Novel vidofludimus-based DHODH inhibitors containing carboxylic acid bioisosters with superior broad-spectrum antiviral activity

Dr. Alexandra Herrmann

NASDAQ: IMUX | Mar/07/2025 | Hamburg

Cautionary Note Regarding Forward-Looking Statements

This presentation contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These include statements regarding management's intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Immunic undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as "anticipates," "believes," "plans," "expects," "projects," "future," "intends," "may," "will," "should," "could," "estimates," "predicts," "potential," "continue," "guidance," and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995.

Such forward-looking statements are based on our expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including, but not limited to, risks relating to strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management. Risks and uncertainties that may cause actual results to differ materially from those expressed or implied in any forward-looking statement include, but are not limited to: Immunic's development programs and the targeted diseases; the potential for Immunic's development programs to safely and effectively target and treat the diseases mentioned herein; preclinical and clinical data for Immunic's development programs; the impact of future preclinical and clinical data on Immunic's product candidates; the timing of the availability of data from Immunic's clinical trials; the availability or efficacy of Immunic's potential treatment options that may be supported by trial data discussed herein; the timing of current and future clinical trials and anticipated clinical milestones; Immunic's ability to protect its intellectual property position; Immunic's plans to research, develop and commercialize its current and future product candidates; the timing of any planned investigational new drug application or new drug application; the development and commercial potential of any product candidates of the company; expectations regarding potential market size; developments and projections relating to Immunic's competitors and industry; the clinical utility, potential benefits and market acceptance of Immunic's product candidates; Immunic's commercialization, marketing and manufacturing capabilities and strategy; Immunic's ability to successfully collaborate with existing collaborators or enter into new collaboration agreements, and to fulfill its obligations under any such collaboration agreements; Immunic's ability to identify additional products or product candidates with significant commercial potential; the impact of government laws and regulations; the COVID-19 pandemic; impacts of the conflicts in Ukraine – Russia and the Middle East; Immunic's listing on The Nasdaq Global Select Market; expectations regarding the capitalization, resources and ownership structure of the company; the executive and board structure of the company; Immunic's estimates regarding future revenue, expenses, capital requirements and need for additional financing, including the ability to satisfy the minimum average price and trading volume conditions required to receive funding in tranche 2 and 3 of the January 2024 private placement; the nature, strategy and focus of the company and further updates with respect thereto; and the other risks set forth in the company's Annual Report on Form 10-K for the fiscal year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission.

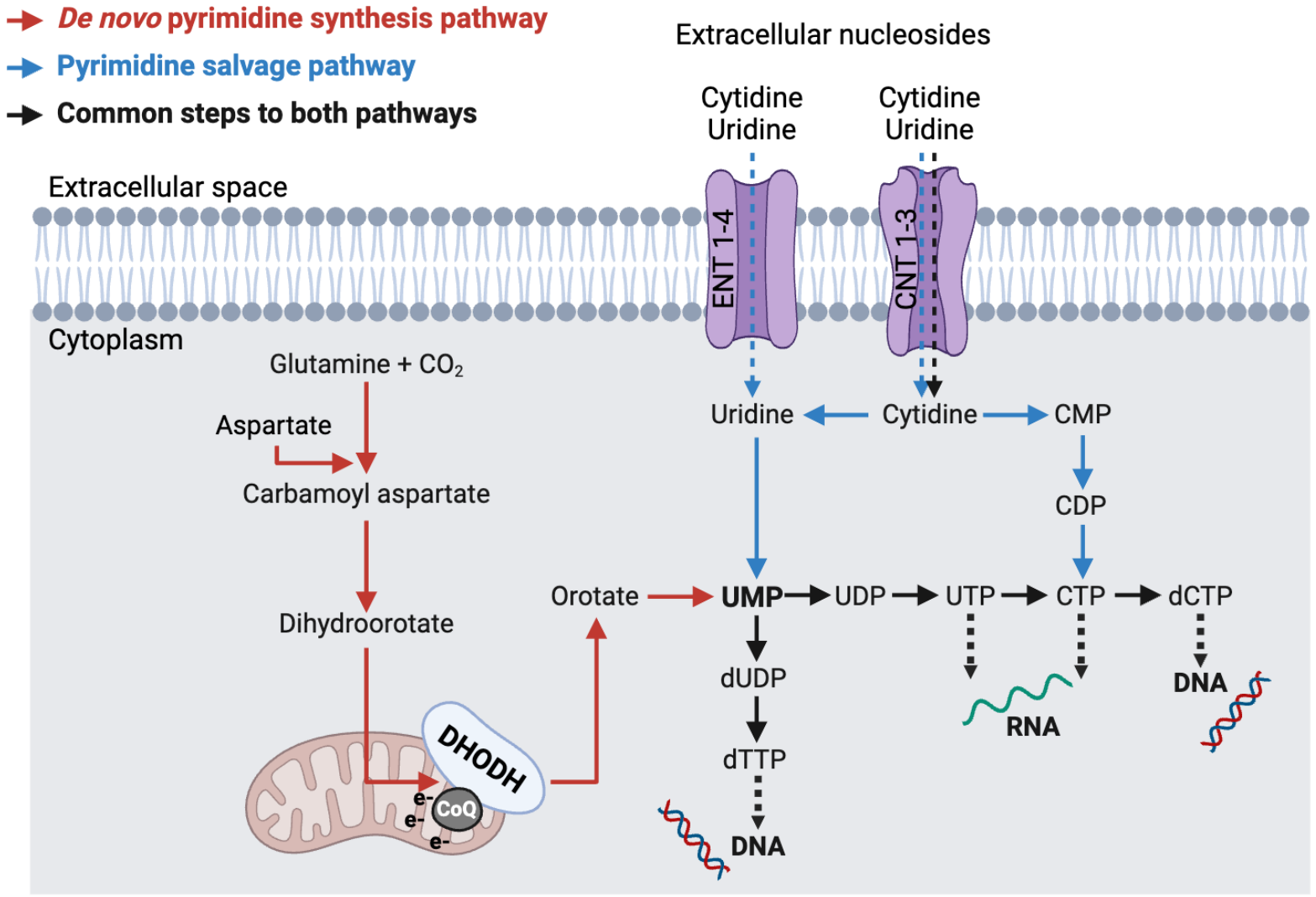
Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.

