



Workshop : Broad-spectrum antiviral therapeutics: a key tool for pandemic preparedness

# Towards broad(er)-spectrum antiviral agents

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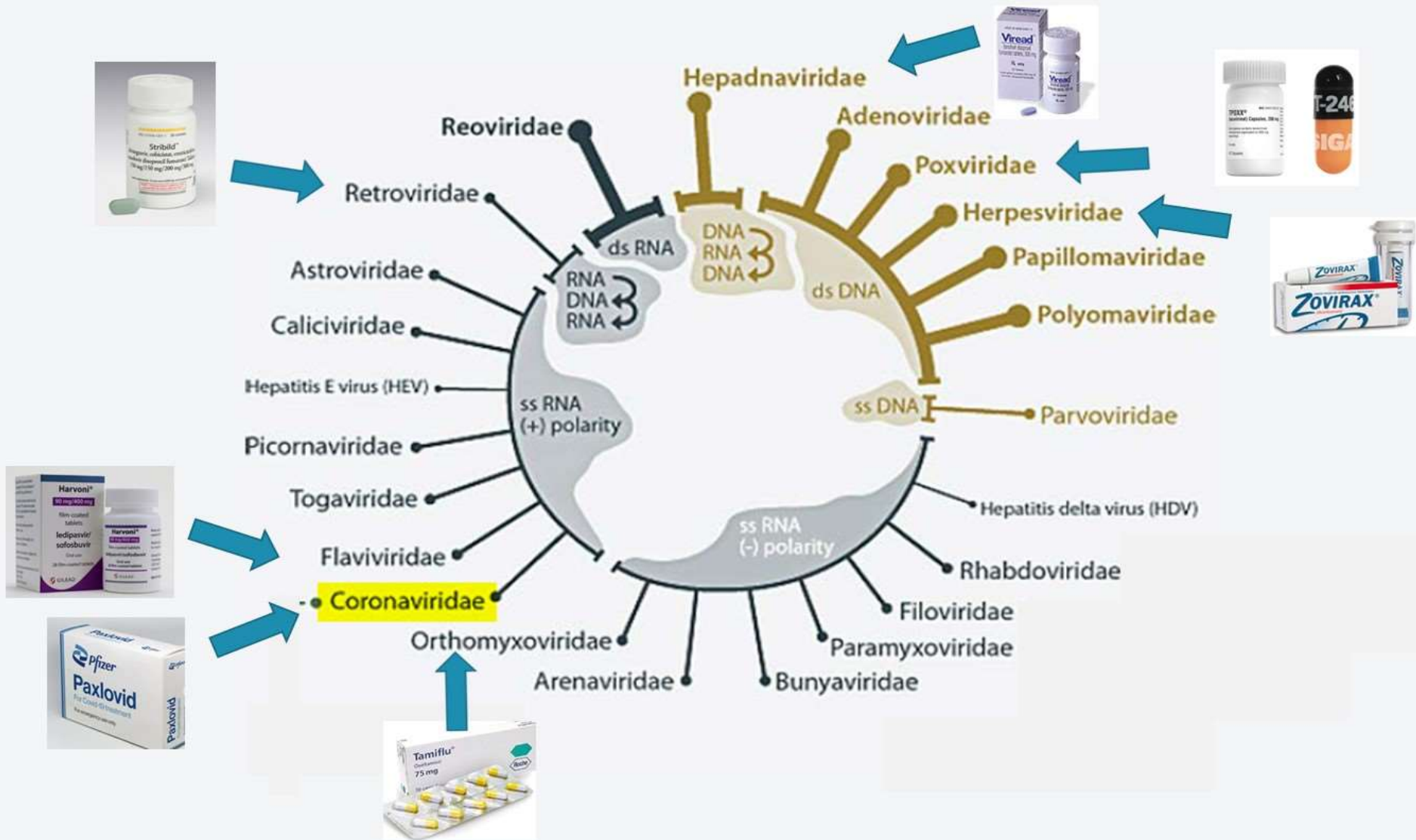
[www.antivirals.be](http://www.antivirals.be)



@neyts\_johan

November 22<sup>nd</sup> 2022

KU LEUVEN



**Current Opinion in Virology 2013, 3:217–224**

**Intervention strategies for emerging viruses: use of antivirals**

Yannick Debing, Dirk Jochmans and Johan Neyts

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An alternative is to develop drugs that have broad-spectrum antiviral activity within a given genus or family (e.g., broad-spectrum flavivirus or paramyxovirus inhibitors). It is probable that novel, potentially highly pathogenic RNA viruses will emerge in the future; consider for instance the recent fatalities with the novel coronavirus-EMC [1]. Having broad-spectrum (pan-genus; pan-family or pan-RNA virus) inhibitors at hand may help to contain such future outbreaks.

