Therapeutics for HBV, HCV, HCC; Biomarkers of HCC & Fibrosis

- 30 faculty and labs dedicated to the pursuit of antivirals
- Focus upon chronic viral diseases (viral hepatitis / herpes simplex)
- Outreach services for chronic viral infection
Disclosures

- Contravir: Board of Directors
- Arbutus: Research Grants & Equity
- Glycotest: Board of Directors
- Your companies name: Here!
Morphogenesis of hepatitis B virus as a therapeutic target
- Essential viral protein (*S* neg virus is not viable)
- Extra virological functions (*immuno evasion*)
Extra virological roles:
Extra virological roles:

Unmasking: too much HBs, HBsAbs are made, but complexed with HBs
Eliminate HBs, and unmask, liberate, present HBsAbs
HBsAb appearance after spontaneous or drug induced HBsAg loss occurs, but can take months to years.

17-76% of those who lose HBsAg spontaneously (~0.1-2.0% per year, peaking age 50) develop detectable HBsAbs within two-ten years.

Chu, C.-M. and Liaw, Y.-F. Antiviral Therapy, 2010
Tolerization
Too much HBs (S): exhaustion of T cells,
HBs as an immunosuppressor

- But, what’s the evidence that an anti-HBs agent would do more than just act as a direct acting antiviral?
Its levels have negative predictive value

- No decline in HBs after 12 weeks of IFN Rx is 90-100% predictive of ineffective Rx (Liaw, 2012; Mocauri, 2009; Rickborst, 2010)
Its levels have positive predictive value

- HBsAg pretreatment and early post treatment levels of HBsAg correlate with NUC long term response (Lee, Ahn, 2011; Shin, 2012)
Less HBsAg, better outcome

- Spontaneous loss of HBsAg associated with greatly reduced risk of liver cirrhosis and liver cancer

*Chu, C.-M. and Liaw, Y.-F. Antiviral Therapy, 2010*
Experimental Evidence

- In vitro experiments show HBsAg suppresses the function of monocytes, dendritic cells (DCs) and natural killer (NK) cells by direct interaction.

Hepatitis B virus surface antigen (HBsAg) and hepatitis B virus (HBV) inhibit antigen presentation capacity of myeloid dendritic cells (mDC).

mDC were activated in the presence of 1 μg/ml HBsAg or HBV particles (multiplicity of infection of 100) or the appropriate controls and cultured for 6 days with allogeneic T cells. (a) Representative experiment of the effect of serum derived-HBsAg on the T-cell stimulatory capacity of mDC, measured by [3H]thymidine incorporation in proliferating T cells (ratio mDC : T cells = 1 : 15.

Op den Brouw et al, 2009, Immunology, 126:2, 280-289
Breaking immune tolerance in mice by neutralizing HBsAg

HBsAg negative virus fail to establish chronic infections in C3H hydrodynamically infected mice (cccDNA established at similar rates)

Poster 91 Lu Gao/Zhipeng Yan (Roche)
And
Similar findings from:
Lin, Chen & Hwang, Abstract
Molecular basis of HBsAg morphogenesis
Secretion of SVPs and Virions

--Budding of viral cores to form virions
--secretion at PM

MVB/ESCRT III

HBV cores

--Golgi processing

Intermediate Compartment

MTP/VLDL

--disulfide bridge formation by PDI
--folding by GRP78, Calnexin
--glycoprocessing of HBsAg
--budding of subviral particles
--Other factors involved??

ER lumen

HBsAg

--Co-translational membrane
--Insertion at ER, glycosylation

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Therapeutic targeting of HBsAg

- Protein folding inhibitors (Blumberg)
- Small Molecule inhibitors (Arbutus, Roche)
- Nucleic Acid Polymers (NAPs) (Replicor)
- mAb
- RNAi, cccDNA inhibitors
Iminosugar
Protein Folding inhibitor (Editope)

Imino sugar cyclo hexyl akyl DNJs
Editope: Therapeutic creation of a novel T cell epitope to by-pass immune tolerance

Only woodchucks treated with protein folding inhibitors generated D epitope lymphocytic reactivity.
Small molecule

- small molecule
  - Blumberg/Arbutus
  - Preclinical
  - Prevents secretion
Blumberg Lipovir, appears to prevent HBsAg interaction with LDL morphogenesis system and inhibit HBsAg

Cuconatti et al 2014
Small Molecule, unreported mechanism

- Roche (Human Trials)
Replicor Nucleic Acid Polymers (NAPs)

Unknown mechanism, but impressive human trials

doi:10.1371/journal.pone.0156667
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0156667
Mono therapy with REP 2139-Ca

Current inhibitors of HBsAg

Cuconatti et al 2014
### Direct Acting inhibitors of HBsAg

<table>
<thead>
<tr>
<th>Rep 2139, Rep2165</th>
<th>Nucleic acid polymers (NAPs)</th>
<th>Phase II</th>
<th>Replicor</th>
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<td>Phase I/II</td>
<td>Roche</td>
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Conclusions

- HBsAg is an essential viral protein, so inhibitors of HBs will be Direct Acting Antivirals
- HBsAg appears to play a role in establishing and, or sustaining, chronicity
  - Perhaps via immuno evasion
  - Perhaps via non immune molecular mechanism
  
  Thus: HBs inhibitors could have direct acting and immuno enhancing antiviral affects

Endpoints: Decline or loss of HBsAg;
Gain of HBsAb; can be observed with people Rx with NUC
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