

Supplementary table 1. List of promising adjuvants tested for intranasal and oral vaccination with protein antigens

Adjuvants	Administration /Animals	Protein antigens	Reported responses	References
Alum				
Alum	Oral/rabbits, monkeys	DT, TT	IgG1,Th2	Mirchamsy et al. 1996
Bacterial toxins and their derivatives				
Cholera toxin	Nasal/mice	SeM	IgG, IgA, Th1, Th2	Florindo et al. 2009
		M2e-HBc(VLP)	IgG, Th1, protection	De Filette et al. 2006
		rUre	IgG, IgA, Th1, Th2	Moschos et al. 2004
		HA	N.A	Ichinoe et al. 2005
Heat-labile enterotoxin	Nasal/mice, rabbits, pigs	HA	IgG, IgA	Singh et al. 2001
	Nasal/rabbits	HagB	IgG, IgA,	Zhang et al. 2003
Bacterial glycolipids				
MPL/LPS	Oral, nasal/mice	OVA	IgG, IgA, Th1, Th2	Sarti et al. 2001, Bal et al. 2012
Bacterial peptidoglycan				
MDP	Nasal/mice	OVA	IgG1, IgA	Bal et al. 2012
Bacterial second messengers				
c-di-AMP	Nasal/mice	β -Gal, OVA	IgG, IgA, Th1/2/17, CTL	Ebensen et al. 2011
		rNP	IgG, IgA, Th1	Sanchez et al. 2014
c-di-IMP	Nasal/mice	β -Gal, OVA	IgG, IgA, Th1/2/17, CTL	Libanova et al. 2010
c-di-GMP	Nasal/mice	β -Gal, OVA	IgG, IgA, Th1, CTL	Ebensen et al. 2007
		HA	IgG, IgA, Th1, Th2	Svindland et al. 2013
	Nasal, sublingual/mice	H5N1 virosomes	IgG, IgA, Th1, Th2, Th17	Pedersen et al. 2011
Synthetic bacterial DNA and viral dsRNA				
CpG	Nasal/mice	HBsAg	IgG, IgA, Th1, Th2, CTLs	McCluskie et al. 1998,
	Nasal/mice	HIV peptides	IgG, IgA	Pun et al. 2009, Buffa et al. 2012
	Oral/mice, rats	HBsAg, TT	IgG, IgA, Th1, Th2, CTLs	McCluskie et al. 2000, Eastcott et al. 2001, Buffa et al. 2012
Poly I:C	Nasal/mice;	SHIV-VLP	IgG, IgA, CTL	Kang et al. 2004
		HA	IgG, IgA, protection	Ichinoe et al. 2005
	Nasal/mice	HPIV-HN	IgG, IgA	Senchi et al. 2013
Virosomes				
Virosomes	Nasal/mice	SHIV-VLP	IgG, IgA, CTL	Kang et al. 2004
Synthetic small organic molecules				
Imidazoquinoline	Nasal/mice	HBsAg	IgG, Th1, Th2	Vicente et al. 2013
C48/80	Nasal/rabbits	BoNT/A-Hcbtre	IgG	Staats et al. 2011

	Nasal/mice	HA	IgG, IgA, Th1, Th2, protection	Meng et al. 2011
Vitamin E TPGS,	Nasal/mice	DT	IgG	Somavarapu et al. 2005
α -GalCer	Nasal, oral /mice;	HIV-gp120 epitopes	Cellular	Courtney et al. 2009
Plant derived molecules				
Saponin	Nasal/mice	HagB	IgG, IgA, Th1, CTLs	Zhang et al. 2003
	Nasal/rabbits	TT	IgA, IgG	Moghadam et al. 2012
Eurocine	Nasal/mice	HA	IgG, IgA, protection	Petersson et al. 2010
Polymers from crustaceans' shell or particles from surf clam				
Chitosan	Nasal/mice	M1	IgG, IgA, protection	Sui et al. 2010
		rUre	IgG, IgA, Th1, Th2, cellular	Moschos et al. 2004
		HA	IgG, IgA, Th1, Th2	Svindland et al. 2013
Surf clam microparticles	Nasal/mice	HA	IgG, IgA	Ichinohe et al. 2006
Cytokines				
IL-1	Nasal/mice	HA	IgG, IgA, protection	Kayamuro et al. 2010
IL-12	Nasal/mice	TT	IgG, IgA, Th1, Th2	Boyaka et al. 1999
TNF and mutants	Nasal/mice	OVA	IgG, IgA, Th2	Kayamuro et al. 2009a, 2009b

