Collaboration in Action: The Investigative Medicines Initiative (IMI2)

Liver Investigation: Testing Marker Utility in Steatohepatitis

2nd International Workshop on NASH Biomarkers, Washington DC, USA, May 2017

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Disclosure Slide

Quentin M. Anstee

Research Grant Funding: Abbvie, GlaxoSmithKline, Allergan/Tobira, Vertex.

The Investigative Medicines Initiative (IMI2) Scheme

- Focus on unmet needs
- Non-competitive collaborative research
- Competitive Calls for proposals
- Pooling expertise, knowledge and resources, cross-fertilisation
- Developing incentives to address major unmet medical needs
- Providing a neutral trusted platform to align public and private interests
Typical IMI2 Two-Stage Call Process

Topic definition

Stage 1
- Identification of topics and willingness to collaborate
- Applicant consortia submit short proposals
- Evaluation

Stage 2
- Applicant consortium
- Full consortium submits full proposal
- Evaluation

Grant award
- Project Agreement
- Grant Agreement

Project launch!

Call launch
Merger: applicants & industry
Finalisation
An important paradox exists: a significant proportion of the population have NAFLD but only a minority progress to advanced liver disease or morbidity/mortality.
The Imperative for Biomarkers in NAFLD

An important paradox exists: a significant proportion of the population have NAFLD but only a minority progress to advanced liver disease or morbidity/mortality.

A lack of tractable non-invasive biomarkers has impeded the diagnosis, risk stratification and monitoring of patients and so many cases remain undiagnosed and present with advanced disease.

The lack of biomarkers has also hampered drug development and the conduct of clinical trials, which still depend on histological effect as an endpoint.
LITMUS Concept

A goal-oriented, tri-partite collaboration is best placed to deliver a definitive and impartial evaluation of available and new biomarkers.

• **End-users of biomarker technologies**
  – Practicing clinicians with expertise in NAFLD
  – Pharmaceutical industry (EFPIA partners & Partners in Research);

• **Independent academics** with expertise in the evaluation of medical test/biomarker performance

• **Biomarker researchers and developers**
  – Academic
  – Commercial
A goal-oriented, tri-partite collaboration is best placed to deliver a definitive and impartial evaluation of available and new biomarkers.

LITMUS Concept

LITMUS will implement a robust ‘technology-unbiased’ platform and conduct the systematic study and validation of a broad range of non-invasive biomarkers and technologies relevant to NAFLD with reference to fully-adjudicated liver biopsy data.

• LITMUS will align with the EMA/FDA accord for Qualification of Biomarkers & Clinical Outcome Assessments, in compliance with:
  – EMA CHMP Guidance on Qualification of Novel Methodologies for Drug Development;
  – FDA 510(k)/PMA pathway or Drug Development Tools (DDT) Qualification Program;

• Generate the requisite level of high-quality data to support biomarker validation and the evidence needed for regulatory qualification.
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LITMUS will implement a robust ‘technology-unbiased’ platform and conduct the systematic study and validation of a broad range of non-invasive biomarkers and technologies relevant to NAFLD with reference to fully-adjudicated liver biopsy data.

Our ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to and/or regression from NAFL through NASH to fibrosis and cirrhosis.

- To assist drug development and the conduct of clinical trials
- To enable the cost-effective management of NAFLD in clinical practice.
Strong Collaborative Foundations in Discovery Science

