DISCLOSURES

The commercial entities with which I/we have relationships do not produce health-care related products or services relevant to the content I am presenting.
Methodology

1. Review of Pub Med/Literature

2. Opinions of investigators in the field

3. Focus on discovery in thyroid hormone action and metabolism

4. Many other significant advances that could not be included.
Thyroid Hormone Action

Thyrotropin releasing hormone (TRH) → Pituitary → Thyrotropin (TSH) → Thyroid → T4/T3

Iodine

T3 → D2 → T3 → D3 → T4 → D3 → rT3 → T2

CoR → PXR → RXR

Bone
Thyroid Development

1/3000 congenital hypothyroidism

* De Felice and Di Lauro, Endocrinology, 2011

Murine ESCs


PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Anthony Hollenberg)
Index family w/congenital hypothyroidism, growth delay and testicular enlargement.

Mutation in IGSF-1 (immunoglobulin Superfamily -1)
Thyroid Axis
Sun et al, Nature Genetics 2012

- Low TH levels and normal TSH
- Defective response to TRH
Type 2 deiodinase plays a critical role in central feedback but where?
Reduction in TSH bioactivity preserves T3 levels

1. Astrocyte KO – normal TFTs.
2. ? Phenotype of tanycyte KO.
Defects in the MCT8 lead to AHD Syndrome. The tissue-specific effects of MCT8 lead to the TH abnormalities and the neurologic effects are likely mediated by the lack of MCT8 centrally.

How does the MCT8 recognize TH? Can we bypass the MCT8?
Cellular Actions of Thyroid Hormone

Groeneweg et al, Endocrinology 2013
Braun et al, Endocrinology 2013

1. His 192 identified by chemical inactivation.
2. Could it occlude the Channel?
3. Could it also effect a clamp?

Martagon et al, Endocrinology, 2013
Cellular Actions of Thyroid Hormone

Verge et al, JCEM 2012
Horn et al, Endocrinology 2013

Can alternative ligands prevent AHDS??

WT  Pax8  MCT8 DKO

Fall in T3 allowed for weight gain; ?long-term safety
Cellular Actions of Thyroid Hormone

$T_3$

HDAC3

CoR

RXR/TR TR

Transcriptional activity

TH-deprived EU TH excess

CoR CoA

spot14 dio1 mod1

TRβ1 TRβ2 TRα1

HAT/MT

CoA

RXR/TR TR

Transcriptional activity

TH-deprived EU TH excess

CoR

trh tshα tshβ

DR+4, PAL, Lys
Cellular Actions of Thyroid Hormone
Chatonnet et al, Proc Natl Acad Sci 2013

Murine cerebellar neurons

ChAP-Seq
1. Positively regulated
2. Isotype-specific binding does not predict response
Resistance to Thyroid Hormone

- Mutations found in the TR\(\beta\) and TR\(\alpha\) ligand-binding domain.

ClinicalPresentation-TR\(\alpha\) resistance
1. normal TSH
2. low T4 and nl to high T3
3. growth delay
4. bradycardia

Mutations impair ligand-binding, and prevent:

2. CoActivator recruitment
Cellular Actions of Thyroid Hormone

Fozzatti et al, Proc Natl Acad Sci 2013

Mouse Models Recapitulate the Human Disease

1. No effect HPT axis
2. Improved growth (bone and weight)

1. Role of SMRT?
2. Role of HDAC3?
Peripheral Actions of Thyroid Hormone
Mittag et al, J Clin Invest 2013

$T_3 \rightarrow \text{Heart rate, blood pressure}$

$TR\alpha^{R384C}$

$T_3 \rightarrow \text{Brain} \rightarrow \text{Heart rate, blood pressure}$
Peripheral Actions of Thyroid Hormone
Mittag et al, J Clin Invest 2013

AHA Parvalbumin

[Images and diagrams related to thyroid hormone actions and parvalbumin expression in the brain are shown.]
Peripheral Actions of Thyroid Hormone
Lin et al, Endocrinology 2012

\[ \text{T}_3/\text{GC-1/KB2115} \]

Liver

Cholesterol
Cyp7A
Bile Acids

LDLR
SR-B1

GC-1/LDL-R -/-

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Peripheral Actions of Thyroid Hormone

Lin et al, Endocrinology 2012

Cyp 7a

Bile Acids

T3, GC-1 > Statin

Cholesterol

Cyp 7a

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Peripheral Actions of Thyroid Hormone

Baliram et al, J Clin Invest 2013
Sun et al, Proc Natl Acad Sci 2013

TSHr absence accelerates osteoporosis

\[ T_3 \]

TSH

TRα1

Bone

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Anthony Hollenberg)
SUPPLEMENTARY FIGURE 1

Quantitative PCR showing the expression of Tshβ in FACS-sorted CD11b+ and CD11b− cells isolated from bone marrow (A), as well as in whole bone marrow isolated from wild type mice on thyroid chow (TH-on), or off thyroid chow (TH-off) for 1 or 2 weeks. Tshβ expression is primarily restricted to the CD11b+ population, and is positively regulated by thyroid hormones, so that decreasing serum T4 levels in TH-off mice are associated with decreased Tshβ expression.

*p<0.05 with respect to CD11b− cells; **p<0.01 with respect to TH-on.
Graves’ Ophthalmopathy
Moshkelgosha et al, Endocrinology 2013

22 female mice immunized hTSHrA plasmid
Variable thyroid response but most hypothyroid

Mouse model of GO
Graves’ Ophthalmopathy
Turcu et al, J Clin Endo Metab 2013

TSHrA1

TSHrA1Blocks M22
Signal Transduction

TSHrA1Blocks M22
induced Hyaluronan

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Anthony Hollenberg)
Conclusions

American Thyroid Association Guide to Investigating Thyroid Hormone Economy and Action in Rodent and Cell Models

Report of the ATA Taskforce on Approaches and Strategies to Investigate Thyroid Hormone Economy and Action

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