Investigational therapies for chronic hepatitis B: will anything really work?

- This presentation will:
  - Describe the basis of therapies for chronic HBV
  - Describe the new therapies in the pipeline for HBV

- Conflicts:
  - Arbutus BioPharma (grant)
  - Contravir Pharma (Board Member)
The secret lives of the hepatitis virus and hepatitis!
The Liver and hepatitis B

Liver Weight: 3-4 lbs ~1.5 kg

Weight of brain: 3 lbs ~1.35 kg

Weight of kidney: 0.26 lbs ~130g
The Liver and hepatitis B

Liver Weight: 3-4 lbs ~1.5 kg

Weight of brain: 3 lbs ~1.35 kg

Weight of Kidney: 0.26 lbs ~130g

Tenofovir approved in US for HBV, in 2008, but not yet approved in China for HBV

All DAAs act on the polymerase (POL)
Revill, Testoni, Zoulim, Locarnini (2016) Nat Revs Gast&Hep

HBs (sAg)

Virions (DNA containing)
Target the virus

HBs (sAg)

Virions (DNA containing)

Revill, Testoni, Zoulim, Locarnini (2016) Nat Revs Gast&Hep
Target the host

Virions (DNA containing)

HBs (sAg)

Hepatocyte

NTCP

HSC

Space of dissec
The phases of chronic hepatitis B

<table>
<thead>
<tr>
<th>Immune tolerance</th>
<th>Immune clearance</th>
<th>Immune control</th>
<th>Immune escape</th>
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**HBsAg**
- Red line indicating presence of Hepatitis B surface antigen (HBsAg)

**HBV-DNA**
- Blue line with fluctuations indicating Hepatitis B virus (HBV) DNA levels

**HBsAb**
- Green line showing antibody response (HBsAb) against HBsAg

**ALT**
- Blue line representing Alanine aminotransferase (ALT) levels

- **HBsAg +ve chronic hepatitis**
- **Inactive (carrier) state**
- **HBeAg –ve active chronic hepatitis**

*Previously considered to be ‘healthy carriers’*
Treatment goals

- Clinically: reduce (eliminate) the clinical consequences of chronic hepatitis B
- Surrogate end points:
  - Eliminate detectable viremia
  - Normalize circulating levels of liver derived enzymes (ALT, AST)
  - Reduce HBs antigenemia
  - Sustained, off drug, beneficial antiviral affect

New DAAs: HBs suppressed
Chronic hepatitis B following Successful Treatment

*Previously considered to be ‘healthy carriers’
Potential new therapies for chronic hepatitis B

**Direct-acting antivirals**
- **Approved:** Polymerase inhibitors
- **Potential:**
  - Prodrugs of polymerase inhibitors
  - HBsAg inhibitors
  - Capsid inhibitors
  - RNaseH inhibitors
  - CRISPR/Cas9 system targeting cccDNA
  - HBV attachment inhibitors

**Host-targeting antivirals**

- **Immunomodulators**
  - **Approved:** Interferons
  - **Potential:**
    - TLR agonists
    - Therapeutic vaccines
    - STING agonists
    - Interleukins, cytokines

- **Targeting host function**
  - **Approved:** None
  - **Potential:**
    - Epigenetic modifiers
    - Entry inhibitors
    - Imino sugar glucosidase inhibitors
The HBV Investigational Development Landscape as of 4. 2005

Pre-clinical

- Isis HBV antisense
- ARC520 RNAi
- TTP sAg
- Rep2139 sAg
- Bay41109 capsid

Indirect Host modifier

Indirect Immunomodulator

Human Phase Trials

- GS4774 vac
- Inovio HBV
- Editop e
- DV501 Vac

DAA

*HDV active
The HBV Investigational Development Landscape as of 4. 2010

Pre-clinical:
- ARB-423 capsid
- Isis HBV antisense
- ARC520 RNAi
- TTP sAg
- ?Bay41109 capsid
- Benza capsid
- CpAMS capsid

Human Phase Trials:
- TAF
- ALN-HBV
- Lonafarin nib*
- DV501 Vac
- HDAC
- CAR
- Chime ne HBV
- GS4774 vac
- Inovio HBV
- HepTcell

Indirect Host modifier
- DAA

Indirect Immunomodulator
- ALN-HBV
- *HDV active
The HBV Therapeutic Development Landscape as of 4. 2015

**Pre-clinical**

- RNase Hi
- TTP sAg
- Benza capsid
- CpAMS capsid
- CRISPC AS (intel)
- CRiSPC AS (intel)
- AGX100 HBV
- cccDNA forma
- DDN RNAi
- Brinipristin SMAC
- HDAC
- CTR431
- NV100
- CTR431
- CAR
- Chimene HBV
- Tomem vax
- STING
- HepTcell
- TG1050
- Inovio HBV
- GS4774 Vac
- GS9620 TLR7
- DV501 Vac
- Roche 7795

