mRNA and adjuvants friends…or foes ?

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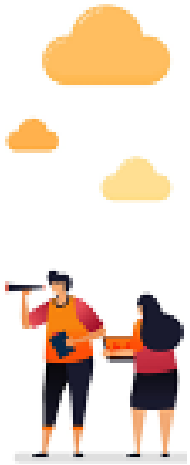
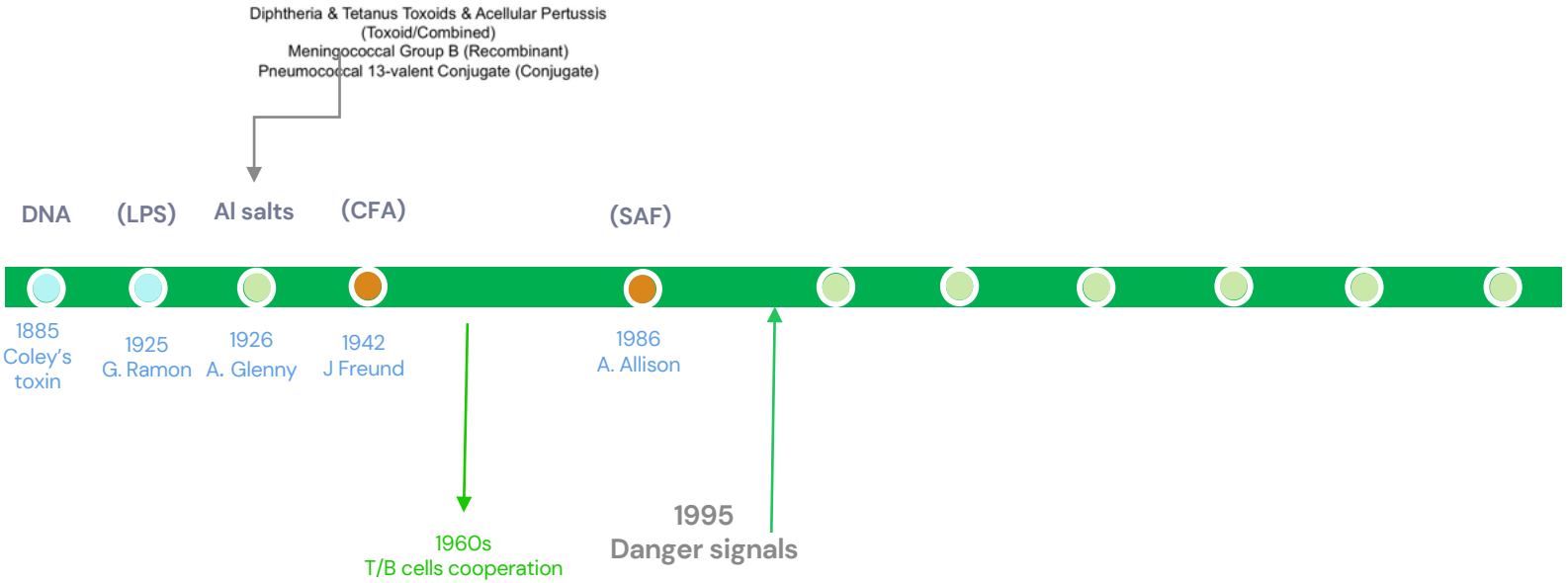
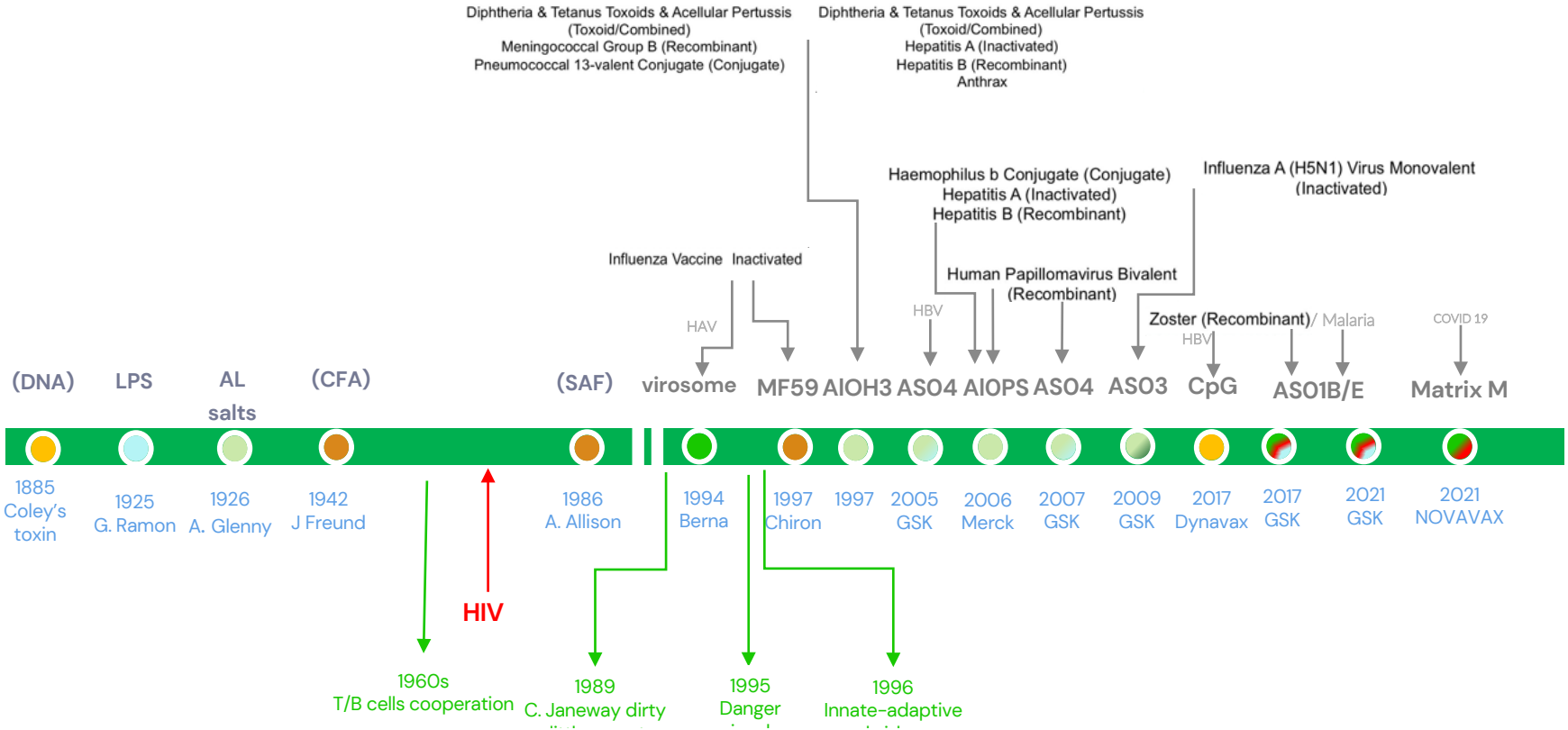


