where the organic waste now overflowing dumps could be burned to provide charcoal. It might even be possible to reclaim cleared land. But because the benefit of increased yields depends on quickly transporting produce and fruit to large markets, the increased costs of terra preta may not be economically viable in remote parts of Amazonia. In addition, Clement argues that any success with terra preta will simply lure more people to work with it and that those people will end up clearing forest in the process. "Terra preta is about making the current process of development more rational and sustainable, not about conservation," he says. "It's about creating the conditions for the forest to return more quickly after it's cleared, not about preserving it from development."

Even if Clement's view is correct, examining terra preta is still worthwhile, according to Susanna Hecht, a geographer at the University of California, Los Angeles. "We have to get over this Bambi syndrome of seeing all development in the tropics as necessarily catastrophic," she says. "People have been farming there—farming hard—for thousands of years. We just have to learn how to do it as well as they did."

–CHARLES C. MANN

STEM CELL LINES

'Show Us the Cells,' U.S. Researchers Say

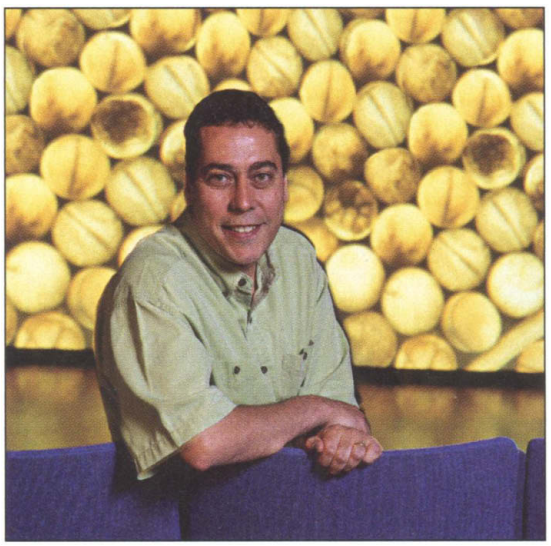
One year after President Bush announced that some 60 human embryonic stem cell lines were available, U.S. scientists have their hands on just four

Ali Hemmati-Brivanlou, a molecular embryologist at Rockefeller University in New York City, has been trying since last September to obtain samples of all the cells listed on the National Institutes of Health's (NIH's) registry of "available" human embryonic stem cell lines—which at the beginning of this month numbered 71. The results: two viable lines, one from WiCell in Madison, Wisconsin, and one from ES Cell International (ESI) in Melbourne, Australia. (ESI sent him two lines, but the other one won't grow, he says.) "Everybody has their own reasons why they should not be sending things out," says Brivanlou.

One year has passed since President George W. Bush announced, after much deliberation, that he would allow federally funded researchers to work with human embryonic stem (hES) cell lines—as long as the cells had been derived before he began his speech at 9:00 p.m. on 9 August 2001. The cell lines, which can in theory develop into any type of cell in the body and thus might someday be useful for treating disease, are controversial because their derivation requires the destruction of week-old embryos. In his speech, Bush also announced that "more than 60" such cell lines were available, taking the research community by surprise. Until then, most researchers suspected that perhaps a dozen hES cell lines had been derived. But a worldwide survey by NIH had turned up at least 64 cell lines on four continents, NIH officials said.

A year later, the scientists' conservative estimate still seems closer to the mark. Although the NIH list has grown to include 71 "eligible" cell lines—derived in accordance with certain ethical standards before the specified date—practical and legal hurdles have kept most of the lines in the labs where they were derived. And because relatively few have been fully characterized, it's not clear that all of them are in fact bona fide hES cells. So far, just 16 cell lines are currently available for distribution, according to their proprietors. Of these, at most four are actually in the hands of U.S. researchers who aren't collaborating with the labs that derived the cells; another seven or so lines are expected to be available to the scientific public in the next few months.

"The whole thing is going pretty slowly," says a scientist who asked not to be identified—and who would like to use up to 10 cell lines in various experiments. He blames the delay on extensive negotiations over rights to the cells and layers of NIH bureaucracy. Even so, much of the community seems to agree with George Daley of the Massachusetts Institute of Technology's Whitehead Institute that, despite the slow progress, "NIH has been doing the best it can."



Cell waiting. Brivanlou, shown here before images of *Xenopus* ova and embryos, so far has received only two cell lines.

