The importance of antivirals in pandemic preparedness

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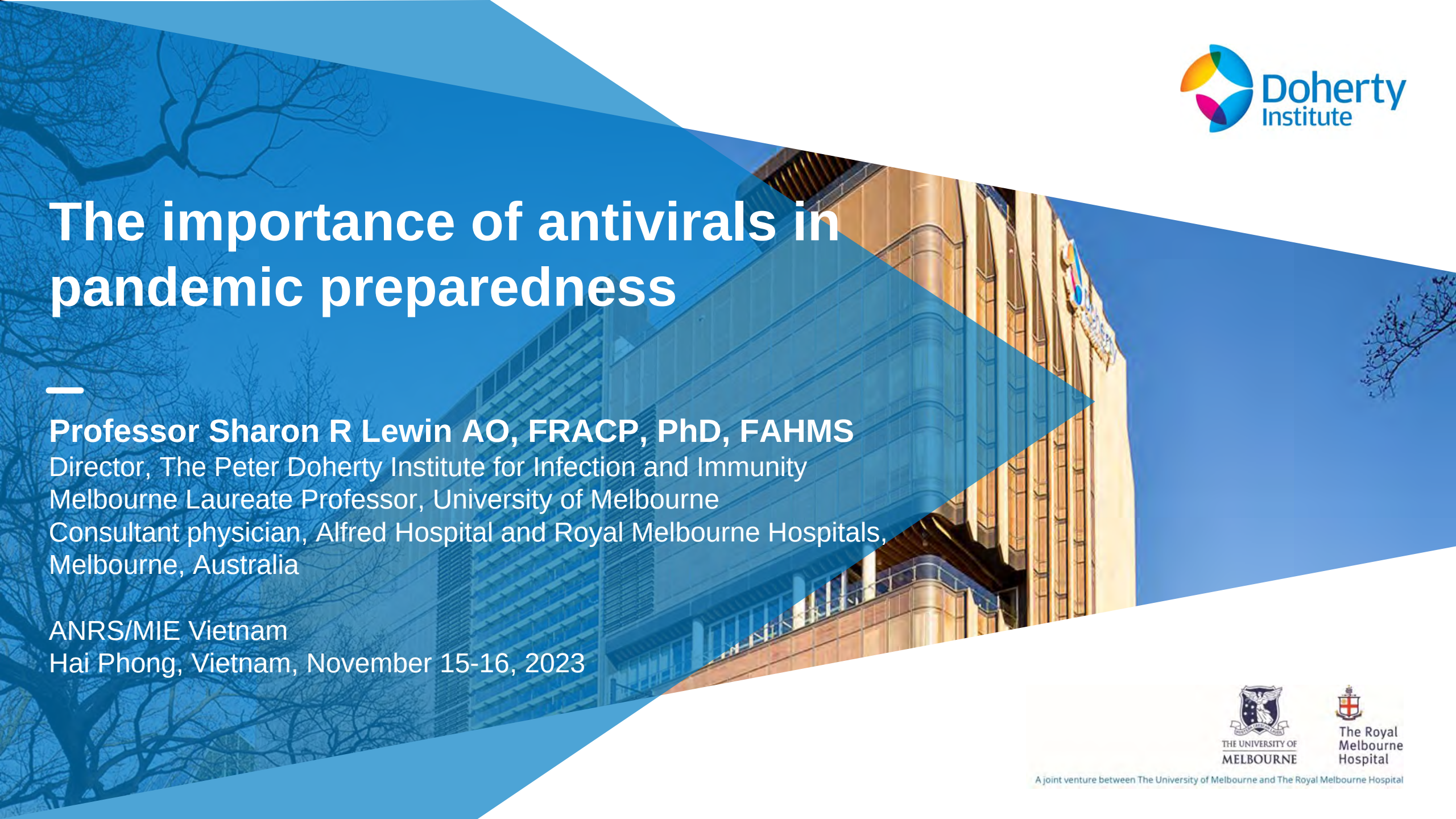
ANRS/MIE Vietnam
Hai Phong, Vietnam, November 15-16, 2023



Doherty Institute

THE UNIVERSITY OF MELBOURNE

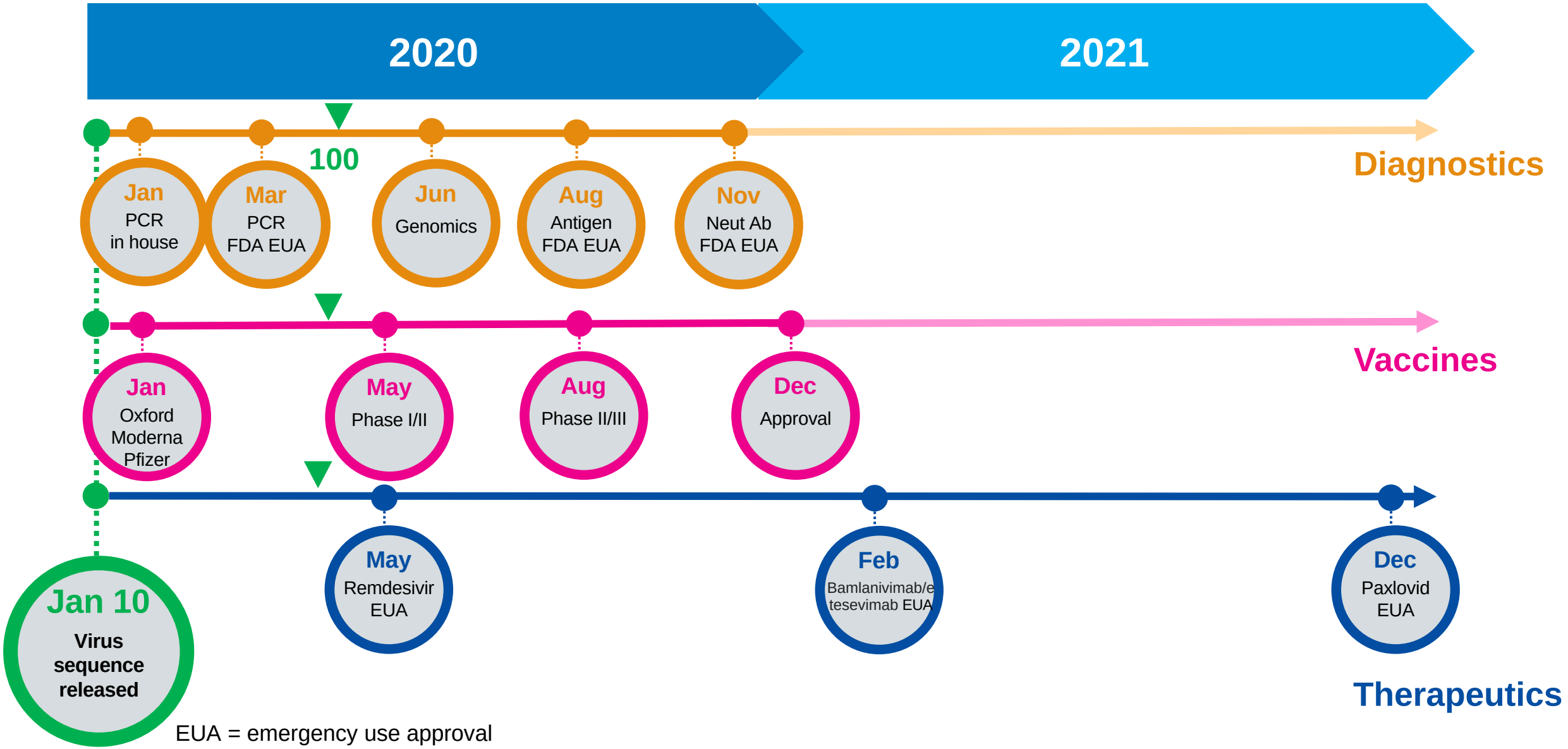
The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

The 100 days mission for vaccines, diagnostics and therapeutics

Coalition for Epidemic Preparedness Innovation (CEPI) aspires for the world to be able to respond to the next Disease X with a new vaccine in just 100 days

The 100 day mission: is it remotely feasible?



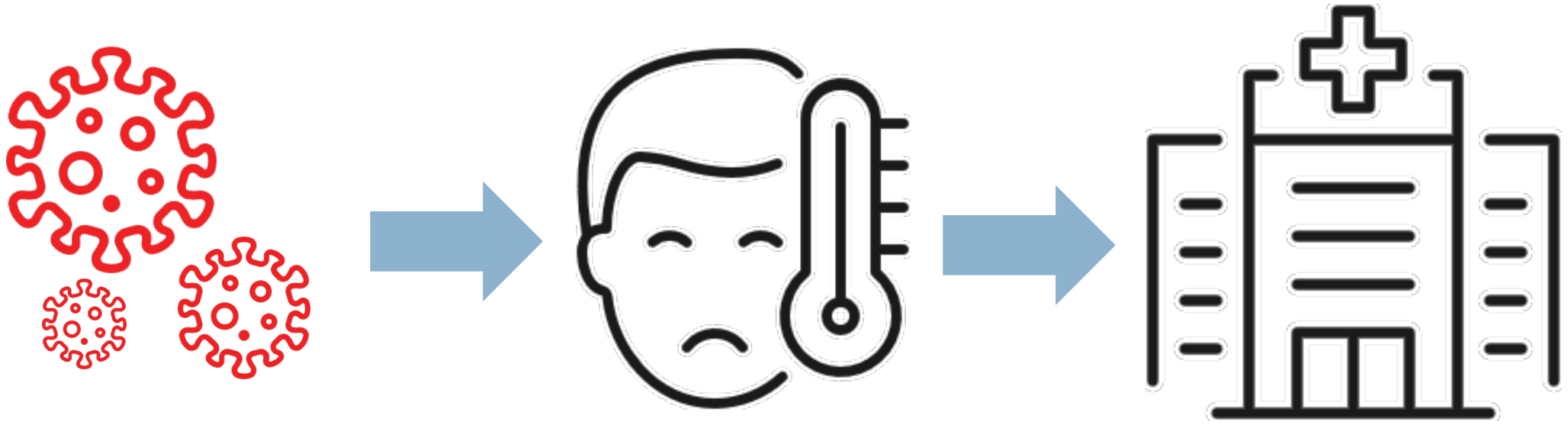
EUA = emergency use approval

Challenges in developing antivirals for SARS-CoV2

- The **pathogenesis of COVID-19 is complex**: the different phases of early viral replication and later immunological disease meant antivirals had to be given early to have an impact
- Current **available technology for antiviral development** takes time and…… can lead to some wrong turns
- No existing models of highly active antivirals for **respiratory pathogens**
- Minimal investment in antivirals relative to vaccines for COVID-19: estimated investment in **vaccines is $137 billion** compared to **antivirals being $7 billion**

. Source: Vanderbilt Vaccine Centre, BMGF; Wellcome Trust; KeNUP Foundation report January 2021. Figures in AU$

Direct acting antiviral therapeutics are important for individuals and population control of a pandemic



Individual risk of acquiring infection

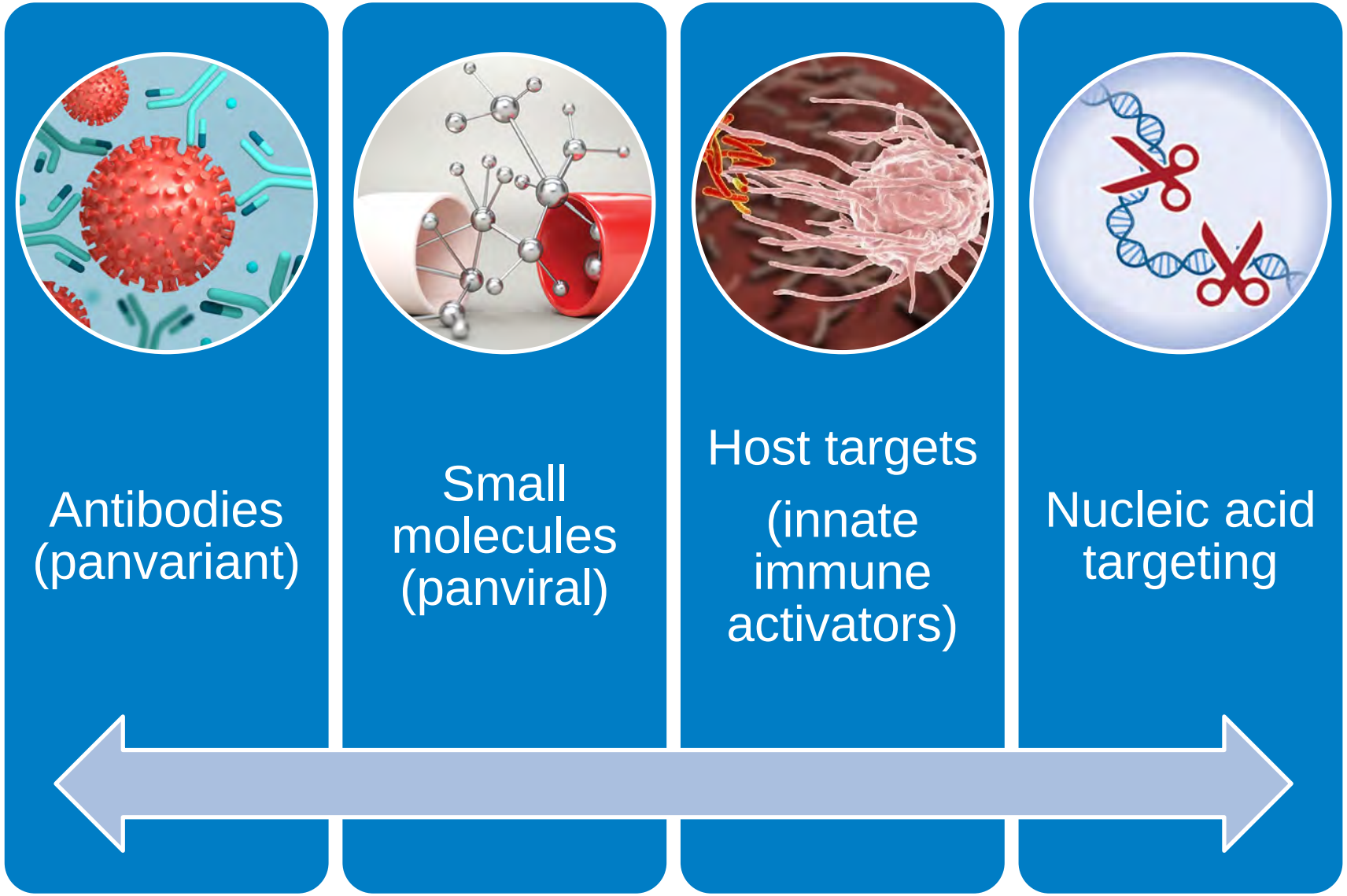
Individual risk of acquiring disease

Individual risk of requiring hospitalization

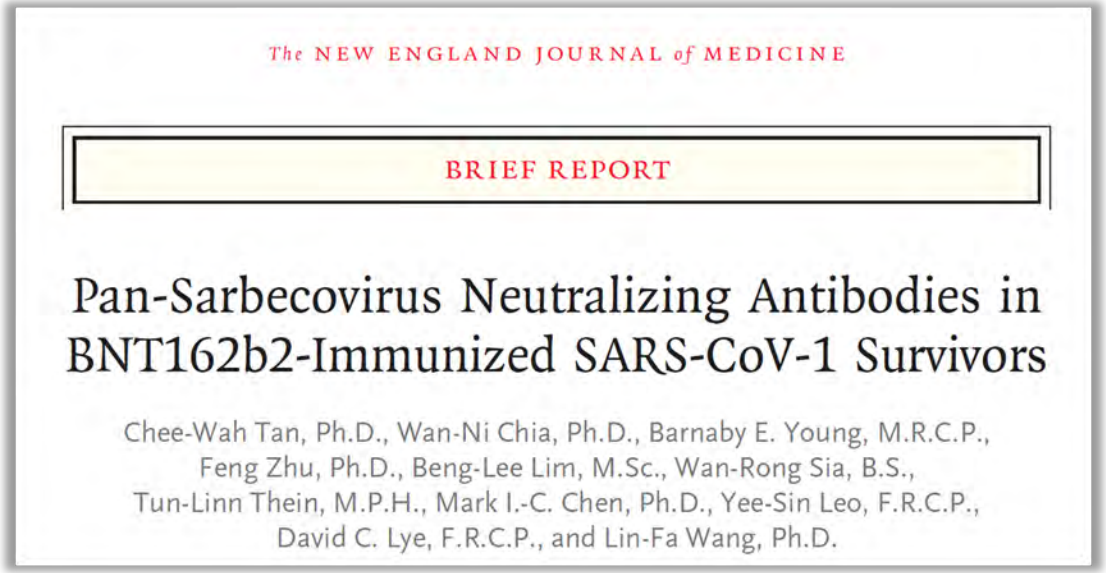
A major advantage is that directing antivirals **act immediately** and are needed if we **dont/cant develop a vaccine**

Meeting the challenge for direct acting antivirals at speed

Potential strategies for direct acting antivirals at speed



Pan-sarbecovirus antibodies are being developed now and need to be available in the future

