Twitter Thread by Billy Bostickson ■■&■ ■

Billy Bostickson ■■&■ ■
@BillyBostickson

PROQUEST RESEARCH THREAD
Mainly DARPA/PREDICT/ECOHEALTH papers
1. PREEMPT Team will study air-borne highly pathogenic avian influenza virus in birds & small mammals, & tick-borne Crimean-Congo hemorrhagic fever virus.
Dr. Peter Barry & Dr. Brian Bird
https://t.co/GOUGRoRGfl

to achieve the greatest health benefits. Interventions under consideration include animal- or insect-targeted vaccines, therapeutic interfering particles, gene editors, and indirect approaches informed by environmental and ecological factors that affect how viruses are spread —for instance, understanding the environmental stressors that drive bats into closer contact with humans and devising mitigating options to reduce the likelihood of that contact.

The research teams' approaches each come with a unique set of potential benefits and challenges, and the teams are responsible for assessing and demonstrating to DARPA the safety, efficacy, stability, and controllability of their proposed interventions. In the future, these considerations could factor into decisions by the ultimate end users —communities, governments, and regulators —on which strategies to pursue to prevent new zoonoses.

DARPA and the PREEMPT teams receive guidance from independent expert advisors in the ethical, legal, social, and regulatory aspects of the life sciences. These individuals include Dr. Claudia Emerson, director of the Institute on Ethics &Policy for Innovation at McMaster University; Dr. Matt Kasper, legislative liaison for the U.S. Navy's Bureau of Medicine and Surgery, and a former deputy director of field laboratory operations at the Naval Medical Research Center; and Dr. Steve Monroe, associate director for Laboratory Science and Safety at the CDC, and a former deputy director of the CDC's National Center for Emerging and Zoonotic Infectious Diseases.

The teams also benefit from established relationships with local universities, communities, and governments based on prior or ongoing research. These relationships will facilitate initial field collection and help to familiarize stakeholders with PREEMPT technologies as they are being developed. DARPA is also beginning outreach to the WHO as a potential avenue for future transition of PREEMPT technologies.

DARPA intends that PREEMPT teams will perform fundamental research and publish results for review by the broader scientific community.

Crédito: DARPA

2. PREEMPT lab teams

https://t.co/GOUGRoRGfI

* Autonomous Therapeutics, Dr. Ariel Weinberger
* One Health Institute UCD, Drs. Peter Barry & Brian Bird
* Institut Pasteur, Dr. Carla Saleh
* Montana State University, Dr. Raina Plowright
* Pirbright Institute, Dr. Luke Alphey

DETAILS

Subject:	Medical laboratories; Laboratories; Mosquitoes; Insects; Medical research; Public health; Viruses; Infectious diseases; Influenza; Researchers; Zoonoses; Teams; West Nile virus; Epidemics; Ebola virus; Medicine
Location:	Cambodia Pennsylvania France Montana Central African Republic United States–US California Los Angeles California Colorado Madagascar Virginia Uruguay Texas French Guiana
Company / organization:	Name: Griffith University; NAICS: 611310; Name: University of Idaho; NAICS: 611310; Name: McMaster University; NAICS: 611310; Name: Cornell University; NAICS: 611310; Name: Centers for Disease Control &Prevention--CDC; NAICS: 923120; Name: University of Glasgow; NAICS: 611310; Name: Montana State University; NAICS: 611310; Name: Mount Sinai School of Medicine; NAICS: 611310; Name: Naval Me dical Research Center; NAICS: 541714; Name: Texas Tech University; NAICS: 611310; Name: Cambridge University; NAICS: 611310; Name: University of Chicago; NAICS: 611310; Name: University of Texas; NAICS: 611310; Name: Department of Defense; NAICS: 928110; Name: Rocky Mountain Laboratories; NAICS: 541714; Name: Pennsylvania State University; NAICS: 611310; Name: Plymouth University; NAICS: 611310; Name: Department of the Navy; NAICS: 928110; Name: University of Nottingham; NAICS: 611310; Name: Colorado State University; NAICS: 611310; Name: University of Tartu; NAICS: 611310; Name: National Institutes of Health; NAICS: 923120; Name: Pirbright Institute; NAICS: 611310; Name: Institut Pasteur; NAICS: 541714; Name: Johns Hopkins University; NAICS: 611310

