Characterization of a novel potentiator series for treating Cystic Fibrosis

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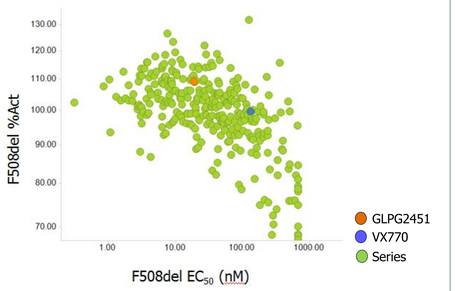
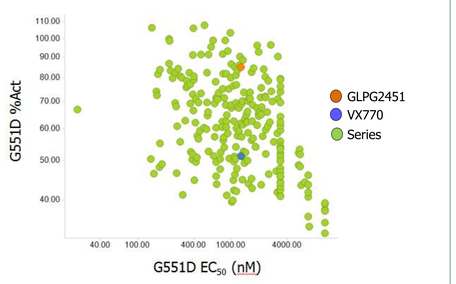
Here, we report the identification and characterization of a novel series of potentiators and the combination of these with corrector(s).

Identification of a novel potentiator series using YFP-Halide assay

LT corrected F508del CFTR



G551D CFTR



Medicinal Chemistry efforts on the series resulted in improved potentiator potency of the compounds on F508del and G551D CFTR.

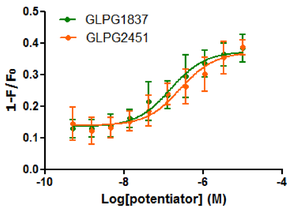
Improving potency in the F508del YFP assay was matched by improvement in the ADME and PK profiles, with good exposure *in vivo* for several compounds within the series.

From this effort, **GLPG2451** was identified and represents a potentiator from a new series distinct from GLPG1837[1].

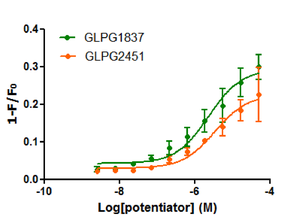
Translation of YFP-Halide activity into Primary Bronchial Epithelial cells derived from patients with ClassIII/ IV CFTR mutations

YFP Halide assay – HEK293

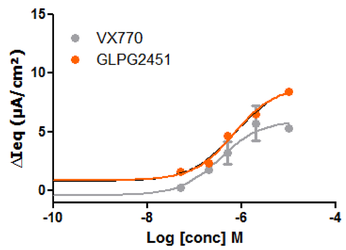
S1251N CFTR



G551D CFTR

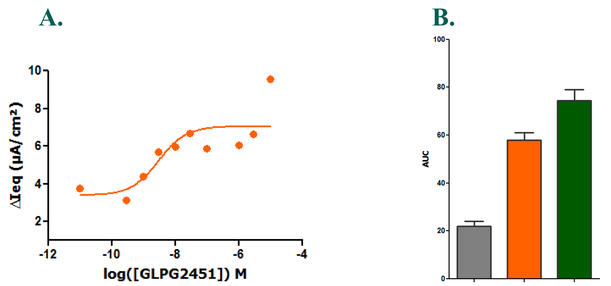


G551D/ F508del HBE



G551D /F508del HBE grown for 21 days in ALI culture, CFTR was activated with forskolin and a dose response of GLPG2451 or VX770. Measurements were done using TECC.

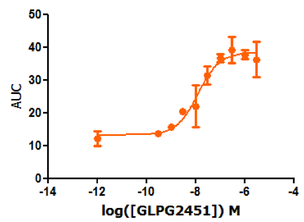
R334W/ F508del HBE



R334W /F508del HBE grown for 21 days in ALI culture, A. CFTR was activated with forskolin and a dose response of GLPG2451. B. Cells were incubated for 24 hours with DMSO (Grey), GLPG2451 (Orange) or GLPG2451 + GLPG2222 (Green). CFTR was activated with forskolin. Measurements were done using TECC.

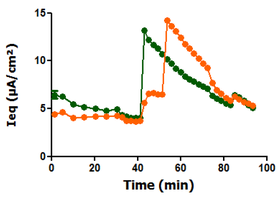
F508del/ F508del Primary Bronchial Epithelial cells

Dose response GLPG2451 on GLPG2222 corrected cells



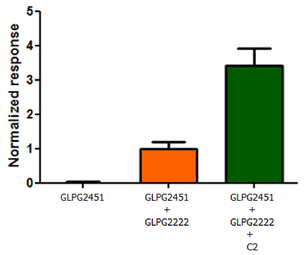
F508del /F508del HBE grown for 21 days in ALI culture, treated with GLPG2222 for 24 hours, CFTR was activated with forskolin and a Dose response of GLPG2451.

Chronic and acute GLPG2451 treatment



Cells were treated with GLPG2222 for 24 hours, and CFTR was activated with forskolin followed by GLPG2451 (Orange)
Cells were treated with GLPG2222 + GLPG2451 for 24 hours and CFTR was activated with forskolin (Green)

Dual and triple combination with GLPG2451



Cells were treated with GLPG2222 + GLPG2451 (Orange) or GLPG2222+GLPG2451 + C2 corrector (Green) for 24 hours. CFTR was activated with forskolin

GLPG2451 exhibits a dose-dependent activity on HBE cells derived from patients harboring CFTR mutations belonging to Class II, III or IV as measured in TECC.

Conclusions

In summary, we describe the identification of a second generation potentiator series with very good channel opening activity. From this series, GLPG2451 was identified and is currently in Phase 1.

Reference

1. Conrath K., *et al.*,(2013) Novel potentiators for treating Cystic Fibrosis NACFC

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