# Liver Forum 5:
# Summary of Proceedings

Thursday, November 10, 2016
Boston, Massachusetts

***Facilitating Collaborative Research in Drug Development and Health Policy***
*1608 Rhode Island Avenue NW, Suite 212, Washington DC 20036*
*(p) 202-833-4617 (f) 202-872-4316*
*www.hivforum.org*

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## ABBREVIATIONS

AASLD, American Association for the Study of Liver Disease
ALT, Alanine Aminotransferase
AST, Aspartate Aminotransferase
BLA, Biologic License Application
BMI, Body Mass Index
BPCA, Best Pharmaceuticals for Children Act
CDRH, Center for Devices and Radiological Health
CHMP, Committee for Medicinal Products for Human Use
CMS, Centers for Medicare & Medicaid Services
COU, Context of Use
CyNCh, Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children
DILI, Drug Induced Liver Injury
EMA, European Medicines Agency
EPoS Project, Elucidating Pathways of Steatohepatitis
FDA, Food and Drug Administration
FLIP Consortium, Fatty Liver Inhibition of Progression
FNIH, Foundation for the National Institutes of Health
HCC, Hepatocellular Carcinoma
HHS, Health and Human Services
IMI, Innovative Medicine Initiative
IND, Investigational New Drug
IRB, Institutional Review Board
LITMUS, Liver Investigation: Testing Marker Utility in Steatohepatitis
LOI, Letter of Intent
NAFLD, Nonalcoholic Fatty Liver Disease
NAS, NAFLD Activity Score
NASH, Nonalcoholic Steatohepatitis
NDA, New Drug Application
PeRC, Pediatric Review Committee
PIP, Pediatric Investigational Plan
PPSR, Proposed Pediatric Study Request
PREA, Pediatric Research Equity Act
PSP, Pediatric Study Plan

## SESSION #1: INTRODUCTION AND UPDATES

**Moderators:** Veronica Miller, Forum for Collaborative HIV Research
Arun Sanyal, Virginia Commonwealth University Medical Center
David Shapiro, Intercept Pharmaceuticals

### Liver Forum Updates

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/01_Miller.pdf
**Presenters:** Veronica Miller, Forum for Collaborative HIV Research

- Welcome and review of the Liver Forum's major operating principles:
  - **"Once new drug candidates and therapeutic strategies are identified, their efficient, safe development is in the best interest of all stakeholders, most of all, the patients".**
  - The intended impact of the Forum on drug development is to increase clarity, efficiency, collaboration, and innovation, and decrease uncertainty, redundancy, development time, and risk. This creates a "win-win" situation for everyone.
  - Each participant has an equal voice in the Forum, and each participant is a co-owner in the process, which encourages open discussion and deliberation.

- Review of the guidelines for participation in the Forum:
  - Due to tremendous growth of the Forum, and number of people attending meetings, there are strict limitations to the number of people that may attend per company.
  - Participation at in-person Liver Forum meetings is limited to 2 people per industry organization, though more than 2 people per company are allowed to log-in to the meeting remotely.
  - In-person attendees should be scientists or clinical researchers, as this is not a meeting for marketing or commercial activity.
  - There is no maximum number of participants per company for participation in the working groups.
  - While companies make contributions to the Forum, they are voluntary and participation is not contingent on financial support.
  - The Forum is a non-competitive, safe zone. What is said at the Liver Forum, stays at the Liver Forum.

- Overview of achievements since Liver Forum 4 in Barcelona:
  - Three manuscripts have been developed by the working groups and are being prepared for submission to both *The Journal of Hepatology*, and *Hepatology* for a possible simultaneous trans-Atlantic publication. The manuscripts are:
    - Disease Case Definitions, Baseline
    - Standardization of Baseline Parameters
    - Pediatric Issues
  - The Forum currently has three "Fellows", and is open to any academic group with fellows or junior faculty that would like to participate.
    - Shadab Siddiqui, working with Arun Sanyal has headed the Disease Definitions manuscript.
    - Yuval Patel, working with Andrew Muir has headed the Baseline Parameters manuscript.
    - Amanda Cheung, working with Brent Tetri will be heading the second definitions manuscript.

  - Planning for new initiatives of the Forum are underway, including
    - **NASH Biomarker Workshop**, Washington, D.C., May 2017- abstract driven workshop that is a collaborative effort between the FNIH Biomarker Consortium, the Liver Forum, and Expert Medical Events.
    - **Adaptive Trial Design Workshop**- focusing on new analytic approaches, and causal inference. To be held between LF 5 and LF 6.
    - **Pediatric Natural History Cohort Workshop**– focusing on challenges, strategies, and innovation. To be held between LF 5 and LF 6.

- Updates to the Steering Committee:
  - Welcome to new Steering Committee members and thank you to out-going members for support and contributions to the Liver Forum.
  - The steering committee rotates members on a regular basis.
  - Thank you to founding industry co-chair Gary Burgess, and welcome to David Shapiro as the new industry co-chair.
  - List of Steering Committee members is available in slides and on website (http://www.hivforum.org/projects/drug-development/liver-forum)

- Update on industry membership and sponsorship:
  - The Liver Forum currently has 96 industry member organizations, ranging from "big pharma" to small start-ups- everyone is welcome.
  - 60 industry organizations were registered for Liver Forum 5
  - Sponsorship has also grown over the years. Sponsorship is voluntary and supports the activities of the Liver Forum.
  - List of Financial sponsors is available in slides and on website (http://www.hivforum.org/projects/drug-development/liver-forum)

- Welcome from Steering Committee Co-Chairs:
  - Dr. Arun Sanyal welcomed all new and returning attendees to Liver Forum 5, and commented that everyone's participation is critical to the success of the group. Dr. Sanyal also thanked Lara Dimick-Santos from the FDA, and Elmer Schabel from the EMA for their commitment and leadership.
  - Dr. David Shapiro remarked that the Liver Forum was created two years ago, and since then had proved to be a very productive organization with real, tangible deliverables.

## Recognition for Outstanding Service

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/03_Davis-Williams.pdf
**Recipient:** Captain Anissa Davis-Williams, U.S. Food and Drug Administration
**Presenters:** Arun Sanyal, Virginia Commonwealth University Medical Center
David Shapiro, Intercept Pharmaceuticals
Lara Dimick-Santos, U.S. Food and Drug Administration

- Captain Anissa Davis-Williams from the FDA was presented with the first iteration of the *Liver Forum Champion of Collaboration* award for outstanding service and commitment in the field of liver disease. (http://www.hivforum.org/forum-news/announcements/1369-liver-forum-champion-of-collaboration-captain-anissa-davis-williams)
  - Drs. Arun Sanyal, David Shapiro, and Lara Dimick-Santos applauded Captain Davis-Williams' for her tireless efforts, positive attitude, dedication to advancing the field, and commitment to patients.

