NEWS

Wartime tactic doubles power of scarce bird-flu drug

Doctors think they have hit on a way to effectively double supplies of a drug that fights bird flu. Administering Tamiflu alongside a second drug that stops it being excreted in urine means that only half doses of the treatment would be needed.

Tamiflu (oseltamivir phosphate) is the main antiflu medicine recommended by the World Health Organization (WHO). The WHO suggests that, in anticipation of a flu pandemic, countries should stockpile enough for at least a quarter of their population. But although Swiss drugmaker Roche, the sole supplier, has quadrupled its production capacity over the past two years, the current supply is thought to cover just 2% of the world population.

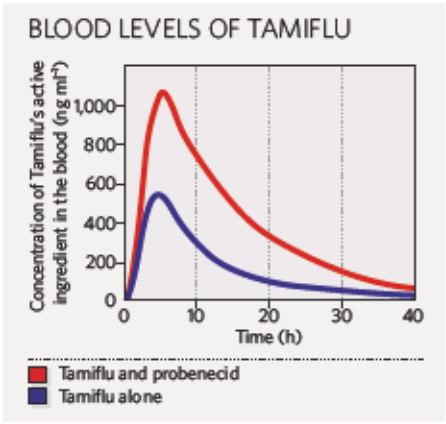
Last week, Joe Howton, medical director at the Adventist Medical Center in Portland, Oregon, suggested a way to double supplies, after browsing basic safety data from Roche for a talk on avian flu.

The technique was invented during the Second World War to extend precious penicillin supplies. Scientists found that a simple benzoic acid derivative called probenecid stops many drugs, including antibiotics, being removed from the blood by the kidneys. Probenecid is readily available and is still widely used alongside antibiotics to treat gonorrhoea and syphilis, and in emergency rooms, where doctors need their patients to have high, sustained levels of antibiotics in their blood.

Howton noticed from Roche's data that Tamiflu, like penicillin, is actively secreted by the kidneys, and that the process is inhibited by probenecid. Giving the flu drug together with probenecid doubles the time that Tamiflu's active ingredient stays in the blood, doubles its maximum blood concentration, and multiplies 2.5-fold the patient's total exposure to the drug (see graph, and G. Hill *et al. Drug Metab. Dispos.* **30**, 13–19; 2002).

In other words, you could get away with using half as much Tamiflu to get the same therapeutic effect. "It dawned on me that the data potentially represented a tremendous therapeutic benefit," Howton told *Nature*.

Given that Roche published the probenecid data in 2002, has it considered this option? "It doesn't seem so," says Martina Rupp, a spokeswoman at Roche's headquarters in Basel. "It is an interesting idea, but we can't really say anything," she adds, claiming that there are insufficient data. The WHO and the US Food and Drug Administration declined to comment when *Nature* asked them about the idea.



SOURCE: G. HILL *ET AL. DRUG METAB. DISPOS.* 30, 13–19 (2002)

Studies are being proposed that will look at safety issues relating to probenecid and Tamiflu, although doctors argue that there are already enough data for the drug combination to be used, even without specific approval from regulatory agencies. Grattan Woodson of the Atlanta Research Center in Decatur, Georgia, has prescribed probenecid for more than 25 years and says he prescribes drugs for such off-label purposes every day. "This is a perfectly acceptable and established practice," he says.

Peter Zed, a specialist in emergency medicine at Vancouver General Hospital in Canada, agrees. He has published studies of the safety of probenecid and antibiotic combinations. "There would be nothing unique about using probenecid with Tamiflu," he says.

Michael Osterholm, director of the US Center for Infectious Disease Research and Policy in Minneapolis, Minnesota, cautions that probenecid alone will not be sufficient to avert a flu pandemic. He points out that the most optimistic estimate of Tamiflu production capacity in the next five years gives enough to treat just 7% of the global population.

Coping with a pandemic will require "launching a worldwide Manhattan-like project for drug production, packaging and distribution today", Osterholm says. "It's not just about having a magic bullet; it's whether you can make it and find enough guns from which to shoot it." Still, doubling the doses available could be crucial for treating people quickly after an outbreak, and Osterholm says the idea definitely merits investigation.

"It's not just about having a magic bullet; it's whether you can find enough guns from which to shoot it."

"This is wonderful," agrees David Fedson, formerly a medical director of the vaccine company Aventis Pasteur, based in Lyons, France. "It is extremely important for global public health because it implies that the stockpiles now being ordered by more than 40 countries could be extended, perhaps in dramatic fashion." He suggests that capsules containing both Tamiflu and probenecid should be developed.

Like many scientists, Fedson is stumped by the apparent lack of interest from Roche, and the relevant authorities. "It's stupefying," he says. ■

Declan Butler

Drug firms donate compounds for anti-HIV gel

Motivated by positive results reported in this week's *Nature*, two drug companies have given away rights to two key compounds, so that they can be developed into gels that protect against HIV.

Such a gel could help many women to protect themselves, as they often find it difficult to get partners to use condoms — particularly in the developing world, where men may disapprove of the practice. Experts say that a microbicide applied to the vagina before sex could save 2.5 million lives in just three years.

