radiotherapy and Gendicine injections showed partial regression of tumors.

Ebola rears ugly head as vaccine enters trials

The Ebola virus resurfaced in November in the Republic of Congo, claiming 29 lives, according to the World Health Organization. In May 2003, the hemorrhagic fever caused 148 infections, including 128 deaths.

Officials say the outbreak might have begun after a group of hunters ate an infected dead boar in the Mbomo region of the country. There is no cure as yet, but scientists at the US National Institutes of Health are conducting the first human clinical trial to test an Ebola vaccine. In November, researchers gave their first volunteer a DNA vaccine—manufactured by California-based Vical—with modified, inactivated genes from the Ebola virus.

The vaccine trial will enroll 27 people, including 6 controls. Volunteers will each get three injections over two months, and scientists will observe their immune reactions to the vaccine for a year.

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News briefs written by Aparna Surendran and Pierrette Lo
Marc Tessier-Lavigne

How do you top solving a century-old riddle in developmental neurobiology? By moving to a company with no commercial interest in neuroscience. For someone as ambitious as Marc Tessier-Lavigne, leaving academia for the biotech giant Genentech could be the perfect choice.

The worst thing anyone has to say about Marc Tessier-Lavigne is that he wants everyone in his laboratory to use 20-point Arial Bold font for their presentations. Or that he has a penchant for bad movies—think Jean-Claude Van Damme—and likes to sing “My Way” at karaoke parties. Beyond that, people consistently describe him the same way.

“The stories about Marc that I can come up with are all essentially about Marc being perfect,” says Cori Bargmann, who for 10 years shared graduate students and laboratory space at the University of California in San Francisco with Tessier-Lavigne. “If there were anything bad to be known about him, I would know about it—and I don’t.”

Tessier-Lavigne’s impeccable reputation matches his image as a brilliant and ambitious scientist. Those who know him well say it was obvious early on that he was destined for great things: he didn’t disappoint them. In 1994, he shot to fame with his discovery of netrins—the chemicals that guide axons to their destinations—solving a problem that had stumped neurobiologists for more than a century.

“Careers had been ruined, tenure had been denied over this problem. No one had succeeded—and somehow he got it done,” says Bargmann. “He has this miraculous ability to get done what needs to be done.”

There was no looking back from that point on. Tessier-Lavigne assembled a fleet of spectacular graduate students and postdoctoral fellows, and carved a place for himself as a pioneer in developmental neurobiology. With good friend and collaborator Corey Goodman, he founded the company Renovis and, two years ago, moved to Stanford University. In September 2003, Tessier-Lavigne once again made a splash in the scientific community when he left Stanford for Genentech.

The biotech giant created a position for Tessier-Lavigne, offering him the chance, as senior vice-president of research drug discovery, to oversee 320 people in oncology, molecular biology, physiology and medicinal chemistry, which comprise two-thirds of the company’s research.

“I thought about [the offer] very seriously. It’s a time when research has been going wonderfully—lab is great, Stanford is great,” says Tessier-Lavigne. “[But] I looked at the opportunity and thought I’d definitely regret it in the future if I didn’t take it. So I decided to take the plunge.”

As part of his agreement with Genentech, Tessier-Lavigne can maintain his own laboratory. Although he says he will continue to solve problems in neurobiology, many scientists expect his contribution will be limited, and question his move to a company with no interest in neuroscience.

To those who have watched Tessier-Lavigne’s career closely, however, the move comes as no surprise. “Marc could lead the country; he’s a natural leader,” says Nobel Laureate Eric Kandel, who has known Tessier-Lavigne since the latter’s days as a postdoctoral fellow at Columbia University. “I knew it was just a matter of time,” Kandel says. “I wouldn’t be surprised if he ended up running the company.”

Tessier-Lavigne had already exhausted the challenges academia offers, adds Martin Raff, emeritus professor of biology at University College, London (UCL). “When a young person does spectacularly well at science, the next challenge is not likely to be all that different,” Raff says. “The best it can be is equally successful.” For someone as ambitious as Tessier-Lavigne, Raff says, going to Genentech is the right decision.

Still, Raff says, Tessier-Lavigne agonized about the move—as he does about every other decision. “For somebody who’s been so successful in every part of his life, Marc is fretting all the time over every step—where to postdoc, who to postdoc with, what problems to tackle,” Raff says. “He tears himself to pieces about every move.”

A closer look at Tessier-Lavigne’s life presents plenty of clues about his constant reach for the next big challenge. Born in Canada, he grew up in London and Brussels and attended French lycées there. “By the time I graduated high school, I didn’t know whether I was Canadian, French, English or Belgian,” he says.

After completing a degree in physics at McGill University in Montréal, he won a Rhodes scholarship for a second degree in philosophy and physiology from Oxford University. He then returned to Canada for a year to run Pugwash, the Nobel Prize–winning organization—and then back to the UK for a Ph.D. from UCL.

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Soon after, UCL offered him a tenure-track position, a rare offer for such a young scientist. Tessier-Lavigne declined and went instead to Tom Jessell’s lab at Columbia University, where he began earning a solid reputation as a developmental neurobiologist.

Once Tessier-Lavigne moved to his own lab, however, he published nothing but reviews for more than three years—an enormous risk for a young researcher. His sights set on isolating the elusive chemoattractants, he recruited students, postdocs, family, friends, family of friends and anyone else he could to help him. Between July 1991 and May 1992, he held 25 ‘Bastille days’, as the students dubbed them, where the volunteers would form an assembly line: some cracked eggs, others pulled out the embryos, and still others extracted the brains and froze them. More than 50 large pizzas and 25,000 chick embryos later, he was well on his way to isolating netrins. Between 1994 and 1995, he published six papers in Cell.

On par with his accomplishments as a scientist, people say, is the importance Tessier-Lavigne places on family. Former students and postdocs fondly say that, one year, the lab produced more babies than it did papers. By all accounts, he is incredibly devoted to his own family and spends most of his free time with them. He and his wife Mary Hynes, also a neurobiologist, have three precocious children—the eldest taught himself calculus at age 10—a beautiful home, and a dog.

“He’s one of those people for whom things always seemed to go just right,” says Tad Homer-Dixon, who has known Tessier-Lavigne since their days at Pugwash in the late 1970s. “There are some people with whom that would be annoying, but Marc’s just a lovely person,” says Homer-Dixon. “He manages to carry it all off with a real sense of interpersonal ability and charm and humility, even.”

Apoorva Mandavilli, New Orleans