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CAM Working Group Update

HBV Forum 8

London UK

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Harry L. A. Janssen MD PHD

Professor of Hepatology

Erasmus University, Rotterdam, Netherlands

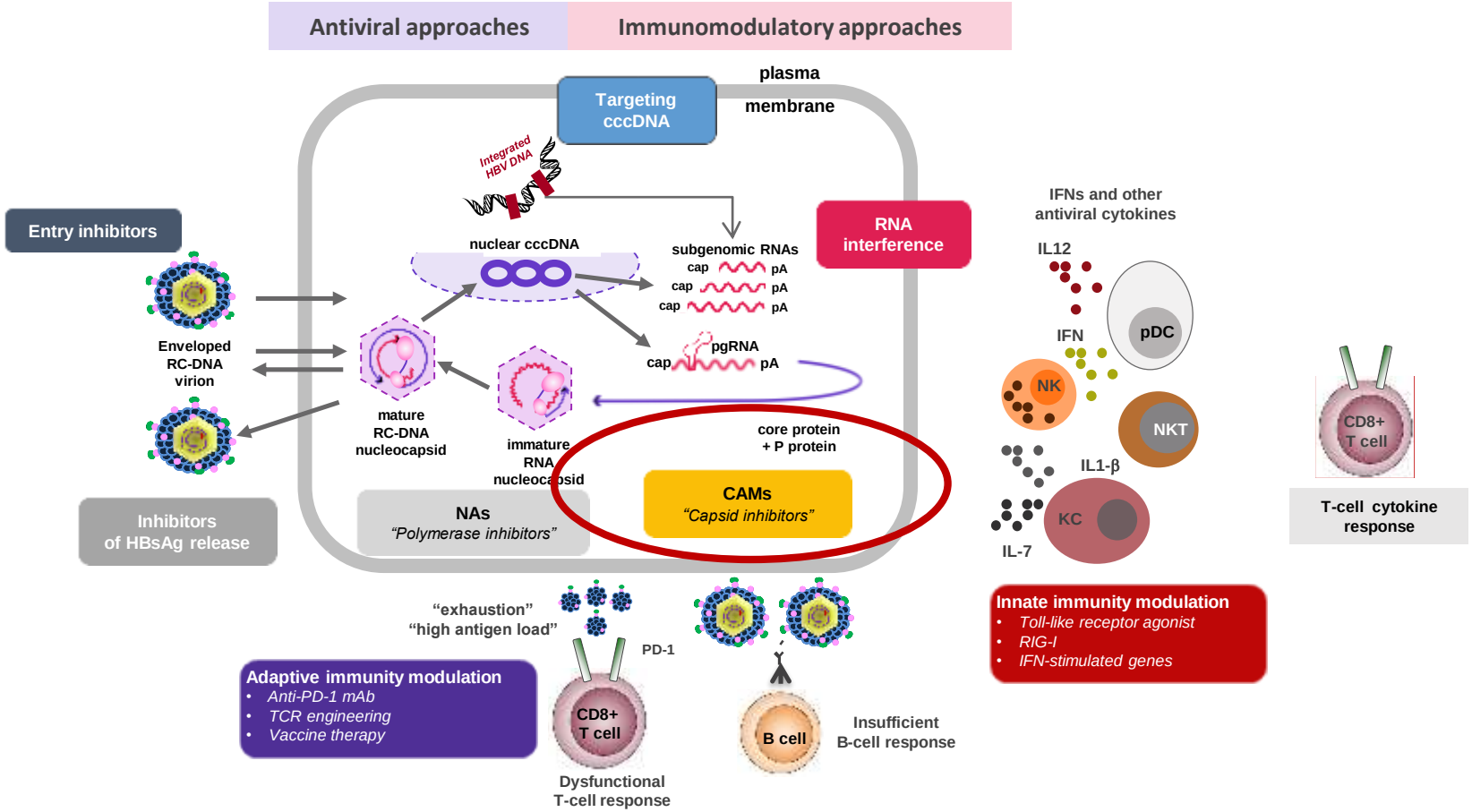
Toronto General Hospital, Toronto, Canada

