Goals of the NASH CRN and Opportunities for Collaboration

Moving Forward: Research Priorities

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Chief, Pediatric GI and Hepatology
Columbia University

STOP NASH

Disclosures

None relevant to this presentation
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Science, July 3, 2013

THE LIVER’S WEIGHTY PROBLEM

As obesity rates soar, a sometimes fatal liver disease is becoming epidemic. In black and white.
Goals of the NIDDK NASH CRN

- Focuses on:
  - Natural history
  - Contributing factors
  - Etiopathogenesis
    - Genetics/epigenetics
    - Environmental contributors/toxins
  - Noninvasive imaging and biomarkers
  - Complications
  - Therapy

NASH CRN Centers

Steering Committee with Pediatric Members Shown

Steering Committee:
- Joel Lavine (co-chair), CU JoW@kumc.edu
- Anur Sanyal (co-chair), VCU lavine@vcu.edu
- Sarah Barlow, BCM sbarlow@bcm.edu
- Nigra Chahlani, IU nchahlani@iu.edu
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- Peter Whitington, NWH peter.whitington@wright.edu
- Stavrou Xanthakis, CINC stavroux@uthscsa.edu
**NASH CRN ORGANIZATION**

![Diagram of NASH CRN Organization]

**NASH CRN Subject Enrollment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients</th>
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<tr>
<td>NAFLD DB</td>
<td>1,503</td>
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<tr>
<td>PIVENS</td>
<td>247</td>
</tr>
<tr>
<td>TONIC</td>
<td>173</td>
</tr>
<tr>
<td>DB2-Adult</td>
<td>1,754</td>
</tr>
<tr>
<td>DB2-Pediatric</td>
<td>675</td>
</tr>
<tr>
<td>FLINT</td>
<td>283</td>
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<tr>
<td>CyNCh</td>
<td>169</td>
</tr>
<tr>
<td><strong>All Studies</strong></td>
<td><strong>4,804</strong></td>
</tr>
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</table>

As of 03Oct15

**Ancillary Studies: Summary**

- Years of studies: 2004 to present and ongoing
- 106 Ancillary Studies:
  - 46 Active
  - 31 Completed
  - 19 Inactive or withdrawn
  - 10 Disapproved
- 12 Pilot and Feasibility Studies:
  - 8 Completed
  - 1 Resubmitted as Ancillary Study
  - 3 Inactive or withdrawn
- 38 Presentations and 35 Publications from Ancillaries
- 19,740 Biosamples and DNA on 1,474 patients analyzed (2013)
Publications (67) and Presentations (91)

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Publications</th>
<th>Presentations</th>
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<tbody>
<tr>
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<td>9</td>
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<td>2008</td>
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<tr>
<td>2009</td>
<td>30</td>
<td>31</td>
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<tr>
<td>2010</td>
<td>28</td>
<td>25</td>
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<td>2011</td>
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<td>17</td>
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<tr>
<td>2012</td>
<td>10</td>
<td>9</td>
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Submitting a Proposal to the Network

- [https://jhuccs1.us/nash/](https://jhuccs1.us/nash/)
- Discuss proposal with liason
- Obtain AS form from liason
- Submit to liason for submission to AS Committee
- Await comments or approval
- Receive data/samples

Ancillary Study Ground Rules

- Involves new data collection
- Funding comes from outside CRN
- Does not use central resources
- Requires Steering Committee liaison
- Ancillary and Steering Committees assess scientific/resource merit
- Publications/presentations from AS needs to be approved prior to submission
Publication Category

<table>
<thead>
<tr>
<th>Type</th>
<th>No. Publications</th>
<th>Average Impact Factor</th>
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<tbody>
<tr>
<td>Clinical Trials</td>
<td>4</td>
<td>21.7</td>
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<tr>
<td>Epidemiologic</td>
<td>21</td>
<td>9.1</td>
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<tr>
<td>Genetics</td>
<td>4</td>
<td>13.2</td>
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<tr>
<td>Histology</td>
<td>7</td>
<td>11.9</td>
</tr>
<tr>
<td>Noninvasive Markers</td>
<td>10</td>
<td>6.5</td>
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<tr>
<td>Translational</td>
<td>7</td>
<td>10.6</td>
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<tr>
<td>Total</td>
<td>53</td>
<td>9.3</td>
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</table>

