A New Approach for Preventing Acute Respiratory Viral Infections in Immunocompromised Individuals

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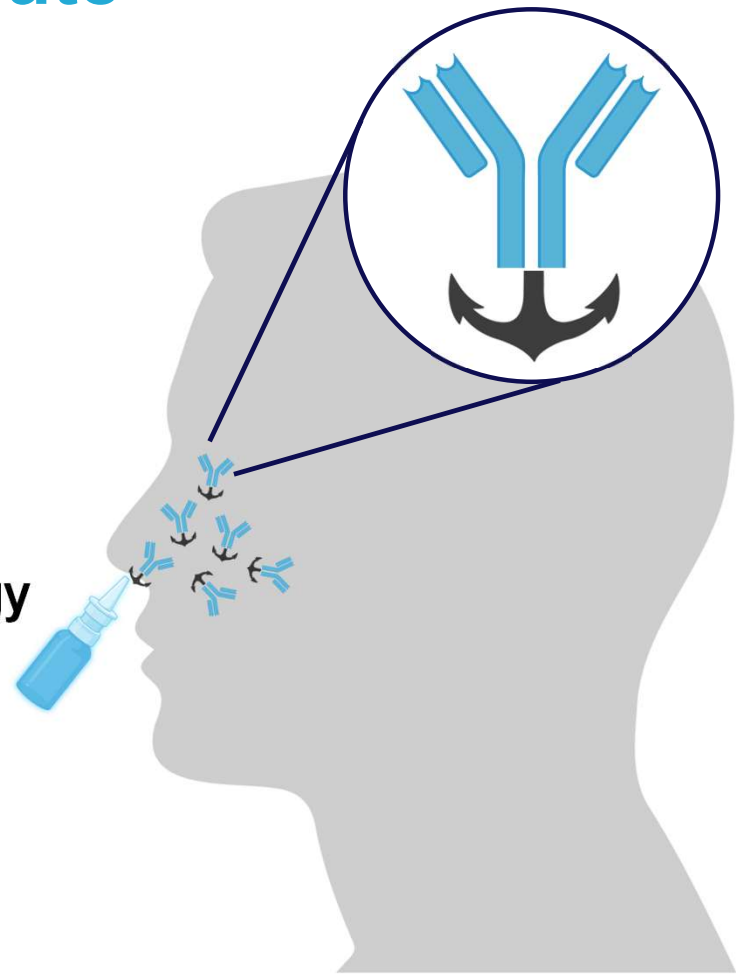


TAVI Forum 11
October 15, 2024

Disclosure

Dr. Warner Greene is a co-founder of InvisiShield Technologies and currently serves as President and Chief Scientific Officer of the company. Dr. Greene was seconded InvisiShield Technologies by the Gladstone Institutes when the company was launched. Dr. Greene currently is salaried by both the company and the Gladstone Institutes and holds equity in InvisiShield Technologies

Intranasal Preventive Biomedicines to Neutralize and Halt Airborne Infections

TAVI Forum 11 Presentation
October 15, 2024

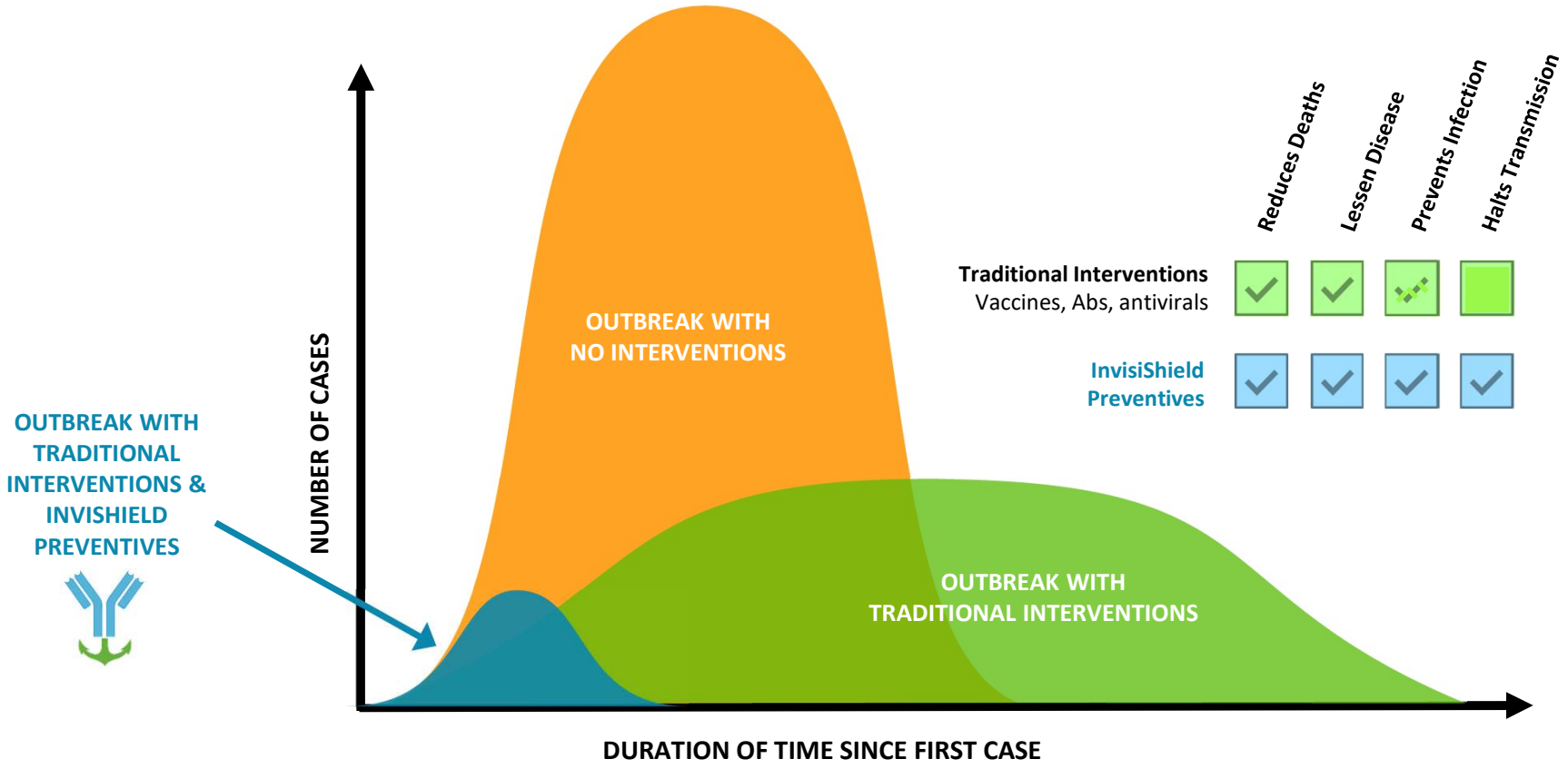
A New Paradigm in Respiratory Virus Prevention

The Respiratory Viral Challenge: Infections Continue as a Leading Cause of Adult and Pediatric Morbidity and Mortality

	SARS-CoV-2	INFLUENZA	RSV
Annual U.S. deaths	75K[1]	21K[1]	10K[1]
Annual U.S. hospitalizations	~450K[1]	~280K[1]	~240K[1]
Vaccine effectiveness: Adults (Year 1 adults >60 for RSV)	 ~48%[1]	 ~40%[1]	 ~81%[3]
Vaccine effectiveness: Immunocompromised SARS-CoV, Flu (Year 2 adults >60 for RSV)	 ~36%[1]	 ~5%[2]	 ~61%[3]
Currently approved / authorized protective antibodies in U.S.	1 (7 previously authorized)	0	2 (None for adults)

1. CDC Estimates
2. Hughes K, et al. Clin Infect Dis. 2021;73(11): e4353-e4360.
3. Ricco, M, et al. Vaccines 2024

Redefining Disease Outbreak Mitigation and Control



INVISISHIELD TECHNOLOGIES

Why prevention is important in the immunocompromised population

Studies have shown that:

- Among people who had either a solid organ transplant or a stem cell transplant, about 65 percent of those who got flu were hospitalized. Clin Infect Dis 2018 Oct 15;67(9):1322-1329
- Risk of death among hospitalized people with COVID-19 was about 1.44 times greater among those who were immunocompromised than those were not. PLoS Med. 2023 Jan; 20(1): e1004086.

Need to respond to an unmet need in a critically vulnerable population—the immunocompromised

- Immune compromised medical conditions include but are not limited to:
  - Active treatment for cancer
  - Receipt of organ transplant
  - Moderate or severe primary immunodeficiency
  - Advanced HIV infection

- Globally, 159M people are immunocompromised and are unlikely to mount strong immune responses to COVID-19 vaccines
- CDC reports: immunocompromised patients are 40% more likely to require ICU admission for COVID and are 87% more likely to die in the hospital

Source:
1. CDC, Special Considerations in People Who Are Immunocompromised (2022) https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised
2. Corey, L., (2021). Immunocompromised People Are Vulnerable To Covid-19. We Owe Them Some Answers. Johns Hopkins University, https://coronavirus.jhu.edu/vaccines/blog/immunocompromised-people-are-vulnerable-to-covid-19-we-owe-them-some-answers
3. CDC, Morbidity and Mortality Weekly Report (MMWR) (July 8, 2022) https://www.cdc.gov/mmwr/volumes/71/wr/mm7127a3.htm

Evusheld was the only authorized COVID-19 preventive on the market, but its efficacy rapidly declined as new immunoevasive variants like XBB.1.5 emerged

- On June 29, 2022, due to increasing viral resistance, FDA recommended doubling the Evusheld dose given every six months to 3 ml of each antibody IM
- Despite declining neutralization, AstraZeneca generated approximately $2B in sales from Evusheld in 2022, validating a significant market for preventives in the immunocompromised population
- **On January 26, 2023, FDA announced that AstraZeneca's Evusheld was no longer authorized due to high level variant resistance**

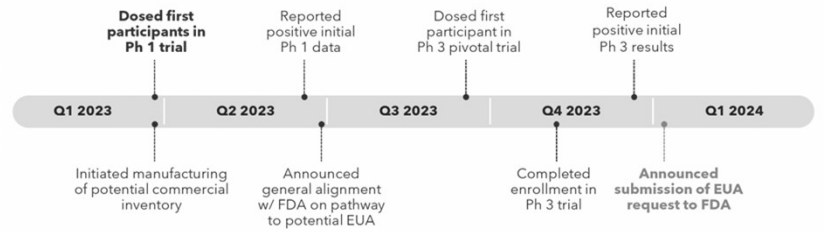
Source:
1. CDC, Variant Proportions, https://covid.cdc.gov/covid-data-tracker/#variant-proportions
2. AstraZeneca, Year-to-date and Q3 2022 Results, https://www.astrazeneca.com/content/dam/az/PDF/2022/Q3/Year-to-date_and_Q3_2022_results_presentation.pdf

