Effective Inhibition of cccDNA derived mRNA/Viral Antigens and Tolerability with ARC-520

25th APASL Conference, 2016

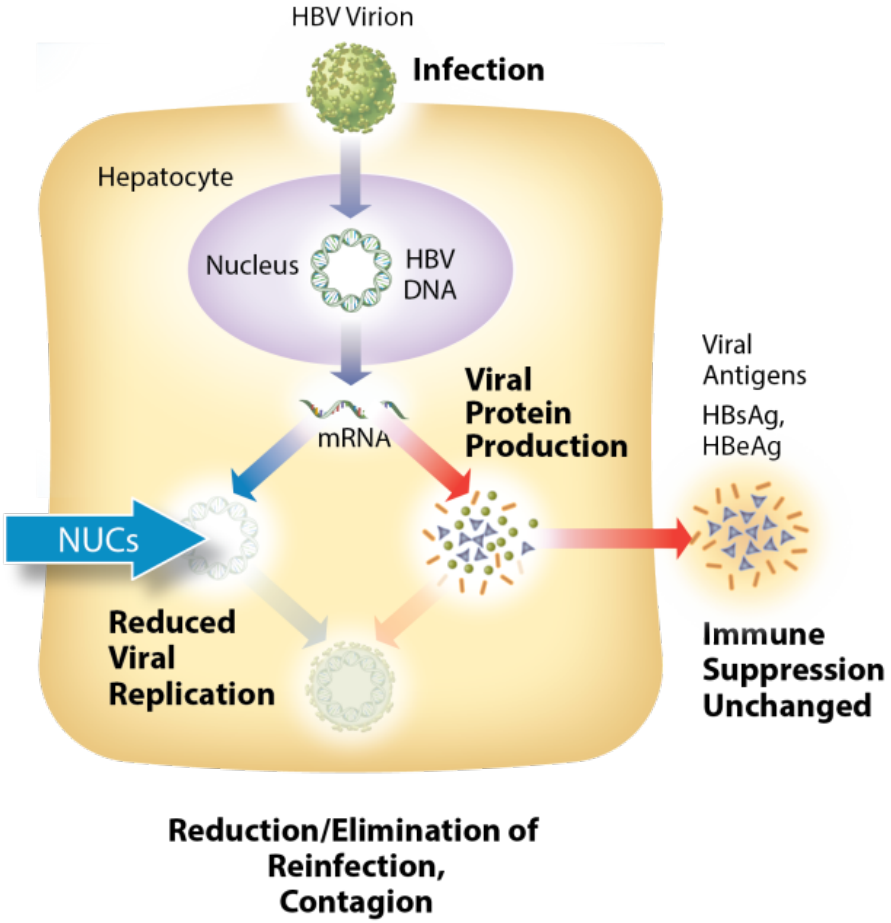
Man-Fung Yuen, MD, PhD

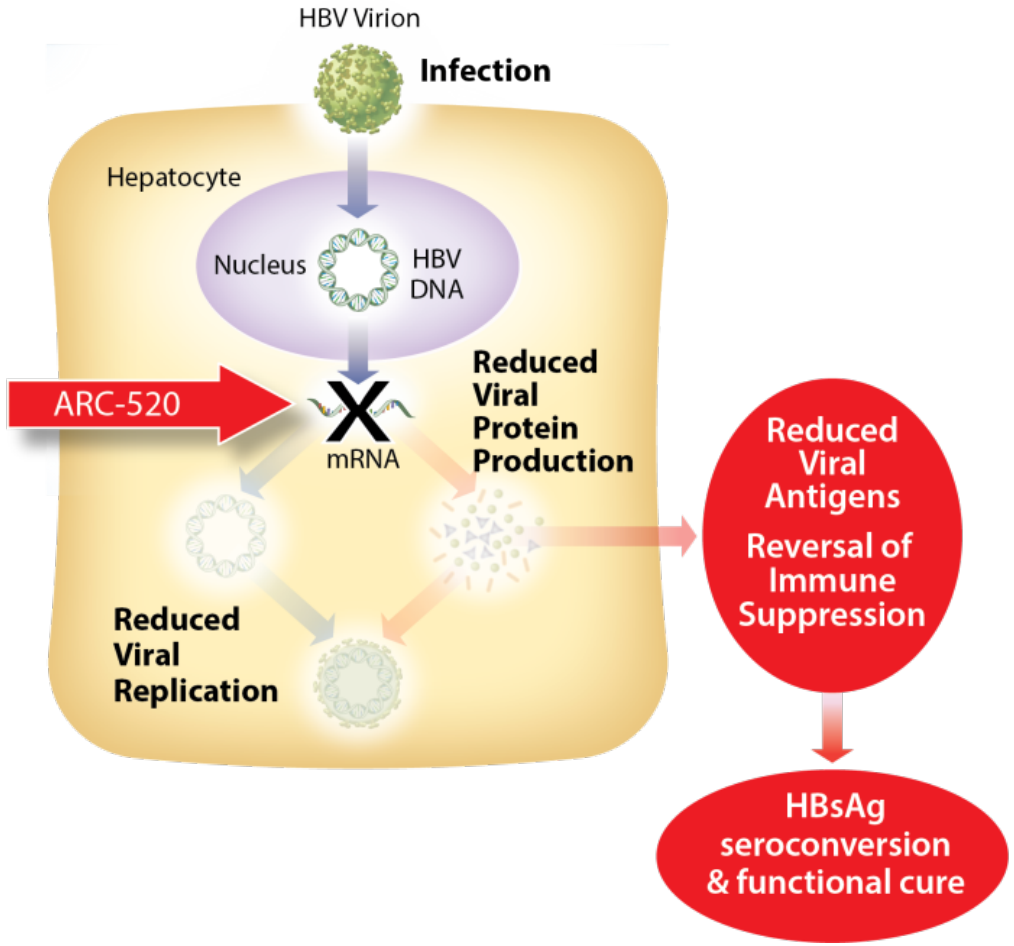
The University of Hong Kong

On behalf of the Heparc-1001 and Heparc-2001 Investigators

