Favipiravir (T-705, commercial name Avigan), a drug developed to treat influenza virus infection, has been used in some countries as an oral treatment for COVID-19; however, its clinical efficacy in this context is controversial. The anti-SARS-CoV-2 effects of favipiravir reported by previous studies are inconsistent. For example, the findings of Jeon et al. reported in this journal (1) and others (2) demonstrate that favipiravir (500 μM) shows negligible effects against SARS-CoV-2 in cultured cells, whereas two other studies reported weak effects, with a 50% effective concentration (EC$_{50}$) ranging from 61.88 to 207.1 μM (3, 4). These discrepancies may result from differences in the assay protocol used.

Here, we compared the effects of favipiravir on replication of SARS-CoV-2 and influenza virus in VeroE6 cells by quantifying the amount of propagated virus in medium via a plaque assay (5). Favipiravir blocked propagation of influenza virus in a concentration-dependent manner; however, it actually enhanced that of SARS-CoV-2 (Fig. 1A). Favipiravir significantly enhanced viral RNA replication in culture medium of VeroE6 cells infected with SARS-CoV-2, SARS-CoV-1, or MERS-CoV (Fig. 1B). Furthermore, favipiravir at 20 to 500 μM slightly, but significantly, enhanced RNA replication of SARS-CoV-2 in differentiated primary human bronchial tracheal epithelial cells cultured at an air-liquid interface (HBTE/ALI cells) (Fig. 1C). Favipiravir can be converted into favipiravir-ribofuranosyl-5'-triphosphate in cells and may influence cellular nucleoside/nucleotide metabolism, which may affect viral replication.

A recent study using hamsters revealed that the effective dose of favipiravir required to suppress replication of SARS-CoV-2 is 1.0 g/kg body weight, administered by intraperitoneal (i.p.) injection (6). Data from another group suggest that hamsters lost 20% of their body weight after i.p. injection of favipiravir at a dose of about 1.0 g/kg body weight (7). Such a high dose may not be practical for use in humans; however, high plasma trough concentrations of favipiravir were reported in clinical trials in Ebola-infected patients. In that study, favipiravir was given orally at a dose of 6 g or 2.4 g/day, after which the median observed trough concentration in blood plasma was 46.1 μg/ml (293 μM) (8). Nevertheless, we found that this concentration was totally ineffective; rather, it was counterproductive, as mentioned above. Recently, the manufacturer reported the results of its own clinical trials showing that symptoms of COVID-19 in a favipiravir-treated group improved after 11.9 days compared with 14.7 days in a placebo-treated group (9). So far, we are unable to provide a scientific rationale for the improved clinical symptoms after treatment with favipiravir.

Regardless of the data presented above, we feel compelled to raise awareness about administration of favipiravir to pregnant women; this is contraindicated due to the known teratogenic side effects of the drug (10).

The pressures brought to bear on societies by the COVID-19 pandemic mean that we may make poor judgments in the hope of identifying a "wonder" drug. Thus, we implore that drug approval is always handled in a manner based on scientific evidence.
statistical significance compared with the DMSO control: *, very highly significant (***) (P < 0.001). Two-tailed Student’s t tests were used to analyze statistical significance compared with the DMSO control: *, significant (P < 0.05); **, highly significant (P < 0.01); and ***, very highly significant (P < 0.001).

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