Supplementary table 2. List of materials and delivery vehicles tested for intranasal and oral vaccination with protein antigens

Materials	Administration/Animals	Protein antigens	Reported responses	Delivery vehicles* and adjuvant if applicable	References	
VLP						
VLP-HBV	Nasal/mice	M2e	IgG, Th1, protection	NPs, CT	De Filette et al. 2006	
VLP-HEV	Oral/mice	HEV	IgG, IgA	NPs	Li et al. 2001, Wu et al. 2012	
VLP-MuPyV	Nasal/mice	GAS-J8i peptide	IgG, IgA	NPs	Rivera-Hernandez et al. 2013	
VLP-NV	Oral, nasal/mice	rNV-VLP	IgG, IgA	NPs, LT/CT	Mason et al. 1996, Ball et al. 1998, Guerrero et al. 2001	
Synthetic polymers						
PLGA	Nasal, oral/mice, rabbits, cattle	F1/V	IgG, IgA	MPs/MSs	Jaganathan et al. 2006	
		Oral/mice	OVA	IgG, IgA	NPs, MPLA	Sarti et al. 2011
			OVA	IgA, CTL	MPs	Maloy et al. 1994
	Nasal, oral/rabbits	Malaria-SPf6 6	IgG, Th1	MPs	Carcaboso et al. 2003	
		SFV-Env E2	Ig, protection	MSs	Brandhonneur et al. 2009	
		Nasal/mice	HBsAg	IgA, cellular	CS-PLGA MSs, CTB	Jaganathan et al. 2006
			BRSV-peptides	IgA, cellular	MPs	Kavanagh et al. 2013
	Nasal/calves	BP13V-peptides	IgG	NPs	Mansoor et al. 2014	
		OVA	IgG, IgA	MSs/MPs	Kavanaagh et al. 2003	
		Nasal/mice	F1/V/(F1+V)	IgG, IgA	MSs	Eyles et al. 2000, Alpar et al. 2001, Tripathi et al. 2006
Nasal/rats	TT		IgG, IgA	PEG-PLA NPs/MPs	Tobio et al. 1998, Vila et al. 2004	
PCL	Oral/mice	HBsAg	IgG, IgA, Th1	PEG-PLA-PEG NPs	Jain et al. 2010	
	Oral/mice	OVA	IgG	RGD peptide, NPs of PLGA/PLGA-PEG/PCL-PEG	Garinot et al. 2007	
		Nasal/mice	DT	IgG	NPs, VE-TPGS	Somavarapu et al. 2005, Singh et al. 2006
			SeM	IgG, IgA, Th1, Th2	NSs, CTB	Florindo et al. 2009
PEI	Nasal/mice, rabbits	HA, HSV-gpD,	IgG, IgA, cellular, protection	Nanoscale complexes	Wegmann et al. 2012	