Henry Lik Yuen Chan, Kevin Liu, Bruce D. Given, Thomas Schluep, James Hamilton, Ching-Lung Lai, Stephen A. Locarnini, Johnson YN Lau, Carlo Ferrari, Robert G. Gish

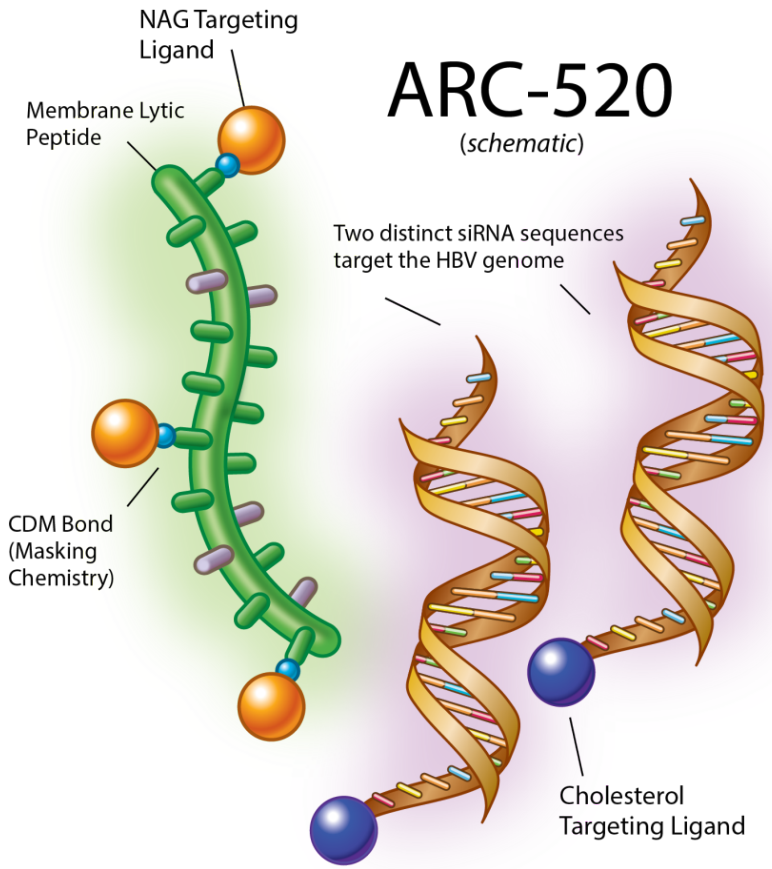
Mechanistic comparison of RNAi therapeutics vs. reverse transcriptase inhibitors (NUCs)