Immunic THERAPEUTICS

Disclosures

Dr. Alexandra Herrmann is an employee of Immunic AG, Gräfelfing, Germany, and owns stock options of the parent company Immunic Inc.

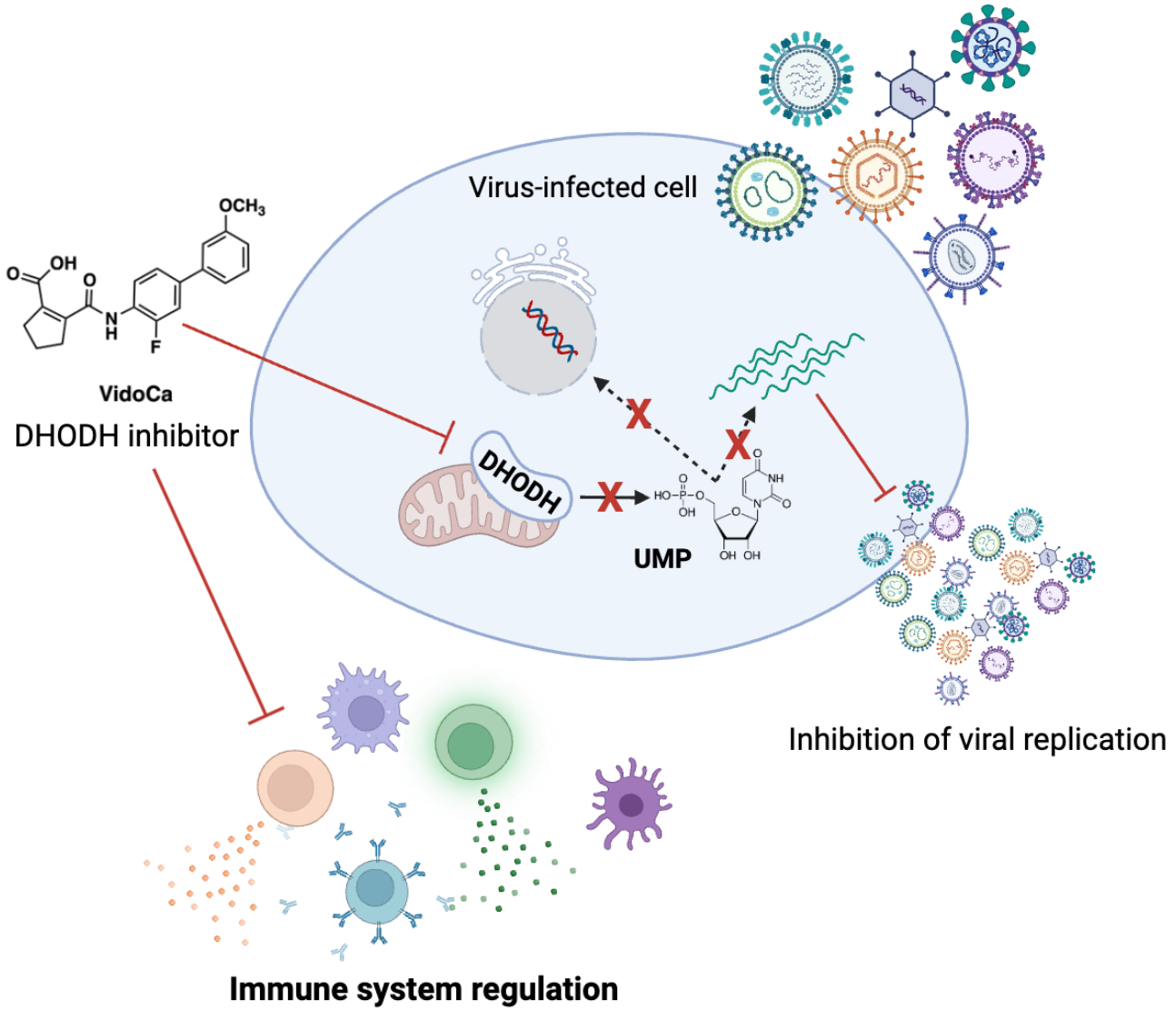
Dihydroorotate dehydrogenase (DHODH)



- DHODH catalyzes the rate-limiting step of the *de novo* pyrimidine synthesis
- UMP: central precursor for DNA and RNA
- *De novo* synthesis pathway required in highly metabolically active cells

Adapted and modified from Luganini et al., 2025; created with BioRender.com

The antiviral mechanism of DHODH inhibitors

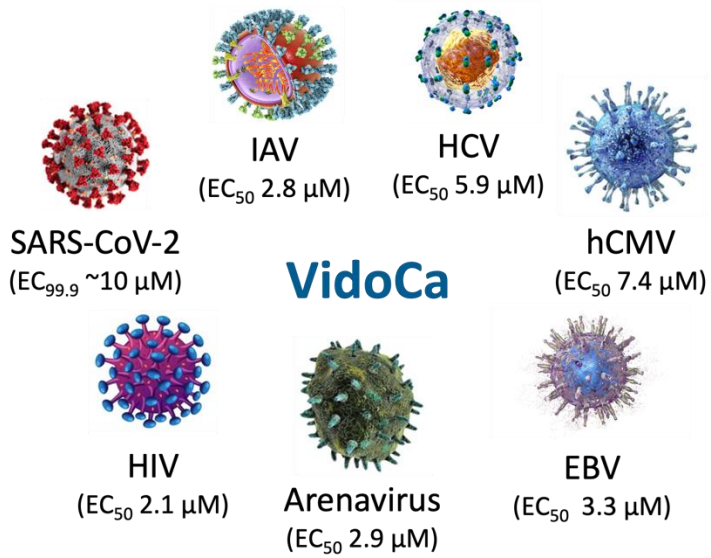


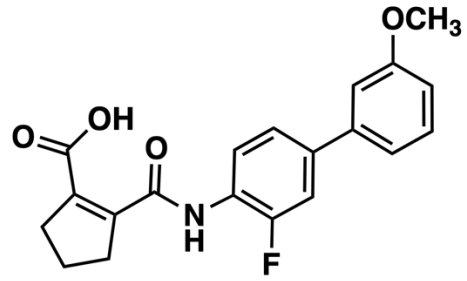
1. Depletion of pyrimidine-containing nucleotides
   → direct effect on expression and replication of viral nucleic acids
2. Secondary activation of interferon-stimulated genes (ISGs)
   → establishment of an antiviral state
3. Inhibition of hyperactive immune cells
   → anti-inflammatory effect