FDA's Recent EUA for PEMGARDA Underscores Urgent Need for COVID Preventive Medications for High Risk, Immunocompromised Populations

- Authorized (EUA) for Pre-exposure prophylaxis of COVID-19 in immuno-compromised patients via immunobridging to prior adintrevimab clinical trial [1, 2]
- Intravenous long-acting (3 mos.) IgG1λ injection
- Anaphylaxis observed in 0.6% of patients
- Three-hour IV administration time
- Cost: $5,775/3 mos.
- **Remains susceptible to future variant mutations**

PEMGARDA
(pemivibart) injection

Ph1 to EUA authorization in ~ 12 months



1. Adults and adolescents who have moderate to severe immune compromise due to medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID vaccination.
2. Immunobridging approach to the EVADE study of adintrevimab which included 2582 randomized patients, including 1,480 in the PrEP setting, conducted over a period of 1 year (Invivyd, NCI)

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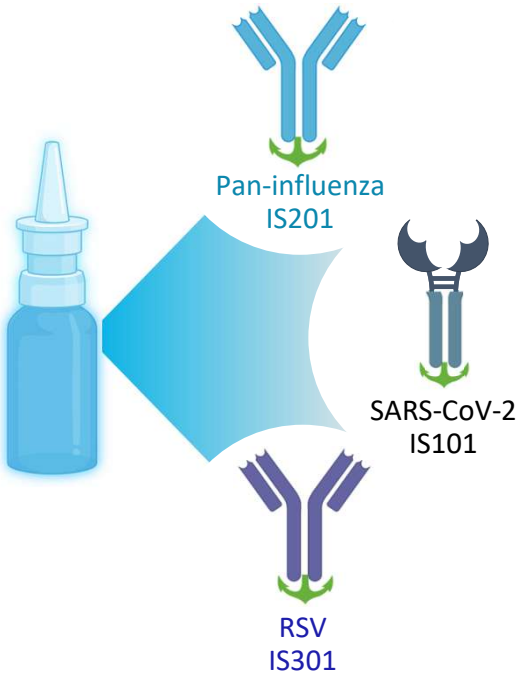
Target Premier Preventive:
All-in-One Single Administration for Influenza, SARS-CoV-2, and RSV



- ✓ In vivo protection established against all three major viral respiratory pathogens
- ✓ Potential to break chains of transmission through treatment of infected individuals—halting of "forward transmission"
- ✓ Favorable potency, absorption, distribution, and safety profile
- ✓ Cost-effective, low-dose, modular manufacturing and formulation

InvisiShield Leadership

Michael P. Smith
CEO
Zogenix, Raptor, Memory Pharma, QLT, Chiron

Warner C. Greene, MD, PhD
Co-Founder, President, and CSO
Founder, Gladstone Institute of Virology & Immunology, Professor of Medicine, UCSF

Cheng Liu, PhD
Co-Founder and Chairman
Eureka Therapeutics, Estrella, Chiron

Jennifer Cook, MBA
Advisor, Strategy
Grail, Roche, Genentech

Jeff Murray, MD, MPH
Advisor, Regulatory
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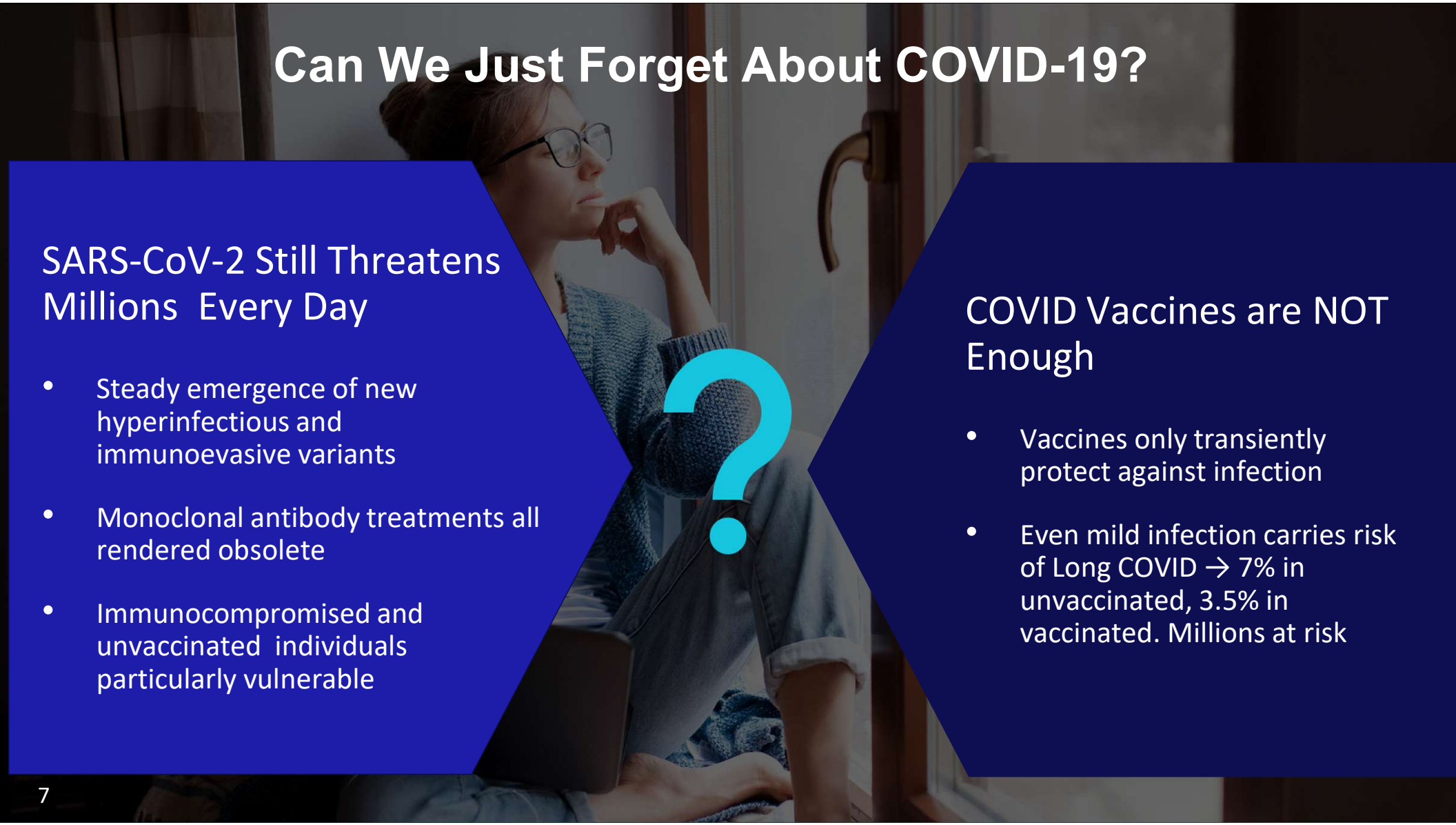
Charles Rice, PhD
Maurice R. and Corinne P. Greenberg Professor, Rockefeller University
2020 Nobel Laureate in Physiology or Medicine

Akiko Iwasaki, PhD
Sterling Professor of Immunobiology and Molecular, Cellular, and Developmental Biology
Yale University

Can We Just Forget About COVID-19?



SARS-CoV-2 Still Threatens Millions Every Day

- Steady emergence of new hyperinfectious and immunoevasive variants
- Monoclonal antibody treatments all rendered obsolete
- Immunocompromised and unvaccinated individuals particularly vulnerable

COVID Vaccines are NOT Enough

- Vaccines only transiently protect against infection
- Even mild infection carries risk of Long COVID → 7% in unvaccinated, 3.5% in vaccinated. Millions at risk

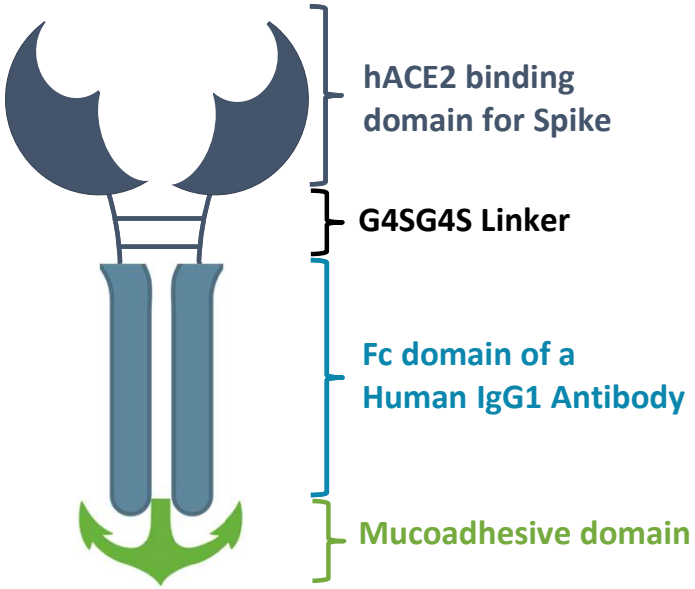
Which Is Worse—COVID or the Flu?

- SARS-CoV-2 is approximately 2.8 fold more infectious than Influenza
- Even in the post-pandemic period, approximately 600 people are dying of COVID each week in the United States
- Rates of hospitalization for individuals over the age of 65 are nearly 10X higher than with Influenza
- Death rates for people older than 65 infected with SARS-CoV-2 are 3-4 times higher than with Influenza
- Infection with SARS-CoV-2, even mild, carries the risk of developing Long COVID
- COVID is less seasonal than Influenza

How to counter the persistent evolution of new variants that consistently outflank anti-Spike monoclonal antibodies?

