NIMBLE
Non-Invasive BioMarkers of MetabOlic Liver Disease

May 5, 2017

Dr. Roberto Calle
For the NIMBLE Program Steering Committee

Confidential
I am an employee and stockholder of Pfizer Inc.
Snapshot of the Foundation for the National Institutes of Health (FNIH)

1996
established by Congress to support NIH in its mission by
advancing biomedical research and training collaborations
among government, universities, industry and not-for-profit organizations

FNIH
Foundation for the National Institutes of Health

$875 million
raised by the FNIH since 1996

501(c)(3)
Non-governmental not-for-profit & independent Board of Directors

Over 550
projects supported

100+
active research partnerships, scientific education/training, conferences/events and capital programs

$0.93
93% of funds directly support programs

13 years
of outstanding Charity Navigator ratings
Biomarkers Consortium

Mission Statement
To discover, develop, and seek regulatory approval for biomarkers to support and accelerate development of new drugs, preventive medicine, and medical diagnostics by combining the forces of the public and private sectors.

Biomarkers Consortium Goals
- Facilitate the development and the seeking of regulatory approval for biomarkers using new and existing technologies;
- Develop evidence to help qualify biomarkers for specific applications in diagnosing disease, predicting therapeutic response or improving clinical practice;
- Generate information useful to inform regulatory decision making;
- Make consortium project results broadly available to the entire scientific community.
- Generate pre-competitive projects; makes consortium project results broadly available to the entire scientific community
- Raise funds from outside sources who support mission (e.g., private industry)
Biomarkers Consortium Governance Structure and Accomplishments

Executive Committee
NIH / FDA / CMS / Industry / FNIH

Cancer Steering Committee

Inflammation & Immunity Steering Committee

Metabolic Disorders Steering Committee

Neuroscience Steering Committee

Multiple Working Groups and Project Teams
Representatives from NIH, FDA, Industry, Subject experts from academia

Academic & Industry Co-chairs:
- Roberto Calle, MD (Pfizer)
- Myrlene Staten, MD (NIDDK)
• Worldwide prevalence of NAFLD in the general population is estimated to be **20 to 30%** in Western countries.
• In the United States, over 64 million people are projected to have NAFLD, with annual direct medical costs of about **$103 billion**.

Liver biopsy; an imperfect gold standard not suitable for large scale application

- Invasive, painful
- Risks- morbidity and mortality
- Sampling variability
- Observer variability
- Limited workforce capacity

Clinical care implications

- Limited capacity for large scale screening
- Limited capacity for definitive diagnosis
- No means to easily assess therapeutic response (e.g., lifestyle or off-label; no approved drugs available)
- Significant limitations to the study of the natural history of the disease

Drug development & clinical study implications

- Slow and expensive screening for studies
- Reduced subject recruitment & retention (prospect of 2nd biopsy)
- Limited capacity for dose selection
- Sampling and observer variability introduce error in the assessment, particularly early studies with smaller sample size
Review of Impact of Biopsy-based Approach on Drug Development

• **Impact on Screening**
  – Nearly half of the biopsies are substandard and there is considerable assessment variability.
  – Increased screen failures, cost, and time needed to perform trials.

• **Impact on Recruitment and Retention**
  – Need for repeat liver biopsies in clinical trials limits subject enthusiasm for participation.

• **Impact on Decision-making and Timelines**
  – Imperfect biopsy data results in imperfect data to support confident decision-making, delaying drug development and potentially resulting in incorrect molecule/dose selection.

• **Impact on Clinical Translation**
  – Even if an effective drug is developed, if correct “at risk” patients are not identified in clinical practice, the drugs impact on burden of disease will be diminished.
Key Non-Invasive Biomarker Needs

Biomarkers that permit:

■ Diagnosis of NASH vs NAFL
■ Staging of disease
■ Classification for risk of progression to adverse outcomes
■ Assessment of response to intervention
The NIMBLE Working Group – Leadership Team

An academic-industry collaborative effort

- **Dr. Arun Sanyal** (Virginia Commonwealth): FNIH NASH Initiative Co-Chair
- **Dr. Sudha Shankar** (Lilly): FNIH NASH Initiative Co-Chair

- **Dr. Rohit Loomba** (UCSD): FNIH NASH Circulating Markers Work Stream Co-Chair
- **Dr. Anthony Samir** (MGH-Harvard): FNIH NASH Imaging Work Stream Co-Chair
- **Dr. Claude Sirlin** (UCSD): FNIH NASH Imaging Work Stream Co-Chair

- **Dr. Roberto Calle** (Pfizer): FNIH Metabolic Disorders Steering Committee Co-chair and NASH Initiative Sponsor
- **Mr. Steve Hoffmann** (FNIH): FNIH Inflammation Steering Committee Scientific Program Manager supporting **NIMBLE** Program
NIMBLE Program Team Organization

NIMBLE Program Steering Committee
Co-chairs: Arun Sanyal and Sudha Shankar
Members: Claude Sirlin, Anthony Samir, Rohit Loomba, Roberto Calle
Scientific Project Manager: Steven Hoffmann

Circulating & Functional Markers Work Stream
Rohit Loomba – Co-chair
Sudha Shankar (Lilly)
Jim Mapes (Myriad – RBM)
Manal Abdelmalek (DCRI)
Mohammad Siddiqui (VCU)
Representatives from 3 companies contributing assays
Others TBD

Imaging Markers Work Stream
Claude Sirlin (UCSD) – Co-chair
Anthony Samir (Harvard/MGH) – Co-chair
Sarah Sherlock (Pfizer)
Roberto Calle (Pfizer)
Others TBD

Pathology Platform Team
Cynthia Guy (DCRI)
Melissa Contos (VCU)
Others TBD

Statistics Platform Team
Derek Leishman (Lilly)
Santos Carvajal-Gonzalez (Pfizer)
Others TBD
Specific Objectives

1. Identify, standardize, and advance qualification of a set of fit for purpose, non-invasive biomarkers (circulating, functional and/or imaging) for the diagnosis and staging of NASH and identification of individuals at risk of progression to adverse outcomes and in need of pharmacological or non-pharmacologic intervention.

2. Identify, standardize, and advance qualification of a set of fit-for-purpose, non-invasive biomarkers (circulating, functional and/or imaging) to assess risk for progression and response to intervention in subjects with various stages of NASH at baseline.

**Stage 1:** standardization and cross-sectional analysis of circulating and imaging biomarkers.

**Stage 2:** most promising candidate biomarkers identified in Stage 1 to be qualified in a prospective longitudinal study.
Interested Partners and Collaborators

- **Eleven** academic investigators (US and ex-US) actively engaged

- Over **thirty** industry partners have expressed significant interest in participating and contributing to the project, including several large pharma as well as imaging companies and companies that have developed functional liver markers

- Offers of data/technology or other in-kind contributions from **eleven** companies

- Offers for samples with matched biopsies from
  - **three** academic collaborators / academic centers (estimated number of samples available approx. 4,000)
  - **three** industry partners (estimated number of samples available approx. 1,000)

- Additional cohorts identified that will be available for validation studies
Collaborative Translational Science

PUBLIC – PRIVATE PARTNERSHIPS WORKING TOGETHER

Academia

INDUSTRY

NIMBLE

FNIH

Liver Forum

IMI

LITMUS

ACADEMIA

INDUSTRY

REGULATORS
NIMBLE Program Timeline and Contact

Program Kick-off projected for 2H-2017

Mr. Steven Hoffmann: shoffmann@fnih.org
FNIH – Scientific Program Manager