mRNA platform for the development of an HIV vaccine: Curb your enthusiasm

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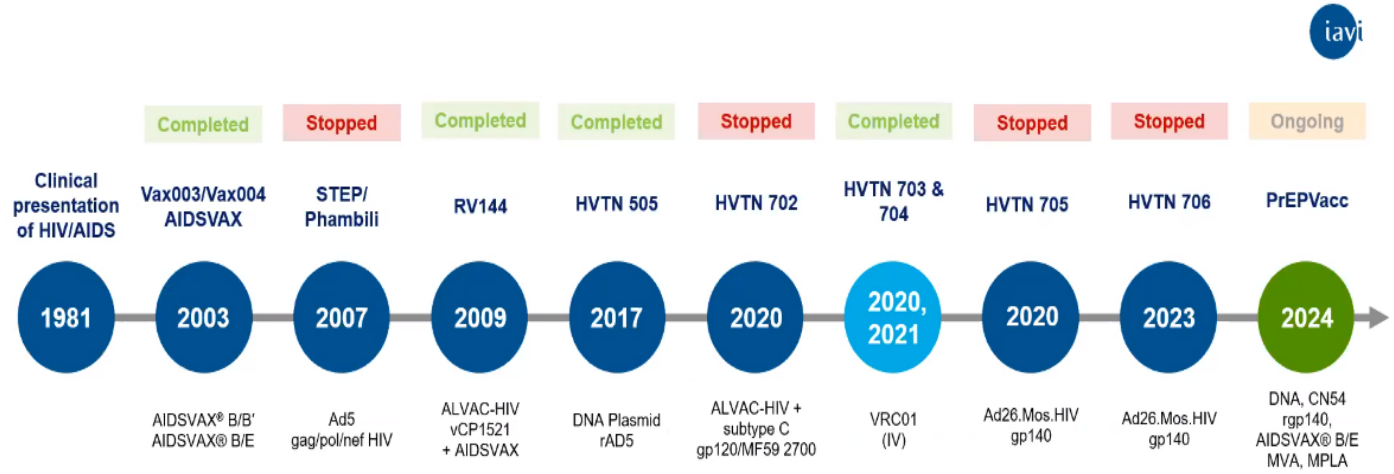
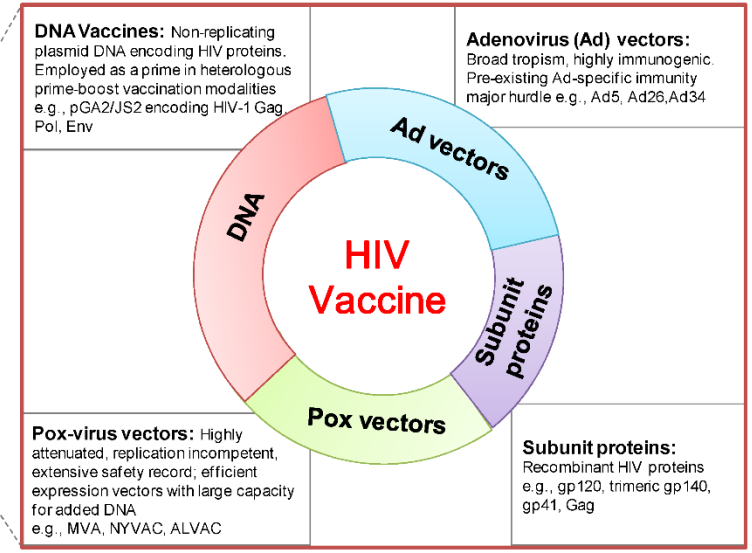
Background

Most candidate HIV-1 vaccines have been designed using a combination of protein subunit, viral vectors or DNA vaccine delivery platforms

History of HIV vaccine efficacy trials



Vaccine Modality	No. of Trials
DNA/Pox Virus	8
DNA/Ad Virus	5
DNA/Pox/Protein	3
Viral vector - Pox	3
Viral vector - Ad	11
Protein	8
Protein/Pox	3



Courtesy: Kundai, LDP workshop, 2023

Covid-19 mRNA vaccines

COVID-19 mRNA vaccine	Target	mRNA dose (μg)	Ref.
mRNA-1273	S-2P	100	[23]
CoV3	S	1	[23]
Ptx-Covid19-B	N.A	16–100	[23]
HDT-301	S	1–25	[23]
BNT1626b2	S-2P	30	
BNT162b1	RBD	1–100	[24]
BNT162a1	RBD	–	
BNT162c2	S-2P	–	
CVnCoV	S-2P	12	[25]
ARCoV	RBD	15	[26]
ARCT-021	S	5&7.5	[27]
LNP-nCoVsaRNA-02	S-2P	0.1–10	[23]
ChulaCov19	S	1–25	[27]
DS5670a	N.A	10–100	[23]
MRT5500	S-2P	15–135	[23]
EXG-5003	RBD	–	[23]

in vitro expression of mRNA molecules in mouse skeletal muscle cells for sensitization purpose was conducted in 1990