A look at the past

From chance ……


Diphtheria & Tetanus Toxoids & Acellular Pertussis
(Toxoid/Combined)
Meningococcal Group B (Recombinant)
Pneumococcal 13-valent Conjugate (Conjugate)
DNA
(LPS)
Al salts
(CFA)
(SAF)
1885
Coley's
toxin
1925
G. Ramon
1926
A. Glenny
1942
J Freund
1986
A. Allison
1960s
T/B cells cooperation
1995
Danger signals

From chance .. to necessity



Understanding the present

An ideal adjuvant

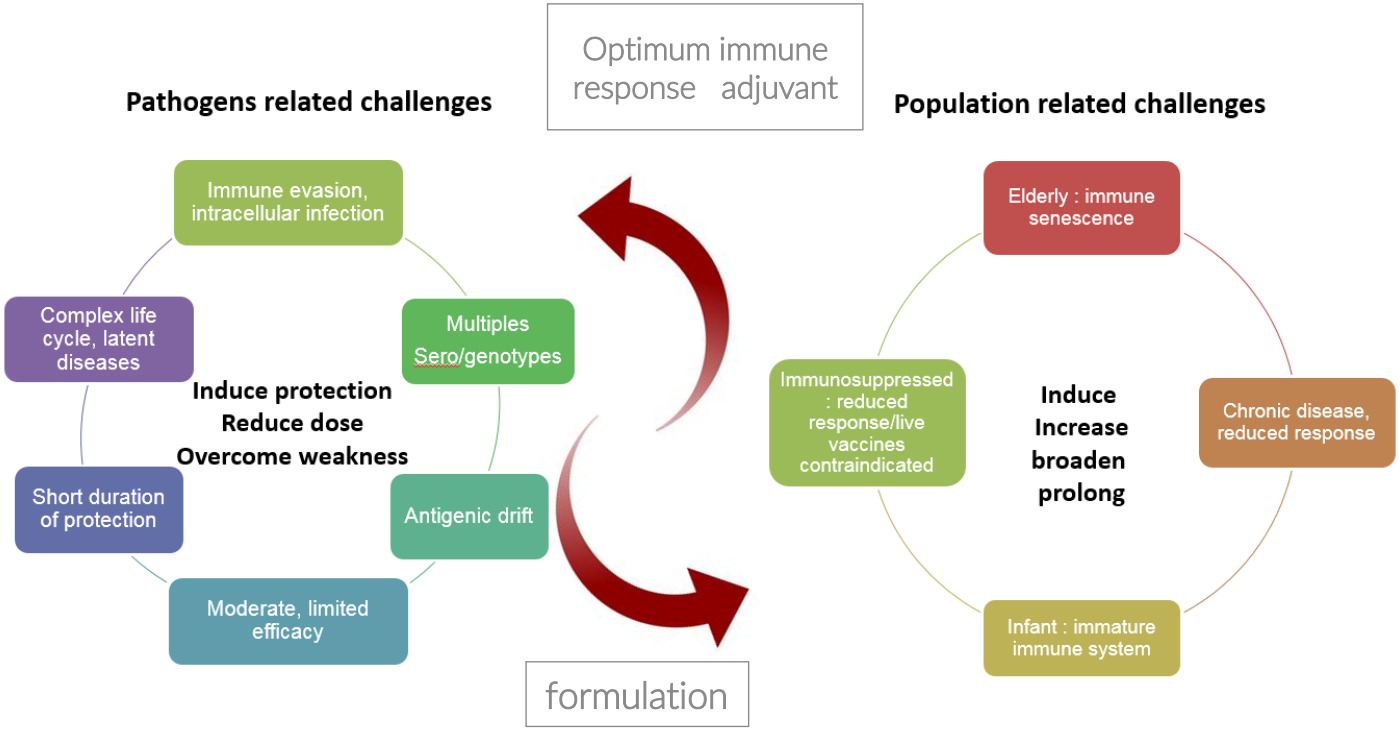
Understanding the present

- Have no bystander adverse effect
- Have a clear mechanism of action
- Effectively activate humoral and cellular immunity with no adverse reaction across populations, if not should be tailored to the population best benefiting from it.
- Be easy to produce, store and administer

Critical part of the adjuvant design

Todays vaccines

development based on the understanding of the host pathogen challenges



What we have learned

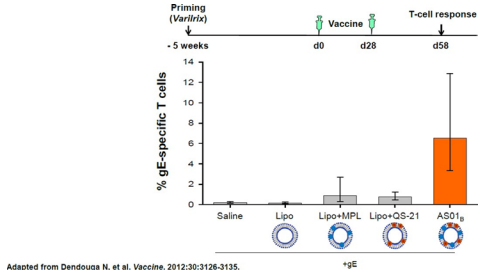
Understanding the present

- Current adjuvants can be natural (part of a plant, microbe), hemi synthetic (built on nature) or synthetic
- The revolution in the understanding of how innate immune system senses microbes brings huge opportunity for their design and development
- One size does not fit all (antigen, or target population, or needed immune modulation)
- Combination can be synergistic through a different mechanism of action (shown with AS01 only so far)

What we have learned

Understanding the present

- The effect of combined adjuvant molecules is superior to the sum of its part



Adapted from Dendouga N. et al. *Vaccine*. 2012;30:3126-3135.

