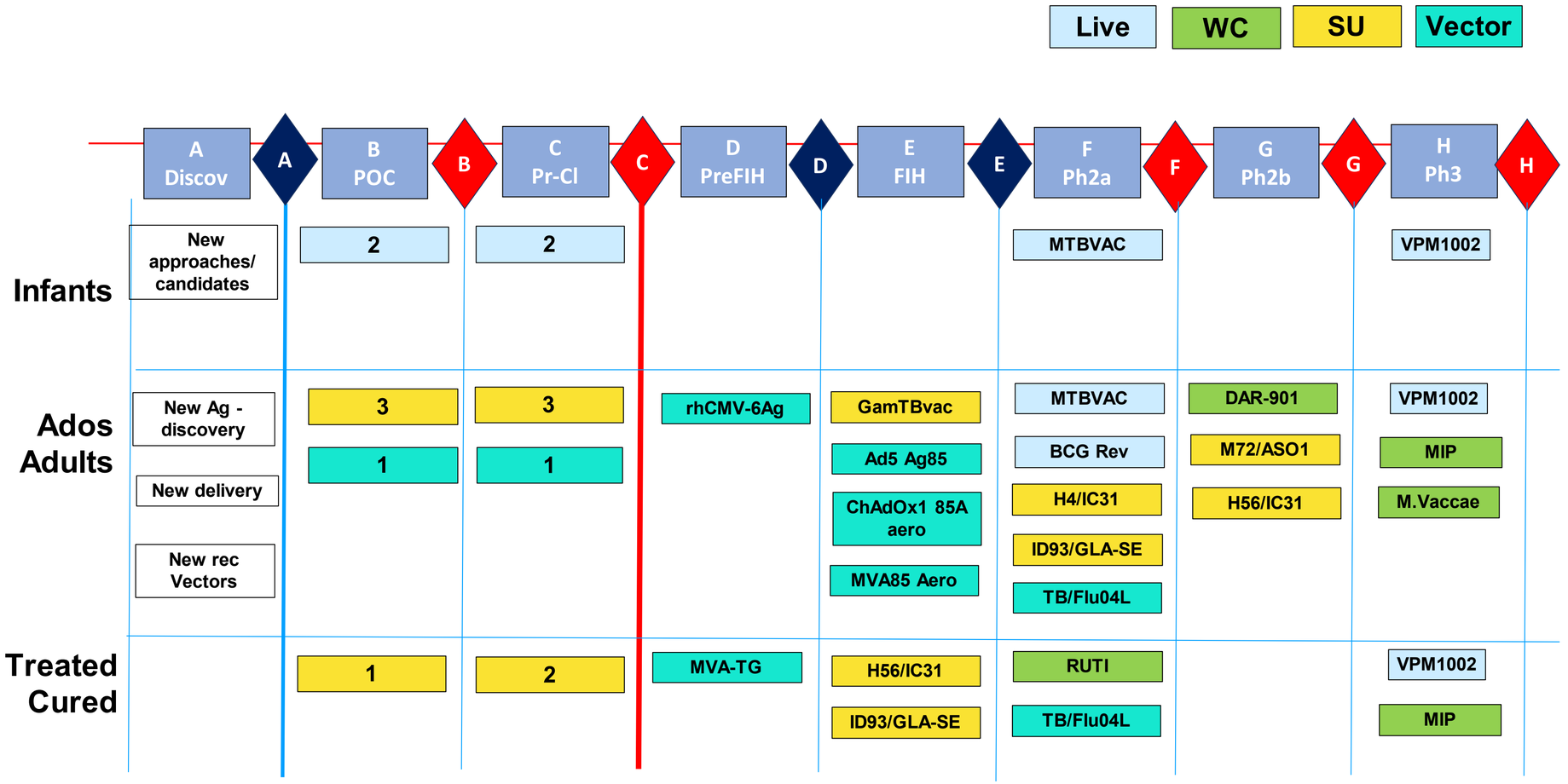
HDT

Pathway to Effective TB Vaccines, 2021

Pipeline of TB vaccines



TBVAC2020 stage gating

H4:IC31 and BCG revaccination

- Phase 2 trial in 990 Quantiferon (QFT)-negative adolescents in South Africa
- Neither vaccine showed significant effect on initial infection
- Both vaccines appeared safe and immunogenic
- H4:IC31 showed a modest signal in prevention of sustained QFT conversion (VE=30.5%; p=0.08)
- BCG revaccination induced statistically significant prevention of sustained QFT conversion (VE-45.4%; p=0.01)
- Considerations