But progress to develop such gels has been slow. Only one microbicide trial has been completed in humans, with disastrous results — the women became more susceptible to HIV because the gel, essentially a detergent that destroys the virus, damaged their vaginal tissue. Five other microbicides are in clinical trials in Africa after proving moderately successful in monkeys, but critics point out that the virus used in those animal tests

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Universities scramble to assess scope of falsified results

Biologists are rushing to quantify the fallout from a case of scientific misconduct unmasked last week. The Massachusetts Institute of Technology (MIT) confirmed on 27 October that it had fired immunologist Luk Van Parijs for fabricating and falsifying data.

The institute said that Van Parijs, an associate professor of biology, had acknowledged to its officials that he altered data in one published article, in unpublished manuscripts and in grant applications. The California Institute of Technology (Caltech) and Harvard University have both now opened inquiries into some of Van Parijs's other published work.

Authorities at all three universities say they have found no evidence that anyone else was involved in the misconduct. Van Parijs previously worked in the labs of Caltech's president, David Baltimore, and physician Abul Abbas, head of pathology at the University of California, San Francisco.

Van Parijs, a 35-year-old native of Belgium who lives in Falmouth, Massachusetts, did not respond to interview requests. His primary studies involved using short pieces of RNA to silence genes that have gone awry in autoimmune diseases. Early indications suggest that his misconduct will not affect his field as dramatically as semiconductor research was affected by Bell Laboratories physicist Jan Hendrik Schön[1]. Colleagues spent years following Schön's line of research until in 2002 it was discovered that he had falsified some of his data.

Van Parijs co-authored a heavily cited paper for *Nature Genetics* in 2003 describing how to use a stripped-down virus, called a lentivirus, as a delivery system for genes that can silence other genes[2]. The paper has not been called into question, and other researchers have shown that the approach works, at least in animal models and cell cultures. Clinical trials in human patients are now being planned.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

E. QUINN

Sacked: Luk Van Parijs, seen as a rising star in biology, was found to have falsified data.

Because of such work, Van Parijs was considered a rising star. "He had incredible potential," says Abbas, who worked with him in 1997 and 1998 at Brigham and Women's Hospital in Boston. "He was a superstar in the making."

But in August 2004, MIT put Van Parijs on administrative leave after some of his lab colleagues made allegations of misconduct to the institute's authorities. After the lab was closed, his students and postdocs scrambled to get jobs elsewhere, and MIT began the inquiry that culminated in his sacking.

Abbas says that Van Parijs has e-mailed him and denied falsifying data in more than one paper. "He apologized for the disappointment he has caused," Abbas says.

MIT officials say that they will submit the results of their investigation to the Office of Research Integrity, the federal agency that monitors research conduct for the US National Institutes of Health. It has been at least a decade since the institute has uncovered a case of misconduct, the officials say.

MIT has not publicly identified the paper that contains the falsified results. But in May, *Current Opinion in Molecular Therapeutics* published a correction to a 2004 review[3,4] on which Van Parijs was the lead author. The note said that unpublished experiments cited in the paper — involving genetically controlling tumour growth in mice — could not be documented.

Investigators are now probing several of Van Parijs's older publications. Caltech is looking at two articles published in *Immunity*, including one co-authored by Baltimore[5,6]. And Harvard is looking into a 1997 paper in the *Journal of Experimental Medicine*[7].

The *Immunity* work dealt with a cell signalling pathway that governs the processes by which cells in the immune system live and die. An expert in the field, who asked not to be named, said that Van Parijs's experiments had never directly been replicated. "We really would like to know if the work is reproducible, so the field can move forward," the immunologist said, "or whether we have to do an about-face." ■

Rex Dalton
Additional reporting by Erika Check

1. Brumfiel, G. *Nature* **419**, 419–421 (2002).
2. Rubinson, D. A. *et al. Nature Genet.* **33**, 401–406 (2003).
3. Nencioni, A. *et al. Curr. Opin. Mol. Ther.* **6**, 136–140 (2004).
4. *Curr. Opin. Mol. Ther.* **7**, 282 (2005).
5. Van Parijs, L., Peterson, D. A. & Abbas, A. K. *Immunity* **8**, 265–274 (1998).
6. Van Parijs, L. *et al. Immunity* **11**, 281–288 (1999).
7. Van Parijs, L. *et al. J. Exp. Med.* **186**, 1119–1128 (1997).

infects cells in a different way from the one that causes AIDS.

John Moore from Cornell University in New York and his colleagues tried a different approach (see page 99). They combined three compounds that each uses a different mechanism to block the virus's entry into cells. Merck's compound CMPD167 competes with the virus for cell receptors inside the vagina. Bristol-Myers Squibb's BMS-378806 interacts with the virus itself, stopping it binding to cells. And a peptide developed by Moore's team inhibits the process used by the virus to enter a cell.

When the researchers tested combinations of the compounds in macaques, they found that they offered at least partial protection against a virus closely resembling HIV. But three animals that received the three compounds together were all protected against infection. These results were enough to persuade the drug firms to give away rights to the compounds, says Moore. "This is the first time there has been a joint announcement like this," adds Mark Mitchnick, chief scientific officer of the International Partnership for Microbicides, the non-profit group that will develop the gel.

Partners including the Bill and Melinda Gates Foundation and the US National Institutes of Health are helping to fund a clinical trial, set to start in 2007. This is estimated to cost between US$150 million and $200 million and will involve about 10,000 women in Africa. ■

Narelle Towie

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