Arrowhead Research
CORPORATION

Arrowhead Analyst and Investor Day
September 24, 2015

Welcome Remarks

Vince Anzalone, CFA - Vice President, IR

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Panelists

- Robert Gish, M.D. – Consultant Professor, Stanford Hospital and Medical Center
- Robert Lanford, Ph.D. – Director, Southwest National Primate Research Center
- Stephen Locarnini, M.D., Ph.D. – Head of Research and Molecular Development, Victorian Infectious Diseases Reference Laboratory
- Chris Anzalone, Ph.D. – President and CEO
- David Lewis, Ph.D. – Chief scientific officer
- Bruce Given, M.D. – Chief operating officer

Agenda

- Introducion – Dr. Chris Anzalone
- Current consensus on HBV - Dr. Robert Gish
- Treatment of chronically infected chimpanzees with ARC-520 – Dr. Robert Lanford
- Key chimpanzee study data and learnings – Dr. David Lewis
- Heparc-2001, exploring new territory – Dr. Bruce Given
- How might we think about HBV now – Dr. Stephen Locarnini
- Closing remarks – Dr. Chris Anzalone
- Q & A – Panel

Introduction

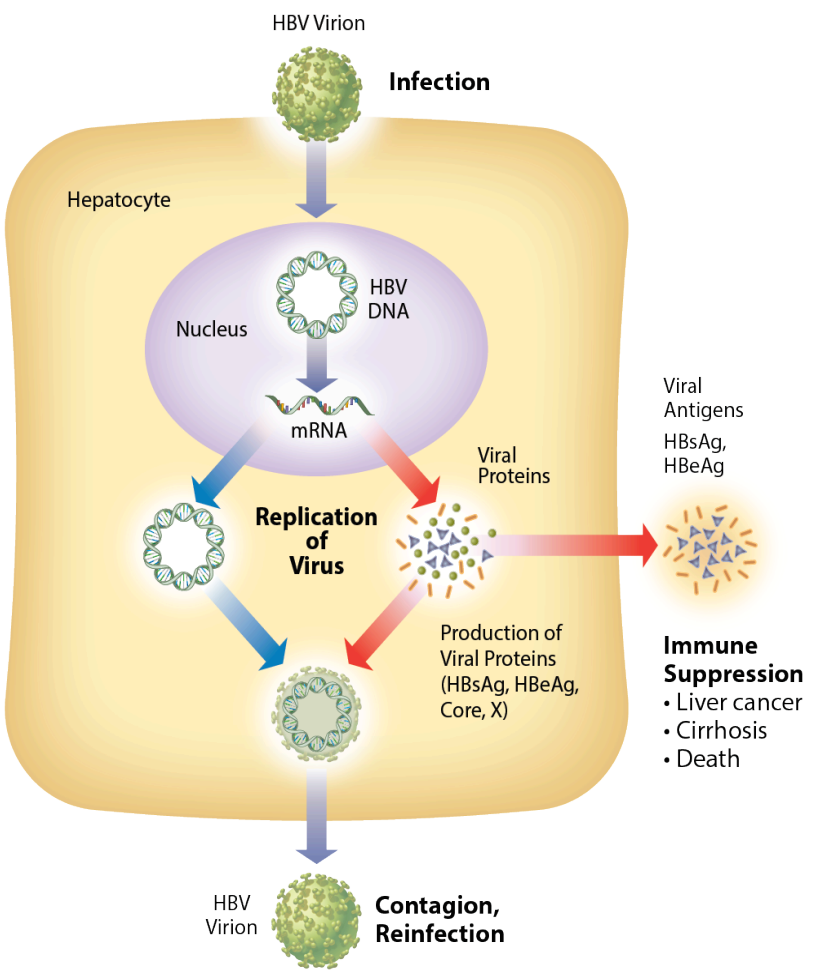
Chris Anzalone, Ph.D. – President and CEO

We have generated a substantial amount of data

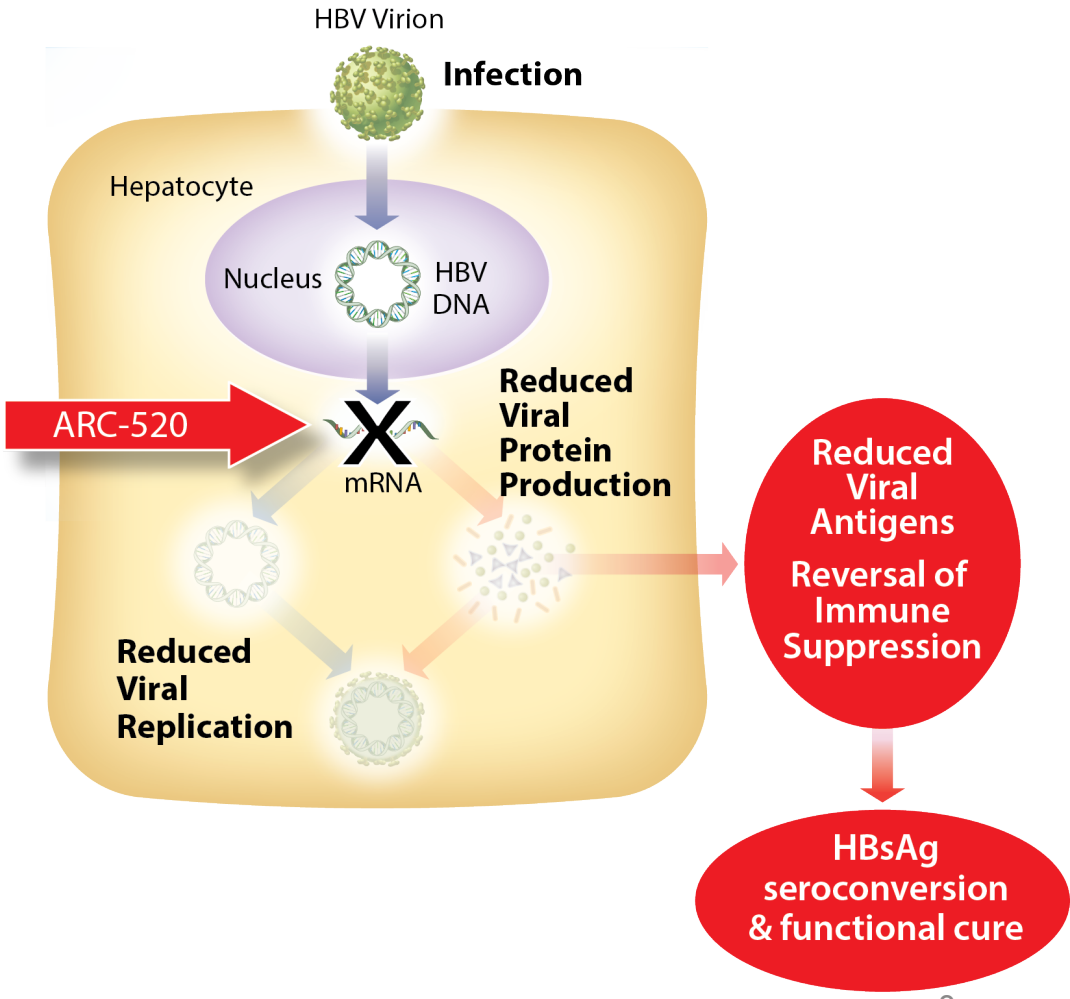
- Today's presentation is a topline summary of some of what we learned
- Chimp data will be presented in detail at AASLD
  - 1 poster and 1 oral presentation
  - Should allow plenty of opportunity for in depth examination/discussion
- Clinical data will be available as soon as accepted and published or presented

HBV Biology and ARC-520 MOA

Untreated



ARC-520



Treatment groups we are discussing today

- Chimp study: 9 CHB chimps suppressed on NUCs then treated monthly for 6-11 months with ARC-520: biweekly blood samples; several biopsies
- 7 cohorts of patients

Cohort	Prior NUCs?	Pat Type	ARC-520 dose	Active	Placebo	Status
1	Yes	HBeAg neg	1.0 mg/kg	6	2	Complete/Unblinded
2	Yes	HBeAg neg	2.0 mg/kg	6	2	Complete/Unblinded
3	Yes	HBeAg neg	3.0 mg/kg	6	2	Complete/Unblinded
4	Yes	HBeAg neg	4.0 mg/kg	6	2	Complete/Unblinded
5	Yes	HBeAg pos	4.0 mg/kg	6	2	Complete/Unblinded
6	Yes	HBeAg pos	2 x 2.0 mg/kg	6	0	Ongoing/Open label
7	No	HBeAg pos/neg	4.0 mg/kg	6 pos/6 neg	0	Ongoing/Open label

New cohorts

5 Questions we will answer today

- Is ARC-520 well-tolerated?
- What did you learn from the chimp study?
- Does the DPC platform work?
- Does ARC-520 work?
- What is the outlook for ARC-520?

Is ARC-520 well-tolerated?

- 84 humans have had single dose to date
  - No AEs rated as serious or severe
  - No discontinuations due to AEs
  - No laboratory signs of end organ tox
- 9 chimps received 6 - 11 monthly doses ARC-520
  - No safety signals detected in any chimp

ARC-520 has been very well tolerated

What did we learn from the chimp study?

1. ARC-520 leads to deep HBsAg reduction

HBeAg status	HBsAg mean peak KD
HBeAg(+): 4 chimps	99% (2 log)
HBeAg(-): 4 chimps	81% (0.7 log)
HBeAg transitional: 1 chimp	87.4% (0.9 log)

2. Evidence of immune reactivation in 1 of the 4 HBeAg(+) chimps

3. We concluded that different responses due to decrease of cccDNA during lifecycle of virus and NUC therapy: significant HBsAg production from integrated DNA

Deep KD with ARC-520 and new paradigm for lifecycle of virus

Does the platform work?

- Our data suggest that integrated DNA becomes an increasingly important source of HBsAg as cccDNA is reduced
- To assess platform activity: look to HBeAg KD in HBeAg(+) patients:
  - ARC-520 silences cccDNA and HBeAg is only expressed by cccDNA
  - HBsAg is expressed by both cccDNA and integrated DNA

Single Dose 4mg/kg ARC-520 in HBeAg(+) Patients		
Antigen	mean max KD	max KD
HBeAg	92% (1.2 log)	98% (1.7 log)

- HBV core-related antigen (HBcrAg) KD was similar to HBeAg in both HBeAg(+) and HBeAg(-) patients

DPC platform is potent and consistent: de-risks ARC-520 and future candidates built on same DPC

Does ARC-520 work?

Reached **99% max KD (1.9 log) HBsAg** after single dose

Highest KD ever reported in a human using RNAi

NUC-naïve HBeAg(+) patients after ARC-520 administration: Just through Day 15: still following patients		
Antigen	Mean max KD	max KD
HBsAg	1.05 log	99% (1.9 log)

…and remember, we are deeply silencing all other viral components as evidenced by HBeAg and core antigen KD: could be powerful disrupter of normal viral function

ARC-520 is very potent at silencing cccDNA expression

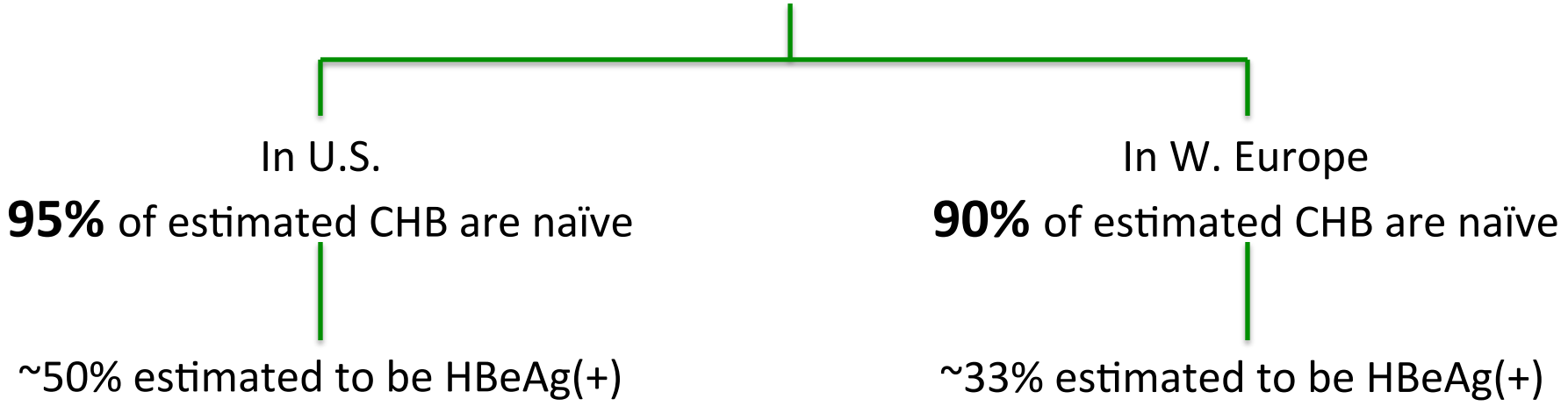
What is the outlook for ARC-520?

HBV will have subpopulations that will respond differently to different treatments

- We identified cccDNA / integrated DNA as determinant of a subgroup:
  - ARC-520 is well tolerated and deeply silences cccDNA expression
  - NUC-naïve HBeAg(+) patients are richest in cccDNA

Important target population for ARC-520, but is it a small slice of a huge market?

