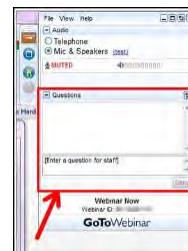
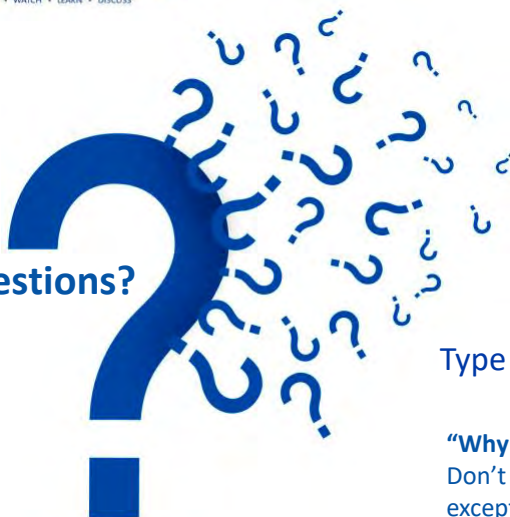




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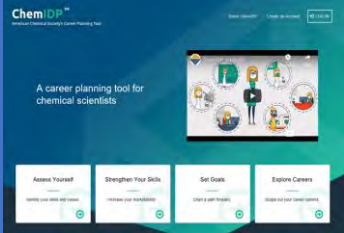
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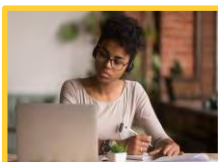


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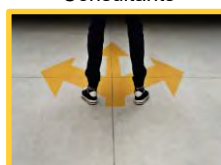
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## ACS Industry Matters Article:

*Pfizer and the COVID-19 Vaccine*

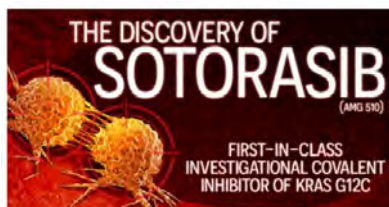


“ Drugs are not simply found ”  
– drugs are invented.

**Mark Noe**, Pfizer's Vice President of Discovery Sciences, takes us behind the scenes to help us better understand how the Pfizer and BioNTech COVID-19 vaccine came to be.

[www.acs.org/Pfizer](http://www.acs.org/Pfizer)

10



Date: Thursday, February 25, 2021 @ 2:30pm ET  
 Speaker: Brian Lanman, Amgen, Inc.  
 Moderator: Ariamala Gopalsamy, AstraZeneca

[Register for Free!](#)

**What You Will Learn:**

- Why identifying a direct inhibitor of KRAS has proven so challenging
- How covalent inhibition helped to turn KRAS G12C into a tractable target
- What hurdles were overcome in turning initial KRAS G12C binders into potential human therapeutics

Co-produced with: ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications



Date: Wednesday, March 3, 2021 @ 2:30pm ET  
 Speaker: Robert Migliorini, Exxon Mobil Corporation  
 Moderator: Bryan Tweedy, American Chemical Society

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**What You Will Learn:**

- Learn about the major sections of a contract and common types of IP related agreements, including confidentiality/non-disclosure, material transfer, and more
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- Know the appropriate type of IP agreement to put in place prior to working with an outside party

Co-produced with: ACS Professional Education



## SCIENCE AS A DIPLOMATIC TOOL



Date: Wednesday, March 10, 2021 @ 11am-12pm ET  
 Speakers: Zafra Lerman, Malta Conferences Foundation / Peter Hotchkiss, Organisation for the Prohibition of Chemical Weapons / Vaughan Turekian, National Academies' Policy and Global Affairs Division  
 Moderator: Lori Brown, American Chemical Society

[Register for Free!](#)

**What You Will Learn:**

- How the OPCW works with the governments of 193 countries to prevent the use of chemical weapons
- How the US National Academies' Policy and Global Affairs office mobilizes experts and networks around the world to increase the use of evidence to advance local, national and global policy and capacity
- How the Malta Conferences uses science diplomacy to overcome cultural, religious, and political barriers in the Middle East

Co-produced with: ACS External Affairs & Communications

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# COVID-19 VACCINES UPDATE

## Emerging Questions & Future Applications



**FREE Webinar** | TODAY at 2:30pm ET



THIS ACS WEBINAR WILL BEGIN SHORTLY . . .

12





## COVID-19 Vaccines Update: Emerging Questions & Future Applications



**Shane Crotty**  
Professor, Center for Infectious Disease and  
Vaccine Research, La Jolla Institute for Immunology



**Yizhou Dong**  
Associate Professor, Pharmaceutics and Pharmacology,  
The Ohio State University's College of Pharmacy



**Angela Zhou**  
Information Scientist,  
Content Operations, CAS

*Presentation slides are available now! The edited recording will be made available as soon as possible.*

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## COVID-19 Vaccines: Emerging Questions & Future Applications



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Journal articles



Understanding the nanotechnology in COVID-19 vaccines



Author Name  
Affiliation

Blog Title

Blog Content

Blogs



Data Sets



Videos



Whitepapers

Explore more COVID-19 information at  
<https://www.cas.org/covid19>



## Welcome & Introductions



**Dr. Shane Crotty**  
Professor

Center for Infectious Disease and Vaccine  
Research at La Jolla Institute for Immunology

@profshaneCrotty



**Dr. Yizhou Dong**  
Associate Professor

Pharmaceutics and Pharmacology,  
The Ohio State University's College of Pharmacy

@yizhoudonglab



**Dr. Angela Zhou**  
Information Scientist

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@profshaneCrotty

Over 2 million views in 24 hours

Picked up by Scientific American and other outlets



### / Are RNA vaccines safe?

I have gotten this question a lot lately, and it is a good question.

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@profshanecrotty

**/ First:** RNA is messages. At any moment a human cell has 5000+ different RNA messages, and they are all temporary messages, like post-it notes that get torn up by the cells within minutes or hours after being read.



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**3/ Or, actually, RNA is like snapchat messages that expire.**

RNA vaccines do NOT become a permanent part of your body. They are temporary messages instructing cells to make one viral protein temporarily.



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**4/ Second, in the case of RNA COVID-19 vaccines, the RNA message is for 1 single coronavirus protein.**

It takes 25 different coronavirus proteins to make a coronavirus, so there is no worry about the RNA making a virus.



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@profshanecrotty

**5/ Third, over 70,000 doses of these COVID-19 RNA vaccines have been given to people now, and the independent safety boards (not controlled by the companies) have reported no serious concerns.**

That's a lot of safety data!

