

The search for antivirals for emerging and neglected viruses at the Rega Institute

Dirk Jochmans

Rega Institute for Medical Research
KU Leuven, Leuven, Belgium

June 9th, 2023

[Home](#)

The Neyts-lab of Virology, Antiviral Drug & Vaccine Research



Virologist Johan Neyts about vaccines and virus inhibitors | KU Leuven

KU LEUVEN

RESEARCH

Vaccine development

Bekijken op  YouTube

FIGHTING COVID-19

Watch our video to discover our search for potent antivirals for COVID-19 patients and learn more about our vaccine candidate.



research group Johan Neyts

Our mission

It is our mission to develop antiviral strategies and vaccines against a range of viruses.

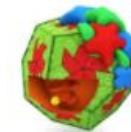
Click the icons below to find out more.



[Flaviviruses](#)



[Enteroviruses](#)



[Noroviruses](#)



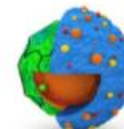
[Paramyxoviruses](#)



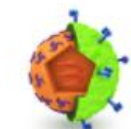
[Rabies](#)



[Coronaviruses](#)



[Hepatitis B virus](#)



[Togaviruses](#)



[Hepatitis E virus](#)



[Bunyaviruses](#)

© Neyts-lab; created by Cimaza

Viral infections against which antiviral drugs (examples) are available....

Herpesvirus



HIV



SARS-CoV2



HBV



HCV



HCV

(near 100% cure rate...)



POX



Influenza

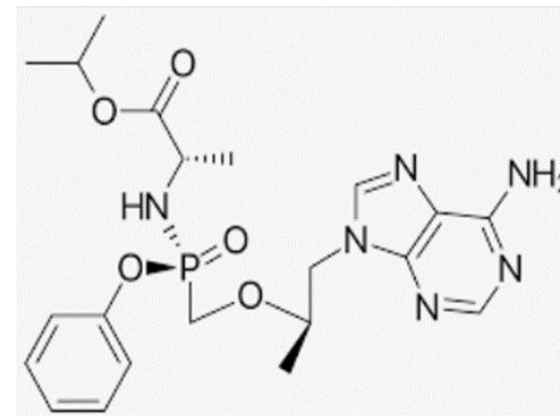


No (small molecule) antiviral drugs for any other virus or virus family

Earlier Antiviral Drug Discovery at KU Leuven: the HIV case



Erik De Clercq : virologist, KU Leuven
John Martin : CEO Gilead Sciences, Foster City
Antonin Holy : medicinal chemist, IOCB, Prague

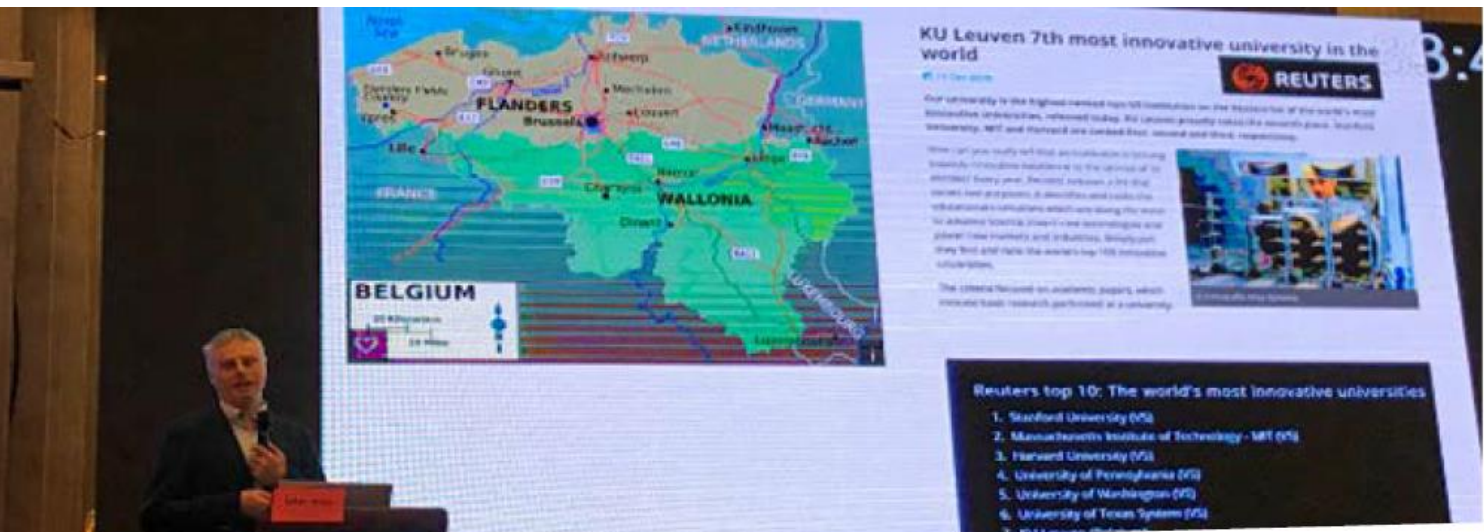


Tenofovir (two prodrugs)



Copyright: Gilead Sciences





Current Opinion in Virology 2013, 3:217–224

Intervention strategies for emerging viruses: use of antivirals

Yannick Debing, Dirk Jochmans and Johan Neyts

The 8th Wuhan International Symposium on Modern Virology

Keynote by Johan Neyts, Wuhan (Sept 2019)

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.

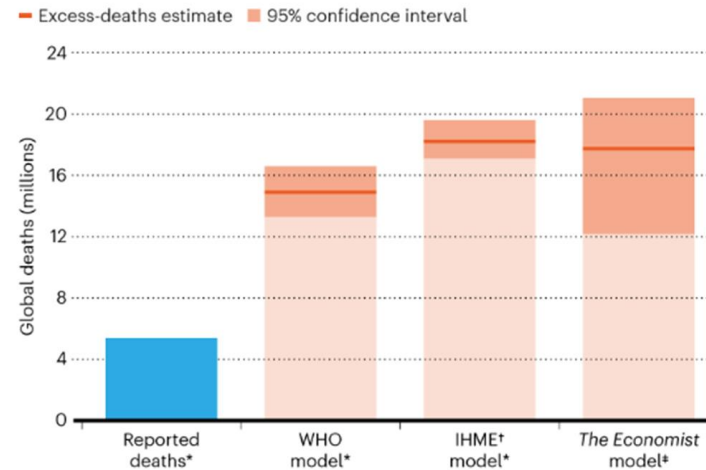
" If anything kills over 10 million people in the next few decades, it's most likely to be a highly infectious virus rather than a war "

Bill Gates,
TED X TALK 2015

**DISEASE
X**

COVID'S TRUE TOLL

The number of confirmed deaths (blue bar) caused by COVID-19 is much smaller than tallies of 'excess deaths' (pink bars), which are those above what is expected, during the pandemic.



