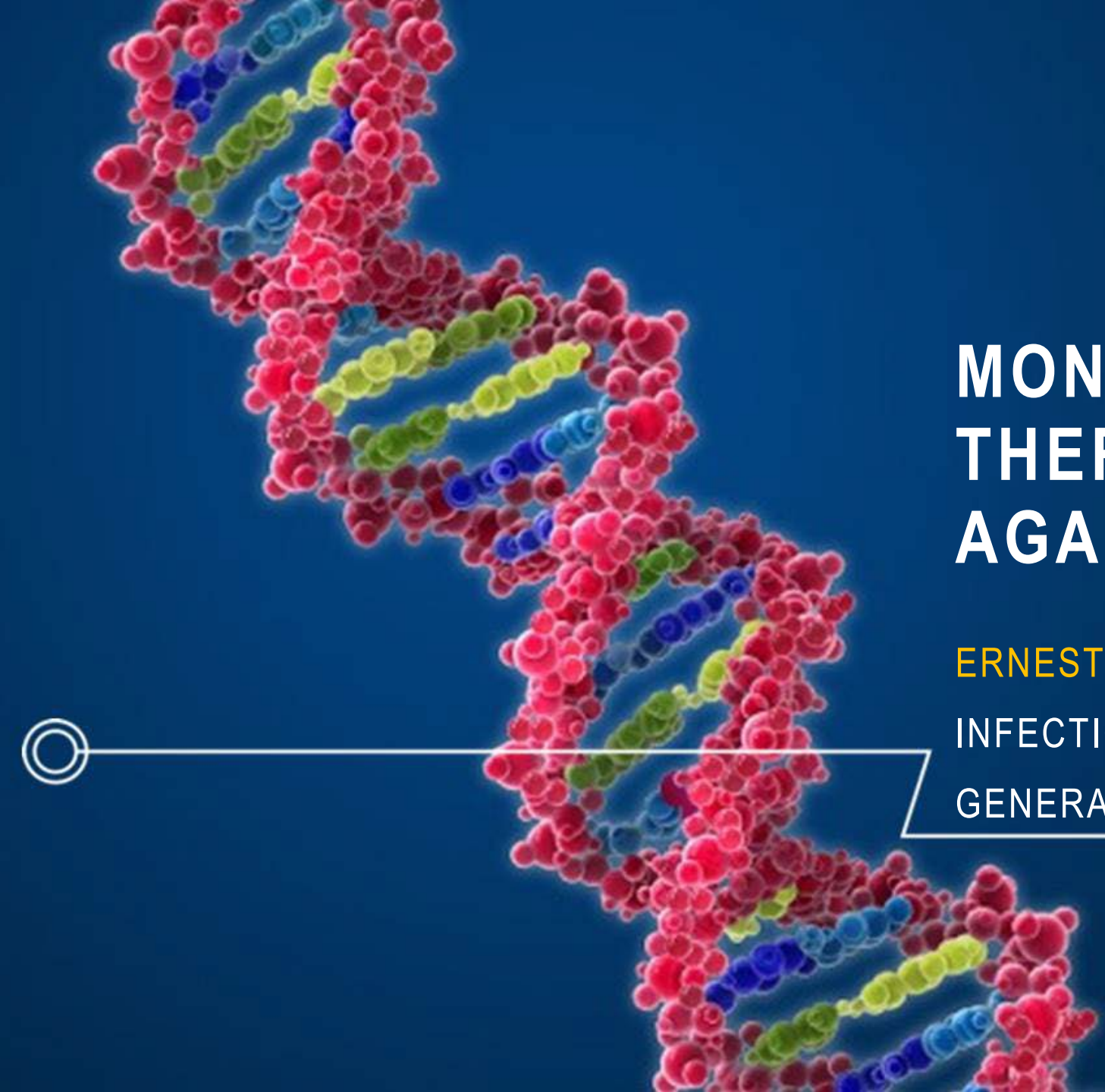

REGENERON
SCIENCE TO MEDICINE®

MONOCLONAL ANTIBODY THERAPIES IN THE FIGHT AGAINST COVID-19

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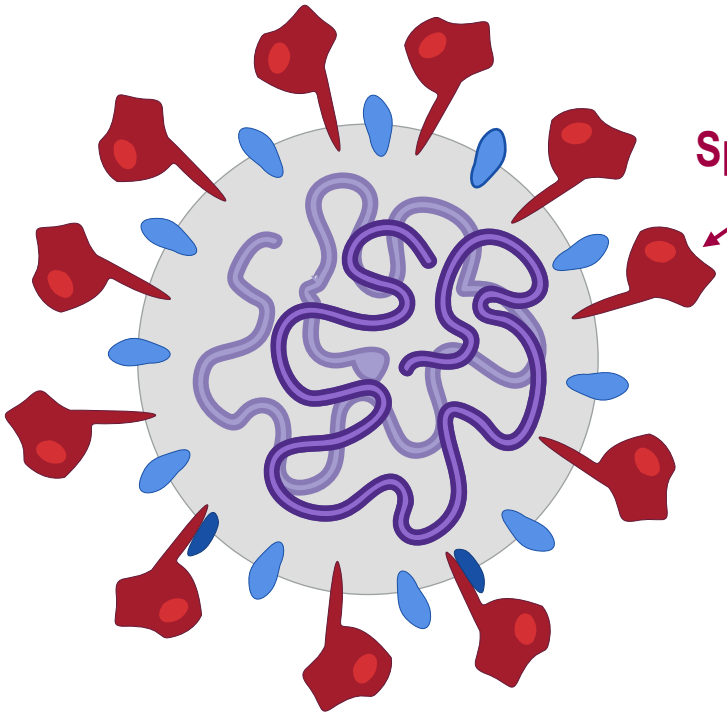
INFECTIOUS DISEASE LEAD.

GENERAL MEDICINE FRANCHISE.

LEGAL DISCLOSURE

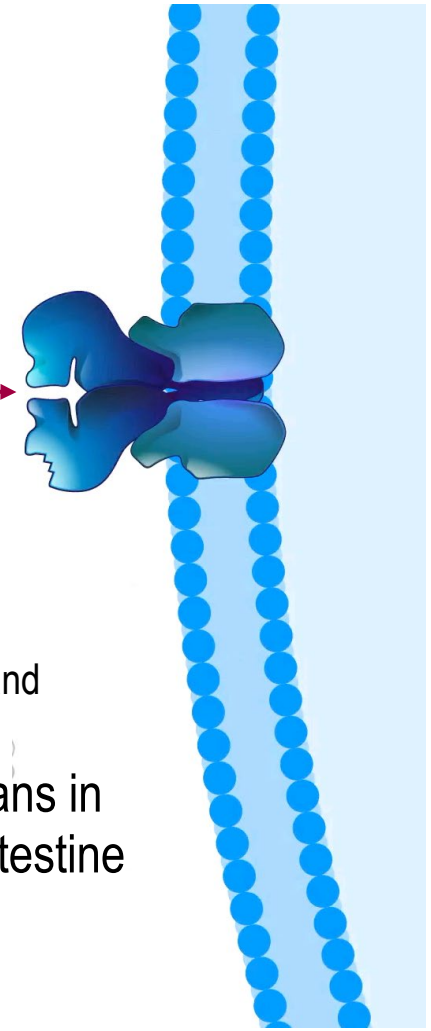
Ernesto Oviedo-Orta is a Regeneron Pharmaceuticals, Inc. employee/stockholder with Regeneron Pharmaceuticals, Inc.

SARS-COV-2 ENTERS HOST CELLS BY BINDING TO THE ACE2 RECEPTOR ON THE CELL SURFACE[1,2]



- Binds to the **ACE2 receptor** to allow virus entry into host cells[1,2]

- **ACE2 receptor**[1]
  - Negative regulator of the renin-angiotensin system
    - Regulates vasodilation
    - Protective role in cardiovascular disease and kidney diseases
  - ACE2 is abundantly present in humans in the epithelia of the lung and small intestine and in the vascular endothelium[3]

