— Special Edition —
WCBP 2021
VIRTUAL SYMPOSIUM

Research and Advanced Technologies Supporting the Accelerated Development of a COVID-19 Vaccine

Workshop Session Four

Academic Knowledge & Innovation to Accelerate Successful Technological Transfer for a COVID-19 Vaccine

Texas Children's Center for Vaccine Development

Maria Elena Bottazzi PhD
Co-director

Baylor College of Medicine
NATIONAL SCHOOL OF TROPICAL MEDICINE
Texas Children's Hospital®

DISCLAIMER: *I am an inventor of patents for non-income generating vaccines to prevent parasitic infections. Baylor College of Medicine has granted a non-exclusive license to a COVID-19 vaccine candidate for an India-based vaccine manufacturer of which I am a developer.*

Texas Children's CVD Mission

A **Product Development Partnership**
Academic Health Center-based
+ 50 scientific and technical staff
> 40 Global Partnerships

Established in DC the year 2000
Moved to **Texas Medical Center** in 2011
Collaboration with Baylor College of Medicine

To develop and test new low-cost and effective vaccines against emerging and neglected tropical diseases

To build capacity for vaccine development locally and with foreign nations

To guide and influence vaccine policy and advocacy

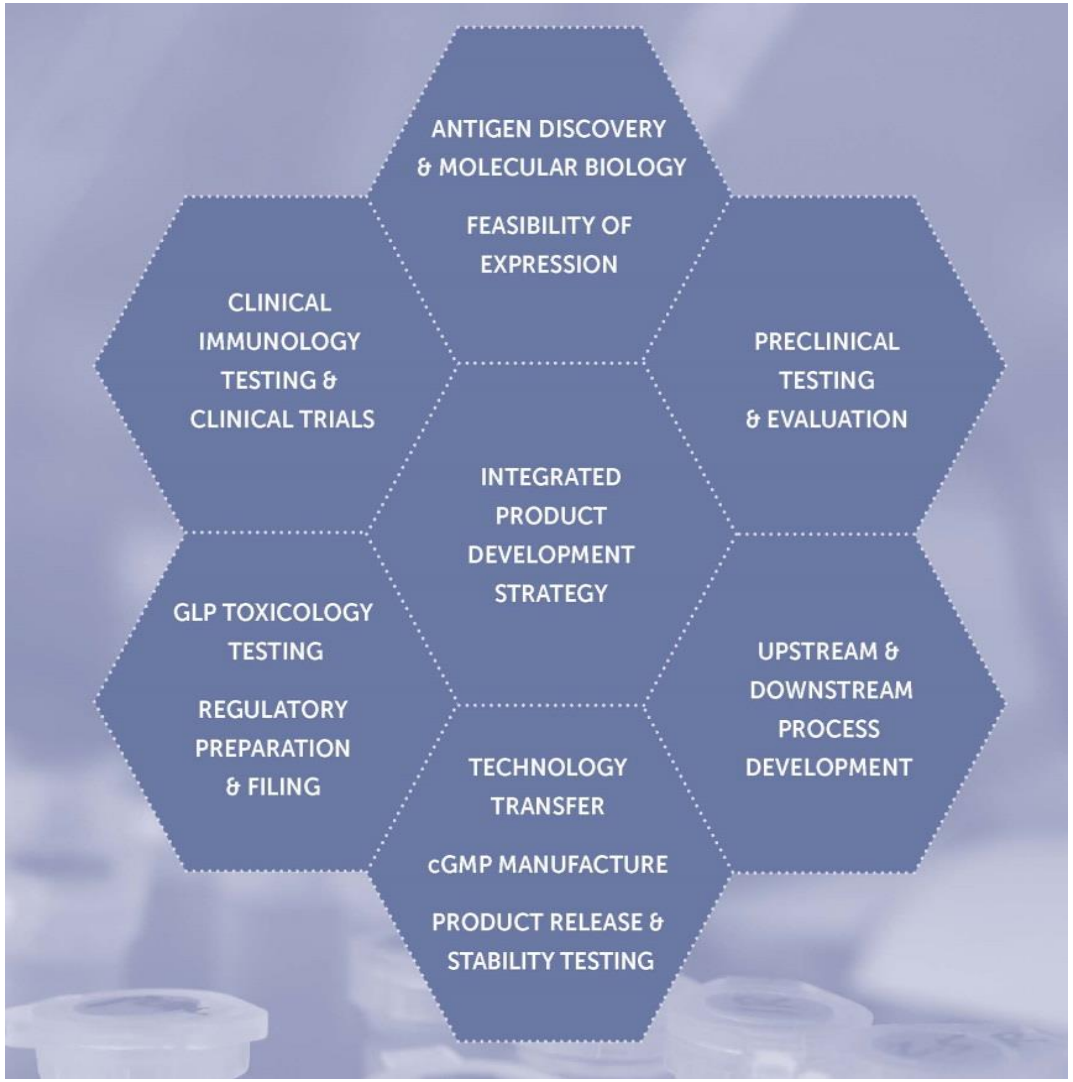
PDPs as Key Accelerators of Vaccine Development

Source of innovation, cut costs and mitigate risks

Specialized knowledge and technologies

From basic research to critical path development:

- Targeted discovery, screening and engineering
- Production process development and scale-up
- Assay and formulation development
- Preclinical models for immunogenicity and efficacy
- Clinical trial networks
- Ethical, regulatory and quality assurance framework



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Portfolio and Major Accomplishments (2011 - 2020)

Human Hookworm Infection

Intestinal Schistosomiasis

Chagas disease

Coronavirus Initiative

Tick-borne and Lyme disease

Cutaneous Leishmaniasis

Soil-transmitted Helminths (Ascaris, Trichuris and Toxocara)

Developed the first vaccine for human hookworm infection now entering phase 2 clinical trials

Developed the first vaccine for intestinal schistosomiasis now entering phase 2 clinical trials

Developed the first vaccine for Chagas disease now entering phase 1 clinical trials

Developed innovative vaccines for emerging coronavirus infections: COVID-19, SARS and MERS

Signed and implemented historic capacity building agreements with Brazil, Mexico, Malaysia and the Kingdom of Saudi Arabia

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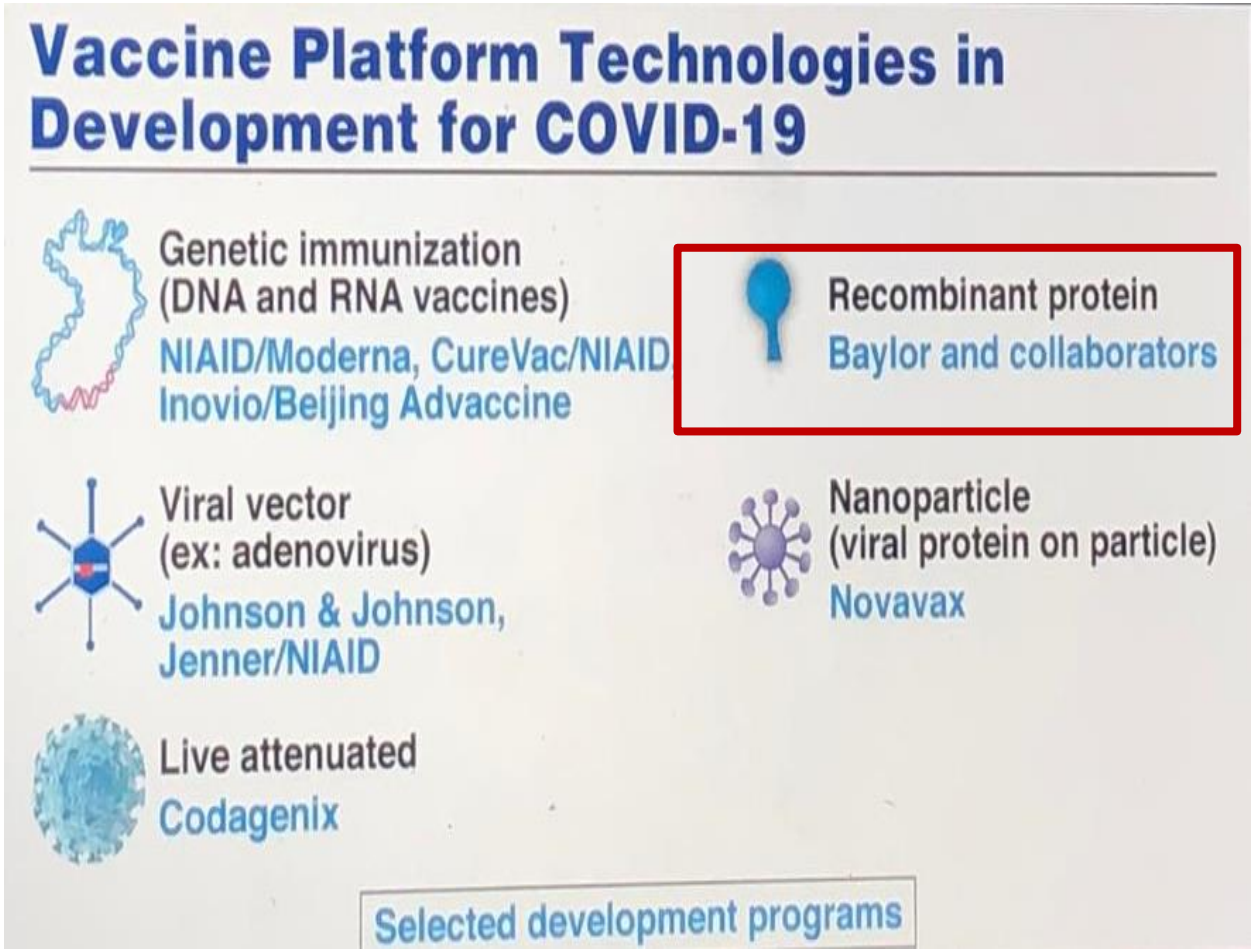
Texas Children's CVD Relies on Subunit Vaccine Technology

