Preclinical Development of Optimized DHODH Inhibitors as Broad-Spectrum Antivirals for the Treatment of Respiratory Virus Infection

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Advanced Clinical Pipeline

Well Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus Calcium (IMU-838)	DHODH	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials				▪ Initial phase 1b celiac disease data of IMU-856 expected in Q2/2023 ▪ Interim analysis of CALLIPER trial in PMS planned after half of the patients completed 24 weeks of treatment, estimated for H2/2023 ▪ CALLIPER trial estimated to readout end of 2024 ▪ Interim analysis of first ENSURE trial in RMS planned after approximately half of the events occurred, estimated for late 2024 ▪ ENSURE-1 trial estimated to readout end of 2025, ENSURE-2 soon thereafter
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
		Ulcerative Colitis (UC) – CALDOSE-1 Trial				
IMU-856	Intestinal Barrier Function	Celiac Disease				

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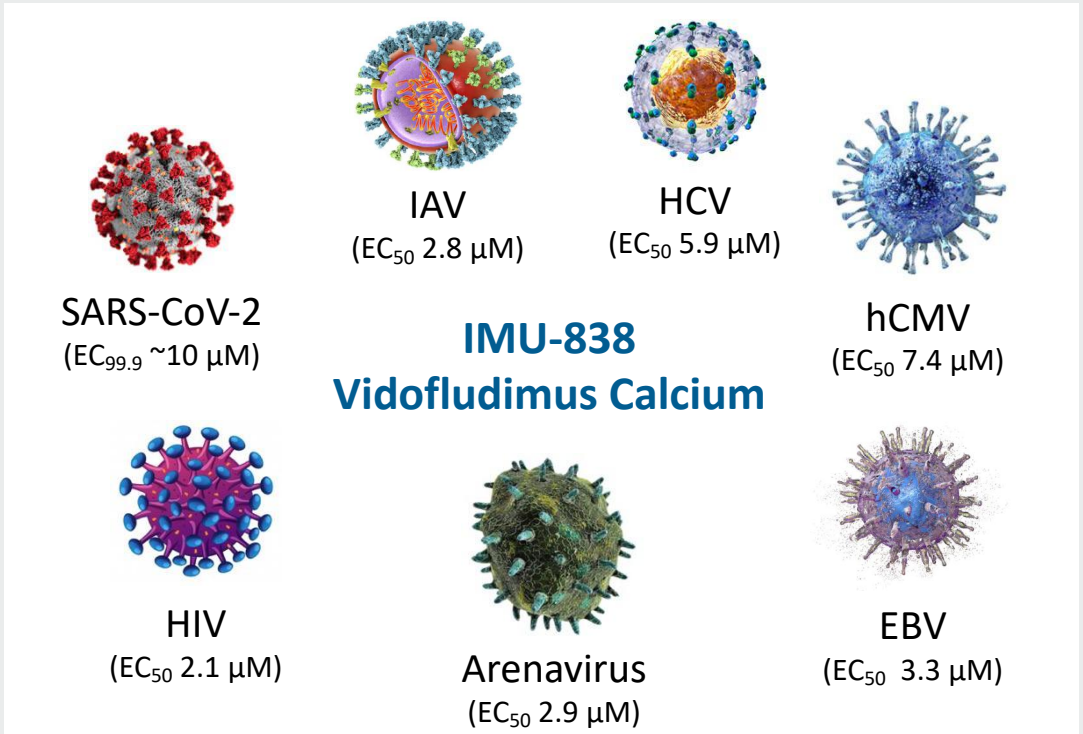
DHODH Inhibition Provides Broad-Spectrum Antiviral Activity Against Different Pathogenic Viruses