Created with BioRender.com

Vidofludimus calcium (VidoCa)

- Orally bioavailable small molecule
- DHODH inhibitor: selectively targets hyperactive immune cells and shows broad-spectrum antiviral activity *in vitro*
- Nurr1 activator: direct and indirect neuroprotective effects *in vitro* and in animal models
- Currently investigated in
  - several phase 2/3 trials for multiple sclerosis (CALLIPER[1], ENSURE[2])
  - a in BMBF-funded phase 2 trial for post-COVID syndrome (RAPID_REVIVE[3])
- Results from the phase 2 CALVID-1 trial in COVID-19 patients revealed[4]
  → shorter time to clinical improvement
  → less patients with fatigue

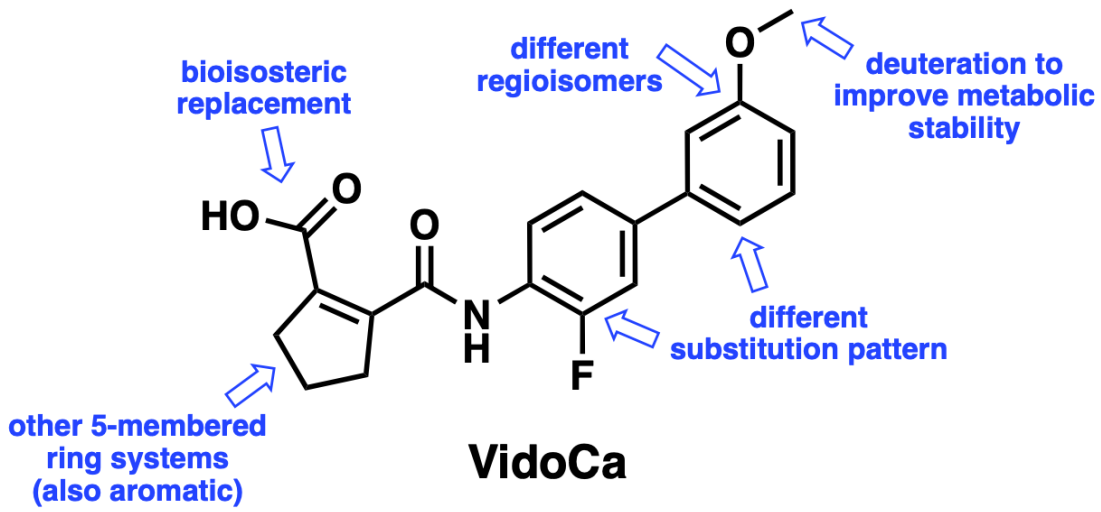




VidoCa

Nurr1: nuclear receptor-related 1; Vietor et al., 2023; [1] NCT05005410, [2] NCT05134441, NCT 05201638, [3] EU CT No. 2024-511628-16-00, [4] NCT04379271, Vehreschild et al., 2022.

Compound optimization of VidoCa



VidoCa		1796
120 nM	IC_{50} hDHODH	1 nM
5,000 nM	IC_{50} mDHODH	2 nM
5,200 nM	EC_{50} SARS-CoV-2	1 nM

Mouse	5 mpk (♀)	PK in mouse	Mouse	5 mpk (♀)
C_{max}	3440 ng/mL		C_{max}	6700 ng/mL
$t_{1/2}$	1.6 h		$t_{1/2}$	2.5 h
AUC	5740 ng*h/mL		AUC	25000 ng*h/mL
F	44 %		F	76 %

C_{max}: maximum serum concentration

AUC: area under the curve; exposure over time

$t_{1/2}$: half-life

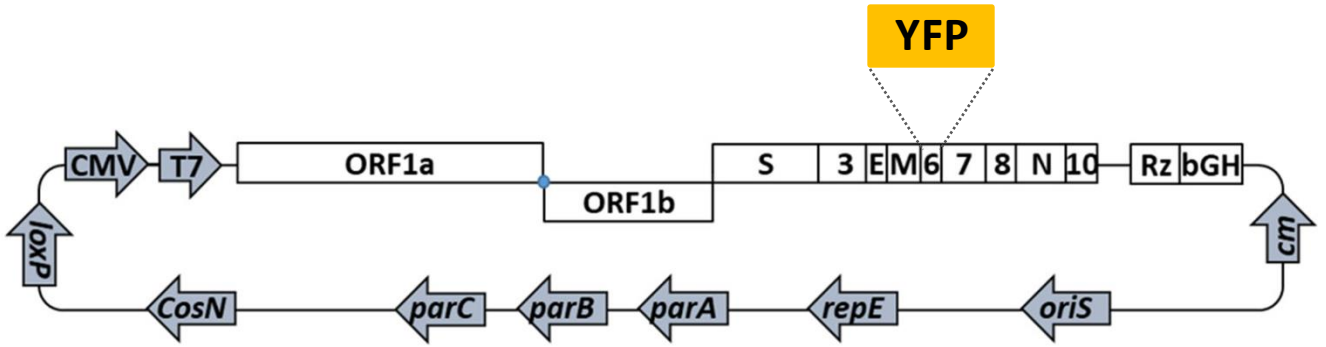
F: bioavailability

- Introduction of bioisosters, modifications at the central phenyl ring, and variations of the 5-membered ring system → improved potency
- Modifications at the central phenyl ring → elimination of species specificity
- Deuteration and modifications at the central phenyl ring → improvement of pharmacokinetic properties