No, it is a large segment of the chronic HBV (CHB) population



Proprietary data from Clarion Healthcare, LLC

ARC-520 also studied in other populations

ARC-520 could be a powerful ant-viral in *low and high* cccDNA patients

1. **ARC-520 appears to deeply silence all cccDNA expression**
   - Even in patients with low cccDNA, ARC-520 should severely disrupt normal viral function (even if HBsAg is not fully suppressed)
     - We expect Core antigen, HBeAg, and X antigen to be strongly silenced in all patients

2. **Clinical data here are single dose: ARC-520 expected to be a multi-dose therapy**
   - Chimp study suggests that KD should increase upon multi-dose
   - Long term disruption of virus could contribute to functional cure

3. **Unclear how much HBsAg needs to be reduced to achieve functional cure, particularly when all other viral proteins are silenced**

Also expanded our HBV portfolio

We nominated an additional candidate: ARC-521

Provides 2 shots on goal

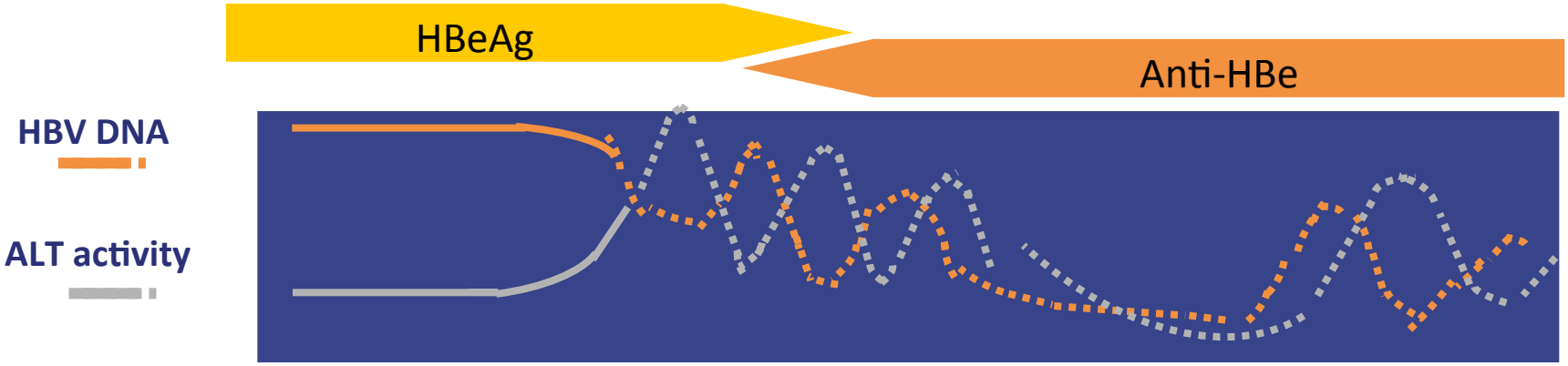
- Same DPC as ARC-520, so safety expected = ARC-520
- Optimized to include integrant KD
- Validated in chimps
  - Multi-log KD
- Complement to ARC-520
- IND or equivalent by mid-year 2016

De-risked program with tolerability/activity of ARC-520, increased ammunition against difficult virus

Current consensus on HBV lifecycle and targets

Robert Gish, M.D.

Phases of Chronic HBV Infection



Phase	Immune Trained	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Optimal treatment times

Yim HJ, et al. *Hepatology*. 2006;43:S173–S181.

A new era in HBV therapeutics is emerging

- There is now HBV drug development beyond NUCs and interferon
  - With the successes in HCV, attention has shifted to HBV and drug development is booming
  - Great and growing diversity in viral targets
- As with HCV, *we anticipate* that HBV will yield to this attack
- As with HCV, *we anticipate* combination therapy for HBV

How the field tends to talk/write about chronic HBV

- HBV chronicity is a failure of the immune system to exert control
  - Resolved acute infection is, by definition, characterized by HBsAg seroclearance
  - Near term goal in chronic HBV is functional cure (HBsAg seroclearance)
  - Sterilizing cure, *if we ever achieve it*, is a more distant goal
- Viral antigens (principally HBsAg) play a dominant role in immune suppression
  - Long-term, complete suppression of circulating HBV DNA does not cure the disease, same for HBeAg loss
  - HBsAg loss shows high persistence and best outcomes off therapy
- cccDNA is central to the lifecycle and the ultimate target of efforts to clear/control the virus

Emerging targets fall into two main categories

- Immune system directed
  - Efforts to reduce antigenemia (HBsAg, HBeAg, HBcAg, HBxAg)
    - Reduce viral protein synthesis (RNAi)
    - Inhibit HBsAg secretion from hepatocytes
  - Efforts to activate immune recognition of HBV
    - Checkpoint inhibitors
    - Drugs aimed at restoring innate immunity
    - Drugs aimed at reversal of apoptosis inhibition
- cccDNA directed agents
  - Entry inhibitors
  - Capsid assembly inhibitors
  - Epigenetic control

Treatment of Chronically HBV-Infected Chimpanzees with ARC-520

Robert Lanford, Ph.D. – Director, SNPRC

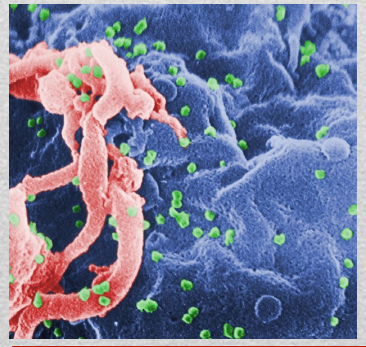
TEXAS BIOMEDICAL RESEARCH INSTITUTE

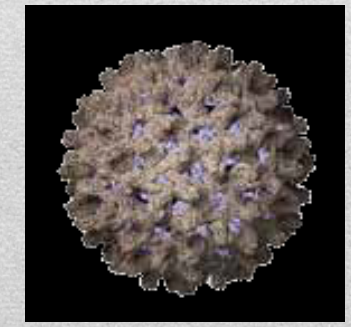
SOUTHWEST NATIONAL SNPRC PRIMATE RESEARCH CENTER

SOUTHWEST NATIONAL SNPRC PRIMATE RESEARCH CENTER

TEXAS BIOMEDICAL RESEARCH INSTITUTE

- Independent Research Institution, founded in 1941
- 350 employees
- 70 doctoral level Investigators
- 200 research projects
- 330 acre campus
- 600,000 square feet of lab, animal and support space
- $50 million annual budget
- $120 million endowment





SOUTHWEST NATIONAL SNPRC PRIMATE RESEARCH CENTER

Chimpanzee Colony

- Preclinical testing on Merck HBV Vaccine in 1970s and 1980s
- First transmission of HIV from man to animal model
- First transmission of nonA, nonB hepatitis to animal model
- Two NIH HCV Cooperative Centers for 15 years
- Preclinical trials for HCV and HBV therapeutics
- 20 sponsors over 10 years with multiple clinical candidates
- One FDA approved cocktail for HCV cure

Veterinary Program

- High quality of animal care to maintain healthy colonies
- High quality of veterinary and technical support of research
- 8 veterinarians, 2 Board Certified in Experimental Medicine (DACLAM), 2 Board Certified in Pathology (DVACP)
- Outstanding clinical and anatomical pathology program
- Behavioral staff of nine individuals for enrichment, training, assessment and intervention.
- AAALAC accreditation renewed in 2015 (highest standard for an animal care program)

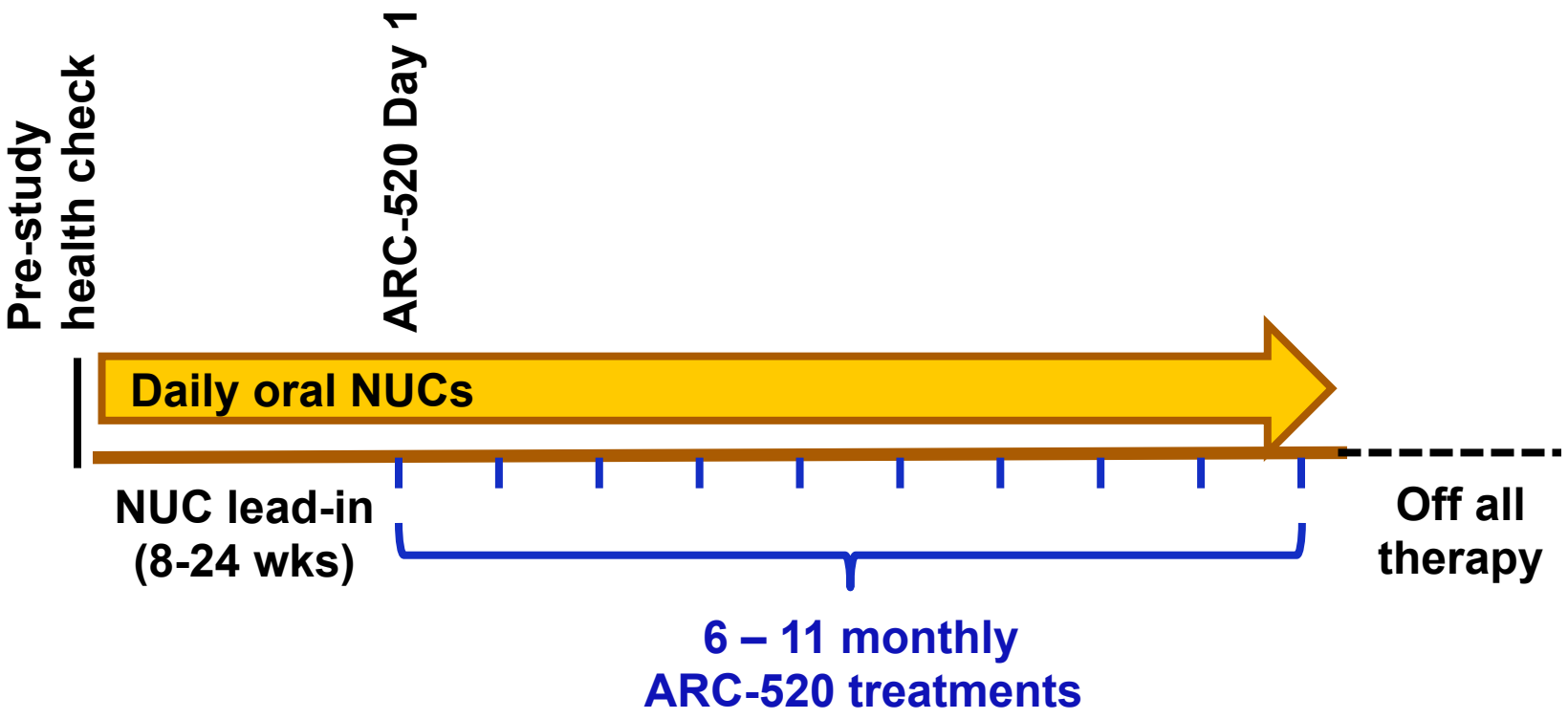
ARC-520 Chimpanzee Study

- 9 chimps used in the study – 5 HBeAg pos, 4 HBeAg neg
- Chronically infected with HBV for multiple years
  - Deep sequencing and phylogenetic analysis (VIDRL) points to variant of human HBV
- Tissue and blood samples assayed at TxBiomed or specialized labs
  - Efficacy readouts: serum viral titer, quantitative HBsAg and quantitative HBeAg, total liver HBV DNA compared to cccDNA, HBV RNA and host RNA transcripts in the liver, and additional readouts
  - Safety labs: Clinical safety parameters included CBC and blood chemistries, daily observation by veterinarian and behavioral staff for normal activity and feeding.

Key chimpanzee study data and learnings

David Lewis, Ph.D. – Chief Scientific Officer

Chimp dosing and sampling timeline

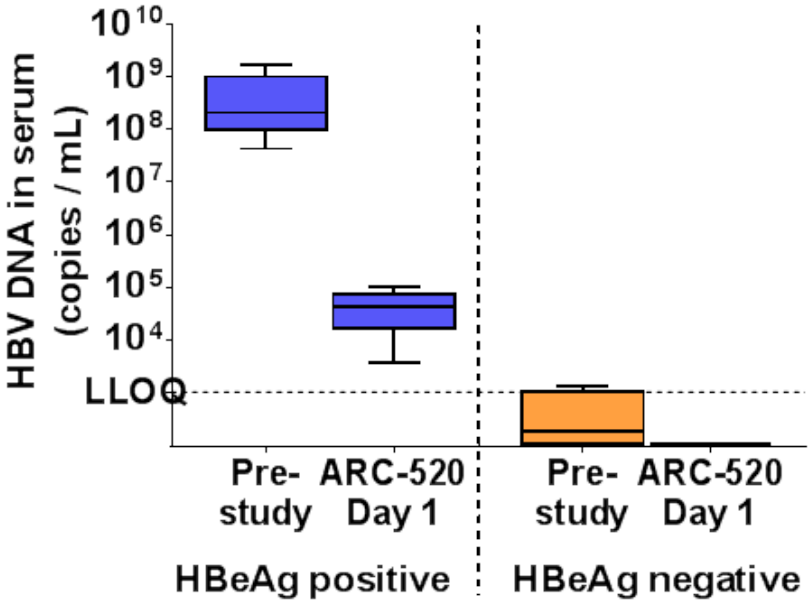


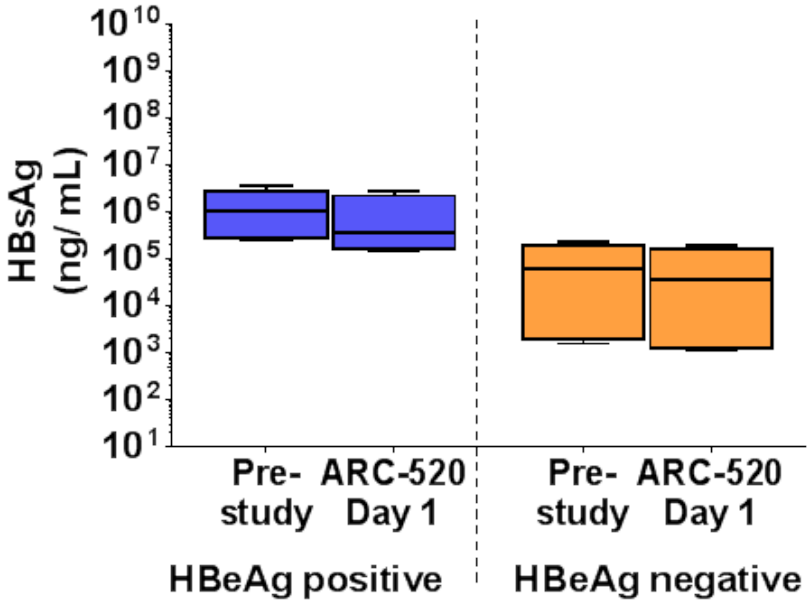
- Chimp study design similar to human clinical trial design
- 2, 3 or 4 mg/kg ARC-520
- Monitor safety and efficacy
  - Blood collection performed regularly throughout study
  - Periodic liver needle biopsies

