How can we stop the next pandemic?

New York Times

Nam-Joon Cho, Ph.D.

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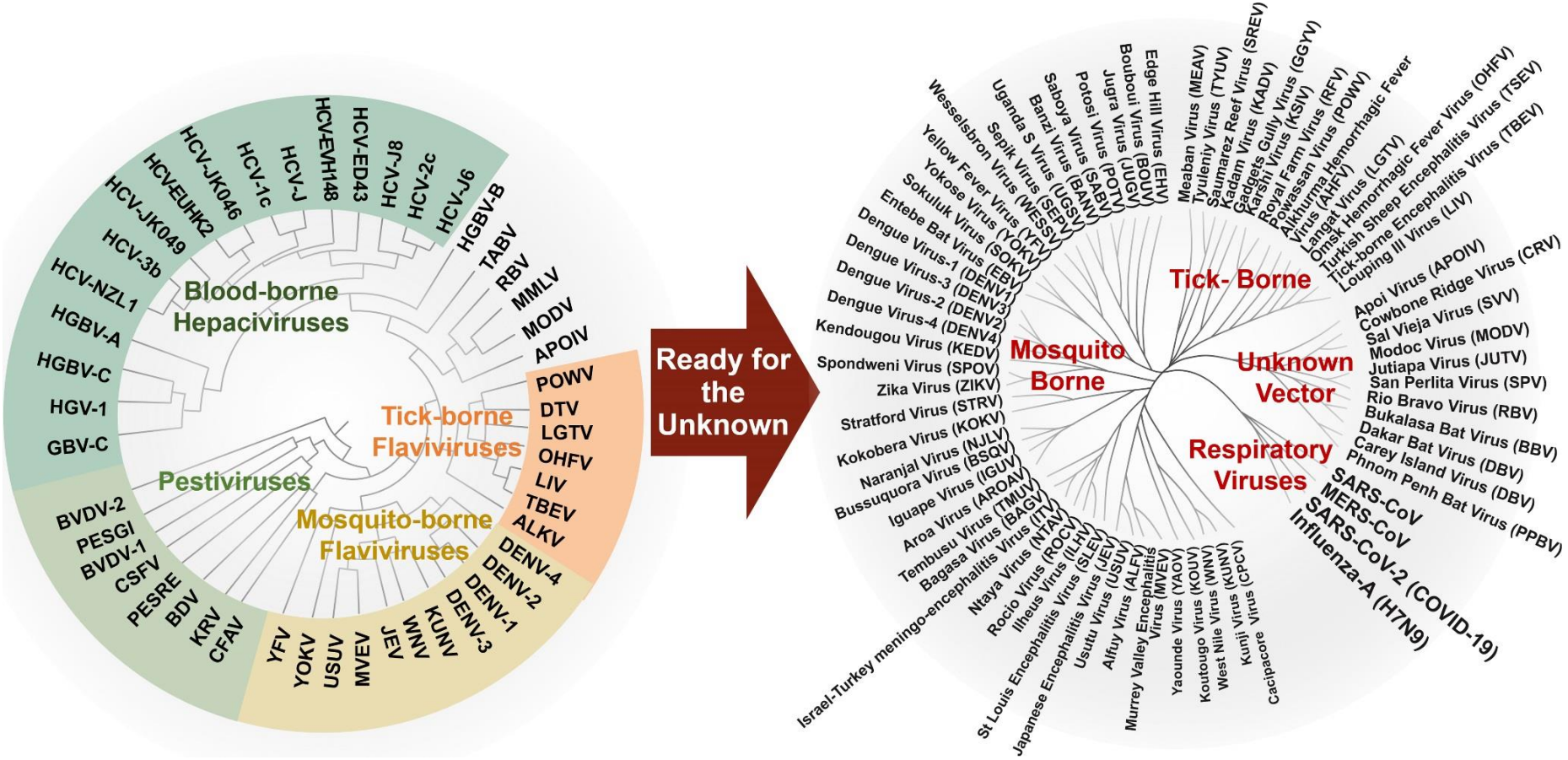
과총-재외과협 온라인 포럼 6.3.2020

We need to confront the "unknown unknowns"



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Preventing Coronavirus Transmission

- An N95 respirator is a respiratory protective device designed to achieve a very close facial fit and very efficient **filtration of airborne particles**.
- The 'N95' designation means that when subjected to careful testing, the respirator blocks **at least 95 percent of very small (0.3 micron) test particles**.

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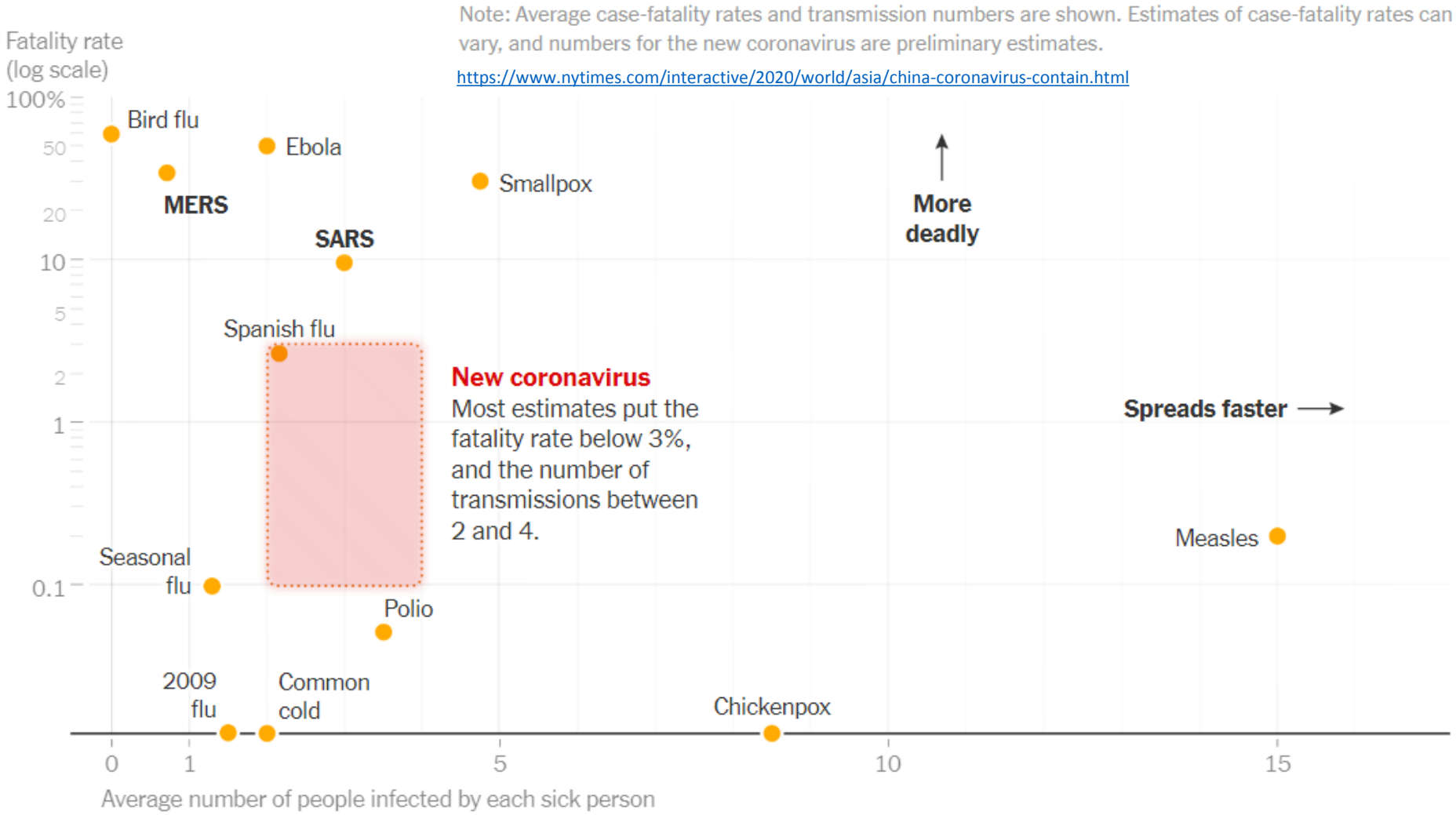
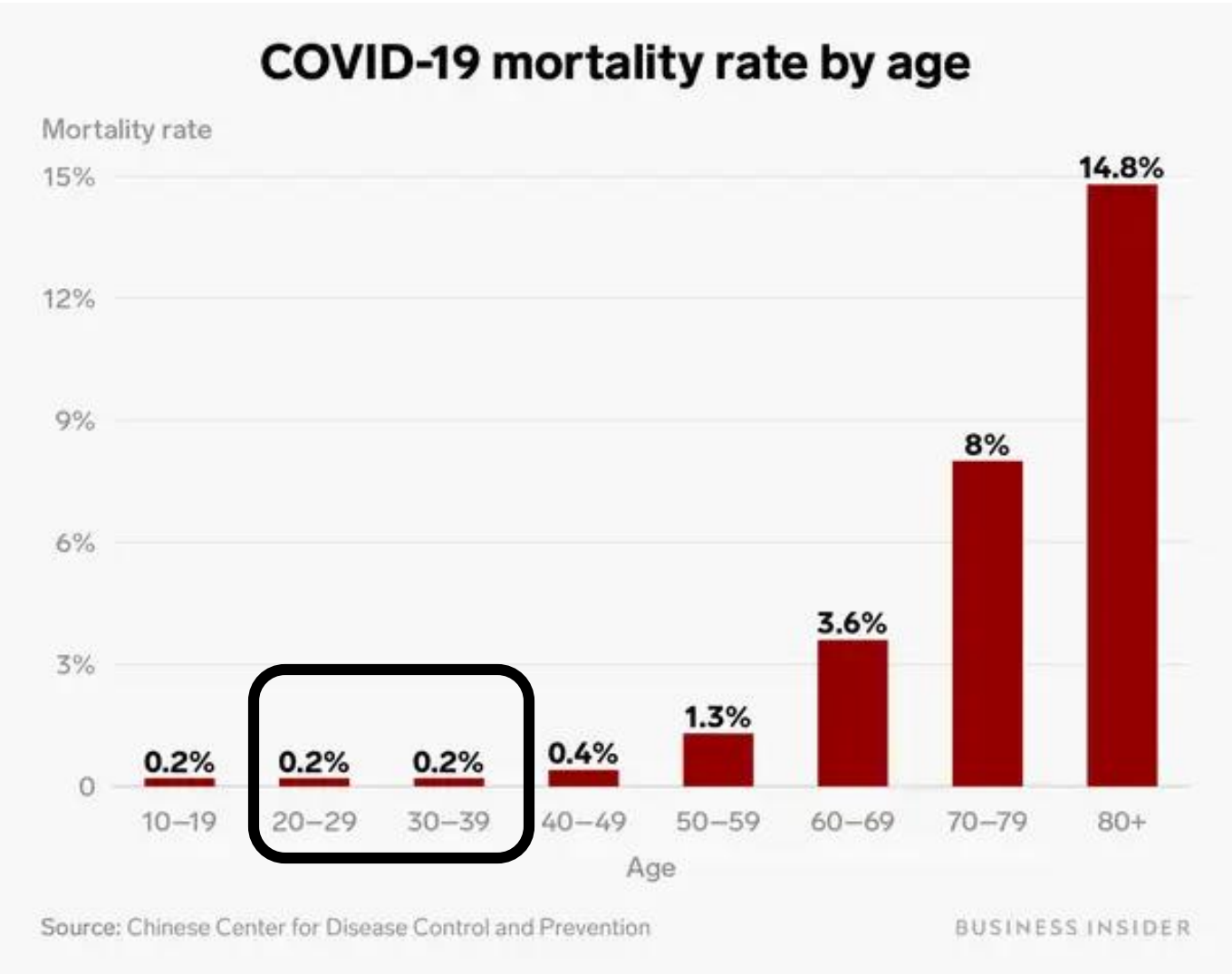
Current Coronavirus vs. Other Viruses



