Cardiac Endocrinology

Heart-derived hormones in physiology & disease

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Goal & Disclosure

- Basic scientific research helps understand pediatric heart biology and disease

- No other disclosures

Outline

Clinical phenomenon associated with CHD/pediatric heart disease

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A heart-derived hormone that regulates body growth

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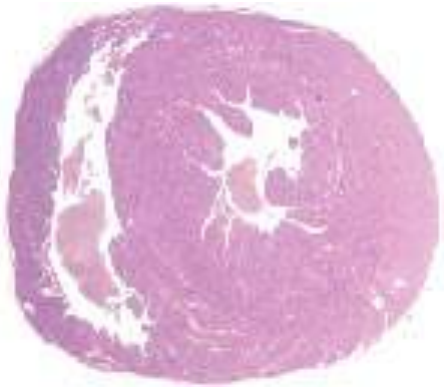
Cardiac Endocrinology

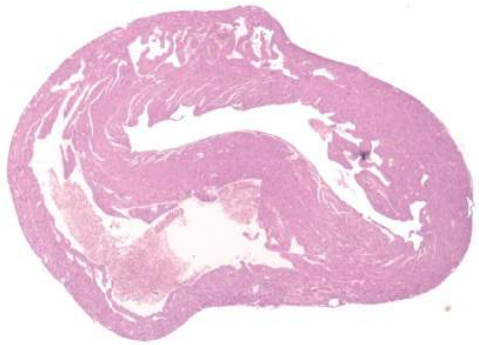
Failure to thrive (FTT) and CHD

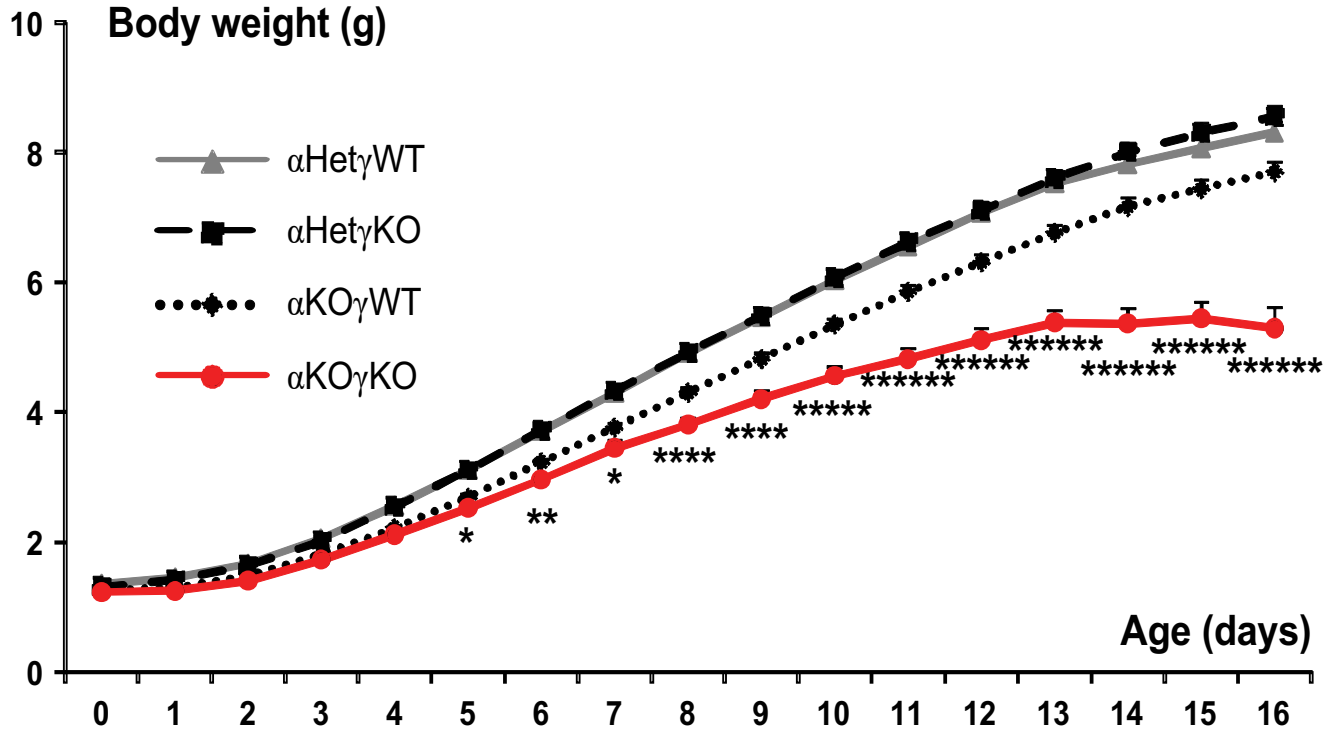
Children with CHD often develop FTT, but the mechanism is not clear.