Multiple doses of ARC-520 well tolerated in chimpanzees

- Regular monitoring of clinical chemistry, coagulation, blood counts, cytokines, complement revealed no evidence of end organ toxicity
- No adverse changes in behavior, body weight, or food consumption noted
- Animals with high transaminases at baseline generally normalized under treatment
- ALT increase observed in one animal coinciding with HBeAg seroconversion and signs of immune reactivation – data to be presented at future medical conference

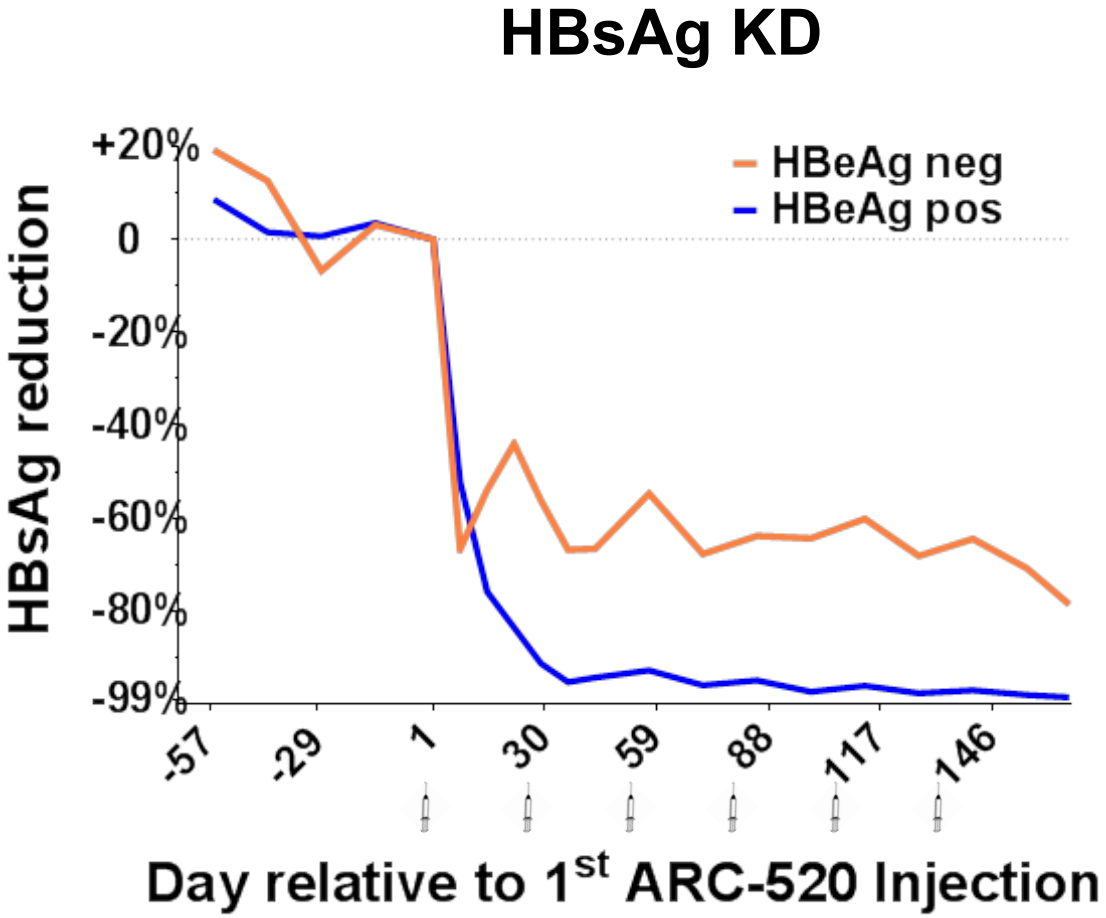
Nuc lead-in period: deep decrease observed in HBV serum DNA but HBsAg relatively unchanged





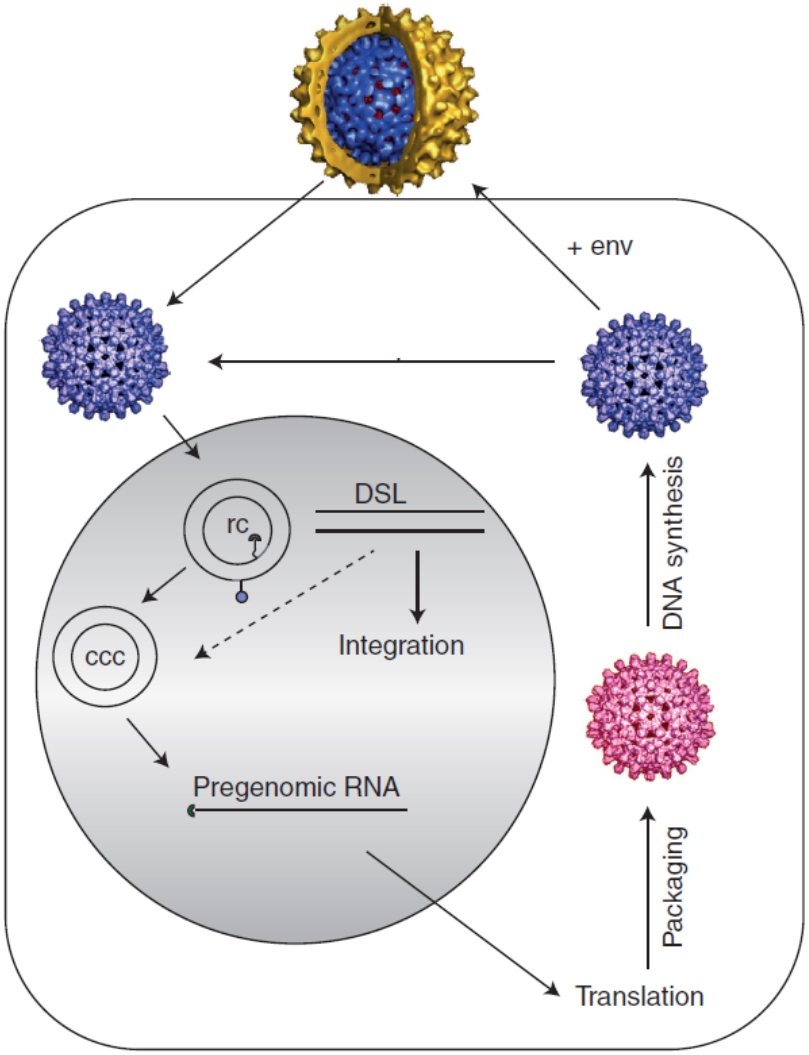
- **Chimp response to NUC therapy similar to humans:**
  - Deep decrease in serum viral titers especially in HBeAg pos chimps
  - Initial serum HBV DNA levels much lower in HBeAg neg, dropping well below the level of quantitation during NUC lead-in phase
  - HBsAg levels were not significantly changed during NUC lead-in

Deep reduction in HBsAg with ARC-520: HBeAg pos chimps are most responsive



- Mean knockdown (nadir)
  - **HBeAg pos**
    99% (2.1 log_{10})
  - **HBeAg neg**
    81% (0.7 log_{10})
- HBsAg trends downward after multiple doses

HBV lifecycle



Hu and Seeger, CSH Perspectives in Medicine, 2015

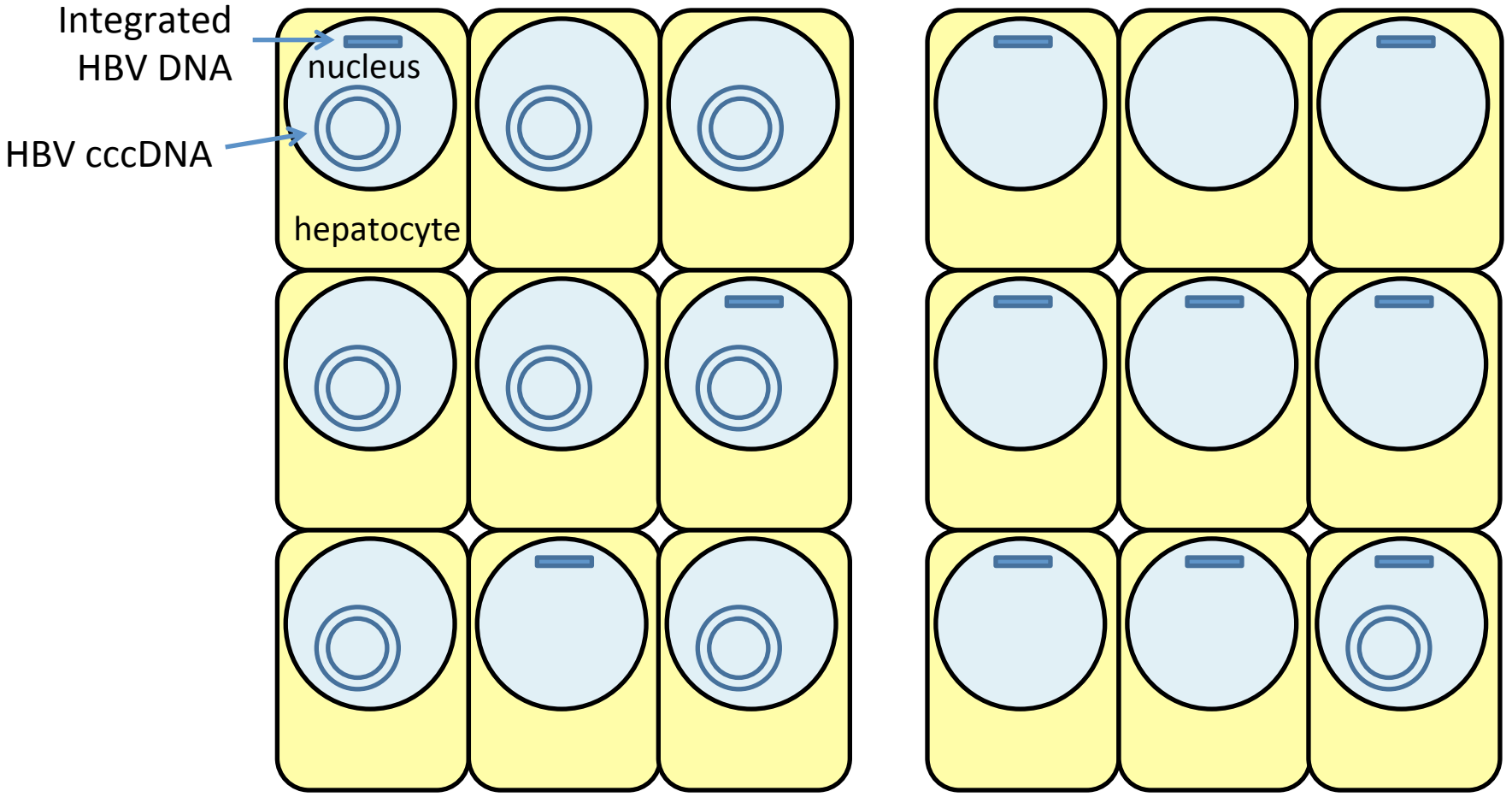
- cccDNA codes for all viral mRNAs and pregenomic RNA (pgRNA)
- pgRNA used in viral replication
  - converted to relaxed circular DNA (rcDNA)
- Another replication product is double-stranded linear (dsl) HBV DNA
  - Less than full genome length
  - Replication defective
  - **10% of replication products are dslDNA**
- rcDNA and dslDNA both transferred to nucleus after infection
- dslDNA can integrate into the host genome
  - Propagated as hepatocytes divide

Novel finding: Predominant liver HBV DNA differs in HBeAg neg and HBeAg pos chimps

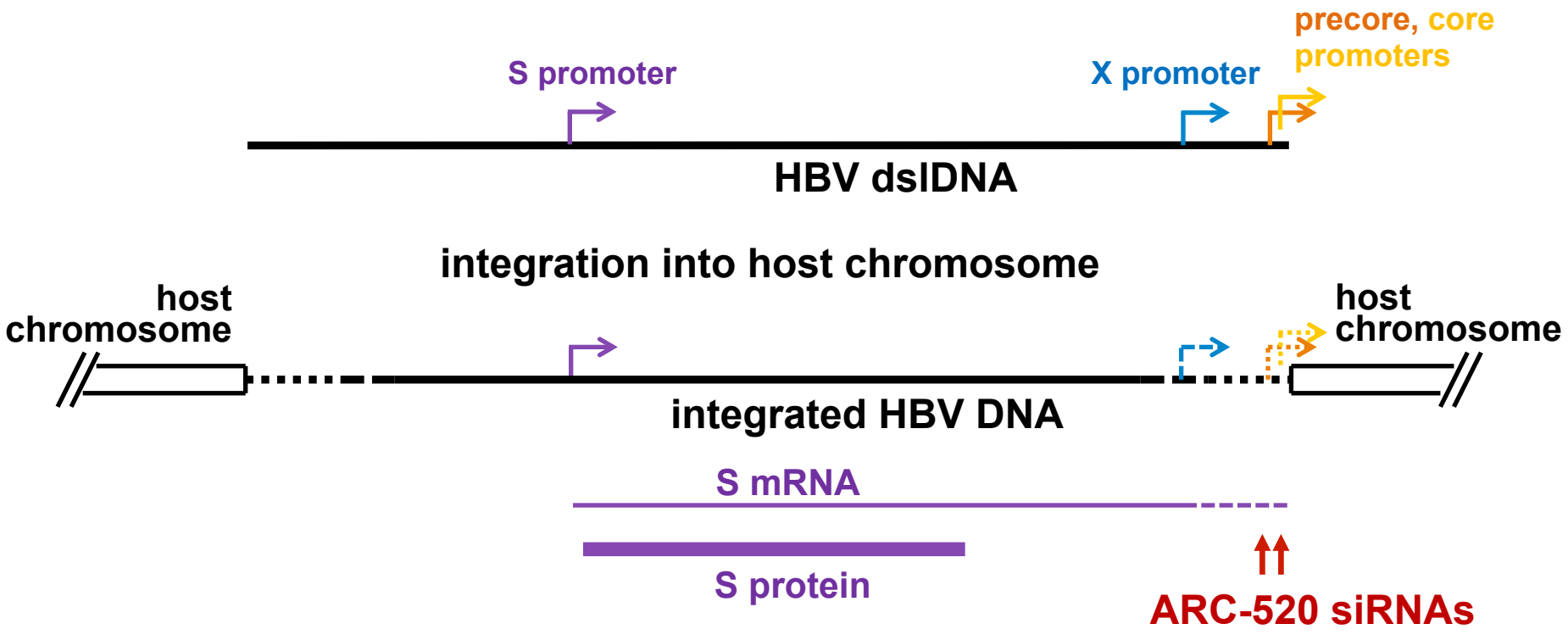
Liver biopsy at initiation of ARC-520 treatment revealed:

- Most HBV DNA in liver of HBeAg pos is cccDNA
- 500-fold less cccDNA in HBeAg neg
  - Only 5% of total HBV DNA in liver in HBeAg neg was cccDNA and total HBV DNA levels were ***not*** affected by NUCs
- ***HBV DNA profile in HBeAg neg chimps is consistent with a high proportion of integrated HBV DNA***

Conceptual representation of HBV DNA in liver lobules of HBeAg pos and HBeAg neg chimps



HBV DNA integrates into the host chromosome *and produces HBsAg*



- HBV DNA integration occurs throughout infection largely via dslDNA and introduces deletions
- Intact S protein ORF and transcriptional control elements allow expression of HBsAg
- Explains persistent expression of HBsAg despite v. low cccDNA in HBeAg neg chimps
- Loss of ARC-520 target sites explains lower KD of HBsAg in HBeAg neg chimps

Deep HBsAg reduction in HBeAg neg chimps treated with siRNA targeting integrated DNA

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- Two HBeAg neg chimps were treated
- Mean nadir of HBsAg after ARC-520 treatment:
  - 77% reduction (7 monthly doses)
- Mean nadir of HBsAg after switching to HBV integrant-targeted siRNA:
  - 99.8% reduction (4 monthly doses)
  - Represents an ***additional 2 log decline*** from end of ARC-520 treatment

Chimpanzee ARC-520 study: interim conclusions

- Robust, sustained direct anti-viral effect on HBsAg production observed in all HBeAg pos and neg chimps
  - HBeAg pos chimps displayed highest levels of HBsAg knockdown - **up to 2.7 log**
  - In HBeAg neg chimps, HBsAg knockdown was also substantial - **up to 0.9 log**
- ARC-520 was well tolerated after multiple doses up to 4 mg/kg ARC-520 (highest dose tested)
- ***Evidence indicates integrated HBV DNA is a significant source of total HBsAg, especially in HBeAg neg chimps***

Heparc-2001
Exploring new territory in HBV

Bruce Given, M.D. – Chief Operating Officer

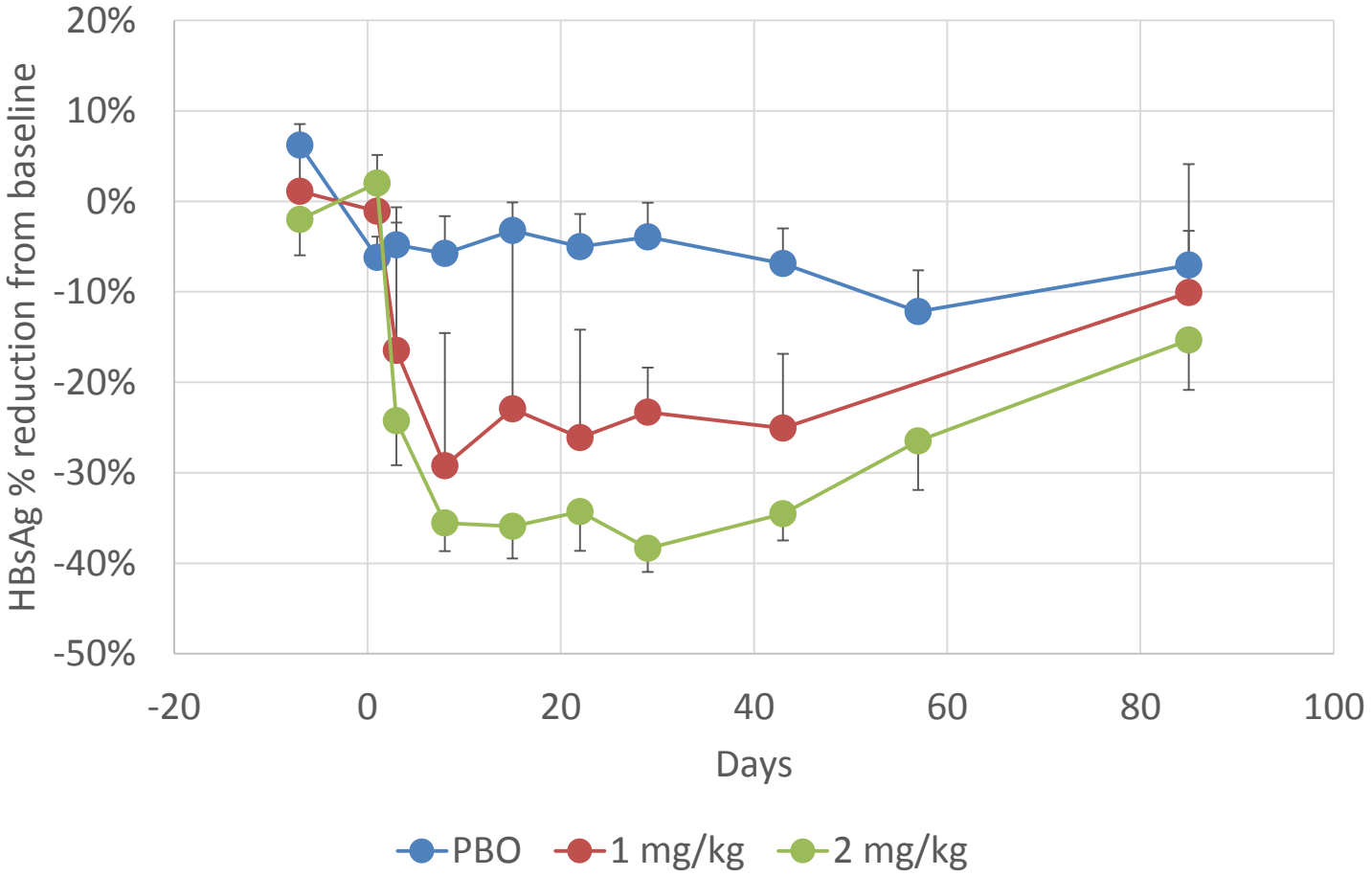
Heparc-2001 Design and Status

Cohort	Prior NUCs?	Pat Type	ARC-520 dose	Active	Placebo	Status
1	Yes	HBeAg neg	1.0 mg/kg	6	2	Complete/Unblinded
2	Yes	HBeAg neg	2.0 mg/kg	6	2	Complete/Unblinded
3	Yes	HBeAg neg	3.0 mg/kg	6	2	Complete/Unblinded
4	Yes	HBeAg neg	4.0 mg/kg	6	2	Complete/Unblinded
5	Yes	HBeAg pos	4.0 mg/kg	6	2	Complete/Unblinded
6	Yes	HBeAg pos	2 x 2.0 mg/kg	6	0	Ongoing/Open label
7	No	HBeAg pos/neg	4.0 mg/kg	6 pos/6 neg	0	Ongoing/Open label

Opening considerations for Heparc-2001

- DPCs had never been in the clinic before ARC-520
  - Activity in humans vs animals unknown
  - 1 and 2 mg/kg starting doses based on data from a single HBV-infected chimpanzee
  - We had good safety and tolerability in healthy subjects through highest dose tested (2 mg/kg)
  - Australian normal volunteer study kept open to dose higher if it looked useful

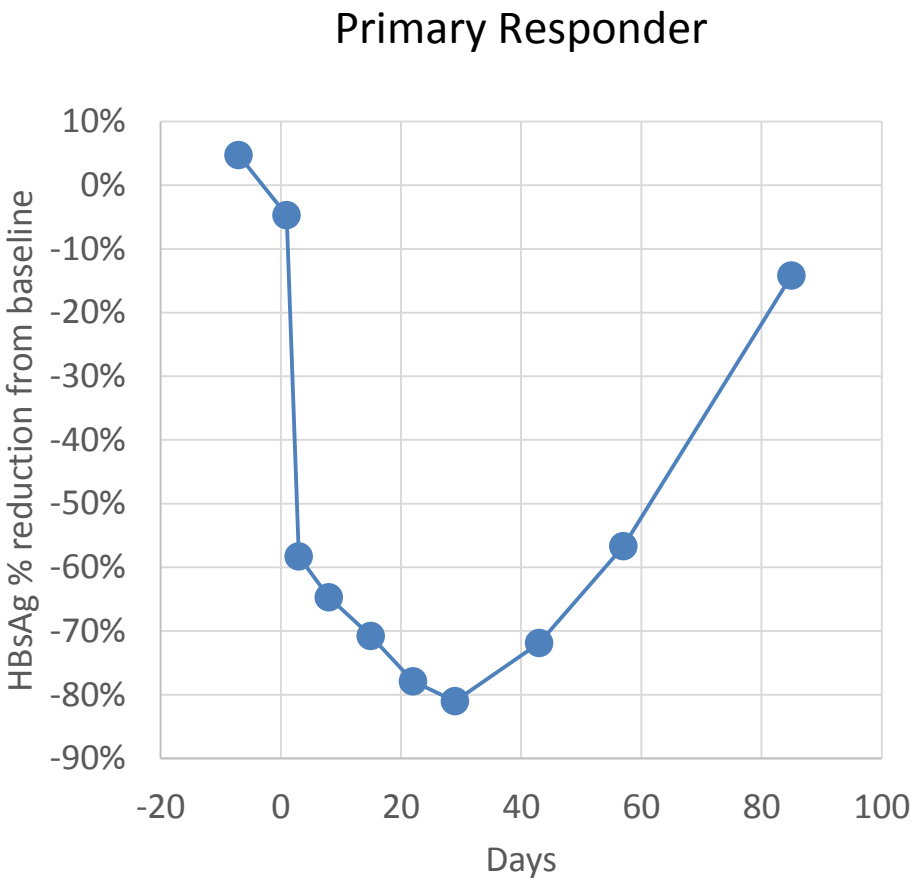
Early data pleases HBV clinicians and gives first report of direct anti-viral HBsAg reduction

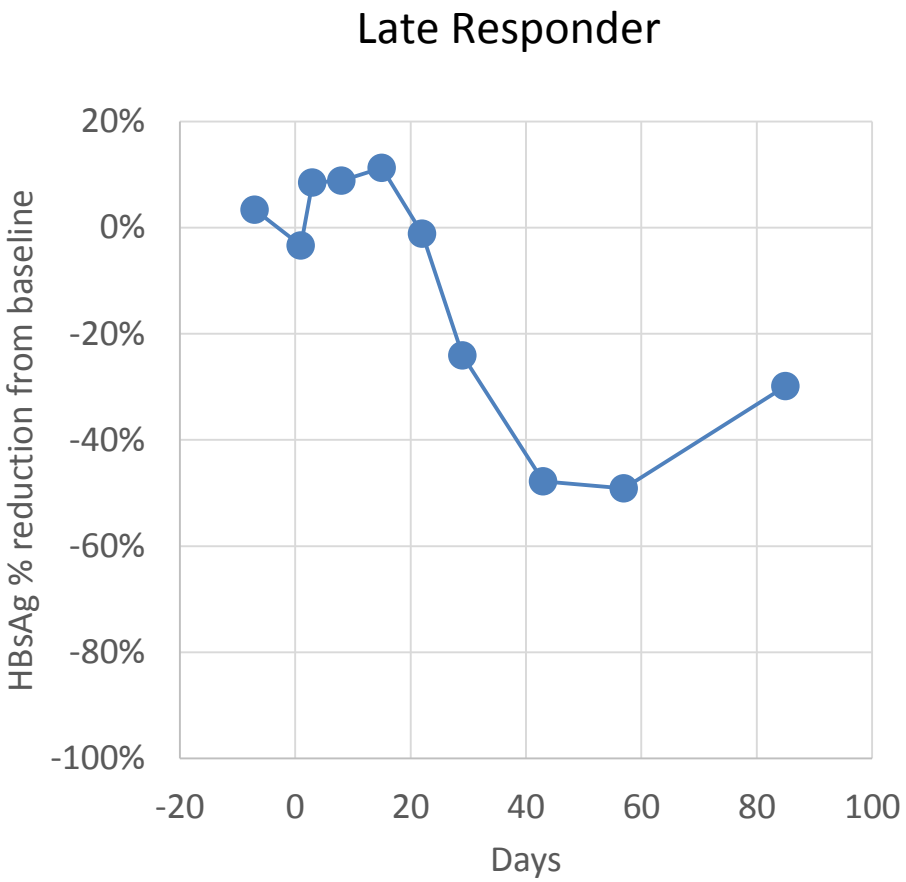


The explorations begin

- Based on every animal model with every gene we had studied, we interpreted the 1 and 2 mg/kg results as indicating we were on the low end of the dose response curve
- Dosing in healthy subjects to 4 mg/kg appeared safe
- We added 3 and 4 mg/kg cohorts, still in HBeAg negative patients on chronic entecavir
- To our surprise, peak knockdown in best responders in cohorts 3 and 4 continued to be around 60%
- Some patients appeared to show a late response that we couldn't explain