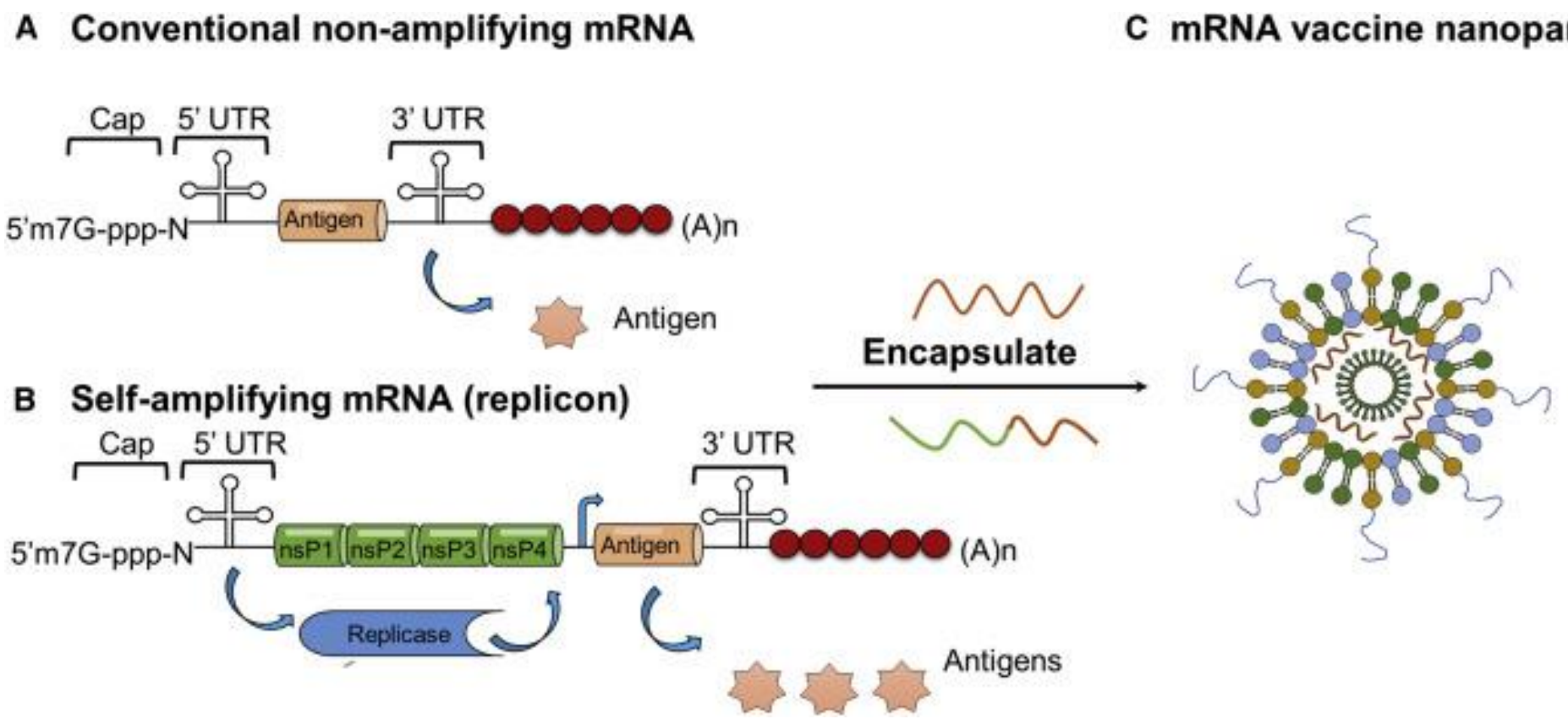
mRNA vaccines have been extensively studied in protection against viral infections caused by ***influenza virus H7N9,***
Zika virus,
Ebola virus,
dengue virus,
respiratory syncytial virus,
cytomegalovirus,
rabies virus,
flaviviruses

Current mRNA HIV-1 vaccines

- tHIVConsrvX
- mRNA-1644 (eOD-GT8 60mer mRNA)
- BG505 MD39.3 mRNA
- BG505 MD39.3 gp151 mRNA
- BG505 MD39.3 gp151 mRNA
- BG505 MD39.3 gp151 CD4KO mRNA