Cardiac ERRαKOγKO mice: a model of primary cardiomyopathy/heart failure and secondary FTT

control **αKOγKO**

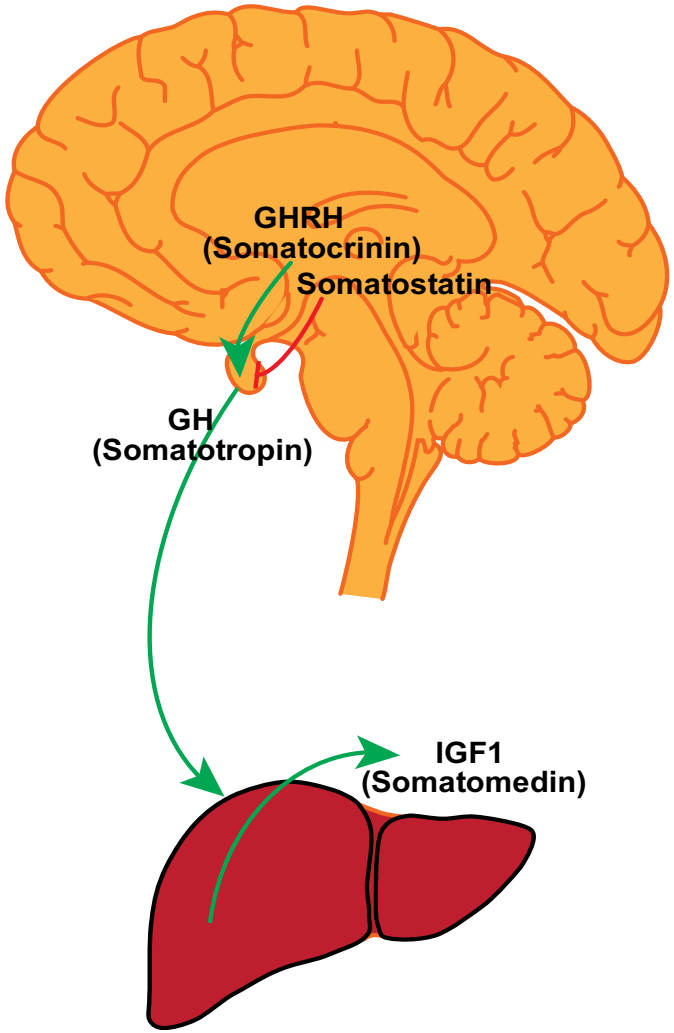


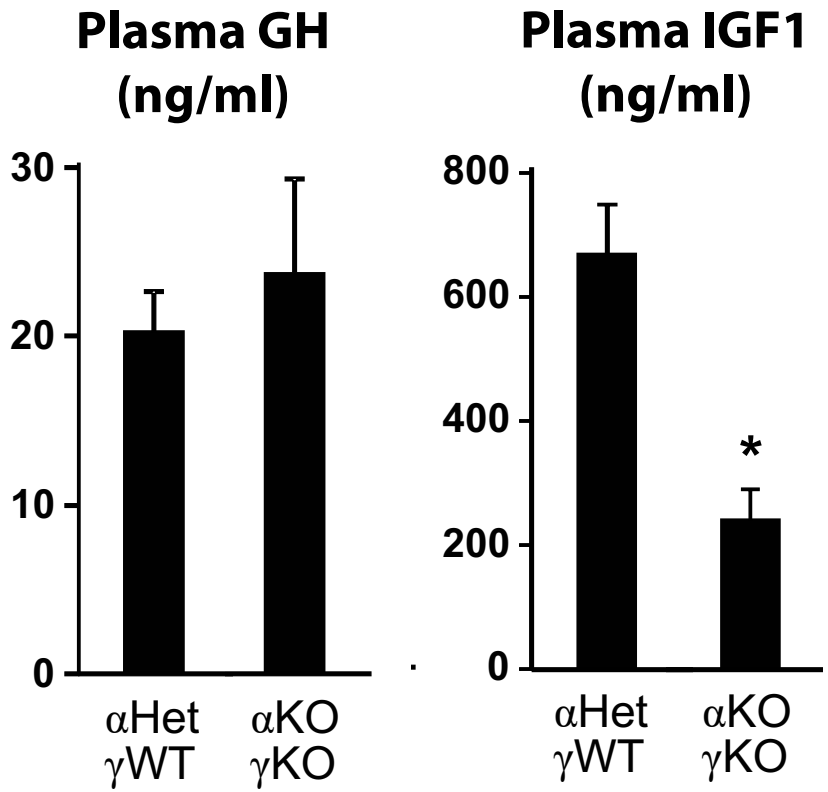




Mechanistic understanding of CHD-associated FTT

1. Why do αKOγKO mice develop FTT?





Liver GH signaling is impaired in αKOγKO mice

Mechanistic understanding of CHD-associated FTT

1. Why are αKOγKO mice develop FTT?

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2. Why do αKOγKO mice have impaired liver GH signaling?

