Strategies For A Pancoronavirus Vaccine

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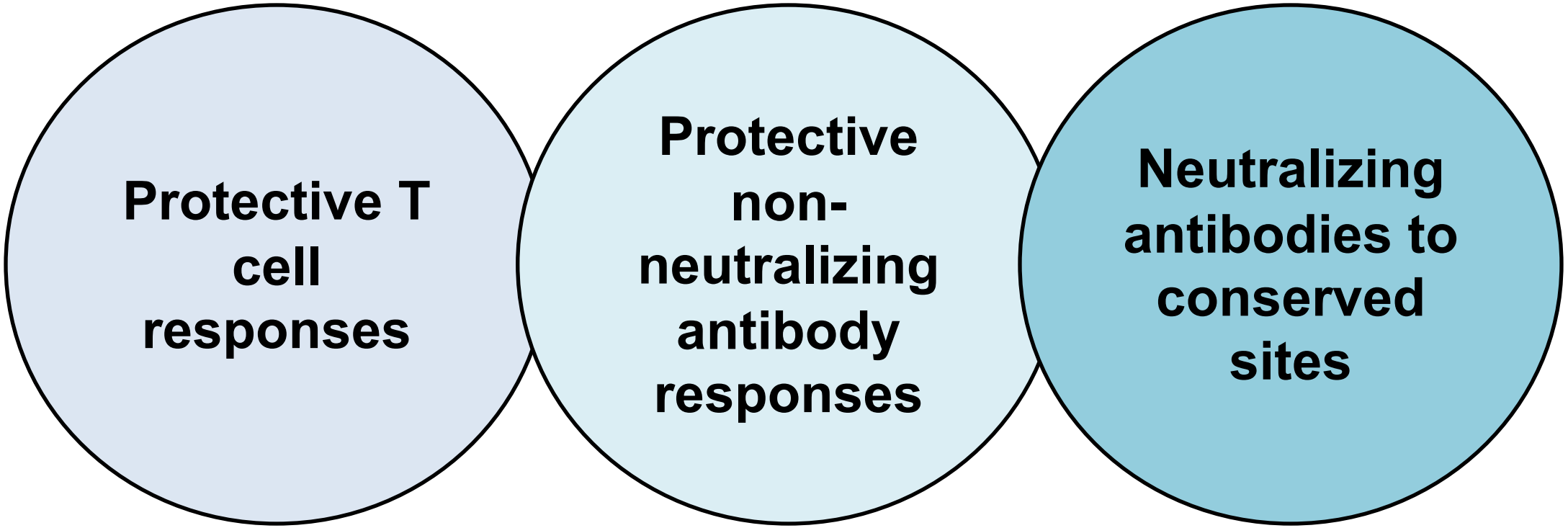
Director of Research, Duke Human Vaccine Institute
Duke University School of Medicine
March 25, 2022

NIH National Institute of Allergy and Infectious Diseases
P01 AI158571, DMID

Hypothesis: Activation of multiple arms of the immune system will lead to the broadest protective immunity

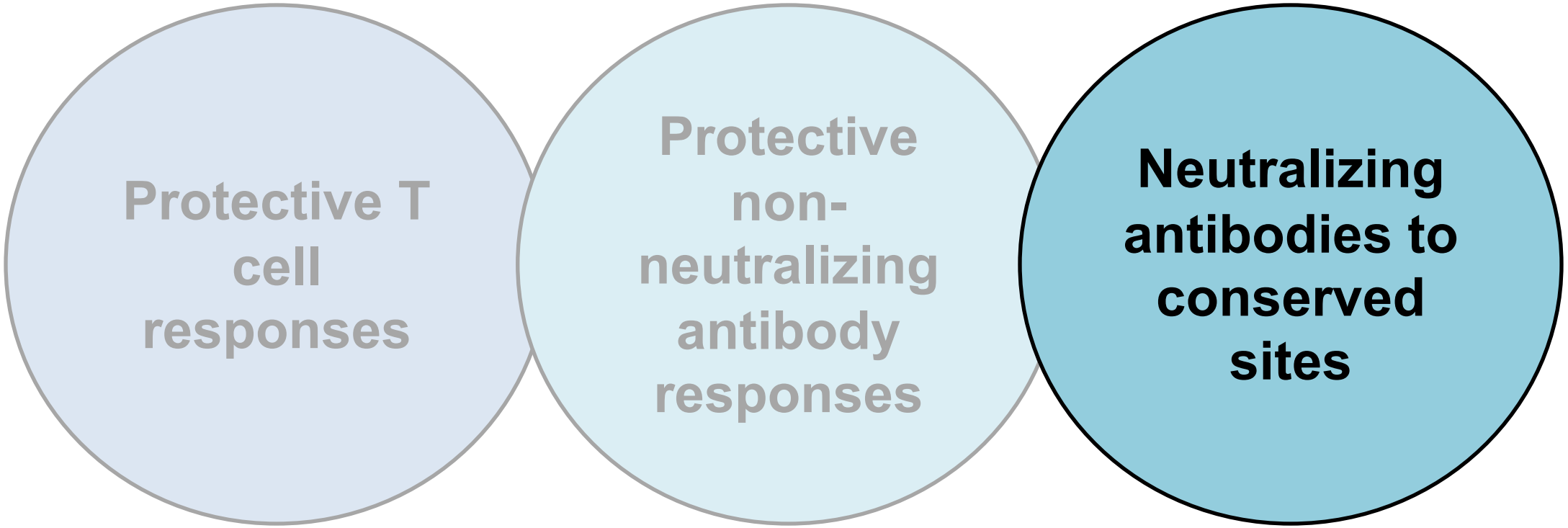


Collaborators:
Bette Korber,
Drew Weissman

Collaborators:
Guido Ferrari

Collaborators:
Priyamvada Acharya,
Kevin Wiehe,
Mihai Azoitei,
Barton Haynes,

Activation of multiple arms of the immune will lead to the broadest protective immunity



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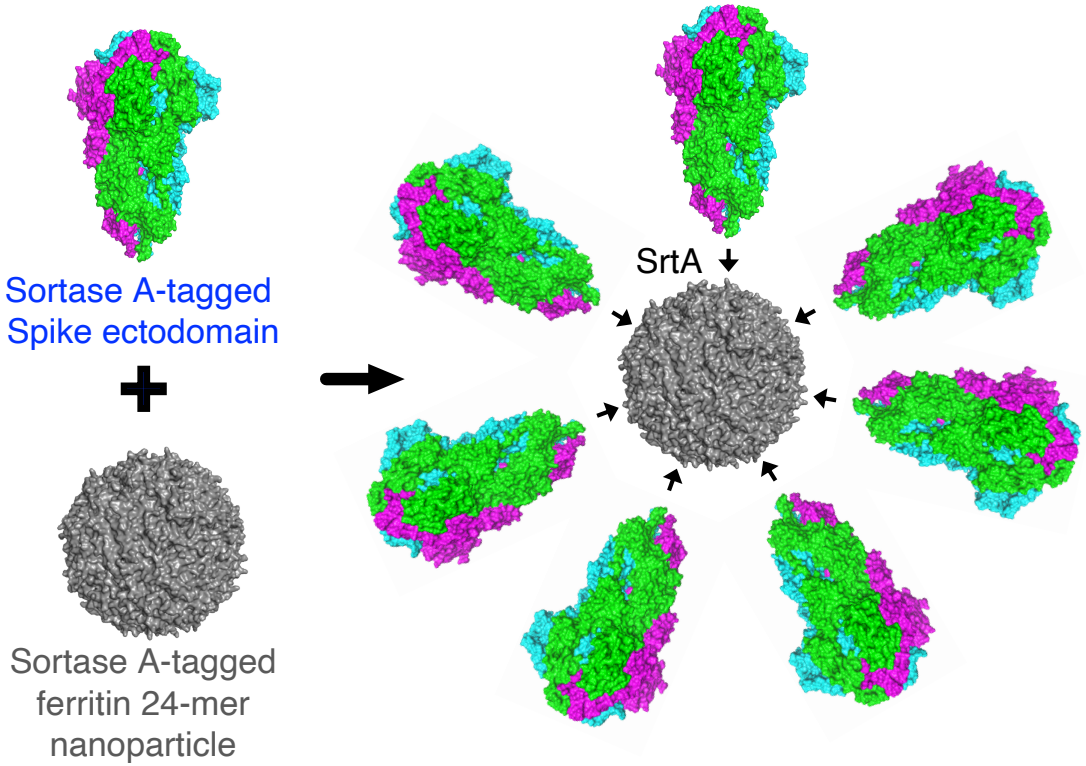
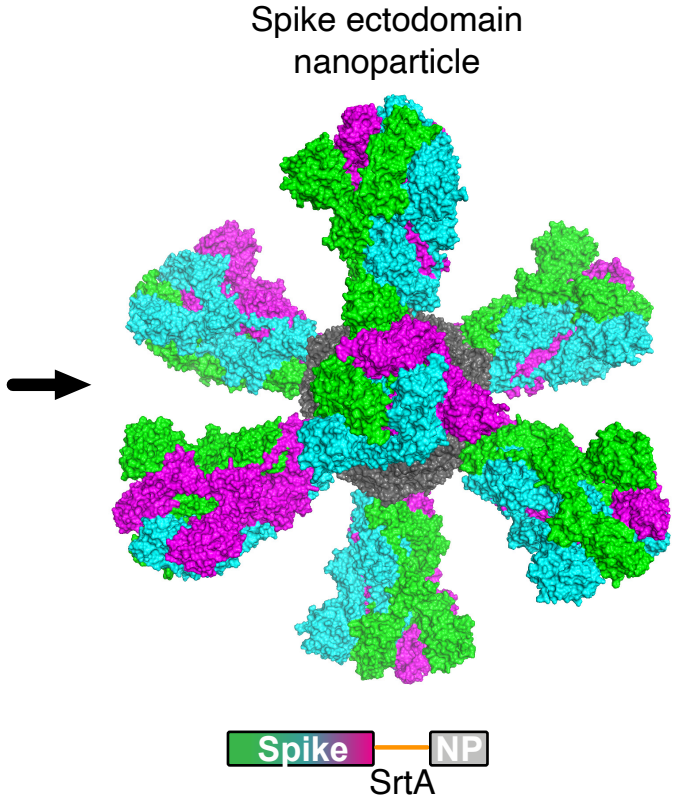
Mihai Azoitei