		HIV-gp140					
Eudragits	Oral/mice	HIV Env epitopes	Colon-targeted, IgG, IgA, cellular, protection	NPs/MPs, TLR ligands		Zhu et al. 2012	
	Oral/human	Bee venom peptide	Colon-targeted	Alginate-liposome		Liu et al. 2003	
Natural polymers							
Chitosan	Nasal/mice	TT	IgG, Th1, Th2	NPs		Sayin et al. 2009	
		HBsAg	IgG, Th1, Th2	Nanocapsules, Imiquimod		Vicente et al. 2013	
Alginate	Nasal, oral/mice	HBsAg	IgG, IgA, cellular	Alginate-chitosan NPs, CpG		Borges et al. 2007,2008	
	Nasal/calves	PSA	IgG	MPs		Rebelatto et al. 2001	
	Oral/mice	BSA	IgG, Th1, Th2	Lectin-alginate NPs		Malik et al. 2012	
Starch	Oral/mice	DT and its mutant	IgG, IgA, Th1, Th2	Polyacryl starch MPs		Rydell et al. 2004	
		HSA	IgG, IgA, Th1, Th2	Polyacryl starch MPs		Wikingsson et al. 2002	
	Nasal, oral/mice	HSA	IgG, IgA, Th2	Silicone-starch MPs		McDermott et al. 1998	
Dextran	Nasal/rabbit	TT	IgG, IgA	MSs		Sajadi et al. 2008	
Hyaluronic acid	Nasal/mice, rabbits, pigs	HA	IgG, IgA	HYAFF MSs, LT		Singh et al. 2001	
Γ-PGA	Nasal/mice	OVA	IgG, IgA, Th1, CTL	NPs		Matsuo et al. 2011	
						Noh et al. 2013	
Lipid based polymers							
Liposome	Oral/mice	BSA	IgG, IgA	UEA1-liposome		Li et al. 2011a, 2011b	
		OVA	IgG, IgA	PEG-liposome		Minato et al. 2003	
	Nasal/mice	HBsAg	IgG, IgA, Th1	IgG-liposome		Tiwari et al. 2011a	
			IgG, IgA, Th1	HA-liposome		Tiwari et al. 2011b	
		OVA	IgG, IgA	Oligomannose-liposome		Ishii et al. 2010	
		HPIV-HN	IgG, IgA	Oligomannose-liposome, Poly I:C		Senchi et al. 2013	
	Oral/rabbits, monkeys, human	DT and TT	IgG	LRS		Mirchamsy et al. 1996	
Niosome	Nasal/mice	HSV-gBs	IgG, Th1, Th2	N.A.		Cortesi et al. 2013	
Bilosome	Oral/mice	HA	IgG, Th1, Th2	N.A.		Mann et al. 2009	
		HBsAg	IgG, IgA	CTB-bilosome		Shukla et al. 2008, 2010	
		TT	IgG, IgA, Th1	N.A.		Mann et al. 2006, Jain et al. 2014	
		DT	IgG, IgA	N.A.		Shukla et al. 2011	
Virosome	Nasal/sublingual	HA	IgG, IgA, Th1, Th2, Th17	c-di-GMP		Pedersen et al. 2011	
ISCOMs	Nasal/mice	RSV Env	IgG, IgA, Th1, Th2	N.A.		Hu et al. 1998	
		MmmSC	IgG, IgA, Th1, Th2, CTL	N.A.		Abusugra et al. 1999	
		HBsAg	IgG, IgA, Th1, Th2, CTL	N.A.		Pandey et al. 2010	

Archaeosome	Nasal/mice	OVA	IgG, IgA, Th1, Th2, CTL	AMVAD	Patel et al. 2007, 2008
Multiple antigen-presenting systems-synthetic peptides					
MAP		MAP-F1	IgG, IgA, Th1, Th2	PLGA MPs, CpG	Ali et al. 2013
Hydrogel of cationic cholesteryl group-bearing pullulan (cCHP)					
cCHP	Nasal/mice	BoHc/A, TT	IgG, IgA,	Nanogel	Nochi et al. 2010
		PspA	IgG, IgA, Th2, Th17	Nanogel	Kong et al. 2013
Inorganic particles					
Gold	Oral/mice	TT	IgG, IgA	CS-AuNPs, QS	Barhate et al. 2013
	Nasal/mice	M2e	IgG, Th1, Th2	M2e-AuNP, CpG	Tao et al. 2014
Receptor-ligand mediated target delivery					
UEA-1	Oral/mice	HBsAg	IgG, IgA, Th1, Th2	UEA1-PLGA NPs	Gupta et al. 2007
		BSA	IgG, IgA	UEA-liposome	Li et al. 2011a, 2011b
RGD peptide	Oral/mice	OVA	IgG	PEG-PLGA NPs	Garinot et al. 2007
Ganglioside	Oral/mice	EGFP	IgG, IgA, Th2	N.A.	Kim et al. 2006
GM1 ligand					
Co1	Oral/mice	EGFP	IgG, IgA, Th2	N.A.	Kim et al. 2010
Fc	Nasal/mice	MERS-RBD	IgG, IgA, Th1, Th2	Fc-RBD, poly I:C	Ma et al. 2014a
Mannose	Nasal/mice	OVA	IgG, IgA	Liposome	Ishii et al. 2010
		HPIV-HN	IgG, IgA	Liposome, poly I:C	Senchi et al. 2013
IgG	Nasal/mice	HBsAg	IgG, IgA, Th1	IgG-liposome	Tiwari et al. 2011a
Transferrin	Nasal/mice	HIV-1 gp140	IgG, IgA	Tf-gp140	Mann et al. 2012
Claudin-4	Nasal/mice	OVA	IgG, IgA, Th1, Th2	OVA-ligands	Nagase et al. 2013

*: MPs: microparticles; NPs: nanoparticles; MSs: Microspheres; NSs: Nanospheres.