Identification and Validation of Non-invasive Biomarkers Across the Spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD)

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innovative medicines initiative

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Central Challenge

NASH is a serious liver disease, substantially more serious than earlier stages of NAFLD. NASH can progress to cirrhosis with attendant morbidities of end-stage liver disease (ESLD) and causes heightened risk for hepatocellular carcinoma (HCC).

Critical need to establish non-invasive biomarkers for diagnosing and classifying subjects within the NAFLD spectrum, and in particular identifying those with NASH and predicting those likely to progress to NASH.

Identifying and validating biomarkers that can be employed to track disease progression, as well as response to intervention is crucial in furthering advances in clinical care and drug development for NASH and will enable clearer understanding of the heterogeneous outcomes of NAFLD.

Current State

The rising prevalence of NAFLD is closely related to the convergent epidemics of obesity, insulin resistance and type 2 diabetes.

World-wide prevalence of NAFLD is approx 30% - doubles within a T2D population.

Not all individuals with NAFLD develop NASH

Imperative that those with NASH can be identified within the NAFLD population

A diagnosis of NASH, its staging and its distinction from NAFLD, is presently based on histological assessment of a liver biopsy.

There is clear consensus that a lack of diagnostic, prognostic and treatment response NASH biomarkers hampers clinical practice and seriously impedes drug development.

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Why the need for public-private collaborative research?

Candidate Biomarkers

- Relatively small studies.
- Rarely been replicated.
- None been validated against liver biopsies
- Need to be studied systematically
- Sufficiently powered investigation.
- collation of relevant existing clinical research
- best addressed by a comprehensive public-private collaboration.

Liver Biopsy

- Currently the basis for diagnosis and staging of severity of NASH.
- Basis for adjudicating effectiveness of intervention
- On-treatment liver biopsy required for registration of novel treatment.

Validating non-invasive biomarkers against liver biopsy in an appropriately designed, sufficiently powered study, is needed to bridge the contemporary standards for clinical practice and drug development.

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What's the purpose of this IMI2 initiative?

Bring together a level of funding and multi-stakeholder commitment sufficient to definitively address biomarker challenges in NAFLD and NASH.

Avail existing NAFLD and NASH research cohorts and access samples that meet carefully considered criteria, importantly including properly adjudicated liver biopsy samples.

Employ standardized laboratory analyses, together with bioinformatics, to harmonize biomarker data, as well as accompanying clinical and liver imaging data.

Transformative for the field - needed to gain consensus acceptance by NAFLD basic and clinical investigators, instill confidence in the use of biomarkers for decision making by drug developers and ultimately, lead to regulatory approval of these biomarkers

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What Kind of Biomarkers?

Diagnostic Biomarkers

Relatively noninvasive (i.e. blood-based/imaging) useful across the spectrum of NAFLD and NASH in particular.

- Identify the severity or stage of ***hepatic fibrosis***
- Pertain to the severity of ***hepato-cellular inflammation.***

Predictive Biomarkers

While cross-sectional data can be employed to validate diagnostic biomarkers, within-subject longitudinal data is needed for qualification of:

- Biomarkers that predict progression from NAFLD to NASH
- Within NASH, progression across stages of disease severity.

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Preclinical Models of NASH

- Significant component will be work on preclinical model development and qualification.
- Test whether biomarkers identified to predict clinical progression back-translate to the preclinical models.
- The preclinical work in models of NAFLD and NASH will increase understanding of the disease mechanisms causing development of NAFLD and its progression to NASH, including the contribution of diabetes to these processes.
- Establishment and characterization of a non-rodent model of NASH; one that incorporates a context of the metabolic syndrome (obesity/insulin resistance).
- Various imaging modalities will be applied to these models (rodent/non-rodent).