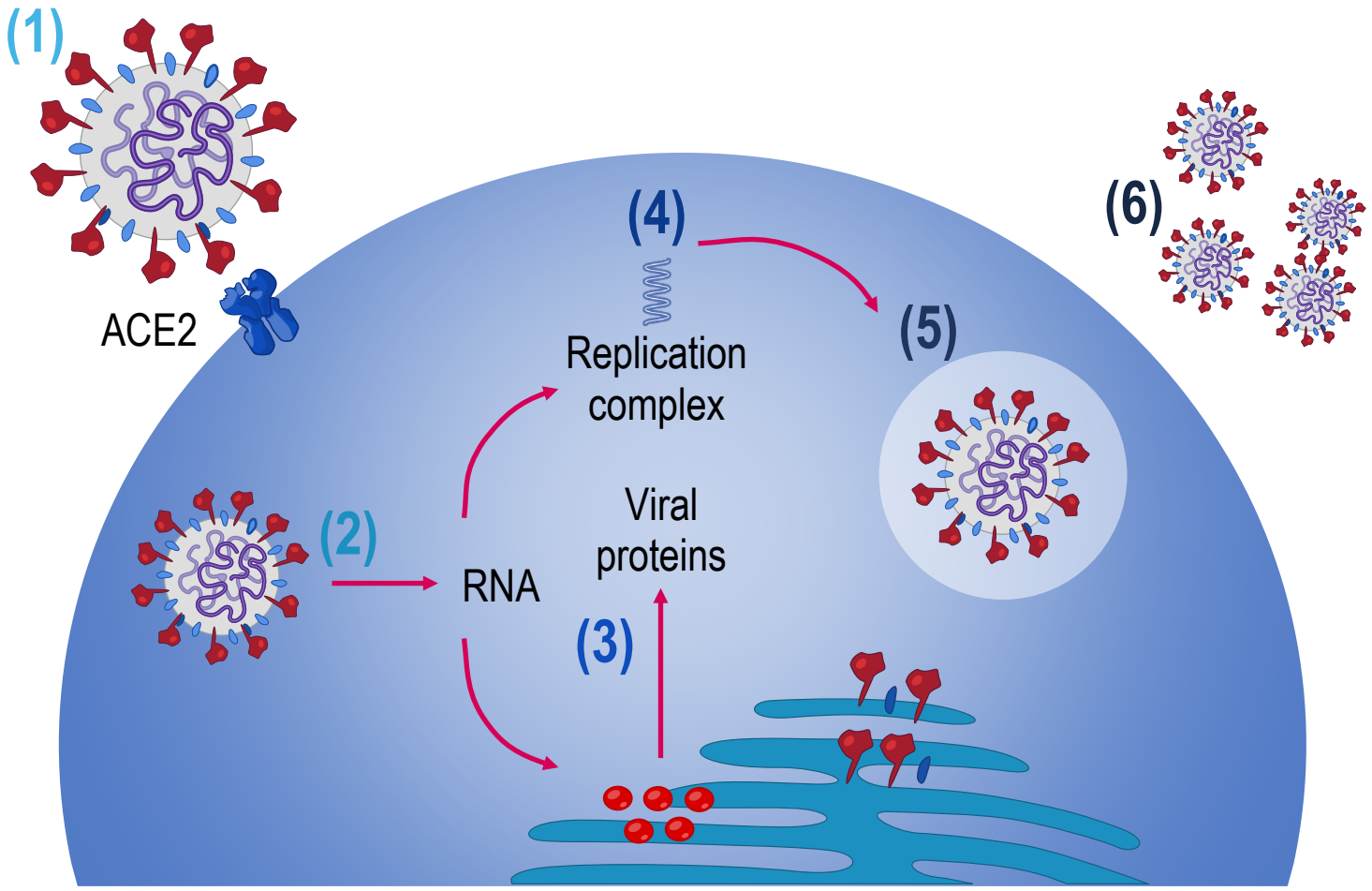


ACE2, angiotensin-converting enzyme 2.

1. Kuba K et al. *Circ J*. 2013;77:301-308. 2. Barnes C et al. *Cell*. 2020;181:271-280. 3. Hamming W et al. *J Pathol*. 2004; 203:631-637.

