Pre-Conference Workshop Discussions

Monday, April 25, 2022

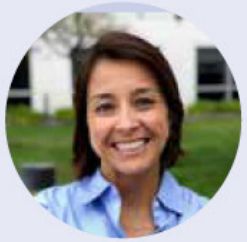
2nd Annual
Chronic HBV Drug Development
From Late Translational to Phase II Clinical Progress

April 25-27, 2022
Boston, MA

Workshop A

8.00AM-11.00AM

Establishing Early Clinical Collaboration to Explore Combination Strategies for Functional Cure for Chronic Hepatitis B



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Chief Scientific Officer
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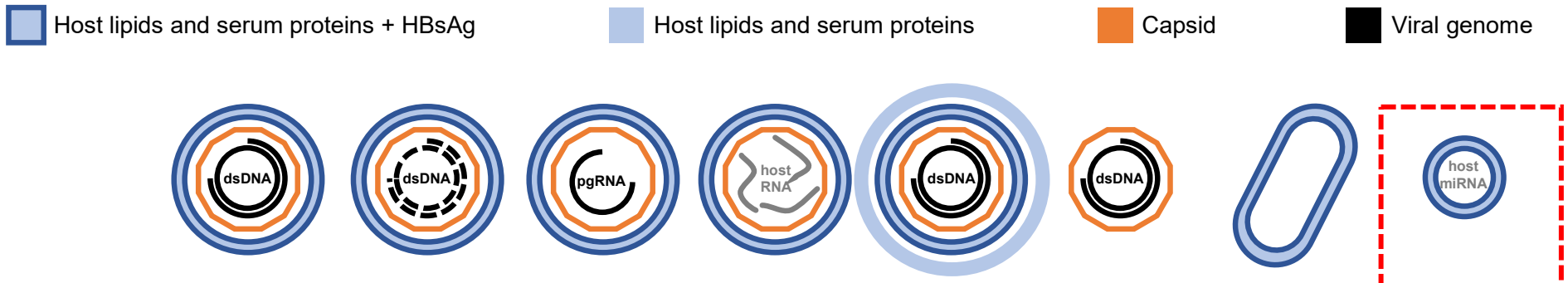
Targeting Hepatitis B surface antigen in combination regimens to achieve functional cure

Particle production in chronic HBV infection



Particle	Dane particle	Quasispecies (mutation)	HBV RNA virion	"Empty" virions	Exosome	"Naked" capsid	SVP (filamentous)	SVP (spherical)
Ratio to Dane particle	1	0.2-0.8	0.001-1	100	unknown	unknown	10	10,000 – 100,000
Size (nM)	44				50-150	27	Ø22	22

99.99% of HBsAg Is derived from subviral particles (SVP)