3. Identifying Suspect Bat Reservoirs of Emerging Infections
https://t.co/lZPBAIjkm7
Defense Advanced Research Projects Agency (DARPA D16AP00113), and DARPA PREEMPT program Cooperative Agreement (DARPA D18AC00031).

Bats host a number of pathogens that cause severe disease and onward transmission in humans and domestic animals. Some of these pathogens, including henipaviruses and filoviruses, are considered a concern for future pandemics. There has been substantial effort to identify these viruses in bats. However, the reservoir hosts for Ebola virus are still unknown and henipaviruses are largely uncharacterized across their distribution. Identifying reservoir species is critical in understanding the viral ecology within these hosts and the conditions that lead to spillover. We collated surveillance data to identify taxonomic patterns in prevalence and seroprevalence and to assess sampling efforts across species. We systematically collected data on filovirus and henipavirus detections and used a machine-learning algorithm, phylofactorization, in order to search the bat phylogeny for cladistic patterns in filovirus and henipavirus infection, accounting for sampling efforts. Across sampled bat species, evidence for filovirus infection was widely dispersed across the sampled phylogeny. We found major gaps in filovirus sampling in bats, especially in Western Hemisphere species. Evidence for henipavirus infection was clustered within the Pteropodidae; however, no other clades have been as intensely sampled. The major predictor of filovirus and henipavirus exposure or infection was sampling effort. Based on these results, we recommend expanding surveillance for these pathogens across the bat phylogenetic tree.

4. Peng Zhou, Linfa Wang, Zhengli Shi, Lijun Wu (WIV)
2104 (CSIRO Australia)

IRF7 in the Australian Black Flying Fox, Pteropus alecto: Evidence for a Unique Expression Pattern and Functional Conservation
https://t.co/UzpI9r0uA7

Zhou, Peng; Cowled, Chris; Mansell, Ashley; Monaghan, Paul; Green, Diane; et al.
PLoS One; San Francisco Vol. 9, Iss. 8, (Aug 2014): e103875. DOI:10.1371/journal.pone.0103875

Full text | Full text - PDF | Abstract/Details | References 45

Abstract

Translate

As the only flying mammal, bats harbor a number of emerging and re-emerging viruses, many of which cause severe diseases in humans and other mammals yet result in no clinical symptoms in bats. As the master regulator of the interferon (IFN)-dependent immune response, IFN regulatory factor 7 (IRF7) plays a central role in innate antiviral immunity. To explore the role of bat IRF7 in the regulation of the IFN response, we performed sequence and functional analysis of IRF7 from the pteropid bat, *Pteropus alecto*. Our results demonstrate that bat IRF7 retains the ability to bind to MyD88 and activate the IFN response despite unique changes in the MyD88 binding domain. We also demonstrate that bat IRF7 has a unique expression pattern across both immune and non-immune related tissues and is inducible by double-strand RNA. The broad tissue distribution of IRF7 may provide bats with an enhanced ability to rapidly activate the IFN response in a wider range of tissues compared to other mammals. The importance of IRF7 in antiviral activity against the bat reovirus, Pulau virus was confirmed by siRNA knockdown of IRF7 in bat cells resulting in enhanced viral replication. Our results highlight the importance of IRF7 in innate antiviral immunity in bats.