Age-Dependent Coronavirus Mortality Rates



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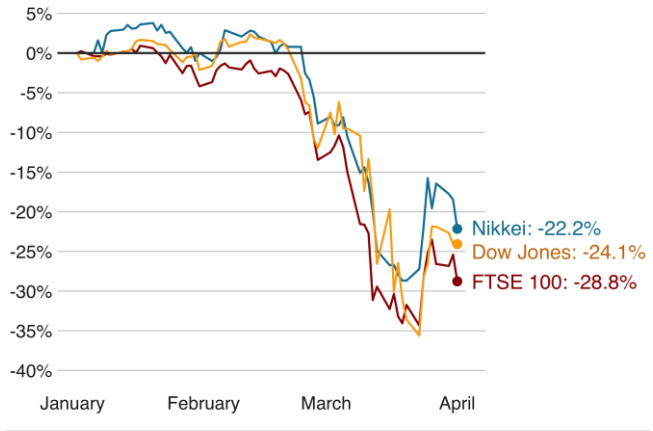
Frozen Economy

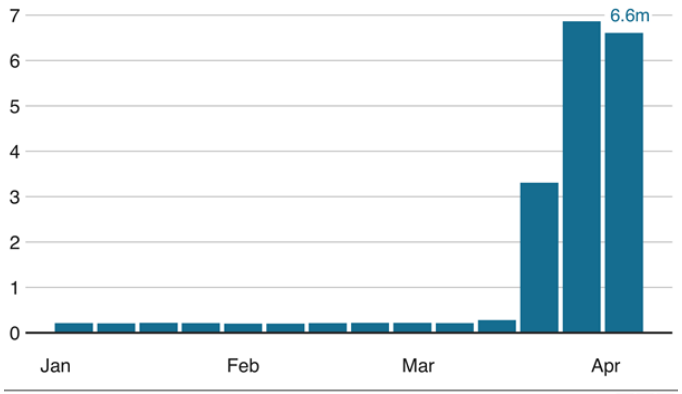
The impact of coronavirus on stock markets since the start of the outbreak



Source: Bloomberg, 01 April 2020, 09:00 GMT BBC

US jobless claims at record high

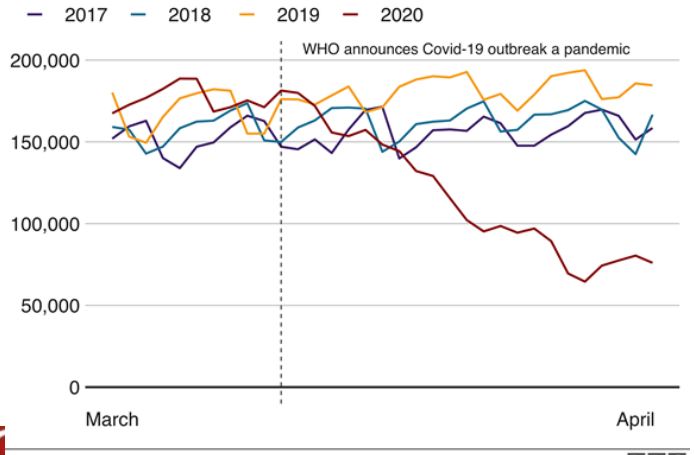
Weekly total of unemployment claims in 2020



