REIMAGINING

antibody medicines

Unleashing the Power of Valency:

A broad coverage, *Receptor Trapping* mechanism realized by the IgM platform for the prevention and treatment of infectious diseases

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San Diego

Forward-looking statements

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Global leaders in the development of IgM antibodies

Oncology

Autoimmunity and Inflammation

Infectious Diseases

IGM Biosciences Overview

Global leaders in engineering and manufacturing IgM antibodies

- IgM antibodies have multiple unique structural attributes that provide advantages over traditional IgG antibodies

Extending our global leadership in IgM antibodies

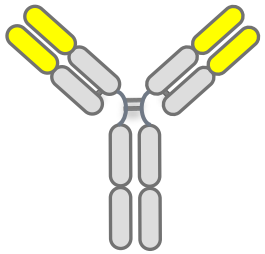
- Two clinical programs, imvotamab (CD20 x CD3) and IGM-8444 (DR5), including ongoing Phase 2 randomized studies (imvotamab in DLBCL/FL)
- Two additional programs, IGM-7354 (IL-15 x PD-L1) and IGM-2644 (CD38 x CD3) with IND submissions planned for 2022
- Partnership with Sanofi to discover and develop agonists against three oncology targets and three immunology/inflammation targets with potential $6B+ in preclinical, clinical, regulatory and commercial milestone payments

World-class team of research, manufacturing and clinical scientists

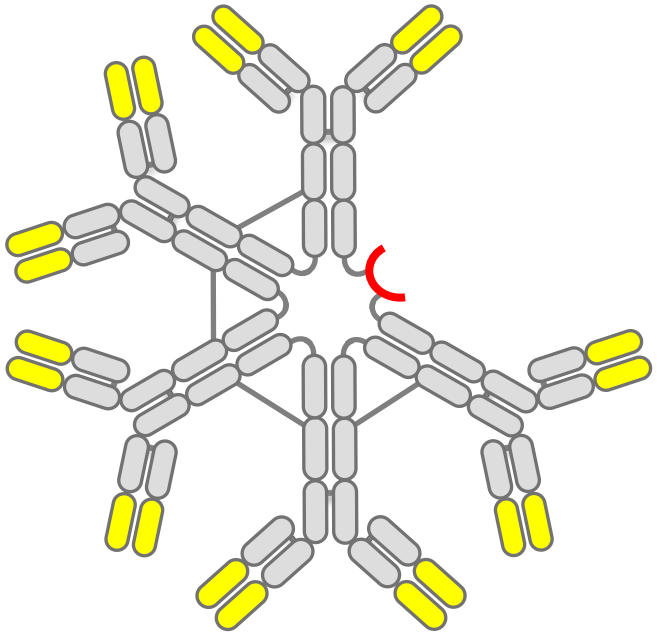
Cash and investments of $469.1 million (as of September 30, 2022)

IgM antibodies have unique structural attributes compared to IgG antibodies

Additional binding sites lead to greatly superior total binding power (avidity)



IgG



IgM

LEGEND | Target binding domains | Constant domains | Joining chain (J chain)

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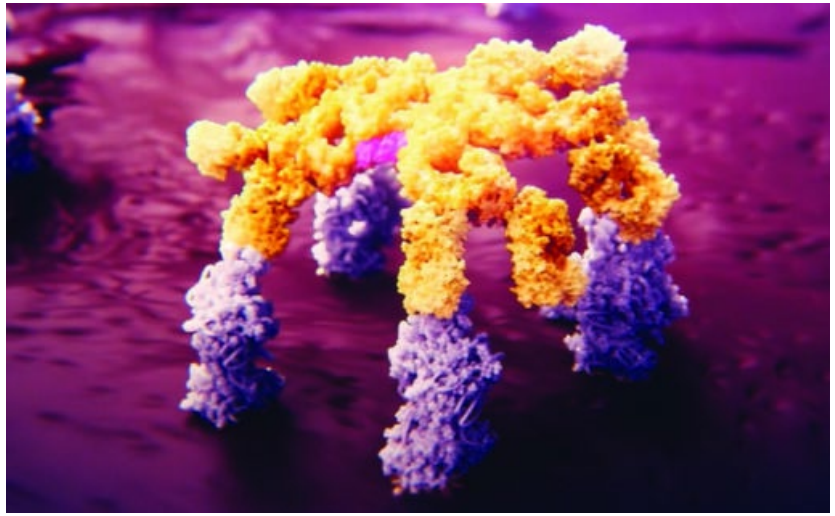
Properties of IgM Antibodies