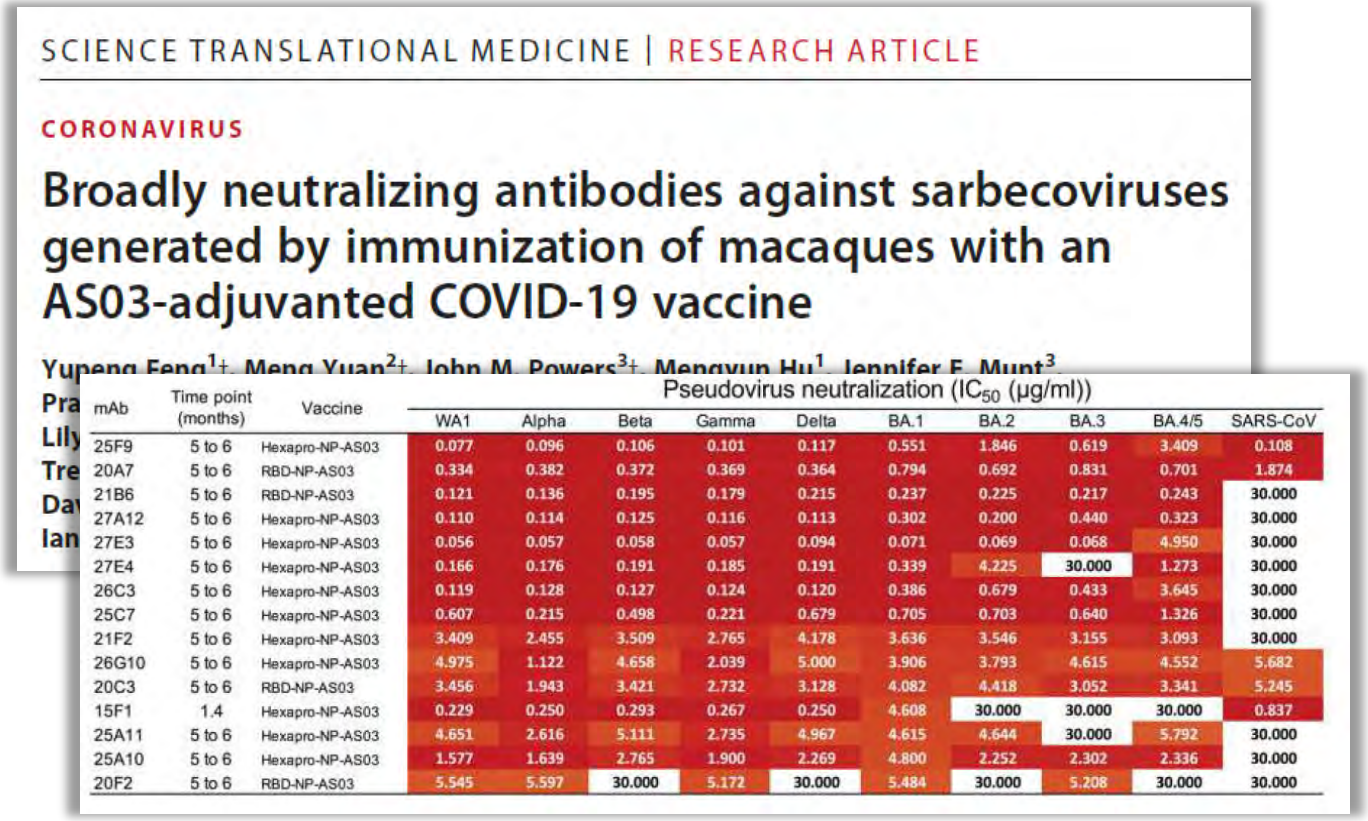


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors

Chee-Wah Tan, Ph.D., Wan-Ni Chia, Ph.D., Barnaby E. Young, M.R.C.P., Feng Zhu, Ph.D., Beng-Lee Lim, M.Sc., Wan-Rong Sia, B.S., Tun-Linn Thein, M.P.H., Mark I.-C. Chen, Ph.D., Yee-Sin Leo, F.R.C.P., David C. Lye, F.R.C.P., and Lin-Fa Wang, Ph.D.



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

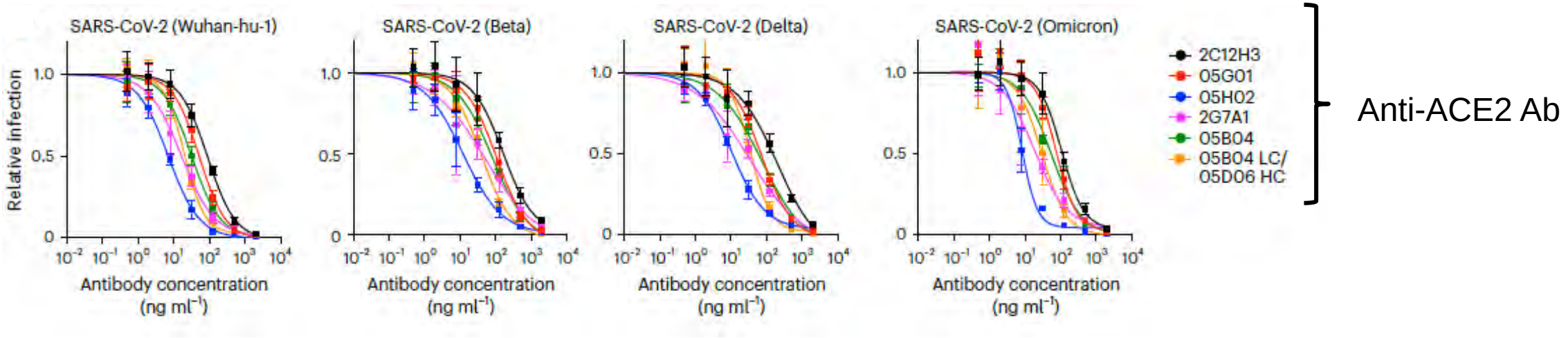
Broadly neutralizing antibodies against sarbecoviruses generated by immunization of macaques with an AS03-adjuvanted COVID-19 vaccine

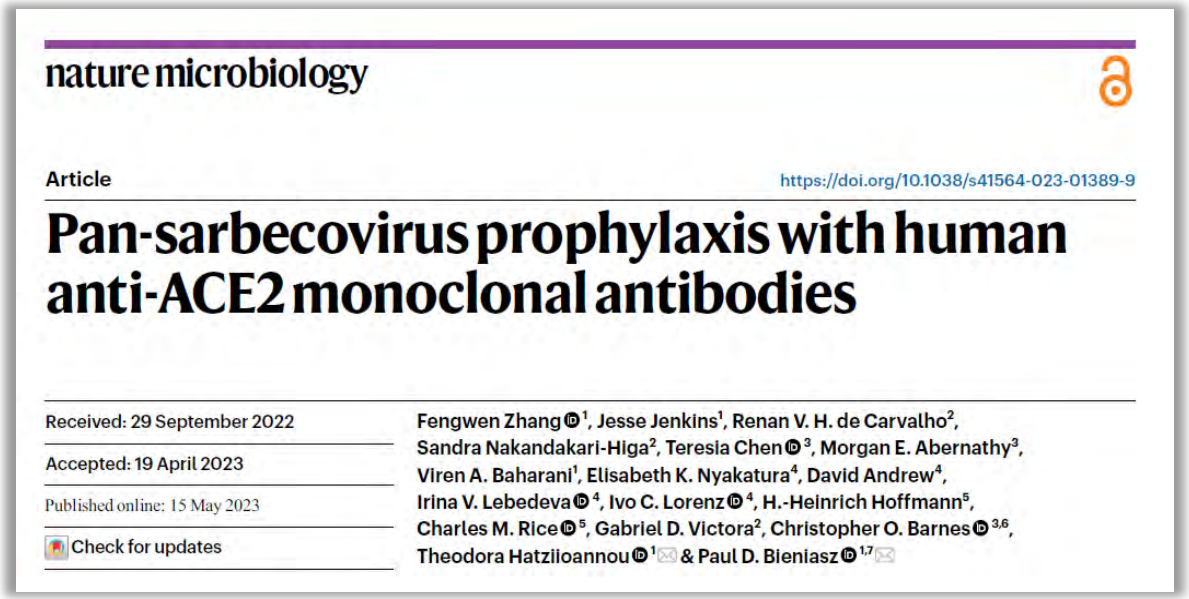
mAb	Time point (months)	Vaccine	Pseudovirus neutralization (IC_{50} (μg/ml))									
			WA1	Alpha	Beta	Gamma	Delta	BA.1	BA.2	BA.3	BA.4/5	SARS-CoV
25F9	5 to 6	Hexapro-NP-AS03	0.077	0.096	0.106	0.101	0.117	0.551	1.846	0.619	3.409	0.108
20A7	5 to 6	RBD-NP-AS03	0.334	0.382	0.372	0.369	0.364	0.794	0.692	0.831	0.701	1.874
21B6	5 to 6	RBD-NP-AS03	0.121	0.136	0.195	0.179	0.215	0.237	0.225	0.217	0.243	30.000
27A12	5 to 6	Hexapro-NP-AS03	0.110	0.114	0.125	0.116	0.113	0.302	0.200	0.440	0.323	30.000
27E3	5 to 6	Hexapro-NP-AS03	0.056	0.057	0.058	0.057	0.094	0.071	0.069	0.068	4.950	30.000
27E4	5 to 6	Hexapro-NP-AS03	0.166	0.176	0.191	0.185	0.191	0.339	4.225	30.000	1.273	30.000
26C3	5 to 6	Hexapro-NP-AS03	0.119	0.128	0.127	0.124	0.120	0.386	0.679	0.433	3.645	30.000
25C7	5 to 6	Hexapro-NP-AS03	0.607	0.215	0.498	0.221	0.679	0.705	0.703	0.640	1.326	30.000
21F2	5 to 6	Hexapro-NP-AS03	3.409	2.455	3.509	2.765	4.178	3.636	3.546	3.155	3.093	30.000
26G10	5 to 6	Hexapro-NP-AS03	4.975	1.122	4.658	2.039	5.000	3.906	3.793	4.615	4.552	5.682
20C3	5 to 6	RBD-NP-AS03	3.456	1.943	3.421	2.732	3.128	4.082	4.418	3.052	3.341	5.245
15F1	1.4	Hexapro-NP-AS03	0.229	0.250	0.293	0.267	0.250	4.608	30.000	30.000	30.000	0.837
25A11	5 to 6	Hexapro-NP-AS03	4.651	2.616	5.111	2.735	4.967	4.615	4.644	30.000	5.792	30.000
25A10	5 to 6	Hexapro-NP-AS03	1.577	1.639	2.765	1.900	2.269	4.800	2.252	2.302	2.336	30.000
20F2	5 to 6	RBD-NP-AS03	5.545	5.597	30.000	5.172	30.000	5.484	30.000	5.208	30.000	30.000

Multiple monoclonal antibodies that can effectively neutralise **all sarbecoviruses tested *in vitro*** identified from patients with COVID-19, SARS-CoV1 survivors and post immunisation of animals and humans

Wang PF et al., Emerging Micro and Infection 2022; Liu et al Science Transl Med 2022; Feng Sci Transl Med 2023

Antibodies to a host target such as ACE2: reduces risk of escape but risk of adverse effects





nature microbiology

Article

https://doi.org/10.1038/s41564-023-01389-9

Pan-sarbecovirus prophylaxis with human anti-ACE2 monoclonal antibodies

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Accepted: 19 April 2023

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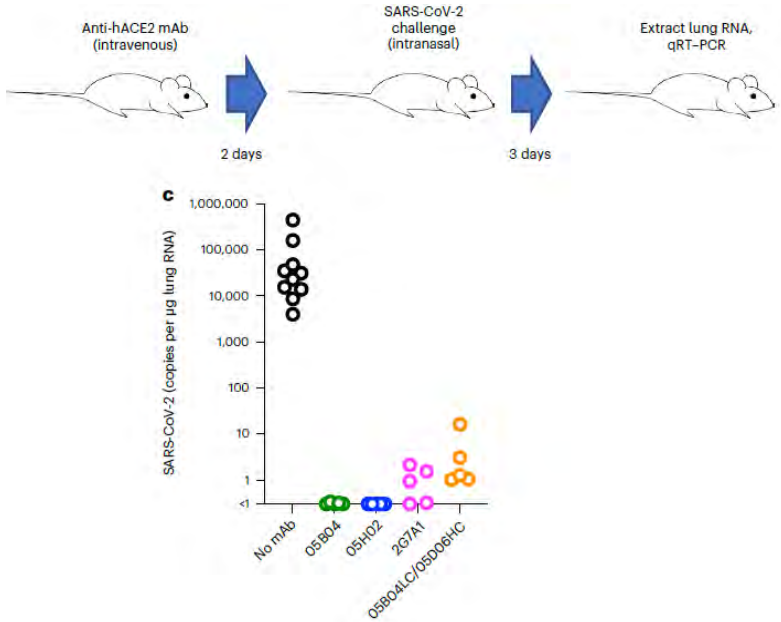
Check for updates

Fengwen Zhang[1], Jesse Jenkins[1], Renan V. H. de Carvalho[2], Sandra Nakandakari-Higa[2], Teresia Chen[3], Morgan E. Abernathy[3], Viren A. Baharani[1], Elisabeth K. Nyakatura[4], David Andrew[4], Irina V. Lebedeva[4], Ivo C. Lorenz[4], H.-Heinrich Hoffmann[5], Charles M. Rice[5], Gabriel D. Victora[2], Christopher O. Barnes[3,6], Theodora Hatziioannou[1] & Paul D. Bieniasz[1,7]



Zhang et al Nat Micro 2023

Significant investment in small molecules that work across whole virus families

Antiviral Drug Discovery Centers

NIH National Institute of Allergy and Infectious Diseases

- Coronaviruses
- Paramyxoviruses
- Bunyaviruses (Bunyavirales)
- Togaviruses
- Filoviruses
- Picornaviruses
- Flaviviruses

$577 million USD for 9 centers

Pandemic Antiviral Discovery

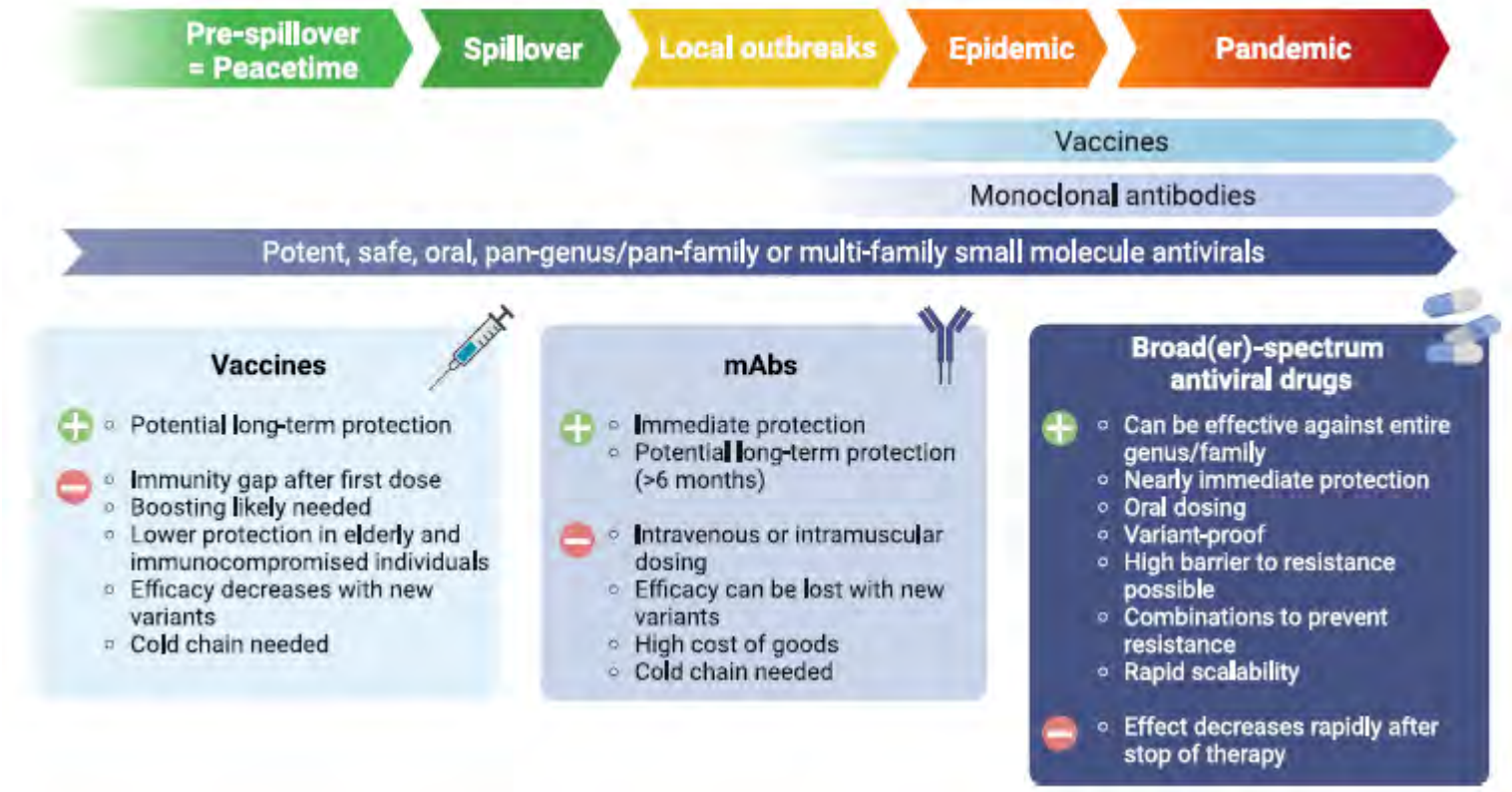
BILL & MELINDA GATES foundation

Open Philanthropy

novo nordisk fonden

www.niaid.nih.gov/research/antivirals

Developing broad spectrum antivirals small molecules



Jochmans et al Cell Host Microbe 2023

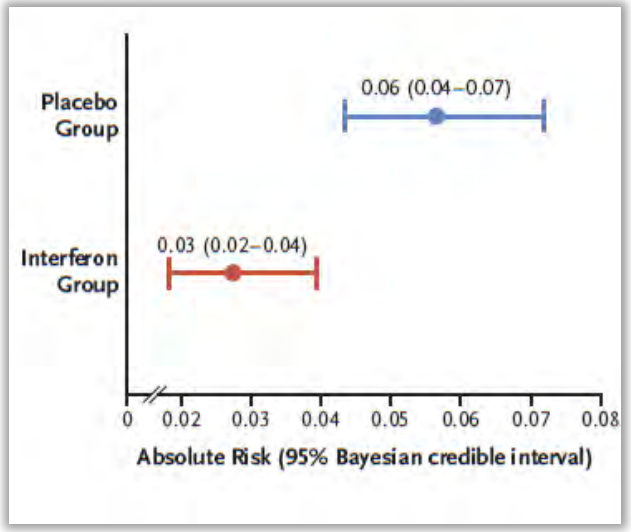
Host factors modification can also act as an antiviral and potentially cross viral families