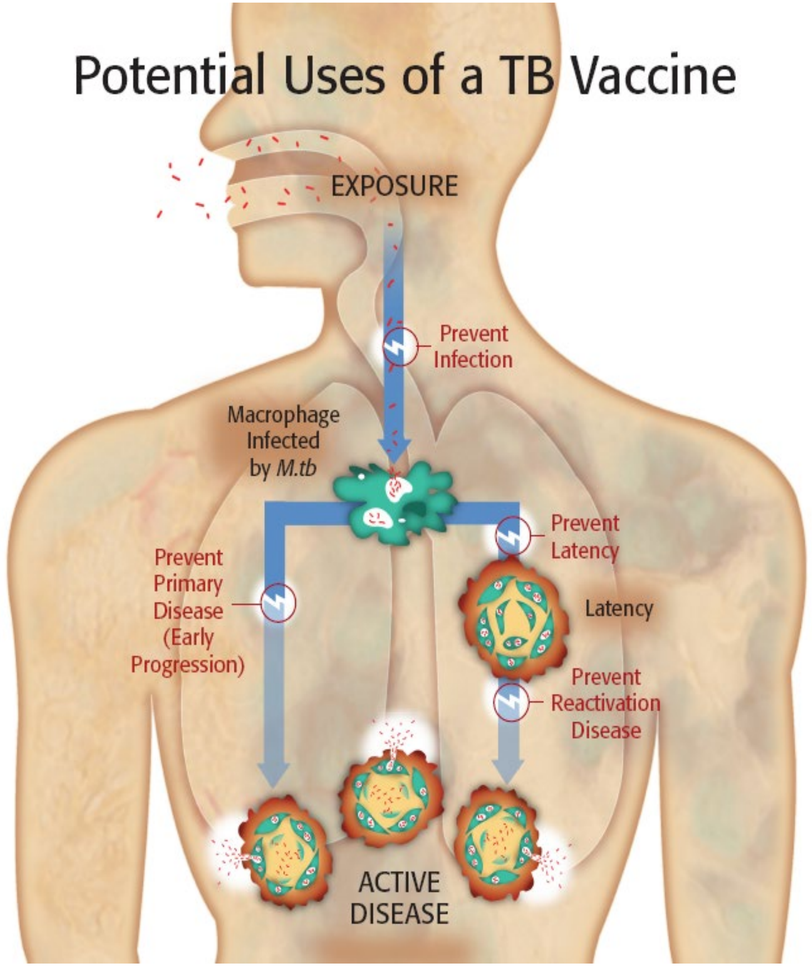
  ✓ POI trial design feasible, tool for decision-making
  ✓ (Immune) correlates of protection
  ✓ Further BCG trial

N Engl J Med 2018;379:138-49

HDT

Strategies for TB Vaccine Development

- **Pre-infection**
  - prevent infection and/or disease (most animal c
  - either initial infection or establishment of the grar
- **Post-infection**
  - prevent disease
  - *after initial infection*
  - reactivation from latency (minimal animal data)
- **Immunotherapeutic**
  - as treatment
  - shorten the course of chemotherapy for active T
  - decrease relapse or reinfection rates



Adapted from BMGF

M72/AS01$_E$

- Phase 2b trial in 3575 quantiferon (QFT)-positive adults in Southern Africa
- The vaccine appeared safe and immunogenic
- M72/AS01$_E$ vaccination induced statistically significant prevention of TB disease (54%)
- Future development path to be determined

N Engl J Med 2018;379:1621-34

HDT

What Next?

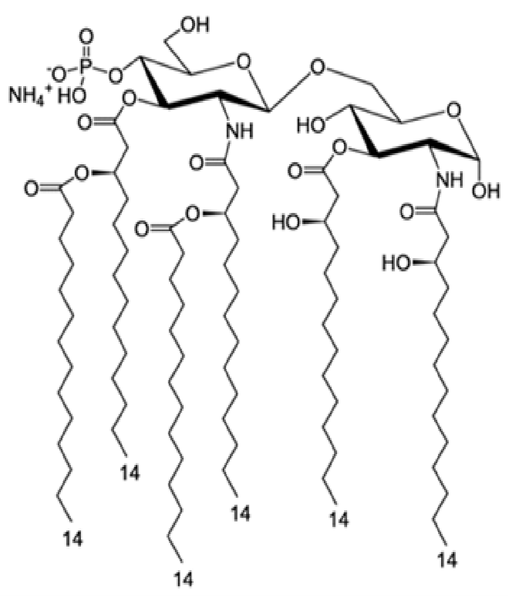
Focus on Effective Adjuvants For Protein Vaccine

✓- ASO1 next gen (synthetic)
✓- Alternative TLR4 formulations
✓- TLR7/8, etc.

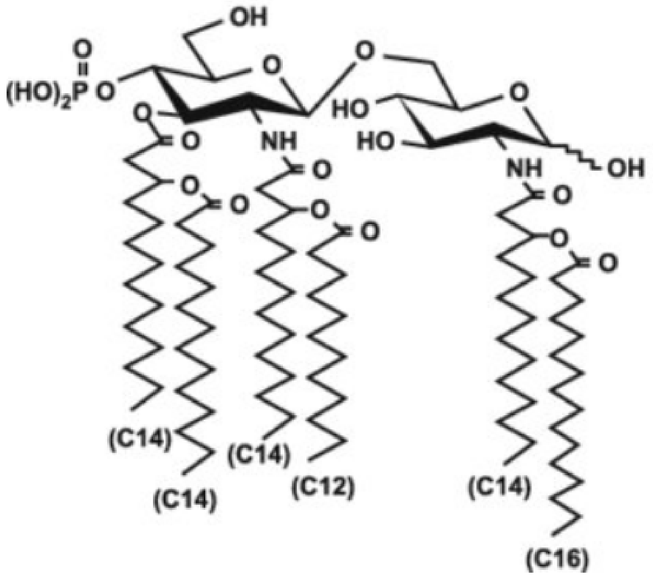
Alternative delivery of Vaccine Antigens

