ORAVAX: A Bacterial DNA Vaccine to Prevent COVID-19

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Course: Vaccines, from Concept to Implementation

Course Directors: Philip LaRussa MD and Lawrence Stanberry MD, PhD

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COLUMBIA | VAGELOS COLLEGE OF PHYSICIANS AND SURGEONS
PROGRAM IN VACCINE EDUCATION

ORA | VAX

The leadership team

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Chief Medical Officer

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Chief Regulatory Officer

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Revolutionizing health through bacteria

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By the end of this presentation, you will understand...

- The unique advantages of our **platform and delivery system**: a bacterial DNA vaccine
- What **preclinical testing** is necessary to demonstrate safety and feasibility
- The **target product profile** we aim to deliver on
- Our plans to conduct **phase 3 clinical trials** to demonstrate efficacy
- General approach to **post-marketing surveillance**
- Anticipated **priority groups for vaccine rollout**

The Platform

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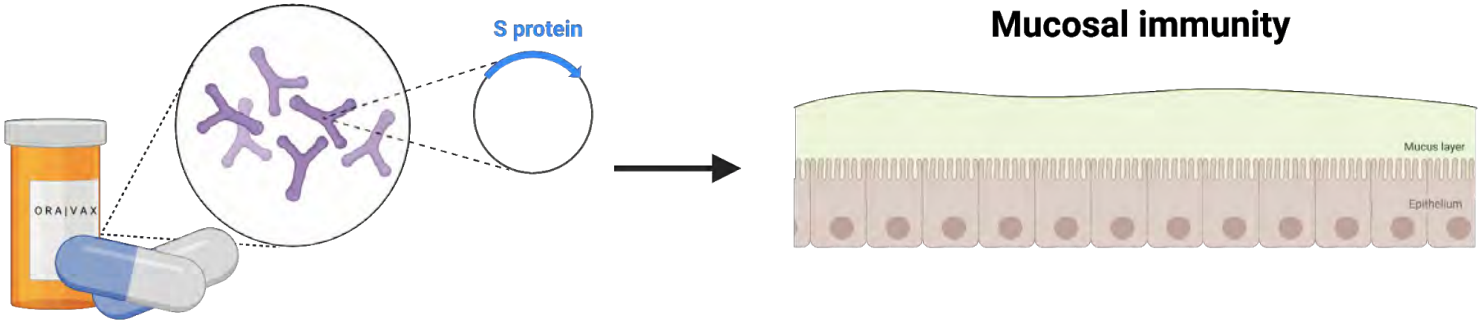
A revolutionary delivery platform



Engineered ***Salmonella typhimurium*** containing synthetic plasmids encoding Spike (S) protein from SARS-CoV-2.

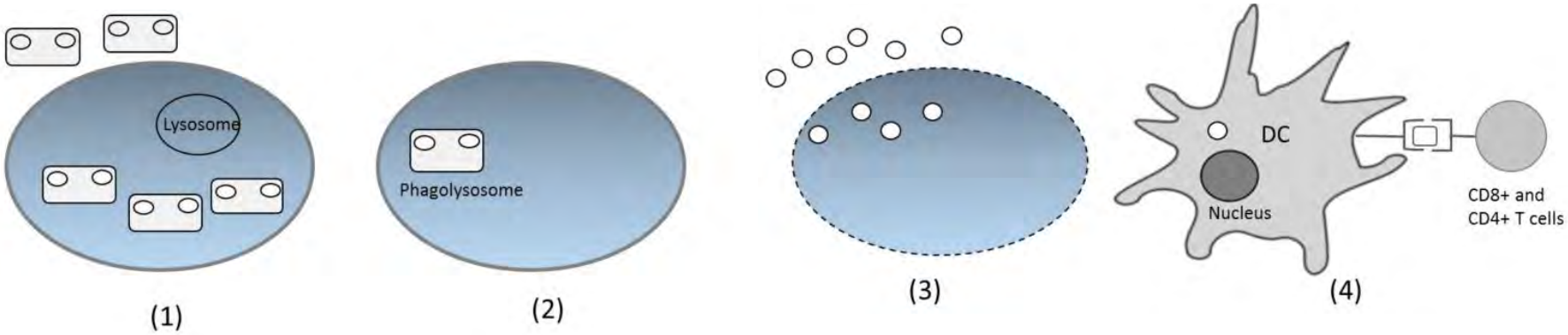
Pros: Bacterial vectored DNA vaccine

DNA vaccines	Bacterial vectors
1. Defined composition 2. Non-replicating platform capable of inducing T-cell immunity 3. Potential application in development of therapeutic vaccines 4. Construct may code for multiple epitopes and also inducers of innate immune responses	1. Directed delivery of target antigen to specific cells including macrophages 2. Large antigen-carry capacity 3. Safety maximized by removing several genes 4. Potential for mucosal immunity 5. Oral delivery possible

