

Thyroid hormone analogue (TRIAC) therapy for resistance to thyroid hormone in children:

proposal for an international multi-center clinical trial

ERICA Research Conference

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&

Endo-ERN THYROID chair

Erasmus MC
University Medical Center Rotterdam



Endo-ERN

Disclosure

Erasmus MC receives royalties from Egetis Therapeutics (no personal benefits)

Outline

Brief context of thyroid hormone signaling

Previous experience: TRIAC in MCT8 deficiency

Proposal for TRIAC in paediatric RTHb

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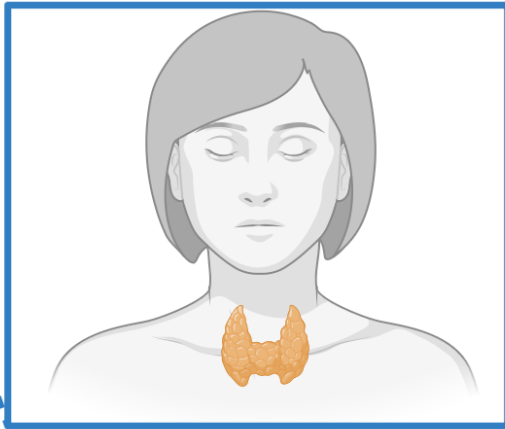
Proposal for TRIAC in paediatric RTHb

