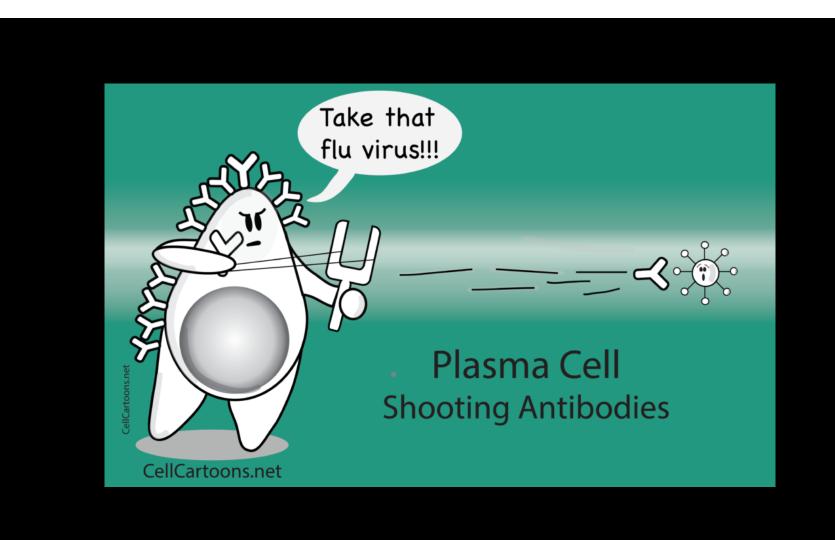
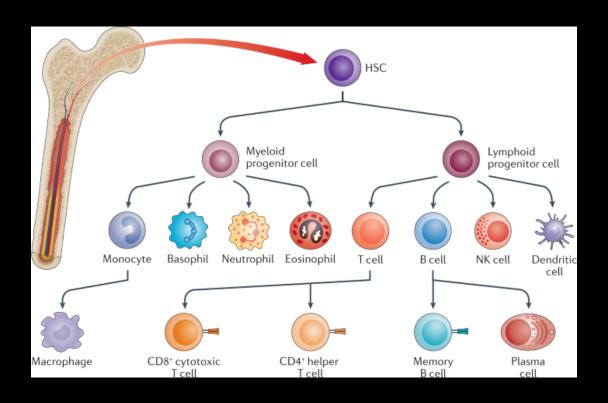
How do antibodies work?

Galit Alter

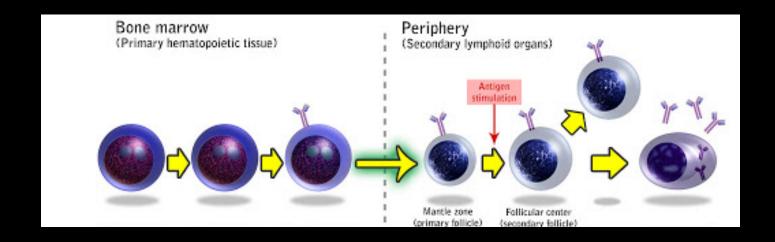
Ragon Institute



Antibodies come from B cells

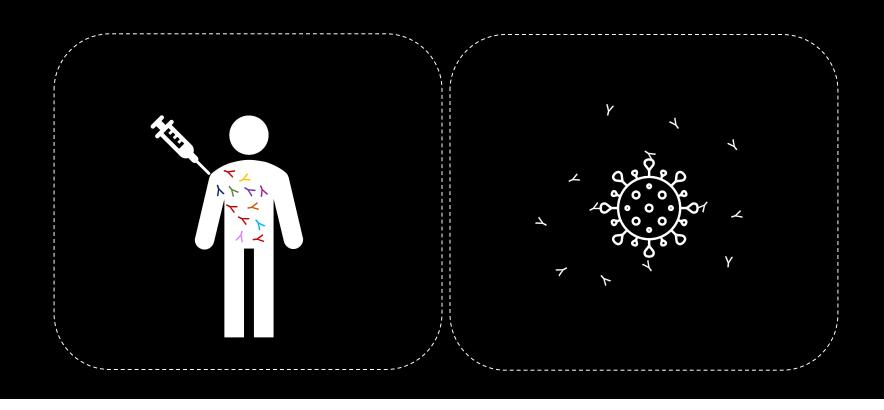


The maturation of the B cell

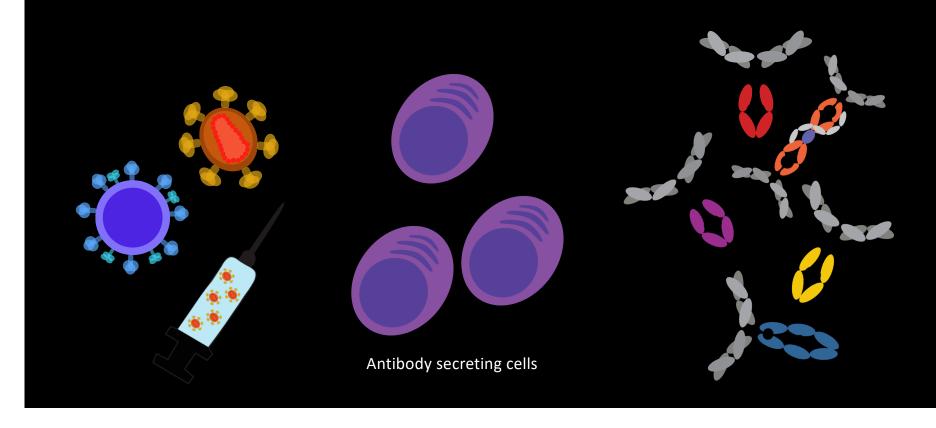


http://hematologyoutlines.com/atlas_topics/69.html

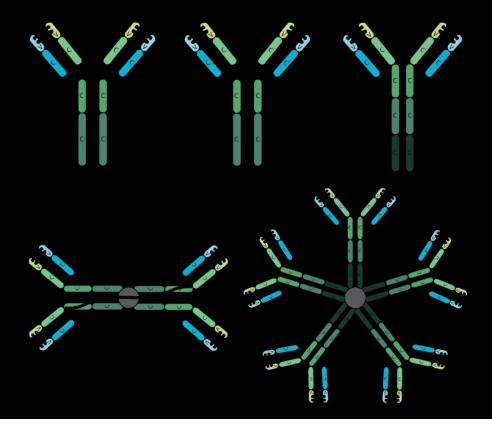
Vaccines and infection lead to the production of antibodies



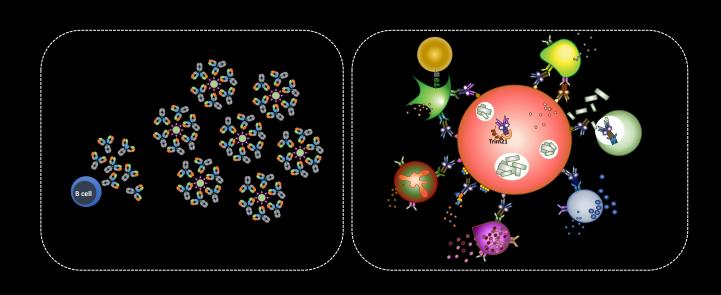
Antibodies are produced by antibody secreting cells and come in different structures and qualities



