

**Response to the recent publication of the effect of the experimental drug,
SPC3649, on Hepatitis C Virus (HCV) infection in Chimpanzees.**

The Humane Society of the United States

On December 3rd, Science Express published an article "Therapeutic silencing of miR-122 in primates with chronic Hepatitis C virus (HCV) infection" (referred to below as "the Article") that describes testing of a new HCV therapy, specifically the drug SPC3649, in chimpanzees. A few weeks earlier, a comprehensive review "[*Chimpanzees in hepatitis C virus research: 1998-2007*](#)" (Journal of Medical Primatology) was published (referred to below as "the Review.") This review argued that there are major scientific problems associated with the application of data from HCV research in chimpanzees to humans. The analysis below examines the claims made in the Article. Many of the shortcomings of the claims in the Article are reflected in the conclusions in the Review.

The following points are pertinent to our analysis of the claims in the Article.

- In vitro experiments as well as clinical trials of SPC3649 in humans were completed or in progress before the chimpanzee study began, making it unclear why the chimpanzee study was conducted at all.
- Chimpanzee liver pathology is significantly different from that of humans suffering from chronic hepatitis C. Consequently, this chimpanzee study does not lend itself to determining possible short- or long-term side effects of treatment with the drug, including effects on human liver carcinomas resulting from Hepatitis C infection.
- The Article reports that a temporary reduction of viremia was observed overall. However, the study results do not support the claim that this might be the predicted clinical response to this drug. Indeed, since only four chimpanzees were used (sample sizes in chimpanzee research projects are usually very small due to prohibitively high costs), it would be difficult to see how any statistically valid predictions could be made. In many measured categories, there are non-

trivial differences between the two chimpanzees in the same dose groups (the two who should “agree”), as well as between the chimpanzees in the high and low dose groups.

- While a key “finding” was reported as the “long-lasting suppression” of the hepatitis C virus, the amount of virus began to rise after the treatment ended and had reached pre-treatment levels in 3 out of the 4 chimpanzees by the end of the study. The treatment lasted only less than three months, and did not provide sufficient data to make conclusions about long-term suppression, with or without continued administration of the drug.
- The Article claims that improved liver biopsy histology was observed in both of the chimpanzees in the high-dose group. The Article shows, in Fig.3 (D-G), improvement in one set of biopsy samples. However, on-line supplemental data shows the samples for the other high-dose chimpanzee, and any substantial improvement in this set is debatable. The liver samples of the two chimpanzees in the low-dose group are not shown at all. In other words, only one in four biopsy sets shows substantial temporary improvement.
- Since chimps do not develop active chronic HCV infection as humans do, testing the drug on them is not predictive of how it would work on chronic HCV human patients. This is particularly relevant as the definitive cause of the damage in human chronic HCV is not fully understood, and relevant confounding variables in the chimpanzee study cannot be controlled or discounted.
- The Article claims that repression of miR-122 (a micro-RNA specific to the liver and the target molecule of SPC3649) led to a concurrent decreased activity of interferon responsive genes (IRG), and that this decreased activity is directly associated with low levels of viremia, and accounts for improved liver histology. Specifically, it noted that serum chemokine IP-10 is a good biomarker of the level of the expression of these genes. However, one of the two chimpanzees in each group (high- and low-dose) had IP-10 levels that did not consistently correspond to the level of viremia (see Fig. 2.C). As a result, the statement

that “the treatment with [the tested drug] results in normalization of IRG levels” is not clearly supported by the published data.

- The properties and functions of miR-122 are not fully understood. We do know that it is implicated in cholesterol regulation and lipid metabolism, and has been associated with resistance to liver cancer. Because chimpanzees are generally resistant to liver cancer, miR-122 studies in chimpanzees do not seem appropriate to clarify whether repression of miR-122 might lead to increased incidences of liver cancer.
- The Article also compares cholesterol effects between the previous African green monkey study and this chimpanzee study, and concludes: “...it is possible that the cholesterol lowering effect of miR-122 antagonism is different in chimpanzees and may better reflect the expected response in man.” There is no supporting data for this statement.