5. Peng Zhou, Linfa Wang, Zhengli Shi
(Sep 2011 - CSIRO Australia)
Type III IFN Receptor Expression and Functional Characterisation in the Pteropid Bat, Pteropus alecto
https://t.co/1S6OrRrtfK

Type III IFN Receptor Expression and Functional Characterisation in the Pteropid Bat, Pteropus alecto

Zhou, Peng; Cowled, Chris; Marsh, Glenn A; Shi, Zhengli; Lin-Fa, Wang; et al.
PLoS One; San Francisco Vol. 6, Iss. 9, (Sep 2011): e25385. DOI:10.1371/journal.pone.0025385

Full text | Full text - PDF | Abstract/Details

Abstract

Translate

Bats are rich reservoir hosts for a variety of viruses, many of which are capable of spillover to other susceptible mammals with lethal consequences. The ability of bats to remain asymptomatic to viral infection may be due to the rapid control of viral replication very early in the immune response through innate antiviral mechanisms. Type I and III interferons (IFNs) represent the first line of defence against viral infection in mammals, with both families of IFNs present in pteropid bats. To obtain further insight into the type III IFN system in bats, we describe the characterization of the type III IFN receptor (IFNλR) in the black flying fox, P. alecto with the characterization of IFNλR1 and IL10R2 genes that make up the type III IFN receptor complex. The bat IFNλR complex has a wide tissue distribution and at the cellular level, both epithelial and immune cells are responsive to IFN-λ treatment. Furthermore, we demonstrate that the bat IFNλR1 chain acts as a functional receptor. To our knowledge, this report represents the first description of an IFN receptor in any species of bat. The responsiveness of bat cells to IFN-λ support a role for the type III IFN system by epithelial and immune cells in bats.

6. ¿Cómo encontrar el origen de los coronavirus?
Qiu, Jane
.Investigación y Ciencia; Dordrecht (Jun 1, 2020).
https://t.co/taZoyHxrqR
and
https://t.co/8FtSri34PX

El Centro para el Control y Prevención de Enfermedades de Wuhan había detectado un nuevo coronavirus en dos pacientes con neumonía atípica ingresados en el hospital y quería que el famoso laboratorio de Shi lo investigara. Antes del SARS, el mundo sabía muy poco sobre los coronavirus —se denominan así porque su superficie con protuberancias se asemeja a una corona solar cuando se examina bajo el microscopio, explica Linfa Wang, directora del programa de enfermedades infecciosas emergentes en la Facultad de Medicina Duke-NUS de Singapur—. Wang, sin embargo, pensó que estos animales podían ser la fuente original. En la cueva de Shitou, donde el minucioso escrutinio ha dado lugar a una biblioteca genética natural de virus presentes en murciélagos, el equipo descubrió una cepa de coronavirus que procedía de murciélagos de herradura y que tenía una secuencia genómica idéntica en un 97

7. BVLPs - Bat Covs + SARS Cov - Baculovirus (WIV 2008)
VLPs of SARS-Like Coronavirus Formed by Membrane Proteins from Different Origins Demonstrate Stimulating Activity in Human Dendritic Cells
https://t.co/eRV8lSyf2P
Bai, Bingke; Hu, Qinxue; Hu, Hui; Zhou, Peng; Shi, Zhengli;

Bai, Bingke; Hu, Qinxue; Hu, Hui; Zhou, Peng; Shi, Zhengli; et al.
PLoS One; San Francisco Vol. 3, Iss. 7, (Jul 2008): e2685. DOI:10.1371/journal.pone.0002685