- Well-established technology
- Considered very safe with widespread use in licensed vaccines
- Suitable for adult & pediatric populations
- Ecosystem of global manufacturers with ease of scalability
- Stable and suitable cold-chain
- Ideal antigen and adjuvant combination for primary or boosting
- Affordable



Anthony Fauci, NIAID, NIH Presentation to National Academies

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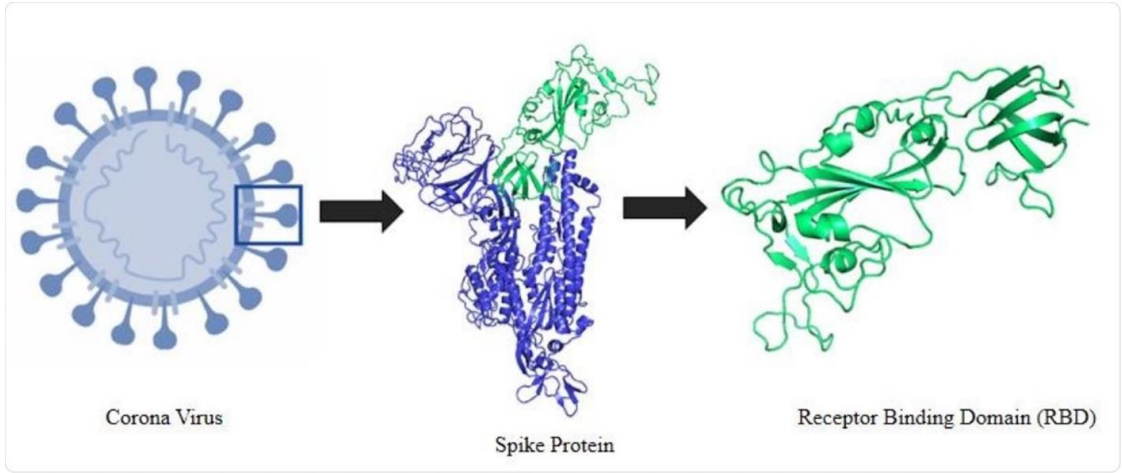
Coronavirus Vaccine Initiative

- Led by Texas Children's CVD
- Develop Low-Cost Coronavirus Vaccines for Global Health by Microbial Fermentation in Yeast
- NIH/NIAID seed funding instrumental
  - **SARS/MERS (2011-16)**
  - **COVID-19 (2020-)**
- Specific coronavirus partnerships launched in 2011 and expanded in 2020



New York Blood Center

utmb Health

Working together to work wonders.™

WRAIR Walter Reed Army Institute of Research

Soldier Health • World Health

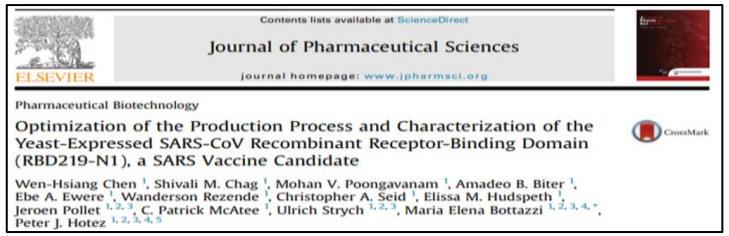
NIH National Institute of Allergy and Infectious Diseases

Grant: R01AI098775, AI14087201

PATH

IDRI TRANSFORMING SCIENCE INTO GLOBAL HEALTH SOLUTIONS

MilliporeSigma


Contents lists available at ScienceDirect

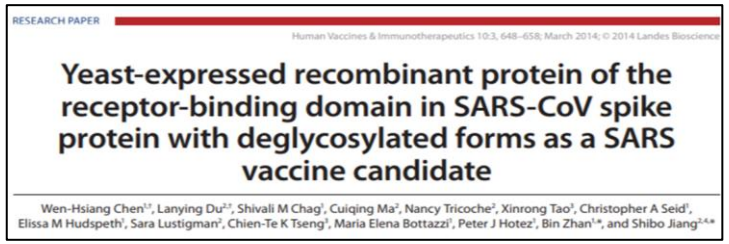
Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutical Biotechnology

Optimization of the Production Process and Characterization of the Yeast-Expressed SARS-CoV Recombinant Receptor-Binding Domain (RBD219-N1), a SARS Vaccine Candidate

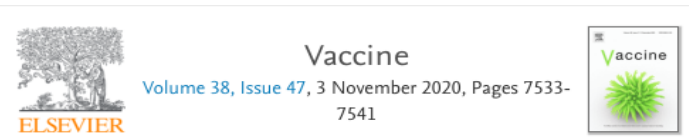
Wen-Hsiang Chen [1], Shivali M. Chag [1], Mohan V. Poongavanam [1], Amadeo B. Biter [1], Ebe A. Ewere [1], Wanderson Rezende [1], Christopher A. Seid [1], Elissa M. Hudspeth [1], Jeroen Pollet [1,2,3], C. Patrick McAtee [1], Ulrich Strych [1,2,3], Maria Elena Bottazzi [1,2,3,4,*], Peter J. Hotez [1,2,3,4,5]


RESEARCH PAPER

Human Vaccines & Immunotherapeutics 10:3, 648–658; March 2014; © 2014 Landes Bioscience

Yeast-expressed recombinant protein of the receptor-binding domain in SARS-CoV spike protein with deglycosylated forms as a SARS vaccine candidate

Wen-Hsiang Chen[1,*], Lanying Du[2,3], Shivali M Chag[1], Cuiqing Ma[2], Nancy Tricoche[2], Xinrong Tao[3], Christopher A Seid[1], Elissa M Hudspeth[1], Sara Lustigman[2], Chien-Te K Tseng[3], Maria Elena Bottazzi[2], Peter J Hotez[2], Bin Zhan[1,*], and Shibo Jiang[2,4,*]


ELSEVIER

Vaccine

Volume 38, Issue 47, 3 November 2020, Pages 7533-7541

Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with aluminum hydroxide induces protective immunity and reduces immune enhancement

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Coronavirus Vaccine Research a Catalyst for COVID-19

2000
Established infrastructure as academic-based PDP with a hybrid business model

2011 TCH CVD recruited to Baylor and Texas Children's and launches the Coronavirus Vaccine Initiative

2020 TCH CVD Accelerates the Development of a COVID-19 Vaccine with a MilliporeSigma Alliance

2010 2012 2013 2015 2017 2018 2019 July

2014 TCH CVD initiates technology transfer of the SARS-RBD Vaccine

2016 TCH CVD manufactures SARS-RBD Vaccine with WRAIR*

2020 TCH CVD alliances with PATH and IDRI*

2020 TCH CVD licenses vaccine to Biological E, Ltd.**

***WRAIR**: Walter Reed Army Institute of Research Pilot Manufacturing Facility; **PATH:** Center for Vaccine Innovation & Access; **IDRI:** Infectious Disease Research Institute

