Nanoparticle Vaccines:

A success story for viral vaccine development

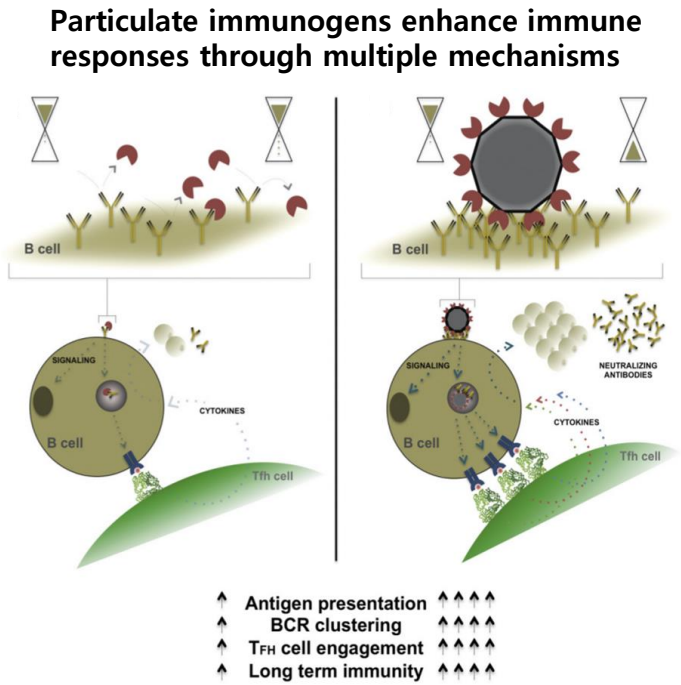
Global Vaccine & Immunization Research Forum
28th March 2023

Harry Kleanthous
Vaccines R&D Strategy & External Innovation

SK bioscience

Key Messages

- Several Virus-Like Particle (VLP)-based vaccines targeting viral infections licensed
- Self-assembling proteins are a promising platform for structure-based vaccine delivery
- Particle-based vaccines deployed during pandemic had key attributes
  - Increased titer, potency, breadth and durability
  - Pre-clinical data predictive of clinical performance



López-Sagaseta J et al. (2016) *Comp. Struct. Biotech. J.* **14**:58-68.
Gause KT et al. (2017) *ACS Nano* **11**:54-68.

BACKGROUND - Licensed/Authorized Products using VLP Technology

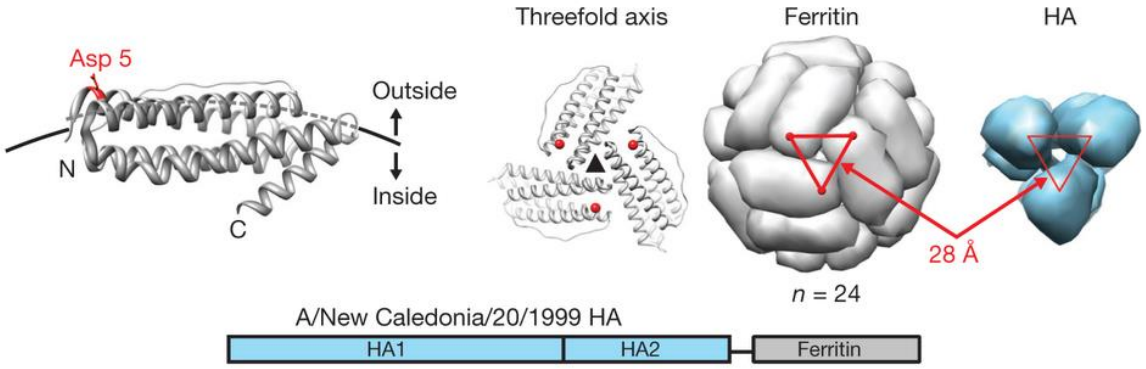
- ~150 VLP/NP vaccines trials listed on ClinicalTrials.Gov (Clinical POC)
- Targets include HPV, HepB, SARS-CoV-2, human and avian influenza, Norovirus, HIV-1, Chikungunya virus, Coxsackieviruses, EBV, as well as against Melanoma, Adenocarcinoma, etc

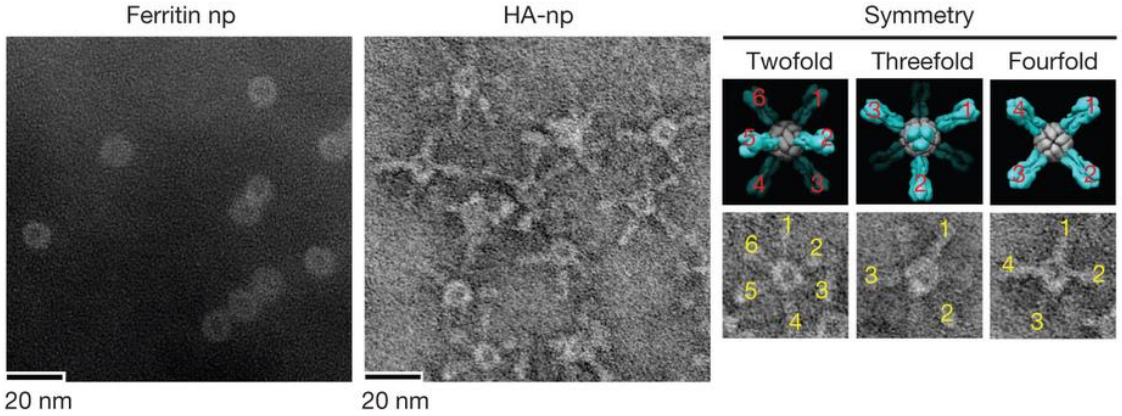
Company	ID Target	Type	Adjuvant	Vaccine	Development Stage	Key Attributes
Merck	HPV tetravalent	VLP	Amorphous Aluminum Hydroxyphosphate Sulfate	Gardasil	Licensed	Safety Potency Efficacy Schedule Dose sparing Breadth Durability Mfgr Scale (Boosters) (Mucosal)
Merck	HPV nonavalent	VLP	Amorphous Aluminum Hydroxyphosphate Sulfate	Gardasil 9	Licensed	
GSK	HPV bivalent	VLP	AS04	Cervarix	Licensed	
Novavax	Influenza SARS-CoV-2	NP NP	Matrix M Matrix M	NanoFlu Nuvaxovid/Covovax*	Phase 3 Approved	
GSK	Hepatitis B	VLP	Alum (PH and OH)	TwinRix	Licensed	
Dynavax	Hepatitis B	VLP	CpG	HEPLISAV-B	Licensed	
Serum Institute	Hepatitis B	VLP	Alum (AlOH)	Genevac-B	Licensed	
SK bioscience	SARS-CoV-2	NP	AS03	SKYCovione	Licensed	

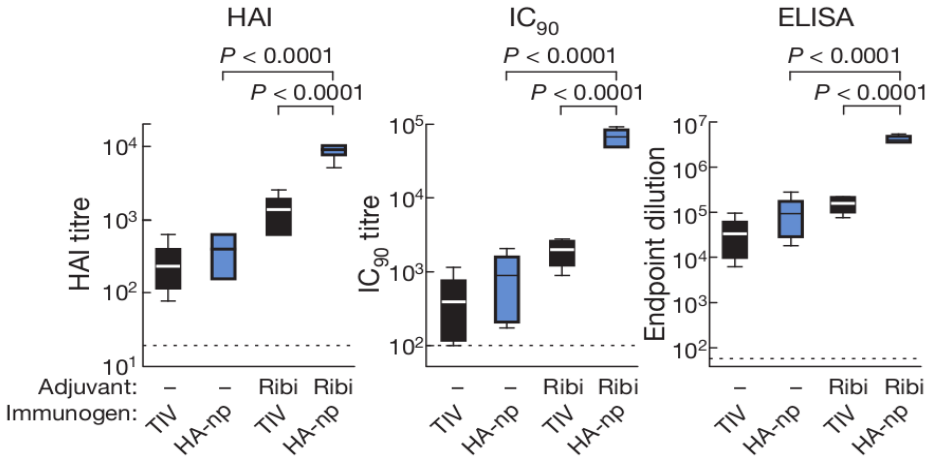
*** SK bioscience CDMO activity during SARS-CoV-2 pandemic**

