LITMUS
Liver Investigation: Testing Marker Utility in Steatohepatitis

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Liver Investigation: Testing Marker Utility in Steatohepatitis

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Clinical Application

Discovery Science

EU FP7 (2010-2013)

Aims of the LITMUS Consortium

1. To leverage existing cross-sectional and longitudinal patient cohorts and bioresources into a single unified resource for biomarker validation.

2. To expand the prospective recruitment of patients with histologically characterised NAFLD to further support validation of candidate biomarkers.

3. To establish a robust technological and methodological platform and use it for the definitive validation of candidate biomarkers.
   – An impartial, technology-unbiased platform for biomarker discovery, assessment and validation.
   – Address all 3 FDA BEST biomarker domains (diagnostic, prognostic and monitoring)
   – Clear line of sight to FDA and EMA regulatory qualification.

4. To define the most accurate and tractable biomarkers relevant to NAFLD.
   – LITMUS will provide validation data of the requisite standard to support regulatory qualification of biomarkers for trial use against both histological/biochemical indices and clinically relevant long-term outcome measures.

5. To develop consensus and qualify preclinical models of NAFLD/NASH and then back-translate biomarkers for validation in these models
   – Supporting pre-clinical drug development and translational drug development.
Biomarker Needs to Address

- **Diagnostic (BIPED ‘Burden/Severity of disease’ and ‘Diagnostic’)**
  - Degree of steatosis,
  - Grade of steatohepatitis,
  - Stage of fibrosis,
  - Discriminating Steatosis (NAFL) vs. Steatohepatitis (NASH)

- **Prognostic (BIPED ‘Prognostic’).**
  - Stratify individuals by fibrosis progression risk,
  - Discriminate fast vs. slow progressors,
  - Predicting long-term outcomes and hard endpoints

- **Dynamic (BIPED ‘Efficacy of Intervention’)**
  - Track progression and/or regression of disease severity
  - Efficacy of intervention
NAFLD REGISTRY

Clinical Data
- Anthropometrics
- Medical History
- Medication
- Hematology & Biochemistry
- Diet/Lifestyle

Histopathology
- Digital Imagery of Histology Slides
- NIDDK NAS Score
- FLIP SAF Score

Biobank Resource
- Serum & Plasma
- Frozen Liver Tissue
- FFPE Liver Tissue
- Urine
- Faeces

Integrated ‘Omics’ Dataset
- SNP variation
- DNA methylation
- Transcriptomics
- Metabolomics/Lipidomics

Longitudinal Follow-up
- Annual Reviews
  - ‘Hard Endpoints’
  - Death/OLT
  - HCC

‘Hard Endpoints’
Work Package Leaders & Key Partners

- **WP1: Project Coordination**
  - Anstee (UNEW) & Wenn (IXS)

- **WP2: Analysis, Evaluation & Evidence Synthesis**
  - Bossuyt (AMC), Boussier (UA)

- **WP3: Patient Cohorts & Bioresources**
  - Ratziu (ICAN), Anstee (UNEW), Bedossa (APHP), Betsou (IBBL), Francque (UZA)

- **WP4: Central laboratory**
  - Karsdal (NB), Leeming (NB), Schuppan (UMC), Daly (UNEW), Hyotylainen (OU), Orsec (OU), Mato (CIC bioGUNE), Clement (ICAN), Geier (UKW)

- **WP5: Imaging**
  - Harrison (UOX), Neubauer (UOX), Banarjee (PERS), Hockings (ANT), Yki-Jarvinen (UHEL), Romero-Gomez (SAS)

- **WP6: Reverse Translation & Pre-Clinical Models**
  - Vidal-Puig (UCAM), Oakly (UNEW), Trautwein (RWTH), Marra (UNIFI), Rodrigues (FML)

- **WP7: ‘QED’ Qualification, Exploitation & Dissemination**
  - Ratziu (ICAN), Sanyal (UNEW), Bossuyt (AMC), Anstee (UNEW), Day (UNEW), Karsdal (NB), Schuppan (UMC), Dufour (UBER)