**6/ Now, it will certainly be good to see the full safety data when the clinical trial results become public, but it looks good.**





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@profshanecrotty

**7-8/ Lastly, regarding these vaccines and vaccines in general, “safe” does not mean the same thing as “did not hurt at all” or “no fever” for a little while.**

The immune system tends to only remember things that hurt somewhat. Not unlike going to the gym and getting exercise and really sore muscles; a bit of pain can be a positive sign that good things are happening. Sometimes you have to earn your immunity, just like you have to earn those biceps you wanted so bad.



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**9/ An immunization is probably going to hurt some, and that’s generally a good sign. You are earning your immunity.**

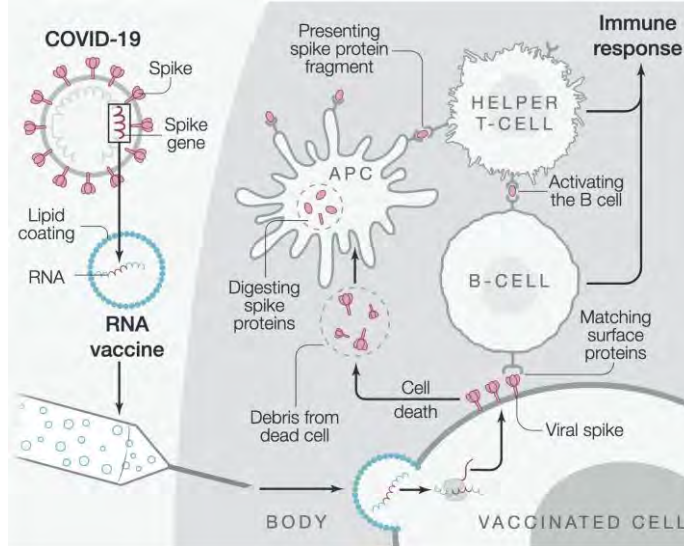




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Eric Topol



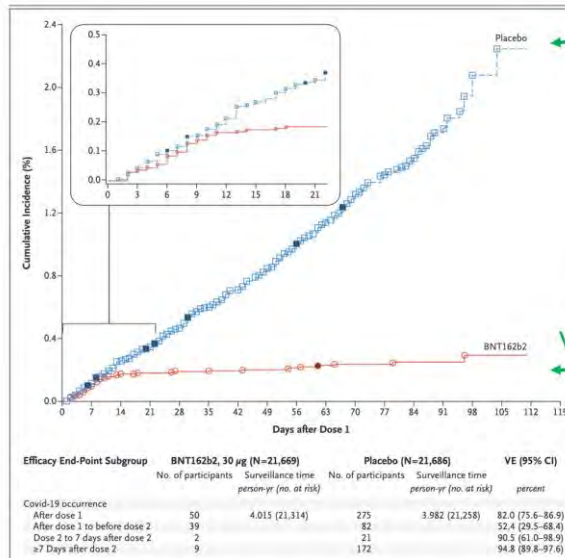
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@profshaneccrotty

# Pfizer vaccine

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← Not vaccinated

← Vaccinated!!!

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@profshaneccrotty

## Vaccine Trial Population Diversity



### These were some of the most inclusive vaccine trials ever.

- Excellent effectiveness in people over the age of 65
- Excellent effectiveness in both men and women
- Excellent effectiveness in Black people
- Excellent effectiveness in Latinos

The FDA has also agreed that pregnant women can receive the vaccine if they wish to, at the advice of their doctor.

There is no effect of the vaccine on pregnancy or fertility.

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"I believe that ethically everyone should take the vaccine."

"There is a suicidal denialism that I wouldn't know how to explain, but today you need to take the vaccine."

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Getting immunized is the kind thing to do.

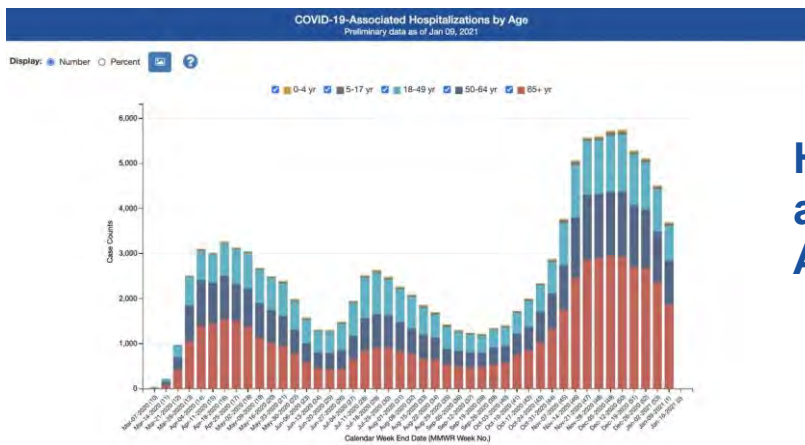
It helps you, your loved ones, your neighbors, and your community.



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@profshanecrotty

Half of COVID hospitalizations in America have been people under age 65

And half of those COVID hospitalizations in the under 65 age are people under 50 years old.



**Half! Over a million Americans**

CDC COVIDWATCH

	0-4 yr	5-17 yr	18-49 yr	50-64 yr	65+ yr	Total
2020	684	1104	30965	32328	53630	118701

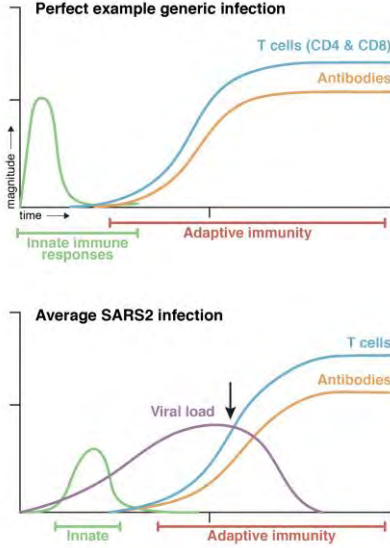


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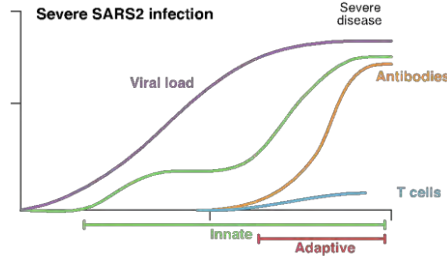
# Immune response trajectories in COVID-19

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\* "Innate" = innate immune response plasma signature



Cell 2021



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# T cell and antibody responses in 'average' cases of COVID-19

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Shane Crotty & Alex Sette

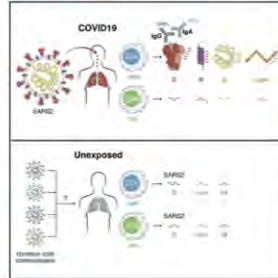
La Jolla Institute  
FOR IMMUNOLOGY

UCSD School of Medicine  
Dept. of Medicine

Cell

## Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

Graphical Abstract



Authors

Alba Grifoni, Daniela Weiskopf, Sydney I. Ramirez, ..., Davey M. Smith, Shane Crotty, Alessandro Sette

Correspondence

shane@lji.org (S.C.), alex@lji.org (A.S.)