BACKGROUND - Self-assembling proteins proven a promising platform for structure-based vaccine delivery

Ferritin nanoparticles (VRC, NIH)







- Form highly ordered, monodisperse structures
- Trafficked like pathogens *in vivo*
- Seamless integration of antigen via genetic fusion
- Can be scalably manufactured
- Non-toxic
- **Enable atomic-level engineering of both antigen and nanoparticle scaffold**

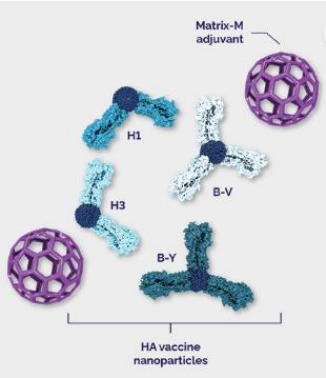
Kanekiyo M, et al. (2013) *Nature* 499: 102-6.

BACKGROUND - VLP Technologies targeting several respiratory viruses

Influenza

qNIV (Novavax)

Vx: rHA + Matrix M



VLP strategy: Budding

Stage of Dev. Phase 3

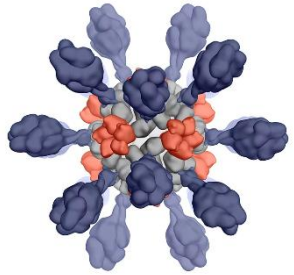
POC:
- Safe & immunogenic in older adults
- More solicited AE
- Non-inferior to licensed INV products
- Qualitative & quantitati vely enhanced humoral & cellular responses

Mgfr: Sf9 insect cells

RSV

IVX-121 (Icosavax)

Vx: Pre-F trimer (no adjuvant)



VLP strategy: i53-50 two component NP

Stage of Dev.: Phase 1/2

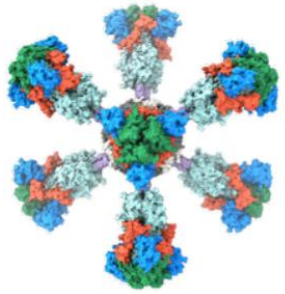
POC:
- Immunogenic in rodent
- Immunogenic in young & Older Adults (RSV A & B)
- Dose sparing
- Durable
- Unadjuvanted

Mgfr: *E. coli* & CHO

COVID-19

SpFN (WRAIR)

Vx: rS2P + ALFQ



VLP strategy: Ferritin NP

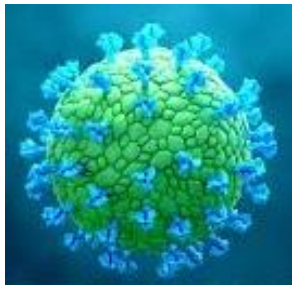
Stage of Dev.: Phase 1/2

POC:
- Rapid protection @ viral replication in LRT & URT of NHPs.
- Protects @ pathology
- Dose sparing
- Safe & immunogenic in Ph 1
- Breadth (VOC & sarb-ecoviruses (3 doses)

Mgfr: CHO

Covifenz (Medicago)

Vx: S2P VLP + AS03



VLP strategy: Budding

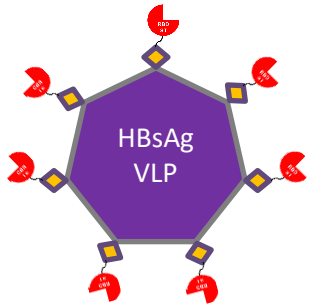
Stage of Dev. : Licensed

POC:
- Robust & durable humoral immunity (Th-1 biased)
- Potent Fc-dependent non-neutralizing Ab
- Breadth against VOC
- Elevated cellular responses

Mgfr: Tobacco plants

RBD-VLP (MIT-SII)

Vx: RBD + Alum



VLP strategy: HBsAg-SpyCatcher-Spytag

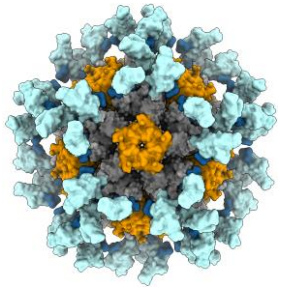
Stage of Dev.: Phase 1

POC:
- Immune-focusing
- Potent CoV-2 specific VN Ab.
- Protects against viral challenge (URT & LRT)
- Dose sparing
- Breadth of immunity against VOC

Mgfr: Yeast

GBP510 (SK bioscience)

Vx: RBD + AS03



VLP strategy: i53-50 two component NP

Stage of Dev.: Licensed

POC:
- Immune-focusing
- Elevated VN Ab titers & protection in NHPs
- Breadth @ VOC
- Pan-sarbecovirus Ab (Het. P-B)
- Safe & Imm (Ph 1/2/3)
- Basis of pansarbeco Vx

Mgfr: *E. coli* & CHO

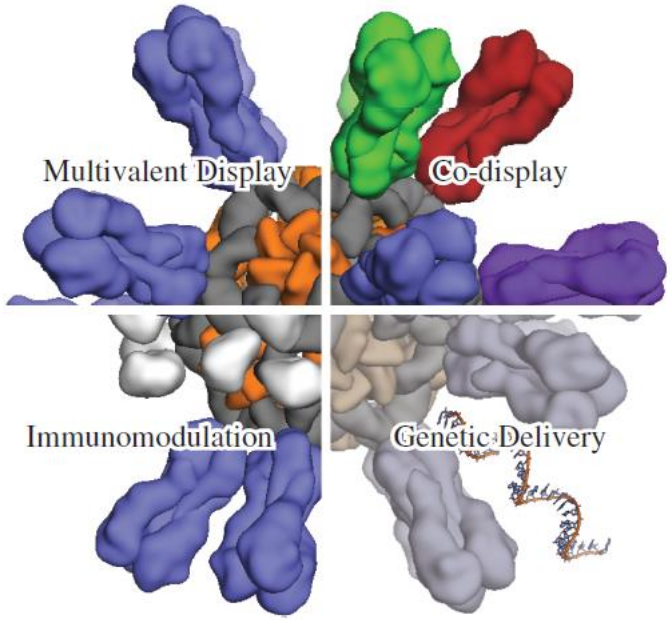
- **VLP delivery being assessed across multiple global health targets (HIV, Malaria, Rotavirus)**

BACKGROUND - Structure-based immunogen design strategies

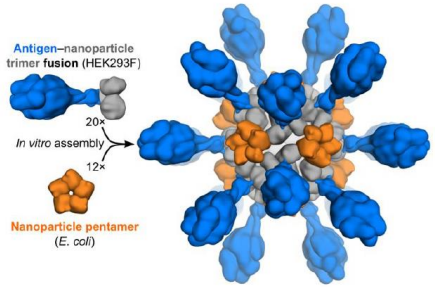
- BMGF invested in novel particle display for next-generation vaccines (subatomic accuracy, predictive algorithms)
- SK bioscience clinically de-risked platform as part of the pandemic response