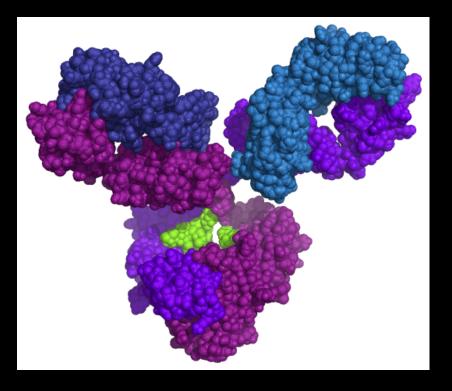
Different flavors of antibodies



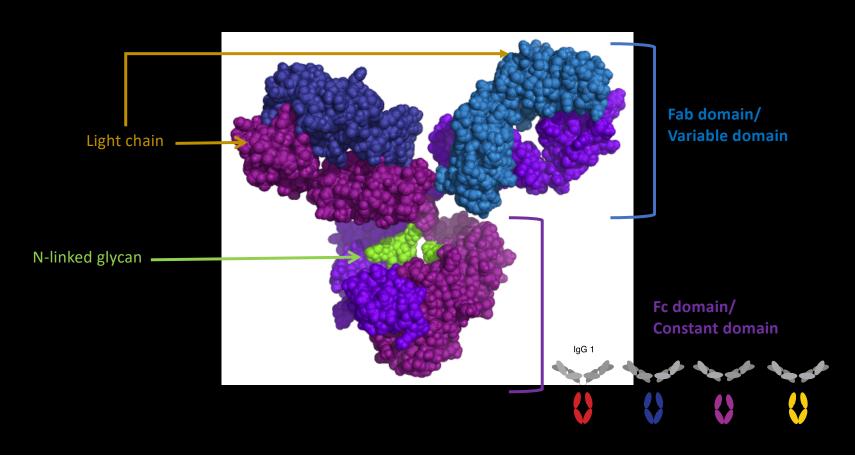
Antibodies can provide protection directly and indirectly