Key biology: All variants continue to utilize a highly conserved viral entry pathway that requires Spike binding to the human ACE2 receptor

IS101 Intranasal Preventive for COVID-19



- 7 previously authorized COVID-19 antibodies have been deauthorized due to loss of activity against variants
- IS101 designed neutralize all variants
- ACE2 extracellular domain (amino acids 1-740) fused to the N-terminus of IgG1 Fc region; IS101 highly potent against every SARS-CoV-2 variant tested and likely all future variants
- Mucoadhesive domain traps IS101 at the point of viral attack and increases the duration of protection

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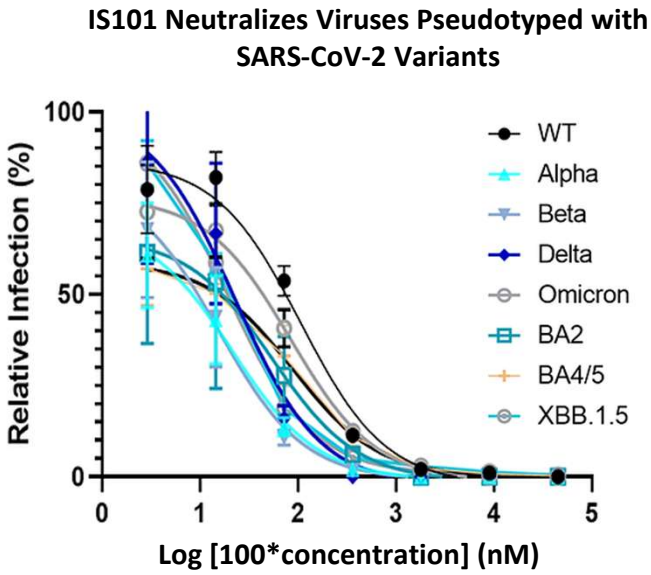
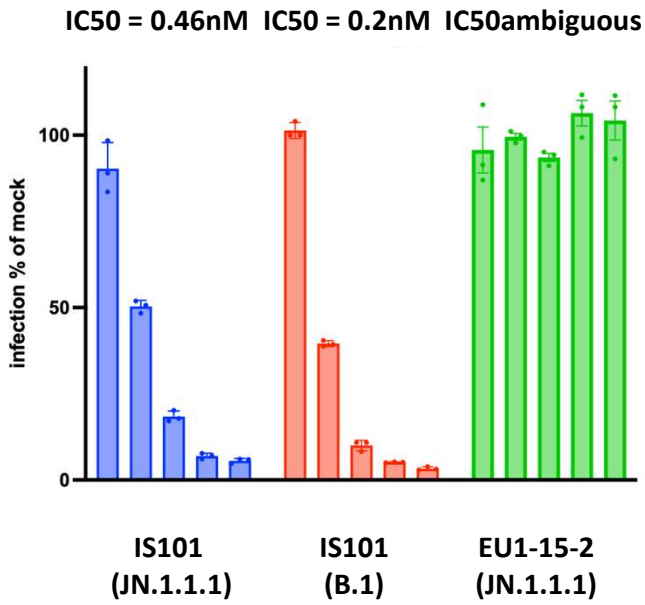
In Vivo and *In Vitro* Properties of IS101

IS101 Potently Neutralizes Viruses Pseudotyped with All Variant SARS-CoV-2 Spikes Tested Including Recent Omicrons



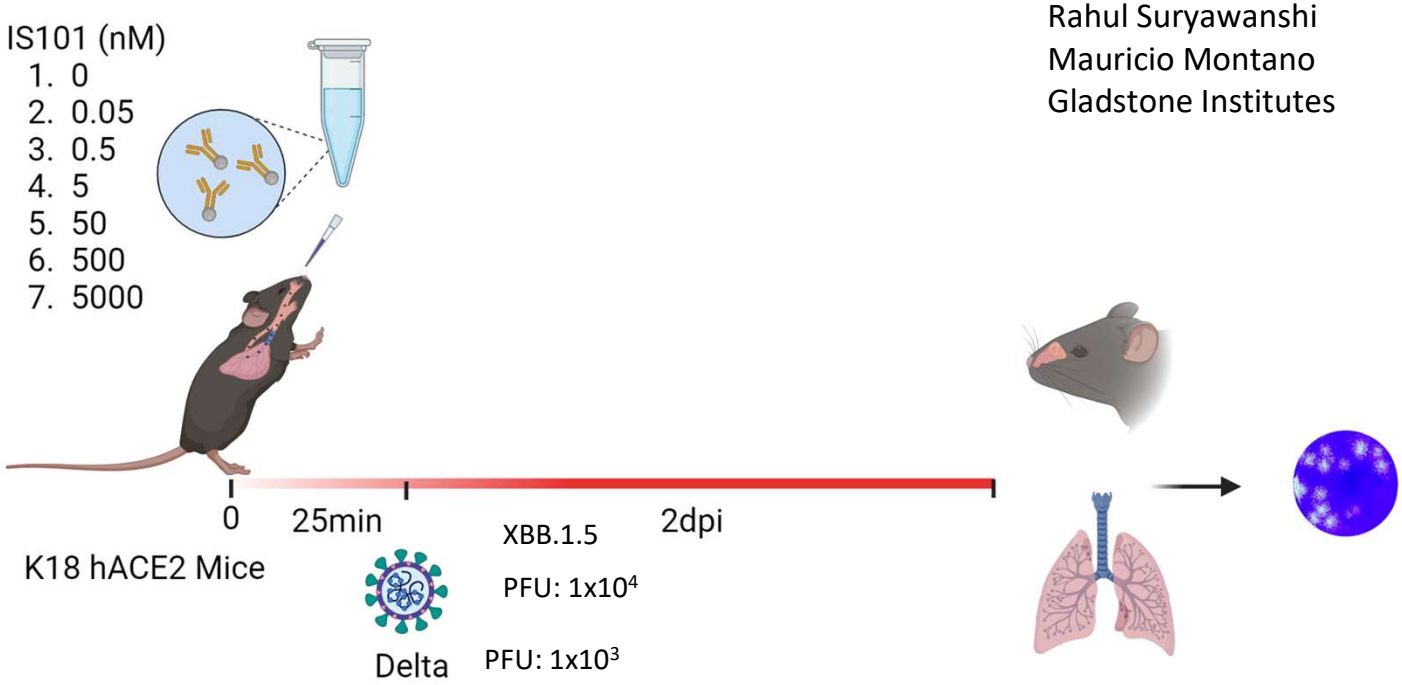


INVISISHIELD TECHNOLOGIES

Evaluating IS101 activity *in vivo*

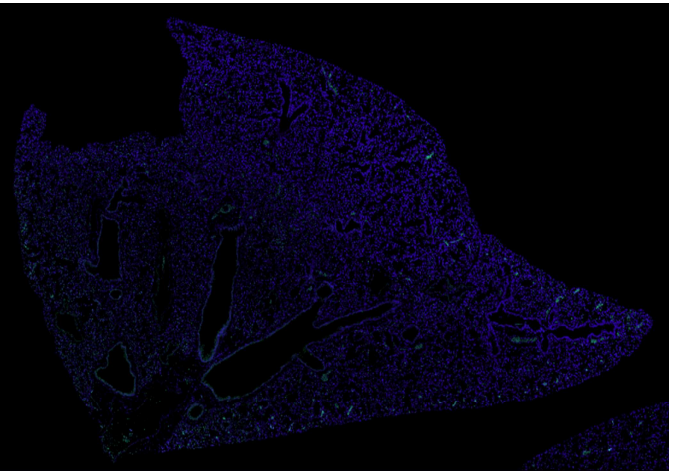
Testing for IS101 Inhibition of SARS-CoV-2 Delta and XBB.1.5 Variant Growth *in vivo* in Human ACE2 Transgenic Mice

Rahul Suryawanshi
Mauricio Montano
Gladstone Institutes

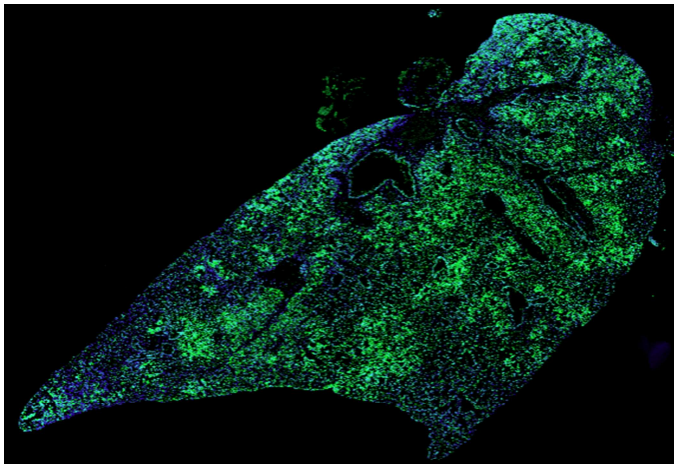


IS101 Blocks SARS-CoV-2-Delta Infection of the Lungs

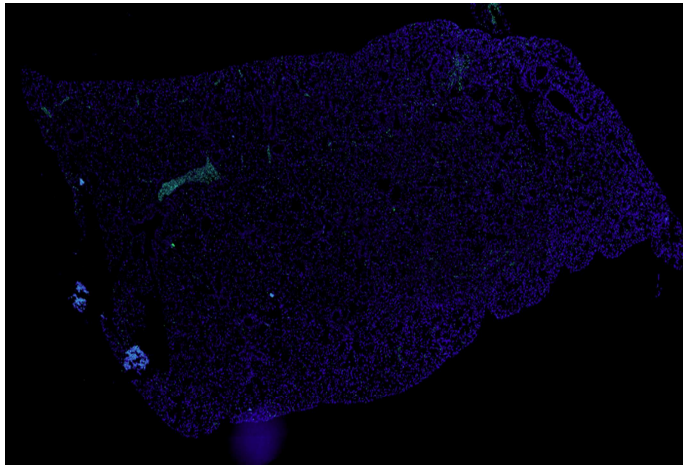
Staining for viral Nucleocapsid protein expression



