"I'm sure this thing will take off," says Froidevaux. "I really hope so. I really hope so." So does Church. "I'll worry in 6 months if we haven't made significant progress," he says. "If by summer we're still struggling, I don't know." **–CHARLES SEIFE**

STEM CELLS

German Researchers Get Green Light, Just

BERLIN AND BONN—German scientists are thankful for small mercies after their country's parliament last week approved some of the world's strictest regulations covering work with human embryonic stem (ES) cells.

The new measure, approved on 30 January, prohibits scientists in Germany from deriving human ES cell lines and "fundamentally bans" the import of these controversial cells. However, the Bundestag left an opening: Researchers can import ES cells if they can demonstrate that there are no feasible alternative ways to conduct the research. But even that comes with a catch: No imports can be approved until the Bundestag passes a new law establishing a national commission to review all import proposals, and the soonest such a commission could be in place is early summer.

Still, researchers are looking on the bright side. "This is a positive signal to scientists, biomedical research, and in the end also to patients," says developmental neuroscientist Oliver Brüstle of the University of Bonn, although he had hoped for a less restrictive vote. "It is the best we could hope for under the circumstances," agreed Rüdiger Wolfrum, a law professor at the University of Heidelberg and vice president of the DFG science funding agency.

Many scientists hope human ES cells, which can in theory transform into any of the body's cell types, might someday produce treatments for dread diseases such as Parkinson's or diabetes. But the cells have stirred controversy because they are derived from week-old human embryos. In Germany, scientists and politicians have argued that the country's embryo protection law, which forbids research on human embryos, does not bar work with stem cell lines that were derived outside the country. Debate on the issue has raged for more than a year, ever since Brüstle proposed importing human ES cell lines from Israel (*Science*, 14 December 2001, p. 2262).

For four and a half hours, Bundestag members debated three proposals, ranging from a complete ban on any import of human ES cells to few import restrictions. The winning compromise follows a formula established by President George W. Bush in August, when he permitted U.S. government-funded researchers to use only cell lines that had already been established (*Science*, 17 August 2001, p. 1242); German researchers will be allowed to import only cell lines established before last week's vote. "Killing of embryos for research purposes must remain illegal," argued Maria Böhmer of the Christian Democratic Union, one of the co-authors of the winning motion. But "we cannot cancel" the fact that embryos were already killed for existing cell lines, she said.

The art of compromise. German Bundestag members vote to allow restricted import of human embryonic stem cells.

CREDIT: MARKUS SCHREIBER/AP

Legislators on all sides of the debate called for generous funding for research into alternatives to ES cells, including stem cells derived from umbilical cord blood and adult tissues.

A day after the Bundestag vote, DFG announced that it would fund Brüstle's work as soon as the national commission is in place to give its stamp of approval. DFG had agreed several times to delay its funding decision until the Bundestag had debated the issue. Asked whether he regretted waiting, DFG president Ernst-Ludwig Winnacker said the result of the debate "shows that it was right to be patient and cautious in this sensitive field. Freedom of research [enshrined in Germany's constitution] is not absolute but is restricted by other rights."

Bundestag leaders have said they hope to have a draft of a new law ready in a few weeks, with final passage possible in a few months. But several scientists warn that this will not be the end of the debate in Germany. Molecular biologist Detlev Ganten of the Max Delbrück Center for Molecular Medicine in Berlin-Buch, a member of the National Ethics Council, said he will push for a review of the embryo protection law after national elections in September. "The discussion will not end here," he says. "From my point of view, import is a step in the right direction, but it leaves a double standard in place." For now, it seems to be a double standard that a majority of German lawmakers can agree on. **–GRETCHEN VOGEL**

With reporting by Sabine Steghaus-Kovac in Bonn.

CANCER RESEARCH

Leukemia Protein Spurs Gene Silencing

Researchers have identified hundreds of genes that can, when mutated, cause uncontrolled cellular growth and other changes that underlie cancer. But in the past few years, increasing evidence has suggested that mutations aren't the only genetic changes that lead to cancer. The addition of certain chemical groups to genes or their associated proteins can also alter gene activity patterns in ways that result in malignancy, without disrupting gene structures. Exactly how cancer-related genes acquire these so-called "epigenetic" alterations hasn't been clear, however.

Now, a team led by Luciano Di Croce and Pier Giuseppe Pelicci of the European Institute of Oncology in Milan, Italy, provides a possible answer for a blood cancer known as acute promyelocytic leukemia (APL). On page 1079, they report that a mutant oncogenic protein involved in APL development recruits enzymes that attach methyl groups to DNA, in this case to a possible tumor suppressor gene called RARβ2. The addition of these methyl groups silences the gene, and that in turn contributes to the malignant transformation of the leukemia cells, the researchers report.

This finding could lead to better APL

therapies aimed at blocking methylation of RARβ2 and other targets of the oncogenic protein. "The implications of the work range all the way from the basic to potential clinical applications," says Stephen Baylin of Johns Hopkins University School of Medicine in Baltimore, Maryland, whose own work focuses on gene methylation.