Thyroid gland produces thyroid hormones

Body

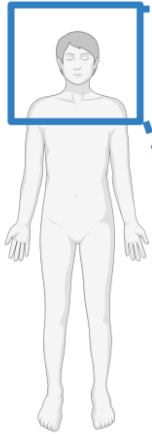


Neck

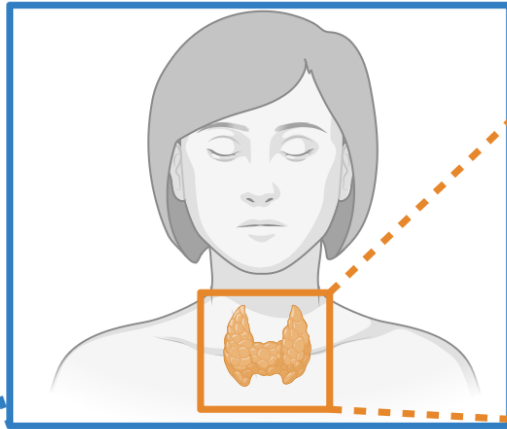


Thyroid gland produces thyroid hormones

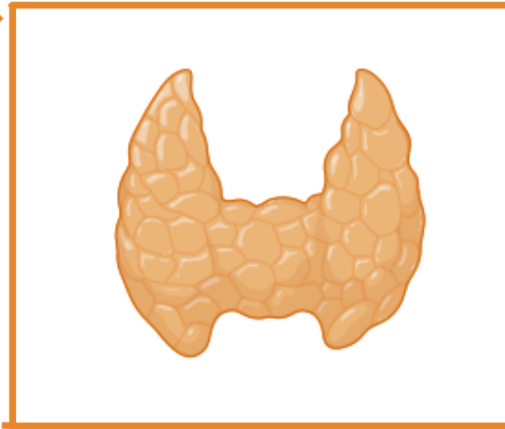
Body



Neck

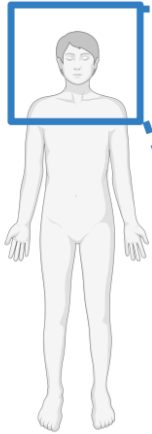


Thyroid