Source: US Bureau of Labor Statistics BBC

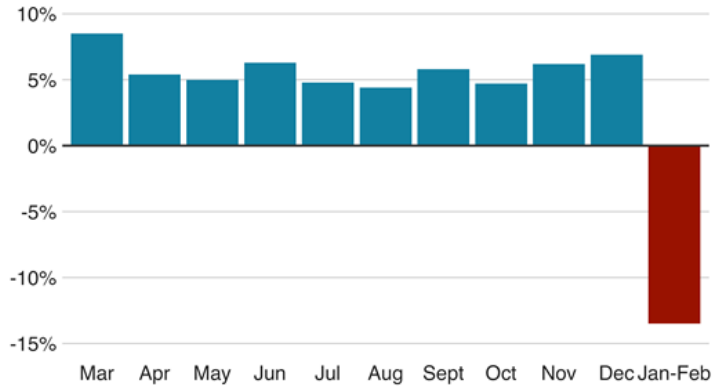
Far fewer flights

Number of total daily flights



Source: Flightradar24, 03 April 2020 BBC

Chinese industrial production fell by 13.5% in the first two months of the year



Source: China National Bureau of Statistics BBC

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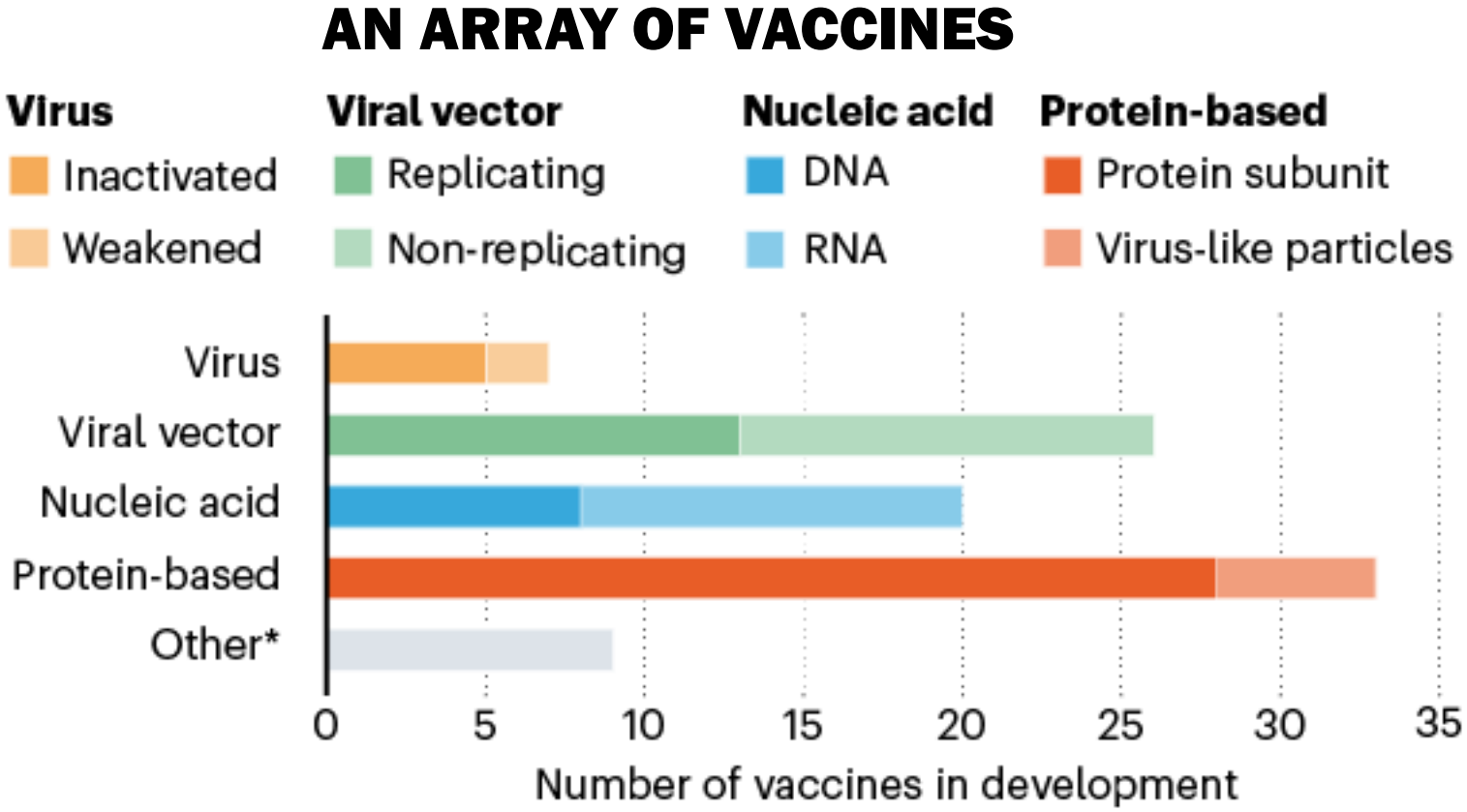
Types of Coronavirus Vaccines in Development



* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

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What could go wrong?

Antibody Dependent Enhancement (ADE)

Vaccines help body produce antibodies to stop viruses and prevent cell infection

Sometimes… antibody binding to virus particles enhances cell infection

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Failure of a Dengue Vaccine

SCIENTIFIC AMERICAN APRIL 2019

How the World's First Dengue Vaccination Drive Ended in Disaster

Is a runaway immune reaction making a dengue vaccine dangerous?

By Seema Yasmin, Madhusree Mukerjee

In December 2015 then president Benigno Aquino III of the Philippines and others negotiated a deal with pharmaceutical company Sanofi to purchase three million doses of Dengvaxia, the first vaccine ever licensed for dengue. The plan was to give a million schoolchildren, nine years of age, three doses of the vaccine each, sparing them from the worst outcomes of dengue: shock, organ failure

COVID-19 Vaccine: Potential ADE Risk (I)

COMMENT

Check for updates

The potential danger of suboptimal antibody responses in COVID-19

Akiko Iwasaki[1,2] ✉ *and Yexin Yang*[1]

There is a desperate need for effective therapies and vaccines for SARS-CoV-2 to mitigate the growing economic crisis that has ensued from societal lockdown. Vaccines are being developed at an unprecedented speed and are already in clinical trials, without preclinical testing for safety and efficacy. Yet, safety evaluation of candidate vaccines must not be overlooked.

https://www.nature.com/articles/s41577-020-0321-6

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Many Challenges to Make Coronavirus Vaccine

Plotting a scientific path to counter COVID-19

HOW COVID-19 RESPONSE IS STIMULATING GLOBAL SCIENTIFIC COLLABORATION

BY STEVE USDIN, WASHINGTON EDITOR | FEB 27, 2020 | 9:55 AM KST

In a global online forum Tuesday night, scientific leaders from companies developing vaccines, therapies and diagnostics to address the COVID-19 outbreak discussed opportunities for collaboration, highlighted challenges, and called for sustained global initiatives to create medical countermeasures to emerging infections.

Participants in the forum, which was sponsored by WuXi Apptec Co. Ltd. (Shanghai:603259; HKEX:2359), provided updates on vaccine development progress, stressed the need to develop multiple vaccines, and called for the establishment of master protocols to efficiently test the candidates.

Vaccine developers and academic opinion leaders said the potential for a COVID-19 vaccine to enhance the severity of infections caused by other coronaviruses, including viruses that are likely to emerge in the future, is a contingency that must be addressed prior to widespread testing of candidate vaccines.

Scientists and business leaders on the ground in China described challenges with available diagnostic technologies and the need for point-of-care diagnostics.

ENHANCEMENT

The need to assess the potential of vaccine candidates to inadvertently worsen future coronavirus infections through a process called antibody-dependent enhancement was a major topic of discussion at the WHO COVID-19 R&D forum on Feb. 11-12, Xuefeng Yu, chairman and CEO of CanSino Biologics, said.

Yu noted that antibody-dependent enhancement has been a major problem with Dengue vaccines. When patients who have not previously been exposed to the virus are vaccinated, there is a risk that some of the antibodies they produce will facilitate virus entry into host cells upon Dengue exposure, causing a much more serious illness than would have occurred in the absence of vaccination.

Antibody-dependent enhancement has also been reported for SARS-CoV, HIV, influenza, other alpha and flaviviruses, and Ebola. SARS-CoV shares a high degree of similarity with SARS-2CoV, the virus that causes COVID-19.

"We should cautiously go into human Phase I trials before we have enhancement models."

Xuefeng Yu, CanSino Biologics

https://www.biocentury.com/article/304521/how-covid-19-response-is-stimulating-global-scientific-collaboration

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COVID-19 Vaccine: Potential ADE Risk (II)

Science

REPORTS

Cite as: Q. Gao *et al.*, *Science* 10.1126/science.abc1932 (2020).

Development of an inactivated vaccine candidate for SARS-CoV-2

Qiang Gao[1]*, Linlin Bao[2]*, Haiyan Mao[3]*, Lin Wang[1]*, Kangwei Xu[4]*, Minnan Yang[5]*, Yajing Li[1], Ling Zhu[5], Nan Wang[5], Zhe Lv[5], Hong Gao[2], Xiaoqin Ge[1], Biao Kan[6], Yaling Hu[1], Jiangning Liu[2], Fang Cai[1], Deyu Jiang[1], Yanhui Yin[1], Chengfeng Qin[7], Jing Li[1], Xuejie Gong[1], Xiuyu Lou[3], Wen Shi[3], Dongdong Wu[1], Hengming Zhang[1], Lang Zhu[1], Wei Deng[2], Yurong Li[1], Jinxing Lu[6]†, Changgui Li[4]†, Xiangxi Wang[5]†, Weidong Yin[1]†, Yanjun Zhang[3]†, Chuan Qin[2]†

[1]Sinovac Biotech Ltd., Beijing, China. [2]Key Laboratory of Human Disease Comparative Medicine, Chinese Ministry of Health, Beijing Key Laboratory for Animal Models of Emerging and Remerging Infectious Diseases, Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences and Comparative Medicine Center, Peking Union Medical College, Beijing, China. [3]Department of Microbiology, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China. [4]Division of Respiratory Virus Vaccines, National Institute for Food and Drug Control, Beijing, China. [5]CAS Key Laboratory of Infection and Immunity, National Laboratory of Macromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China. [6]National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Changping, Beijing, China. [7]Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, Beijing, China.

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) has resulted in an unprecedented public health crisis. There are currently no SARS-CoV-2-specific treatments or vaccines available due to the novelty of the virus. Hence, rapid development of effective vaccines against SARS-CoV-2 are urgently needed. Here we developed a pilot-scale production of a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc), which induced SARS-CoV-2-specific neutralizing antibodies in mice, rats and non-human primates. These antibodies neutralized 10 representative SARS-CoV-2 strains, suggesting a possible broader neutralizing ability against SARS-CoV-2 strains. Three immunizations using two different doses (3 μg or 6 μg per dose) provided partial or complete protection in macaques against SARS-CoV-2 challenge, respectively, without observable antibody-dependent enhancement of infection. These data support clinical development of SARS-CoV-2 vaccines for humans.