Active cccDNA

? Integrated HBV DNA

Vaillant, ACS Inf Dis 2021; 7: 1351-1368

Production of SVP drives chronicity of HBV infection

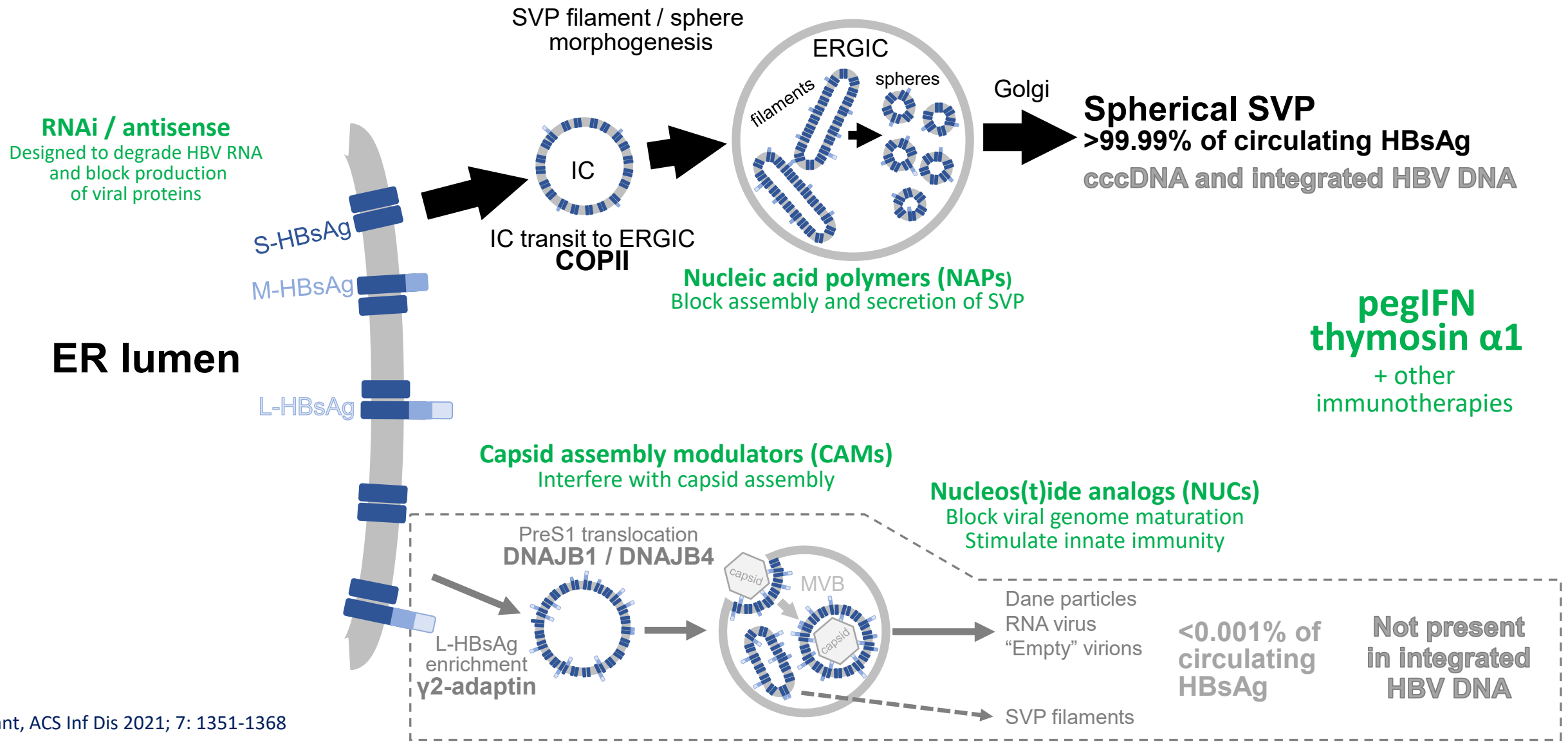
Immunoinhibitory properties of SVP

Immune function	Target of inhibition	Effect observed
Innate HBsAg blocks inactivation of cccDNA	TLR function	*In vitro, in vivo*
	Cytokine signalling	*In vitro*, in humans
	Monocyte and macrophage function	*In vitro*
	Dendritic cell function	*In vitro*
	NK cell function	*In vitro, in vivo,* in humans
Adaptive HBsAg inhibits clearance of integrated HBV DNA	Sequester anti-HBs	*In vitro*
	HBV specific B-cell function	In humans
	HBV specific CD4+ T-cell function	In humans
	HBV specific T-cell tolerance	*In vitro, in vivo*
	HBV specific T-cell exhaustion	*In vivo*, in humans