# Target based drug discovery

## **Polymerase & reverse transcriptase inhibitors\*\*\***

(nucleoside analogues and non-nucleosides)

Herpesviruses

HIV

HBV

HCV

Coronaviruses

## **Protease inhibitors**

HIV

HCV

Coronaviruses

## **Neuraminidase inhibitors**

Influenza viruses

## **Terminase inhibitors**

HCMV

## **Integrase inhibitors**

HIV

## **CXCR5 inhibitors**

HIV

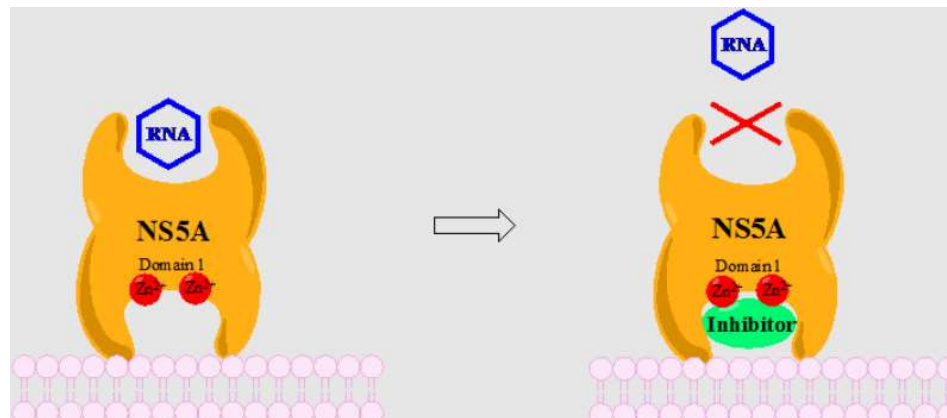
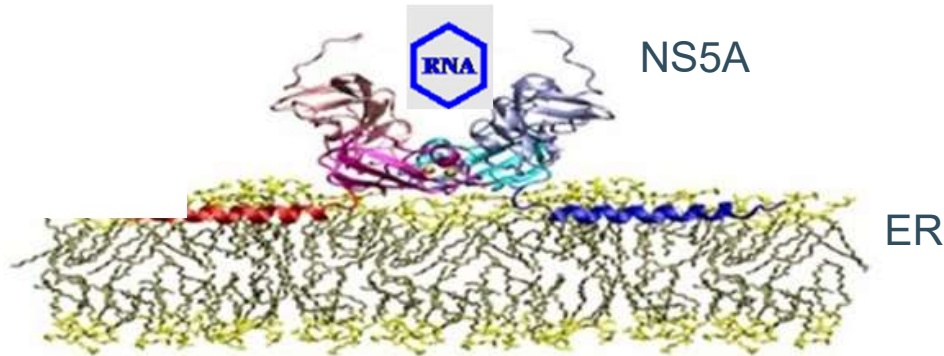
\*\*\* certain nucleoside analogues exert broader-spectrum antiviral activity, e.g.

Remdesivir : filoviruses, paramyxoviruses, coronaviruses...

Molnupiravir : influenza, alphaviruses, coronaviruses....

# Phenotypic based drug discovery

# The HCV NS5A as an excellent antiviral target

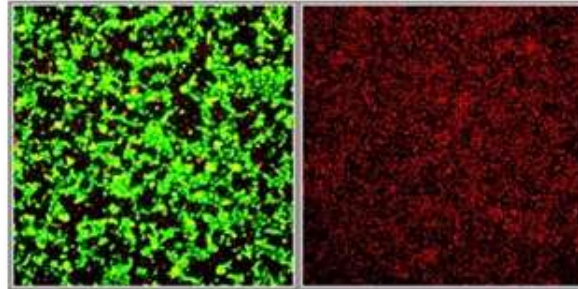
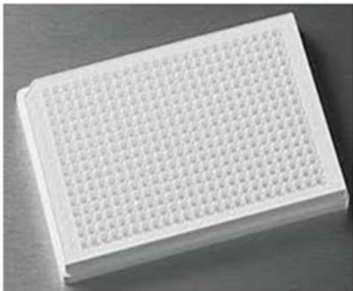