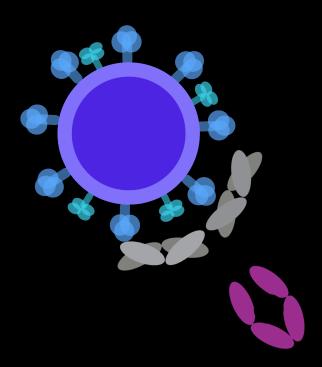
Antibody anatomy

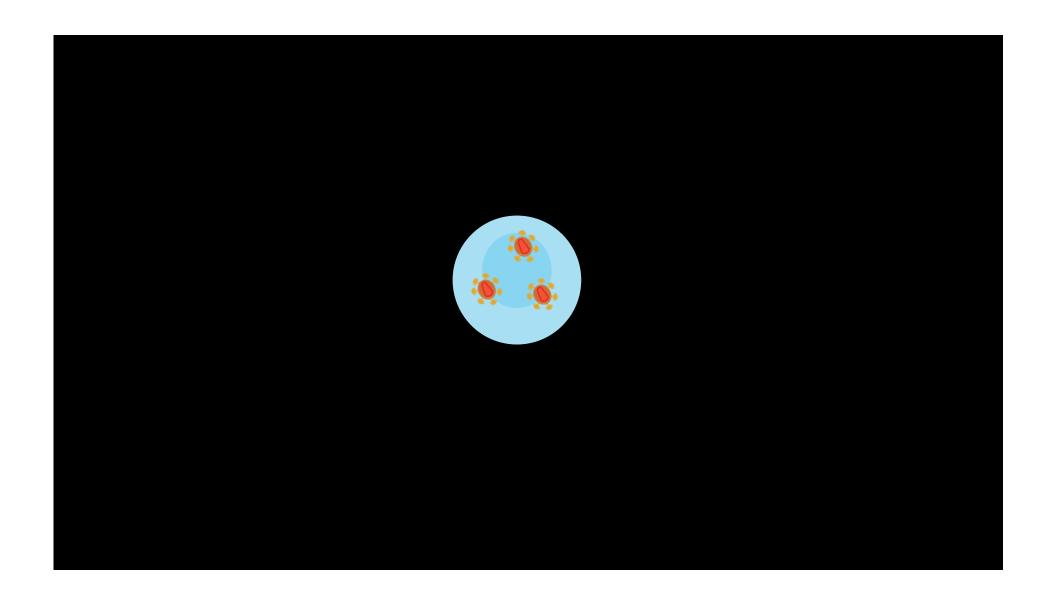


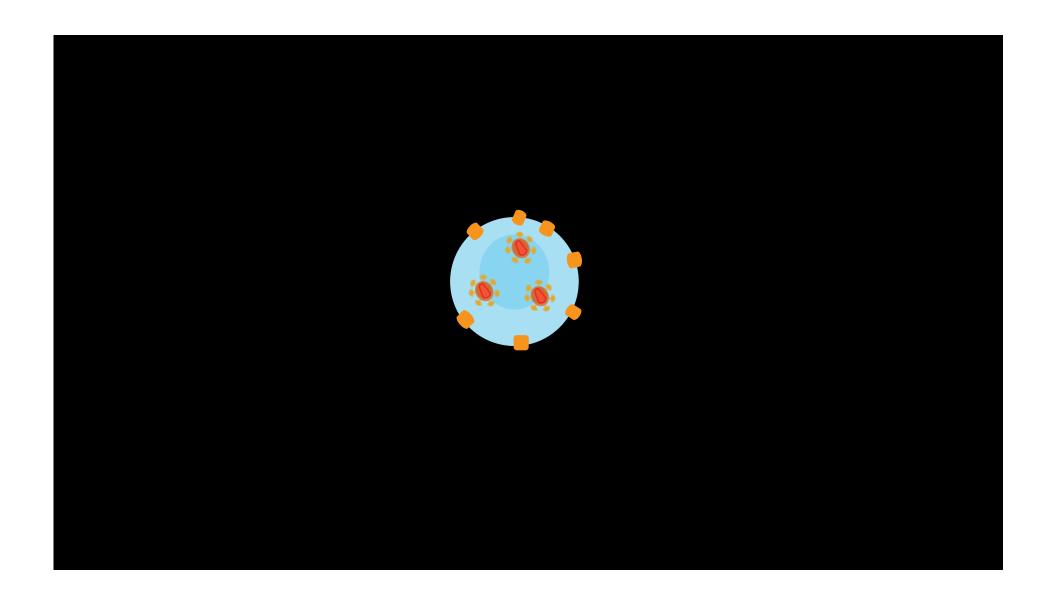
Antibody architecture

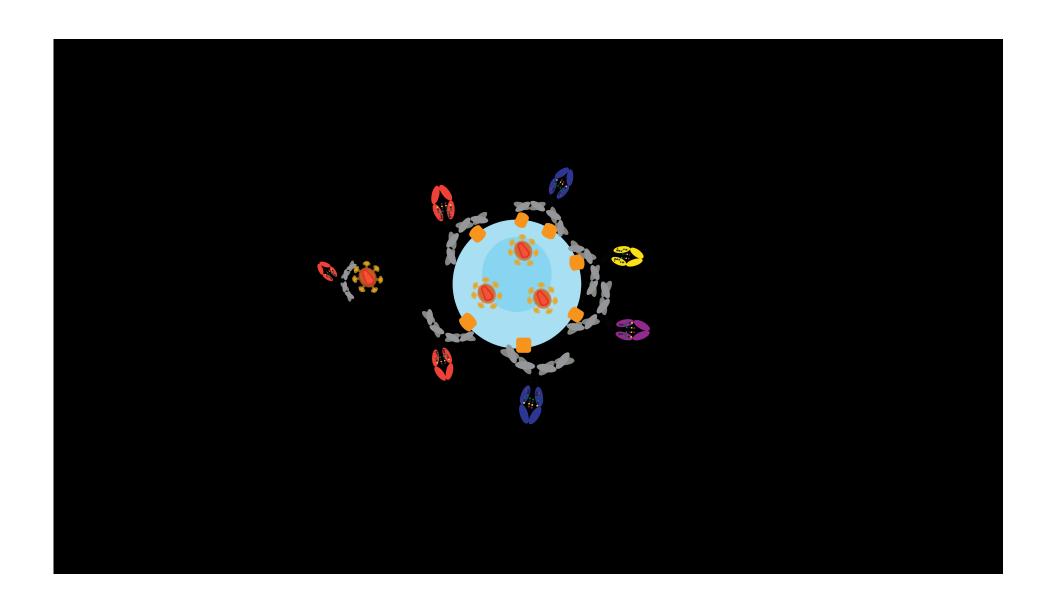


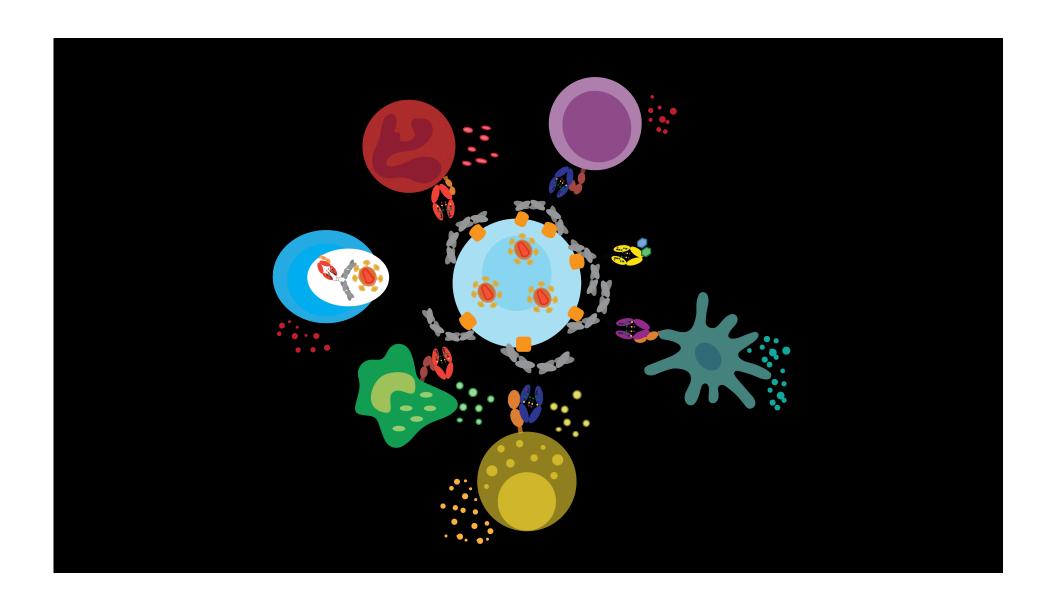
Antibodies bind and neutralize viruses





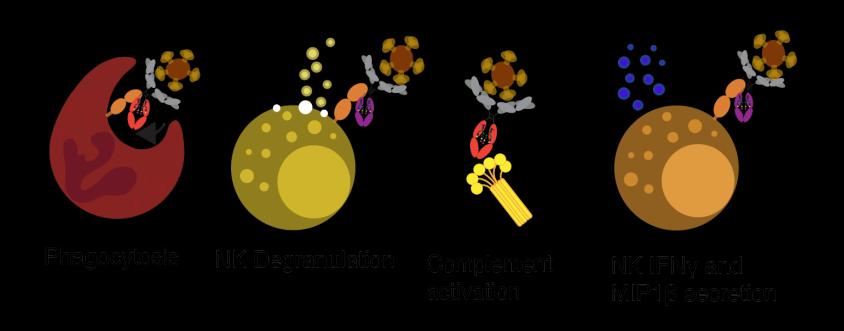


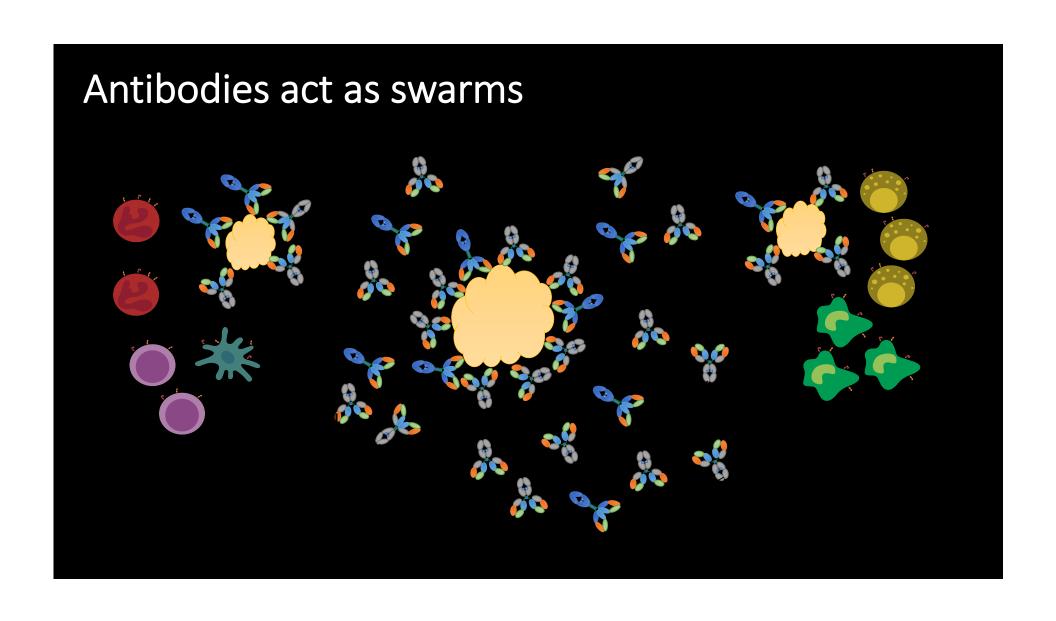




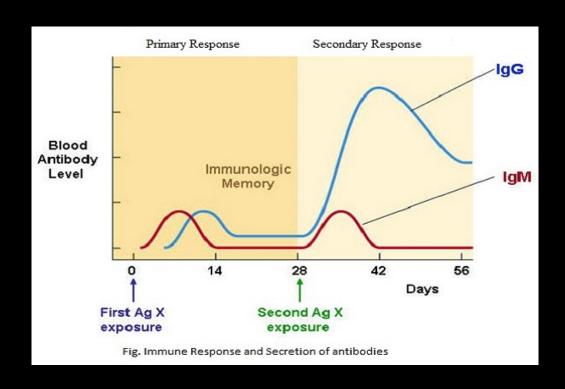
Antibodies recruit the innate immune system to direct killing FcγRIIa, FcγRIIb, FcγRIIc FcγRI FcRn FcγRIIIa, FcγRIIIb