**** Biological E: India-based Industrial Vaccine Manufacturer**

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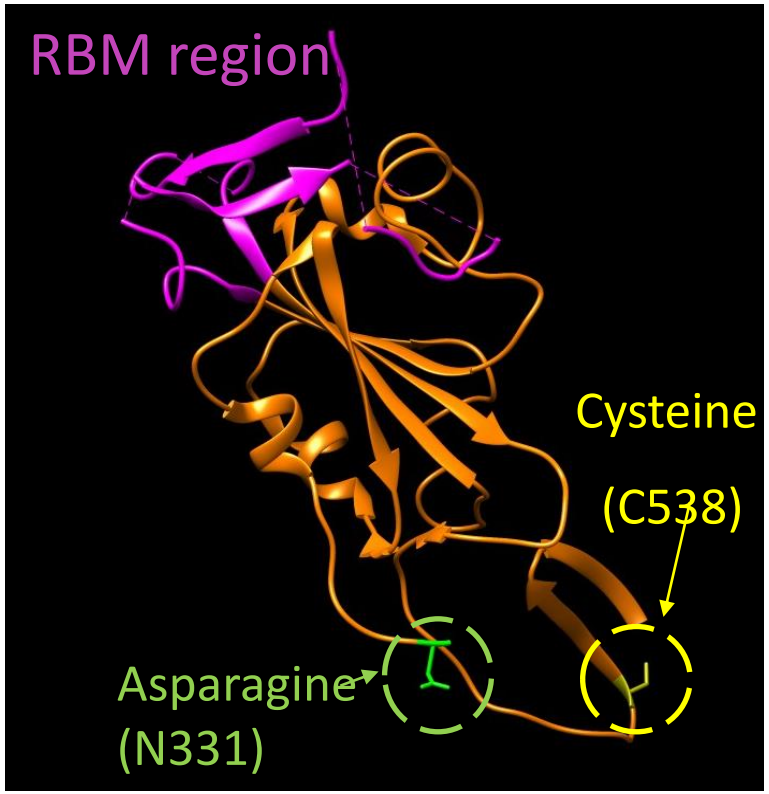
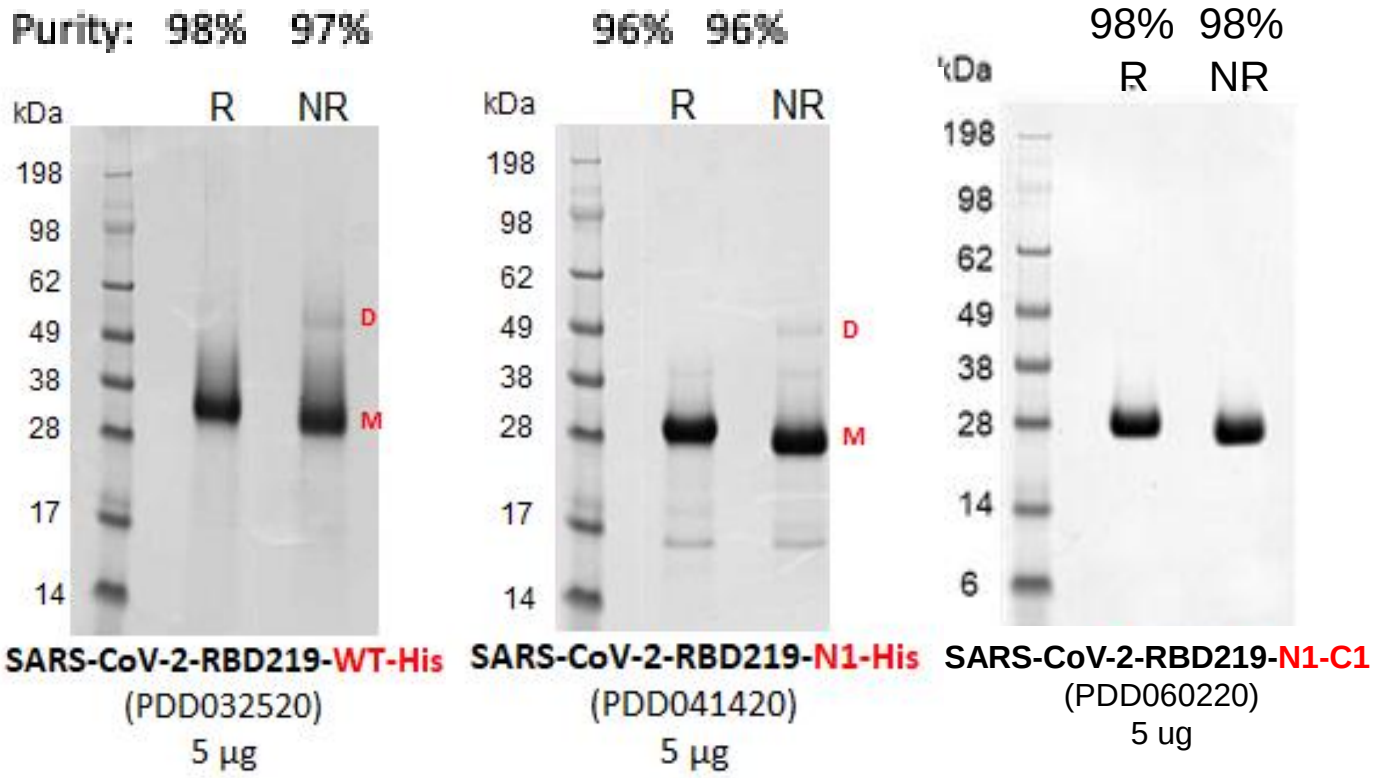
Cloning and Expression Strategy for the CoV-2 Vaccine Candidate



219 WT, 219 N1 and 219 N1C1



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https://www.biorxiv.org/content/10.1101/2020.11.09.373449v1

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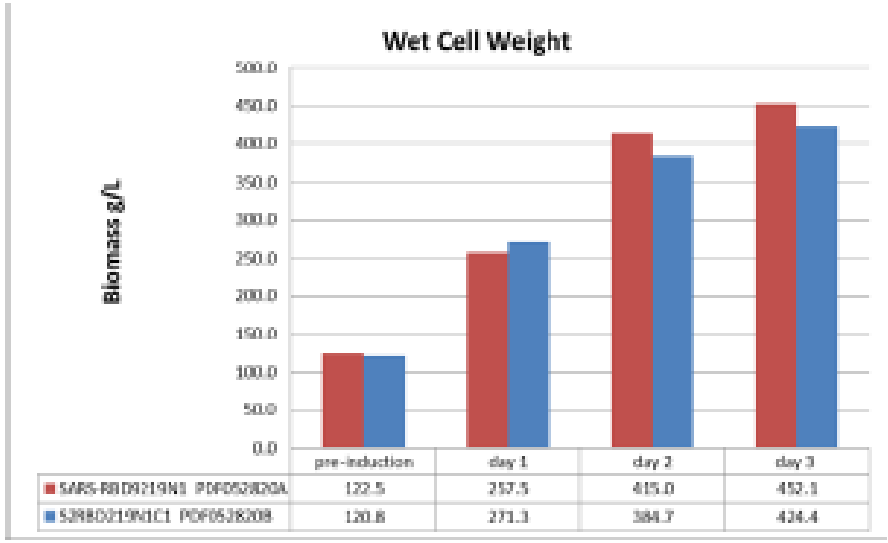
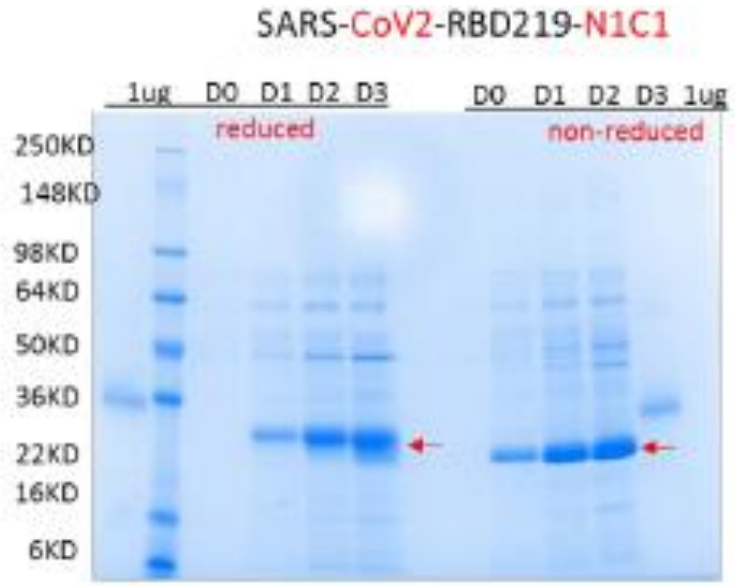
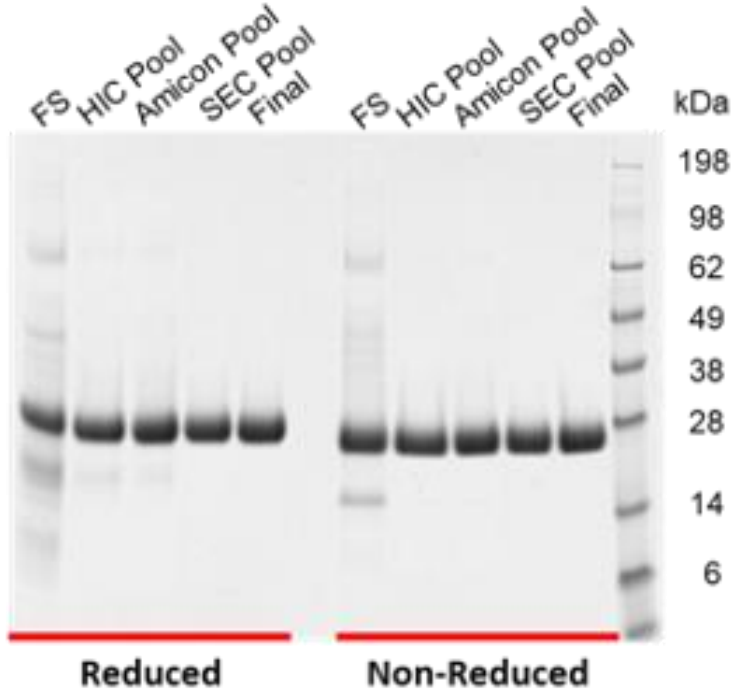
CoV-2-RBD219-N1-C1 Process Development and Scale up Production