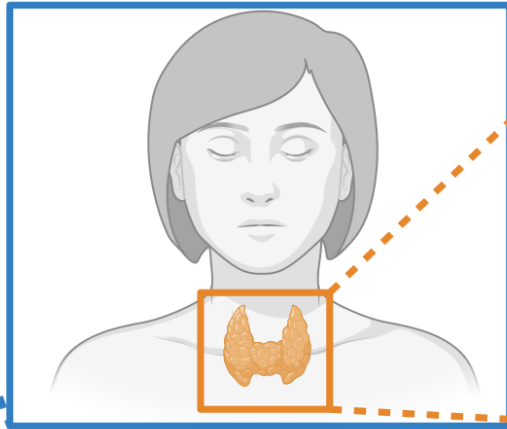


Thyroid gland produces thyroid hormones

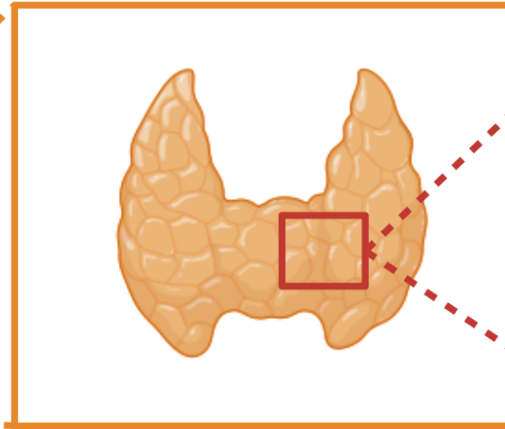
Body



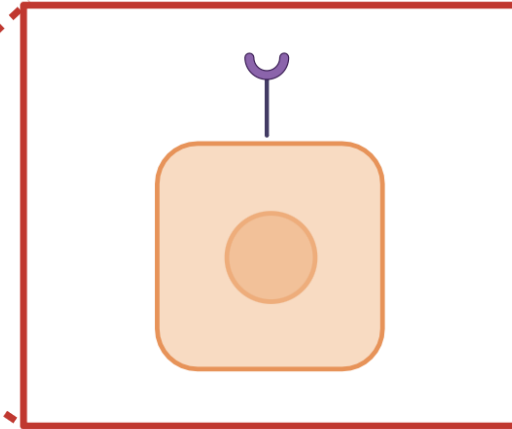
Neck



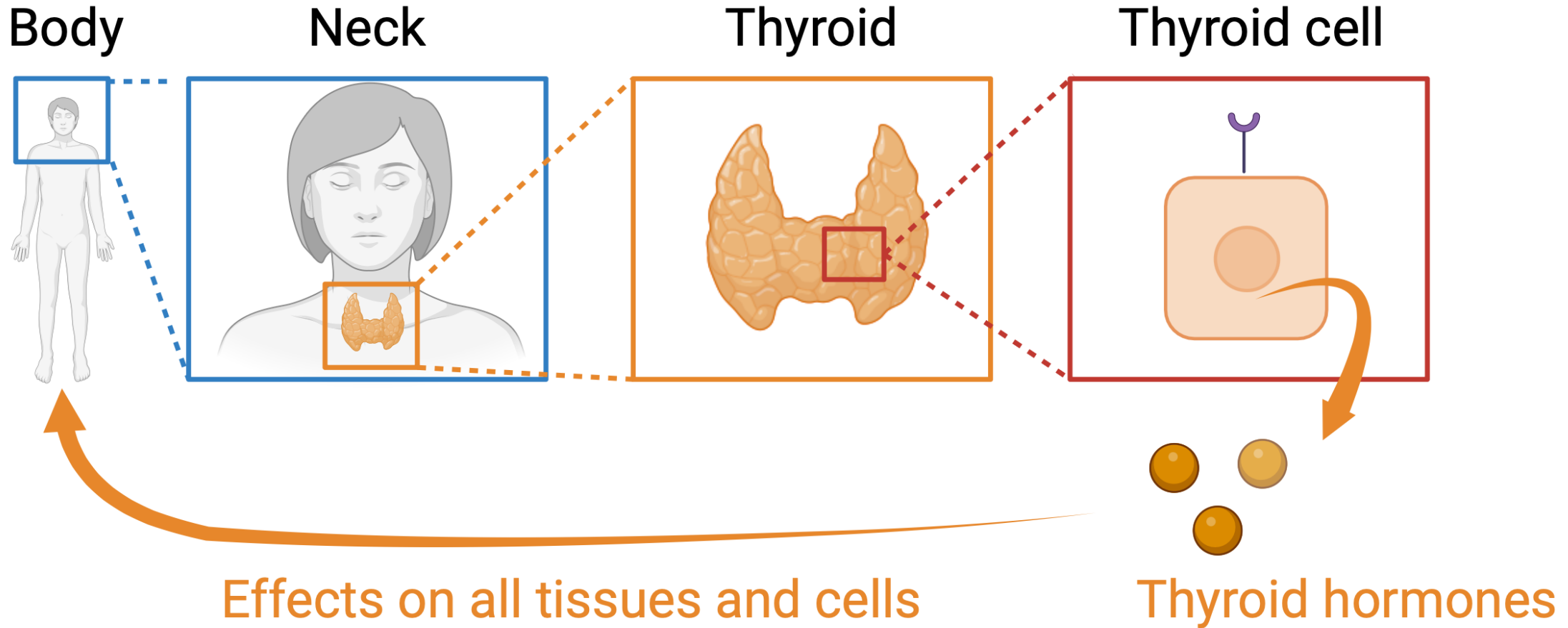
Thyroid



Thyroid cell



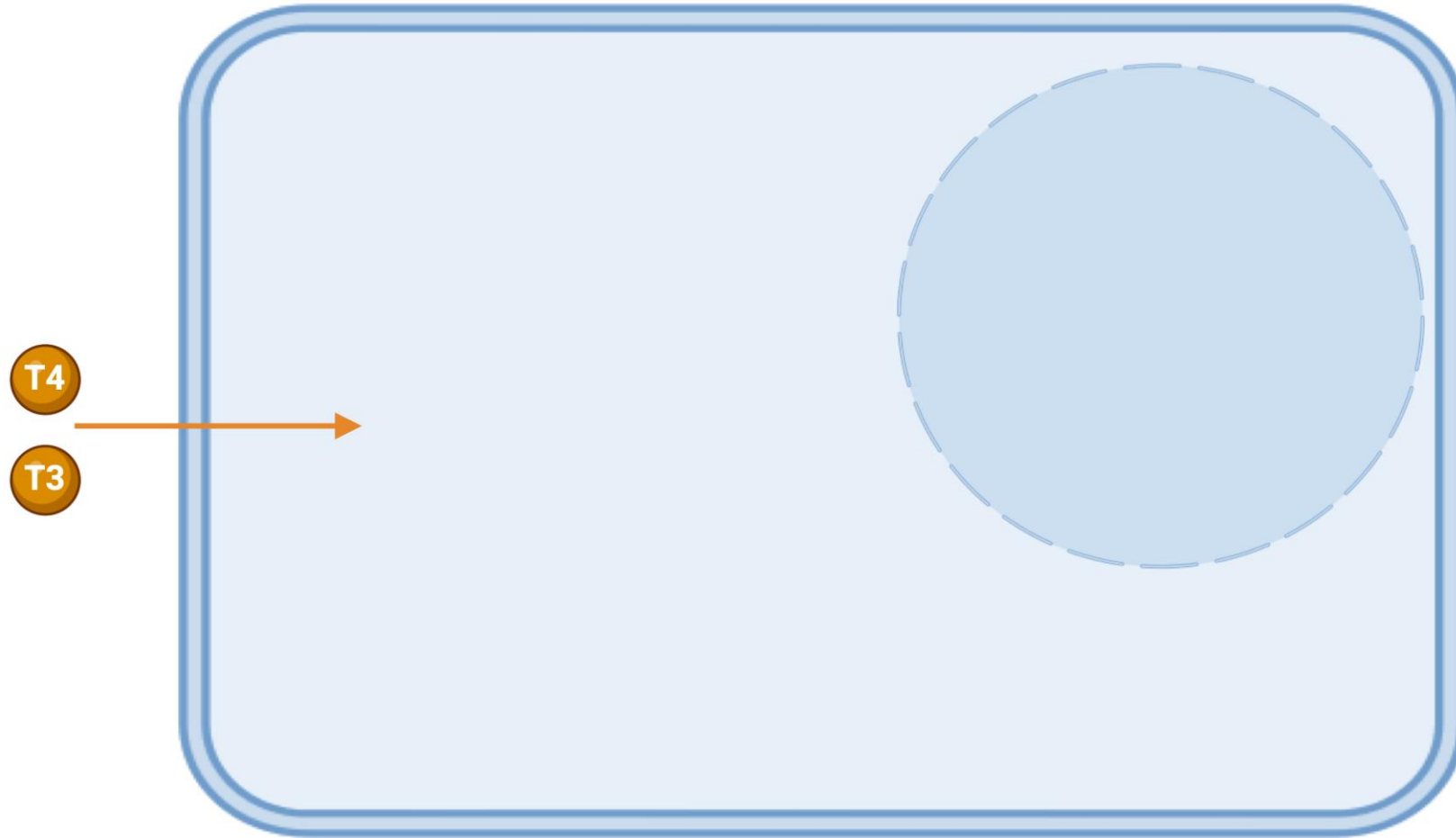
Thyroid gland produces thyroid hormones