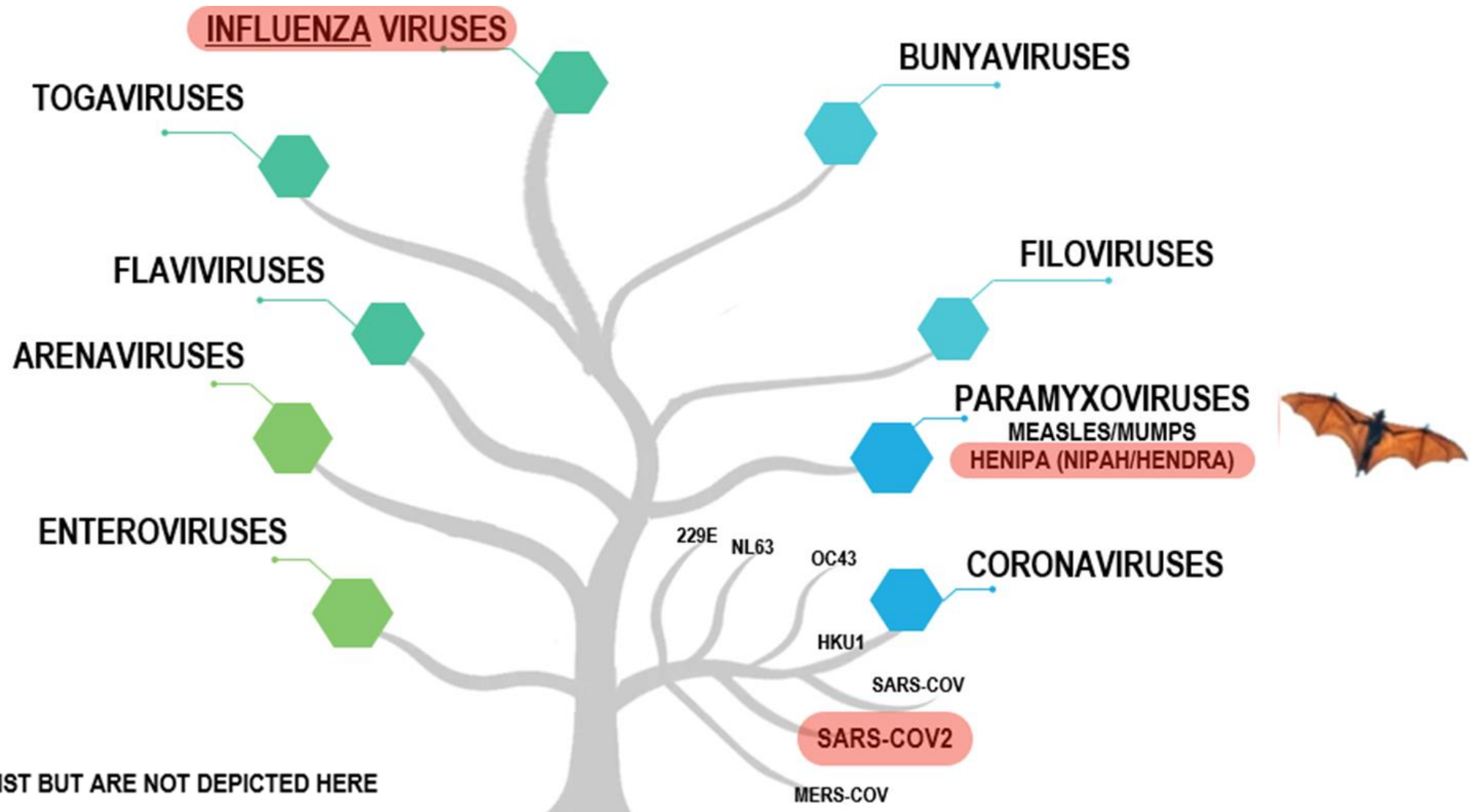
©nature

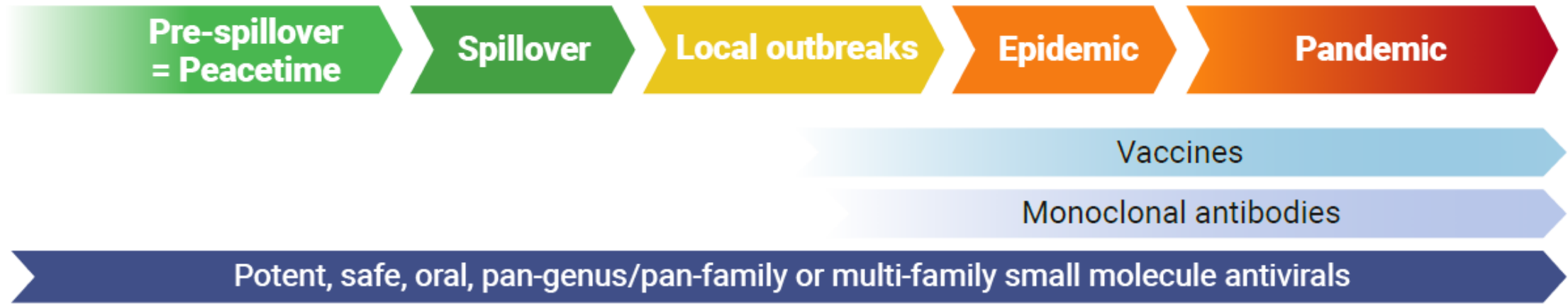
*Up to 31 December 2021; †Institute for Health Metrics and Evaluation; *up to 27 December 2021.

Sources: Our World in Data/The Economist/IHME/WHO



Need for broader-acting antivirals (pan-genus/pan-family)





Joining forces with CD3



CD3

CENTRE FOR
DRUG DESIGN
AND DISCOVERY

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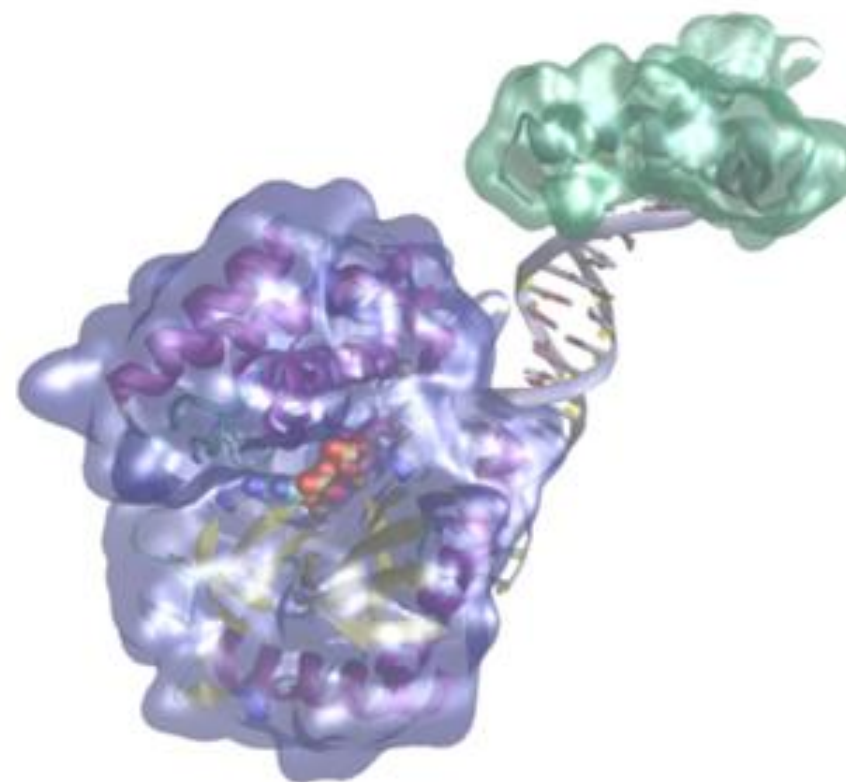
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COLLABORATE WITH US

Turning promising science into the medicines of tomorrow

CD3 is an investment fund and drug discovery center focusing on the discovery of new drugs based on innovative science from our partners. We bridge the gap between innovative biomedical research emerging from academic institutes or biotechs and the pharmaceutical industry, and create value for all stakeholders.

DISCOVER OUR PORTFOLIO



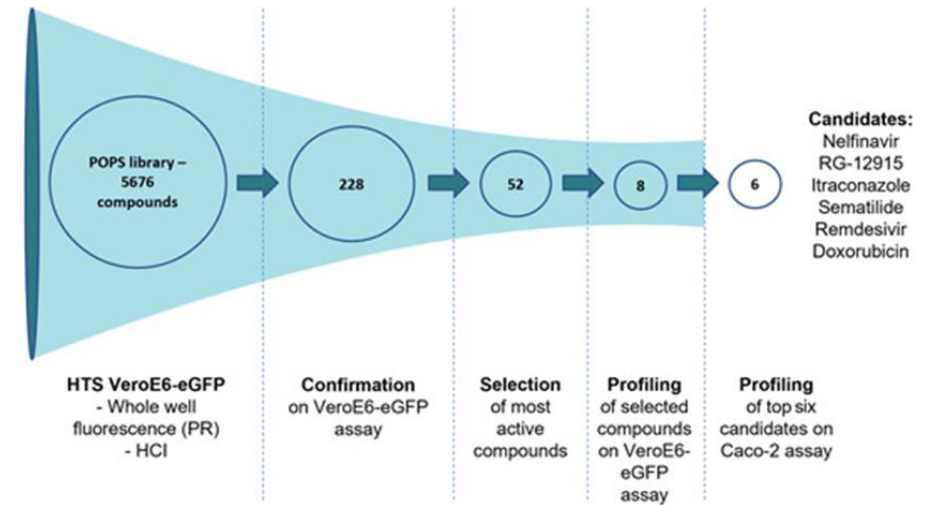
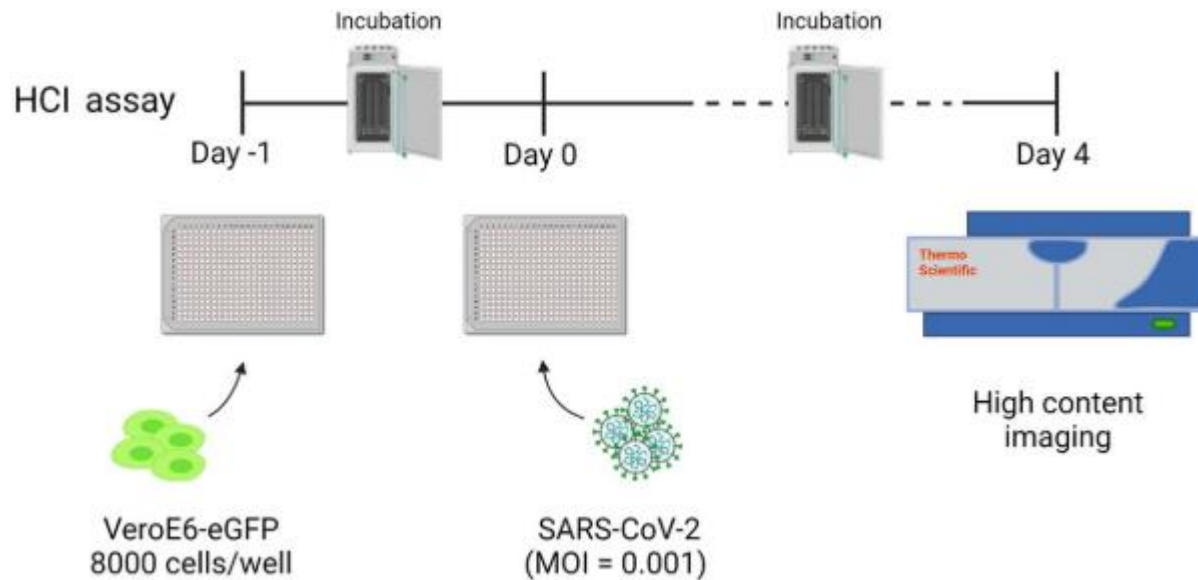
www.cd3.be

High-Throughput Antiviral Screening finding the needle in the haystack

Development and optimization of a high-throughput screening assay for in vitro anti-SARS-CoV-2 activity: Evaluation of 5676 Phase 1 Passed Structures

J Med Virol. 2022;1-11.