The anticipated deliverable is to establish a consensus recommendation of animal model(s) suitable to use in support of development of novel therapeutics for NAFLD/NASH

Proposed Stages

Validation of a Priori Hypotheses (Stage 1a)

- Identification of top markers from existing data
- Qualify by pooling available datasets
- Conduct standardized assays as needed
- Common data repository

Confirm and Complement (Stage 1b)

- Establish a prospective Global NAFLD Cohort (GNC) across the full spectrum of disease (detailed phenotyping, histology, biomarkers specimens, imaging).
- Expected to extend existing studies
- Confirm the identified top candidates in the GNC

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What Will the Applicant Consortium Look Like?

- Led by scientists/physicians who are recognized experts in liver disease and specifically in NAFLD and NASH
- Encompass subjects with the full spectrum of NAFLD (informed consent).
- Cohorts selected for Stages 1a and 1b should be longitudinal research efforts with high quality follow-up procedures together with a high level of participant retention.
- Liver biopsy data must be available
- Enriched with later stages to support NASH biomarker qualification.
- Size estimated to be 1,500 to 2,500 subjects

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Applicant Consortium Cont'd?

- Clinical data (including imaging data) needs to be available
- Data that exclude causes of liver disease other than NAFLD and NASH.
- All liver related biomarker data need to be made available.
- The interval between the two liver biopsies should be at least two years.

Expected Deliverables

1. Baseline characteristics/biomarkers of patients with NAFLD that can diagnose NASH and predict better disease progression across the spectrum of NAFLD;

2. Validation of non-invasive biomarkers for stratification of subjects (e.g. fast progressors) for clinical trial inclusion and

3. The identification of candidate biomarkers that can serve as surrogate markers for clinical outcomes of NASH

Expected Impact

It is expected that this program which seeks to identify and qualify non-invasive biomarkers for NAFLD and NASH will be transformative for clinical management of patients and profoundly enabling for drug development for treatment of NASH. Accurate diagnosis, effective treatment and effective tools to monitor disease response are the three pillars essential in support of medical practice. The unmet need that is present with regard to NAFLD and NASH cannot be effectively addressed without the elucidation of validated biomarkers.

Suggested Architecture of the Full Proposal

WP1 – Overall project co-ordination, integration and dissemination

WP2 – Management and integration of existing databases with key focus upon identification of candidate NAFLD and NASH biomarkers

WP3 – Central laboratory assay development and implementation.

WP4 – Clinical replication and validation of the biomarker(s) identified in Stage 1a data in a separate Stage 1b cohort. Patient reported outcomes

WP5 – Qualification of clinical imaging modalities of NAFLD and NASH within the context of relationship to liver biopsy data and soluble biomarker data, together with other ancillary data including genetic information.

WP6 – Development and qualification of relevant preclinical disease models (rodent and non-rodent) for NAFLD and NASH.

Indicative Duration

- Indicative duration is 5 years
- At the end of this period and ONLY if there is sufficient new information, collectively deemed of value, would there be justification to extend the study beyond year 5 with a restricted call and additional funds.
- Stage 2, the focus would be on delivering and validating surrogate makers of clinical outcome such that they are ready for regulatory acceptance

Participating Companies

Pharmaceutical Companies

MSD
Pfizer
Lilly
BI
Novo Nordisk
Sanofi
Novartis

Partners in Research

Somalogics
Ellegaard

Deliverables

The key deliverable for Stage 1a is to identify and qualify diagnostic biomarkers for NASH and across the spectrum of NAFLD

- Access samples/existing biomarker data from extant cohorts of NAFLD and NASH.
- Perform centralized assays on plasma and serum samples, on liver biopsy samples if available, and genotyping (e.g. for PNPLA3).
- Bioinformatics and biostatistics analyses will drive biomarker qualification.
- Identified biomarkers will then be validated in a separate cohort in Stage 1b.

The two key deliverables for Stage 1b are:

1) to provide validation of the previously identified diagnostic NASH and NAFLD biomarkers using an independent cohort, and

2) collect and extend longitudinal clinical data to identify biomarkers that predict disease progression

- Commencement of accruing the "validation cohort" will be contingent upon making meaningful progress in Stage 1a.
- Validation cohorts(s) should have broad ethnic and demographic diversity.