ALEH-AASLD Research Workshop 2018

Research in Hepatology
What is hot and what is not

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What is **Hot** and what is not ..... 

**Training level:**
- Trainees
- Post Doc
- KOL
- Policy makers
- Industry

**Type of audience:**
- Basic scientists,
- Bench to bedside
- Clinicians, surgeons,
- ID, GI, Onco, Radio
  and Epidemiologists

**Disease nitches interest:**
- Viral, metabolic, autoimmune
- Biliary tract, Cirrhosis, Tumours
- Liver transplantation
Different steps for research interventions in Liver diseases

- Vaccination & Policies
- Viral hepatitis therapy
- NASH treatment & antifibrotics
- Transplantation & Immuno oncology

HEALTHY LIVER
CIRRHOSIS
HCC
CLD: INFLAMATION
What is **Hot** what´s not: Topics

**Research Consortiums in Latin America:**
- Opportunity for multicentric and or proof the concept studies
- Ready for Basic research Networks?
What is HOT and what’s not in Microbiota in Liver Diseases
Gut microbiome and liver diseases

Herbert Tilg, Patrice D Cani, Emeran A Mayer

Gut microbiota contributes to the regulation of de novo hepatic lipogenesis.
Specific nutrients such as fat and alcohol change microbiota composition in a harmful manner, whereas prebiotics counteract these effects.
Both innate immune system and xenobiotic metabolism control liver lipid metabolism via mechanisms involving bacterial components and metabolites.
Hepatic innate immunity controls liver bioactive lipids production and contribute to switch from NAFLD to non-alcoholic steatohepatitis.
Gut microbiome and liver diseases

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Box 5 Gut-brain axis and microbiota

- There are bidirectional communication channels between the gut, its microbiota and the brain
- The trafficking in these channels is significantly altered in hepatic encephalopathy (HE) due to alterations in the gut microbiota and their metabolites, as well as to increased permeability of the epithelial barrier and the blood-brain barrier
- In HE, both inflammatory signal as well as neuroactive microbial metabolites reach the brain and can induce regional neuroinflammation in the brain
- Both structural and functional brain alterations have been reported in patients with HE, and these alterations show correlations with behavioural alterations and symptoms
- Altered brain gut microbiome interactions in HE provide targets for novel treatment approaches, including prebiotics and probiotics, and microbe-specific antibiotics
Microbiota and the Liver at the 6th World Congress

- **MAIT cells (Mucosal-Associated Invariant T cells)** in liver disease and antibacterial response. Riva A, Institute of Hepatology London, Foundation for Liver Research, United Kingdom
- **Using germfree animal models to prove the role of the gut microbiota in liver diseases.** Philippe Gérard, INRA, France
- **Delayed liver regeneration** in germ-free mice is normalized following colonization with conventional mouse microbiota. Wheatley AM, National University of Ireland, Ireland
- **Gut dysbiosis and altered barrier function** precedes the appearance of **metabolic syndrome** in a rat model of maternal food-restriction. Paula Martínez-Oca, University Complutense of Madrid, Spain
- **Fecal Microbiota Transplant 2018: What’s next?.** Peter Konturek, Teaching Hospital of the University of Jena, Germany
What is HOT and what’s not in Hepatic Encephalopathy
Microbiota and sarcopenia link in HE pathogenesis

- Ammonia is produced from nitrogenous products by gut bacterial metabolism of proteins and from deamination of glutamine in the small intestine. Normally, ammonia is cleared by liver and kidneys and metabolized in skeletal muscle.
- However, as a result of liver dysfunction and shunting, ammonia cannot be cleared adequately. Increased ammonia levels in the plasma increases glutamine (via glutamine synthetase) in astrocytes, which subsequently causes intracellular swelling and edema.

Hepatic Encephalopathy: Probiotics and Fecal Transplantation

Update on the Therapeutic Management of Hepatic Encephalopathy

Linda Skiested Kornerup¹ · Lise Lotte Gluud² · Hendrik Vilsstrup¹ · Gitte Dam¹

Abstract

Purpose of Review Hepatic encephalopathy (HE) is a common and devastating complication to chronic liver disease. In this paper, we summarize the latest research and evidence of both conventional and up-coming treatments.