Two profiles of HBsAg response observed

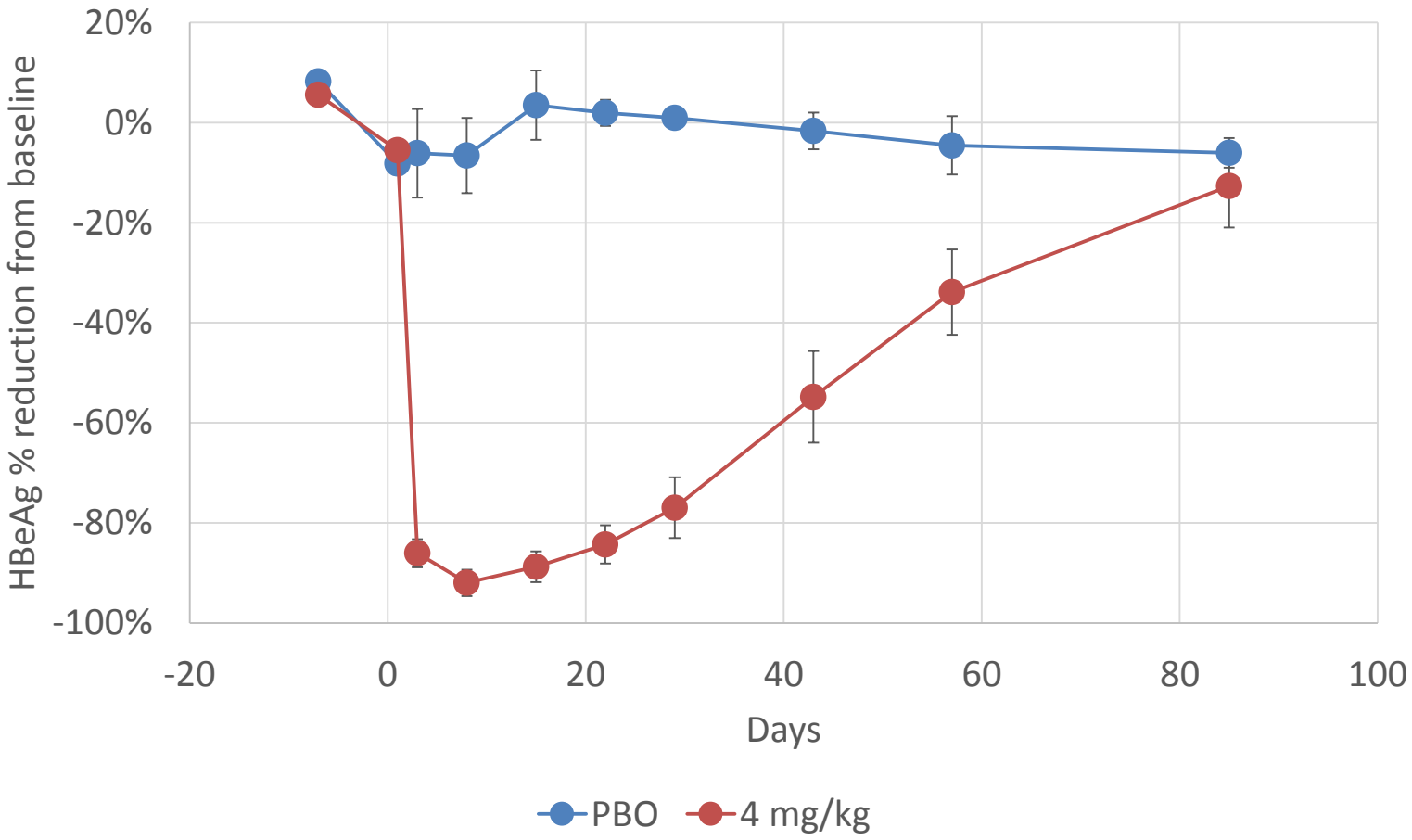




Meanwhile, we started to receive multi-dose chimp data

- HBeAg pos chimps showed greater HBsAg KD than HBeAg neg chimps
- Pointed us toward testing ARC-520 in HBeAg pos patients
- We looked at 4.0 mg/kg in single and divided doses on a background of chronic entecavir
  - Enabled testing of HBeAg +/- hypothesis
  - **HBsAg responses looked complex – HBeAg provided an additional endpoint to test platform activity**

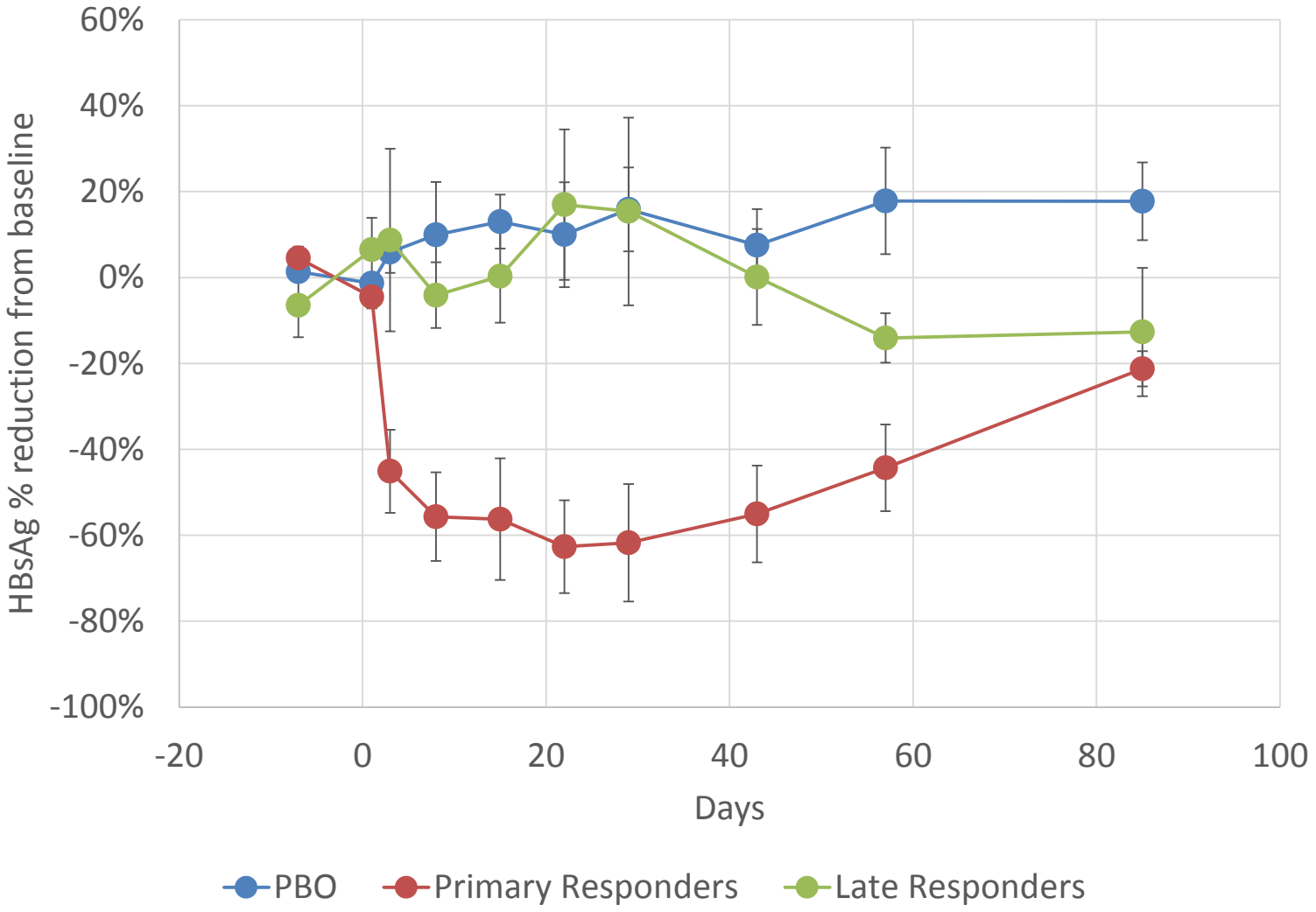
The Platform Works! HBeAg drops deeply



Results in HBeAg pos patients confirm the DPC technology

- HBeAg drops rapidly and deeply, demonstrating reductions of 83-98% (0.8 – 1.7 logs) after a single dose (cohort 5)
  - Confirms that the RNAi triggers in ARC-520 were reaching the cytoplasm and effectively engaging RISC
- We think the technology is validated, confirming deep knockdown of a target mRNA in humans
- Subsequently also shown for HBcrAg in HBeAg pos and neg patients
- We believe that favorable tolerability and deep KD de-risks future candidates using this DPC (ARC-AAT, ARC-F12)

Surprisingly, in cohort 5 HBsAg shows best knockdown of only 80% after a single dose



We are faced with a conundrum

- HBeAg results clearly validate the drug
- \
- ….But why isn’t HBsAg falling in a similar fashion and why 2 patterns of KD?
  - Points to biology specific to HBsAg

Chimp data emerges that changes our thinking about HBV biology and lifecycle

- *Complements newly published human biopsy data*

- NUC treatment and HBeAg loss associated with sharp reductions in cccDNA
- As cccDNA is reduced, integrated DNA emerges as unexpected source of persistent HBsAg production
- ARC-520 was optimized to silence expression from cccDNA
  - As expected shows deep KD of cccDNA-derived gene products as exemplified by HBeAg
  - Would not be expected to silence most integrated-derived HBsAg

What would this mean for the patients in cohorts 1-6 ?

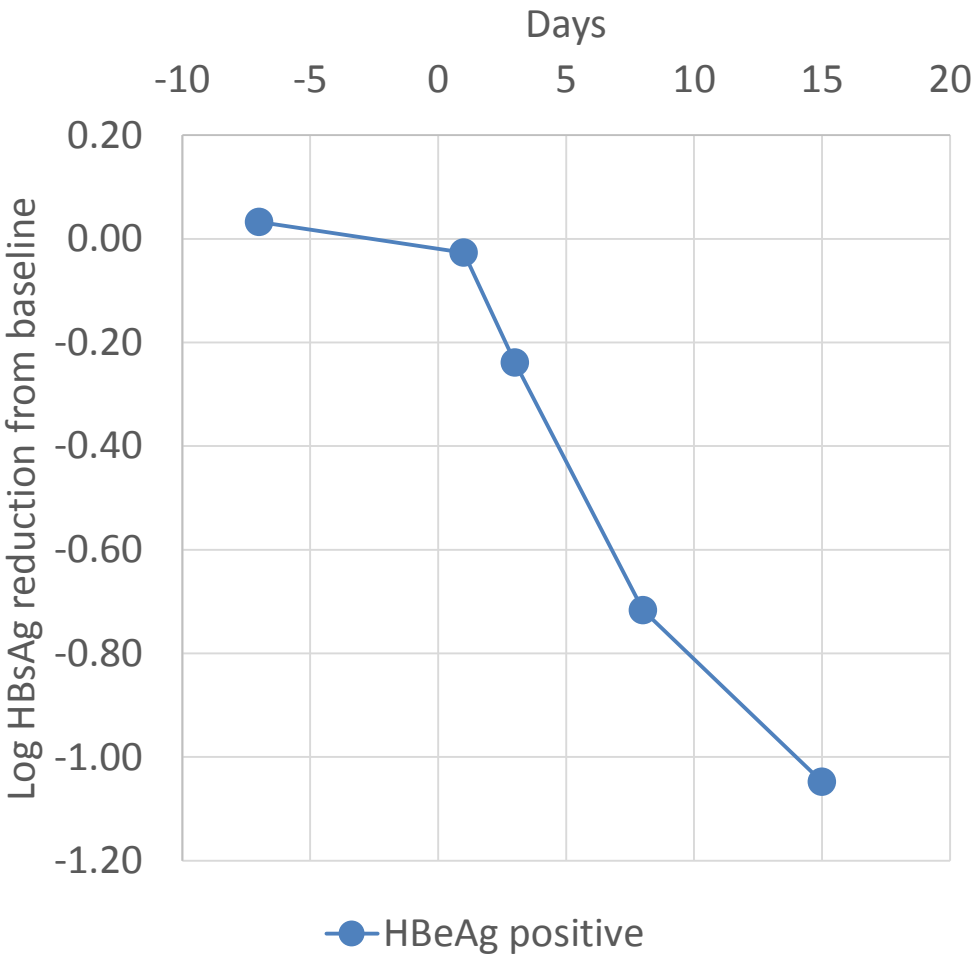
- Prior entecavir treatment ranged from 2 – 8 years, with a median of 5 years
- Based on prior research by C.L. Lai et al at Queen Mary Hospital (Hong Kong), we would expect that cccDNA concentrations in these patients would have been reduced to undetectable levels on liver biopsy
  - Dr. Lai's work violates conventional wisdom that NUCS lead to minimal reduction of cccDNA

Lai, C.-L., et al. (2014) Hepatology v. 60 n. suppl. S1, p. 1090A, abstract no. 1855

We developed a new hypothesis

- Integrated DNA was placing a floor under the HBsAg response in chronic NUC-treated patients, especially HBeAg negative
- The chimps would be analogous to patients naïve to prior therapy
- We decided to study naïve patients both HBeAg pos and neg at baseline with ARC-520
  - We further theorized that the HBeAg pos group would have a deeper response than the HBeAg neg group

Naïve HBeAg positive patients show deep HBsAg reduction



Single dose of 4 mg/kg results in a mean HBsAg reduction of more than 1 log at Day 15

Peak KD likely not yet achieved

Data are still maturing

Maximum KD to date is 1.9 log (99%)

What the clinical data has told us

- ARC-520 has shown good single dose tolerability in 84 humans and good multi-dose tolerability in 9 chimps
  - Still no serious or severe AEs or dropouts due to AEs
  - Still no suspected signs of end-organ toxicity on labs
- ARC-520 can produce deep and sustained KD of cccDNA-derived mRNA/proteins
  - HBeAg, core antigen, HBsAg
- *The technology works! Highest reported single dose KD in humans with RNAi therapeutic*

Brief update on the clinical program

- First Monarch cohorts (multi-drug cocktail study) planned to be in naïve patients
  - Expect deep KD of all gene products, esp. in HBeAg pos
  - Large pool of patients because <15% of patients are treated
- Heparc-2002 (HBeAg neg) and -2003 (HBeAg pos) continue as planned
  - ARC-520 clearly disrupts HBV as evidenced by deep KD of HBeAg and HBcrAg – we think may be important for achieving seroclearance
  - Hard to predict multiple dose effects or chances for seroclearance
  - Extension will only include HBsAg strong responders (>70% reduction in HBsAg after 4 doses)

… and, we added an additional product to the program

- We have combined the best trigger from ARC-520 with our best trigger targeting integrated DNA to produce ARC-521
- This product is in GMP manufacturing now and is expected to enter GLP tox this fall
- Assuming all goes well, we anticipate filing to commence clinical studies around mid-year 2016
- ARC-521 is expected to be more active against HBsAg derived from integrated HBV DNA

How Might We Think About HBV Now?

