Quantitative Imaging Goals for NIDDK

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Monitor progression and response to therapy of disease in
- liver
- kidney and urological organs
- bone marrow
- bowel
- exocrine pancreas

Measure pancreatic islet beta cell mass and inflammation to monitor diabetes progression and response to therapy

Monitor mass and activity of human brown and beige fat

Enable brain research in metabolic diseases
- Regulation of energy balance and metabolism
- Alterations caused by disease state
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Goal: replace diagnostic biopsy with independent measures of the common events in disease progression
- **fat deposition**
- **inflammation**
- **fibrosis**
- changes in architecture
- dysfunction
- dysregulated proliferation (cancer)

NIDDK Activities focused on tissue fibrosis

<table>
<thead>
<tr>
<th>Nonalcoholic Steatohepatitis Clinical Research Network</th>
<th><a href="https://jhuccs1.us/nash">https://jhuccs1.us/nash</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials in adults and children</td>
<td>Elucidate disease pathogenesis</td>
</tr>
<tr>
<td></td>
<td>Improve diagnosis, treatment and clinical management</td>
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</tbody>
</table>

ChiLDReN: Childhood Liver Disease Network
- Biliary Atresia Research Consortium (BARC)
- Cholestatic Liver Disease Consortium (CLiC)
- Cystic Fibrosis Liver Disease (CFLD)

Hepatitis B Clinical Research Network
[http://www.hepbnet.org](http://www.hepbnet.org)

Drug-induced Liver Injury Network (DILIN)
[https://dilin.dcri.duke.edu/](https://dilin.dcri.duke.edu/)

NIDDK Fibrosis Biomarker Consortium
- biomarkers of fibrosis in kidney, urological and bone marrow disease (4 sites)

RFA-DK-13-026

Upcoming NIDDK Workshop:
Advances in Biomedical Imaging, Bioengineering and Related Technologies for the Development of Biomarkers of Pancreatic Disease
- July 22, 2013
- University of Pittsburgh
Nonalcoholic Fatty Liver Disease
(~80M in US)        Alcohol & other diseases
Nonalcoholic Steatohepatitis
(10-15M in US)

Liver Injury

Hepatitis B Virus
~300M worldwide
Hepatitis C Virus
~300M worldwide

Hepatic stellate cells (HSCs): activation in response to liver injury
inactivation with therapy

Can we image disease progression and regression?
Many mechanisms for fibrosis regression have been identified

**Major studies with liver fibrosis as primary or co-primary endpoint**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/primary endpoint</th>
<th>Hepatitis</th>
<th>Year of publication</th>
<th>No. of patients</th>
<th>NCT no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngmin A Lee et al. Gut 2015;64:830-841</td>
<td>Naive patients</td>
<td></td>
<td></td>
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</tbody>
</table>
Urgent need for a toolkit of validated biomarkers of liver fibrosis

US shear-wave elastography

MR Molecular Imaging of mouse liver collagen (fibrosis)

MR elastography

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**PET/SPECT Tracers Show Promise for Endogenous Human β-Cell Mass**

- **18F-FP-(+)-DTBZ**
- **111In-labelled Exendin**
- **[11C]5-HTP**

**Barriers to validation: Beta cell mass is non-zero in T1D**

- Many (54/74) T1D patients secrete c-peptide
- β cell mass (insulin stain) in long duration (1-35 yrs) T1D
- Many pancreata from T1D have islets with β cells.

Therefore, data in T1D are insufficient for validation of β cell mass biomarkers.
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**Human brown fat can be detected using FDG-PET**

NIDDK Workshop, Bethesda, MD, November 4, 2014:
Consensus Recommendations for Standardized FDG-PET of Human Brown Fat
(manuscript in preparation)

Novel detection techniques for hBAT mass and/or activity

NET ligand $^{11}$C-MRB detects inactive hBAT

Hwang JJ et al, Metabolism. 2015 Jun;64(6):747-55. Imaging human brown adipose tissue under room temperature conditions with $^{11}$C-MRB, a selective norepinephrine transporter PET ligand.

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**Brain research in metabolic disease**

**Key challenges:**
- Adequate temporal/spatial resolution for structure, biochemistry, function
- Standardized protocols to relate metabolism, cognition and quantitative neuroimaging
- Diabetes is associated with impaired cognition, but does diabetic microvascular dysfunction interfere with functional imaging outcomes?

 DMN resting state functional connectivity reduced in T2DM despite unimpaired cognition

Reduced working memory BOLD activation in MetS, despite unimpaired cognition


Gail Musen et al. Diabetes 2012;61:2375-2379
MR Imaging Shows Promise for Measures of Pancreatic Inflammation

Visualizing Pancreatic Inflammation

Recent onset T1D    Healthy

High               Low

MRI Inflammation Signal

T1D    Control

Groups

P = 0.0007
ROC AUC = 0.91