Recent Findings Meta-analyses report beneficial effects of lactulose, branched-chain amino acids, rifaximin, and to some degree L-ornithine L-aspartate on the manifestations of HE in patients with cirrhosis, and generally the numbers needed to treat are low. Recent studies on newer HE treatments including ornithine phenylacetate, spherical carbon, and fecal microbiota transplant also report potentially beneficial effects on HE manifestations.

Summary The conventional treatments benefit patients with HE. Newer treatments are under study and more research is needed for their validation.
What is HOT and what’s not in NAFLD, Hepatic Fibrosis
Modeling the Epidemic of NAFLD Demonstrates an Exponential Increase in Burden of Disease

Distribution of NASH population by fibrosis stage in the United States for 2015 and 2030.

Chris Estes, et al HEPATOLOGY, VOL. 67, NO. 1, 2018
There are a number of anti-fibrotic therapies entering clinical trials in NASH patients, but a major obstacle to their development is the lack of sensitive and noninvasive tools for assessing fibrogenesis. Here, we discuss our preclinical work to develop molecular imaging of collagen as a biomarker.

Development of Dual PPAR Agonist and IVD in NASH
Dean W. Hum, PhD, CSO, Genfit

Elafibranor is a first-in-class PPARα/δ agonist which has demonstrated in a Phase IIb study NASH resolution without the worsening of fibrosis while also improving cardio-metabolic risk. NASH resolution correlated with fibrosis improvement. Elafibranor is now being investigated in Phase III. GENFIT is also developing a blood-based in vitro diagnostic to identify NASH patients who are at risk of disease progression— a key unmet clinical need.

Other companies involved in NASH research: Gilead, BMS, Novartis, Novo Nordisk...
Hepatic Fibrosis: New Concepts and Controversies

AASLD Single Topic Conference, September 14th & 15th, 2018

I: Biology of Organ Fibrosis, What’s New?
Moderators: Don C. Rockey, MD, FAASLD and Rebecca G. Wells, MD

II: Microbiome, Immunity, and Fibrosis: The Gut-Liver Axis
Moderators: Meena B. Bansal, MD, FAASLD and Bernd Schnabl, MD

III: NASH, Fibrosis Progression and HCC in NAFLD
Moderators: Ekihiro Seki, MD, PhD and Robert F. Schwabe, MD

IV: Nonparenchymal Cells and Fibrosis
Moderators: Rebecca G. Wells, MD and Cynthia Ju, PhD

V: Emerging Concepts in Liver Fibrosis
Moderators: David Brigstock, PhD, FAASLD and Jelena Mann, MD

VI: Moving from Bench to Bedside in Fibrosis
Moderators: Meena B. Bansal, MD, FAASLD and Manal F. Abdelmalek, MD,
Cell-free nucleic acids (RNA and DNA) are released from a variety of dying hepatic cells; these nucleic acids then enter systemic circulation where they can be isolated from serum or plasma and quantified using a number of methods. Screening cell-free nucleic acids for specific epigenetic modifications, such as DNA methylation, as well as sequence alterations can aid fibrosis grading and early HCC detection and/or recurrence.

What is HOT and what’s not in HCC
FDA approves NIVOLUMAB for HCC previously treated with Sorafenib

- On September 22, 2017, the FDA granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for the treatment of HCC in patients who have been previously treated with sorafenib.

- 154-patient subgroup of CHECKMATE-040 (NCT 01658878), a multicenter, open-label trial conducted in patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib. The trial enrolled patients with either active HBV (31%) or HCV (21%) but not those with active co-infection or with HDV infection. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks.

- The overall response rate, assessed with RECIST 1.1, was 14.3% (95% CI: 9.2, 20.8), with 3 complete responses and 19 partial responses. Response duration ranged from 3.2 to 38.2+ months; 91% of responders had responses lasting 6 months or longer and 55% had responses lasting 12 months or longer.
FDA approves REGORAFENIB for HCC previously treated with Sorafenib

• On April 27, 2017 the FDA expanded the indications of Regorafenib to include the treatment of patients with HCC who have been previously treated with Sorafenib.

• An multicenter, randomized, double-blind, placebo-controlled trial of 573 patients with Child-Pugh A and BCLC Stage B or C with disease progression following Sorafenib.

• Regorafenib160 mg PO qd plus best supportive care (BSC) vs matching placebo plus BSC for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity.