Molecule	Fermentation yield* (mg RBD/L of FS)	Level of Impurity on SDS-PAGE	Hyperglycosylation on WB	Dimer formation on WB
RBD219-WT	142 ± 8	High	Yes	Yes
RBD219-N1	50 ± 13	Mid	No	Yes
RBD219-N1C1	280 ± 70	Low	No	No

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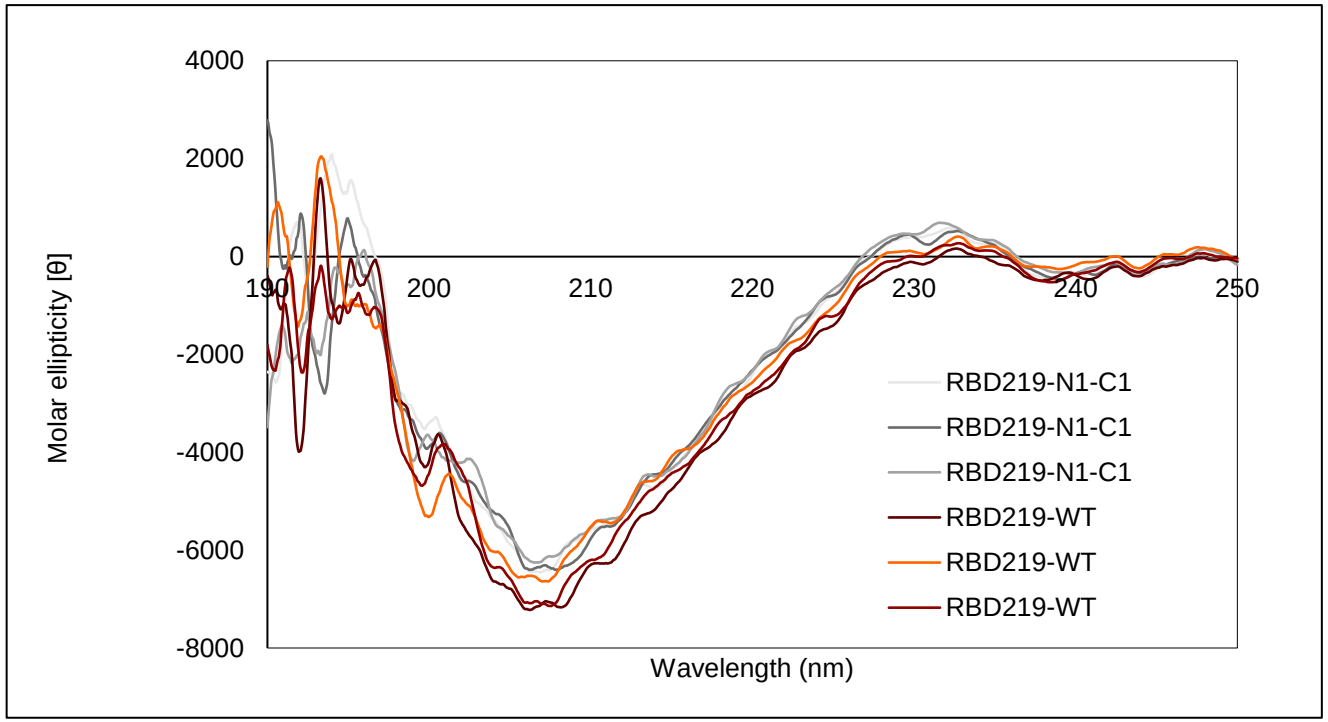
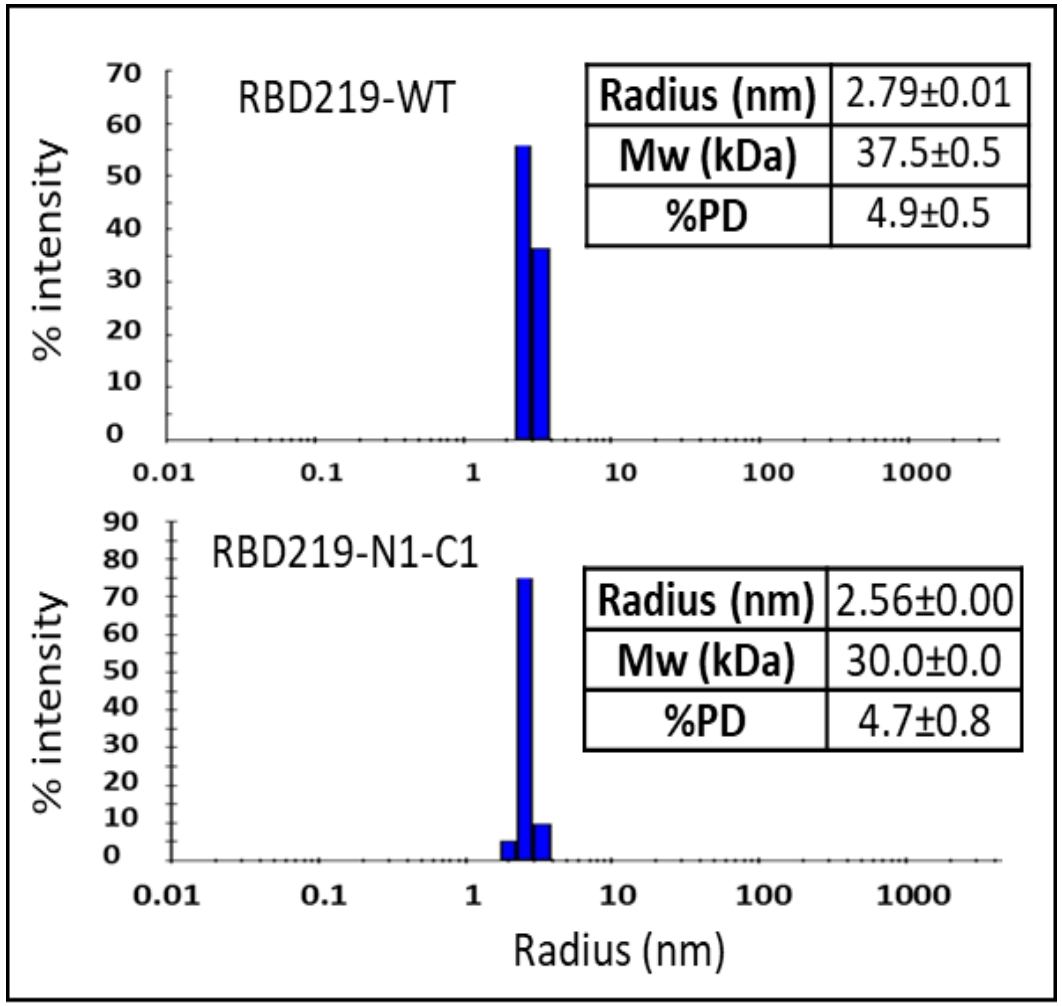
Biophysical Comparison using Dynamic Light Scattering and Circular Dichroism





