NEUROBIOLOGY

New Lead to an Alzheimer's Mouse?

If an Alzheimer's researcher were to make a wish list, chances are good that a small animal model for the disease would be near the top. Alzheimer's develops naturally only in humans and higher primates, and the desire for an animal model—which would allow scientists to test theories about the cause of the disease as well as potential treatments—has spurred several efforts over the past few years to genetically engineer mice that would mimic Alzheimer's symptoms. Unfortunately, those efforts have not met with much success.

Now two groups of researchers may have taken a step toward fulfilling the wish for an "Alzheimer's mouse," by transferring into mice a human gene that's a prime suspect in Alzheimer's pathology. But it's only a first step: Although the gene is highly active in the animals, it has not yet produced pathological changes. The preliminary state of the research, combined with the troubled history of previous work— which includes retractions of two models, one amid concerns that tissue purporting to show Alzheimer's pathology in mice may have been of human origin (*Science*, 6 March 1992, p. 1200)—makes everyone cautious. "I really don't want to oversell it," says Alzheimer's expert Sam Sisodia of Johns Hopkins University School of Medicine, a member of one of the groups working on the current models. "It would be great if it works, but there's [no pathology] yet."

To try to create the mouse models, the two teams, one led by Johns Hopkins developmental geneticist John Gearhart and the other by Ted Choi of GenPharm International in Mountain View, California, used the human gene for the amyloid precursor protein (APP). APP may play a role in formation of the plaques that are one of the characteristic pathological features of Alzheimer's brains. Plaques consist of a protein core, composed mainly of the peptide β-amyloid, surrounded by degenerating nerve terminals. One school of thought holds that the deposition of β-amyloid, which is split from APP, causes the nerve degeneration of Alzheimer's, although the β-amyloid deposition might instead be merely the result of that degeneration.

Because of its proposed role in Alzheimer's, previous attempts at mouse model-making also used the APP gene, but the new work differs from those efforts in a significant way. The earlier research did not use the full APP gene because its 400-kilobase-length greatly exceeds the capacity of the vehicles then available for cloning DNA. Instead, researchers used DNA copies of APP messenger RNAs lacking the gene's usual control sequences as well as the noncoding introns needed for normal patterns of gene expression. Presumably as a result, the animals produced little human APP protein.

But earlier this year, several groups, including Choi's at GenPharm, developed methods of introducing into mice genes cloned in yeast artificial chromosomes (YACs). YACs have the capacity to handle full-length genes, and the Gearhart and Choi groups were able to use the new methods to put the complete APP gene into their mice. This makes it the largest gene genetically engineered into those animals to date. (The Gearhart team describes its work in the September *Nature Genetics* and Choi and GenPharm colleague Barbara Pearson have a paper in press at the *Proceedings of the National Academy of Sciences*.)

Both Gearhart and Choi say the initial results are encouraging. In particular, the animals make almost as much human APP protein as they do mouse protein. "We can show nicely that we have the human protein in neurons of the major cell groups in the animals' brains," says Gearhart. Nonetheless, neither group has yet seen any sign that their mice are developing plaques or other types of Alzheimer's pathology. It is possible that excess APP production may not be at fault in the first place, although Gearhart notes that people with Down's syndrome, who have an extra copy of the gene, develop Alzheimer's pathology early, around age 35. Or, the mice may simply be too young to show plaque formation: The oldest are 7 months old (mice usually live 2 to 3 years). But without the pathology, both groups acknowledge, they can't claim to have an Alzheimer's model.

Buoyed by the early findings, however, both teams are moving ahead to the next step, which is to insert into mice the mutant APP genes that have been linked to hereditary early-onset Alzheimer's in some families. Says Sisodia: "the strongest feature of the approach is that it allows us to test whether these mutations can cause pathology." If the efforts to produce an Alzheimer's mouse succeed, it would be "fantastic," says Zaven Khachaturian, who heads up the Alzheimer's research program at the National Institute on Aging. So, along with everyone else, he's watching closely. And hoping that the latest efforts don't follow the trend in this field—early promise followed by a quick flameout.

–Jean Marx

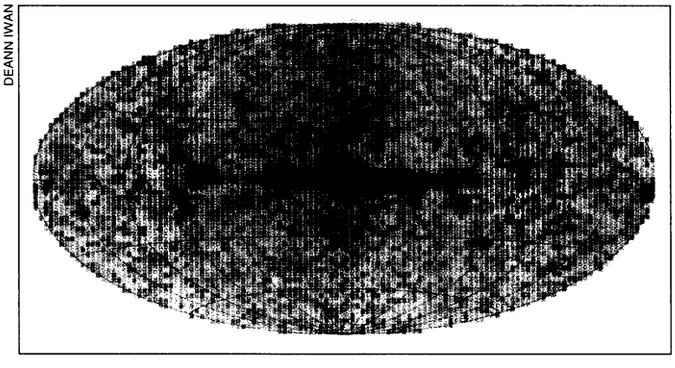
ASTRONOMY

Closing In on X-Ray Background Origins

When astronomers first ventured above the atmosphere with rockets and satellites 30 years ago, their instruments caught a cacophony of x-rays and gamma-rays. X-rays appeared to drizzle in from all directions in the universe, forming a ubiquitous but mysterious "x-ray background."

Now one group of astronomers think they have finally discerned the background's source: galactic powerhouses known as active galactic nuclei (AGN). These are powerful radiation-emitting sources such as quasars. In last week's *Astrophysical Journal*, Julian Krolik of Johns Hopkins University and his colleagues report that they analyzed new x-ray data from detectors on the Japanese Ginga satellite and NASA's Compton Gamma Ray Observatory that sampled a variety of these AGNs. The researchers made some assumptions about the general distribution of AGNs in the universe and concluded that the combined emissions of these sources would closely match the spectrum of the x-ray background. "Once we saw that the data did match, everything fell into place fairly quickly," Krolik said in a press statement.

Though some astronomers agree, critics point out that Krolik's calculations of AGN distribution rest on assumptions about the curvature of space and density of matter. Different assumptions have led another team to conclude that an additional class of sources may also contribute to the background.



DEANN IWAN

The x-ray sky. Powerful x-rays come from sources in our galaxy *(pink)*, and from beyond comes a background x-ray glow *(blue)*.

But whether or not Krolik and colleagues manage to satisfy their critics on the fine points, they are closing in on a longstanding question. The astronomer who first detected the x-ray background, Riccardo Giacconi,