Uninfected

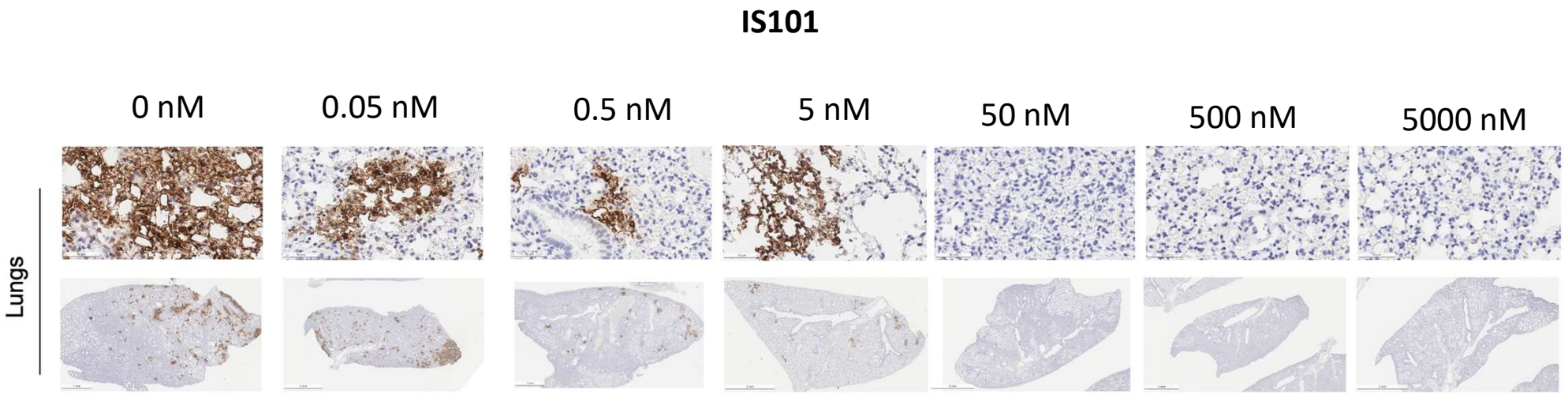


Delta Infected



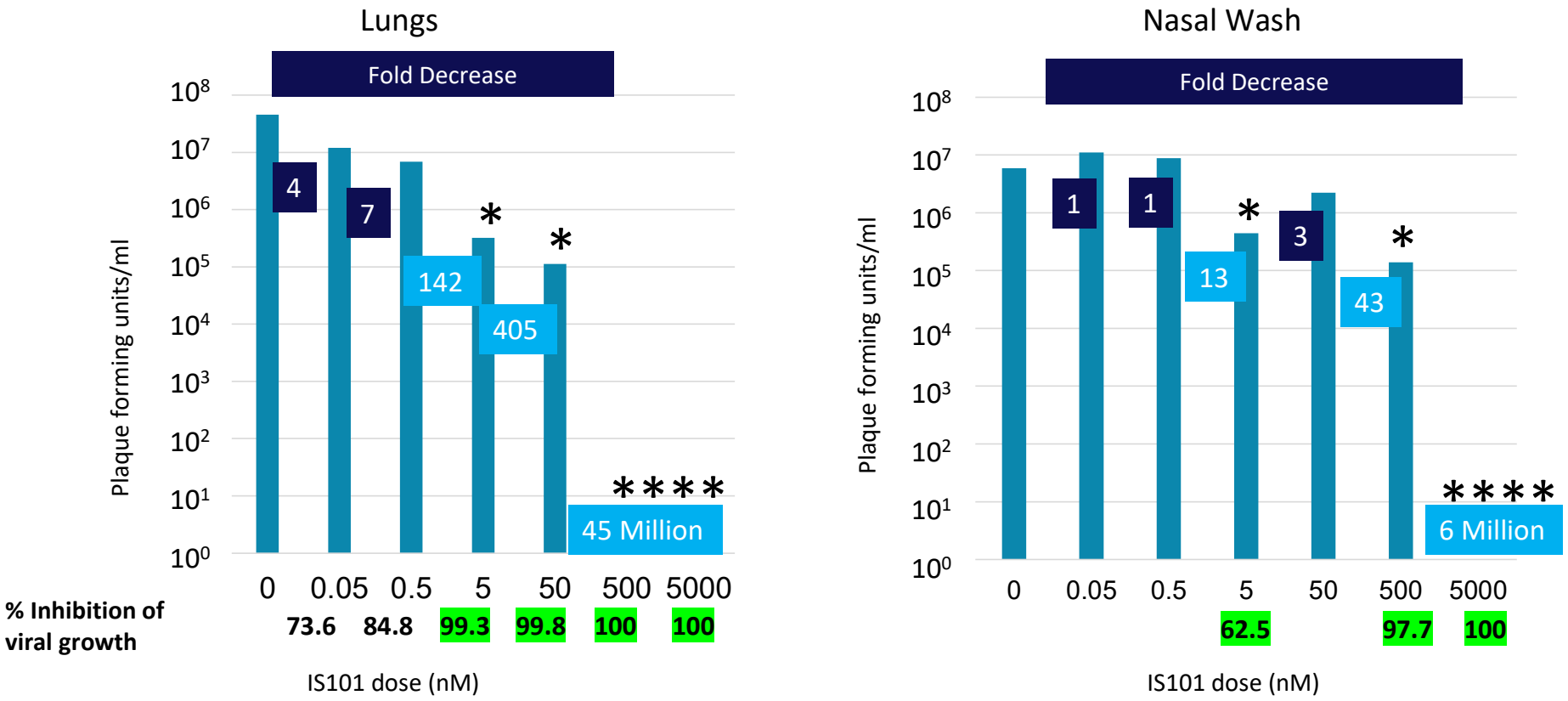
Delta Infected in presence of IS101 (500 nM)

IS101 at Concentrations ≥50 nM Strongly Protect Lungs from *in vivo* SARS-CoV-2 Delta Infection



SARS-CoV-2 Nucleocapsid Staining performed 48 hours after infection

IS101 Completely Protects Against Infection of the Lung: (500 nM) and Sterilizes the Nasal Cavity at 10X Higher Dose



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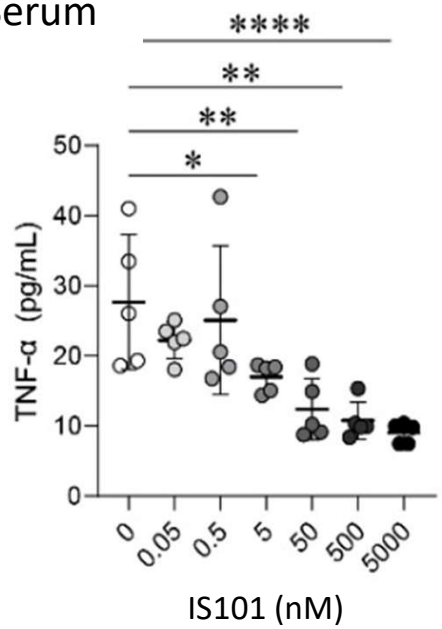
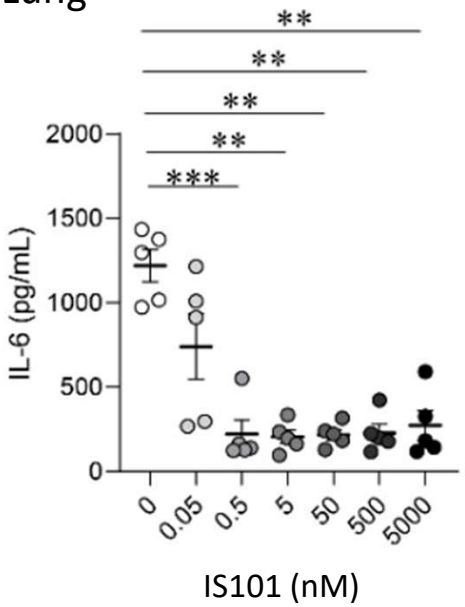
Does IS101 alter the expression of virus-induced proinflammatory cytokines *in vivo*?

IS101 Treatment Reduces Proinflammatory Cytokine Production in the Serum, Lung, and Nasal Wash in a Dose-Related Manner

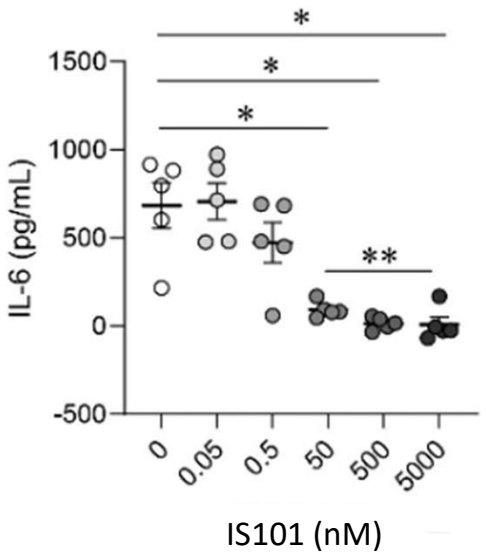
Serum



Lung



Nasal Wash



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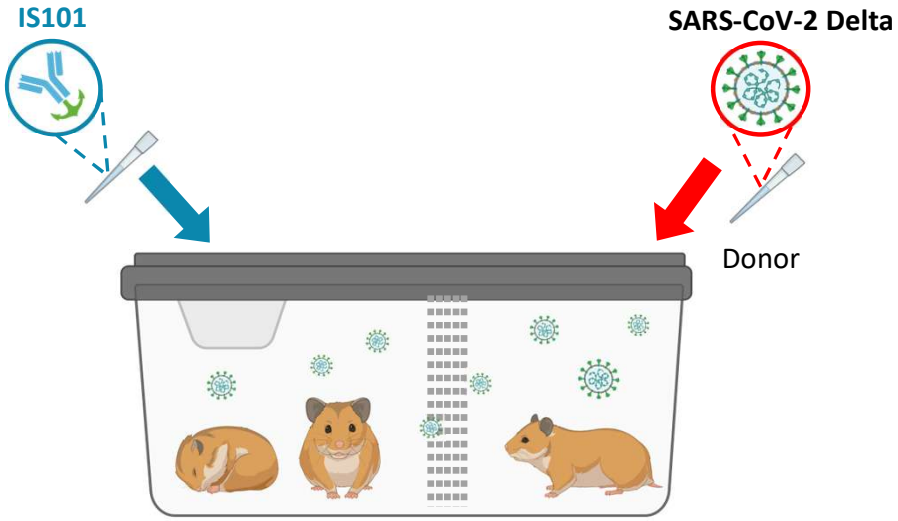
Can IS101 inhibit airborne transmission of SARS-CoV-2?