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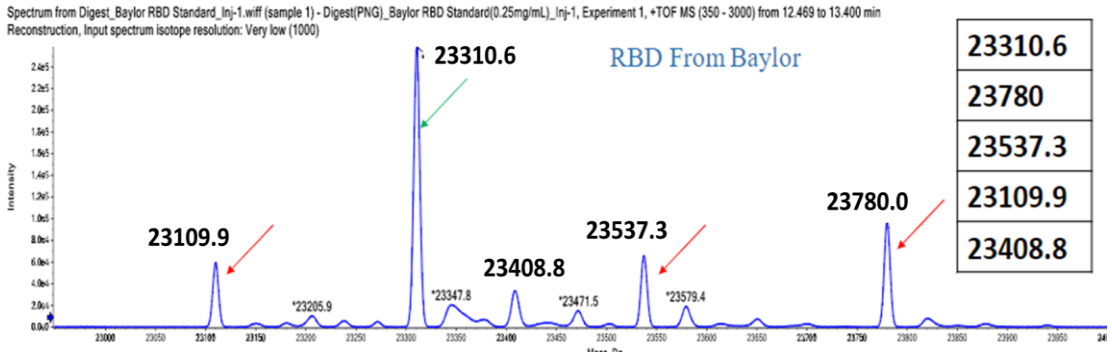
Continuous improvement and re-design strategies to enable robust CMC

>RBD219-N1C1

EAEAEFITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSP
TKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDS
KVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNG
VGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKAVNFNFNGLTGT

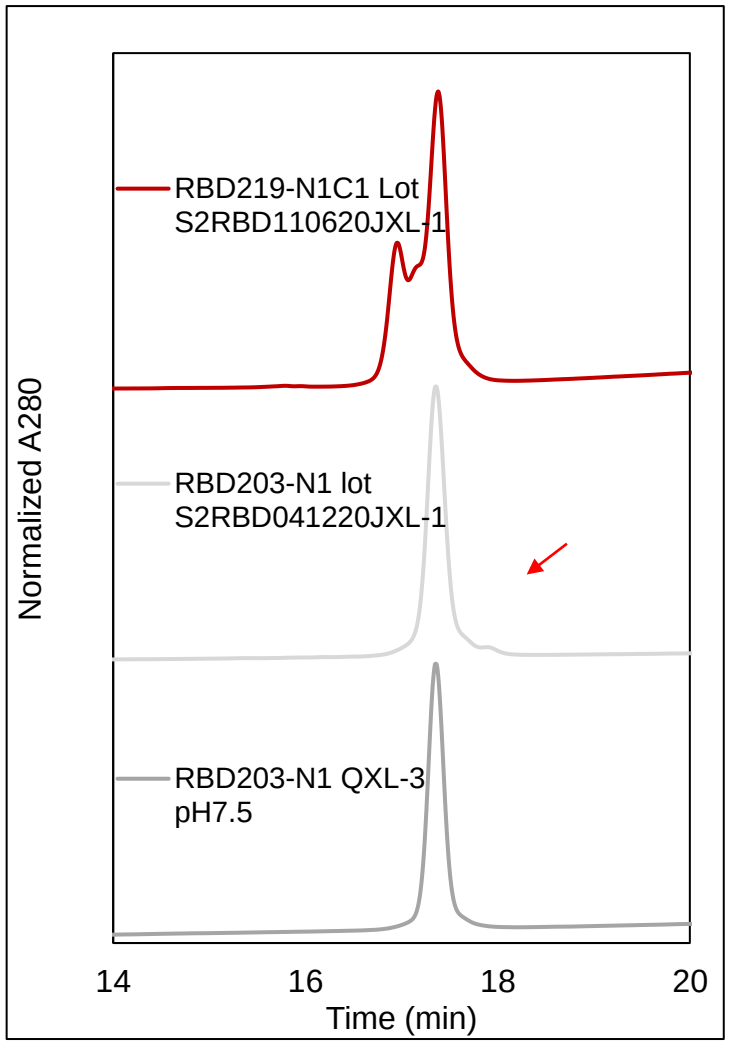


Molecular weight observed by mass spectrometry (kDa)	N-terminal variants	C-terminal variants	Expected Molecular weight (kDa)
23310.6	EAEAEF	STNL	23310
23780	EAEAEF	STNLVKNK	23779
23537.3	EAEAEF	STNLVK	23537
23109.9	EAEF	STNL	23110
23408.8	EAEAEF	STNLV	23409

>RBD203-N1

EAEAEFITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSP
TKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDS
KVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNG
VGYQPYRVVVLSFELLHAPATVCGPKKSTNL

RP-HPLC



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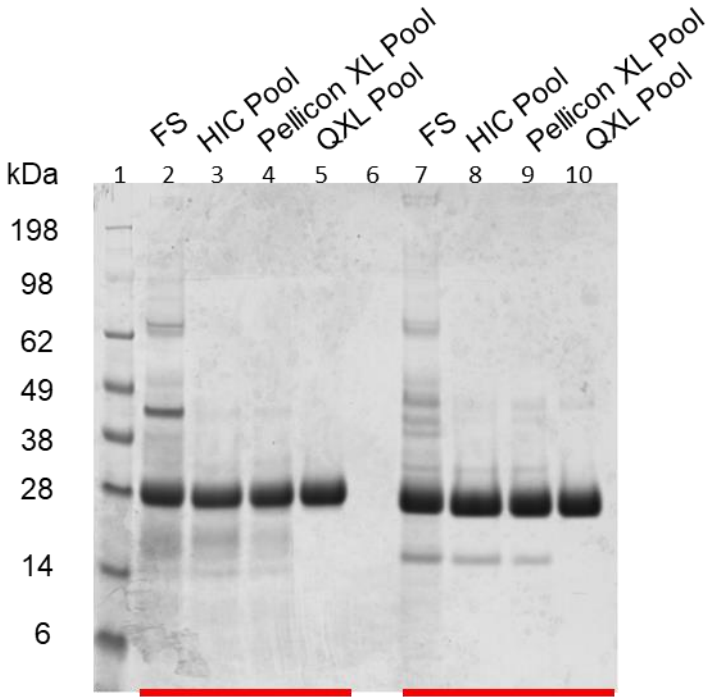
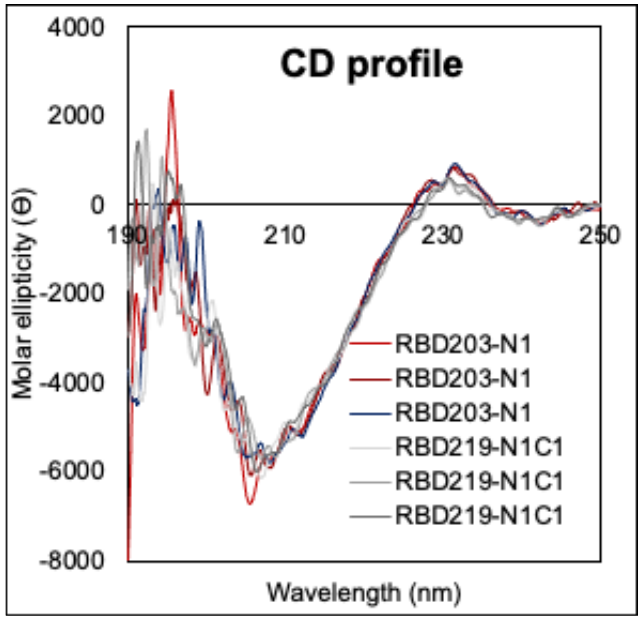
CoV-2-RBD203-N1 Process Development and Scale up Production



