Preclinical Development of Dual Host Targeting Small Molecule Inhibitors as Broad-Spectrum Antivirals

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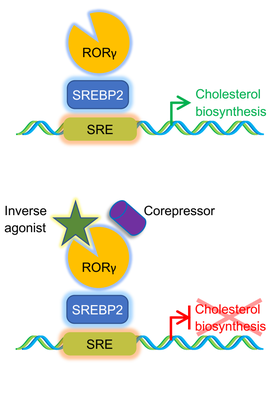
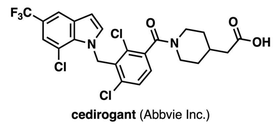
Background

Target 1: RORγ

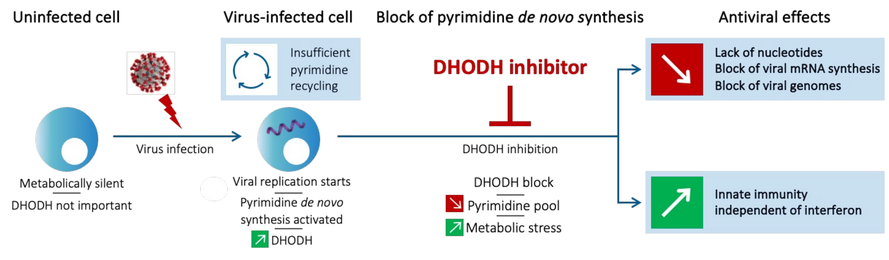


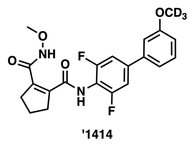
- Inverse agonists of retinoic acid-related orphan receptor gamma (RORγ) (e.g. cedirogant) inhibit different viruses *in vitro*[1]
- RORγ1 is the responsible isoform for the antiviral effect *in vitro*[1]
- RORγ2/t is only expressed in several immune cells, but modulation might be advantageous *in vivo*
- Antiviral effect depends (at least partially) on the depletion of cellular cholesterol[1]



cedirogant (Abbvie Inc.)

Target 2: DHODH

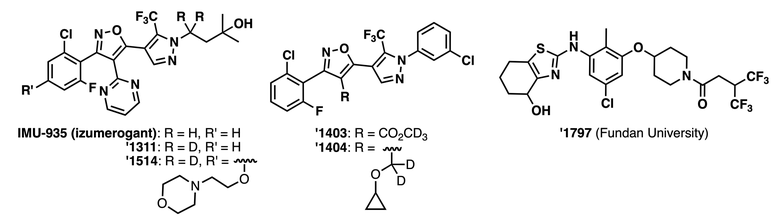




'1414

- Inhibitors of dihydroorotate dehydrogenase (DHODH) block the replication of distinct viruses *in vitro* and *in vivo*[2,3]
- DHODH inhibitors might prevent overshooting immune responses and cytokine storms in response to viral infections

Objectives



IMU-935 (izumerogant): R = H, R' = H
'1311: R = D, R' = H
'1514: R = D, R' =
'1403: R = CO_2CD_3
'1404: R =
'1797 (Fundan University)

- Izumerogant (IMU-935, 0732) has already demonstrated clinical safety and tolerability in phase 1 trials[4]
- Izumergant potently inhibits the host targets RORγ and DHODH simultaneously

➢ **Investigation of the antiviral activity of RORγ/DHODH dual inhibitors in cell culture and an animal model**

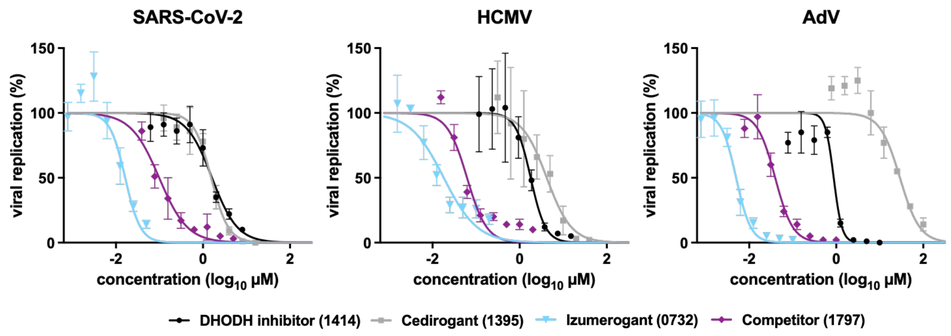
Results

Single target activity of RORγ/DHODH inhibitors

Compound	IC_{50} DHODH (µM)	IC_{50} RORγ (µM)
DHODH inhibitor (1414)	0.15	n.a.
Cedirogant (1395)	>100	0.03
Izumerogant (0732)	0.04	0.06
deut. Izumerogant (1311)	0.04	0.02
1514	2.08	0.27
1404	0.13	0.01
Competitor (1797)	0.51	0.04