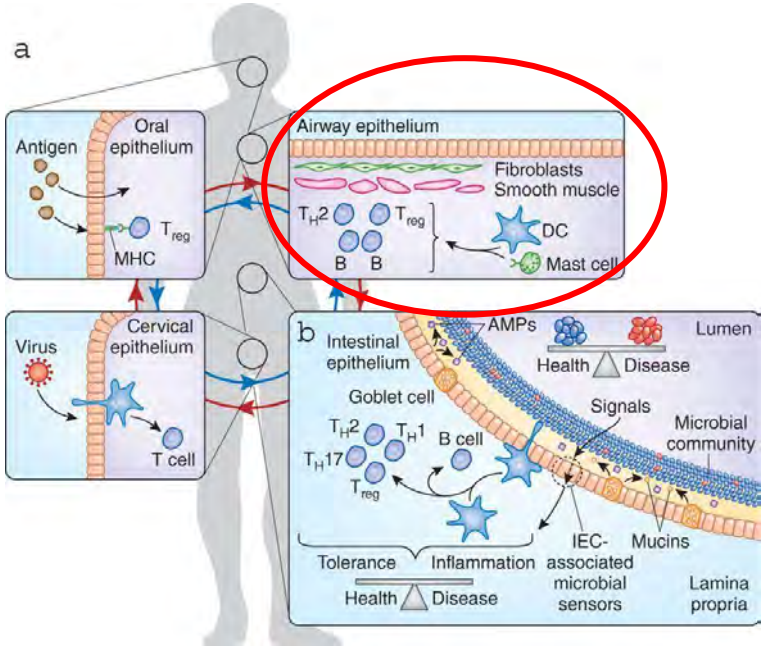
Cons: Bacterial vectored DNA vaccine

DNA vaccines	Bacterial vectors
1. Poor immunogenicity in humans 2. Concerns/issues regarding potential for construct to integrate with host genome	1. Possible genomic instability at the site of insertion giving low antigen expression levels 2. Expression of bacterial antigens may further reduce vaccine-specific immunogenicity 3. Efficacy decreased by existing vector immunity 4. Difficult to optimize engineering without conducting a number of clinical trials

Proposed DNA vaccine delivery system using a live bacterial vector

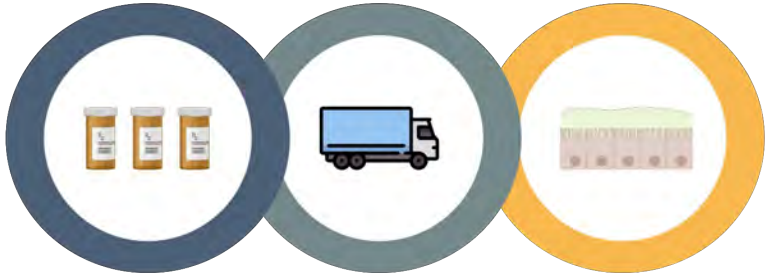


Mucosal immunity is the largest component of the immune system



Oral delivery is the most desirable and patient-accepted route

Pros: A rapid, cost-effective vaccine for the globe

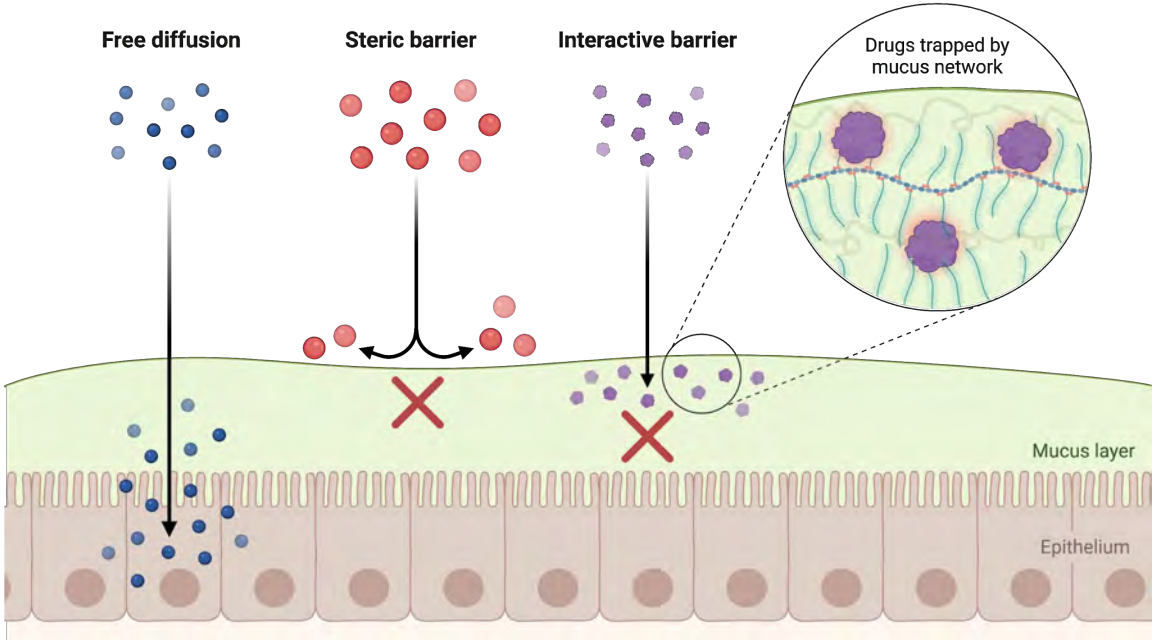


Cost-effective production

Improved distribution

Mucosal immunity

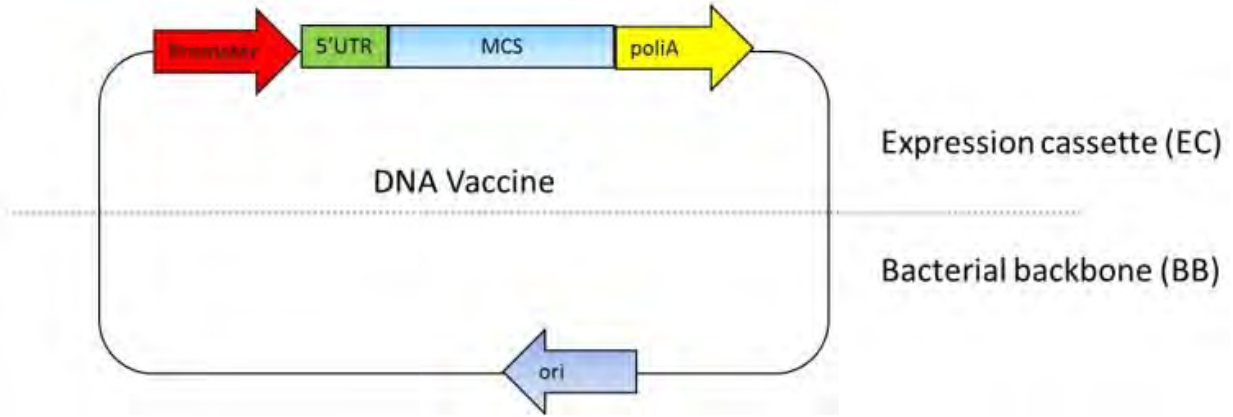
Cons: a promising but largely untested technology