These are just a few examples but i think you can add more

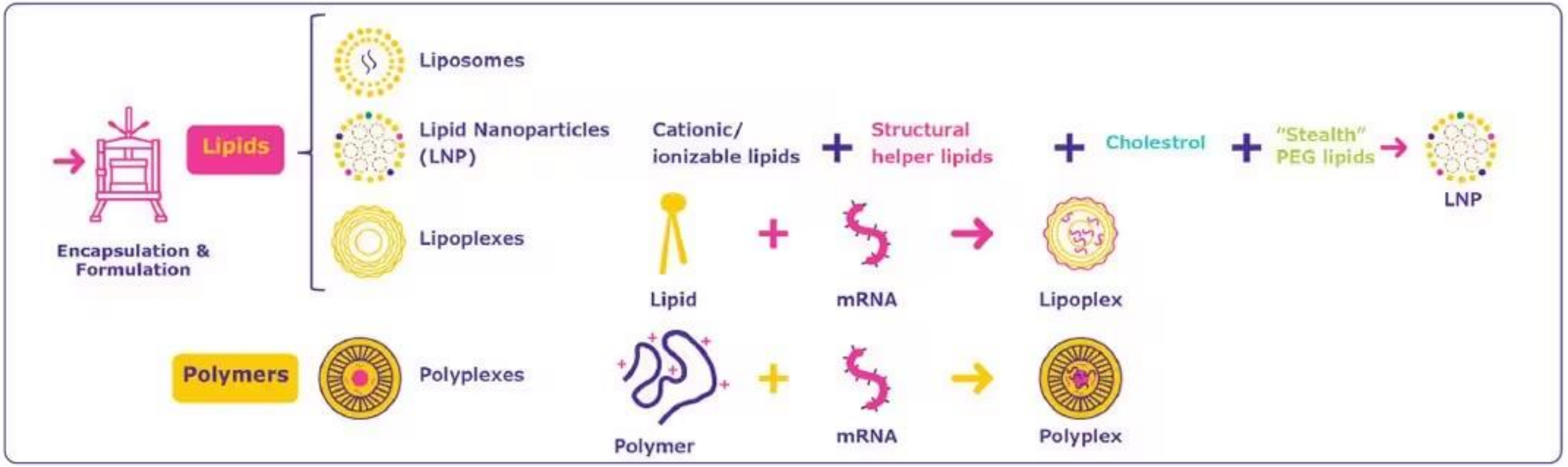
RECAP: mRNA vaccine structure



Adapted from: Kowalski et. al., 2019, Advances in Technologies for Therapeutic mRNA Delivery

Modified nucleosides such as pseudouridine (Ψ) and 5-methylcytosine are commonly used in non-amplifying mRNA to reduce innate immune response stimulation and proinflammatory responses

RECAP: mRNA formulation methods



https://www.sigmaaldrich.com/UG/en/technical-documents/technical-article/pharmaceutical-and-biopharmaceutical-manufacturing/vaccine-manufacturing/manufacturing-strategies-for-mrna-vaccines

Advantages

The greatest advantage is that the mRNA platform allows rapid iteration of candidate vaccines

HIV env trimer synthesis using protein subunit and viral vectors is relatively complex and time-consuming while pre-existing immunity against viral vectors and poor immunogenicity of DNA are key limitations of these platforms

mRNA enables the rapid synthesis of safe vaccines using a cell/virus culture-free process

mRNA vaccines can induce both B and T-cells;
nucleoside-modified LNP mRNA can activate Tfh cells

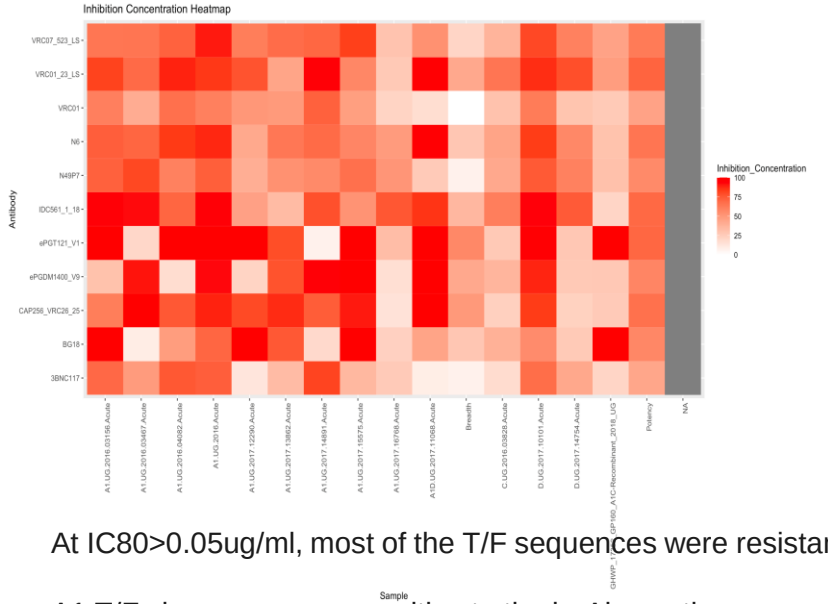
The ease and speed of production as well as the robust immunogenicity provided by mRNA make it an ideal platform for the in vitro and in vivo evaluation of HIV env trimers

Disadvantages

You could also talk about the cold chain requirement for mRNA vaccines which could limit their accessibility in resource-limited settings

- allergy, renal failure, heart failure, and infarction remain a risk, the vaccine mRNA may also be degraded quickly after administration or cause cytokine storms.