• Results: significant improvement in overall survival (OS) (HR=0.63, 95% CI: 0.50, 0.79, p<0.0001) with an estimated median OS for patients in the Regorafenib arm of 10.6 months vs 7.8 months for patients in the placebo arm.

• Significant improvement in progression-free survival (PFS) on modified RECIST (HR=0.46, 95% CI: 0.37, 0.56, p<0.0001), an estimated median PFS of 3.1 and 1.5 months in Regorafenib and placebo arms.

• The overall response rate, based on modified RECIST, was 11% in Regorafenib arm and 4% in the placebo arm.
FDA approves LEVANTINIB as first-line therapy for unresectable HCC:

- On August 16, 2018, the FDA approved lenvatinib capsules (Lenvima, Eisai Inc.) for first-line treatment of patients with unresectable HCC.

- International, multicenter, randomized, open-label, non-inferiority trial (REFLECT; NCT01761266) conducted in 954 patients with untreated, unresectable HCC. Patients were randomized (1:1) to lenvatinib (12 mg PO qd for patients with a baseline body weight of ≥60 kg and 8 mg PO qd for patients with a baseline body weight of <60 kg) or sorafenib (400 mg orally twice daily). Treatment continued until radiological disease progression or unacceptable toxicity.

- REFLECT demonstrated that lenvatinib was non-inferior but not statistically superior to sorafenib for overall survival (OS) (HR 0.92; 95% CI: 0.79, 1.06)
Sorafenib & Nivolumab as first-line therapy for unresectable HCC Trial

**Sponsor:** University of California, San Francisco

**ClinicalTrials.gov Identifier:** NCT03439891

**Study Type:** Interventional (Clinical Trial)

**Estimated Enrollment:** 40 participants

**Allocation:** Non-Randomized

**Intervention Model:** Sequential Assignment

**Masking:** None (Open Label)

**Primary Purpose:** Treatment

**Official Title:** Multicenter Pilot Study of the Safety, Efficacy, and Immune Cell Profiling in Advanced HCC Patients Treated with the Combination of Sorafenib Plus Nivolumab as First-Line of Systemic Therapy

**Actual Study Start Date:** February 21, 2018

**Estimated Primary Completion Date:** May 29, 2020

**Estimated Study Completion Date:** December 31, 2020
Despite the rarity of circulating tumor cells (CTC), in the region of one per billion blood cells in patients with metastatic disease, advances in technologies now enable their detection and isolation, supporting both biomarker and mechanistic biology studies. HCC, hepatocellular carcinoma.

What is HOT and what’s not in Viral Hepatitis
Micro-elimination – A path to global elimination of hepatitis C

Jeffrey V. Lazarus\textsuperscript{1,2,*}, Stefan Wiktor\textsuperscript{3}, Massimo Colombo\textsuperscript{4}, Mark Thursz\textsuperscript{5}, on behalf of the EASL International Liver Foundation

\textsuperscript{1}Barcelona Institute for Global Health (ISGlobal), Hospital Clinic, University of Barcelona, Barcelona, Spain; \textsuperscript{2}CHIP, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; \textsuperscript{3}Department of Global Health, University of Washington, USA; \textsuperscript{4}Clinical and Research Center Humanitas, Rozzano, Italy; \textsuperscript{5}Division of Digestive Diseases, St Mary's Hospital, Imperial College London, London, UK
Background: Molecular testing at the point-of-care may turn out to be game changer for HCV diagnosis and treatment monitoring. One such assay GeneXpert® has recently been released.

Objectives: Comparative analysis between GeneXpert® and Abbott HCV-RNA was done. Perfect correlation between the assays in the course of therapy at different treatment time-point in genotypes 3 and 1 was seen.

Conclusion: The study demonstrates excellent performance of the Xpert® HCV assay in viral load assessment and in treatment course monitoring consistency.
In this review, we summarized new therapeutic approaches and novel molecular targets for anti-HBV drug development.

To achieve a more sustained and effective control of HBV infection, a combination of the existing HBV therapies and one or more of the above modalities, either small-molecule drugs or biologics, will be necessary.

The next milestone in the therapy of HBV infection, a functional “cure” that has remained elusive, is likely within our grasp within the next decade.
rüd

R&D in HBV therapy: still in process

ILC, April 2018, Parallel Session: HBV Cure
Encouraging developments towards an HBV cure. There are now almost 50 new anti-HBV and anti-HDV treatments being openly investigated, and 17 of these are already undergoing phase II clinical trials.