- The award was presented on behalf of the Liver Forum and AASLD.

## Regulatory Updates

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/02_Dimick-Santos.pdf
**Presenters:** Lara Dimick-Santos, U.S. Food and Drug Administration
Elmer Schabel, Bundesinstitut für Arzneimittel und Medizinprodukte

- Types of endpoints that can be used for approval of drugs:
  - Confusion amongst the field about clinical benefit, validated surrogates, and surrogates reasonably likely to predict. Not straightforward at FDA either, and is a moving target.
  - Clinical benefit: How a patient feels, functions, or survives.
    - Examples of clinical benefit in NASH: reduction in all-cause mortality, prevention of liver transplant, prevention or reduction in decompensation events.
  - Surrogates reasonably likely to predict clinical benefit: each drug and combination of disease can be different, since the metabolic pathway has to be taken into account. There might be other surrogates that might be reasonable depending on the metabolic pathway.
    - Potential examples for NASH: complete resolution of steatohepatitis and no worsening of liver fibrosis; at least 1 point improvement in fibrosis and no worsening of steatohepatitis.
  - Validated surrogates: require clinical trial to validate, and are for a specific disease setting and class of interventions. There are no validated surrogate endpoints currently for NASH.
    - Have been recognizing the progression to cirrhosis on histology as a clinical endpoint- though histology is really a surrogate. Still under discussion and depends on drug and mechanism.

- Verification trials under accelerated approval:
  - Two ways to perform verification trials
    - Entirely new trial. Stop and enroll new population with same disease, and start new trial.
    - Seamless phase 3/4 design (many in NASH are doing this because of long natural history) and roll patients over from phase 3 to 4.
  - One trial requires lower alpha than if two trials, due to risk for bias. To be persuasive, the trial needs to be large, multi-centered, internal consistency, evidence of efficacy based on multiple endpoints, and statistically very persuasive.
  - For two seamless design trials, the alpha needs to be controlled at or below 0.05 and split the alpha between phase 3 trial and phase 4 trial.
    - One way to split the alpha is 0.01 for phase 3, and 0.04 for phase 4. Other ways to split could also be proposed.
  - For one trial, a smaller overall alpha, less than 0.05 is needed, but no specific guidance on what it should be. The lower the alpha, the more persuasive the results are. A very, very persuasive alpha could be 0.00025, but this may not be practical.

- **Questions and Discussion:**
  - Q: *What is the origin of the combined alpha of 0.05 for the seamless 3/4 trials?*
    - The 0.05 alpha gives 95% confidence internal, and with two trials there is less bias. The alpha of 0.05 is somewhat artificial, but is accepted across drug development world and is a standard alpha value being used in most phase 3 trials.

        - When there are two trials where the alpha is split, there is essentially the same degree of certainty as one trial that's highly statistically significant, if those two trials are conducted independently.

    - Q: *What is the general recommendation for one study, is it 0.025?*
        - 0.025 is high for most recommendations. Drugs have been approved at 0.01, though it is not a definite number and depends on other items such as power, length of trial, and population.

    - Q: *What about when something demonstrates an effect on mortality (ex. elevated serum ALT), but its reduction isn't considered appropriate for a clinical trial?*
        - Determined on a case-by-case basis- in the process of trying to write guidelines, but has been in process for a while because it's subjective. Look at a totality of the data, consult with outside experts, and determine if it's reasonably likely to predict clinical benefit.
        - Using example of ALT, would need to demonstrate that reduced ALT results in improved survival before it can be used as a surrogate.
        - The reasonably likely to predict clinical endpoints using for NASH are based on theoretical plausibility, because the only way to diagnose the disease is histologically.

    - Q: *Would a reduction in liver-related mortality without an impact on overall mortality be accepted as an appropriate surrogate?*
        - It is difficult to identify what is liver-related mortality, and what was cardiovascular-related mortality, so in general overall mortality should be the first endpoint, and the specific disease mortality should be a secondary endpoint. The endpoint will be driven by progression to cirrhosis, not mortality.
        - Tend to forget that histology is not a gold standard but a surrogate.

    - Q: *Would a seamless phase 2, 3, 4 trial be something that would be considered appropriate for approval?*
        - It would be considered, but it all comes down to the details and requires individual assessment.

- No fixed solution. Have presented a path forward, but happy to listen and have discussions about other ways to proceed. Flexibility and creative thinking are at the center of fields like NASH which are moving without having any precedent.

## SESSION #2: FOCUS ON BIOMARKERS

**Moderators:** Veronica Miller, Forum for Collaborative HIV Research
Quentin Anstee, Newcastle University Medical School

### FDA's Biomarker Qualification Program

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/04_Amur.pdf
**Presenter:** Shashi Amur, U.S. Food and Drug Administration

- Updated definition for biomarkers derived from FDA/NIH biomarker working group: "**A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions**". (https://www.ncbi.nlm.nih.gov/books/NBK326791/)

  - Types include molecular (e.g., blood glucose), histologic (e.g., biopsy-proven acute rejection), radiographic (e.g., tumor size), or physiologic (e.g., blood pressure).

- Biomarkers:
  - Categories: Diagnostic, Susceptibility/ Risk, Prognostic, Predictive, Pharmacodynamic/ Response, Monitoring, Safety.
    - There is overlap in biomarker categories.
  - Key contributors to drug development success: Right Target, Right Tissue, Right Safety, Right Patients, Right Commercial Potential

- Integrating biomarkers into drug development:
  - Drug Approval Process (IND/NDA/BLA)
    - Strengths: Biomarker use generally has a well-defined purpose; clinical trial information is available to developer; opportunities to bring in outside experts; company retains marketing advantage.
    - Limitations: Biomarker use may not always be generalizable; limited opportunities for additional data sources; the company is responsible for all development costs; limited opportunities for engagement with outside groups due to confidentiality issues; biomarker information on drug labels and reviews available only upon drug approval.
  - Scientific Community Consensus
    - Strengths: Researchers publish papers and generate an extensive knowledge base of exploratory biomarker data in published literature; opportunity for broad and multiple community inputs.
    - Limitations: Published data may not be reproducible (possibly up to 80% of published data); time to regulatory acceptance; variability of study designs, populations, and analytics; applicability to regulatory paradigms.
    - Example: ALT was discovered in 1955, but took nearly 50 years to be established into regulatory use.
  - Biomarker Qualification Program: Meant for establishing the use of a biomarker in drug development for a specific context of user purpose. Outside of the IND/NDA/BLA process.
    - Strengths: Biomarker use is very generalizable; opportunity to pool resources, share costs, and bring in outside experts; opportunity for systematic biomarker development with regulatory advice; outcome is a public biomarker guidance, and an executive summary and supporting reviews.
    - Limitations: Part of a group effort, where stakeholders may have differing goals and levels of commitment; data may not be readily available; data sharing an aggregation may be challenging.