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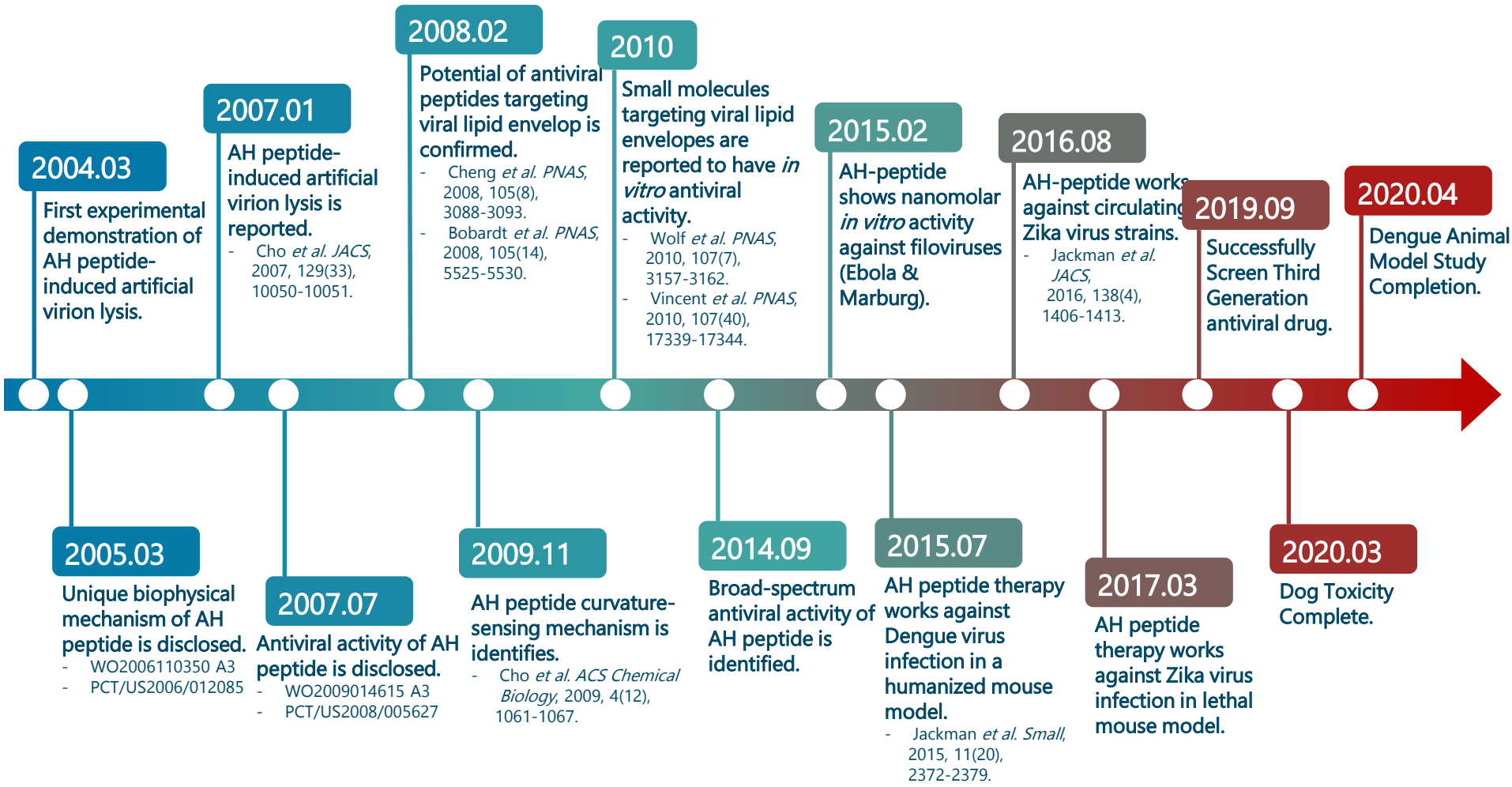
Discovery of Antiviral Drug Platform



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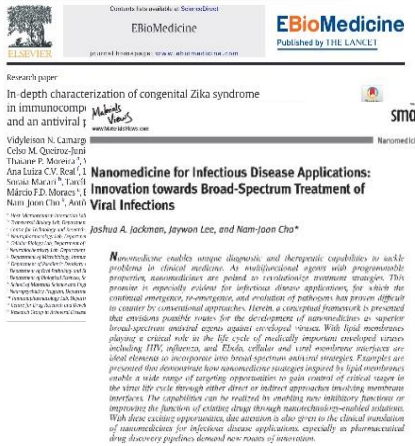
Lipid Enveloped Antiviral Disruption "LEAD" Concept

- **Publications**


EBioMedicine

EBioMedicine
Published by THE LANCET

Research paper

In-depth characterization of congenital Zika syndrome in immunocompe... and an antiviral ...

small

Nanomedicine

Nanomedicine for Infectious Disease Applications: Innovation towards Broad-Spectrum Treatment of Viral Infections

Joshua A. Jackman, Jaywon Lee, and Nam-Joon Cho*


nature materials

LETTERS

Therapeutic treatment of Zika virus infection using a brain-penetrating antiviral peptide

Joshua A. Jackman[1,10], Vivian V. Costa[2,3,4,10], Soohyun Park[1], Ana Luiza C. V. Real[2], Jae Hyeon Park[1], Pablo L. Cardozo[2,5], Abdul Rahim Ferhan[1], Isabella G. Olmo[2], Thaiane P. Moreira[4,6], Jordana L. Bambirra[4,6], Victoria F. Queiroz[4,6], Celso M. Queiroz-Junior[7], Giselle Foureaux[7], Danielle G. Souza[6], Fabiola M. Ribeiro[6], Bo Kyeong Yoon[1], Evelien Wynendaele[8], Bart De Spiegeleer[8], Mauro M. Teixeira[2,3] and Nam-Joon Cho[1,9]*

Zika virus is a mosquito-borne virus that is associated with neurodegenerative diseases, including Guillain–Barré syndrome and congenital Zika syndrome. As Zika virus targets the nervous system, there is an urgent need to develop therapeutic strategies that inhibit Zika virus infection in the brain. Here, we have engineered a brain-penetrating peptide that works against Zika virus and other mosquito-borne viruses. We evaluated the therapeutic efficacy of the peptide in a lethal Zika virus mouse model exhibiting systemic and brain infection. Therapeutic treatment protected against mortality and markedly reduced clinical symptoms, viral loads and neuroinflammation, as well as mitigated microgliosis, neurodegeneration and brain damage. In addition to controlling systemic infection, the peptide crossed the blood–brain barrier to reduce viral loads in the brain and protected against Zika-virus-induced blood–brain barrier injury. Our findings demonstrate how engineering strategies can be applied to develop peptide therapeutics and support the potential of a brain-penetrating peptide to treat neurotropic viral infections.

- Jackman *et al.* *Nature Materials 2018; 17, 971–977.*
- Jackman *et al.* *Nature Materials 2018; 17, 950–957.*
- Camargos VN *et al.* *EBioMedicine 2019; 44, 516-529.*
- Jackman *et al.* *Advanced Therapeutics 2018; 1(5), 1800045.*
- Nam Joon Cho *et al.* *Nature Materials 2020;* https://doi.org/10.1038/s41563-020-0698-4


Check for updates

comment

Materials science approaches in the development of broad-spectrum antiviral therapies

The COVID-19 pandemic has reignited efforts to develop materials science innovations aimed at stopping viral infections. One of the greatest opportunities lies in developing broad-spectrum antiviral technologies that work against many viruses, which could be the key to thwarting outbreaks in the future.

Nam Joon Cho and Jeffrey S. Glenn

- **Medias**


EurekAlert!
The Global Source for Science News

Peptide engineered by NTU Singapore successfully exploits Achilles' heel of Zika virus

ScienceDaily
Your source for the latest research news

Science News from research organiz...