CREDIT: YANIK WAGNER

In an attempt to speed access to the cell lines, NIH has crafted a model materials transfer agreement (MTA) and funded a half-dozen groups that have derived cell lines so they can ramp up production. The agency has also procured cells for six intramural labs and given supplementary funds to close to 20 researchers so they can add hES cells to their ongoing research.

But none of these efforts can ensure the quality of the cell lines, many of which are not ready for prime time. A San Diego company called CyThera, for example, is listed as having nine lines, but none is available yet. "We first have to find out whether the derivations will result in bona fide human embryonic stem cells," says the company's president Lutz Giebel. Of the 19 lines listed at the University of Göteborg in Sweden, only three will be available in the near future, says neuroscientist Peter Eriksson; 10 others are on hold until the Swedish researchers develop new protocols for growing them more easily. And at Stockholm's Karolinska Institute, all six NIH-approved lines are frozen while work focuses on newer lines. "It is an open question if the 'NIH' lines can be successfully thawed," says researcher Michael Andäng.

Brivanlou points out that both commercial and academic cell providers have little or no incentive to supply cells to competing groups—particularly at the modest going rate of $5000 per sample. Many of the labs holding the cells "are not at the outset thinking of supplying the scientific community," Wendy Baldwin, NIH's deputy director for extramural research, admitted to the president's bioethics council in early July. Some plan to supply only collaborators, she said.

Right now, four groups are emerging as the main suppliers of hES cells to U.S. researchers: WiCell; ESI; the University of California, San Francisco (UCSF); and the Athens, Georgia, branch of the Australian company BresaGen. WiCell and ESI are al-

Regulations Constrain Stem Cell Research Across the Globe

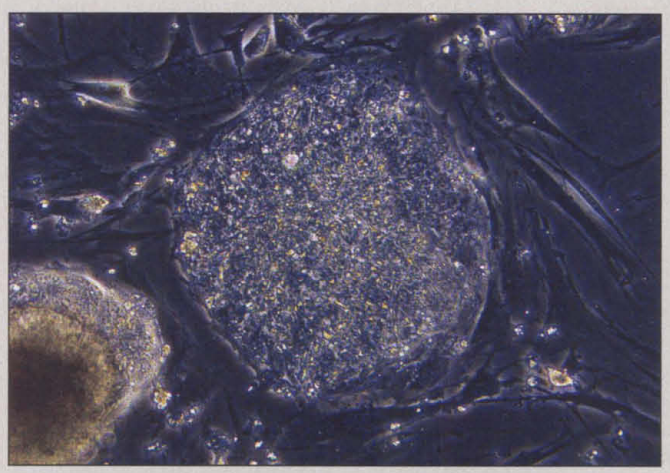
U.S. researchers aren't the only ones facing delays acquiring human embryonic stem (hES) cells (see main text). Many of their colleagues in Europe and Asia are constrained by similar government regulations, and some still face outright bans on the work, which is controversial because it entails the destruction of an embryo but promises new types of treatments for a host of diseases. Following is a snapshot of various regulations, many of which are still in flux.

European Union: The E.U. has been struggling to find common ground among states with very different laws. The latest proposal, suggested last week by the office of the Danish president of the E.U., would impose a moratorium on the derivation of new hES lines until at least 31 December 2003. Specifically, the proposal would preclude support by the E.U.'s new $17 billion Framework 6 research program for any new research that would harm embryos. Like the Bush compromise, the proposal—expected to be accepted—would allow research to continue on existing hES cell lines.

United Kingdom: As amended in 2001, the law governing embryo research allows the use and derivation of hES cell lines, as well as the use of nuclear transfer techniques to create such cells. Despite the liberal regulations, scientists don't seem to be lining up for the chance to derive new lines. The national oversight body, the Human Fertilisation and Embryology Authority, has granted only two licenses for such work, and an HFEA spokesperson says none is pending.

Netherlands: Under a new law that will take effect in September, research is allowed on human embryos when there is no reasonable alternative. The law prohibits so-called reproductive cloning.

Sweden: Swedish law allows embryo research, and several groups have derived hES cell lines that are eligible for funding by the U.S. National Institutes of Health. In fall 2001, a national advisory committee recommended leaving current guidelines in place but outlawing reproductive cloning.



Stuff of life. Dense, rounded masses of human embryonic stem cells rest on elongated "feeder" cells.

CREDIT: UNIVERSITY OF WISCONSIN, MADISON

Belgium and Israel: Research on embryos is allowed, under rules similar to the liberal Swedish policies.

