Correspondence

DAS181 and H5N1 Virus Infection

To the Editor—Belser et al. [1] reported that DAS181, a novel sialidase fusion protein, could protect mice from lethal avian influenza H5N1 virus infection. The authors mentioned in their abstract that “when used to treat mice daily beginning 1 day before infection with A/Vietnam/1203/2004(H5N1) virus, DAS181 treatment at 1 mg/kg/day protected 100% of mice from fatal disease” [1, p. 1493]. In table 1 of their article, they showed that 12 (100%) of 12 challenged mice survived after receiving DAS181 treatment at 1 mg/kg/day for 7 days, beginning 1 day before virus challenge [1, p. 1495]. However, as shown in table 2 of the same article [1, p. 1496], 19 (95%) of 20 mice survived under the same conditions [1]. It will be important to determine the percentage of protection offered when the number of mice is increased from 20 to 50 or more. Showing 100% protection in 1 experiment that involved only 12 mice is neither necessary nor sufficient to establish the conclusion that DAS181 treatment at 1 mg/kg/day protects 100% of mice from fatal disease.

In the introduction of their article, Belser et al. state that DAS181 “has reduced replication of H1N1 viruses in mice and ferrets” [1, p. 1494] and cite an article by Malakhov et al. [2]. Actually, this statement is imprecise because the ferret studies used DAS178 instead of DAS181 [2]. Even though their functions are said to be similar, DAS178 and DAS181 are 2 different molecular entities. Consequently, Belser et al. should change “DAS181” to “DAS178” in their statement.

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Reply to Zhang

In his letter to the editor, Dr. Zhang suggests that the study by Belser et al. [1] used an inadequate number of mice to evaluate the antiviral efficacy of DAS181 against lethal influenza A H5N1 virus infection. In fact, the study by Belser et al. [1] used over 30 animals in 2 independent experiments to demonstrate an efficacy of 95%–100% for DAS181 in the prevention of lethal H5N1 disease when administered at a dose of 1 mg/kg/day in starting 1 day prior to infection. Previous publications evaluating the efficacy of antiviral treatments against influenza viruses consistently used 8–12 mice per group to assess protection from fatal disease, placing our study within, and even above, accepted standards [2–6]. Scientists who perform animal research have an ethical obligation to use the minimum number of animals needed to achieve valid, reproducible, and statistically rigorous results. We believe we have used a sufficient number of mice in this preclinical evaluation to convincingly demonstrate the powerful antiviral effect of DAS181 against an H5N1 virus with pandemic potential.

A second criticism from Dr. Zhang focuses on a citation of the study by Malakhov et al. [7], which indicated that DAS181 “reduced replication of H1N1 viruses in mice and ferrets” [1, p. 1494]. Dr. Zhang is correct in pointing out that DAS178, a precursor of DAS181, was used in the ferret experiments detailed in the Malakhov et al. [7] article. However, as also described in the article, DAS178 and DAS181 possess identical sialidase catalytic domains and have indistinguishable activities in cell-based assays [7]. Taken together, the preclinical studies of Malakhov et al. [7] and Belser et al. [1] clearly demonstrate the potential of this novel class of broad-spectrum influenza antiviral drugs to meet an urgent public health need. The next step in determining the safety and efficacy of this drug for humans is not further efficacy testing in animals, but rather the evaluation of DAS181 in humans. The first Phase 1 clinical trial of DAS181 is nearing completion and results are anxiously awaited. Such studies are of increasing importance, given the recent emergence and spread of oseltamivir-resistant influenza A (H1N1) viruses [8].

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Potential conflicts of interest: D.F.W., M.Y., and F.F. declare that they have competing financial interests. NexBio holds the rights to the potential product, DAS181; M.Y. and F.F. own the founder shares of common stock of NexBio; and D.F.W. owns the options of NexBio’s common stock. J.M.K. received funding from NexBio to cover the costs of this research. J.A.B. and X.L. declare that they have no relevant conflicts of interest.

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