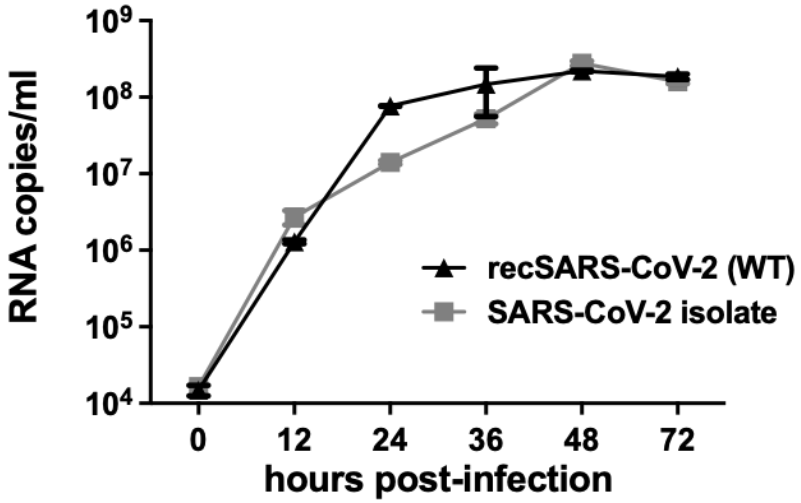
→ Optimization resulted in a large chemical space with >300 novel DHODH inhibitors

Immunic THERAPEUTICS

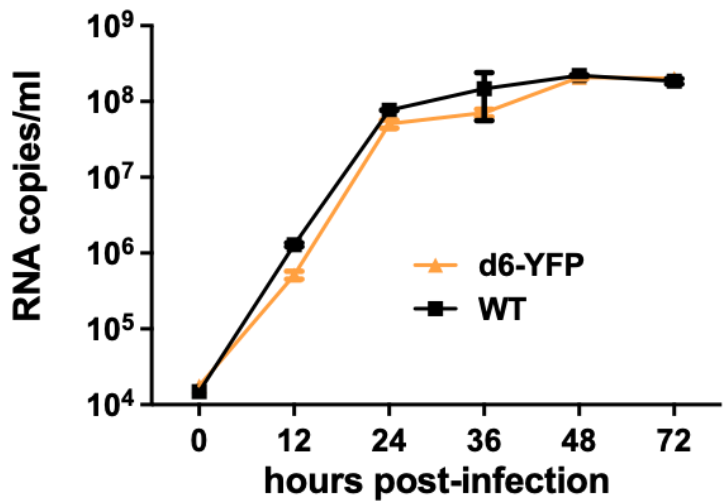
Recombinant SARS-CoV-2 reporter viruses for compound screening



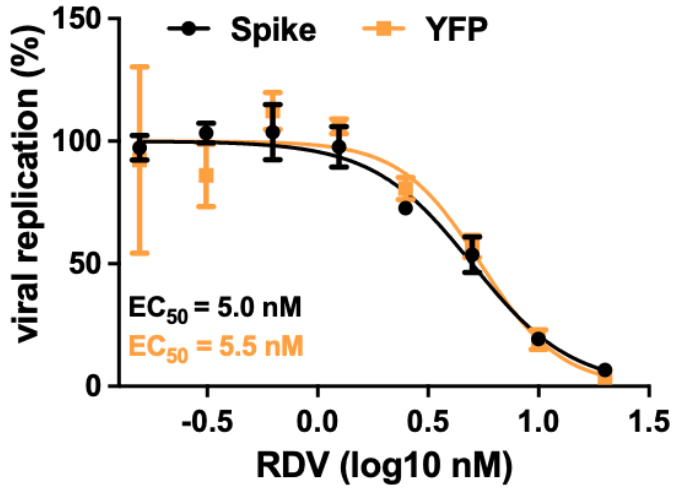
CaCo-2 cells, MOI = 0.005



CaCo-2 cells, MOI = 0.005



CaCo-2 cells, MOI = 0.005, 30 hpi

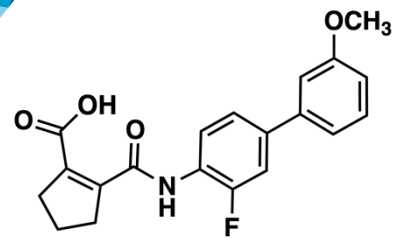


→ Recombinant SARS-CoV-2 WT and the d6-YFP reporter virus exhibit similar replication characteristics

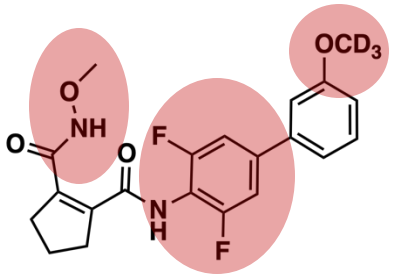
→ The d6-YFP mutant displays comparable sensitivity to antiviral drugs like RDV

Herrmann et al, 2021; Hahn et al., 2021

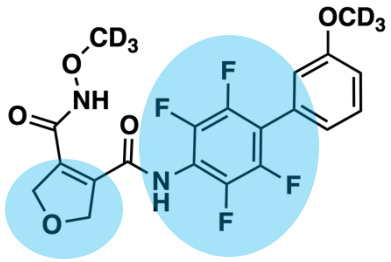
Effect of optimized DHODH inhibitors on SARS-CoV-2 replication