SVP must be cleared for immunotherapy to achieve its full potential

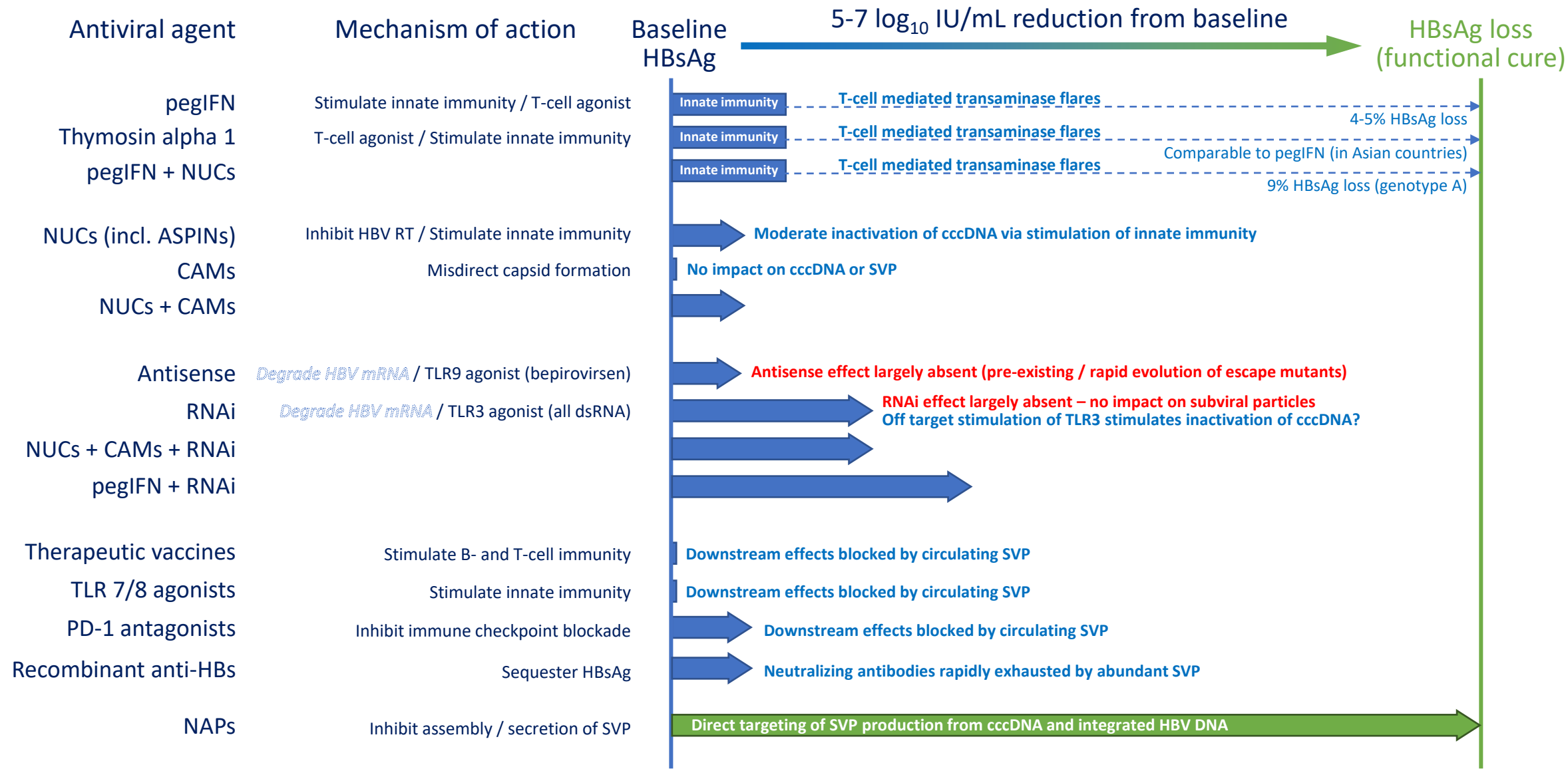
Vaillant, ACS Inf Dis 2021; 7: 1351-1368

Impact of investigational approaches on HBsAg



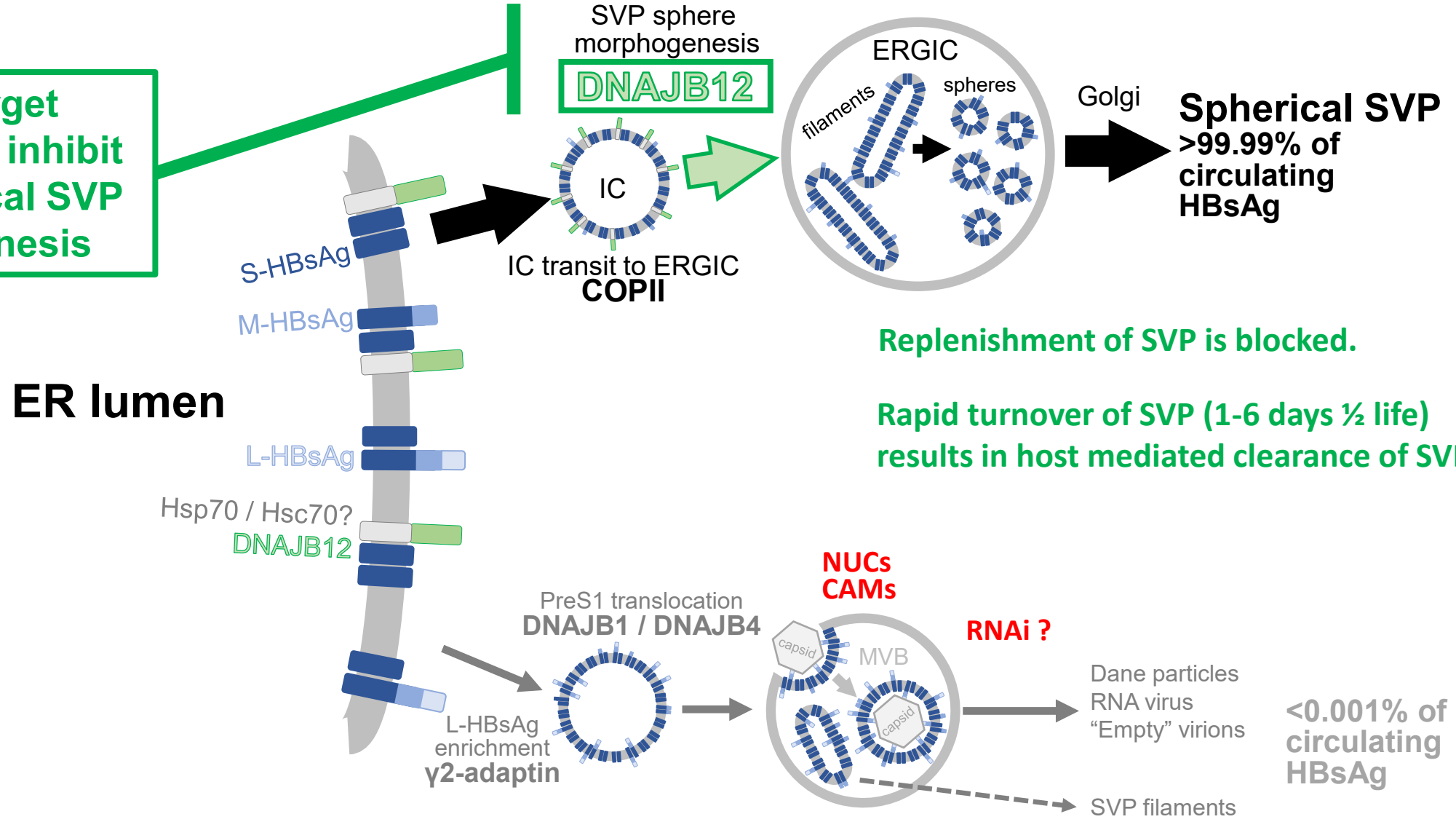
Vaillant, ACS Inf Dis 2021; 7: 1351-1368