Preclinical Testing

Toxicology

- Stability of the plasmid



Toxicology

- Stability of the plasmid
- C57BL/6 mice
- 3 billion CFUs vs 10 billion CFUs
    - Single vs. Repeat Dose

Toxicology

- Stability of the plasmid
- C57BL/6 mice
- 3 billion CFUs vs 10 billion CFUs
    - Single vs. Repeat Dose

Single/Repeat Dose Study in Baboons

Vaccination

3 or 10 CFU units

Monitor

6, 24, 48, 72h

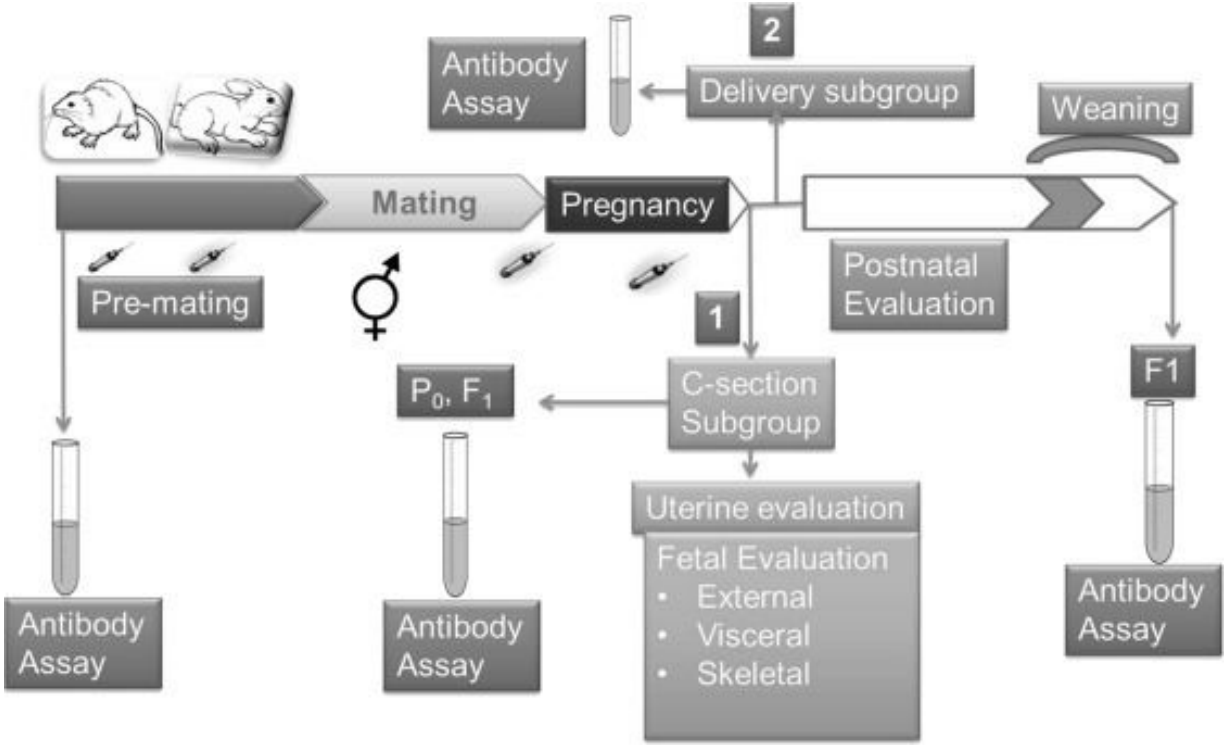
Evaluate

Blood & Immune

Pathology

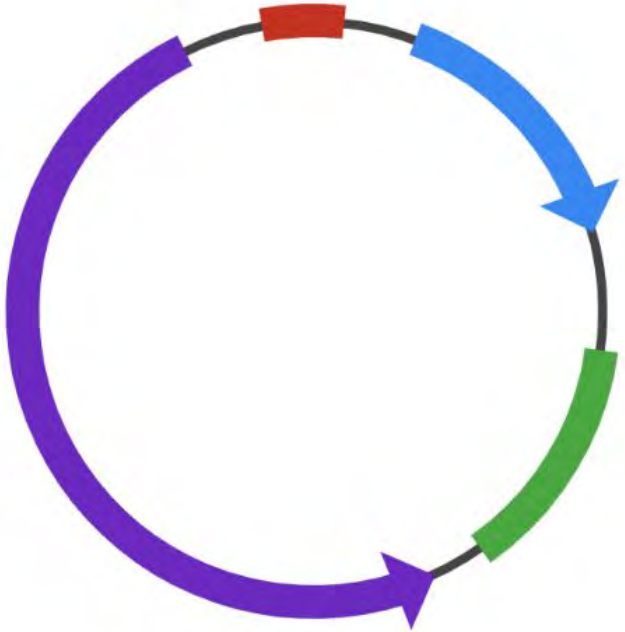
Critical Organs

Toxicology: Reproductive/Developmental



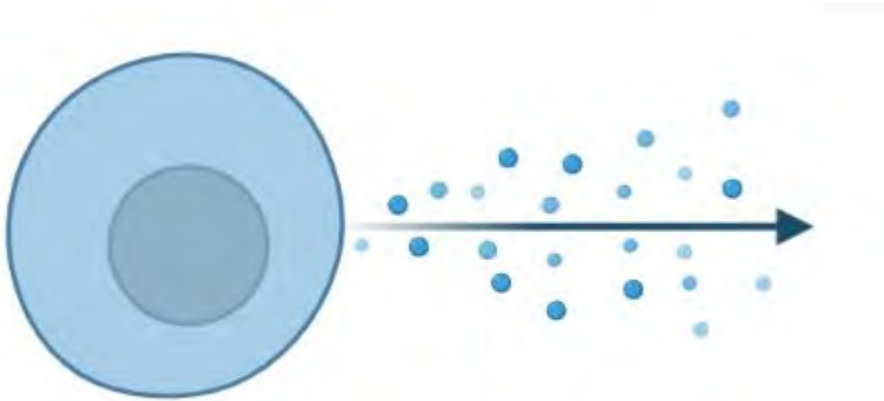
Toxicology

- Mutagenicity
- Biodistribution
  - Integration
- Carcinogenicity
- Testing bulk plasmid products



