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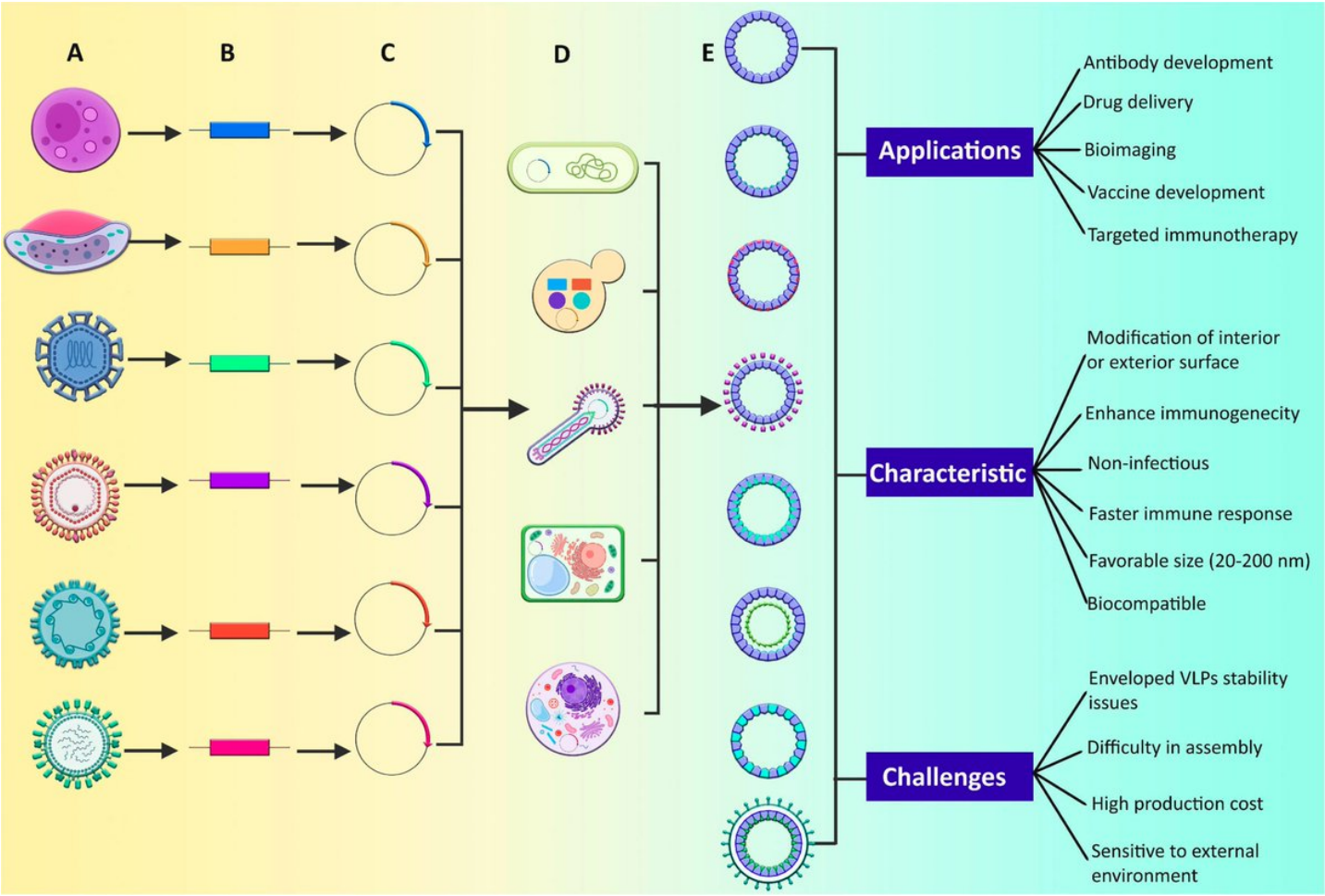