Professor Stephen Locarnini
WHO Regional Reference Centre for Hepatitis B
Victorian Infectious Diseases Reference Laboratory,
Peter Doherty Institute
Melbourne, Victoria 3000, AUSTRALIA

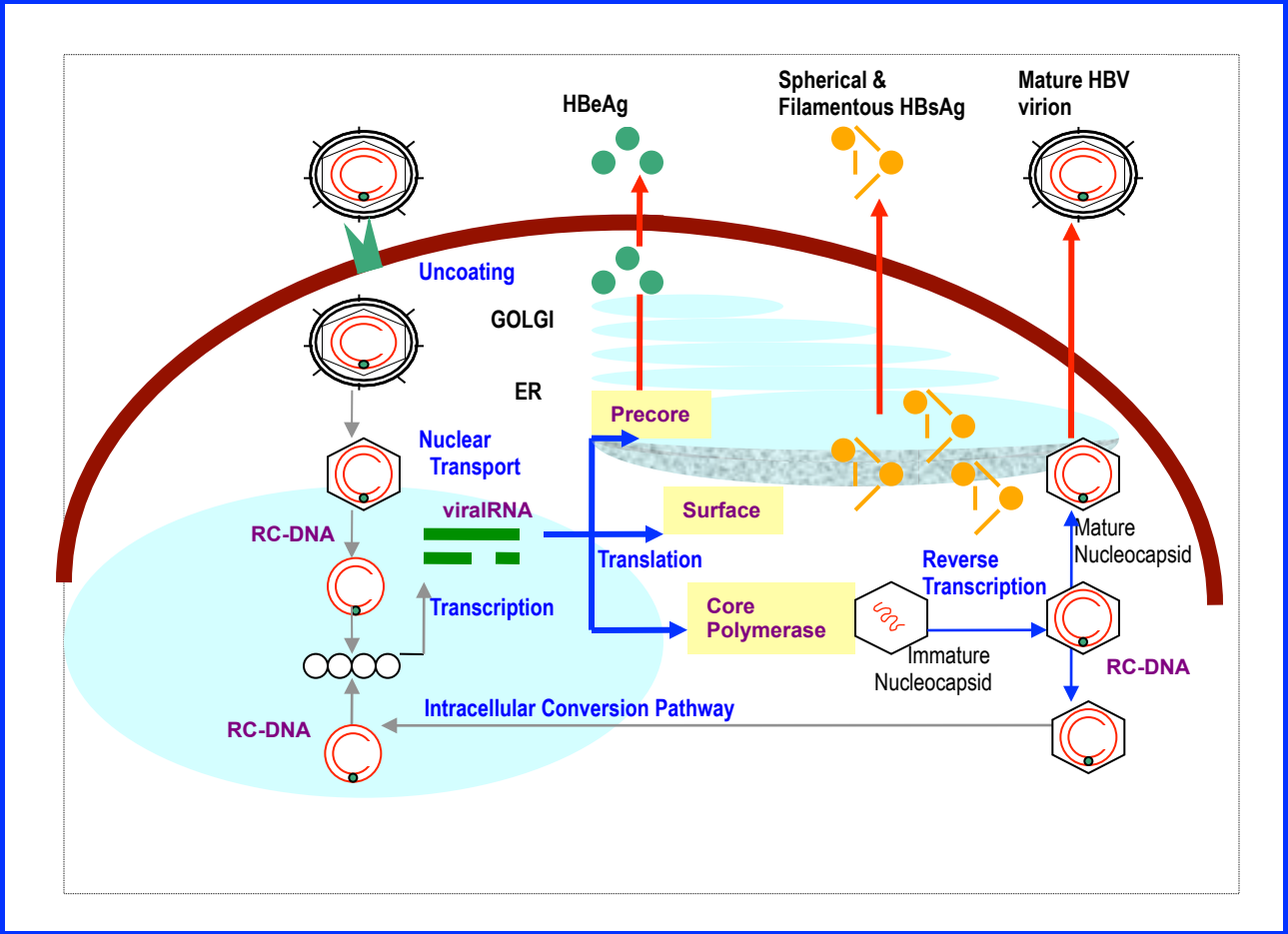
Doherty Institute
A joint venture between the University of Melbourne and Melbourne Health

Founding Director: Professor Sharon Lewin
Patron: Professor Peter Doherty (Nobel Laureate)

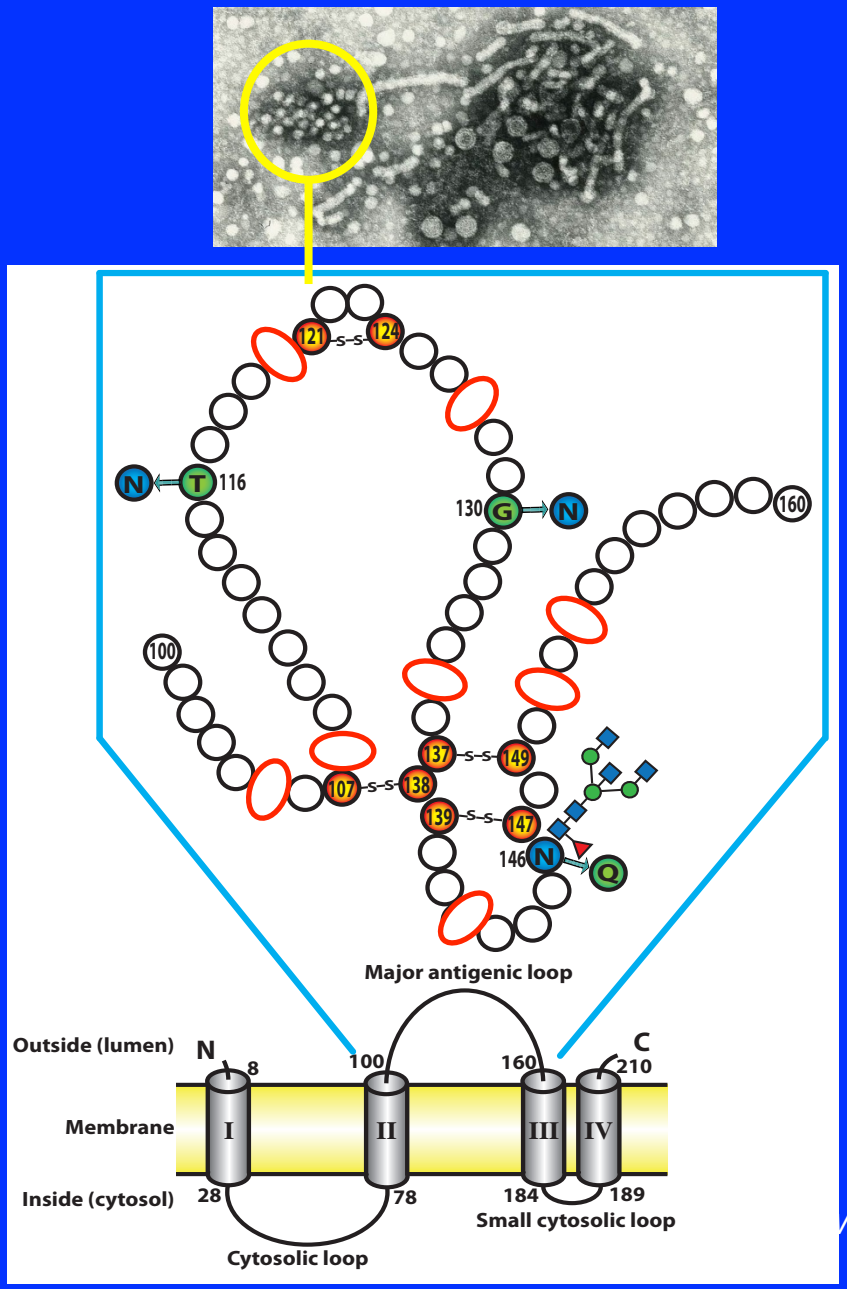
Doherty Institute for Infection & Immunity

- Partnership of The Royal Melbourne Hospital (RMH) and University of Melbourne (UoM).
- Located in the Parkville healthcare, tertiary education and biomedical research precinct.
- Integration of infectious diseases research, teaching, diagnostic and public health capability.
- Five partner organisations have combined to form the Doherty:
  - Victorian Infections Diseases Reference Laboratory (VIDRL)
  - Victorian Infectious Diseases Service (VIDS)
  - Victorian Nosocomial Infection Surveillance System (VICNISS)
  - Department of Microbiology and Immunology (DMI)
  - Microbiological Diagnostic Unit (MDU)
- The Doherty has been fully operational since April 2014

HBV Replication: Pre ARC-520 Era



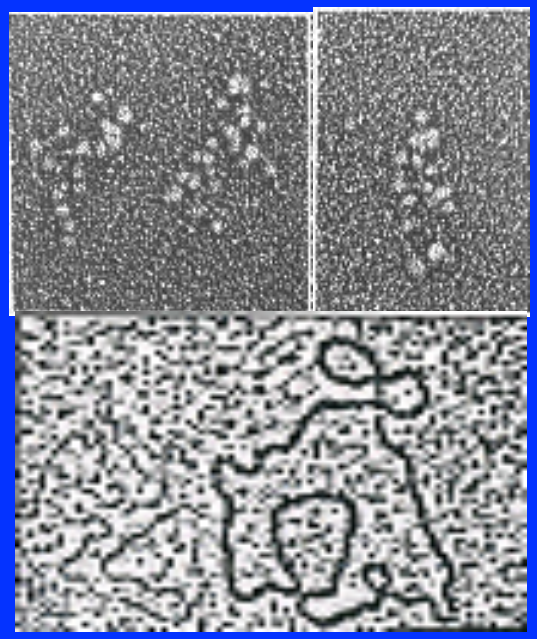
Immune Regulation by HBsAg



- HBsAg secreted in vast excess over virions (>10^3 fold)
- Circulate in blood 100-400 μg/ml (1% of total serum protein)
- Unique conformational structure (8 cysteines ● and 8 prolines ⬮)
- Associated with increased risk of HCC *(Yuen, MF. et al 2008. Gastro;135:1192–1199)*
- Plays a key role in HBV persistence
- Suppress both innate (TLR-2, TLR-9 and IFN-α) as well as adaptive (mDC) responses to infection

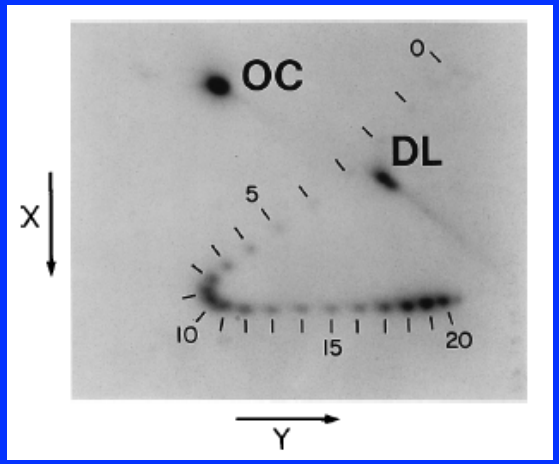
Wang, S et al 2013. J Immunol;190:5142.; Xu, Y et al 2009. Mol Immunol; 46:2640.; Op den Brouw, ML et al 2009. Immunol;126:280.