- HIV-1 Diversity



- At IC80>0.05ug/ml, most of the T/F sequences were resistant.
- A1 T/Fs became more sensitive to the bnAbs as the concentration increased (1 to 50ug/ml)
- A1 T/F sequences from the GHWP are more sensitive to N6, VRC07_523_LS, N49P7, VRC01, 3BNC117, and ePGDM1400_V9 than CAP256_VRC26_25, ePGT121_V1, BG18 (IC80>50ug/ml).

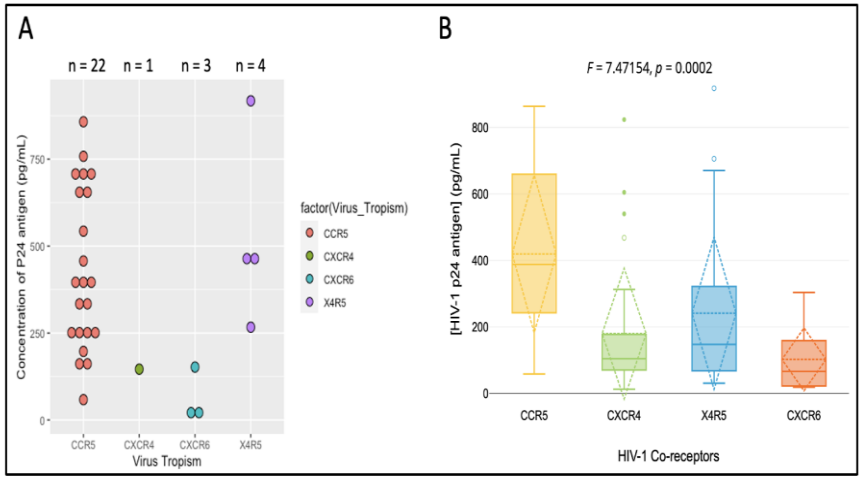
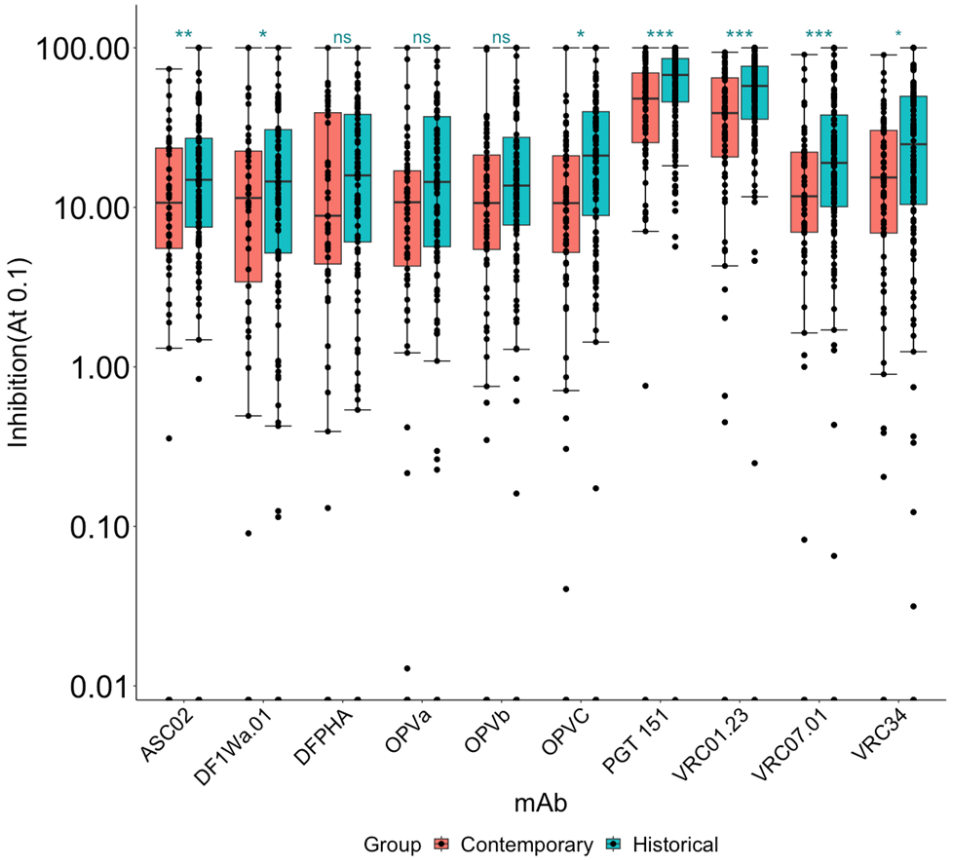