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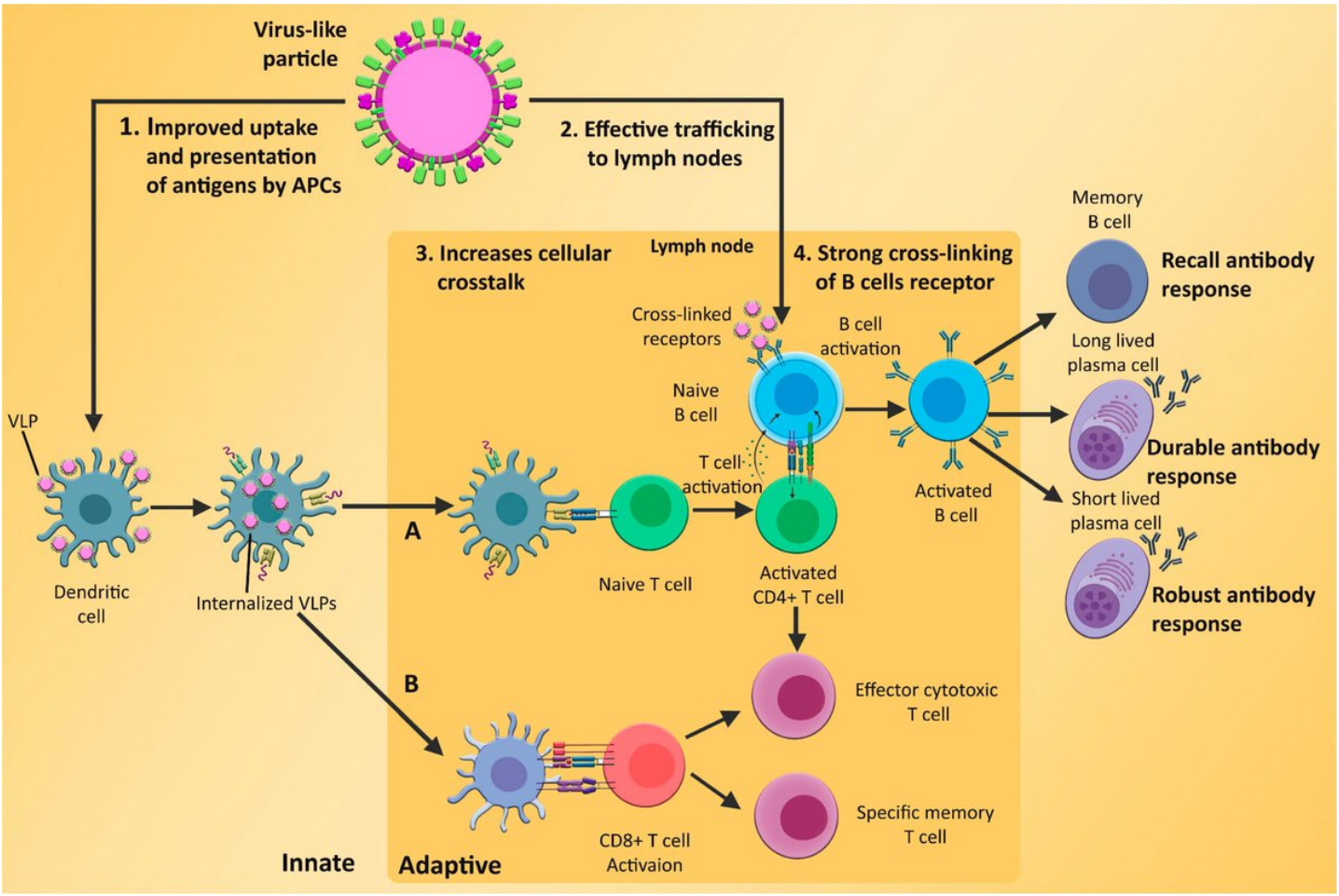
Virus-Like Particles: Revolutionary Platforms for Developing Vaccines Against Emerging Infectious Diseases
https://t.co/gm76Pzw0KT

In memoriam Nicola Bidoli

VLP applications characteristics challenges



VLP Induction of innate and adaptive immunological responses (A) humoral immunity; (B) cell-mediated immunity) by VLPs



VLPs Advantages and limitations of different expression systems for the development of virus-like particles.