- Qualification vs. Validation:
  - Validation: Establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose.
    - Analytical Validation: Establishing that the performance characteristics which include sensitivity, specificity, accuracy, precision, and others of a test, tool, or instrument are acceptable.
    - Clinical Validation: Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

        - In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state or experience that the assessment is intended to capture or reflect.
    - Biomarker Qualification: A conclusion that, within a carefully and specifically stated "Context of Use", the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development.
        - Context of Use (COU): A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.
            - COU drives the level of evidence needed, amount of data, and type of data, which then drives the qualification process. This establishes that the biomarker assay is performing correctly.
            - Differs from validation, which shows that there is a correlation between the biomarker and the clinical outcome.

- Biomarker Qualification Process:
    - Three stages: Initiation, Consultation and Advice, and Review.
        - Initiation: Submit a letter of intent (LOI), a 2-5 page document providing background on biomarker, why it should be used in drug development, and how the submitter plans to use it in drug development. FDA determines the acceptability of the LOI into the program.
        - Consultation and Advice: Submit preliminary data or data summaries in a briefing package. Collaborative discussion with FDA about the biomarker development plan, how to proceed, and when ready with data, invite to send in full qualification package.
        - Review: Submit full qualification package, and FDA reviews to make a yes or no decision to qualify. If qualified, FDA drafts guidance document.
            - FDA then needs to post guidance to Federal Register.
    - Currently 13 unique qualified biomarkers, 10 of which are non-clinical.
    - Submitter can be submitted by any individual or group, there are no fees for submissions, and qualification is voluntary. Once biomarkers are qualified, they can be used in any drug development program under the context for which it obtained qualification.

- Other initiatives:
    - Critical Path Innovation Meeting: non-binding meeting meant for the discussion of the science, medicine, and regulatory aspects of innovation in drug development that includes early biomarkers.
    - FDA Letter of Support: issued to a requester and is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.
        - Have issued 11 letters
    - Limited Context of Use: limited amount of data- smaller context of use. Can initially qualify as a response biomarker, and then when sufficient data is available, qualify it as a surrogate endpoint.

- **Questions and Discussion:**
    - Hoping that Liver Forum can qualify some biomarkers, such as elastography. While validated to measure kilopascals, not qualified to measure fibrosis or cirrhosis.

- Q: *Is there guidance on how to go from these biomarkers from drug development to general biomarkers that can be used as diagnostic out in clinical? Or is that the role of professional societies to move it into clinical practice?*
  - Qualification is solely for drug development and not for clinical practice. When a biomarker is qualified, the biomarker assay is not also qualified. This type of question can be directed to CDRH.

- Many biomarkers used in niche areas start in academia before they make their way into a drug label. Data can be accumulated over time by incorporating these tests early, and eventually used to support qualification.

## FNIH: NASH Biomarker Consortium

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/05_Calle.pdf
**Presenter:** Roberto Calle, on behalf of Foundation for the National Institutes of Health

- Foundation for the National Institutes of Health (FNIH) Overview:
  - FNIH created as Congressional mandate in 1996 with the goal of advancing biomedical research and training researchers in collaborations that spanned all stakeholders.
  - Non-profit organization supporting over 550 projects, one is the Biomarkers Consortium (http://www.fnih.org/what-we-do/biomarkers-consortium).

- Biomarkers Consortium:
  - Mission: to discover, develop, and seek regulatory approval for biomarkers to support and accelerate development of new drugs, preventive medicine, and medical diagnostics by combining the forces of the public and private sectors.
  - Role of FNIH is to bring together stakeholders to work in a pre-competitive space where all parties have common interest of advancing the field to facilitate the development of new therapies for patients.
  - Output of collaborations is public, and everything is generated for the purpose of sharing with general scientific and medical community and published in peer-reviewed journals.
  - Governed by executive committee with members from the NIH, FDA, CMS, Industry, and FNIH.
    - Divided into four areas of interest, each with own steering committee: Cancer, Inflammation and Immunity, Metabolic Disorders, and Neuroscience.
    - Steering committees are in charge of a portfolio of projects, submitted by members, or project concepts submitted by non-members.
    - Steering committees are led by co-chairs from industry and academia, and consist of members from academia, industry, and regulatory authorities.
  - Direct impact on the development of 6 drugs, 4 guidance documents, and over 40 publications including work by the steering committees and project teams.

- FNIH Biomarker Consortium NASH Working Group:
  - Goal: advance the qualification of one or more, fit-for-purpose, non-invasive tools, that integrate both circulating and quantitative imaging markers.
  - Limitation to field is absence of non-invasive biomarkers that allows a move away from liver biopsy.
  - Priorities: biomarker qualification that identifies patients at risk, evaluates disease progression vs. regression, and evaluates response to treatment.
  - Work together with the different initiatives (e.g., Liver Forum, IMI) in the field to ensure that the work is complementary and not repetitive.

- Dr. Sanya Whitaker is the scientific program manager- contact her if interested in joining the project.

## Liver Forum- FNIH Collaborations

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/06_Sanyal.pdf
**Presenter:** Arun Sanyal, co-chair FNIH Biomarker Consortium

- FNIH Biomarker Consortium:
  - Scientific leadership is multi-disciplinary and includes all perspectives and expertise- clinical, technical, analytic, and strategic.
  - FDA, Liver Forum, and EMA are involved in process and provide feedback so that the scientific content is aligned with regulatory requirements.

- Work Plans:
  - Phase 1: establish collaborative partnerships; ensure working groups have right mix of expertise; conduct comprehensive literature analysis to determine short list of candidates for further validation.
    - Objective is advanced validation, not discovery of new biomarkers.
  - Phase 2: engage retrospective-prospective validation studies; develop and complete standardization of methods that can be translated into clinical practice; analyze existing data sets of cross-sectional and longitudinal cohorts where there are samples and clinical data available.
  - Phase 3: engage in a cross-sectional prospective validation
  - Phase 4: possible future longitudinal validation relating things to outcomes.