Antiviral Activity With EC_{50} Values in Single Digit µM Range



Vidofludimus Calcium Inhibits Virus Replication and Reactivation

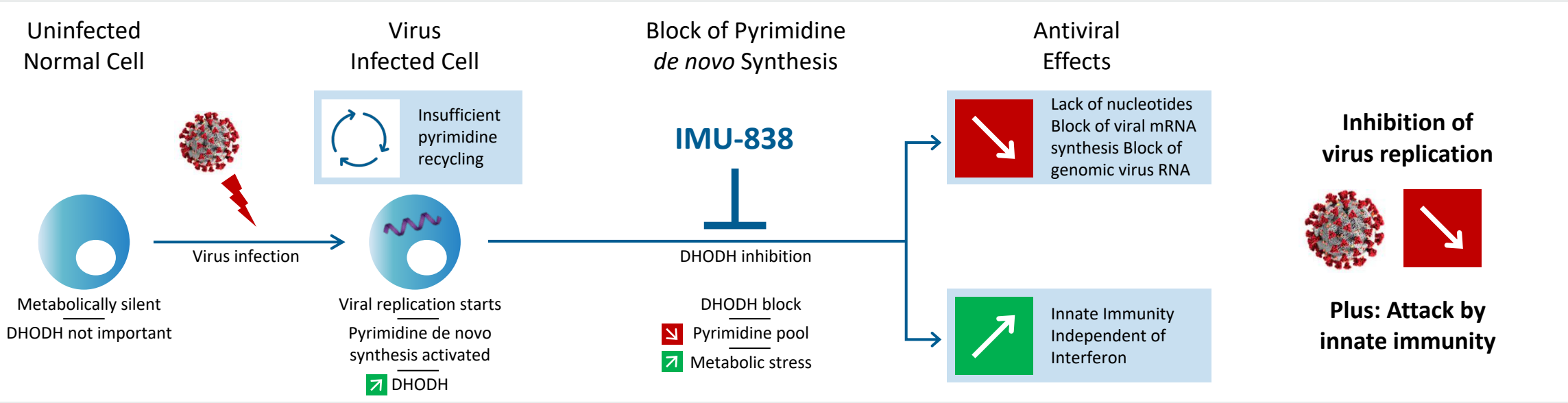
- Viruses rely on the host cell's infrastructure for replication
- Inhibition of DHODH leads to a depletion of pyrimidine nucleotides that are needed for the
  - Production of viral RNA and DNA (virus genome)
  - Production of viral proteins (via mRNA)
- By targeting the host cell metabolism, vidofludimus calcium has shown to be active against different RNA and DNA viruses *in vitro*

Left: Hahn F et al. (2020) Viruses. 12:1394 / Right: Eur J Clin Invest. 2020;50:e13366

Vidofludimus Calcium: Summary of Rationale in COVID-19

Dual mode of action: orally available DHODH inhibitor with both, antiviral and anti-inflammatory effects

Host-based mechanism avoids dependence on specific viral proteins and, therefore, offers broad-spectrum antiviral activity



Vidofludimus Calcium Reduces Viral Load in COVID-19 Patients

Infect Dis Ther
https://doi.org/10.1007/s40121-022-00690-0

ORIGINAL RESEARCH

Safety and Efficacy of Vidofludimus Calcium in Patients Hospitalized with COVID-19: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Trial

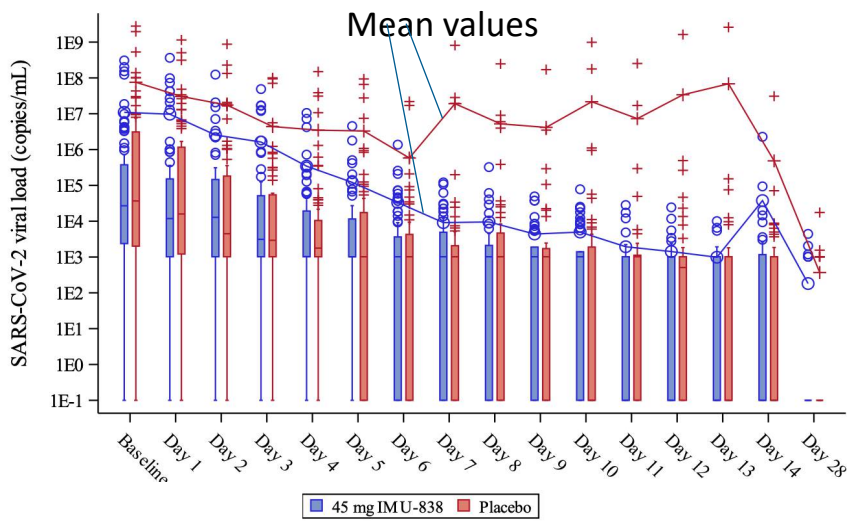
Maria J. G. T. Vehreschild · Petar Atanasov · Kateryna Yurko · Cristian Oancea · Georgi Popov · Valentina Smesnoi · Gheorghe Placinta · Hella Kohlhof · Daniel Vitt · Evelyn Peelen · Jelena Mihajlović · Andreas R. Muehler