Full text | Full text - PDF | Abstract/Details

Abstract

Translate

The pathogenesis of SARS coronavirus (CoV) remains poorly understood. In the current study, two recombinant baculovirus were generated to express the spike (S) protein of SARS-like coronavirus (SL-CoV) isolated from bats (vAcBS) and the envelope (E) and membrane (M) proteins of SARS-CoV, respectively. Co-infection of insect cells with these two recombinant baculoviruses led to self-assembly of virus-like particles (BVLPs) as demonstrated by electron microscopy. Incorporation of S protein of vAcBS (BS) into VLPs was confirmed by western blot and immunogold labeling. Such BVLPs up-regulated the level of CD40, CD80, CD86, CD83, and enhanced the secretion of IL-6, IL-10 and TNF-α in immature dendritic cells (DCs). Immune responses were compared in immature DCs inoculated with BVLPs or with VLPs formed by S, E and M proteins of human SARS-CoV. BVLPs showed a stronger ability to stimulate DCs in terms of cytokine induction as evidenced by 2 to 6 fold higher production of IL-6 and TNF-α. Further study indicated that IFN-γ+ and IL-4+ populations in CD4+ T cells increased upon co-cultivation with DCs pre-exposed with BVLPs or SARS-CoV VLPs. The observed difference in DC-stimulating activity between BVLPs and SARS CoV VLPs was very likely due to the S protein. In agreement, SL-CoV S DNA vaccine evoked a more vigorous antibody response and a stronger T cell response than SARS-CoV S DNA in mice. Our data have demonstrated for the first time that SL-CoV VLPs formed by membrane proteins of different origins, one from SL-CoV isolated from bats (BS) and the other two from human SARS-CoV (E and M), activated immature DCs and enhanced the expression of co-stimulatory molecules and the secretion of cytokines. Finding in this study may provide important information for vaccine development as well as for understanding the pathogenesis of SARS-like CoV.

8. Above paper cited by 7 in Pro Quest
https://t.co/8Jr9lCSZu4

1. Virus like particle-based vaccines against emerging infectious disease viruses

Liu, Jinliang; Dai Shiyu; Wang Manli; Hu, Zhihong; Wang, Hualin; et al. **Virologica Sinica; Heidelberg** Vol. 31, Iss. 4, (2016): 279-287.
Get full text

2. Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice

Coleman, Christopher M; Liu, Ye V; Mu, Haiyan; Taylor, Justin K; Massare, Michael; et al. **Vaccine; Kidlington** Vol. 32, Iss. 26, (May 30, 2014): 3169-74.

3. Identifying SARS-CoV Membrane Protein Amino Acid Residues Linked to Virus-Like Particle Assembly

Tseng, Ying-Tzu; Chia-Hui, Chang; Shiu-Mei, Wang; Kuo-Jung, Huang; Chin-Tien, Wang. **PLoS One; San Francisco** Vol. 8, Iss. 5, (May 2013): e64013. Show Abstract
References (59) Abstract/Details Full text Full text - PDF (2 MB)

4. Development of Virus-Like Particle Technology from Small Highly Symmetric to Large Complex Virus-Like Particle Structures

Pushko, Peter; Pumpens, Paul; Grens, Elmars. **Intervirology; Basel** Vol. 56, Iss. 3, (May 2013): 141-65.

9. Immunogenicity of spike glycoprotein of Bat SARS-like coronavirus
https://t.co/3PQkkYHSjQ
Insect cell technology - versatile & robust vaccine manufacturing platform
https://t.co/d8WKHrXz0V
VLP-based vaccines against emerging infectious disease viruses
https://t.co/gSVag3xAul

Virol Sin. 2010 Feb; 25(1): 36–44.
Published online 2010 Feb 12. doi: 10.1007/s12250-010-3096-2
PMCID: PMC7090579
PMID: 20960282

Immunogenicity of the spike glycoprotein of Bat SARS-like coronavirus

Yu-xuan Hou,[1] Cheng Peng,[1] Zheng-gang Han,[1] Peng Zhou,[1] Ji-guo Chen,[2] and Zheng-li Shi[1]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Abstract

Go to:

