ic researchers have identified, but it is more specific in its action than the others. "They've taken a prototype drug and shown that it has therapeutic activity in animals," says John Groves, a chemist at Princeton University.

To come up with their compound, the MetaPhore team started with manganese, the least toxic of the three metals that can perform SOD catalytic activity. By trial and error, the researchers produced a ring structure that holds onto manganese reasonably well. Then, by computer modeling and with many animal tests, they developed a derivative that was even more stable and more effective in breaking down superoxide. This compound, known as M40403, transforms superoxide at rates similar to those of native SOD, and without acting on other related compounds such as peroxynitrite. In addition, it proved stable when injected into animals, indicating that the compound itself, and not a breakdown product, produces any pharmacologic effects. "M40403 is excreted intact," says Riley.

The investigators then tested whether M40403 would protect animals against the kind of damage thought to be caused by superoxide. In one set of experiments, they induced inflammation in the footpads of rats by injecting them with the polysaccharide carrageenan. M40403 injections given 30 minutes before the carrageenan greatly decreased several key indicators of inflammation such as swelling, tissue damage, white blood cell accumulation at the site of the injury, and production of certain cytokines, immune regulators that contribute to the damage.

In another series of tests, the researchers evaluated M40403's effects on perfusion injury. They used clamps to shut off blood supply to the intestines of rats for 45 minutes, and then released the clamps to allow the blood to flow. Such rapid restoration of circulation produces a spike of superoxide radicals as the tissue goes into high metabolic gear to make up for its previous lack of oxygen. The resulting damage killed most of the control animals within 2 hours and none survived more than 4 hours, but about 90% of the treated animals lasted that long. Analysis of blood and tissue samples again showed that M40403 reduced the typical signs of inflammatory damage.

Salvemini says the team hopes to conduct safety studies and then determine whether the compound has therapeutic value in humans. But no matter what, she adds, because M40403 is very specific in its actions, it should at least be possible to use it to dissect out which of the many changes contributing to inflammation are due to superoxide. "This compound will help [researchers] discover and deconvolute this very difficult-to-untangle set of interactions of these very short-lived, very reactive molecules," says Groves. Indeed, the MetaPhore team's results have already indicated that superoxide is involved in the regulation of cytokines. "That's important," says Matthew Grisham, a biochemist at Louisiana State University Medical Center in Shreveport. "No one has made that connection before." –EVELYN STRAUSS

GENOMICS

Mouse Genome Added To Sequencing Effort

Even as the largest academic genome sequencing centers scramble to generate a rough draft of the human genome by March 2000, they have taken on another monumental task: producing a preliminary sequence of the mouse genome sequence by 2003, followed by a high-quality version 2 years later. On 5 October, the National Human Genome Research Institute (NHGRI) awarded $21 million over the next 7 months to jump-start the mouse effort at 10 laboratories across the United States with a total of $130 million to be spent through 2002 (see chart). The initial amount "was less than what we might have hoped for," says NHGRI director Francis Collins, which is why the grants of all groups but one are for 7 months. But NHGRI wanted the groups to ramp up quickly. "I'm so tickled to be able to start the mouse [sequencing] now," says Collins.

MOUSE GENOME GRANTS (1999–2002)

Principal Investigator	Institution	Amount (in millions)
John D. McPherson	Washington Univ. School of Med.	$24.642
Richard A. Gibbs	Baylor College of Medicine	$22.344
Eric S. Lander	Whitehead Inst. for Biomedical Rsrch.	$21.507
Eric Green	Natl. Human Genome Research Inst.	$16.060
Douglas R. Smith	Genome Therapeutics Corp.	$12.874
Bruce A. Roe	Oklahoma University	$12.192
William R. McCombie	Cold Spring Harbor Laboratory	$6.874
Raju S. Kucherlapati	Albert Einstein College of Medicine	$6.127
Robert B. Weiss	University of Utah	$6.067
William C. Nierman	The Institute for Genomic Research	$1.60 (1 yr)

SOURCE: NHGRI

Both human and mouse geneticists share that sentiment. At an estimated 3 billion bases, the mouse genome is comparable in size to the human's and is sometimes described as the human genome chopped into 150 pieces and put back in a different order along the mouse's 21 chromosomes. Because the mouse is so well studied, its sequence will speed the understanding of how our own genes work, says mouse geneticist Barbara Knowles, director of research at the Jackson Laboratory in Bar Harbor, Maine. And Richard Gibbs, whose sequencing center at Baylor College of Medicine, Houston, was one of the big winners, agrees: "To ensure that we can interpret the human sequence with maximum efficiency, there's nothing quite like the mouse genome," he says.

The three centers that pulled down the biggest grants for what will be known as the Mouse Genome Sequencing Network are those doing the lion's share of the U.S. contribution to the human genome sequence: Baylor and the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, each received $4 million while Washington University School of Medicine in St. Louis got $2.7 million. The three centers will have help, however, from a cadre of teams including some that are relatively new to large-scale sequencing.

Genome mappers Raju Kucherlapati, a geneticist at Albert Einstein College of Medicine in New York, and NHGRI genomicist Eric Green have both signed on to the mouse effort. "We've never had support for sequencing in the past," says Kucherlapati, whose group has only about 1 million bases of sequence from various organisms under its belt, "but it was a natural evolution from mapping." Over the next 7 months, he expects to complete about 12 million bases of the rough draft, while Green, who has done some sequencing, hopes to do 25 megabases over the next year.

Unlike the Human Genome Project, in which the sequencers took on entire chromosomes or parts of chromosomes, those tackling the mouse genome will do a mix of randomly chosen DNA and DNA of biological interest, such as regions in which the mouse genes are in the same order as those in regions of human chromosomes that contain disease genes. The network will meet at the end of the month to choose those regions and decide how mouse researchers can request that regions containing genes they are interested in be sequenced first. Says Kucherlapati: "If the consortium can move top priority mouse projects along [with the sequencing], that will be a great strategy." –ELIZABETH PENNISI