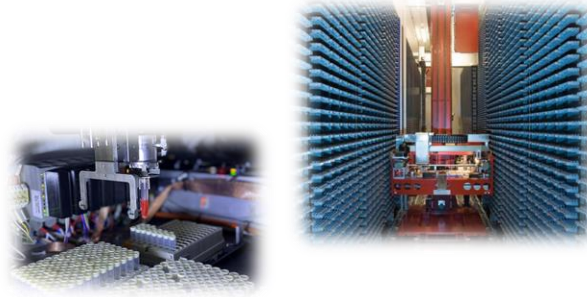
Winston Chiu¹ | Lore Verschueren² | Christel Van den Eynde² |
Christophe Buyck² | Sandra De Meyer² | Dirk Jochmans¹ | Denisa Bojkova³ |
Sandra Ciesek³ | Jindrich Cinatl³ | Steven De Jonghe¹ | Pieter Leyssen¹ |
Johan Neyts¹ | Marnix Van Lookk² | Ellen Van Damme²



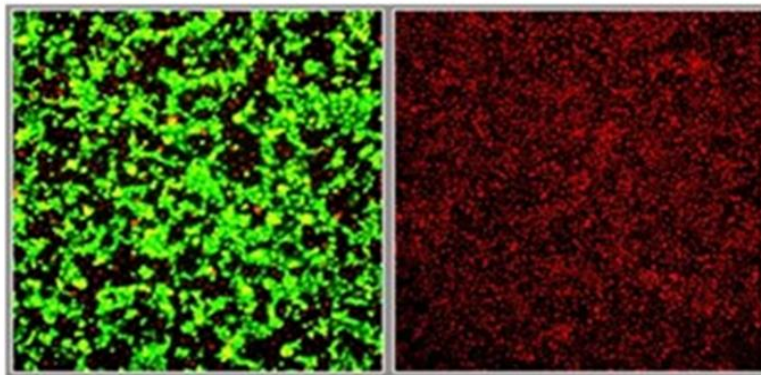
High-Throughput Antiviral Screening finding the needle in the haystack



Compound Libraries (~300.000 molecules)

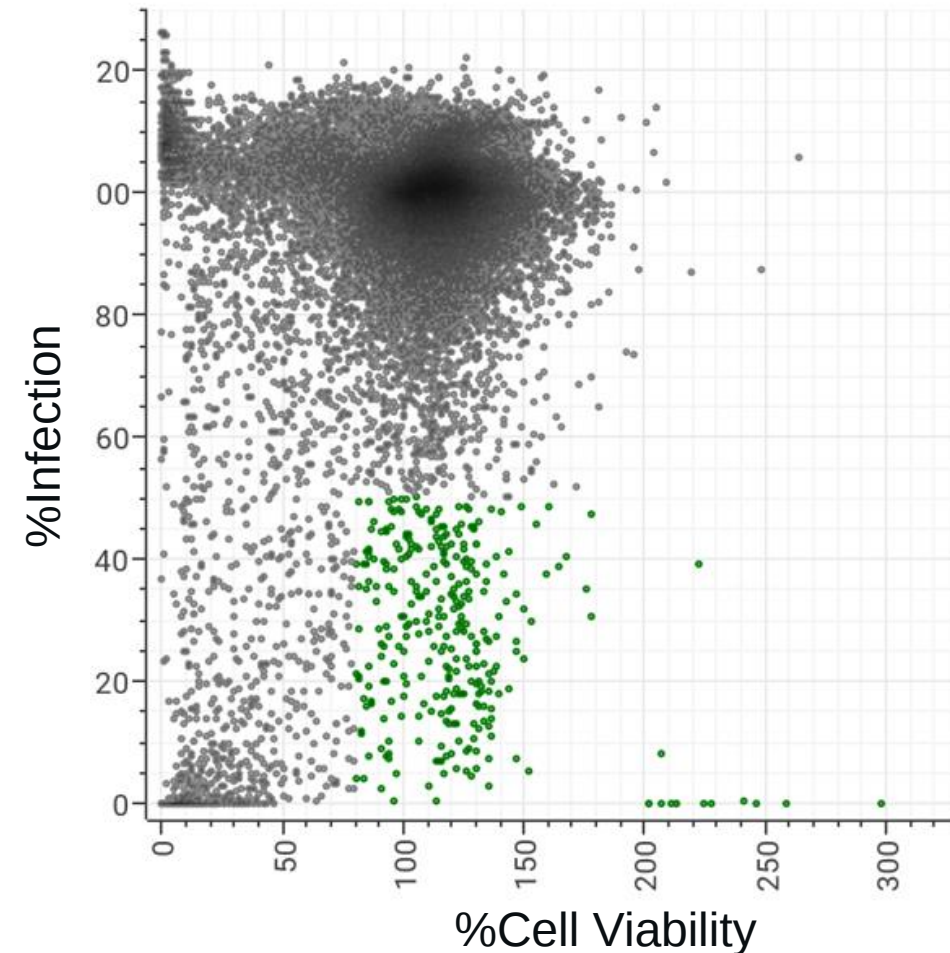
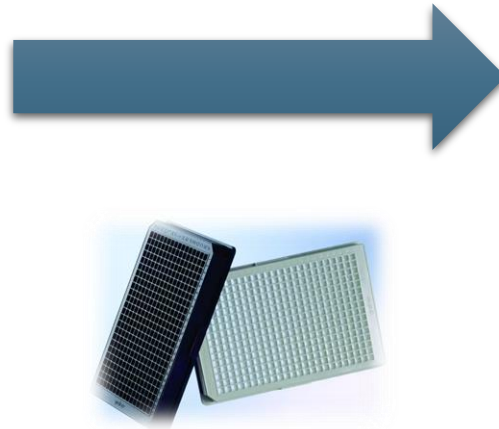


Antiviral Assay



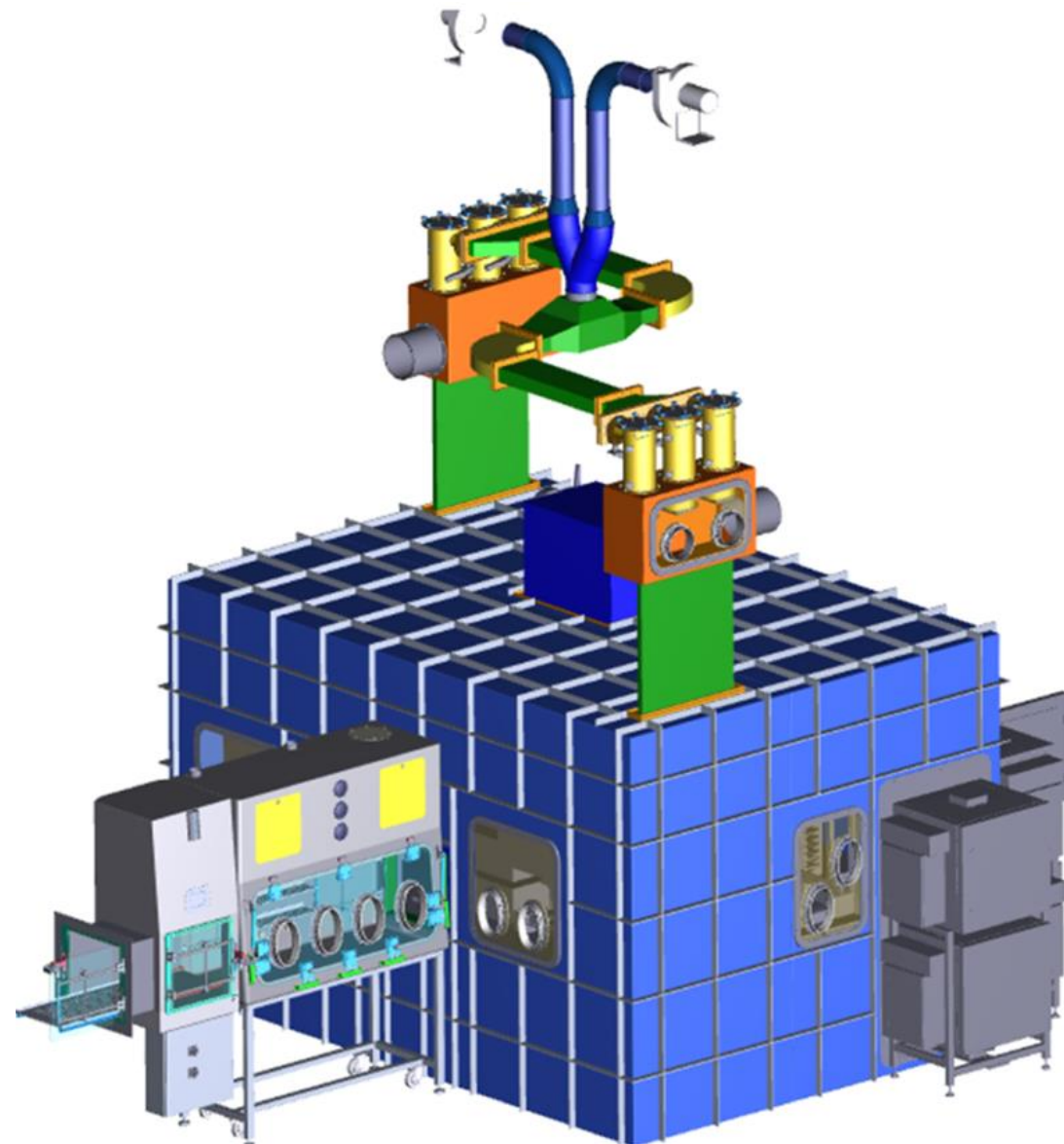
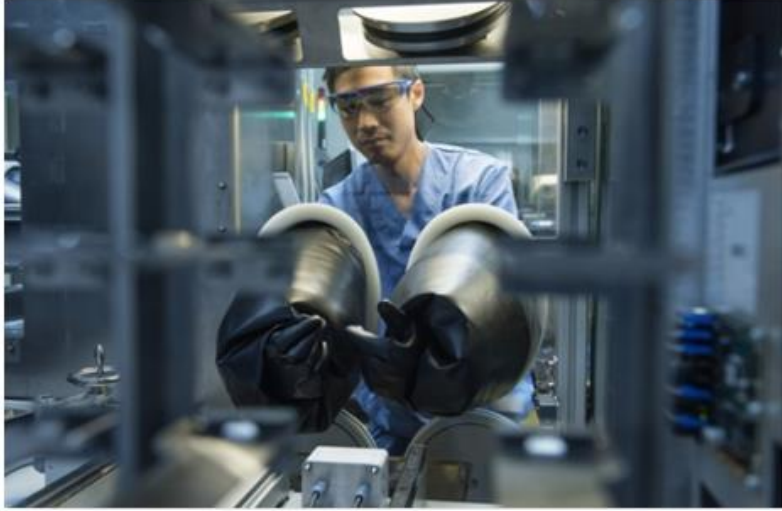
Virus control