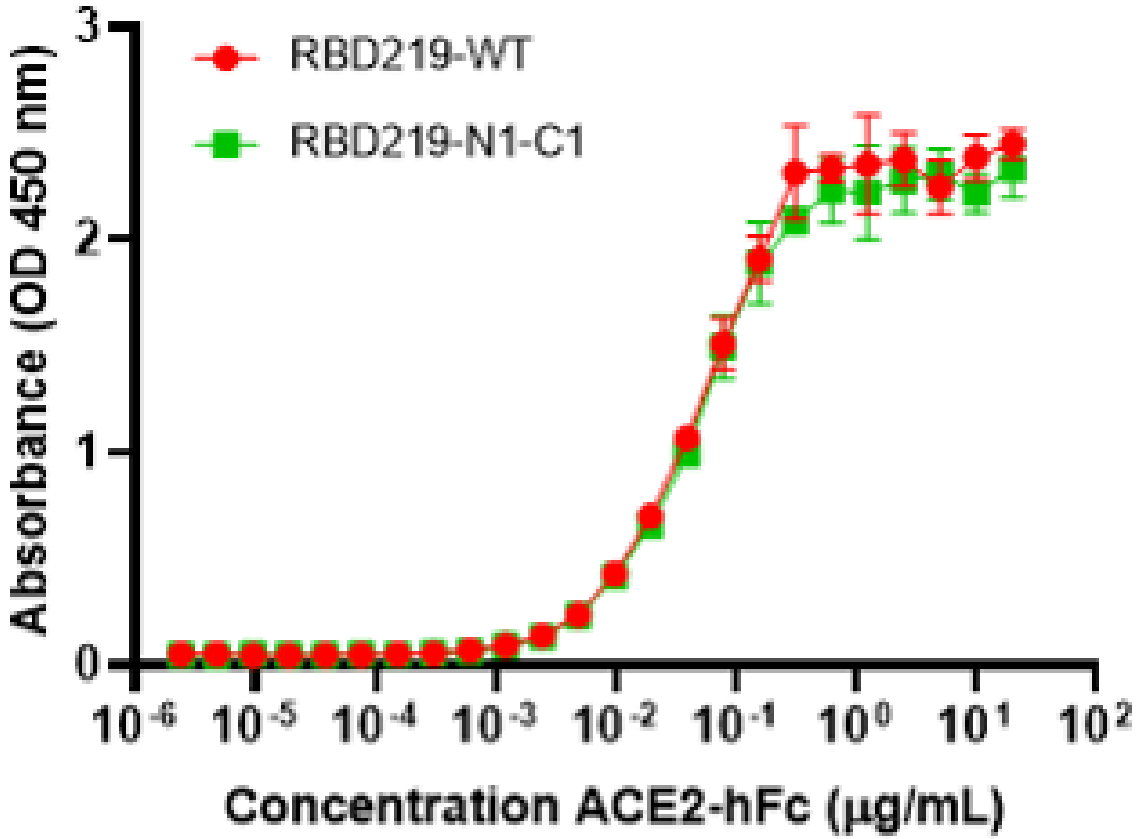
4-12% SDS-PAGE

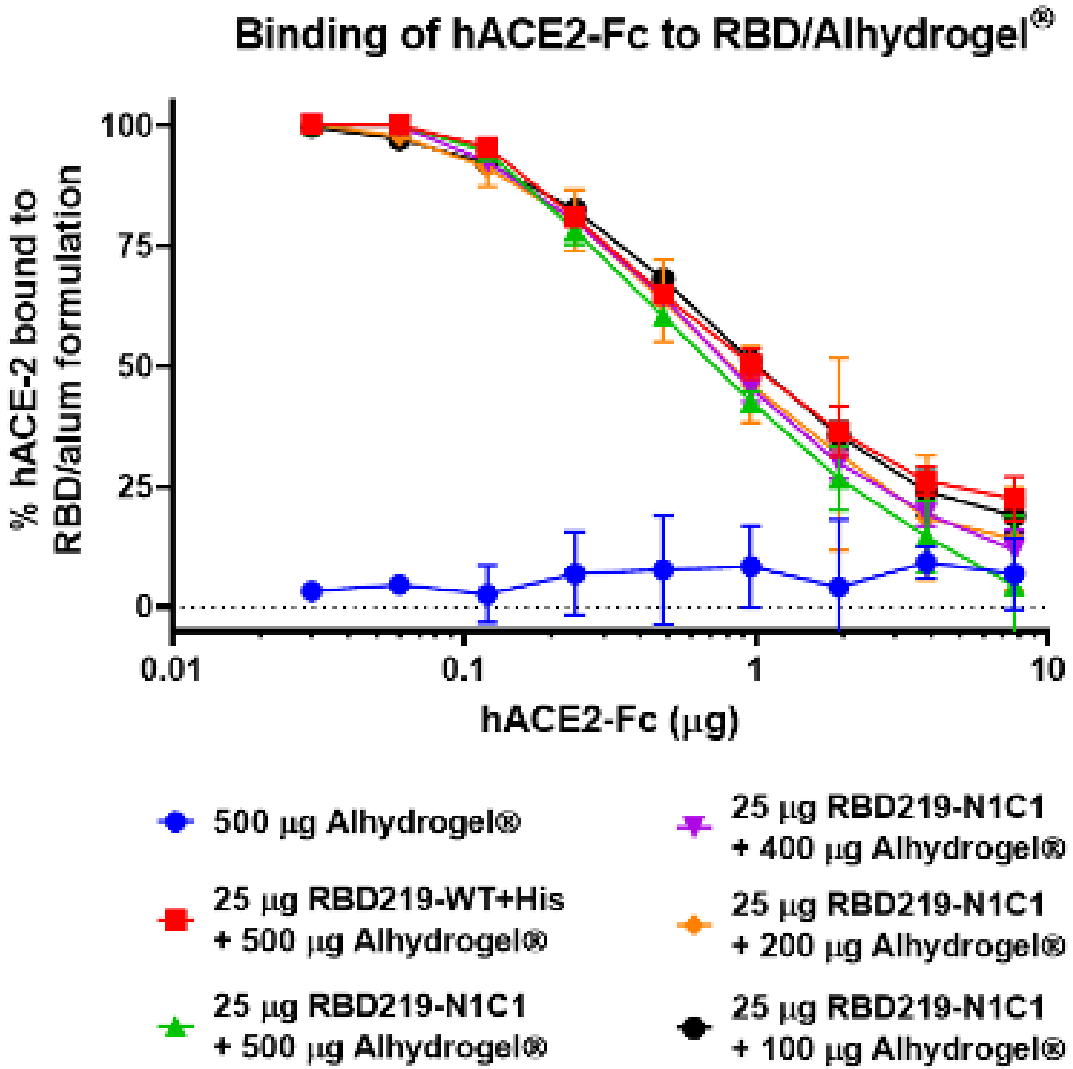


Protein	Tm (°C)
RBD219-N1C1	51.9
RBD203-N1	50.8

	SARS-CoV-2-**RBD-219-N1-C1** (PDD120220)	SARS-CoV-2-**RBD203-N1** (PDD081120)
Yield BEFORE Purification	428 mg/L FS	540 mg/L FS
Overall Recovery	39 %	49 %
Yield AFTER Purification	135 mg/L FS	265 mg/L FS
Purity (Non-Reduced)	95.1 %	94.7 %

Receptor Binding Assays and Functional Comparison





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https://www.biorxiv.org/content/10.1101/2020.11.09.373449v1
https://www.biorxiv.org/content/10.1101/2020.11.04.367359v1