➢ **Izumerogant (0732) and its deuterated analog 1311 display the most potent inhibition considering both targets**

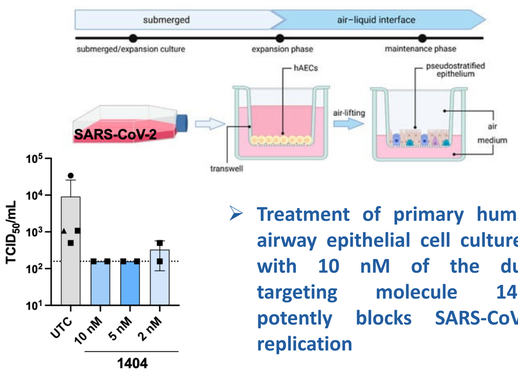
Antiviral effect of dual host targeting molecules



Virus	Compound	EC_{50} (µM)	CC_{50} (µM)	SI
SARS-CoV-2 (enveloped RNA virus)	1414	1.6 ± 0.6	>100	>63
	1395	2.4 ± 0.4	35 ± 3	14
	0732	0.017 ± 0.006	24 ± 8	1400
	1797	0.90 ± 0.021	31 ± 6	344
HCMV (enveloped DNA virus)	1414	3.0 ± 0.8	>100	>33
	1395	4.0 ± 0.5	40 ± 5	10
	0732	0.015 ± 0.006	93 ± 3	6623
	1797	0.16 ± 0.09	79 ± 22	479
AdV (non-enveloped DNA virus)	1414	2.1 ± 0.3	>100	>86
	1395	26 ± 13	24 ± 2	1
	0732	0.0035 ± 0.0021	>100	>28571
	1797	0.030 ± 0.014	39 ± 3	1300

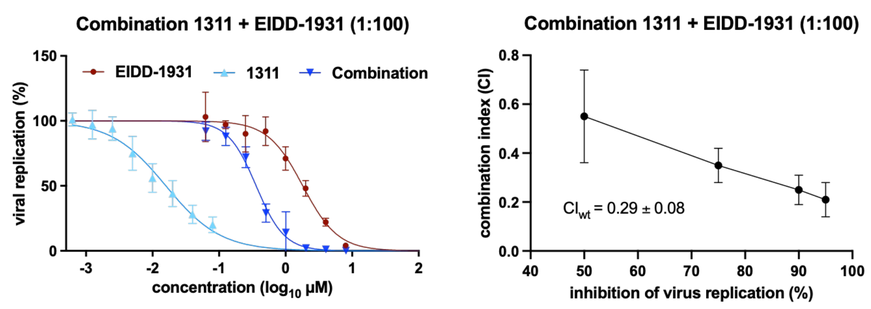
➢ **Izumerogant (0732) potently restricts replication of enveloped DNA and RNA as well as non-enveloped viruses**

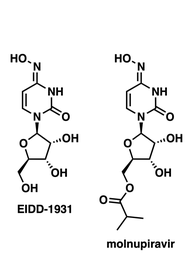
Antiviral effect on SARS-CoV-2 in hAECs

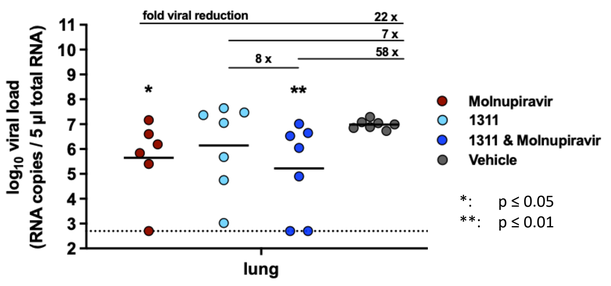


➢ **Treatment of primary human airway epithelial cell cultures[6] with 10 nM of the dual targeting molecule 1404 potently blocks SARS-CoV-2 replication**

Drug interaction of dual host targeting molecules with nucleoside analogs *in vitro* and *in vivo*



