Prospects in Vaccine Development for Prevention of Infectious Diseases and Treatment of Cancers

NAPPSA

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NAPPSA

Introduction

- Effective new vaccines have hit the market, e.g pneumonia, shingles, RSV , Covid-19 etc. This is just the beginning.
- About 258 vaccines were in development as of 2020 (PhRMA), and It found that $406 billion in direct medical costs were saved due to routine childhood vaccination of U.S. children born from 1994 to 2018.
- Pharmaceutical companies are currently developing everything from personalized cancer vaccines that could cost tens of thousands per patient to vaccines that prevent developing-world diseases like malaria or tuberculosis. Improved flu, pneumonia, and meningitis vaccines will also be available in your neighborhood pharmacy (www.msm.com/en-us/health/medical/a-golden-age-of-vaccines-is-here-what-it-means-for-you).
- Consider cancer, a hot spot in vaccine research, according to PhRMA. Preventive vaccines against hepatitis B and the HPV viruses, first approved in 1981 and 2006, respectively, have reduced rates of liver and cervical cancer.
- Whereas vaccines have traditionally been used to prevent infectious diseases, scientists have begun researching therapeutic vaccines to treat people who are already sick, including cancer patients.
- In 2023, Moderna and Merck conducted a trial in which personalized vaccines that used genetic sequencing to target specific mutations in each patient's cancer helped slash the recurrence rate for metastatic melanoma. The two pharmaceutical companies plan to try the same approach on lung cancer and other carcinomas.

Introduction (Cont'd)

- Even though antigen types vary among different vaccines, the vaccine manufacturing process, in general, is similar for all types, i.e. upstream generation of antigen, downstream separation of antigen and formulation combining all components.
- This presentation will focus on the challenges and prospects of vaccine development and manufacturing using different vaccine platform technologies. It will highlight the various strategies in vaccine development, possible vaccine candidates, and vaccine production process based on the knowledge acquired in vaccine development in the past.
- I will also make a case for the need for Nigeria to focus on domestication of local vaccine manufacturing and briefly share our efforts in building an end-to-end vaccine manufacturing facility in Nigeria.

What is a Vaccine?

- A vaccine is a biological preparation that when inoculated or administered induces antibodies and cellular immune response to a pathogen

That protects against the pathogen or suppress chronic infection.

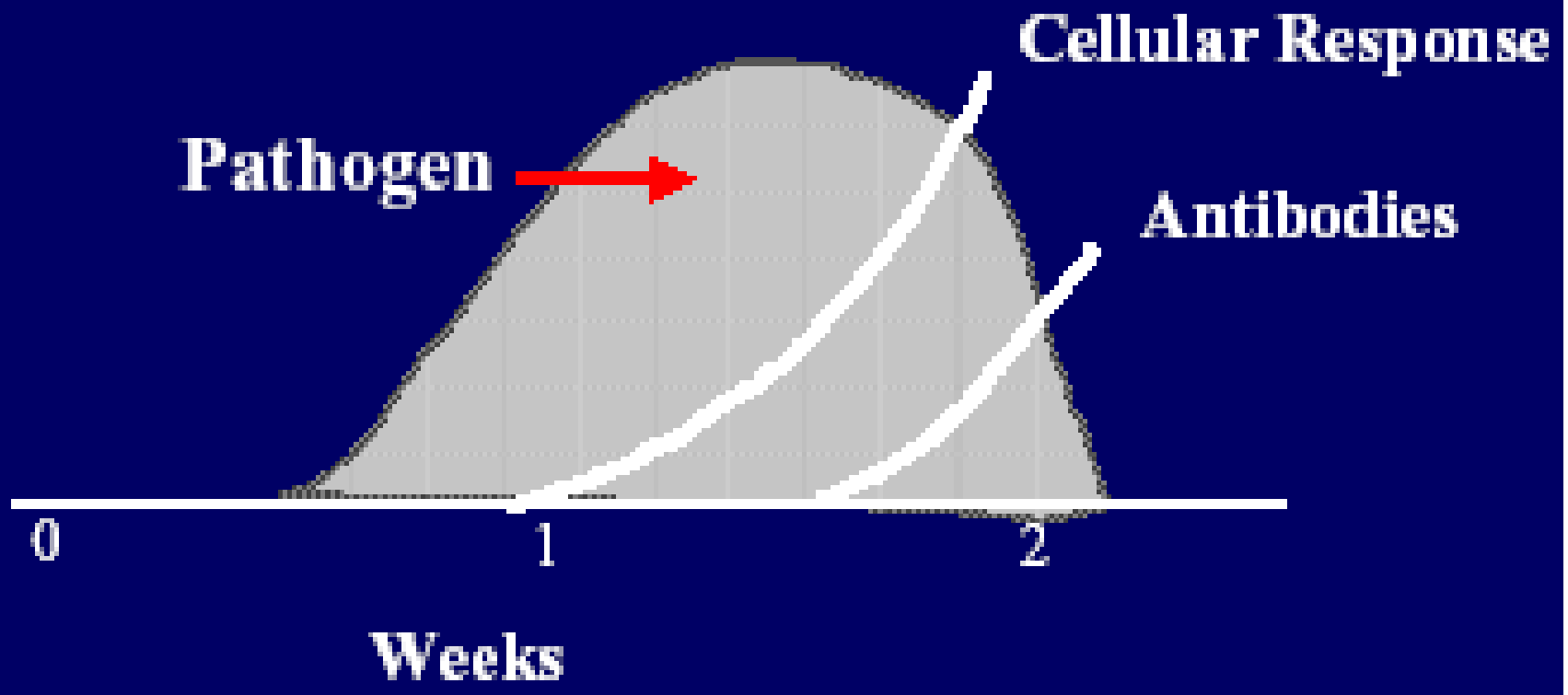
VACCINES

Vaccines are presently the most powerful and cost effective health interventions

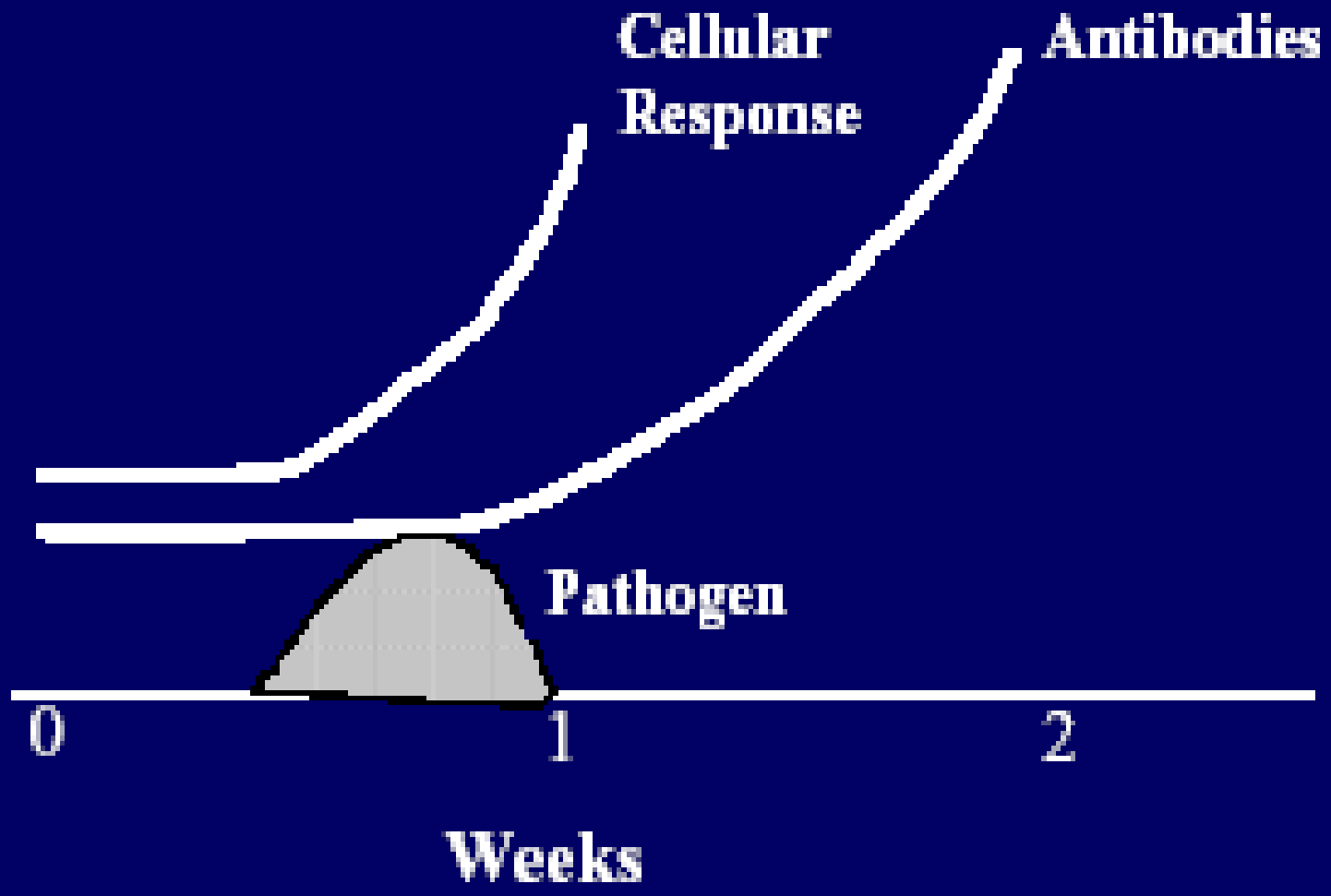
Successful in the global eradication of some transmissible diseases