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Treatment with Pegylated Interferon Lambda for Covid-19

G. Reis, E.A.S. Moreira Silva, D.C. Medeiros Silva, L. Thabane, V.H.S. Campos, T.S. Ferreira, C.V.Q. Santos, A.M.R. Nogueira, A.P.F.G. Almeida, L.C.M. Savassi, A.D. Figueiredo-Neto, A.C.F. Dias, A.M. Freire Júnior, C. Bitarães, A. C. Milagres, E.D. Callegari, M.I.C. Simplicio, L.B. Ribeiro, R. Oliveira, O. Harari, L.A. Wilson, J.I. Forrest, H. Ruton, S. Sprague, P. McKay, C.M. Guo, E.H. Limbrick-Oldfield, S. Kanters, G.H. Guyatt, C.R. Rayner, C. Kandel, M.J. Biondi, R. Kozak, B. Hansen, M.A. Zahoor, P. Arora, C. Hislop, I. Choong, J.J. Feld, E.J. Mills, and J.S. Glenn, for the TOGETHER Investigators*

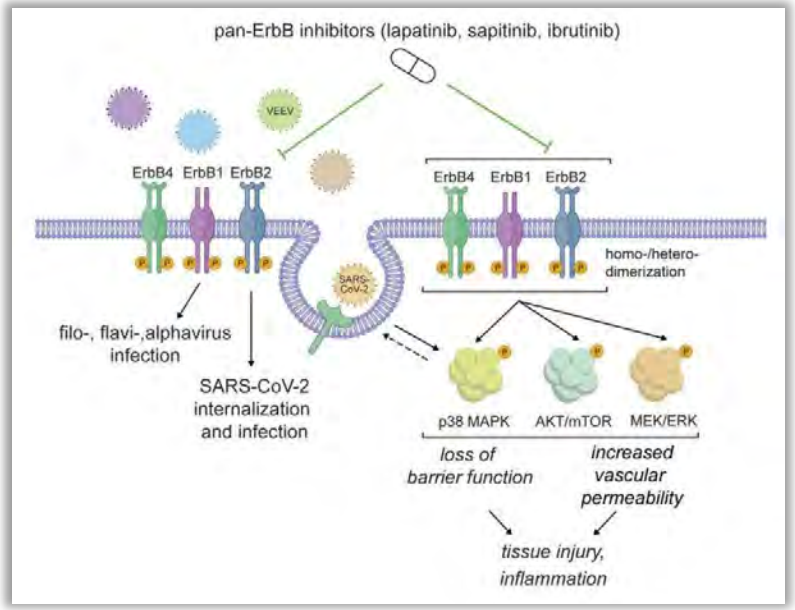


The Journal of Clinical Investigation

RESEARCH ARTICLE

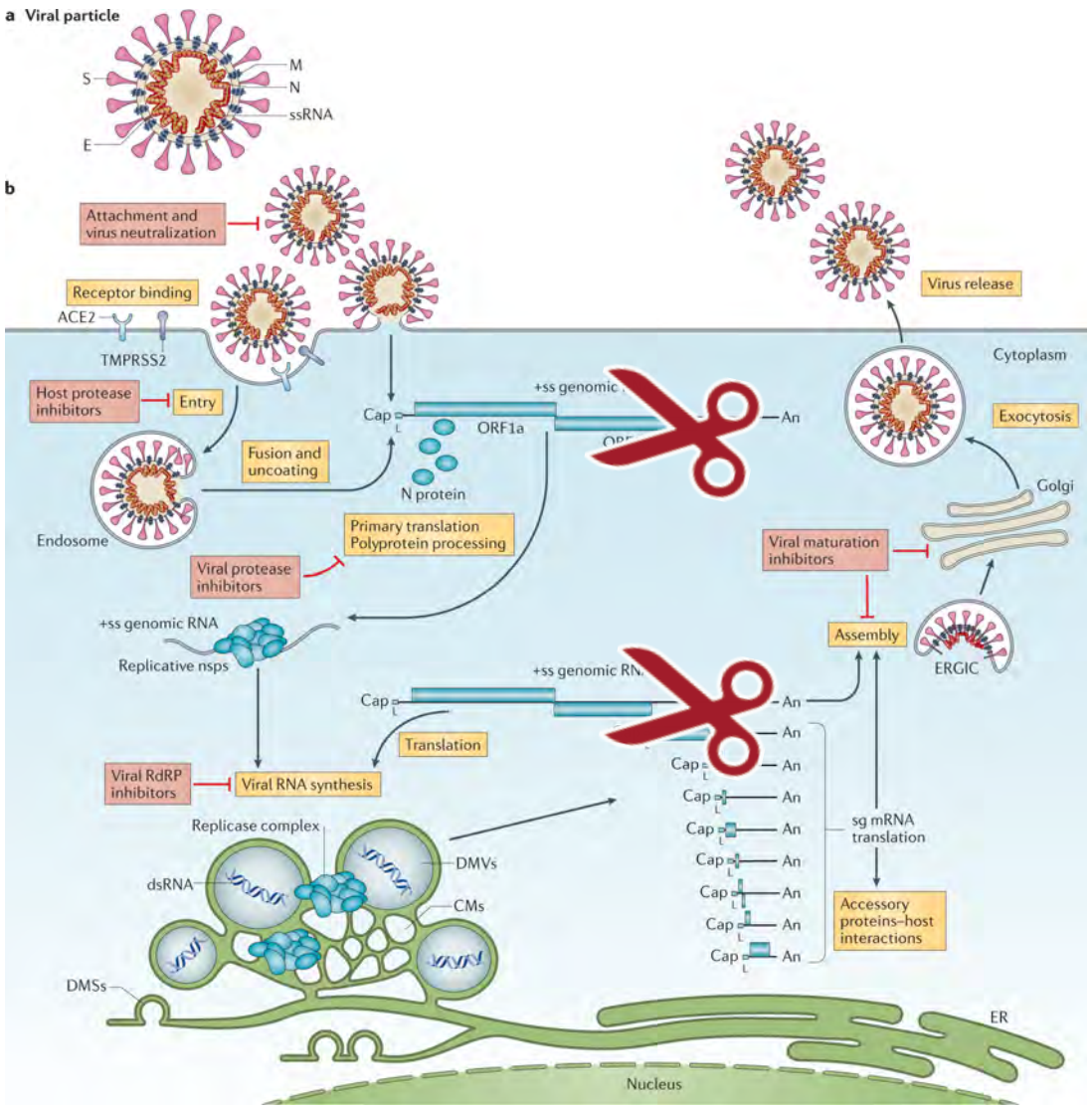
Anticancer pan-ErbB inhibitors reduce inflammation and tissue injury and exert broad-spectrum antiviral effects

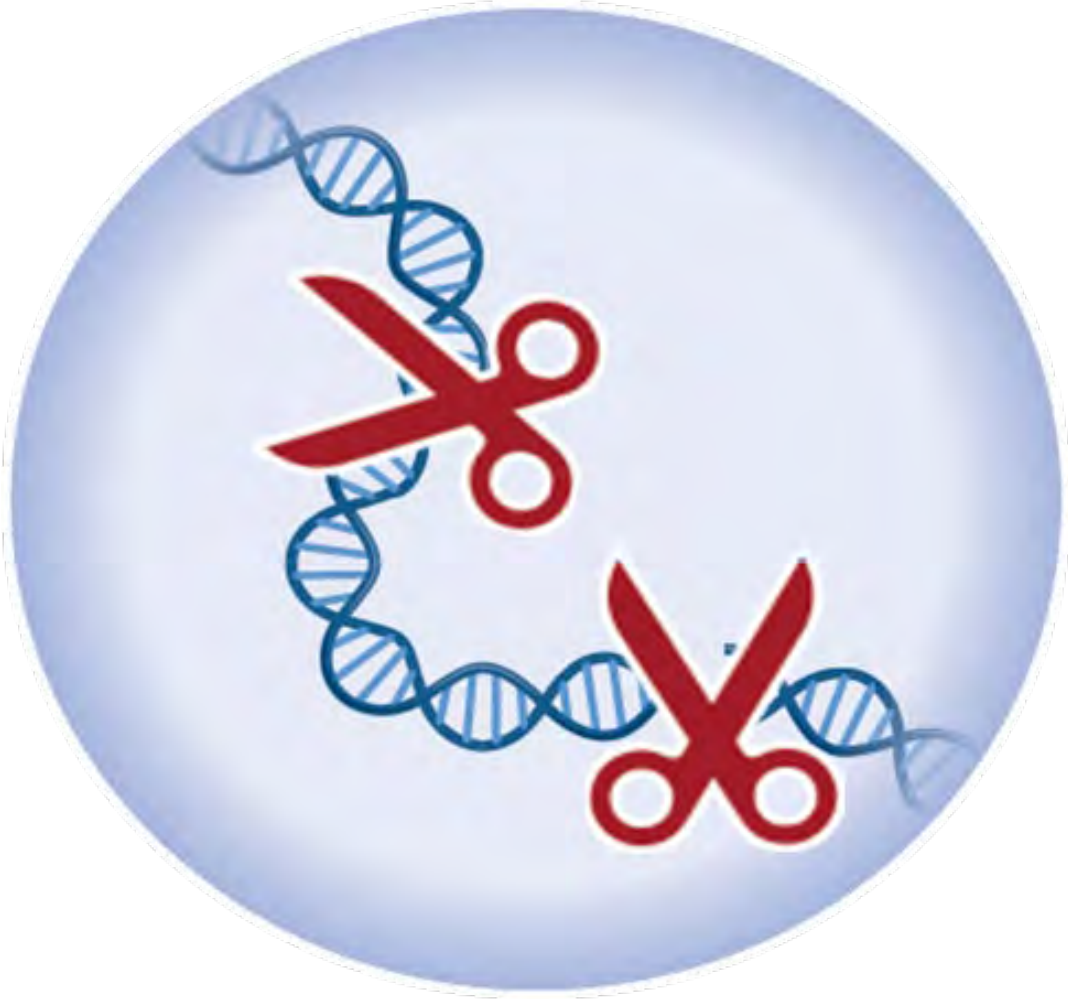
Sirle Saul,[1] Marwah Karim,[1] Luca Ghita,[1] Pei-Tzu Huang,[1] Winston Chiu,[2] Verónica Durán,[1,3] Chieh-Wen Lo,[1] Sathish Kumar,[1] Nishank Bhalla,[4] Pieter Leyssen,[2] Farhang Alem,[5] Niloufar A. Boghdeh,[5] Do H.N. Tran,[1] Courtney A. Cohen,[6] Jacquelyn A. Brown,[7] Kathleen E. Huie,[6] Courtney Tindle,[8,9] Mamdouh Sibai,[10] Chengjin Ye,[11] Ahmed Magdy Khalil,[11] Kevin Chiem,[11] Luis Martinez-Sobrido,[11] John M. Dye,[6] Benjamin A. Pinsky,[1,10] Pradipta Ghosh,[8,9,12] Soumita Das,[9,13] David E. Solow-Cordero,[14] Jing Jin,[15] John P. Wikswo,[16] Dirk Jochmans,[2] Johan Neyts,[2] Steven De Jonghe,[2] Aarthi Narayanan,[4,17] and Shirit Einav[1,3,18]



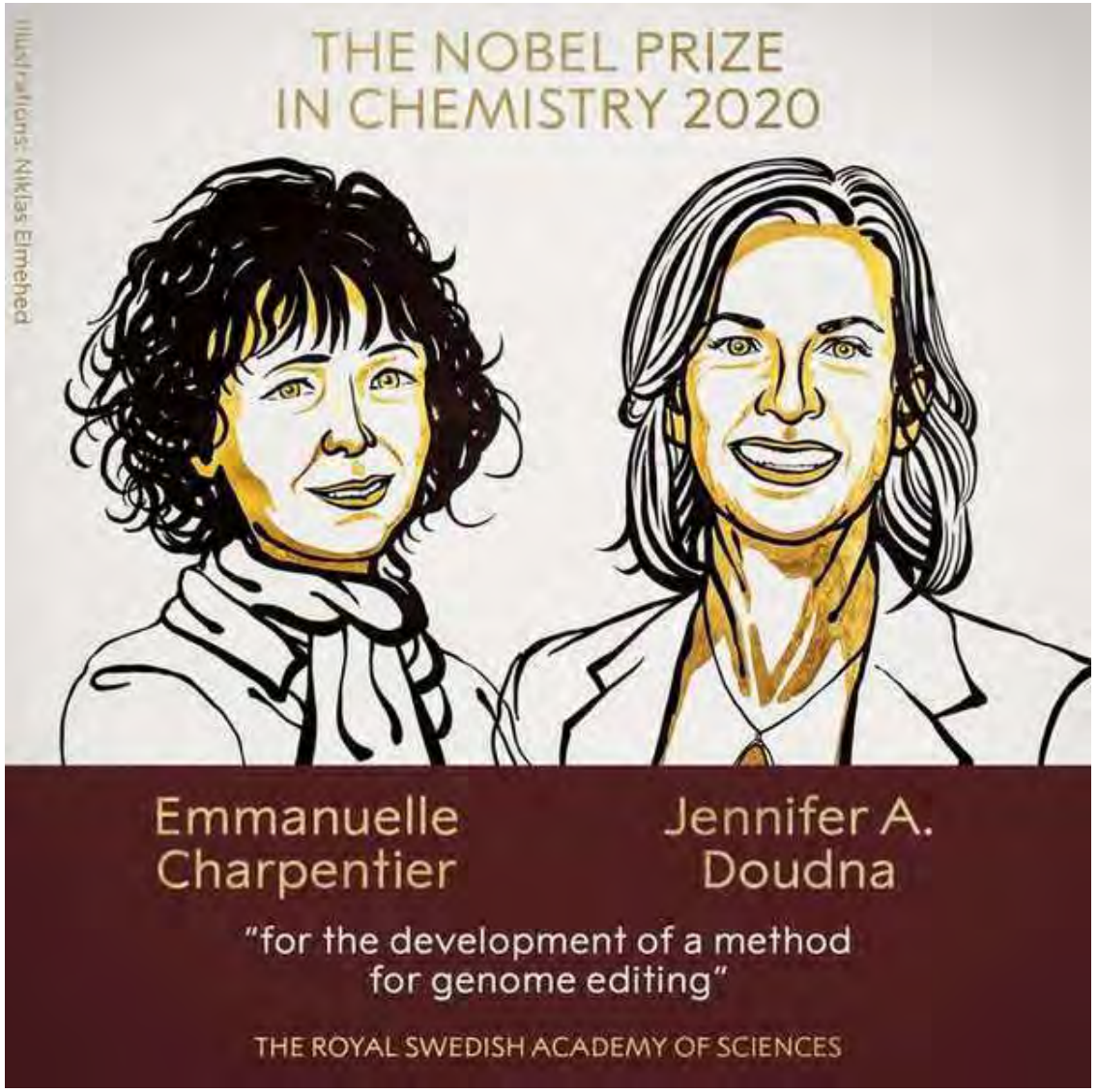
Reis et al., NEJM 2023; Saul et al., J Clin Inv 2023

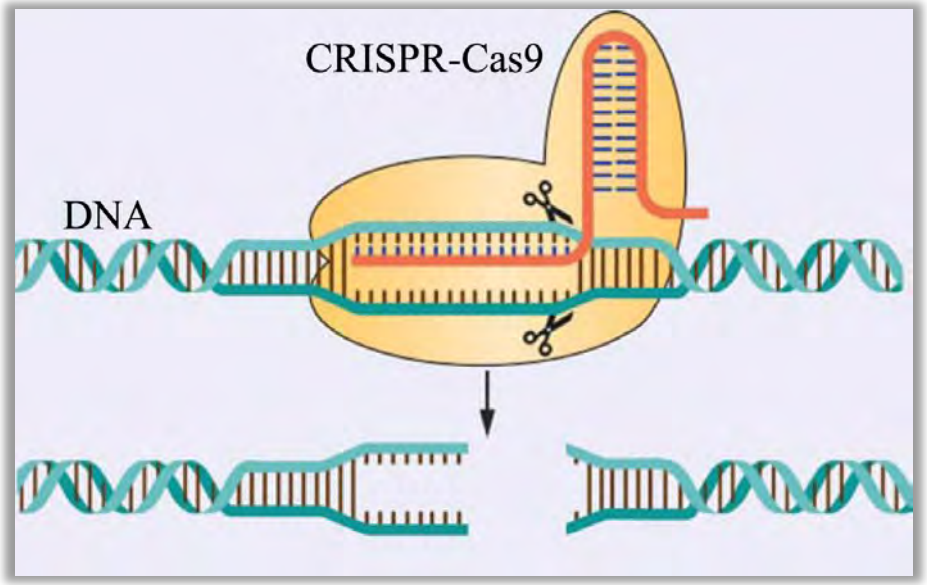
Direct acting antivirals: targeting viral RNA