In Brief

An analysis of immune cell responses to SARS-CoV-2 from recovered patients identifies the regions of the virus that is targeted and also reveals cross-reactivity with other common circulating coronaviruses

Highlights

- Measuring immunity to SARS-CoV-2 is key for understanding COVID-19 and vaccine development
- Epitope pools detect CD4<sup>+</sup> and CD8<sup>+</sup> T cells in 100% and 70% of convalescent COVID patients
- T cell responses are focused not only on spike but also on M, N, and other ORFs
- T cell reactivity to SARS-CoV-2 epitopes is also detected in non-exposed individuals



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Tony Fauci. Congress, August 2020

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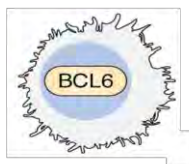
## Do people develop immunity to COVID-19?

- ❖ COVID-19 is an acute infection that resolves/cures in most humans
- ❖ What kind of immunity is important against COVID-19?



**Antibodies**  
(from B cells)

- ❖ Important in almost all currently licensed human vaccines



**Helper T cells**

- ❖ Critical for antibody responses
- ❖ Protect independent of antibodies in SARS mouse model



**Killer T cells**

- ❖ Important in many viral infections
- ❖ Agammaglobulinemic individuals survive COVID19

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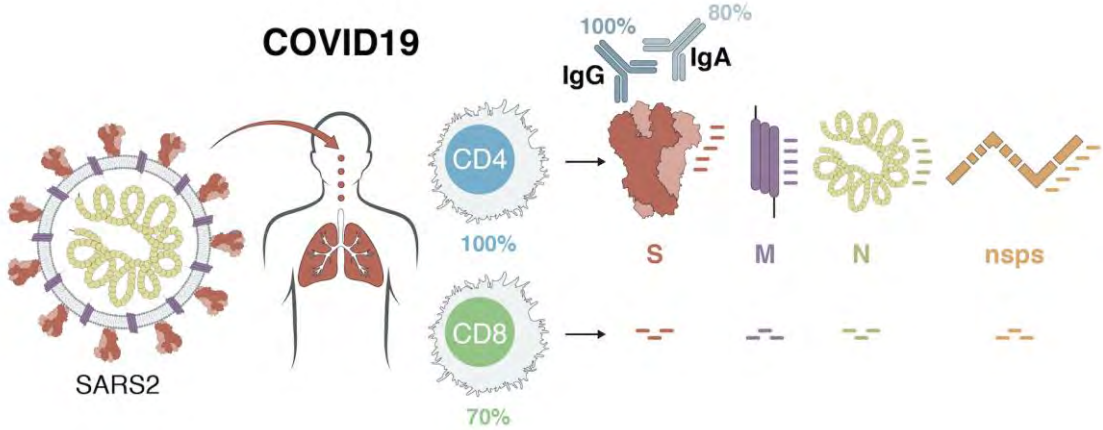


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@profshaneccrotty

# The Good News!



## Antiviral immunity that matches expectations

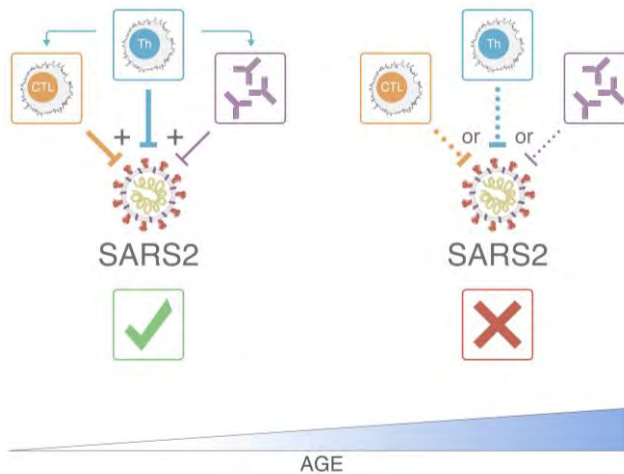


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## Adaptive immune responses to SARS-CoV-2 in acute COVID-19 and associations with disease severity



Moderbacher / Ramirez / Dan et al., Cell 2020

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## How long does immunological memory to SARS-CoV-2 last?

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COVID-19 (n = 188)	
Age (years)	19 - 81 [Median = 40]
Gender	
• Male (%)	43% [80/188]
• Female (%)	57% [108/188]
SARS-CoV-2 PCR positivity	
• Positive	77% [145/188]
• Not performed	20% [37/188]
• Negative	1% [2/188]
• Unknown	2% [4/188]
Peak disease severity	
• Asymptomatic	2% [4/188; 2F, 2M]
• Mild	90% [170/188; 100F 70M]
• Moderate	3% [6/188; 3F, 3M]
• Severe	4% [7/188; 3F, 4M]
Days post symptom onset at collection (n = 254)	6– 240 [Median = 88] 8 months

### SARS-CoV-2 specific



Science. Jan 6, 2021

Biorxiv Nov 16, 2020



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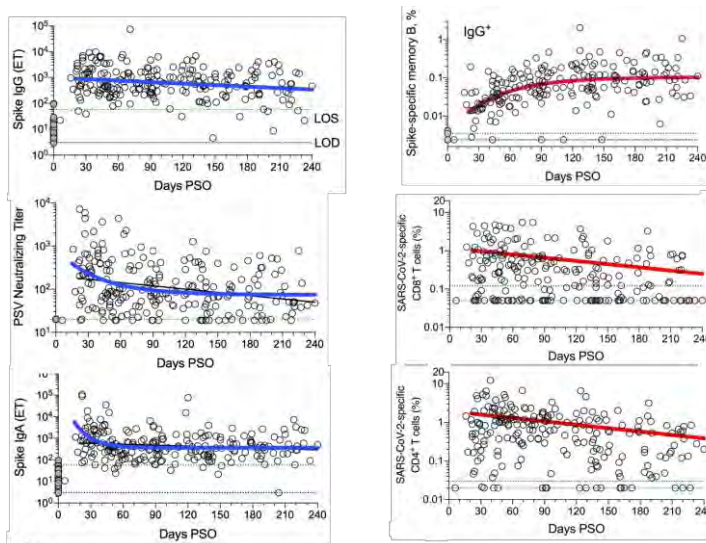


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## How long does immunological memory to SARS-CoV-2 last?