HBsAg loss – a critical milestone for functional cure of HBV

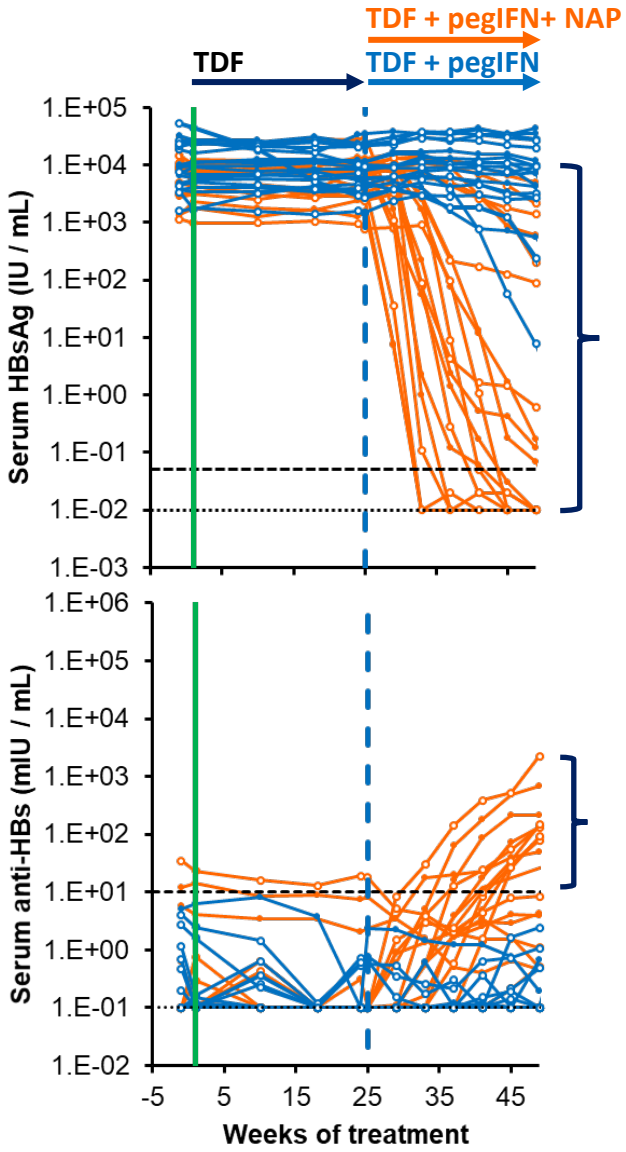


Why do NAPs allow clearance of SVP?