Cell control



DE VIRUSBUNKER: bestbeveiligde labo ter wereld staat in Leuven

07/10/2017 om 03:01 door Kristof Bohez



Pieter Leyssen

Winston Chui, Joost Schepers, Thibault Francken



China releases genetic data on new coronavirus, now deadly

Lisa Schnirring | News Editor | CIDRAP News, January 11, 2020

Topics: [COVID-19](#), [SARS](#), [MERS-CoV](#)

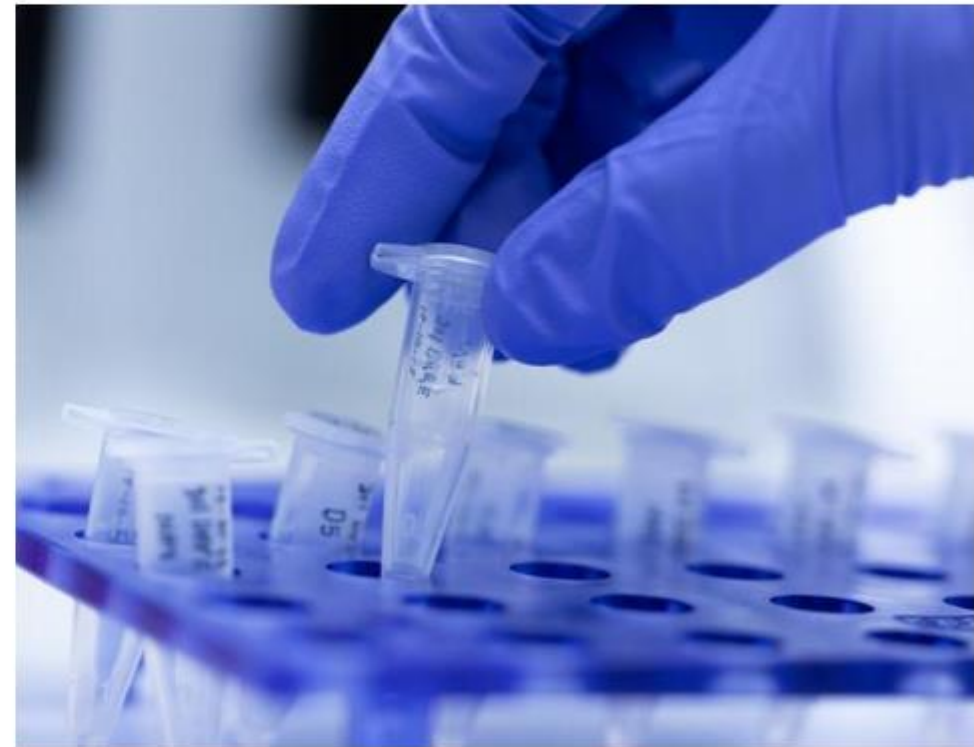


SHARE

In quickly moving developments last night, health officials from Wuhan, China, posted a novel coronavirus (nCoV) pneumonia outbreak update, which scaled back the number of cases to 41 and noted the first death, and researchers from China released the genetic sequence of the nCoV.

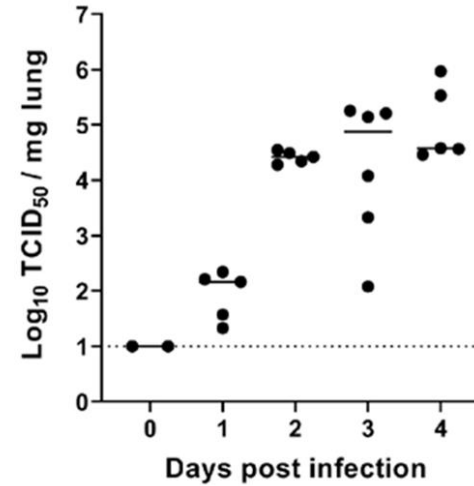
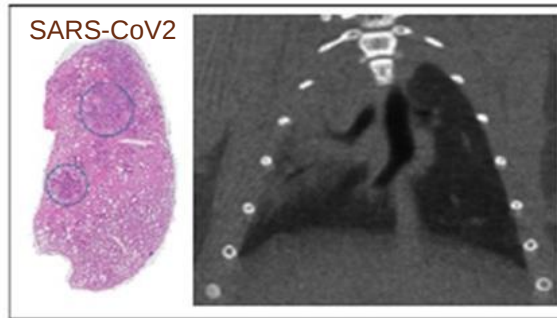
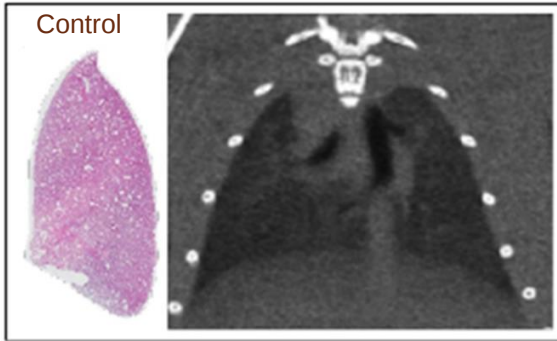
And this morning the World Health Organization (WHO) released several interim guidance documents, including advice on travel, lab testing, and medical evaluation.

Michael T. Osterholm, PhD, MPH, said he's pleased to see that health officials and scientists in China have released as much information as they have. He said the main focus now turns toward identifying the animal species that transmitted nCoV to humans and determining whether exposure to those animals poses a threat of outbreaks in other areas.