- Largest naturally occurring antibody (~1000 kDa)
- First line of defense upon pathogen infection
- Secreted from plasma cells as pentamer or hexamer
- Strong binding to difficult targets, for example:
  - Tumor associated antigens
  - Antigens expressed at low level
  - Viral antigens
- Cross-linking targets to enhance signaling
- Stronger complement fixation than IgGs



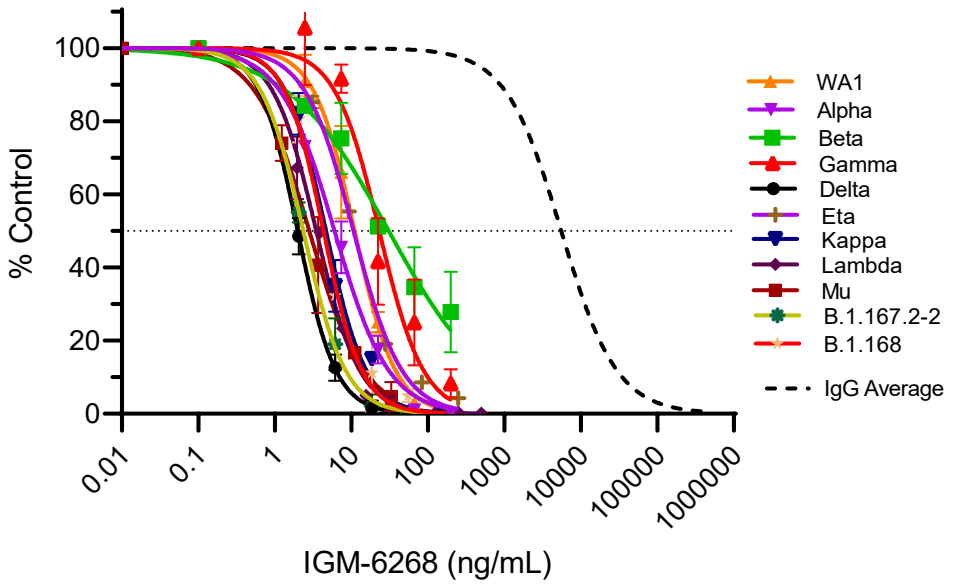
The polyvalency of IgM molecules gives them high-avidity binding to their targets

Traditional Monoclonal Antibody Approach: Our Initial Strategy for Leveraging Polyvalency to Address SARS-CoV-2

IGM-6268 is an engineered monoclonal IgM antibody developed in collaboration with UT/UTMB that targets the RBD of the SARS-CoV-2 Spike Protein

IGM-6268 can be viewed as a POC molecule for IgM-based therapeutics targeting respiratory viruses via intranasal delivery

- Significantly robust neutralization of SARS-CoV-2 in mouse models
- Robust *in vitro* neutralization of variants Alpha, Beta, Gamma and Delta
- Robust *in vitro* neutralization of antibody escape mutants, including those for the EUA-approved IgGs
- Highly active for prophylaxis and treatment in mouse models when administered intranasally
- Well tolerated during Phase 1 study in healthy volunteers



Nasal delivery of an IgM offers broad protection from SARS-CoV-2 variants, Nature, 2021, 595, 718-723

Traditional Monoclonal Antibody Approaches Have Demonstrated Significant Limitations for Durably Addressing SARS-CoV-2

- SARS-CoV-2 continues to evolve and evade immune responses
- Bebtelovimab demonstrates diminished efficacy against BA.2.75, a variant-of-concern lineage being monitored

Table 1. IC50s of ten therapeutic monoclonal antibodies against BA.2.75. (ng/mL)

	B.1.1	BA.2	BA.4/5	BA.2.75
Adintrevimab	6.3 ± 1.7	> 2750	> 2750	> 2750
Bamlanivimab	6.7 ± 1.1	> 4725	> 4725	> 4725
Bebtelovimab	2.4 ± 0.9	1.7 ± 0.8	1.3 ± 0.3	34 ± 6.9 *†
Casirivimab	3.4 ± 1.2	> 5042	> 5042	2303 ± 2570
Cilgavimab	14 ± 1.7	21 ± 7.9	305 ± 127	479 ± 154 *
Etesevimab	12 ± 1.6	> 4600	> 4600	> 4600
Imdevimab	8.0 ± 3.1	> 5000	> 5000	> 5000
Regdanvimab	1.0 ± 0.4	> 4025	> 4025	42 ± 14 *†
Sotrovimab	47 ± 50	1213 ± 224	1149 ± 159	240 ± 56 *†
Tixagevimab	1.5 ± 0.6	3815 ± 1032	> 4375	45 ± 8.2 *†
Ronapreve (casirivimab+imdevimab)	3.9 ± 2.3	> 5000	> 5000	> 5000
Evusheld (cilgavimab+tixagevimab)	4.7 ± 1.1	42 ± 17	586 ± 193	113 ± 31 *
Etesevimab+bamlanivimab	8.3 ± 1.0	> 4600	> 4600	> 4600