Berkeley Public Health

Background

- Different nomenclature in use for drugs interfering with nucleocapsid assembly and disassembly processes
  - CAMs (Capsid Assembly Modulators)
  - CpAMS (Core Protein Allosteric Modulators)
  - Core Inhibitors
  - Different/inconsistent sub-classification
- Confusion!
  - Different names used by industrial partners
  - Clear and agreed-upon nomenclature needed

HBV replication cycle



Background

Capsid Assembly Modulators, CAMs, are small molecules that have two well-established mechanisms of action against HBV:

- Stimulate HBc assembly to decrease formation of RNA-filled capsids, resulting in loss of new virus
- CAMs can bind mature HBV cores and prevent them from properly uncoating, preventing new infection analogous to an entry inhibitor

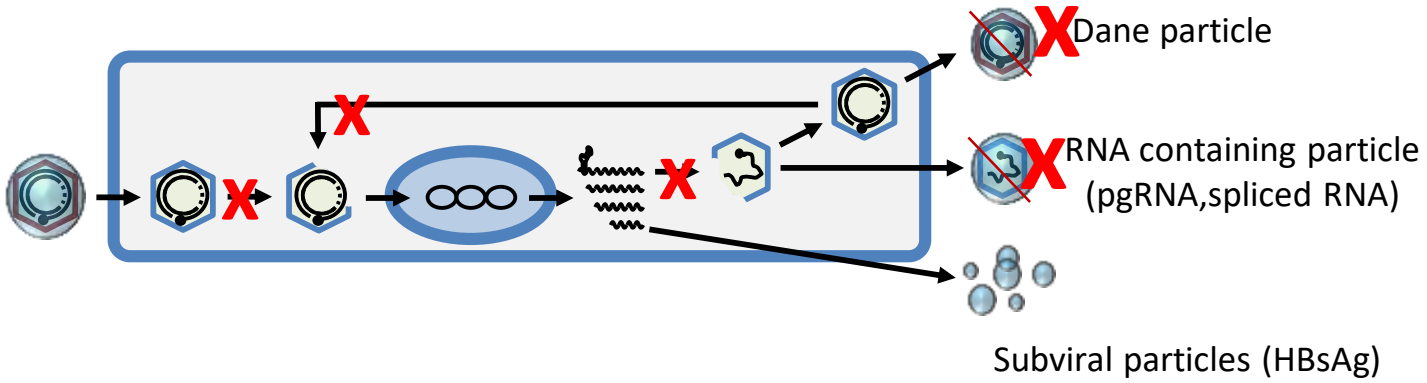
By decreasing formation of new virus and decreasing new infections by disrupting DNA release, CAMs by themselves or in combination therapy offer two routes to suppress HBV infection and may contribute to an HBV cure

Background

- Capsid assembly modulators disrupt the HBV lifecycle by destabilizing the nucleocapsid and/or by blocking RNA packaging.

- Reduce HBV genome replication and viral assembly, leading to HBVDNA and HBVRNA decline **and** hopefully blockage of cccDNA replenishment and hepatic reinfection cycles?

- -Forms aberrant non-capsid polymers (impair capsid assembly) Class 1 or A
- -Forms empty capsids devoid of pg RNA/rcDNA (block encapsidation) Class 2 or E
- The next generation CAMs have in vitro antiviral potency 2-3 logs greater than other CAMs.



Background

- Once daily oral regimen: easy to use
- Monotherapy: HBVDNA and HBVRNA decline ± 3 logs in 4 wk
- In combination with NA: HBV DNA decline 6 logs at 48 wks
- No or modest HBsAg or HBeAg decline thus far.
- HBVRNA decline suggests decreased cccDNA activity: will longer therapy really lower cccDNA pool and HBsAg?
- Risk for initial non-response and resistance
- Many CAMs are in preclinical or clinical development
- Side effects: thus far limited. Most frequently rash (self limited) and ALT flares