Antibodies recruit the innate immune system to direct killing

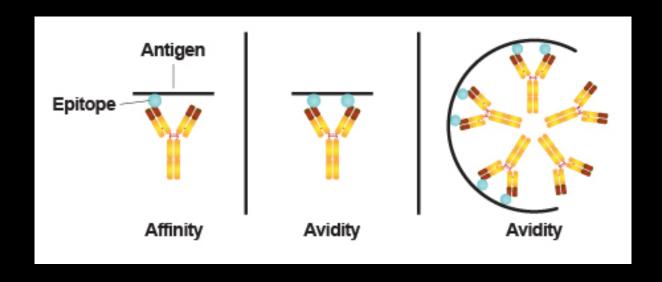




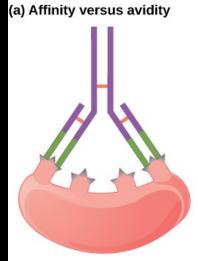
Kinetics of the antibody response



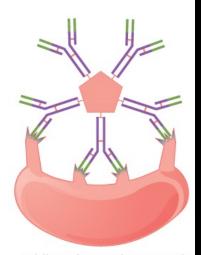
Advantage in numbers



Avidity before affinity...

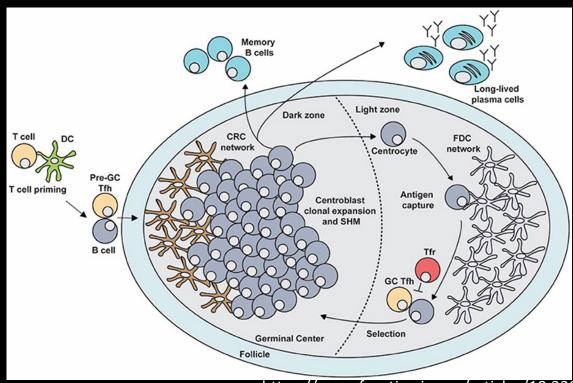


Affinity refers to the strength of a single antibody-antigen interaction. Each IgG antigen binding site typically has high affinity for its target.



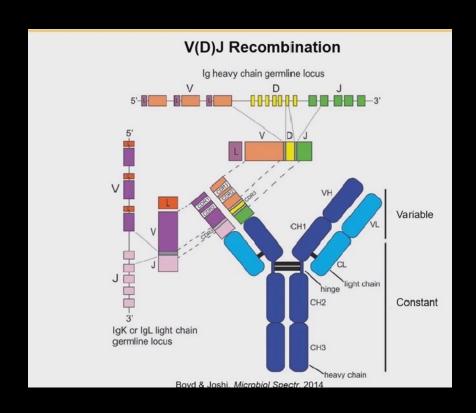
Avidity refers to the strength of all interactions combined. IgM typically has low affinity antigen binding sites, but there are ten of them, so avidity is high.

Somatic hypermutation and clonal selection

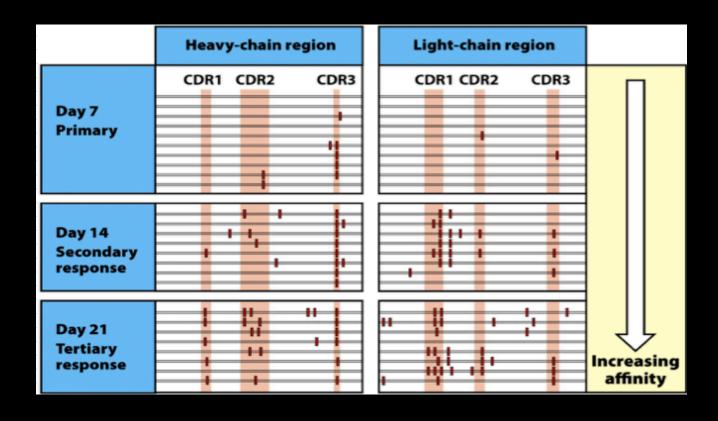


https://www.frontiersin.org/articles/10.3389/fimmu.2018.02469/full

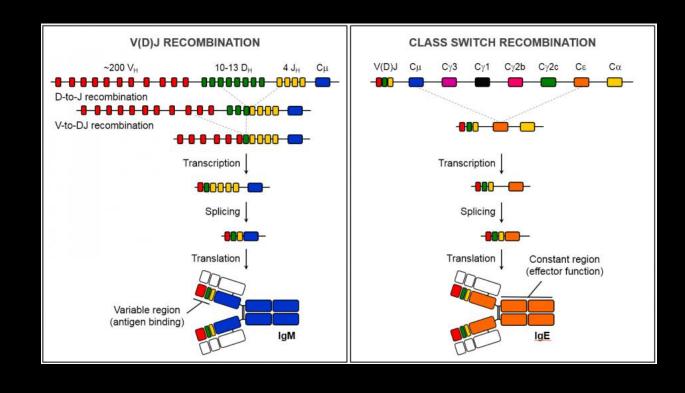
Generating diversity



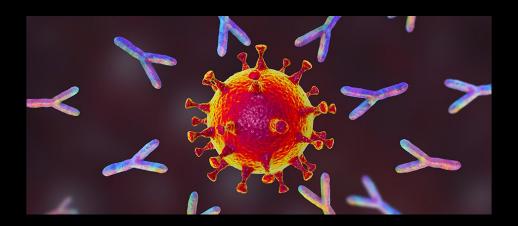
Affinity maturation



Making a B-cell receptor



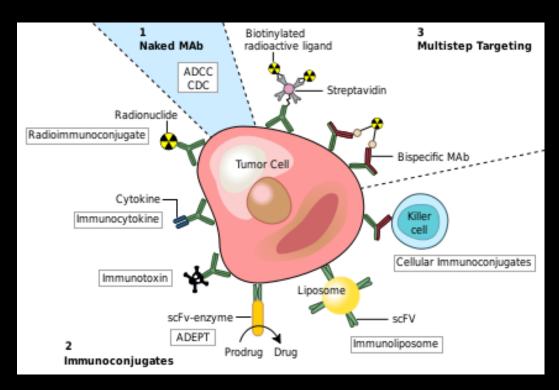
Antibodies as drugs



Fastest growing class of drugs...