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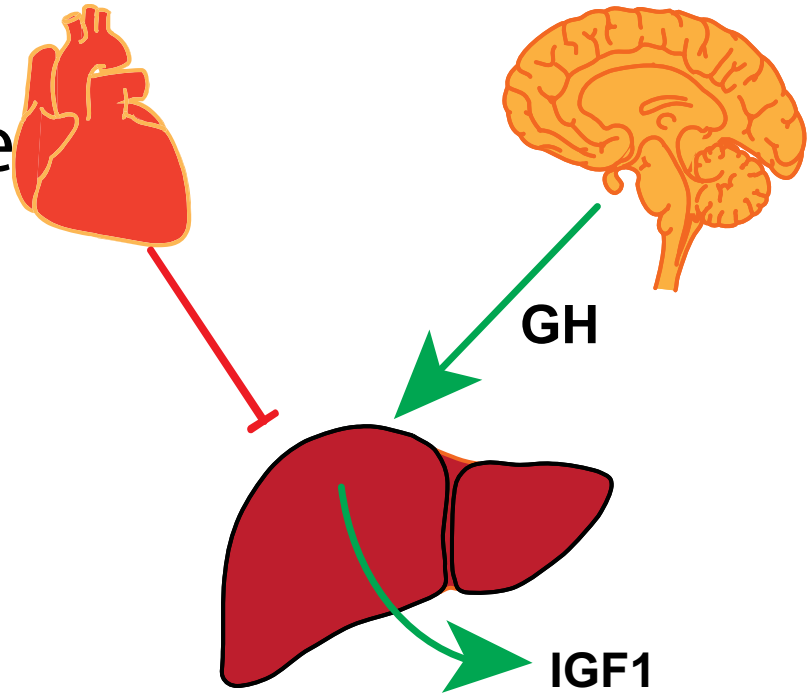
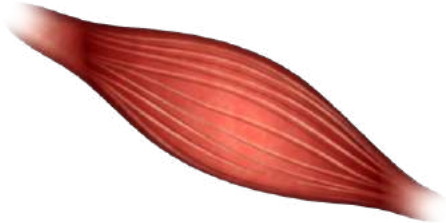
3. αKOγKO mice plasma contains substance that inhibits liver GH signaling



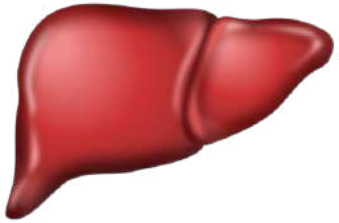
This substance has high molecular weight, mostly likely a protein

Endocrine function of the heart

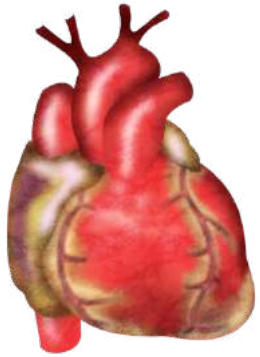
Leptin, TNFα, adiponectin, resistin, etc.