Sinhyu / iStock

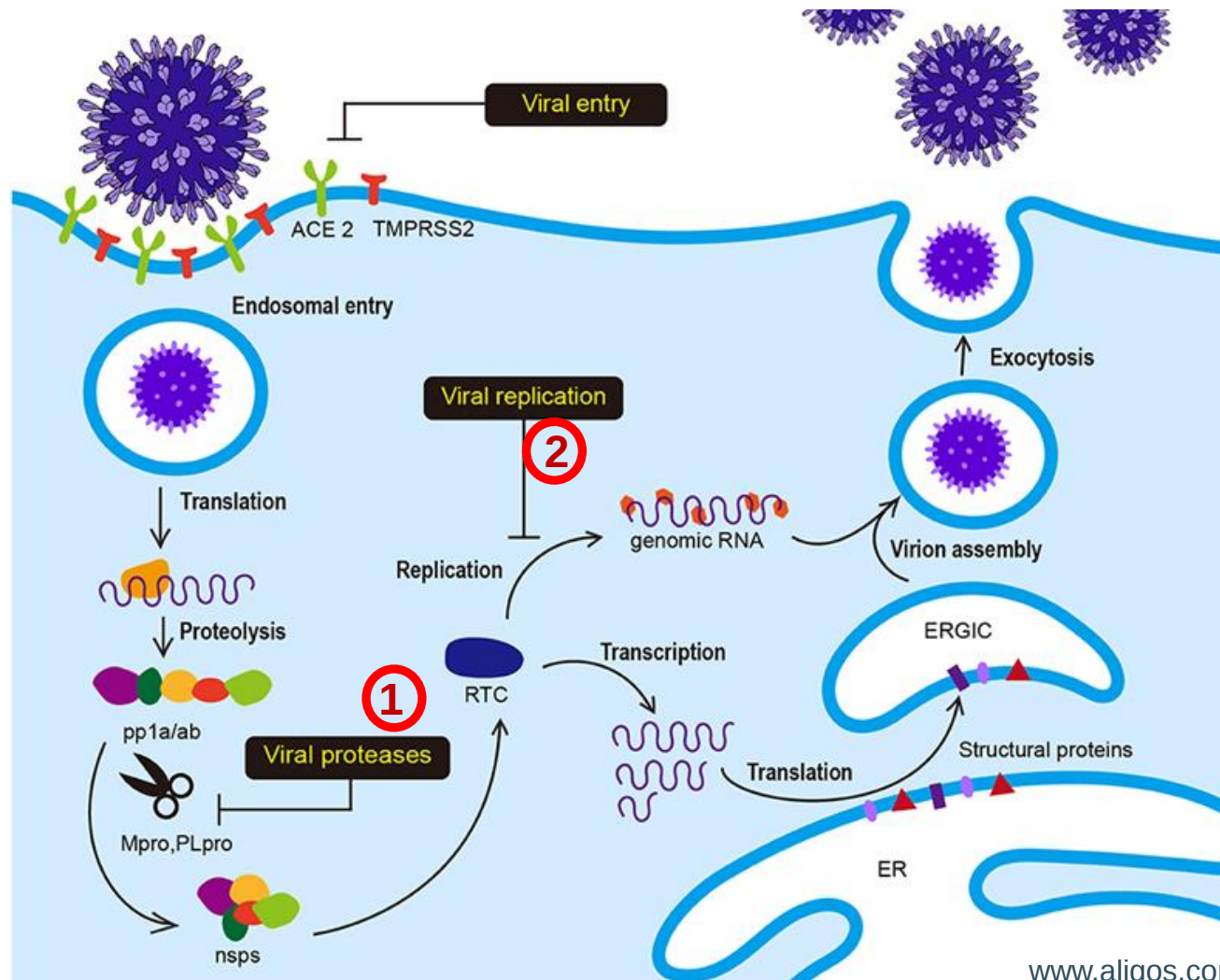
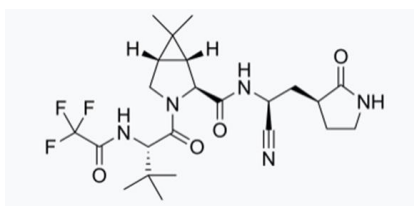
The COVID hamster model



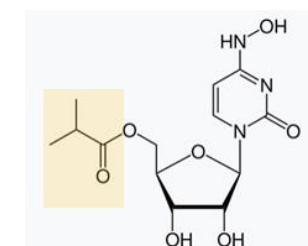
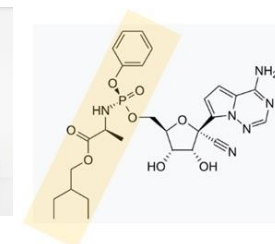


Small molecule antivirals against SARS-CoV2

1. Protease inhibitor



2. Polymerase inhibitors



www.aligos.com

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

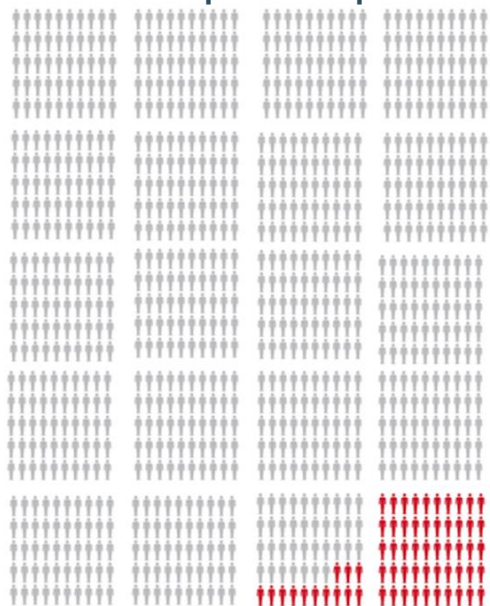
APRIL 14, 2022

VOL. 386 NO. 15

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

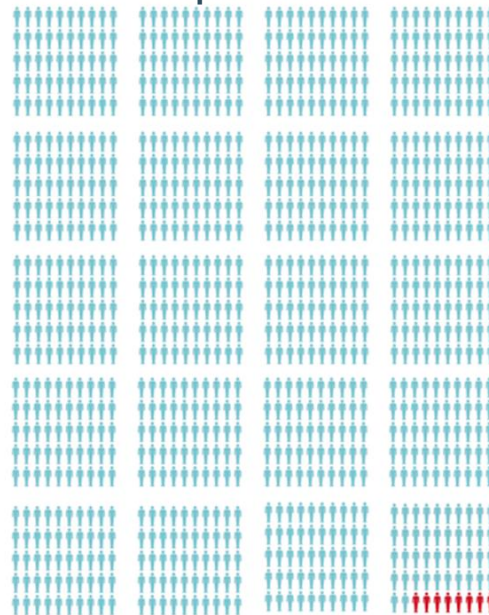
Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

1000 at risk patients : placebo



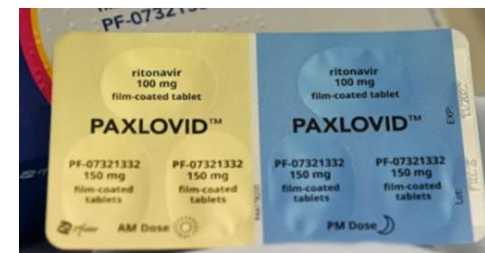
63 hospitalizations/death = 6.3%

1000 at risk patients : Paxlovid



8 hospitalizations/death : 0,8%

Paxlovid (nirmatrelvir + ritonavir)

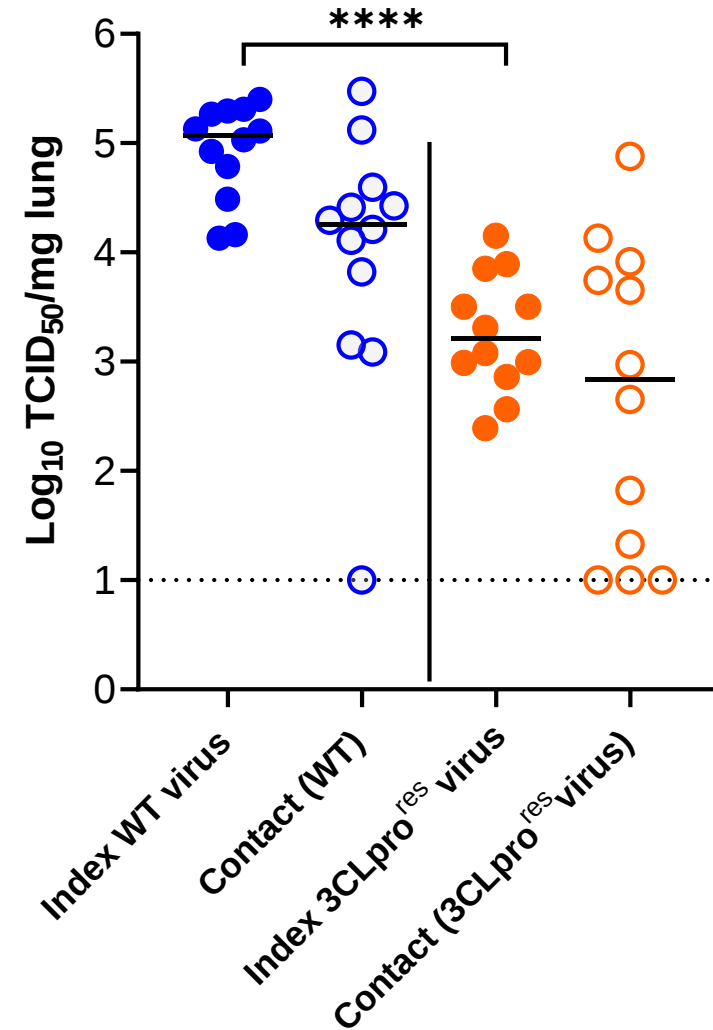
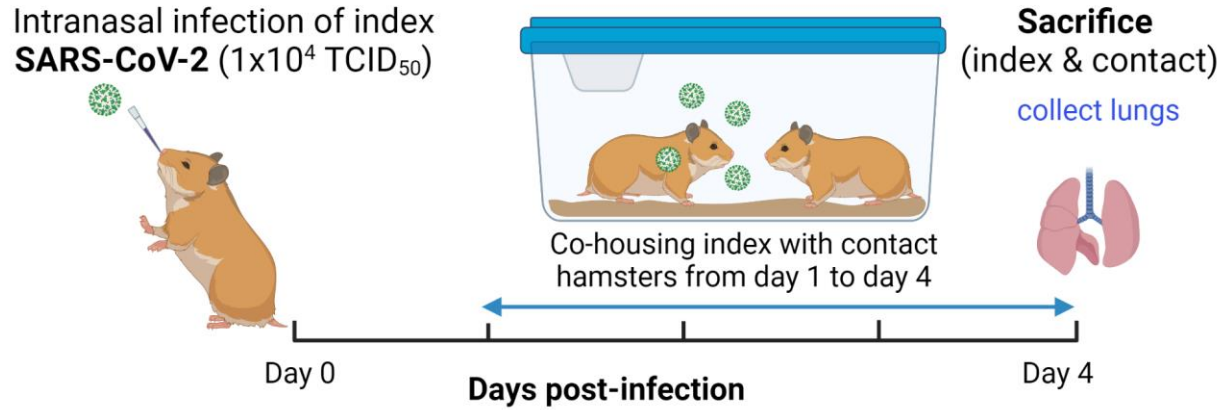


Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Before prescribing ritonavir-boosted nirmatrelvir, **clinicians should carefully review the patient's concomitant medications**, including over-the-counter medications, herbal supplements, and



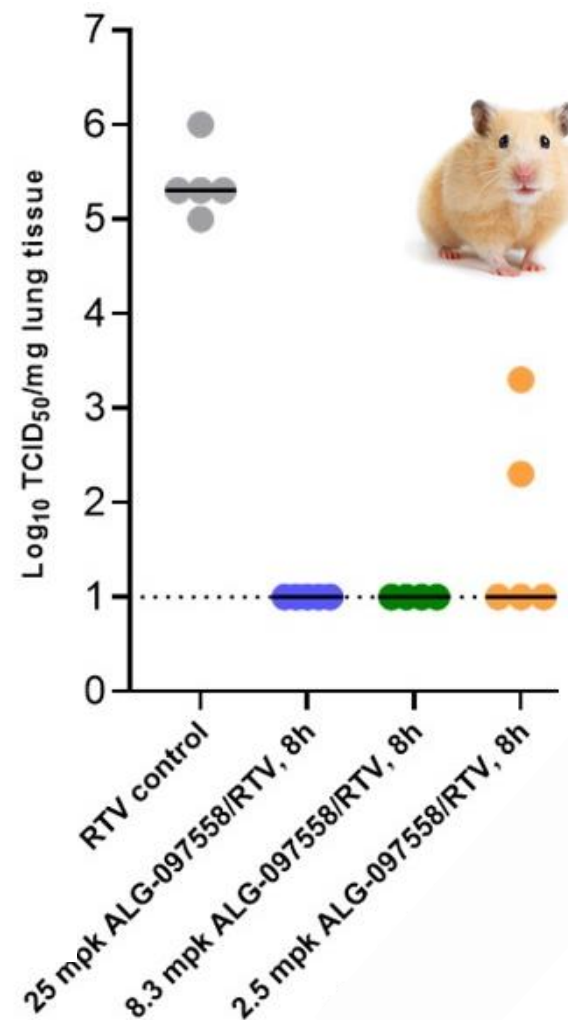
Transmission of nirmatrelvir resistant SARS-CoV2



ALG-097558 a ritonavir-free coronavirus protease inhibitor

Virus	Variant	EC ₅₀ (μM)	EC ₅₀ (μM)
		ALG-097558	Nirmatrelvir
SARS-CoV-2	03021/2020 (ancestral) ¹	0.012	0.114
	B.1.1.7 (alpha) ²	0.011	0.106
	B.1.617.2 (delta) ²	0.013	0.217
	B.1.1.529 (omicron) ¹	0.008	0.069
	BA.2 ¹	0.007	0.045
	BA.5 ¹	0.013	0.089
SARS-CoV-1	Isolate Vietnam ¹	0.022	0.173
MERS	EMC ¹	0.005	0.025
β-hCoV	OC43 ³	0.009	0.047
α-hCoV	229E ⁴	0.017	0.476

Cell lines used: (1) VeroE6-eGFP or Vero76 (in presence of 2 μM of P-glycoprotein inhibitor CP-100356), (2) A549-ACE2-TMPRSS2, (3) HeLa, (4) Huh-7; No cytotoxicity was detected for ALG-097558 at concentrations up to 100 μM.



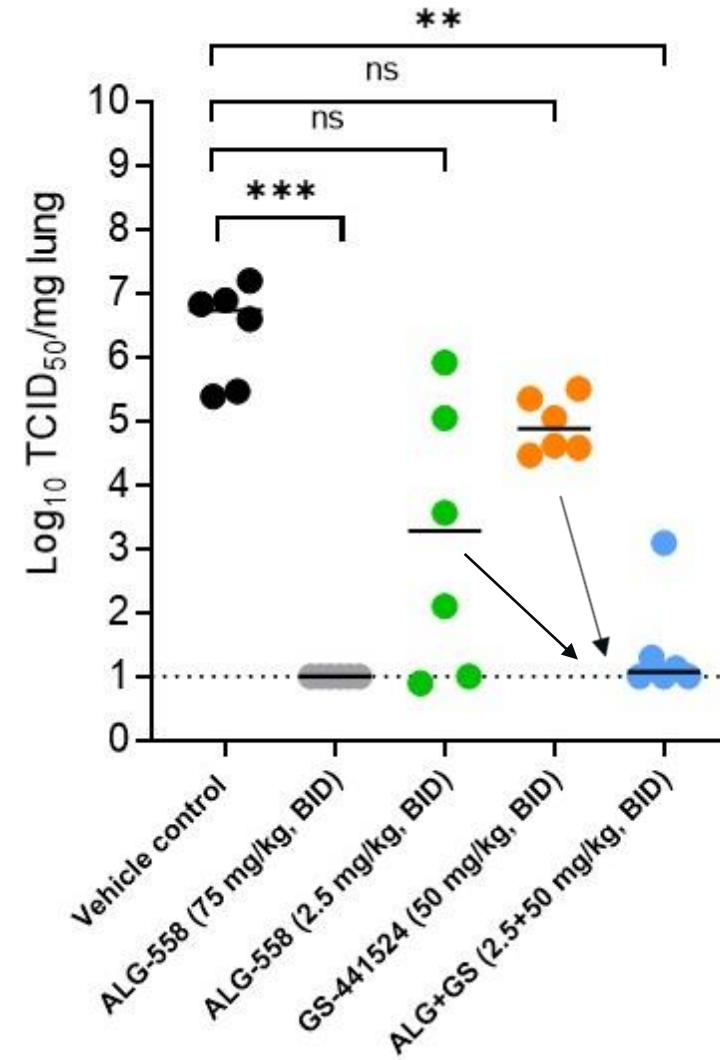


The power of combinations (1)

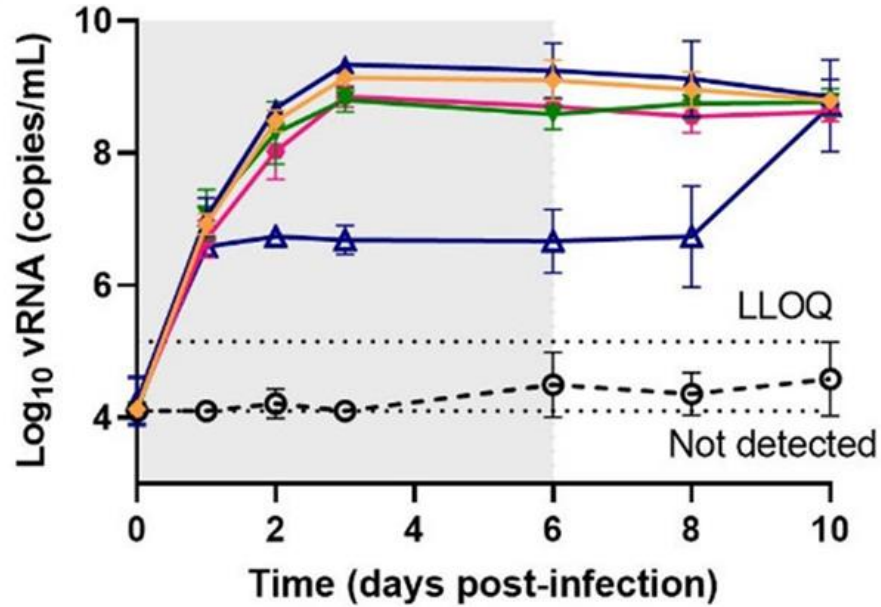
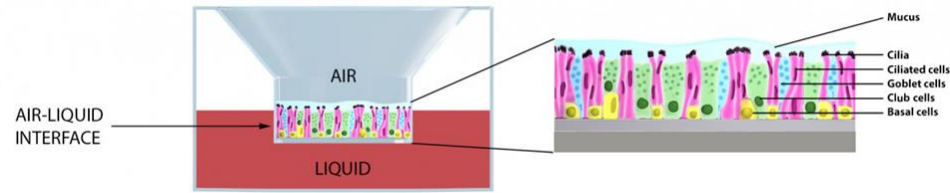
ALG-097558 +