**Human Phase Trials**

- Roche 7834 (sAg)
- ARC520 RNAi
- Isis HBV antisense
- GLS-4 capsid
- TLR7
- Vac
- Rep213 capsid
- 9 sAg
- ARB-423 capsid
- ABI 703 capsid
- ?Bay41109 capsid
- ?Bay41109 capsid
- ARB-423 capsid
- ARB174 0,1467 MycB entry*
- Lonafarinib*
- SB920
- Roche 7834 (sAg)

**Indirect Host modifier**

- DAA

**Indirect Immunomodulator**

- HDV active
Entry

• Pros:
  • Clinical validation
  • Anti-HDV
  • Stops life cycle from the beginning

• Cons:
  • Doesn’t affect established infection
  • MyrB: NTCP receptor targeted (?affect on bile)
  • CTR432: cell chaperons affected (tox?)

Pre-clinical

Contravir

- MycB receptor
- Small mol, oral

Human Phase Trials

Heptera

- Peptide, iv
- MycB entry

H Weidemeyer, S Urban
AASLD, 2018
Capsid/Core modifiers/uncoating

Pros
- Multiple, Essential viral function
- Validated clinically
- Extra-virological affects?
- Escape mutants rare

Cons
- ?replication inhibitor
- Resistance possible

Programs:
- Assembly
- Blumberg/Arbutus,
- Novartis
- Novira
- Roche
- Sunshine

Pre-clinical
- ARB-423 capsid
- ABI 7031 capsid
- Benza capsid
- CpAMS capsid
- Roche

Human Phase Trials
- GLS-4 capsid
- J&J capsid
- Novartis
- Bay411 capsid

HBV core protein dimers
- Phenylpropenamide and sulfamovibenamamide derivatives
- Heteroarylpirimidined derivatives
- Functional nucleocapsids
- Aberrant core protein aggregates that are subsequently degraded

Classes:
- Class I CpAM
- Class II CpAM

 créé par Romain Boissonnault
http://www.sciencemag.org/collection/4666
Capsid/Core modifiers/uncoating

HBs Ag inhibitors

Pre-clinical
- TTP sAg
- BSBI 259 sAg
- CRV43 1
- Rep213 9 sAg

Human Phase Trials
- Rep213 on-treatment antiviral response
  Courtesy: A Vailliant

DAA

HBV integration

Programs:
- Blumberg/Arbutus
- Contravir
- Replicor

RNA Degrading

Zhou et al, AVR (2017)
Mueller et al, J.Hep (2017)

Hu-mouse

Serum HBsAg (% Baseline)

Study Day

Roche DHQ
AB452
Arbutus

Pre-clinical

Zhou et al, AVR (2017)
Mueller et al, J.Hep (2017)
Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

Durable reduction of HBsAg, HBeAg, and serum HBV DNA increasingly reduced with each injection

HDI minicircle HBV1.3 (n=6), 3 x Q3Q doses, Day 57 evaluation

- S trigger alone effectively reduced HBsAg but not as effective for HBeAg
- Addition of small amount X trigger resulted in significantly greater HBeAg reduction

Acknowledgement: IHEP group
RNAi + Therapeutic vaccination (AAV model)

reduces HBs
cccDNA

Programs:
?Gilead, ?Arbutus, Assembly, ?Others
Blumberg, Fox Chase, Duke, Rockefeller
Immune Modulators as of Jan, 2017

Pre-clinical

- CAR
- Chimge ne HBV
- Tomega vac
- STING

Human Phase Trials

- Opdivo + GS4774
- SB9200
- Roche 7795
- GS4774 vac
- GS9620 TLR7
- DV501 Vac

Programs:
- Akshaya
- Arbutus/Blumberg
- BMS
- Dynavax
- Gilead
- HepTcell
- Inovio
- Roche
- Springbank
- Tomegvax

Chang & Liu, 2016
Normal induction of immune clearance
Homeostatic Tolerance

GS-9620 (vesatolimod), TLR 7 agonist, in CHB pts (not on antiviral Rx)
Springbank’s putative RIGI/STING acting small molecule first in class in people

Yuen et al, AASLD, 2018
Checkpoint intervention

Nivolumab (Anti PDL-1) in HBe neg CHB

M-2
N=12
N=10 (GS 4774+)
Combination for efficacy, not to repress resistance

Repress viremia and antigenemia (2 complimentary DAAs)
This could be sufficient for a large % of people

Enhance host immune mediated antiviral response
patient select
after antigen control
Stair way to a cure!!!
Each new drug will be a step up clinical benefit
Acknowledgement

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