www.wikipedia.org

# High throughput phenotypic antiviral drug discovery

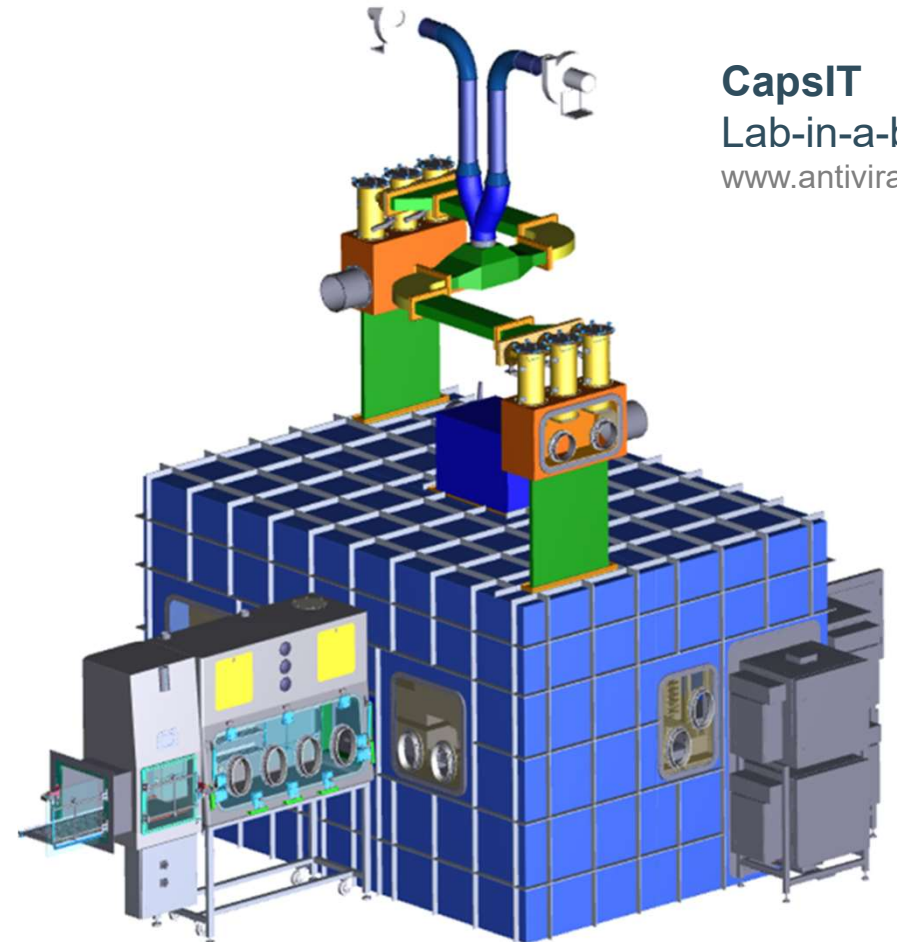


 **CD3**  
CENTRE FOR  
DRUG DESIGN  
AND DISCOVERY



Infected (SARS-CoV2)

Uninfected



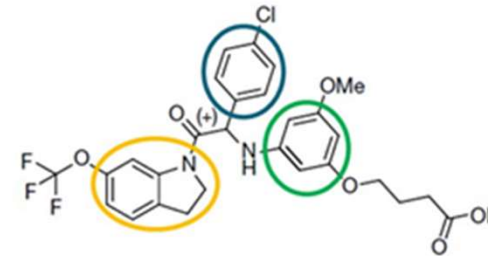
**CapsIT**  
Lab-in-a-box  
[www.antivirals.be](http://www.antivirals.be)