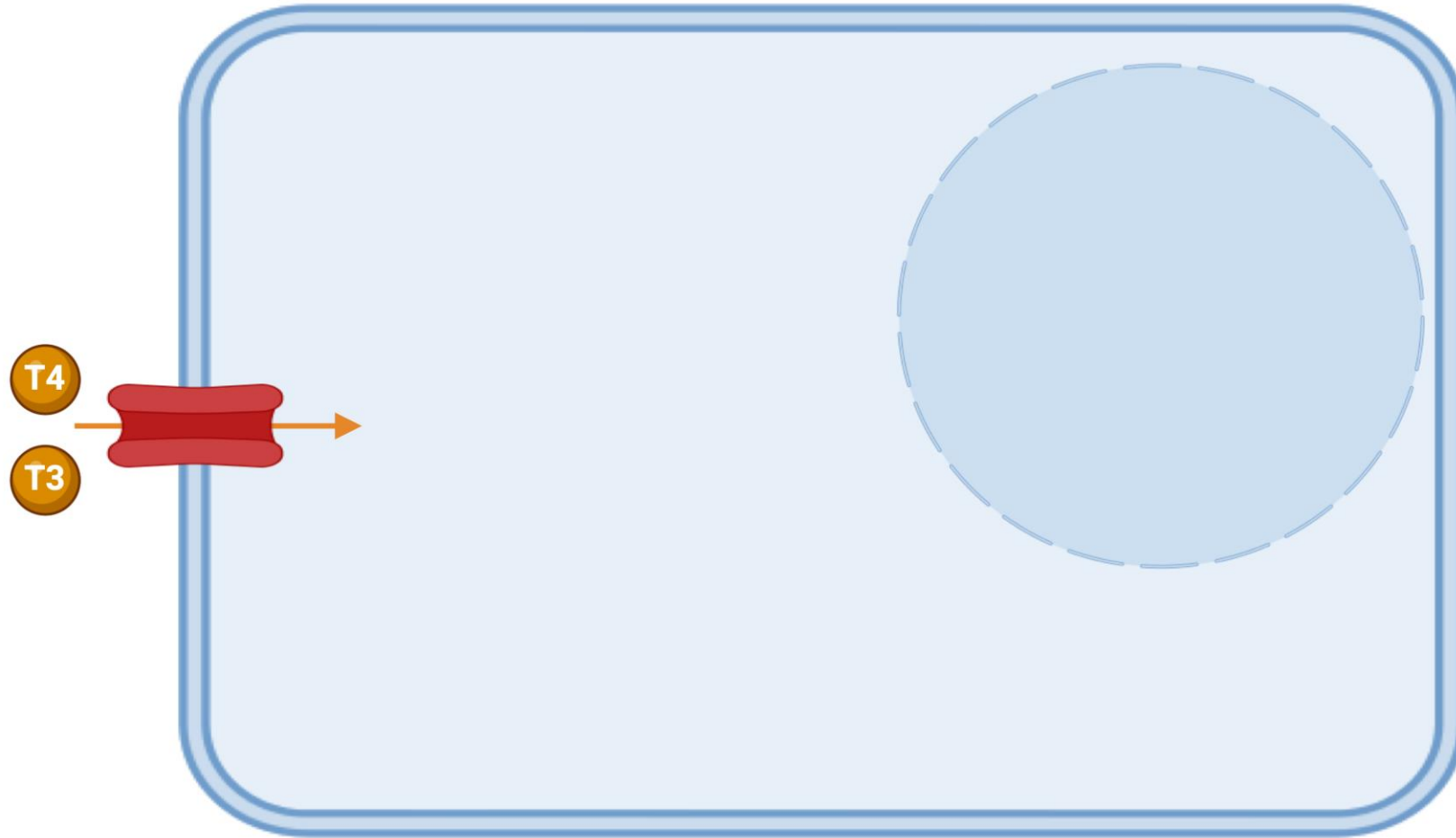
T3 target cell



T3 target cell: hormones enter

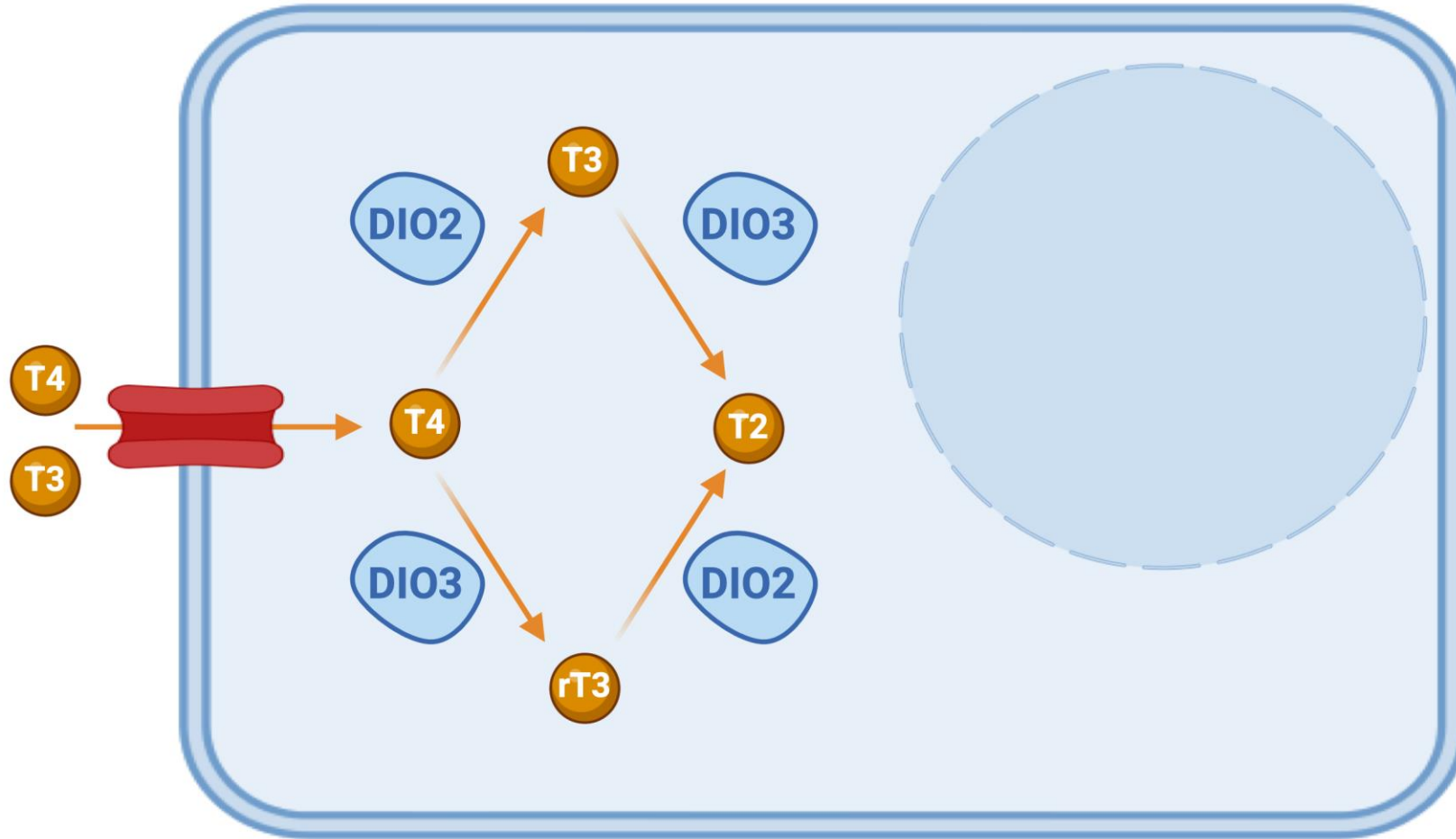


T3 target cell: hormones enter by transporter proteins



Transporter

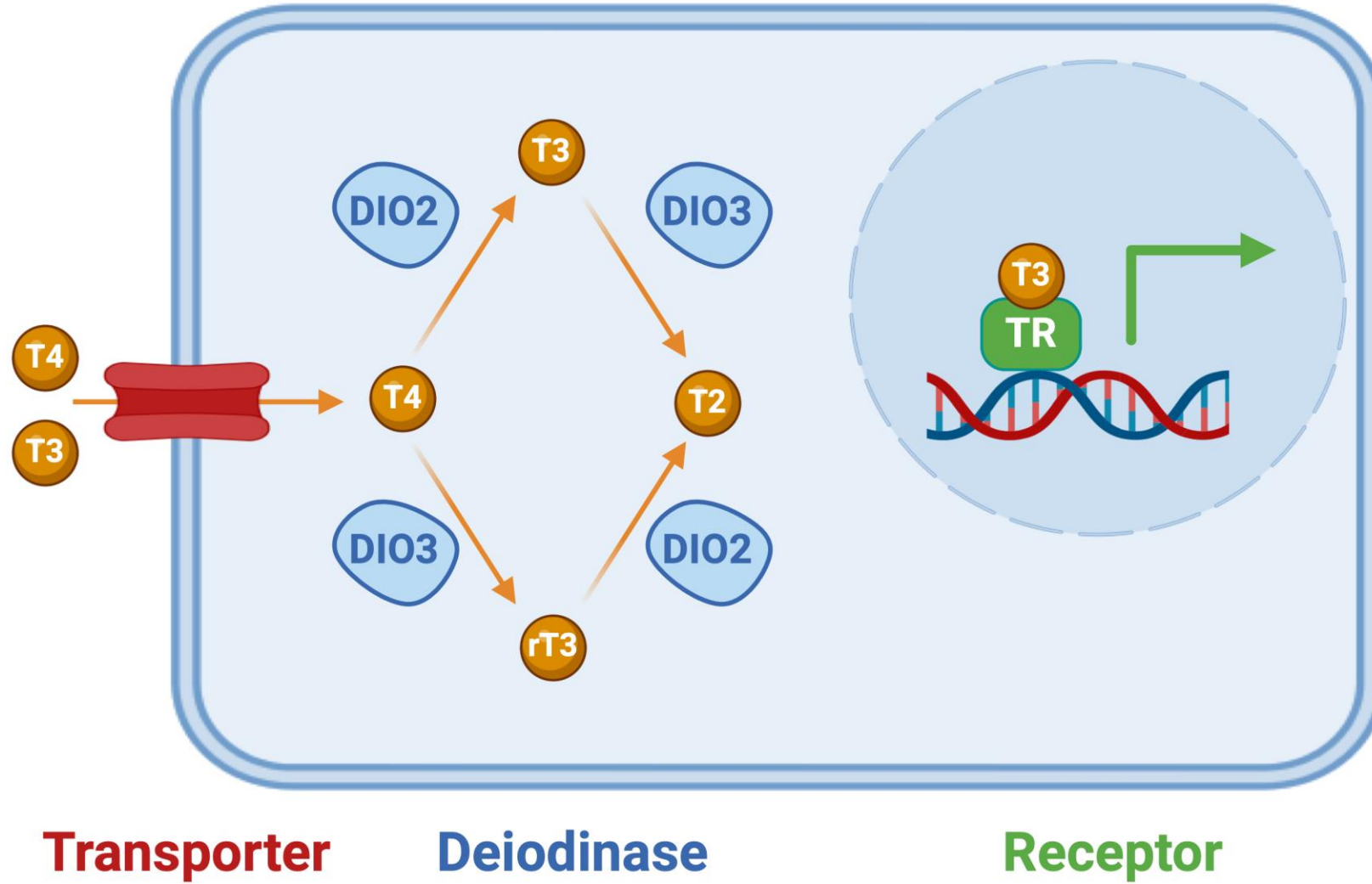
Thyroid hormone activating and inactivating enzymes