Expression Systems for VLP Production

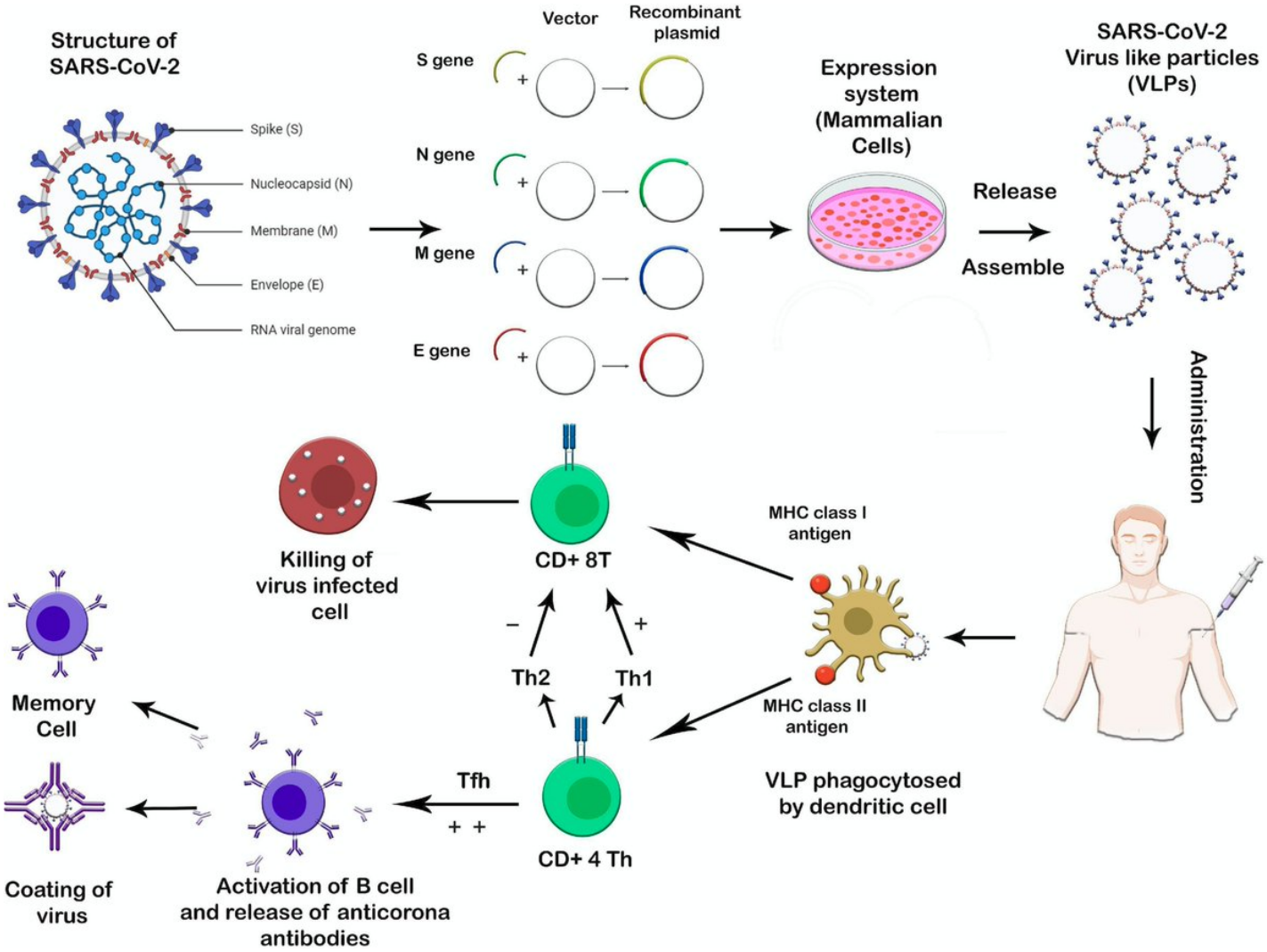
Expression systems	Bacteria	Yeast	Insect cells	Mammalian cells	Plant cells
Advantages	• Cost-effective • Scalable • Rapid growth • Easy manipulation • High-level expression • Genetic stability	• Low production cost • No endotoxins contamination • High-density fermentation • Support most protein folding	• Carry and deliver large amount of DNA • High protein expression • Support eukaryotic protein PTMs • Proper protein folding and assembly	• Perform proper folding, assembly, and PTMs of proteins	• Highly scalable • Cost-effective • Carry out N-glycosylation • High expression • Correct folding and assembly
Limitations	• Poor immunogenicity • Recombinant proteins lack PTMs • Protein solubility issues • Contamination by bacterial endotoxins • Inability to create di-sulfide bonds	• Vlp yield lower than E. coli • High mannose modification • Lack mammalian like PTMs	• Difficult to scale up • High production cost • Baculoviruse contamination • Simpler N-glycosylation than mammalian cells • Incomplete modification of proteins	• Require large-scale production facilities • Lengthy expression time • Low yield • Contamination by mammalian pathogens	• Low yield than mammalian cells • Technical and regulatory issues