Peptide successfully exploits Achilles' heel of Zika virus


PHYS.ORG

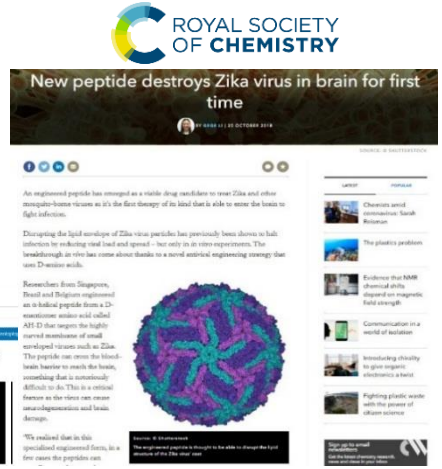
Peptide exploits Achilles' heel of Zika virus


Pesquisa
FAPESP

Nova estratégia inibe replicação do zika


THE STRAITS TIMES

NTU scientists discover new drug to fight Zika virus


ROYAL SOCIETY OF CHEMISTRY

New peptide destroys Zika virus in brain for first time

Asia&Pacific

Singaporean scientists invent peptide to prevent Zika infections


China.org.cn

Singaporean scientists invent peptide to prevent Zika infections

INFECTION CONTROL TODAY

Engineered Peptide Successfully Exploits Achilles' Heel of Zika Virus

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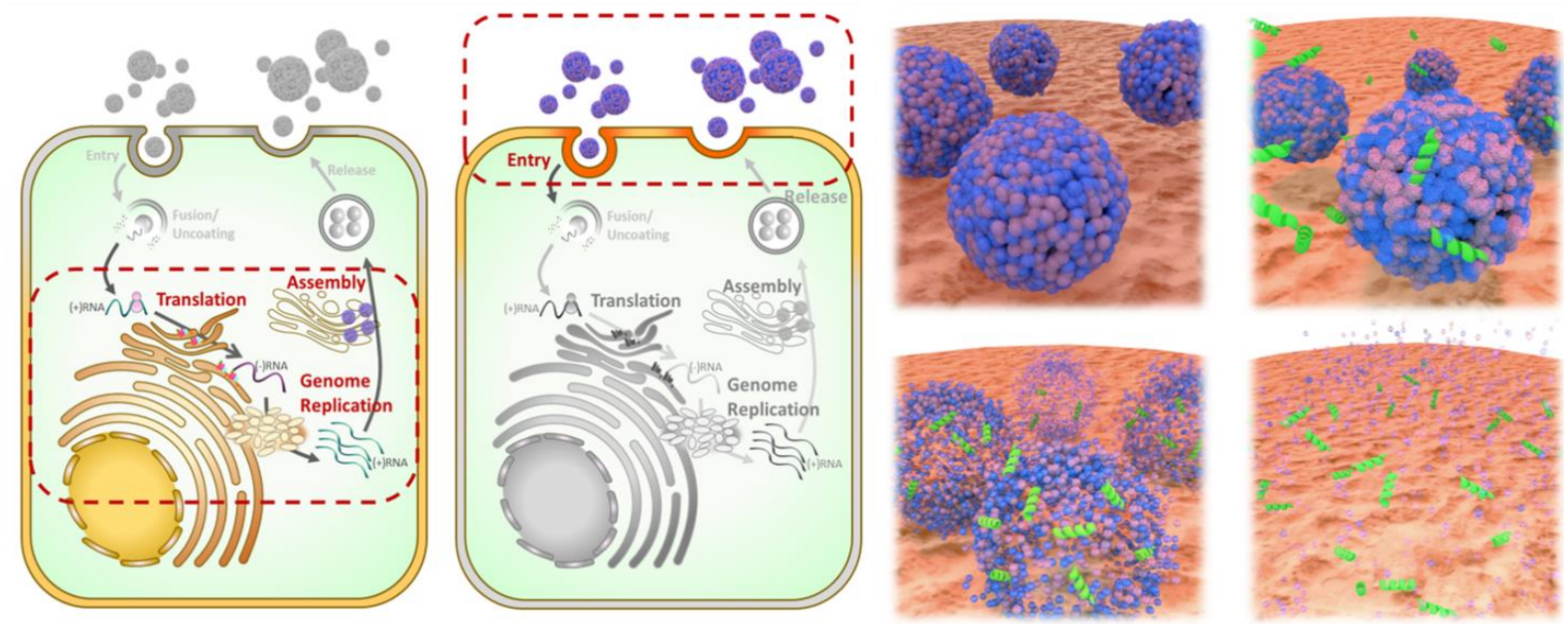
Next –Generation Antiviral Technology



- Enveloped viruses are membrane-enclosed objects that infect cells.
- Antiviral peptide for **L**ipid **E**nvelope **A**ntiviral **D**isruption (LEAD)

World Health Organization

NIH National Institute of Allergy and Infectious Diseases

USAMRIID United States Army Medical Research Institute of Infectious Diseases

Public Health England

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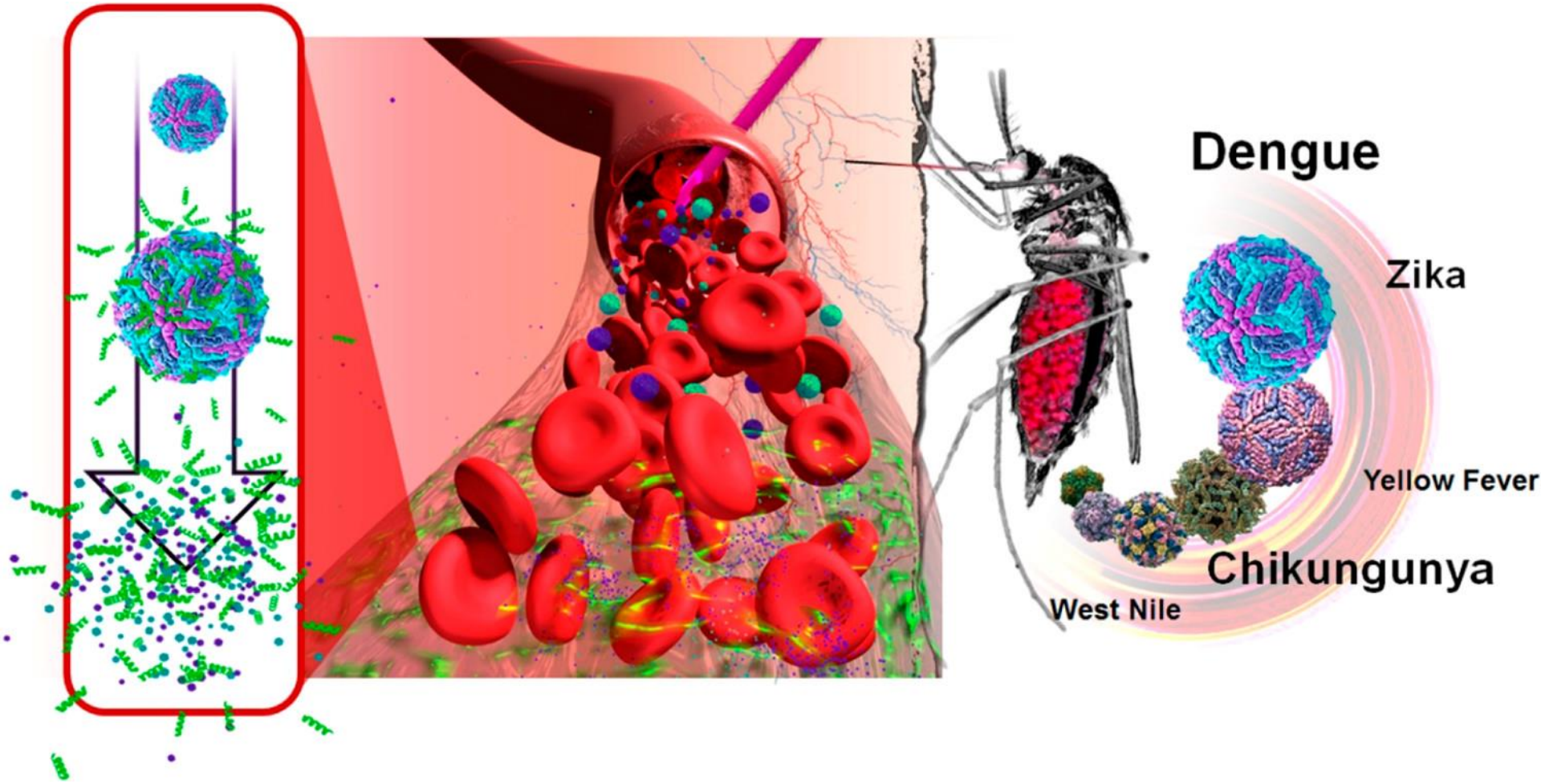
LEAD Concept: Mosquito-Borne Viruses