- RNA
- DNA

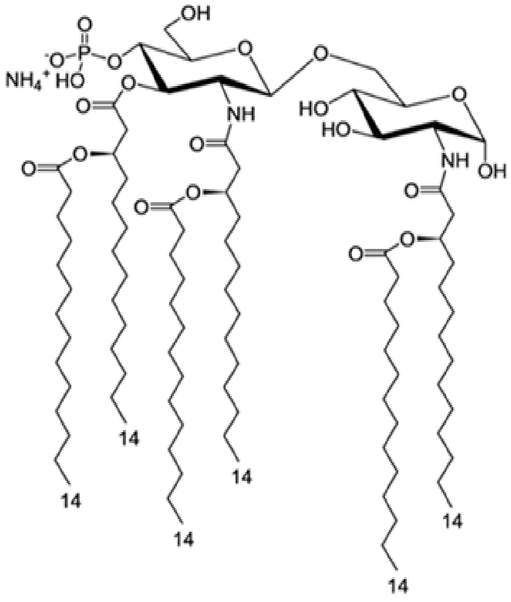
IP Issues with Current TLR Agonists



GLA



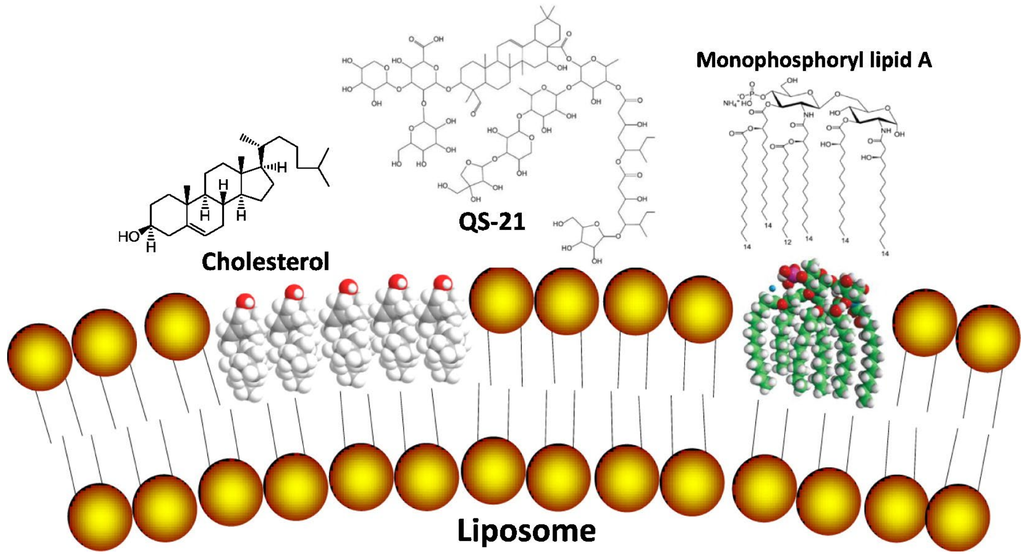
MPL

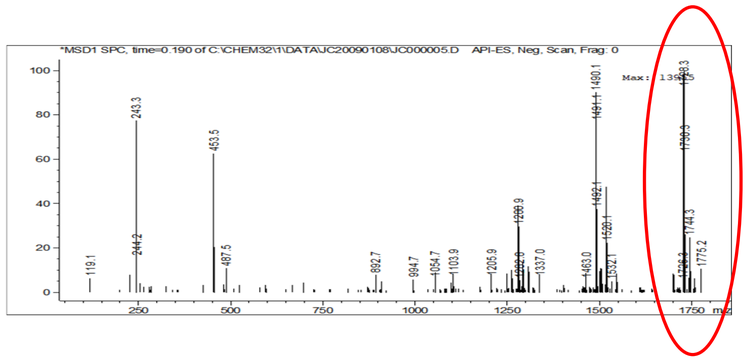


3D(6acyl) PHAD

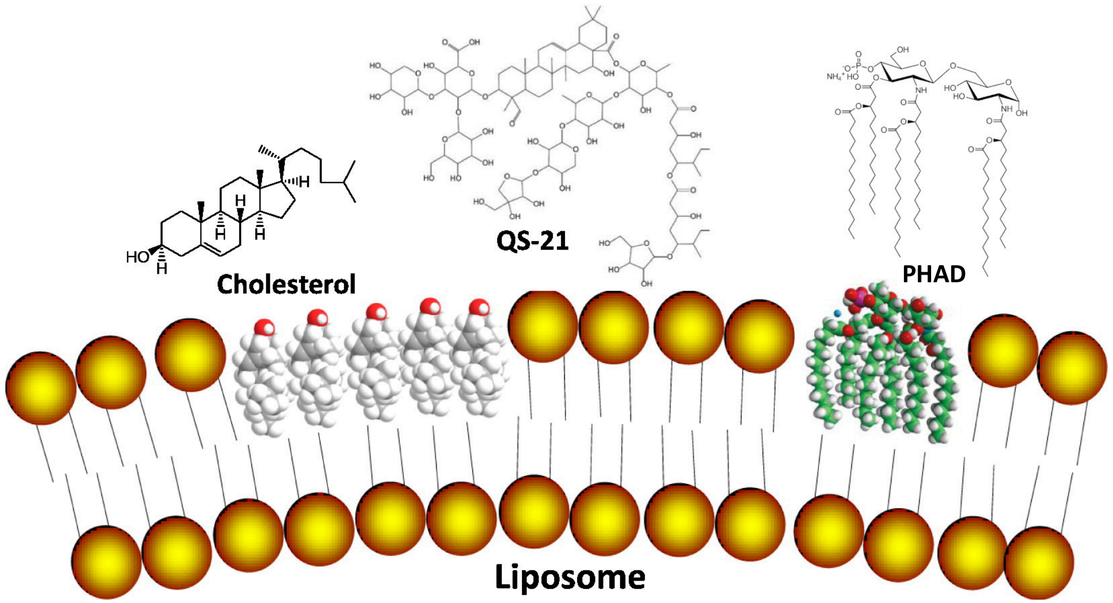
Many TLR4 agonists are encumbered by patent issues and can face deployment problems related to freedom to operate, manufacture, and/or distribute

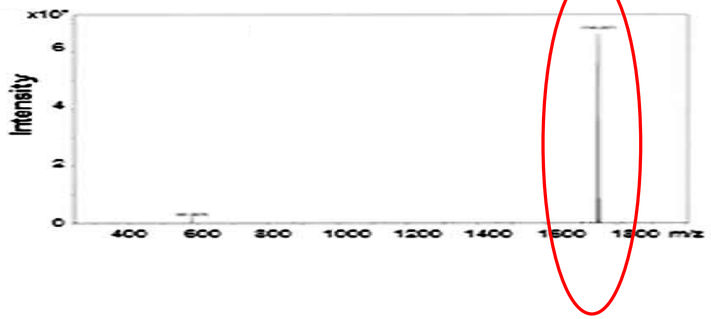
Next Gen AS01





MPL (Hexa-acyl component circled in red)