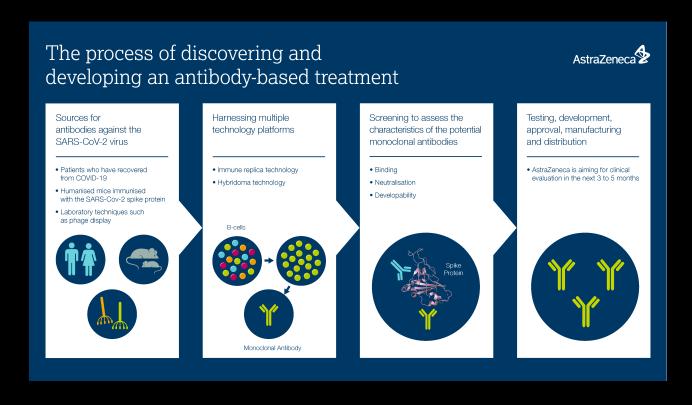
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Belantamab mafodotin ⁽⁵⁾	Dicesop	mab	humanized	S-cell materation y antique (DCMA)	relapsed or refractory multiple musloma	Cabinalzumab ^[21]		mab humanized	CSE1R	metastatic pancreatic cancer B-cell Hodgkin's lumphoma, non-				Sosue factor							personnel nodumel	Gallookurumab PM	_	meb burnanized	MUCI	_	cancer
	-	_		R-cell activating	systemic lucus erythematosus	Camidaniumab testrine ^(CS)		mab feman	CD25 (a chain of IL-2 receptor)	Hodgkin lymphoma, acute lymphoblastic loukemia, acute	ConctramabPR		mab humanized	pathway inhibitor	blee	eding	Eculturab/M	Soliris ma	humanized	CS Y	hemoglobinura, atypical hemolytic uremic syndrome	Continued N	_	nab nouse	00147 (basic		graft versus host disease
Belimemab ⁽²⁷⁾	Denlysts	mab	human	factor (BAFF)	without renal or CNS involvement				5.5.ms880	myoloid loukomia	ContrologoupPf		mab chimeric	etolorius	-	ola virus	Cataman		- manu	entotrain	sepsis caused by Gram-negative	Gedyamab ⁽²⁾	_	mab human	Nemaggistini		par vesas nos oscase
Remarkszumab/28		mah	humanized	rorre	gastric cancer or gastrossophapeal kendion	Camealcumab(PR)		mab humanized	PD-1	hepatocellular carcinoma				glycoprotein			Edobacomab			ALMANIA .	bacteria	Genturant organicm ⁽¹⁶⁾	Mylotera	net turnanced	C033	v	acuto myologenous leukemia
OCTATION NAMED IN			TOTAL CO.	TOTAL STREET	adinocarcinoma	Canakinumab ^{EES}	fais	mab human	IL1 Y	cryopyrin-associated periodic	Consequential		mab humanized	1-40-\$-amytoid		themer's disease	Edrecolomab	Panores III		EpCAM	colorectal carcinoma	Gerolizanab oroganicas in	Mything	meb humanicad	4.40	,	dabetes etc.
Denralizamab ⁽³⁹⁾	Fasensa	mab	humanized	CD125 Y	asthma		_		CanAs (a	W-1010	Crizanizumabi19	Adakveo	mab humanized	selectin P Y	983	Ne-cell disease	Etalcumab(2)	Reptive in		LFA-1 (CD11a)	psoniasis (blocks T-cell migration)	Gitvetrophi ⁽²⁾	_	nab veterinary	PODOI		2
_				Staphylococcus aureus bi-		Confecumeb mertansine(30)		mab humanized	glycotorm of MUC1)	colorectal cancer etc.	Croledurab ^[21]		mab human	glacagon receptor (GCGRI)	dat	betes	Chaganat (C)	Mycograb sc	v human	Hopeo	invasive Condute infection	Girnsternab (2)	_	nab human	COED		theumatoid arthritis
Berlinstownsb ²⁷⁸		mab	human	component louisocidin	,	4	_		Canno fa		CR6261		meb human	Influence A	into	octious disease/efluenza A	Elderunb/S	ma	human	interferon gamma- induced peoples	Crofte's disease, alcorative colitis				carbonic		
Bernotimas/25	Xionis	mab	human	B.IA	colcerctal cancer	Conference revisioning [12]		mab humanized	glycoform of	cancers				terragglutinin						reputsive guidance	spinal cord injury and multiple	Cirentosmab(26)	Rescarex	mab chimeric	anhydrane 9	(CA-	dear cell renal cell carcinoma ^[53]
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Bettinunet ^{ES}			turas	CCL11 (extrain-1)	severe allergic discoders	CaptacizunabPff	Cabevi	SEAD NUMBERONS		purpura, thrombosis	Deceturaryab(**)		mab humanized	CD40		matologic cancers	Elgenterno[60]	n n	human	ERBRO (HERO)	CARCEL		Simponi	nab human			therapatoid arthetis, escalatio
	_		-	Carcinoembryonic		Capromability	Prostascint	mab mouse	Citutamate carbonypeptidase Y	prostate cancer (detection)	Dackzwnab ^{DM}		mab humanized	CDS5 (a chain of E-2 receptor)	pres	prevention of organ transplant rejections, multiple scherosis cancer etc.	Dokumab	Emplicit m	humanized	SLAMF7 Y	multiple myeloma	Golmunab ⁽⁴⁵⁾	amp08	- Janes	TNF-o	- '	arthitis, ankylosing spondylitis
Besilesomab PNI	Scellmun	mab	mouse	ontigen (CEA)- mistrel antigen	inflammatory lesions and metastases (detection)						Dalotucumab		mab humanicad	IGE-1 receptor	can		Elsimorrab	n n	mouse	11-6	2	Gomilaimab		mab chimeric	CD23 (NE receptor)		allergic authma
			hamanian d		metastatic cancer, retinopathy of	Carturooh [14]		mab human	MCP-1	oncology/mmune indications				(CD(221) CD154 (CD40L)	- 1		Emacturamab ⁽⁵⁾	n.	humanized	CSF1R	cancer	Cosuranomab		mab humanicad	tau protein		progressive supranuclear paley
Sevectromab(12)	Avastin		humanized	YESFA Y	prematurity	Casoluximab(PS)		mab chimeric	endoglin	angiosarcoma	Depinolizameb pago#5		mab humaniced mab human	0000 V		ficie roveioma	Crepatores (19)	Garefast m	human	interferon gamma Y	hemophagocytic lymphohistocytosis	Gusekumab	Tremtys	mab human	6.23	Y	pscrissis
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Bickonab ⁽²⁸⁾	FibilScint			fibrin II, beta chain	tronbormbolism (dagnosis)	c0795-doxorabicis		mab humanized	Lewis-Yantigen	CARCEL	Demonstration		mab humanized	DLI4	can		Enricomes ^{2/8}	Hernitera m	humanized	activated F9, F10 Y	baerophila A	Dalzwast ²⁰	Trogerzo	mab humaniced	004	Y	HIV infection
Binegunet ^{DS}			human	ACVR09	myostatin inhibitor	immunocorpagate	_	Intrastice	same anger	provention of capan transplant	Denintrounab matodotni ²³	_	map humanized	CD19	can		Executanal vedotal ²		berran	ANL	CARON	19000		7 human	PD-1		squamous cell non-small cell lung cancer