- **Small pox**
- **Polio**
- **Measles**

Unimmunized Person



Immunized Person



The Road to Vaccine Development

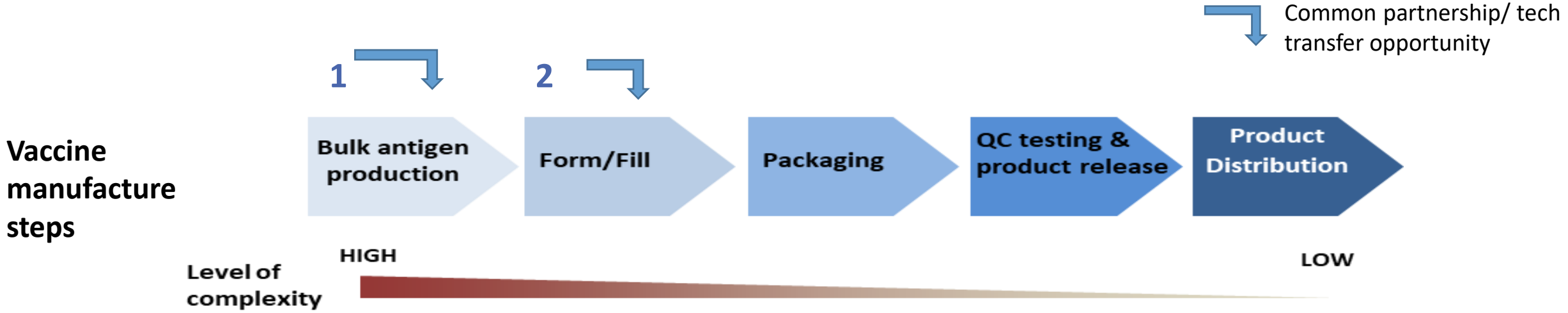
Academic

- Identify the natural mechanism of protection (correlates of protection).
- Isolate the antigen(s) responsible for the protection.
- Show in animal models that the vaccine is protective.
- Find the best method to present the antigen (e.g. vectors, DNA, RNA, inactivated, protein subunit etc) .

Industry

- Increase yield and purity (process optimization and scale-up).
- Show the safety of the antigen in animal models (preclinical).
- Produce a lot under GMP for clinical trials.

Full manufacture versus form/fill?



1. **Full manufacture**: more difficult from technical perspective but more value captured
2. **Form/fill only**: technically less challenging but captures less value; relies on partner to provide bulk material

- Tech transfer partnership may involve recipient initially performing only form/ fill before developing bulk manufacture capability later during collaboration

Accelerating the pathway to clinic and commercialization

MilliporeSigma process Development

Pre-clinical | **Ph I** | **Ph II** | **Ph III** | **Commercial**

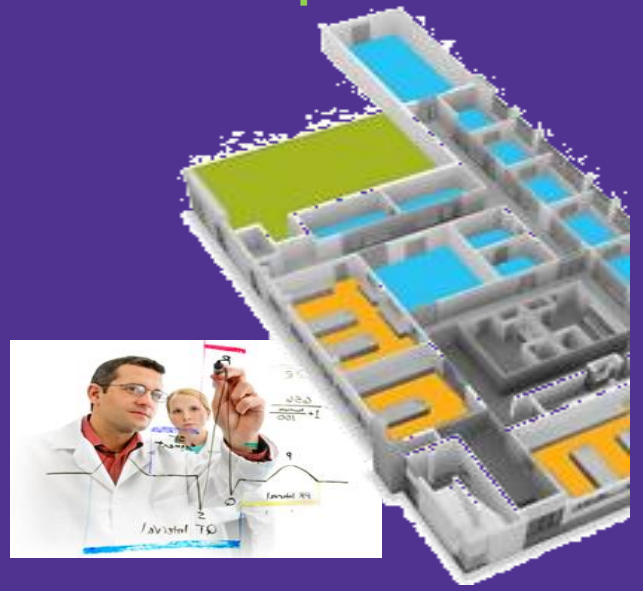
USP/DSP Process development TOOLBOX

Integrated Single-Use process at < 2kL

Media

Buffers & CIP

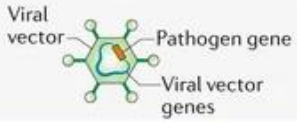
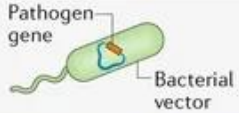
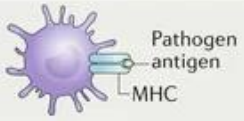
Facility Design, Build & start up



Support your process development for Ph1 trials (GMP)

Proven, ready to use, single-use USP/DSP template at ≤ 2kL

Design & validate an entire single-use process or integrate individual unit operations

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Nature Reviews Immunolo L474-1733 (print)

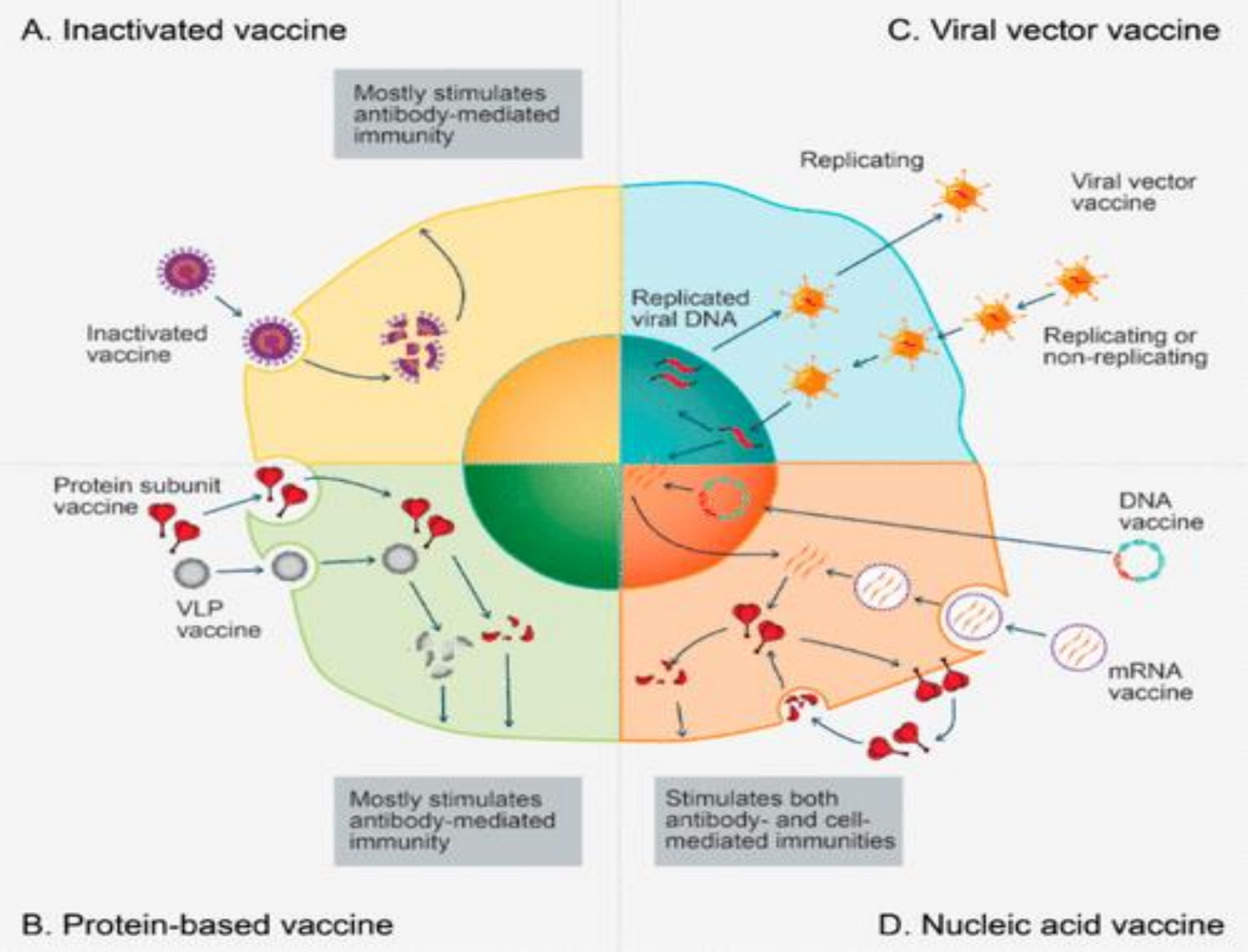


Fig.:Vaccine platforms and their ways of producing immunogen in cells.
Li et al. 2021 (Preprint). ACS Cent. Sci.

Local Efforts

(Vaccine Development and Manufacturing)

Innovative Biotech

How Innovative Biotech Collaborated to Navigate their Path to Commercialization

EIB

Innovative Biotech

Bringing International Vaccine Development and Manufacturing Expertise to Nigeria

About Innovative Biotech LTD (INNOVATIVE)

- Incorporated in 2006
- Was founded to apply the advances made in biotech industry toward pioneering biotech and vaccine development in Nigeria
- Privately held Nigerian/USA company and operates with its own seed fund raised by local investors. It is the first private biotech company in Nigeria.

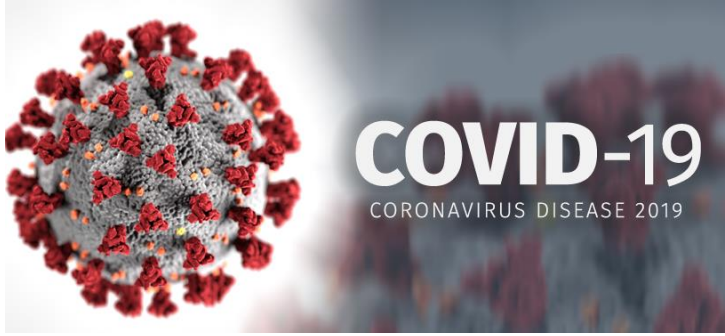
Mission:

- To provide and enhance better health and life expectancy by eradication of diseases in Africa through innovative production of biotech products and services

- Clear objectives in order to fulfil its participation and success in a growing market share of this exciting industry:

1. **Market Leader:** Provide High Quality and Affordable vaccines, across all critical disease segments
2. **Leadership Development:** Develop one of the first modern African owned vaccine of international standards with world-class business leadership
3. **Sustainable Growth:** Deliver and maintain growth at a minimum of 10% CAGR over the next 10 years

The Journey
Vaccine Development



- Previous work on Baculovirus expression system (HIV and Ebola)
- COVID-19 was the Catalyst to accelerate the Mission
- Engaged with Merck KGaA, Germany/ MilliporeSigma Emerging Biotech, USA and other Biotech Tech companies.