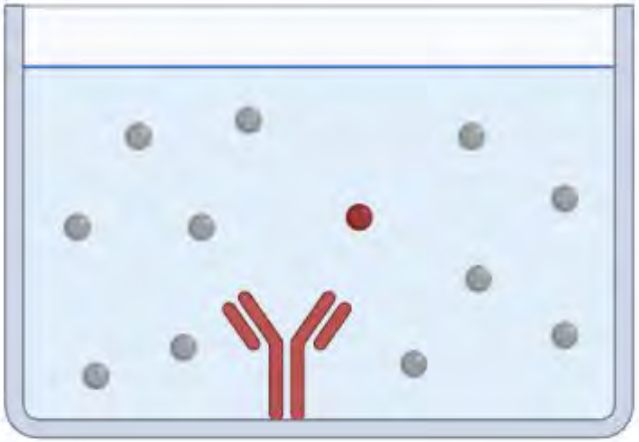
Immunology

- Evaluate the production of pro-inflammatory cytokines in vitro



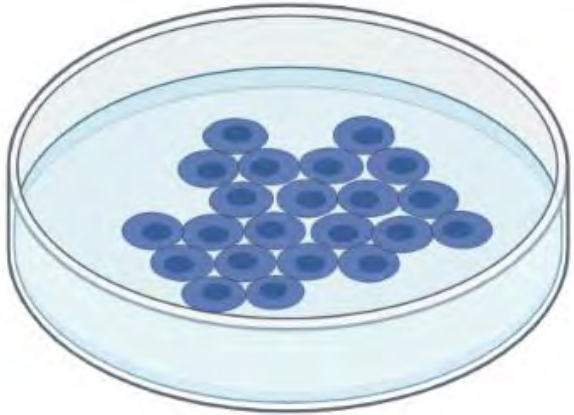
Immunology

- Evaluate the production of pro-inflammatory cytokines in vitro
- Evaluate antibody titers in vivo
  - IgA
  - IgG & Isotypes



Immunology

- Evaluate the production of pro-inflammatory cytokines in vitro
- Evaluate antibody titers in vivo
  - IgA
  - IgG & Isotypes
- Evaluate cytokines post-vaccination in vivo



Immunology

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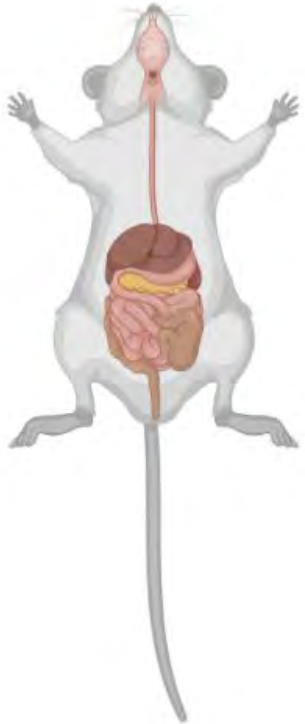
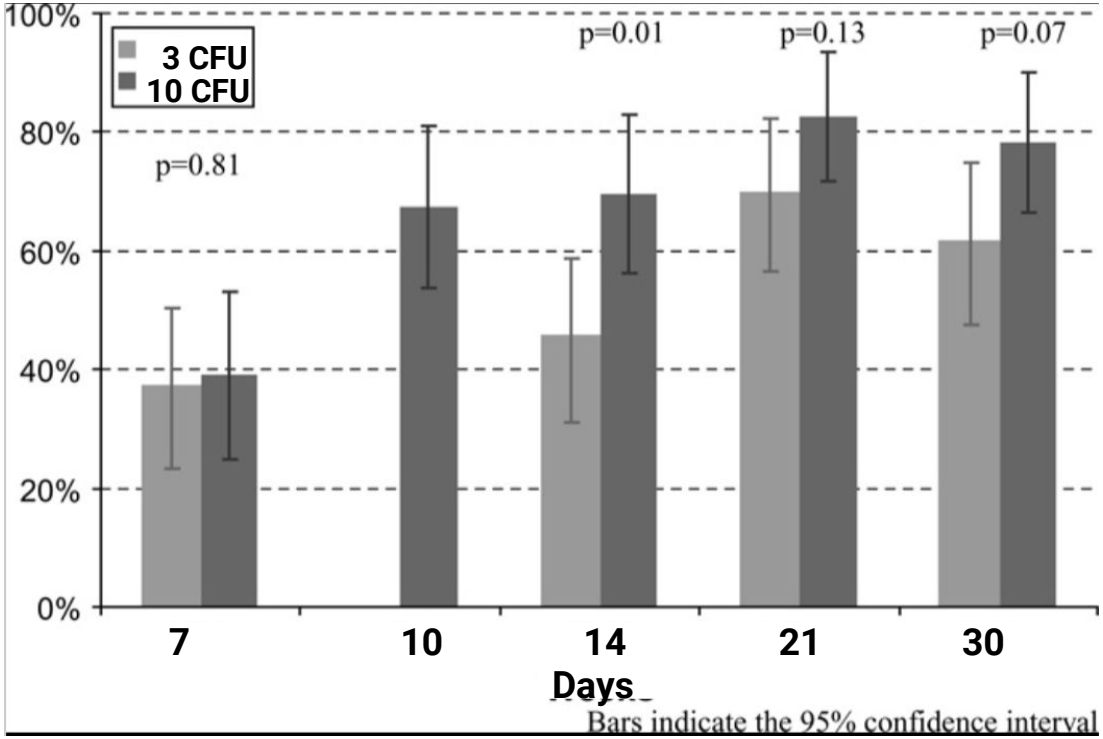
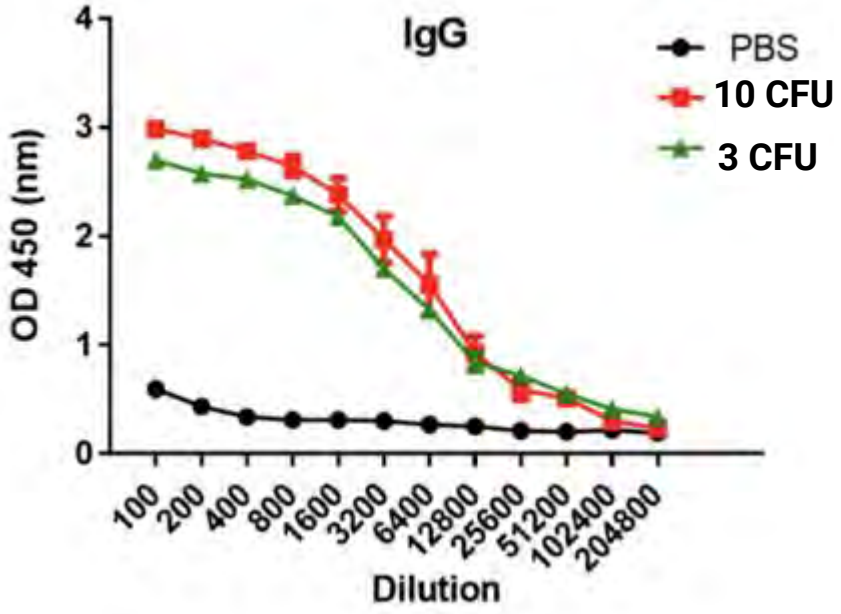