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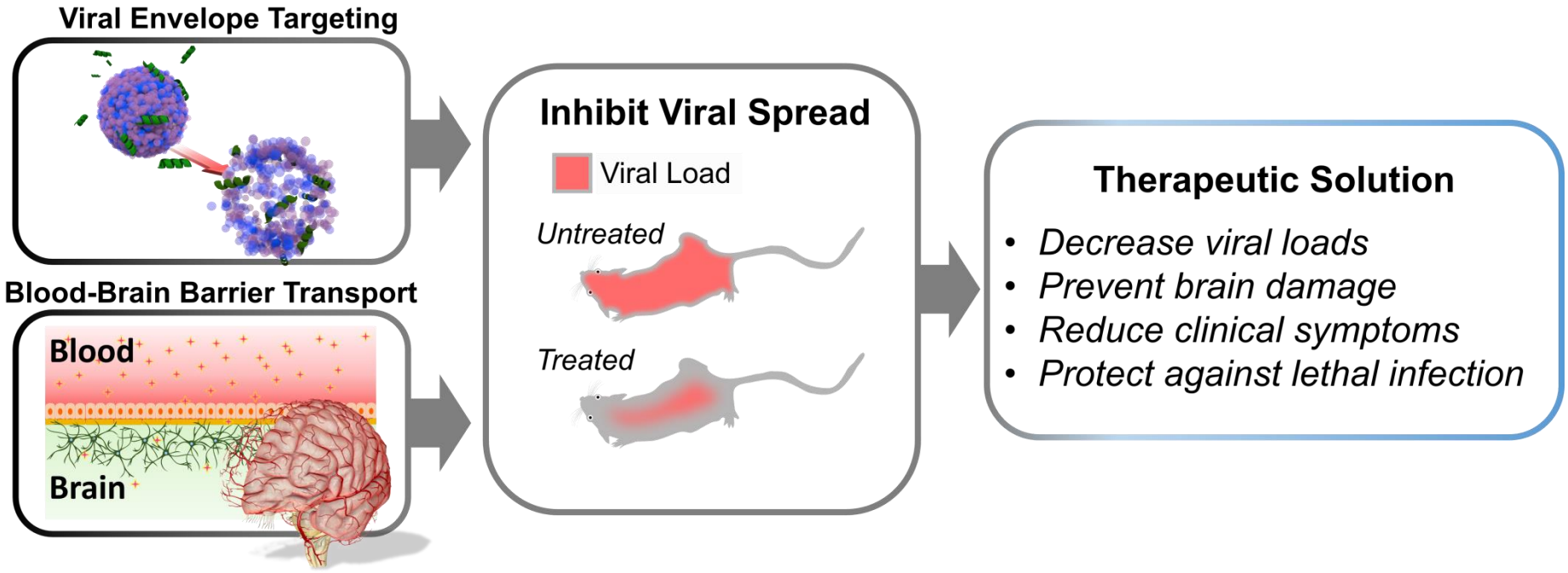
LEAD Concept



- **Lipid Envelope Antiviral Disruption = "LEAD"**
- **Selected amphipathic, α-helical (AH-D) peptide as LEAD candidate.**
- **Evidence of some peptides crossing blood-brain barrier.**

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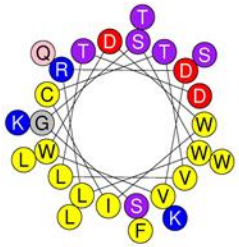
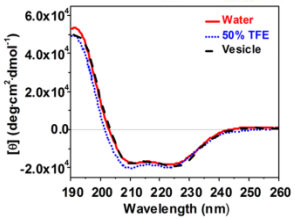
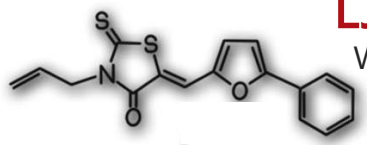
Target Achilles' Heel of Antiviral Agents





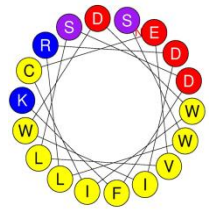
AH Peptide

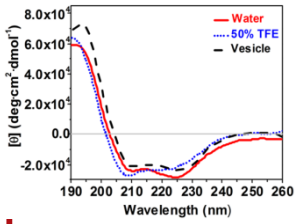
Cho et al. (2009). *ACS Chemical Biology*, 4(12), 1061-1067.



LJ001

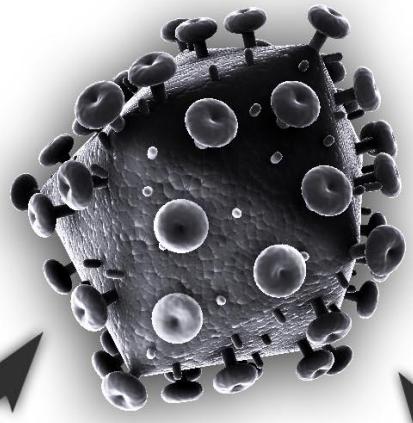
Wolf et al. (2010). *PNAS*, 107(7), 3157-3162.



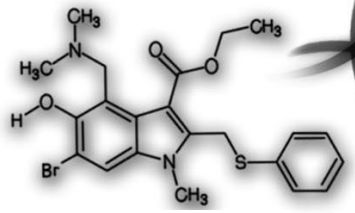


C5A Peptide

Cheng et al. (2008). *PNAS*, 105(8), 3088-3093.

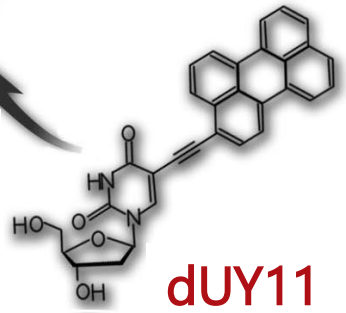


Virus Envelope



Arbidol

Villalaín et al. (2010). *J Phys Chem B*, 114(25), 8544-8554.



dUY11

Vincent et al. (2010). *PNAS*, 107(40), 17339-17344.

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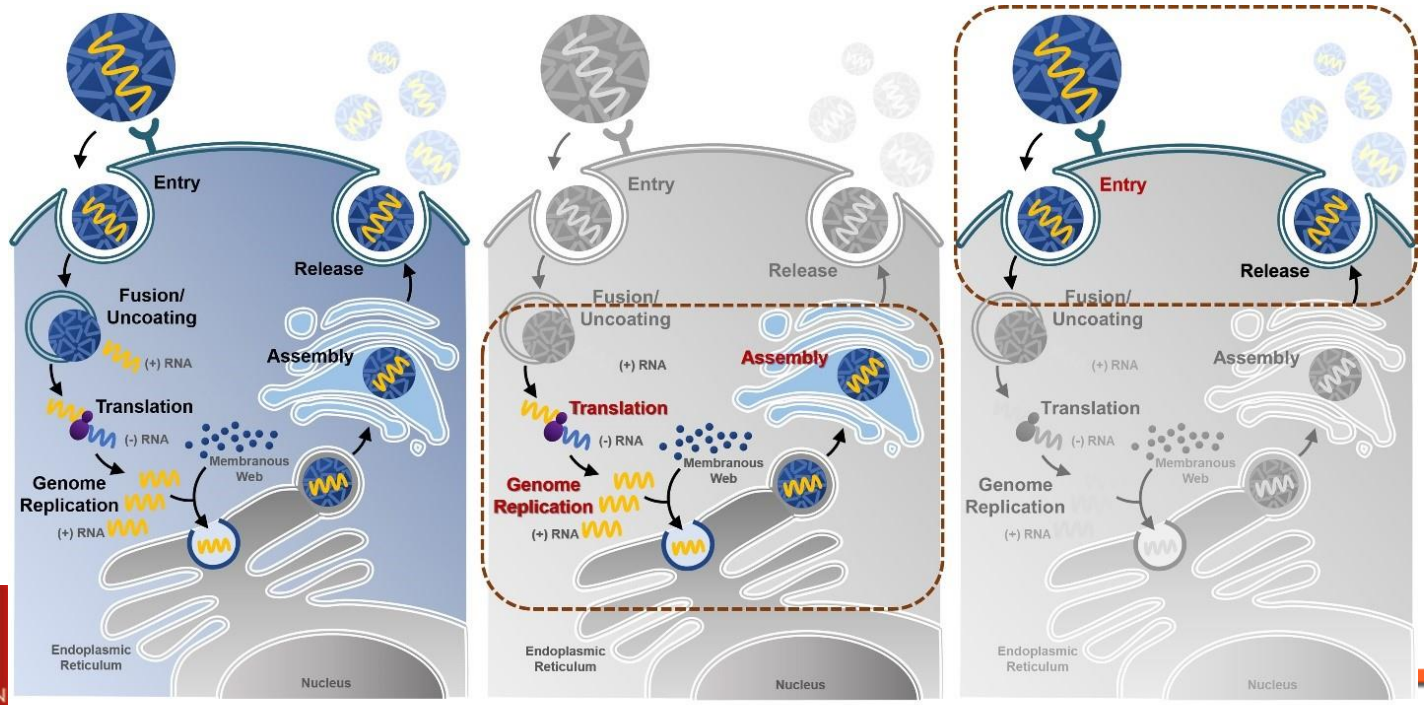
Therapeutic Treatment of Zika Virus Infection Using a Brain-Penetrating Antiviral AH-D Model Peptide