NAPs target DNAJB12 to inhibit HBV spherical SVP morphogenesis



REP 401 study:
NAPs dramatically improve response to TDF + pegIFN



Up to 8 $\log_{10}$ decline from baseline (to < 0.005 IU/mL)
Potent HBsAg decline

Rapid HBsAg seroconversion

NAP monotherapy:
REP 2055 = REP 2139
Up to 7 $\log_{10}$ HBsAg reduction at 12 weeks
HBsAg seroconversion
Low rates of HBV functional cure

NAPs + TDF + pegIFN
HBsAg < 0.005 IU/mL (60%)
HBsAg seroconversion
Inactivation of cccDNA
Host mediated transaminase flares (95%)
High rates of HBV functional cure (39%)
No further therapy required in 78% of patients

GT D functional cure rate
TDF + pegIFN = 0%
(Marcellin et al, Gastroenterology 2016; 150: 134-144)
NAPs + TDF + pegIFN = 39%

Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Al-Mahtab et al., PLoS One; 2016; 11: e0156667

REP 401 study:
Outcomes after removal of all therapy

Completed treatment and 24-48 weeks of follow-up		36
Clinical response	Normal ALT	89%
	Normal liver median stiffness	56%
HBsAg response	< 1000 IU/mL	72%
	< 1 IU/ml	50%
	≤ LLOQ (0.05 IU/mL)	42%
	Seroconversion	53%
HBV DNA response	≤ 2000 IU/mL	78%
	Target not detected (TND)	47%
Virologic response	Partial cure (Inactive HBV) (HBV DNA ≤ 2000 IU/mL, normal ALT)	39%
	Functional cure (HBsAg < LLOQ, HBV DNA TND, normal ALT)	39%
	Clinical benefit, no therapy required (low risk of progression, reduced risk of HCC)	**78%**

→ **Reversal of liver inflammation / fibrosis**

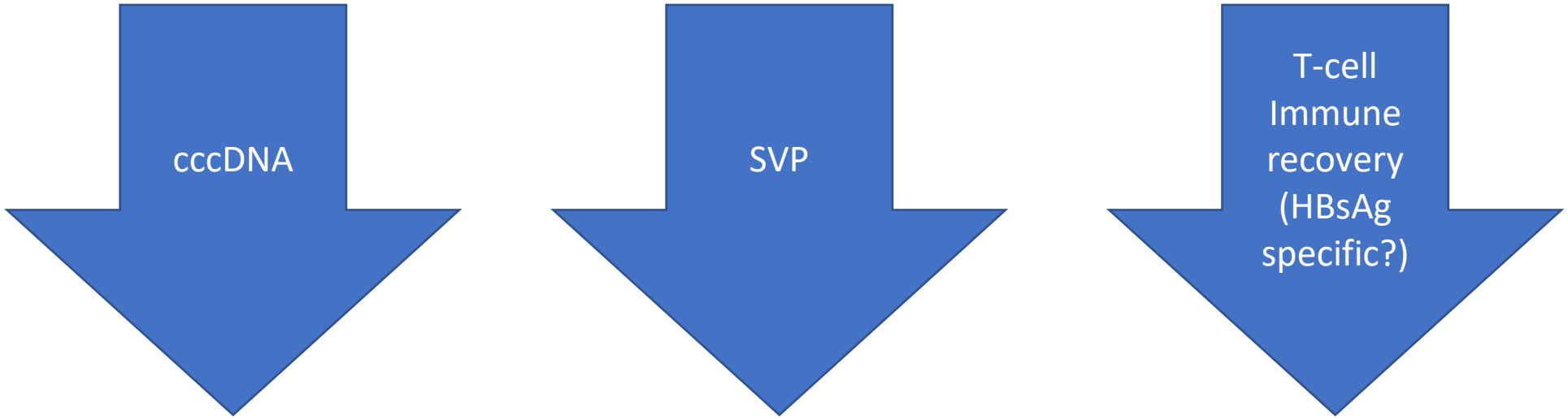
All with:
- **HBsAg < 0.005 IU/mL (ARCHITECT® NEXT)**
- **No HBsAg immunocomplexes**
- **HBV RNA target not detected**
- **HBcrAg < LLOQ**

Efficient silencing of cccDNA
Removal of integrated HBV DNA

Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Bazinet et al., Hepatol Comm 2021, 5: 1873-1887

Combination therapy in the context of HBsAg loss

Optimizing regimens for functional cure



NUCs (ASPINs) (inactivation)
Novel CAMs?
TLR agonists (inactivation)
HBV RNA destabilizers?
Other agents?

NAPs
Novel agents?

pegIFN / thymosin α1
Therapeutic vaccines?
CAR / TCR T-cell therapy?
PD-1 agonists?