- T cells grafted with HBV-specific T-cell receptors of high functional avidity achieve functional cure of HBV infection in humanized mice. Karin Wisskirchen K et al

- Preclinical antiviral drug combination studies utilizing novel orally bioavailable investigational agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, a HBV RNA destabilizer. Nagraj Mani et al

- Discovery of a novel core inhibitor EP-027367 with potent antiviral activity both in vitro and in a humanized mouse model. Michael Vaine et al
What is HOT and what’s not in Liver Transplantation
The Role of Humoral Alloreactivity in Liver Transplantation: Lessons Learned and New Perspectives

- Preformed DSA are present in 13–17% of LT recipients, and an additional 8% will develop de novo DSA within the first year after transplant.
- Yet chronic rejection for allograft loss following LT, affects only 3-4% of liver allografts among adult maintained on tacrolimus.
- Furthermore, results from immunosuppression withdrawal trials in pediatric LT recipients indicate that even operationally tolerant patients may harbor DSA.
- The presence of DSA does not necessarily correlate with progressive increase in histologic inflammation or fibrosis.
Immunosuppressant agents in liver transplantation: Less is more

- Immunosuppressive medications landscape remains steadfast clinicians stay up to date on best practices.
- While HCV is nearly subdued as a post-transplant complication,
- MS is increasingly harming patients exacerbated by immunosuppression.
- Finally, given the confluence of MS and CI side effects, treatment of early ACR could be excessive and must be reevaluated in light of today’s average
- Less is more: an opportunity for clinical research

What is HOT and what’s not in research networks
Already well established Liver Research Consortiums
TARGET: Public-Private-Partnership RWD for HCV Direct Acting Antivirals

Figure 1. (A) The Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) is led by the University of Florida and the University of North Carolina. The Clinical and Data Coordinating Centers (blue) are responsible for the overall management of the study. The Steering Committee (red) is consulted on all matters having network-wide scientific or operational impact. (B) HCV-TARGET clinical sites across North America, Europe, and Israel including academic sites (green triangle) and community sites (yellow circle).
HEP-NET: a Research network with horizontal and vertical integration

- Acute Hepatitis B and C
- Co-infections (HBV/HCV, Delta)
- Special patient groups
- … Registration trials in these fields are not pushed by the industry

Investigators initiated trials only possible with a structure such as HEP-NET or other networks

More than 20 clinical trials since 2002
Developing Research Consortiums in Latin America: LALREAN’s experience

**Developing Multicenter Consortia in Liver Disease in Latin America: Challenges and Opportunities**

Manuel Mendikal intuition and Marcello O. Siloto

Liver Transplantation, Vol. 23, No. 9, 2007

**LIVER TRANSPLANTATION**

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Multicenter consortia are usually composed of a group of people or associations with similar interests and a common mission. These partnerships allow for coordination of efforts and resources in pursuing pre-established goals. While some biomedical scientists in general and in the field of hepatology in particular, several consortia have emerged to pursue similar solutions that are either specific to hepatobiliary and liver diseases, as well as to the general scientific community.

The purpose of this article is to describe those difficulties we continue to face today and to discuss the opportunities for improvement.

**Where Do We Stand in Latin America?**

Latin America is a heterogeneous region comprised of 20 countries with more than 600 million people. The region presents significant disparities in economic resources, with most of the population living in low- and middle-income range. As a result, the availability of tertiary care and advanced diagnostic and therapeutic services is limited, making the region a prime candidate for collaborative research initiatives.

In this context, the PAN Liver consortium was established in 2006, with the aim of strengthening liver research and care in Latin America. Since its inception, the consortium has played a pivotal role in advancing liver research and improving patient outcomes.

**Opportunities**

In the described scenario, the development of a consortium for studying liver diseases or any other pathology would seem to be an essential step. However, to achieve this, there are several challenges that need to be addressed.

1. **Insufficient grants and funding to maintain academic career development.**
   - To address this issue, it is crucial to obtain funding from various sources, such as government agencies, private foundations, and international organizations.

2. **Migration of qualified physicians and researchers to countries with greater resources.**
   - Implementing policies that attract and retain talent is essential. This can be achieved through competitive salary packages, research grants, and opportunities for professional development.