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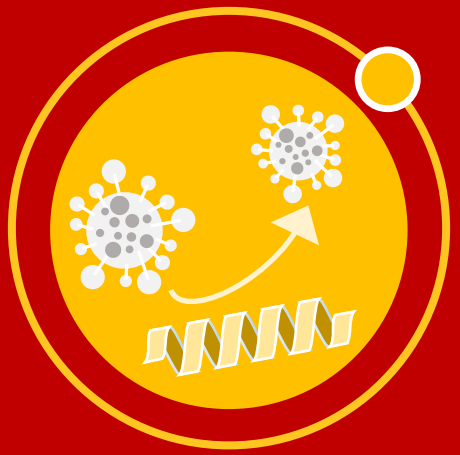
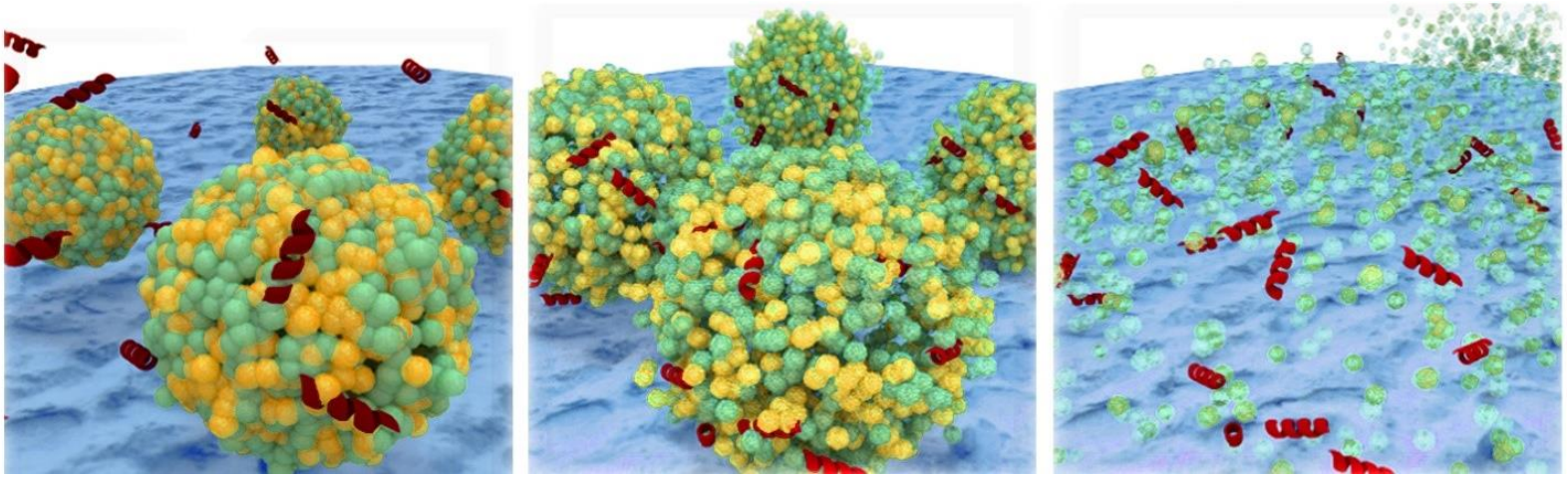


Engineering Short Amphipathic Peptides with Antiviral Properties

Antiviral Peptide Series



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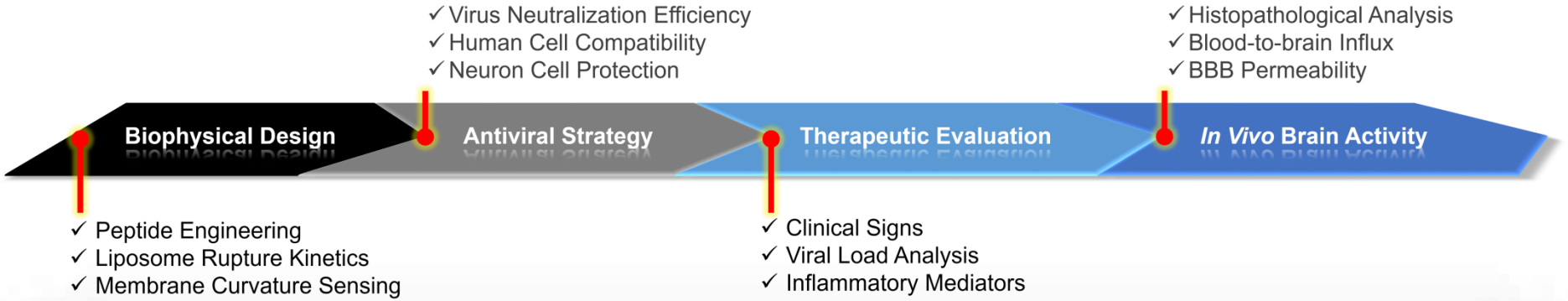
Experimental Strategy



Biophysical Design	Characterize selective disruption of curved membranes and predict range of effective peptide concentrations.
Antiviral Strategy	Measure inhibitory concentrations against ZIKV and other mosquito-borne viruses.
Therapeutic Evaluation	Determine if peptide's activity can improve outcomes in mouse model with high viral burden in brain.
In Vivo Brain Activity	Investigate brain penetration of peptide and protective effects against ZIKV-induced BBB injury.

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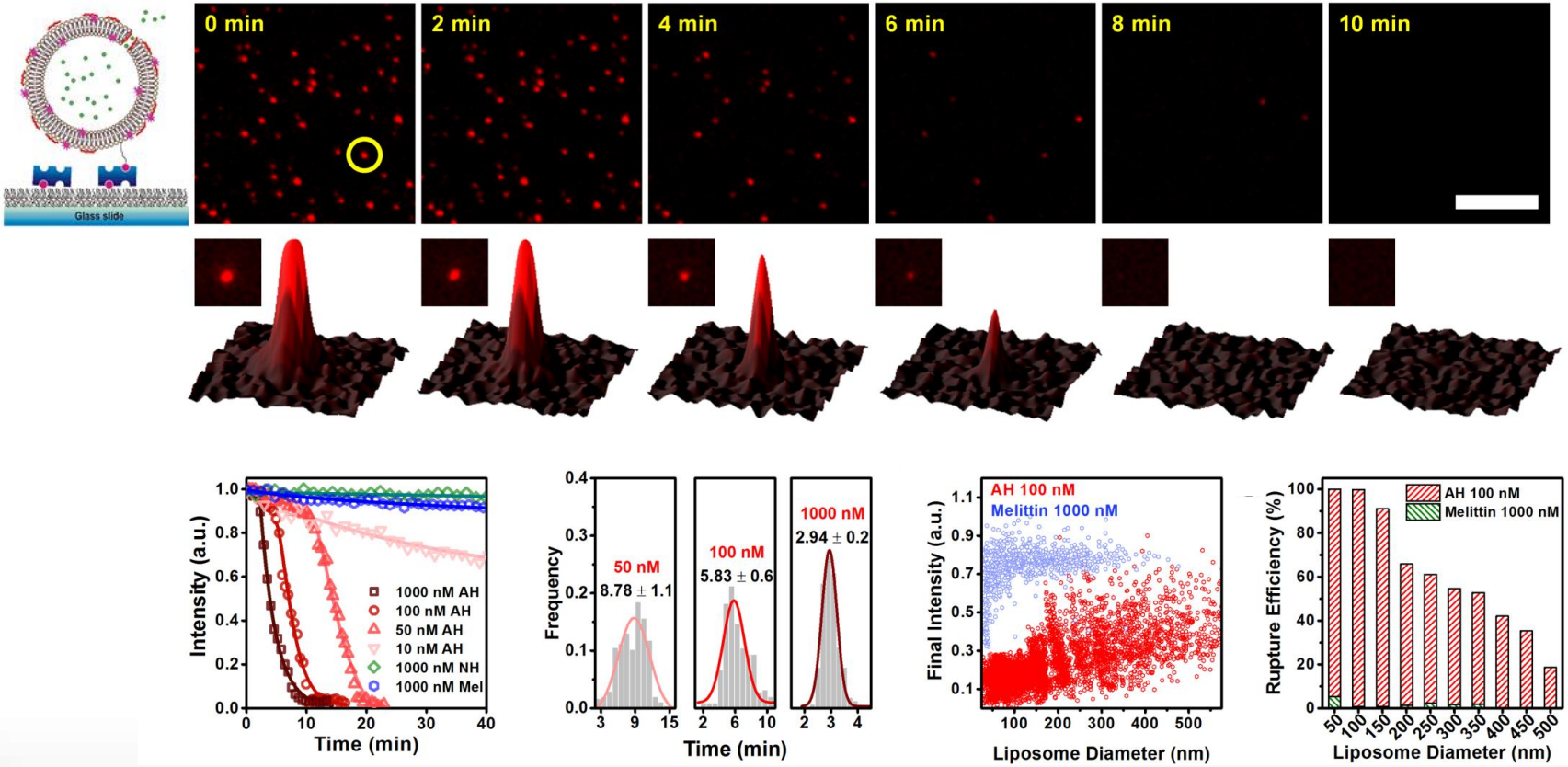
In Vitro Antiviral Activity