Syrian Golden Hamster Model of Airborne SARS-Co-2 Infection

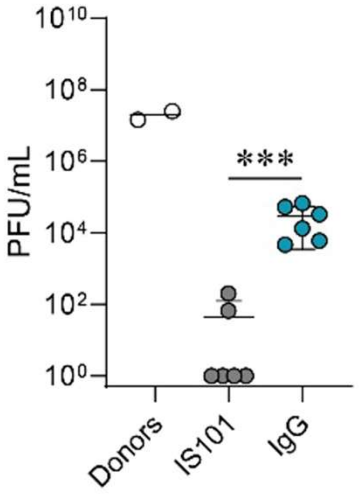
- Testing the ability of IS101 to **prevent aerosol infection following treatment of uninfected hamsters** that share a common air supply with infected animals (preventive effect)
- Testing whether IS101 **can interrupt forward viral transmission by treatment of infected animals**

IS101 Protects Bystander Hamsters from Airborne Transmission of SARS-CoV-2 Delta (PreP)

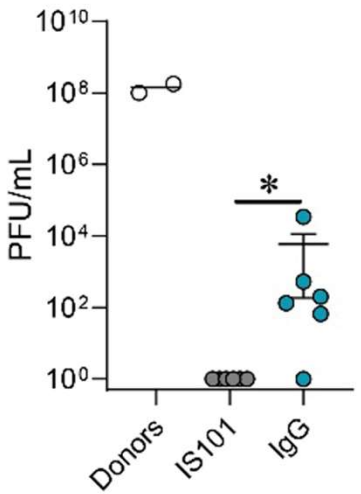
Donor co-housed with IS101/IgG control-treated recipients



Nasal wash



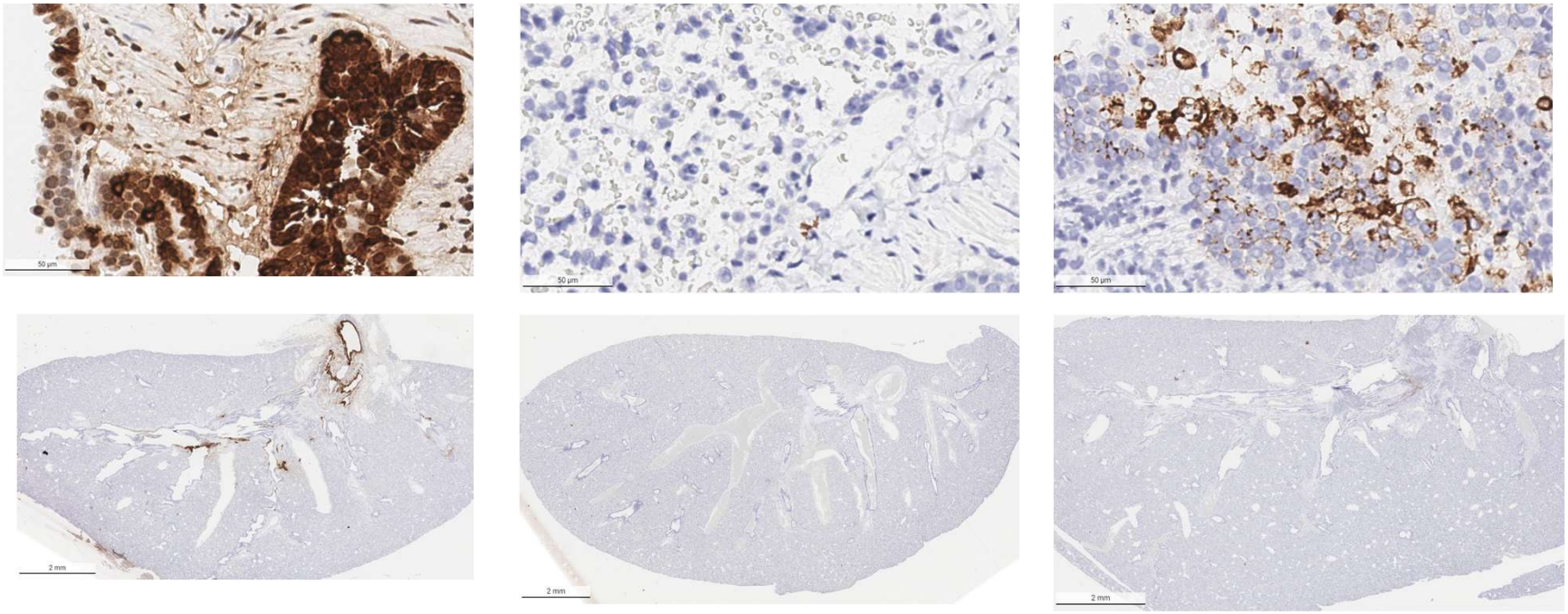
Lungs



INVISISHIELD TECHNOLOGIES

IS101 Protects Bystander Hamsters from Airborne Transmission of SARS-CoV-2 Delta (PrEP)

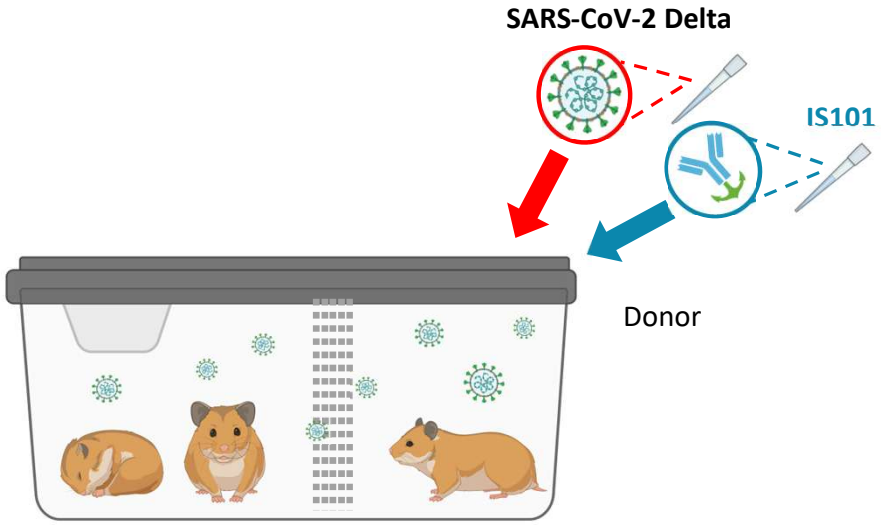
Lungs

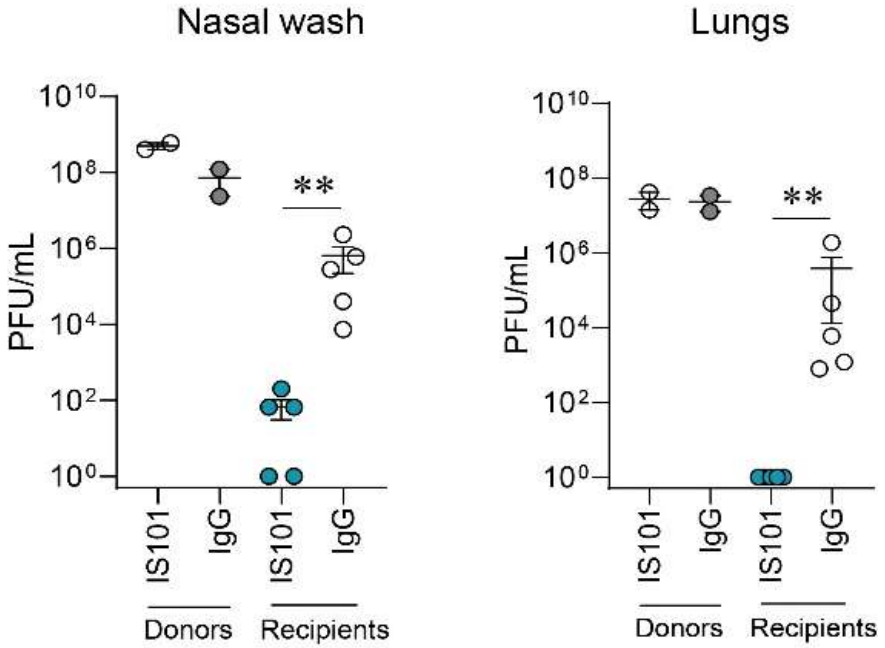


Donor | IS101 | IgG

IS101 Treatment pf Infected Hamsters Prevents Airborne Transmission to Untreated Hamsters (Inhibition of Forward Viral Transmission)

Donor treated with IS101/IgG control and co-housed with uninfected, untreated recipients