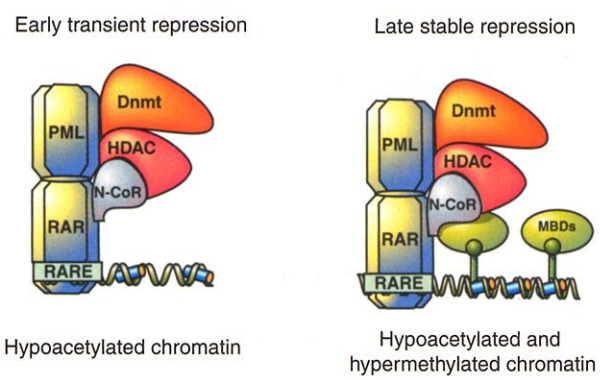
On the basic side, the discovery helps resolve a paradox concerning gene methylation in cancer cells. The genomes of cancer cells usually carry fewer methyl groups than normal, but particular genes—including several tumor suppressors whose loss or inactivation contributes to excessive cell growth—often have more than their share of the chemical additions. This presumably shuts down the genes' activity. "The big question is what targets methylation to [those] specific sites," says Peter Jones, a methylation expert at the University of Southern California in Los Angeles.

To address that question, Di Croce, Pelicci, and their colleagues turned to APL cells. They carry an oncogenic protein, named PML-RAR because it's the product of an abnormal gene formed by fusing two genes, one encoding the α form of the retinoic acid receptor (RAR) and the other encoding the so-called promyelocytic leukemia protein (PML). Normal RAR, when bound to retinoic acid, alters gene expression in immature white blood cells, causing them to mature and stop dividing. PML-RAR has the opposite effect: It blocks the development of immature white blood cells, which consequently grow out of control. The protein apparently does this by suppressing gene activity, and the Milan team wanted to find out whether it might do so by facilitating methylation of its target genes.

Several lines of evidence suggest that it does. For example, the researchers found that in immature white blood cells, PML-RAR binds to a DNA segment needed for the expression of one of its targets, the gene for the β form of the retinoic acid receptor (RARβ). And once the protein binds to the regulatory site, Pelicci says, "we see hypermethylation of this target promoter." This in turn silences the gene.

Further work indicated that PML-RAR triggers hypermethylation by drawing in two methylating enzymes. The enzymes bound to the RARβ promoter only when PML-RAR is present. "It's the first example in a human tumor where a genetic change [formation of the PML-RAR fusion gene] is setting up an epigenetic change," Baylin says.

What's more, that epigenetic change seems to be what holds the cells in the immature, dividing state seen in APL: Di Croce and his colleagues showed that once the epigenetic changes were established, the fusion protein was no longer necessary. They did this by setting up the experiments so that the PML-RAR gene was expressed in the white cell precursors only in the presence of zinc ions. If they turned off PML-RAR production after 48 hours by removing the zinc, the cells remained locked in their undeveloped condition.



Gene lock-up. On binding to its target promoter, PML-RAR attracts an enzyme (HDAC) that removes acetyl groups from histone proteins and also enzymes (Dnmt) that add methyl groups to the DNA. The actions of these enzymes, together with the proteins (MBDs) attracted by the added methyl groups, eventually shut down the gene.

Conversely, the team found, treatments known to return APL cells to a more normal behavior demethylate the RARβ gene and increase its activity. This can be done, for example, by treating the cells with both retinoic acid, which makes PML-RAR behave more like normal RAR, and the drug 5-Aza-dC, which removes methyl groups from DNA.

Although intrigued by the findings, some researchers want to see more evidence of PML-RAR's ability to recruit methylating enzymes to its target genes. "I would be more convinced if they had been able to show that for more than one gene," says Jean-Pierre Isse of the University of Texas Southwestern Medical Center in Dallas. "RARβ is methylated in a lot of cancers without PML-RAR."

Still, Baylin says, researchers interested in epigenetic events in cancer now have a new line of investigation to follow. He points out that many leukemias and lymphomas feature both fusion proteins and hypermethylated tumor suppressor genes. The question now is whether any of them work the same way that PML-RAR does in transforming cells to malignancy. **–JEAN MARX**

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ScienceScope

Nuclear Shutdown Operations at a research nuclear reactor in the Netherlands were set to shut down this week after Dutch and European authorities expressed concerned about its safety. The High Flux Reactor (HFR) in Petten, owned by the European Union's Joint Research Centre, will remain closed pending a review by outside experts.

The 40-year-old reactor is used for energy-related research and makes more than half of all medical isotopes used in Europe. The apparent growth of a tiny, 18-year-old crack in the reactor vessel plus allegations by an operator of unsafe practices triggered the shutdown.

NRG, the company that operates HFR, claims the reactor is safe and says the whistleblower acted as part of a long-running labor conflict. Although he agrees that the crack is harmless, Dutch environment minister Jan Pronk last weekend said he wants experts to examine the lab's "safety culture."

Water Warning The National Academy of Sciences has waded into a battle over water policy in Northern California and Oregon with a report criticizing the judgment of federal fisheries biologists.

Last year, the U.S. Fish and Wildlife Service and National Marine Fisheries Service recommended water restrictions to protect two endangered species of suckerfish in Upper Klamath Lake and a downstream species of Coho salmon. The recommendations came in the middle of a regional drought and touched off angry protests by farmers and calls for an independent review of the move.

The committee's report, issued this week, found no clear connection between water levels and conditions that promote algal blooms and other problems that degrade water quality and can kill fish. At the same time, the committee said there was no evidence to support an alternative plan from the Bureau of Reclamation to release more water than normal to farmers.

Glen Spain, a fisheries expert with the Institute for Fisheries Resources in Eugene, Oregon, says the academy's conclusions put federal biologists in "a difficult box." The report suggests they shouldn't raise or lower Klamath Lake water levels, Spain says, although current levels contributed to the fish's plight. The agencies must come up with a new plan by 1 April to protect the fish during the upcoming growing season.