Advantages:

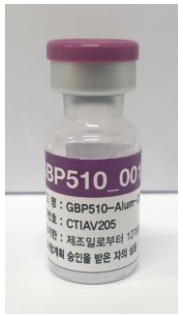
- VLP display of immunogens are superior vaccines (HPV, HBV)
- Design of novel self-assembling protein scaffolds to control size, shape, # subunits, location & orientation of Ag precisely at atomic-level accuracy (complex Ag)
- Highly ordered, mono-disperse immunogens that are stable
- A repetitive array of Ag drives robust B cell activation (BCR clustering) and induces potent & durable immunity
- Co-display of multiple antigens (genetic fusion or 'Plug-and-display' approach)
- Inclusion of immunostimulatory molecules to exploit signaling pathways (molecular adjuvant)
- Genetic immunization (mRNA) using single-component nanoparticles



I53-50 two-component icosahedral nanoparticle



60 monomers, 20 trimers
~50 nm diamter



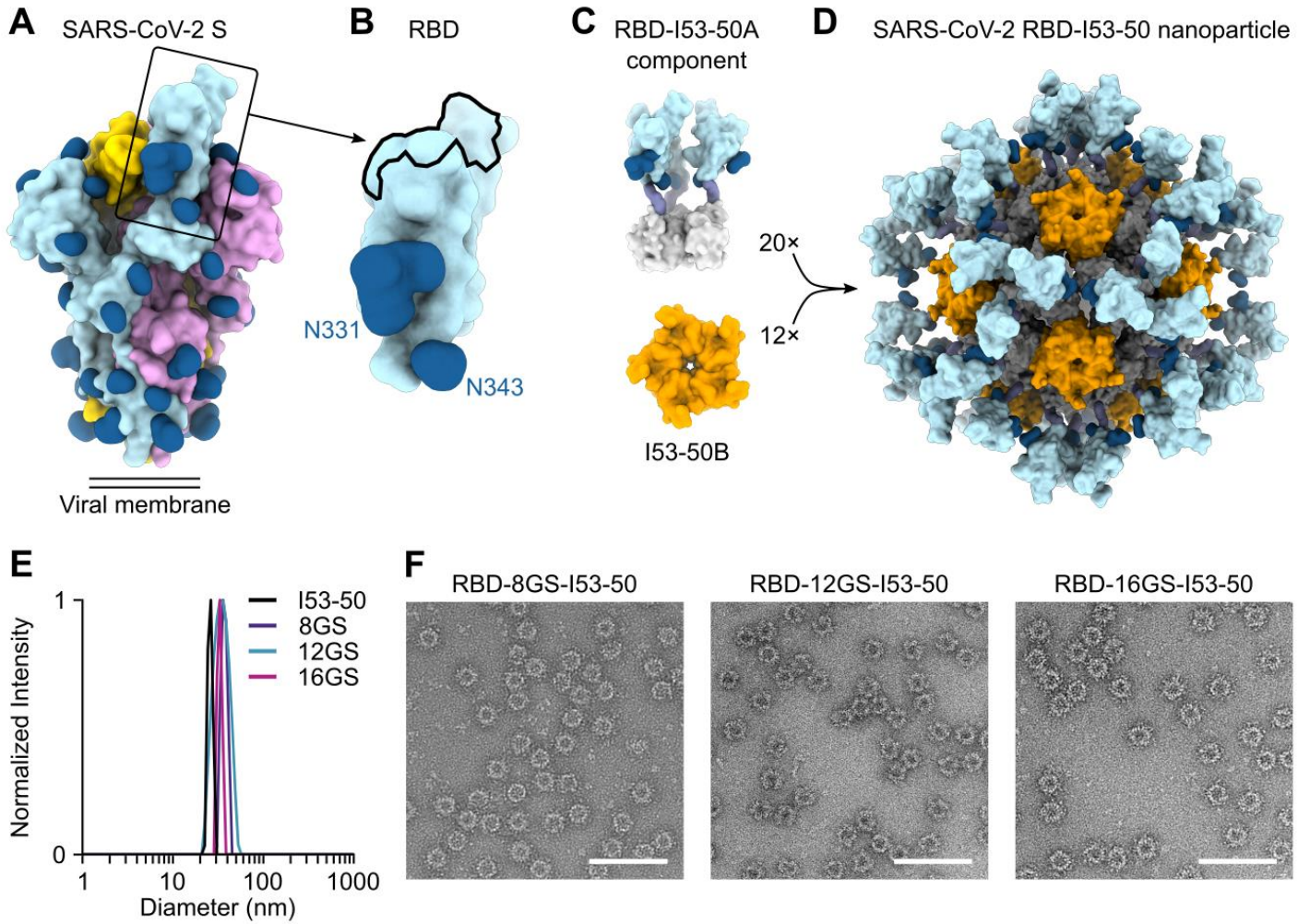
Institute for Protein Design – Structure-based Immunogen Design Strategies

- **SARS-CoV-2 RBD-I53-50 nanoparticles are produced in high yield and are highly monodisperse**