- Deliverables:
  - Key data on biomarkers to support non-invasive case definition; algorithm; key data towards biomarker qualification; key data for imaging to assess suitability for large scale application; publish along the way in peer-reviewed publications and white papers; data made publicly available.
    - Metrics of success: achievement of specific aims, generation and publication of scientific findings, and incorporation of qualified biomarkers into clinical trials.
    - Long term impact: incorporation into clinical practice guidelines.

## IMI: Accelerated Drug Portal

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/07_Brosnan.pdf
**Presenter:** Julia Brosnan, on behalf of Innovative Medicines Initiative

- The Innovative Medicine Initiative (IMI):
  - Created by the European Union Central Government to drive drug development. Funding comes from private industry, and then funds are matched by the European Union.
  - Strategic Governing Group determined that establishing non-invasive biomarkers for diagnosing and classifying subjects within the NAFLD spectrum was a Central Challenge. Identifying and validating biomarkers can be employed to track disease progression as well as response to intervention.
  - The lack of diagnostic, prognostic, and predictive biomarkers is hampering clinical practice and drug development, which resulted in IMI publishing a call for proposals (https://www.imi.europa.eu/content/imi-2-call-9).

- Public-Private Collaborative Research:
  - There are many biomarker candidates out there; however the studies have been relatively small, have rarely been replicated, and have not been validated against liver biopsy. By working together and pooling funding, can create a well-designed and large enough study to validate noninvasive biomarkers against liver biopsy.
  - Not starting from scratch – using existing research cohorts and samples (including properly adjudicated liver biopsy samples) and using standardized laboratory analysis to harmonize biomarker data.
  - Start with validation stage, and then confirm and complement- need to be able to replicate in additional studies.

- Applicant Consortium:
  - Led by scientists and physicians who are recognized experts, bringing together subjects and data from a cohort across the full spectrum of NAFLD, though enriched with later stages to support NASH biomarker qualification.
  - The cohorts should be longitudinal research units already underway, with high-quality follow-up procedures, and high participant retention.
  - Liver biopsy and clinical data must be available, and causes of liver diseases other than NASH and NAFLD will be excluded.
  - Will have a cross-sectional cohort, and could be continued as longitudinal with greater than 1500 biopsy validated samples.

- Expected Deliverables:
  - Baseline characteristics/ biomarkers of patients with NAFLD that can diagnose NASH and predict better disease progression across the spectrum of NAFLD.
  - Validation of non-invasive biomarkers for stratification of subjects for clinical trial inclusion.
  - The identification of candidate biomarkers that can serve as surrogate markers for clinical outcomes of NASH.

- The winning consortium is called LITMUS, and the PI is Quentin Anstee.

## Liver Investigation: Testing Marker Utility in Steatohepatitis

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/08_Anstee.pdf
**Presenter:** Quentin Anstee, Newcastle University Medical School

- LITMUS consortium builds on a number of previous EU-funded consortia. First the FLIP consortium (http://www.flip-fp7.eu/consortium.html) that was coordinated by Vlad Ratziu and subsequently the EPoS project (http://www.epos-nafld.eu/).

- Aims of LITMUS Consortium:
  - To leverage existing cross-sectional and longitudinal patient cohorts and bio-resources into a single unified resource.
  - Expand that resource through additional prospective recruitment of patients with histologically characterized fatty liver disease.
  - Establish a robust technological and methodological platform and use it for the definitive validation of candidate biomarkers.
    - Need to separate out the people who are doing the ultimate assessment of the quality of the biomarker from those individuals who may have a vested interest in

it- have a built-in firewall between the biomarker data and the phenotype data to which it will be measured so that the two only are put together at a later stage down the line.
        - Need to address all three of the FDA BEST biomarker domains—diagnostic, prognostic, and monitoring.
        - Want very clear line of sight towards the FDA and the EMA for regulatory qualification.
    - Need to define the most accurate and tractable biomarkers relevant to fatty liver disease and generate data of the requisite standard to do that.
        - This is a key goal of the LITMUS consortium.
    - Need to develop and qualify pre-clinical models of fatty liver disease and back-translate the biomarkers into these models to determine whether they can support the pre-clinical drug development pipeline as well.

- Biomarker Needs to Address:
    - Want to address the diagnostic, the prognostic, and the dynamic or monitoring biomarkers. It is key to be able to discriminate between steatosis and steatohepatitis.
    - Want to be able to develop biomarkers and validate biomarkers that can track disease.
    - Want to look at prognostic biomarkers, biomarkers that may come and be useful at predicting long-term outcomes and hard endpoints.
        - Already have large OMICs data sets on many of the patients in our registry which we can draw on.

- NAFLD Registry:
    - Registry established during the FLIP consortium, brings together extensive clinical data in biopsy characterized patients, which have been centrally read. Originally developed to support discovery science but is now being repurposed for additional roles
    - Patients have been under longitudinal follow-up.
    - Necessary to expand our patient recruitment, strong links with investigators in US and China, the idea of forming international chain to build up the global NAFLD network.

- QED work package:
    - Qualification, exploitation, and dissemination. This important work package brings together experts both from Europe and the United States and from the inception of the project will be reaching out to the Liver Forum, to the EMA, and the FDA to make sure that we are generating the forms of data that will be fit for purpose.

## SESSION #3: DISEASE DEFINITIONS WORKGROUP UPDATE

**Moderators:** David Shapiro, Intercept Pharmaceuticals
Stephen Harrison, University of Oxford

### Disease Definitions Working Group

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/09_Megnien.pdf
**Presenter:** Sophie Megnien, Genfit Corp
**Discussants:** Pierre Bedossa, University of Paris Diderot
Vlad Ratziu, Hôpital Pitié Salpêtrière et Université Pierre et Marie Curie
Brent Tetri, Saint Louis University School of Medicine
Saul Karpen, Emory University School of Medicine
Jeff Schwimmer, University of California, San Diego School of Medicine

Vincent Wong, The Chinese University of Hong Kong

- Working Group Updates:
  - The general objective of the working group is to define clinical endpoints for clinical trials, and the first stage was to have base definitions for the level of disease.
  - The Working Group has developed a manuscript on case definitions, to be submitted for publication: "*An evaluation of case definitions for inclusion and analysis of endpoints in clinical trials for non-alcoholic steatohepatitis through the lens of regulatory science*".
  - The next stage of the Working Group is to get deeper into the details and coming to a consensus on how to define the resolution of NASH, "no worsening", and "worsening".
  - Amanda Cheung has joined the Working Group and will be heading the writing of the second manuscript.
  - Definitions for NASH resolution, worsening, and no worsening, need to be "Fit-for-Purpose" – clear clinical endpoints to use in trials that are precise, quantifiable, reproducible, and acceptable to regulatory agencies.
    - Need to make sure that the surrogate endpoint that will be used will be acceptable and will be reasonably likely to predict the final outcome. Therefore, will need to measure at baseline and the end of treatment.