- The effect of combined adjuvant molecules can be different than their single parts
  - MPL : TLR4
  - QS21 : Caspase 1
  - MPL/QS21 : Syk activation
- Adjuvants can bring pan protection and increase the breadth of the response
  - Alum/MPL : HPV
  - O/W emulsion : influenza
- Adjuvant can protect better than the original pathogen in frail population
  - MPL/QS21 : protection over 90% against zoster over 80 years of age
  - Attenuated virus : protection bellow 30% over 80 years of age

What we have learned

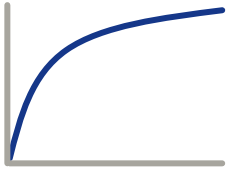
Understanding the present

Overcome poor **immunogenicity**

O/W , AS01, CpG

✓

Recombinant antigen



Increased **duration** of immune response

Alum, AS04

✓

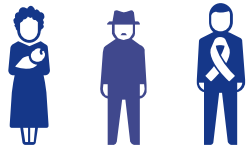
HPV

Dose reduction and **antigen sparing**

MF59/AS03

✓

Pandemic Flu



Improved immune responses in **special populations**

AS01

✓

Zoster

The power of formulation

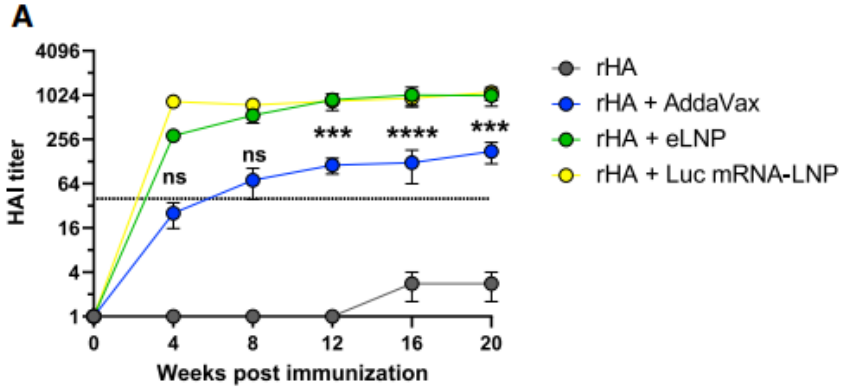
What about combinations?

Could adjuvant and mRNA be the best of both world ?

LNP can act as adjuvant with rec proteins (mice)

Demonstrated with rHA recombinant antigen

(when using high doses)



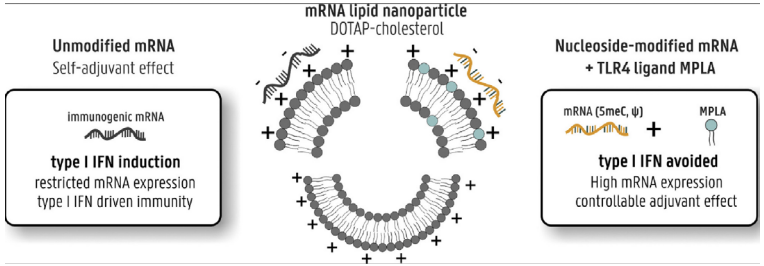
Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral response. Alameh et al., 2021, Immunity 54, 2877–2892 December 14, 2021

What does this means for mRNA?

Humoral response needs to be improved (level, breadth, duration)

Increase APC targeting and cytokine expression

Improving current LNP



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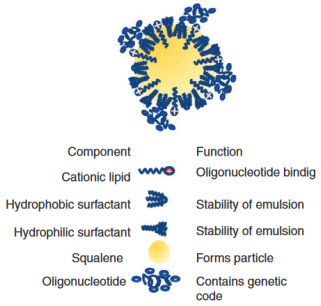
What does this means for mRNA?

Humoral response needs to be improved (level, breadth, duration)

Improving current LNP

Addition of exogenous adjuvant



Gemcovac (lyophilized samRNA, emulsion adjuvant)

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Beyond current approaches

What is next ?

What is next ?

- Current mRNA technology ***as clearly demonstrated its value*** for fast emerging response
- ***Strengths*** (CD8 in naïve individuals) and ***weaknesses*** (low quantity and persistence versus recombinant/adjuvant and reactogenicity) have been highlights thanks to never before reached amount of vaccinated people within a short time has given a view on its strengths and weaknesses
- ***It is possible today*** to combine existing adjuvant technologies to new mRNA platform and may reach the best of both world

THANK YOU