Current CAMS under Investigation

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Product Name	Company	Phase	Trial ID	N	Trial Status	Product Name
ABI-H3733	Assembly Bio	Phase 1	NCT04271592	120	Completed	ABI-H3733
Vebicorvir (ABI-H0731)	Assembly Bio	Phase 2a (Triple Combination)	NCT04820686 (Verbicorvir + NA + siRNA (Arbutus)	60	Recruiting	Vebicorvir (ABI-H0731)
Vebicorvir (ABI-H0731)	Assembly Bio	Phase 2a (Triple Combination)	NCT04781647 (Verbicorvir + ETV + PEG-IFN)	60	Recruiting	Vebicorvir (ABI-H0731)
AB-836	Arbutus	Phase 1a/2a	NCT04775797	60	Recruiting	AB-836
bersacapavir (JNJ-6379)	Janssen	Phase2b (Combination)	NCT04129554	130	Recruiting	JNJ-6379
bersacapavir (JNJ-6379)	Janssen	Phase2a (Combination)	NCT04667104 (PENGUIN)	50	Recruiting	JNJ-6379
bersacapavir (JNJ-6379)	Janssen	Phase 2b (Combination)	NCT03982186 (REEF-1)	471	Active, not recruiting	JNJ-6379
VNRX-9945	Venatorx	Phase 1	NCT04845321	80	Recruiting	VNRX-9945
EDP-514	Enanta	Phase 1b	NCT04008004(NUC-suppressed)	98	Completed	EDP-514
EDP-514	Enanta	Phase 1b	NCT04470388 (Viremic)	24	Completed	EDP-514
ALG-000184	Aligos	Phase 1	NCT04536337	156	Recruiting	ALG-000184
ZM-H1505R	ZhiMeng Bio	Phase 1	NCT04220801	64	Completed	ZM-H1505R
Morphothiadine (GLS4)	HEC Pharm	Phase 2b (Combination)	NCT04147208 (GLS4 + Ritonavir + Entecavir)	250	Recruiting	Morphothiadine (GLS4)
RG-7907	Roche	Phase 2 (Combination)	NCT04225715	210	Recruiting	RG-7907
HRS5091	Hengrui, CN	Phase 1	NCT04480294	98	Not yet recruiting	HRS5091
GST-HG141	Fujian Cosunter, CN	Phase 1	NCT04868981	30	Not yet recruiting	GST-HG141

Combo Vebicorvir plus NA in HBeAg positive CHB

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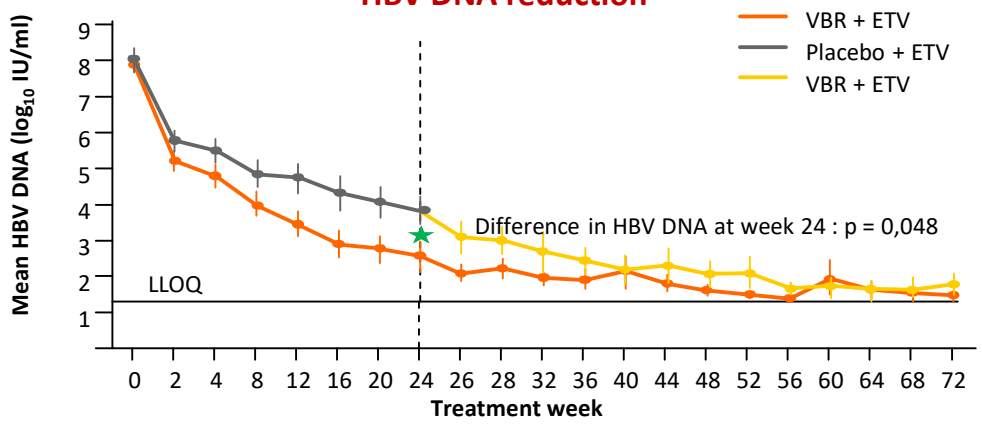
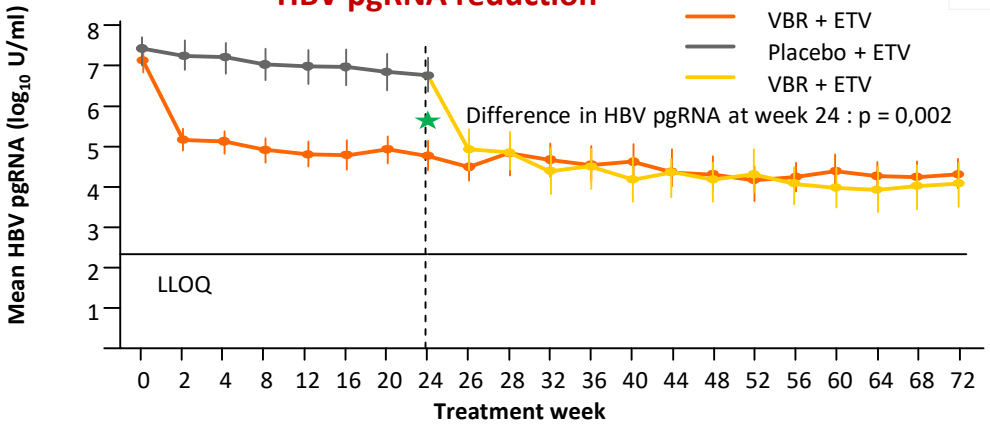
Treatment-naive patients