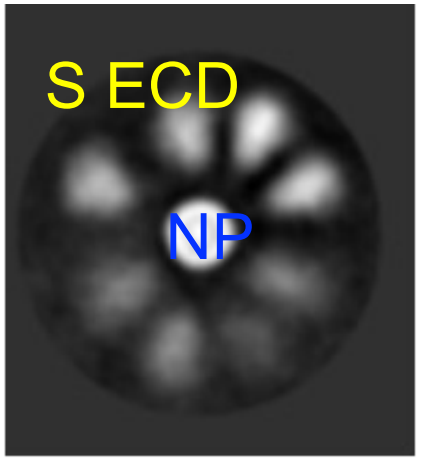
Multimerization of antigen to induce potent humoral immunity

Multimerization of SARS-CoV-2 S ectodomain to make virus-like particles





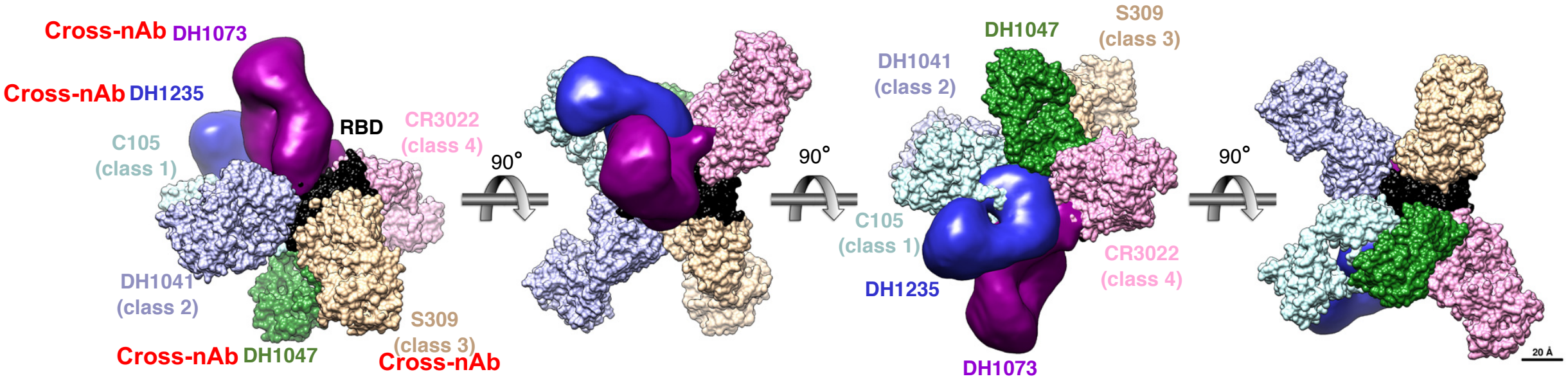
Ectodomain nanoparticles



Electron microscopy of nanoparticle immunogen

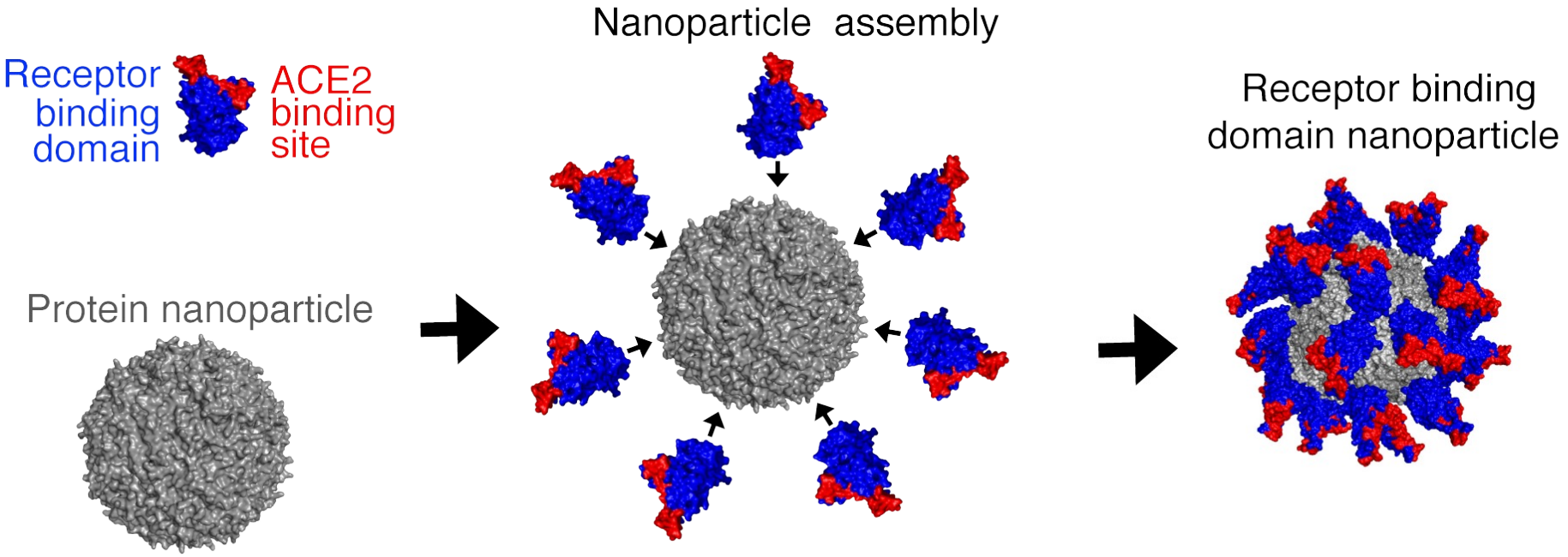
Li D et al Biorxiv 2022

Structures of cross-neutralizing antibodies define multiple broadly neutralizing epitopes on RBD

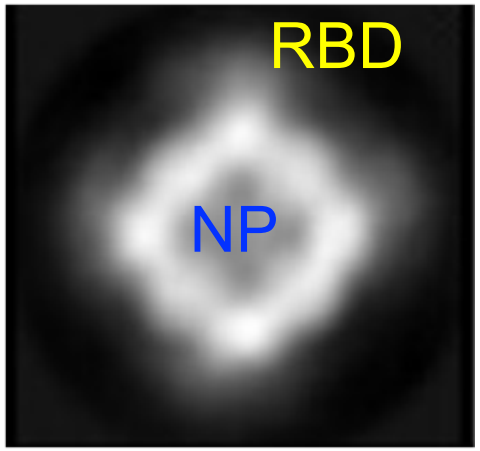


RJ Edwards

Multimerization of SARS-CoV-2 RBD to focus antibodies on the RBD



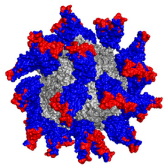
Receptor-binding domain nanoparticles



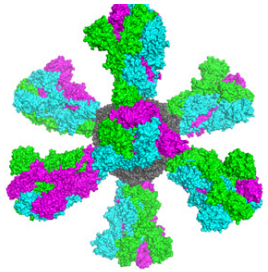
Electron microscopy of nanoparticle immunogen

Esther Lee, Haiyan Chen, RJ Edwards, Mihai Azoitei
Saunders et al Nature 2021

Can nanoparticle vaccines protect against SARS-CoV-2 Beta variant of concern?