Received: June 3, 2022 / Accepted: August 17, 2022

- 223 patients randomized in Europe and the United States
- June to December 2020, 14 days of treatment
- Time to clinical improvement
  - Median: similar for both groups
  - Early treated patients (< 9 days after symptom start): 3.8 days for vidofludimus calcium treated patients in the 75% percentile

Vidofludimus calcium was safe and showed clinical antiviral activity

S Figure 1: Time course of SARS-CoV-2 viral load (copies/mL) (modified intention-to-treat population n=198)



From day 6 on, vidofludimus calcium shows clear differentiation in viral load in COVID-19 patients

Vehreschild et al., 2022, Infect Dis Ther

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Vidofludimus Calcium Showed Interesting Hints for Clinical Anti-SARS-CoV-2 Activity and Maintenance of Humoral Response

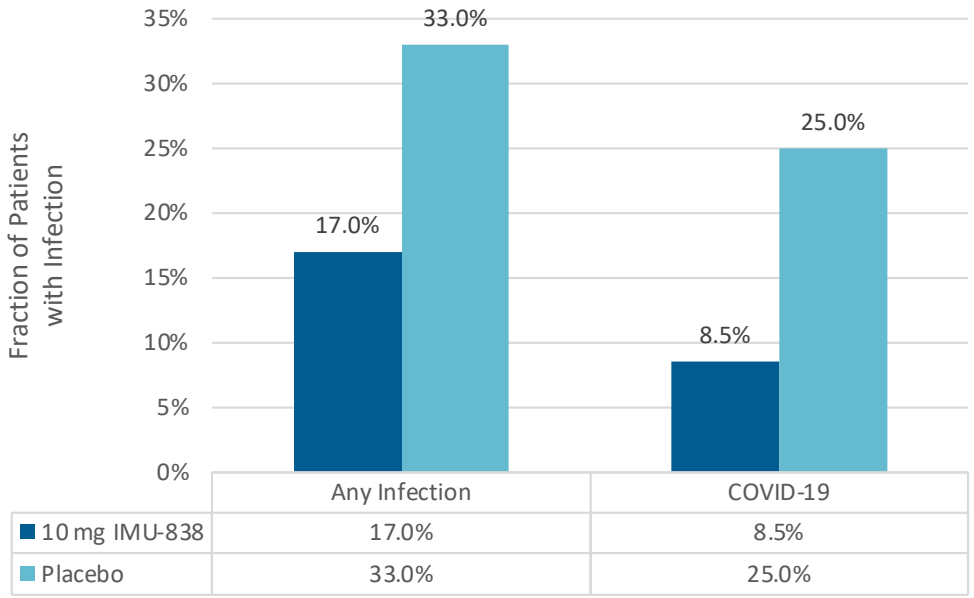
Treatment Does Not Interfere With Antibody Development During SARS-CoV-2 Infection

	Day 6		Day 14		Day 28	
	IgA	IgG	IgA	IgG	IgA	IgG
Placebo	84%	88%	94%	94%	97%	99%
Vidofludimus Calcium	86%	93%	97%	97%	95%	100%

Phase 2 CALVID-1 Trial in COVID-19

Proportion of patients with anti-SARS-CoV-2 IgA or IgG antibodies

Treatment Corresponds With Decreased Number of Opportunistic SARS-CoV-2 Infections



