Robinson and colleagues planned to test this approach by "challenging" the vaccinated monkeys with an inoculum of SHIV placed in the animals' rectums. This is a more real-world test than injecting the virus under the skin or into a muscle. To do the experiment, the researchers needed a "challenge stock," a batch of SHIV that had been tested on monkeys to determine the minimum amount of virus needed to establish an infection rectally. After she had started vaccinating monkeys, Robinson realized that she would have to make the challenge stock herself, which took three tries.

By the time they challenged the 24 vaccinated monkeys, 7 months had elapsed since the animals had received a booster shot. "Originally we had planned to challenge at 3 months," laughs Robinson. The vaccinated animals became infected with the SHIV, but 20 weeks later, 23 of 24 monkeys had controlled the infection and had suffered no immune damage, the researchers report. All four of the unvaccinated control animals, in contrast, had consistently high levels of SHIV in their blood, and their immune systems steadily declined; all the control monkeys subsequently died from AIDS. "This is the closest thing to a real-life challenge that we've seen yet," says James Bradac, who heads the NIAID division that oversees monkey trials of AIDS vaccines.

An HIV version of this DNA/MVA vaccine—which has no company behind it but is being manufactured under contract—is slated to begin human trials in the United States by early next year. **–JON COHEN**

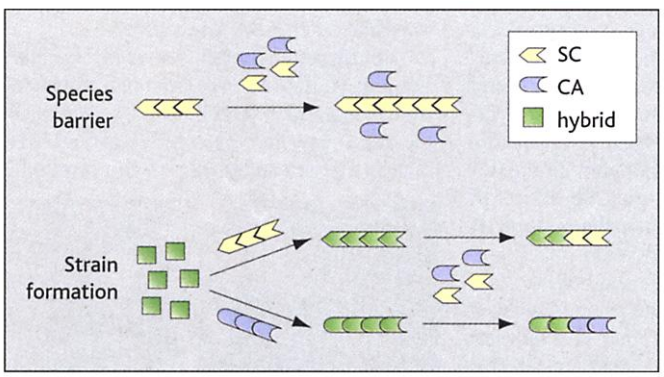
PRION RESEARCH

Getting Yeast Prions to Bridge the Species Gap

The sheep disease scrapie has been around for centuries without infecting humans. But the strikingly similar "mad cow disease," a progressive and ultimately fatal neurodegenerative condition, has apparently slipped from infected cattle into the human population. Both scrapie and mad cow disease are almost certainly transmitted by an abnormally folded form of a protein, known as a prion. That has left researchers with the problem of trying to figure out what determines whether a particular prion disease can spread from one species to another. New results with yeast prions may now provide a clue.

Although yeast prions are not infective, their behavior resembles that of mammalian prions in some ways. Both form when a normal prion protein adopts an abnormal shape or conformation. This abnormally folded protein can then induce the same shape change in other normal copies of the same protein, causing them all to clump together in insoluble aggregates. In the case of mammalian prions, these may damage the brain, while the aggregated yeast prion proteins lose their normal activity.

Ordinarily, a yeast prion from one species of yeast cannot induce the shape change in the corresponding prion protein from another species. But work reported in the 8 March issue of *Nature* by Jonathan Weissman and Peter Chien of the University of California, San Francisco, indicates that this species barrier can be overcome if the prion protein can adopt multiple structures and can thus interact with prion proteins from more than one species. If something similar happens with the prion that causes mad cow disease, it might explain how it is able to cause disease in humans as well as cattle.



A promiscuous prion. *S. cerevisiae* (SC) and *C. albicans* (CA) prions won't mix (top), but both will coax a hybrid protein into prion fibers that remember the shape of the protein that seeded them (bottom).

Weissman and Chien performed their experiments on the yeast prion protein Sup35. Previous work had shown that the Sup35 proteins from the yeast species *Saccharomyces cerevisiae* and *Candida albicans* can't induce one another to change shape and form insoluble prion aggregates. To figure out the structural basis for this species barrier, the researchers replaced the normal *SUP35* gene of *S. cerevisiae* with a three-part hybrid gene consisting of the DNAs encoding 40 amino acids from the *Saccharomyces* protein, 100 amino acids from the *Candida* protein, and the portion of Sup35 responsible for its normal biological function, which is turning off protein synthesis at certain sequences. They also added to these cells a separate piece of DNA encoding the prion-forming part of either the *Candida* Sup35 or of the *Saccharomyces* Sup35. The researchers wanted to see if either of the proteins made by these DNAs could push the hybrid protein into a prion state.

The *Candida* protein and the *Saccharomyces* protein turned out to be equally effective in switching the hybrid protein into the prion form in cells. But the phenotype of those cells, a result of the biologically active domain of the hybrid being turned off, was more severe in the cells induced with the *Candida* protein.

To determine whether these differences, reminiscent of prion strains previously seen in both yeast and rodent models, were due to different conformations of the hybrid prion, Weissman and Chien turned to the test tube, where prion proteins form long, organized fibers. Consistent with their results in yeast cells, the researchers found that fragments of prion fibers, made up of either the *Saccharomyces* protein or the *Candida* protein, could accelerate the hybrid protein's incorporation into prion fibers.

The real surprise came when the researchers let these test tube polymerization reactions run until essentially no remnants of the original *Saccharomyces* or *Candida* fibers remained. Chimeric fibers that had been seeded by *Saccharomyces* fibers would in turn trigger prion formation only by the *Saccharomyces* protein. Likewise, chimeric fibers seeded by the *Candida* protein would seed soluble *Candida* protein but not soluble *Saccharomyces* protein. The chimeric fibers, apparently, could "remember" the shape of the protein that had originally seeded them even though that protein was gone.

How the hybrid protein is able to structurally adapt to prions from both species is unclear. "We have to start looking at this experimentally," Weissman says. He hopes to get structural information about the chimeric fibers by examining them using atomic force microscopy or cryo-electron microscopy.

Researchers are already intrigued, however, by what the results suggest about the source of the species barrier. "It's not just the differences in amino acid sequences, but also the differences in conformation that the prion takes" that may establish that barrier, says yeast prion researcher Susan Liebman of the University of Illinois, Chicago.

The big question now is whether something similar can explain why the mad cow disease prion, but not the one that causes scrapie, can cause disease in humans. "Yeast is a simple way to carve out one step, and that's conversion of normal protein into another, oligomeric [prion] form," says physical biochemist Peter Lansbury of Harvard Medical School in Boston. "Beyond that, people really need to think about the huge differences [between yeast and mammalian prions]." **–R. JOHN DAVENPORT**

ILLUSTRATION: ADAPTED FROM CHIEN *ET AL.*, *NATURE* 410 (8 MARCH 2001)