Lexi Walls

Brooke Fiala

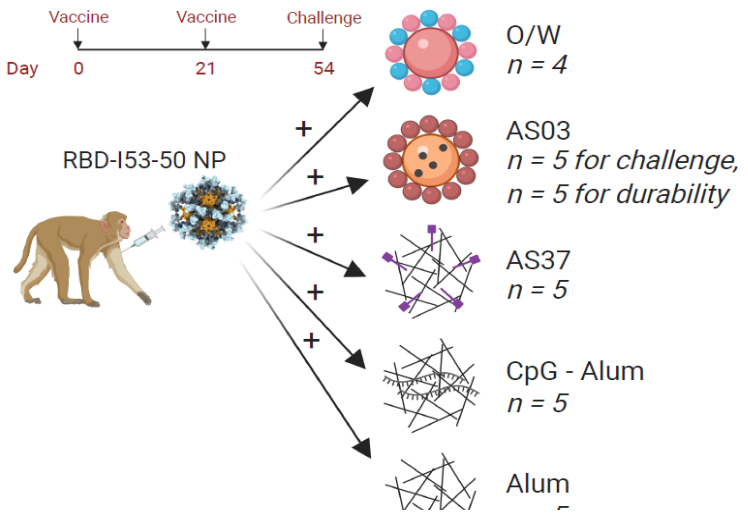
David Veesler

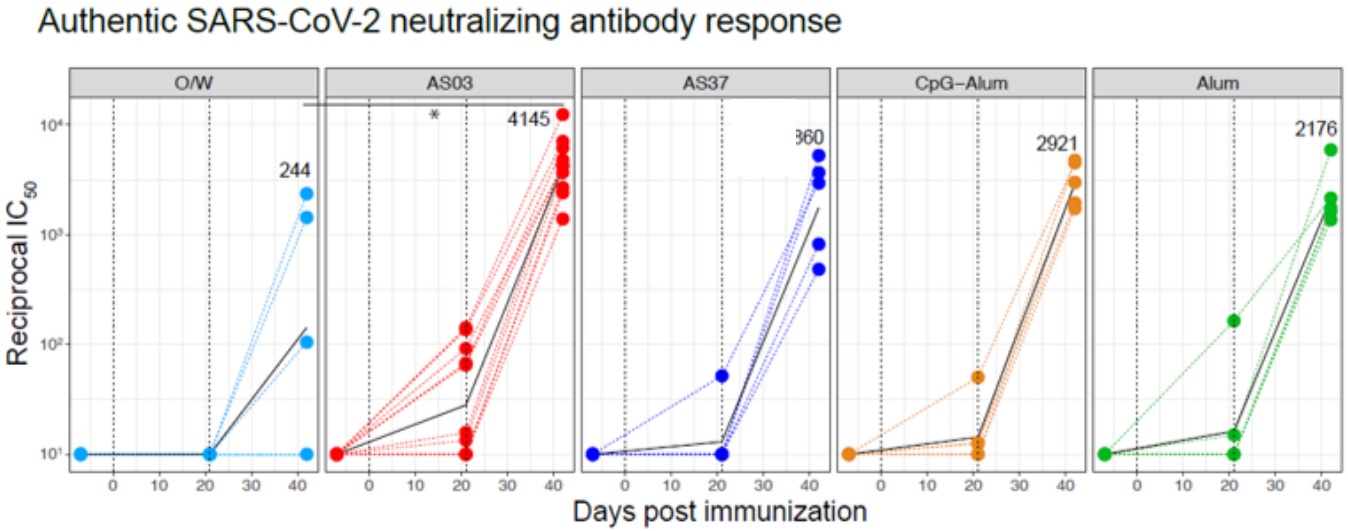


Walls AC & Fiala B et al. (2020) *Cell* 183: 1367-82.

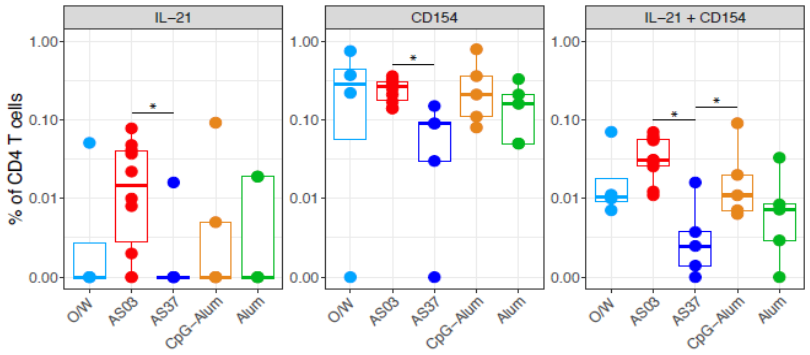
RBD-Nanoparticle Vaccines induce protective immunity (Stanford)

- **RBD NPs elicit potent humoral & cellular immune responses (AS03, GSK; Alum-CpG, Dynavax)**
- **Protection in the LRT & URT (sub-genomic PCR & PET-CT)**



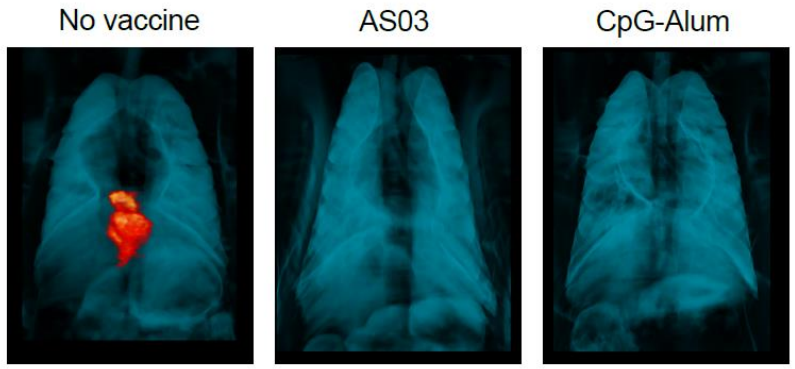


CMI responses (IL-21 & CD154)

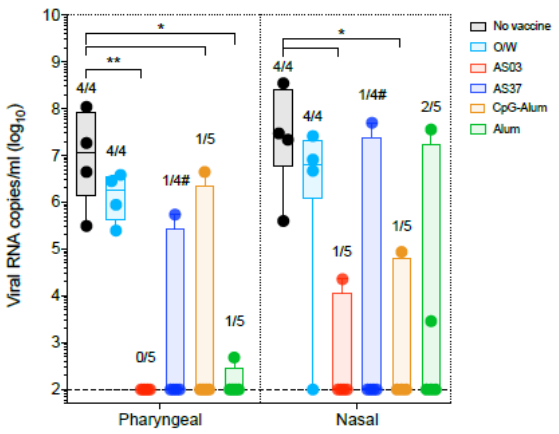


- Markers of **formation** and persistence of **germinal centers,** critical for generation of affinity-matured plasma cells and memory B cells capable of mediating **durable** immunity

Efficacy (lungs, PET-CT)



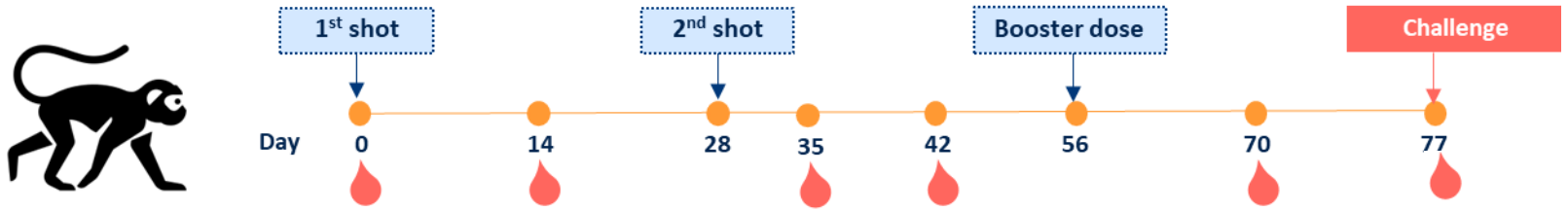
Efficacy in URT (N-gene sub-genomic PCR)



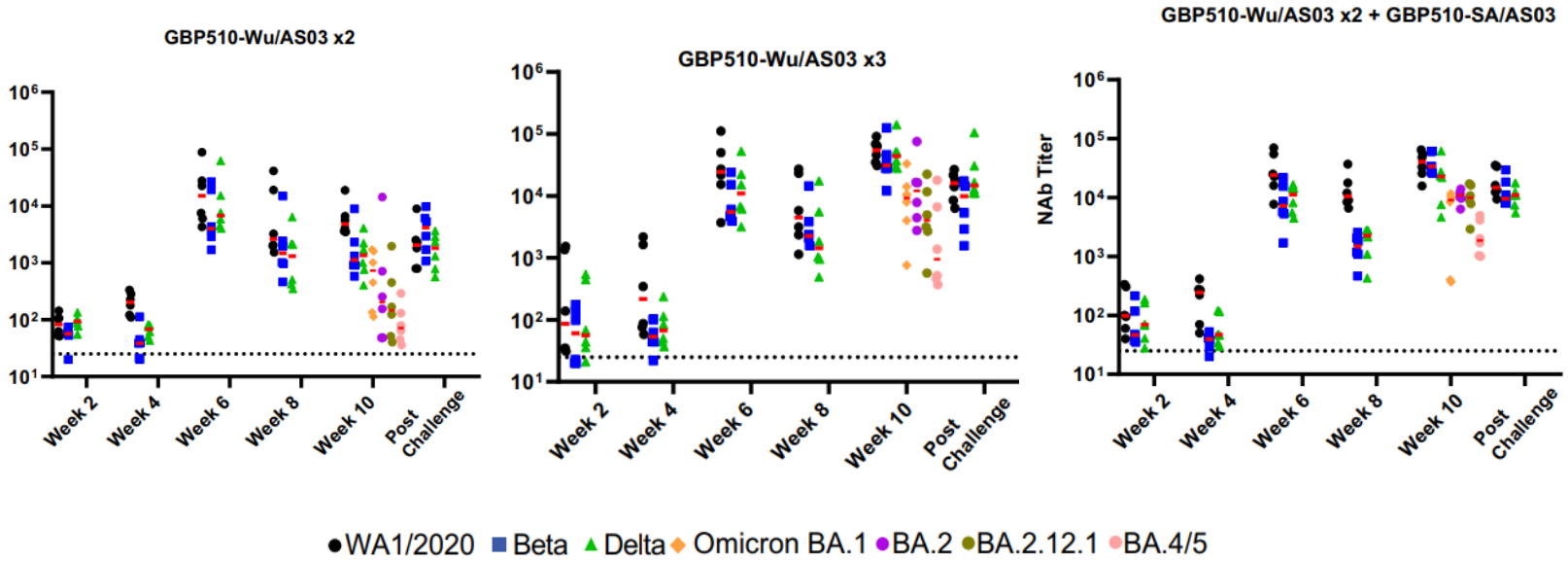
Arunachalam et al. (2021) *Nature* 594: 252-258.