VLP vaccines against different viruses and parasites.

VLP vaccine	Antigens displayed by VLP vaccine	Expression system	Targeting pathogen	Mechanism of action	References
M-HBsAgS-N4, M-HBsAgS-N9 VLPs	NANP repeats from circumsporozoite protein (CSP) and small HBV envelope protein (HBsAgS)	HEK 293F cells	*Plasmodium falciparum*	Induced anti-NANP Abs with the potential to initiate the complement system, which led to the inactivation of invading parasitic sporozoites.	Kingston et al., 2019
STh and STh-A14T VLPs	Human heat-stable toxins (STh) and STh-A14T toxoid	*E. coli*	Enterotoxigenic *Escherichia coli* (ETEC)	Both VLPs showed immunogenicity in mice and neutralized the native STh's toxic activities completely.	Govasli et al., 2019
CV-B4 VLPs	VP1	Insect cells	Coxsackievirus B4 (CV-B4)	Showed antigenic reactivity with specific antibodies.	Hassine et al., 2020
RVFV VLPs	Gn, Gc, and N proteins	Sf9 insect cells	Rift Valley fever virus (RVFV)	Produced RVFV neutralizing antibodies in mice and stimulated spleen cells in the mouse to produce high cytokines levels (IL-4 and IFN-γ).	Li et al., 2020
Genogroup II, genotype 17 (GII.17) VLPs	Major capsid protein (VP1)	sf9 insect cells	Noroviruses (NoVs)	Mice immunized with purified and sterile VLPs developed specific GII.17 sera and effectively blocked GII.17 VLPs bound to antigen of the saliva histo-blood group.	Chen et al., 2020
JEV genotype III (GIII) VLPs	Envelope (E) protein and Precursor membrane protein (prM)	Mosquito cell lines	Japanese encephalitis virus (JEV)	A specific immune response has been developed against a stable IgG2a/IgG1 ratio. This response essentially nullified both Japanese encephalitis virus GIII and GI and triggered a hybrid response of Th1/Th2 in a mice model.	Chang et al., 2020
SAG1-VLPs	Surface antigen 1 (SAG1)	Sf9 insect cells	*Toxoplasma gondii*	After immunization, IgG, IgG1, IgG2a, and IgA were significantly enhanced, and *T. gondii* endurance rates were severely constrained by the immunized sera.	Choi and Park, 2020
VLP-gG and VLP-gB	ILTV glycoproteins B (gB) or G (gG)	LMH cells	Infectious laryngotracheitis virus (ILTV)	VLPs displayed no noticeable adverse effects *in vivo* and appeared to induce an antibody-based immune response.	Schädler et al., 2019
Chimeric VLP (Pfs230 and Pfs25), genetically fused to dS of the duck HBV	Pfs25 and Pfs230	Auxotrophic *Hansenula polymorpha* strain ALU3	*Plasmodium falciparum*	Exhibited reactivity with transmission-blocking antibodies and established the malaria antigens exhibition on the native VLP surface.	Wetzel et al., 2019b
Triple chimeric AHSV-6 VLPs	VP2, VP3, VP5, and VP7	*Nicotiana benthamiana* dXT/FT plants	African horse sickness virus (AHSV)	Able to stimulate a poor neutralizing humoral immune response against homologous AHSV virus in target animals.	Rutkowska et al., 2019
Codon-optimized AMA-1 VLP	Apical membrane antigen 1 (AMA-1)	Sf9 insect cells	*Plasmodium berghei*	Vaccination with codon-optimized AMA-1 VLPs, mediated elevated levels of B cells, $CD8^+$ T cells, germinal center cells, and $CD4^+$ T cell responses relative to non-codon optimized VLPs.	Lee et al., 2019