A group of SARS-like coronaviruses (SL-CoV) have been identified in horseshoe bats. Despite SL-CoVs and SARS-CoV share identical genome structure and high-level sequence similarity, SL-CoV does not bind to the same cellular receptor as for SARS-CoV and the N-terminus of the S proteins only share 64% amino acid identity, suggesting there are fundamental differences between these two groups of coronaviruses. To gain insight into the basis of this difference, we established a recombinant adenovirus system expressing the S protein from SL-CoV (rAd-Rp3-S) to investigate its immune characterization. Our results showed that immunized mice generated strong humoral immune responses against the SL-CoV S protein. Moreover, a strong cellular immune response demonstrated by elevated IFN-γ and IL-6 levels was also observed in these mice. However, the induced antibody from these mice had weaker cross-reaction with the SARS-CoV S protein, and did not neutralize HIV pseudotyped with SARS-CoV S protein. These results demonstrated that the immunogenicity of the SL-CoV S protein is distinct from that of SARS-CoV, which may cause the immunological differences between human SARS-CoV and bat SL-CoV. Furthermore, the recombinant virus could serve as a potential vaccine candidate against bat SL-CoV infection.

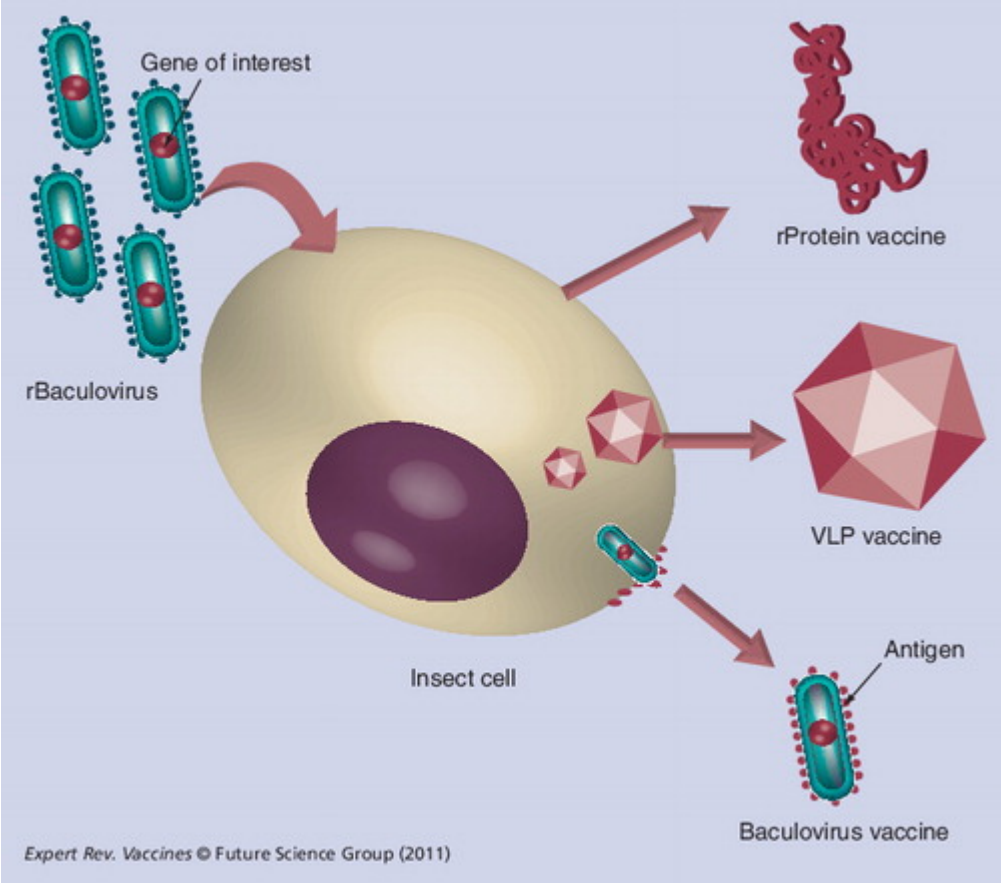
10. Insect Cell Technology & Vaccine Development

Paper in Tweet 9 is a useful 2014 review of vaccines based on baculovirus systems with 5 tables showing all vaccine projects for humans & animals

https://t.co/uDjmxl7sZD

Tables 1, 2, 3 shown here

Text only: https://t.co/VRlG1itgDY



11. Tables 4 and 5

Table 4. Baculovirus-expressed virus-like particles for veterinary immunization

Table 5. Baculovirus vaccines under development.