RBD-Nanoparticle Vaccine + AS03 protects against a CoV-2 VOC (Harvard)

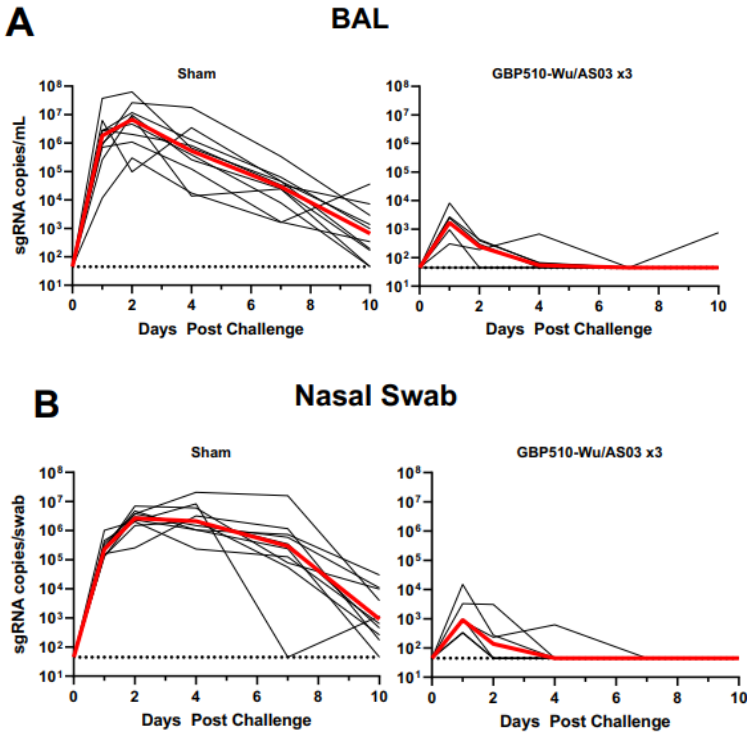
- **Two or three dose immunization regimens (homologous & heterologous) elicit broad neutralizing Ab in NHPs against circulating CoV-2 variants**
- **Significant protection in the LRT and URT against a heterologous Delta challenge**



- **PSV neutralization confirms response against Omicron lineages**



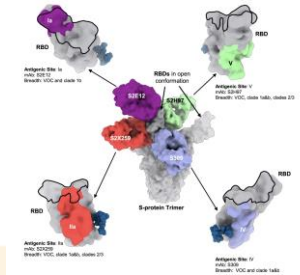
- **Protection @ Delta virus CoV-2 VOC in URT & LRT**



Jacob-Dolan *et al.* (2023) NPJ 8: 23.

RBD-Nanoparticle Vaccines induce durable & pan-sarbecovirus bnAbs (Stanford)

- **AS03-adjuvanted NP immunization elicits potent and durable serum antibody responses & protects @ heterologous challenge**
- **Booster vaccination after primary immunization promotes bnAb's that target conserved regions of RBD with femtomolar affinity**
- **Passive immunization with 25F9 bnAb supports pan-sarbecovirus breadth**



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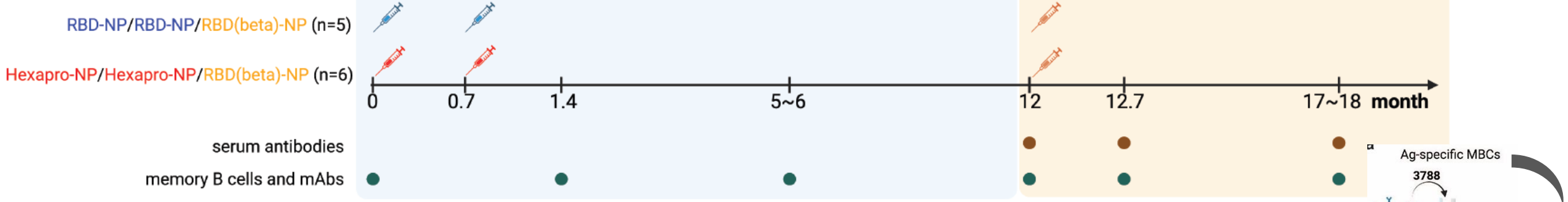
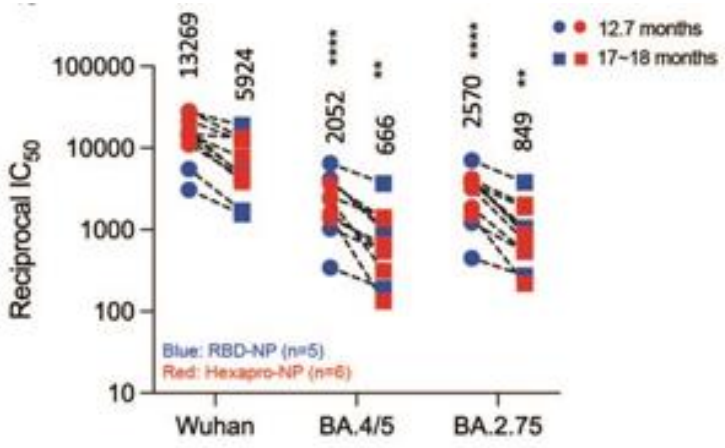
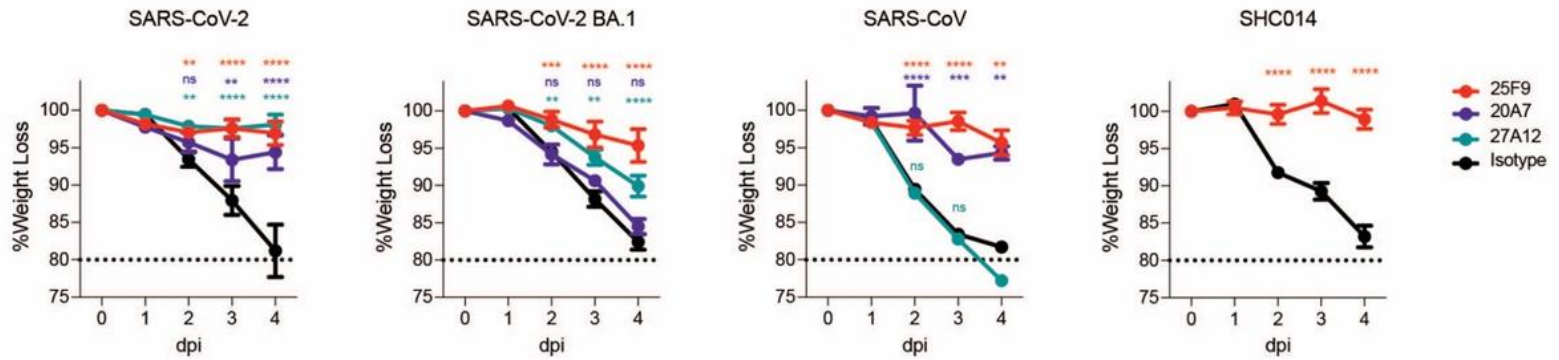


