WELCOME

Happy New Year 2019
Acknowledgements - Conflict of interest

• Investigator/speaker/grant from: Gilead, Merck, Abbvie, Janssen, Intercept, Genfit, Eiger
Hepatology
Today and the Future
We have to look at the Past to optimize Today the management of patients and to imagine the Future.
The Model of Hepatitis C: The Past

We can celebrate today the 30th Anniversary of the discovery of HCV

From non-A, non-B hepatitis to HCV
The Model of Hepatitis C: The Past

Award PHC 2009
We celebrated the 20th Anniversary of the discovery of HCV

Harvey Alter
Michael Houghton
Leonard Seeff
The Model of Hepatitis C: The Past

Hepatitis C is a model. In twenty years, we moved from a misunderstood and untreatable disease to a well described disease with more than 50% cure. Soon, 70% with triple therapy with protease inhibitors. And why not, almost 100% within the next 10 years. Rendez-vous at the Paris Hepatitis Conference in 2019!

Introduction of the PHC 2009
The Model of Hepatitis C: Today

- Almost 100% cure
- Cure means:
  - viral eradication
  - regression of fibrosis/cirrhosis
  - improved quality of life
  - improved outcome

Marcellin, Gastroenterology 2009   Kutala, AAC 2015
Cure with DAAs is associated with improved survival

DAAs improve survival (French Hepather cohort)

Backus et al. Hepatology 2018
Hepatitis C: The Future

- Cure does not mean elimination
- Barriers to elimination
  - Awareness
  - Information
  - Education
  - Screening
  - Access to therapy
The WHO Programme
Elimination of HCV by 2030

Chronic Liver Diseases (CLDs) a major Public Health problem
CLDs compared with other major chronic diseases

Global epidemiology of CLDs

- Prevalence of CLDs: 18.5%
- Number with CLD: 0.84-1.13 billion
- Prevalence of cirrhosis: 4.5% to 9.5%
- Incidence of HCC: 5.6%/year

Estimated increase within the next decade
CLDs today

Non Viral CLDs

1/3

- NASH; 10%
- ALD; 19%
- Other; 5%

Viral CLDs

2/3

- HBV; 43%
- HCV; 24%

Marcellin and Kutala. Liver Int. 2018
CLDs in the Future (5 years)
A Changing Pattern

Decrease of viral CLD
Increase of non viral CLD

Vaccination
Prevention
Screening
Treatment

Non Viral CLDs
1/2

Viral CLDs

Information
Education
Screening
Change in lifestyle
Treatment

NASH; 20%
ALD; 25%
HCV; 15%
HBV; 35%
Other; 5%

Decrease of viral CLD
Increase of non viral CLD

Marcellin and Kutala. Liver Int. 2018
HBV
The next Challenge

- Therapeutic vaccines
- cccDNA Inhibitors
- SiRNAs
- Entry inhibitors
- Capside inhibitors
- HBsAg inhibitors
- Immune system activators
### Compounds in Development for Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Silencing RNA’s (siRNAs): Interferes and destroys viral RNA</th>
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</thead>
<tbody>
<tr>
<td><strong>ARB-1467</strong> RNAi gene silencer (1.0)</td>
<td>Arbutus Biopharma, USA</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>RG6004</strong> RNAi gene silencer</td>
<td>Roche, Switzerland</td>
<td>Phase I/II</td>
</tr>
<tr>
<td><strong>ARO-HBV</strong> RNAi gene silencer</td>
<td>Arrowhead Pharma, USA</td>
<td>Phase I/II</td>
</tr>
<tr>
<td><strong>AB-729</strong> RNAi gene silencer</td>
<td>Arbutus Biopharma, USA</td>
<td>Phase I</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Entry Inhibitors: Interferes with HBV getting into liver cells</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Myrcludex B</strong> Entry inhibitor</td>
<td>Hepatera, Russia with MYR GmbH, Germany</td>
<td>Phase II</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Capsid Inhibitors: Interferes with the viral DNA protein shield</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Morphothiadin (GLS4)</strong> Capsid inhibitor</td>
<td>HEC Pharma, PR China</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>JNJ 56136379</strong> Capsid inhibitor</td>
<td>Janssen, Scotland</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>ABI-H0731</strong> Capsid inhibitor</td>
<td>Assembly Biosciences, USA</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>AB-506</strong> Capsid inhibitor</td>
<td>Arbutus Biopharma, USA</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>ABI-H2158</strong> Capsid inhibitor</td>
<td>Assembly Biosciences, USA</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>RG7907</strong> Capsid inhibitor</td>
<td>Roche, Switzerland</td>
<td>Phase I</td>
</tr>
</tbody>
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<thead>
<tr>
<th>HBsAg Inhibitors: Interferes with production of HBV surface antigen (sAg)</th>
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</thead>
<tbody>
<tr>
<td><strong>REP 2139 / REP 2165</strong> sAg inhibitor</td>
<td>Replicor, Canada</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><strong>Antisense Molecules: Binds to the viral mRNA to prevent it from turning into viral protein</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>IONIS-HBVRx (GSK3228836)</strong> Viral protein inhibitor</td>
<td>Ionis Pharma, USA with GSK</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>IONIS-HBVLRx (GSK33389404)</strong> Viral protein inhibitor</td>
<td>Ionis Pharma with GSK</td>
<td>Phase II</td>
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# New Treatments on the Horizon for Hepatitis Delta