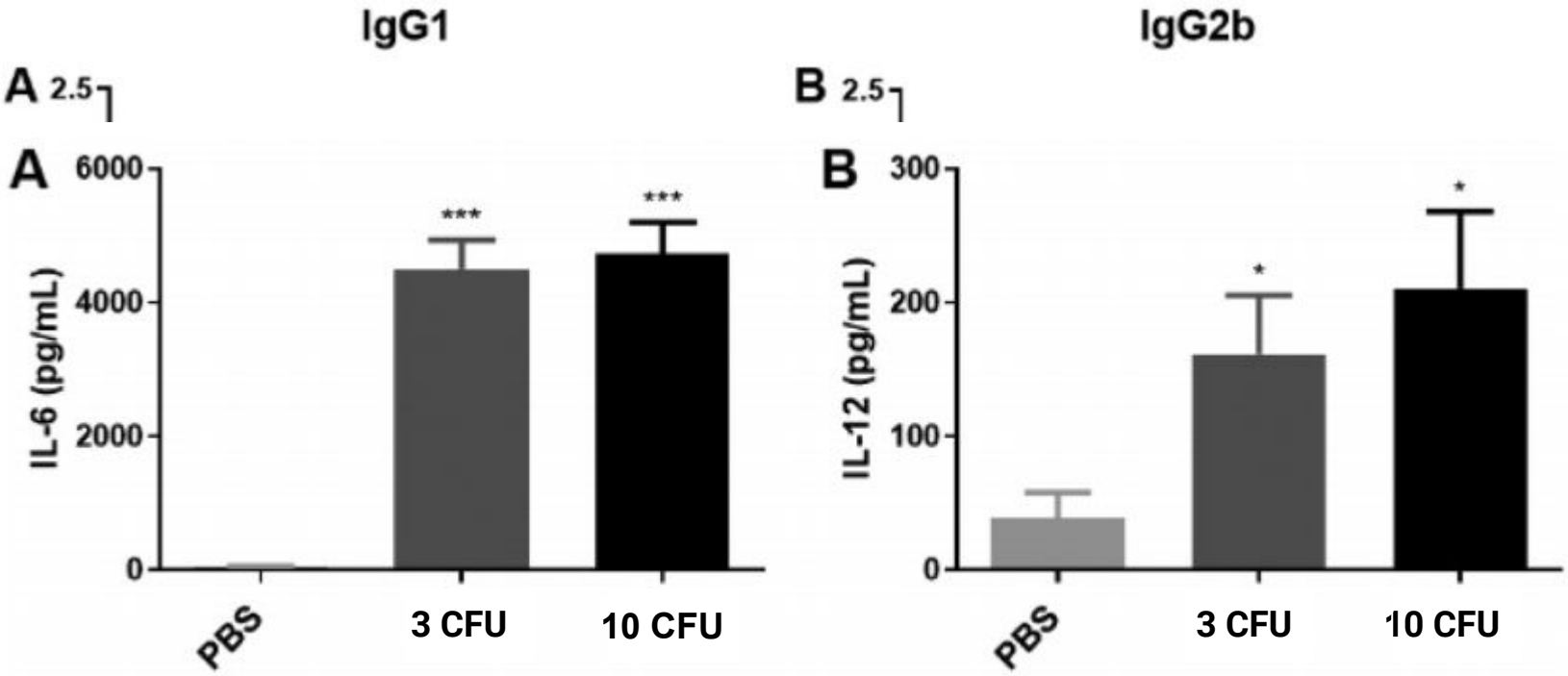
Immunology


100%
80%
60%
40%
20%
0%
3 CFU
10 CFU
p=0.81
p=0.01
p=0.13
p=0.07
7
10
14
21
30
Days
Bars indicate the 95% confidence interval

Immunology


IgG
PBS
10 CFU
3 CFU
OD 450 (nm)
0
1
2
3
4
100
200
400
800
1600
3200
6400
12800
25600
51200
102400
204800
Dilution