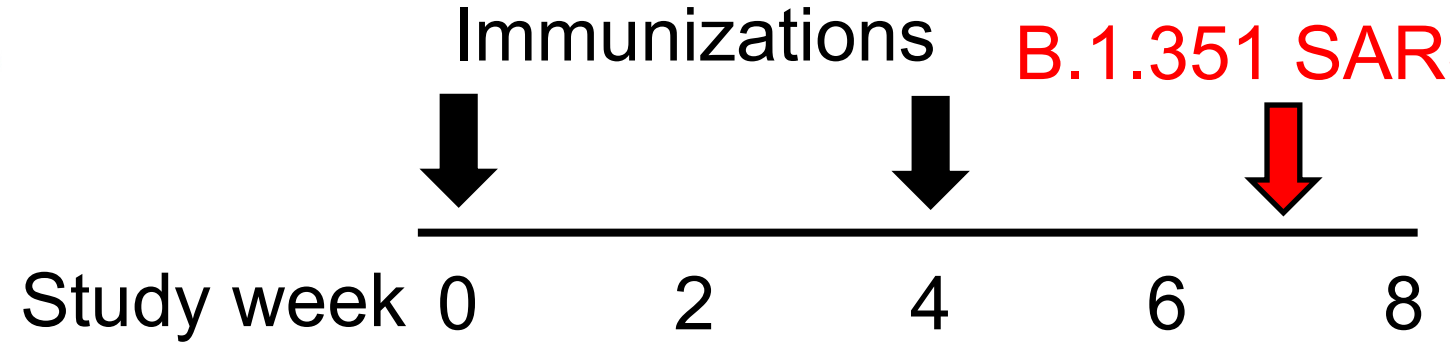


WA-1
or
B.1.351

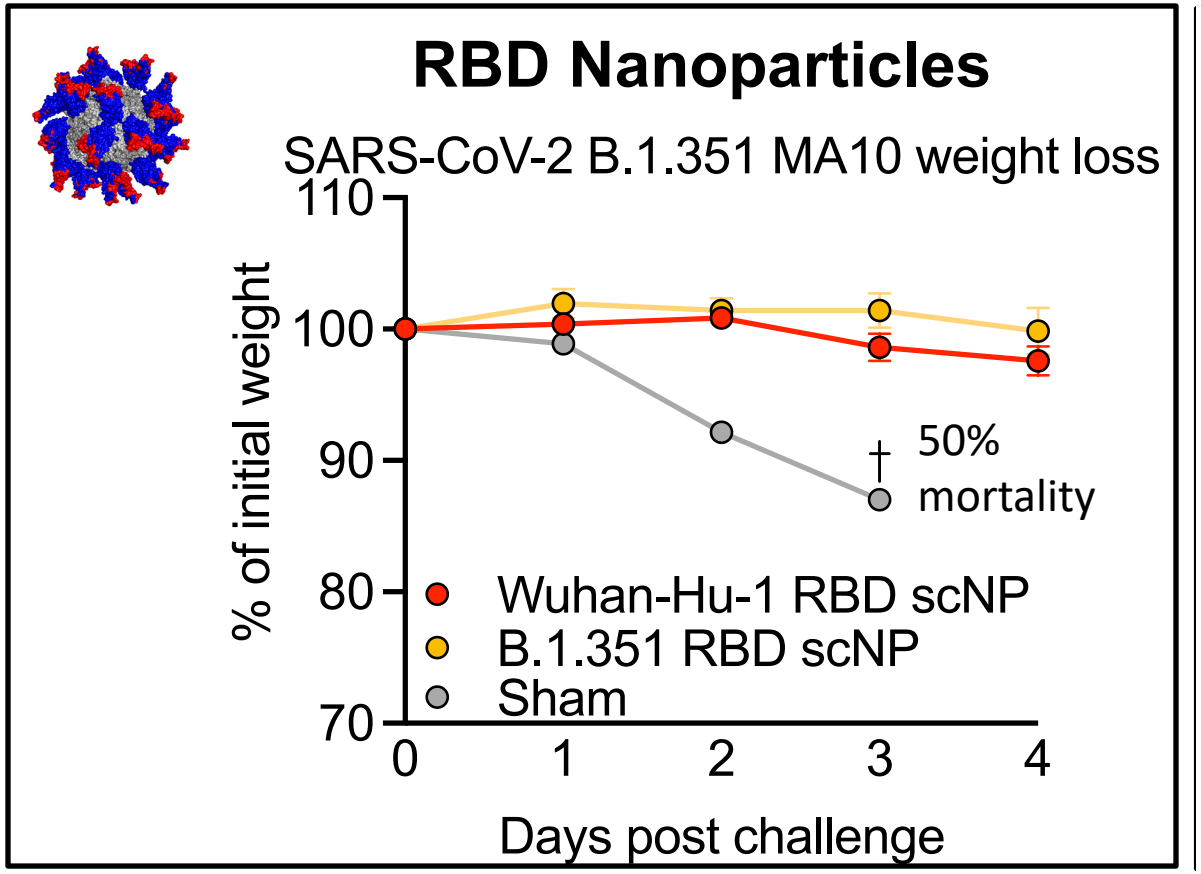


WA-1
or
B.1.351

Aged BALB/c

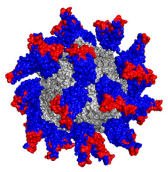


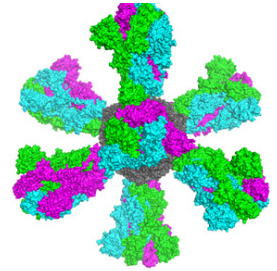
Nanoparticle vaccines protect against lethal challenge with the Beta variant of SARS-CoV-2



David Martinez, Ralph Baric, Barton Haynes

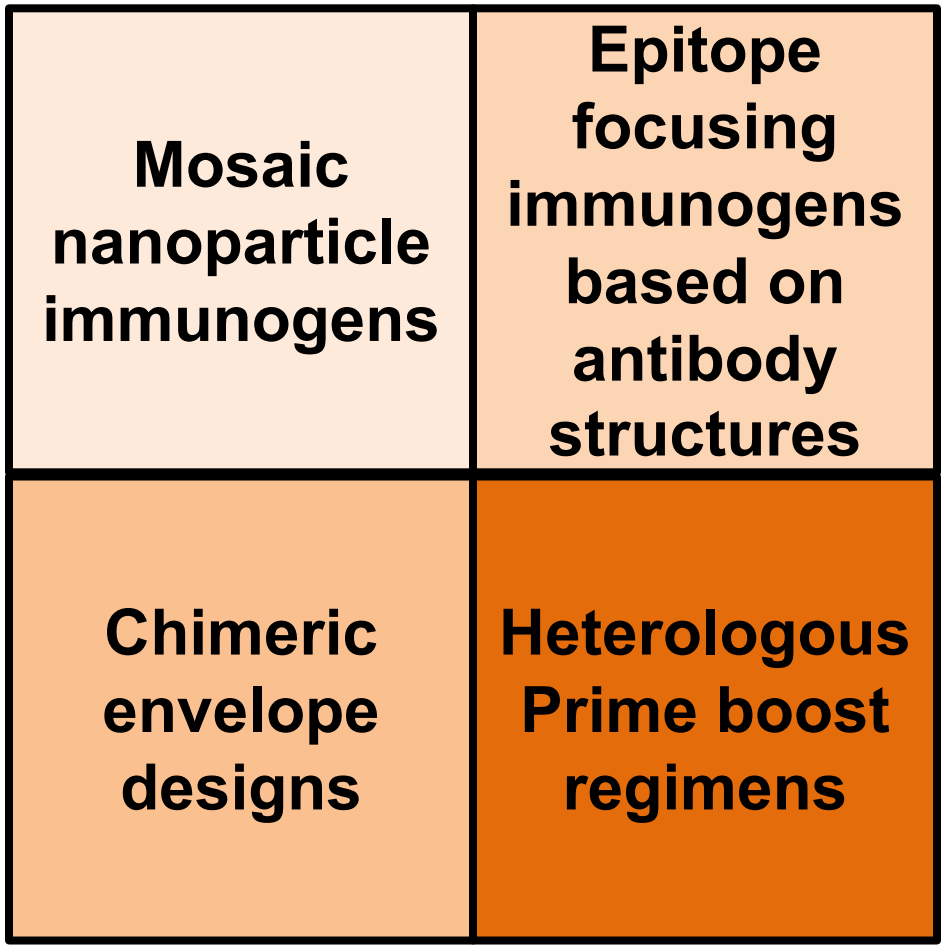
Nanoparticle vaccines protect against lethal challenge with the Beta variant of SARS-CoV-2





David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes

Approaches for broadening potent antibody responses



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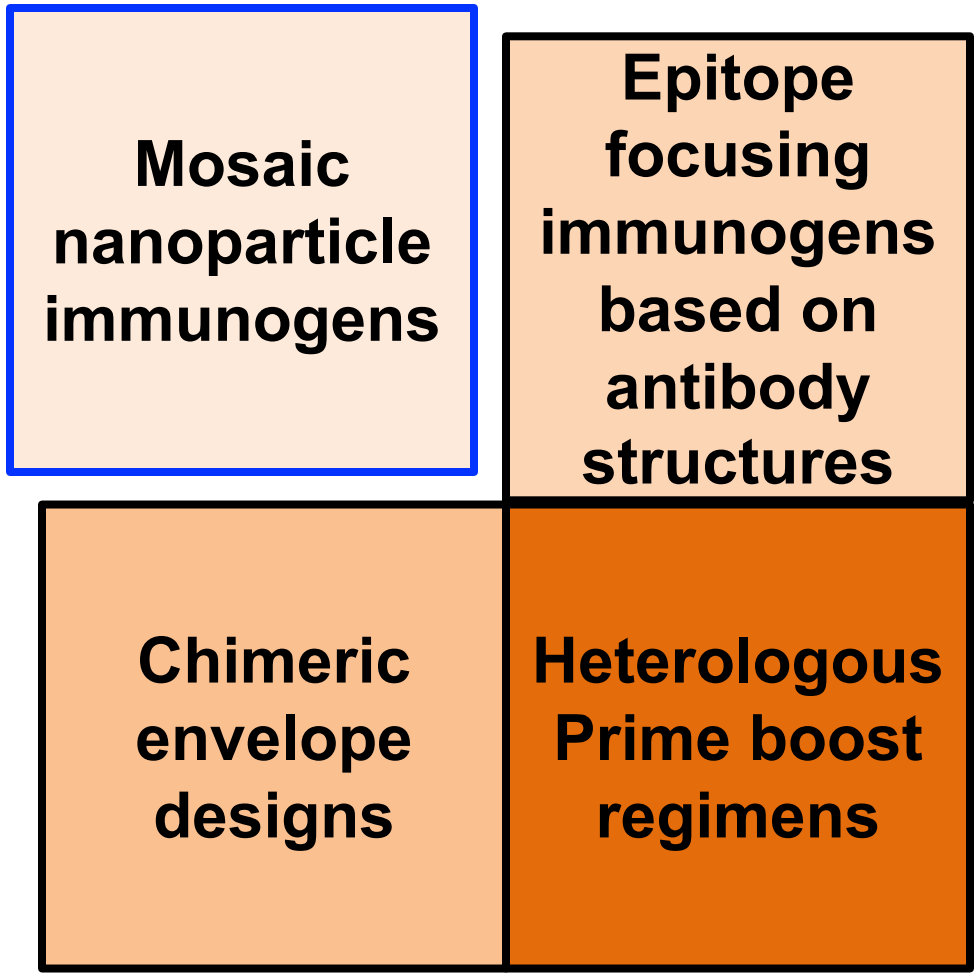
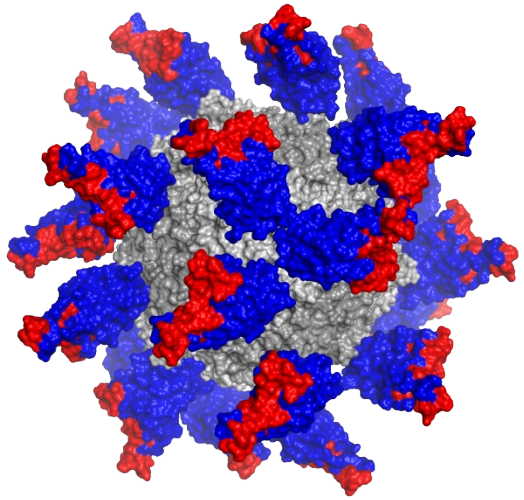