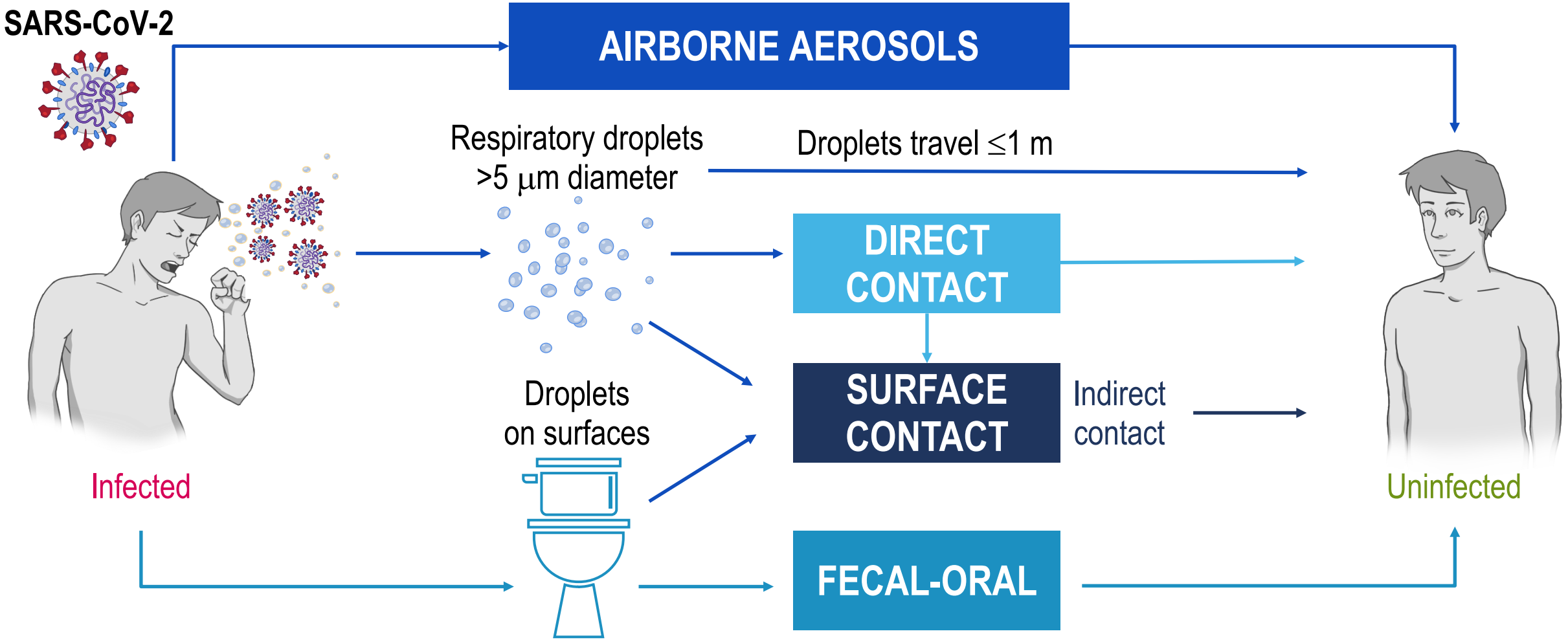
SARS-COV-2 REPLICATES WITHIN HOST CELLS TO FORM NEW VIRUS PARTICLES

1. The virus enters the host by first binding to ACE2 on the cell surface[1]
2. Once inside the cell, the virus releases its RNA[1]
3. Some RNA is translated into proteins by the cell's machinery[1]
4. Some of these proteins form a replication complex to make more viral RNA[1]
5. Proteins and RNA are assembled into new virus particles[1]
6. New virus particles are released from the cell and proceed to infect other cells[2]



1. Romano M et al. *Cells*. 2020;9:1267 doi:10.3390/cells9051267. 2. Garoff H, et al. *Microbiol Mol Biol Rev*. 1998;62:1171-1190.

THERE ARE MULTIPLE ROUTES OF HOST-TO-HOST TRANSMISSION



Modified from: Harrison AG et al. *Trends Immunol*. 2020. doi:10.1016/j.it.2020.10.004.

COVID-19 COURSE OF DISEASE VARIES

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Viral Replication	+	+ + +	+ + +	+ +	+

COVID-19, Coronavirus Disease 2019.

Gandhi RT et al. *N Engl J Med*. 2020;383:1757-1766.

PASSIVE IMMUNITY AND ACTIVE IMMUNITY ARE BOTH PATHOGEN-SPECIFIC PROCESSES BUT DIFFER IN THE DURATION OF THE PROTECTIVE RESPONSE[1-4]

Temporary protection conferred by using an external source of pathogen-specific antibodies, including transplacental transfer of maternal antibodies or injection of antibodies

Passive Immunity

Immediate immunity by neutralization, opsonization, or direct killing of the target pathogen, which prevents infection