Text version: https://t.co/VRlG1itgDY

CSVs: https://t.co/uDjmxl7sZD

Only a few coronavirus vaccines mentioned, next tweet

Insect cell technology is a versatile and robust vaccine manufacturing platform

Jimmy A Mena & Amine A Kamen

https://doi.org/10.1586/erv.11.24

PUBLISHED ONLINE:
09 January 2014

Table 4 of 5
Table 4. Baculovirus-expressed virus-like particles for veterinary immunization.

Virus-like particles	Virus	Vaccine name/animal model (manufacturer)	Ref.
Veterinary vaccines commercially available			
Circovirus VLPs	PCV-2	Porcilis® PCV (Intervet/Schering-Plough)	[122,123]
Veterinary vaccines in field trials			
Circovirus VLPs	PCV-2	Mouse, pig	[124–126]
Parvovirus VLPs	Porcine parvovirus	Pig	[127]
Bluetongue VLPs	Bluetongue virus	Sheep	[128]
Foot and mouth VLPs	Foot-and-mouth disease virus	Cow	[131,166]
Influenza VLPs	Avian influenza virus	Chicken, duck	[129,130]

PCV: Porcine circovirus; VLP: Virus-like particle.

12. WIV Baculovirus based Cov Vaccine Project (1)

1. WIV 2008 - Mice- Insect Cells - Bat Covs- Sars

Vaccination of mice with recombinant baculovirus expressing spike or nucleocapsid protein of SARS-like Cov generates humoral & cellular immune responses

https://t.co/bTn9INxo1w

› Mol Immunol. 2008 Feb;45(4):868-75. doi: 10.1016/j.molimm.2007.08.010. Epub 2007 Oct 1.

Vaccination of mice with recombinant baculovirus expressing spike or nucleocapsid protein of SARS-like coronavirus generates humoral and cellular immune responses

Bingke Bai [1], Xinya Lu, Jin Meng, Qinxue Hu, Panyong Mao, Baojing Lu, Ze Chen, Zhiming Yuan, Hanzhong Wang

Affiliations – collapse

Affiliation

1 State Key Laboratory of Virology, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, 430071 Hubei, PR China.

PMID: 17905435 PMCID: PMC7112626 DOI: 10.1016/j.molimm.2007.08.010

13. SARS-HIV Baculovirus based Cov Vaccine Project (2)

Peking (2006)

Baculovirus surface display of SARS coronavirus (SARS-CoV) spike protein and immunogenicity of the displayed protein in mice models
https://t.co/RjrMb0YYZG
full text: https://t.co/iQYr3GDq1z

› DNA Cell Biol. 2006 Dec;25(12):668-73. doi: 10.1089/dna.2006.25.668.

Baculovirus surface display of SARS coronavirus (SARS-CoV) spike protein and immunogenicity of the displayed protein in mice models

Qian Feng [1], Yingying Liu, Xiuxia Qu, Hongkui Deng, Mingxiao Ding, Terence L T Lau, Albert Cheung-Hoi Yu, Jianguo Chen