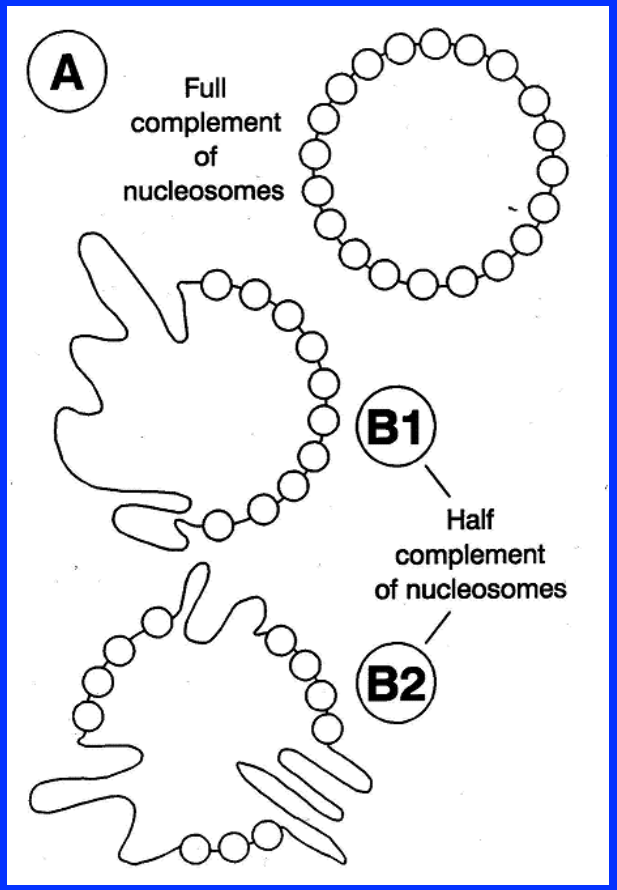
The cccDNA is a Minichromosome



Bock, T. et al 1994. Virus Genes;8:215

Bock, T. et al 2001. JMB;307:183





"CLOSED"

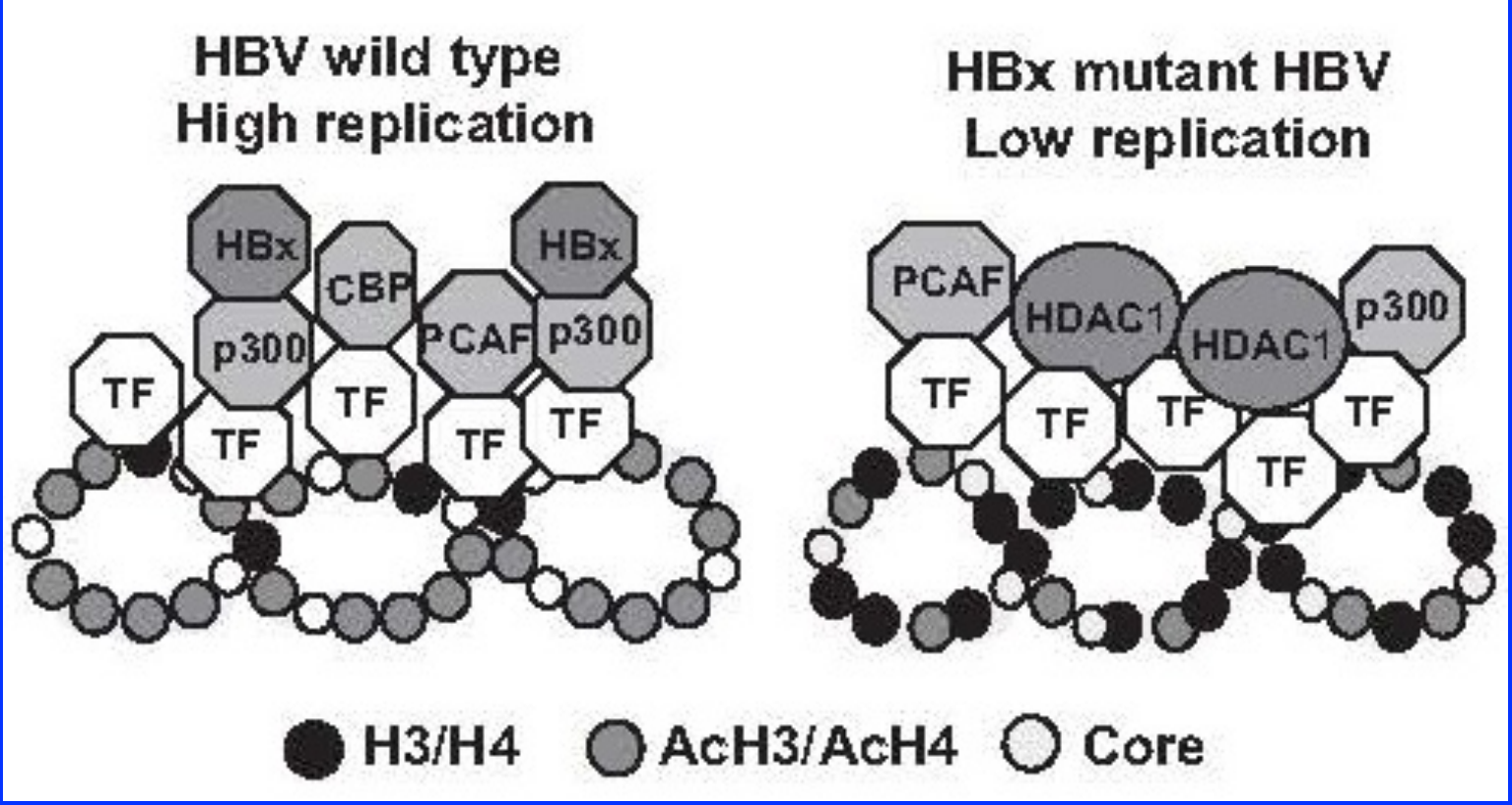
Low Replication Phenotype
Quiescent or active
Medium to Low Viraemia

"OPEN"

High Replication Phenotype
Transcriptionally Active
High Viraemia

Newbold, J and Locarnini, S 1995. J. Virol;69:3350

HBcAg and HBx are key Components of the HBV Minichromosomes



HBx blocks methylation complex

HBcAg binds cccDNA and up-regulates transcription of MC

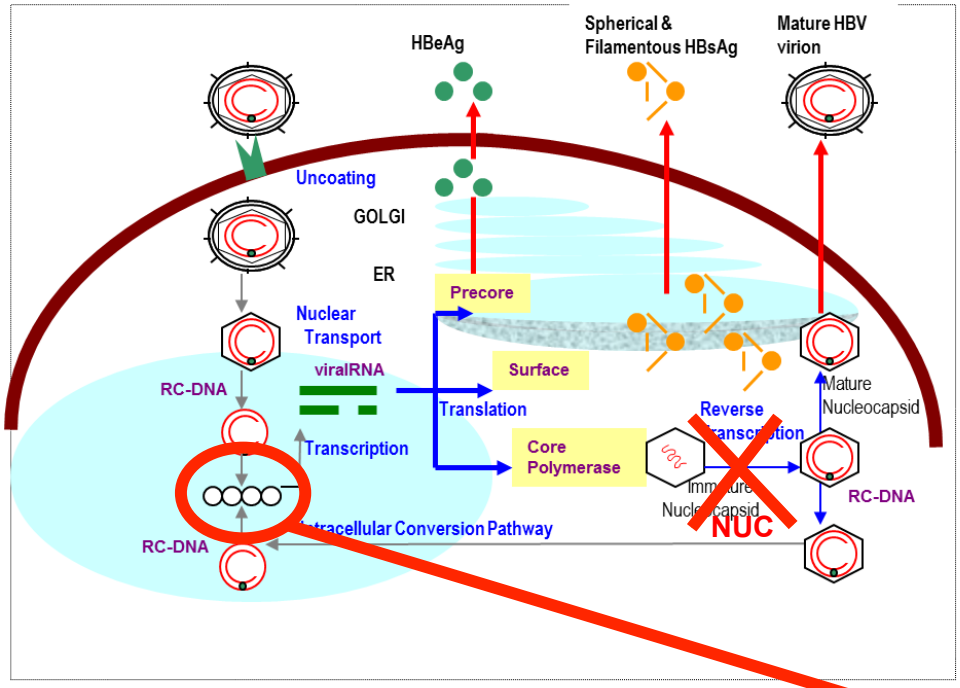
HBx and HBcAg knock-out result in transcriptional arrest of MC

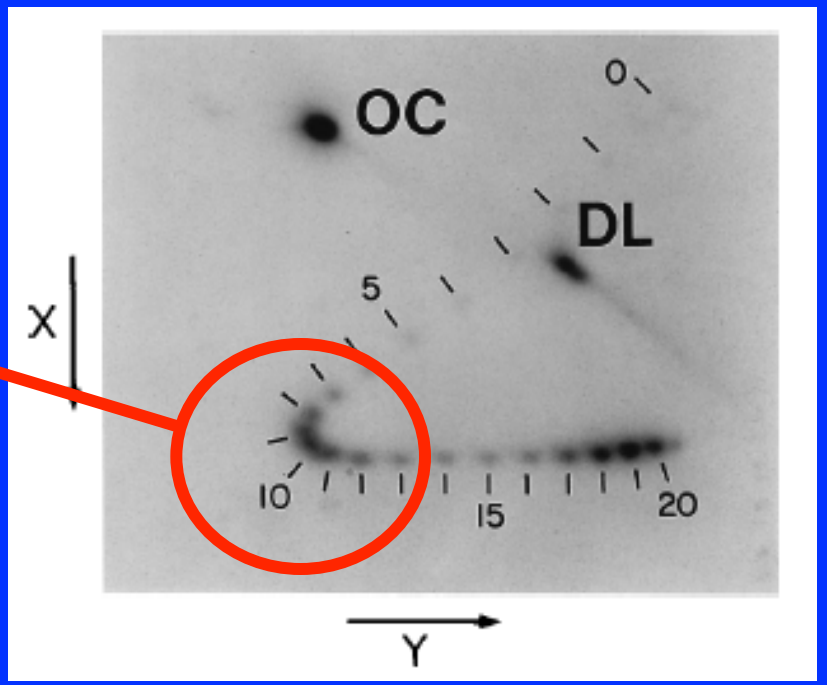
Bock, T. et al 2001. JMB;307:183;
.Belloni, L et al 2009. PNAS;106:19975-19979

A Complex Virus Becomes More Complex

- We've known about integrated DNA for quite a while
  - Thought to perhaps play an important role in HCC tumorigenesis
  - Minimal attention as a source of mRNA transcription or as critical component of chronic HBV persistence
  - Even at baseline, HBeAg negative chimps were near/below LLOQ for cccDNA in hepatocytes
- And…most have thought that NUCs did not effect cccDNA levels
  - Data has emerged this year from two sources showing large reductions in cccDNA levels with NUC therapy in humans – and now in Arrowhead chimps
- ***This forces us to rethink the role of integrated DNA in chronic HBV (beyond its proposed role in tumorigenesis)***

Partial Reduction of cccDNA by NUCs

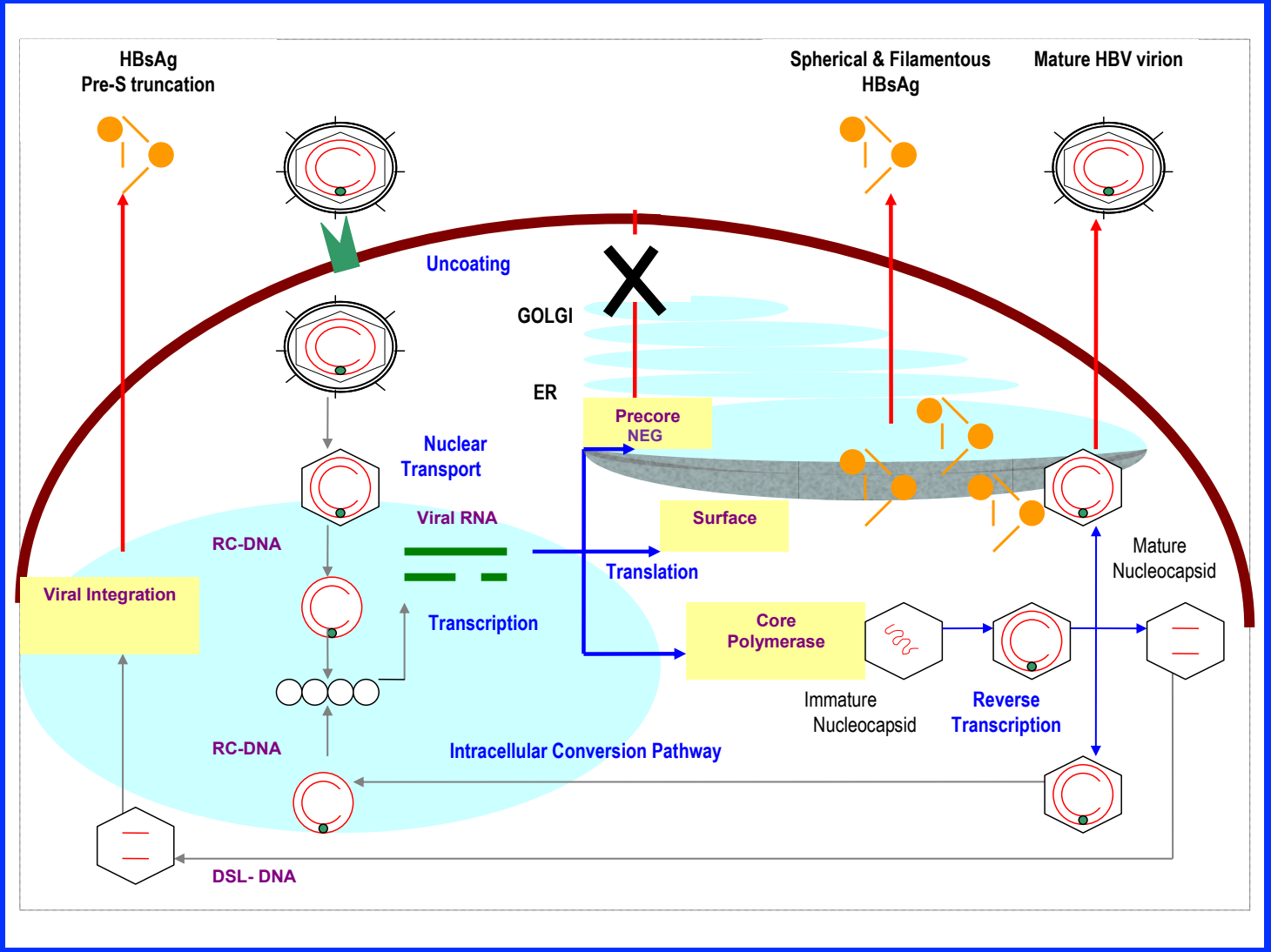




Newbold, J. et al 1995. J.Virol;69:3350

What I Think About Integrated HBV DNA Now

HBV Replication: ARC-520 Era



And What About RNAi ?