Temporary protection, as the antibodies are not produced by the host

Active Immunity

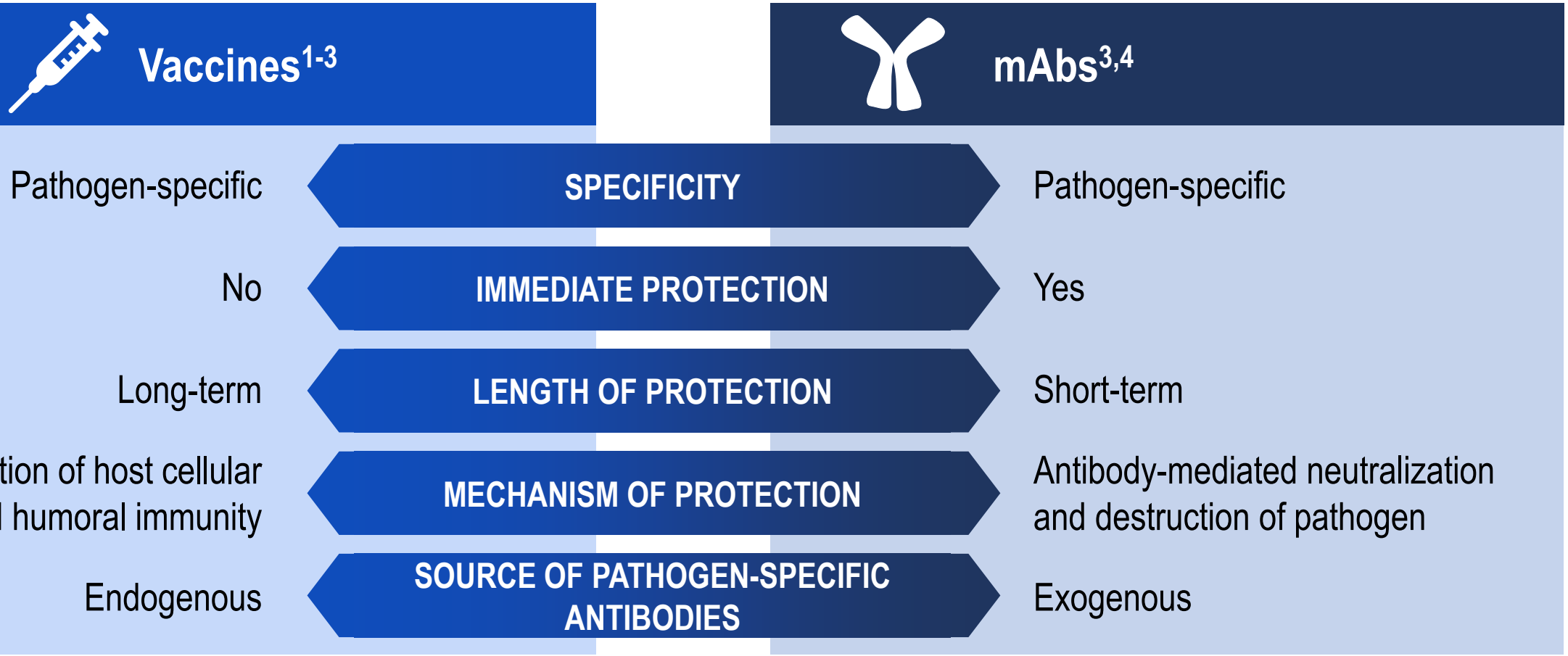
Requires time to build up after recognition of the pathogen

Longer-lasting protection as host develops immune memory cells specific to the pathogen

Pathogen-specific and long-lasting protective immune response developed by the host in response to natural infection or administration of a vaccine

1. Marshall JS et al. *Allergy Asthma Clin Immunol*. 2018;14(Suppl 2):49. 2. Clem AS. *J Glob Infect Dis*. 2011;3:73-78. 3. CDC. Immunity types. March 10, 2017. https://www.cdc.gov/vaccines/vac-gen/immunity-types.htm. Accessed December 17, 2020.
4. Marcotte H et al. Passive immunization. In: Mestecky J, et al, eds. *Mucosal Immunity*. 4th ed. Vol 2. 2015:1403-1434.