- Potent membrane-disruptive activity in nanomolar range
- Selective activity against curved membranes (= virus particles)

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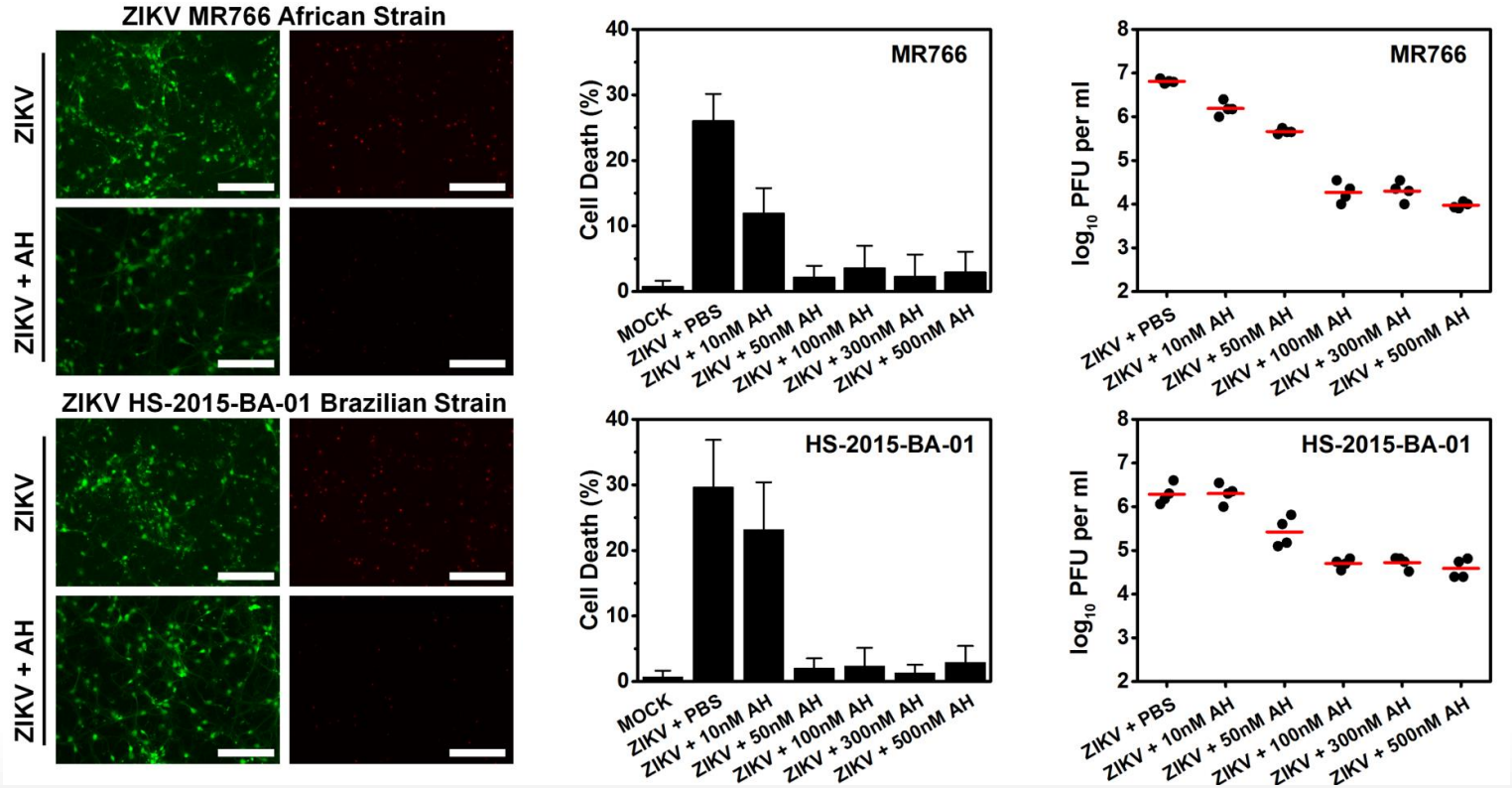
In Vitro Antiviral Activity



- Protects against ZIKV-induced death in primary neuronal cultures
- Inhibitory against Zika, Dengue, Chikungunya, Japanese Encephalitis, Yellow Fever (Selectivity Index: 337 to 5422)

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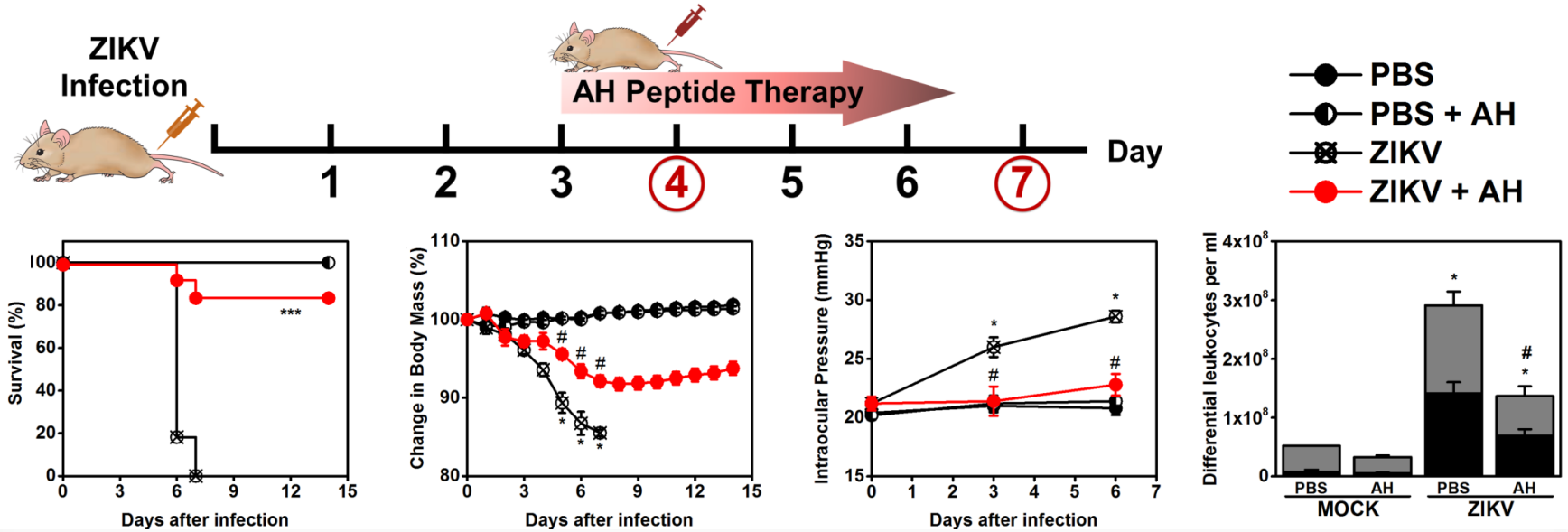
In Vivo Therapeutic Efficacy



- Type I interferon receptor-deficient mice were i.v. inoculated with 4 x 103 PFU of Brazilian ZIKV strain (HS-2015-Ba-01 isolate).
- Therapy started on day 3 post-infection (i.p. administration) and 18 out of 22 mice survived.
- Protected against weight loss, eye pressure change, and leukocytosis.

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Our Strategy Works Against Many Viruses

Works against a wide range of viruses that are of importance to clinical medicine and biodefense.

Virus	EC_{50} (μM)
Zika (FSS13025)	0.960
Zika (PRVABC-59)	1.240
Zika (MR766)	1.040
Dengue-1 (PRS41393)	2.040
Dengue-2 (New Guinea C)	1.950
Dengue-3 (H87)	1.900
Dengue-4 (H241)	1.640
Yellow Fever (17D)	0.098
Japanese Encephalitis (SA 14-14-2)	0.150
Powassan Virus (BL)	5.170
Chikungunya (181/25)	2.520
Ebola (Zaire)	0.930
Marburg (Angola)	0.640
Rift Valley Fever Virus (MP12)	0.260
Human cytomegalovirus (AD169)	<4
Vaccinia Virus (NYCBH)	>12
Polio Virus (Malhoney)	>30

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Concluding Remarks

- "LEAD" therapy inhibits ZIKV infection in mice through a combination of systemic control and inhibitory activity in organs, including the brain.

- Might also address other ZIKV-related medical complications such as viral persistence in tissues, maternal-fetal and sexual transmission, and eye infections.

- Motivates new antiviral strategies for treating mosquito-borne virus infections and possibly other classes of neurodegenerative diseases with possible viral etiologies.

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Thank You