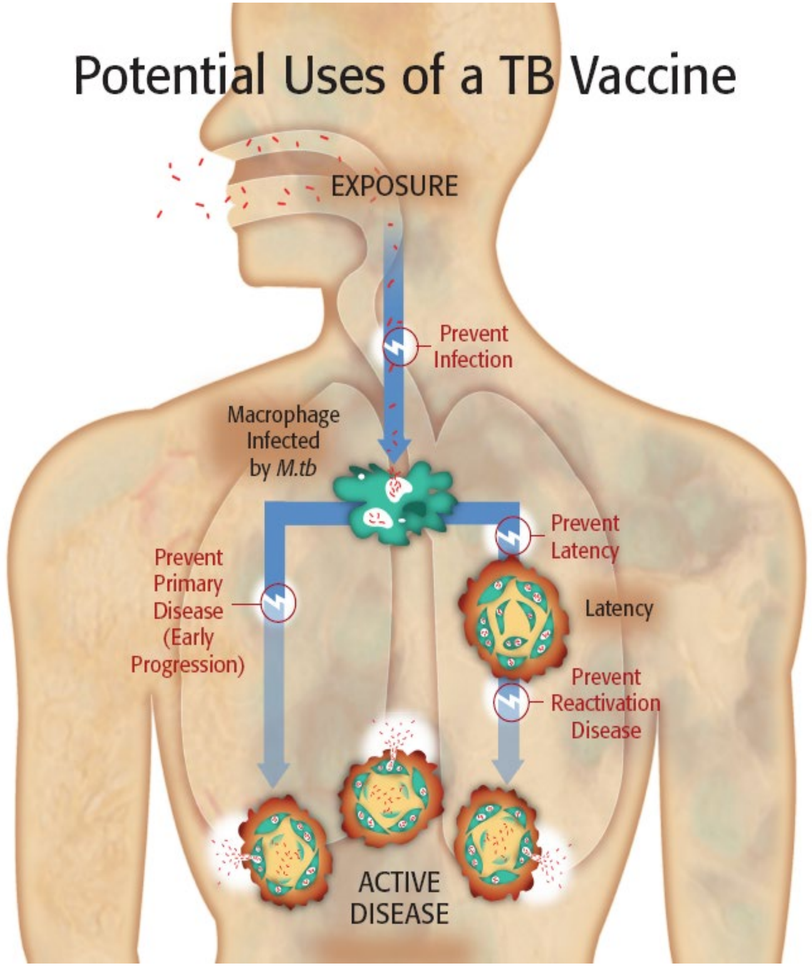
PHAD (Hexa-acyl component circled in red)

MS adapted from: “Development and Characterization of Synthetic Glucopyranosyl Lipid Adjuvant System as a Vaccine Adjuvant” Coler RN, Bertholet S, Moutaftsi M, Guderian JA, Windish HP, et al. (2011) PLOS ONE 6(1): e16333.

HDT

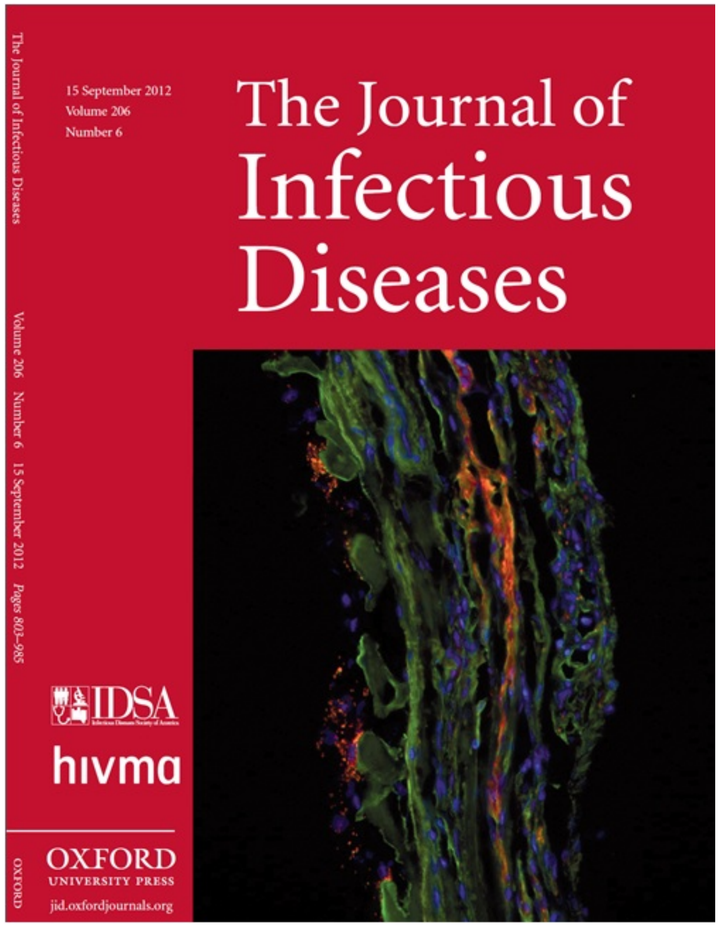
Strategies for TB Vaccine Development

- **Pre-infection**
  - prevent infection and/or disease (most animal c
  - either initial infection or establishment of the grar
- **Post-infection**
  - prevent disease
  - *after initial infection*
  - reactivation from latency (minimal animal data)
- **Immunotherapeutic**
  - as treatment
  - shorten the course of chemotherapy for active T
  - decrease relapse or reinfection rates



Adapted from BMGF

Immune Therapy for TB



Journal of Infectious Diseases Advance Access published August 13, 2012

MAJOR ARTICLE

Therapeutic Immunization against *Mycobacterium tuberculosis* Is an Effective Adjunct to Antibiotic Treatment

Rhea N. Coler, Sylvie Bertholet,[a] Samuel O. Pine, Mark T. Orr, Valerie Reese, Hillarie Plessner Windish, Charles Davis, Maria Kahn, Susan L. Baldwin, and Steven G. Reed

Infectious Disease Research Institute, Seattle, Washington

Background. Recent advances in rational adjuvant design and antigen selection have enabled a new generation of vaccines with potential to treat and prevent infectious disease. The aim of this study was to assess whether therapeutic immunization could impact the course of *Mycobacterium tuberculosis* infection with use of a candidate tuberculosis vaccine antigen, ID93, formulated in a synthetic nanoemulsion adjuvant, GLA-SE, administered in combination with existing first-line chemotherapeutics rifampicin and isoniazid.