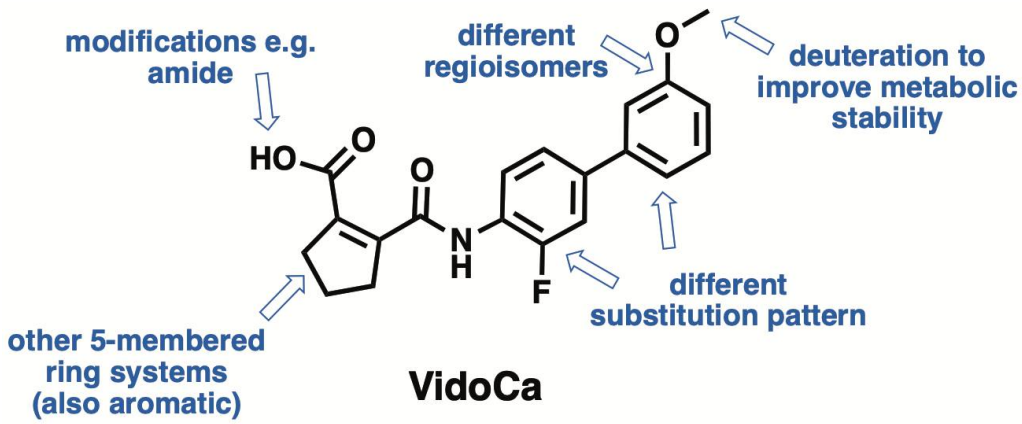
Phase 2 EMPhASIS Trial in Relapsing-Remitting Multiple Sclerosis

Number of reported COVID-19 cases in Cohort 2

IgA: immunoglobulin A; IgG: immunoglobulin G

DHODH Inhibitors 2.0: Successful Optimization Process

Compound Optimization Options



Topics For Improvement

- Improved DHODH inhibition
  - Addressing strong species specificity
- Enhanced cellular antiviral activity
- Improved drug-like properties
  - Solubility
  - ADME parameters
  - PK properties

ADME: Absorption, Distribution, Metabolism, Excretion; PK: pharmakokinetic

Optimization Significantly Increases Antiviral and Drug-Like Properties

VidoCa			XAVI-101	
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 %

Cmax: maximum plasma drug concentration; t1/2 = terminal elimination half-life; AUC: area under the curve; F: bioavailability; PK: pharmakokinetics

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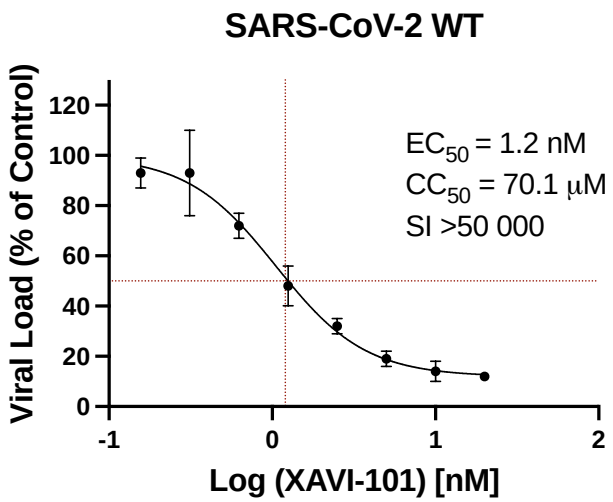
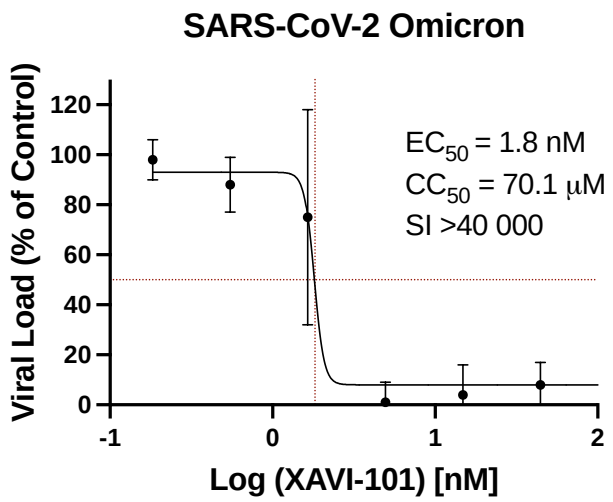
DHODH Inhibition Acts Independent of Virus Mutations and Reduces Viral Load in Infected Mice