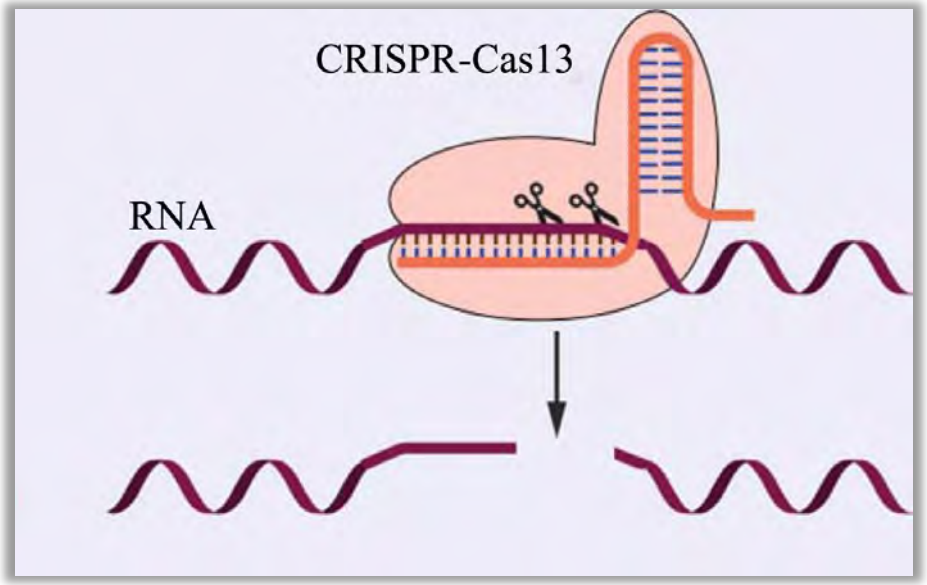




Targeting viral RNA: CRISPR technologies







CRISPR-Cas 13 is an effective antiviral in vitro

nature COMMUNICATIONS

ARTICLE

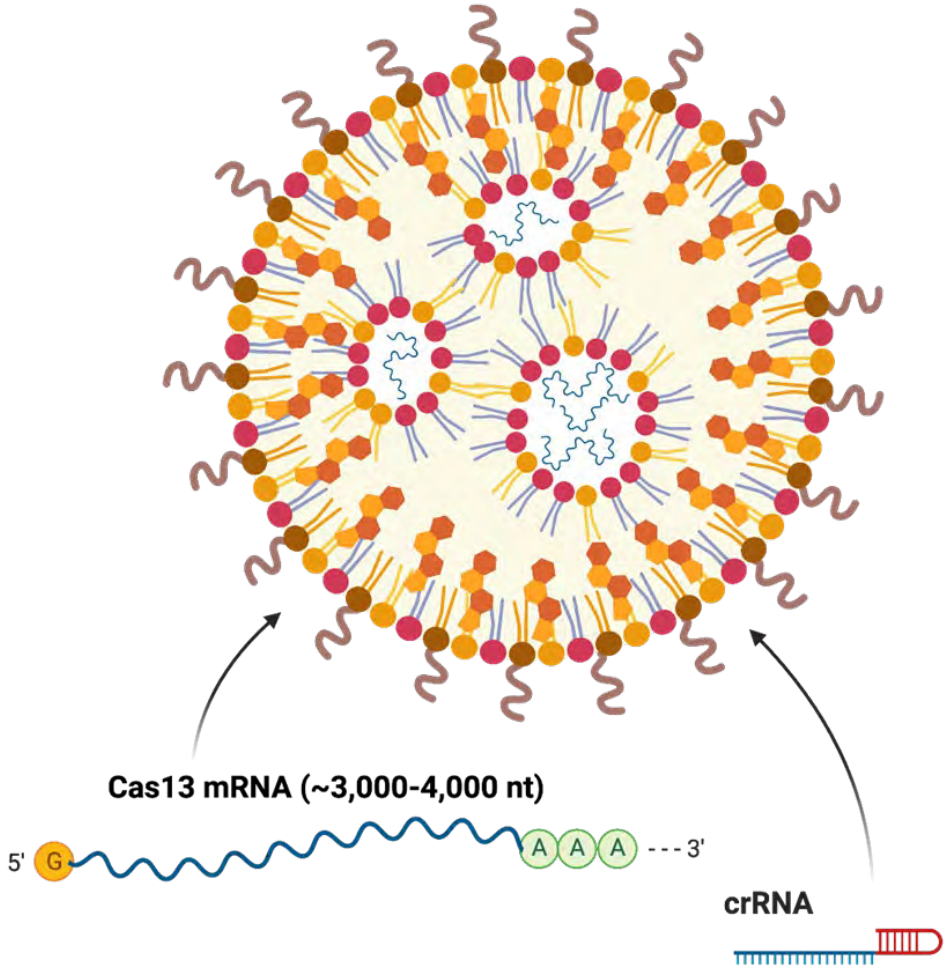
https://doi.org/10.1038/s41467-021-24577-0 OPEN

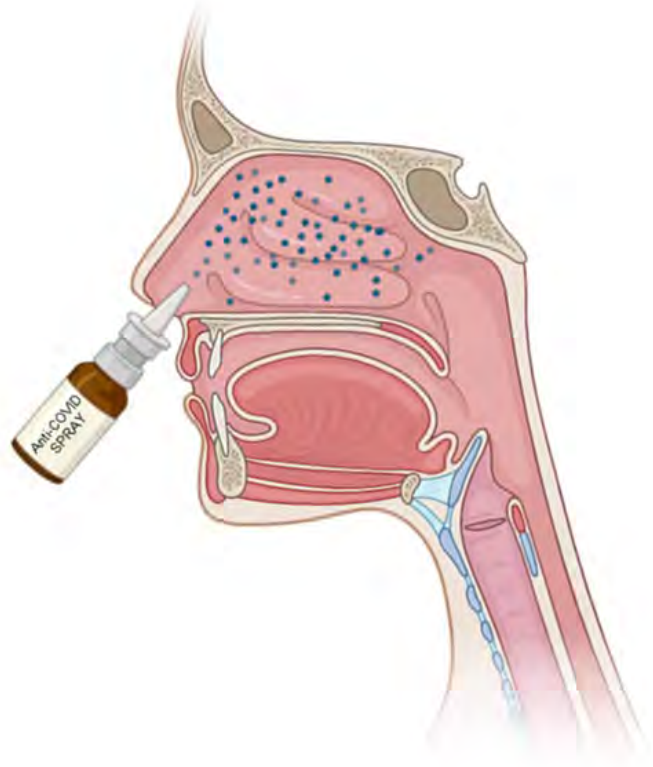
Check for updates

Reprogrammed CRISPR-Cas13b suppresses SARS-CoV-2 replication and circumvents its mutational escape through mismatch tolerance

Mohamed Fareh[1,2✉], Wei Zhao[3], Wenxin Hu[1,2], Joshua M. L. Casan[1,2], Amit Kumar[1,2], Jori Symons[3], Jennifer M. Zerbato[3], Danielle Fong[3], Ilia Voskoboinik[1,2], Paul G. Ekert[1,2,4,5], Rajeev Rudraraju[3,6,7], Damian F. J. Purcell[7], Sharon R. Lewin[3,8,9,10✉] & Joseph A. Trapani[1,2,10]

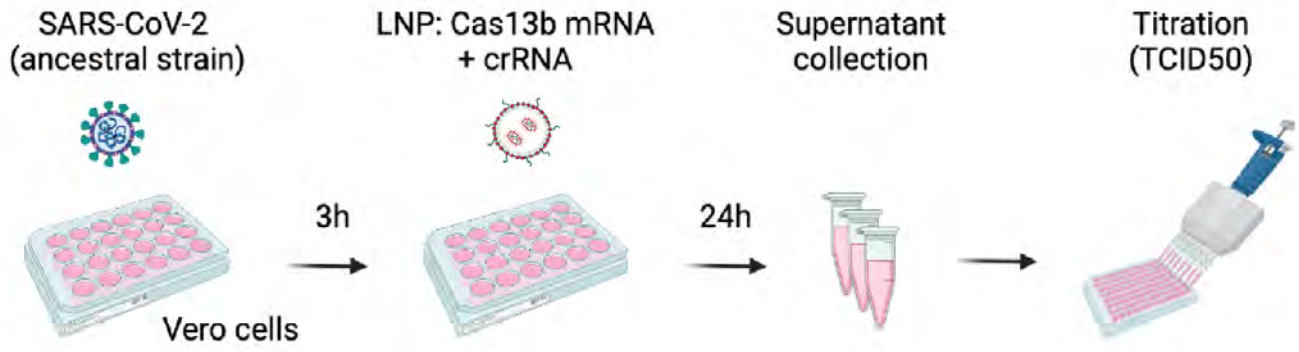
Delivery of CRISPR-Cas13 in vivo

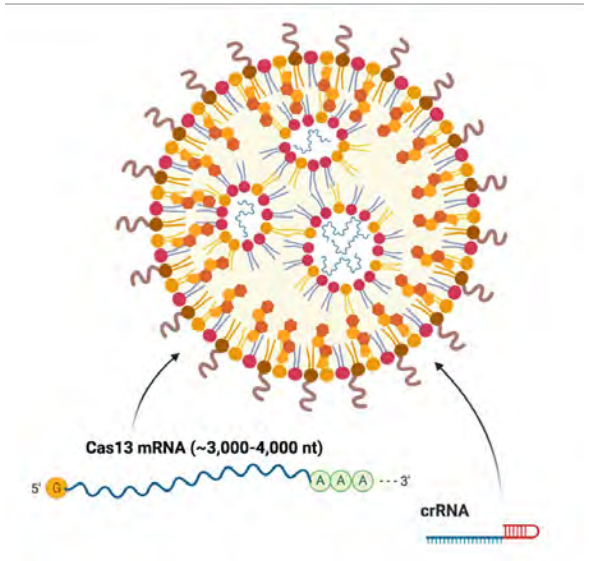




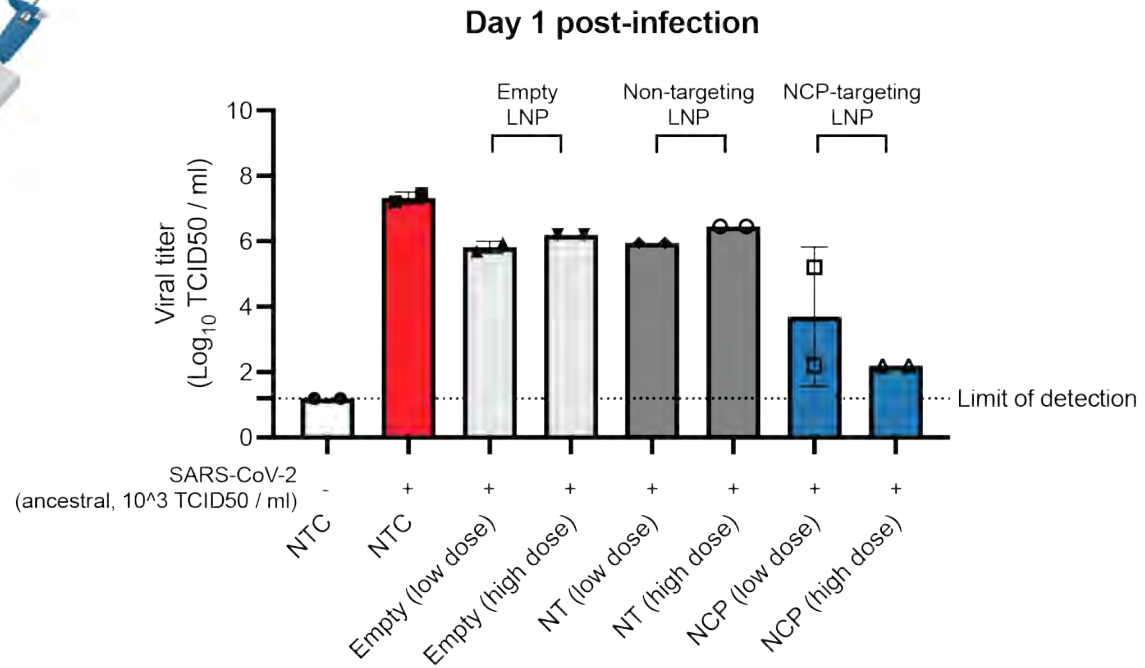
SARS-CoV-2 CRISPR/Cas13
Aerosolised and potentially delivered as a nasal spray

mRNA-LNP can deliver CRISPR-Cas13 as an antiviral





Empty LNP
Non-targeting crRNA
NCP crRNA

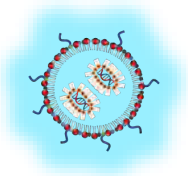


NTC = no template control; NT = non targeting; NCP = nucleocapsid

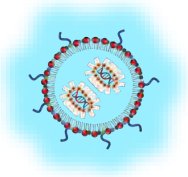
Kan, Zhao, Fareh et al (unpublished)

In vivo delivery of mRNA LNP to the respiratory tract

Day 0 –Luciferase mRNA-LNP labelled with DiD dye

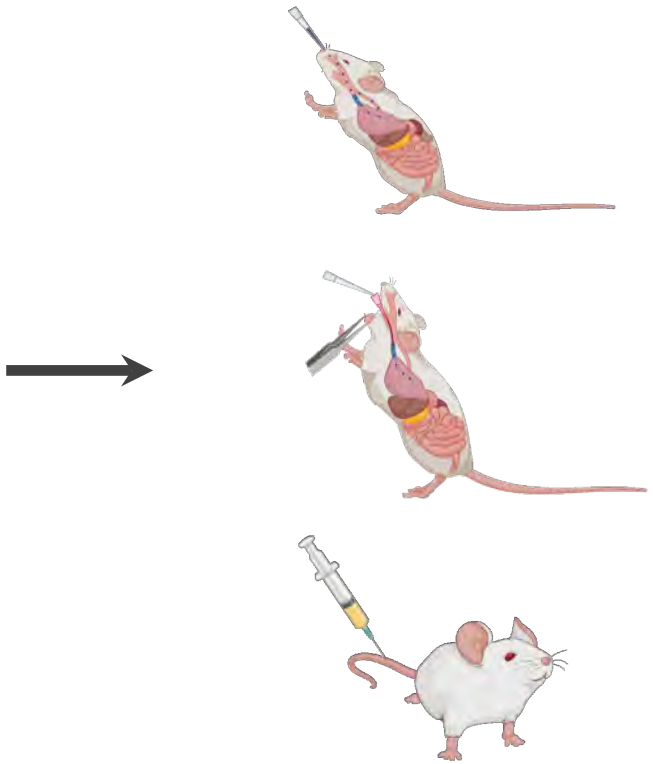


Lipid 1 mRNA LNP



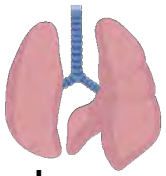
Lipid 2 mRNA LNP

Day 1 – Administration of mRNA-LNP (2 ug/mouse) Intranasal, intratracheal or intravenous



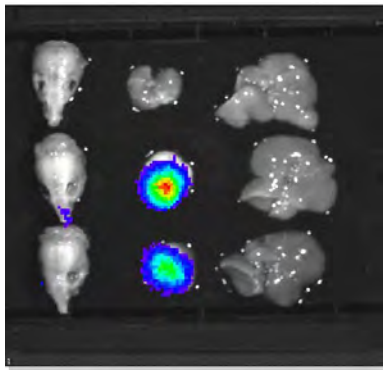
Day 1 - 7 h post-treatment Organ harvesting and imaging

Head



Lung

Liver

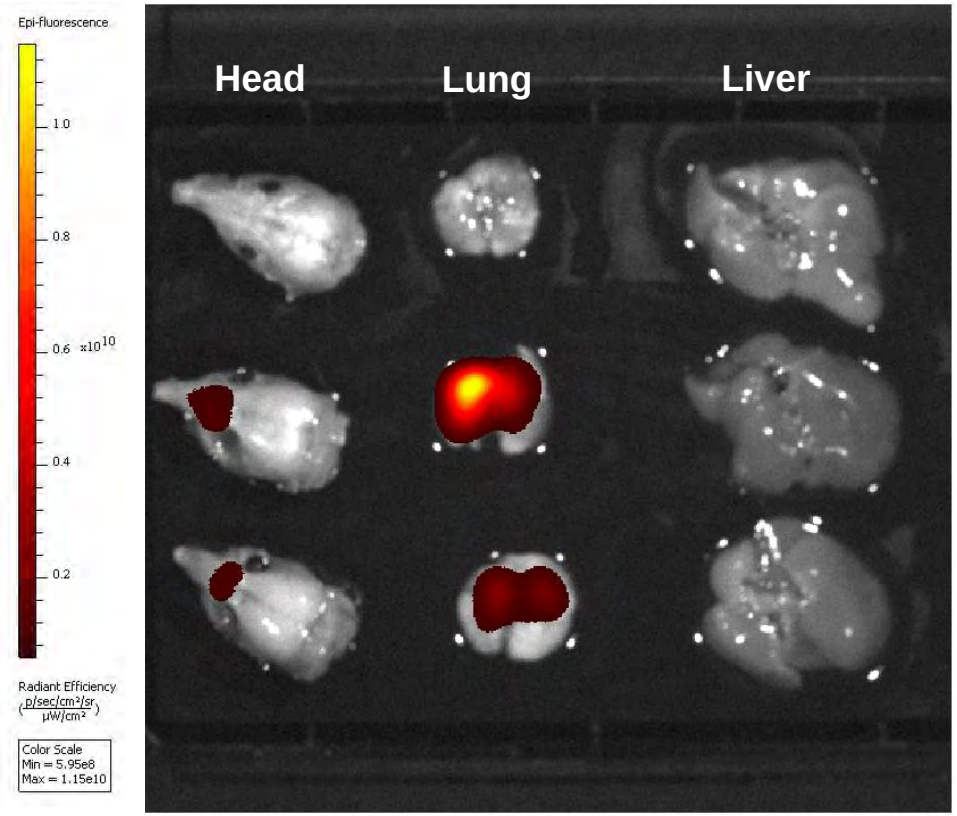


IVIS imaging DiD and Luc

Stan Kan, Rob DeRose, Wei Zhao, Zhenjun Chen and others

High specificity of Lipid 1 - LNP for mRNA expression in lung following intranasal delivery

Biodistribution (DiD)



PBS

Lipid 1 - LNP

Lipid 2 - LNP

Kang, de Rose Zhao, Fareh and others; provisional patent submitted

RNA targeting strategies for COVID-19 treatment: a new paradigm?