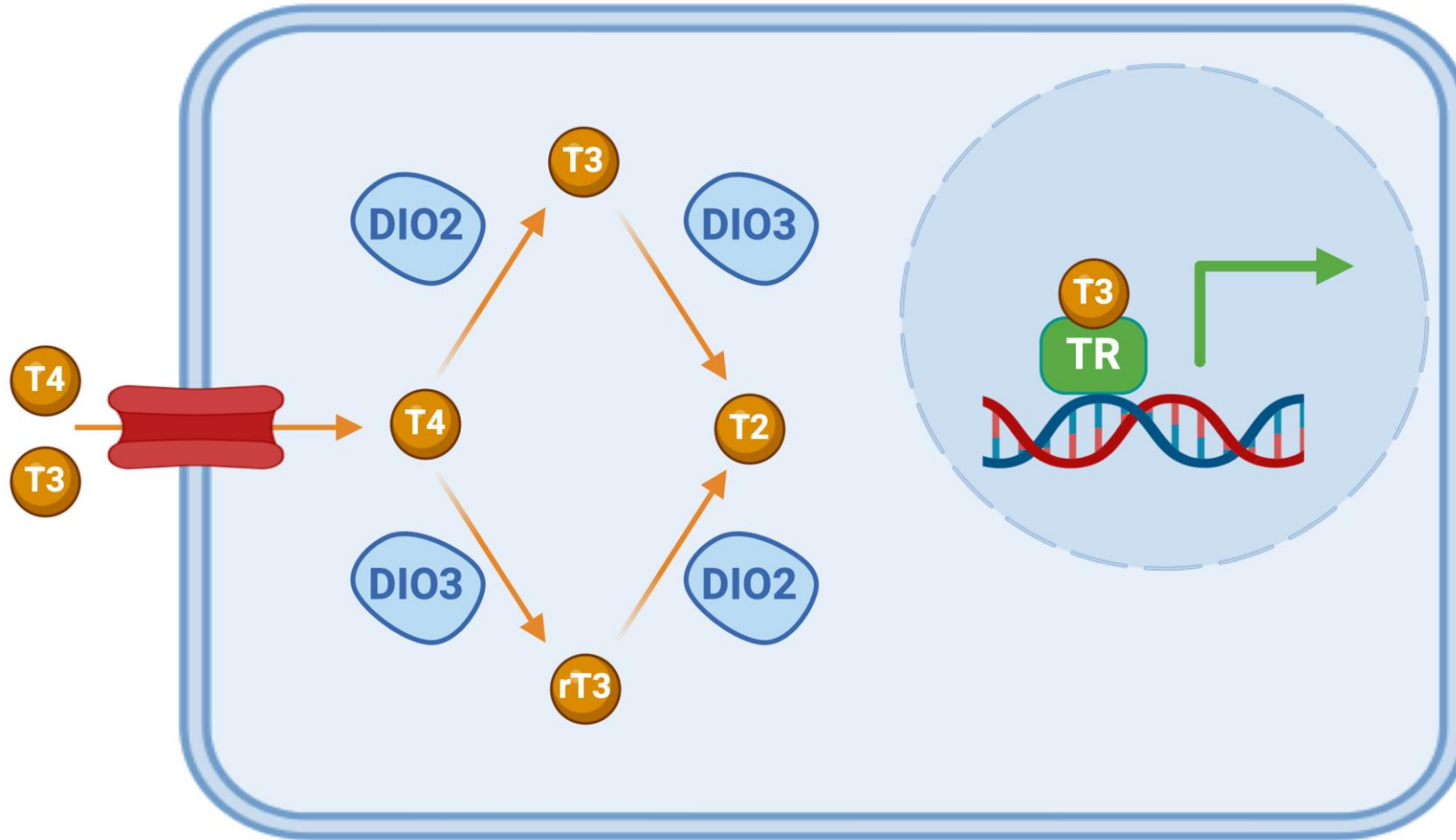
Transporter

Deiodinase

Thyroid hormone action in the nucleus



Thyroid hormone signaling disorders



Transporter

MCT8 deficiency
OATP1C1 deficiency

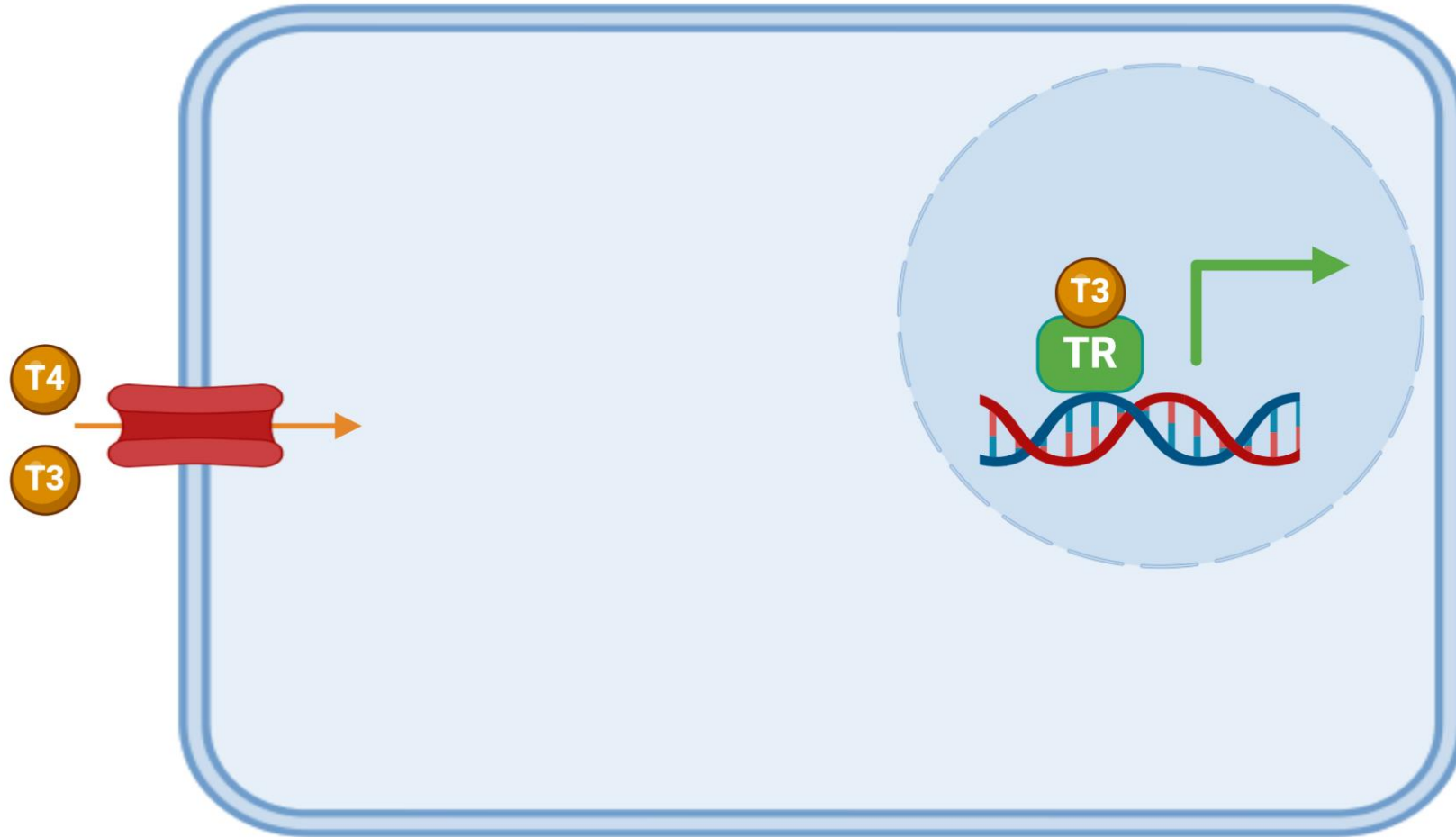
Deiodinase

SBP2 deficiency

Receptor

RTH α
RTH β

Today



Transporter

**MCT8 deficiency
(Example)**

Receptor

**RTH β
(Proposal)**

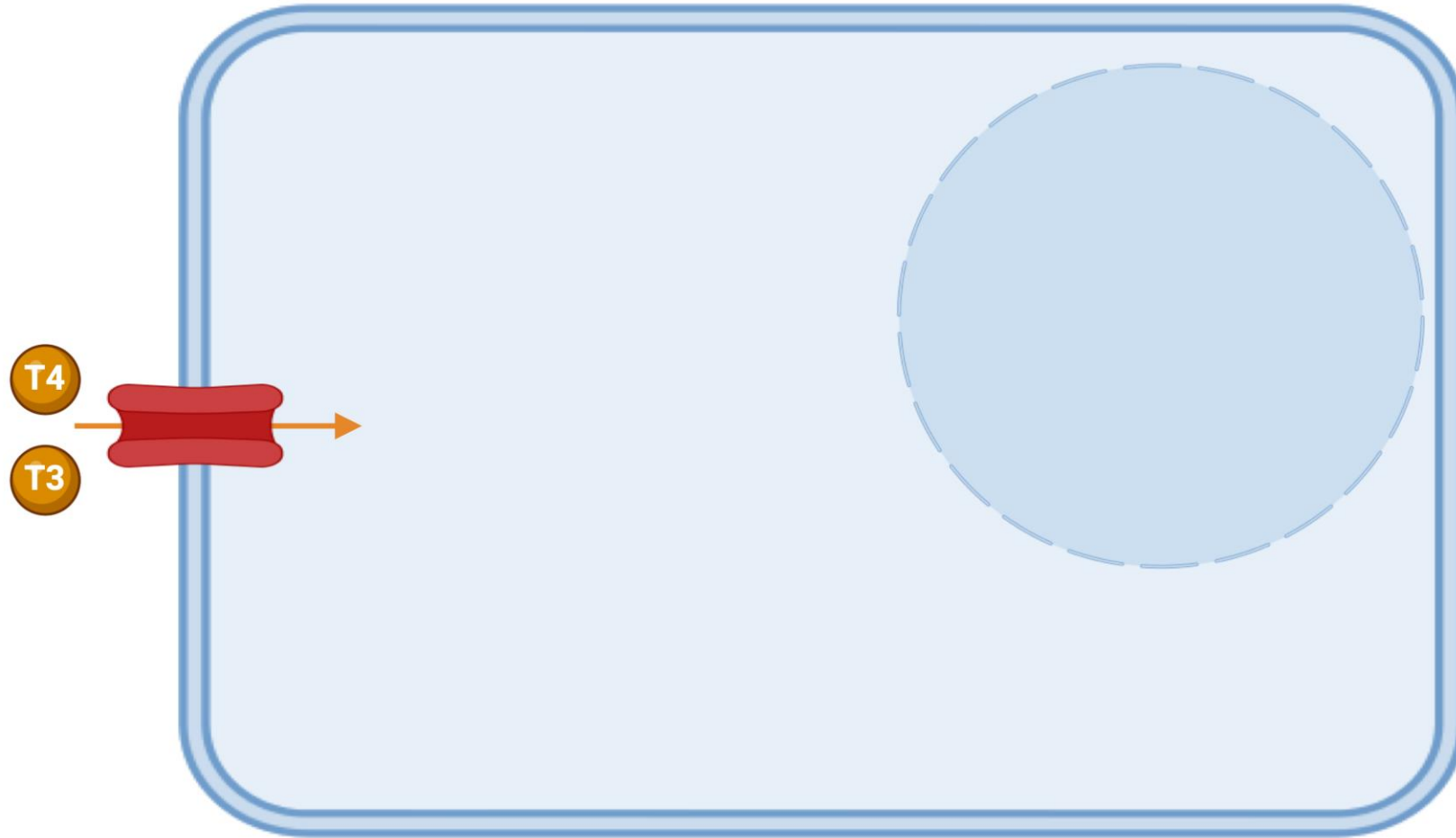
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Brief context of thyroid hormone signaling

