NIMBLE Leadership Team

Arun J Sanyal MD
Virginia Commonwealth University
Academic Co-Chair NIMBLE

Sudha Shankar, MD
AstraZeneca
Industry Co-Chair NIMBLE

Roberto Calle, MD,
Pfizer
Industry Co-Chair NIMBLE/MDSC Co-Chair

Tania Kamphaus, PhD
Scientific Program Manager
Overall Goals for the Project and for Today’s Presentation

- **Overarching Project Goal**: to leverage state of the art contemporary scientific tools to qualify strategically relevant biomarkers to enable timely development of NASH therapeutics

- **Today’s Discussion**:
  - Update on evolving NIMBLE organization
  - The scientific approach to develop a stepwise plan to qualify select non-invasive biomarkers to enable accelerated drug development and increased access to care for patients with NASH
  - What has been accomplished so far
  - Next steps- analysis of barriers and solutions
NIMBLE Program Team Structure

NIMBLE Program Leadership Team
Project Co-chairs: Arun Sanyal, Sudha Shankar, Roberto Calle
Members: Claude Sirlin, Anthony Samir, Rohit Loomba, Sarah Sherlock
Scientific Program Manager: Tania Kamphaus

Circulating & Functional Markers Work Stream
Rohit Loomba (UCSD) – Co-chair
Sudha Shankar (Astra Zeneca) – Co-chair
Roberto Calle (Pfizer)
Academic collaborators

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

Data Analysis & Modeling Expert Team
Nancy Obuchowski (Cleveland Clinic)
Santos Carvajal-Gonzalez (Pfizer)
Statistical CRO

Imaging Markers Work Stream
Claude Sirlin (UCSD)– Co-chair
Anthony Samir (Harvard/MGH) – Co-chair
Sarah Sherlock (Pfizer) – Co-Chair
Academic collaborators
NIMBLE PROJECT TEAM

12 Funding Companies
9 Academic Centers
FDA, NIH
Biomarker Companies
Rationale For Approach Being Taken
Key Biomarker related Questions in NASH: A Clinician’s Perspective

- Is NAFLD/NASH likely to develop?
- Is NAFLD Present?
- Is the patient likely to die from NASH?
- What intervention is needed?
- Is the disease trajectory changing?
The Development of Cirrhosis is a Key Milestone in the Course of Cirrhosis

**Causes of death:**
- Cardiovascular
- Cancer
- Rare HCC

**Causes of death:**
- Cardiovascular
- *Liver-related*
- HCC

**NASH**
- Reduced progression to cirrhosis

**CIRRHOSIS**
- reduced outcomes

**DEATH**
NASH (F4) – Prevalence by disease state – 2015 & 2030 (US)

Estes et al, Hepatology, 2018 Jan;67(1):123-133
## Priorities in Biomarker Development for NIMBLE- based on Biggest Impact on Patients Life and Field

<table>
<thead>
<tr>
<th>Biomarker “fit for purpose” use</th>
<th>Impact</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Low due to knowledge gaps and genetics based therapeutics</td>
<td>5</td>
</tr>
<tr>
<td>Is NAFLD present?</td>
<td>Low, can be easily predicted from clinical risk factor profile, does not correlate well with outcomes</td>
<td>4</td>
</tr>
<tr>
<td>What is the risk of liver outcome?</td>
<td>Very high- critical to determine who requires drug/surgical/endoscopic intervention</td>
<td>1</td>
</tr>
<tr>
<td>Can we match drug to patient?</td>
<td>Intermediate- more work needed to validate molecular classification</td>
<td>3</td>
</tr>
<tr>
<td>Is disease trajectory changing (with or without intervention)</td>
<td>High- needed to determine when to intervene, assess disease progression/regression and impact of therapy</td>
<td>2</td>
</tr>
</tbody>
</table>
Administrative Update

Tania Kamphaus PhD
Helen Heymann PhD
Joe Menetski PhD
NIMBLE- SOME KEY MILESTONES – Since Launch Q4 2018 and Q2 2019

Contracting
- Academic Centers
- Key Collaborators
- CROs and Vendors
- Sample Cohorts

Protocol and Study Design
- Draft SAP Design
- Draft Protocol Design
- Updating Imaging Study Design

Regulatory
- LOI for circulating BMx
- Planning submission to EMA

Governance
- New NIMBLE PM
- COI policies signed
- Engaging Patient Representatives
NIMBLE Approved Project Plan

Program Launch

Year 1

STAGE 1 – Retrospective Analysis & Method Studies

1. Sample recovery & analysis
2. Data integration & analysis
3. Methodology imaging studies

Year 2

QC datasets & samples

Biomarker selection For Stage 2

Year 3

Cross-sectional analysis of baseline data

Year 4

Pubs & final data release

STAGE 2 – Prospective study including Circulating, Functional and Imaging markers

Planning

Study Execution & Interim Readout

- Cross-Sectional
- Longitudinal, interventional trial

Analysis & Reporting

Project Milestones
Conflict of Interest Policy

- COI document has been previously circulated to all project team members and signed by members

- Levels of COI:
  - Academic investigators: low, intermediate and high levels of COI defined
  - Industry investigators: low and high levels
  - All key collaborators are considered to have a high level of COI
Engaging Patient Representatives and FDA