Molecular Therapy

Original Article

A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19

Adi Idris,[1,5] Alicia Davis,[2,3,5] Aroon Supramaniam,[1,5] Dhruba Acharya,[1] Gabrielle Kelly,[1] Yaman Tayyar,[1] Nic West,[1] Ping Zhang,[1] Christopher L.D. McMillan,[4] Citradewi Soemardy,[2] Roslyn Ray,[2] Denis O'Meally,[2] Tristan A. Scott,[2] Nigel A.J. McMillan,[1] and Kevin V. Morris[1,2]

Cell

Article

Identification of a therapeutic interfering particle—A single-dose SARS-CoV-2 antiviral intervention with a high barrier to resistance

Idris et al., Molecular Therapy 2021; Chaturvedi et al., Cell 2022

Cumming Global Centre for Pandemic Therapeutics

In September 2022, Geoff Cumming, a Canadian philanthropist now based in Melbourne, announced a gift of $250 million to the Doherty Institute.

The gift will establish the Cumming Global Centre for Pandemic Therapeutics.

The centre will provide long term mission based funding to researchers to develop novel platform technologies for therapeutics for pathogens of pandemic potential.

Funding principals include 20% for discovery research and 30% will be spent externally to the Doherty Institute

Summary and implications

- Antivirals can play a **critically important role in a pandemic response**, in addition to vaccines. For COVID-19, therapeutic development was slow given disease complexity and limitations of existing antiviral drug development approaches

- In addition to an expanded tool box of broad spectrum antiviral drugs, substantial investment is now needed in **adaptable platform technologies** that would allow for rapid development of therapeutics for a novel pathogen

- CRISPR-Cas13 RNA editing **has high specificity and potency** allowing for control of SARS-CoV2 replication in vitro. Exciting advances in **mRNA lipid nanoparticles** have high relevance for RNA targeting therapeutics, in addition to vaccines.

- Barriers to **global access** of products due to cost and patents remain a major challenge that must be addressed in addition to investment in science and innovation

Acknowledgements

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Christina Cortez
Rob De Rose

Peter MacCallum Cancer Centre
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Mohamed Fareh
Wenxin Hu
Joshua Cassan

Monash University
Colin Pouton
Stewart Fabb
Angus Johnson

APPRISE executive
Miranda Smith
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Australian Government
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paulramsay FOUNDATION
PARTNERSHIPS FOR POTENTIAL

Tầm quan trọng của thuốc kháng vi rút trong ứng phó với đại dịch

Professor Sharon R Lewin AO, FRACP, PhD, FAHMS
Director, The Peter Doherty Institute for Infection and Immunity
Melbourne Laureate Professor, University of Melbourne
Consultant physician, Alfred Hospital and Royal Melbourne Hospitals, Melbourne, Australia

ANRS/MIE Vietnam
Hai Phong, Vietnam, November 15-16, 2023

Doherty Institute

THE UNIVERSITY OF MELBOURNE

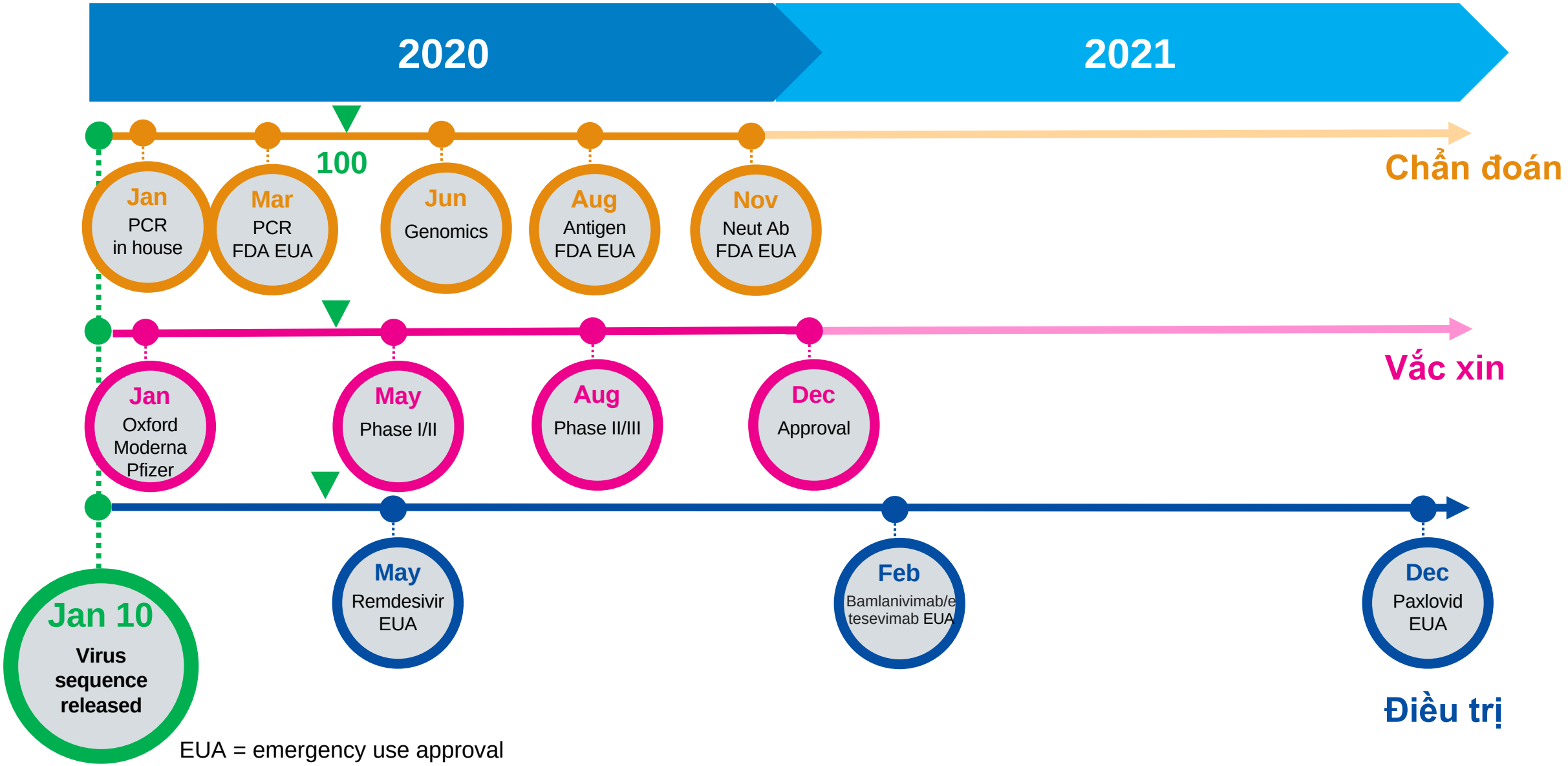
The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Tầm quan trọng của thuốc kháng vi rút trong việc ứng phó với đại dịch

Liên minh đổi mới chuẩn bị phòng chống dịch bệnh (CEPI) mong muốn thế giới có thể ứng phó với bệnh X tiếp theo bằng một loại vắc xin mới chỉ sau 100 ngày

Nhiệm vụ 100 ngày: liệu nó có khả thi?



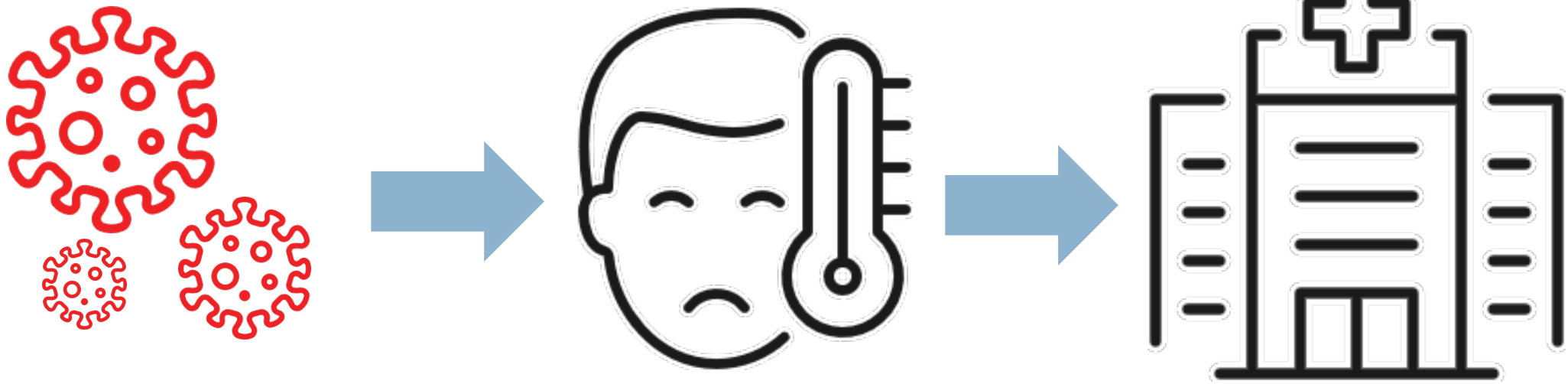
EUA = emergency use approval

Những thách thức trong phát triển thuốc chống virus SARS-CoV2

- Cơ chế bệnh sinh của Covid-19 rất phức tạp: các giai đoạn khác nhau của quá trình nhân lên của vi rút sớm và bệnh miễn dịch sau này nên thuốc kháng vi rút phải được tiêm sớm đê có tác dụng
- Công nghệ hiện có để phát triển thuốc kháng vi rút cần có thời gian và có thể dẫn đến một số sai lầm.
- Hiện chưa có mô hình thuốc kháng vi rút có hoạt tính cao đối với các mầm bệnh đường hô hấp
- Đầu tư tối thiểu vào thuốc kháng vi rút so với vắc xin ngừa Covid-19: ước tính đầu tư vào vắc xin là 137tyr USD, so với thuốc kháng vi rút là 7 tỷ USD

. Source: Vanderbilt Vaccine Centre, BMGF; Wellcome Trust; KeNUP Foundation report January 2021. Figures in AU$

Phương pháp điều trị bằng thuốc kháng vi rút tác động trực tiếp , rất quan trọng đối với việc kiểm soát đại dịch của cá nhân và cộng đồng



Nguy cơ nhiễm trùng cá nhân

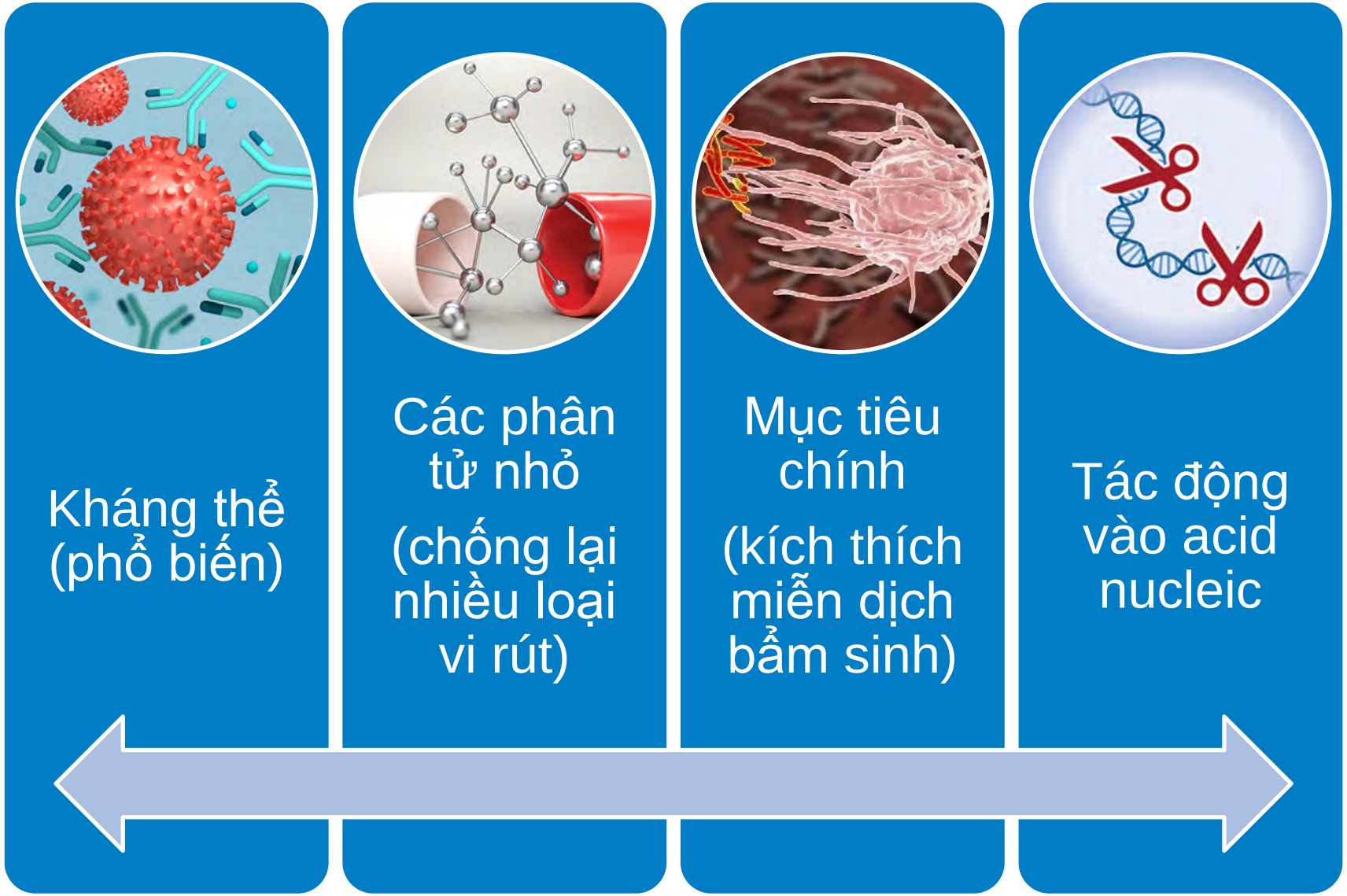
Nguy cơ mắc bệnh của cá nhân

Nguy cơ cá nhân phải nhập viện

Ưu điểm chính của thuốc kháng vi rút là có thể sử dụng ngay lập tức và là cần thiết nếu chúng ta không/ không thể phát triển vắc-xin

Đáp ứng thách thức về thuốc trực tiếp tác động vào vi rút với tốc độ cao

Một số chiến lược tiềm năng để phát triển thuốc trực tiếp tác động vào vi rút



Kháng thể Pan-sarbecovirus hiện đang được phát triển và cần có sẵn trong tương lai

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors

Chee-Wah Tan, Ph.D., Wan-Ni Chia, Ph.D., Barnaby E. Young, M.R.C.P., Feng Zhu, Ph.D., Beng-Lee Lim, M.Sc., Wan-Rong Sia, B.S., Tun-Linn Thein, M.P.H., Mark I.-C. Chen, Ph.D., Yee-Sin Leo, F.R.C.P., David C. Lye, F.R.C.P., and Lin-Fa Wang, Ph.D.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

Broadly neutralizing antibodies against sarbecoviruses generated by immunization of macaques with an AS03-adjuvanted COVID-19 vaccine