# The flavivirus NS4b as an excellent antiviral target

Serotype	Genotype	Strain	EC <sub>50</sub> (µM)
DENV-1	G1	Djibouti	<0.00006 ± 0.00004
DENV-1	G3	Malaysia* <sup>o</sup>	0.0003 ± 0.00007
DENV-1	G4	Indonesia	<0.00008 ± 0.00005
DENV-1	G5	France - Toulon	<0.00003 ± 0.00001
DENV-2	Asian America	Martinique <sup>o</sup>	0.004 ± 0.005
DENV-2	American	Trinidad	<0.00004 ± 0.000009
DENV-2	Cosmopolitan	France - Toulon	<0.00007 ± 0.00005
DENV-2	Asian I	Thailand <sup>o</sup>	0.001 ± 0.0002
DENV-2	Asian II	Papua New Guinea*	<0.00004
DENV-2	Sylvatic	Malaysia*	<0.00006 ± 0.00003
DENV-3	G1	Malaysia	0.0005 ± 0.0002
DENV-3	G2	Thailand	0.001 ± 0.0007
DENV-3	G3	Bolivia	0.0005 ± 0.0003
DENV-3	G5	H87 <sup>o</sup>	0.001 ± 0.0005
DENV-3	G5	Brazil* <sup>^</sup>	0.0002 ± 0.0002
DENV-4	G1	India	<0.00004
DENV-4	G2a	Malaysia	0.003 ± 0.003
DENV-4	G2b	Martinique	<0.0001 ± 0.0001
DENV-4	G2b	Brazil	<0.0002 ± 0.0001
DENV-4	G3	Thailand*	0.006 ± 0.006
DENV-4	Sylvatic	Malaysia*	0.0003 ± 0.00002



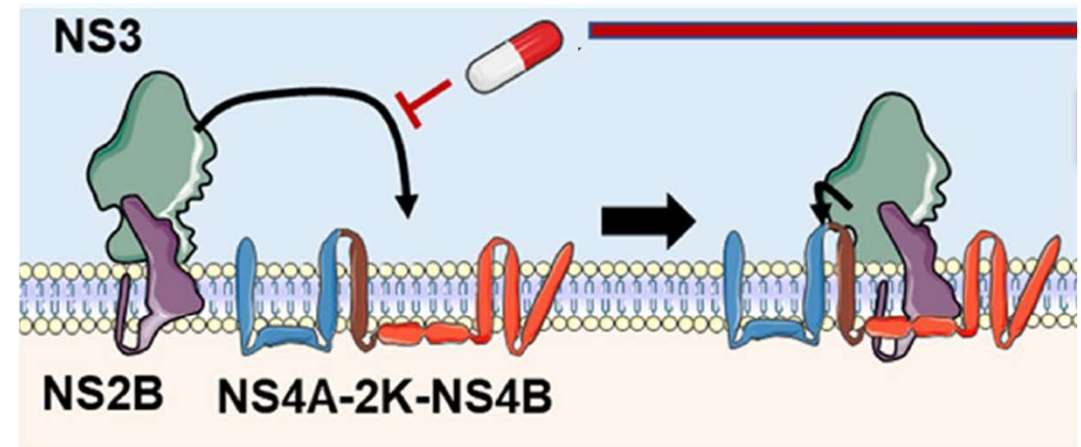
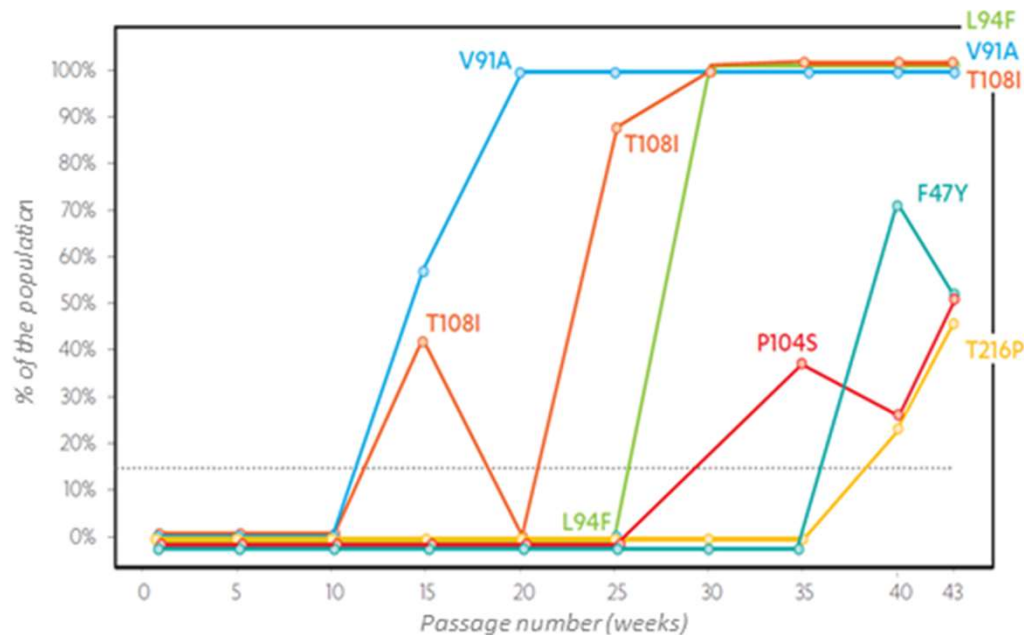
KU Leuven, the Wellcome Trust and Janssen are together joining the fight against Dengue fever (breakbone fever)