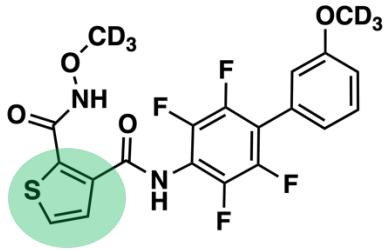
VidoCa



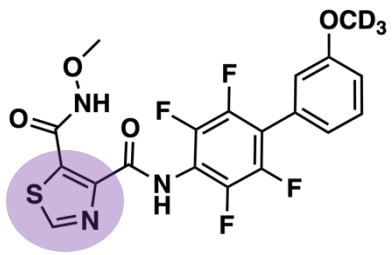
1414



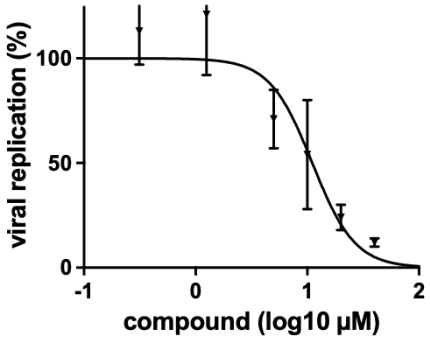
1738



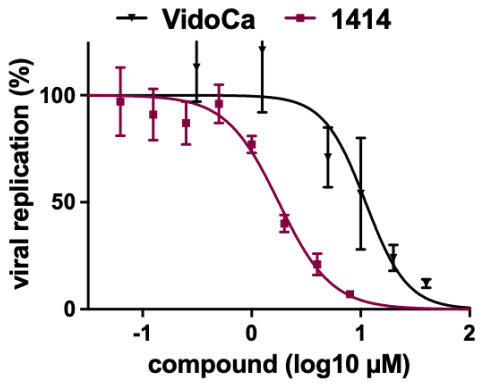
1796



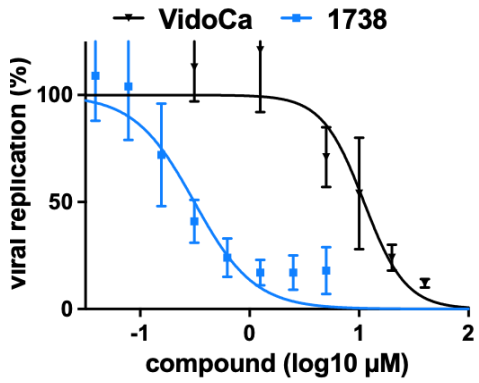
1864



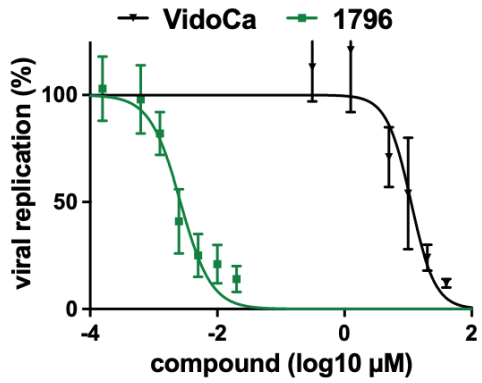
11.1 µM
SI >9



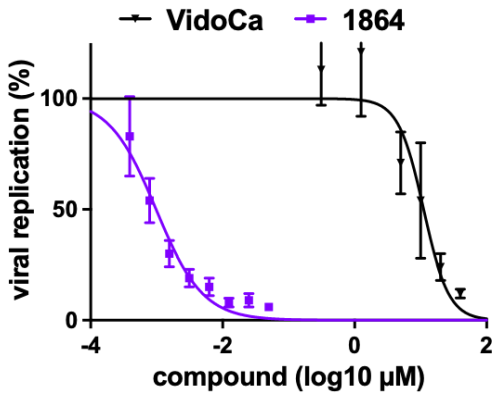
1.77 µM
SI >56



0.31 µM
SI >320



0.0026 µM
SI >38,000



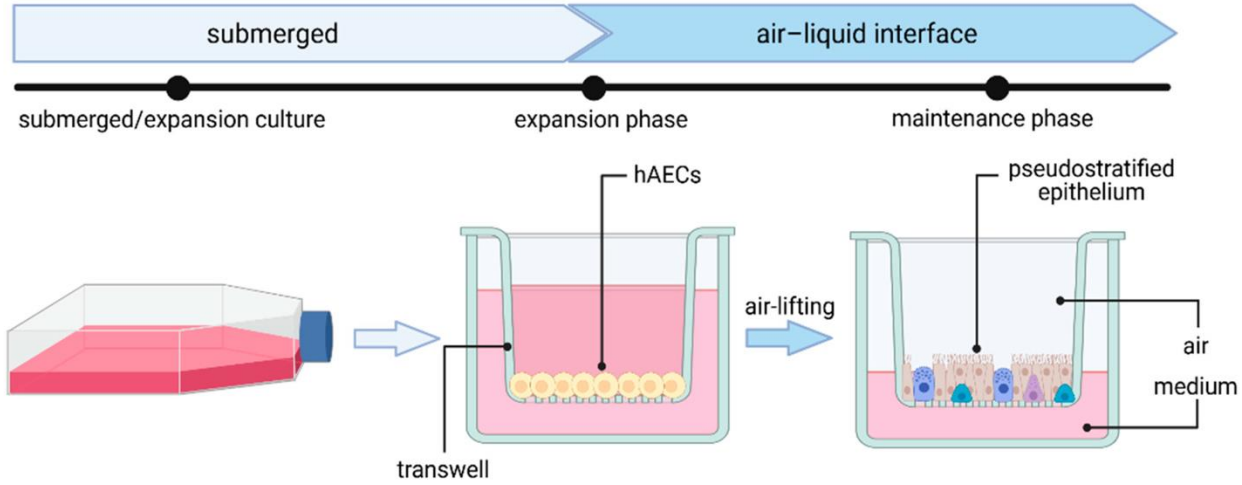
0.00098 µM
SI >100,000

→ Compound optimization resulted in a more than 10,000-fold improvement of SARS-CoV-2 inhibition *in vitro*