• NIMBLE has invited Global Liver Institute to participate in and provide feedback at a steering level

• Drs. Lara Dimick and Veronica Pei will serve as FDA representatives and provide guidance for regulatory submissions and study design
Contracting

Academic Centers

• VCU (Arun Sanyal)
• UCSD (Rohit Loomba & Claude Sirlin)
• MGH (Anthony Samir)
• Case Western (Nancy Obuchowski)

Contractors and CROs

• AG MedNet
• CRC Pharma (CRO)
• Celerion (CRO)
• Statistical CRO (SAP planning)
Imaging work stream update (Oct 2018-current)

- Imaging Protocol **draft** ✓
- Imaging service identified and contracting underway ✓
- Quality control documents developed ✓
- Chain of custody of data established ✓
- Statistical analysis subgroup established with inclusion of Dr. NANCY OBUCHOWSKI ✓
- Site selection RFP for stage 1.1 and 1.2 ✓
- Study design and sample size for stage 1.1 and 1.2 ✓

- Establishment of SAP and ICF
- Site finalization ✓
- Registration of study
Imaging Study Updates

Initial Proposal 1.1
- Test-retest repeatability (US and MRI)
- Temporal reproducibility (US and MRI)
- Scanner reproducibility (US)

Initial Proposal 1.2
- Scanner reproducibility (MRI)

Updated Proposal 1.1 – Ultrasound Only
- Test-retest repeatability (US)
- Temporal reproducibility (US)
- Scanner reproducibility (US)

Updated Proposal 1.2 – MRI Only
- Scanner reproducibility (MRI)
- Test-retest repeatability (MRI)
- Temporal reproducibility (MRI)

Proposed updates will simplify the study design and should have favorable impacts on subject recruitment, study timelines and cost.
Proposed Activities in the next 6 Months

- Imaging Biomarkers:
  - a. Finalization of protocol with SAP (underway)
  - b. Contract between participating sites and FNIH (underway)
  - c. ICF approval
  - d. Patient recruitment
Circulating Markers
Work Stream Update

Dr. Arun Sanyal, MD
Dr. Sudha Shankar, MD
Dr. Roberto Calle, MD
Dr. Rohit Loomba, MD
Circulating Biomarkers Work Stream Update (Oct 2018-current)

- Circulating biomarkers (applications received after project plan approval) flagged for review and inclusion based on thorough literature review ✓
- Protocol Drafted ✓
- Statistical CROs finalized ✓
- Biomarker vendors identified, under contracting ✓
- Operations CROs identified (pending contracts) ✓
- Quality control documents under development ✓
- Chain of custody of data under developments ✓
- Identification of cohorts with “intended use” populations in different clinical settings and establishing collaborative contracts – near finalization ✓
- Submission of draft LOI to FDA ✓

Next Steps (Q3-4 2019)

- Biosample repositories ideal for protocol: discussions ongoing between academic PI and cohort leads
- Protocol finalization WITH SAP
- Contracting with sample cohorts
- Contracting with Key Collaborators
Critical Steps in Qualification of Circulating Biomarkers-II

Methodological issues (being standardized and aligned by working group):

- Sample collection
- Storage and transport
- Analysis
- Quantification and internal/external controls
- Data reporting

Study Design (retrospective data will inform prospective study):

- Populations to be interrogated
- Standardization of collection of meta-data
- Analytic issues:
  - determination of disease activity
  - separation from F0 or F1 vs higher stages
  - separation of F4 from lower stages
Identification of NASH with NAS ≥ 4 and Fibrosis stage 2-3, Cirrhosis due to NASH

Criteria used to pick which sample sets will be interrogated for circulating biomarkers:

- time from sample collection to liver biopsy
- amount of meta-data collected
- data on storage conditions available
- cross-sectional vs longitudinal data available with accompanying biopsy
- availability of biopsy for scan and re-read
FDA LOI Update

- NIMBLE Letter of Intent (LOI) -
  - Submitted: 02-26-2019
  - Confirmation of Receipt: 02-26-2019
  - Initial Feedback: April 2019
  - Revision of LOI ongoing – due to be submitted this week
- LOI markers -
  - NIS4
  - Nordic Panel: Pro-C3-C6
  - OWL Liver Test
  - ELF
Proposed Activities in the next 3 Months

- Circulating Biomarkers:
  - a. Finalization of protocol with initial SAP
  - b. Establish contract between biosample cohorts and VCU
  - d. Finalizing contract between vendors and FNIH
### STRENGTHS
- Many tools available
- Disease biology increasingly well understood
- Large clinical cohorts available
- Active drug development space
- Growing consensus on endpoints and case-definitions
- Integrated approaches to get read out for liver and other end organs

### WEAKNESSES
- Paucity of longitudinal data sets
- “Concrete” thinking with respect to fibrosis implications
- Suboptimal therapeutics
- Challenges in histological assessment
- Bidirectional natural course
- Primary care MDs overwhelmed with work
- Burden of diagnostics for patient

### OPPORTUNITIES

### THREATS
NIMBLE and LITMUS are Collaborative Activities that Build Synergy and are Working in Concert with Regulators to Accelerate Biomarker Development
NIMBLE: A True Public - Private Partnership

NIMBLE Co-chairs