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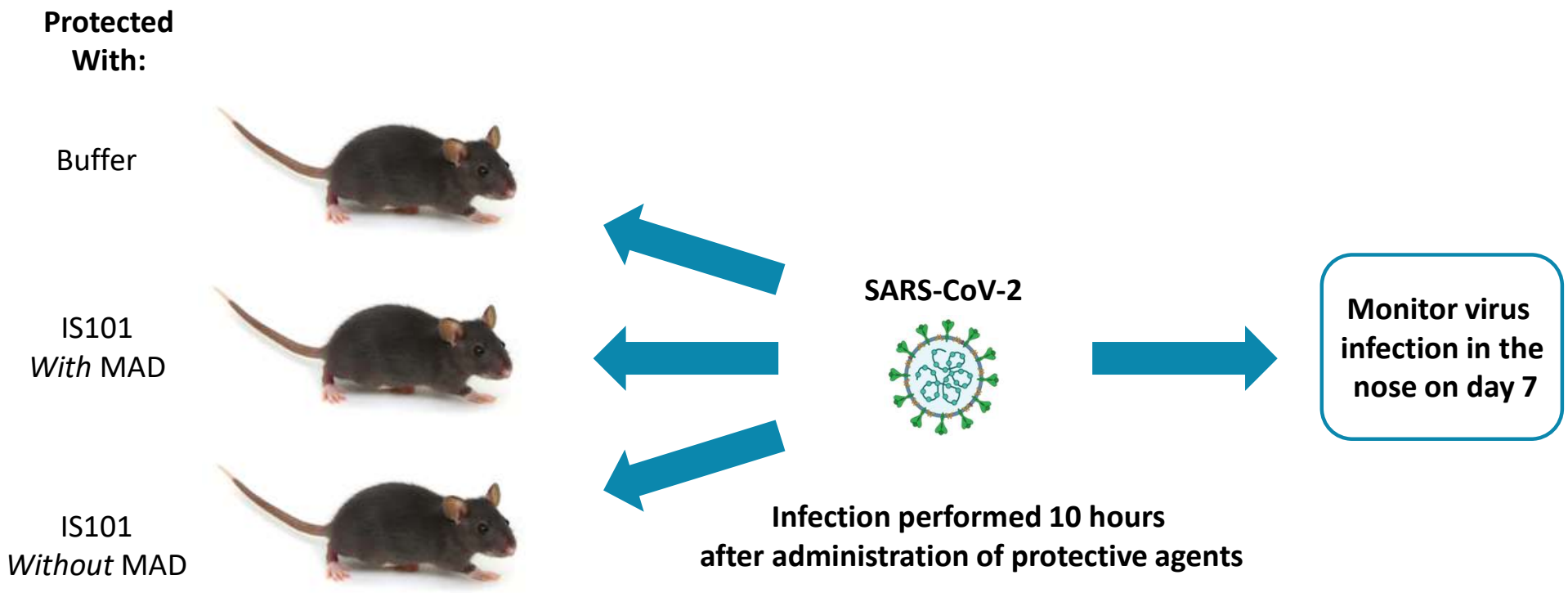
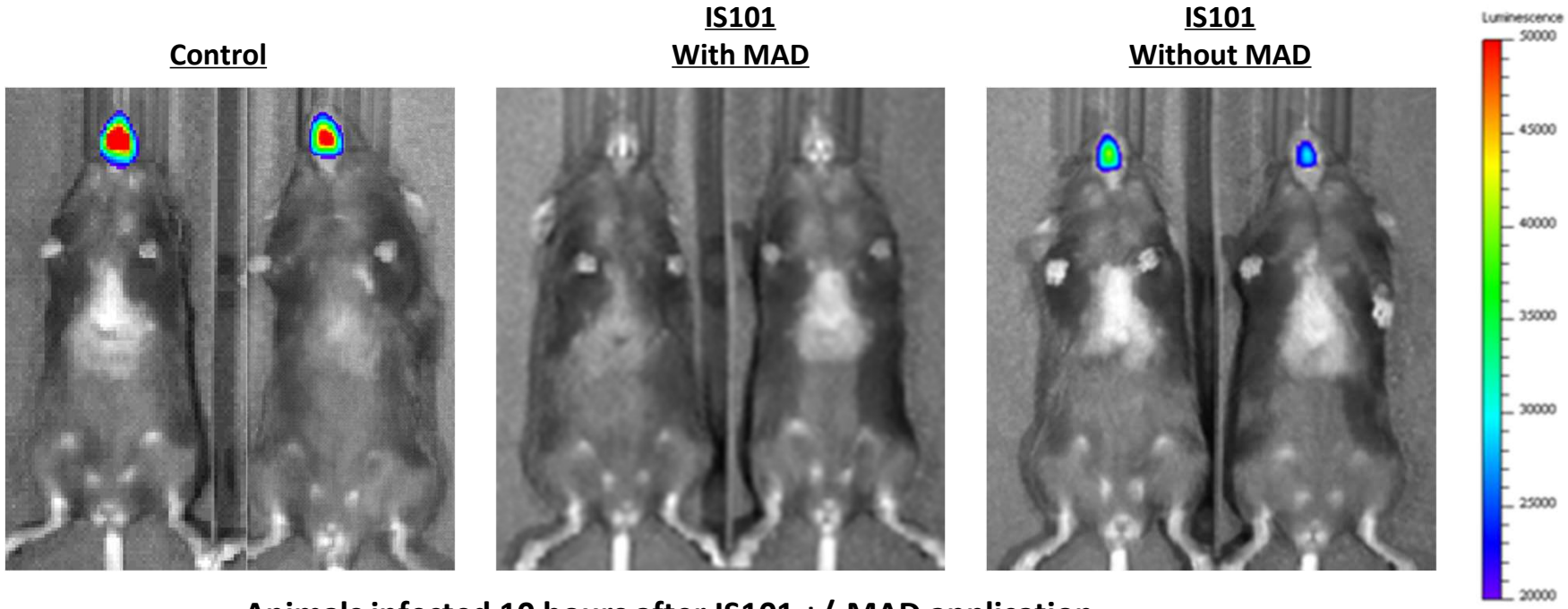
Does InvisiShield's Proprietary Mucoadhesive Domain Convey Favorable Properties?

Testing Effectiveness of Mucoadhesive Domain (MAD) To Extend Durability of Protection by IS101



Presence of Mucoadhesive Domain (MAD) Extends IS101's Duration of Action



Animals infected 10 hours after IS101 +/-MAD application

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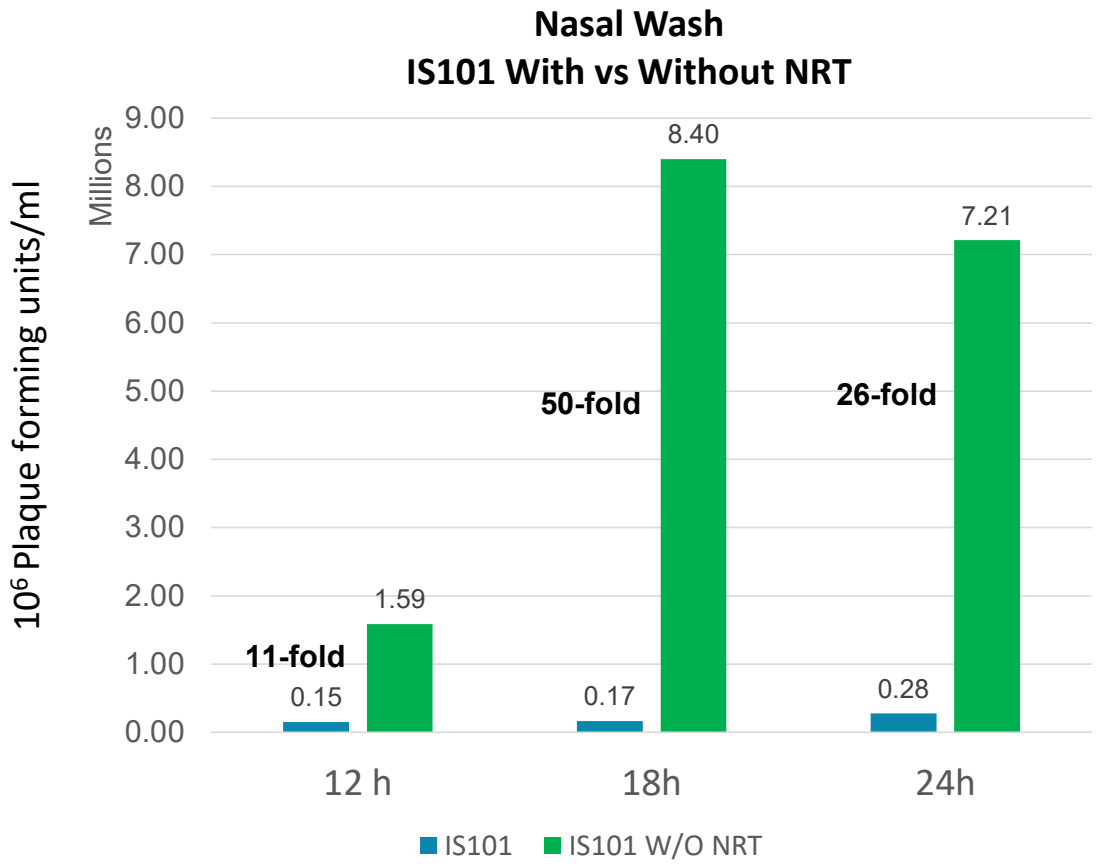
Lack of Nasal Retention Technology Reduces IS101 Inhibition Between 12 to 24 Hours — IS101 Remains Effective Through 24 Hours



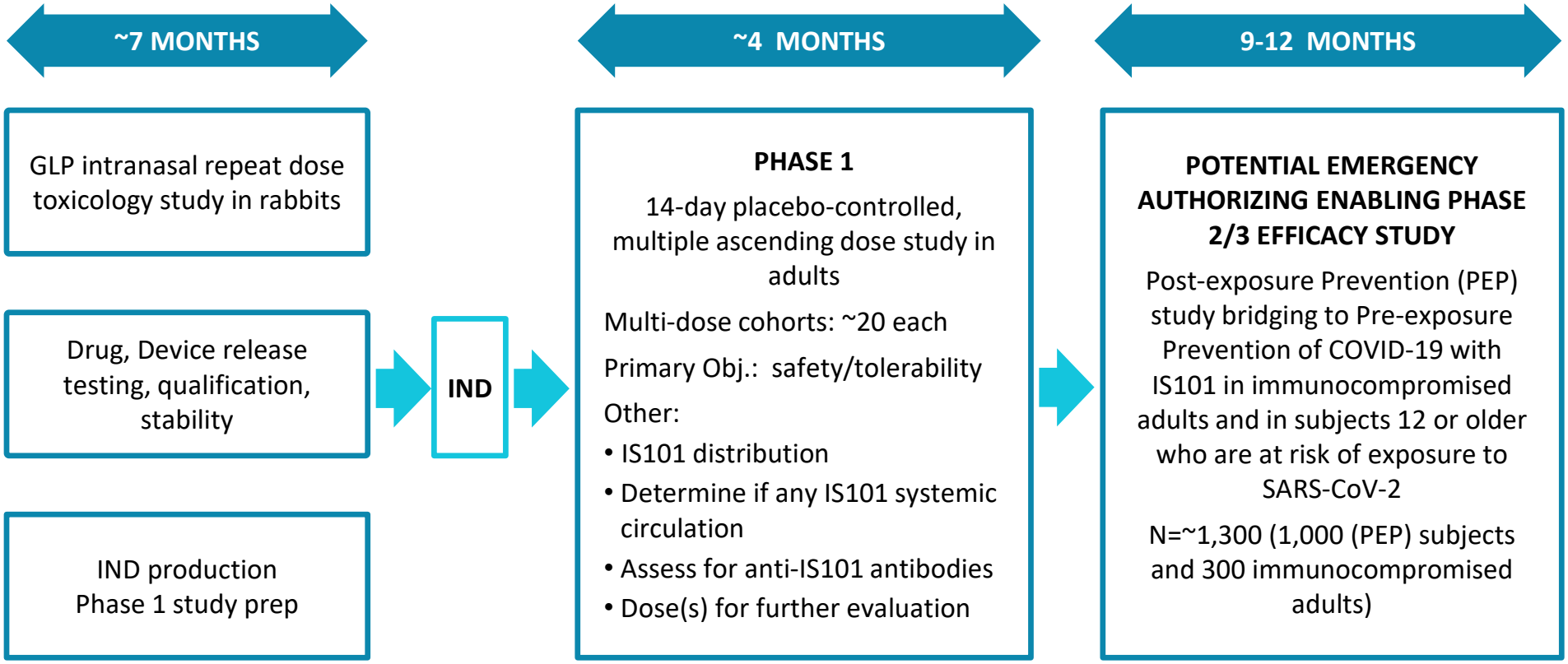
INVISISHIELD TECHNOLOGIES

Manufacturing Summary

- 21 CFR 210,211 current GMP-compliant facility in Sacramento, California
- CHO based IS101 Master Cell Bank (generated and released by Charles River) used for two 30-liter scale GMP manufacturing runs
- Sufficient IS101 available for Phase I trial (production level = 100 mg/liter
- Manufacturing strategy readily adaptable to influenza and RSV preventives for which Master Cell Banks are being produced
- Favorable properties: 1) only low amounts of preventive are required for high level protection in the nose compared to systemically administered antibodies resulting in lower overall costs; 2) agile platform