Target Vaccine Portfolio (1/3) – Overview

There are two key sources of vaccines for Innovative Biotech:

In-licensed vaccines

Addressing calls for endemic vaccines with strong market demand

Available vaccines:

IPV, HPV-2, Hexavalent, TCV, PCV-14, Rotavirus, OCV

Owned vaccines

Developing IP for Virus Like Particle (VLP) Vaccines for critical diseases

Vaccines in development:

Lassa, Ebola, YF, VLP Covid, VLP HPV, VLP HIV

Bringing International Vaccine Development Expertise to Nigeria through Partnerships and Tech Transfer

Novel HIV VLP Based Vaccine

Induced broadly Neutralizing antibodies in Mice model

Novel Ebola VLP Based Vaccine

Highly immunogenic in mice model. Plans are underway to developed a bivalent VLP Ebola

Novel Cell-based Yellow Fever Vaccine

Licensed a novel cell based YF vaccine - combines characteristics of DNA and live-attenuated vaccines. The iDNA YF vaccine induced high neutralizing antibodies in mice. Can be formulated for storage at RT.

Novel Reassortant Lassa Vaccine

Licensed a Lassa Candidate Vaccine based on reassortant technology. GMP material is now available for tox study and clinical trials.

Novel HPV Vaccine

Developing a trivalent 16,18 and 35 HPV vaccine based on African HPV serotypes. Could protect over 90% of HPV serotypes circulating in Africa based on cross-protections

Partners:

Merck KGaA, MilliporeSigma, Technovax LLC, Medigen LLC., Lion's Head UK, Afreximbank Cairo, ITC Geneva, Bbio The Netherlands, Bharat Biotech India, Walvax etc

Development of HIV VLP candidate Vaccine

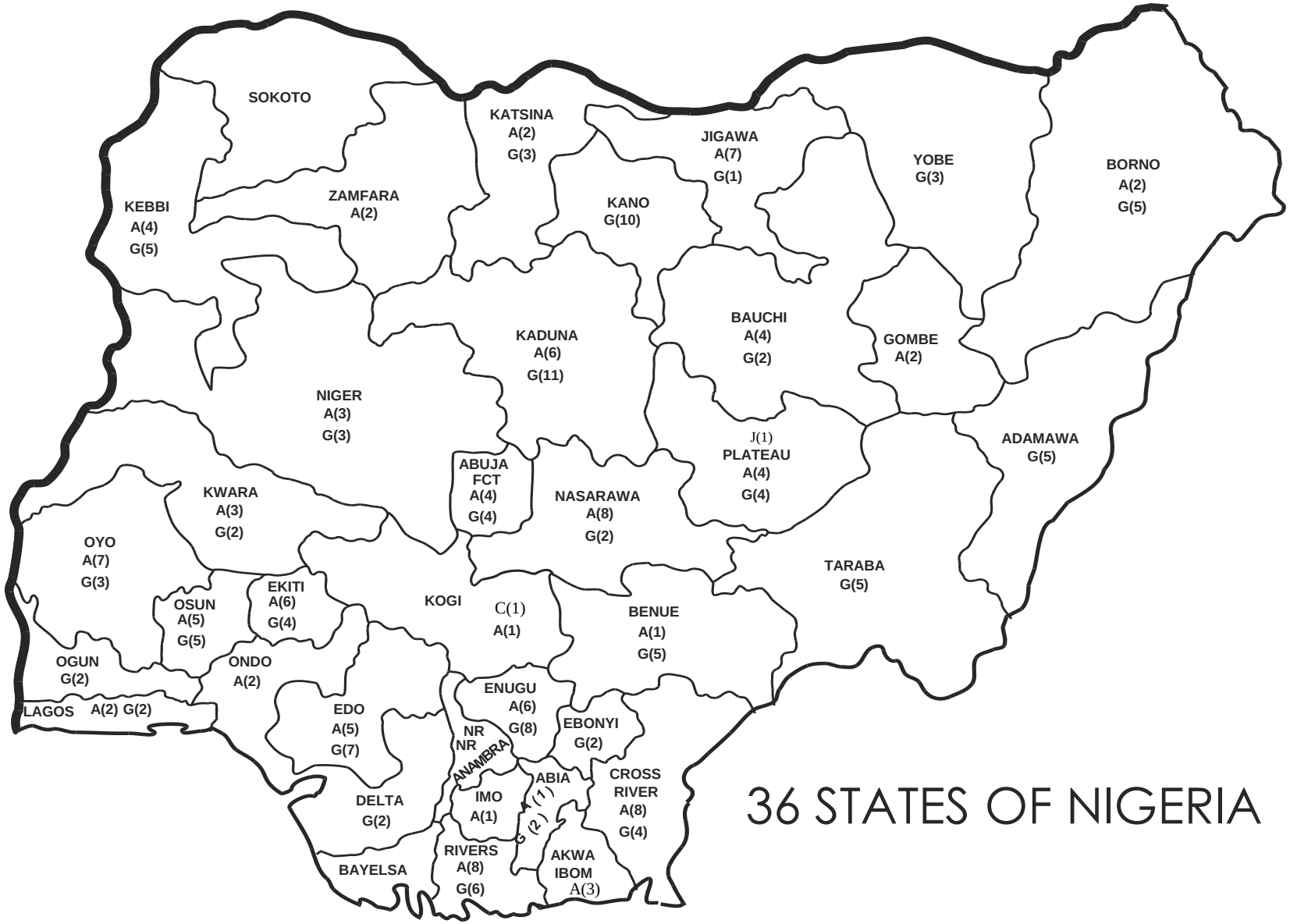


Fig. Map of Nigeria Showing the Distribution of HIV-1 Subtypes

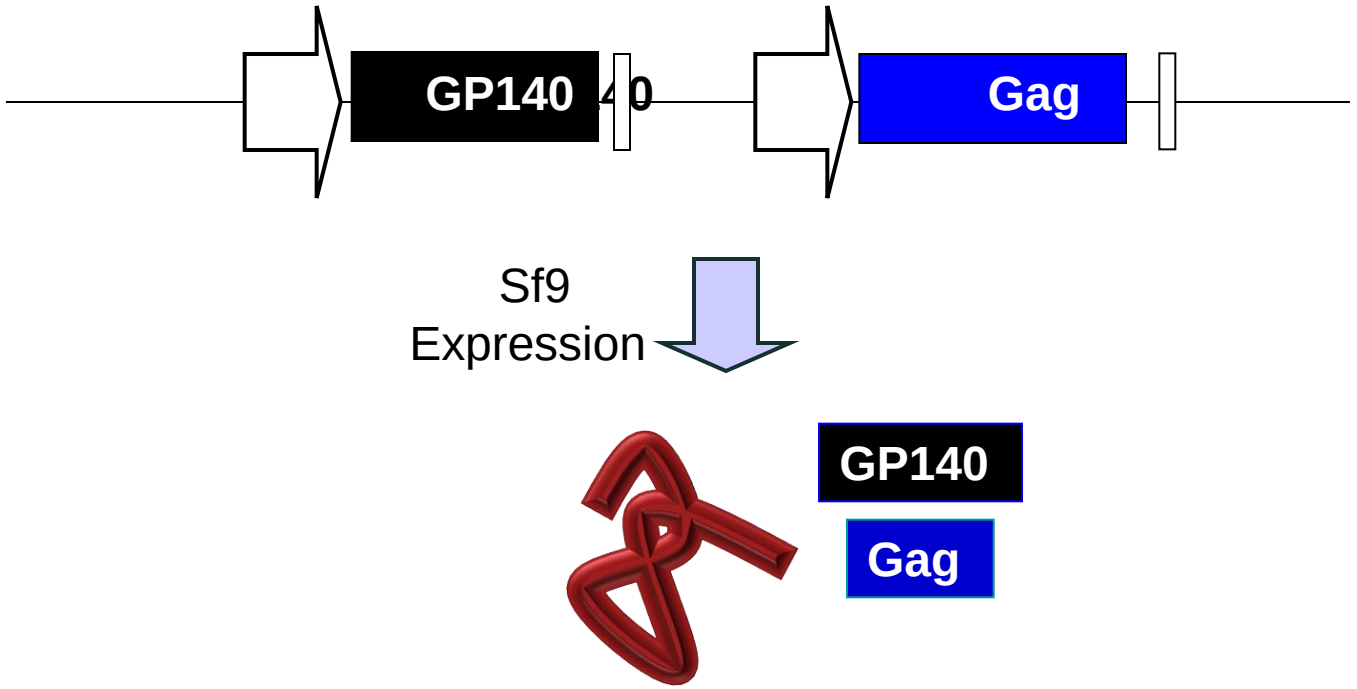
Agwale *et al*. (2002).Vaccine; 20: 2131-2139

Antibody neutralization titer against heterologous viruses

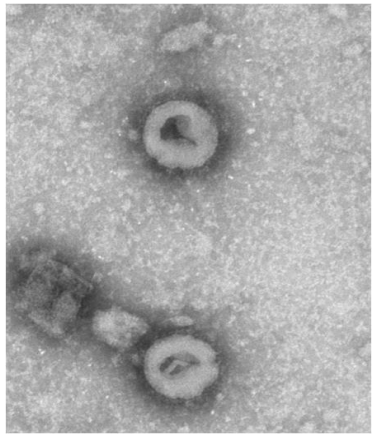
Agwale et al. 2011. Plos One: 6:

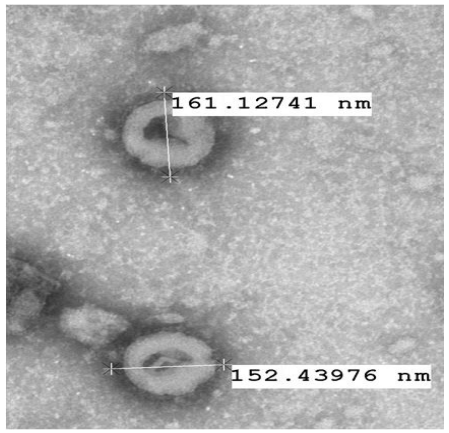
	Plasmas/Sera (IC50 1/diln)																						
	FU	MD	NB	NIPRD/CBN /015802	NIPRD/CBN /017302	NIPRD/GSH /0169/02	NIPRD/GSH /0408/02	NIPRD/SHC /030402	NIPRD/SSC /0175/02	NIPRD/VRC/ 001	NIPRD/VRC/ 033	NIPRD/VRC/ 034	NIPRD/VRC/ 039	NIPRD/VRC/ 043	NIPRD/VRC/ 044	NIPRD/VRC/ 045	NIPRD/VRC/ 055	NIPRD/VRC/ 059	NIPRD/VRC/ 061	NIPRD/VRC/ 064	NIPRD/VRC/ 067	NIPRD/VRC/ J/O	NIPRD/VRC/ Jacob/Onah	
MD	33	146	70			166	193	52	89	339	139	224	67	100	59	61	107	34	61	247	347		205/190*	*IC50s from replicate runs
NIPRD/GSH/0169/02	43	305	44			96	189	122	28	324	97	219	47	152	42	42	55	37	51	176	336		213/136	
NIPRD/SSC/0175/02	37	305	58			159	323	56	79	398	172	295	47	86	39	57	107	46	90	351	591		234/237	
NIPRD/VRC/033	45	183	117	360	23	90	194	59	206	288	97	349	57	88	46	70	57	44	33	237	350	172	210/135	
NIPRD/VRC/033	<20	151	192			55	177	24	177	331	24	143	23	41	22	35	22	<20	22	232	462	155		
NIPRD/VRC/039	31	316	115			120	290	79	49	406	424	290	50	513	45	100	65	48	56	250	438		263/258	
NIPRD/VRC/045	52	122	97			143	211	101	321	335	356	227	61	221	79	84	86	64	61	214	368		290/182	
NIPRD/VRC/055	46	343	152			126	234	79	479	337	269	345	70	153	44	95	168	33	55	188	495		311/256	
NIPRD/VRC/059	20	198	189	241	85	78	329	190	255	617	226	257	21	253	34	33	91	37	44	471	398	232/257		
NIPRD/VRC/061	45	516	63			195	242	181	181	445	529	220	79	210	64	63	141	55	133	292	411		202/169	
NIPRD/VRC/J/O-1	39	63	68	168	60	58	324	27	176	414	44	205	21	28	30	23	41	<20	26	224	496	164/184		
NIPRD/VRC/J/O-2	23	106	46	283	80	72	241	46	220	368	40	140	21	56	27	24	25	<20	27	203	443	196/239		
NIPRD/VRC/Jacob/Onah	49	111	99			178	177	112	201	371	182	271	81	88	39	36	74	37	47	212	394		270/186	
NL43 - CONTROL - Replicate #1	64	2165	1399	2564	1457	1375	2808	1048	1219	1372	708	1295	178	384	247	654	1116	516	218	594	1141	521	518	
NL43 - CONTROL - Replicate #2	74	2730	1078			1480	3800	1320	1302	1552	715	1448	210	328	272	713	982	476	214	709	1476	591	449	
JRCSF - CONTROL - Replicate #1	42	377	<20	243	<20	115	167	192	257	319	187	246	75	258	65	71	96	63	80	189	312	155	219	
JRCSF - CONTROL - Replicate #2	<20	200	49			27	174	74	163	249	33	131	<20	95	<20	21	<20	<20	<20	149	315	171	151	
aMLV - control - Replicate #1	61	90	<20	243	<20	79	135	60	23	399	192	323	100	150	112	96	138	102	73	248	378	145	284	
aMLV - control - Replicate #2	53	61	31			<20	171	42	22	228	20	164	<20	43	35	42	30	22	25	186	295	214	203	

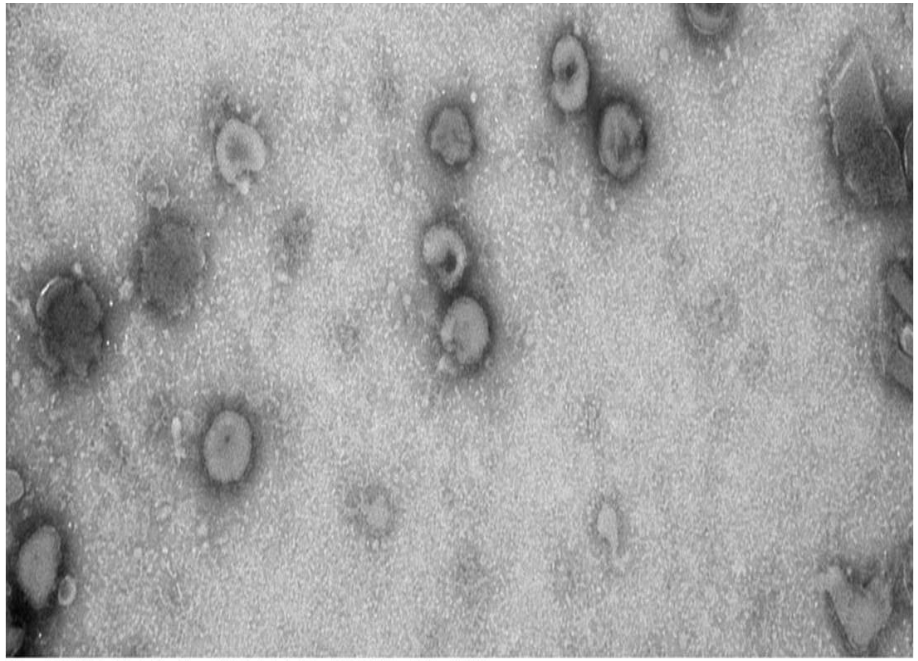
Baculovirus Expression of HIV VLP



Electron micrographs of HIV VLP





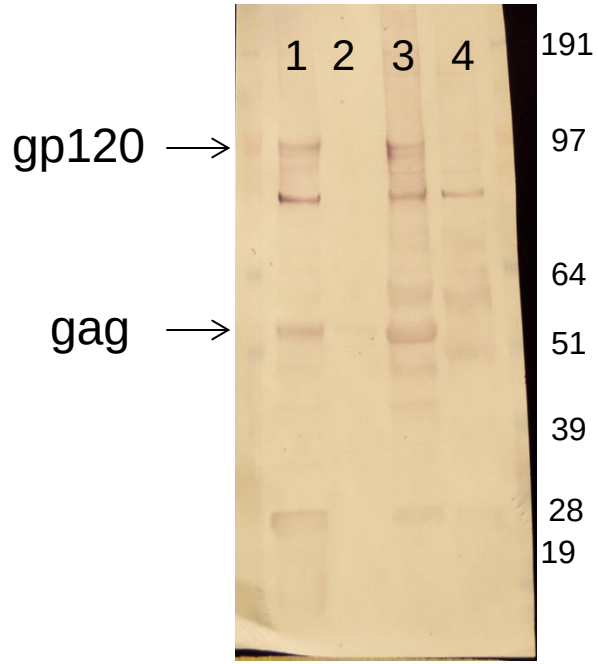


HIV sera test

Medigen, Inc.

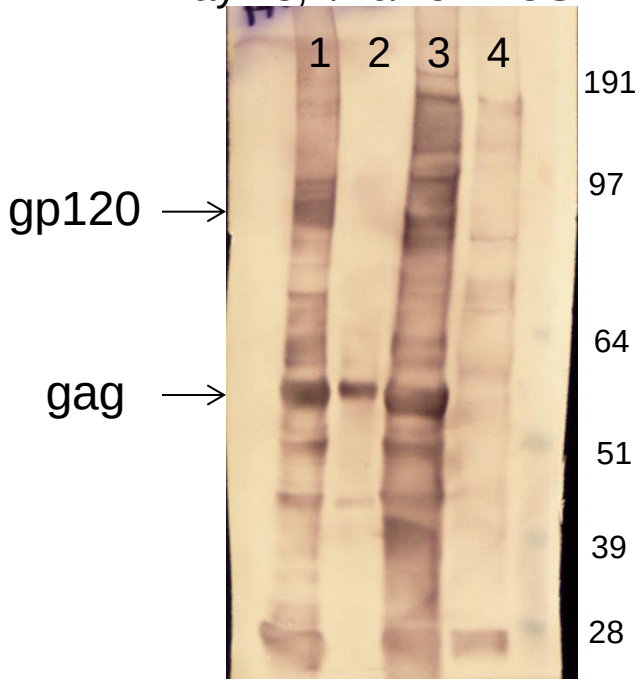
Antigens:
1) HIV-VLP cell lysate 11/3/14, 10µl 2x
2) Flu/gag VLP control 1:100, 10µl 2x
3) HIV-VLP 7/7/14, 10µl 2x
4) Flu VLP control 1:5, 5µl 2x