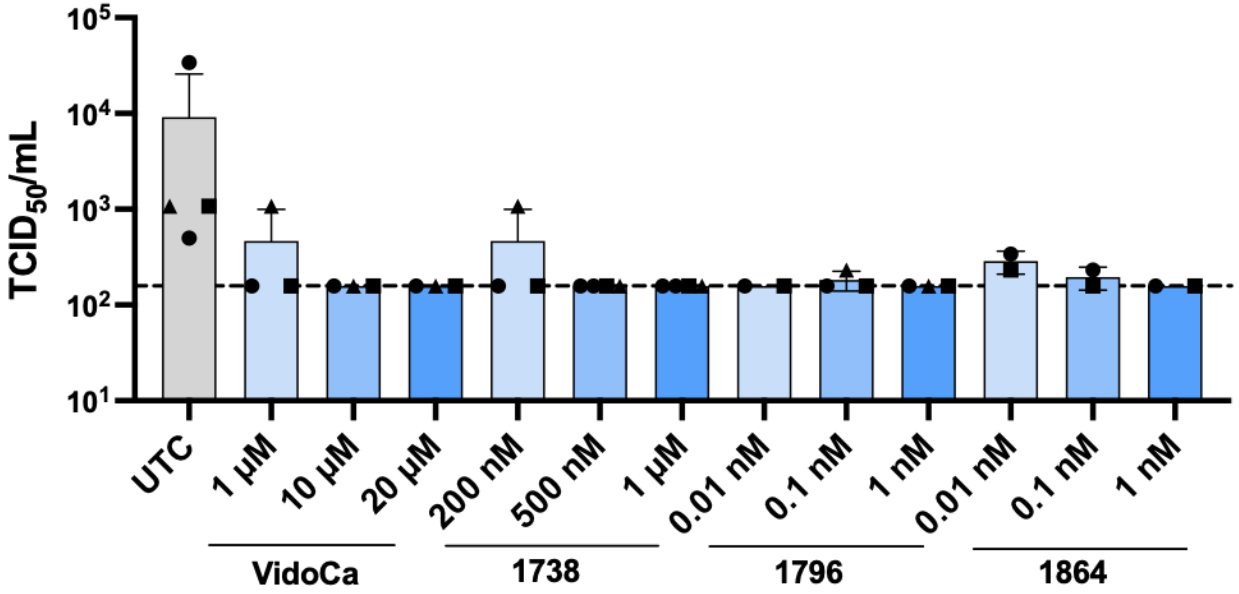
Analyses performed by Marschall lab, Erlangen, Germany.

CaCo-2 cells, d6-YFP, MOI = 0.003; 30 hpi

Analysis of DHODH inhibitors in human airway epithelial cells



Human airway epithelial cells (hAECs) treated with inhibitor from the basolateral site, 3x10^4 PFU SARS-CoV-2 from the apical site; 48 hpi

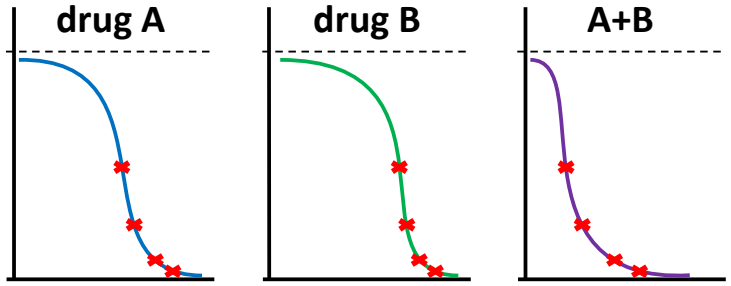


→ Optimized DHODH inhibitors potently restrict SARS-CoV-2 replication at nanomolar to sub-nanomolar concentrations

Analyses performed by Pfänder lab, Bochum/Hamburg, Germany; Heinen et al., Viruses, 2021.

Drug interactions of DHODH inhibitors and nucleoside analogs during SARS-CoV-2 infection

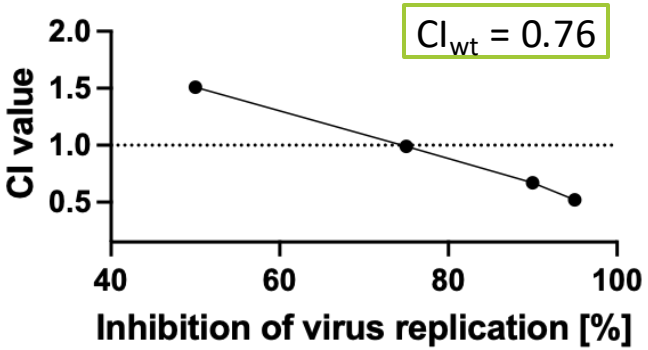
Loewe additivity fixed-dose ratio method



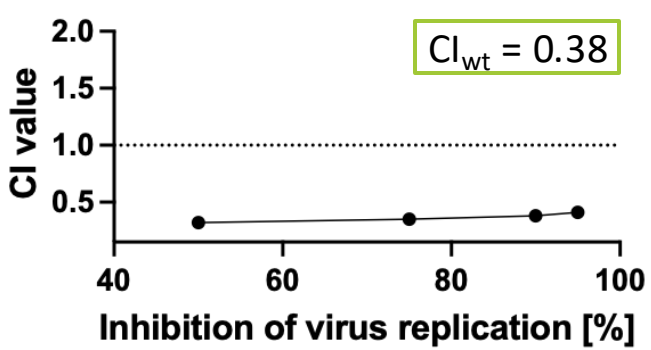
A	B	A+B	A+B		
EC_{50}	EC_{50}	EC_{50}	CI_{50}	×0.1	
EC_{75}	EC_{75}	EC_{75}	CI_{75}	×0.2	
EC_{90}	EC_{90}	EC_{90}	CI_{90}	×0.3	CI_{wt}
EC_{95}	EC_{95}	EC_{95}	CI_{95}	×0.4	

>1.2	antagonistic
0.8-1.2	additive
<0.8	synergistic

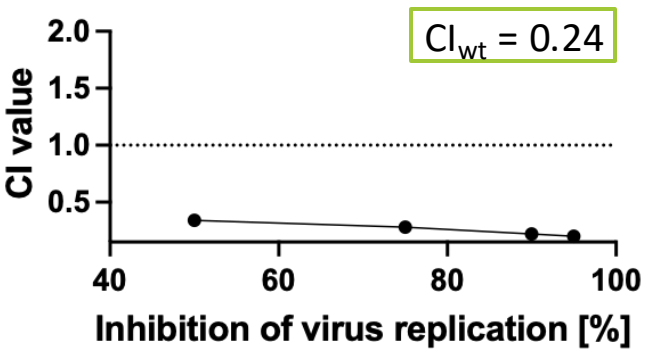
Gemcitabine + VidoCa-D_3 (1:20)



EIDD-1931 + VidoCa (1:5)