Methods. We used a mouse model of fatal tuberculosis and the established cynomolgus monkey model to design an immuno-chemotherapeutic strategy to increase long-term survival and reduce bacterial burden, compared with standard antibiotic chemotherapy alone.

Results. This combined approach induced robust and durable pluripotent antigen-specific T helper–1-type immune responses, decreased bacterial burden, reduced the duration of conventional chemotherapy required for survival, and decreased *M. tuberculosis*–induced lung pathology, compared with chemotherapy alone.

Conclusions. These results demonstrate the ability of therapeutic immunization to significantly enhance the efficacy of chemotherapy against tuberculosis and other infectious diseases, with implications for treatment duration, patient compliance, and more optimal resource allocation.

HDT

RNA Vaccines

Advantages

- Synthetic process, cost effective
- Can encode multiple antigens
- Safe
- Potent antibody responses

Open Questions

- T cell responses?
- Durability?

Nucleic Acids as Vaccine Platforms

DNA

- DNA encoding antigen
- Efficient protein expression requires nuclear delivery

Transcription

RNA

- RNA encoding antigen
- Efficient expression only requires cytoplasmic delivery

Translation

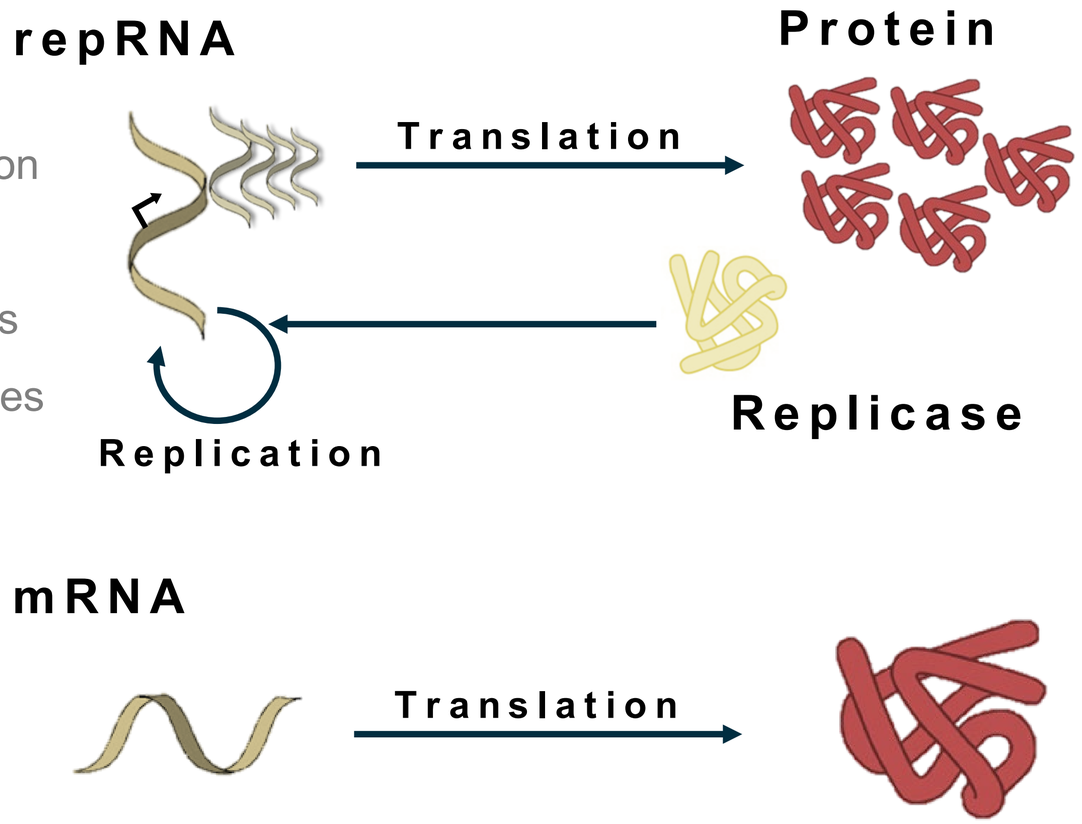
Protein

- Traditional vaccine antigen
- Requires cell-based manufacturing process

HDT

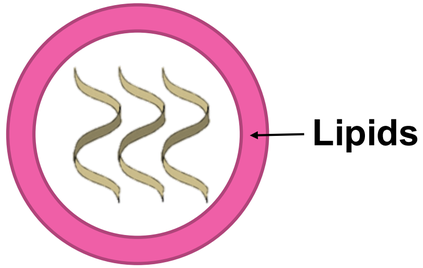
repRNA More Potent than mRNA

- RNA encodes replicon and antigen
- Replication increases number of RNA copies by >10^4