https://doi.org/10.1101/2022.07.14.500041

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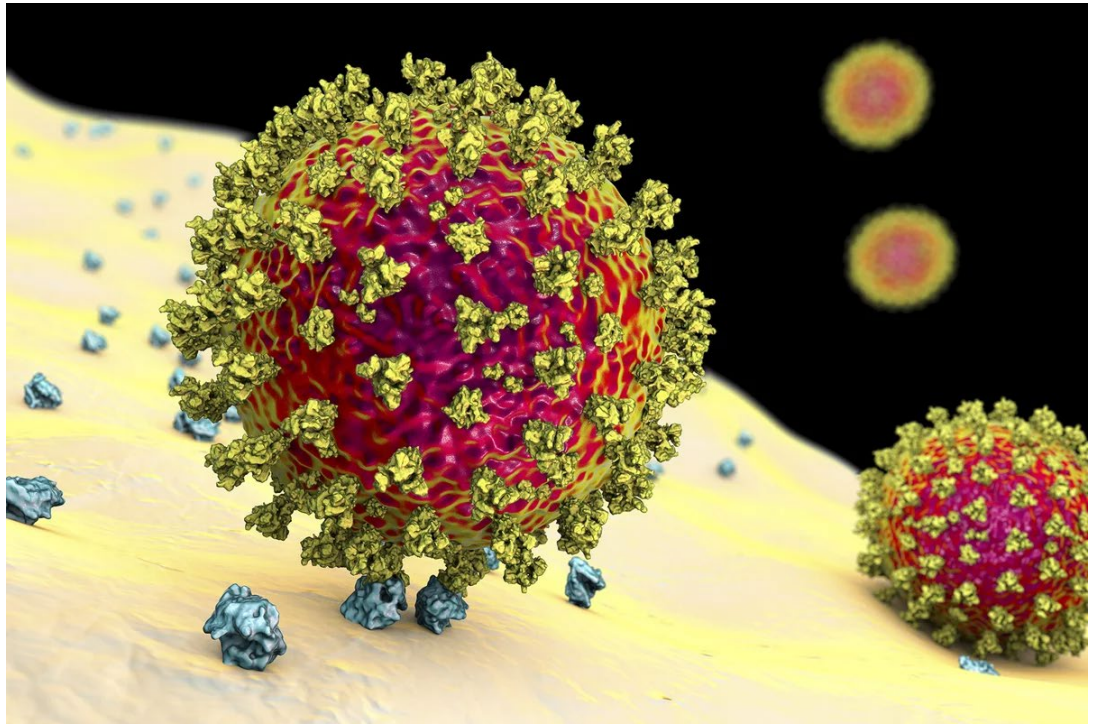
Receptor Trapping Approach: Our Refined Strategy for Unleashing the Power of Valency to Address SARS Family Viruses



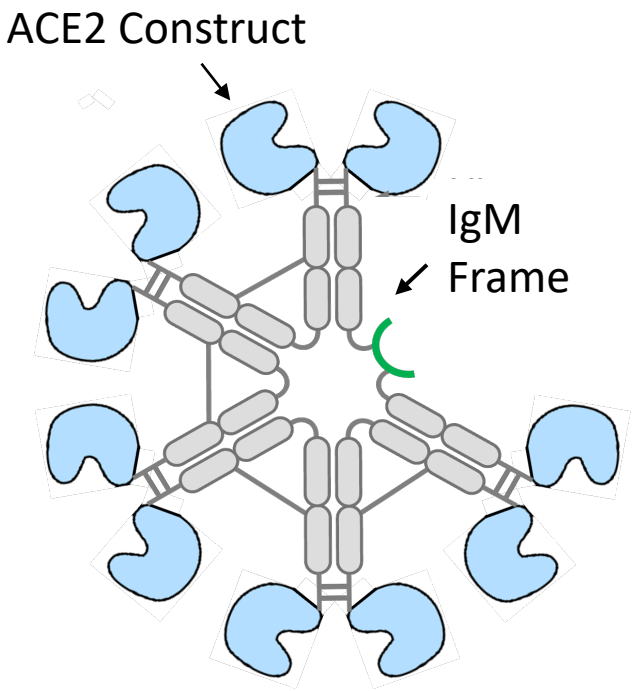
Kateryna Kon/Science Photo Library via Getty Image