- NASH Resolution:
  - Working Group Consensus: Resolution of NASH is defined as an expert liver pathologist assessing the overall pattern of injury, reporting the disappearance of hepatocyte ballooning (grade 0) and the disappearance of persistence of minimal lobular inflammation (grade 0 or 1).
    - Overall diagnosis of no NASH, plus the absence of ballooning, plus the absence or minimal residual lobular inflammation.
    - This is difference than complete resolution of NAFLD, which requires disappearance of steatosis.
    - The definition needs to be data-driven and will be an evolving definition as more data become available.
  - Gaps, Needs, Questions:
    - Need to standardize how ballooning is assessed by pathologists and from one trial to the next in order to improve reproducibility.
    - Need more data on portal inflammation to make sure it is a driver of NASH. Recommend to collect data on portal inflammation, but not include it in the definition yet.
    - Need to develop a definition for NASH resolution in pediatric populations- different drivers of disease.
    - Need to continue to correlate this definition with new biomarkers and surrogates as data become available.

- Worsening and No-Worsening of NASH:
  - Two separate definitions with different metrics.
  - No Worsening of Nash in the context of the endpoint that is used with improvement of fibrosis without worsening of NASH.
    - Starting definition: No worsening of either ballooning or inflammation by 1 point.
      - Need to consider the relative contribution of ballooning and inflammation to the progress of disease – different relative scales.

- Need more data to see how the worsening of ballooning or inflammation relates to the severity of disease to evolution of fibrosis.

- **Questions and Discussion:**
  - Q: *Do clinicians understand the issues of histology adequately? And are there things that clinicians are failing to weigh or think about sufficiently?*
    - Yes, they understand. Clinicians receive a biopsy with chronic liver disease and some degree or steatosis and fibrosis, and the difficult part is to determine if it is NASH or not. They can assess overall pattern of histology, or use an algorithm using clear definitions of ballooning, inflammation, and steatosis.
    - To ensure understanding between clinicians and pathologists, it is important that the language used for definitions be precise, quantifiable, and not just overall impressions.

  - Q: *Is pediatric NASH the same disease? Are different criteria needed and does the whole process need to be done again for pediatricians and for the pediatric disease?*
    - It is more complicated. There are between 20-40% of children who have what looks like NASH as would be seen in adults, and between 30-40% who will have a portal or a zone one or borderline steatohepatitis. Though term borderline is used, between 10-20% of these children are more likely to have advanced fibrosis. A one-size-fits-all approach might not be appropriate for children.
    - Trouble with real resolution and disappearance of inflammation. This will be almost impossible bar to maintain as it is hard for a pathologist or clinicians to say something looks normal. “Disappearance” may also be problematic. Agree that pediatric presentation of disease is very different.

  - Q: *In paired biopsies in kids, how often does the phenotype shift between portals (the portal based versus the classic lobular), and whether it has to do with aging?*
    - A presentation about this question 2 years ago showed that the pattern (borderline zone one, or type two) does shift to an adult pattern in a percentage of people, and then about 40 or 50% resolved over time. But it was a small sample size, and need to look at it further because there’s just not that many children that get longitudinal biopsies outside of a histology-based clinical trial.

  - Q: *Most of the trials that have been done have been done with therapeutics in North America or in Europe. Is the disease the same in Asian patients in Asia and in Asian patients in North America and Europe?*
    - Both for Asian patients in Asia as well as Asian patients in North America or Europe, we see the full spectrum of NAFLD from NASH, fibrotic disease, or even cirrhosis. Asian patients tend to have central obesity at a lower BMI; therefore, the definition of overweight and obesity would be slightly different in Asian patients. For example, a BMI of 23 would be overweight, and 25 would be obesity. The major problem is that if a clinical trial uses a BMI as the cut-off or the inclusion criteria, many of our patients with active disease may be excluded because of slightly lower BMI.
    - There are no studies published on NASH of cohorts from Africa, India, and South America, and if kids are different, there is a possibility that different ethnicities could be different, we just haven’t studied yet.

- Q: *How much work has been done to look at subcutaneous fat biopsies and correlate that with the inflammation that is seen in the liver?*
  - Bedossa et al. have had a paper accepted to Gut recently (https://www.ncbi.nlm.nih.gov/labs/articles/27884920/) on the correlation between subcutaneous adipose tissue and evolution, where the size of adipose fat is assessed.

- Q: *Is there a database of human liver biopsy specimen photomicrographs, each of which has been scored by a professional expert NASH pathologist and has the vector of the necessary scores? Is this something that a machine could learn?*
  - There is no public database available as far as is known, but would be very useful to develop for this type of approach. Have previously tried to do this with simple lesions such as gynecological cytology, and have not progressed much.
  - FLIP Consortium has an expanded set of slides from different phenotypes throughout NAFLD spectrum, might be available for this type of data analysis. They are scanned, but not in public domain.

## SESSION #4: PEDIATRIC ISSUES WORKGROUP UPDATE

**Moderators:** Joel Lavine, Columbia University Medical Center
Richard Torstenson, Novo Nordisk

### Law and Regulations for Trials in Pediatric Patients

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/10_Mehta.pdf
**Presenter:** Ruby Mehta, U.S. Food and Drug Administration

- Pediatric Drug Development:
  - Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) were introduced to foster drug development for children.
    - "Children" defined as between 0-16 years old, or persons who have not attained the legal age for consent to treatment or procedures.
  - Ultimate goal of BPCA and PREA is to encourage the appropriate use of medications in children, and help inform labeling and prescribing information.
  - BPCA
    - Provides financial incentive for companies and is voluntary.
    - The FDA and NIH partner to obtain studies.
  - PREA
    - Companies are required to assess the safety and effectiveness of new drugs and biologics in pediatric patients.
    - Proposed Pediatric Study Request (PPSR) can be submitted to the FDA by the sponsor, and the FDA issues a written request.
      - PPSR should include rationale for study design, detailed study design, and formulation for each age group.
  - BPCA vs. PREA
    - Both apply to drugs and biologics, but BPCA is voluntary where PREA is mandatory.
    - BPCA studies can be conducted for indications other than what the adult trials were conducted, and PREA requires studies only for indication under review.
      - BPCA example: an anti-estrogen drug that is approved for treating breast carcinoma was the BPCA and studied in pediatric condition with excess estrogen production.