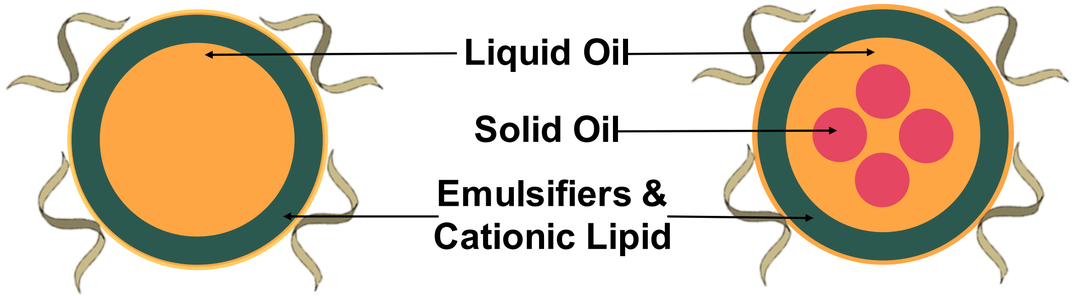
- Amplified vaccine antigen expression
- Replicon proteins, dsRNA, and ssRNA activate innate immune response

RNA Vaccines Require Formulation



Lipid Nanoparticles (LNPs) (Malone *et al*, 1989)

- Encapsulated RNA
- Single-vial presentation
- Complex to



Cationic Nanoemulsions (CNEs) (Brito *et al*, 2014)

- Binds RNA
- Two-vial presentation
- Allows for stockpiling of

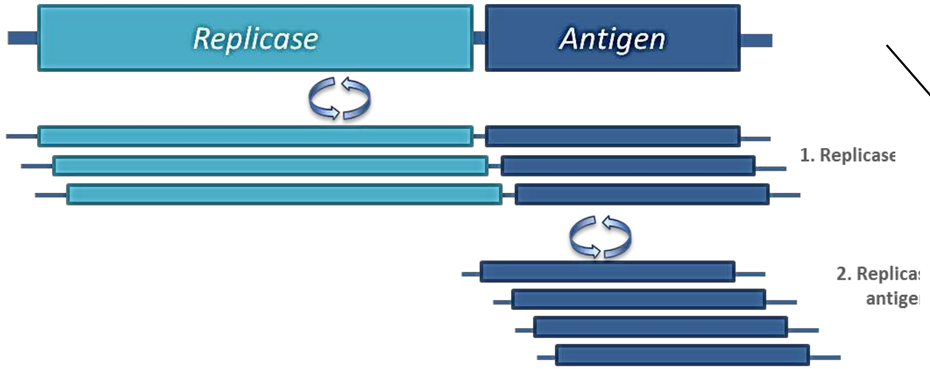
Nanostructured Lipid Carriers (NLCs)

- Historically used for delivery of lipophilic small-molecule drugs

HDT

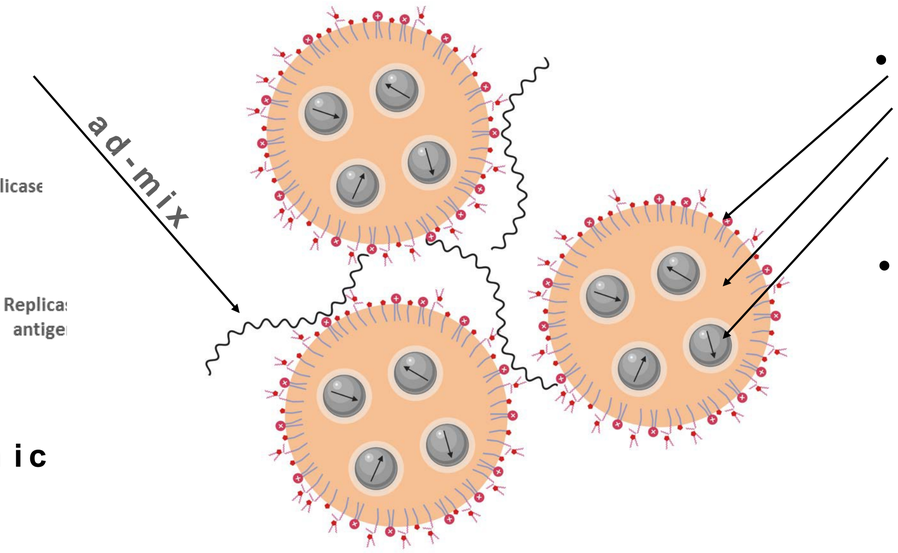
LION RNA Formulation

repRNA: self-amplifying antigen



- Replicase amplifies the genomic RNA creating >100k copies
- Replicase amplifies the antigen RNA leading to high-level, sustained immune activation

