Antiviral evaluation of compounds against SARS-CoV-2

Molecule tested: mirtazapine

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Introduction

In response to the recent emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the Unité des Virus Émergents performed preclinical evaluation of drug candidates against SARS-COV-2. **This interim report has not been peer-reviewed.** The data of this report are available upon request.

The molecule tested here is the mirtazapine, a synthetic tetracyclic derivate of the pipazino-azepines with antidepressant activity.

In vitro evaluation of efficacy of mirtazapine

Mirtazapine was identified as a potential hit by an antiviral screen based on the SARS-CoV-2 cytopathic effect inhibition (Touret et al., 2020).

In vivo evaluation of efficacy of mirtazapine

Experiments were approved by the local ethical committee (C2EA—14) and French authorities (APAFIS#23975). Four-week-old female Syrian hamsters were intranasally infected with 10^4 TCID50 of the BavPat1 SARS-CoV2 strain as described previously (Driouich et al., 2020). To assess the efficacy of mirtazapine, a group of 6 hamsters received the drug, orally, two times a day (BID). We used one dose of 4 mg/day (around 75 mg/kg/day). Treatment was initiated at day of infection, ended at 2 day post infection (dpi) and animals were sacrificed at 3 dpi. A control group of 6 infected/untreated animals received, orally, 0.9% Sodium Chloride solution. Viral replication was measured in lungs (infectious titres and viral RNA yields) and in plasma (viral RNA yields).

Results showed no significant reduction of viral replication in lungs and plasma compared to control group (**Figure 1**).

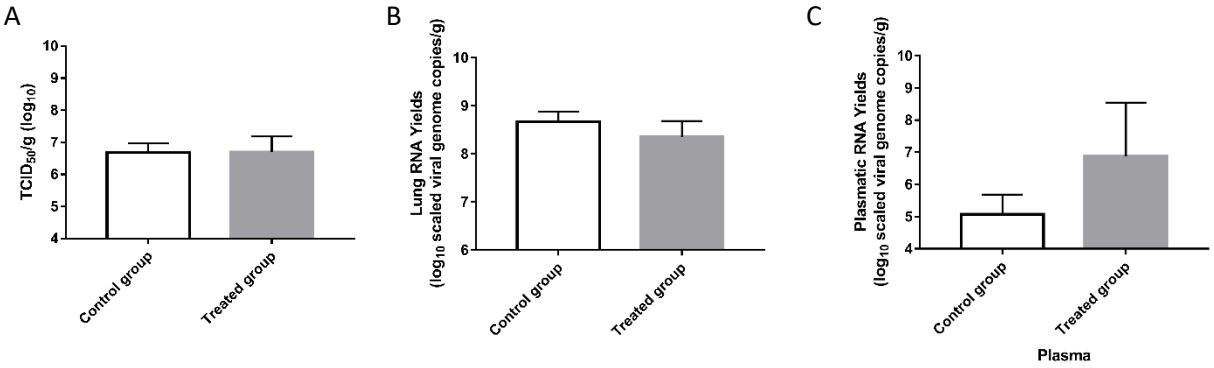

Figure 1: Viral replication in lungs (A-B) and in plasma (C). Lung infectious titers were measured using a $TCID_{50}$ assay and viral RNA yields were using an RT-qPCR assay as previously described (Driouich et al., 2020).

Conclusion

Mirtazapine was found as a primary hit in our screen. However, results obtained using a hamster model suggest that this molecule is a poor inhibitor of SARS-CoV-2 replication *in vivo.*

References

DRIOUICH, J.-S., COCHIN, M., LINGAS, G., MOUREAU, G., TOURET, F., PETIT, P. R., PIORKOWSKI, G., BARTHÉLÉMY, K., COUTARD, B., GUEDJ, J., DE LAMBALLERIE, X., SOLAS, C. & NOUGAIRÈDE, A. 2020. Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model. *bioRxiv***,** 2020.07.07.191775.

TOURET, F., BARONTI, C., GOETHALS, O., VAN LOOCK, M., DE LAMBALLERIE, X. & QUERAT, G. 2019. Phylogenetically based establishment of a dengue virus panel, representing all available genotypes, as a tool in dengue drug discovery. *Antiviral Res,* 168**,** 109-113.

TOURET, F., GILLES, M., BARRAL, K., NOUGAIREDE, A., VAN HELDEN, J., DECROLY, E., DE LAMBALLERIE, X. & COUTARD, B. 2020. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. *Sci Rep,* 10**,** 13093.