- All viruses need to bind to specific host cell receptors to initiate infection
  - It is unlikely that viruses can mutate to escape their specific receptors
- Soluble receptor ACE2 (APN01) can neutralize SARS-CoV-2 VOCs*
- Clinical IV dosing of rACE2 is well tolerated #
- **HOWEVER, weak interactions between receptor and viruses may limit the therapeutic efficacy of soluble receptors**

** Clinical grade ACE2 as a universal agent to block SARS-CoV-2 variants. EMBO Molecular Medicine, 2022, 14: e15230*

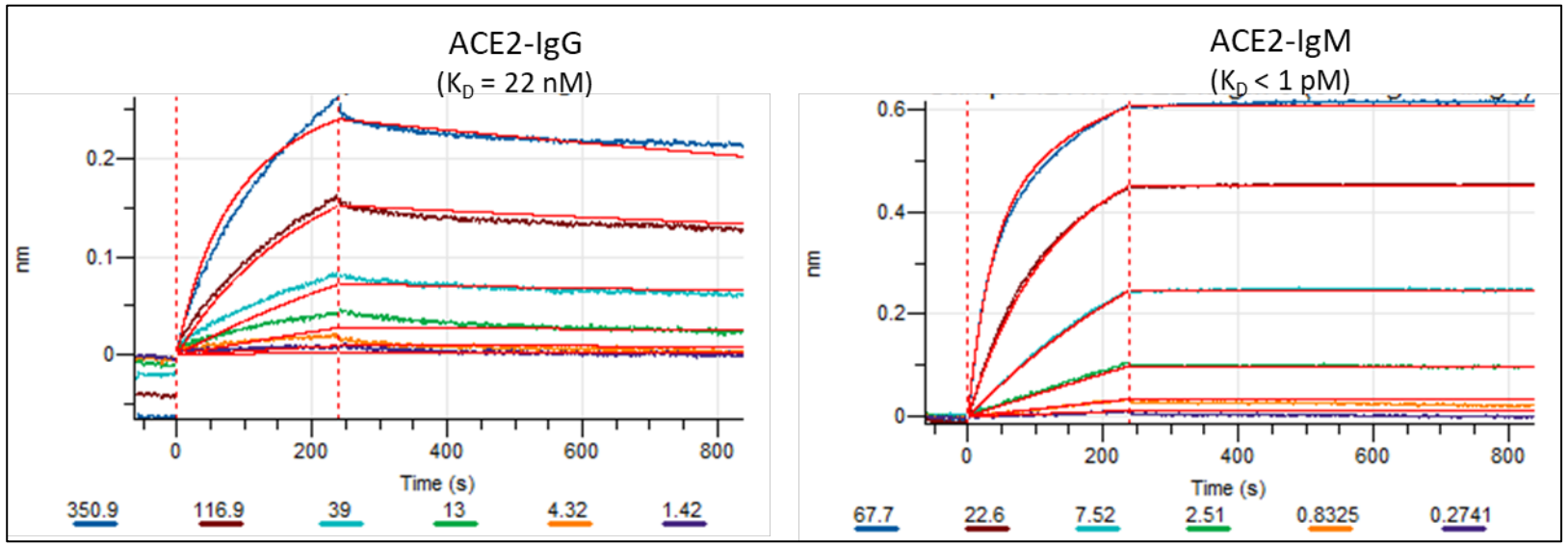
 # A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Critical Care, 2017, 21:234

ACE2-IgM Fusion Protein: A Molecule Designed to Enable Highly Efficient Receptor Trapping of SARS Family Viruses