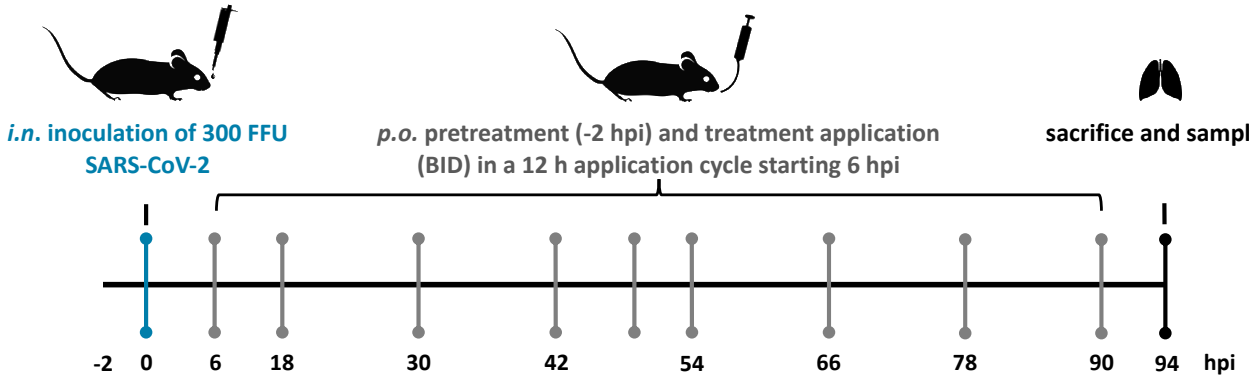
EIDD-1931 + 1796 (1000:1)



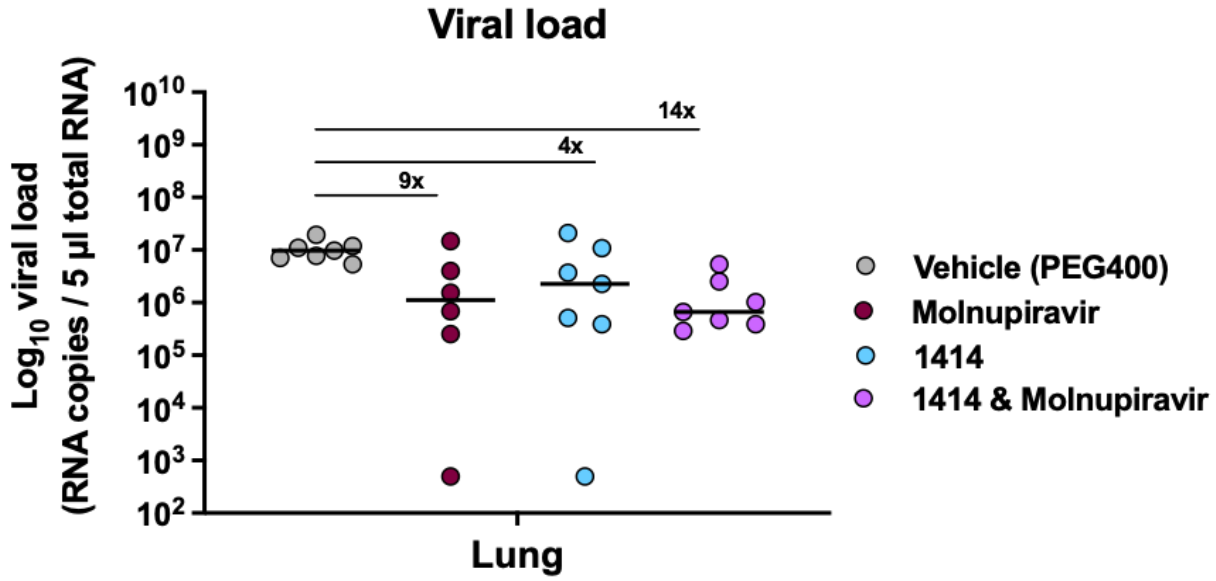
→ Optimized DHODH inhibitors act synergistically with nucleoside analogs *in vitro*

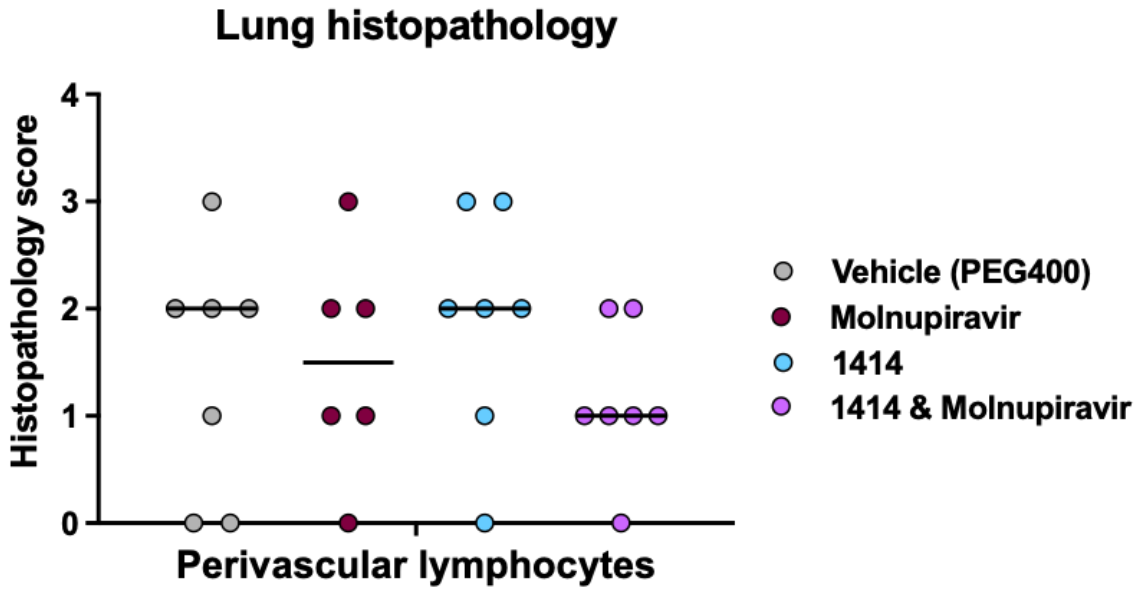
VidoCa-D_3: deuterated analog; EIDD-1931: N^4-Hydroxycytidine, active metabolite of molnupiravir; Analyses performed by Marschall lab, Institute of Clinical and Molecular Virology, Erlangen, Germany