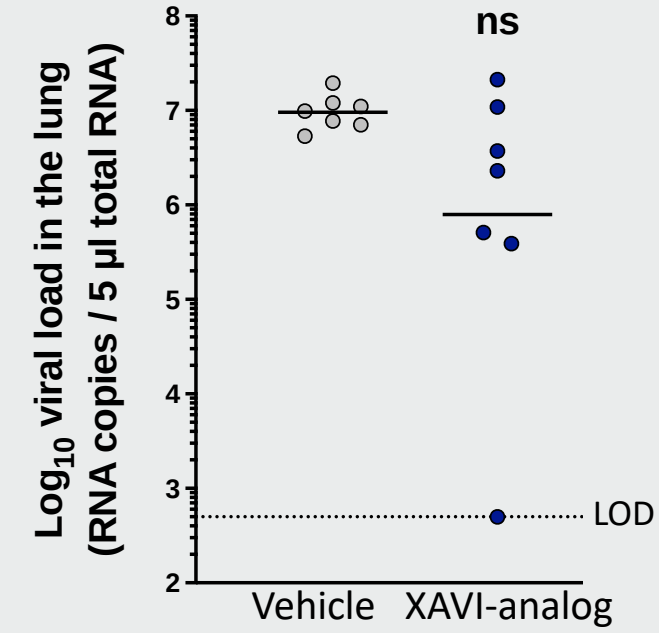
XAVI-101 Is Highly Active Against SARS-CoV-2 wt and Omicron Variant





Virus mutations do not impair activity of XAVI-101 as a potent DHODH inhibitor

Mice Were Infected With SARS-CoV-2 Wuhan Strain

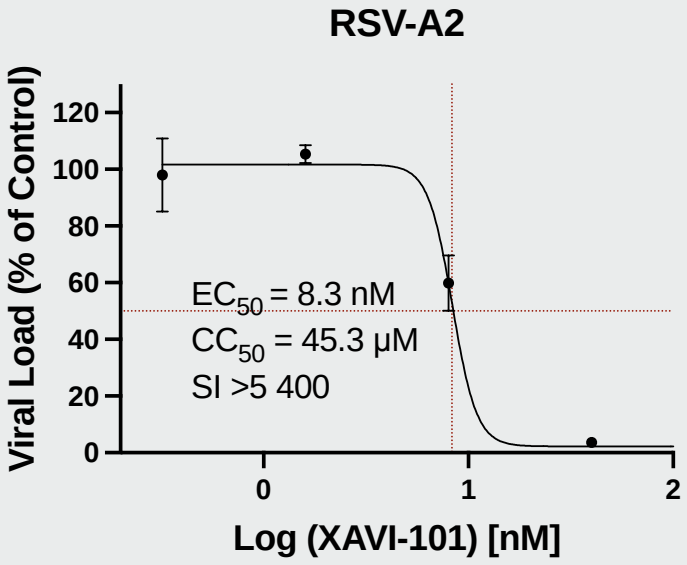


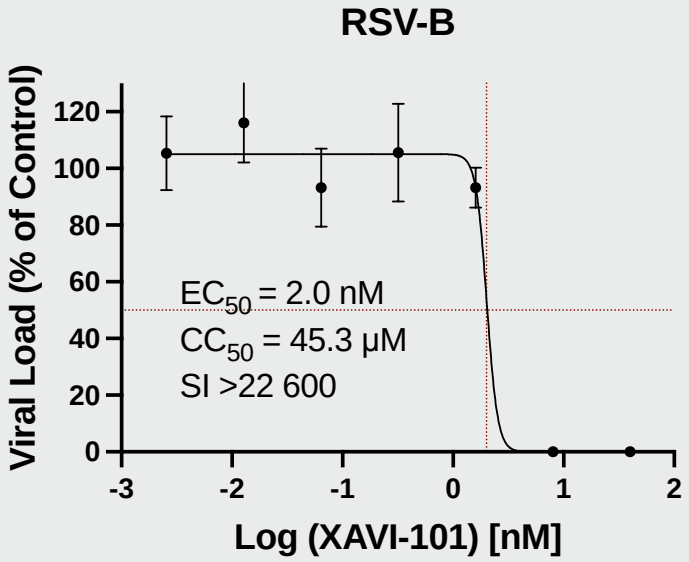
XAVI-101 analog reduces SARS-CoV-2 viral load in lungs of K18 hACE2 mice