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❖ 188 subjects. 41 subjects @ 6 to 8 months post-infection



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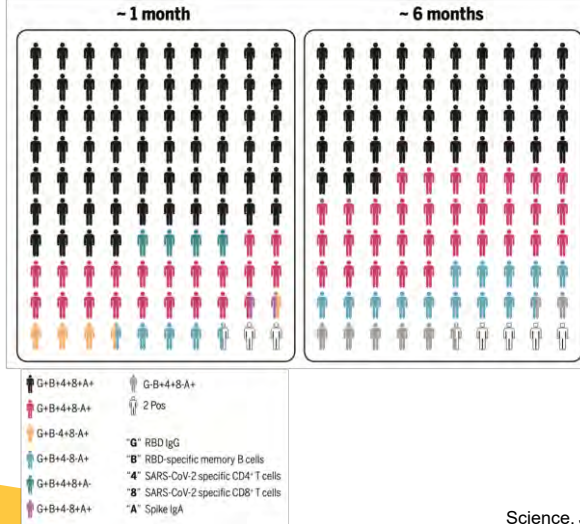
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# Immunological Memory

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The largest ever study of its kind, for any viral infection



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Science, Jan 6, 2021

## The New York Times

### Immunity to the Coronavirus May Last Years, New Data Hint

Blood samples from recovered patients suggest a powerful, long-lasting immune response, researchers reported.



Blood was drawn for a Covid-19 antibody test at the University of Arizona in Tucson earlier this year. (Christie Gray/Reuters)

By Apoorva Mandavilli

Nov. 17, 2020, 12:20 p.m. ET

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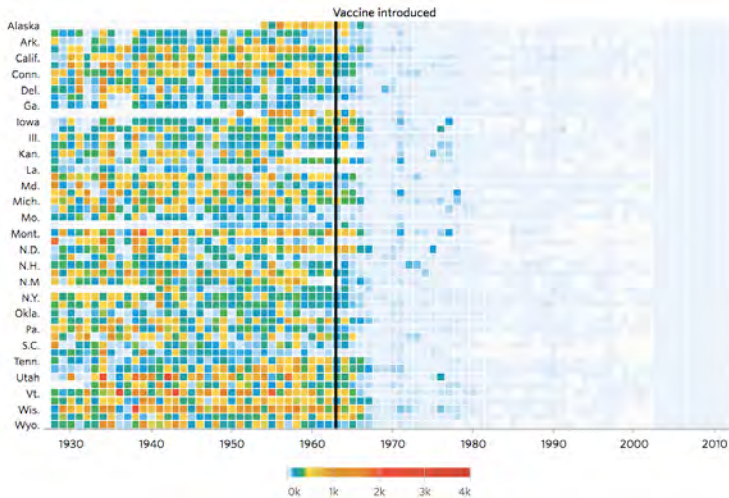
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# How effective are vaccines?

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## Measles



The measles vaccine has saved an estimated 14.1 million lives since 2011

# cases per 100,000 people.

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Elvis received the polio vaccine live on the Ed Sullivan show



CREDIT: SEYMOUR WALLY/NY DAILY NEWS ARCHIVE VIA GETTY



Arnold @Schwarzenegger - Jan 20  
Today was a good day. I have never been happier to wait in a line. If you're eligible, join me and sign up to get your vaccine. Come with me if you want to live!  
[Show this thread](#)



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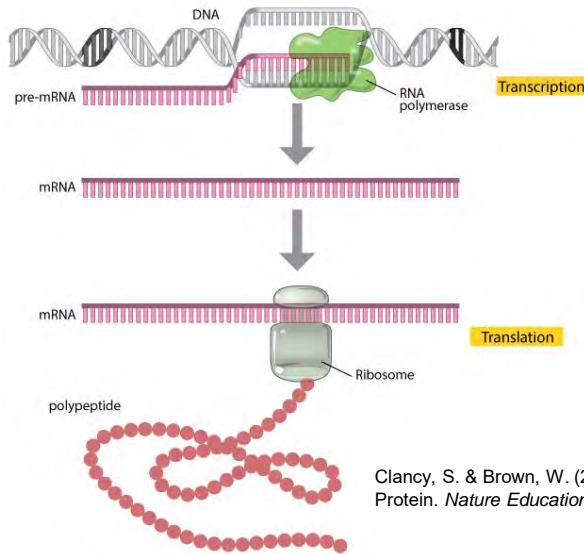
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Yizhou Dong  
@yizhoudonglab

### Translation: DNA to mRNA to Protein

THE OHIO STATE UNIVERSITY  
COLLEGE OF PHARMACY



Clancy, S. & Brown, W. (2008) Translation: DNA to mRNA to Protein. *Nature Education* 1(1):101

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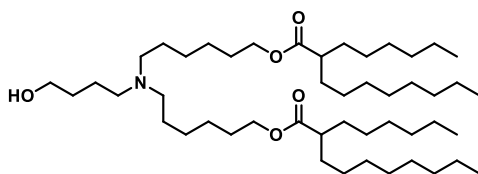
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## Ingredients of COVID-19 mRNA vaccines

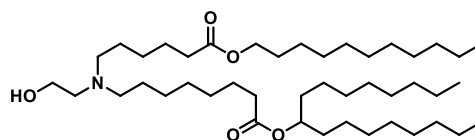


**Active agent:** Nucleoside-modified mRNA encoding SARS-CoV-2 spike protein

**Lipid components:** Ionizable lipid, Cholesterol; Phospholipid; PEG2000-lipid



ALC-3015 used in BNT162



SM-102 used in mRNA-1273

**Cryoprotectant:** Sucrose, a sugar molecular.

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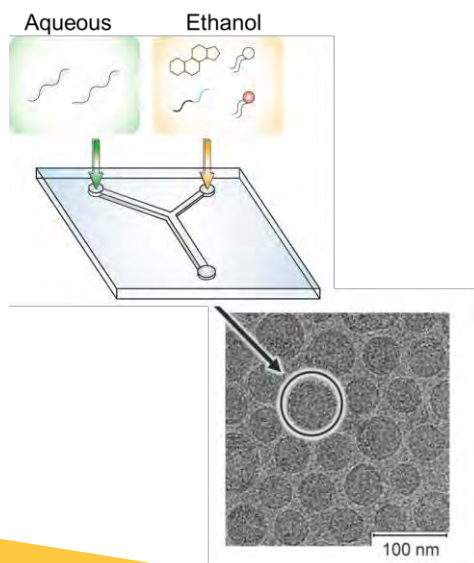


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@yizhoudonglab

## Formulation of lipid-mRNA nanoparticles used for COVID-19 vaccines



FDA Vaccines and Related Biological Products Advisory Committee  
December 17, 2020;  
Chan, C., Du, S., Dong, Y\*, Cheng, X\*, Current Topics in Medicinal  
Chemistry, 21(2):92-114 (2021).