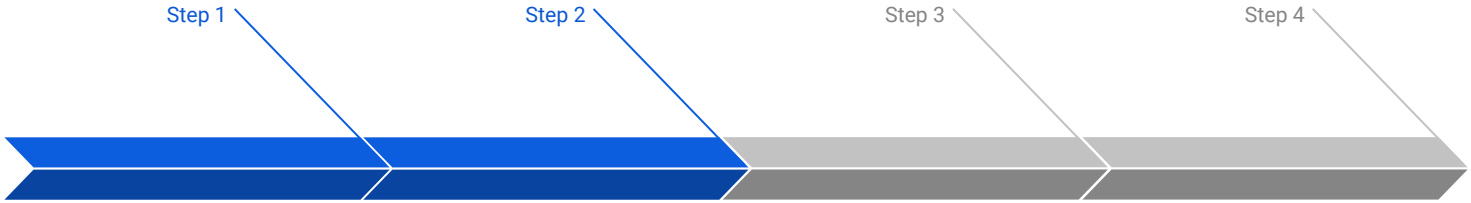
Immunology


IgG1
A
A 2.5
6000
4000
2000
0
IL-6 (pg/mL)
***
***
PBS
3 CFU
10 CFU
IgG2b
B
B 2.5
300
200
100
0
IL-12 (pg/mL)
*
*
PBS
3 CFU
10 CFU

Pre-Clinical Efficacy

- Build on our single/repeat dose study
- Baboons as our model organism
- Central idea is to “challenge”

Pre-Clinical Efficacy



Vaccinate

One dose of the oral vaccine

20 Baboons

Challenge

2 weeks post vaccination

Monitor

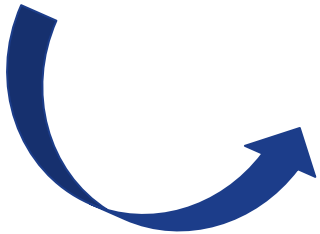
Survival & disease monitored for 14 days post

Assay

Collect organs at 2, 5, 7, 9 DPI for virus titration

Pre-Clinical Efficacy

- Response of baboons to the challenge
- Effect of vector priming?



Future Studies!

Target Product Profile

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TPP 1 - Indication for Use

Preferred	**Critical or Minimal**
Immunization **protects against** COVID-19 infection	Immunization reduces the severity of COVID-19

TPP 2 - Target Population

Preferred	Critical or Minimal
All ages and medical profiles, except for pregnant women	Adults, including the elderly, except for individuals who are pregnant or have a history of GI disease

TPP 3 - Contraindications

Preferred	Critical or Minimal
Pregnancy	Pregnancy, history of GI disease, & immunocompromised patients

TPP 4 - Safety/Reactogenicity

Preferred	Critical or Minimal
No serious adverse events	Safety and reactogenicity profile whereby the vaccine benefits still outweigh the safety risks

TPP 5 - Efficacy

Preferred	Critical or Minimal
>70% efficacy on a population basis >70% efficacy on the elderly	>70% efficacy on a population basis >60% efficacy on the elderly

TPP 6 - Dose Regimen

Preferred	Critical or Minimal
Single-dose regimen	No more than two doses, 21 days apart

TPP 7 - Durability of Protection

Preferred	Critical or Minimal
Lifetime immunity	Protection for at least 12 months

TPP 8 - Route of Administration

Preferred	Critical or Minimal
Oral	Oral

TPP 9 - Coverage

Preferred	Critical or Minimal
Multivalent	Monovalent

TPP 10 - Product Stability/Storage

Preferred	Critical or Minimal
Shelf life >24 months at room temperature Stability > 6 months at room temperature	Shelf life >12 months at room temperature Stability > 1 month at room temperature

TPP 11 - Co-Administration

Preferred	Critical or Minimal
Can be given with other vaccines without affecting immunogenicity, safety, or efficacy of the vaccines	Must be used as a stand-alone vaccine

TPP 12 - Presentation

Preferred	Critical or Minimal
Solid pill product in mono-dose presentation	Solid pill product in multi-dose presentation

TPP 13 - Production

Preferred	Critical or Minimal
7 billion doses	350 million doses

TPP 14 - Registration/ Prequalification

WHO and International Regulatory Authorities
WHO prequalified and/or Emergency Use Assessment & Listing Procedure (EUAL)

TPP 15 - Post-Marketing Surveillance

WHO and International Regulatory Authorities
Post-marketing surveillance will include an evaluation of all serious adverse effects, as well as vaccine effectiveness. Emergence of vaccine-resistant SARS-CoV-2 mutants will also be assessed, following the WHO’s prequalification requirements.

Phase 3 Testing

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Goal for phase 3: demonstrate vaccine efficacy in large, representative populations

- Randomized, double blinded, **placebo-controlled**, multicenter trial
- **Global consortium of sites** representing target populations
- Approximately **26,000++ participants** to be enrolled
- Duration follows adaptive **event-driven design**
  (expected 2 year follow-up for safety, but efficacy endpoints reached sooner)

Primary efficacy outcome: how effective is our vaccine at preventing moderate/severe disease?

OUTCOME	MEASUREMENT
First occurence of confirmed moderate-to-severe (or critical) COVID-19 (>21 days post-vaccination), as per recommended US FDA case definitions*	• Regular symptom screening by text-message monitoring system and participant phone-calls • All symptom reports investigated by clinical team • Cases confirmed by molecular diagnostic test (nasal swab PCR) at 2 independent labs (in cases of discrepancy, central lab results will prevail) • Cases adjudicated by a blinded central clinical committee

Secondary outcomes: will our vaccine prevent infection, transmission, and/or hospitalization?