Figure 2: HIV-1 T/F coreceptor usage. TF virus tropism (A) and Differences in the HIV-1 TF virus infectivity for different coreceptors (B)

- ❖ Most TF virus variants were more CCR5 tropic followed by dual tropism (X4R5), CXCR6 and CXCR4 (Figure 2A) respectively
- ❖ All the TF virus variants identified as R5 tropic, X4 tropic and dual tropic were resistant to both Maraviroc and AMD3100

Historical and Contemporary Inhibition at 0.1 concentration



Overall, Inhibition is higher in historical (7 of 10 mAbs) than in contemporary strains

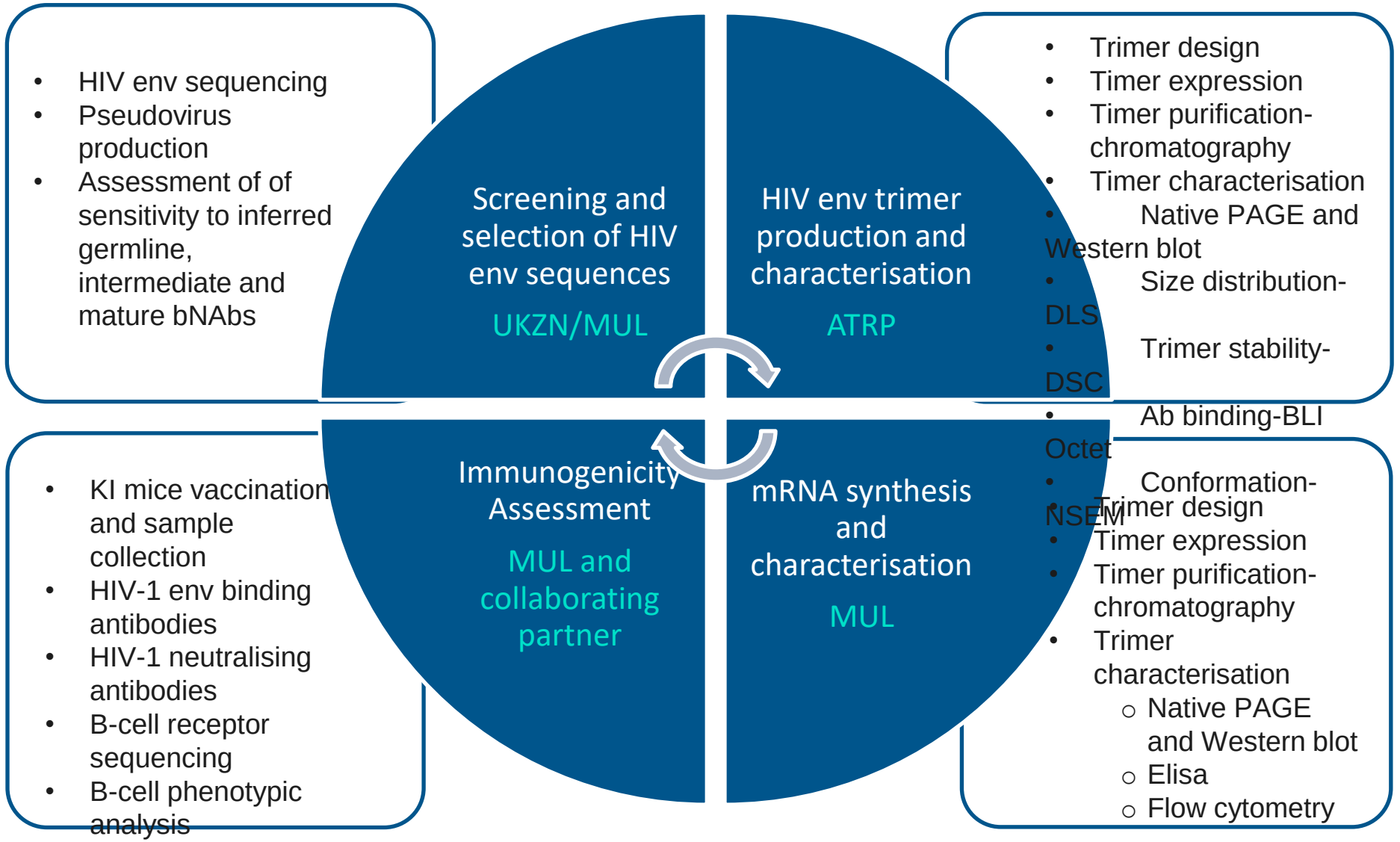
PGT 151, VRC01.23 and other VRC mAbs are the most potent