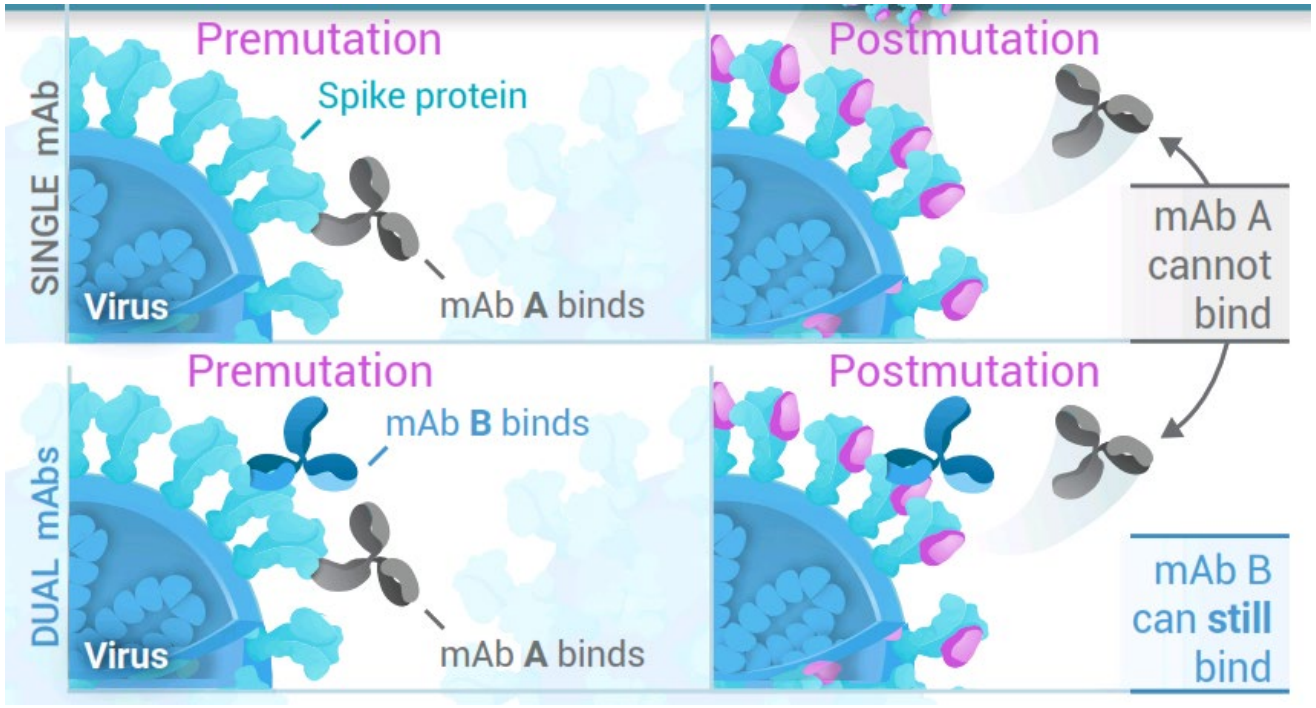
KEY DIFFERENCES BETWEEN VACCINES AND mAbs



1. Clem AS. *J Glob Infect Dis*. 2011;3:73-78. 2. Morris L et al. *PLoS Med*. 2017;14:e1002436. doi:10.1371/journal.pmed.1002436. 3. Pelegrin M et al. *Trends in Microbiol*. 2015;23:653-665. 4. CDC. Immunology and vaccine-preventable diseases. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf. Accessed December 17, 2020.