IL6, αKG, Metrnl, etc.



IGF1, FGF21, IGFBP1, etc.



ANP and BNP discovered over 40 years ago: vasodilators

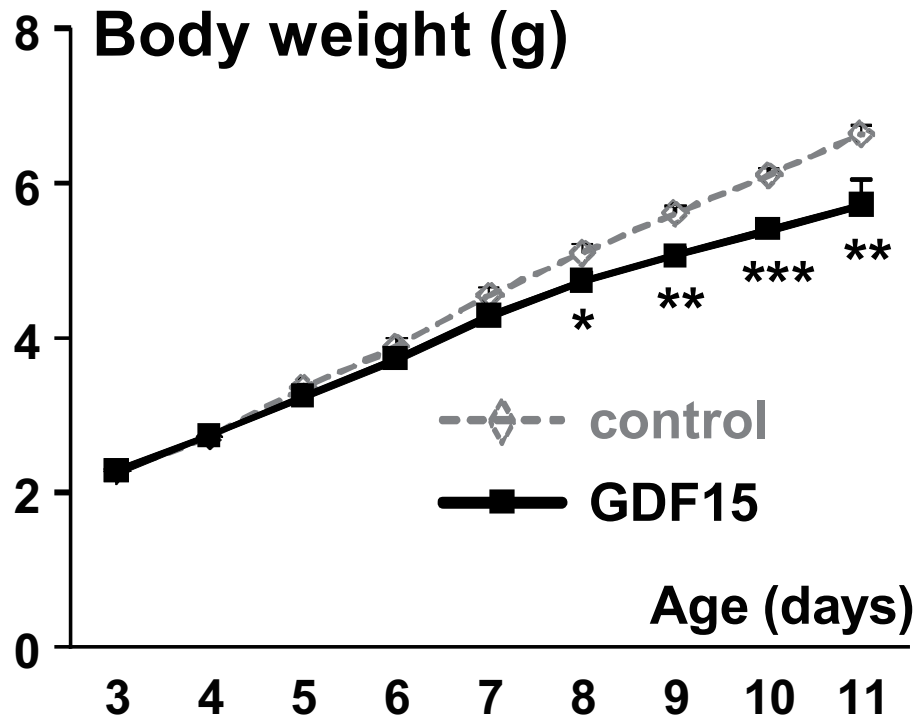
Identifying heart-derived hormone that inhibits liver GH signaling