STAGES OF TRANSLATIONAL SCIENCE

<table>
<thead>
<tr>
<th>STAGES OF TRANSLATIONAL SCIENCE</th>
<th>ACHIEVED and PROPOSED ACTIVITIES</th>
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</thead>
<tbody>
<tr>
<td>T1: BASIC SCIENCE</td>
<td>Genetics and Systems biology: genetics, microbiome, lipidome, transcriptome, proteome Biomarker discovery: integration of “omics” approaches, Identification of targets: for diagnostics and therapeutics</td>
</tr>
<tr>
<td>T2: EARLY TRANSLATION</td>
<td>Partnership with industry: Pharmavite, Intercept, Raptor, Takeda, Echosens, GE, Somalogic Partnerships with other NIH consortia: NURSA, LIPIDMAPS CHILDREN, TEENLABS Validation of diagnostic targets: Fibroscan, MRI, biosamples Phase 2 A trials: ASBT inhibitor, NHR agonists/antagonists</td>
</tr>
<tr>
<td>T3: LATE TRANSLATION</td>
<td>Phase 2b trials: pentoxifylline, vitamin E, obeticholic acid</td>
</tr>
<tr>
<td>T4: DISSEMINATION</td>
<td>Inform practice guidelines and remove barriers to drug development by improved diagnostics</td>
</tr>
<tr>
<td>T5: ADOPTION</td>
<td>Outcomes and validation of quality of care in NAFLD- standard of care development</td>
</tr>
</tbody>
</table>

Sample of Pediatric Ancillary Studies (in progress)

- Hepatic nuclear hormone receptor expression related to NAFLD severity
- The microbiome in development and progression of NAFLD
- Sleep apnea relation to NAFLD histology
- Altered drug metabolism in pediatric NAFLD
- Proteomic biomarkers for NAFLD discrimination
- Hormonal influences on histology
Ancillary Study Ideas for Consideration

- Environmental endocrine disruptors
- Genetic variants explaining ethnic predisposition
- Maternal factors predisposing to NAFLD
- Epigenetic modifications affecting NAFLD
- Novel safe phase I therapeutics
- Sleep apnea interventions on NAFLD
- Lifestyle intervention effects on NAFLD

The NASH CRN is uniquely suited to perform such studies

- Diverse expertise in NASH
- Expertise in metabolism, development
- Pathology consensus and expertise
- Pioneers in liver imaging
- Expertise in gut endocrine function
- Subjects of varying ethnicity/races/geography/ages
- Strong record of collaborative research
- Superb biostatistical support via DCC

Severity of NAFLD in Biopsied Children in Comparison to Adult Enrollees

<table>
<thead>
<tr>
<th>NAS</th>
<th>Adult (n=3,885)</th>
<th>Pediatric (n=1,236)</th>
<th>Total (n=5,111)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>0</td>
<td>25 (1)</td>
<td>11 (7)</td>
<td>36 (1)</td>
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<tr>
<td>1</td>
<td>134 (4)</td>
<td>64 (8)</td>
<td>198 (5)</td>
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<tr>
<td>2</td>
<td>444 (15)</td>
<td>157 (14)</td>
<td>601 (15)</td>
</tr>
<tr>
<td>3</td>
<td>471 (16)</td>
<td>213 (19)</td>
<td>684 (17)</td>
</tr>
<tr>
<td>4</td>
<td>448 (22)</td>
<td>214 (22)</td>
<td>662 (22)</td>
</tr>
<tr>
<td>5</td>
<td>542 (18)</td>
<td>236 (20)</td>
<td>778 (19)</td>
</tr>
<tr>
<td>6</td>
<td>419 (14)</td>
<td>135 (12)</td>
<td>554 (17)</td>
</tr>
<tr>
<td>7</td>
<td>351 (9)</td>
<td>76 (6)</td>
<td>427 (7)</td>
</tr>
<tr>
<td>8</td>
<td>44 (2)</td>
<td>19 (2)</td>
<td>63 (2)</td>
</tr>
</tbody>
</table>
Pediatric NASH CRN Investigators

The NASH CRN is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Clinical Centers:

Principal Investigators:
- BCM: Sarah Barlow
- Cincinnati: Stavra Xanthakos
- CU/UCSD: Joel Lavine/Jeff Schwimmer
- EU: Saul Karpen
- IU: Jean Molleston
- JHU: Ann Scheimann
- NWU: Peter Whitington
- SLU: Ajay Jain
- UCSF: Philip Rosenthal
- UW: Karen Murray

Clinical Coordinators:
- BCM: Leanel Fairly
- CWRU: Judy Whitwell
- IU: Ann Klipsch
- JHU: Kimberly Pfeifer
- SLU: Joan Siegner
- CU/UCSD: Elena Reynoso/Janis Durelle
- UCSF: Danuta Filipowski
- UW: Melissa Young
- VCU: Sherry Boyett

Pathologists:
- Elizabeth Brunt (WU)
- David Kleiner (NCI)
- Cynthia Behling (CU/UCSD)
- Melissa Contos (VCU)
- Oscar Cummings (IU)
- Linda Ferrell (UCSF)
- Cynthia Guy (DUKE)
- Matthew Yeh (UW)

Data Coordinating Center (JHU):
- Patricia Belt
- Jeanne Clark
- Milana Isaacson
- James Tonascia
- Mark Van Natta
- Laura Wilson
- Katherine Yates

This man is overworked

YES YOU CAN