Report to the **Community** 2013

Economic Sustainability



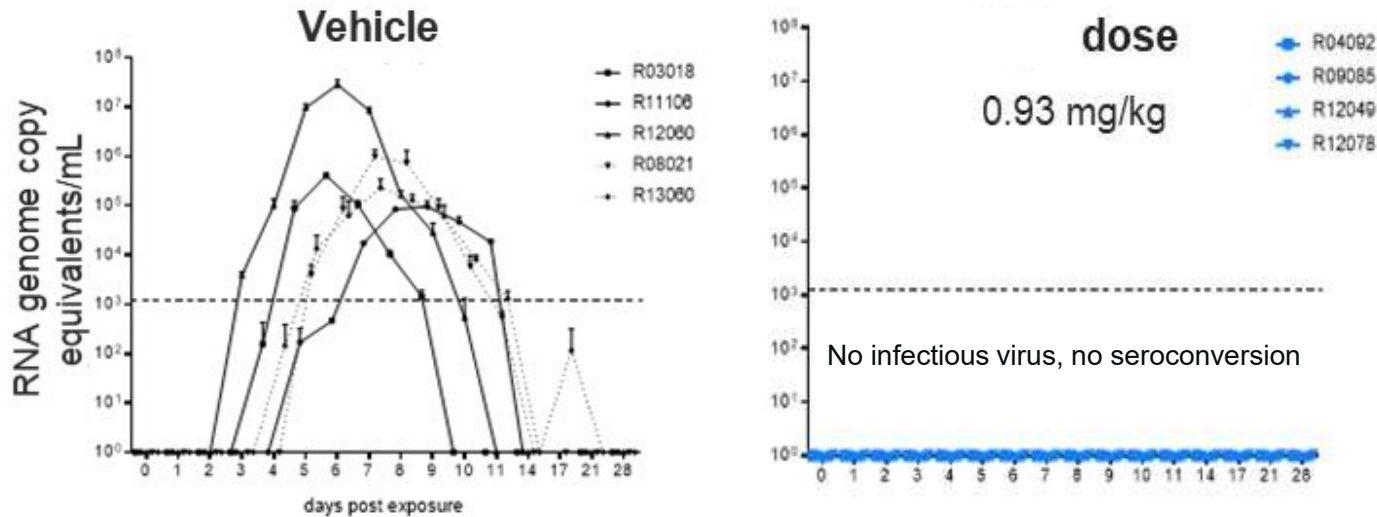
# An ultrapotent pan-serotype dengue inhibitor with a high barrier to resistance targeting NS4b



# Highly effective in preventing DENV in rhesus monkeys



DENV-2  
DENV-1



**Pre-exposure prophylaxis study - two-stage adaptive design:** STAGE 1: Vehicle (n=3), JNJ-1802 (n=3, each) once daily at 0.01 mg/kg (low), 0.18 mg/kg (mid), 3 mg/kg (high) STAGE 2: Vehicle (n=2), JNJ-1802 (n=3, each) once daily at 0.024 mg/kg (low), 0.09 mg/kg (mid), 0.93 mg/kg (high)

Also highly effective against DENV-1 rhesus monkeys

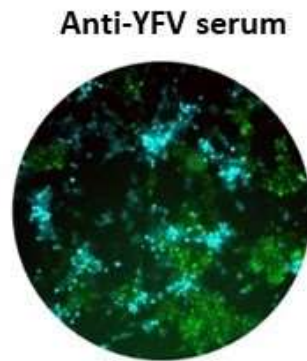
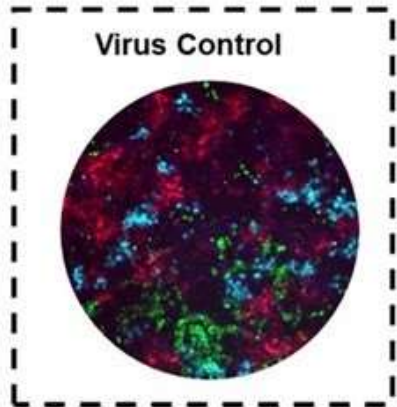