Heart RNA-seq

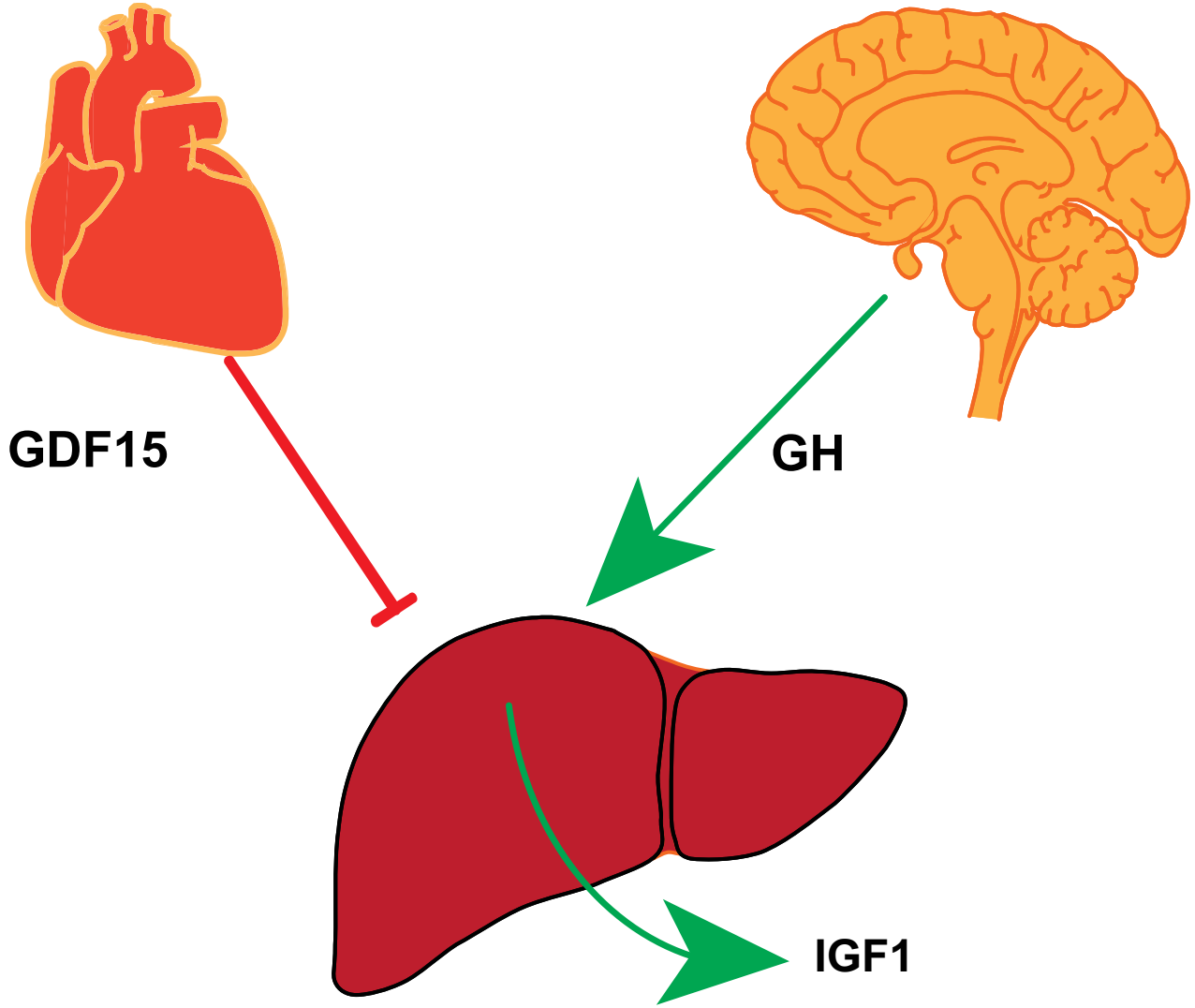
Plasma proteomics

Test whether candidate inhibits liver GH signaling and body growth in mice

GDF15: circulating GDF15 is highly elevated in heart failure patients

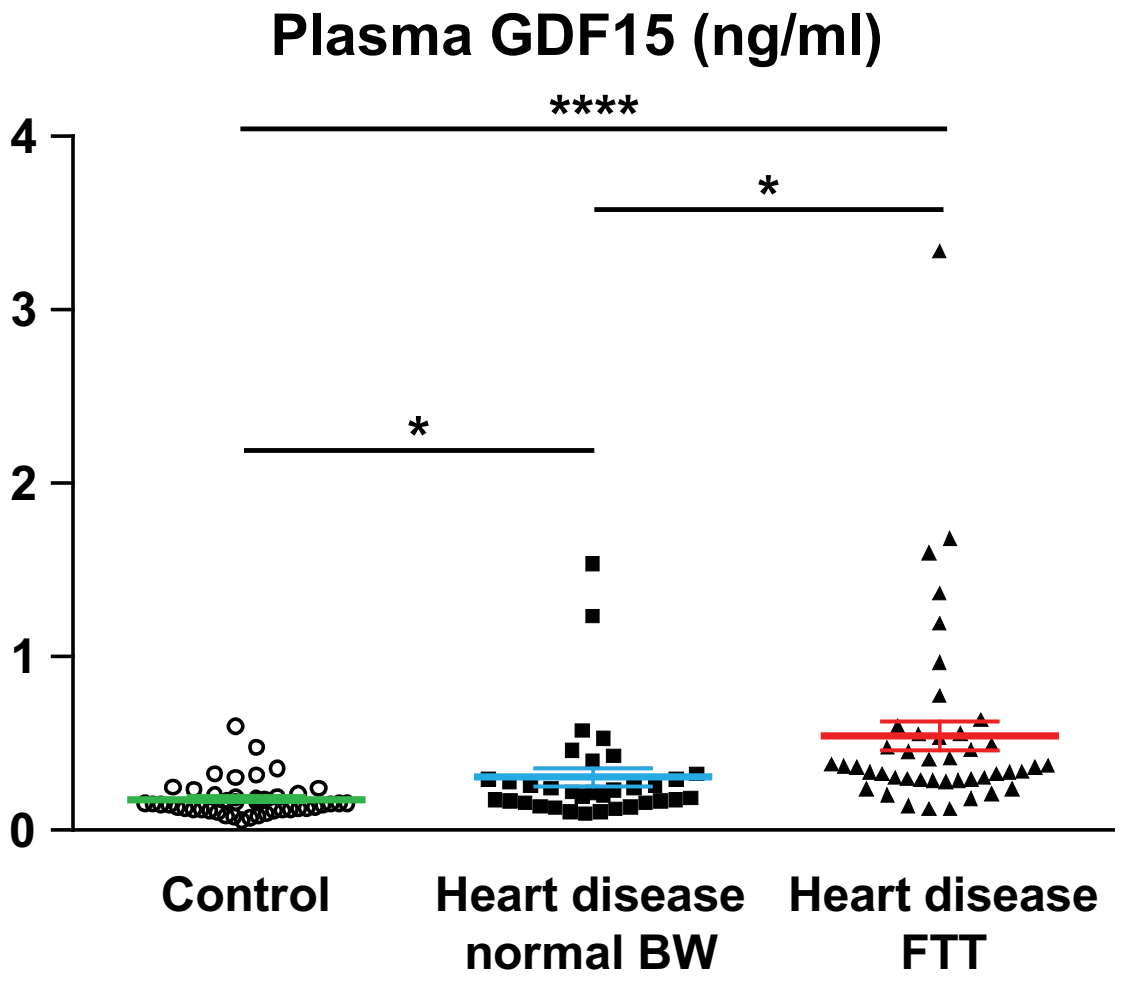


Mechanistic understanding of CHD-associated FTT

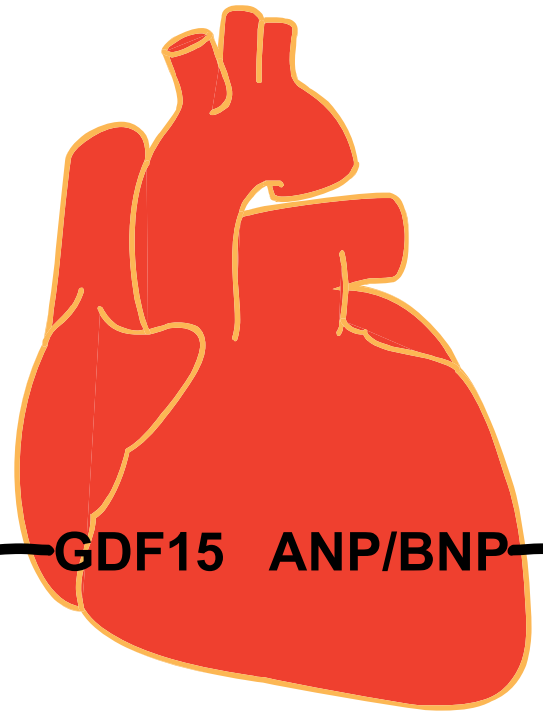


Blocking heart synthesized GDF15 normalizes liver GH signaling and body growth

Plasma GDF15 is elevated in children with CHD and FTT



Cardiac Endocrinology: a unified mechanism



Coordinate cardiac function and body growth; Relieve cardiac burden (inhibit body growth)

Coordinate cardiac function and hemodynamics; Relieve cardiac burden (decrease blood pressure)

GDF15 is clinically important:

1. Many clinical trials ongoing (up to Phase 2): obesity/diabetes/fatty liver; cancer/heart failure cachexia.

2. Develop GDF15 diagnostic method at CHOP

Wang et al, EmboMolMed 2017; Hu et al G&D 2018; Li et al MCB 2018; Zhao et al, JACC BTS 2020

Cardiac Endocrinology: the next

We are currently using advanced chemical biology method to unbiasedly label all heart-secreted proteins in mice

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Plasma mass spectrometry to identify new heart-secreted proteins

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Understand their biology, mechanism, importance in disease (CHD)

Summary

CHD and FTT

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GDF15 is a heart-derived hormone that regulates body growth

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Cardiac Endocrinology

Acknowledgement

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Ben Wilkins

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Matt Weitzman

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Mitch Lazar

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