Topic: Identification and Validation of Non-invasive Markers across the Spectrum of Nonalcoholic Fatty Liver Disease (NAFLD)

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Topic details

Action type: Research and Innovation Actions (RIA)
Submission & evaluation process: 2 Stages

Specific challenges to be addressed

Aim:
The central challenge to be addressed is to establish and validate non-invasive markers for classifying and evaluating subjects with NAFLD, and in particular to identify amongst those with NAFLD, individuals who have Nonalcoholic steatohepatitis (NASH). Identifying and validating these biomarkers will be crucial in furthering an understanding of the factors that drive the heterogeneity of NAFLD and in enabling accurate diagnosis of those with NASH. The ultimate challenge that will be addressed is to validate one or more NAFLD biomarkers that can serve as surrogates for development of clinically meaningful outcomes.

Current State:
NAFLD is not an uncommon disease. The rising incidence of NAFLD is closely related to the convergent epidemics of obesity, insulin resistance and type 2 diabetes. The estimated world-wide prevalence of NAFLD is approximately 30%; yet not all individuals with NAFLD develop NASH. It is estimated that the prevalence of NASH is approximately 7%. A diagnosis of NASH (and hence its distinction from NAFLD) is at present based on histological assessments of liver biopsies. The procedure is invasive and associated with a risk, even if it is small. Moreover, while regarded as a gold standard for diagnosis of NASH, a liver biopsy can be subject to sampling variability and some variability in interpretation (or scoring). Given these and other related challenges, including notably that there are few efficacious therapies, only a small proportion of patients who potentially have NASH is given this diagnosis. Given that around 1/3 of subjects with NASH go on to progress to late stage liver disease such as cirrhosis and hepatocellular carcinoma it is rapidly emerging as a major public health problem. This proposal aims to reverse the lack of non-invasive biomarkers that hamper clinical practice and seriously impede drug development, and, thereby remove a major barrier that limits appropriate treatment for patients with NASH.
Need and opportunity for public-private collaborative research

There are a plethora of candidate biomarkers that have already been identified, or at least empirically nominated. It is quite plausible that one or more of these candidate biomarkers could address the gaps outlined above. However, to date the effort toward identifying and validating NAFLD and NASH biomarkers has been dispersed and each contribution relatively small, conducted largely by academic laboratories and rarely replicated. There is a true need for a comprehensive public-private collaboration to enable and support a bona fide systematic approach to validate candidate markers. To this point, gaining a consensus within the NAFLD field amongst researchers and clinical investigators, drug developers and regulators on the qualifications and utility of key biomarkers across the spectrum of NAFLD and for the diagnosis of NASH will be pivotal in the acceptance of these biomarkers for regulatory approval. Without collaborative, large scale, public-private research effort it seems unlikely that acceptance of these biomarkers as criteria for participant inclusion in clinical trials, for tracking disease (and response) progression and for evaluating endpoints will be possible. The purpose of this ambitious IMI2 initiative is to bring together contemporary, but disparate activities, across the NAFLD field with a level of funding and multi-stakeholder commitment commensurate to build a database that is comprehensive in scale and scope to definitively answer the key biomarker questions in NAFLD. Without such a concerted effort it is unlikely that transformative progress can be made in this disease area.

Scope

The scope of this proposed biomarker collaborative research for NAFLD and NASH will encompass three aspects, which are outlined below.

1. Diagnostic and staging biomarkers that can separate NASH from NAFLD, and more specifically, identify the presence and severity of inflammation and fibrosis. This will serve to help identify the most appropriate population for a particular treatment.

2. Biomarkers that can predict progression. It is recognized that in general, NASH progresses slowly toward End-Stage Liver Disease (ESLD). However, there do appear to be subgroups that progress fairly rapidly. Accordingly, there is a clear need to qualify biomarkers that can identify “fast progressors” amongst those who meet criteria for a diagnosis of NASH.

3. An ultimate goal of biomarker research is to provide research findings that validate with Regulatory agencies the acceptance of non-invasive biomarkers as surrogates for clinically important endpoints. It will be a long-term goal of this collaborative research to validate biomarkers that reliably identify and predict risk for cirrhosis and complications of ESLD (e.g. varices, ascites) and that reliably identify and predict risk for hepatocellular carcinoma (HCC).

Expected key deliverables

The expected deliverables are:

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

2. validation of noninvasive markers for stratification of subjects (e.g. fast progressors) for clinical trials; and

3. the identification of candidate biomarkers that can serve as surrogate markers for clinical outcomes of NASH.
It is planned that deliverables 1-3 will be achieved in Stage 1 (the focus of this application) but that full validation of markers that can be regarded as surrogates for clinical outcomes by regulatory bodies, will require a longer period of work than can be accomplished during these first 5 years. Sufficient promising data from Stage 1 is expected to lead to an additional Stage 2 call for full clinical validation (by the launching of a restricted call).

