the Max Planck Institute for Biophysical Chemistry in Göttingen, West Germany, have used gene targeting to knock out certain homeobox-containing genes in mouse embryonic stem cells. Homeobox genes play important roles in fruit-fly development, but the functions of the mammalian genes are not known.

The researchers may be able to dissect the roles of the mammalian homeobox genes, by making mice in which the genes have been inactivated. The Toronto and Göttingen workers have produced chimeric mice with the altered embryonic stem cells, and are carrying out breeding experiments to see if the mutated homeobox genes have made it into the germline of the chimeras.

Meanwhile, at the International Genetics Congress that was held in Toronto in August, Berg described his group's recent progress in achieving targeted gene transfer. In one set of experiments, Maria Jasin of the Berg laboratory introduced a bacterial gene into a line of cells carrying a copy of the genome of simian virus 40 (SV40). The bacterial gene and the vector used to transfer it were designed in such a way that the gene was supposed to be expressed only if it inserted into the SV40 DNA. Jasin found that about half the cells that expressed the bacterial gene had it integrated in the desired SV40 site, although other integration sites also conferred activity on the gene.

In another set of experiments, David Strehlow of the Berg group showed that plasmid and cellular DNA could mutually exchange genetic material to correct defective antibiotic resistance genes. "The two genes talk to each other and repair each other's defects," Berg says.

Most of the genes that researchers are going to want to correct or inactivate, as the case may be, do not offer ready selection opportunities, such as those provided by the HPRT and antibiotic resistance genes. Also at the genetics congress, Capecchi described a method that should allow the targeting of any gene in the genome.

The method depends on the use of two selectable genes, one positive and one negative, that are incorporated into the gene transfer vector. The vector is designed so that the negative selection gene can go into the genome only at incorrect sites, allowing those cells to be killed while positive selection can also be applied to identify cells that have the correct integration site. The Capecchi group has used the method to inactivate a mouse homeobox gene and also an oncogene, both of which are otherwise not selectable. All in all, researchers should soon have the ability to apply targeted gene transfer to modify whatever genes they want.

■ JEAN L. MARX

Similar Experiments, Dissimilar Results

Two recent experiments added to the confusion about how high-temperature superconductivity works by reporting inconsistent measurements and coming to opposing conclusions

CONFLICTING RESULTS APPEARED this past week from two experiments designed to test how high-temperature superconductors work. Two groups of researchers, one at AT&T Bell Labs and the other at Argonne National Laboratory, performed similar experiments but obtained different data and came to opposing conclusions. The results reflect the confusion that still exists about the mechanisms behind high-temperature superconductivity.

At issue is why the recently discovered high-temperature materials become superconducting—lose their resistance to electrical current—when cooled past a certain critical temperature. Until 1986, the only known superconductors had to be cooled to at least 23 K (23° above absolute zero, or −418°F), and many scientists thought it might be impossible to find superconductors that worked at significantly higher temperatures. But 2 years ago, IBM's Georg Bednorz and Alex Muller found superconductivity at 30 K in a Ba-La-Cu-O material. The discovery set off a flurry of research that produced several superconductors with much higher critical temperatures, and the current record is 125 K (−235°F) in a Tl-Ba-Ca-Cu-O material.

The problem is that the standard theoretical explanation for superconductivity does not seem to apply to the new materials. Scientists have offered several alternative theories, and experiments such as the Bell Labs and Argonne work are aimed at testing them, with the goal of determining which (if any) of the competing explanations reveal why the new materials work.

The accepted theory for low-temperature superconductors is the Bardeen-Cooper-Schrieffer theory (BCS). BCS traces superconductivity to an interaction between conduction electrons and quantum vibrations (or phonons) in the lattice of atoms that make up the superconductor. This electron-phonon interaction causes the conduction electrons to travel through the superconductor in pairs rather than singly, and this pairing combined with a second effect causes electrical resistance to disappear if the material is cooled to a low enough temperature.

Experiments on Y-Ba-Cu-O superconductors that have a critical temperature of 90 K indicate that the electrons in these materials do travel in pairs but that an electron-phonon interaction plays little or no role in causing the pairing. The recent discovery of a 30 K Ba-K-Bi-O superconductor provided an opportunity to learn more about what is going on, since the new material is not a copper oxide like all other high-temperature superconductors but is still superconducting at relatively high temperatures. The Bell Labs and Argonne groups both looked at the Ba-K-Bi-O material to get clues about the mechanism behind its superconductivity.

To sort out which team is right, the experiment will probably have to be repeated by other groups.

Both groups used a standard test for electron-phonon interactions called the isotope effect test. If electron-phonon interactions are behind the superconductivity of a material, then the critical temperature should vary with the strength of the phonons, or lattice vibrations. One can modify the frequency (and thus the strength) of the lattice vibrations by changing the mass of the atoms in the lattice, which can be done by substituting one isotope for another in the atoms of the material. (Different isotopes of an element have different masses.) Although there are various subtleties, the basic idea is that if electron-phonon interactions play a role, then changing isotopes in a superconductor should modify its critical temperature in a certain, predictable way.

The Argonne and Bell Labs researchers both performed this test on the Ba-K-Bi-O superconductor by substituting ^{18}O for ^{16}O and looking for changes in the critical temperature.

The Argonne group, led by Dave Hinks, found a large isotope effect—the critical

temperature was about 1.4 K less in the ^{18}O sample than in the ^{16}O sample—and concluded that this was evidence that the material's superconductivity is caused by a phonon-mediated mechanism. At Bell Labs, Bertram Batlogg, Robert Cava, and coworkers found a much smaller isotope effect and concluded from this and other measurements and calculations that a completely different mechanism is at work.