Manufacturing Facility
located in Sacramento, CA

IS101 Development Plan

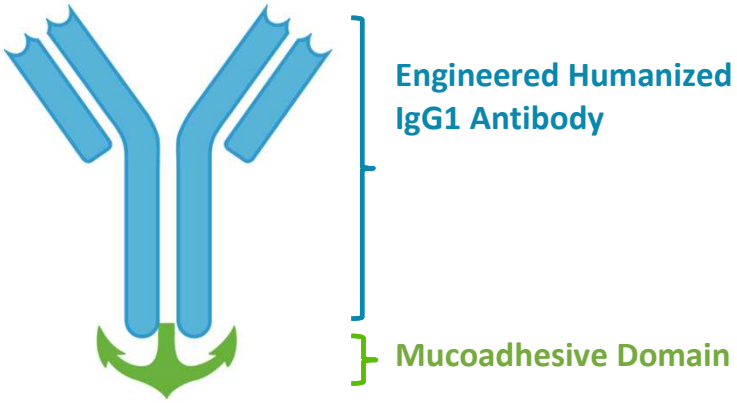


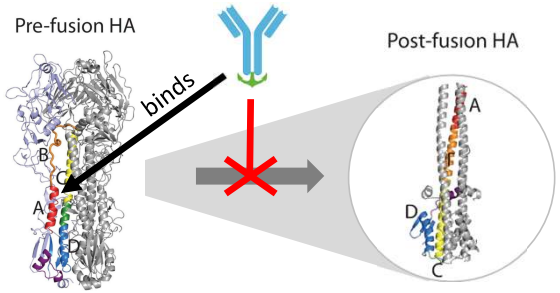
IS101 Communications with FDA

- InvisiShield submitted 2nd Pre-IND package in Aug 2023
- FDA provided positive feedback in subsequent correspondence in Dec 2023:
  - ✓ Agreed with InvisiShield's Phase 1 clinical trial design
  - ✓ Agreed with InvisiShield's manufacturing plan
  - ✓ Agreed with InvisiShield's delivery device for IS101
  - ✓ Agreed with current and planned preclinical virology and toxicology data
  - ✓ Clear runway to IND submission

Developing broadly neutralizing intranasal preventives for Influenza and RSV

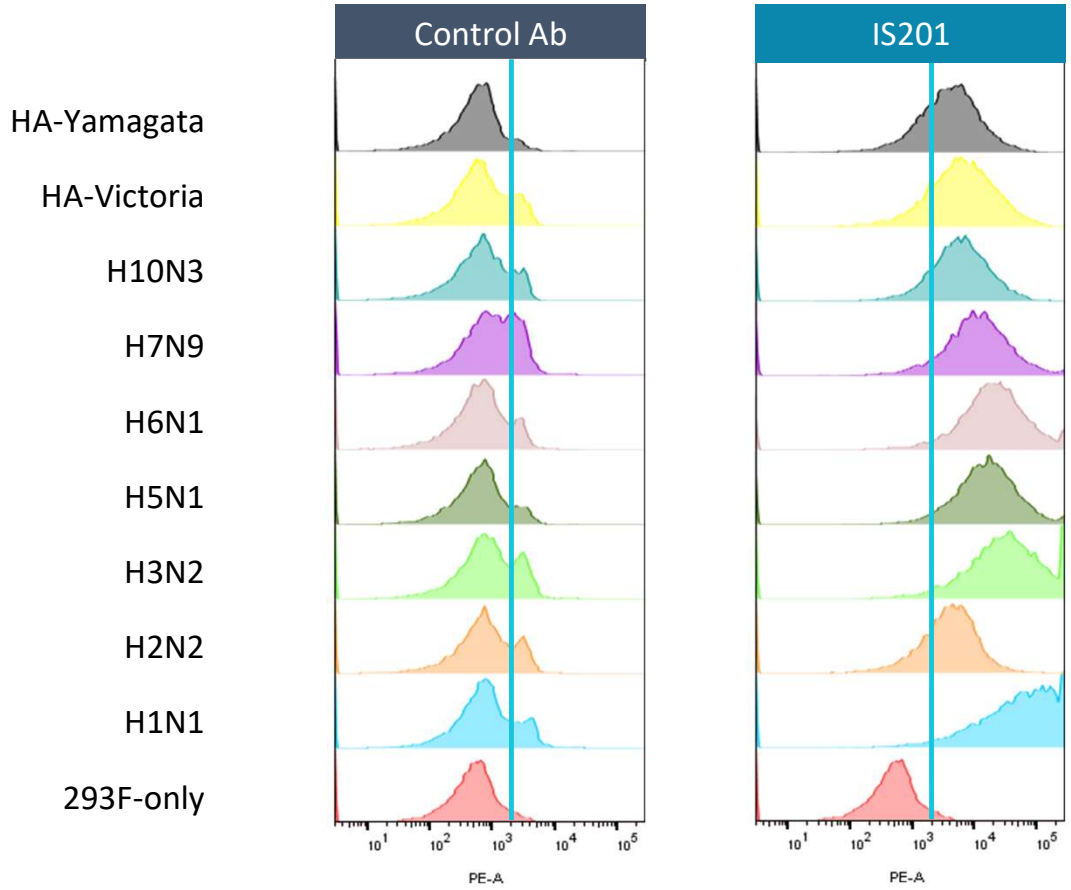
IS201: Pan Influenza A and B Intranasal Preventive





- Limited preventive agents other than vaccines (no antibodies approved)
- Vaccines provide limited protection; particularly for highly vulnerable elderly and immunocompromised populations
- IS201 a proprietary engineered humanized antibody with broad neutralizing activity against influenza A and B
- IS201 blocks virion entry at level of fusion
- Binds to stem of HA holding HA in prefusion, non-extended conformation
- Mucoadhesive domain: C-terminal modification to target, prolong protection

IS201 Exhibits Broad and High Level Binding to the Hemagglutinins of Both Influenza A and B Strains Measured by Flow Cytometry



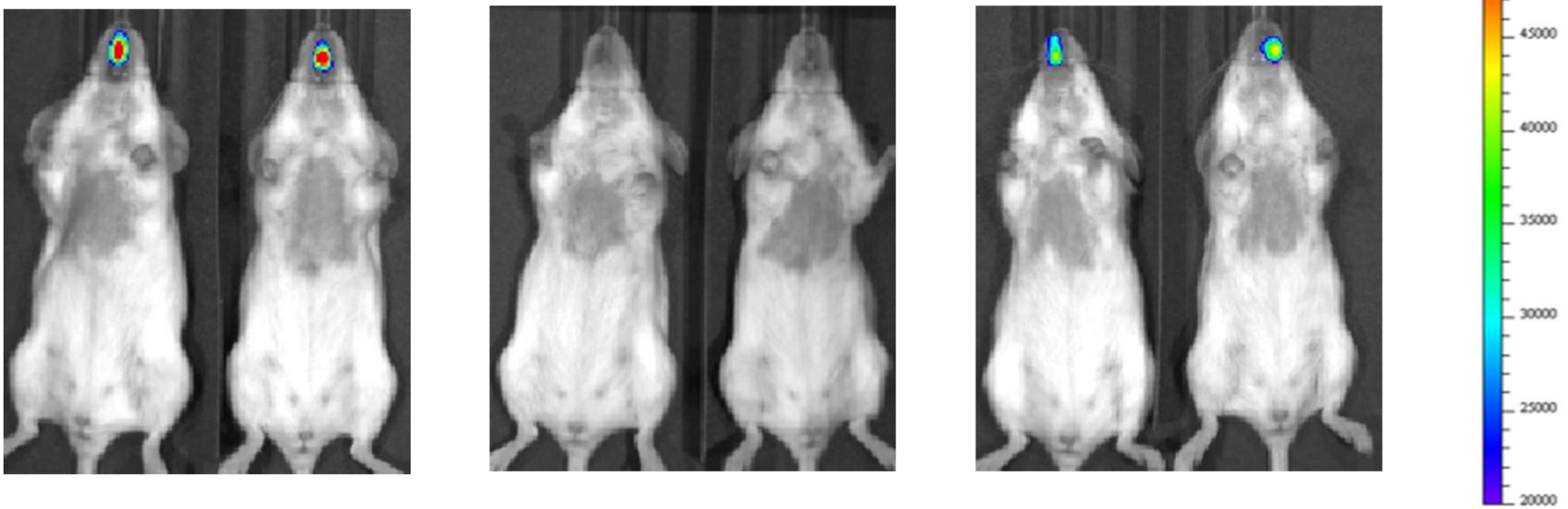
INVISISHIELD TECHNOLOGIES

InvisiShield's Mucoadhesive Domain (MAD) is Effective for Extending Antibody Protection Against Influenza Infection

Control

Pan-variant anti-Flu Ab CR9114 With MAD

Pan-variant anti-Flu Ab CR9114 Without MAD



Pan-variant anti-Flu Ab CR9114 +/- MAD administered 10 hours before virus inoculation

Testing Whether a Bivalent Preventive With Nasal Retention Technology Can Neutralize both SARS-CoV-2 and Influenza

Protected With:

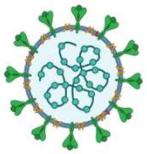
IS101
(SARS-CoV-2 Inhibitor)