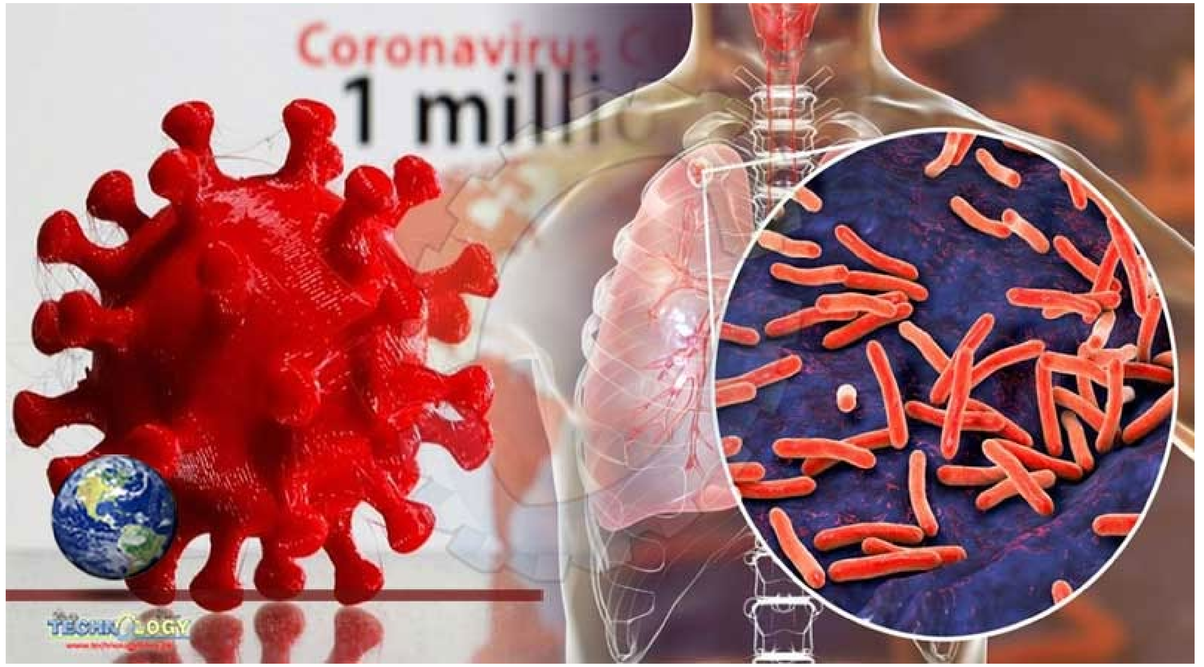
LION™: lipid inorganic nanoparticle



- Cationic lipids surround adjuvant oils and inorganic metal particles
- Nanoparticles protect the repRNA while driving delivery to the immune system

Enabling Global Protection Against Covid: Lessons for TB

- LION Formulation Enables Protective Response in Clinical Trial
- Lowest RNA Dose of any RNA Vaccine



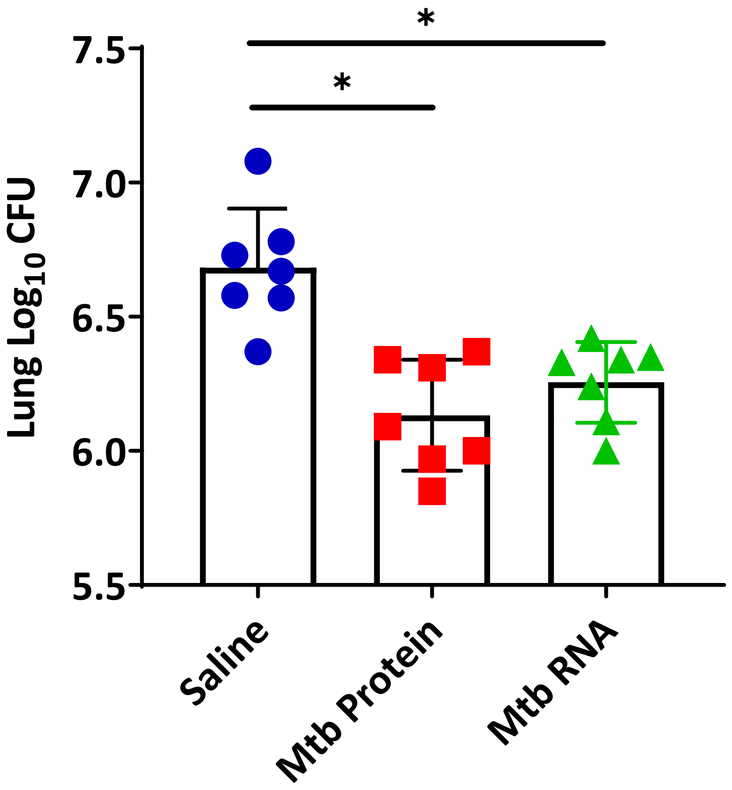
Global TB Fight Set Back 12 Years by COVID Pandemic, Doctors Warn

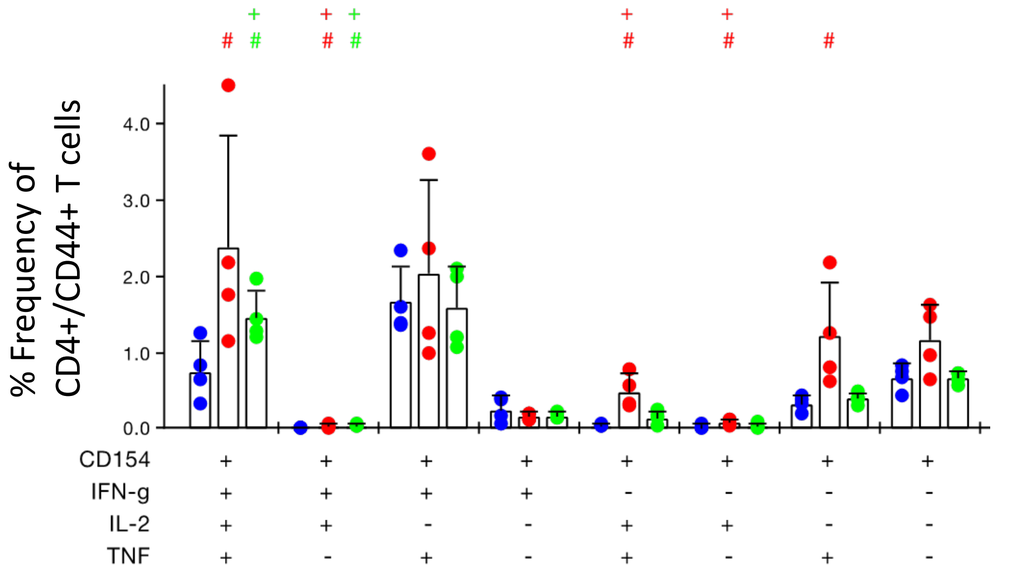
https://www.voanews.com/science-health/global-tb-fight-set-back-12-years-covid-pandemic-doctors-warn