SARS-COV-2 HAS THE POTENTIAL TO MUTATE, DECREASING THE NEUTRALIZATION ABILITY OF THERAPEUTIC ANTIBODIES

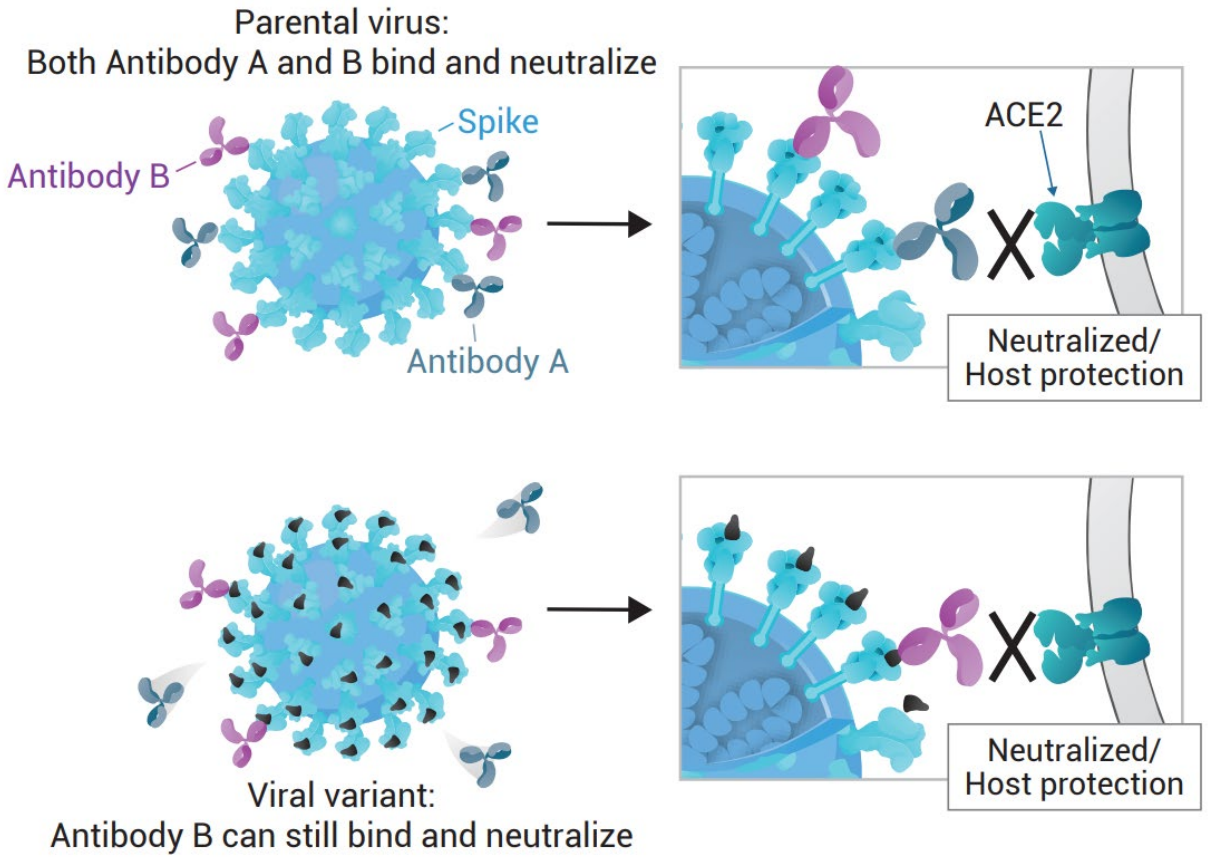
- RNA viruses are known to mutate because of the lack of fidelity in replication due to the RNA-dependent RNA polymerase[1-3]
- Mutations in spike RBD can lead to a structural change that weakens antibody recognition, thus decreasing the neutralization ability of the antibody[1,4,5]
- The new variant may quickly replace the wild-type virus due to selective pressure by a neutralizing antibody[1,4,6]
- The probability of a virus mutating multiple antibody-binding sites is lower than a single binding site[1,4,7]
- Using more than one antibody lowers the risk of SARS-CoV-2 escape variants[1]



mAb, monoclonal antibody.

1. Baum A et al. *Science*. 2020;369:1014-1018. 2. Smith EC et al. *PLoS Pathog*. 2017;13:e1006254. doi.org/10.1371/journal.ppat.1006254. 3. Sanjuán R et al. *Cell Mol Life Sci*. 2016;73:4433-4448. 4. Tai W et al. *J Virol*. 2016;91:e01651-16. doi:10.1128/JVI.01651-16. 5. Sui J et al. *J Virol*. 2014;88:13769-13780. 6. Kim Y-S et al. *Emerg Infect Dis*. 2019;25:1161-1168. 7. Coughlin MM et al. *Virology*. 2009;394:39-46.

DUAL mAb TREATMENT MAKES IT HARDER FOR SARS-CoV-2 TO BECOME RESISTANT TO TREATMENT



- The probability of a virus mutating multiple antibody-binding sites on Spike RBD is lower than the probability of the virus mutating a single binding site[1,2]
- Therefore, it is less likely that a viral variant will have mutations that affect both antibodies in a combination treatment[2,3]

1. Tai W et al. *J Virol*. 2016;91:e01651-16. 2. Baum A et al. *Science*. 2020;369:1014-1018. 3. Coughlin MM et al. *Virology*. 2009;394:39-46.