- **PSV serum neutralization of Omicron lineages**



- **Passive immunization with bnAbs protects against different sarbecoviruses**

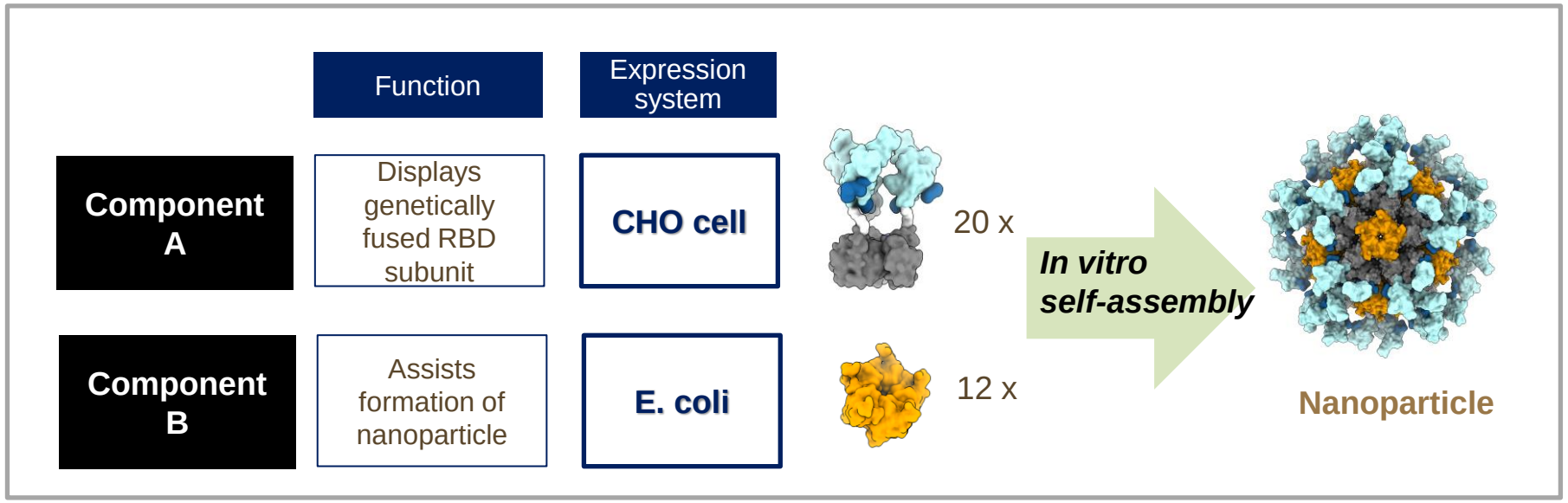


Arunachalam et al. (2022) *Sci. Transl. Med*.14, 658: 1-16, Feng et al. (2023) *bioRxiv*. Jan 20.

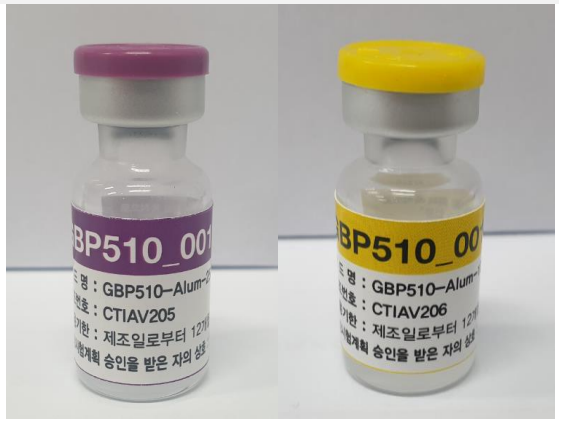
SK bioscience – COVID-19 Vaccine: (GBP-510)

Project Overview

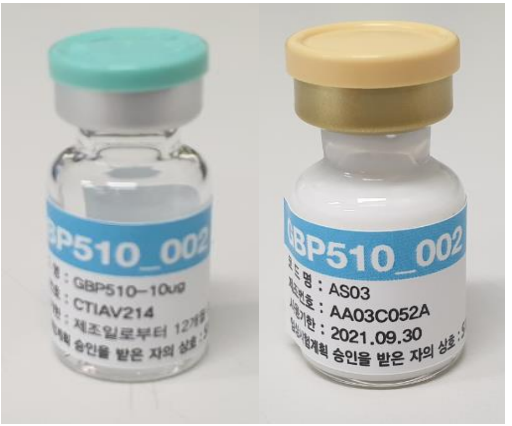
- SK bioscience (SK) has developed a novel nanoparticle vaccine candidate targeting the receptor binding domain (RBD) of SARS-CoV-2 Spike protein
- GBP510 consists of a self-assembling, two-component nanoparticle (RBD-16GS-I53-50) that was developed by the Institute for Protein Design (IPD) at the University of Washington using its synthetic structure-based vaccine design techniques.
  - Component A displaying genetically fused RBD protein
  - Component B forming a core pentametric nanoparticle structure, which self-assemble to display 60 copies of the SARS-CoV-2 Spike protein's RBD. Candidate vaccine tested with Alum and AS03.
- GBP510 provokes an enhanced immune response due to its molecular structure optimally displaying multiple antigens allowing affordable market access due to high productivity.