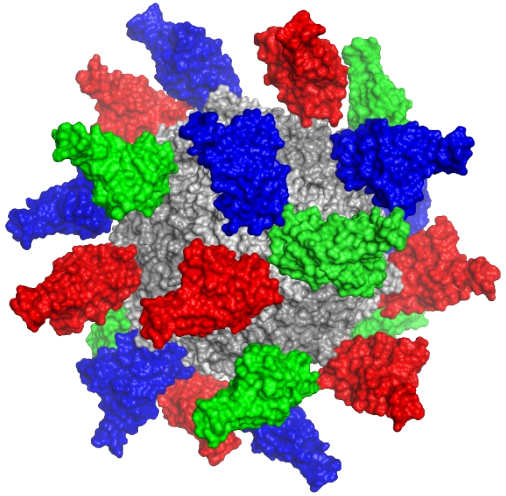
Mosaic conjugate nanoparticle immunogens

Monovalent RBD nanoparticle



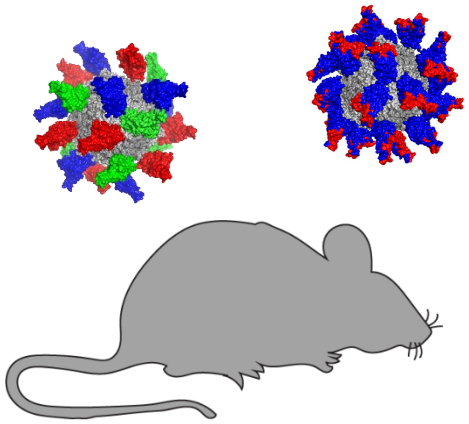
SARS-CoV-2 WT
RBD 24-mer

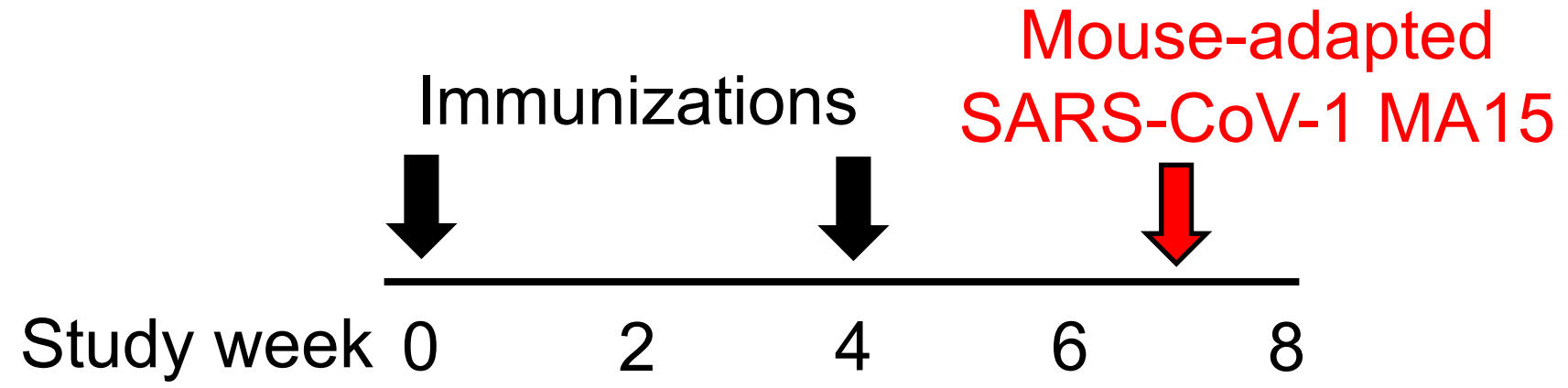
Trivalent Mosaic RBD nanoparticle



Groups 2b + 2c
MERS
SHC014
SARS-CoV-2
RBD 24-mer

Can mosaic nanoparticle vaccines protect against a heterologous betacoronavirus?