Biomedical Primate  
Research Centre

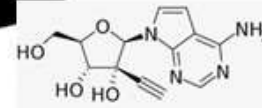
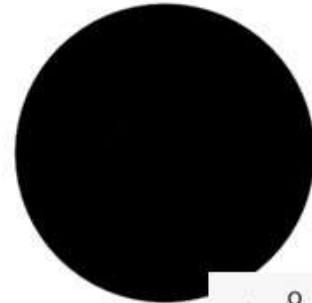
# Rainbow (multiplex) antiviral assays

An example for flaviviruses

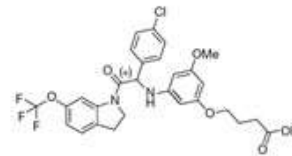
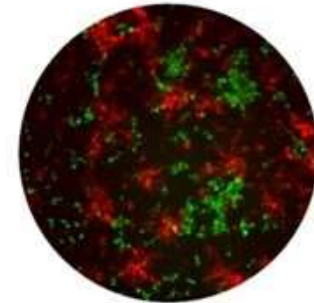
Dengue, Japanese encephalitis, Yellow fever



NITD-008 Pan-flavirus inhibitor



JNJ-A07 Dengue inhibitor



# The need for pan-enterovirus drugs

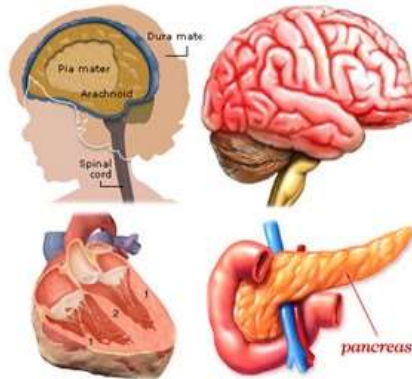
Enteroviruses, 10 species, > 100 sero/genotypes

Hand-Foot-and-Mouth Disease



*EV-A species*

Enterovirus A71



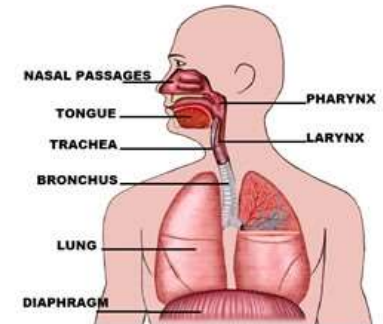
*EV-B species*

Coxsackievirus



*EV-C species*

Poliovirus



*EV-D species*

Enterovirus D68

## Highly potent pan-enterovirus inhibitor, with high barrier to resistance that targets the viral helicase

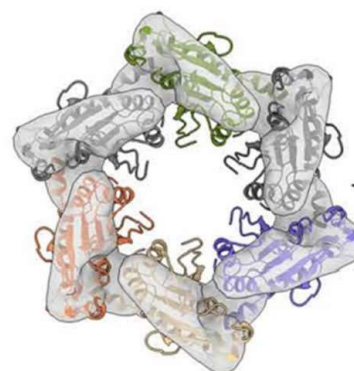
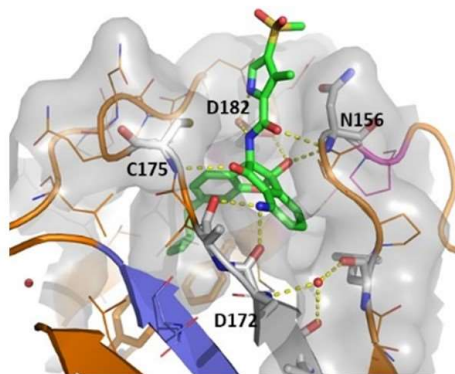
	CV-B3	CV-B4	Echo3	Echo9	Echo11	Echo30	EV-A71	CV-A9	CV-A21	EV-D68
Compound A (nM)	2.6	1.0	3.0	3.5	2.3	2.0	3.1	1.7	74	<1
Pleconaril (μM)	>25	ND	ND	0.19	<0.010	ND	>10	0.23	<0.010	0.4