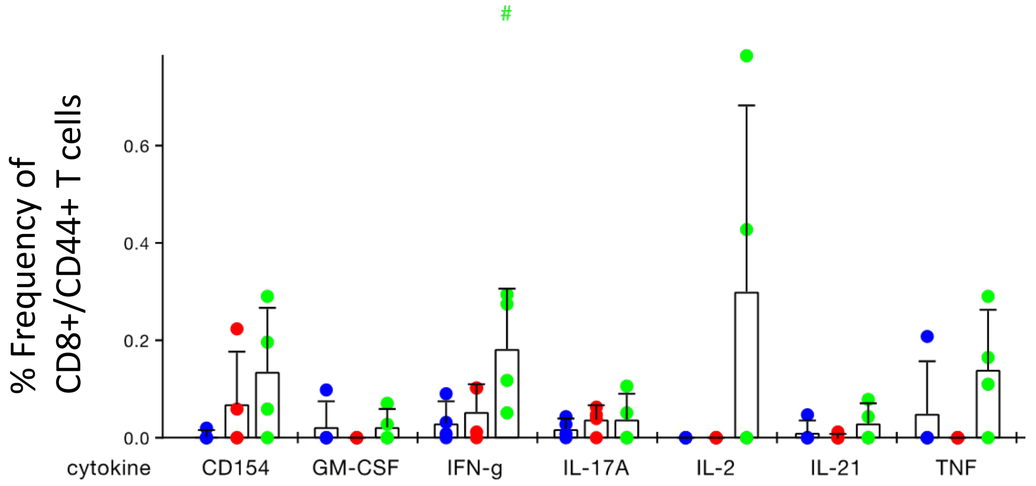
Spike Protein IgG Titer

Groups	GMT (95% CI)		
	Day 1	Day 29	Day 57
Placebo	398.2 (253 - 626.5)	419.7 (250.2-704.2)	781.2 (397.4-1535)
5 µg Dose	375.5 (198.2-711.3)	2255 (713.2-7127)	6408 (2330-17624)
10 µg Dose	496.2 (341.2-721.4)	2368 (728.1-7705)	17013 (7115-40682)
25 µg Dose	699.6 (419.4-1167)	4207 (1450-12210)	16266 (5777-45801)

Single Shot Protection with TBRNA

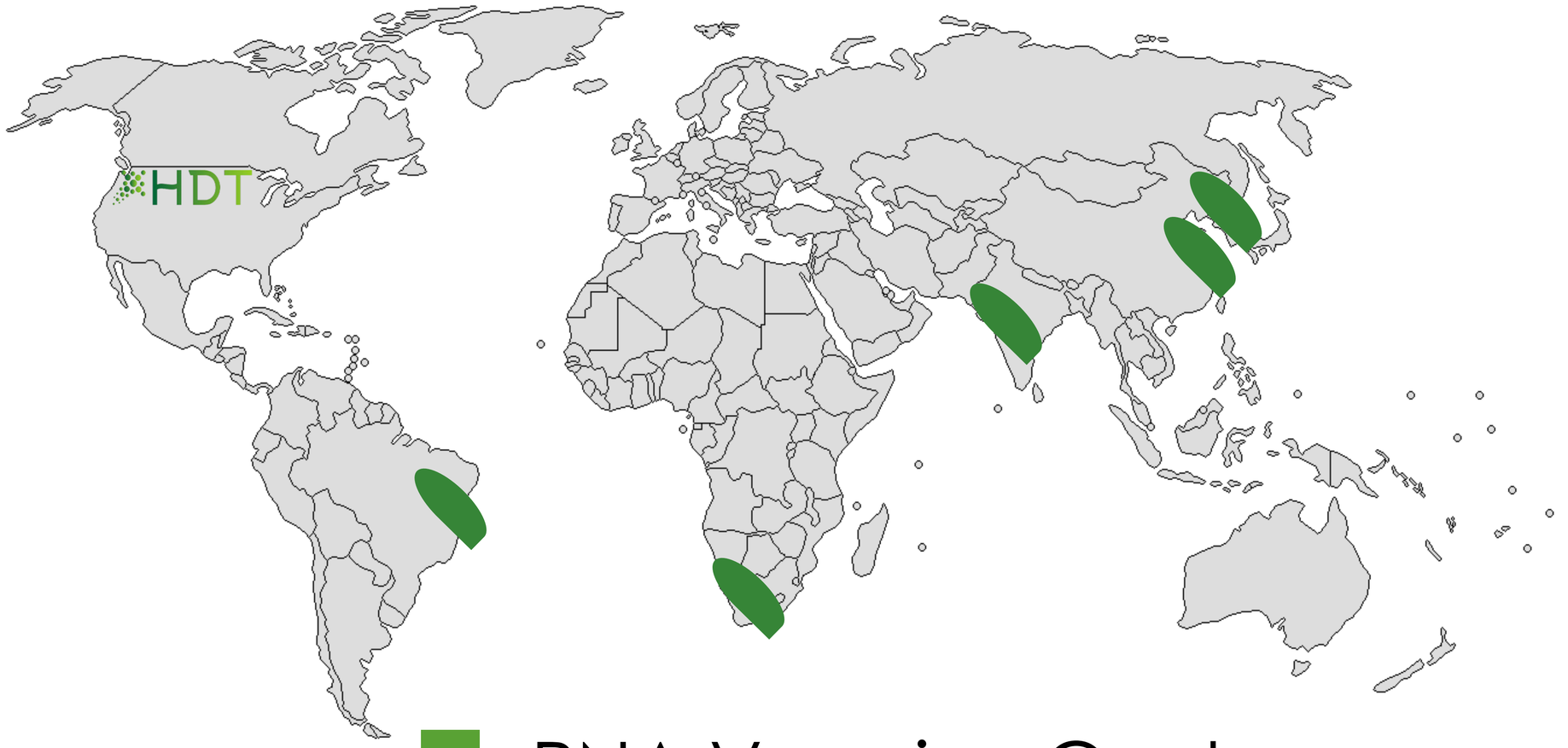






Technology Transfer, Capacity Development

Lesson From Covid， Critical For Global Vaccine Solutions



HDT

Inauguration of Adjuvant Center in India