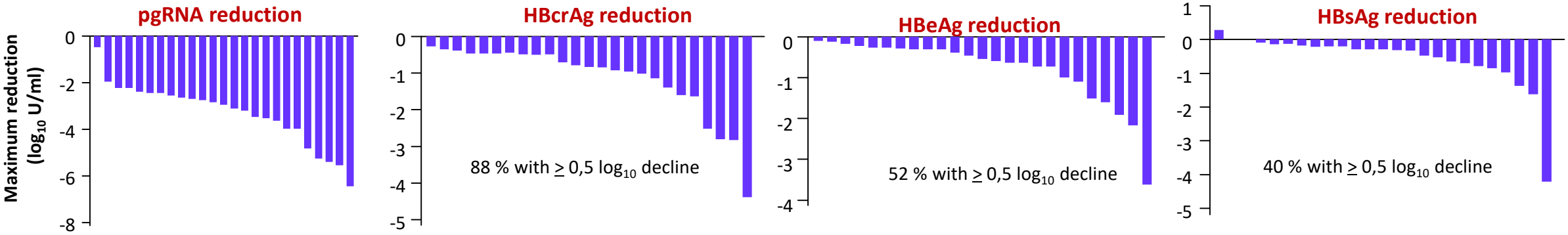
HBV DNA reduction



HBV pgRNA reduction



Change from baseline for individual patients

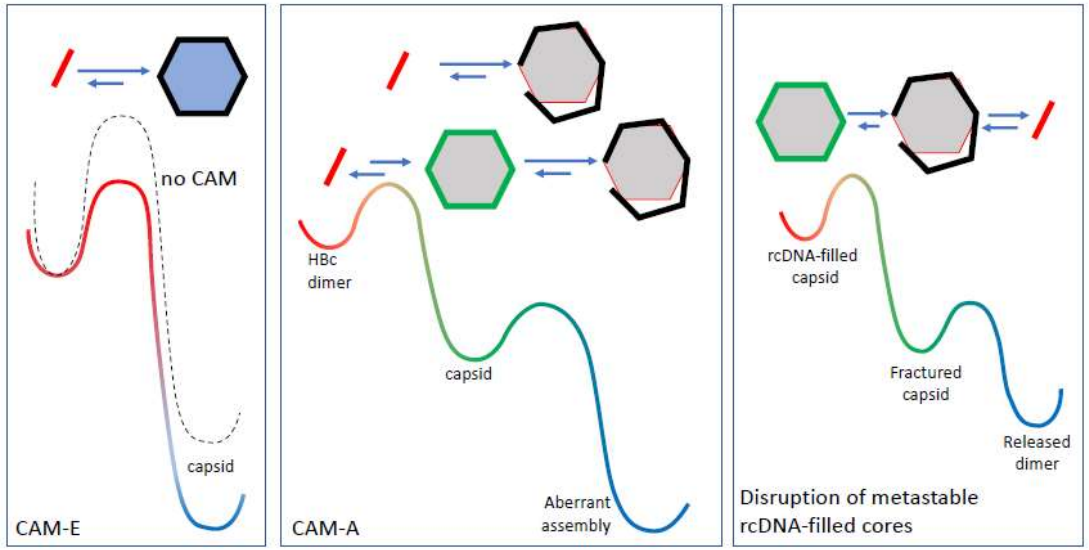


No sustainable response off-treatment

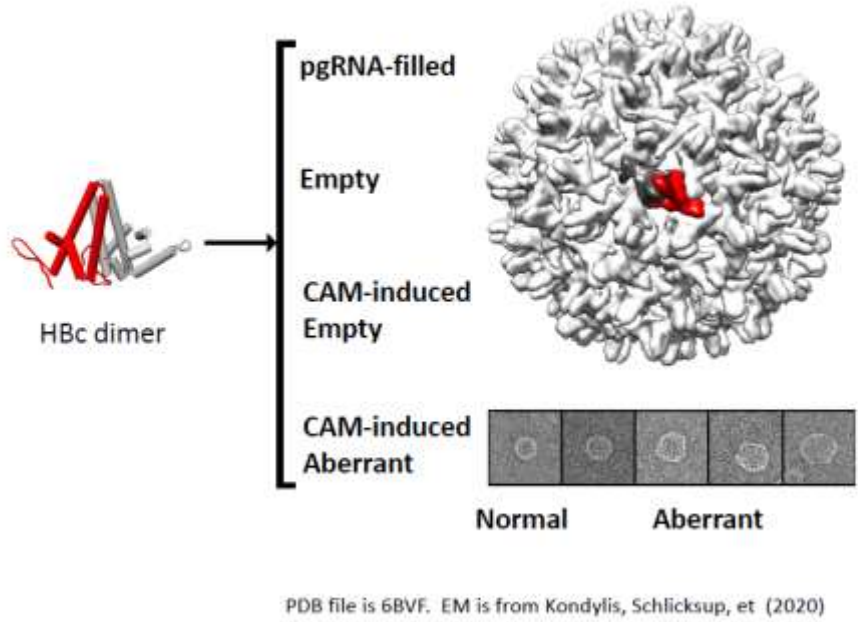
Yuen MF et al. EASL 2020, Abs. LP30

Figure 1: mode of action of CAMs supporting the proposed nomenclature

Panel A



Panel B



PDB file is 6BVF. EM is from Kondylis, Schlicksup, et (2020)

Adam Zlotnick

CAM Working Group
HBV Forum & ICE-HBV

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- Establish naming convention – appropriate categorization
  - Reduce confusion
  - Provide clarity & precision
  - Accommodate mechanism of action

CAM Working Group
HBV Forum & ICE-HBV

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- Co-chairs:
  - Fabien Zoulim, Harry Janssen
- Core writing group:
  - + **Adam Zlotnick**, Veronica Miller

Nomenclature of HBV Core Protein Targeting Antivirals

Author List

Fabien Zoulim (INSERM), Adam Zlotnick (Indiana University), Stephanie Buchholz (Federal Institute for Drugs and Medical Devices, BfArM), Eric Donaldson (US FDA), John Fry (Aligos), Anuj Gaggar (formerly at Gilead), Jianming Hu (Penn State University), Michael Kann (University of Gothenburg), Oliver Lenz (Janssen), Kai Lin (Atea), Nagraj Mani (Arbutus), Michael Nassal (University of Freiburg), William Delaney (Assembly Biosciences), Su Wang (Center for Asian Health, Saint Baranabas Medical Center), Gabriel Westman (Swedish Medical Products Agency), Veronica Miller (University of California, Berkeley), Harry Janssen (Erasmus Medical Center)

Process

- Invite experts to participate
  - Scientists from all companies developing CAMs
  - Academics with expertise in molecular biochemistry and clinical research
  - Regulators from US and EU
  - Patient representative

Process - 2

- Review of literature and scientific discussion
- Two voting procedures
  - Most appropriate nomenclature
  - Scientific rationale
- Considerations
  - Similarities with MOA and nomenclature in other viral diseases
  - Current state of science
  - Potential for future therapies
    - Need to be flexible

Consider the audience

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- Clinicians
- Researchers
- Policy makers
- HBV-affected community

Easy to understand and remember, but also scientifically sound

Simple, but not oversimplified

Consensus questions (2nd round)