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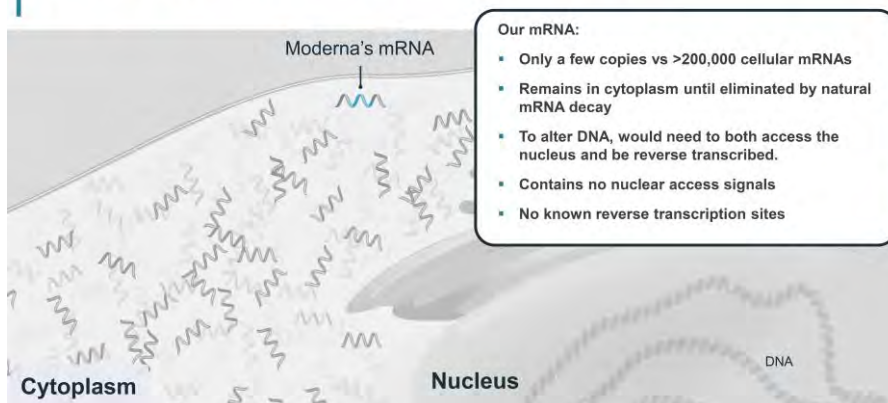
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## mRNA Platform and Mechanism of Action of mRNA-1273



CO-18

### Our mRNA Vaccine Cannot Alter DNA



FDA Vaccines and Related  
Biological Products Advisory  
Committee December 17, 2020



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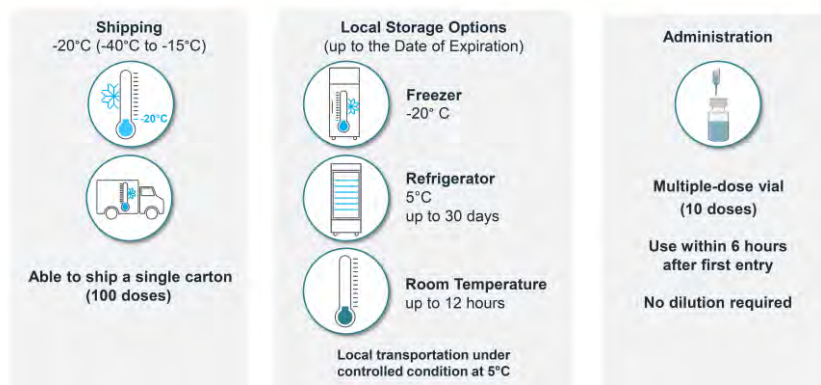
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### mRNA-1273 Shipping, Storage and Administration



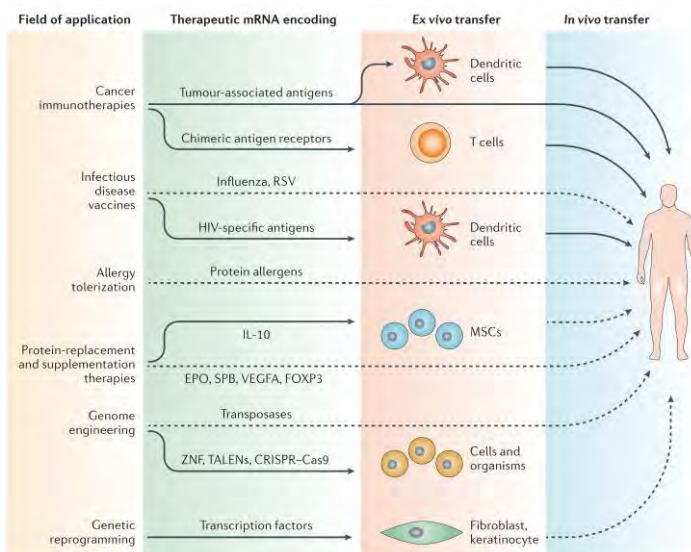
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## mRNA-based vaccines and therapeutics



Nature Reviews Drug Discovery 13, 759–780 (2014)

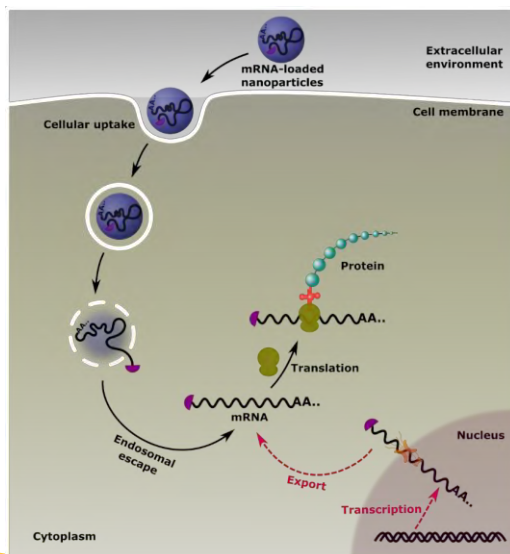


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## Delivery – a Key Challenge for mRNA Therapeutics



Li, B., Zhang, X., Dong, Y.\*. Nanoscale platforms for messenger RNA delivery, *Wiley Interdiscip Rev Nanomed Nanobiotechnol.*, e1530. PMID: 29726120



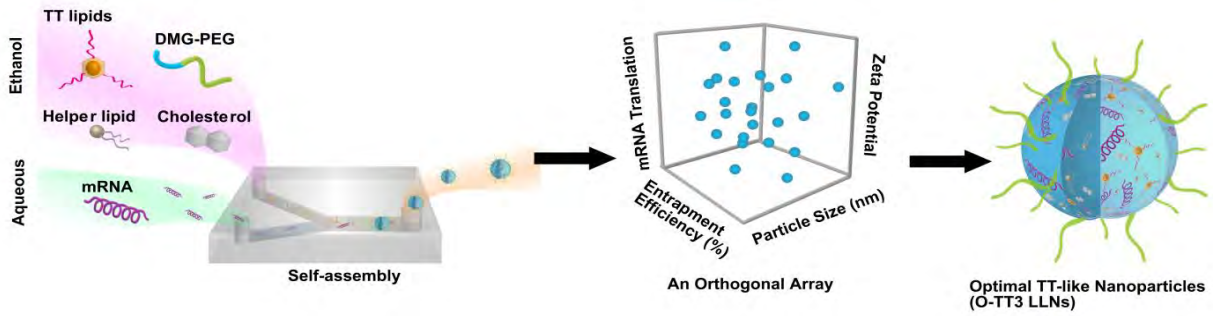
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# An orthogonal array optimization of lipid nanoparticles for mRNA delivery in vivo



Li, B., Luo, X., Deng, B., Wang, J., McComb, D. W., Shi, Y., Gaensler, K. M. L., Tan, X., Dunn, A. L., Kerlin, B. A., Dong, Y.\* *Nano Letters*, 15 (12), 8099–8107 (2015). Dong, Y.; Li, B., WO 2016187531.