DHODH inhibition diminishes SARS-CoV-2 replication *in vivo*



Female K18-hACE mice, 25 mg/kg/bid molnupiravir, 50 mg/kg/bid DHODH inhibitor 1414; or combination of both; analysis 4 dpi





→ Combination of a DHODH inhibitor with a nucleoside analog has a superior antiviral effect compared to single treatment *in vivo*

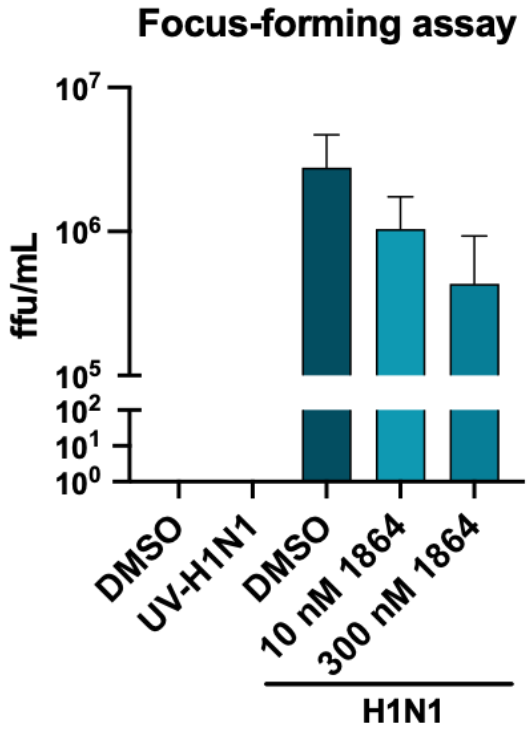
Analyses performed by Fraunhofer IZI, Leipzig, Germany, and Prof. Klopfleisch, Freie Universität Berlin, Germany.

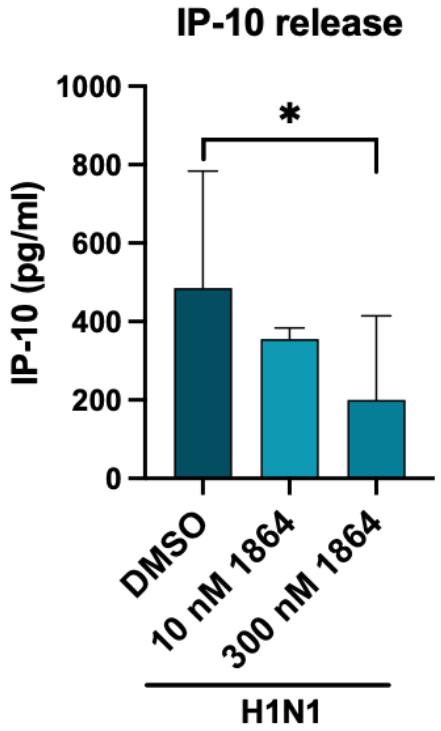
Effect of DHODH inhibition on influenza virus replication in *ex vivo*-cultivated human lung tissue

Ø 8-10 mm

~ 300 µm

Human precision cut lung slices (PCLs), A/H1N1/California/4/2009pandemic, 72 hpi





→ The optimized DHODH inhibitor 1864 inhibits influenza virus replication in human lung tissue and reduces the release of pro-inflammatory cytokines

IP-10: Interferon gamma-induced protein 10. Analyses performed by Fraunhofer ITEM, Hannover, Germany.

Immunic THERAPEUTICS

Optimized DHODH inhibitors show potent broad-spectrum antiviral activity in cell culture

	Baltimore	VidoCa (nM)	1738 (nM)	1864 (nM)
		non-enveloped		
HAdV	I	6400	350	0.4
		enveloped		
CMV	I	7000	670	-
MPXV	I	700	58.2	0.5
SARS-CoV-2	IV	5200	330	1.0
CoV-229E	IV	-	172	3.4
CoV-OC43	IV	-	172	4.1
ZIKV	IV	-	470	44.2
IAV	V	2200	460	3.0
MeV	V	-	295	3.1
RSV	V	-	19.9	-
HIV-1	VI	2100	8.7	0.001

-, not determined

- → Inhibition of non-enveloped and enveloped viruses
- → Inhibition of DNA and RNA viruses
- → Inhibition of a retrovirus

Summary: Design, screening and characterization of optimized DHODH inhibitors

1. Improvement of drug-like properties, target engagement, and antiviral activity

2. Synergistic activity with nucleoside analogs
   - ➢ Promising treatment option for vulnerable patient population or severe course of viral infections

3. Reduction of viral load in lungs of SARS-CoV-2-infected mice and influenza virus-infected human lung tissue slices

4. Potent restriction of diverse viruses in cell culture
   - ➢ Promising approach for host-directed broad-spectrum antivirals with regard to pandemic preparedness

Acknowledgements

Immunic AG, Gräfelfing

Hella Kohlhof

Daniel Vitt

Christian Gege

Evelyn Peelen

Institute of Virology, Erlangen

Manfred Marschall

Friedrich Hahn

Christina Wangen

Sabrina Wagner

Melanie Kögler

Matthias Tenbusch

Pascal Irrgang

Armin Ensser

Arne Cordsmeier

Doris Jungnickl

Institute of Molecular Virology, Ulm

Konstantin Sparrer, Jan Münch, Frank Kirchhoff, Tatjana Weil, Victoria Hunszinger, Rüdiger Groß

Fraunhofer Institute for Cell Therapy and Immunology, Leipzig

Thomas Grunwald, Nadja Uhlig, Valentina Eberlein, Leila Issmail

Fraunhofer Institute for Cell Therapy and Immunology, Halle

Holger Cynis, Benjamin Hietel

Ruhr-University Bochum/LIV Hamburg

Stephanie Pfänder, Natalie Heinen

Leibniz Institute of Virology, Hamburg

Thomas Dobner, Wing-Hang Ip

Freie Universität Berlin

Robert Klopfleisch

Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover

Sebastian Konzok, Helena Obernolte

University Hospital Essen

Sebastian Reuter

Thank you for your attention!