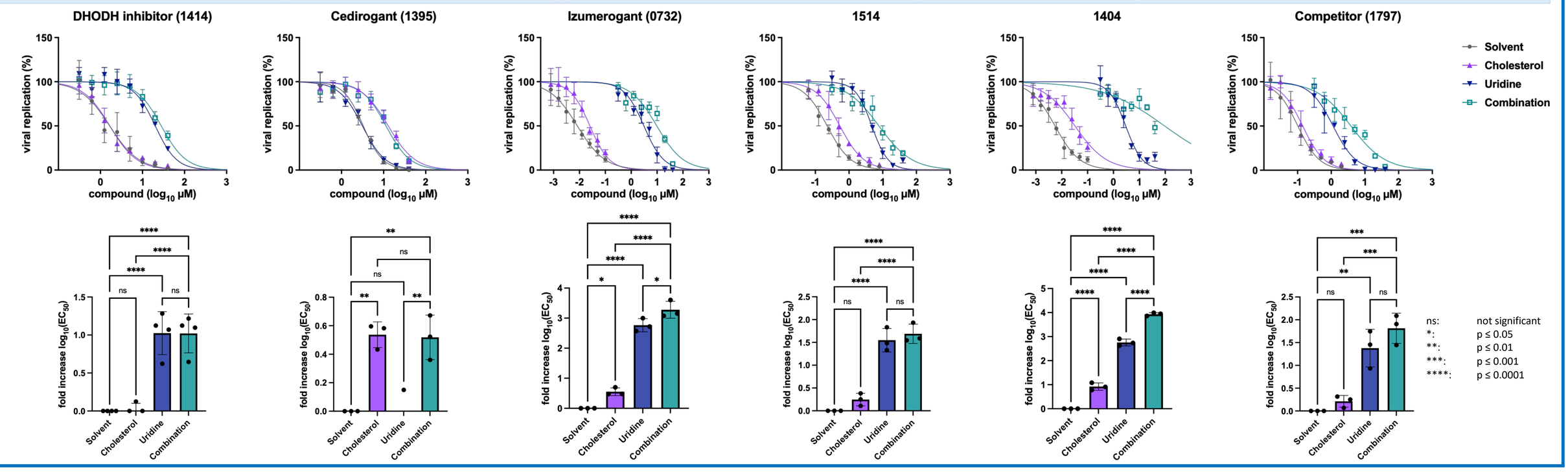




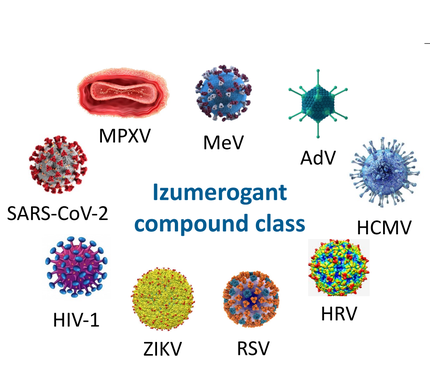
➢ **Combination of deuterated izumerogant (1311) with the active metabolite of molnupiravir (EIDD-1931) revealed strongly synergistic to synergistic effects against SARS-CoV-2 *in vitro***

➢ **Deuterated izumerogant reduces SARS-CoV-2 viral load in lungs of hACE2-transgenic mice**
➢ **Combination treatment with molnupiravir enhances the antiviral activity of deuterated izumerogant *in vivo***

Impact of uridine and cholesterol supplementation on the antiviral effect of RORγ/DHODH dual inhibitors against SARS-CoV-2



Summary and conclusions



	Izumerogant (0732)	1311	1403	1404	1514	Competitor (1797)
SARS-CoV-2	17.0 nM	15.0 nM	12.0 nM	13.0 nM	356.0 nM	90.2 nM
CoV 229E	-	-	5.3 nM	6.5 nM	-	22.1 nM
CoV OC43	-	-	7.8 nM	7.5 nM	-	67.6 nM
IAV	75.0 nM	-	29.0 nM	110.0 nM	-	1200.0 nM
RSV	-	-	7.3 nM	3.3 nM	-	75.0 nM
HRV-14	-	-	-	1.0 nM	-	-
AdV	3.5 nM	-	5.8 nM	6.2 nM	-	30.0 nM
MeV	-	-	3.3 nM	7.5 nM	-	67.0 nM
ZIKV	-	-	42.8 nM	17.9 nM	-	35.0 nM
HIV-1	-	-	1.4 nM	1.2 nM	-	10.8 nM
HCMV	13.0 nM	-	-	12.0 nM	360.0 nM	11.0 nM
MPXV	-	1.8 nM	2.3 nM	3.2 nM	-	2.5 nM

- **Dual-targeting compounds that simultaneously modulate DHODH and RORγ exhibit potent broad-spectrum antiviral activity *in vitro***
- **Combination treatment with nucleoside analogs further enhances the antiviral activity *in vitro* and *in vivo***
- **Supplementation experiments with uridine (DHODH) and cholesterol (RORγ) confirm both host targets are required for the antiviral activity**

➢ **Due to the broad-spectrum antiviral activity, the izumerogant compound class represents a promising treatment strategy for seasonal infections and pandemic outbreaks**

References:
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