Germany: A new law permits scientists to import hES cell lines that were created before 1 January 2002, if approved by a national review committee. The committee will soon consider its first application; two more are expected soon. The first, from Oliver Brüstle and colleagues at the University of Bonn, might be approved this fall—2 years after he first applied for federal funds for the project, igniting heated public debate.

France: A proposed law that would remove the ban on human embryo research—it would allow researchers to use embryos for medically important research—was put on hold when a new government came to power in June. The new government also suspended a regulation that would have let researchers import hES cell lines until the law was passed. The health minister, Jean-François Mattei, has said he will not push for drastic changes in the proposed law. But his view might not be shared by President Jacques Chirac, who is opposed to embryo research.

Spain: Research on viable human embryos is banned. However, the 1988 law does not mention stem cells, so a few scientists assumed they would be allowed to work with lines derived elsewhere. When their research on hES cells made front-page headlines, the government stopped the work; the health ministry claims no work is now under way on hES cells. An advisory body created in late July will compare the promise of stem cells from adults and embryos and propose new rules governing the research.

Italy, Austria, and Ireland: Embryo research, including work on hES cells, is not allowed.

Canada: Since March, Canadian scientists have been able to derive hES cells from human embryos left over after fertility treatment. The health ministry has ruled out research on human somatic cell nuclear transfer—whether for research leading to the derivation of stem cells or for reproductive purposes (*Science*, 8 March, p. 1816).

Singapore: Although a half-dozen hES cell lines were derived in Singapore, the legal status of embryonic research is murky, as no laws cover the topic. In July, the government accepted the recommendations of the Bioethics Advisory Committee, permitting hES cell research and therapeutic cloning under the oversight of a national licensing body. Legislation, which includes a complete ban on human reproductive cloning, is being drafted.

Japan: A 2-year-old law bans all human cloning experiments. Guidelines enacted last fall (*Science*, 3 August 2001, p. 775) permit the creation and use of hES cells. Researchers must receive approval from a local and a national ethics review board.

Korea: Proposed legislation, expected to be introduced this fall, would allow research on surplus human embryos but prohibit reproductive cloning. Deciding whether to allow the use of somatic cell nuclear transfer procedures to create stem cells will be left to a bioethics committee not yet in place.

India: No specific law governs embryo research, although guidelines issued in 2000 permit derivation and use of hES cells, subject to the approval of the bioethics committee at the scientist's institution. It is unclear whether scientists who develop hES cell lines will be able to send them abroad.

Australia: A nationwide policy might soon replace the current patchwork of state regulations. A proposed law, expected to be debated this month, would permit researchers to work with hES cells and derive new cell lines from excess embryos created for fertility treatments. All research on nuclear transfer in human cells would be outlawed (*Science*, 12 April, p. 238).

—GRETCHEN VOGEL

With reporting by Michael Balter in France, Pallava Bagla in New Delhi, Xavier Bosch in Barcelona, Dennis Normile in Tokyo, and Mark Russell in Seoul.

ready distributing cells; the others plan to come on line soon.

NIH has signed MTAs—which assign rights to discoveries made with the cells—with all four groups. (The agreements apply to NIH employees and serve as a model for researchers at other institutions.) And all four have NIH grants to help them characterize and boost their cell supplies. "It's very labor-intensive to expand those lines," says Andrew Cohn of the Wisconsin Alumni Research Foundation (WARF), which owns WiCell. Jennifer O'Brien, a spokesperson at UCSF, explains that hES cells are far trickier to grow than mouse cells. They grow more slowly, and they also require so-called feeder cells to keep them in their undifferentiated state. They have to be watched constantly: If colonies are too sparse, growth is retarded; if cells are grown too close together, they differentiate.