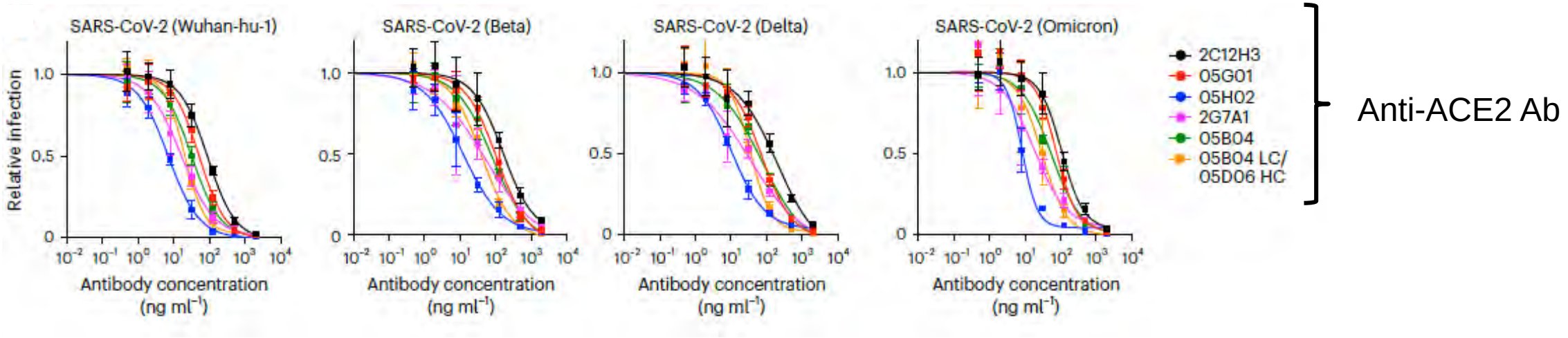
Yupeng Feng[1]†, Meng Yuan[2]†, John M. Powers[3]†, Mengyun Hu[1], Jennifer E. Munt[3]

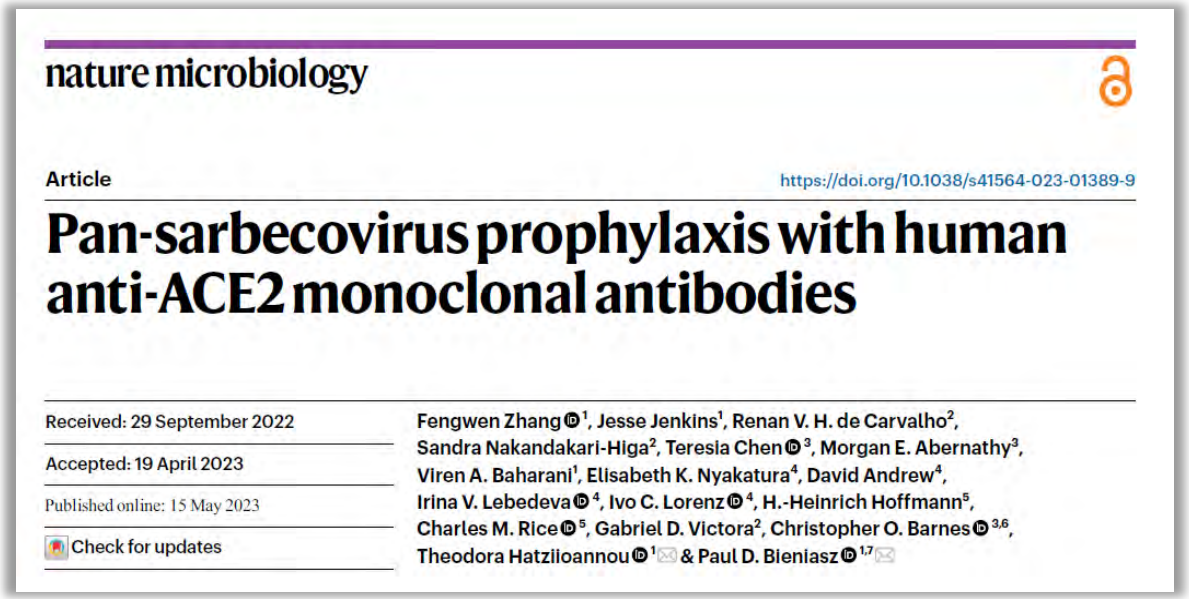
mAb	Time point (months)	Vaccine	Pseudovirus neutralization (IC_{50} (μg/ml))									
			WA1	Alpha	Beta	Gamma	Delta	BA.1	BA.2	BA.3	BA.4/5	SARS-CoV
25F9	5 to 6	Hexapro-NP-AS03	0.077	0.096	0.106	0.101	0.117	0.551	1.846	0.619	3.409	0.108
20A7	5 to 6	RBD-NP-AS03	0.334	0.382	0.372	0.369	0.364	0.794	0.692	0.831	0.701	1.874
21B6	5 to 6	RBD-NP-AS03	0.121	0.136	0.195	0.179	0.215	0.237	0.225	0.217	0.243	30.000
27A12	5 to 6	Hexapro-NP-AS03	0.110	0.114	0.125	0.116	0.113	0.302	0.200	0.440	0.323	30.000
27E3	5 to 6	Hexapro-NP-AS03	0.056	0.057	0.058	0.057	0.094	0.071	0.069	0.068	4.950	30.000
27E4	5 to 6	Hexapro-NP-AS03	0.166	0.176	0.191	0.185	0.191	0.339	4.225	30.000	1.273	30.000
26C3	5 to 6	Hexapro-NP-AS03	0.119	0.128	0.127	0.124	0.120	0.386	0.679	0.433	3.645	30.000
25C7	5 to 6	Hexapro-NP-AS03	0.607	0.215	0.498	0.221	0.679	0.705	0.703	0.640	1.326	30.000
21F2	5 to 6	Hexapro-NP-AS03	3.409	2.455	3.509	2.765	4.178	3.636	3.546	3.155	3.093	30.000
26G10	5 to 6	Hexapro-NP-AS03	4.975	1.122	4.658	2.039	5.000	3.906	3.793	4.615	4.552	5.682
20C3	5 to 6	RBD-NP-AS03	3.456	1.943	3.421	2.732	3.128	4.082	4.418	3.052	3.341	5.245
15F1	1.4	Hexapro-NP-AS03	0.229	0.250	0.293	0.267	0.250	4.608	30.000	30.000	30.000	0.837
25A11	5 to 6	Hexapro-NP-AS03	4.651	2.616	5.111	2.735	4.967	4.615	4.644	30.000	5.792	30.000
25A10	5 to 6	Hexapro-NP-AS03	1.577	1.639	2.765	1.900	2.269	4.800	2.252	2.302	2.336	30.000
20F2	5 to 6	RBD-NP-AS03	5.545	5.597	30.000	5.172	30.000	5.484	30.000	5.208	30.000	30.000

Nhiều kháng thể đơn dòng (được xác định từ bệnh nhân sống sót sau Covid-19, SARS-CoVid1 và sau tiêm chủng cho động vật và con người) có thể làm giảm hoạt tính tất cả các loại sarbecovirus khi được thử nghiệm trong môi trường in vitro

Wang PF et al., Emerging Micro and Infection 2022; Liu et al Science Transl Med 2022; Feng Sci Transl Med 2023

Kháng thể nhắm vào vật chủ như ACE2: giảm nguy cơ bỏ sót vi khuẩn nhưng có nguy cơ gây ra tác dụng phụ





nature microbiology

Article

https://doi.org/10.1038/s41564-023-01389-9

Pan-sarbecovirus prophylaxis with human anti-ACE2 monoclonal antibodies

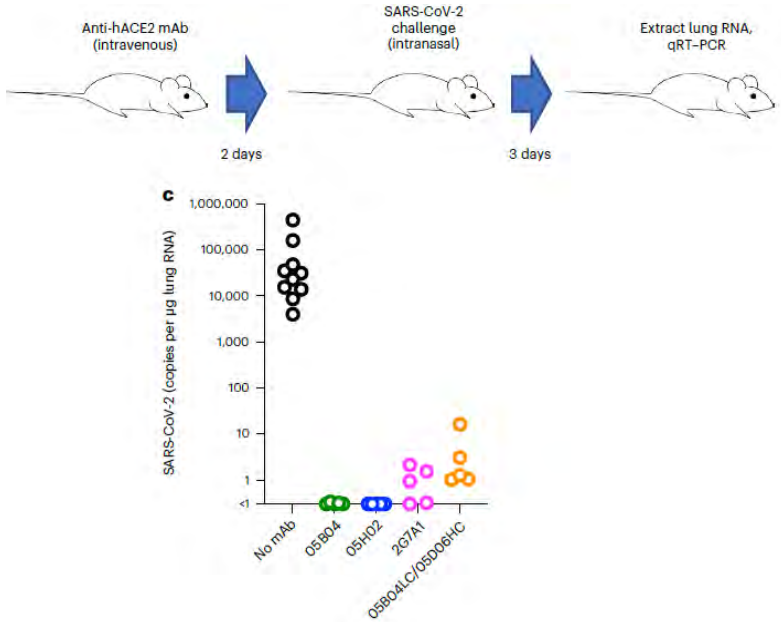
Received: 29 September 2022

Accepted: 19 April 2023

Published online: 15 May 2023

Check for updates

Fengwen Zhang[1], Jesse Jenkins[1], Renan V. H. de Carvalho[2], Sandra Nakandakari-Higa[2], Teresia Chen[3], Morgan E. Abernathy[3], Viren A. Baharani[1], Elisabeth K. Nyakatura[4], David Andrew[4], Irina V. Lebedeva[4], Ivo C. Lorenz[4], H.-Heinrich Hoffmann[5], Charles M. Rice[5], Gabriel D. Victora[2], Christopher O. Barnes[3,6], Theodora Hatziioannou[1] & Paul D. Bieniasz[1,7]



Zhang et al Nat Micro 2023

Đầu tư đáng kể vào việc phát triển các phân tử nhỏ có khả năng tác động trên toàn bộ một họ vi rút

Antiviral Drug Discovery Centers

NIH National Institute of Allergy and Infectious Diseases

- Coronaviruses
- Paramyxoviruses
- Bunyaviruses (Bunyavirales)
- Togaviruses
- Filoviruses
- Picornaviruses
- Flaviviruses

$577 million USD for 9 centers

Pandemic Antiviral Discovery

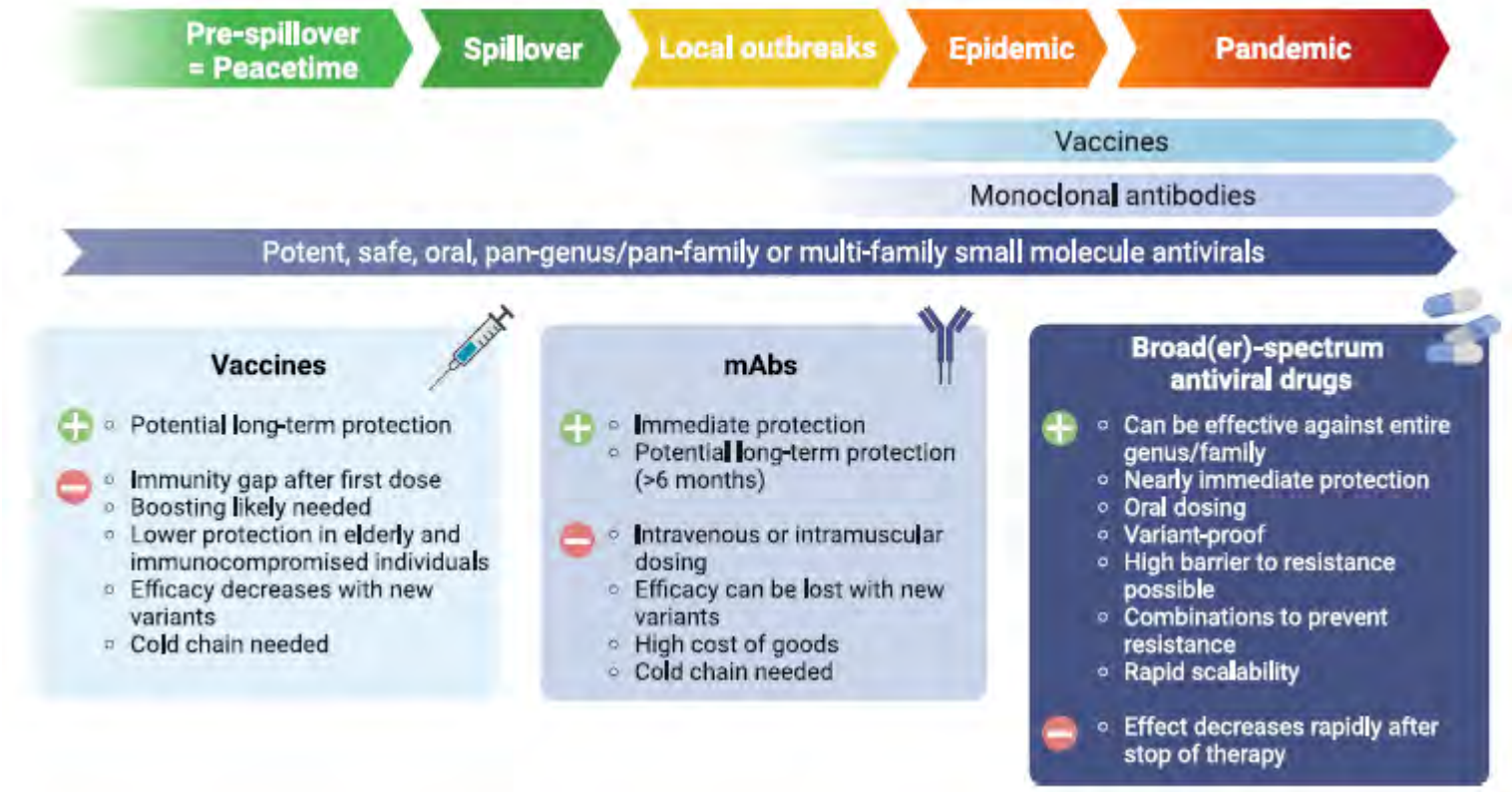
BILL & MELINDA GATES foundation

Open Philanthropy

novo nordisk fonden
Benefiting people and society

www.niaid.nih.gov/research/antivirals

Phát triển các phân tử nhỏ có khả năng kháng vi rút phổ rộng



Jochmans et al Cell Host Microbe 2023

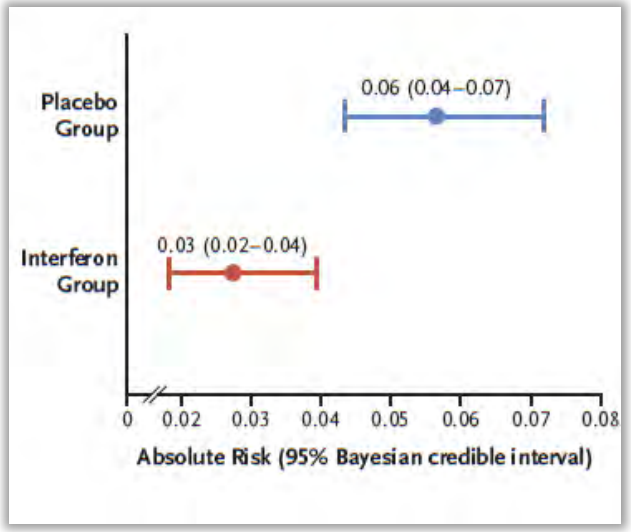
Việc sửa đổi các yếu tố của vật chủ có thể hoạt động như một chất chống vi rút và có hiệu quả ở các họ vi rút khác nhau

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Treatment with Pegylated Interferon Lambda for Covid-19

G. Reis, E.A.S. Moreira Silva, D.C. Medeiros Silva, L. Thabane, V.H.S. Campos, T.S. Ferreira, C.V.Q. Santos, A.M.R. Nogueira, A.P.F.G. Almeida, L.C.M. Savassi, A.D. Figueiredo-Neto, A.C.F. Dias, A.M. Freire Júnior, C. Bitarães, A. C. Milagres, E.D. Callegari, M.I.C. Simplicio, L.B. Ribeiro, R. Oliveira, O. Harari, L.A. Wilson, J.I. Forrest, H. Ruton, S. Sprague, P. McKay, C.M. Guo, E.H. Limbrick-Oldfield, S. Kanters, G.H. Guyatt, C.R. Rayner, C. Kandel, M.J. Biondi, R. Kozak, B. Hansen, M.A. Zahoor, P. Arora, C. Hislop, I. Choong, J.J. Feld, E.J. Mills, and J.S. Glenn, for the TOGETHER Investigators*