- What should the overarching class of molecules be named?
  - Core Protein Targeting Antivirals
  - Capsid Targeting Antivirals
  - Other
- What should the class of molecules be named?
  - Capsid Assembly Modulators (CAMs)
  - Capsid Protein Allosteric Modulators (CpAMs)
  - Core Inhibitors
  - Other
- Do we have sufficient data to sub-categorize?
  - Class I-Class II; CAM E-CAM A; CAM A-CAM N

Consensus

- Overarching Class: Core Protein Targeting Antivirals
- CAM: Capsid Assembly Modulators
- Sub-classification: More data needed
  - Interim recommendation
    - CAM-A (aberrant)
    - CAM-E (empty)

Discussion

- HBV Forum and ICE-HBV recommendations meant to facilitate efficiency and clarity in HBV drug development
  - Standardized nomenclature reflecting the science on which drug development is based
- Recommendations based on Working Group review of available data
  - To be updated when more information becomes available

Publication status

- Invitation to submit to Nature Review Gastro/Hep
- Comments on draft manuscript received from all Working Group members
- Writing group finalizing revisions
- Submit June 2022

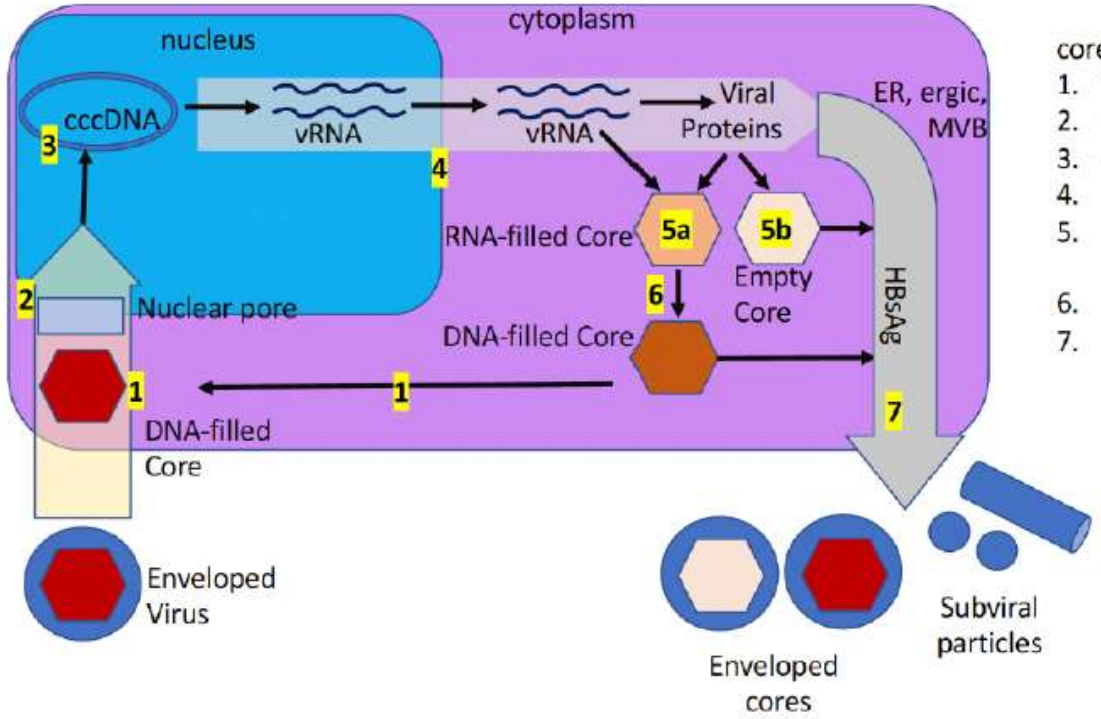
Special thanks

- Adam Zlotnick
  - Extensive biochemical background and figure

- Jessica Weber, Emily Gainor, Chelsey Campillo
  - Manuscript development support

Thank You!

Supplementary figure 1: the role of core protein in the HBV life cycle



core protein and core mediated activity:

1. Transport to nucleus
2. Core dissociation, uncoating DNA
3. cccDNA
4. RNA export
5. a. nucleation by RNA+polymerase
   b. Spontaneous nucleation
6. Reverse transcription
7. Binding surface antigen

Adam Zlotnick