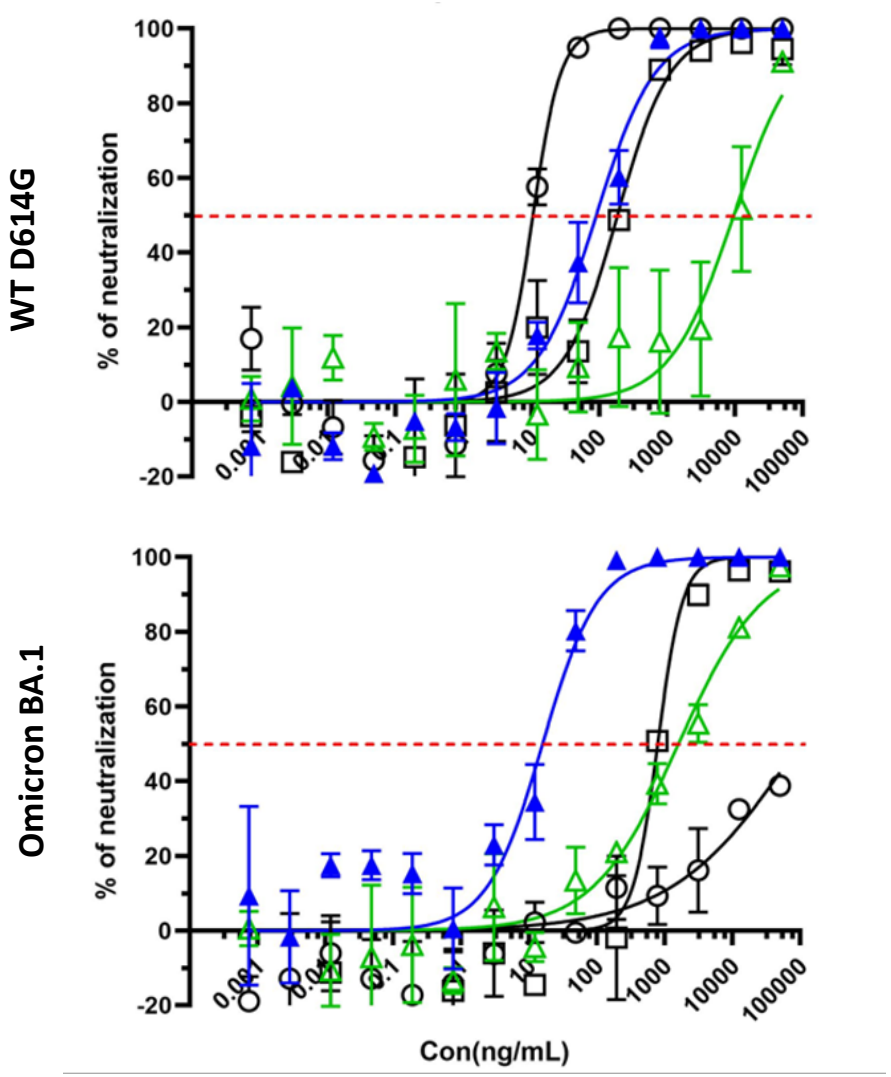


ACE2-IgM is a recombinant fusion protein designed for receptor trapping SARS family viruses. *Ten copies of the monomeric human angiotensin converting enzyme 2 (ACE2) soluble domain, the cellular receptor for SARS viruses, are fused to the human IgM Fc frame via engineered linkers.*

ACE2-IgM binds to Omicron RBD with sub-pM avidity



ACE2-IgM Exhibits High *in vitro* Potency Against SARS-CoV-2 Variants (authentic virus)



Neutralization IC50 (ng/mL)

	WT D614G	Omicron BA.1
ACE2-IgM ▲	49	9
ACE2-Fc △	3768	1143
IGM-6268 ○	12	>10,000
S309 IgG □	224	794

ACE2-IgM exhibits enhanced potency against live Omicron virus, while IGM-6268 and S309 (Sotrovimab) showed significantly reduced potency

ACE2-IgM Exhibits Broad *in vitro* Neutralization Coverage with High Potency Against SARS-Family Viruses

Pseudovirus neutralization IC50 (ng/mL)

Pseudovirus	ACE2-IgG	ACE2-IgM
Wuhan-Hu-1 D614G	1526.0	5.0
Alpha (B.1.1.7)	132.0	1.1
Beta (B.1.351)	506.4	0.8
Gamma (P.1)	260.8	1.2
Delta (B.1.617.2)	262.4	2.1
Omicron BA.1 (B.1.1.529.1)	852.3	2.5
Omicron BA.2	356.1	0.9
Omicron BA.2.12.1	563.6	5.2
Omicron BA.2.75	84.08	7.7
Omicron BA.4/5	299.3	8.3
SARS-CoV-1 Urbani	2370.0	11.9

ACE2-IgM is potent against all known SARS-CoV-2 variants, as well as SARS-CoV-1, in pseudovirus neutralization assays

