Bench to Bed:

Relevance of biomarkers used
in *in vitro* and *in vivo* model
systems to the clinic

Dieter Glebe

Institute of Medical Virology,
National Reference Centre (NRC) for Hepatitis B Viruses and Hepatitis D Viruses,
Justus Liebig University Giessen, Germany
Overview of HBV-related biomarkers

Serum markers

- HBV DNA
- HBsAg
- HBeAg
- anti-HBc
- anti-HBs
- anti-HBe

Liver enzymes: ALT, etc.

Liver biopsy
HBV-related biomarkers during occult HBV infection (OBI)

**Occult hepatitis B infection**
- Liver cccDNA+
- Serum HBV DNA+

**Overt hepatitis B infection**
- Liver cccDNA+
- Serum HBV DNA+
- Serum HBsAg+

*Dotted line in occult hepatitis B infection denotes that serum HBV DNA is detected intermittently and is usually at low levels <200 IU/ml*
HBV-related biomarkers during occult HBV infection (OBI)

Occult hepatitis B infection

Liver cccDNA+

*Serum HBV DNA+

Overt hepatitis B infection

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Serum HBsAg+

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Mak et al., JHep 2020
Challenges for HBV biomarkers to predict HBV cccDNA loss

Serum markers
- HBV DNA
- HBsAg
- HBeAg
- anti-HBc
- anti-HBs
- anti-HBe

Liver biopsy

Testoni et al., 2018
Challenges for HBV biomarkers to predict HBV cccDNA loss

**Serum markers**

**HBV DNA**
- Decline during NUC therapy does not correlate with cccDNA loss
- Complete HBV DNA suppression during NUC therapy?

**HBsAg**
- Seroclearance – “functional cure”?
- Quantitative HBsAg (qHBsAg)

Testoni et al., 2018
Virus and host factors determining HBsAg production and secretion

# Role of qHBsAg and composition of HBsAg

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
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</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-positive infection</td>
<td>HBeAg-positive hepatitis</td>
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<td>Immune tolerant</td>
</tr>
<tr>
<td>Immune tolerant</td>
<td>Immune active</td>
<td>Inactive</td>
<td>Immune active</td>
<td>HBsAb ±</td>
</tr>
</tbody>
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- **qHBsAg**
- **HBV DNA**
- **ALT**

**Treatment indication**

Charre et al., Antiviral Research 2019
### Role of qHBsAg and composition of HBsAg

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- **HBsAg**
- **HBsAb**

#### Virion

<table>
<thead>
<tr>
<th>SHBs</th>
<th>MHBs</th>
<th>LHBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>preS2</td>
<td>preS1</td>
<td>S</td>
</tr>
</tbody>
</table>

#### Subviral particles

- Transmembrane domains: 1, 2, S, and L
- 106/118/119 aa
- 55 aa
- 226 aa

- myr

#### Literature References

- Charre et al., Antiviral Research 2019
- Glebe and Bremer, Semin Liver Dis 2013
- Pfefferkorn et al., Gut 2018
Role of qHBsAg and composition of HBsAg

Charre et al., Antiviral Research 2019
Glebe and Bremer, Semin Liver Dis 2013
Pfefferkorn et al., Gut 2018
Role of qHBsAg and composition of HBsAg

Charre et al., Antiviral Research 2019
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Pfefferkorn et al., JHep 2020
Role of HBcrAg and HBV RNA for predicting cccDNA

Serum markers

HBV RNA
- Decrease indicate IFN response
- Low HBV RNA predicts sustained virological control off-treatment
- Low pre-genomic HBV RNA predicts low cccDNA levels/activation in the liver

HBcrAg
- Correlation with intrahepatic cccDNA during NUC therapy
- Prediction of clinical relapse after stopping NUC treatment
- Sensitivity should be improved
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Test requirements

Specificity
- Controls (avoid false-pos./false-neg.)
- point-of-care (POC) tests
- HBV genotype panel similar to HBV DNA/HBsAg assays

Sensitivity
- Test-dependent
- point-of-care (POC)
- HBV genotype panel similar to HBV DNA/HBsAg assays