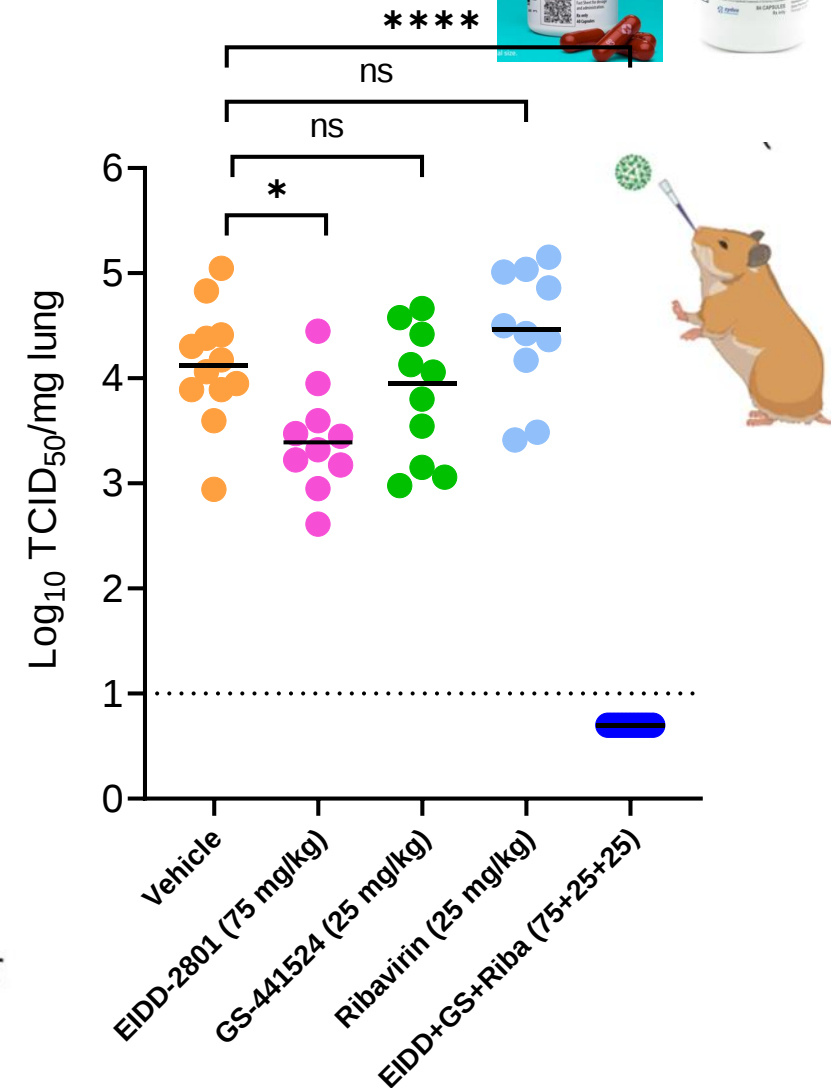
Combinations to (i) improve potency and (ii) prevent emergence of variants



The power of combinations (2)



- ◆— Infected untreated control
- Uninfected control
- ▲— Ribavirin 10 µM
- ▼— GS-441524 1 µM
- Molnupiravir 1 µM
- ▲— GS-441524+Ribavirin+Molnupiravir 1µM+10µM+1µM



Ultrapotent dengue inhibitor



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

Report to the
Community

2013

Economic Sustainability

janssen



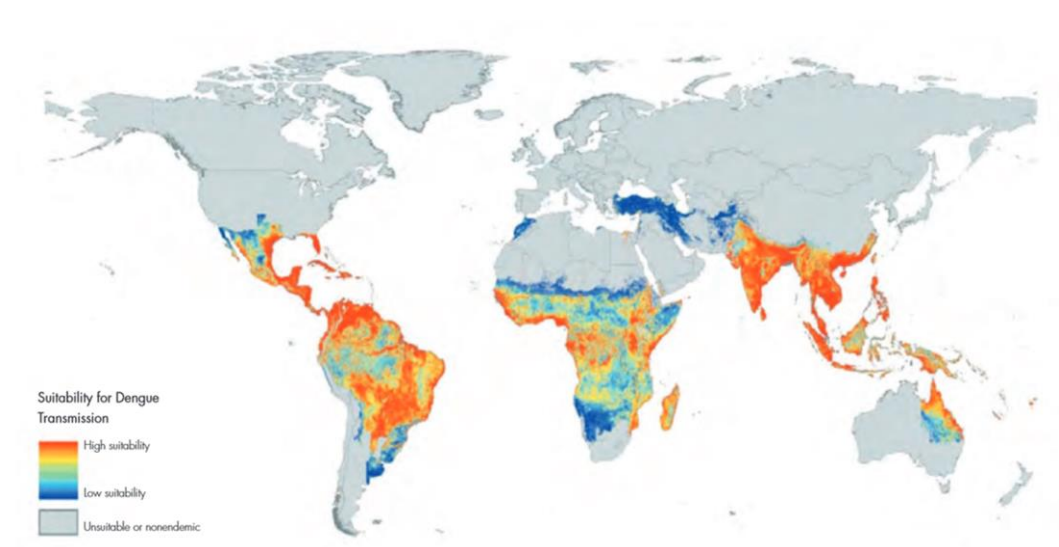
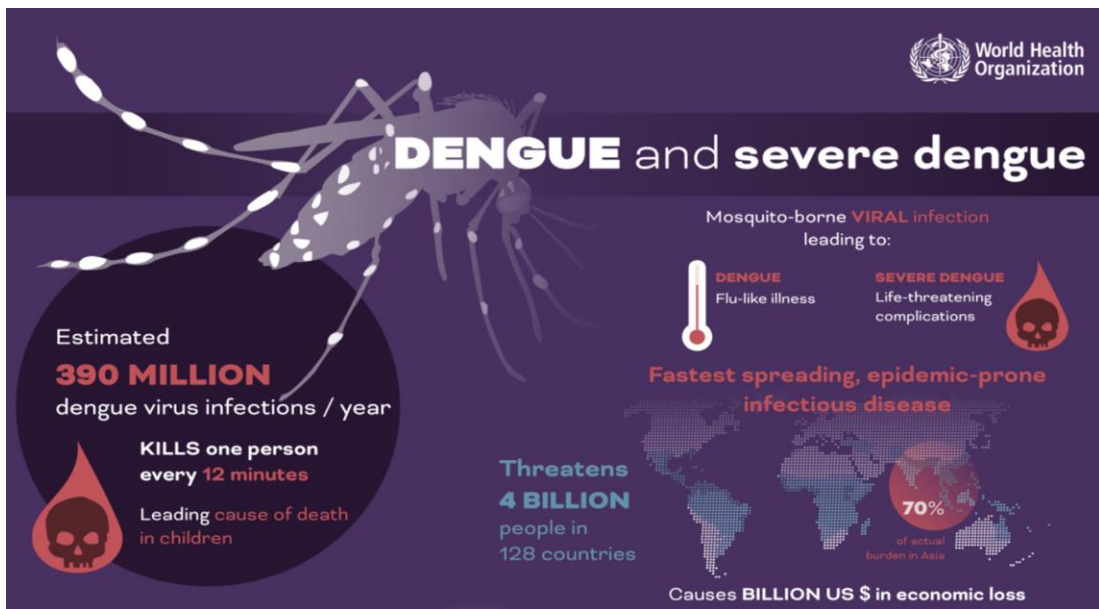
DE TIJD DONDERDAG 7 OKTOBER 2021

Belgen ontwikkelen krachtig middel tegen dodelijke tropische ziekte



Cientistas descobrem inibidor do vírus da dengue capaz de frear infecção

Estudo da Universidade de Leuven, na Bélgica, testou molécula que se mostrou 'altamente potente' na redução da carga viral da dengue e suas variantes em camundongos



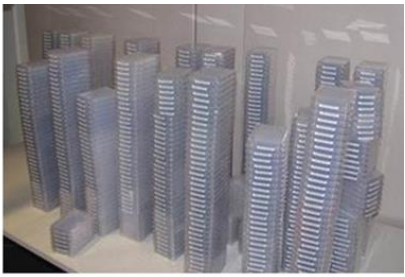
Courtesy of Dr. Trung Dinh The (Ho Chi Minh City, Vietnam)