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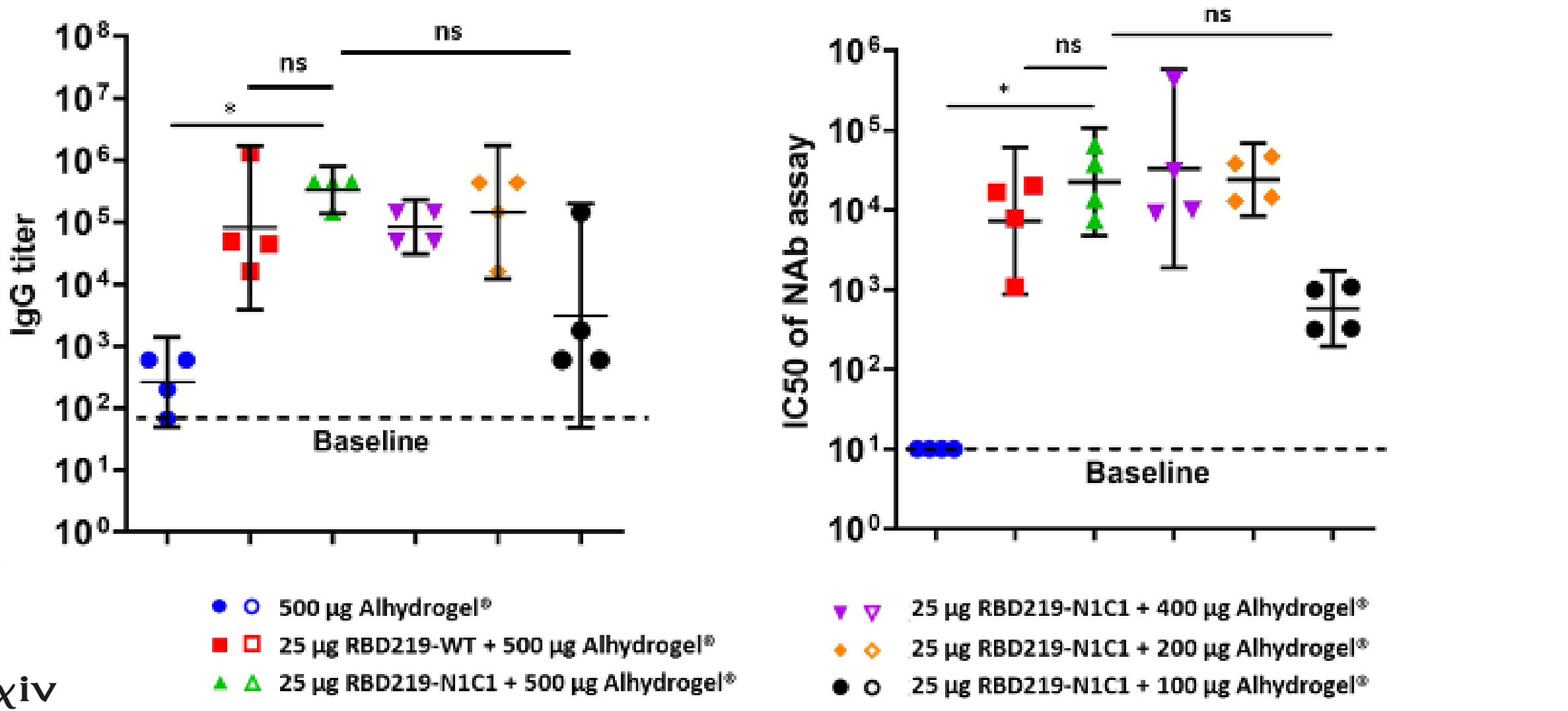
Preclinical Functional Comparison



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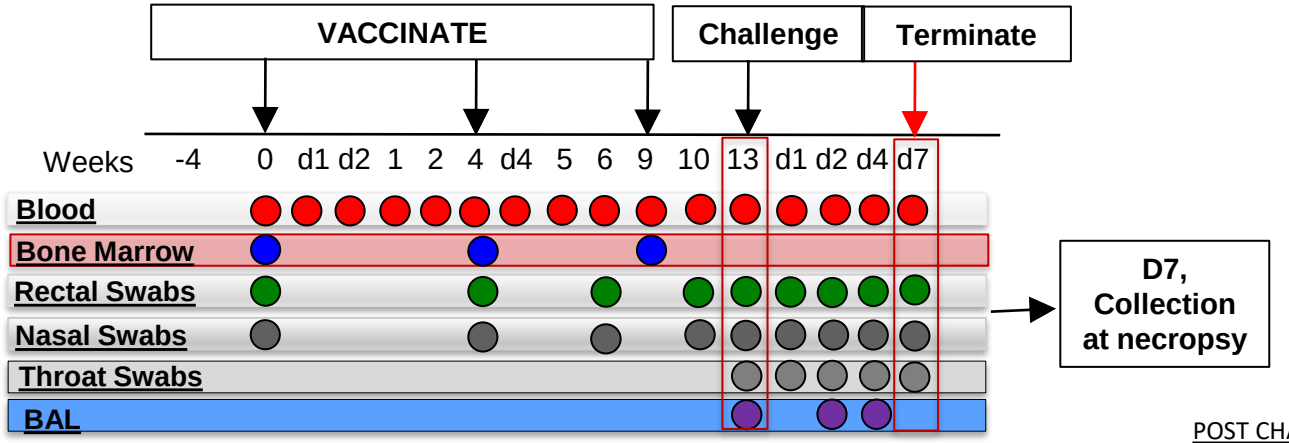
Efficacy and Safety in a NHP Model

EMORY UNIVERSITY

Dr. Sudhir Kasturi



Blood

- Innate responses by Flow, transcriptomics
- CD4+ and CD8+ T cell responses
- Serology (binding, neutralization, ADCC)
- Plasmablast analysis by ELISPOT and FACS

Bone Marrow

- Plasma cell analysis by ELISPOT

Mucosal assays

- IgG and IgA binding antibody
- BAL collections for immune phenotyping

POST CHALLENGE
Frequency of collections TBD

- Nasal swabs (PCR)
- Throat swabs (PCR)
- Serum/plasma (SEROLOGY)
- PBMCs
- BAL (Immune cell phenotyping)
- H&E (Immunepathology at necropsy)

A seminal and strategic partnership for industrial scale

THE HINDU

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Coronavirus | U.S.-based Baylor College of Medicine ties up with India's Biological E for COVID-19 vaccine

Photo: Reuters

Biological E gets CDSCO panel's nod for human trial of Baylor's covid vaccine

2 min read . Updated: 28 Oct 2020, 05:28 PM IST

Leroy Leo

http://gbchealth.org/crossing-the-valleys-of-death-in-tb-from-development-to-roll-out/

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A COVID-19 for Global Health – Latin America, India, Africa