Bimekizumab ⁽⁹⁾	_	mab	humanized	ii. 17A and ii. 17F	ankylosing spondylitis, psoriasis	Cedelzumab ^{DS}		mab humanized	CD4	resections, treatment of						ostecoorosis, bone metastases	Enevelopment		humanized	TWEAK receptor	cancer etc.	Enhancement Secretors	Zevalin	nab nouse	COSS	v	concer con-Hodekin's lymphoma
Difaminsb		mab	chimeric	serum amyloid A protein	arryloidosis		_			cultureous staumous cell	Denosumabl ^{MS} Pro		mab human	RANKI Y	etc		Enfortumab vedotin	Padoev m	human	necte-4 Y	urothelial cancer	torounab rations	coradi	neb human	VEGER 1		cancer etc.
Diversorab ⁽¹⁹⁾		mab	humanized	CD44 v6	squamous cell carcinoma	Complinat PS	Libtayo	mab human	PDCD1 Y	cascinoma equamous ces	Depahakizumab mafodotisi ⁽¹⁴⁾		mab chimeric/humanize	d EGFR		oblastoma	Entimorrato pegoliffili	n n	mouse	ICAM-1 (CD54)	2		Creation	mab humanized	debastes		reversal of anticoagulant effects of
Dieselumab ⁽¹⁾		mab	human	CD40	organ transplant rejection	Cerguturumab amunaleukin ^[10]		mab humanized	112	CARON	Deriotaximab biotin		mab chimeric	historia complex		surrent glioblastoms multiforme	Enobiliurumabil/H	n	humanized	C0276	cancer	idaractramab ⁽⁴⁾	r sanding			- '	6sbigatran
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Biontovetrosb ⁽²⁾			velocity	com	Inukemia (ALL) (CD19+)	Centralization pegalitini	Const.				Decamicsmabl/H	n Manusia	mab humanized	serum amyloid P component	7		Enoticumat/P8	ns.	human	00.4	?	tgovornab	Indimacis- 125	F(ab1)2 mouse	CA-125		ovarian cancer (diagnosis)
Biontavetrosb ⁽²⁾	picebiss	-		SOST		Cebelmabilis		mab human	PD-1	CRACCE	Diretorimab	Unitorin	mab chimoric	802 ganglioside With	odawn nes	unblastoma	Ensiturinab	rs.	chimeric	MUCSAC	cancer	findaturumab vedotia ^[22]		mab humanized	C0798		cancer
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Bocockwast ^{OS} Beschungt ^{OS}	-		humanized	PCSK9	dyslpidemia Crohn's disease				(DGFR)	head and neck cancer	Diridevemeb		mab human	bernagglutnin	Influenza A	benza A	Epratucumab	mal	humanized	C088	cancer, systemic lapus erothernalcoso (SUE)	4	_		mecrophage	_	and pancreatic tumor
Contraction of	-	-480	- Committee	· ·	Hodgiin's lymphoma	Cibisatamab ⁽⁵⁾		mab humanized	CEACAM5	CARCOF	Domagrozumab#1		mab humanized	00F-8	Dec	cheese muscular dystrophy	Eptinezumab(7)5	Vest m	humanized	calcitonin gene-		malumat/S		mab human	rigistion inhibitory fact	_	cancer
Reenhailmab wedotin@9				CD30 (TNPHSPR) Y SNSP NTD		Climburumab ^{DM}	mapes	7 humanized	RORI	chronic lymphocytic laukamia	Dorlmomab antox ^{N1}		Flab1 ₂ mouse	2	7		Ephrezuranen	vyepa n	ramanzea	related peptide	migraine				(MF)		
	Adcentris	mab	chimeric		anapiastic large-cell lymphoma	Citatuzumab bogatosi ^(M) Citatuzumab ^(M)	-	Fab humanized	EpCAM	ovarian cancer and other solid tumors	Dostarimab ^{NE}		mab humanized	PCDP1	can		Exercipabilitis	Almovig m	ab human	calcitonin gene- related peptide receptor (CORP)	migraine	(macrolimatel [®])		mab humanized	melanoma cell adhesion molecule	d Gode	
								mab barran	IGF-1 receptor	sold tumors	Droziturnob		mab human	086		ncer etc.						- majorana and d			(MCAM)		'
DrinkleumabPS		mab	human	£-12, £-23	psodasis, rheumaloid arthritis, effaminators bowel diseases.				(00221)		08-8201		? humanized	HER2	gast	stric or gastroesophageal ctice adenocarcinoma	Entrumabl ⁴⁵	F	t) ₂ humanized	(1002 (0010)	hearl affack, stroke, traumatic shock	Imcironab	Myoscint	mab mouse	cardiac myos		cardiac imaging
					multiple sclerosis	Clazakizumab(P2)		mab humanized	Infledoukin 6 (E-6)	rheematoid arthritis	Outlgotscursat 258		mab humanized	ERBBO (HERB)	test	dicular cancer	Erlamaxomab@5	Resomun Stur	nct ratinouse hybrid	HERSheu, COS Y	breast cancer etc.	Imgeturumeb178		mab humanized	Epidermal gro factor receptor		concer
Brodatumab(ISI	Siliq	mab	human	L-17 Y	Plaque psodasis	Clesolximab@9		mab chimeric	CD4	rheematoid arthritis	Dupliumat/PS	Decement	meb human	6-4flo Y		pic dematits, asthma, nasal	Etanacipumab	Abeato m	burnanized	integrin o ₄ B ₂ Y	melanoma, prostate cancer,				(EGFF0)		
Brotucizumab ^[29]	Beovu	scPv	humanized	vescular endothelial growth factor A (VEGFA)	wet age-related macular degeneration	Chroticoneb totsavday(2)	hPAM4-Cide		MUC1	pancreatic cancer					poly		Etolinub ²⁵	-	humanized	nor	ovarian cancer etc.	Indecumeb(Pf)		mab human	selectin P		cordiovascular disease
	_	-				Codniturumabi ⁴		mab humanized	glypican 3	CARON	Dervetemeb ^(A)		mab human	PO-L1 Y		ncer cell malignancies	Etglimab(1)	_		Integrin (b)	inflammatory bowel disease	indetunimeb sevtensime ^(CC)		mab chimeric	80C1		cancer
Bootictusumab ²⁵	_		humanized	Notch 1	CHROIT	Coletuzumab pelidotin ^[2]	_	mab humanized	PTIC	CRECK	Dunighamab Dayorkasiyamab ⁽²⁻⁴⁾		mab human scfy chimeric/humanica		Gan-		Evineoureb	n	humanized human	angiopoietin 3	dysloidemia	indusatumab vedotin ^[22]		mab burson	BUCY2C		cancer
Burosumab ^[M]	Crysvita	mab	human	FGF 23 Y	X-linked hypophosphalemia	Coltumb savtersine ⁽⁵⁾	_	mab chimeric	CD19	CARCET	Devortainmab(5)		serv emerchanance	a constade	can	NOM .	Caseman		nerel	argrepowers 3	90000000	nebilcurat/PB	Uplens	mab humanized	CD19	٧	cancer, systemic sclerosis,