HIV-VLP Vaccine Study
Mice Serum (GR.A;pull)
Day 28;2/26/15.IB USA



Mouse sera α HIV1 1:100

HIV-VLP Vaccine Study
Mice Serum (GR.C;pull)
Day 28;2/26/15.IB USA



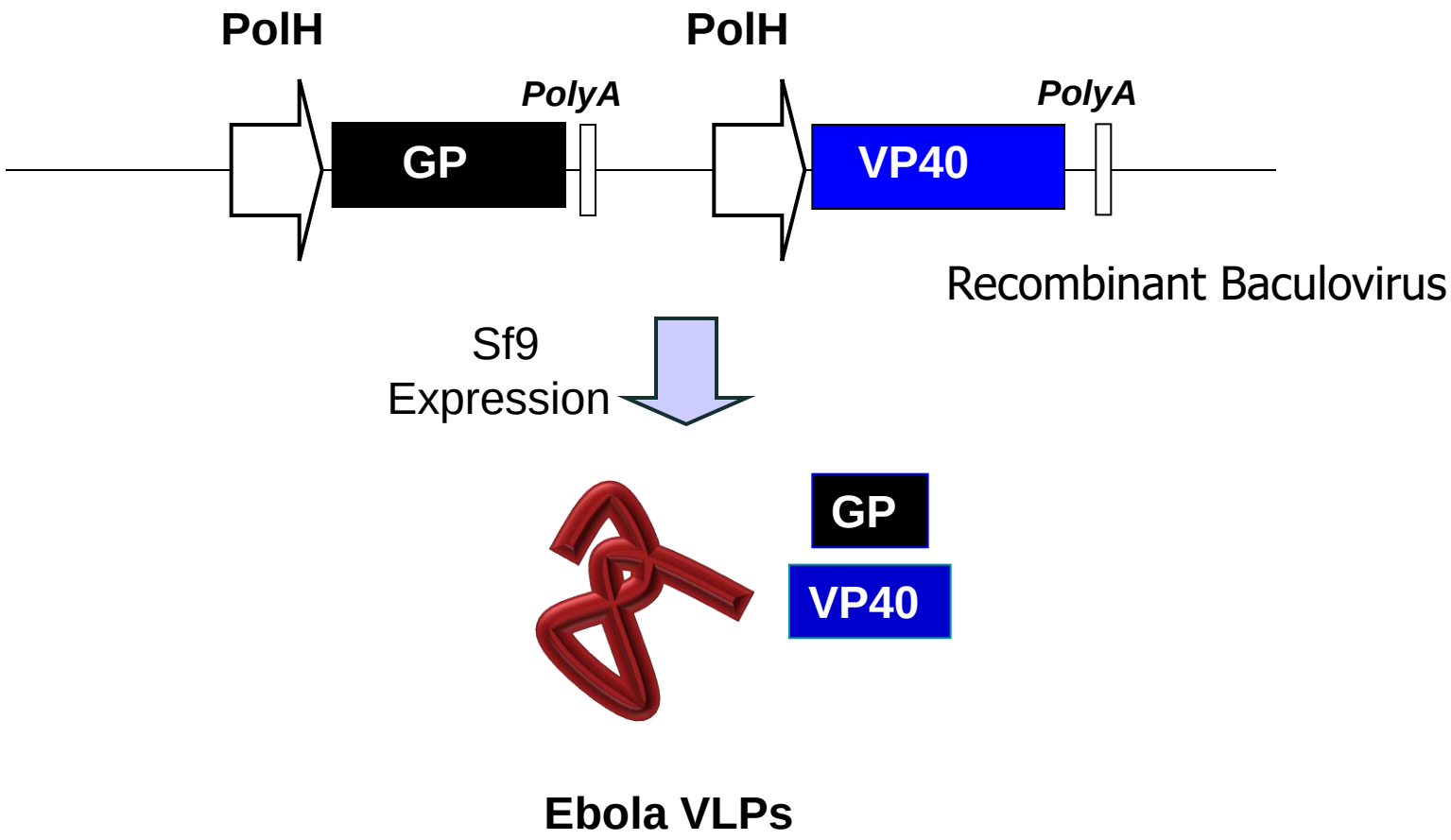
Mouse sera α HIV2 1:100

HIV CRF02_AG VLP Candidate vaccine induced broadly neutralizing antibodies in mice model

	IC50 (1/diln)					
	IBHIV001	IBHIV002	IBHIV003	IBHIV004	IBHIV005	Z23
SF162	<100	<100	<100	<100	<100	20773
MN	2506	1454	1811	4129	2846	8840
BAL	<100	<100	<100	<100	<100	919
MGRM-AG-002	5580	3048	3944	7915	5412	387
MGRM-AG-006	7930	3010	3697	9477	6280	227
94UG103	7366	3042	3112	6437	5972	149
MGRM-C-026	3578	2092	1641	3499	3128	299
92TH021	4939	2205	1945	7008	4820	233
93IN905	2613	2232	1654	3831	3171	523
6535.3	596	247	321	1126	549	312
VSVg	1208	494	775	2063	920	<100
aMLV	13228	6150	7218	17153	14331	<100
JRCSF	3277	1636	2397	5377	4286	199
NL43	<100	<100	<100	<100	<100	2047
SIVmac239	559	328	387	1088	523	<100

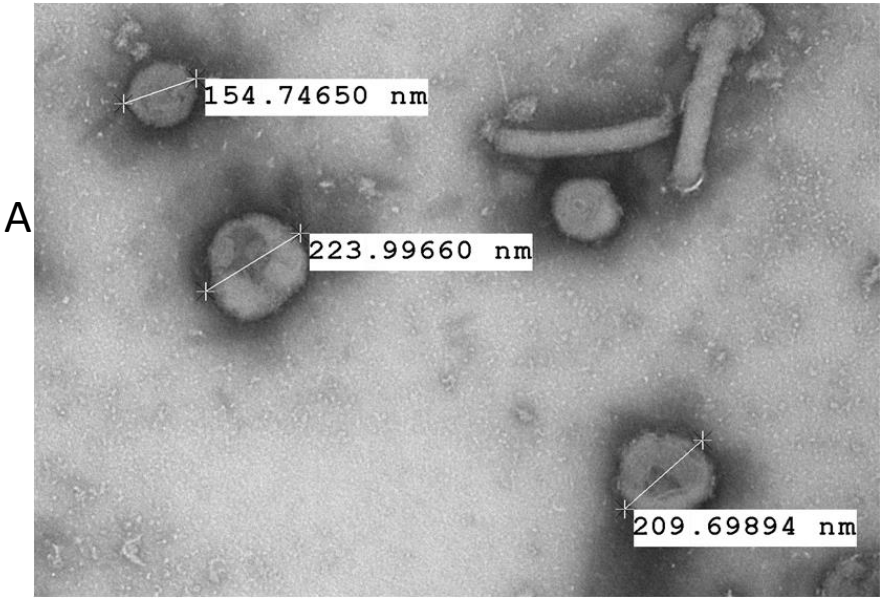
Development of EBOLA VLP candidate Vaccine