$HBc_{\Delta R82}$, $HBc_{\Delta H301}$, $HBc_{\Delta H82}$, and $HBc_{\Delta R301}$ VLPs	$CD4^+$ cell epitope (AS15), B cell epitope ($SAG1_{301-320}$ or $SAG1_{82-102}$), and a $CD8^+$ cell epitope (ROP7 or HF10)	*Escherichia coli*	*Toxoplasma gondii*	High titers of IgG Ab and production of interferon (IFN)-p, resulted in reduced brain parasite load.	Guo et al., 2019
PPRV VLPs	Hemagglutinin (H), PPRV matrix (M), nucleocapsid (N), and fusion (F) proteins	Baculovirus-insect cell	Peste des petits ruminants virus (PPRV)	Induced antibodies production specific for F and H proteins and provoked a cellular immunological response in goats.	Yan et al., 2019
EV71-VLPs	VP0, VP1, and VP3	*Pichia pastoris*	Enterovirus 71 (EV71)	Both maternally transferred Ab and passive transfer protection mouse models stimulated a robust neutralizing Ab response and offered effective protection against lethal challenge.	Yang et al., 2019
CJaYZ vaccine	CprME-IRES-NS2B-3, (C-E3-E2-6K-E1)	293?T stable cell lines	ZIKV, CHIKV, JEV, and yellow fever virus (YFV)	The tetravalent VLPs supplied highly neutralizing Ab titers against the viral strains tested.	Garg et al., 2020
Chimeric BTV-4 and BTV-3 VLPs	VP3, VP7, VP2, and VP5	*N. benthamiana*	Bluetongue virus (BTV)	Induced long-lasting serotype-specific neutralizing Abs in sheep like the monovalent live attenuated vaccine controls.	Mokoena et al., 2019
AP205 capsid-based VLPs	The VAR2CSA PM antigen and HPV RG1 epitope	*E. coli*	Human Papillomavirus and placental malaria	Reduced *in vivo* HPV infection and induced IgG antibodies against VAR2CSA.	Janitzek et al., 2019
CVB1-VLPs	CVB1 capsid proteins (VP0, VP1, and VP3)	Baculovirus-insect cell	Type B Coxsackieviruses (CVBs)	CVB1-VLP vaccines were extremely immunogenic, and their immunogenicity and stability improved with formalin treatment.	Hankaniemi et al., 2019
HCV VLPs	E1 and E2 glycoproteins	Huh7 cells	Hepatitis C virus (HCV)	Produced robust HCV multi-genotypic neutralizing Ab (NAb), as well as cell mediated immunity responses in pigs.	Earnest-Silveira et al., 2016; Christiansen et al., 2019
Hepatitis B core (HBc) VLPs and Recombinant immune complexes (RIC)	Minor CP (L2 or L2 fused with an immunoglobulin)	*N. benthamiana*	Human Papillomavirus (HPV)	Both candidates for the vaccine showed potent immunogenicity in a mice model but were particularly so when delivered together, producing very high and consistent HPV L2-directed antibody titers, which associated with the neutralization of viruses.	Diamos et al., 2019

VLP - how to produce them

Proposed production system and mechanism of action of SARS-CoV2 virus-like particle vaccine. Plasmids encoding the structural proteins (S, N, M, and E) of the SARS-CoV2 can be transfected into an appropriate mammalian cell line.


Structure of SARS-CoV-2
Spike (S)
Nucleocapsid (N)
Membrane (M)
Envelope (E)
RNA viral genome
Vector
Recombinant plasmid
S gene
N gene
M gene
E gene
Expression system (Mammalian Cells)
Release
Assemble
SARS-CoV-2 Virus like particles (VLPs)
Administration
MHC class I antigen
MHC class II antigen
VLP phagocytosed by dendritic cell
CD+ 8T
Killing of virus infected cell
Th2
Th1
CD+ 4 Th
Tfh
Memory Cell
Coating of virus
Activation of B cell and release of anticorona antibodies