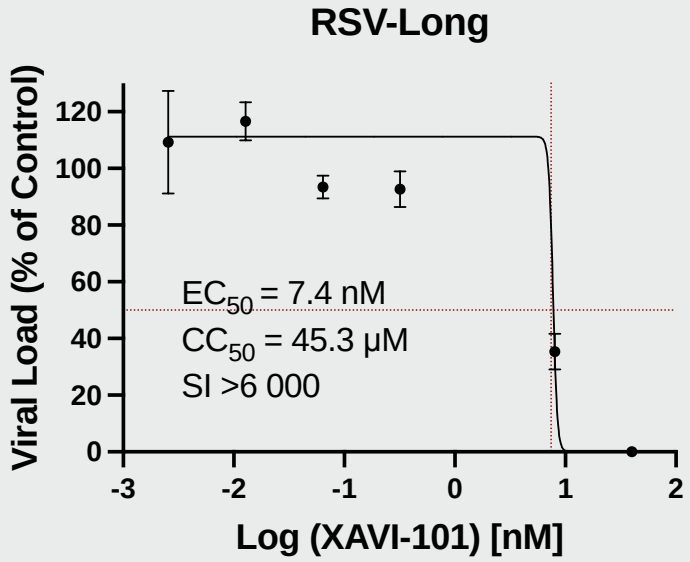
Left: Marschall Lab, Erlangen, Germany/Right: Grunwald Lab, Leipzig, Germany; SI: Selectivity Index

XAVI-101 Inhibits Diverse Respiratory Syncytial Virus (RSV) Strains *In Vitro*

- HepG2 cells were infected with three different RSV strains





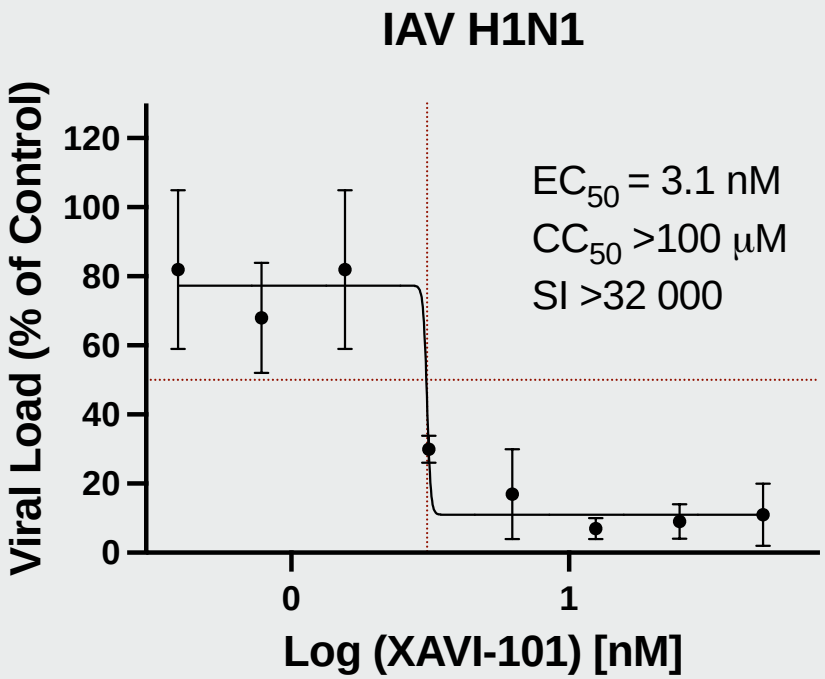


XAVI-101 is highly active against different strains of RSV

Marschall Lab, Erlangen, Germany; SI: Selectivity Index

XAVI-101 Inhibits Influenza Virus Replication *In Vitro*

- HEK293T cells were transfected with a GFP-based reporter systems, sensitive for IAV polymerase
- Cells were treated with XAVI-101 and infected with IAV H1N1/PR8 isolate