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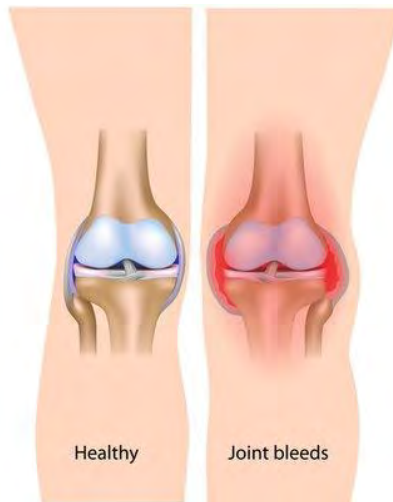


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# Hemophilia-a genetic disorder



Dreamstime.com



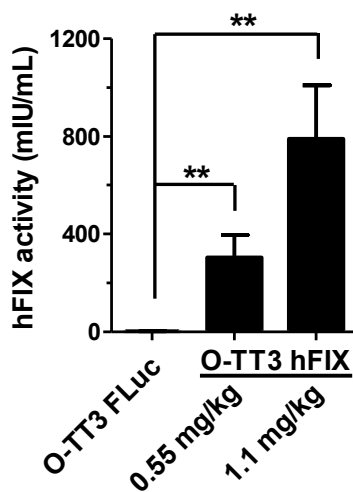
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TT3 lipid nanoparticles are able to fully recover the human factor IX activity to a normal level



FIX-knockout mice



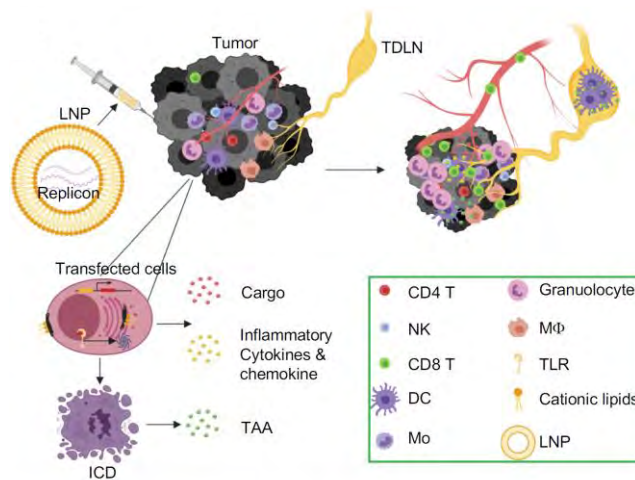
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TT3 LNP deliver self-replicating IL-12 RNA for cancer immunotherapy



Li, Y., Su, Z., Zhao, W. *et al.* Multifunctional oncolytic nanoparticles deliver self-replicating IL-12 RNA to eliminate established tumors and prime systemic immunity. *Nat Cancer* (2020).



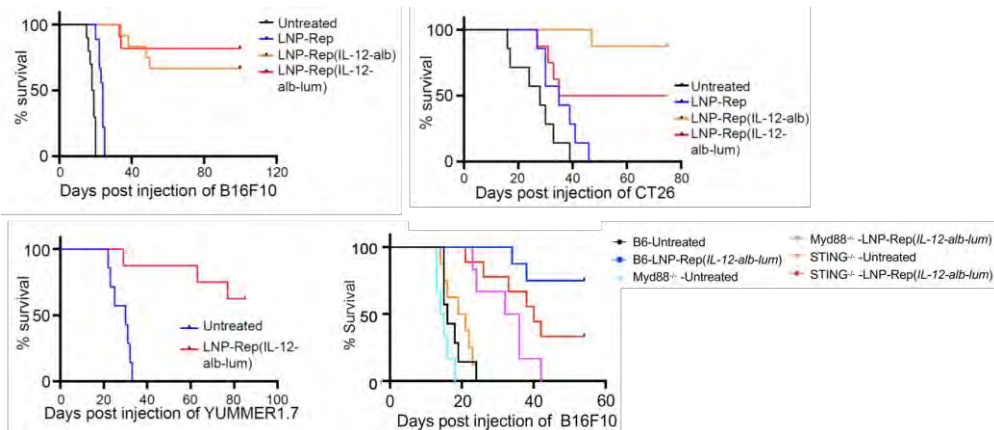
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## A single injection of LNP-replicons encoding IL-12-alb or IL-12-alb-lum can eradicate large established tumors



Li, Y., Su, Z., Zhao, W. *et al.* Multifunctional oncolytic nanoparticles deliver self-replicating IL-12 RNA to eliminate established tumors and prime systemic immunity. *Nat Cancer* (2020).



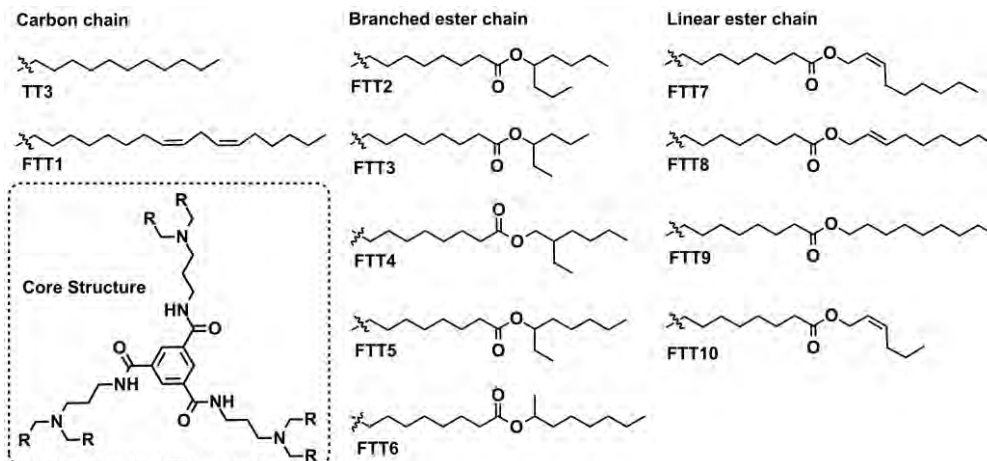
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## Functionalized lipid-like nanoparticles



Zhang, X., Zhao, W., Nguyen, G.N., Zhang, C., Zeng, C., Yan, J., Du, S., Hou, X., Li, W., Jiang, J., Deng, B., McComb, D. W., Dorkin, R., Shah, A., Barrera, L., Gregoire, F., Singh, M., Chen, D., Sabatino, D.E. \*, Dong, Y. \*, Functionalized lipid-like nanoparticles for in vivo mRNA delivery and base editing. *Science Advances*, (2020), in press.