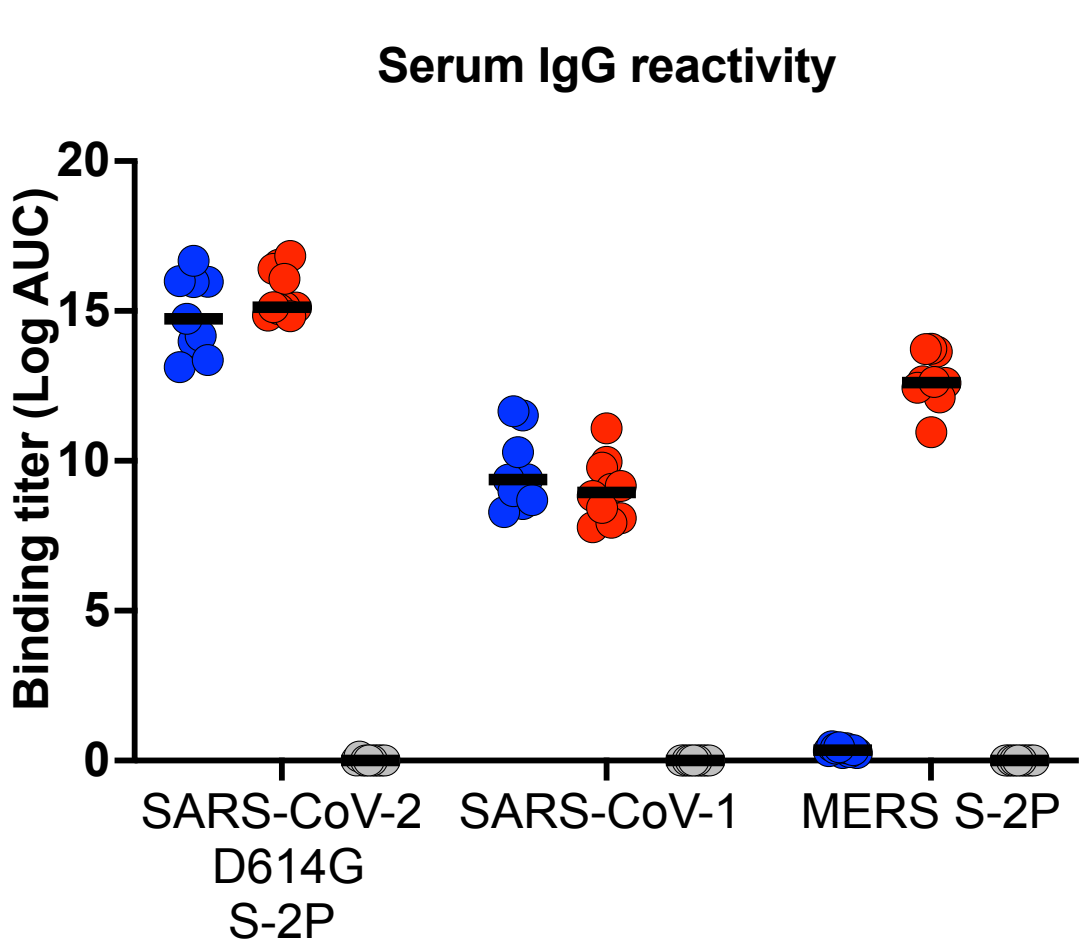


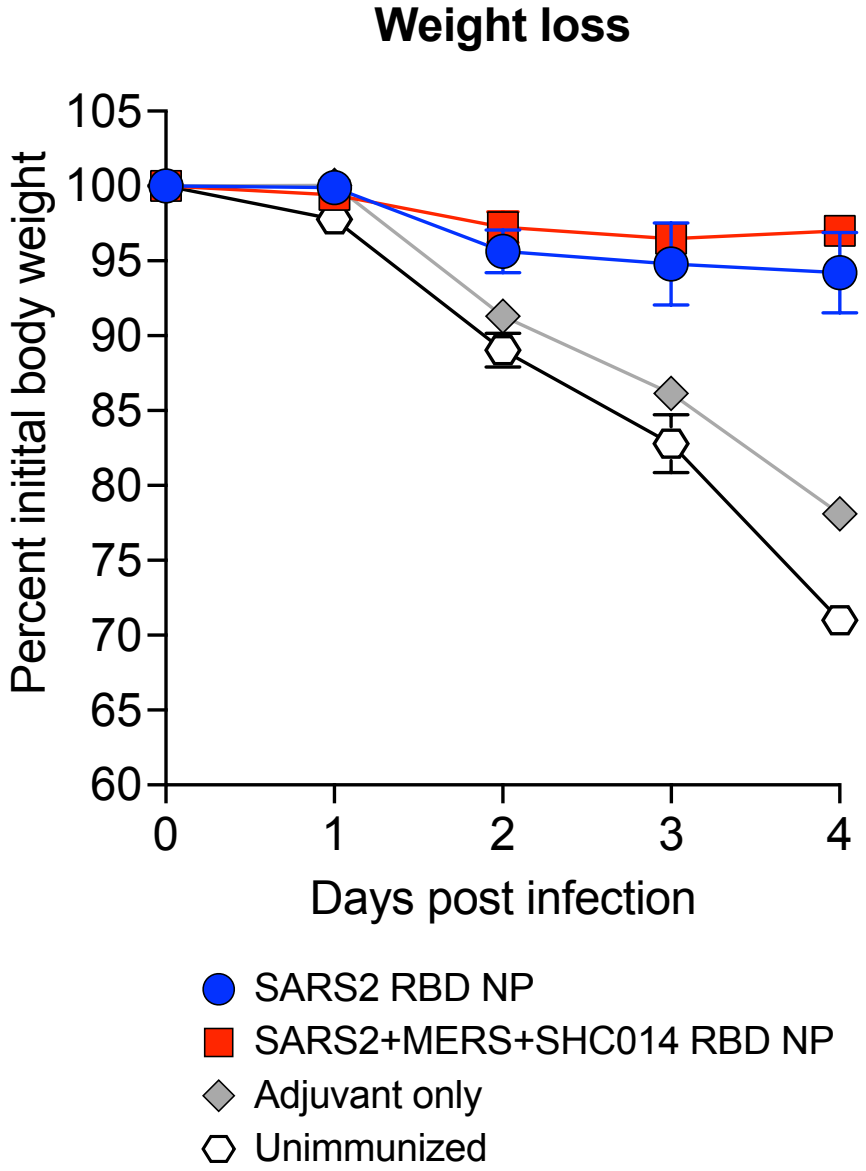


Immunogen: 10mcg
Adjuvant: 5mcg GLA-SE (IDRI-EM082)
Route: 2 sites IM (50mcl)

Haiyan Chen, Esther Lee, Amanda Newman, Cynthia Bowman,
David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes

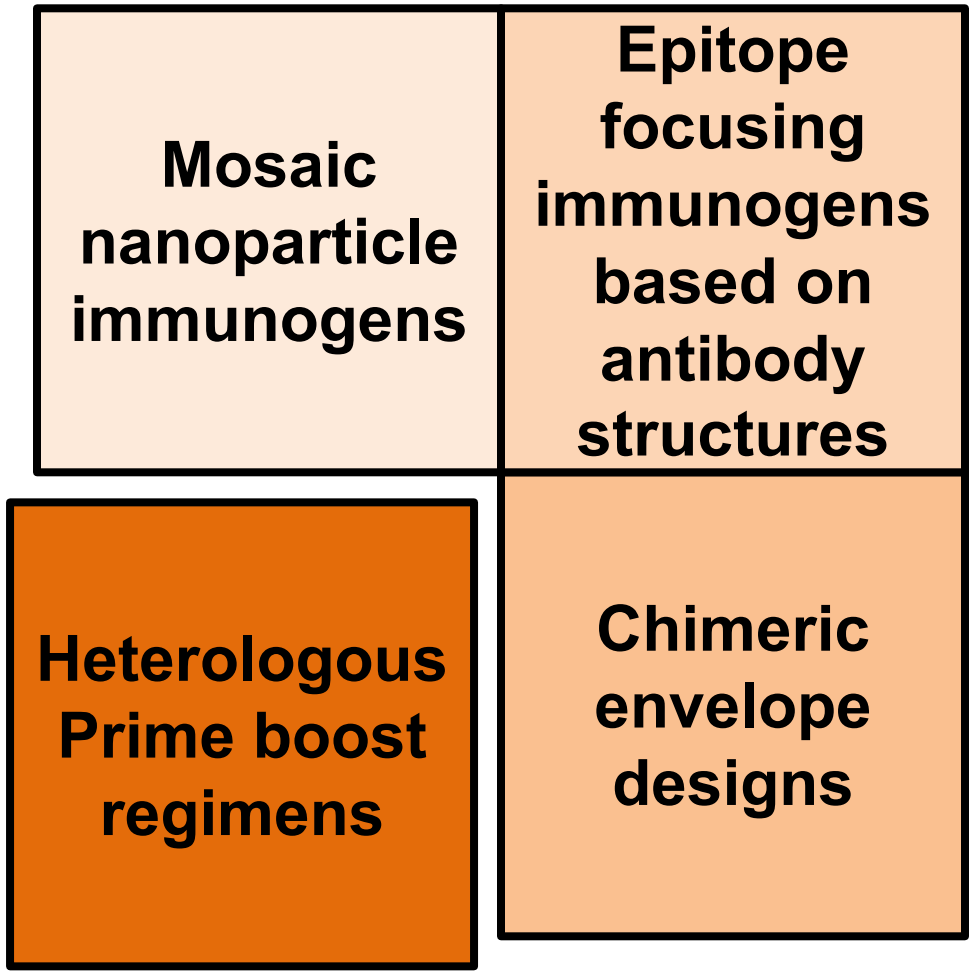
Mosaic NP immunization generates Group 2B+2C reactive antibodies and protects against heterologous betacoronavirus infection





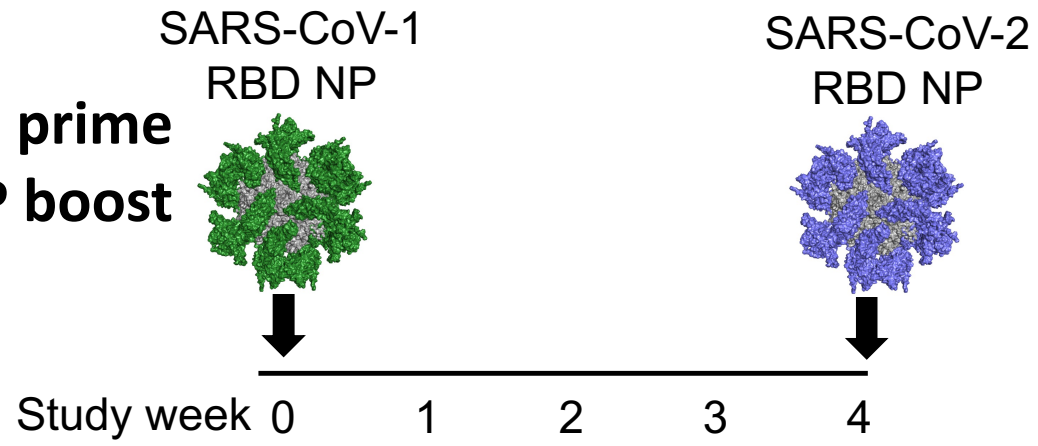
David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes

Approaches for broadening potent antibody responses

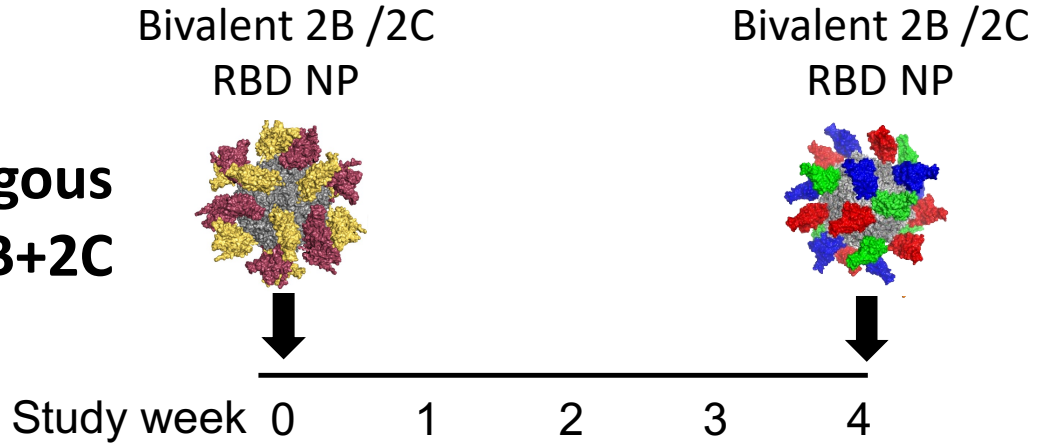


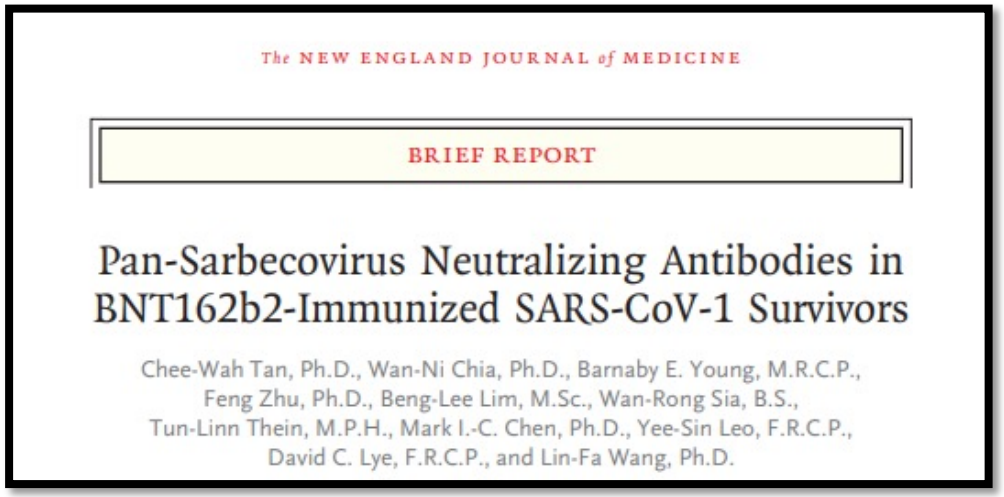
Optimization of heterologous prime boost regimens to increase neutralization breadth

