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An RNA Replicon System to investigate promising Inhibitors of Feline Infectious Peritonitis Coronavirus

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Question: Feline Infectious Peritonitis (FIP) is a fatal feline disease, caused by a Feline Coronavirus (FCoV), namely Feline Infectious Peritonitis Virus (FIPV). It is of great significance in the cat population around the world, causing 0.3 % to 1.4 % of feline deaths (Thayer et al. 2022). As there are neither effective preventive measures nor approved treatment options available, there is a huge need in identifying antiviral drugs against FIPV. In this context, we posed the question, if a FCoV replicon system could be used as a valuable tool for drug discovery *in vitro*; in the hopes of finding potential compounds for future clinical use to save cats suffering from FIP.

Material and Methods: Due to the lack of cell culture systems for Serotype I FCoVs (which is the Serotype most prevalent in the feline population; Thayer et al. 2022), a different system is needed to study these viruses. A viral replicon system, as first described for Hepatitis C research (Lohmann et al. 1999), is a valuable tool to study FCoVs. We show a green fluorescent protein (GFP) expressing Serotype I FCoV replicon RNA stably expressed in baby hamster kidney cells and used it as an *in vitro* screening system to test different antiviral compounds. We also infected felis catus whole fetus 4 (FCWF-4) cells with the FIPV Black strain expressing GFP and treated these cells with the most promising compounds. To measure the inhibitory effect, we quantified the GFP signal via flow cytometry for both systems and defined infectious titers for the FIPV infected FCWF-4 cells.

Results and Discussion: We exposed the FCoV replicon to Remdesivir, GC376, Nirmatrelvir and Amodiaquine. As expected, the polymerase inhibitor Remdesivir and protease inhibitors GC376 and Nirmatrelvir showed a high inhibitory effect. Contrary to prior studies, Amodiaquine did not increase the inhibitory effect of GC3763 (Delaplace et al. 2021) nor Nirmatrelvir when combined. To avoid antiviral resistance development, combination therapy might be the best long-term therapeutic plan. Therefore, we tested and found different effective combinations: combining Remdesivir with either GC376 or Nirmatrelvir increased the individual inhibitory effect. For all tested compounds showing inhibition, cytotoxic concentrations were all well above the inhibitory concentrations, and therefore show great potential for future *in vivo* use. Independent of the used system or read-out method the inhibition curves overlapped very well.

Conclusion and Clinical Relevance: Overall, these results demonstrate the utility of the serotype I feline coronavirus replicon system for antiviral screening as well as to study this virus in general. Also, we suggest that several compounds represent promising candidates for future clinical use to treat and finally save cats suffering from FIP.

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