Up to 1000-fold more potent than reference cmpd

	PV1 (Sabin)	PV1 (Chat)	PV2 (Sabin)	PV2 (W2)	PV3 (Sabin)	PV3 (Fox)
Compound A (nM)*	21	21	21	20	20	20
Pleconaril (μM)	>25	>25	1.8	16	0.17	15

Up to 1000-fold more potent than reference cmpd

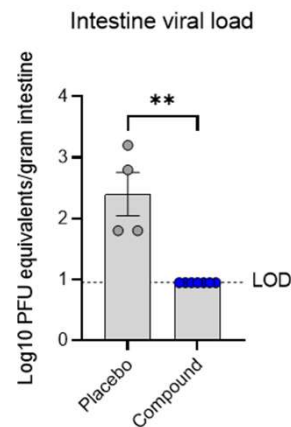
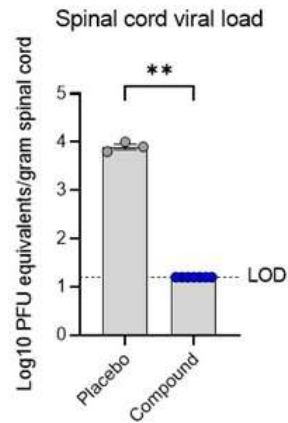
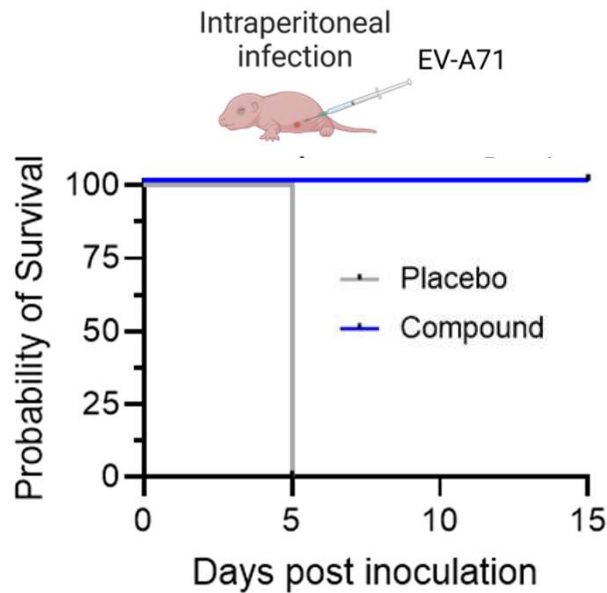
High *in vitro* barrier to resistance : ~20 weeks



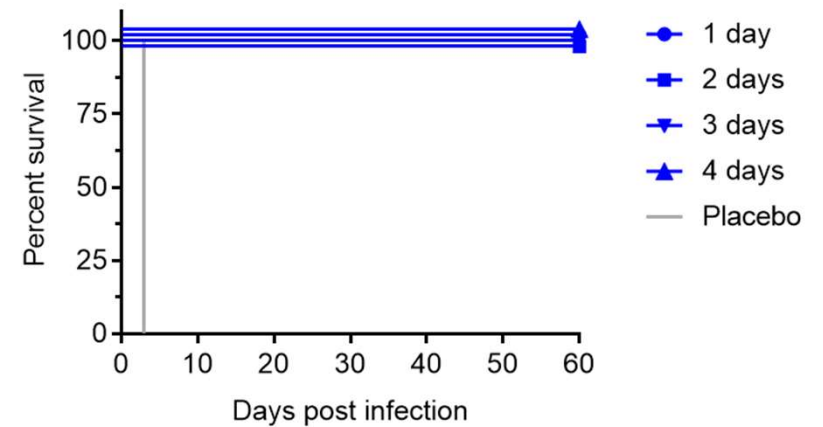
Hurdis et al., Sci Advances (2022)

