Genomic Approaches to Cancer Cachexia: Validating Models

Summer Research Program in Genomics 2011

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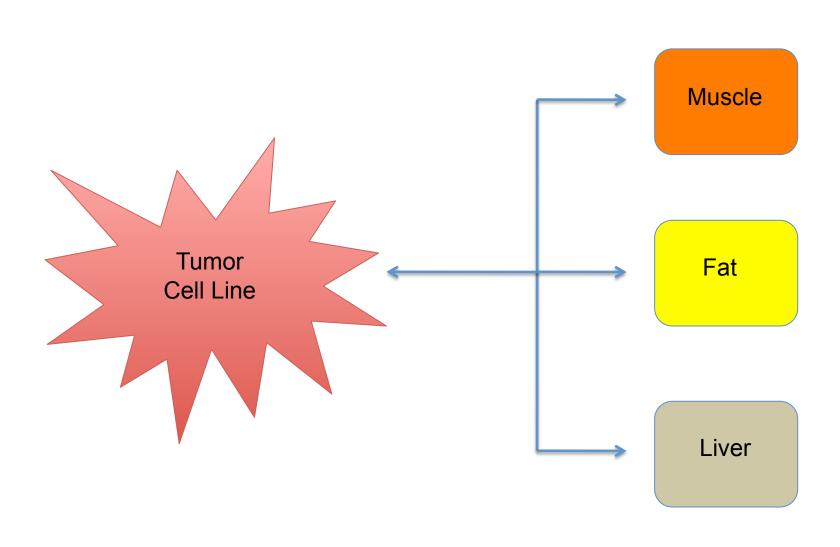David K. Thomas, M.D.

Todd R. Golub, M.D.

Background

Clinical description:
Syndrome of progressive muscle and fat wasting,
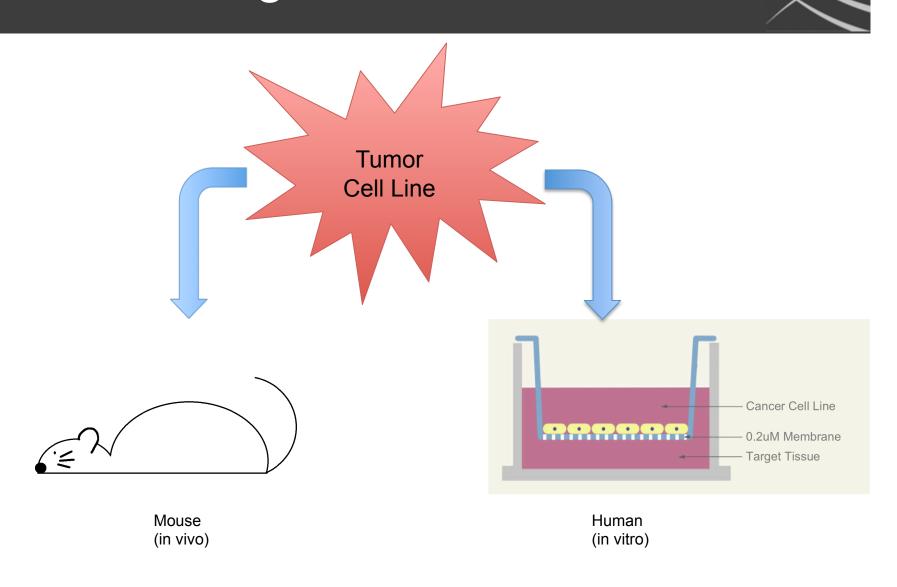with gross weight loss of > 5%

Scope:
> 50% of all cancer patients will develop cachexia
   leading to fatigue, weakness, immobility, and psychosocial distress

> 25% of all cancer deaths are directly caused by cachexia
   via respiratory failure, cardiac failure, and metabolic derangement…
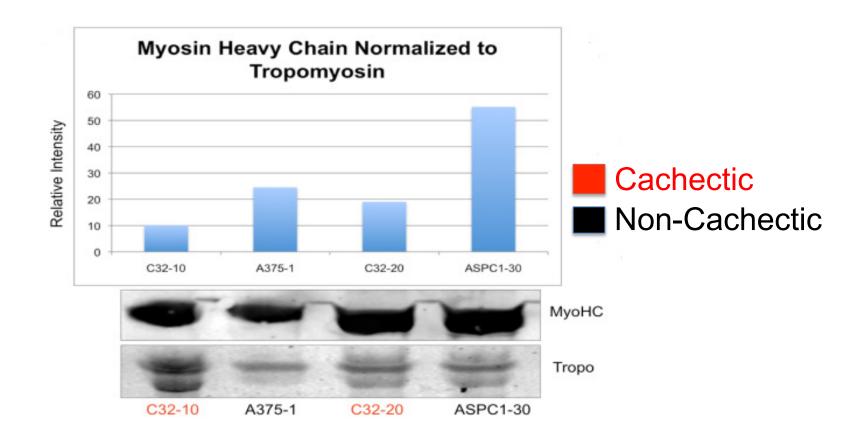
Building Relevant Models