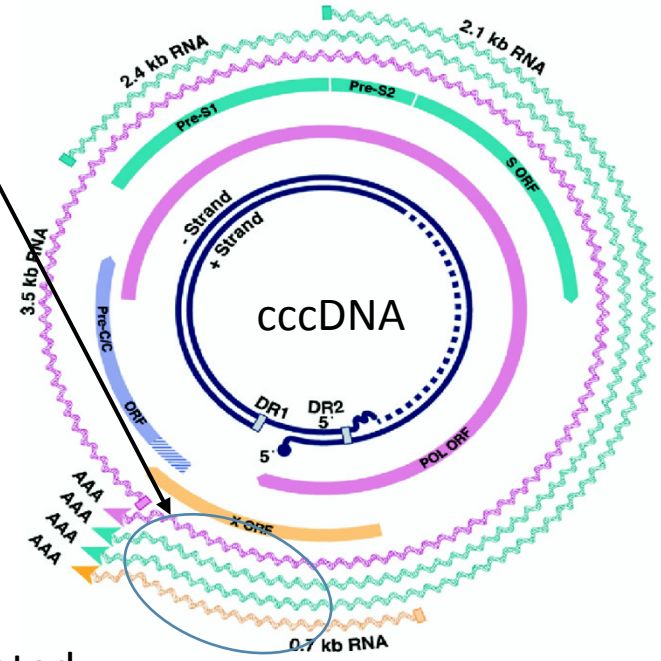
RNA interference therapeutic ARC-520 for chronic HBV infection

Designed to reduce all transcripts from HBV cccDNA



- **ARC-520 Excipient**
  - Hepatocyte-targeted DynamicPolyConjugate™ peptide (NAG-MLP) to enhance siRNA delivery
- **ARC-520 API**
  - Mixture of 2 cholesterol-conjugated siRNAs in solution
  - Inclusion of two siRNAs gives broader genotype coverage (>99%)

HBV Transcript Map



Study Design

- Heparc-1001: Placebo controlled, single dose escalation study in healthy volunteers
  - Primary Objectives: Safety, tolerability and pharmacokinetics
  - 54 subjects randomized (36 IV ARC-520 / 18 IV PBO)
  - 9 dose levels between 0.01 to 4.0 mg/kg
  - Subjects in cohorts 7-9 were pretreated with oral antihistamine
- Heparc-2001: Phase II study in patients with chronic hepatitis B
  - Primary Objective: Depth and duration of HBsAg reduction in response to a single dose or two doses (cohort 6) of ARC-520 in combination with entecavir.
  - Adult patients with HBeAg negative or positive chronic HBV, ALT/AST < 100 IU/mL and Fibroscan ≤ 8 at screening
  - 58 patients have been successfully dosed with 48 receiving drug and 10 receiving placebo.
  - 4 dose levels between 1.0 and 4.0 mg/kg ARC-520
  - All patients pretreated with oral antihistamine

ARC-520 cumulative exposure

Dose (mg/kg)	0.01	0.1	0.3	0.6	1.0	1.2	2	3	4
# Subjects Receiving Single Dose	4	4	4	4	6	4	14	10	34*
# reported Treatment Emergent Adverse Events	1	9	12	3	1	6	13	2	8