SARS-CoV-1 NP prime
SARS-CoV-2 NP boost



Heterologous Group 2B+2C




The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

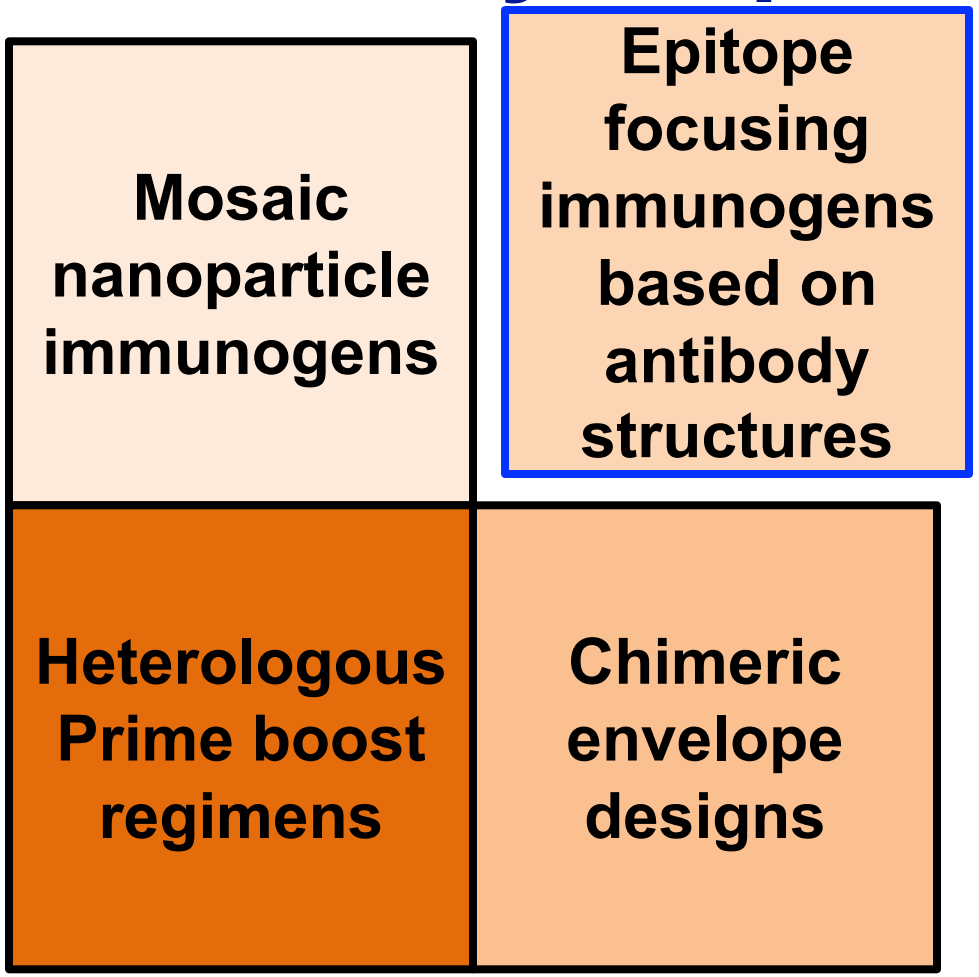
Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors

Chee-Wah Tan, Ph.D., Wan-Ni Chia, Ph.D., Barnaby E. Young, M.R.C.P., Feng Zhu, Ph.D., Beng-Lee Lim, M.Sc., Wan-Rong Sia, B.S., Tun-Linn Thein, M.P.H., Mark I.-C. Chen, Ph.D., Yee-Sin Leo, F.R.C.P., David C. Lye, F.R.C.P., and Lin-Fa Wang, Ph.D.

Tan, CW, Wang, L et al NEJM, 2021

Defining the rules for which spikes work best as primes versus which spikes work best as boosts

Approaches for broadening potent antibody responses



Broadly neutralizing antibodies can serve as immunogen targets

Neutralization titers (PsVNA50) against SARS-CoV-2 variant strains (IC50 mcg/mL)											
Ab	WA-1	Alpha B.1.1.7	Beta 1.351	Gamma P1	Epsilon 1.429	Iota 1.526	Kappa 1. 617.1	Delta 1.617.2	Omicron BA.1	BA.3	BA.3
DH1284	0.0034	0.0042	0.0249	0.0530	0.0034	0.0044	0.0040	0.0067	0.017	0.03	0.02
DH1047	0.1214	0.1233	0.1238	0.1631	0.1475	0.1585	0.1328	0.1609	>25	NT	NT

Neutralization titers against betacoronaviruses (IC50 mcg/ml)						
Ab	SARS-CoV-2 D614G peudovirus	SARS-CoV-2 WT MN titer (IC99 mcg/ml)	SARS-CoV-2 2AA MA	SARS-CoV-1 MA	WIV-1	SHC014
DH1047	0.09	0.12	0.40	0.03	0.19	0.20
DH1073	6.79	3.22	0.81	0.008	0.27	>10

David Montefiori, Surender Khurana, Ralph Baric, Barton Haynes

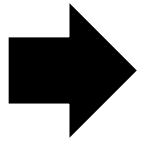
Structure-guided, epitope focused immunogens

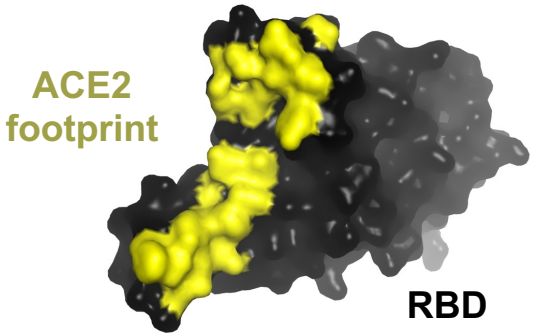
DH1284

SARS CoV-2
S-2P trimer

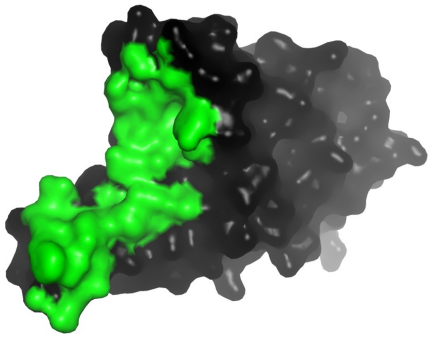
DH1047

SARS CoV-2
S-2P trimer

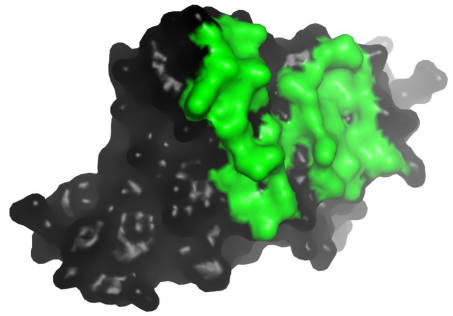


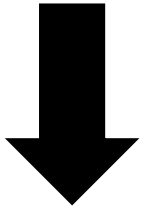


DH1284



DH1047





Epitope-focused immunogens

Collaborator: Mihai Azoitei

Priyamvada Acharya unpublished, 2021

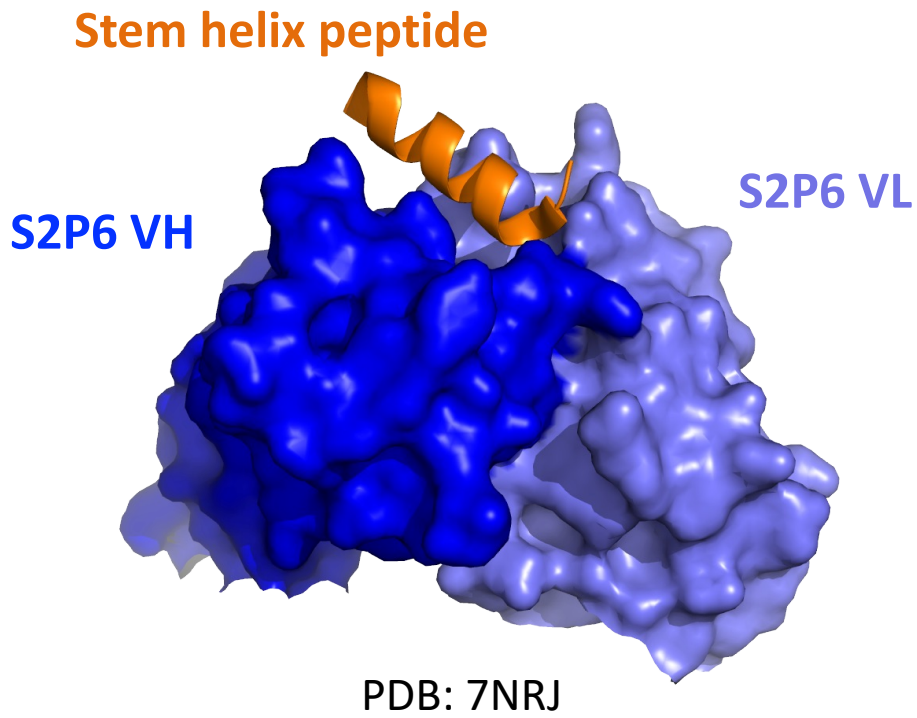
S2 region includes highly conserved neutralizing epitopes