    - Orphan indications are exempt from PREA, but can be studied under BPCA.
    - Both inform the labeling.

- PREA:
    - Triggered in the following circumstances: new indication, new dosage form, new dosing regimen, new route of administration, new active ingredients.
        - Retroactive going back to 1999.
    - Data is used to assess the safety and effectiveness, and support dosing administration and inform the label.
    - Pediatric deferrals requirements:
        - Sponsor must submit: certification of the grounds for deferring the assessment; pediatric study plan; evidence that studies are being conducted or will be conducted with due diligence and at the earliest possible time; a timeline for the completion of such study.
    - Pediatric waiver:
        - A waiver can be requested if: the necessary studies are impossible or highly impracticable; evidence strongly suggests the drug/biologic would be ineffective or unsafe; drug does not represent a meaningful therapeutic benefit over existing therapies in pediatric patients and is not likely to be used by a substantial number of pediatric patients; reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

- Pediatric Review Committee (PeRC):
    - PeRC reviews the pediatric plans of both that are submitted to the FDA for both BPCA and PREA.
    - Committee members are required to include expertise in pediatrics, neonatology, pediatric ethics, biopharmacology, statistics, chemistry, and law. And have appropriate expertise related to the product under review.
    - Pediatric Study Plan (PSP)
        - Submitted and reviewed of PeRC outlines the pediatric study that the sponsor intends to conduct.
        - The intent is the encourage trials as early as possible in the product development, and conduct these studies- when appropriate- prior to submitting the NCA/BLA.
        - Strict timelines, and must be reviewed and agreed upon by FDA.
    - Extrapolation: if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients such as PK studies and safety.

- Research Involving Children:
    - Subpart D: ethical framework proposed by the National Commission, adopted by HHS in 1983.
    - Children are vulnerable and require additional safeguards. Ethical issues can be offset by establishing conditions that research must satisfy to be appropriate for the involvement of children.
    - Two types of pediatric research:
        - Research that does no present greater than minimal risk

- Research where an intervention presents greater than minimal risk, but where the risk is justified by the anticipated direct benefit to the enrolled children and the relation of the anticipated benefit to such risk is at least as favorable as that presented by available alternative approaches.
- If there is no prospect of direct benefit and procedure presents greater than minimal risk, the key protocol issue goes to the Federal panel for review. This request is made by IRB not FDA.
    - Key elements considered when federal panel reviews a procedure or an intervention: presents reasonable opportunity to further the understanding of prevention or alleviation of a serious problem affecting the health or welfare of children; consultation with a panel of experts in pertinent disciplines; opportunity for public review and comment; conducted in accordance with sound ethical principles; adequate provisions made for soliciting the assent of children and the permission of their parents; administration of an intervention that present a minor increase over minimal risk to children lacking a disorder or condition.

- Ethical Principles of Liver Biopsy:
    - Key elements are: Prospect of benefit, and the risk.

## Regulatory Update from Europe: Paediatric NASH

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/11_Schabel.pdf
**Presenter:** Elmer Schabel, Bundesinstitut für Arzneimittel und Medizinprodukte

- Pediatric Regulation in Europe:
    - Pediatric regulation 1901/2006 has similar objectives as the US regulations presented previously, and is nearly ten years old.
        - In Europe, the PeRC is called “Pediatric Committee”, and includes experts from the national agencies of the European Union member states, CHMP members, and other patient and health care professional representatives.
    - Pediatric Investigational Plan (PIP) applies to every new substance, and includes quality, safety, and efficacy.
        - Contains administrative information, waiver requests, overall strategy, details of individual studies, and timelines.
        - The opinion on PIP is not given by the European Commission but by EMA.
        - Procedure takes 60 days, with potential 3-month clock-stop and further 60 day extension.
        - The final decisions on the agreed PIP are published
        - Waiver and deferral elements of PIP are very similar to US procedure.
            - Obligations
                - Must submit and agree to PIP at the end of Phase 1, and undergo validation/ check for compliance with the PIP.
            - Incentives
                - Supplementary protection certificate extension of 6 months (patent extension), provided only when compliance has been verified.
                - Market exclusivity protection extended for 1 year if new indication.
                - Orphan Exclusivity extended for 2 years (medicinal products only).
                - Off-patent medicinal products have a special type of license called PUMA and theoretically can give a 10-year protection period.

- PIP Applications:
  - Regulatory experience with PIP applications is very limited
    - Currently two agreed PIPs, one for NASH (Elafibranor), one for hepatic fibrosis (Simtuzumab).
    - Currently two ongoing procedures
      - Elafibranor
        - Waiver for patients under two; proposed indications are NASH and NAFLD
      - Simtuzumab
        - Waiver for patients less than 28 days old, and the proposed indications are treatment of advanced hepatic fibrosis and cirrhosis
      - Substance XXX
        - Still under discussion, name blocked. Proposed waiver for patients under 12, and proposed indication for treatment of NASH with stage 2-3 fibrosis.
      - Substance YYY
        - Still under discussion, name blocked. Proposed waiver of patients under two years old, and proposed indication for treatment of NASH.

## Status of Pediatric NASH Research

**Panelists:** Miriam Vos, Emory University School of Medicine
Jeff Schwimmer, University of California, San Diego School of Medicine
Ruby Mehta, U.S. Food and Drug Administration
Rajarshi Banerjee, Perspectum Diagnostics

## Pediatric Issues Workgroup Update

**Presenter:** Miriam Vos, Emory University School of Medicine

- Working Group Update:
  - The pediatric regulatory guidance manuscript is completed and undergoing review before submission.
  - Planning a one-day working group meeting on pediatric issues prior to the next Liver Forum meeting, and encourage those interested in pediatric aspects to attend.
  - Several pediatrics working group members have joined disease definitions working group to provide pediatric experts involved in those conversations about definitions of NASH.

## Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children (CyNCh)

**Slides:** http://www.hivforum.org/storage/documents/2016/LF5/12_Schwimmer.pdf
**Presenter:** Jeff Schwimmer, University of California, San Diego School of Medicine

- CyHCh Trial: (see more: https://clinicaltrials.gov/ct2/show/NCT01529268?term=cynch&rank=1)
  - Conducted by the NIH NASH CRN, with many different centers involved.
  - First trial in pediatric liver disease designed with liver histology as the primary outcome.
    - Proportion of children with histologic improvement in NAFLD between baseline liver biopsy and a follow-up biopsy after 52 weeks of treatment. Improvement defined as decrease in NAS score of 2 points, and no worsening of fibrosis.