Baculovirus Expression of Ebola VLP

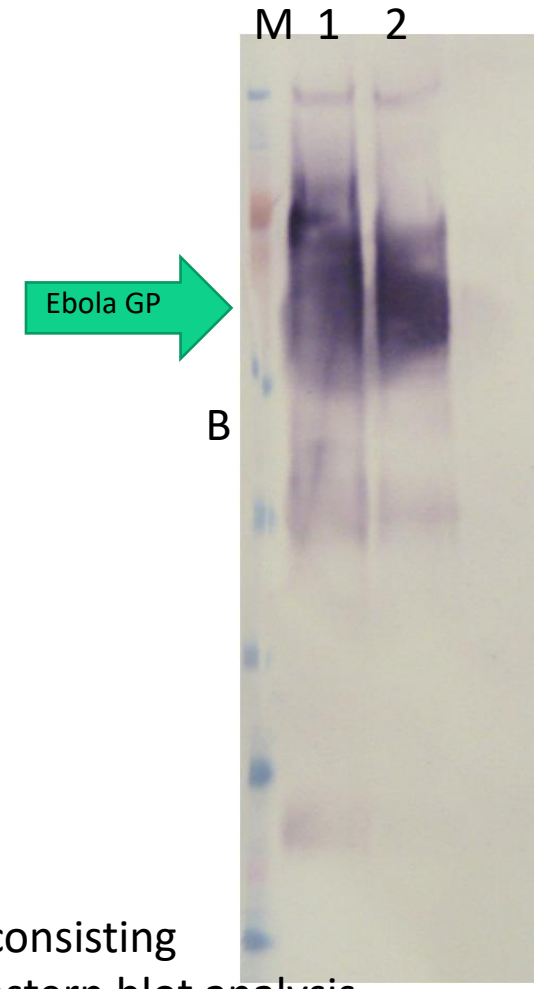


Electron Microscopy of Ebola VLP

A



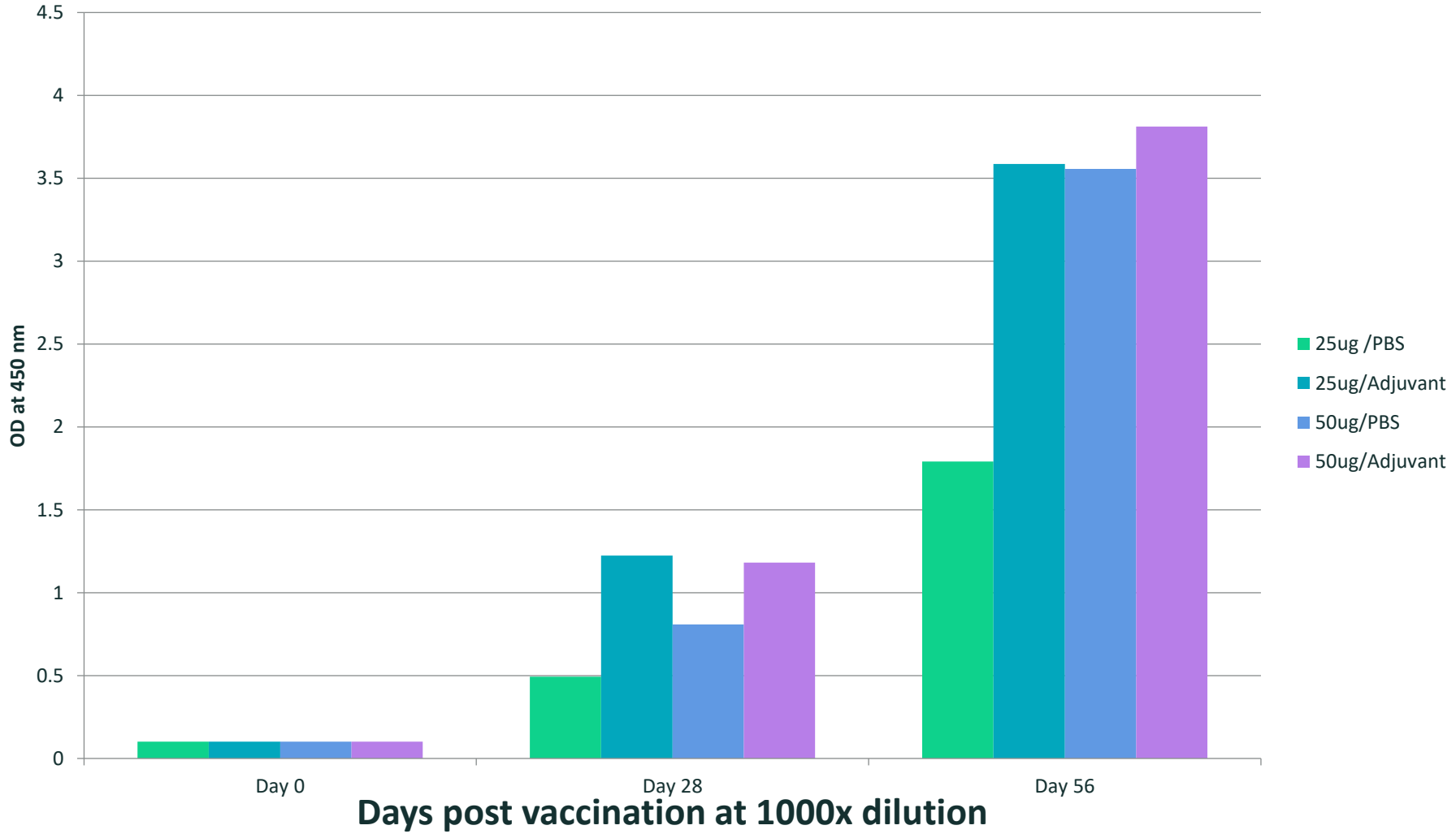
B



M. SeeBlue® Plus2 protein standard
1. Ebola VLP, diluted 5x
2. Ebola VLP, diluted 10x

Figure: (A). Electron microscopy of Ebola VLP consisting Of GP and purified from sf9 insect cells, (B) western blot analysis Of Ebola VLP expressing GP using antigen-specific sera.

Agwale et al. Construction and evaluation of a highly immunogenic Ebola VLP vaccine candidate, Poster #17. Targeting Ebola International conference, Paris, France May, 2015)



Novel HPV Vaccine

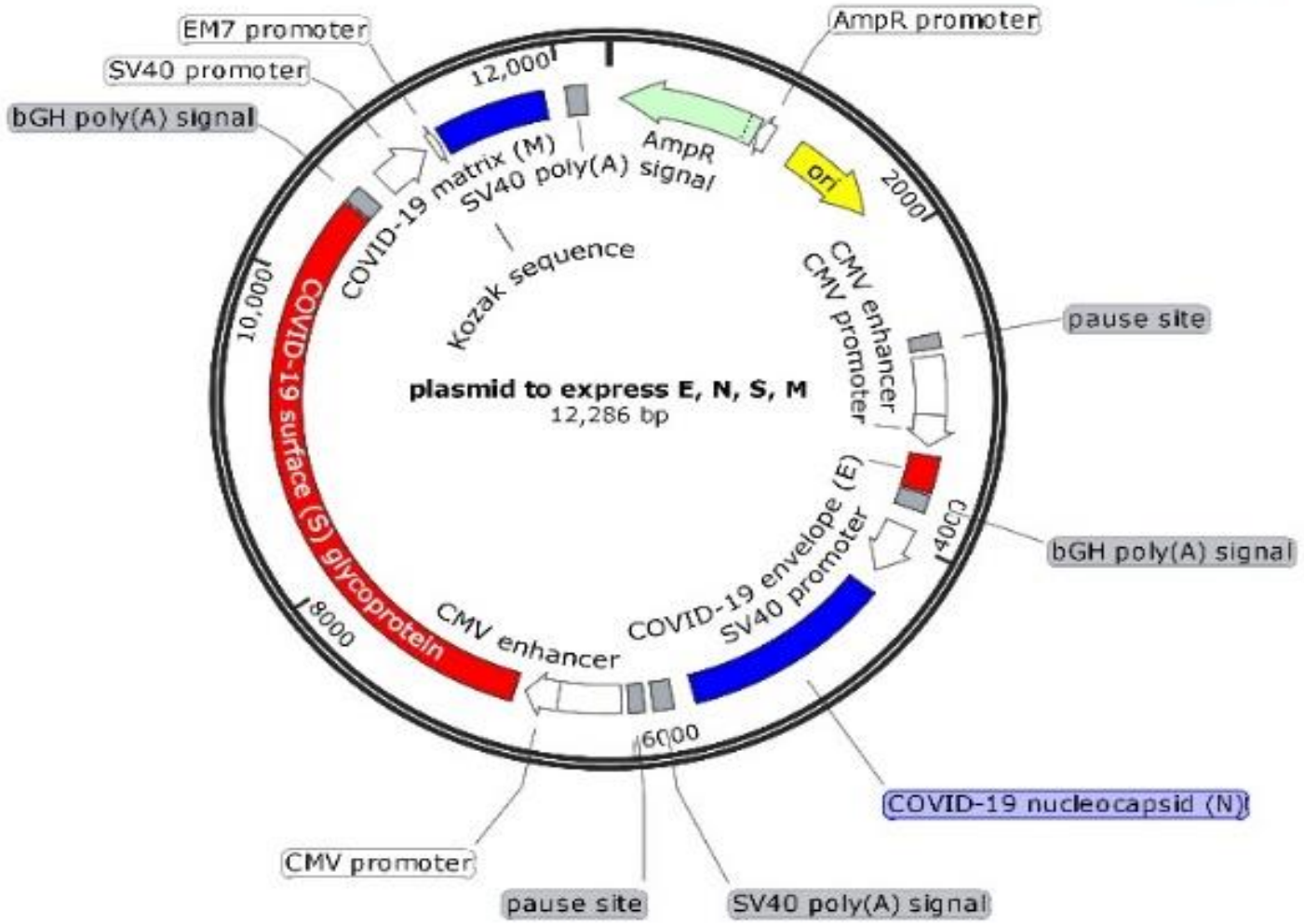
- Current Vaccine: Cervarix (16/18); Gardasil (6/11/16/18); Gardasil-9 (6/11/16/18/31/33/45/52/58).
- Cross Protection: HPV31/33/45,lesser extent HPV35/58. Tsang et al., 2020. JNCI J Natl Cancer Inst. 112(10).
- Africa: 16(48%), 18(23%), 31(2%), 33(1%), 35(5%), 45(10%), 51(2%), 52(3%), indeterminate(3%): Sanjose et al., 2010.Lancet Oncol 2010; 11: 1048–56.
- New Vaccine: HPV16/18/35.

APPROACH; Baculovirus expression system to purify L1 protein of types 16, 18 and 35.

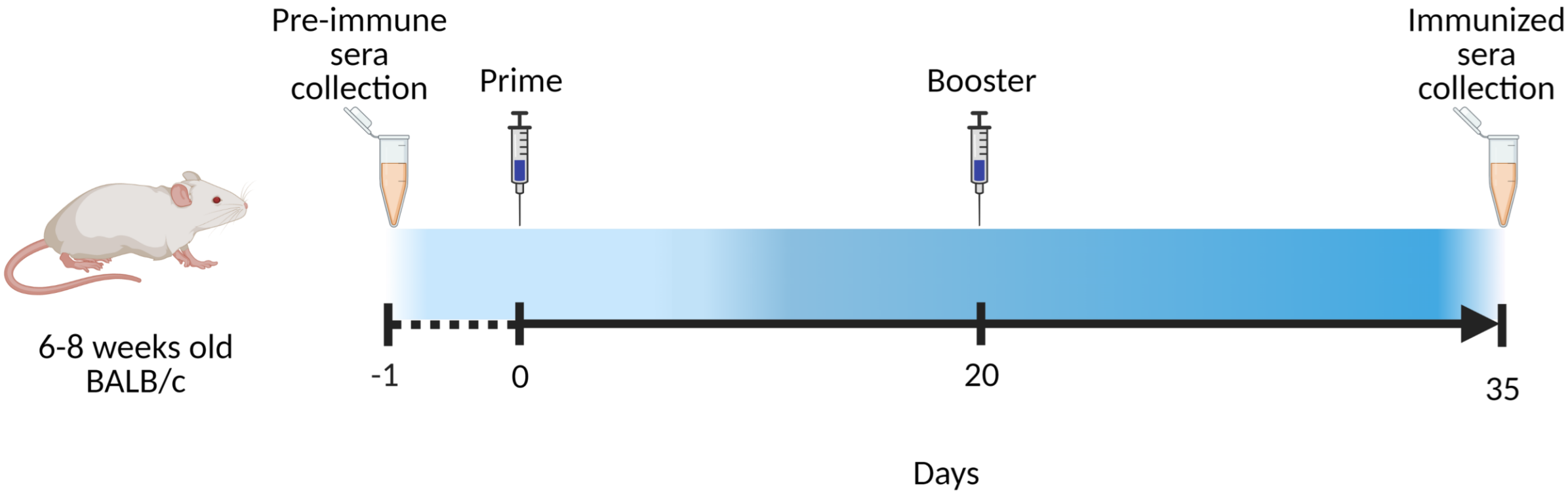
Development and Manufacturing of a Multivalent COVID-19 Vaccine

