

SPECIAL EDITION THE FUTURE OF MEDICINE

# Newsweek

Summer 2005

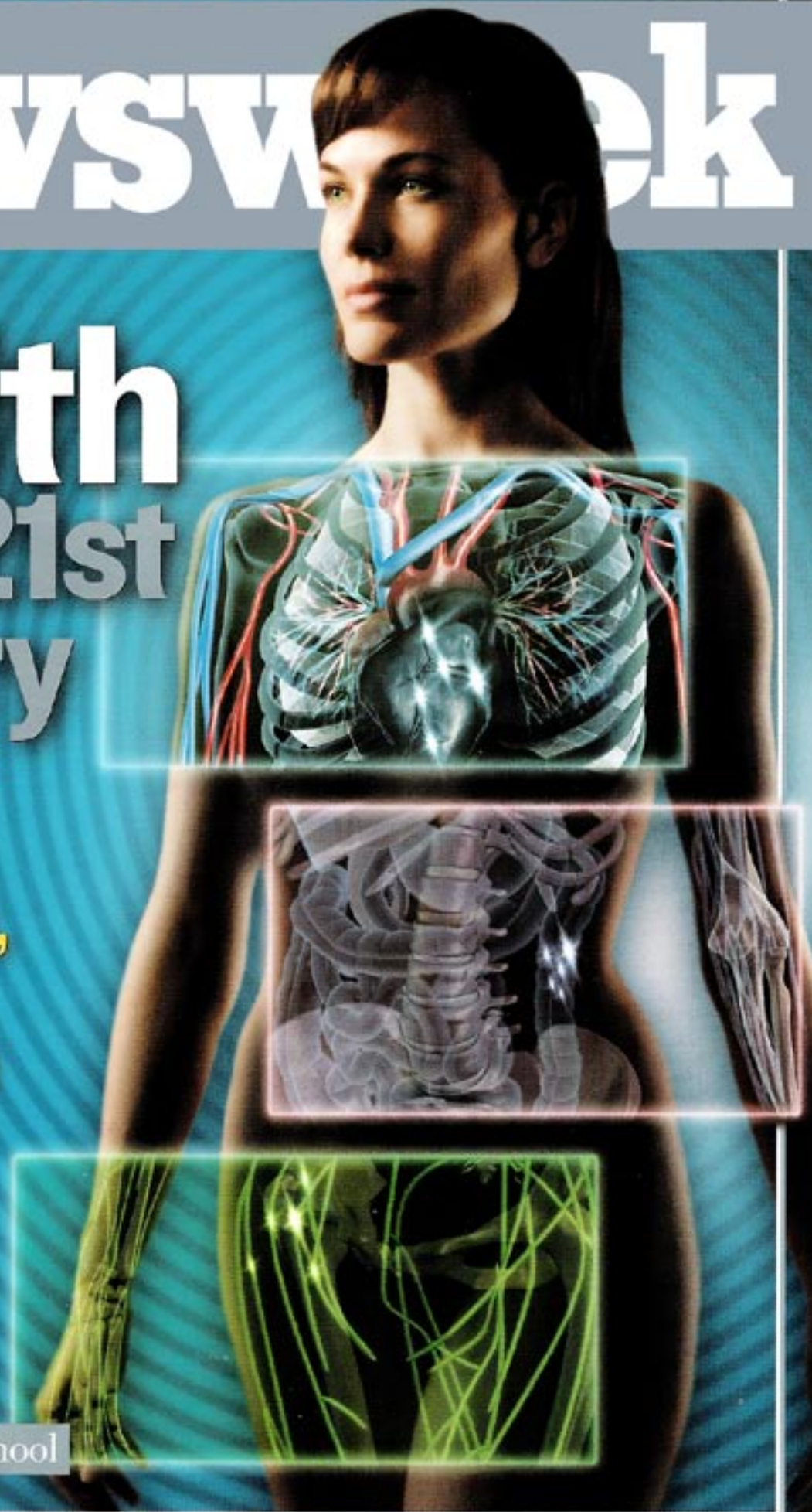
## Your Health In the 21st Century

NEW TREATMENTS

For Cancer,  
Alzheimer's,  
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The Science  
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With Harvard Medical School



# Newsweek

FROM HARVARD MEDICAL SCHOOL

## A Fix for Faulty Proteins

By Peter T. Lansbury, Ph.D.,  
and Tom Fagan, Ph.D.

**W**hat do Alzheimer's disease, type 2 diabetes and amyotrophic lateral sclerosis (ALS), better known as Lou Gehrig's disease, have in common? On the face of it, not much. But at the molecular level, these and many other diseases do share something: toxic, misfolded proteins trigger the pathology. Our recent understanding about the importance of protein folding in disease, and the use of new tools to try to fix misfolded proteins, is one of the hottest areas in medicine.

There are as many as 100,000 different proteins in humans. After each protein is formed, it must be twisted, bent and folded into just the right shape to be functional. Mistakes happen, which is why evolution has endowed cells with sophisticated housekeeping mechanisms to repair or destroy poorly formed proteins before they do any harm. Occasionally, however, a misfolded protein evades these controls and accumulates in sufficient quantities to clump together and poison or even kill the cell. This event is so rare that our cellular housekeeping systems can keep up while we are young, but not as we age. That's why diseases caused by aberrantly folded proteins normally begin in middle age and take time to progress.

One way to treat diseases caused by misfolded proteins would be to stimulate the housekeeping processes. Another would be to prevent protein misfolding in the first place. Scientists around the world are determining the three-dimensional structures of normal and abnormal proteins. They are using that information to identify small molecules, some that keep the normal proteins from misfolding and others that prevent misfolded proteins from clumping together.



Recently we identified several molecules (after screening 2 million with computers) that show promise as potential treatments for certain inherited cases of ALS. In these cases, ALS is caused by the misfolding and aggregation of an enzyme called superoxide dismutase (SOD). We created a picture of the three-dimensional structure of SOD and found a little crevice between the two halves of the protein. Lab tests have shown that the small molecules we identified nestle in that crevice and keep SOD from falling apart. The compounds are now being tested in animals that develop ALS. Misfolded proteins cause other brain diseases, including Parkinson's, as well as diseases that damage the heart, spleen and liver. Each of these misfolded proteins is a target for treatment.

LANSBURY is a professor of neurology at Harvard Medical School, and FAGAN writes for the school's publications.