AVAILABILITY OF HUMAN EMBRYONIC STEM CELL LINES

Institution	Listed	Currently available
UCSF	2	0
Plans to start distributing one line in the fall. NIH infrastructure award.		
WARF	5	1
Has executed agreements with 90 researchers, more than 70 in the U.S., and has shipped 57 batches. So far shipping only one line; plans to ship all five by January. NIH infrastructure award.		
Arcos/CyThera	9	0
Might have cells characterized and ready to distribute in 2 years. Seeking NIH infrastructure award.		
Geron	7	0
Has WARF's five cell lines plus two subclones; supplying only NIH and collaborators.		
BresaGen Inc.	4	1
Has supplied one cell line only to collaborators. NIH infrastructure award.		
ES Cell International	6	4
Two lines should be characterized in a few weeks. Has sent cells to 30 groups so far, 10 in the U.S. NIH infrastructure award.		
University of Göteborg (Sweden)	19	3
Has not distributed any cells to U.S. researchers but plans to start a collaboration in the fall with researchers in California. One paper involving the cells is currently under review.		
Karolinska Institute (Sweden)	6	0
NIH-approved lines are currently frozen. NIH infrastructure award.		
National Centre for Biological Sciences/ Tata Institute, Bangalore (India)	3	0
None is yet fully characterized; is waiting for government guidelines on export.		
Reliance Life Sciences, Mumbai (India)	7	0
None is yet fully characterized; no export plans at present.		
Technion University, Haifa (Israel)	4	3
Is distributing only to collaborators.		
Maria Biotech Co. Ltd., Seoul (South Korea)	3	3
Cells are available to collaborators; no plans to ship cells abroad at present.		
Seoul National University (South Korea)	1	1
Plans to distribute worldwide.		
Pochon CHA University, Seoul (South Korea)	2	0
Is still characterizing the cell lines; hopes to start distributing in a year. Is applying for NIH infrastructure grant.		

WiCell now dominates the landscape with its cells, which were first derived at the University of Wisconsin, Madison, in 1998. WiCell also holds a U.S. patent on hES cells—an issue that has complicated some MTA negotiations. Cohn says that WiCell has executed agreements with 90 researchers, more than 70 of them in the United States. So far, they've sent out 57 batches of cells. Once the agreement is signed and payment is in hand, Cohn says, the cells ship within a week. But although the registry says WARF has five eligible cell lines, Cohn says they've only been sending out one type. The other four should be available by January, he says.

The other current supplier for U.S. researchers is ESI, a company created by researchers at Monash University in Australia, whose cell lines were derived at the University of Singapore. ESI is listed as having six lines, four of which are viable and available, according to Chief Operating Officer Catriona King. The company has provided cells to 30 groups of researchers, including 10 in the United States. Another 30 deals are in the works, she says. It's slow going, says Daley, who has been waiting for 2 months for three ESI cell lines he has requested.

This fall, UCSF will begin distributing one of its two cell lines, according to O'Brien. The fourth outfit, BresaGen, has so far sent its cells to only "two or three" collaborators, says Mike McDonell, vice president for cell services. McDonell says BresaGen has characterized all four but at the moment has just one line growing for distribution. The company has been waiting for an NIH grant that will enable it to scale up production. "Getting federal funding is the only way that we'll be able to pursue the development of the cells, and I think that's true of most of those who have cells on the registry," agrees Jeanne Loring, founder of Arcos, the parent organization of CyThera.

Questions about commercial rights to the cells have also dampened some researchers' enthusiasm. "The whole [intellectual property] issue hangs like a pall over a lot of the work," says Daley. WARF's broad patent covers all import and use of hES cells in the United States—so technically, institutions that send cells to U.S. researchers could run afoul of WARF's patent. WARF has said it will defend its patent claims and the rights of its licensee, Geron Corp. in Menlo Park, California. But it has also said it has no objection to U.S. researchers acquiring cells from other sources for research purposes as long as the agreement is "substantially similar" to the agreement between WiCell and NIH. Any exceptions require a separate agreement between the cell provider and WARF, says Cohn, noting that both ESI and UCSF already have such agreements.

To respond to researcher concerns about how the government is handling stem cells, Baldwin says NIH director Elias Zerhouni has appointed a "SWAT team." NIH will also soon be adding details to its stem cell registry, says Baldwin—for instance, information on publications and names of researchers using particular lines. Baldwin suspects that the list will ultimately include about 80 lines.

Ascertaining how many of the cell lines actually work as advertised will take longer. To nudge this process along, Brivanlou is organizing a conference, to be held in November at the New York Academy of Sciences, where he hopes researchers can agree on a set of molecular markers to be used to evaluate stem cells. "If I send for a cell line from India, how do I know they are really undifferentiated?" he says. With mice and other vertebrates, "one can test molecular markers and correlate them directly" with the development status of the embryo. With hES cells, though, "this is uncharted territory."

–CONSTANCE HOLDEN AND GRETCHEN VOGEL

With reporting by Pallava Bagla in New Delhi and Mark Russell in Seoul.