The Power of Valency

VALENCY

Valency	1	2	3	4		10
	$ACE2_{615}$*	$ACE2m_{615}$-Fc*	$ACE2_{615}$-foldon *	ACE2-Fc-TD#		ACE2-IgM
Avidity K_D (nM)	76.8	22.3	1.15	0.20 – 0.87		<0.001
IC_{50}, Wuhan D614G Pseudovirus Neutralization (nM)	~980	~43	~2.3	0.25		0.0051
IC_{50}, Wuhan D614G Pseudovirus Neutralization (ng/mL)	67700	8400	690	110		5.0
		8-fold	12-fold	6-fold	22-fold	

Total of 10,000-fold increase in potency

*A trimeric human angiotensin-converting enzyme 2 as an anti-SARS-CoV-2 agent. Nature Structural & Molecular Biology, 2021, 28, 202-209

A tetrameric ACE2 protein broadly neutralizes SARS-CoV-2 spike variants of concern with elevated potency. Antiviral Research, 2021, 194, 105147

The innovative approach of utilizing the IgM antibody frame, with 10 ACE2 receptors per molecule, harnesses the power of valency to increase the effective concentration of ACE2 at the viral contact point, greatly increasing potency and enabling therapeutic dosing

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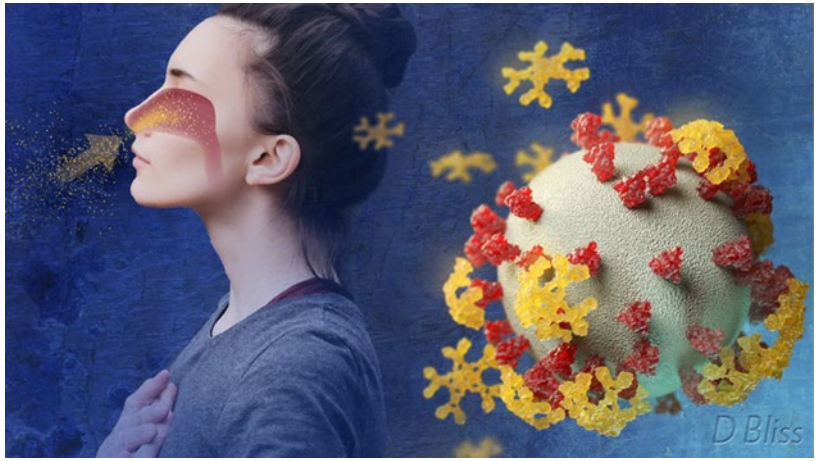
Manufacturability of ACE2-IgM

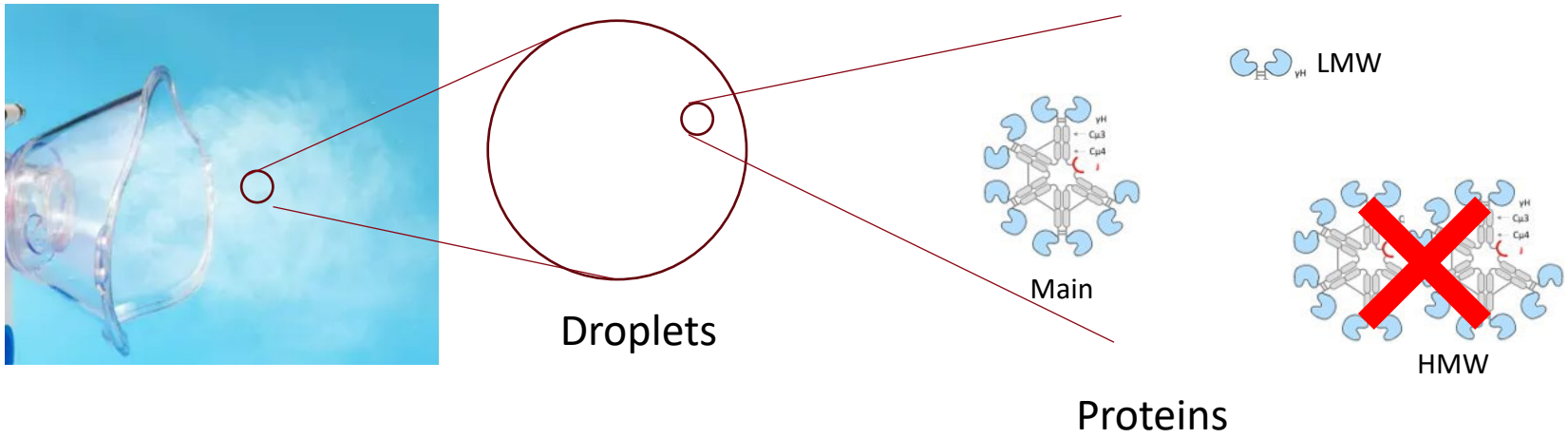
- Expressed at high level in correctly assembled form
- Can be purified to >98% purity
- High degree of homogeneity in the pentameric form
- Suitable for large scale production
- Formulated to be stable outside of ultra-low temperature freezers