- Histologic entry criteria used was NAS score ≥ 4. The mean NAS score was 4.7, with most coming from steatosis or lobular inflammation.
- Weight-based dosing strata was used, for a total of three groups: ≤ 65kg, >65 to 80kg, >80 kg.
- 230 children were assessed for eligibility, 61 were excluded, for a total of 169 that were randomized and assigned to either cysteamine bitartate or placebo.
  - 19% in the treatment group did not have follow-up biopsy, compared with 7% in placebo group, though all included in intention-to-treat analysis.
- Treatment did not improve NAFLD activity score; however, treatment significantly decreased both ALT and AST compared to the placebo group.
  - Even when stratified by weight for dose, there was still a significant difference in the amount of drug that the lighter children received.
  - The more drug those in the treatment group received, the more likely they were to respond to the treatment.
- The lightest weight group had to take 8 capsules a day, and the highest weight group had to take 12 a day.
- Over the course of 52 weeks, there was a mean weight gain of 7.1kg, about 1.3 pounds per month.
- Children who had borderline portal NASH or type 2 NASH who received the active drug had the highest odds ratio of improvement.

- **Questions and Discussion:**
  - Q: *Was there any relationship between likelihood of improvement or decrease in ALT and change in body mass index?*
    - Don't know the answer yet, looking deeper at what does ALT tell us in this context. Children who lose weight were more likely to have a response, but with caution due to smaller analyses.

  - Q: *How was compliance assessed, and are there data associating PK data with compliance or number of capsules?*
    - Compliance was assessed by pill count- at each visit the bottle had to be returned and the pulls were counted and a new bottle was provided. There were issues with compliance, and was statistically significantly better in the placebo group than in the active drug group.
    - Children more often chew their pills or keep them in their cheeks, so if there is a taste difference between the placebo content and the drug content, then that can drive compliance differences in the two groups.

  - Q: *To what extent do psychosocial issues and family dynamics play a role? Is there a way to tease apart the relationship of age and family dynamics (younger, more influence from parents; older, more rebellious).*
    - The younger age group- disproportionately the lighter group- is more likely to be under greater parental control. It is yet another confounder, and difficult to tease apart.

  - Q: *If this study had been successful, what would've been the next step for the FDA and the EMA respectively in terms of marketing authorizations? Would it be that the marketing indications would require a biopsy?*

- In the US we would use the subpart D to think through a liver biopsy. Some people would consider liver biopsy to be greater than minimal risk and some people would not. The protocol needs to articulate an adequate justification of a repeat biopsy.
- Repeat biopsies have also been controversially discussed in the Pediatric Committee- there is no dedicated legal framework, but general ethical requirements in a situation with more than minimal risk. In this situation, there is no chance to refer to any adult data, so there is no way of extrapolation. In this situation, would maybe say yes to this kind of procedure because there is otherwise no reliable measure to assess the benefit associated or the risks associated with this compound.
- The trial was kind of an early phase 2 trial in a fairly small population. Had it succeeded, probably would want more data from a phase 3 trial. If it were a drug that had more adult data, as much pediatric data might not be needed.

## SESSION #5: MECHANISM OF ACTION AND SURROGATE ENDPOINTS

**Moderators:** David Shapiro, Intercept Pharmaceuticals
Arun Sanyal, Virginia Commonwealth University Medical Center

### Linking Mechanism of Action to Endpoint Selection in NASH Trial

**Panelists:** Laurent Fischer, Allergan
Rob Myers, Gilead Sciences, Inc.
Scott Friedman, Icahn School of Medicine at Mount Sinai
Anna Mae Diehl, Duke University Medical Center
Detlef Schuppan, Mainz University Medical Center
Eileen Navarro, U.S. Food and Drug Administration

- **Questions and Discussion:**
  - Q: *For endpoints in terms of early phase development versus more advanced phase development, does one size fit all? Or should there be a closer linkage to the mechanism of action?*
    - Phase 2a trials have a different purpose which is to show proof of mechanism or target engagement. Often, it's to generate some traction for a small company to justify moving to phase 2b or phase 3. Ultimately, it has to converge on the endpoints that confer subpart H approval.
    - Endpoints should be different for different drugs, because the endpoint needs to makes sense within the drug mechanism. So, no. There's not one-size-fits-all. There have been examples of surrogates that are reasonable for the different categories of anti-inflammatory and anti-fibrotic, but that doesn't mean there couldn't be a differently constructed endpoint. In early phase trials, should look at things that show whether the drug mechanistically works well.
    - Two components: One is does the drug attack the target as thought/intended? And two, if it does, does that have any impact on the disease course? And they're separate questions.

  - Q: *What's the best way for a drug that has anti-inflammatory target to be evaluated beyond looking at it under the microscope?*
    - Need to know where the inflammation is and what cells are involved, and what the time period is. Inflammation in the short time is protective against insulin resistance and possibly fibrosis in animal experiments; however, chronic

inflammation can be pro-fibrotic and NASH progression. Think there needs a redefinition, and that progression of the disease towards cirrhosis is the relevant inflammation linked component.
    - Want to know if the tissue is responding in a way that engages pathways that collectively show benefit, which is a much more holistic approach. It's not a regulatory endpoint, but it certainly will provide comfort that the pathways engaging could ultimately culminate in improved fibrosis.
    - Looking at NASH under the microscope is the histologic manifestation of a wound healing responses, and inflammation and scarring are both part of that.
    - Clinical pharmacology guidance that reviews how to describe mechanism of action for a product, starting with the accumulation of information from the most granular description of what its effect is, all the way to its effect particularly for a chronic disease on the whole organism

- Q: *In a subpart H or a phase 2b trial, how does one link mechanism of action data to provide some evidence that the drug is beneficial?*
    - Have to link anti-inflammatory effects of a drug on other endpoints, for example looking at both the metabolic situation and fibrosis- have they improved or worsened? It could be different for each endpoint.
    - Doing transcriptomics to have a more sophisticated way to look at what's happening in these patients who've been treated and whether we can correlate the mechanism of action with what we've seen- which is an improvement in fibrosis without worsening of NASH. We do need to have better tools, highlighting the important role of identifying biomarkers so that early on we can show more than target engagement.
    - Consensus across the groups that fibrosis is important. Of the available instruments- noninvasive, serum, imaging- which ones in a phase 2 would provide the most confidence for going into a definitive study?
        - Gets back to the proof of mechanism. If the drug is an anti-inflammatory, would want to know that inflammatory markers are being affected, preferably in the circulation.
        - Jury is out on anything other than biopsy, though MRE has the most data, and is most rigorous. Serum markers still need to be validated.
        - More optimistic about serum markers, and would like to see these markers in addition to the imaging studies. Imaging is not as sensitive because they are static.
        - Function studies, particularly in more advanced patients, because in the end it's pretty clear that function will predict outcome. These need to be validated further.