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MCT8 deficiency



MCT8

MCT8 deficiency: developmental & metabolic disorder

MCT8 deficiency: developmental & metabolic disorder

T4 ↓

T3 ↑

TSH =

Epilepsy



No head control

Hypotonia

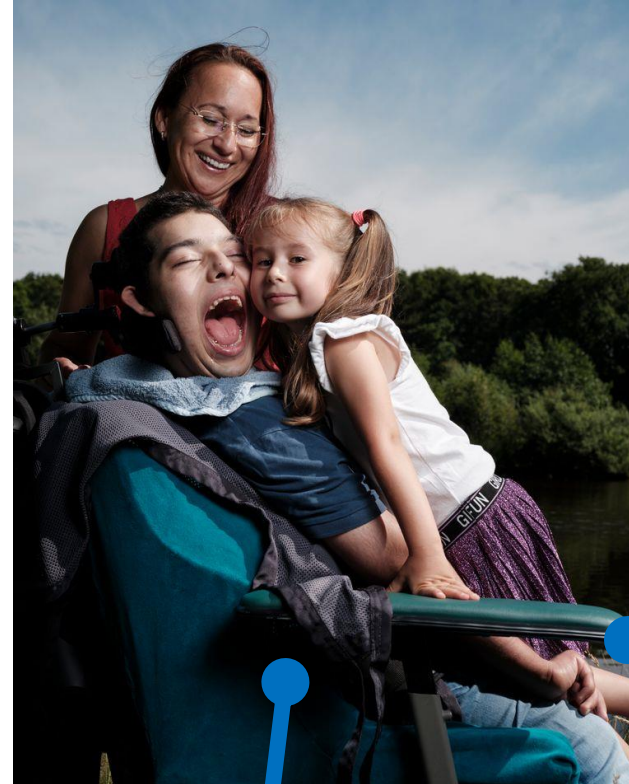
Hypokinesia

Low body weight & feeding problems

Sleep disturbance

Tachycardia

Frequent infections



Dystonia

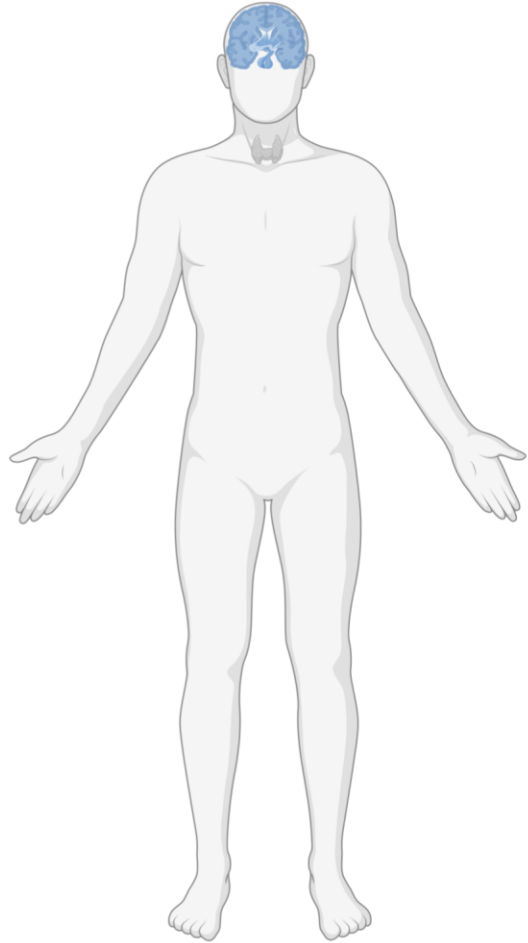
Scoliosis

Low muscle mass

Wheel chair bound

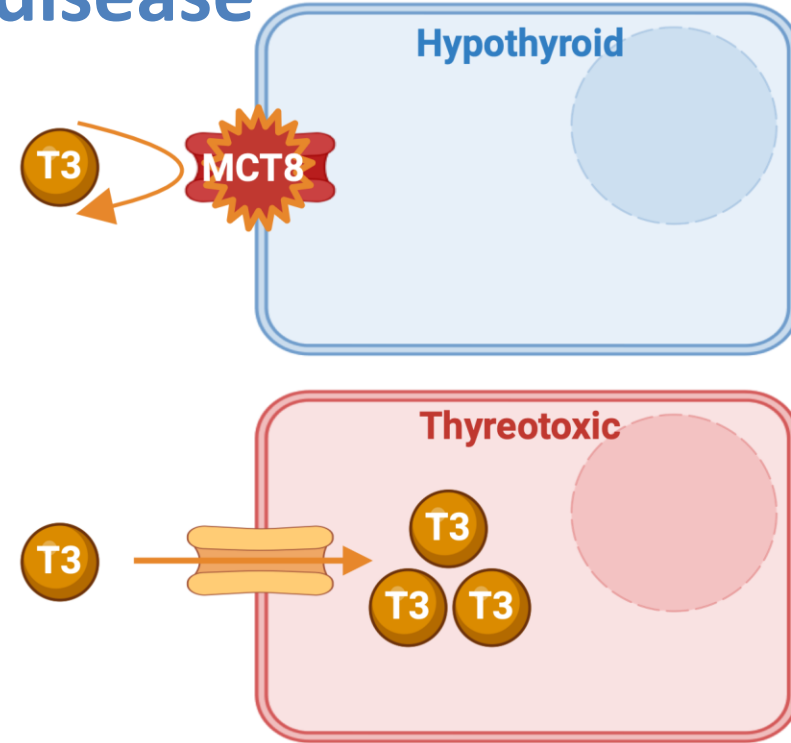
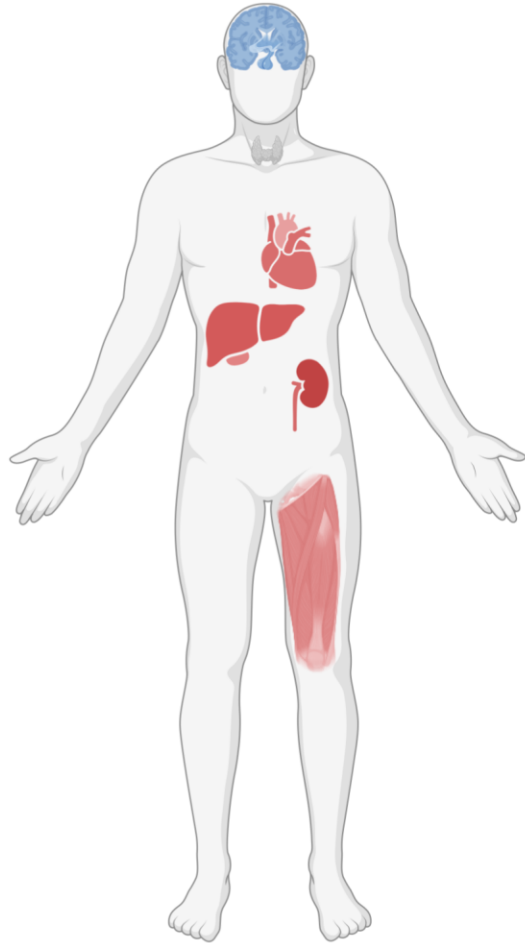
MCT8 deficiency: mechanisms of disease