## Hepatitis Delta Drug Watch

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>COMPANY</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambda (Pegylated Interferon)</td>
<td>Immune Response Stimulator</td>
<td>Elger BioPharma, USA</td>
<td>FDA Orphan Drug Designation Phase III (Projected 2018)</td>
</tr>
<tr>
<td>Myrcludex B</td>
<td>Entry Inhibitor</td>
<td>MYR-GmbH, Germany</td>
<td>EMA PRIME Eligibility Phase II</td>
</tr>
<tr>
<td>Lonafarnib</td>
<td>Prenylation Inhibitor</td>
<td>Elger BioPharma, USA</td>
<td>FDA Fast Track Designation Phase II</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>NTCP Inhibitor</td>
<td>Ziauddin University Hospital, Pakistan</td>
<td>Phase II</td>
</tr>
<tr>
<td>REP 2139 REP 2165</td>
<td>HBsAg Inhibitor</td>
<td>Replicor, Canada</td>
<td>Phase II</td>
</tr>
<tr>
<td>GI-18000</td>
<td>Immune Response Stimulator</td>
<td>GlobeImmune, USA</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>ALN-HDV</td>
<td>RNAi Gene Silencer</td>
<td>Alnylam, USA</td>
<td>Pre-clinical</td>
</tr>
</tbody>
</table>
NAFLD
A silent epidemic

United States 31%¹
Mexico 16%²
Italy 23%²
Israel 30%²
Japan 18-29%

NASH
A huge burden

Estimation in the US

- NAFLD: \(~80\) million Americans
- NASH: \(~16\) million Americans
- Cirrhosis: \(~1–3\) million Americans
NASH
An increasing indication for liver transplantation

UNOS Registry 2004-2013

Wong et al. Gastroenterology 2015
## Drugs and Development Status in NASH

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Phase</th>
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<tbody>
<tr>
<td>FXR agonist</td>
<td>Obeticholic acid</td>
<td>III</td>
</tr>
<tr>
<td>Anti-LOXL2 monoclonal antibody</td>
<td>Simtuzumab</td>
<td>IIb</td>
</tr>
<tr>
<td>Fatty acid/bile acid modifier</td>
<td>Aramchol</td>
<td>IIb</td>
</tr>
<tr>
<td>Dual inhibitor of CCR2 and CCR5</td>
<td>Cenicriviroc</td>
<td>IIb</td>
</tr>
<tr>
<td>Dual PPAR alpha/delta agonist</td>
<td>Elafibranor</td>
<td>III</td>
</tr>
<tr>
<td>Galectin-3-inhibitor</td>
<td>GR-MD-02</td>
<td>Ib</td>
</tr>
<tr>
<td>ASK1-Inhibitor</td>
<td>Selonsertib</td>
<td>III</td>
</tr>
</tbody>
</table>

Abbreviations: FXR, Farnesoid X receptor; LOXL2, Lysyl oxidase-like 2; CCR2, C-C chemokine receptor types 2; CCR5, C-C chemokine receptor types 5; PPAR, peroxisome proliferator-activated receptor.
HCC
The major Public Health issue

• Incidence: 800 000/year
• 750 000 deaths/year
• 20 Million disability-adjusted life-years
• 1.7 million new cases of HCC due to NAFLD over the next few decades
• Total cost $850 billion

**Future promising therapies for HCC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Key action</th>
<th>Country</th>
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<tbody>
<tr>
<td><strong>Oncolytic virus therapy</strong></td>
<td></td>
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<tr>
<td>JX-594 (&lt;i&gt;pexastimogene devacirepvec&lt;/i&gt;)</td>
<td>Vaccinia virus</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>Reolysin (pelareorep)</td>
<td>Reovirus</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>CC0070 (Adenovirus)</td>
<td>Adenovirus</td>
<td>USA</td>
</tr>
<tr>
<td>T - Vec (talimogene laherparepvec)</td>
<td>HSV - 1</td>
<td>USA</td>
</tr>
<tr>
<td>G47Δ</td>
<td>HSV - 1</td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Immunotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Targeting T cells</td>
<td>USA /Europe</td>
</tr>
<tr>
<td>Durvalumab</td>
<td></td>
<td>USA</td>
</tr>
<tr>
<td>Nivolumab</td>
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<td>USA</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td></td>
<td>USA</td>
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<tr>
<td>BMS-986016</td>
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<td>USA/Europe</td>
</tr>
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New technologies for the Future Hepatology

• Genomic
• Proteomic
• Big data
• Artificial intelligence

New tools for more accurate markers, imaging and logarithms for an optimal personalized diagnosis, prognosis and therapy
Conclusion
Today and the Future

• HCV: good job!
  Objective: elimination

• HBV: the next challenge!
  Combination available within 5 years?
    Antiviral + anti-protein + immune stimulator?