XAVI-101 is highly active against influenza H1N1 virus replication

Marschall Lab, Erlangen, Germany; SI: Selectivity Index

DHODH Inhibitors for the Treatment of Different Respiratory Infections

High Medical Need

- For potential future **pandemics**
- In general, for **vulnerable patients**
  - Immunocompromised patients under certain therapies
  - Elderly patients
  - Patients with Asthma and Chronic Obstructive Pulmonary Disease (COPD)
  - Newborns

Antiviral Treatment Option

- **Acute therapy** for different respiratory viruses due to host-based approach
- **Prevention therapy**
  - Based on the clean safety profile of vidofludimus calcium it can be used as
    - Prevention therapy in seasons with higher respiratory tract infection risk
    - Prevention therapy for health care personnel

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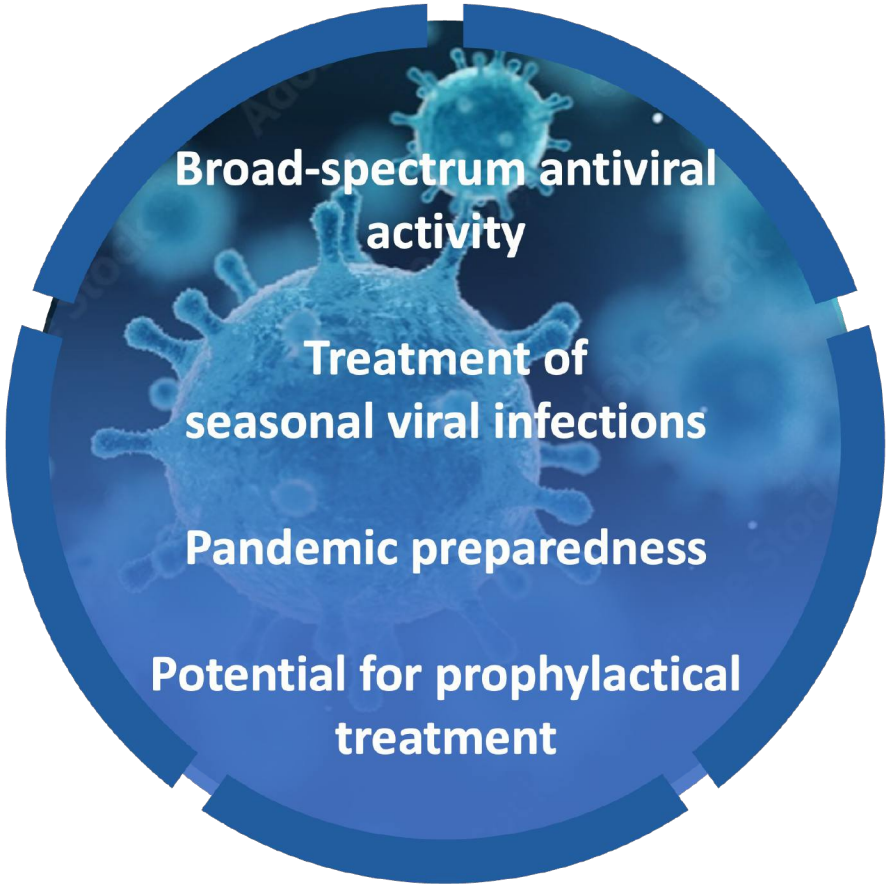
XAVI-101: In Development as Potential Broad-Spectrum Antiviral Drug

- **XAVI-101** shows improved target engagement and pharmaceutical properties compared to vidofludimus calcium (currently tested in phase 2 and 3 clinical trials in multiple sclerosis)
- **XAVI-101** potently restricts replication of different respiratory viruses in single-digit nanomolar range *in vitro*
- **XAVI-101** analog reduces the viral load in lungs of SARS-CoV-2 infected mice
- **XAVI-101** represents a promising candidate with broad-spectrum antiviral activity for future clinical development



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Thank You!

Collaboration Partners

Universitätsklinikum Erlangen

Fraunhofer IZI

Thank You!

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