CR9114
anti-Flu Ab

IS101
+
CR9114
anti-Flu Ab

Dual infection performed at T_{10hr}

SARS-CoV-2



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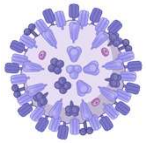
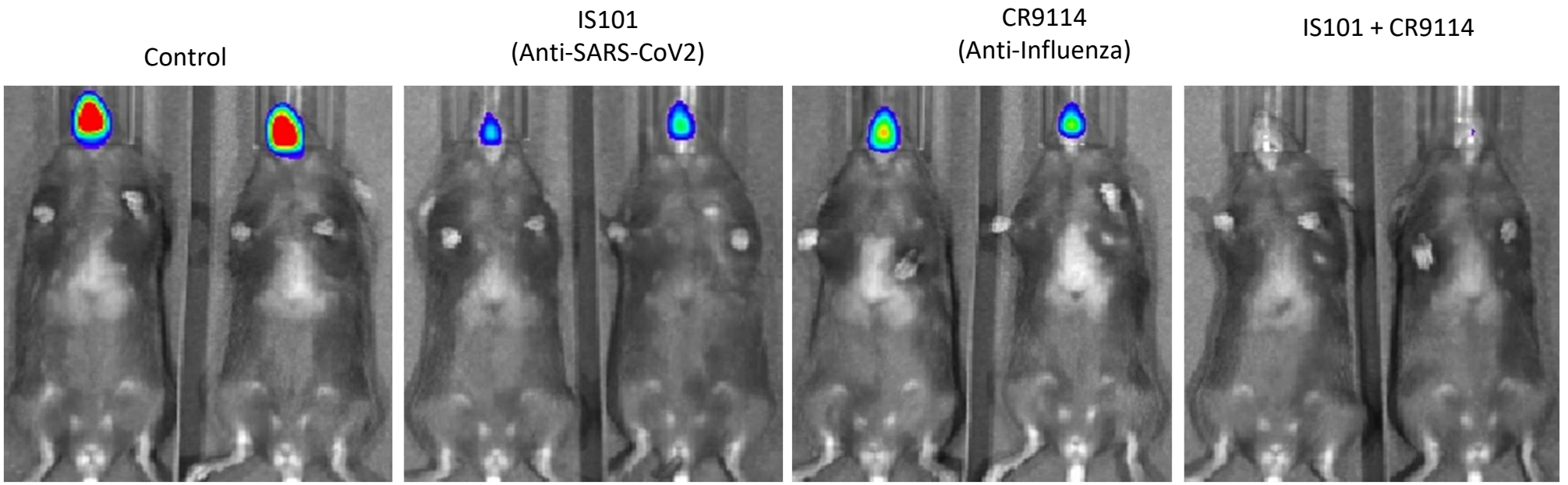


H3N2 Influenza

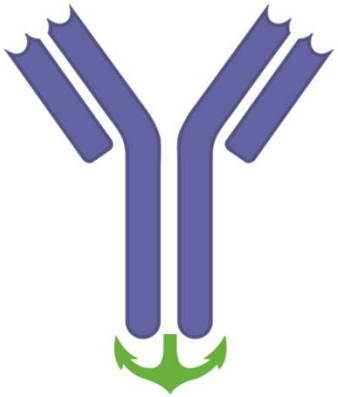
Monitor virus replication in the nose on day 7

Proof-of-Concept: Bivalent SARS-CoV-2/Influenza Intranasal Preventive Blocks Infections by Both Viruses



All mice dosed with SARS-CoV-2+H3N2 influenza at Day 0 (10 hrs after pre-treatment with candidate preventives); mice analyzed on Day 7

IS301 RSV Intranasal Preventive

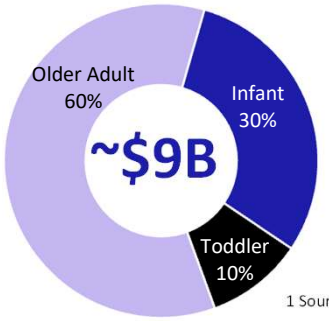


Palivizumab, humanized IgG1 Antibody

Binds to RSV F protein inhibiting fusion

Mucoadhesive Domain

Global RSV Market 2030 [1]



1 Source: Sanofi Corporate Presentation, June 2023

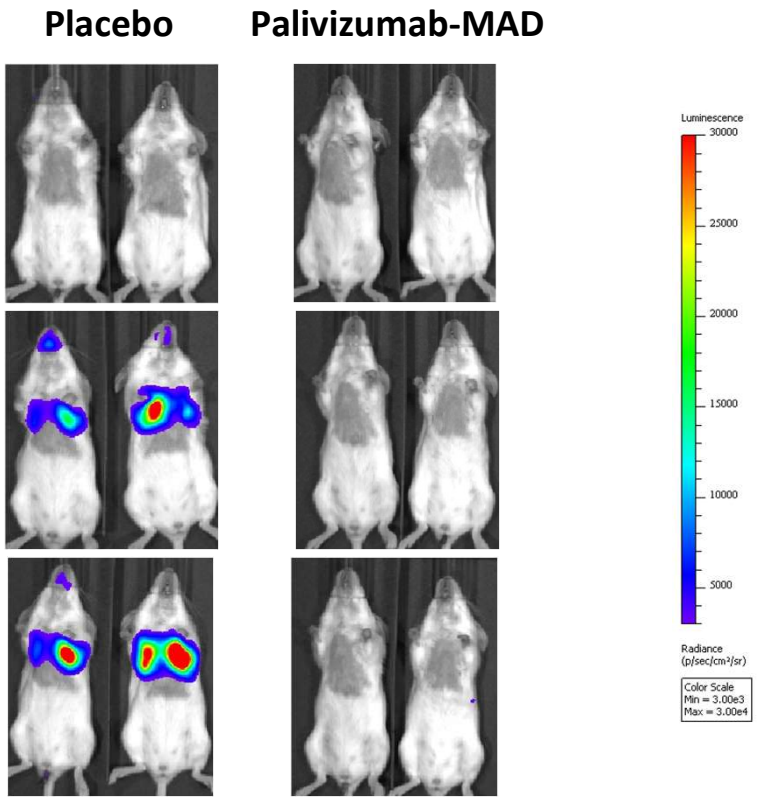
- No approved preventive agents other than vaccines for adult populations
- More solutions needed in highly vulnerable, elderly adults, immunocompromised populations
- Engineered humanized antibody incorporating palivizumab (Synagis)
- Palivizumab is approved as an intramuscular injection for the prevention of serious lower respiratory tract disease caused by RSV in infants (now off patent)
- Mucoadhesive Domain attached to C-terminal to prolong protection

Palivizumab with Mucoadhesive Domain Inhibits Live Intranasal RSV Infection Delivered 10 Hours after Treatment

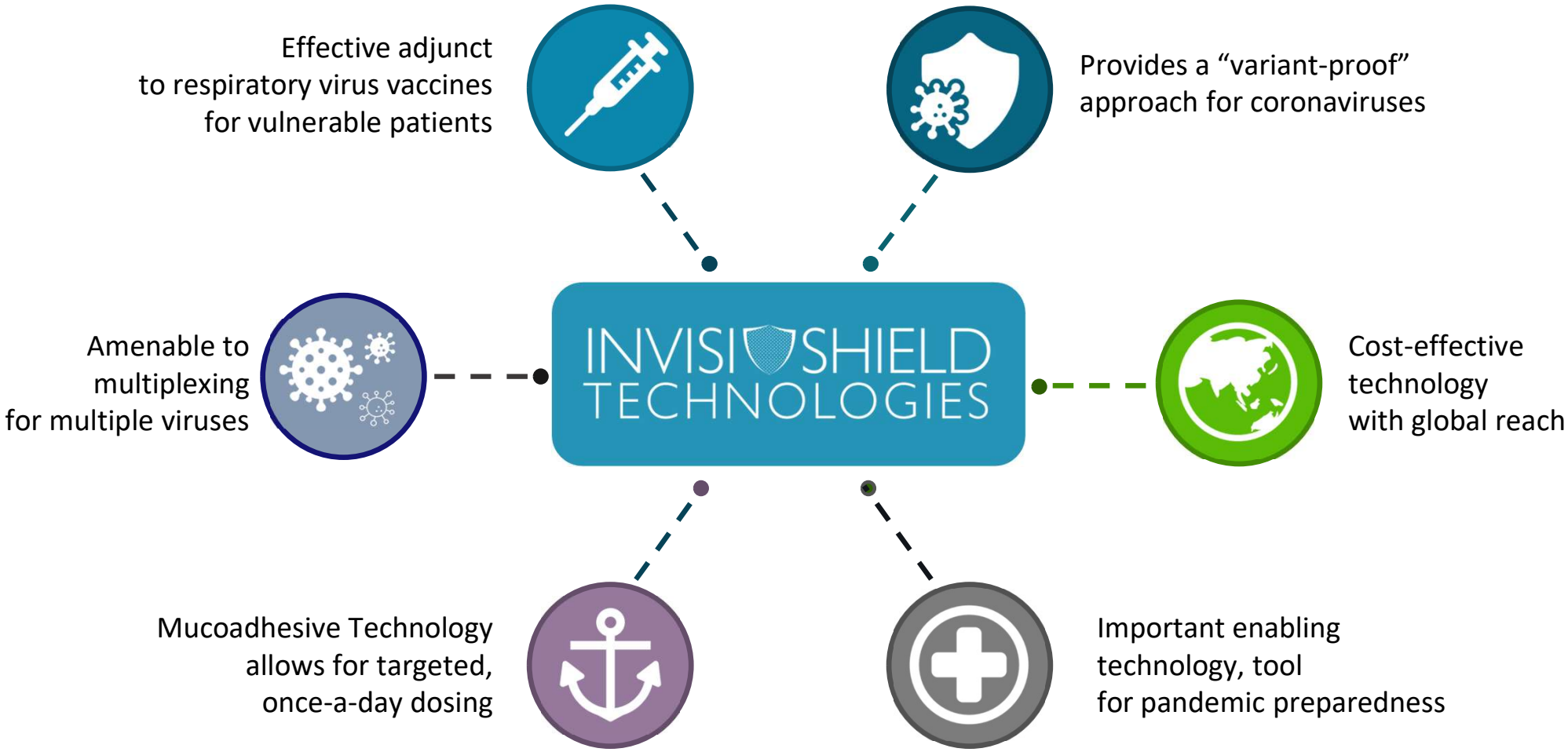
All mice were dosed intranasally with Placebo or Palivizumab-MAD on Day 0

Infected intranasally with RSV 10 hours later

Note complete protection of Palivizumab-MAD treated mice



INVISISHIELD TECHNOLOGIES


Effective adjunct
to respiratory virus vaccines
for vulnerable patients
Provides a “variant-proof”
approach for coronaviruses
Amenable to
multiplexing
for multiple viruses
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TECHNOLOGIES
Cost-effective
technology
with global reach
Mucoadhesive Technology
allows for targeted,
once-a-day dosing
Important enabling
technology, tool
for pandemic preparedness

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Thank you