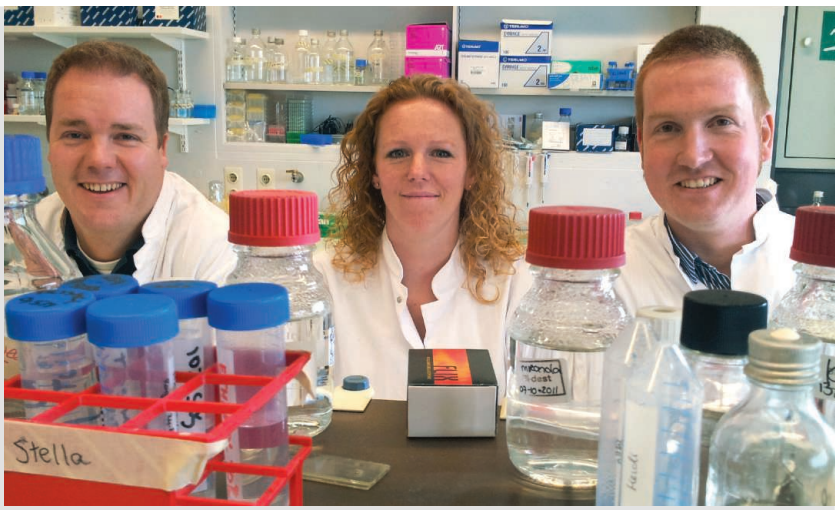
For Young Scientists, A Wild Ride



In the background. Sander Herfst, Eefje Schrauwen, and Martin Linster did the hands-on work in Ron Fouchier's laboratory in the Netherlands.

ROTTERDAM, THE NETHERLANDS—They've become known as the Kawaoka and Fouchier papers. But Yoshihiro Kawaoka and Ron Fouchier rarely set foot in the high-security labs where the experimental work on their two highly controversial H5N1 studies was done. That work—concocting mutant viruses, inoculating ferrets, and testing whether they'd infect others—was carried out by younger researchers who have remained invisible during the past 8 months. Yet for them, the stakes were just as high—higher, perhaps, because a paper in *Science* or *Nature* can be a critical career booster.

Earlier this week, Sander Herfst, a virology postdoc at Erasmus MC here and the first author of Fouchier's paper, published on page 1534 of this issue of *Science*, was getting the champagne ready and announcing a lab party on the bulletin boards. "We're incredibly happy," he says.

While Fouchier gave interviews, traveled to meetings, and lobbied to get his paper published, Herfst stayed in the background, as did Ph.D. students Eefje Schrauwen and Martin Linster, the second and third authors, respectively. Once the National Science Advisory Board for Biosecurity (NSABB) got involved, "it was clear that this was being discussed at a level where we didn't belong," Schrauwen says.

The same was happening at the University of Wisconsin, Madison, where foot soldiers in Kawaoka's lab spent months waiting and worrying whether their paper would ever get published, Masaki Imai, the first author, wrote in an e-mail to *Science*. (*Nature* finally published it last month.) Imai, who is Japanese, obtained a Ph.D. at the University of Hokkaido in Japan, as did the second and third authors, Tokiko Watanabe and Masato Hatta.

In both studies, it was these bench scientists who saw the first signs that they had created new strains of the H5N1 virus that were transmissible from one ferret to another through sneezing and coughing—a finding they realized would be huge news. In Rotterdam, it happened in late June 2011, when a PCR test suggested that a ferret housed in a cage adjacent to an infected one had traces of the H5N1 virus in its airways. "We were very excited," Herfst says. "When we showed it to Ron, he just said: 'Calm down, and do it again. It may be an error.' "

It wasn't. But while he expected to make headlines, Herfst says he never imagined that the paper would get a red light from the NSABB and become the focus of a heated international debate about the limits of academic freedom. Watching the flood of news coverage on TV, "it was strange to think that we had created all of that in our lab," Schrauwen says. "I thought that people would understand how important this kind of work is," Watanabe wrote.

The issue dominated lunch breaks at the lab but began to surface in private conversations, as well. A friend who had read the news stories but didn't know Herfst was involved warned him to watch out "because they are doing some pretty dangerous things at Erasmus." Others asked critical questions: Was this study really necessary? Linster says he could usually convince them. "Debates about animal experiments are more difficult," he says.

Members of both teams, however, worry that the controversy may deter budding scientists from entering the field. "They might be afraid or feel anxious or apprehensive about rejection of papers as a result of biosecurity concerns," Imai wrote. Indeed, a postdoc planning to come to Rotterdam won't work on H5N1, Herfst says. But Hatta thinks it won't be a problem. "Seeking the truth is the job of the scientists. I think nothing affects their motivations," he wrote.

Now that both papers are published, Herfst hopes the moratorium on H5N1 transmissibility studies will be lifted soon (see p. 1496). "We have a long list of interesting things we'd like to do," he says. But Herfst and his colleagues realize that that debate, too, is held well above their pay grade.

–M.E.

that makes first contact with the host cell; scientists already knew that two mutations there can make the virus prefer mammalian cells over bird cells. Another mutation, in the polymerase protein complex, allows the virus to replicate in the cool environment of the human upper respiratory tract rather than in bird intestines, the much warmer environment where it usually resides.

These initial mutations alone didn't do the trick, however, so Fouchier's team decided to try a time-honored method to encourage a pathogen to adapt to a new host: They passed the virus from ferret to ferret by directly inoculating uninfected animals with nasal samples from infected ones and repeated the procedure a total of 10 times. (In his Malta talk, Fouchier called this a "really stupid" approach, a phrase widely interpreted to mean he regretted it. In fact, he says, he just meant that the technique, called passaging, is a simple one compared to the sophistication of creating targeted mutations. The confusion may have stemmed in part from the fact that the Dutch word for "stupid" can also mean "simple.")

The end result was a virus that could move through the air from one caged ferret to another right next to it; in a first experiment, the virus transmitted from cage to cage in three out of four instances.

Prior to publication, media reports suggested that airborne transmission required five mutations. The reality is more complex. Each of Fouchier's transmissible viruses had at least nine mutations, five of which were shared by all. This core quintet may be sufficient, the team writes, but the big question is whether one or more of the other changes also plays an important role, Peiris says.

Fouchier already knows part of the answer. Once his team achieved transmission in the summer of 2011, the researchers began additional experiments to identify the minimum set of mutations needed to make the virus airborne. But before those experiments were finished, they submitted their manuscript to *Science*, worrying that Kawaoka or other scientists might beat them

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