Ways antibodies are used as drugs

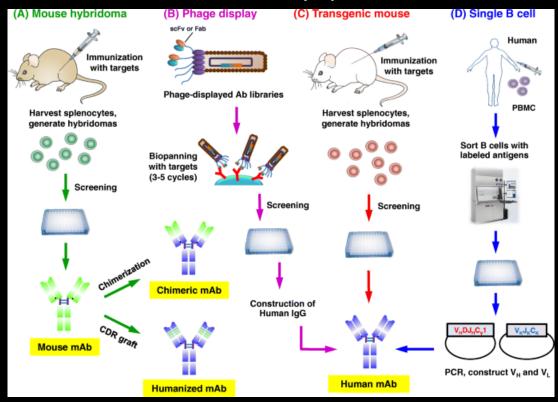


https://en.wikipedia.org/wiki/Monoclonal_antibody

Antibody drug discovery process



Deeper view of discovery process...



https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z

The Lilly COVID antibody drug

Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting

September 16, 2020



Primary endpoint of viral load change from baseline at day 11 was met for one of three doses;
 consistent effects of viral reduction seen at earlier time points



- Rate of hospitalizations and ER visits was 1.7 percent (5/302) for LY-CoV555 versus 6 percent (9/150) for placebo--a 72 percent risk reduction in this limited population

The Regeneron antibody drug

REGENERON

◀ Back

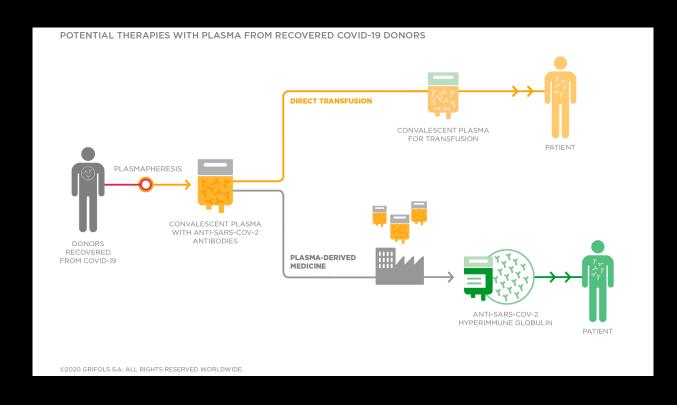


September 29, 2020 at 4:01 PM EDT

REGENERON'S REGN-COV2 ANTIBODY COCKTAIL REDUCED VIRAL LEVELS AND IMPROVED SYMPTOMS IN NON-HOSPITALIZED COVID-19 PATIENTS

called seronegative group. The monoclonal cocktail showed little effect on people who already had antibodies against the virus. But it appeared to help the seronegative patients, powerfully reducing the amount of virus found in nasopharyngeal swabs and alleviating symptoms more quickly. "These are provocative results," says Myron Cohen

An alternative to single antibody drugs



Serum transfer results

Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study

Hassan Abolghasemi, ^a Peyman Eshghi, ^b Abdol Majid Cheraghali, ^{c,*} Abbas Ali Imani Fooladi, ^a
Farzaneh Bolouki Moghaddam, ^d Sina Imanizadeh, ^d Matin Moeini Maleki, ^d Mohammad Ranjkesh, ^d
Mohammad Rezapour, ^d Ali Bahramifar, ^e Behzad Einollahi, ^f Mohammad Javad Hosseini, ^g Nematollah Joneidi Jafari, ^h
Mohamad Nikpouraghdam, ⁱ Nariman Sadri, ^j Mokhtar Tazik, ^j Shanaz Sali, ^k Shamsi Okati, ^l Elham Askari, ^m
Payam Tabarsi, ^m Jafar Aslani, ⁿ Ehsan Sharifipour, ^o Mohammad Hossein Jarahzadeh, ^p Nastaran Khodakarim, ^q
Mahmood Salesi, ⁿ Ramezan Jafari, ⁿ and Samira Shahverdi^r

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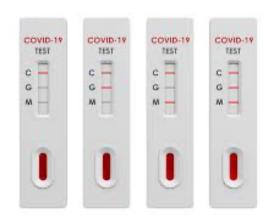
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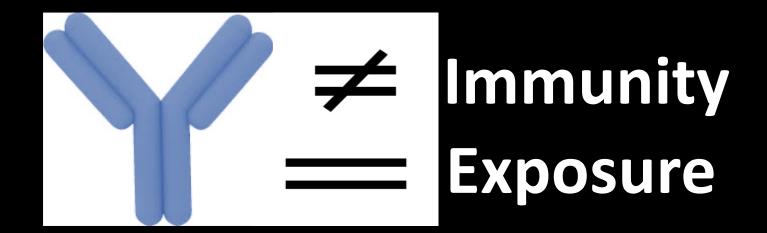
✓

Since Dec. 2019 the new coronavirus (SARS-CoV-2) has infected millions and claimed life of several hundred thousand worldwide. However, so far no approved vaccine or drug therapy is available for treatment of virus infection. Convalescent plasma has been considered a potential modality for COVID-19 infection. One hundred eighty-nine COVID-19 positive patients including 115 patients in plasma therapy group and 74 patients in control group, registered in the hospitals with confirmed COVID-19 infection, entered this multi-center clinical study. Comparison of outcomes including all-cause mortality, total hospitalization days and patients' need for intubation between the two patient groups shows that total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20 % in control group. This clinical study provides strong evidence to support the efficacy of convalescent plasma therapy in COVID-19 patients and recommends this treatment for management of these patients. Clinical efficacy, immediate availability and potential cost effectiveness could be considered as main advantages of convalescent plasma therapy.



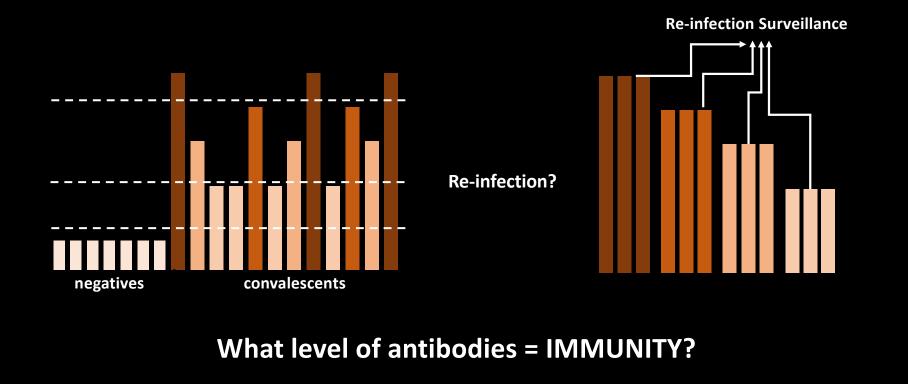
What does a SARS-CoV-2 antibody test result mean?

What does a positive antibody test mean?