# Highly potent in various mouse enterovirus infection models

## EV71 in SCID pups



## Coxsackie B4 in SCID mice



# Combinations...?

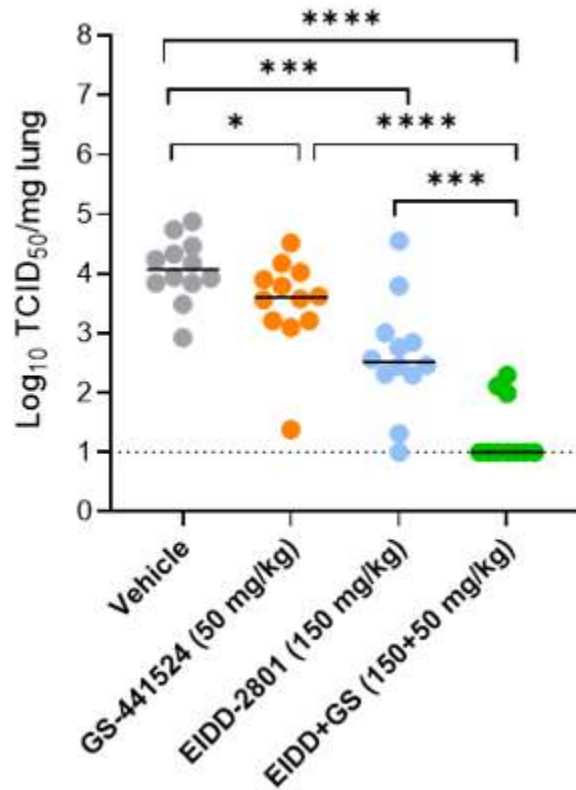
1. To increase coverage
2. increase potency
3. To avoid resistance to develop



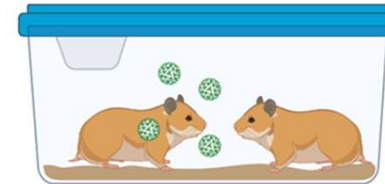
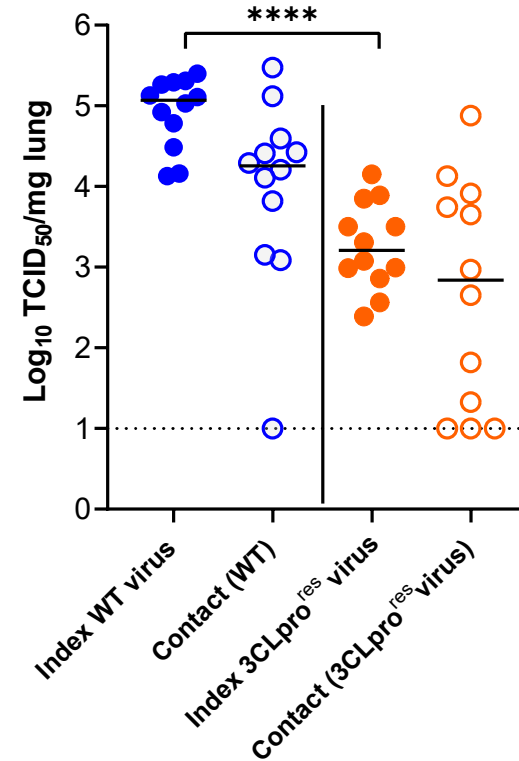
# Combinations to increase potency and to avoid resistance

## Increased potency of combination against SARS-COV2

Intranasal infection of index SARS-CoV-2 ( $1 \times 10^4$  TCID<sub>50</sub>)



## Transmission of Paxlovid resistant virus



Co-housing index with contact hamsters from day 1 to day 4



Pieter Leyssen, Lotte Coelmont, Dirk Jochmans, Kai Dallmeier, Suzanne Kaptein, Steven De Jonghe, Rana Abdelnabi, Robbert Boudewijns, Sapna Sharma, Jana Van Dycke, Lorena Sanchez Felipe, Lanjiao Wang, Laura Vangeel, Kim Donckers, Li-Hsin Li, Sander Jansen, Sebastiaan ter Horst, Ji Ma, Lana Langendries, Xinyu Wang, Viktor Lemmens, Arno Cuvry, Nguyen Dan Thuc Do, Xin Zhang, Nanci Dos Santos Ferreira, Emma Roux, Maïlis Charlotte Darmuzey, Lara Kelchtermans, Yuxia Lin, Zhen Wu, Caroline Collard, Carolien De Keyzer, Katelijne Haepers, Katrien Geerts, Jasper Rymenants, Sarah Debaveye, Kayvan Abbasi, Tina Van Buyten, Lindsey Bervoets, Elke Maas, Thibault Francken, Niels Cremers, Stijn Hendrickx, Winston Chui, Joost Schepers, Hendrik Jan Thibaut



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