Building Relevant Models

Tumor Cell Line

Mouse
(in vivo)

Human
(in vitro)

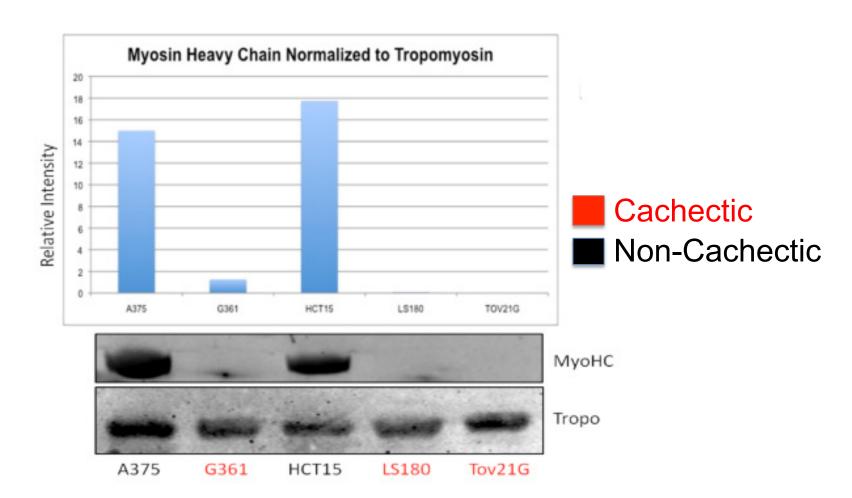Cancer Cell Line

0.2uM Membrane

Target Tissue

Specific Loss of Myosin Heavy Chain Occurs in In Vivo Models of Cachectic Muscle
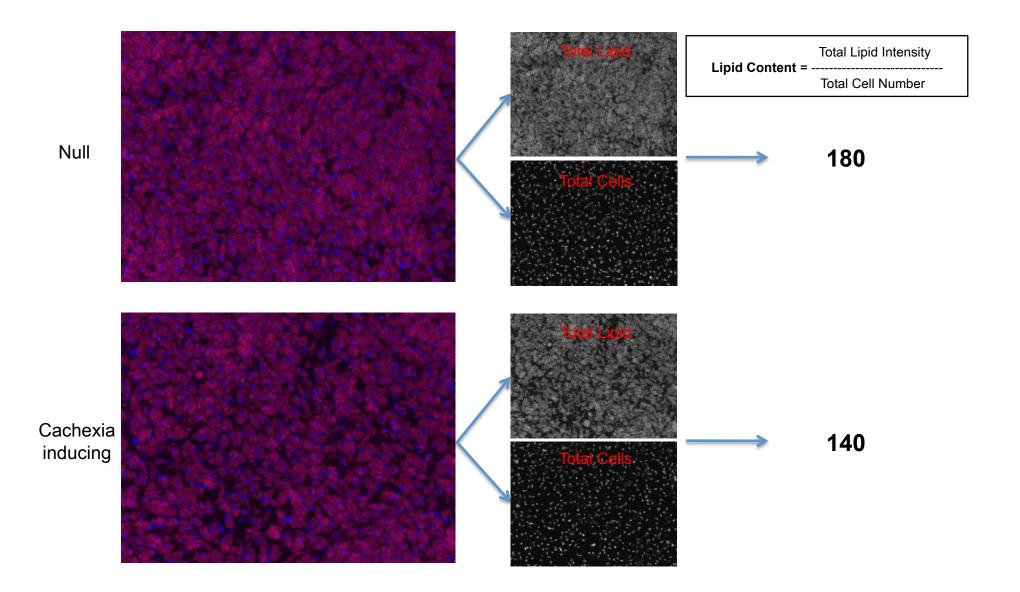
Specific Loss of Myosin Heavy Chain in In Vitro Samples Validates Model