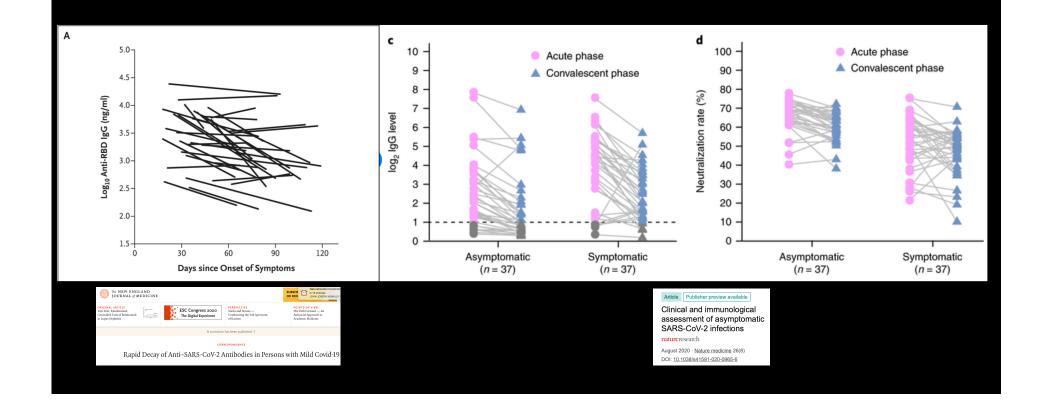


Sero-Epidemiological studies are needed to establish a threshold of immunity.

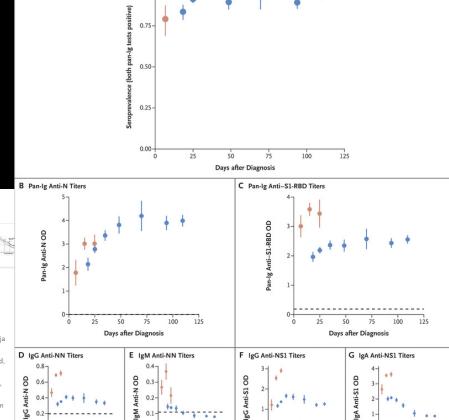
Defining a protective titer...



Evidence of waning immunity???



Stability of humoral immune responses over time



0 25 50 75 100 125

Days after Diagnosis

25 50 75 100 125

25 50 75 100 125

Days after Diagnosis

A Seroprevalence among SARS-CoV-2 Infected Persons

0 25 50 75 100 125

Days after Diagnosis

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First case of SARS-CoV-2 re-infection

NEWS

HEALTH & MEDICINE

A man in Hong Kong is the first confirmed case of coronavirus reinfection

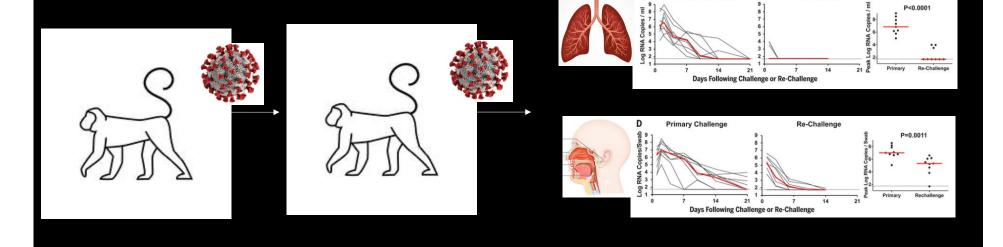
A 33-year-old got sick during his first round with the virus, but wasn't ill the second time

The first time the man was infected, he had a fever, cough, sore throat and headache for three days. He tested positive for the coronavirus on March 26 and was admitted to a hospital in Hong Kong three days later. At that point his symptoms had gone away. He was discharged on April 14 after he tested negative for the virus twice. But the man tested positive again more than four months later on August 15, when officials screened him upon returning to the Hong Kong airport from Spain. The second time, he never showed any indication of being sick — a sign that his immune system kicked in enough to protect him from the disease because he remained asymptomatic but not enough to prevent reinfection.

SARS-CoV-2 infection protects against rechallenge in

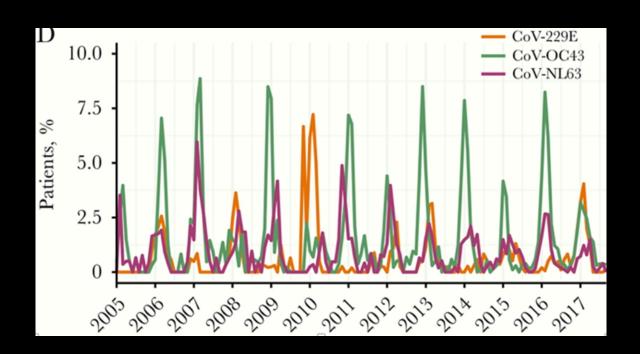
rhesus macaques

Dabishek Chandrashekar^{1,*}, Dinyan Liu^{1,*}, Amanda J. Martinot^{1,2,*}, Katherine McMahan^{1,*}, Noe B. Mercado^{1,*}, Lauren Peter^{1,*}, Lisa H. Tostanoski^{1,*}, Dinyou Yu^{1,*}, Zoltan Maliga³, Michael Nekorchuk⁴, Kathleen Busman-Sahay⁴, Margaret Terry⁴, Linda M. Wrijil², Sarah Ducat², David R. Martinez⁵, Caroline Atyeo^{3,6}, Stephanie Fischinger⁶, John S. Burke⁶, Matthew D. Slein⁶, Laurent Pessaint⁷, Anthony Cook⁷, Matthew D. Slein⁶, Laurent Pessaint⁷, Anthony Cook⁷, Brad Finneyfrock⁷, Anthony Cook⁷, Brad Finneyfrock⁷, Renita Brown⁷, Elyse Teow⁷, Jason Velasco⁷, Roland Zahn⁸, Frank Wegmann⁸, Peter Abbink¹, Esther A. Bondzie¹, Gabriel Dagotto^{1,3}, Makda S. Gebre^{1,3}, Xuan He¹, Catherine Jacob-Dolan^{1,3}, Nicole Kordana¹, Zhenfeng Li¹, Michelle A. Lifton¹, Shant H. Mahrokhian¹, Lori F. Maxfield¹, Ramya Nityanandam¹, Joseph P. Nkolola¹, Aaron G. Schmidt^{6,9}, Andrew D. Miller¹⁰, Ralph S. Baric⁵, Galit Alter^{6,9}, Peter K. Sorger³, Jacob D. Estes⁴, Hanne Andersen⁷, Mark G. Lewis⁷, Dan H. Barouch^{1,6,9,†}

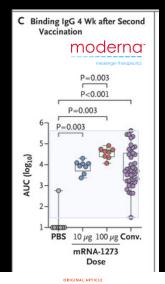


Primary Challenge

Does Coronavirus-specific immunity exist?



Vaccine Immunity is widely different than Natural Immunity



Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates

Kizzmekia S. Corbett, Ph.D., Barbara Flynn, M.S., Kathryn E. Foulds, Ph.D., Joseph R. Francica, Ph.D., Seyhan Boyoglu-Barnum, Ph.D., Anne P. Werner B.S., Britta Flach, Ph.D., Sarah O'Connell, M.S., Kevin W. Bock, M.B., Mahnaz Minai, M.S., Bianca M. Nagata, M.S., Hanne Andersen, Ph.D., <u>et al.</u>