ACE2-IgM Can be Self-Administered Without Needles

- ACE2-IgM formulation has been optimized to enable respiratory delivery via aerosolization
- Initial PK modeling supports intranasal delivery with single dose exceeding therapeutic concentrations for 24 hours
- Two different respiratory delivery routes enable options for prophylaxis and therapeutic treatment
  - Delivery depth is determined by aerosolization device
  - Early-stage treatment or prevention using atomization may be possible
  - Therapeutic window to treat acute infection will need to be established



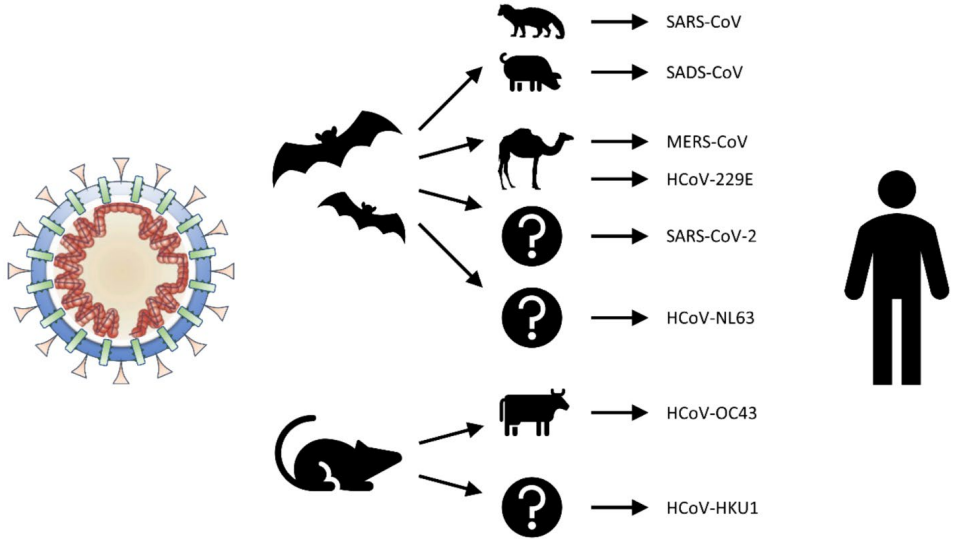
ACE2-IgM Can Be Aerosolized



- Achieved molecular integrity post aerosolization – no shear stress induced aggregation
- Achieved high degree of mass and potency recovery post aerosolization