VLP Vaccine Development

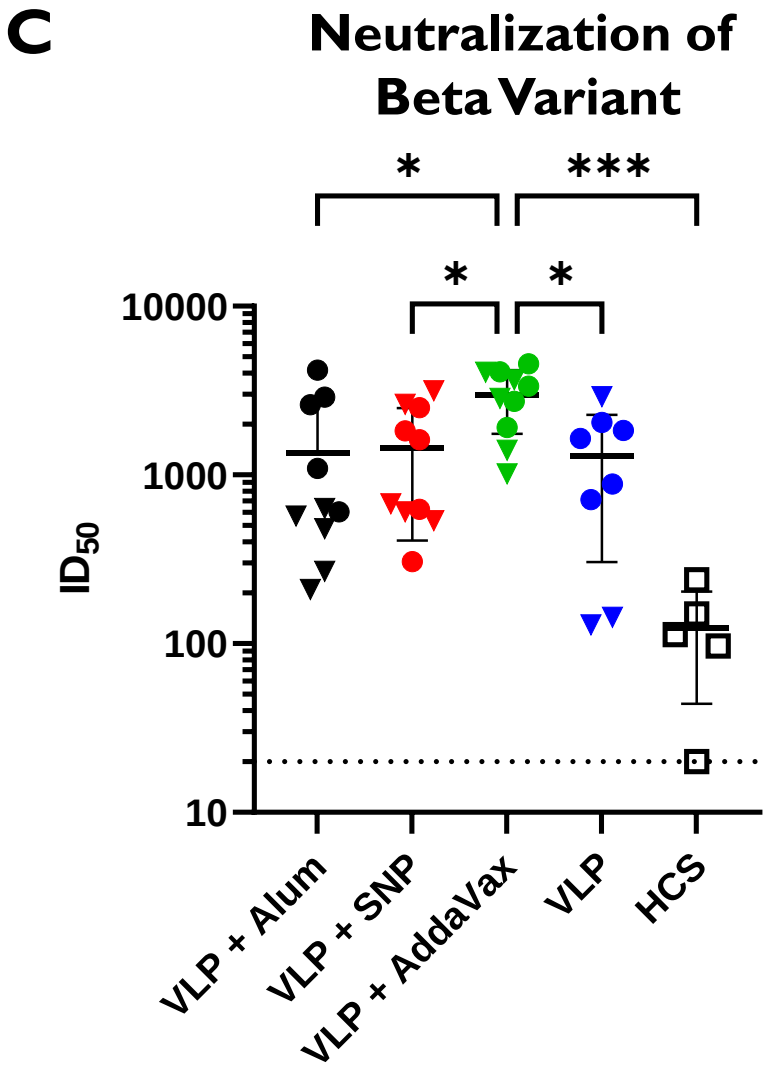
- Structure mimics the native virus
- Contains all viral structural components
  - S, M, E, and N
- Assembled in mammalian cell culture
  - VLPs released into culture medium and then purified

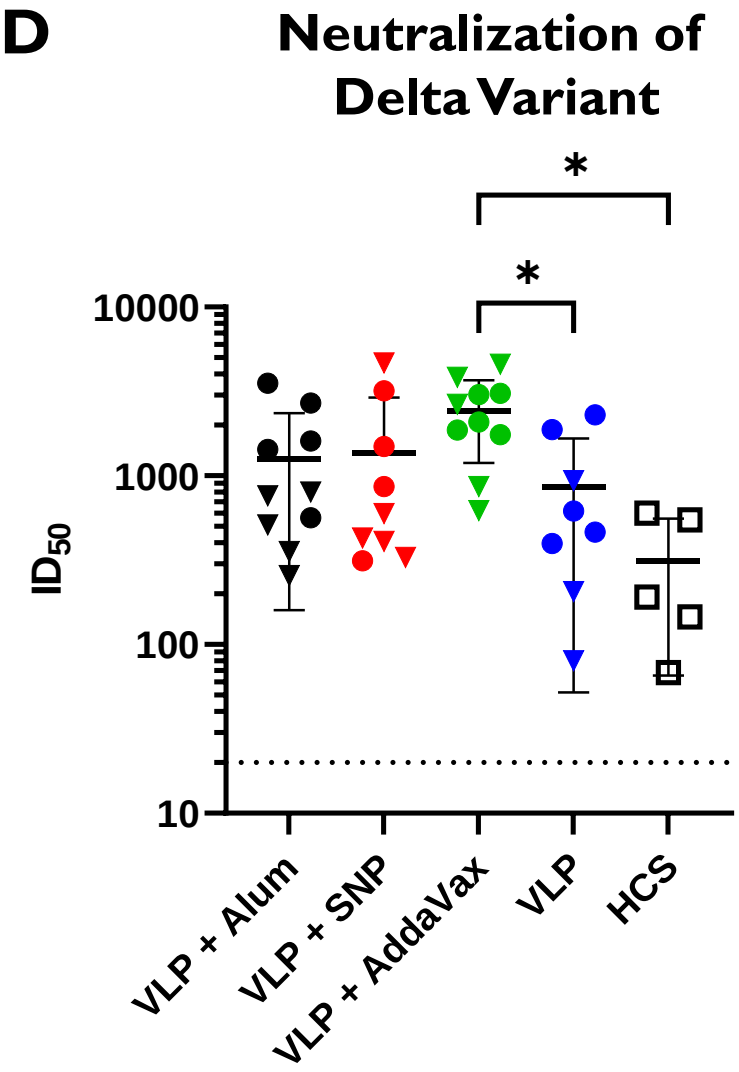


VLP Immunization Schedule



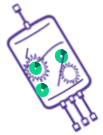
SARS-CoV-2 VLP Vaccine – Comparison of Neutralization of Beta and Delta Variants





VLP Process Template 500L Scale – Mobius Single-use Systems

Phase 2 Manufacturing Facility



Cell Culture 3L

50L Bioreactor

200L / 100L Bioreactor

DNA Digestion

Clarification

Ultrafiltration

Chromatography Steps

Phase 1 Final Fill Facility

Novel Yellow Fever Vaccine

- Current Vaccine: Production in eggs, risk for supply chain.
- Novel YF Vaccine: Cell based production, so no eggs needed.
- It is a live attenuated vaccine, similar to 17D vaccine.
- iDNA immunization approach combines characteristics of DNA and attenuated vaccines, so it can be formulated for storage at room temperature.
- Serum free production, therefore increased safety.
- Close disposable manufacturing technology, i.e quality by design.
- Proprietary technology.

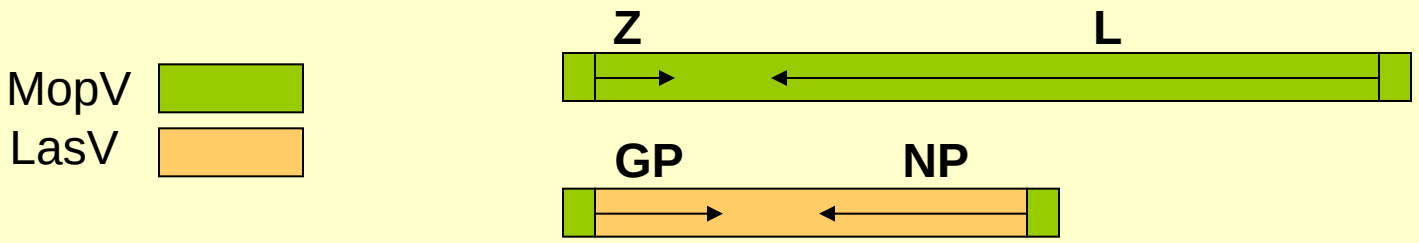
APPROACH

- Developed using iDNA technology.
- The iDNA represents genetically stable DNA that encodes the full-length RNA genome of YF17D vaccine.
- Safety of the vaccine was confirmed in AG129 mice.
- Vaccination of mice resulted in seroconversion and elicitation of virus-specific neutralizing antibodies (Tretyakova et al., Virology, 2014).
- Next steps: Prepare cGMP material for bridging studies.

LasV Vaccine:
Live Reassortant Mopeia Virus (MopV) Expressing Lassa Fever Virus Structural Proteins