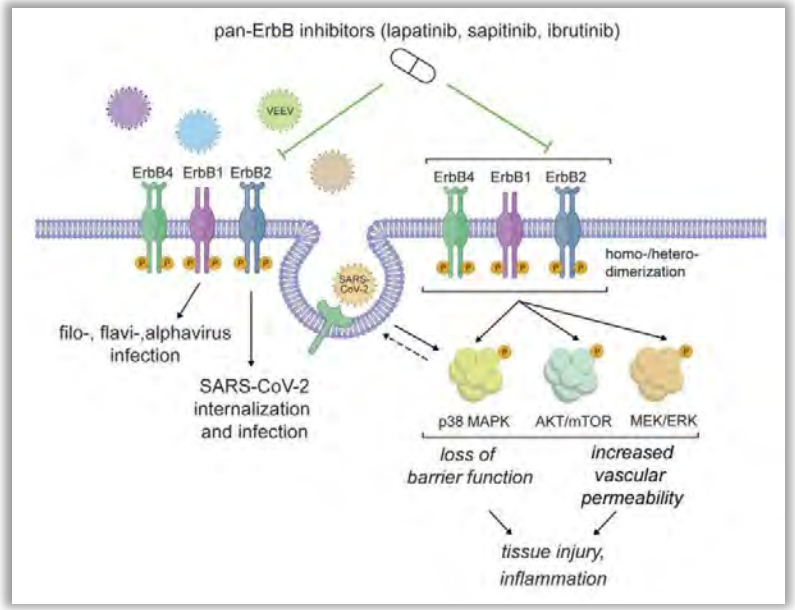


The Journal of Clinical Investigation

RESEARCH ARTICLE

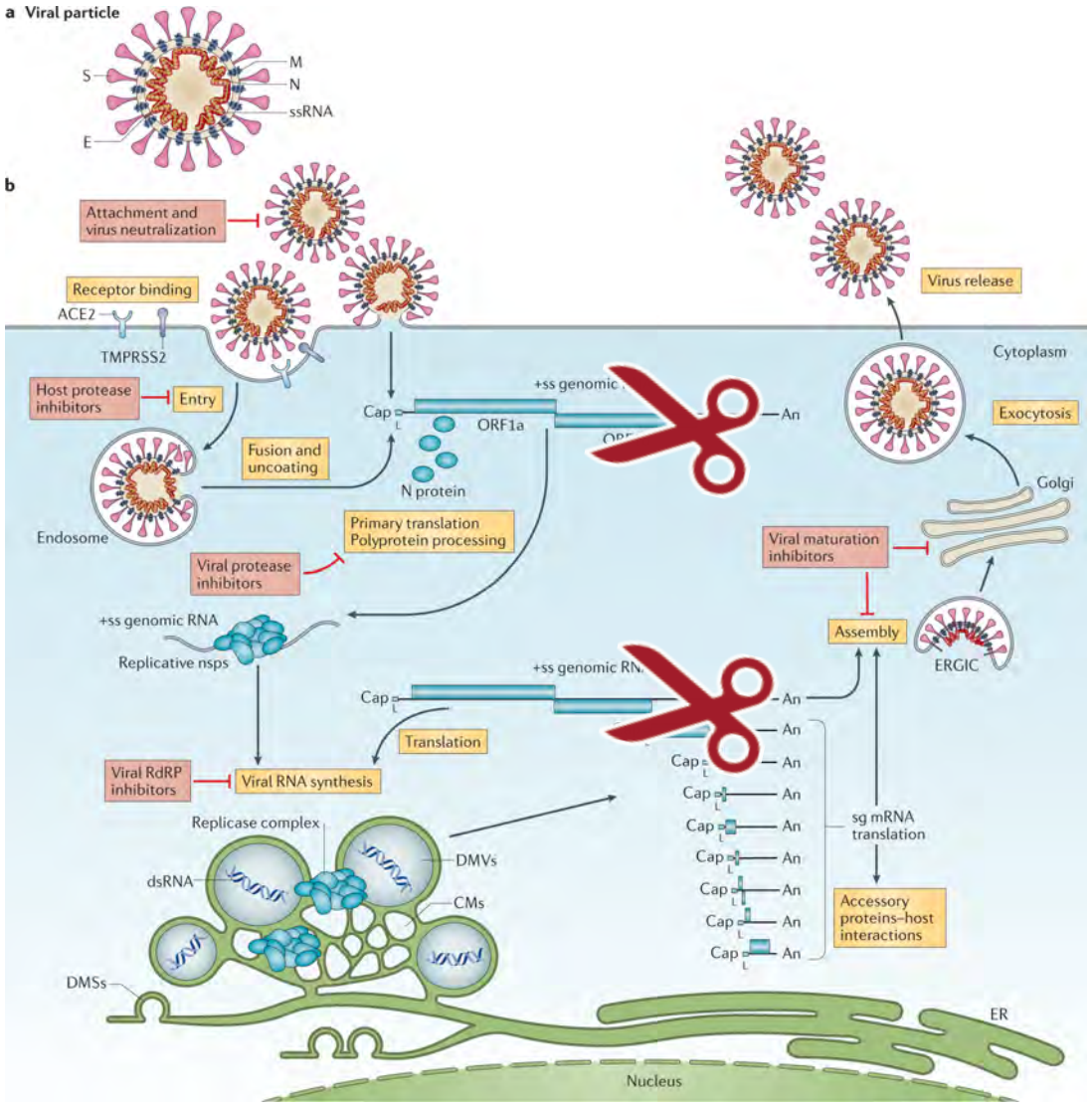
Anticancer pan-ErbB inhibitors reduce inflammation and tissue injury and exert broad-spectrum antiviral effects

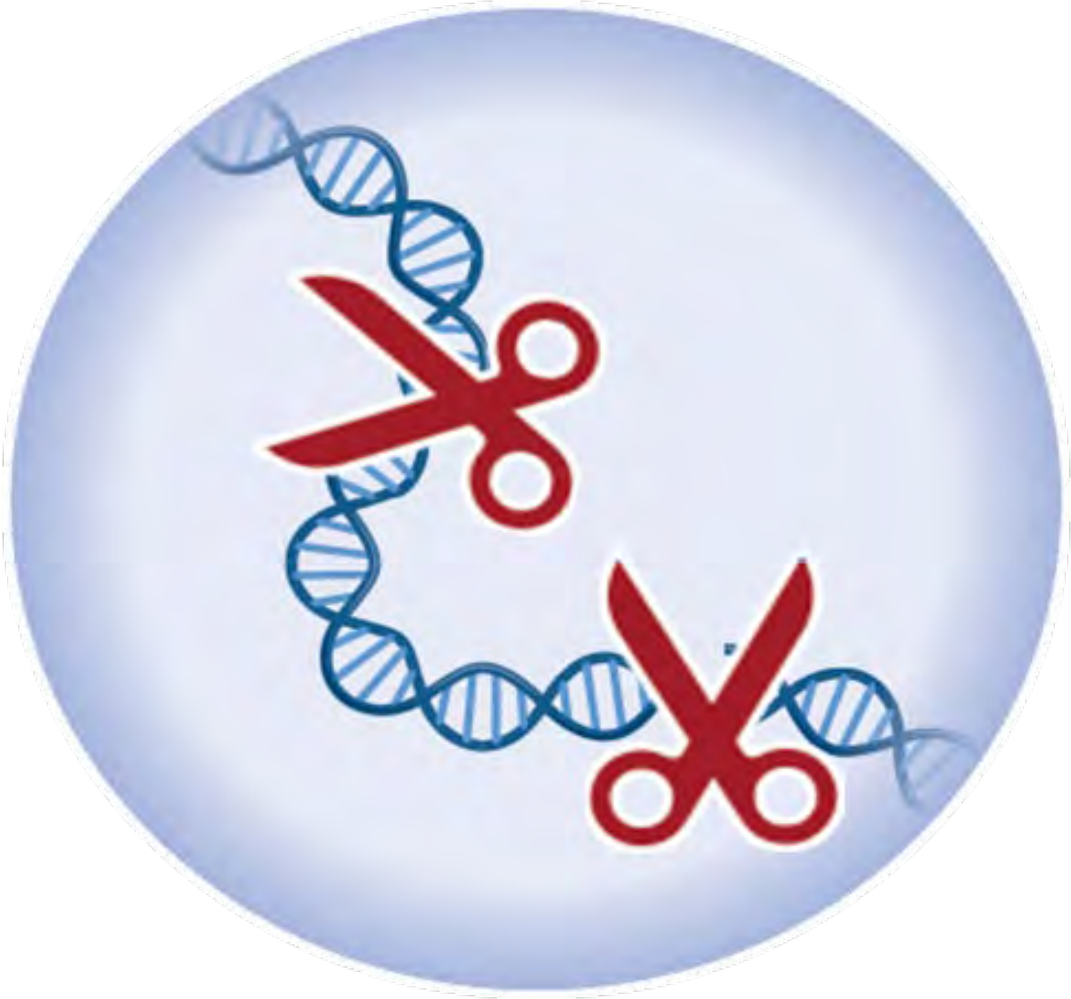
Sirle Saul,[1] Marwah Karim,[1] Luca Ghita,[1] Pei-Tzu Huang,[1] Winston Chiu,[2] Verónica Durán,[1,3] Chieh-Wen Lo,[1] Sathish Kumar,[1] Nishank Bhalla,[4] Pieter Leyssen,[2] Farhang Alem,[5] Niloufar A. Boghdeh,[5] Do H.N. Tran,[1] Courtney A. Cohen,[6] Jacquelyn A. Brown,[7] Kathleen E. Huie,[6] Courtney Tindle,[8,9] Mamdouh Sibai,[10] Chengjin Ye,[11] Ahmed Magdy Khalil,[11] Kevin Chiem,[11] Luis Martinez-Sobrido,[11] John M. Dye,[6] Benjamin A. Pinsky,[1,10] Pradipta Ghosh,[8,9,12] Soumita Das,[9,13] David E. Solow-Cordero,[14] Jing Jin,[15] John P. Wikswo,[16] Dirk Jochmans,[2] Johan Neyts,[2] Steven De Jonghe,[2] Aarthi Narayanan,[4,17] and Shirit Einav[1,3,18]



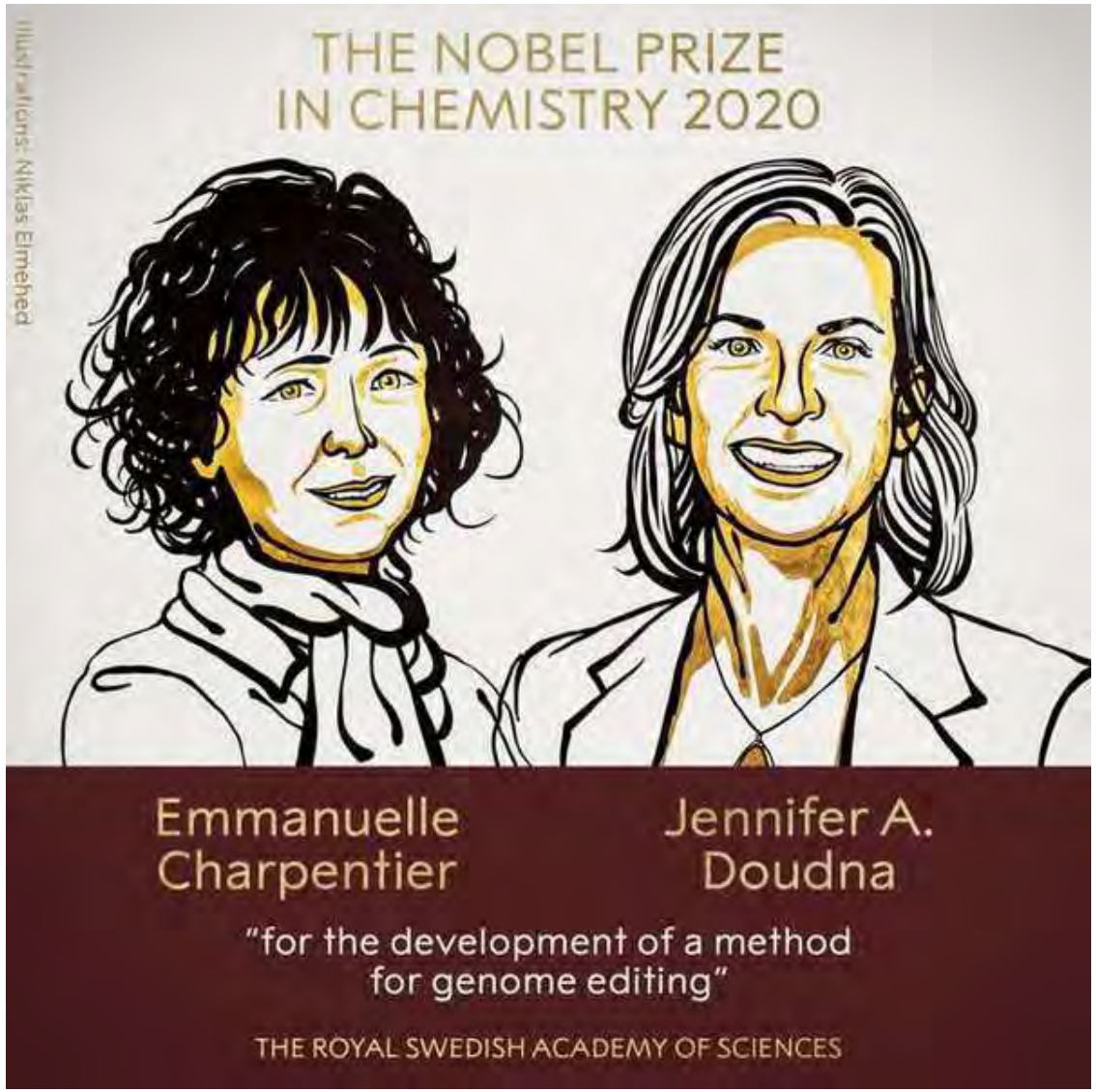
Reis et al., NEJM 2023; Saul et al., J Clin Inv 2023

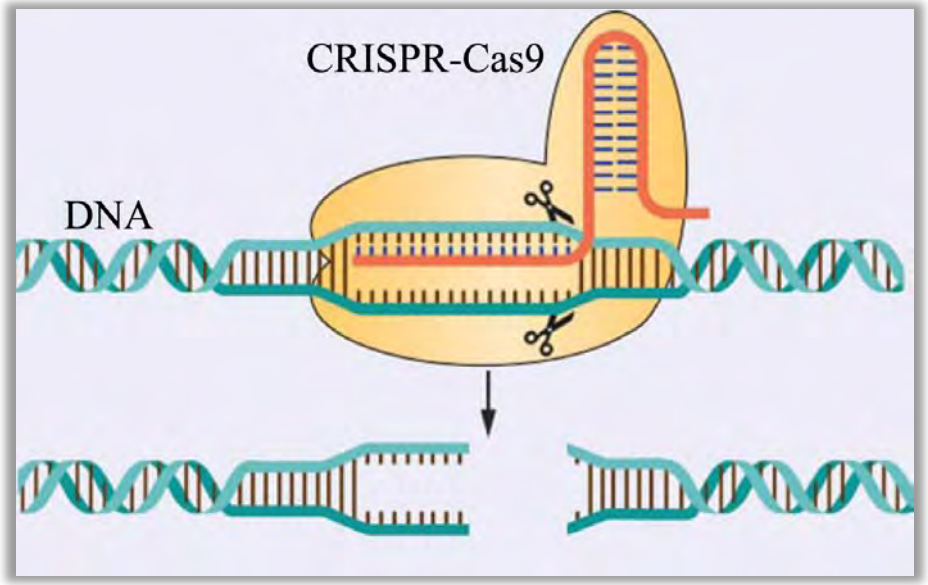
Thuốc chống vi rút tác động trực tiếp: nhắm mục tiêu vào RNA vi rút

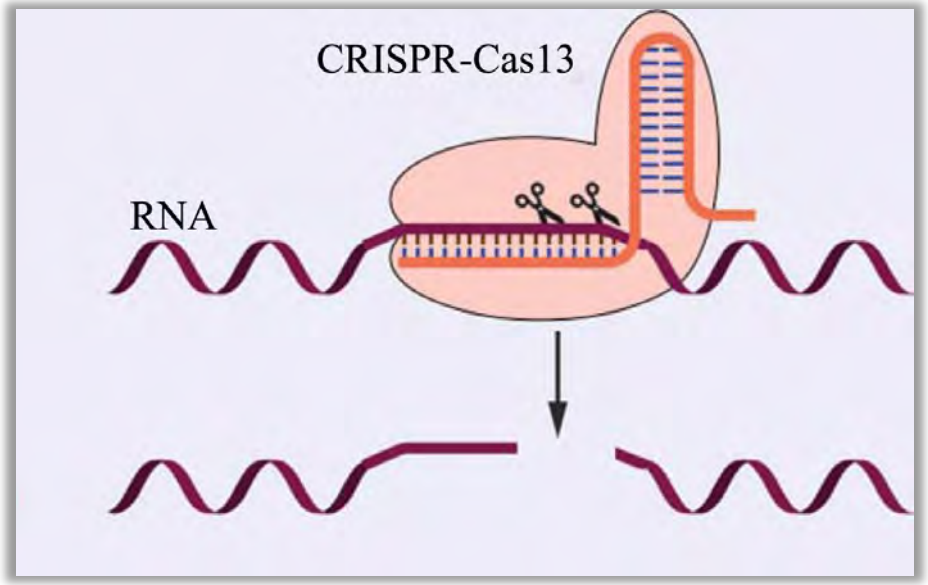




Nhắm mục tiêu vào RNA vi rút: Công nghệ CRISPR







CRISPR-Cas 13 là thuốc kháng vi rút hiệu quả trong thí nghiệm

nature COMMUNICATIONS

ARTICLE

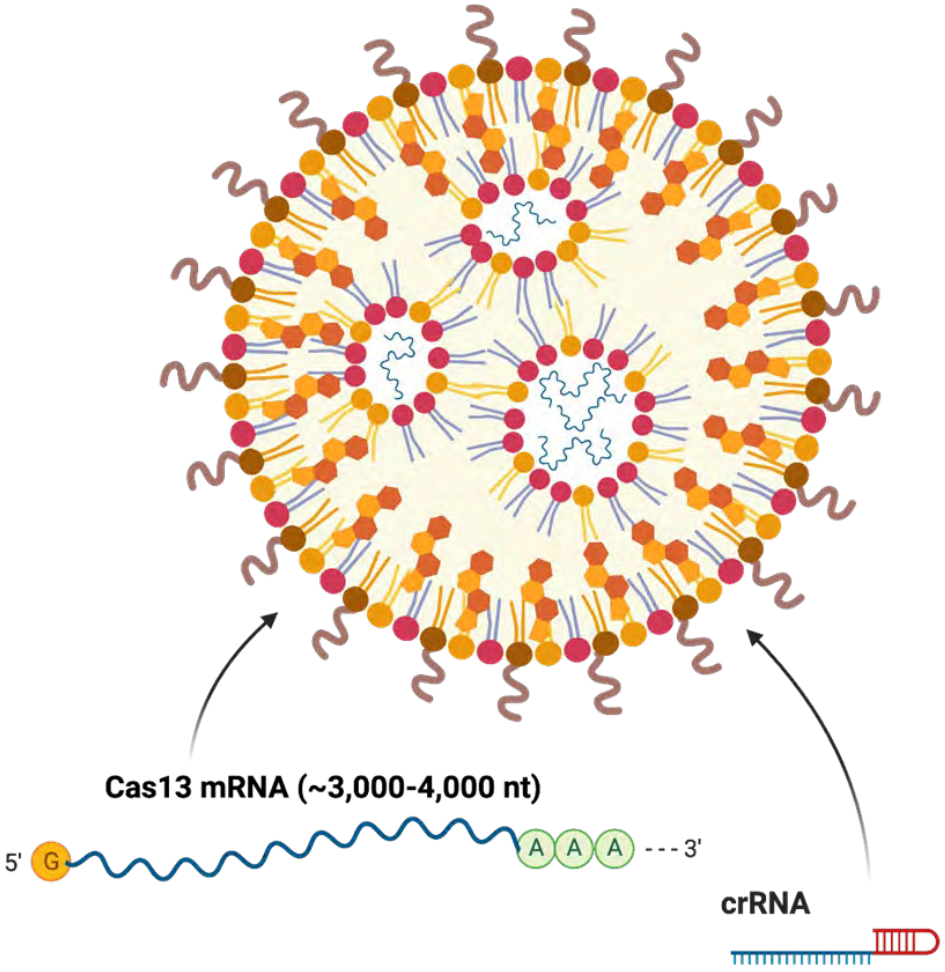
https://doi.org/10.1038/s41467-021-24577-0 OPEN