Affiliations – collapse

Affiliation

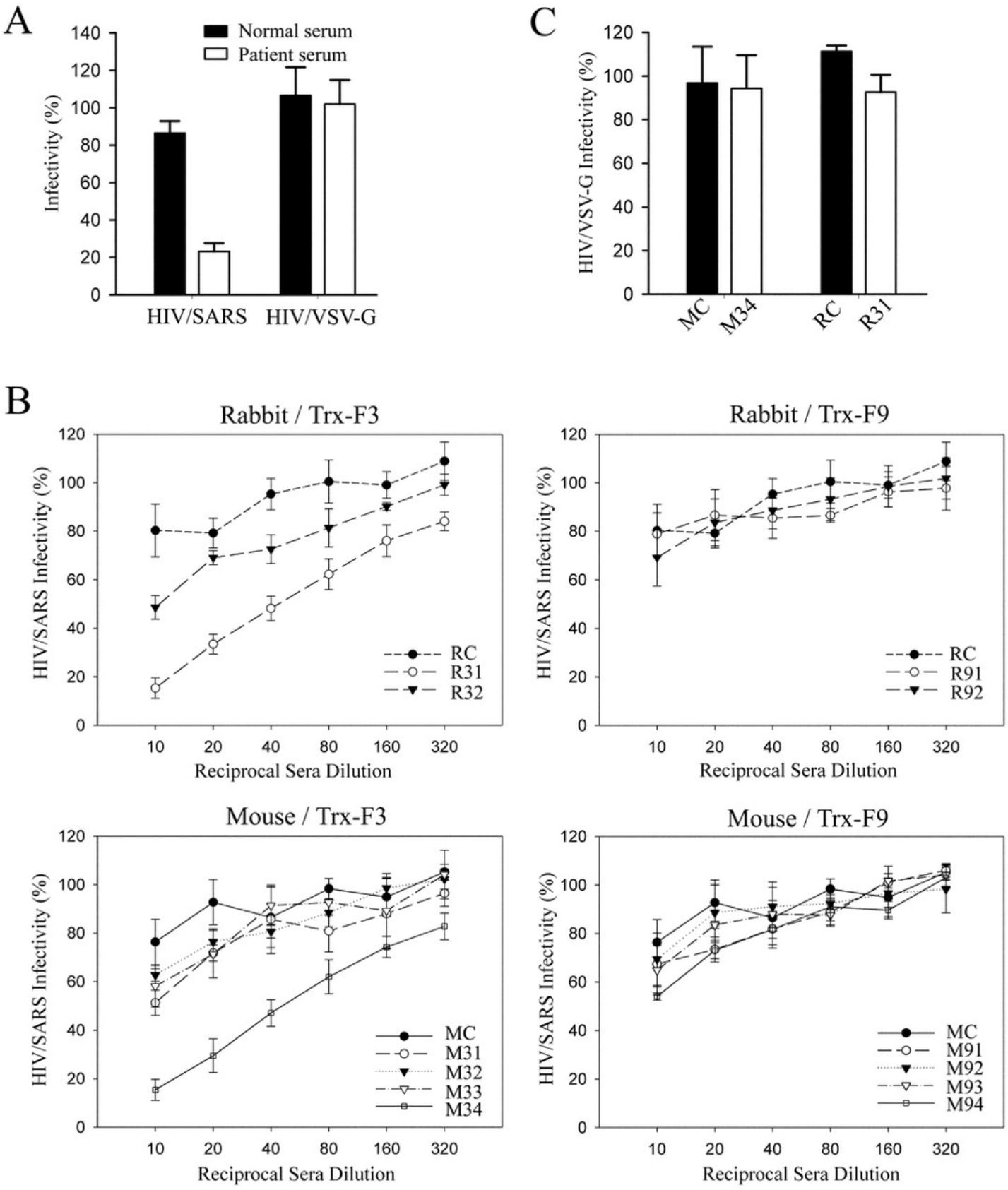
1 The Key Laboratory of Cell Proliferation and Differentiation of Ministry of Education, Department of Cell Biology and Genetics, College of Life Sciences, Peking University, Beijing, People's Republic of China.