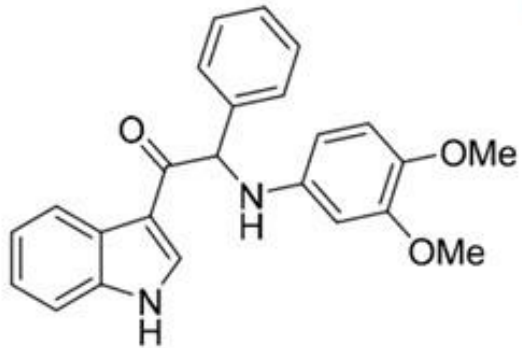
Toward antiviral therapy

Safe
Pan-serotype (1,2,3,4)
Oral once daily
Treatment & prophylaxis

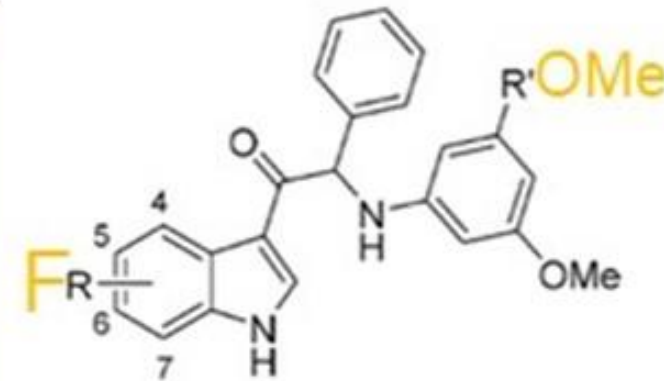




Screening followed by large medchem effort



DENV2 : 0,08 μ M
DENV1: 1,6 μ M
DENV3: 29 μ M
DENV4: 4,5 μ M



DENV2 : 0,007 μ M
DENV1 : 0,25 μ M
DENV3 : 0,68
DENV4 : 4,8 μ M

An ultrapotent pan-serotype dengue inhibitor



Suzanne Kaptein

Article

A pan-serotype dengue virus inhibitor targeting the NS3–NS4B interaction

<https://doi.org/10.1038/s41586-021-03990-6>

Received: 30 June 2020

Accepted: 1 September 2021

Published online: 6 October 2021

Suzanne J. F. Kaptein¹, Olivia Goethals², Dominik Kiemel³, Arnaud Marchand⁴, Bart Kesteleyn⁵, Jean-François Bonfanti^{6,11}, Dorothée Bardiot⁴, Bart Stoops⁵, Tim H. M. Jonckers⁵, Kai Dallmeier¹, Peggy Geluykens^{5,12}, Kim Thys⁵, Marjolein Crabbe⁵, Laurent Chatel-Chaix¹³, Max Münster², Gilles Querat⁷, Franck Touret⁷, Xavier de Lamballerie⁷, Pierre Raboisson^{5,14}, Kenny Simmen⁵, Patrick Chaltin^{4,8}, Ralf Bartenschlager^{3,9}, Marnix Van Loock^{2,15} & Johan Neyts^{1,10,16}

Article

Blocking NS3–NS4B interaction inhibits dengue virus in non-human primates

<https://doi.org/10.1038/s41586-023-05790-6>

Received: 29 June 2022

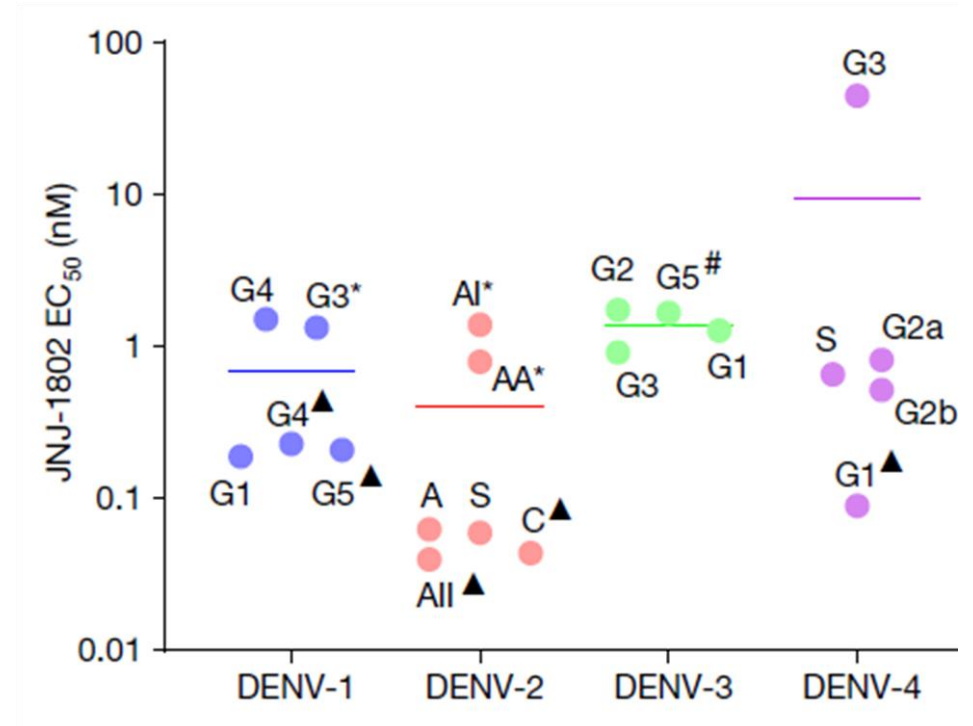
Accepted: 3 February 2023

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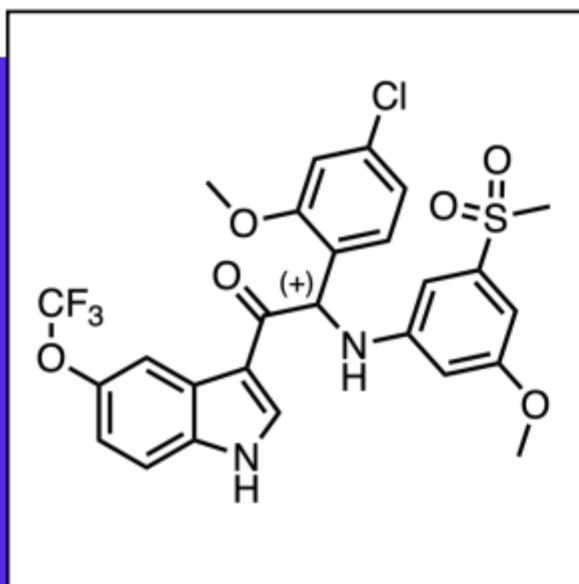
Check for updates

Olivia Goethals¹, Suzanne J. F. Kaptein², Bart Kesteleyn³, Jean-François Bonfanti^{4,5}, Liesbeth Van Wesenbeeck³, Dorothée Bardiot⁶, Ernst J. Verschoor⁷, Babs E. Verstrepen⁷, Zahra Fagrouch⁷, J. Robert Putnak⁸, Dominik Kiemel⁹, Oliver Ackaert¹⁰, Roel Straetemans¹¹, Sophie Lachau-Durand³, Peggy Geluykens^{3,12}, Marjolein Crabbe¹¹, Kim Thys³, Bart Stoops³, Oliver Lenz³, Lotke Tambuyzer³, Sandra De Meyer³, Kai Dallmeier², Michael K. McCracken⁸, Gregory D. Gromowski⁸, Wiriya Rutvisuttinunt⁸, Richard G. Jarman⁸, Nicos Karasavvas⁸, Franck Touret¹³, Gilles Querat¹³, Xavier de Lamballerie¹³, Laurent Chatel-Chaix¹⁴, Gregg N. Milligan¹⁵, David W. C. Beasley¹⁵, Nigel Bourne¹⁵, Alan D. T. Barrett¹⁵, Arnaud Marchand⁶, Tim H. M. Jonckers³, Pierre Raboisson^{3,16}, Kenny Simmen¹⁷, Patrick Chaltin^{6,18}, Ralf Bartenschlager^{9,19}, Willy M. Bogers⁷, Johan Neyts^{2,20} & Marnix Van Loock^{1,20}



Small Molecules of the Month

March 2023
drughunter.com



JNJ-1802

DENV

oral first-in-class DENV (NS3-NS4B) inhibitor

Ph. I for dengue

from a DENV-2 phenotypic antiviral screen

Nature, March 15, 2023

JANSSEN, BE + FR

Other Antiviral Targets in the Neyts-lab

KU Leuven announces collaboration and license agreement with Gilead Sciences for the development of new antivirals against the respiratory syncytial virus

17 May 2022



Acknowledgements

Neyts-lab Pieter Leyssen, Lotte Coelmont, Dirk Jochmans, Kai Dallmeier, Suzanne Kaptein, 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, Mailis 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

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Heidelberg University, Germany
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Olivia Goethals, Bart Kesteley, Jean-François Bonfanti, Bart Stoops, Peggy Geluykens, Kim Thijs, Marjolein Crabbe, Tim Jonckers, Pierre Raboisson, Kenny Simmen, Marnix Van Look

KRICT, Daejeon, South Korea
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Christopher Cawthorne – Georg Schramm – Koen Van Laere

Biomedical MRI and MoSAIC – KU Leuven
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Department of Animal, Dairy and Veterinary Sciences, Utah State University, USA
Yanan Liu – Rong Li – Zhongde Wang

Division of Translational Cell and Tissue Research – KU Leuven
Birgit Weynand

Department of Virology, Biomedical Primate Research Centre (BPRC), Rijswijk, The Netherlands
Babs E. Verstrepen – Kinga Böszörmény – Gwendoline Kiemenyi-Kayere – Nikki van Driel – Willy Bogers – Ernst Verschoor

Department of Viroscience, Erasmus University Medical Center, Rotterdam, The Netherlands
Thijs Kuiken

Leuven University Vaccinology Center (LUVAC), and KU Leuven Department of Public Health and Primary Care – KU Leuven
Corinne Vandermeulen



THANK YOU TEAM !!



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