RESEARCH

CORONAVIRUS

Broad betacoronavirus neutralization by a stem helix–specific human antibody

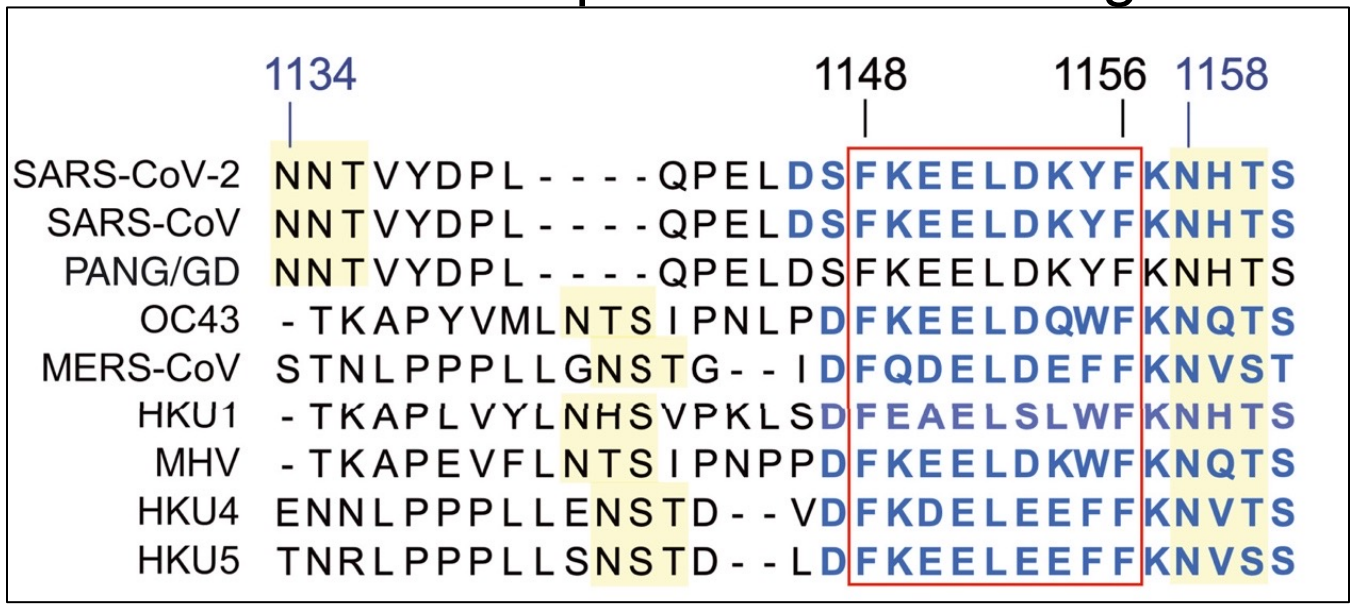
Dora Pinto[1]†, Maximilian M. Sauer[2]†, Nadine Czudnochowski[3]†, Jun Siong Low[4]†, M. Alejandra Tortorici[2], Michael P. Housley[3], Julia Noack[3], Alexandra C. Walls[2], John E. Bowen[2], Barbara Guarino[1], Laura E. Rosen[3], Julia di Iulio[3], Josipa Jerak[4], Hannah Kaiser[3], Saiful Islam[3], Stefano Jaconi[1], Nicole Sprugasci[1], Katja Culap[1], Rana Abdelnabi[5], Caroline Foo[5], Lotte Coelmont[5], Istvan Bartha[1], Siro Bianchi[1], Chiara Silacci-Fregni[1], Jessica Bassi[1], Roberta Marzi[1], Eneida Vetti[1], Antonino Cassotta[4], Alessandro Ceschi[6,7,8,9], Paolo Ferrari[9,10,11], Pietro E. Cippà[10,12], Olivier Giannini[9,10], Samuele Ceruti[13], Christian Garzoni[14], Agostino Riva[15], Fabio Benigni[1], Elisabetta Cameroni[1], Luca Piccoli[1], Matteo S. Pizzuto[1], Megan Smithey[3], David Hong[3], Amalio Telenti[3], Florian A. Lempp[3], Johan Neyts[5], Colin Havenar-Daughton[3], Antonio Lanzavecchia[1], Federica Sallusto[4,16], Gyorgy Snell[3], Herbert W. Virgin[3,17,18], Martina Beltramello[1], Davide Corti[1]*, David Veesler[2]*



PDB: 7NRJ

Stem helix region represents a conserved site for epitope-focusing immunogens

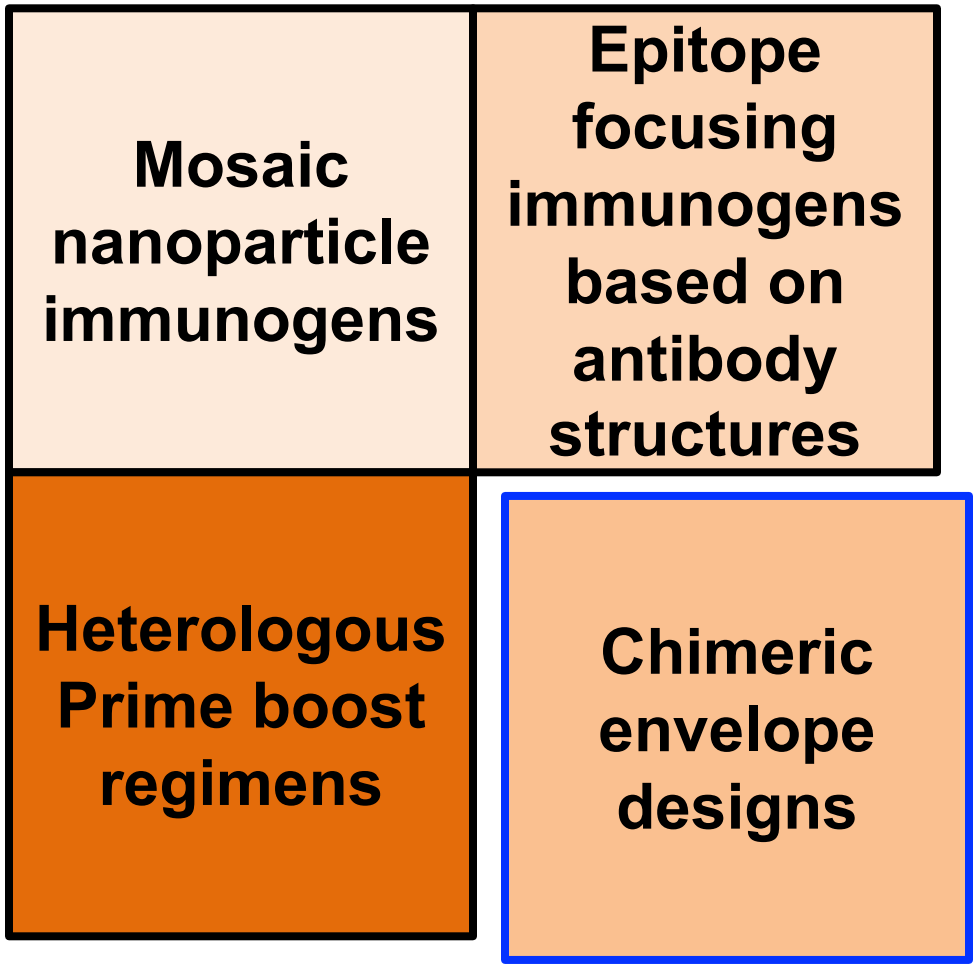
S2 of coronavirus spike amino acid alignment



Epitope-focused immunogens

Collaborator: Mihai Azoitei

Approaches for broadening potent antibody responses



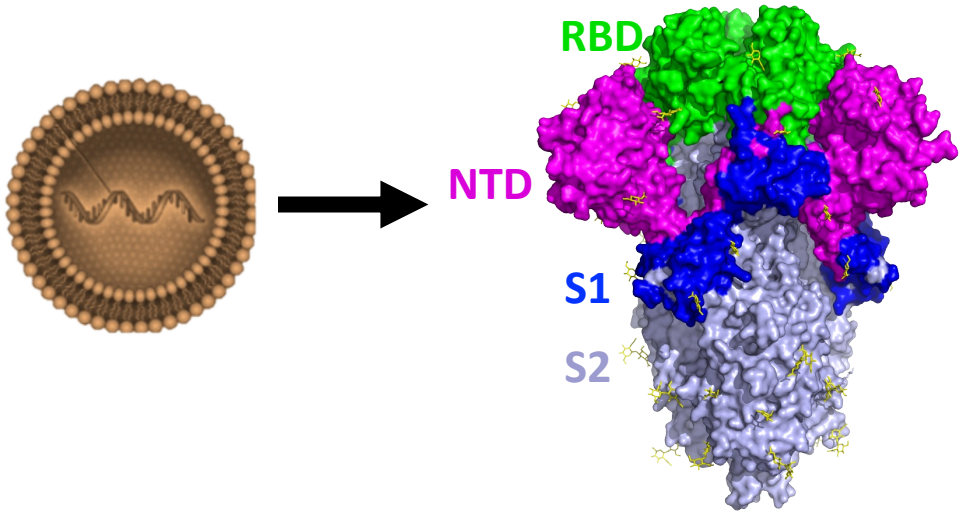
RESEARCH

CORONAVIRUS

Chimeric spike mRNA vaccines protect against Sarbecovirus challenge in mice

David R. Martinez[1]*, Alexandra Schäfer[1], Sarah R. Leist[1], Gabriela De la Cruz[2], Ande West[1], Elena N. Atochina-Vasserman[3], Lisa C. Lindesmith[1], Norbert Pardi[3], Robert Parks[4], Maggie Barr[4], Dapeng Li[4], Boyd Yount[1], Kevin O. Saunders[4], Drew Weissman[3], Barton F. Haynes[4], Stephanie A. Montgomery[5], Ralph S. Baric[1]*