*<0.05; ** , 0.001; *** < 0.0001; ns >0.05

- 10 mAbs; 226 Viruses (80 Contemporary and 146 Historical, 8 HIV Clades) screened
- Overall, PGT151 and VRC01.23 are the most potent inhibitors across historical and contemporary
- Clade differences are evident across A1 and C
- Statistically meaningful Clade-based Comparisons only possible for clades A1 and C
- Critical relevance gaps (clades D, A/D and A) which circulate in this region are underrepresented and not statistically analysable

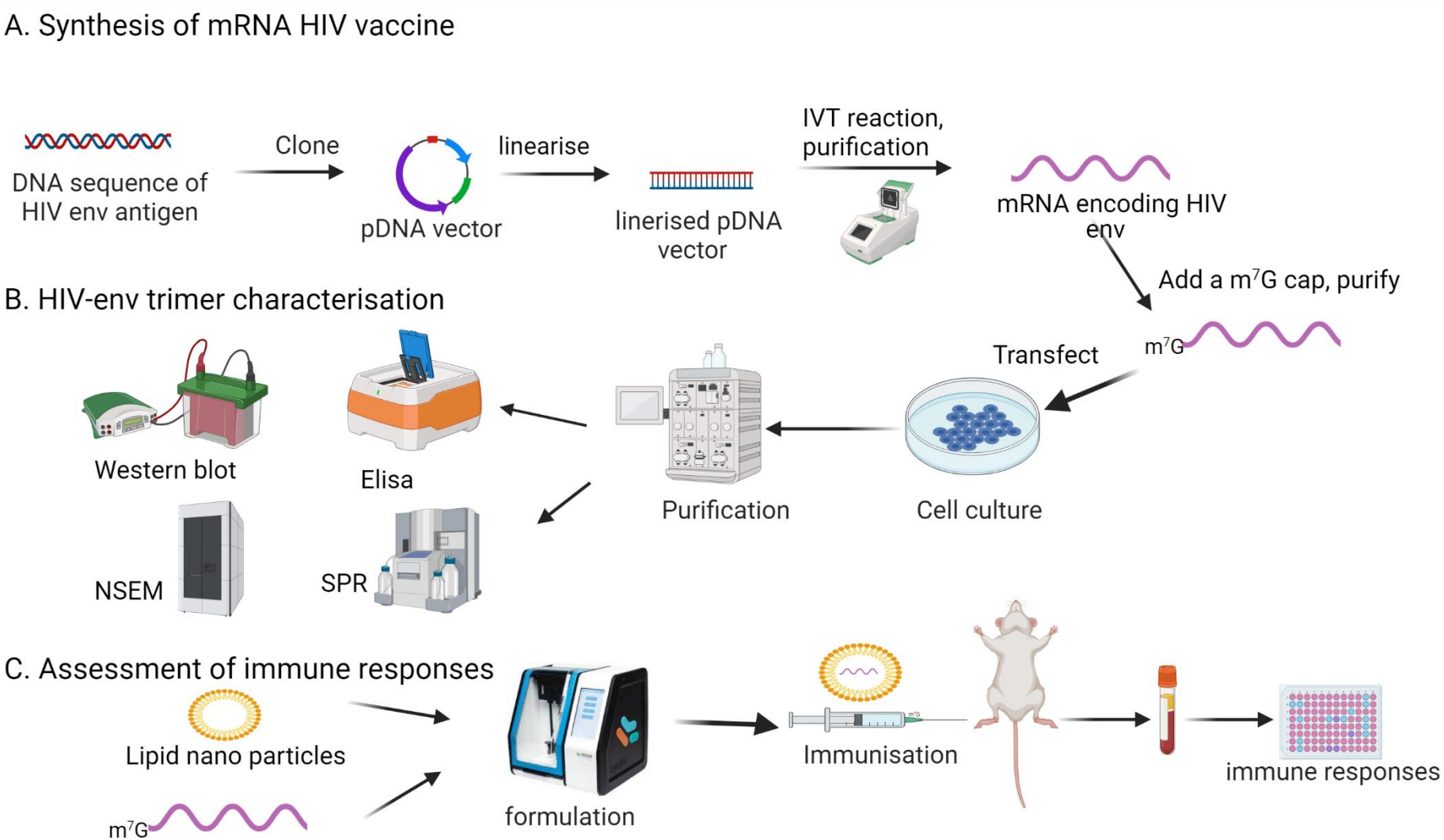
Establishment of an mRNA vaccine platform at MUL to support the preclinical evaluation of HIV-1 immunogens