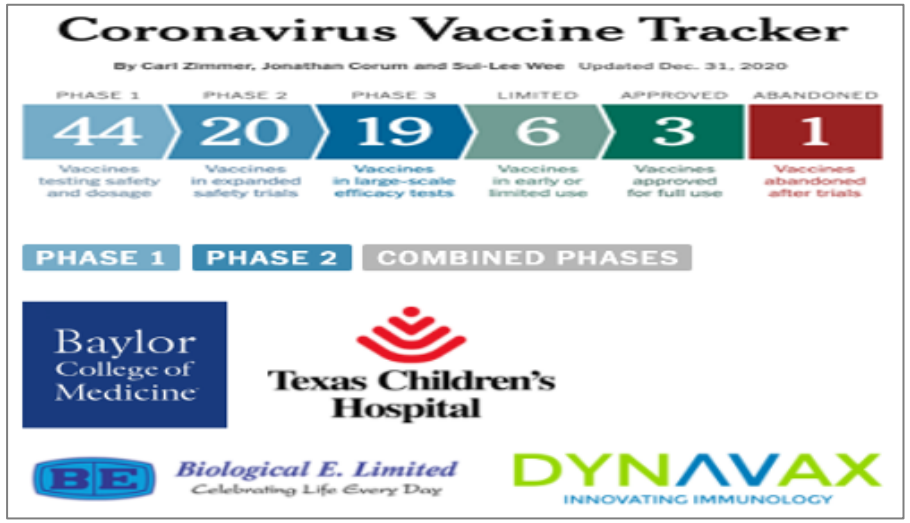
Bio E

APPROACH

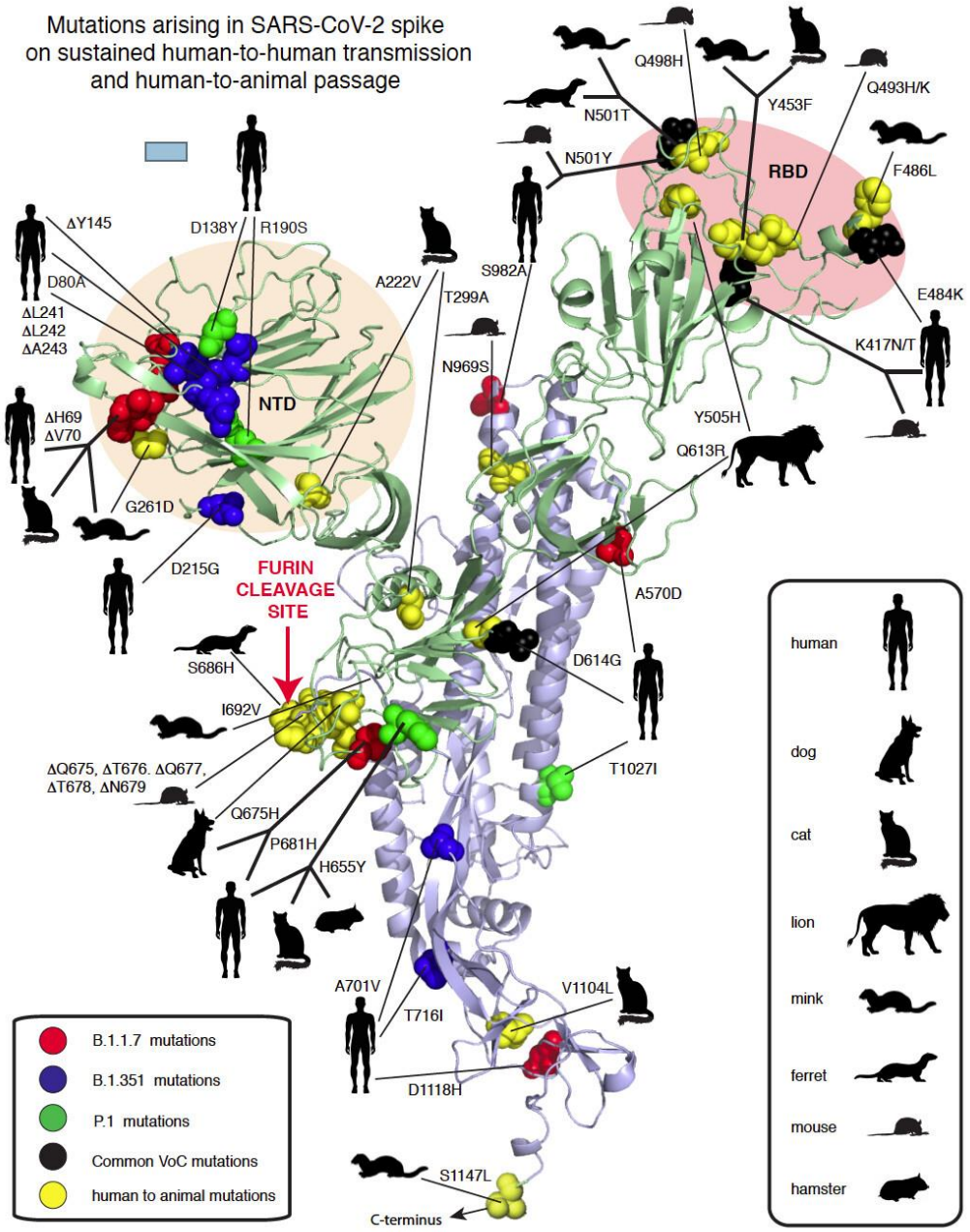
Classical vaccine with established infrastructure and manufacturing platform.

- ✓ *Millions of doses of Hep B vaccine manufactured and distributed.*

Collaboration with Baylor College of Medicine (Peter Hotez, Maria-Elena Bottazzi)



- The candidate cell bank and its production process were developed at Texas Children's CVD
- The vaccine or closely related prototype induces high levels of protection in mice and NHPs
- Biological E scaling up production and advancing its Ph 1/2 clinical testing in seven sites in India
- Ease of production, scalability and storage at 4ºC



Emerging Strains of SARS-CoV-2

Residues within the Receptor Binding Domain (RBD) sequence

- B.1.1.7 ("UK strain"):
N501Y, delH69, delV70, delY145, A570D, P681H, T716I, S982A D1118H

- **B.1.351 (501Y.V2, "South Africa strain"):**
D80A, D215G, K417N, E484K, N501Y, and A701V

- P1/2 ("Manaus/Brazil strain")
E484K

- L425R ("California strain")
L425R

- 20G/677H ("Ohio strain I")
Q677H (plus mutations in M: A85S and N: D377Y)

20G/501Y (Ohio strain II")
N501Y (plus mutations in ORF1AB)

Mutations arising in SARS-CoV-2 spike on sustained human-to-human transmission and human-to-animal passage, Robert F. Garry
https://virological.org/t/mutations-arising-in-sars-cov-2-spike-on-sustained-human-to-human-transmission-and-human-to-animal-passage/578

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Do the mutations allow the virus to evade the immune system?

Mutant RBD proteins under development

High Priority:

- **UK-RBD:** RBD203-N1, N501Y
- **ZA-RBD:** RBD203-N1, K417N+E484K+N501Y
- **Brazil-RBD:** RBD203-N1, E484K

Lower Priority:

- Mink/DK RBD: RBD203-N1, N501Y+Y453F
- RBD203-N1, Y453F

Criteria for prioritization

- Prevalence
- Potential for immune evasion
- Potential for increased infectivity

Pseudovirus Generation

Mutations	Status
D614G	Completed
N501Y-D614G (UK)	Completed
Δ69-70-N501Y-D614G (UK)	Near completion
Δ69-70-N501Y-D614G-P681H (UK)	In progress
E484K-N501Y-D614G (ZA)	Near completion
K417N-E484K-N501Y-D614G (ZA)	Near completion
E484Q-D614G	Near completion
K417T-E484K-N501Y-D614G	Under consideration
L452R (CA)	Starting

Courtesy Dr. Jason Kimata, BCM

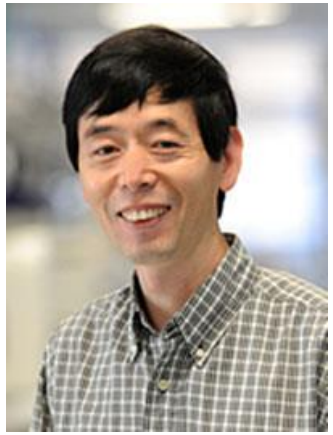
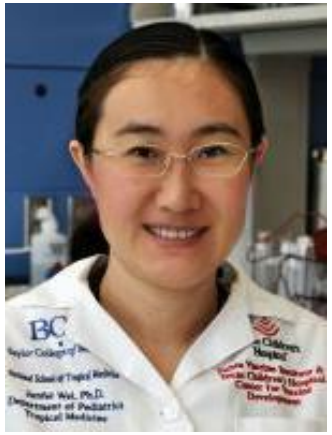
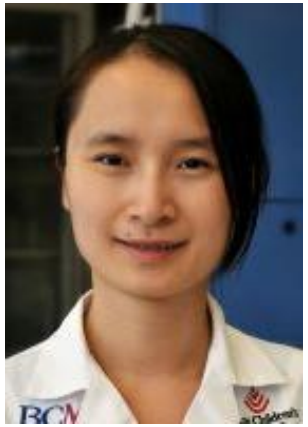
A COVID-19 Vaccine for Global Use

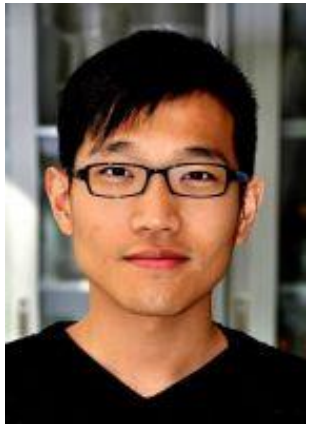
- Leveraged a path for a COVID-19 vaccine from prior experience
- Exploring a US strategy including pediatric and maternal immunization vaccine suitability
- Exploring other delivery and adjuvant systems
- Interest in evaluating as boosters for OWS vaccines
- Expanding to universal coronavirus vaccine development
- Interest in expanding partnerships with US pharma and investors

Coronavirus Vaccines in Development Team Leads

A SARS CoV Vaccine as a potential heterologous vaccine against SARS-2 CoV

A SARS-2 CoV Vaccine leveraging the knowledge gained from SARS CoV




And many other staff and faculty behind the scenes

Collaboration with BCM Cores Dr. Kimata and others

This work was supported by Robert J. Kleberg Jr. and Helen C. Kleberg Foundation, Fifth Generation, Inc. (Tito's Handmade Vodka), JPB Foundation, NIH-NIAID (AI14087201) and Texas Children's Hospital Center for Vaccine Development Intramural Funds.

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