

# Virus paper reignites prion spat

Mention the name Laura Manuelidis to a prion researcher, and you will almost certainly get a strong reaction. For years the Yale University neuropathologist has ruffled feathers by arguing that a virus causes neurological conditions such as Creutzfeldt-Jakob disease in humans and scrapie in animals, rather than an infectious protein, or 'prion', as most researchers believe.

That argument is decades old, and the prion hypothesis has been steadily winning converts. But the publication of a paper from Manuelidis in the *Proceedings of the National Academy of Sciences* last week served as a reminder that the debate is not over<sup>1</sup>. The paper, which shows pictures of virus-like particles in infected cells in culture, hardly overturns the prion hypothesis, but it does show how hard it can be to pin down the source of a disease.

There was a time when the tables were reversed. Stanley Prusiner from the University of California, San Francisco, fought for years to win acceptance for his idea that a misshapen protein was the cause. When he got a Nobel prize in 1997, the fight for public opinion was won but scientific skirmishes continued.

Researchers had shown that infecting animals with purified prions could cause disease, but some still questioned whether a virus particle or two could have slipped undetected through the purification process. But in 2004 Prusiner's lab showed that prions synthesized in a test tube — and so free of virus — could cause disease in mice<sup>2</sup>.

A year later, Claudio Soto, a neurologist at the University of Texas in Galveston, selectively amplified prions from diseased mouse brains. He diluted his solutions until they could not contain any molecule from the brain sample other than prions. The solutions also infected mice<sup>3</sup>.

That work silenced much of the debate, says Neil Cashman, scientific director of PrionNet Canada in Vancouver. "I really feel that these viral people are swimming upstream," he says. "But some highly regarded people do not think the prion hypothesis has been proven."

Prusiner's work was important but flawed, says Robert Rohwer, a neurovirologist at the Veterans Affairs Medical Center in Baltimore, Maryland. The amount of synthetic prion needed to infect the mice was a million times higher than would be required using brain isolates. And the mice were engineered to produce high amounts of the

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prion's natural form, making them prone to developing prion disease spontaneously.

If the synthetic prion can be shown to infect normal mice, Rohwer says he will be convinced. "If it's successful and can be reproduced by others, then it really does close the issue as far as I'm concerned," he says.

Prusiner's results have not yet been verified by other labs, and some researchers have complained that the transgenic mice he used were not made available. Iliia Baskakov, a lead author on Prusiner's paper who is now at the University of Maryland in Baltimore, says they used transgenic mice because these had the strongest response, but he hopes to replicate the work in wild-type animals soon.

Baskakov says the synthetic prion probably had low activity because it was not folded into an optimally infectious form. "This is an extremely complex problem," he says. "I would not expect that somebody would just generate 100% infectious prions in their first experiment."

Meanwhile, Bruce Chesebro, chief of the Laboratory of Persistent Viral Diseases in Montana, is concerned that the infectivity of Soto's prion solutions didn't increase proportionally with their concentration. Soto says this was unique to the prion strain used for those experiments, and that subsequent, unpublished, work with other prions has shown that virulence does increase with concentration.

For some researchers, these are mere details, and they clearly wish that Manuelidis and her arguments would just go away. Two refused to speak to *Nature*, because they did not want to play any role in publicizing her work. Charles Weissmann of Scripps Florida in Jupiter says the evidence in favour of prions is incontrovertible. Although Manuelidis claims in her paper that virus-like particles from infected cells can infect other cells in culture, Weissmann says the findings are meaningless until she can purify her particles and show that they can cause disease and that they are free of the prion protein — something he does not expect to happen.

Manuelidis believes that her criticism of prions has made it harder for her to publish in top journals. "It's not very politically correct if you don't believe in prions," she says. "It means that you won't get any grant money."

Although many disagree with her, several prion researchers say that Manuelidis's scepticism keeps the field on its toes. "To me the prion issue is settled, but it's good to have this type of person," says Soto. "This issue is so important that you have to be very rigorous." ■

Heidi Ledford

1. Manuelidis, L., Yu, Z.-X., Banquero, N. & Mullins, B. *Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.0610999104 (2007).
2. Legname, G. *et al. Science* **305**, 673–676 (2004).
3. Castilla, J., Saá, P., Hetz, C. & Soto, C. *Cell* **121**, 195–206 (2005).

## NUMBER CRUNCH

**98 billion** is the mass, in tonnes, of one square kilometre of the United Kingdom, say geologists who have weighed up Europe's countries by evaluating the thickness of Earth's crust in different regions.

**112 billion** is the mass of the same area of Austria, which, thanks largely to the Alps, is Europe's densest country.

**78.4 billion** is the corresponding figure for Germany, which, despite being an economic heavyweight, is less well endowed in the geological stakes.

## SCORECARD



### Eagle-eyed diagnosis

An unnamed Irish surgeon has been congratulated for spotting a tumour in government minister Conor Lenihan's cheek while watching him on television. He called Lenihan's office to urge him to see a specialist; the tumour has now been successfully removed.



### Negative calories

Coca-Cola and Nestlé are being sued by advocacy group the Center for Science in the Public Interest over claims that Envigo, the 'negative-calorie' drink, can help people lose weight by speeding up their metabolism.



## WORDWATCH

### Google bombing

The trick used by webmasters to code links into their websites in sufficient numbers to manipulate search engines, ensuring, for example, that the term 'miserable failure' links to George W. Bush's biography. Google has pledged to tackle the practice, leading to accusations that it is censoring its results.

## ON THE RECORD

**"All food for purchase in the UK is 110% safe."**

Nigel Horrox, president of the British Veterinary Poultry Association, seems to think that the arrival of the H5N1 flu virus at a British turkey farm has boosted food quality to an unprecedented degree.

Sources: Ananova Science, *The Guardian*, CSPI, UPI.com, Science Media Centre