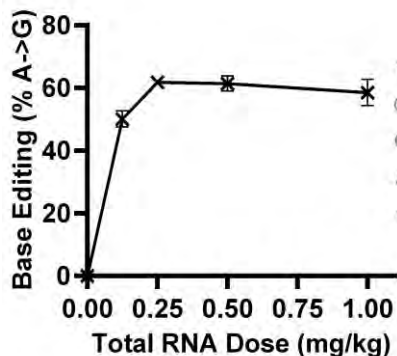
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## Efficient base editing of PCSK9 gene in mice



T	0.01%	0.01%	0.04%	0%	99.99%	0.02%	0.02%	0.03%	99.99%	99.95%
G	0.04%	0.04%	0.01%	5.09%	0%	52.29%	0.04%	0.04%	0%	0.04%
C	99.94%	99.94%	99.93%	0%	0.01%	0%	99.87%	99.91%	0.01%	0.01%
A	0.01%	0.01%	0.03%	94.91%	0%	47.68%	0.07%	0.02%	0.01%	0%
#	53798	53848	54069	54092	54078	51505	54697	54550	54723	54724

Target site sequence (including PAM region):  
5'-CCCATACCTTGGAGCAACGGCGG-3'

Zhang, X., Zhao, W., Nguyen, G.N., Zhang, C., Zeng, C., Yan, J., Du, S., Hou, X., Li, W., Jiang, J., Deng, B., McComb, D. W., Dorkin, R., Shah, A., Barrera, L., Gregoire, F., Singh, M., Chen, D.\*, Sabatino, D.E. \*, Dong, Y.\*. Functionalized lipid-like nanoparticles for in vivo mRNA delivery and base editing. *Science Advances*, (2020), in press.

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## Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection



**30 MILLION** people worldwide are affected by sepsis

**#1 CAUSE** of death in hospitals

**25-30% MORTALITY RATE**

**1.5% ANNUAL RATE OF INCREASE**

Reinhart, K., et al. (2017). Recognizing sepsis as a global health priority—a WHO resolution. *New England Journal of Medicine*, 377(5), 414-417.

Hotchkiss, R. S., et al. (2013). Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *The Lancet infectious diseases*, 13(3), 260-268.

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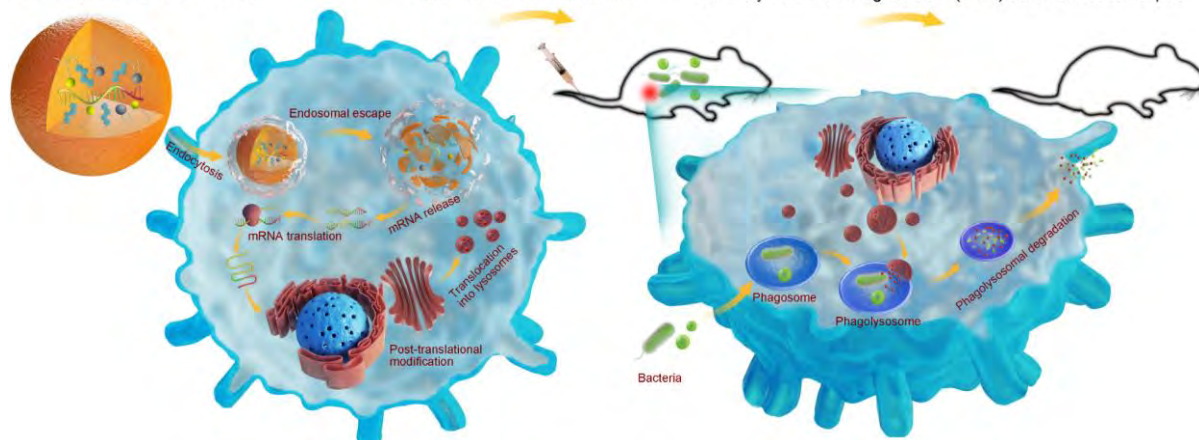
## Engineered macrophages containing antimicrobial components for treating sepsis



Vitamin lipid nanoparticle (VLNP)

Adoptive macrophage transfer

Recovery from multi-drug resistant (MDR) bacteria-induced sepsis



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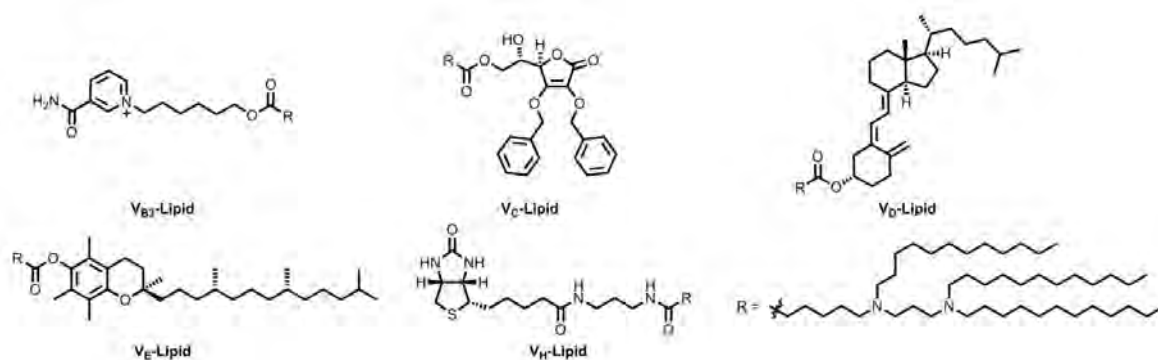


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## Synthesis of vitamin-derived lipids



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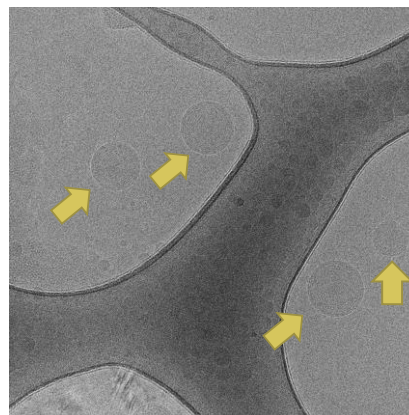
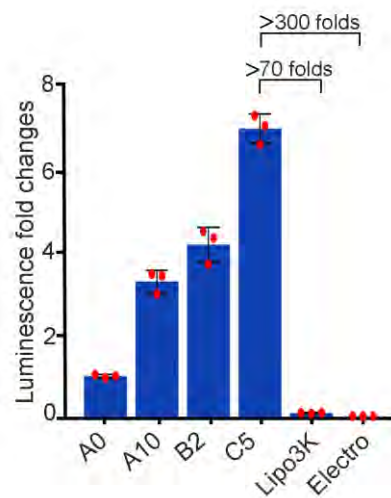