The researchers were uncertain about why their measurements of the isotope effect differed. The two labs use different techniques to make their Ba-K-Bi-O compounds, and the compositions of the two materials probably varied somewhat. Even if the compositions differed, however, the two materials should have been similar in structure and should have shown similar isotope effects.

Since the results depend strongly on how much of the ^{16}O was replaced by ^{18}O, an overestimate of the replacement percentage would lead to an underestimate of the isotope effect. And Hinks pointed out that since the critical temperature depends on the potassium content, any replacement technique that accidentally removed some of the potassium could skew the results. The Argonne team had this problem originally, caused by an impure ^{18}O supply.

To sort out which team is right on the magnitude of the isotope effect, the experiment will probably have to be repeated by other groups.

The Argonne and Bell Labs groups also differ on their interpretation of the data. The Argonne researchers see the isotope effect as strong evidence for a phonon mechanism. "If the isotope effect is there, it generally means the phonons are doing something," Hinks said.

The Bell Labs workers disagree. "Nobody argues that the phonons are not involved," said Cava, but measurements of the electronic density of states in the Ba-K-Bi-O material lead them to the conclusion that the mechanism is not conventional electron-phonon interactions. The Bell Labs group believes instead that the pairing is caused by electronic excitations, which as a secondary effect create lattice distortions, or phonons. Thus the phonons would just be "along for the ride" and would not be a primary cause of the electron pairing.

"The mechanism is not going to be resolved by one experiment," Cava said. There remains a struggle ahead as the superconductivity community argues whether the Ba-K-Bi-O materials are superconducting because of the well-known, comfortable electron-phonon mechanism or whether it is something different, challenging, and exciting. ■ **ROBERT POOL**

Joint Soviet–U.S. Attack on Heart Muscle Dogma

Under certain experimental conditions scientists can prod heart muscle cells to divide; whether the research will lead to new therapies remains to be seen

"WE SHOULD BE AWAKENED from a state of dogmatic slumber," says Alexander Mauro, paraphrasing Immanuel Kant but referring to the prevailing state of mind about heart muscle. A long-held conviction is that adult cardiac muscle cells have lost the ability to divide. Because of this, the reasoning goes, people with massively damaged hearts need artificial ones or transplants in order to live.

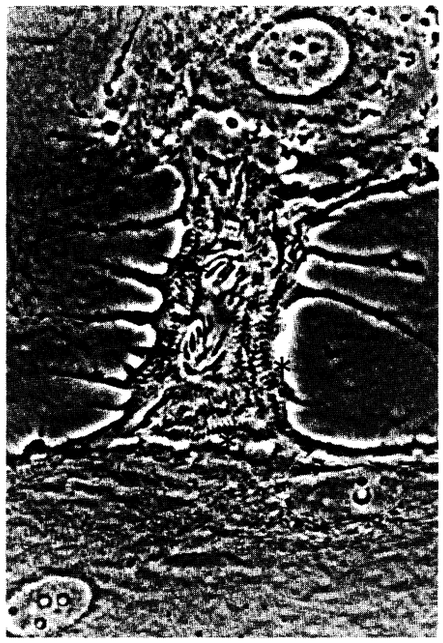
Mauro, of Rockefeller University in New York, and about 25 other researchers met recently to challenge this dogma.* The group, inspired by Pavel Rumyantsev, a Soviet scientist from the Academy of Sciences in Leningrad, is exploring new techniques to trigger mitosis-reluctant cardiac muscle cells into dividing again after they mature. As yet, the field of research is in an early stage. It is not widely recognized and not heavily funded, but its proponents envision future therapies for heart disease patients if some of the new techniques can be applied to human heart tissue.

"The interest in this field is just dawning," Eugene Braunwald of Harvard Medical School told *Science*. "Of all the medical subspecialities, cardiology has really been the slowest to take advantage of recent progress in cell biology and molecular biology." Cardiology, he says, has been dominated by the view that the heart is an electrically driven pump, so much of the research has focused on biophysics, hydraulics, and engineering. Today, that view is changing, but it is a slow process.

The question everyone wants to answer is whether it is possible to repair damaged tissue in the human heart after a heart attack. As yet no answer exists. But basic research on myocytes, the contracting muscle cells that make up about 25% of all the cells in the heart, is in a new phase. Current studies address two fundamental issues: why do heart muscle cells stop dividing shortly after birth and can they be stimulated to divide again? In practical terms most of the research falls into three categories—experiments on intact animals, studies of myocytes in tissue culture, and experiments with transgenic mice that have been induced to grow unusual heart tumors.

Until about 25 years ago, no one had evidence that mature heart myocytes retain the capacity to divide. Then in the early 1960s, Rumyantsev showed that they do. He cut off the blood supply to the left ventricle in young rats, which triggered DNA synthesis and nuclear division in muscle cells of the left atrium. Much of the cardiology community remained unaware of the work until 1977 when Rumyantsev wrote a review on the subject. The work not only stimulated the field, it also established one major experimental approach, namely research on intact animals.

Rumyantsev's experiments raised problems that still exist today. For example, atrial myocytes divide more in young rats, possibly because their regenerative potential is greater than that of older animals. Also, as Victor Ferrans of the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Maryland, points out, "You would like to



Newt ventricular myocyte *dividing in a 12-day culture. Both chromosomes (arrows) and myofibrils (asterisks) are visible (×1250).*

*The "Workshop on Myocardial Regeneration" was held on 20 and 21 June at Rockefeller University.