THE FDA HAS GRANTED EMERGENCY USE AUTHORIZATIONS FOR SEVERAL THERAPIES TO ADDRESS COVID-19 PANDEMIC[1-2]

Vaccines	Monoclonal antibodies	Convalescent plasma	Antivirals
Pfizer/BioNTech	Casirivimab with imdevimab	REGENERON science to medicine®	
Moderna	Bamlanivimab	Lilly	
Johnson & Johnson / Janssen	Bamlanivimab with etesevimab	gsk VIR	
	Bebtelovimab		
	Sotrovimab		
	Evusheld	AstraZeneca	

Prevention — Treatment

1. FDA. FDA combating COVID-19 with therapeutics. FDA website. Updated December 2, 2020. https://www.fda.gov/media/136832/download. Accessed December 4, 2020. 2. FDA. Emergency Use Authorization. Updated March 15, 2021. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

OTHER RECENT MAB / BIOLOGICS

Monoclonal Antibodies / Biologics

Molecular Partner/Novartis confirmed EUA submission for ensovibep (trispecific DARPin) for the treatment of mild to moderate outpatient COVID-19

Celltrion announced it has submitted an IND to conduct a global Ph3 trial to evaluate the efficacy and safety of an inhaled COVID-19 antibody cocktail for patients with mild to moderate symptoms of COVID-19

Emerging data suggests Adagio's ADG20 has markedly reduced activity vs. the BA.2 lineage of Omicron, introducing further delays and modifications to its clinical development program

SAB provided an update on SAB-185 (polyclonal mAb) that is being evaluated in NIH's Ph3 ACTIV-2 trial for mild to moderate COVID-19 where the design will be changed from non-inferiority vs. REGEN-COV to superiority vs. placebo

	Monoclonal Antibodies / Biologics								
	REGENERON	**LILLY**	**LILLY**	**GSK/VIR**	**AZ**	**CELLTRION**	**BRIIBIO**	**ADAGIO**	**NOVARTIS**
	REGEN-COV (casivirimab + imdevimab)	**bamlanivimab + etesevimab**	**Bebtelovimab**	**Xevudy (sotrovimab)**	**Evusheld (tixagevimab + cilgavimab)**	**Regkirona (regdanvimab)**	**amubarvimab + romlusevimab**	**ADG20**	**ensovibep**
PrEP	-	-	-	Ph3 planned 2Q22	EUA (12yr+)	-	Trial ongoing in China	**Ph3 stopped early due to Omicron Date expected late-March**	-
PEP	Not authorized due to Omicron *EUA (12yr+)*	Not authorized due to Omicron *EUA (all ages)*	-	-	Failed Ph3	-	-		-
Outpatient	Not authorized due to Omicron *EUA, high-risk (12yr+)*	Not authorized due to Omicron *EUA, high-risk (all ages)*	**EUA, high-risk When other therapies not available (12yr+)**	EUA, high-risk (12yr+)	Positive Ph3	Positive Ph3	Positive Ph3; Submitted EUA	**Ph3 stopped early due to Omicron Date expected late-March**	**Positive Ph2 Submitted EUA** Ph3 in planning
Inpatient	Positive Ph3	Failed ACTIV-3	-	RECOVERY ongoing Failed ACTIV-3	ACTIV-3 ongoing	-	Failed ACTIV-3	-	Failed ACTIV-3
Dose	1200mg 600mg Q4W repeat PrEP	700mg bam 1400mg ete	**175mg**	500mg	**600mg (previously 300mg Q6M)**	40mg/kg	2000mg	300mg stopped; Ph1 higher dose planned	75mg
Administration	IV or SC (4x injection)	IV	**IV injection**	IV (IM 2x injection submitted)	IM (2x injection)	IV	IV	IM (1 injection)	IV (exploring SC)
Activity vs. Omicron	No	No	**Yes**	Yes **No (BA.2)**	**Yes (Reduced)** **Yes (BA.2)**	No	Yes	Yes (Reduced) **No (BA.2)**	Yes
Next-gen	Pre-clinical	-	-	VIR-7832 enhanced T cell protection; 2 mAbs combo w/ sotrovimab	-	**Ph3: inhaled regdanvimab + CT-P63**	-	Structural enhancements to ADG20; assessing library of new mAbs	Future DARPin to address VOCs

Antibody medicines could serve as an important bridge to a vaccine, and may have utility beyond for certain people, such as those who are immuno-compromised or do not respond to a vaccine. Both approaches are important and necessary to hopefully end the COVID-19 pandemic.

https://www.usatoday.com/pages/interactives/sponsor-story/How-antibodies-fight-pathogens-like-coronavirus/