- Q: *is it important to get a better, more granular understanding of the cellular nature of inflammation in NASH (macrophage vs. neutrophil, vs. lymphocyte)?*
    - Classical wound healing M2 macrophages are supposed to improve the metabolic syndrome, fatty tissue inflammation, as well as fatty liver inflammation. But there is also some indication that these cells might promote fibrosis at the same time, at least a variant of these cells. So when we hit the metabolic consequences by increasing M2s, we might also promote fibrosis. I think this is not really clear yet, and we don't understand this very well.

- Unless there is a robust circulating marker of a particular inflammatory cell that correlates with what's going on in the liver, they are just really investigational and they can illuminate the mechanism of action. But they're not going to translate into clinical diagnostics or meaningful endpoints.
- Probably histology is not the best way to assess a granularity in the different type of inflammation. For example, don't know any good immunological chemical marker for between M2 or M1.

- Q: *Should other quantitative measures of the liver be included in phase 2 programs to give support that things are moving in the right direction, or is more validation of those tests needed before getting to this point?*
  - Histology sometimes might not be sensitive enough to demonstrate a beneficial anti-inflammatory effect. Maybe everybody that does basic research could set up a list of things that are well validated in terms of their biological impact and properties in the different inflammatory or cell injury pathways and that can be demonstrated through particular stains or different biological methods. Then decide on which are the best validated, observable, and quantifiable. And then go ahead in the future trials, when it's needed, to assess them and then later on to correlate them with some outcomes. A little bit of standardization here of the best methods could be useful, knowing that it can only serve as supporting evidence for methods of action, cannot serve for demonstrating efficacy unless it is linked to what is well known and well discovered as efficacy criteria.

- Q: *Are there lessons to be learned from other areas and other organs? Other things that should be being thought about?*
  - We might be able to learn quite a bit if we draw parallels between what we find from the impact of whatever markers are common here to how a patient feels, functions, or maybe even survives.
  - Difficulty of trying to use histology to approve biomarkers, because a really great biomarker could be missed because the histology is not good. What kind of gold standard can we use to measure a liver function test against? If there is a new test, what can it be compared to, to say it's really testing liver function?
    - The problem with function testing right now is having the right comparator that would be an easy way to go to regulatory agencies and say this is performing at some comparator level that would pass agency approvals.
  - In animals, it's been demonstrated that during significant inflammation and fibrosis progression, there is de-differentiation of hepatocytes. And one of the things that get down-regulated is a transcription factor- HNF4A- that is easily stained for on liver biopsy. And they demonstrated that if HNF4A was restored, there could be a recovery of liver function. In the beginning, at least, we should see does HNF4A staining on liver biopsy correlate with transcriptomics with outcome?
  - The obvious answer for patients with more advanced disease is the kind of endpoints discussed: progression to cirrhosis and certainly clinical decompensation. That's where those tests are going to have the first validation. If they don't work there, it would seem there's less value in developing them for earlier stages of liver disease

## SESSION #6: NEW WORKGROUP PRIORITIZATION

**Moderators:** Veronica Miller, Forum for Collaborative HIV Research
Arun Sanyal, Virginia Commonwealth University Medical Center

### Possible New Working Groups

**Discussants:** Claudia Filozof, Covance
Donna Cryer, Global Liver Institute
Peter Traber, Galectin Therapeutics, Inc.
Robert Arch, Takeda Pharmaceuticals International, Inc.
Sudha Shankar, FNIH
Claude Cohen-Bacrie, SuperSonic Imagine
Claude Sirlin, University of California, San Diego
Erwin de Buijzer, Humedics GmbH
Arie Regev, Eli Lilly and Company
Joanne Imperial, FibroGen, Inc.

**Discussion:**

1. Efficiency in Trial Recruitment
2. Framework for Placebo Arm Cohort
3. Adaptive trial design and new analytic approaches
4. Biomarker Surrogate Endpoints
5, DILI/NASH
6. HCC and Other Disease States
7. Other?

- DILI/NASH:
    - IQ DILI Consortium, trying to address questions and issues that are not currently covered by existing guidance and position papers on drug-induced liver injury. Very common for patients to have underlying liver diseases, and populations do not behave like the guidance recommends. Populations include oncology patients, hepatitis B patients, NASH patients, who have pre-existing CLD.
    - Questions include: which levels do we use as threshold for a signal for drug-induced liver injury? What do we use as baseline? And do we adjust this baseline along the treatment? When ALT improves, do we then use a different type of baseline? And when do we discontinue treatment?
    - 12 companies part of the consortium, can contact Arie Regev if interested or have questions.

- Efficiency in Trial Recruitment:
    - This Working Group could include Framework for Placebo Arm Cohort, and Adaptive Trial Design. Adaptive design allows for prospectively pre-planned adaptations, and keeps the robustness of the data. This is useful in disease areas where there is a limited number of patients and low prevalence. Patients with biopsy confirmed NASH is very limited.
        - Another thing that can be an objective of this working group is to define the best tool or algorithm that can help pre-identify the patients that will finally have NASH with F2 or 3. There are some algorithms ongoing there, but getting consensus and informing everyone which is the best one will be very helpful.

  - In order to really become efficient in trial management, patients have to be stratified in the best possible way to identify those patients that will benefit from the therapy, and be able to measure it. As a result, a biomarker that really can be used at the beginning and also at the end of the study needs to be found.
  - There could be a better way to use the placebo group, both using it to perform some sub studies for natural history purposes but also considering one placebo group for several different trials to speed up the enrollment- because that's really a big problem. Not only would it speed up enrollment but also reduce cost dramatically and hopefully get us to the end quicker.

- Biomarkers Surrogate Endpoints:
  - Forum has covered that area fairly well. There is a lot of good work and good thinking going on around biomarkers and so forth, but still a long way off from having sufficient information to guide drug development in totality.
  - Liver Forum has made a lot of progress in circulating biomarkers area, but not much attention to the imaging biomarkers.
  - Need to expand the group of biomarkers to include also the functional liver tests

- Other:
  - Refining patient reported outcome measures
  - Need patients not only participating in trials but in the full drug development process.
  - Socioeconomic impact of NASH and its related sequelae.
  - Will be picking back up request that IOM do a study about the state of the liver in the US and call attention to this.