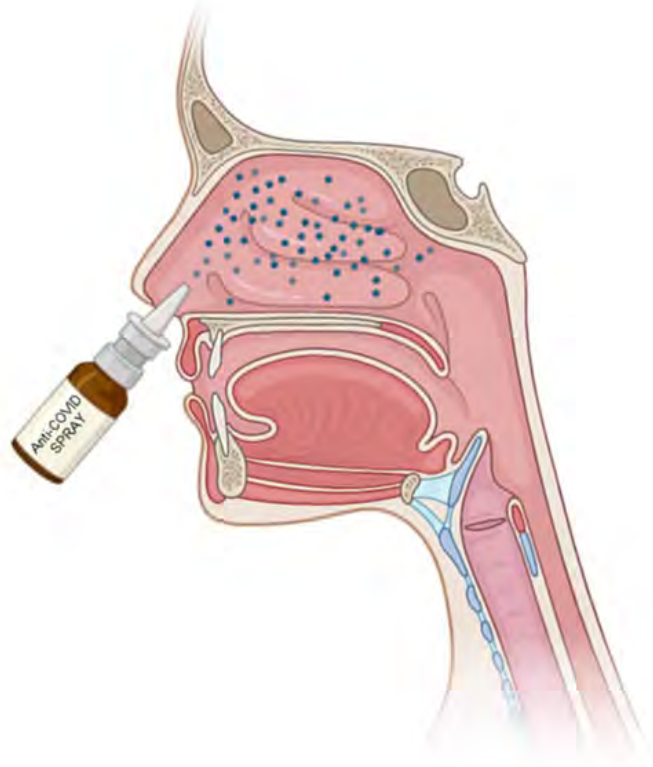
Check for updates

Reprogrammed CRISPR-Cas13b suppresses SARS-CoV-2 replication and circumvents its mutational escape through mismatch tolerance

Mohamed Fareh[1,2✉], Wei Zhao[3], Wenxin Hu[1,2], Joshua M. L. Casan[1,2], Amit Kumar[1,2], Jori Symons[3], Jennifer M. Zerbato[3], Danielle Fong[3], Ilia Voskoboinik[1,2], Paul G. Ekert[1,2,4,5], Rajeev Rudraraju[3,6,7], Damian F. J. Purcell[7], Sharon R. Lewin[3,8,9,10✉] & Joseph A. Trapani[1,2,10]

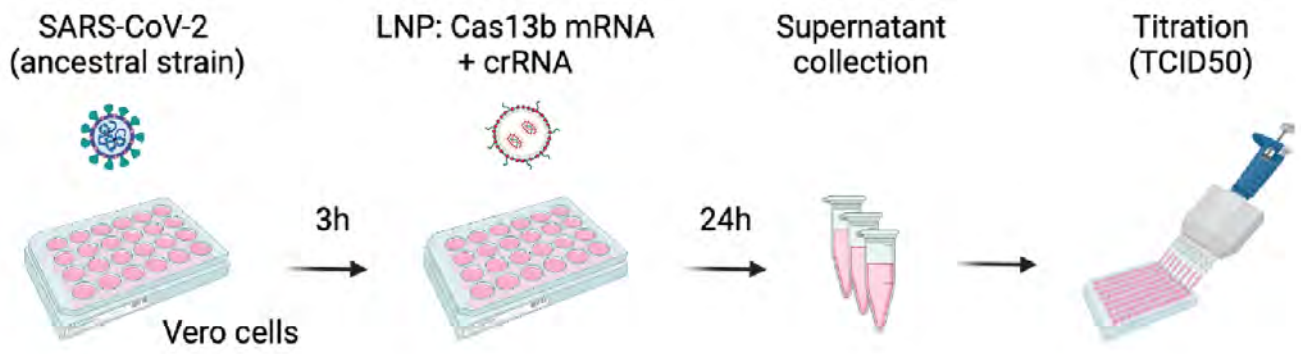
Cung cấp CRISPR-Cas13 in vivo

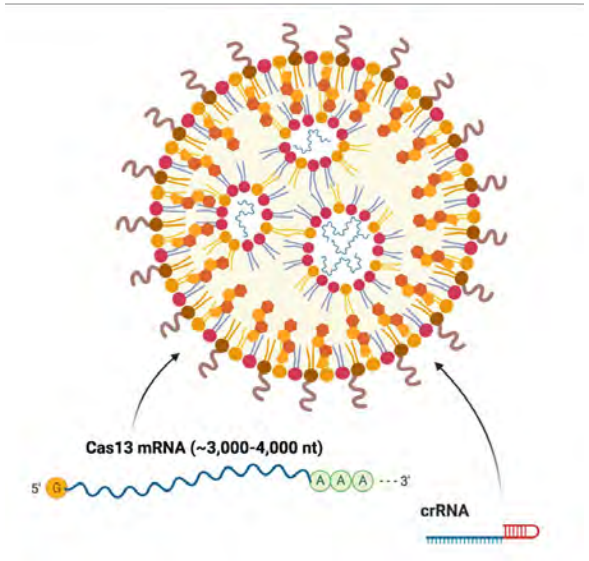




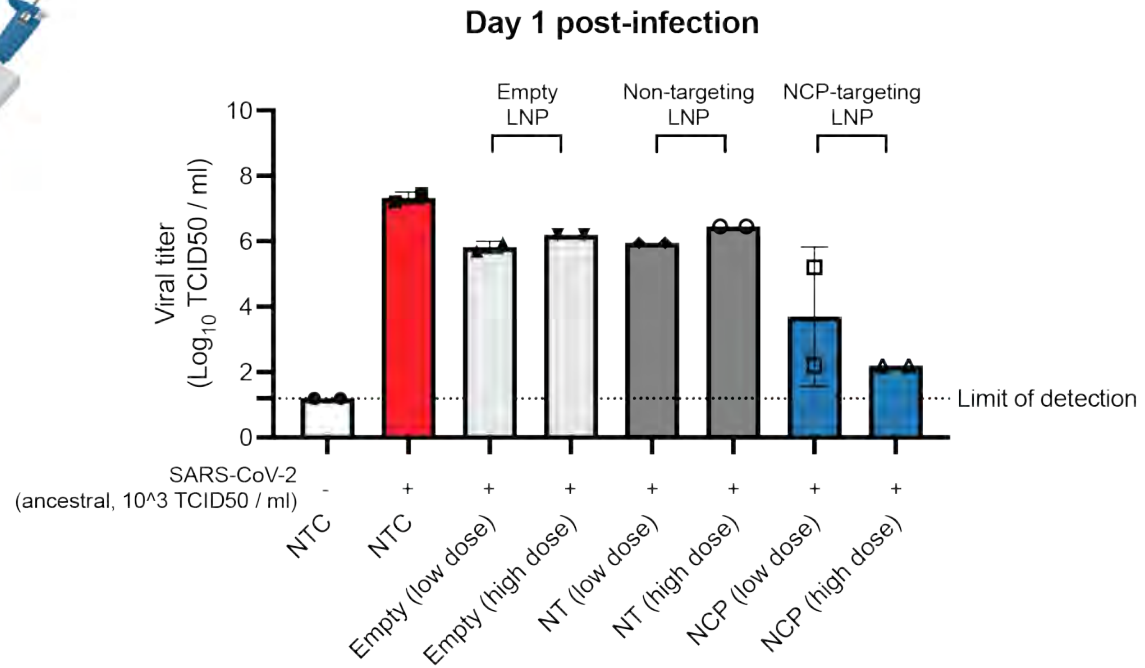
SARS-CoV-2 CRISPR/Cas13
Aerosolised and potentially delivered as a nasal spray

mRNA-LNP có thể cung cấp CRISPR-Cas13 dưới dạng thuốc chống vi rút





Empty LNP
Non-targeting crRNA
NCP crRNA

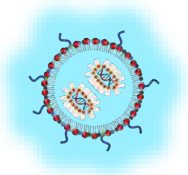


NTC = no template control; NT = non targeting; NCP = nucleocapsid

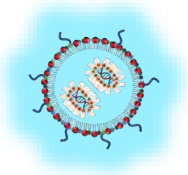
Kan, Zhao, Fareh et al (unpublished)

Cung cấp mRNA LNP in vivo đến đường hô hấp

Day 0 –Luciferase mRNA-LNP labelled with DiD dye

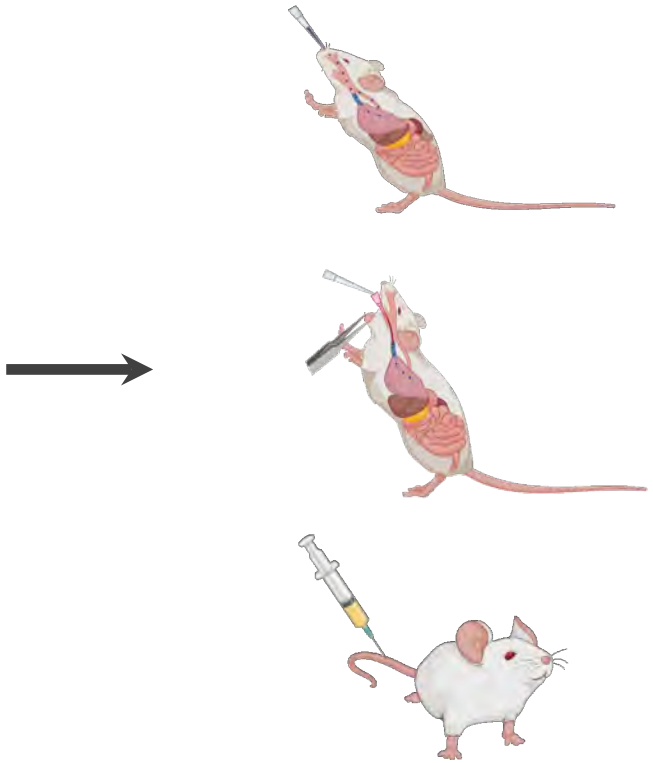


Lipid 1 mRNA LNP



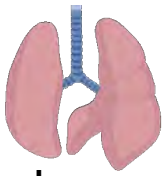
Lipid 2 mRNA LNP

Day 1 – Administration of mRNA-LNP (2 ug/mouse) Intranasal, intratracheal or intravenous



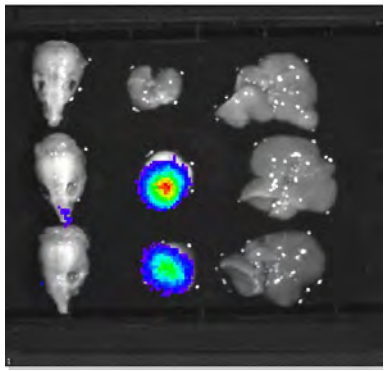
Day 1 - 7 h post-treatment Organ harvesting and imaging

Head



Lung

Liver

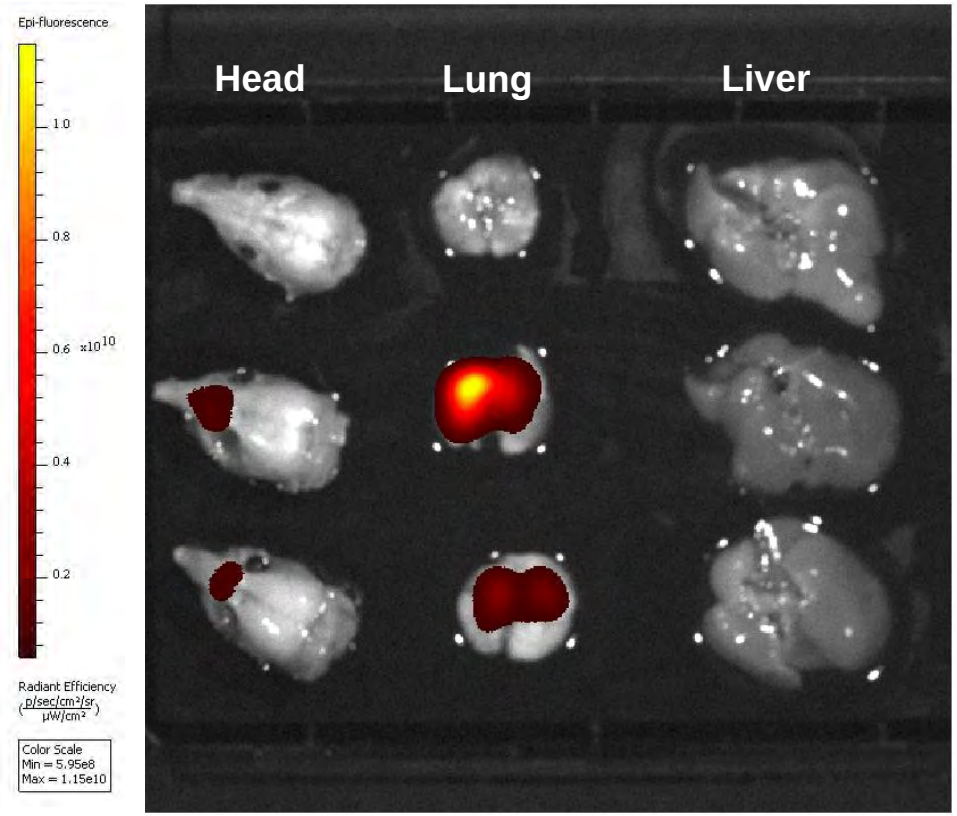


IVIS imaging DiD and Luc

Stan Kan, Rob DeRose, Wei Zhao, Zhenjun Chen and others

Độ đặc hiệu cao của Lipid 1_LNP đối với biểu hiện của mRNA ở phổi sau khi truyền qua đường mũi

Biodistribution (DiD)



PBS

Lipid 1 - LNP

Lipid 2 - LNP

Kang, de Rose Zhao, Fareh and others; provisional patent submitted

Chiến lược sử dụng RNA để điều trị COVID-19: một mô hình mới?

Molecular Therapy
Original Article

A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19

Adi Idris,[1,5] Alicia Davis,[2,3,5] Aroon Supramaniam,[1,5] Dhruba Acharya,[1] Gabrielle Kelly,[1] Yaman Tayyar,[1] Nic West,[1] Ping Zhang,[1] Christopher L.D. McMillan,[4] Citradewi Soemardy,[2] Roslyn Ray,[2] Denis O'Meally,[2] Tristan A. Scott,[2] Nigel A.J. McMillan,[1] and Kevin V. Morris[1,2]

Cell
Article

Identification of a therapeutic interfering particle—A single-dose SARS-CoV-2 antiviral intervention with a high barrier to resistance

Idris et al., Molecular Therapy 2021; Chaturvedi et al., Cell 2022

Trung tâm ứng phó đại dịch toàn cầu

In September 2022, Geoff Cumming, a Canadian philanthropist now based in Melbourne, announced a gift of $250 million to the Doherty Institute.

The gift will establish the Cumming Global Centre for Pandemic Therapeutics.

The centre will provide long term mission based funding to researchers to develop novel platform technologies for therapeutics for pathogens of pandemic potential.

Funding principals include 20% for discovery research and 30% will be spent externally to the Doherty Institute

Tóm tắt và ý nghĩa

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- Chỉnh sửa RNA CRISPR-Cas13 RNA có độ đặc hiệu và hiệu lực cao cho phép kiểm soát sự sao chép của SARS- Covi2 trong ống nghiệm. Những tiến.bộ trong các hạt nano lipid mRNA có liên quan mức độ cao đối với phương pháp điều trị nhắm mục tiêu RNA.

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