3. **Lack of consortia or interest groups that are sustainable over time.**
   - The sustainability of consortia is critical for long-term success. Building strong networks and fostering collaborations with other regions can help ensure the longevity of these initiatives.

4. **Consequently, what has been the specific situation here in Latin America regarding liver consortia?**
   - A very frustrating aspect is that most of the initial impressions have been focused on the development of collaborative groups established to investigate a particular topic. In this sense, there have been some publications, but none of the questions have been answered, groups were dissolved, and lost continuity.

5. **Opportunities**
   - In the described scenario, the development of a consortium for studying liver diseases or any other pathology would seem to be an essential step. However, to achieve this, there are several challenges that need to be addressed.

6. **One way of facing this problem is by providing medical education and research opportunities for the training of young physicians in academic careers.**
   - This can be achieved with simple, low-cost interventions, such as the introduction of bedside teaching, which can be done in hours outside of regular patient care. For example, research methodology, or the assignment of a tutor with an academic vocation that can coach and guide students in the research area. We are certain that with more physicians interested in academic career, scientific production would increase. A necessary strategy to maintain productivity of young physicians in academic careers in their inclusion in clinical and epidemiological research. Many of them will desert if they do not have incentives that can help ensure their professional development. This scenario is where consortia may offer an appropriate academic environment and support by facilitating the cultivation of interest in a systematic and reliable way. With this structure, the research model can provide opportunities for the development of research projects and the implementation of educational programs.
What is HOT what’s not conclusions

- Liver Research is HOT
- Feel free to pick up your own choice
- Be smart, choose:
  - The right research question and study design
  - A friendly and trained support team
    - scientists, epidemiologists, statisticians
  - Appropriate logistics and financial support
  - Network through ALEH/ASLD
- Do not give up!
Back up slides
Extracellular vesicles (EVs) are released from a variety of different cell types in the liver under physiological and pathophysiological conditions into the extracellular space where they interact with neighbouring target cells, as well as into the systemic circulation where they can be isolated and quantified. EV surface markers and cargo may reflect the cell of origin as well as the specific stress that induces their formation and release.

Cell-free DNA methylation as liquid biopsy for the assessment of fibrosis in patients with nonalcoholic steatohepatitis: a gap between innovation and implementation

Silvia Sookoian¹, Carlos J. Pirola¹,²

Hepatobiliary Surg Nurs 2017;6(2):117-121

Figure 1: Obstacles to translating the concept of cell free DNA (cfDNA) methylation into the clinical setting for the stratification of liver fibrosis. This image illustrates the three main pitfalls that must be overcome before cfDNA methylation could be employed as a fibrosis biomarker, namely: (I) cfDNA is at very low concentrations; isolation and quantitation; (II) highly fragmented DNA; and (III) conversion of DNA.
Core tip: Accumulating evidence about circulating tumor cells and cell-free nucleic acids in the blood of cancer patients has suggested their potent clinical utilities as novel biomarker. This concept, so-called “liquid biopsy” is widely known as an alternative approach to cancer tissue biopsy. This method might facilitate a more sensitive diagnosis and better decision-making by obtaining genetic and epigenetic aberrations that are closely associated with cancer initiation and progression. In this article, we review recent developments based on the available literature on both circulating tumor cells and cell-free nucleic acids in cancer patients, especially focusing on Hepatocellular carcinoma.
Liquid Biopsy for HCC

Circulating Tumor DNA Analysis for Liver Cancers and Its Usefulness as a Liquid Biopsy


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CONCLUSIONS: The presence of ctDNA reflects tumor progression, and detection of ctDNA can predict VP and recurrence, especially extrahepatic metastasis within 2 years. Our study demonstrated the usefulness of ctDNA detection and sequencing analysis of cell-free DNA for personalized treatment of liver cancer. (Cell Mol Gastroenterol Hepatol 2015;1:516–534; http://dx.doi.org/10.1016/j.jcmgh.2015.06.009)
Liver antibody-mediated rejection

- Antibody-mediated rejection of the allograft liver is a diagnosis that requires both clinical and histologic correlation.
- The criteria for diagnosing acute antibody-mediated rejection include serum donor–specific antibodies, C4d staining, specific histologic findings, and exclusion of other entities.
- There are several treatment options for acute and chronic antibody-mediated rejection.