**EU FP7**
- €6 million
- (2010-2013)

**EU H2020**
- €6 million
- (2015-2019)

**EU IMI2**
- €34 million
- (2017-2022)
The EPoS European NAFLD Registry
• Clinical recruitment to use a ‘hub and spoke’ model
  – National ‘hub’ centre(s) with feeding ‘spoke sites’
  – Performance management for recruitment
    • Quentin Anstee (UNEW) – UK
    • Vlad Ratziu (ICAN) – France
    • Jorn Schattenberg (UMC) – Germany
    • Andreas Geier (UHW) – Germany
    • Jean-Francois Dufour (UBE) – Switzerland
    • Michael Trauner (MUV) – Austria
    • Sven Franque (UZA) – Belgium
    • Elisabetta Bugianesi (UNITO) – Italy
    • Manuel Romero-Gomez (SAS) – Spain
    • Helena Cortez-Pinto (FML) – Portugal
    • Mattias Ekstedt (LIU) – Sweden
    • Hannele Yki-Jarvinen (UHEL) – Finland
    • Van Mil (UMCU) – Netherlands
    • George Papatheodoridis (NKUoA) – Greece

Additional Links to initiate a ‘Global NAFLD Network’ with USA (Harrison and Sanyal)
The Registry is configured for both cross-sectional and longitudinal data collection.

Standardised data include anthropometric, lifestyle/diet, co-morbidity, pharmacotherapy, clinical biochemistry, histological indices and incident disease/events.
8. Processing of Research Samples

NOTE: All samples must be handled in accordance with local handling/dilution protocols for biological samples. Samples are to be collected after an overnight fast.

8.1 Serum Sample Preparation from SST II (Gold) Tubes

- Label sample tubes clearly with patient's name and ID number.
- Draw blood into SST II (Gold) tubes and immediately place in ice.
- Centrifuge blood samples at 3,000 rpm for 10 minutes.
- Transfer the serum fraction to a clean tube and store at -80°C.
- Ensure samples are not exposed to light.

Cholesterol and Triglyceride Assays

- Serum samples should be assayed for cholesterol and triglyceride concentrations within two hours of taking the sample.
- Serum reference ranges for cholesterol and triglyceride are as follows:
  - Cholesterol: 150-200 mg/dL
  - Triglycerides: 50-150 mg/dL

Diabetes Testing

- Fasting plasma glucose should be measured for all patients.
- Reference range for fasting plasma glucose is 80-110 mg/dL.

HbA1c Testing

- HbA1c is a measure of glycemic control over the past 2-3 months.
- Reference range for HbA1c is 4.0-6.0%.

Hyperlipidemia

- Hyperlipidemia is a condition characterized by high cholesterol and/or triglyceride levels.
- Management includes dietary changes, weight loss, and possibly medication.

Hypertension

- Hypertension is defined as a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher.
- Management includes lifestyle changes, appropriate medications, and regular monitoring.

Mediterranean Diet Score (MDS)

- The Mediterranean Diet Score assesses adherence to the Mediterranean Diet.
- The score is calculated based on the frequency of consumption of specific food groups.
- A score of 0-5 is considered low adherence, 6-10 is moderate adherence, and 11-15 is high adherence.

For detailed instructions and protocols, refer to the Investigator Handbook & Laboratory Manual.

EASL

European Association for the Study of the Liver
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<tr>
<th>WP#</th>
<th>Coordinator/Industry Lead</th>
<th>Project Manager</th>
<th>Academic Lead</th>
<th>Industry Lead</th>
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<td>Quentin Austee (UNEW)</td>
<td>David Wean (IXS)</td>
<td>Julia Brosnan (PFE); Manu Chakravarthy (LLY)</td>
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Conclusions

• LITMUS is a focused, pragmatic and goal-oriented programme, founded on a strong track-record of NAFLD research, that addresses the pressing need for validated non-invasive biomarkers.

• The LITMUS ambition is to make a fundamental difference to the way NAFLD/NASH is diagnosed, clinical trials are conducted and the way patients are managed.

• LITMUS offers the promise of a decisive advance in NAFLD biomarker development and regulatory qualification and will thus facilitate therapeutics discovery and support the targeting of medical care to those at greatest risk.

LITMUS has the demonstrable capacity to provide much needed clarity on biomarker validity at scale and pace and thus deliver a step change in drug development and the care of patients with NAFLD