

Project R&R's Complete Response to Hepatitis C Drug

Scientists at the Southwest Foundation for Biomedical Research (SFBR) recently reported that a new drug developed by Santaris Pharma, SPC3649, is effective against hepatitis C in chimpanzees (1). By interacting with a molecule in the liver called miRNA-122 that is involved in the replication of the hepatitis C virus (HCV), the drug caused a substantial decrease in the level of virus present in the blood of the infected chimpanzees. Further, the drug exhibited a significant barrier to resistance, which viruses often develop against antiviral therapies.

The scientists hope – as does **Project R&R** - that their results will be mirrored in humans, thus providing the first effective and specific new drug for the treatment of hepatitis C. Such a new drug is urgently needed, due to the only existing therapy being highly toxic and efficacious in only 50% of patients. However, we strongly question why this chimpanzee study was at all necessary.

The role of the target molecule of the drug – miRNA-122 – in HCV replication was described in 2005, via elegant tissue culture experiments involving human liver cells (2). Subsequent experiments in 2006 also demonstrated the therapeutic potential of agents very similar to SPC3649 in decreasing the level of HCV infection (3). Further, the drug is already being tested in human clinical trials, which began as long ago as May 2008: single-dose Phase I trials were completed this year (2009) with results imminent (4), and another multi-dose Phase I human trial is in progress, due to finish next summer (2010) (5). Further still, testing of SPC3649 has already complied with regulatory toxicology requirements, having been tested in African green monkeys (6) as well as mice (7).

Even putting to one side the tests on monkeys and mice, we believe the *in vitro* data and the fact that the drug is already in human trials is sufficient evidence against any proffered justification of these recently conducted chimpanzee experiments. The chimpanzee experiments must be redundant: if the human trials show the drug is safe, it *will* progress to efficacy trials - and would have done whether or not the chimpanzee tests had been successful. If the clinical trials show the drug has serious human side effects, its development will not progress - and would not have done so regardless of the results from the chimpanzee experiments. The monkey and mice data, in addition, should give even any advocate of animal testing sufficient cause for concern that the chimpanzee research was still pursued.

Given what we already know about the significant biological differences between humans and chimpanzees regarding the course

of HCV infection, as well as the lack of human relevance and predictive nature chimpanzee data provides (for example, in HIV/AIDS vaccine research), there can be no rational defence of this unnecessary use of chimpanzees in such invasive experiments. This will be illustrated in early 2010 when **Project R&R's** next scientific paper is published. This latest investigation has analyzed the use of chimpanzees in hepatitis C research past and present, and demonstrates that future chimpanzee use is redundant and unnecessary given the comprehensive human-specific research approaches at our disposal.

References

1. Southwest Foundation for Biomedical Research. (2009). New drug technology produces marked improvement in hepatitis c therapy in animals; may be useful for a wide range of diseases. Available at: <http://www.sfbr.org/News/detail.aspx?id=167>
2. Jopling, C.L., Yi, M., Lancaster, A.M., Lemon, S.M., Sarnow, P. (2005). Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* **309**, 1577-1581.
3. Jopling, C.L., Norman, K.L., Sarnow, P. (2006). Positive and negative modulation of viral and cellular mRNAs by liver-specific microRNA miR-122. *Cold Spring Harb Symp Quant Biol* **71**, 369-376.
4. ClinicalTrials.gov. Safety Study of SPC3649 in Healthy Men. Available at: <http://clinicaltrials.gov/ct2/show/NCT00688012?term=SPC3649&rank=2> (Accessed 7-12-2009).
5. ClinicalTrials.gov. SPC3649 Multiple Dose Study in Healthy Volunteers. Available at: <http://clinicaltrials.gov/ct2/show/NCT00979927?term=SPC3649&rank=1> (Accessed 7-12-2009).
6. Elmen, J., Lindow, M., Schutz, S., Lawrence, M., Petri, A., Obad, S., Lindholm, M., Hedtjarn, M., Hansen, H.F., Berger, U., Gullans, S., Kearney, P., Sarnow, P., Straarup, E.M., Kauppinen, S. (2008). LNA-mediated microRNA silencing in non-human primates. *Nature* **452**, 896-899.
7. Elmen, J., Lindow, M., Silaharoglu, A., Bak, M., Christensen, M., Lind-Thomsen, A., Hedtjarn, M., Hansen, J.B., Hansen, H.F., Straarup, E.M., McCullagh, K., Kearney, P., Kauppinen, S. (2008). Antagonism of microRNA-122 in mice by systemically administered LNA-antimiR leads to up-regulation of a large set of predicted target mRNAs in the liver. *Nucleic Acids Res* **36**, 1153-1162.