OUTCOME	MEASUREMENT
Asymptomatic infection	Positive nasal RT-PCR at any time *or* antibody test (performed pre-vaccination, 1 wk, 1 mo, 3 mo, 6 mo, 1 year, 2 years - Abs reactive to an antigen not included in vaccine)
Critical illness	Hospital admission or death with positive SARS-CoV2 RT-PCR test (see FDA recommended case definitions)
Viral shedding	Presence of viable SARS-CoV2 virus in saliva, NP samples, and sputum as detectable by culture and/or other assays (assessed at intervals as noted above)

Plan for recruitment

Inclusion criteria

- **Age 12+**
- **Willing and able** to comply with all requirements (tests, in-person visits, etc)
- Medically **stable**
- Able to give **informed consent**

Exclusion criteria (abbreviated)

- **Immunosuppressed** or known immune disease
- **GI disease** (celiac, IBD, ulcers, etc)
- Current or recent **antibiotic treatment**
- **Pregnant** or **breastfeeding**
- Other **unstable chronic disease***
- Active or **prior COVID infection**
- Already **vaccinated** with any COVID vaccine
- Known **allergy** to a vaccine component
- Past **serious adverse reaction** to any vaccine

**i.e. requiring hospitalization or change in therapy due to deterioration in 2 mo prior to enrollment*

Proposed dosing and schedule

Goal: single dose regimen
- 1-10 billion cfu, dosing studies underway

If early immunogenicity trials show poor response…
- **2 doses** (prime and boost) **separated by 21 days**

Adaptive design Phase II/III design may be warranted

Measuring the immunological response

- Assessing short term **reactogenicity**:
  - 30 min observation period on-site
  - Daily, weekly, monthly symptom logging via text-message system

- Participants will undergo additional **immunogenicity** analyses at pre-specified intervals (pre-vaccination, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years)
  - Antibody titers (IgM, IgG, IgA) - and mucosal vs. systemic
  - Ab neutralization assays
  - Cell-mediated immunity
  - Cytokine levels

- If constrained by budget, immunogenicity testing to be performed only on subset of first ~5000 enrolled participants (across pre-defined age and per-center quota)

Statistical power and duration of study

Necessary events: ~350	**Number of participants needed: ~26,000**
Assumptions *2-sided t-test* • VE ≥ 30% (relative hazard 0.7) • Significance level (α): 5% • Power (β): 90% • Allocation groups: 2:1 (intervention:control)	**Assumptions** • Follow-up period: 2 years • Attrition/censoring: 10% / yr • Baseline event rate (incidence): 1% / yr

Factors that could increase speed of trial:

- Higher than expected **efficacy**: if VE ≥ 70%, only **32 events** needed (i.e. **2 months**)
- Higher than expected **attack rate**
- More enrolled **participants**

Safety & pre-specified analyses

- Independent DSMB to be commissioned
- Interim analyses to be performed at pre-specified intervals (i.e. 25, 50, 100, 200 events) for safety and efficacy stoppage
- Both intention-to-treat (ITT) and per-protocol analyses to be reported

Ethics

- If vaccine is proven safe and effective in preliminary analysis (in consultation with DSMB and applicable regulators), placebo group participants may be offered option of vaccine

- If another vaccine (Pfizer, Moderna, Janssen) is given full biological license approval (BLA) by US-FDA before study commencement, design can be switched over to non-inferiority trial

Post-Marketing Surveillance

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Continuing pharmacovigilance

- Given the novel platform, we intend to conduct robust post-marketing surveillance activities for safety issues

- Particular outcomes of interest:
  - Incidence of **inflammatory gastrointestinal conditions** (inflammatory bowel disease, gastroenteritis, irritable bowel syndrome, etc)
  - Incidence of **gastrointestinal cancers**, other **neoplasms,** or anything suggestive of integration into host genome
  - Incidence of **autoimmune conditions**
  - **Persistent infection** with the bacterial vector
  - Prevalence and duration of potential milder side effects including: constipation, diarrhea, abdominal pain, etc

Methods

Safety:

- **Passive surveillance** for any **unexpected adverse events** using provider/patient-driven reporting systems (i.e. US VAERS and similar)
- **Active surveillance** for **outcomes of special interest**—those described previously, as well as general AEs associated with COVID vaccines—using large patient data pools (i.e. VSD and similar systems)
- Specific **patient registries** to be utilized as needed to examine **special populations** (pregnant, immunocompromised)

Effectiveness (confirmatory):

- Large post-marketing prospective cohort study (cases identified by active surveillance)

Recommendations for implementation

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Priority groups

1) **Health workers** at high to very high risk of becoming infected & transmitting disease
   - Frontline healthcare workers
   - Front desk hospital staff
   - Custodial staff
   - Security & emergency staff

2) **Adults above age 50** with risk factors for severe disease and death:
   - Hospitalized or in a long-term care facility
   - Serious comorbid chronic illness

3) **Middle age Employers**
   - >50 with moderate to high illness actively working in crowded workplace

4) **Other social/employment groups** at elevated risk of acquiring & transmitting infection

- Group of people who are unable to effectively maintain physical distance
- For example: bus drivers, truck drivers, Uber drivers, high priority school staff, Military staff who living in tight quarters

5) **Essential workers outside health and education sections**

●Child care providers, government workers, food and agriculture workers, people living in detention facility, incarcerated people, dormitories, Urban slums, dense urban neighbourhood

Rationale & other ethical considerations

Evolution and Development of Human Health

Thank you!