HIV env trimer development under ADVANCE

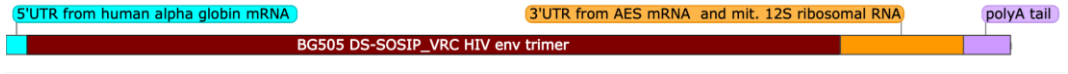


mRNA synthesis laboratories set up

mRNA vaccine development pathway



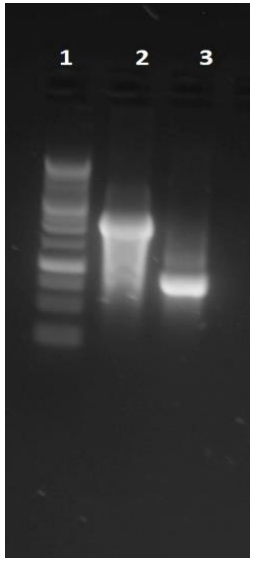
BG505 DS-SOSIP mRNA & saRNA characterisation



BG505 DS-SOSIP mRNA (2.4Kb)

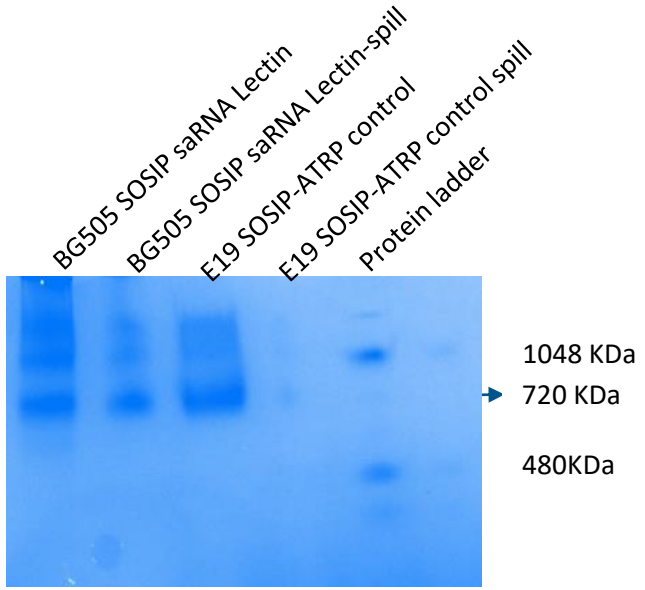
BG505 DS-SOSIP saRNA (9.7Kb)

HIV env trimer sequence design

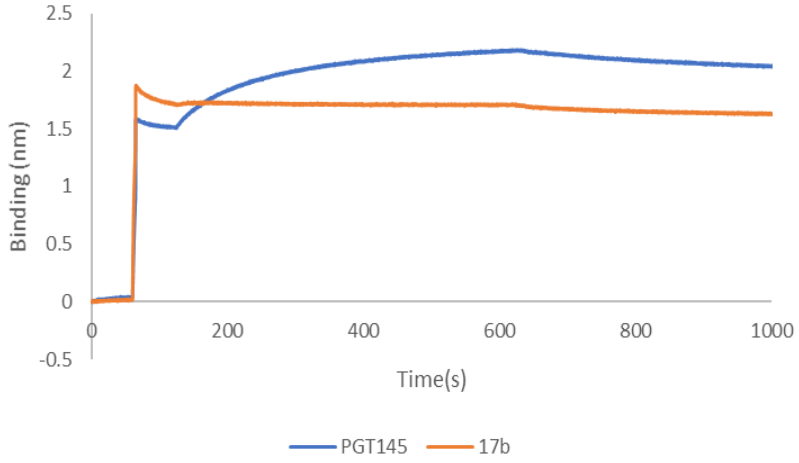


1. 1 kb DNA loading ladder
2. BG505 DS-SOSIP_VRC VEEV
3. BG505 DS-SOSIP_VRC pCDNA3.1+

BG505 DS-SOSIP saRNA & mRNA denatured agarose gel



Native PAGE BG505DS-SOSIP



BLI octet showing binding of BG505 DS-SOSIP saRNA HIV env to PGT145 bNAb

Summary progress

Sub-Activity	Description	Status
1	Training of a laboratory technologist in saRNA/mRNA production, development of SOPs and set up of equipment	Completed
2	Cloning BG505 DS SOSIP into mRNA and saRNA pDNA vector	Completed
3	Synthesis of mRNA & saRNA encoding BG505 DS-SOSIP	Completed
4	Assessing in vitro antigen expression of saRNA and mRNA encoding BG505 DS-SOSIP HIV env immunogen	Ongoing
5	Synthesize mRNA encoding HIV env trimers selected from the HIV trimer workstream and characterize expressed proteins	Pending

Challenges, mitigation & next steps

- Limited capacity of characterisation of HIV-env trimers
  - HIV env trimer purification
  - Antibody binding assays such as SPR
  - Negative stain electron microscopy
- Lack of LNP formulation equipment
- Challenges with obtaining suitable animal models
- Humanised mice required to test germline targeting vaccine approach
- High background in local BALB/c mice