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## V<sub>C</sub>LNP formulation C5 significantly improved mRNA delivery



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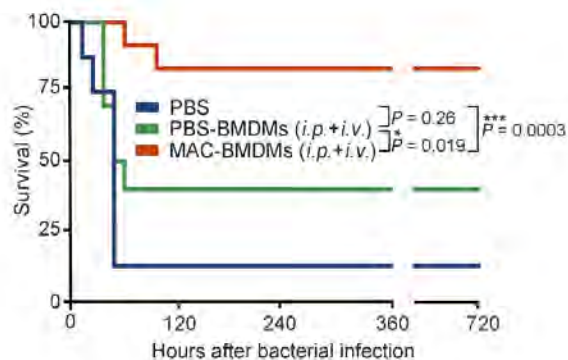
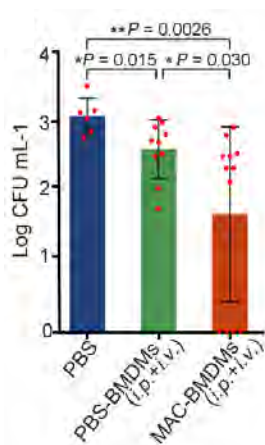


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## Engineered macrophages reduced bacterial burden and improved survival rate in mixed MDR bacteria (*S. aureus* and *E. coli*)-induced sepsis mice



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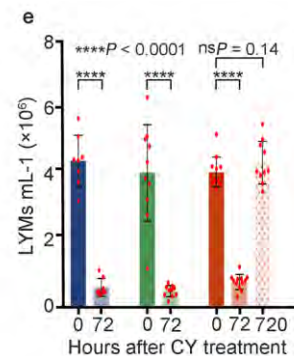
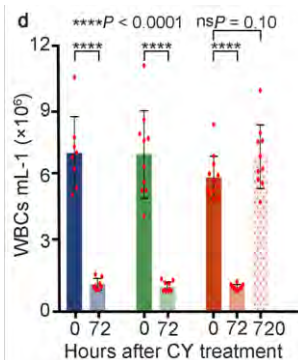
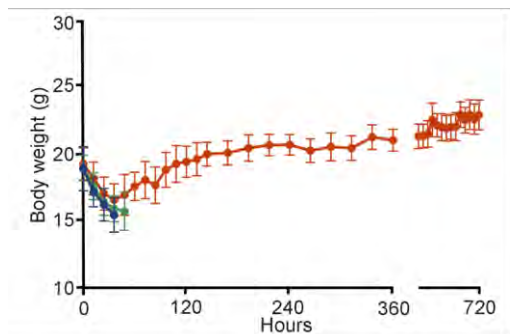


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## Engineered macrophages restored body conditions: body weight, white blood cells, and lymphocytes



Hou, X., Zhang, X., Zhao, W., Zeng, C., Deng, B., McComb, D. W., Du, Shi., Zhang, C., Li, W., Dong, Y\*, Vitamin lipid nanoparticles enable adoptive macrophage transfer for the treatment of multidrug-resistant bacterial sepsis. *Nature Nanotechnology*. 15, 41–46 (2020).



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# Questions?



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# COVID-19 VACCINES UPDATE

## Emerging Questions & Future Applications

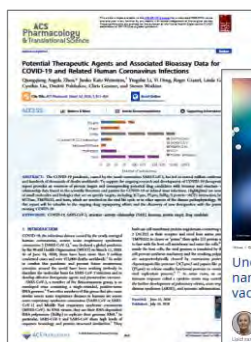


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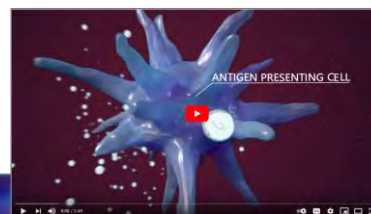


Understanding the nanotechnology in COVID-19 vaccines

Blogs



Data Sets



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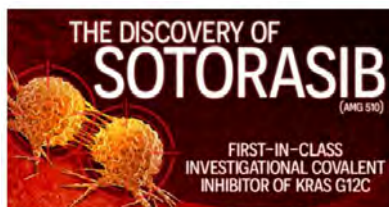


Whitepapers

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<https://www.cas.org/covid19>







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 Moderator: Ariamala Gopalsamy, AstraZeneca

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- Why identifying a direct inhibitor of KRAS has proven so challenging
- How covalent inhibition helped to turn KRAS G12C into a tractable target
- What hurdles were overcome in turning initial KRAS G12C binders into potential human therapeutics

Co-produced with: ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications



Date: Wednesday, March 3, 2021 @ 2-3pm ET  
 Speaker: Robert Migliorini, Exxon Mobil Corporation  
 Moderator: Bryan Tweedy, American Chemical Society

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#### What You Will Learn:

- Learn about the major sections of a contract and common types of IP related agreements, including confidentiality/non-disclosure, material transfer, and more
- Understand the various types of IP agreements, the business and technical use of each type of agreement and the important provisions for each type of IP agreement
- Know the appropriate type of IP agreement to put in place prior to working with an outside party

Co-produced with: ACS Professional Education



Date: Wednesday, March 10, 2021 @ 11am-12pm ET  
 Speakers: Zafra Lerman, Malta Conferences Foundation / Peter Hotchkiss, Organisation for the Prohibition of Chemical Weapons / Vaughan Turekian, National Academies' Policy and Global Affairs Division  
 Moderator: Lori Brown, American Chemical Society

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- How the OPCW works with the governments of 193 countries to prevent the use of chemical weapons
- How the US National Academies' Policy and Global Affairs office mobilizes experts and networks around the world to increase the use of evidence to advance local, national and global policy and capacity
- How the Malta Conferences uses science diplomacy to overcome cultural, religious, and political barriers in the Middle East

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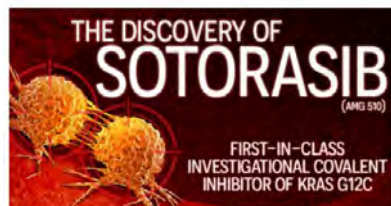


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- Know the appropriate type of IP agreement to put in place prior to working with an outside party

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