T4 ↓
T3 ↑
TSH =

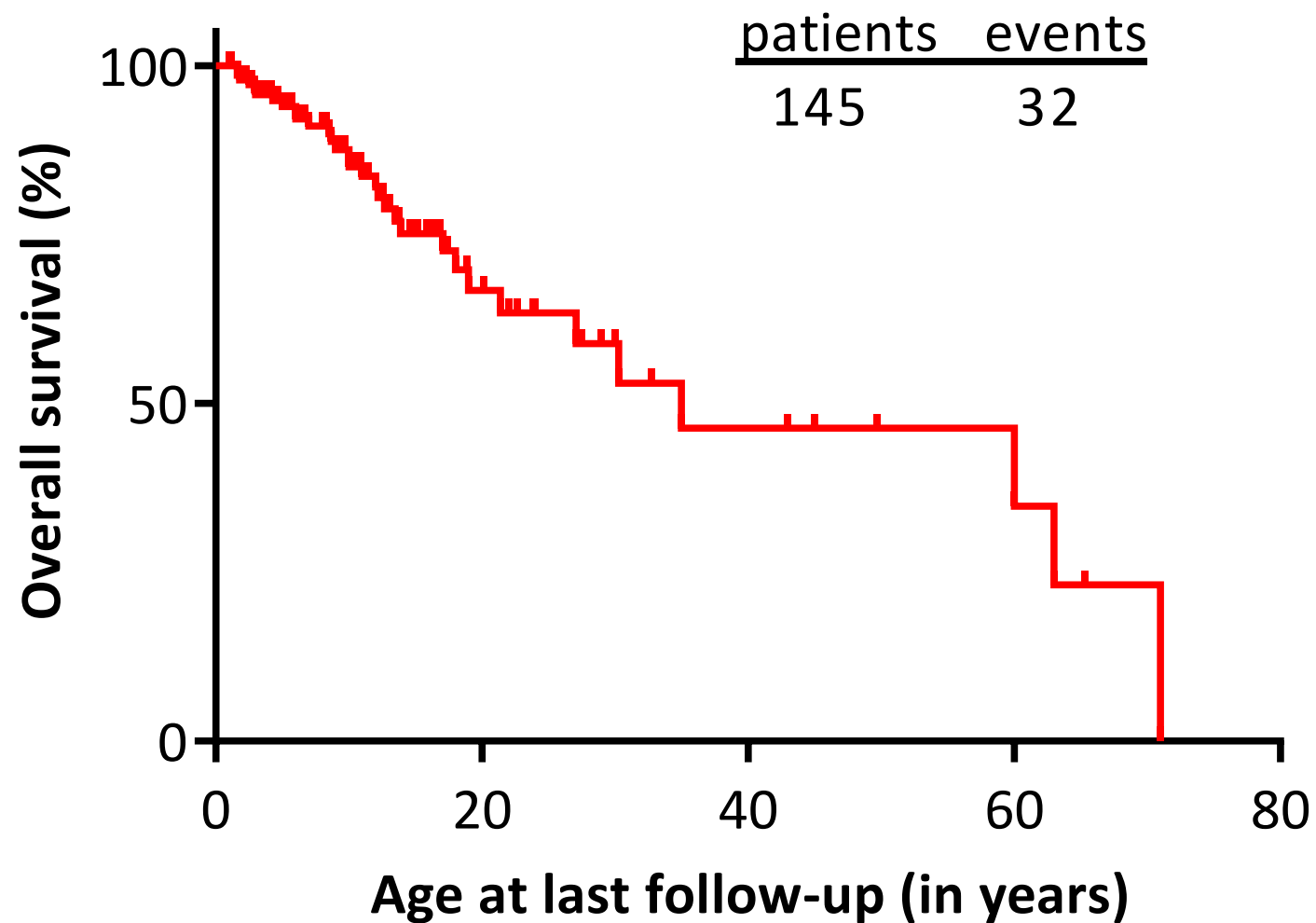


MCT8 deficiency: mechanisms of disease

T4 ↓
T3 ↑
TSH =



High mortality

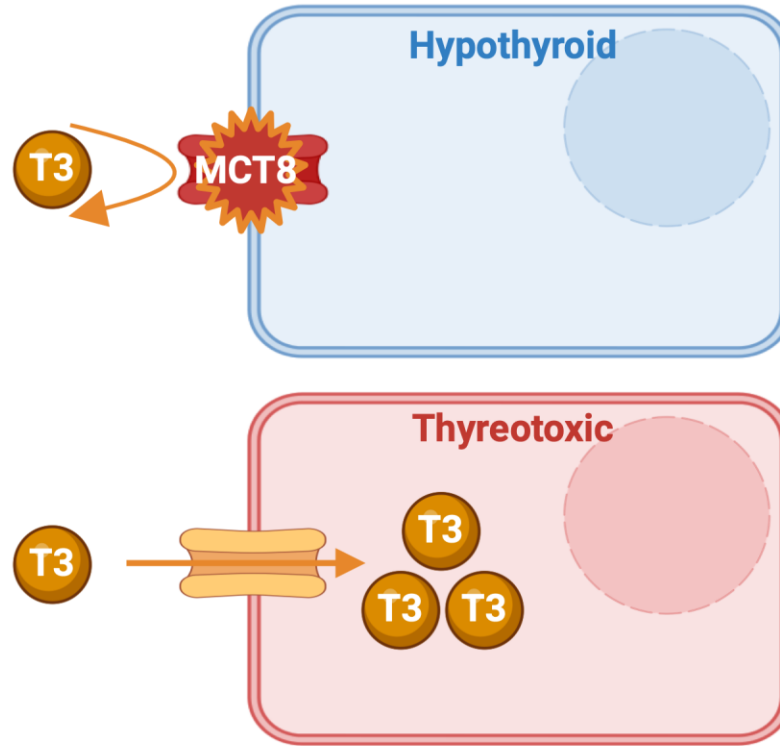
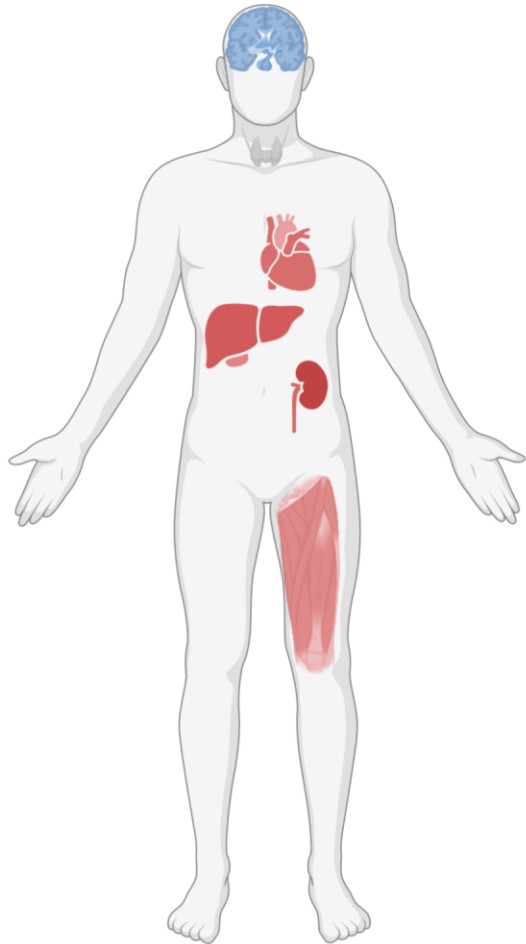