• NASH: understand!
  know the epidemiology, learn the natural history,
  understand the mechanisms, develop effective drugs
  > change of lifestyle

• Alcohol: not forget!
The Future

The new technologies thanks to translational research will accelerate the progress to reach Personalized Hepatology
Wish you a good PHC
Characteristics patients with CLD in the future

Work-up in patients with CLD: a multiorgan approach

Extrahepatic comorbidities
- Type 2 diabetes
- Sleep apnea
- Hypertension, arterial
- Dyslipidemia

Liver condition
- Cofactors of fibrosis
- Pathological form
- Stage
- Prognosis

NAFLD
- Cofactors of fibrosis
- Pathological form
- Stage
- Prognosis

HVB
- Cofactors of fibrosis
- Pathological form
- Stage
- Prognosis

ALD
- Cofactors of fibrosis
- Pathological form
- Stage
- Prognosis
NAFLD – Center stage of the metabolic syndrome?

Hypertension

- Prevalence essential HTN

Diabetes

- Incident diabetes
- Insulin requirements

Cardiovascular

- Endothelial & coronary dysfunction
- Carotid plaques
- Impaired ventricular function and metabolism
- CV events

NAFLD – Center stage of the metabolic syndrome?
The future seen from the inside

- Palliative care in hepatology
- Hepatotoxicity
- Physio-pathological
- Pharmacogenetics
- New drugs
- Biomarkers
- Molecular hepatology
- New technology
CLDs: The Future
A Changing Pattern

Screening + change in lifestyle + education + DRUGS

Increase of non viral CLD

Screening + prevention + DRUG COMBOS

HBV; 35%
HCV; 15%
ALD; 25%
NASH; 20%
Other; 5%

Decrease of viral CLD
Increase of non viral CLD
“If one wishes to contemplate the future of hepatology, one may want to climb several mountains to survey the entire panorama which may be distorted by the view from a particular peak.”

The new technology in the future hepatology

Epigenetic landscape influences the liver cancer genome architecture

Theranostics 2018; 8(6):1740-1751. doi:10.7150/thno.22010
Research Paper
Genomic analysis of liver cancer unveils novel driver genes and distinct prognostic features
Xiangchun Li, Wei Qi Xu, Wei Kang, Sunny H. Wong, Mengyao Wang, Yong Zhou, X
Number of patients with CLD (million)

- HBV: 43%
- HCV: 24%
- ALD: 19%
- NASH: 10%
- Other: 5%
Alcohol: the Neglected Problem

- 3.3 million deaths (6% of all global deaths). WHO source
- 88,000 deaths/year (US)
- 229 billion $/year. Increasing
- Effective alcohol policy measures have been shown to reduce alcohol mortality, including ALD-related mortality
- Cost effective measures include increase in taxes on sales of alcohol drinks, minimum sale price for alcohol, raising the legal age for buying alcohol, low level interventions from clinicians
Primary care setting UK
Asymptomatic, low risk CLD
N=1118

- NALD: 25%
- ALD: 26%
- No cause: 45%
- Classic CLD: 4%

Advanced fibrosis 2%

Armstrong et al., J Hepatol 2013

Tertiary care setting France
Increased ALT, histology
N=274

- NASH: 32%
- Steatosis: 26%
- Normal: 19%
- Other: 23%

Advanced fibrosis 24%

De Ledinghen et al. J Hepatol 2006
Inflammation
The key of CLD progression

Future Hepatology needs a solid foundation of progress in basic and translational research on inflammation and fibrosis.
The primary tests for diagnosing liver disease include liver function tests to test the enzymes.

Measures of inflammation: Liver cell enzymes (GGT, ALT, CDT).

Liver ultrasound to see any damage.

Many liver screening tests routinely check for liver function since many of the symptoms do not show until damage to the liver has already happened.
Criteria WHO for HCV screening test

• Focused testing in most-affected populations regardless of whether delivered through facility- or community-based testing
• General population testing in region with a $\geq 2\%$ or $\geq 5\%$ HCV antibody seroprevalence
• Birth cohort testing for older persons with higher risk of infection and morbidity within populations that have an overall lower general prevalence.
• Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.
• Routine testing of pregnant women for HCV infection is currently not recommended.
Transaminases meet all criteria (WHO) for validation of a universal screening test for all CLDs

✓ The test must be simple, reliable, fast and inexpensive

✓ The test must have good sensitivity, specificity, positive and negative predictive values

✓ The test must have a sensitivity of at least 75%, a false-positive rate of < 10% and a rate of invalid results < 5%
Different roles and level to achieve the awareness

- Information to the public
- The role of medical profession
- The health authorities with their policy
- Available and effective health care system
“The future hepatology, the art of solving the same problems with a little more ability until the last hepatotoxic agent or the spirit of metabolic syndrom will be died” Said Patrick Marcellin
HCC
The landscape of treatment will change

Radiofrequency ablation (RFA)
Trans-arterial chemoembolization (TACE)
Highly-focused ultrasound (HIFU),
Microwave ablation (MWA)
Irreversible electroporation (IRE)
Selective internal radiation therapy (SIRT)
Oncolytic virus therapy
Immunotherapy

Han et al. Cancer 2017