* Includes Heparc-2001 cohort 6: 2 mg/kg q2wk x 2 doses

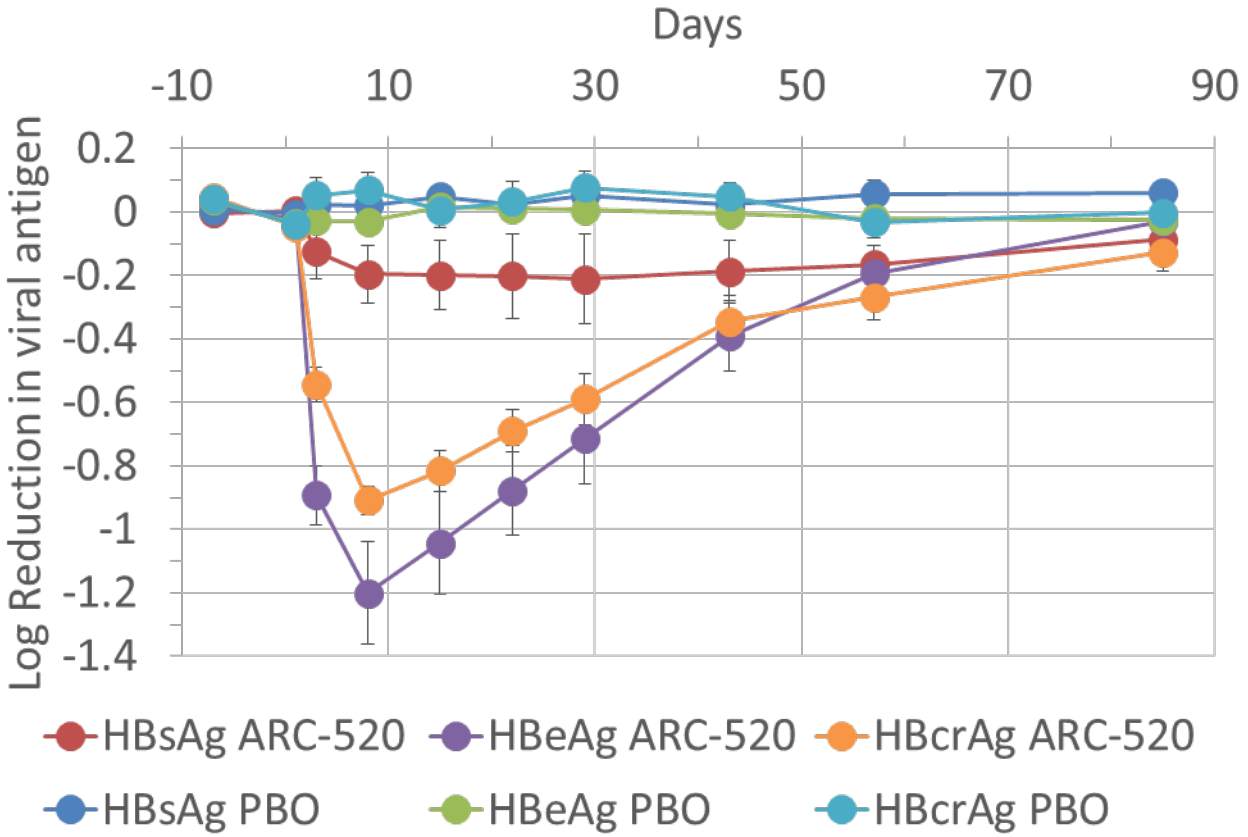
- Total exposure: 84 subjects
- No AEs rated as serious or severe
- No discontinuations due to AEs
- Modest, random occurrence of abnormal laboratory results
- No laboratory signs of end organ toxicity

Treatment related AEs in > 1 subject in Heparc-1001 and Heparc-2001

	PBO n=28	0.01 mg/kg n=4	0.1 mg/kg n=4	0.3 mg/kg n=4	0.6 mg/kg n=4	1.2 mg/kg n=4	2.0 mg/kg n=4	1.0 mg/kg +DPH n=6	2.0 mg/kg +DPH n=10	3.0 mg/kg +DPH n=10	4.0 * mg/kg +DPH n=34
Adverse Event	Number of subjects with AEs related to study drug (n>1)										
Dizziness							2				
Headache	3		1			1					
Creatinine increase	1										2

- 67% of healthy volunteers and 14% of CHB patients reported at least one mild or moderate AE
- Two healthy volunteers reported a moderate hypersensitivity reaction (urticarial rash, flushing) during infusion at 0.3 and 2 mg/kg
- After pretreatment with oral antihistamine (diphenhydramine or chlorpheniramine), no hypersensitivity reactions were seen in CHB patients or healthy volunteers

Deep and sustained reduction of viral antigens in ETV experienced, HBeAg-positive CHB patients



- Single 4 mg/kg IV dose

HBeAg reduction:

- Max = 1.7 log
- Mean max. = 1.2 log

HBcrAg reduction:

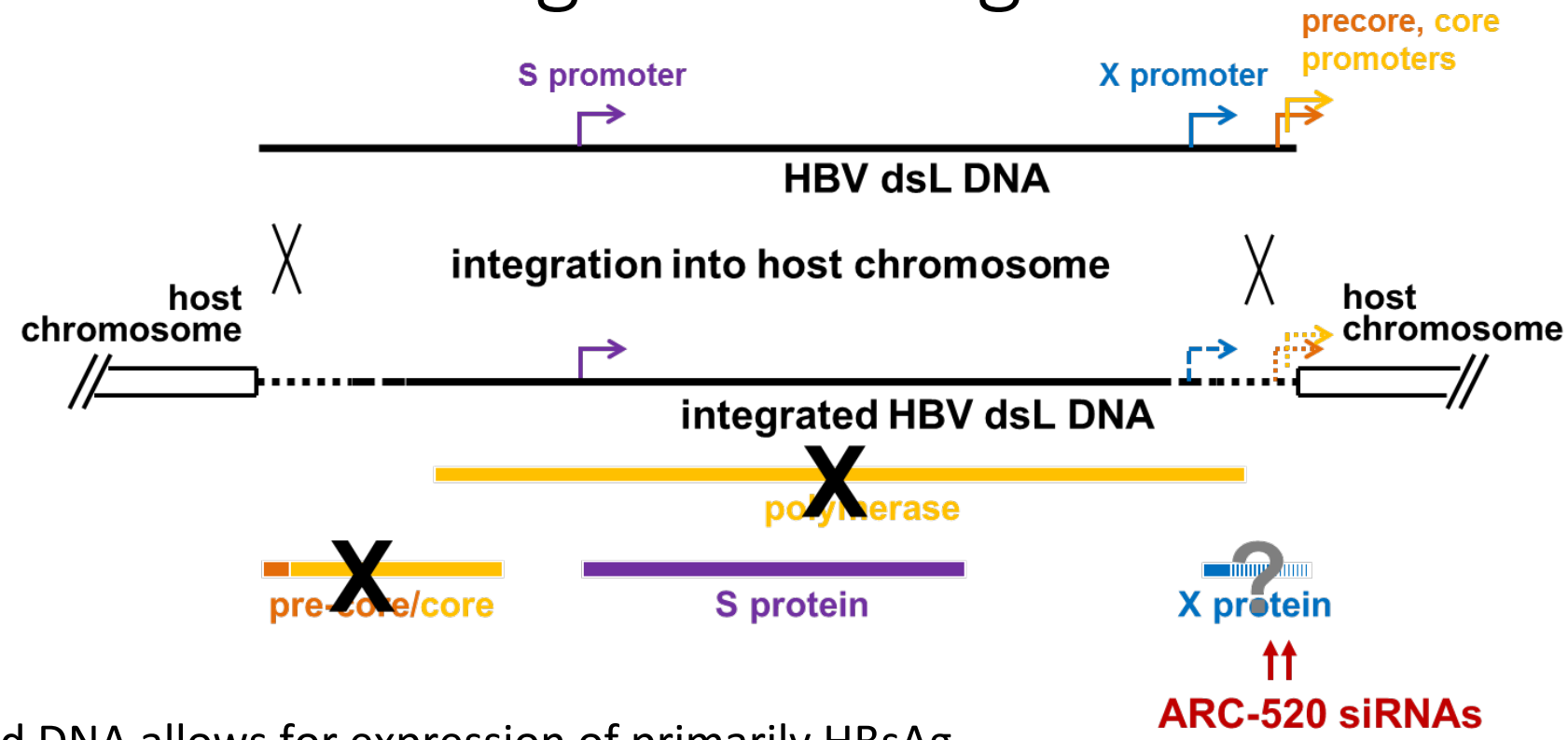
- Max = 1.1 log
- Mean max = 0.9 log

HBsAg reduction:

- Max = 0.7 log
- Mean max = 0.3 log

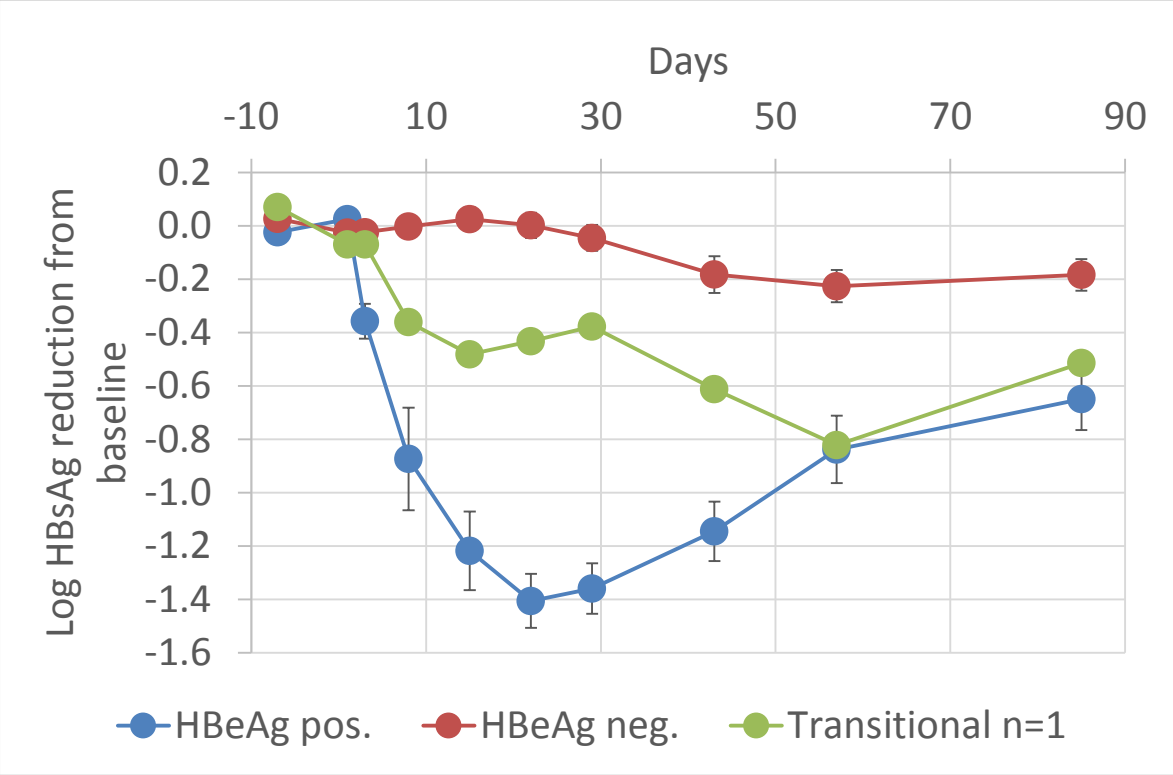
- Substantially higher reduction in HBeAg and HBcrAg compared to HBsAg

Process of HBV dsL DNA integration and theoretical production of HBsAg from integrated DNA



- Integrated DNA allows for expression of primarily HBsAg
  - Expression of truncated X protein also possible
- Explains persistent HBsAg expression despite low cccDNA in HBeAg- chimps [AASLD Abstract: Wooddell et al. (2015) Hepatology 62, 1 (Suppl), 32]
- Loss of ARC-520 target sites explains lower HBsAg KD in HBeAg- chimps and NUC experienced patients

HBsAg reduction in treatment naïve CHB patients



- Single 4 mg/kg IV dose

<u>HBsAg reduction in HBeAg-pos</u>:

- Max = 1.8 log
- Mean max = 1.5 log

<u>HBsAg reduction in HBeAg-neg</u>:

- Max = 0.5 log
- Mean max = 0.3 log

Transitional patient was HBeAg-pos. at baseline and HBeAg negative at days 3 to 43

- Variations in viral antigen reduction are consistent with lower levels of cccDNA derived mRNA transcripts in chronic ETV patients and HBeAg-neg

Summary

- ARC-520 effectively reduced viral antigens derived from cccDNA by up to 1.8 logs (98%)
- ARC-520 was well tolerated
- Direct antiviral effect lasted up to 57 days after a single dose, delayed response duration >57 days
- Findings consistent with higher cccDNA-driven antigen production in naïve HBeAg-pos. CHB
- Chronic ARC-520 studies aimed at producing HBsAg seroclearance are underway

Acknowledgments

- The University of Hong Kong, Queen Mary Hospital
  - Kevin Liu
  - Wai Kay Seto
  - Lung Yi Mak
  - Kwan Lung Ko
  - Wai Pan To
  - Ka Ho Wong
  - Ringo Wu
  - John Yuen
  - Charles Cheng
  - Lily Wang
- The Chinese University of Hong Kong, Prince of Wales Hospital
  - Henry LY Chan
  - Vincent WS Wong
  - Grace LH Wong
- Nucleus Network, Melbourne
  - Jason Lickliter
- Advisors
  - Robert G. Gish
  - Stephen Locarnini
  - Ching-Lung Lai
  - Johnson YN Lau
  - Carlo Ferrari
- Arrowhead Research Corp
  - Christine I. Wooddell
  - David L. Lewis
  - Ryan M. Peterson
  - Zhao Xu
  - James Hamilton
  - Thomas Schluep
  - Diamond Martin
  - Bruce D. Given