PMID: 17184168 DOI: 10.1089/dna.2006.25.668

14. Previous paper used SARS-HIV technique based on work in 2004 by Peking Uni Researchers
Identification of Antigenic Determinant on S2 Domain of Severe Acute Respiratory Syndrome Coronavirus Spike Glycoprotein Capable of Inducing Neutralizing Antibodies
https://t.co/dNh985mjMA

Neutralizing activity of the polyclonal antisera. To study the specificity of our neutralization assay, we first preincubated the SARS-CoV S protein pseudotyped particles (HIV/SARS) with the sera from convalescent SARS patients or the healthy human sera before incubating them with Huh-7 cells for infection. Huh-7 cells have been found to express a high level of the SARS-CoV receptor ACE2 and could be effectively infected by HIV/SARS (**46**). We have also demonstrated that Huh-7 cells could be infected by the pseudotype particles bearing the vesicular stomatitis virus G glycoprotein (HIV/VSV-G) (our unpublished data). As shown in Fig. **5A**, the sera of convalescent SARS patients had an obvious neutralizing activity on HIV/SARS but failed to neutralize HIV/VSV-G, whereas the healthy human sera could not neutralize either of these two pseudoviruses. This suggested that our neutralization assay could be used to detect SARS-CoV-specific neutralizing antibodies.

15. This HIV-SARS technique was based on paper (Ref 46) (2004)
Expression cloning of functional receptor used by SARS coronavirus
https://t.co/q5halBhjFa
"ACE2 mediated entry of HIV/SARS pseudovirus & goat anti-human ACE2 polyclonal antibody abrogates entry of HIV-luc/SARS"



16. The above was partly based on similar research in 2004:

Highly infectious SARS-CoV pseudotyped virus reveals the cell tropism and its correlation with receptor expression

https://t.co/bBIWIHMgn2

In this study, we generated a SARS-CoV pseudotyped virus HIV/SARS using a synthetic codon-optimized SARS-CoV S gene, and showed that the entry of HIV/SARS was mediated by the S protein and was a pH-dependent process; we also showed that the entry of HIV/SARS into host cells could be blocked by the convalescent sera from SARS patients. Most importantly, our cell tropism analysis indicated that multiple tissues besides the lung might be susceptible to SARS-CoV infection because of the specific expression of ACE2. Finally, this SARS-CoV pseudotyped virus we generated in this study can be used as an efficient and safe system for analyzing the character of SARS-CoV infection including immune responses to SARS-CoV infection, development of neutralizing antibodies, and detailed characterization of the S protein function.

17. This research ties in with another previous thread I did on the so-called HIV inserts, vaccine development, horizontal gene transfer, contamination and VLPs:

https://t.co/P7QbDEBG52

> HIV "Inserts" Thread
> This Thread will examine in tedious detail:
> 1. HIV based Virus Like particles (VLPs) & Lentiviruses used mainly for vaccine development
> 2. Important papers & analyses published on HIV "inserts"
> 3. Claims & Arguments made
> 4. Counter Arguments
> 5. Conclusions pic.twitter.com/yDyRIjqjKJ
>
> — Billy Bostickson \U0001f3f4\U0001f441&\U0001f441 \U0001f193 (@BillyBostickson) July 12, 2020

18. That thread's main focus is on possibility of HIV artefacts appearing in SARS-COV-2 through horizontal gene transfer during vaccine development using HIV vlps and SARS spike proteins
https://t.co/G39nSzmqmj

> 11. (Continued from Above)
> "A major safety concern with LV vectors is the risk for potential mutagenesis caused by insertion of the viral genome into the host genome.
> The risk of insertional mutagenesis remains controversial to date." pic.twitter.com/qTkl6JAmWB
>
> — Billy Bostickson \U0001f3f4\U0001f441&\U0001f441 \U0001f193 (@BillyBostickson) July 12, 2020

19. Enough, time for a break https://t.co/JlAPbg25Zb

> 24. WIV Pseudoviruses
> 1. WIV used HIV-1 derived plasmids, co-transfecting them along with SARS-like virus derived spike gene plasmids, into human embryonic kidney (HEK) cells.
> 2. They created pseudoviruses to perform experiments under BSL-2 instead of BSL-4 (required for SARS)
>
> — Billy Bostickson \U0001f3f4\U0001f441&\U0001f441 \U0001f193 (@BillyBostickson) July 15, 2020