Updates from NASH Biomarkers Consortia

LITMUS
Quentin Anstee, Newcastle University
Detlef Schuppan, Mainz University Medical Center
Collaboration in Action: The Investigative Medicines Initiative (IMI2)

Liver Investigation: Testing Marker Utility in Steatohepatitis

Liver Forum #8, Paris, April 2018

Prof Quentin M. Anstee PhD, FRCP
Project Coordinator (Newcastle University, UK)

Dr Julia Brosnan PhD
Project Lead (Pfizer, USA)
Disclosure Slide

Research Grant Funding
Abbvie, Allergan/Tobira, Astra Zenica, GlaxoSmithKline, Novartis Pharma AG, Pfizer Ltd., Vertex.

Active Research Collaborations (including research supported through the EU IMI2 LITMUS Consortium*)

Consultancy

Speaker
Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Genfit SA, Gilead.
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 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*
- Generate the requisite level of high-quality data to support biomarker validation and the evidence needed for regulatory qualification.
LITMUS Concept

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

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**.
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
Strong Collaborative Foundations in Discovery Science

EU FP7 (2010-2013)


Expanded Partner Network

Clinical Application

EU IMI2 (2017-2022)
Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)

FACTS & FIGURES

- **Start Date**: 01/11/2017
- **End Date**: 31/10/2022
- **Contributions**: €
  - **IMI Funding**: 15 797 881
  - **EFPIA in kind**: 15 571 213
  - **Other**: 1 103 310
  - **Total Cost**: 32 472 404

PROJECT LINKS

- **Project website**: www.litmus-project.eu
- **Twitter**: @LITMUS_IMI

**47 Partners***
- 29 Academic,
- 17 EFPIA/Industrial,
- 1 Professional body

**14 Countries for Clinical Recruitment**
- UK, France, Germany, Italy, Switzerland, Netherlands, Austria, Luxembourg, Sweden, Finland, Greece, Spain, Portugal, USA

**True Public-Private co-funding model**
- Effective budget >€34 million
  (includes >€20 million ‘cash’ from EU & Industry)

* Membership expanding due to addition of more industrial partnerships.
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<thead>
<tr>
<th>WP</th>
<th>Coordinator/Project Lead:</th>
<th>Academic Lead</th>
<th>Industry Lead</th>
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<tbody>
<tr>
<td>WP1</td>
<td>Quentin Anstee (UNEW)</td>
<td>David Wenn (IXS)</td>
<td>Julia Brosnan (PFE); Kevin Duffin (LLY)</td>
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<td>David Manner (LLY)</td>
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<td>Quentin Anstee (UNEW); Vlad Ratziu (ICAN)</td>
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<td>Remy Hanf (GNFT)</td>
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<td>Luke Vale (UNEW)</td>
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<td>Fay Betsou (IBBL)</td>
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<td>Pierre Bedossa (APHP); Dina Tiniakos (UNEW)</td>
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<td>Central Labs:</td>
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<td>Diana Leeming (NB)</td>
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<td>Protein/Collagen:</td>
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<td>Jessica Ash (SOMA)</td>
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<td>Pierre Chaumat (GNFT); Melissa Miller (PFE)</td>
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<td>Melina Arazy (EXA)</td>
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<td>Theresa Tuthill (PFE)</td>
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<td>Pre-Clinical Models:</td>
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<td>Haiquin Hua (LLY)</td>
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<td>Qualification, Exploitation &amp; Dissemination (QED)</td>
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<td>Richard Torstenson (NOVO); Morten Karsdal (NB)</td>
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<td>WP8</td>
<td>Ethics Lead:</td>
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Two-day Project Kick-Off Meeting
- November 2017
- Newcastle, UK
- 128 delegates across all partners in attendance
LITMUS Progress (Y1H1)
✓ Initiate LITMUS specific Ethics Applications across all sites.
✓ Inventory & Centralisation of existing Bioresources
✓ Upgrading the European NAFLD Registry Database

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

Histopathology
Digital Imagery of Histology Slides
Central Reading by Expert Pathologists
NIDDK NAS Score
FLIP SAF Score

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

Biobank Resource
Serum & Plasma
Frozen Liver Tissue
PEPE Liver Tissue
Urine
Faeces

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

NAFLD REGISTRY

LITMUS Central Biobank

IBBL

National Lead Clinical Centre
Collaborative Recruiting Centre
Non-Clinical Centre

LITMUS PARTNERS

IMI
innovative medicines initiative
The European NAFLD Registry

INVESTIGATOR HANDBOOK & LABORATORY MANUAL

The European NAFLD Registry and LITMUS consortium are funded by the Innovative Medicines Initiative (IMI) Program of the European Union (Grant Agreement 777377).

Funders:

The European NAFLD Registry www.litmus-project.eu

INVESTIGATOR HANDBOOK & LABORATORY MANUAL

The European NAFLD Registry www.litmus-project.eu

INVESTIGATOR HANDBOOK & LABORATORY MANUAL

The European NAFLD Registry www.litmus-project.eu
Prospective Recruitment & Follow-up of Existing Patients in the European NAFLD Registry already ongoing throughout the LITMUS set-up process
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 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

• Following project kick-off in November 2017, LITMUS has made rapid progress across both the clinical platform and the evaluation platform – establishing a sound foundation for the project.
The LITMUS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777377. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

www.litmus-project.eu
www.imi.europa.eu