A key step towards achieving these deliverables will be the identification of the top biomarker candidates that currently and collectively are regarded as leading candidates and qualify these by pooling available data sets. This will be supported by conducting standardized assays as needed, and by using a common data repository. This will be the main goal of STAGE 1A (validation of a priori hypotheses). The key deliverables for STAGE 1B (confirm and complement) will be to confirm the identified top candidates using a prospectively developed global NAFLD cohort. This will be done by establishing a Global prospective longitudinal NAFLD Cohort (GNC) across the full spectrum of disease with detailed phenotyping, including histology, imaging, and bio-specimen banking. It is anticipated that individuals from existing consortia will contribute towards the GNC.

**Expected impact**

It is expected that this program 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 and effective treatment are the twin pillars that support medical practice and the unmet need that is present with regard to NAFLD and NASH cannot be effectively addressed without the elucidation of validated biomarkers.

**Potential synergies with existing consortia**

This call topic will invite bidding consortia to launch a cross-functional research initiative with overall objectives to address the above gaps. A key aspect of achieving the first objective, that of qualifying candidate biomarkers, will be to pool all available information from existing participating clinical databases. There will be a robust and concerted effort to develop synergies with existing consortia, even or perhaps especially if such consortia have as their respective goal the identification of critical pathobiology process of NAFLD and NASH rather than the identification of candidate biomarkers per se. Indeed, it will be through alignment and collaboration with such existing consortia that synergies valuable to all parties can be achieved. For example, by combining efforts, it will be feasible to use standardized methods/platforms that enhance validation. It will also be possible that consortia contributing these databases will be expanded, and/or extended, further by these efforts. It is also expected that identified biomarkers can be incorporated into ongoing clinical trials in order to enhance the precision of application and chances of success of future novel therapeutics aimed at slowing and/or reversing this disease. Finally it is anticipated that these candidate biomarkers will be evaluated in the preclinical space by the applicant consortium.

**Indicative duration of the project**

The indicative duration of the project will be for 5 years. At the end of this period and only if there is sufficient new information that is collectively deemed of value, would there be justification to extend the study beyond year 5 with a restricted call and additional funds. Thus, in STAGE 2 (which would constitute a separate restricted call), the effort will focus upon delivering and validating surrogate markers of clinical outcome such that these are ready for regulatory acceptance.
Future Project Expansion

In the context of this topic, the EFPIA companies envision the possibility to expand those work packages designed to build and prospectively follow the GNC to in the future support the construction and maintenance of a longstanding clinical data repository to serve as a future source of biomarker identification and/or validation. Leveraging any success in this first program, as long as the results are positive, such further work would be the natural progression of the project. Building on these prior successes would maximise the long term impact of the larger project, and engender continued future successes in making clinical development of new therapeutics, as well as their application in the clinic, both more fruitful and more efficient. This proposed project extension would also take advantage of already established collaborations and networks forged in the overall project, thereby maximising efficiency on time and resources. A restricted call may allow achieving this in the most efficient way. The detailed scope of the call will be described in the relevant annual work plan.

Applicant consortium

Applicant consortium should have clinical and research expertise in NAFLD and NASH with proven access to the recruitment and longitudinal follow up (> 3 years) of large numbers (>1500+) of research participants with these disorders. The applicant consortium will need to have an established expertise in developing and maintaining the clinical database for research participants that is relevant to an in-depth characterization of the presentation of NAFLD. The applicant consortium should hold, or have ready access to, the histology obtained from the initial diagnostic liver biopsy and any follow-up liver biopsy, together with access to serum and plasma samples that can be used for central laboratory determinations.

As outlined above, in Stage 1A, the intent is to pool extant data on NAFLD and NASH biomarkers, so applicant consortium for this aspect of the call must have full access to an existing longitudinal cohort with documented ethical consent to share data and samples. In contrast, the aim of Stage 1B is to prospectively recruit a cohort of research participants with NAFLD and NASH. All of the expertise described above pertains here, in Stage 1B, and additionally, the applicant consortium should have expertise in clinical research recruitment and follow up, including access to needed clinical research facilities. Ideally, an applicant consortium would be able to contribute to both Stage 1A and 1B. A critical need for success of this call will be access to state-of-the-art laboratory facilities and expertise in measuring, in a standardized manner, the top nominated candidate biomarkers in a large cohort. Based upon a survey of published literature, it is anticipated that a cohort of 2,500 to 3,000 research participants will be needed. It is expected that subjects from already existing cohorts will be recruited into the GNC for further follow-up. The applicant laboratory consortium need not also be a clinical site applicant.

Glossary

NAFLD: Non-alcoholic fatty liver disease  
NASH: Non-alcoholic steatohepatitis  
ESLD: end-stage liver disease  
GNC: Global prospective longitudinal NAFLD Cohort