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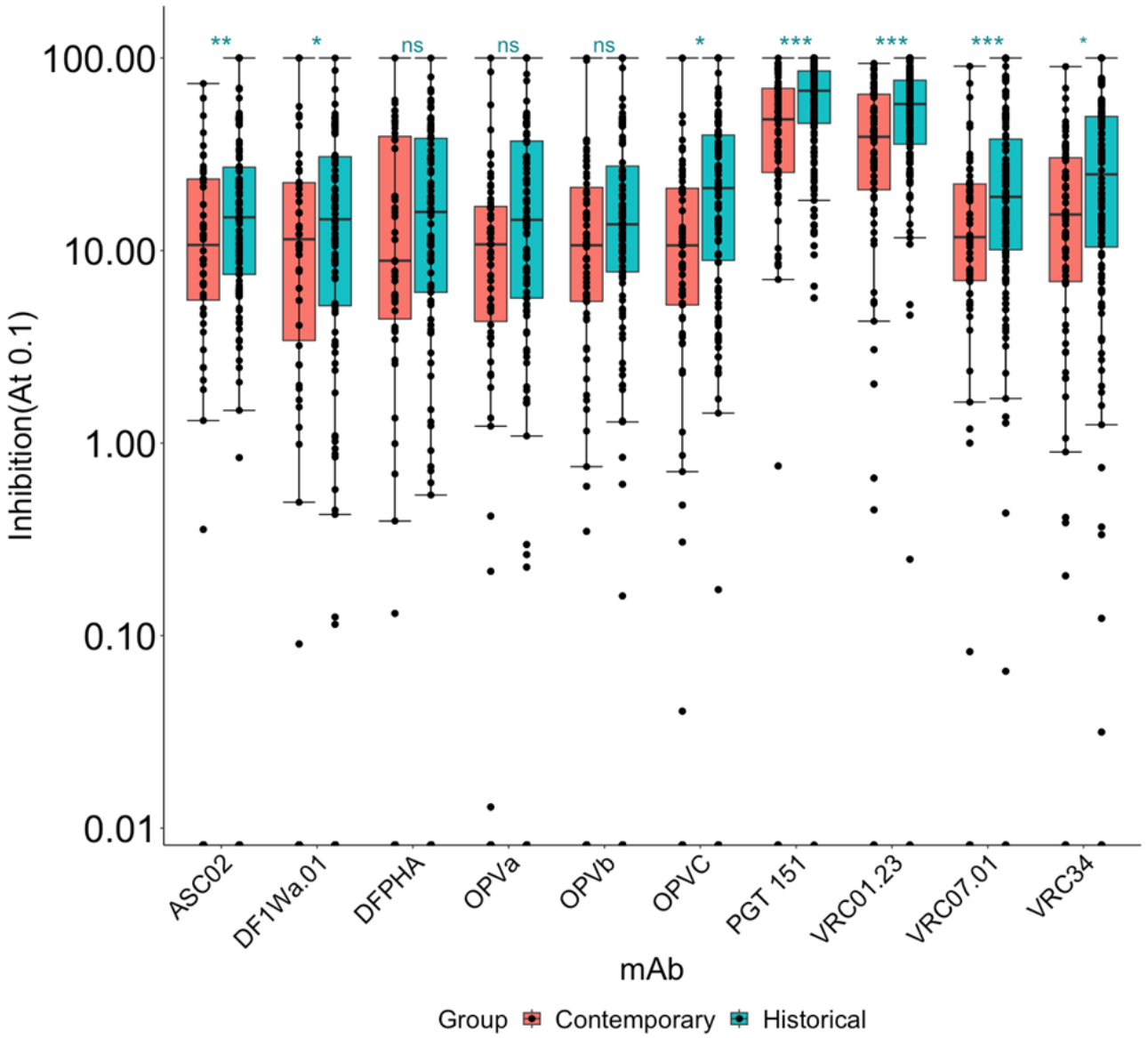
As of July 2023

Historical and Contemporary Inhibition at 0.1 concentration



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MUL Summary: Virus Surveillance progress

- 10 mAbs; 226 Viruses (80 Contemporary and 146 Historical, 8 HIV Clades) screened
- 2 Historical Envs to be repeated
- Neutralising TCID50 and TCID80 for PGT151 and VRC01.23 against the Historical and contemporary panel is next
- Overall, PGT151 and VRC01.23 are the most potent inhibitors across historical and contemporary
- Clade differences are evident across A1 and C
- Statistically meaningful Clade-based Comparisons only possible for clades A1 and C
- Critical relevance gaps (clades D, A/D and A) which circulate in this region are underrepresented and not statistically analysable; thus, the sensitivity of the local region virus epidemic is not addressed