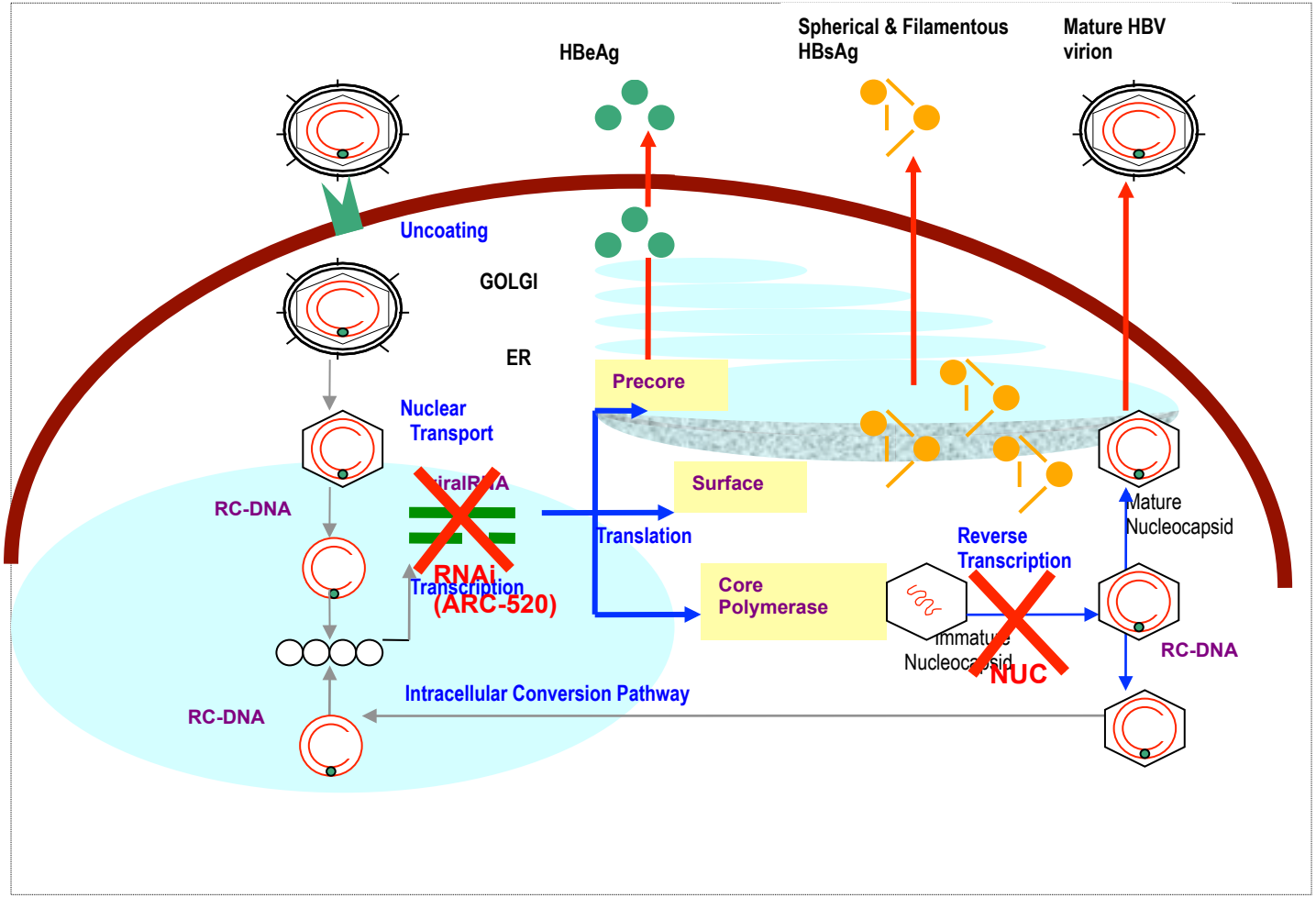
- In addition to HBsAg, ARC-520 is expected to have other important antiviral effects
  - HBeAg
  - HB core antigen
  - X antigen
- The “late responders” for HBsAg are intriguing
  - Due to reduction in other antigens affecting expression of HBsAg off integrated DNA?

This Raises Some Interesting Questions…..

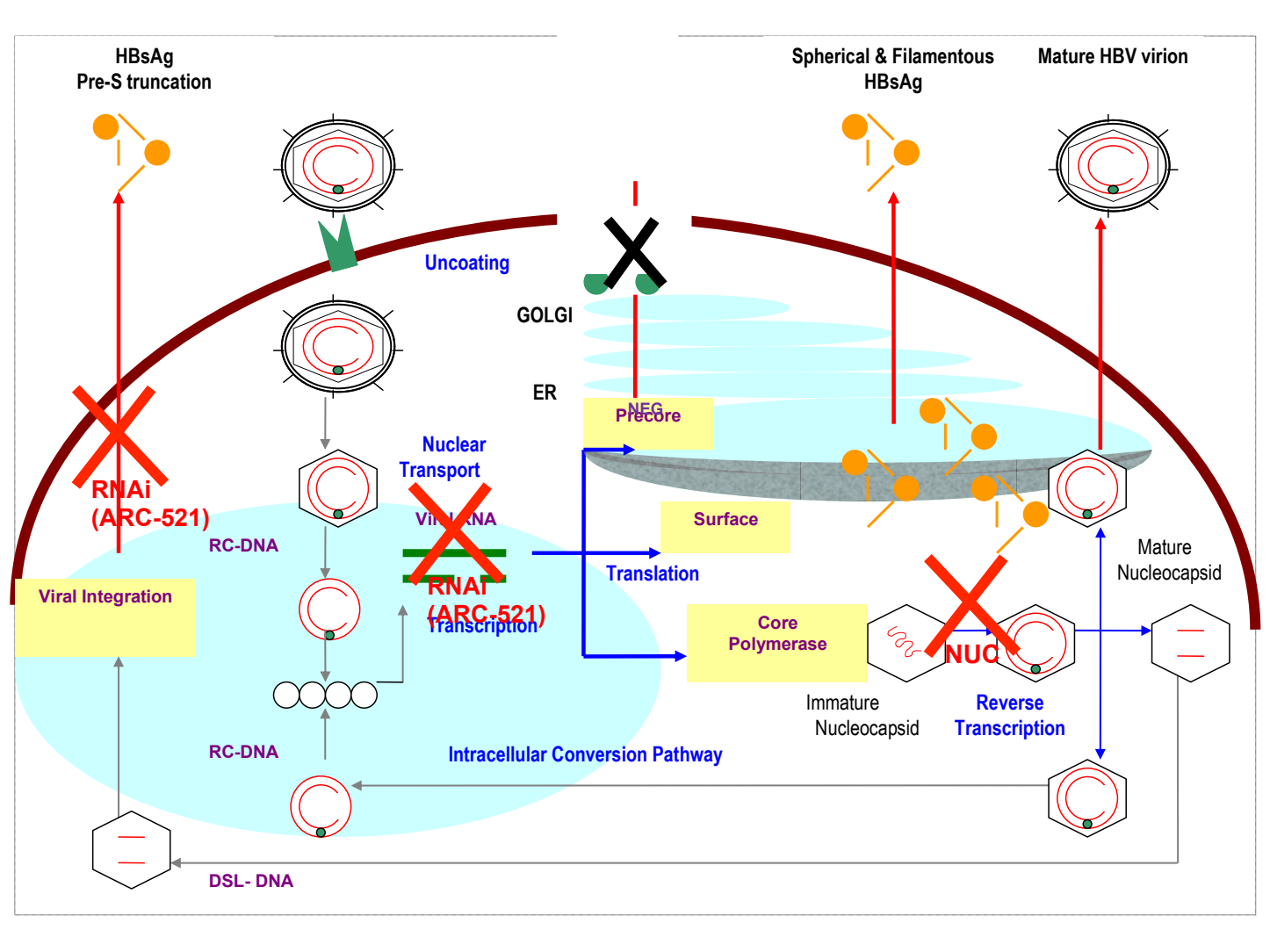
- Will capsid inhibitors have impact in the context of NUC effects on cccDNA?
- Can we quantitate changes in cccDNA in HBeAg negative patients in the context of clinical trials?
- For sterilizing cure, do we need to also get rid of integrated DNA?
  - How will we prove that we have achieved it?
- Will epigenetic approaches also have to account for integrated DNA?
- *And most crucial of all*, what are we learning from pre-clinical models that don't include integrated DNA? Will they be predictive of human clinical trials?

New Therapeutic Approaches to HBeAg-Pos AND HBeAg-Neg HBV

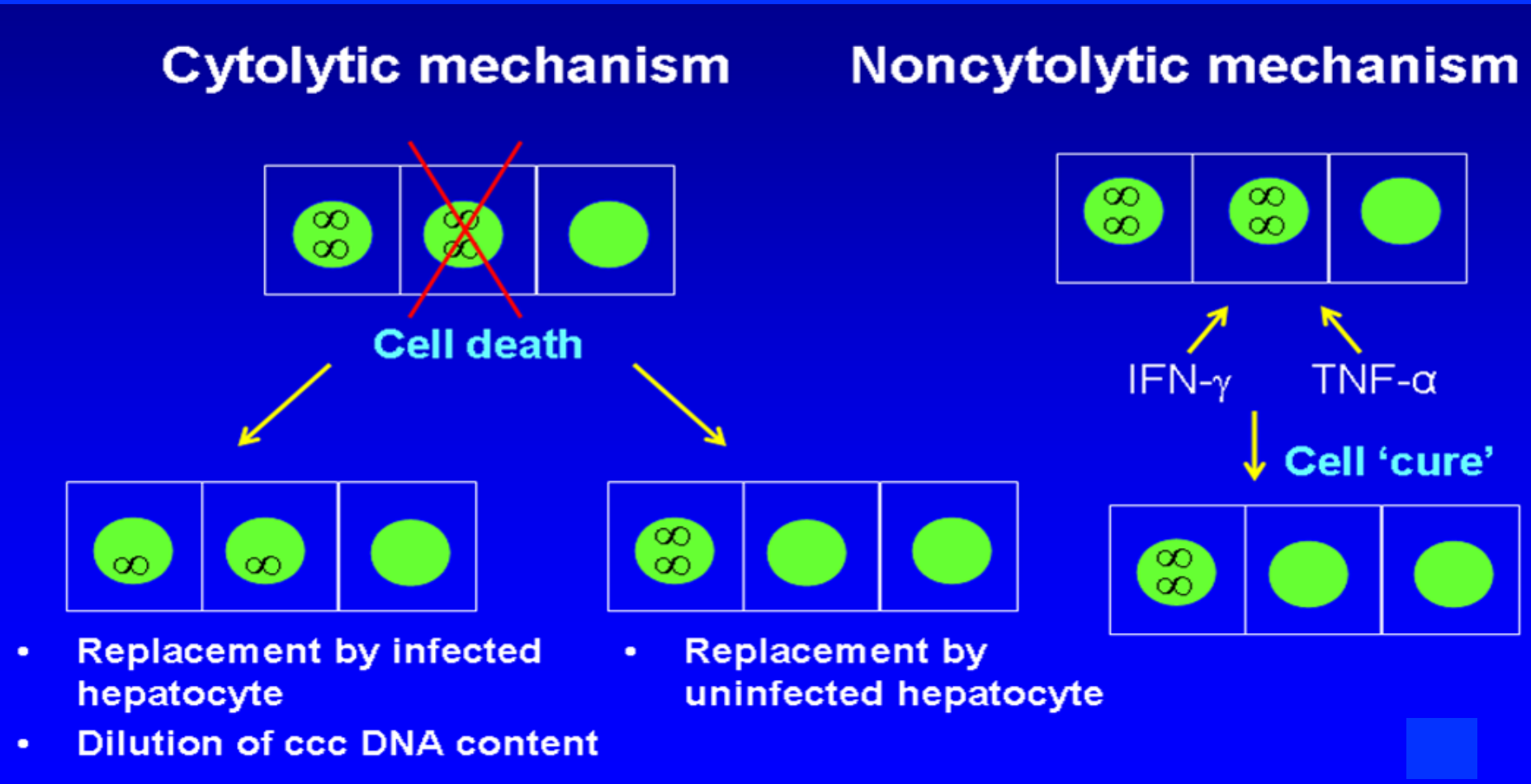
Targets in HBeAg-Pos HBV: ARC-520 + NUC



New Targets in HBeAg-Neg HBV: ARC-521 + NUC



How can we achieve HBsAg seroclearance? An immunological perspective



Lok, A 2005

Summary

Key Virological Findings for ARC-520

- Direct antiviral effect on serum HBsAg, HBeAg, and HBcrAg levels which are substantial
- HBeAg-Pos CHB and HBeAg-Neg CHB have very different viral patho-physiologies
- This has important therapeutic and prognostic significance

Closing Remarks

Chris Anzalone, Ph.D. – President and CEO

What have we done?

1. Demonstrated that DPC platform works in humans

- Deep and consistent target knockdown
- De-risks ARC-520, ARC-521, ARC-AAT, ARC-F12

2. Demonstrated that ARC-520 works in humans

- Deep HBsAg knockdown in treatment-naïve HBeAg(+) patients
  - Deepest RNAi knockdown ever reported in humans
- Deep knockdown of all other antigens tested in all cohorts
  - Indicates substantial disruption of virus

3. ARC-520 is well tolerated

- De-risks ARC-520, ARC-521, ARC-AAT, ARC-F12

4. New Paradigm for HBV lifecycle

- cccDNA decreases over time and with NUC treatment, integrated DNA becomes increasingly important source of HBsAg production

5. Expanded HBV pipeline with ARC-521

Stay Tuned

- Chimp data will be presented
  - 1 poster and 1 oral presentation at AASLD
  - Plan for additional submissions to journals and conferences
- Clinical data will be submitted for multiple publications and presentations
- Multiple dose P2b studies started for ARC-520
- Monarch combination studies with ARC-520 start shortly
- ARC-521 IND or equivalent in May 2016

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Q & A


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