GBP510-Alum 10μg and 25μg



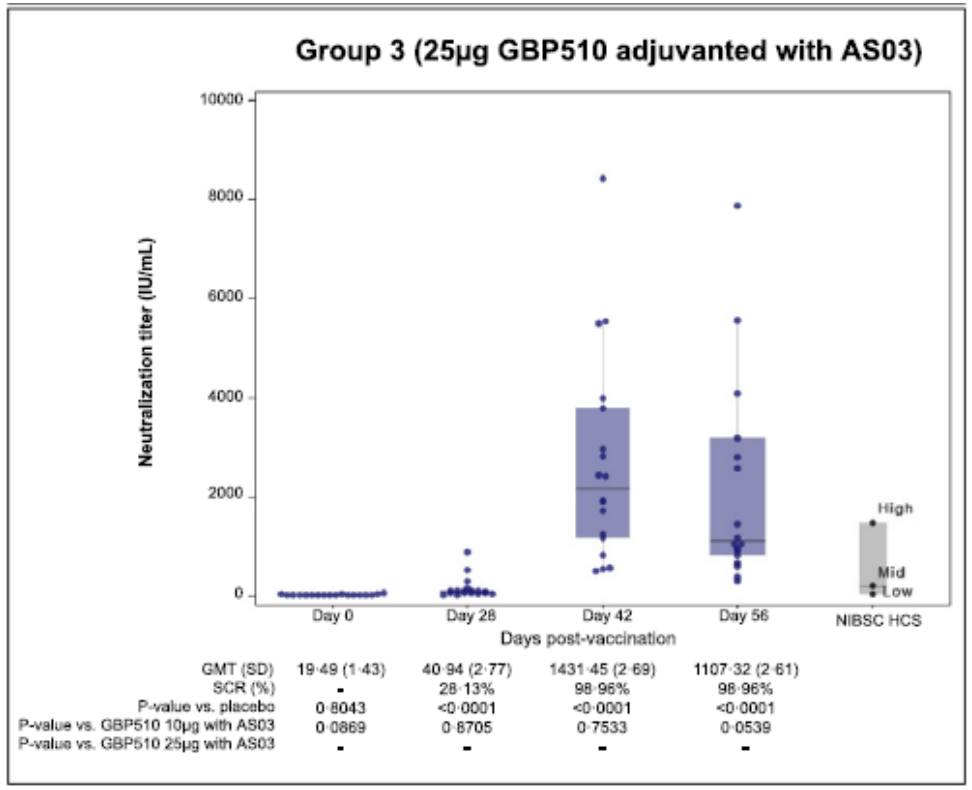
GBP510-AS03 10μg or 25μg



Phase 1/2/3: Safety & immunogenicity of synthetic NP GBP-510/AS03

- **Phase 1/2: Randomized, placebo-controlled, observer-blind study of GBP510- (2 doses; 28 d apart) in healthy adults (19 - 85)**
  - Solicited events: mild-to-moderate in severity and transient; Higher reactogenicity in adjuvanted groups (post-dose 2)
  - 100% SCR (≥ 4-fold rise from baseline) after a 2-dose regimen (adjuvant required), PSV neutralization titers > NIBSC human convalescent sera standard
- **Phase 3: Randomized, active-controlled (Vaxzevria), observer-blind multinational study in 4036 subjects (≥18 +, including > 65)**
  - 1° endpoint met - Superiority in GMT VN titers (FRNT) & non-inferiority in SCR (≥ 4-fold rise from baseline) of GBP510/AS03 compared to ChAdOx1-S

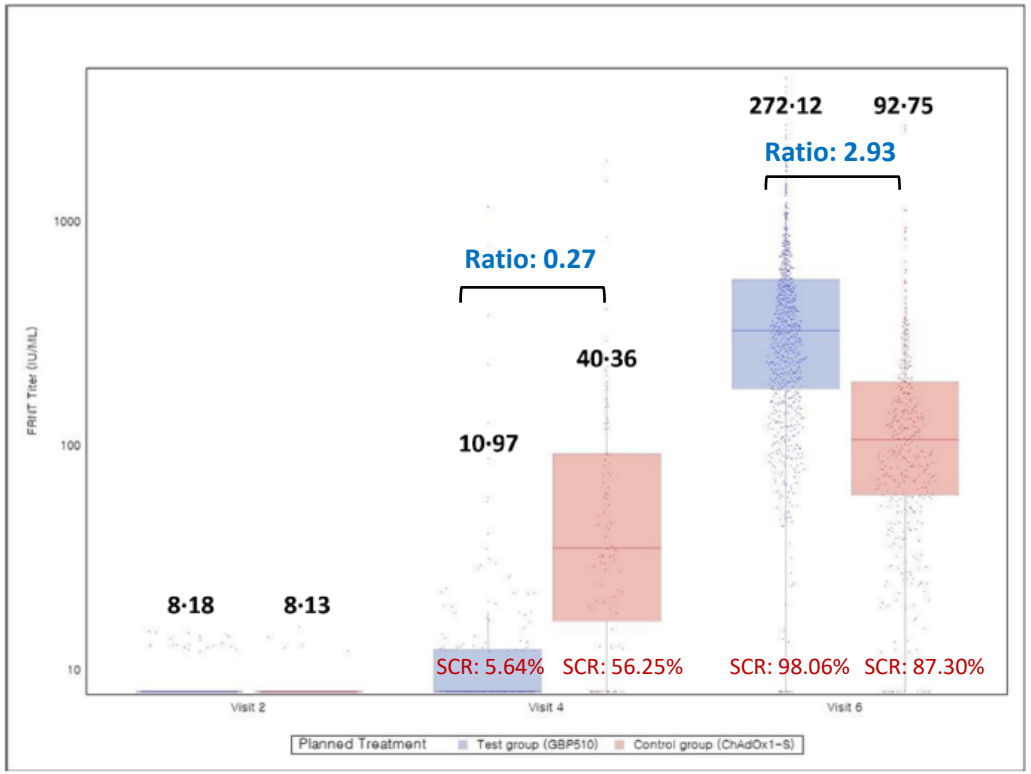
Phase 1/2: Immunogenicity (dose-finding)



Boxplot showing individual neutralizing antibody titer to SARS-CoV-2 by PBNA (converted to IU/ml) for all participants (19-85).

GMTs and SCRs of neutralizing antibody to the SARS-CoV-2 by pseudovirus-based neutralization assay (per-protocol set)

Phase 3: Immunogenicity



Boxplot showing individual neutralizing antibody titer to SARS-CoV-2 by Focus Reduction Neutralization Test (FRNT) converted to IU/ml

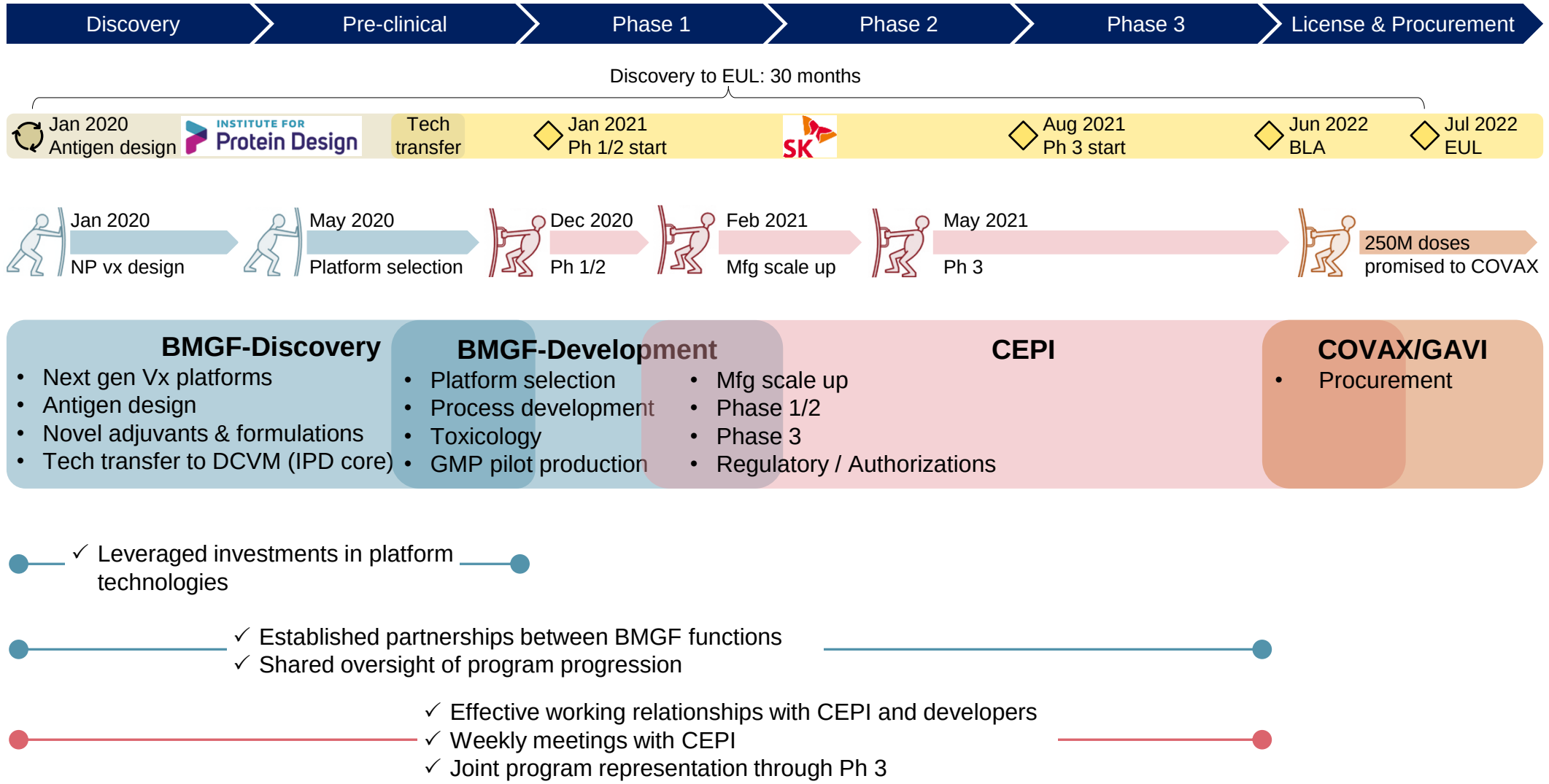
ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate. aGMT (adjusted)