ORAVAX:
Revolutionizing health through bacteria

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References

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Appendices

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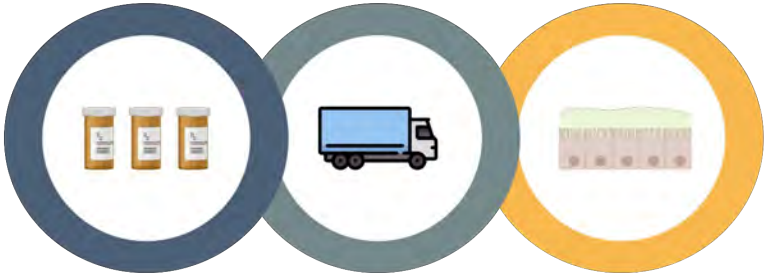
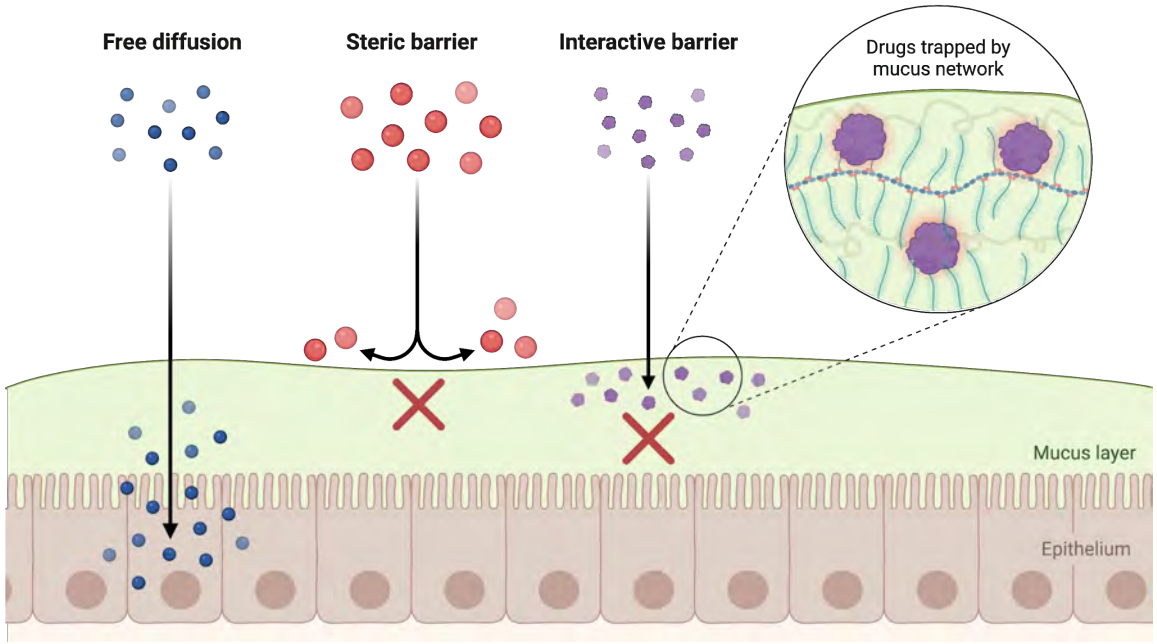
Appendix I. Pros: a rapid, cost-effective vaccine for the globe



Cost-effective production | Improved distribution | Mucosal immunity

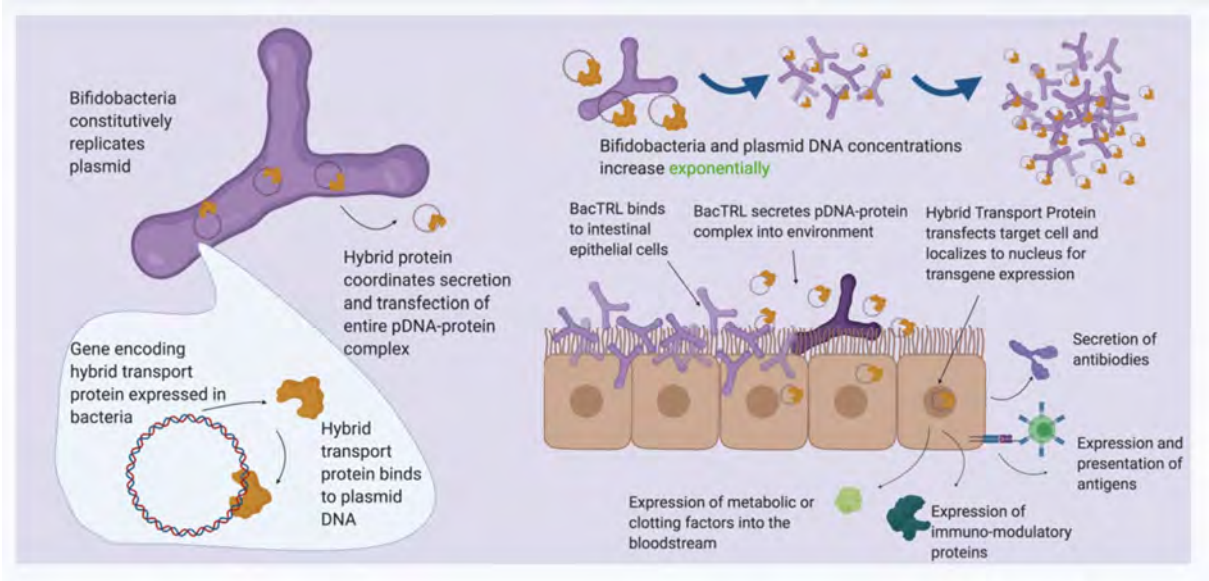
- **Enhanced immune response** due to presence of bacterial danger signals
- Constitutive, **targeted expression** of DNA construct at sites of interest
- **Multivalent potential** (multiple antigens in one payload)
- Built-in **failsafe:** bacterial vector easily killed by routine antibiotics

Appendix II. Cons: a promising but largely untested technology



- No **human** DNA vaccines currently with full FDA approval
- Considerable diversity in gut + respiratory tract microbiome
- Potential issues with low absorption/transfection in gut mucosa (solved by proprietary tech)
- Adjuvants? Extent of systemic protection?
-

Appendix III. A revolutionary delivery platform: bacterial DNA system



- Live bacteria carrying plasmid of interest ingested via oral pill
- Bacteria transit upper GI then colonize gut epithelia
- Transgenes taken up by local host cells, causing expression of target antigens (i.e. SARS-CoV-2 spike protein)
- Systemic and mucosal immune response induced