Emerging Zoonotic Coronavirus Threat

Diverse zoonotic sources makes coronavirus a pandemic threat beyond COVID-19

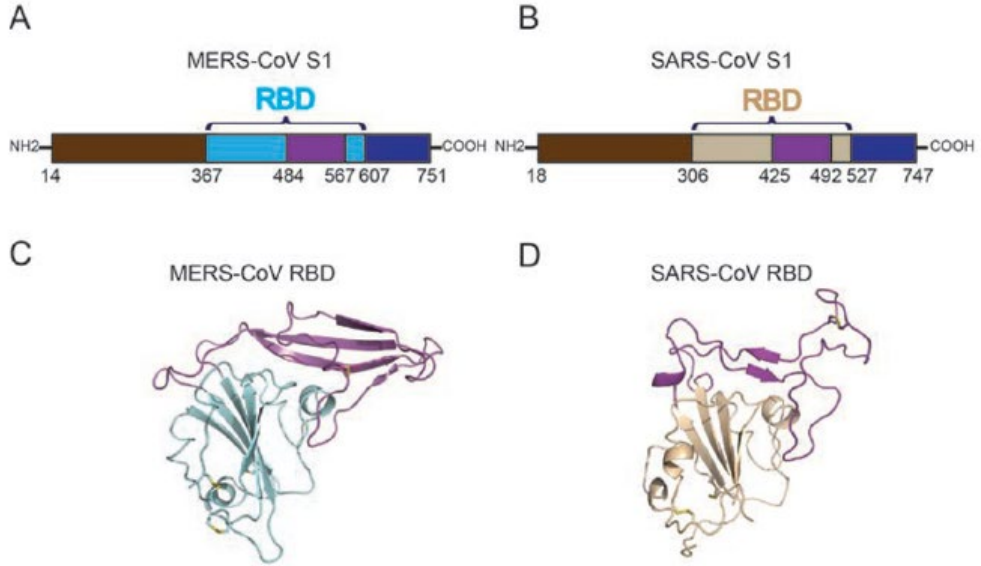


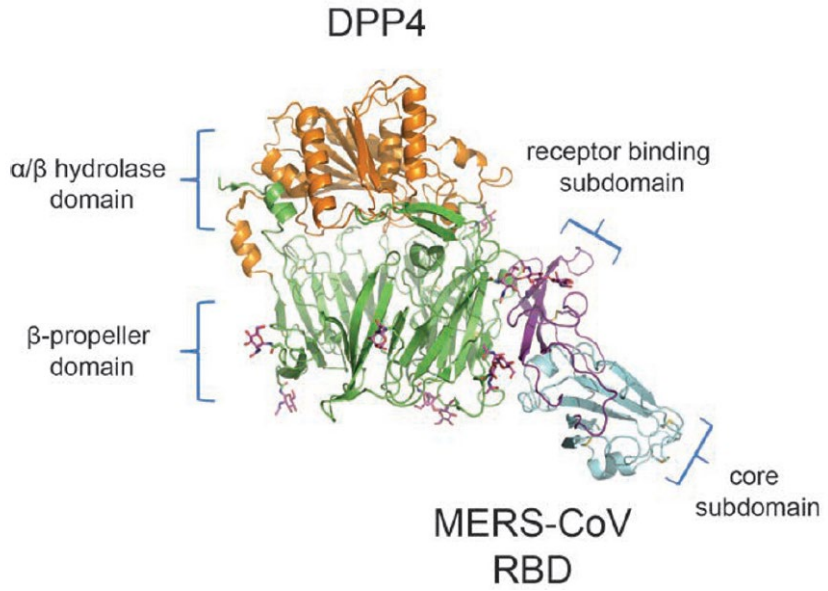
"Innovative approaches are clearly needed to induce ***broad and durable*** protection against coronaviruses known and unknown"

- National Institute of Allergy and Infectious Diseases Director Dr. Anthony Fauci, 26 July 2022

Receptor Trapping May Be Applied to Other Zoonotic Coronavirus Threats

- Most coronaviruses depend on a single receptor for infection
- Although coronavirus spike proteins are prone to accumulate mutations to escape existing immunities, it is unlikely for the spike proteins to adapt to a new host receptor
- Receptor trapping may potentially provide broad and durable protection against other coronaviruses

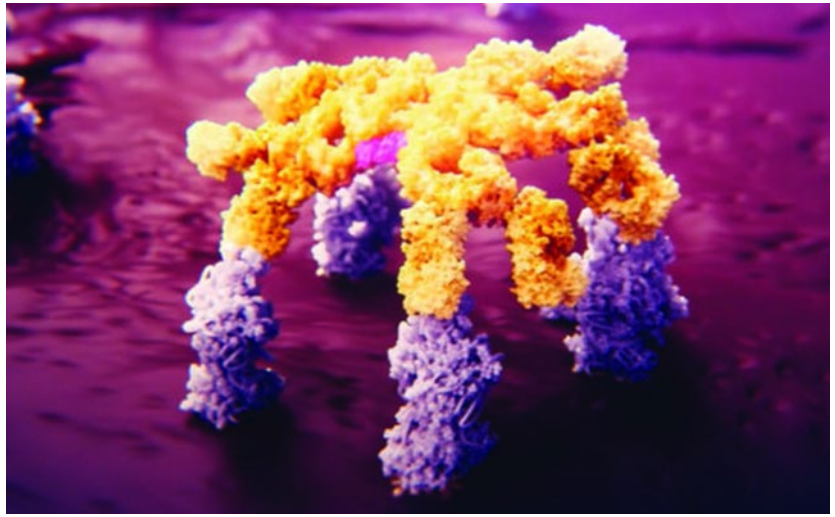




Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4. Cell Research, 2013, 23, 986-993

Summary

- Traditional antibody approach to infectious diseases has significant limitation due to rapid virus evolution
- Receptor trapping mechanism through IgM platform:
  - Overcomes virus evolution and provides broad coverage against virus mutants
  - Increases potency and potentially enables therapeutic dosing
  - May be applied to additional respiratory viruses
- Receptor trapping IgM molecule:
  - Can be expressed and purified, suitable for clinical and commercial development
  - May be self-administered through inhalation, enabling virus neutralization directly at the site of infection



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