Visit 2: Baseline
Visit 4: 4 weeks after 1st dose.
Visit 6: 4 weeks after 2nd dose

Song JY et al. (2022) *eClinicalMedicine* 51: 1-13, Song JY et al. (2023) *medRxiv*.

COVID-19 Response: A roadmap for a new Operating model

- **Aligning novel technologies and academia to industry partners and funding agencies was key to successful partnership**

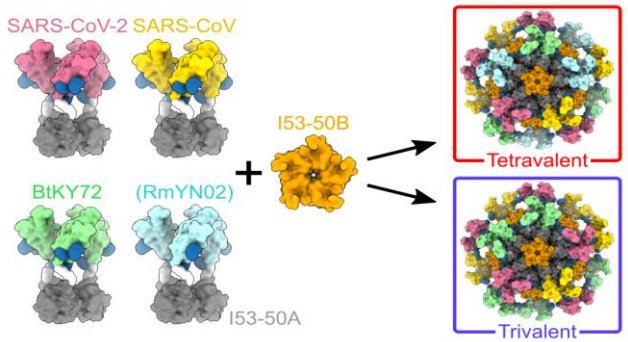


Nanoparticle Technology Advancements

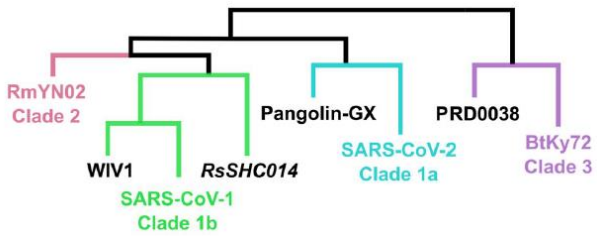
Mosaic Nanoparticles: A Pan-sarbecovirus Vaccine strategy

- Pre-clinical studies support breadth

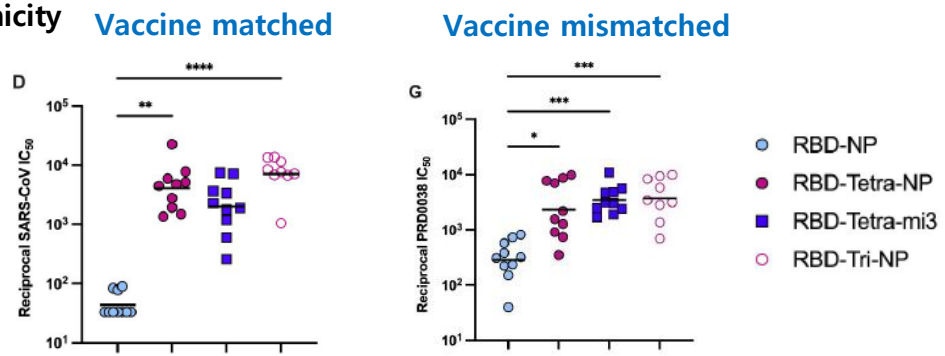
Tri-valent & Tetravalent NP



Sarbecovirus clades



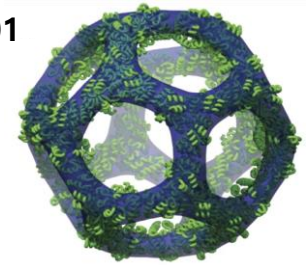
Pre-clinical immunogenicity

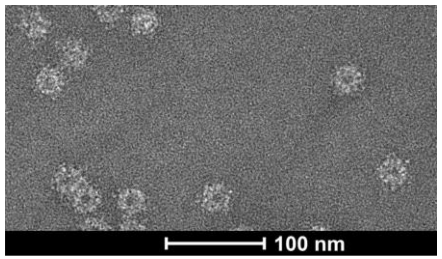


mRNA Nanoparticles: Enhancing titer & longevity of immunity

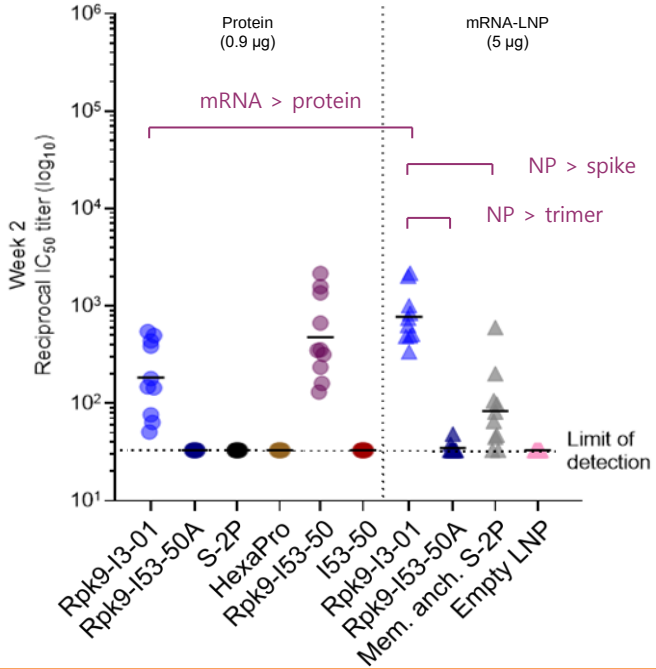
- De-greased single-component NP for efficient cellular secretion
- POC met with RBD vaccines (single-dose vaccination)

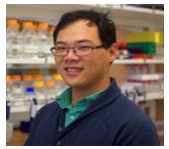
i3-01





Post-prime





John Wang

Alena Khmelinskaia

Grace Hendricks

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Concluding remarks

- **Computationally designed protein nanoparticles are a clinically validated vaccine platform**
- **SK bioscience successfully de-risked a novel synthetic NP platform for a SARS-CoV-2 vaccine**
- **Pre-clinical data recapitulated in clinical trials**
  - Homologous & heterologous prime-boost data pending
- **The platform has potential to address breadth & durability of immunity (Pan-Coronavirus Vx)**
- **Successfully partnership ensured licensure in 30 months**
- **Technology advancements show application to other platforms to enhance immunity**

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