- **Developed chimeric spike designs of RBD, NTD and S2 components.**
- **Induced panSarbecovirus cross-reactive responses.**
- **Current work has expanded to including other betacoronaviruses to make chimeras.**

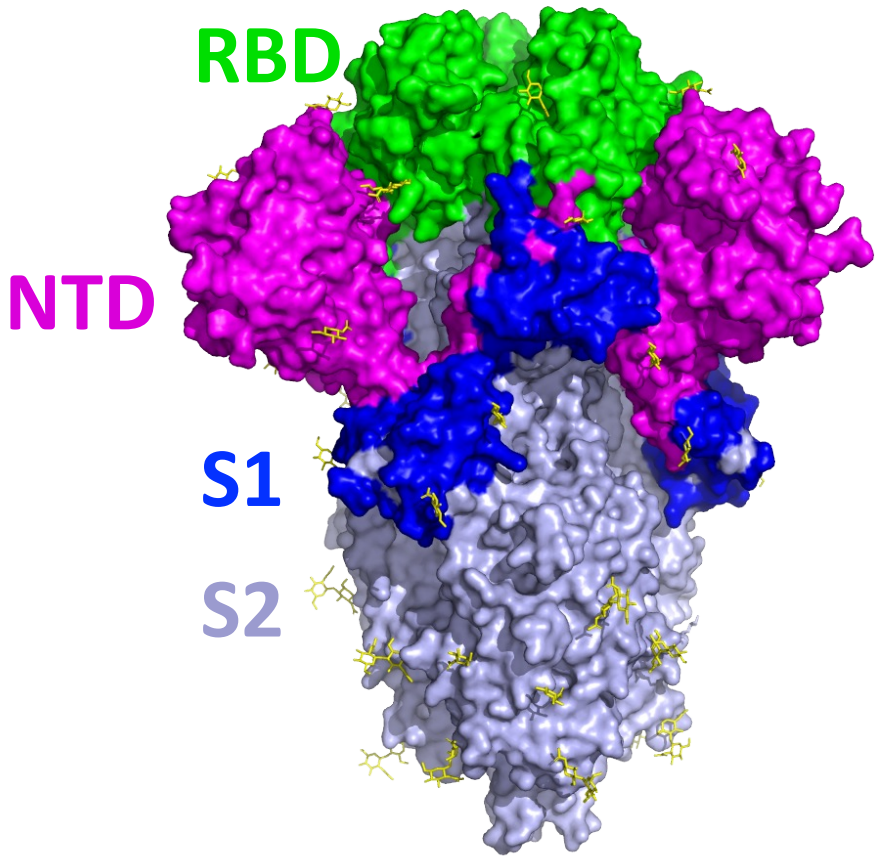


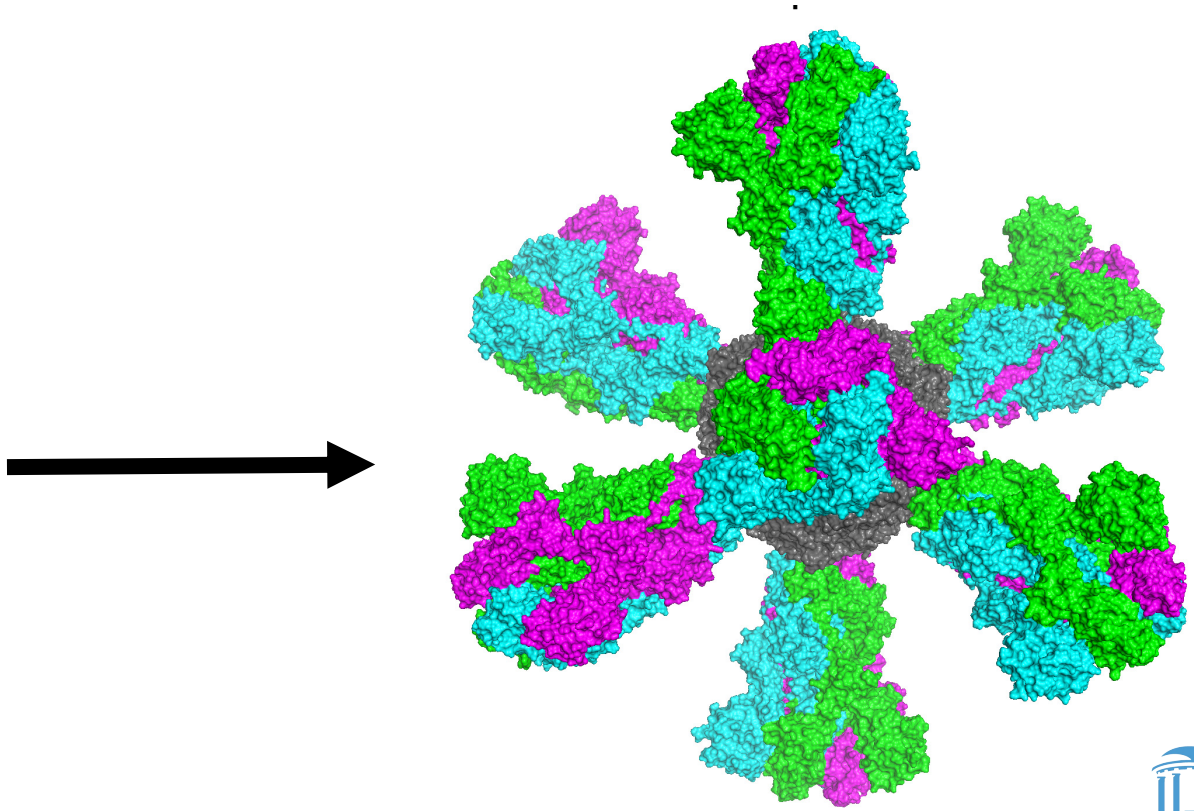
SARS-CoV-2 Coronavirus Spike PDB: 6VXX

Drew Weissman, David Martinez, Ralph Baric P01 AI158571, DMID

Combining chimeric Spike ectodomains with multimerization to induce broad and potent antibody responses

SARS-CoV-2 Coronavirus Spike PDB: 6VXX





David Martinez, Ralph Baric, Kevin Saunders

Duke Human Vaccine Institute
Duke University School of Medicine
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Implications for Pancoronavirus vaccine design

Our design goals include integrating each of the aforementioned concepts. In brief:

- Combining T cell immunogens with antibody immunogens to activate multiple arms of the immune system.
- Designing antibody-based immunogens that focus antibodies to conserved epitopes.
- Broaden the reactivity by increasing epitope diversity present during vaccination with heterologous prime-boost regimens.

Collaborators

Duke Human Vaccine Institute

- **Barton Haynes**
  - Dapeng Li
  - Robert Parks
  - Maggie Barr
  - Laura Sutherland
  - Cynthia Bowman
  - Grace Stevens
  - Charlie Mu
  - Richard Scearce
  - Victoria Lee
  - Meg Deyton
  - Amanda Newman
  - Whitney Edwards
- **Priyamvada Acharya (Structural Biology)**
  - Kartik Manne
- **Rory Henderson (Molecular Dynamics)**
- **Kevin Wiehe (Bioinformatics)**
  - Sravani Venkatayogi
  - Madison Berry
- **David Montefiori (Neutralization)**
  - Amanda Eaton

Duke Human Vaccine Institute

- **Kevin Saunders**
  - Esther Lee
  - Haiyan Chen
  - Alecia Brown
  - Xiaozhi Lu
  - Dylshan Malewana
  - James Counts
  - Beth Bryan
  - Nolan Jamieson
  - Lena Smith
  - Jingjing Li
  - Aja Sanzone
  - Andrew Foulger
  - Chuancang Jiang
  - Elizabeth Donahue
  - Christine Daniels
  - Fangping Cai
  - Shi-Mao Xia
- **RJ Edwards (Negative Stain EM)**
  - Katayoun Mansouri

Duke Human Vaccine Institute

- **Mihai Azoitei**
- **Derek Cain (Flow Cytometry)**
  - Aria Arus-Altuz
  - Steve Slater
- **Wes Rountree**
- **Tony Moody**
  - Yousef Abuhamad
- **Munir Alam**
  - Kara Anasti
  - Advaiti Khanore
- **Wilton Williams**

Upenn (mRNA vaccines)

- **Drew Weissman**
  - Norbert Pardi

UNC Chapel Hill (CoV mouse and neutralization)

- **Ralph Baric**
  - David Martinez
  - Alexandra Schaefer

DMID Program and Product Development teams

P01 AI158571