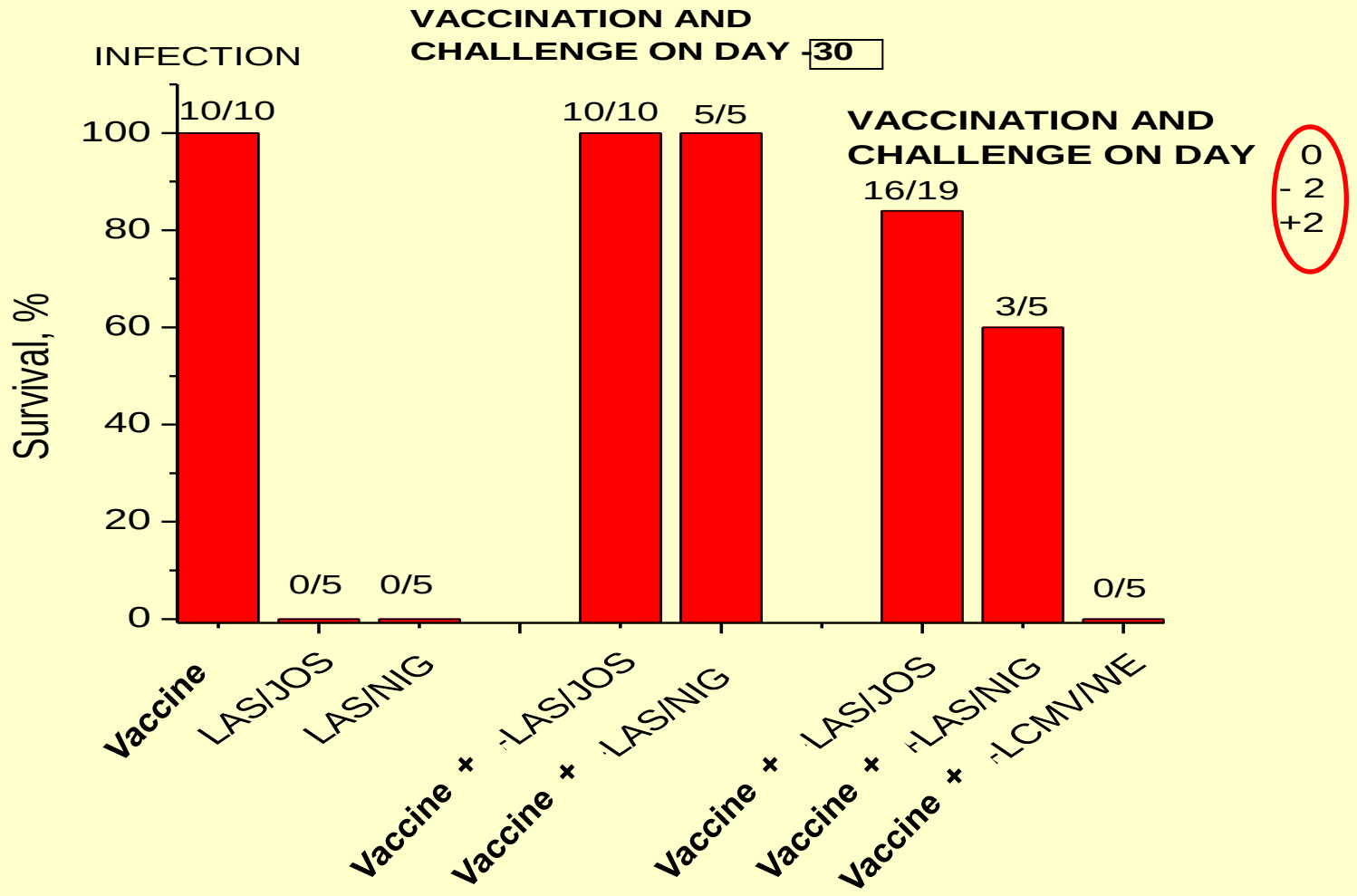
- LasV ML29 Vaccine: 68% MopV genome + 32% LasV Genes
- Reassortant vaccine against Lassa fever
- Vaccine is safe in rodent and NHP models

Genetic Structure of Reassortant Vaccine against LasV



Medigen LLC.
University of Maryland

Vaccination-Challenge Experiments in Guinea Pigs: Preventive and Therapeutic Applications of LasV Vaccine



Medigen LLC.
University of Maryland.

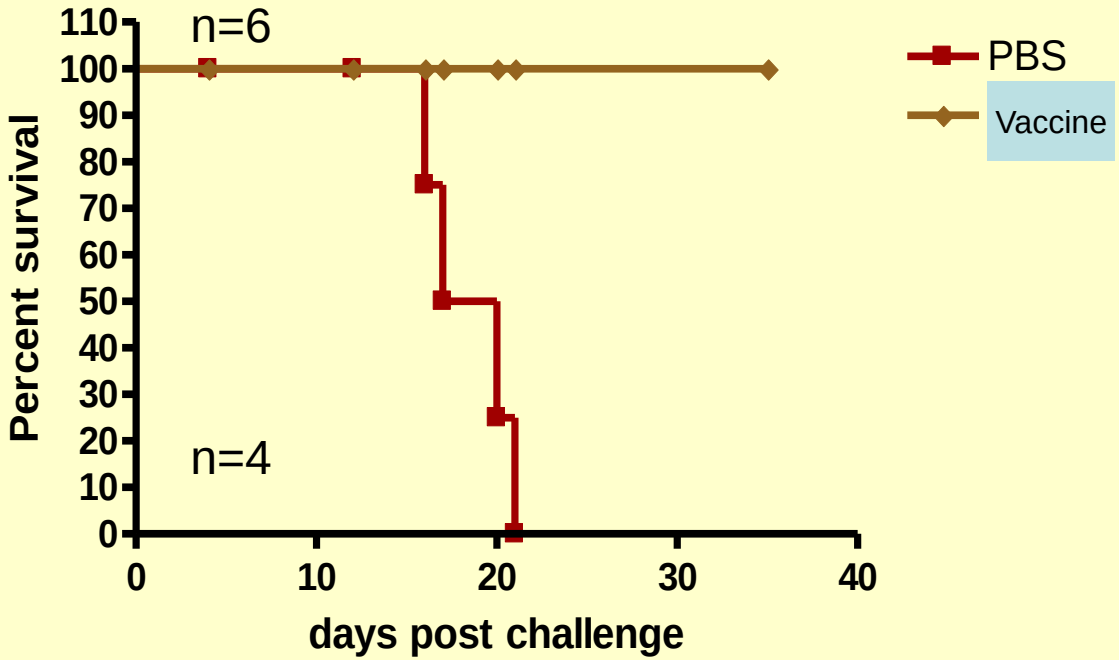
Vaccination with reasortant vaccine protects marmosets against fatal disease

Vaccination
1,000 PFU, s.c.

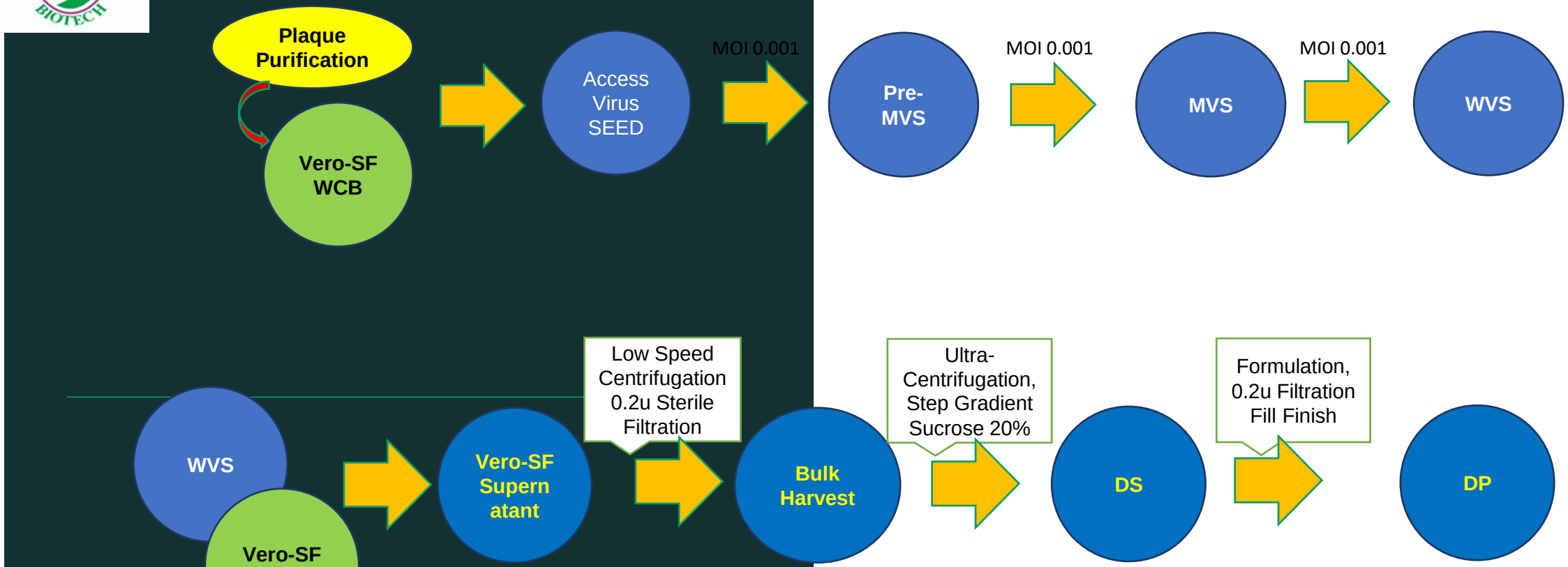
Challenge
1,000 LD50, s.c.

0 30 35 45 50 65 bleed. days

Efficacy in Marmosets



ML29 Lassa Vaccine cGMP Manufacturing



Medigen

Innovative Biotech's Development Impact – Jobs, Training and Expertise to Nigeria

Theme	Description
Technical Partnerships and Training	• Innovative Biotech will bring new science and manufacturing skills to Africa through its partnerships with global pharma companies that will train staff and provide technical expertise to the project. Key Partners include Merck, Unizima and NAFDAC
Vaccination and Education Programs	• IB has been working with hospitals to establish vaccination centers • In past 2 years, IB have carried out vaccination programs for government agencies and conducted community outreach and education programs about vaccines. • 36 States of Nigeria are currently part of their program to educate community on vaccines, their processes, usages, importance, etc.
Health Sovereignty	• The project aims to strengthen African and Nigerian Health Sovereignty by making locally-manufactured vaccines available to the continent. • This is especially important given that Nigeria is expected to graduate from GAVI in 2030, after which Nigeria will need to procure is vaccines independently and may be subject to higher prices if it does not procure locally
Direct employment benefits	• Innovative Biotech will create over 100 jobs in Nigeria and over 100 jobs more broadly across the vaccines supply chains in Africa

Conclusions

- There is now acute awareness of the importance of vaccine production given the Covid-19 Pandemic.
- Covid-19, GAVI graduation and global production capacity shortages can be a big driver for localized production.
- A successful facility will need to have a strong 10+ year strategic plan to have a chance of being viable.
- Modular facilities provide the rapid deployment of flexible production capacity that is needed today.
- Governments and regional trade organizations will need to commit to supporting R and D and manufacturing.
- Private and public firms will need to develop robust business cases for localized vaccine production.
- Technology transfer partners need to provide vital know-how and experience to new localized production efforts.
- **In order to be self-reliant and benefit from the billions of USD health market in Africa by 2030-Africa needs to build an ecosystem that allows Scientists to develop IP that can be used locally.**