Cachectic

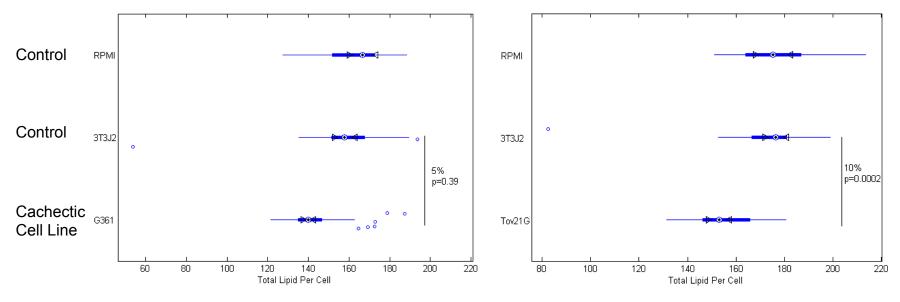Non-Cachectic

High-Content Imaging of In Vitro Adipocyte Models

Null

Total Lipid

Total Cells

$$\text{Lipid Content} = \frac{\text{Total Lipid Intensity}}{\text{Total Cell Number}}$$

180

Cachexia inducing

Total Lipid

Total Cells

140

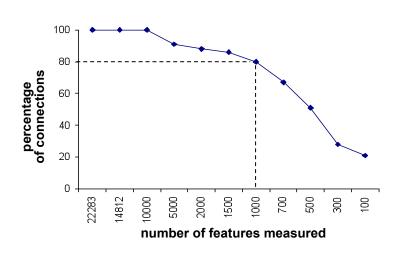# Total Lipid Loss in In Vitro Human Adipocytes is Quantifiable

5% Lipid Loss in Cachectic
Vs. Null Samples
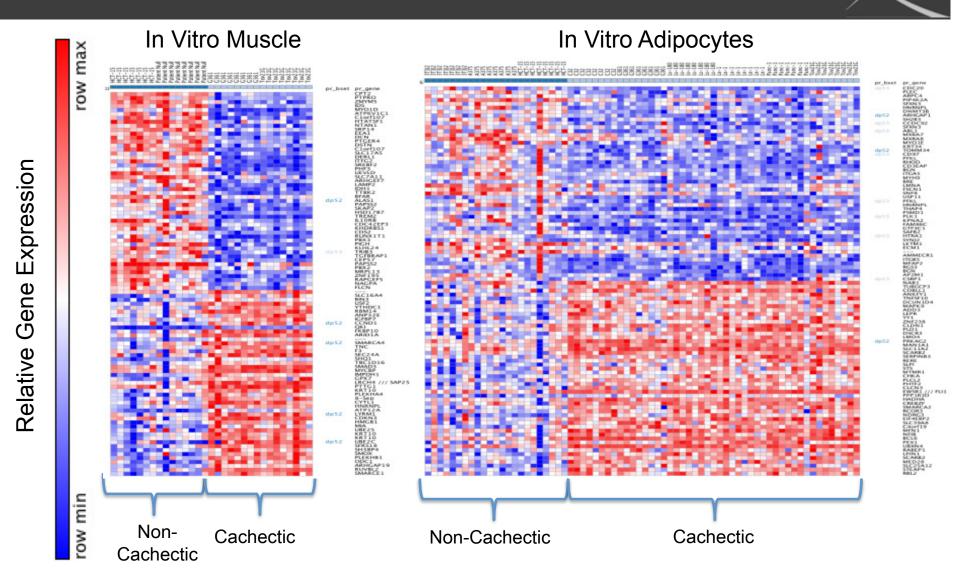
10% Lipid Loss in Cachectic
Vs. Null Samples

MATLAB ver. 7.12

Luminex 1000 Profiling Approach

- Gene expression is correlated

- Effective dimensionality of is < 21,000

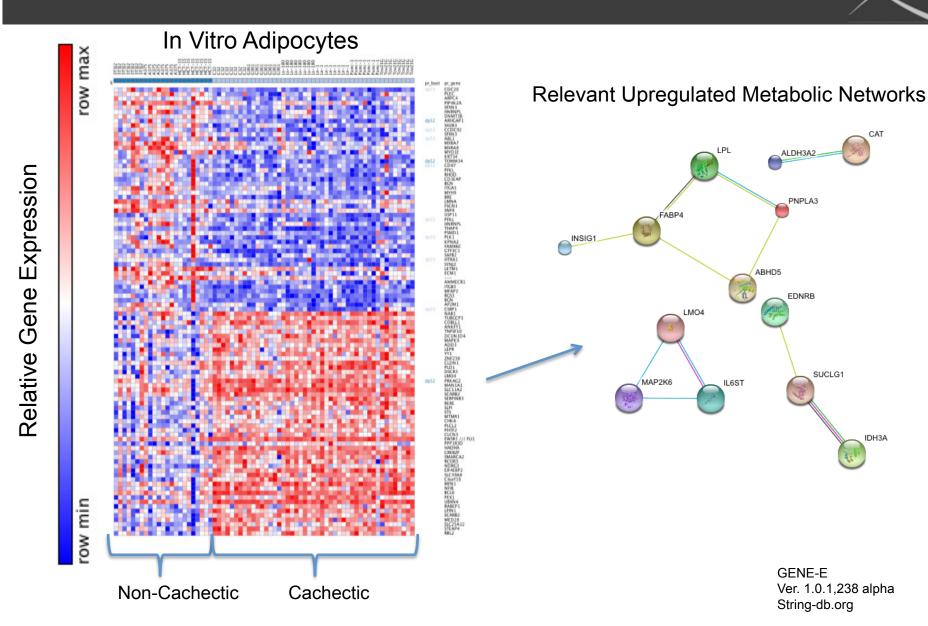- Sufficient to measure ~1000 *Landmark* genes

$$\left[\begin{array}{c} \textbf{1000 Landmark Genes} \end{array} \right] + \left[\begin{array}{c} \textbf{Inference model for genes not explicitly measured} \end{array} \right] = \textbf{Expression profile}$$

Gene Expression Signatures of Cachexia in In Vitro Muscle and Adipocyte Models

In Vitro Muscle

In Vitro Adipocytes

Relative Gene Expression

row max

row min

Non-Cachectic

Cachectic

Non-Cachectic

Cachectic

GENE-E
Ver. 1.0.1,238 alpha

Upregulated Genes in Cachectic Adipocytes Reveals Relevant Biology

In Vitro Adipocytes

Relative Gene Expression

row max

row min

Relevant Upregulated Metabolic Networks

Non-Cachectic   Cachectic

GENE-E
Ver. 1.0.1,238 alpha
String-db.org

Summary

- We have created both in vivo and in vitro models of cachexia

- We have shown that our models recapitulate relevant biology

- These models will enable us to generate a molecular definition of this disease

- These models and readouts will also enable us to use genomic approaches to analyze the secreted factors that drive this process and the genetic programs that initiate it

Acknowledgements
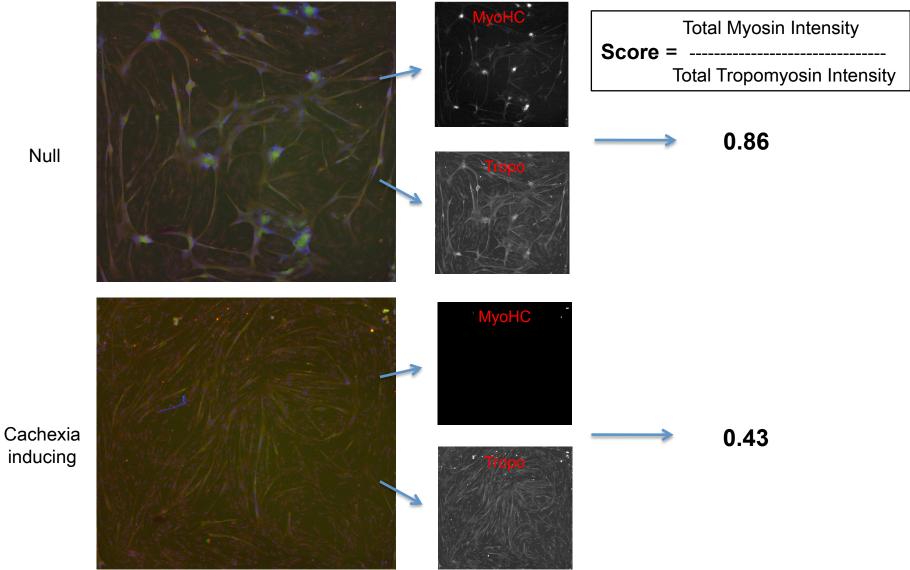
High-content screening of in vitro myotubes models

Null

MyoHC

Tropo

$$\text{Score} = \frac{\text{Total Myosin Intensity}}{\text{Total Tropomyosin Intensity}}$$

0.86

Cachexia inducing

MyoHC

Tropo

0.43

Ligation Mediated Amplification