Individuals at risk

Age (years)	0	10	20	30	40	50	60	70
Total	145	68	23	8	4			

Therapy: dual action

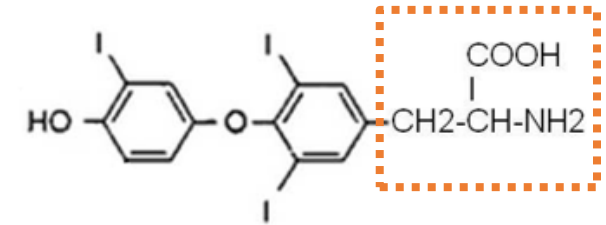
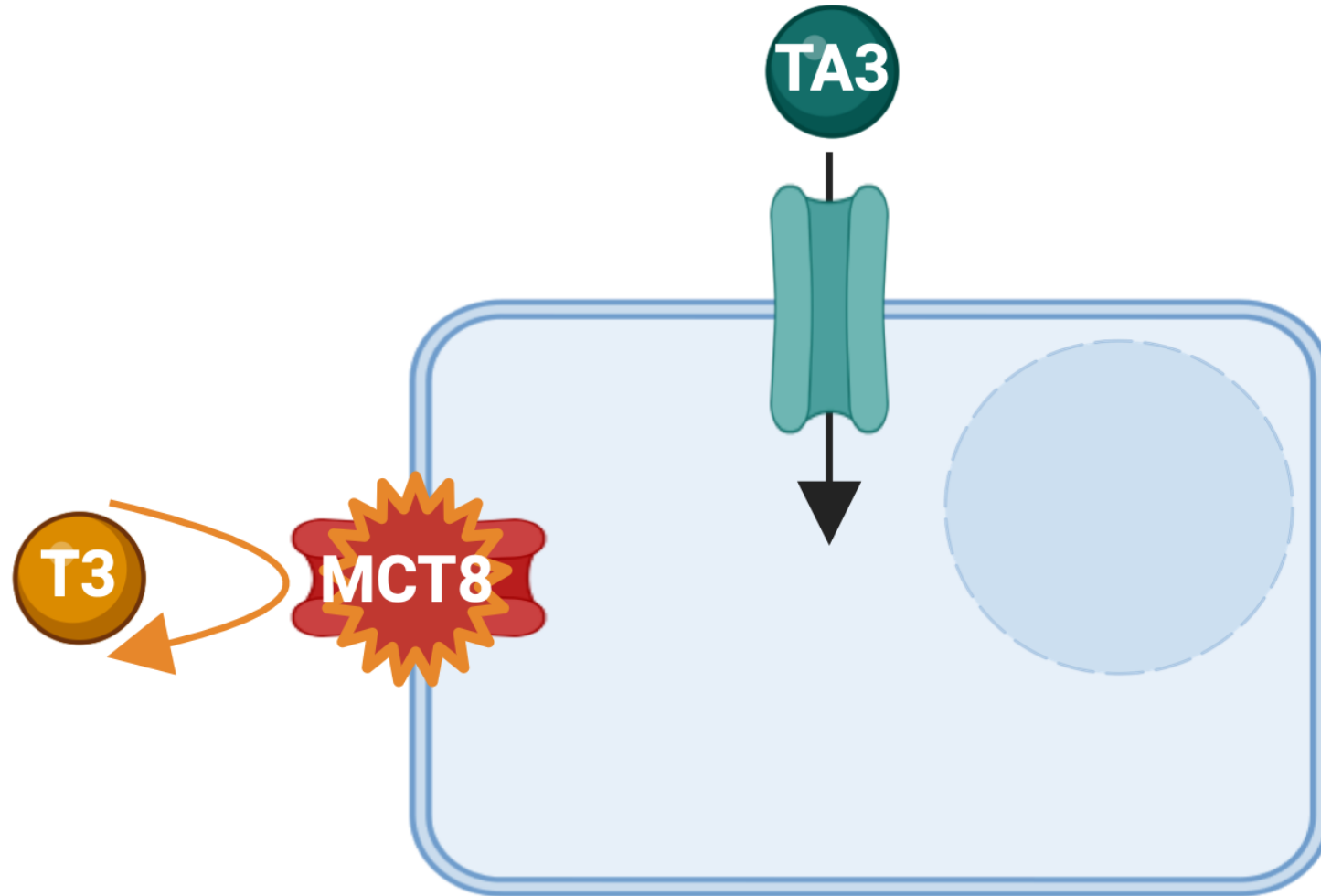
T4 ↓
T3 ↑
TSH =



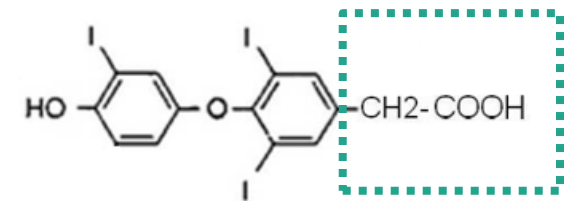
Increase thyroid hormone action

Reduce thyroid hormone action

T3 analogs (Triac) – principle in MCT8 defective cells



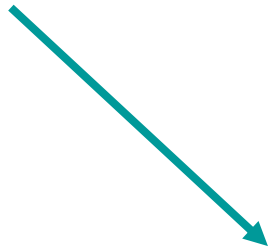
T3



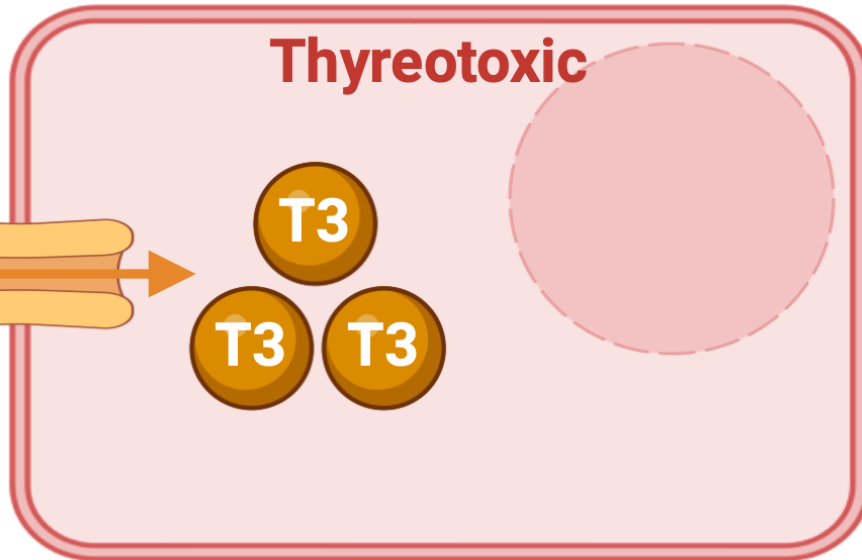
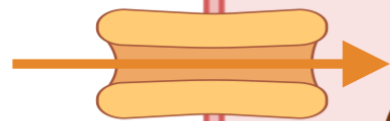
Triac (TA3)

Is Triac effective in patients with MCT8 deficiency?

Triac

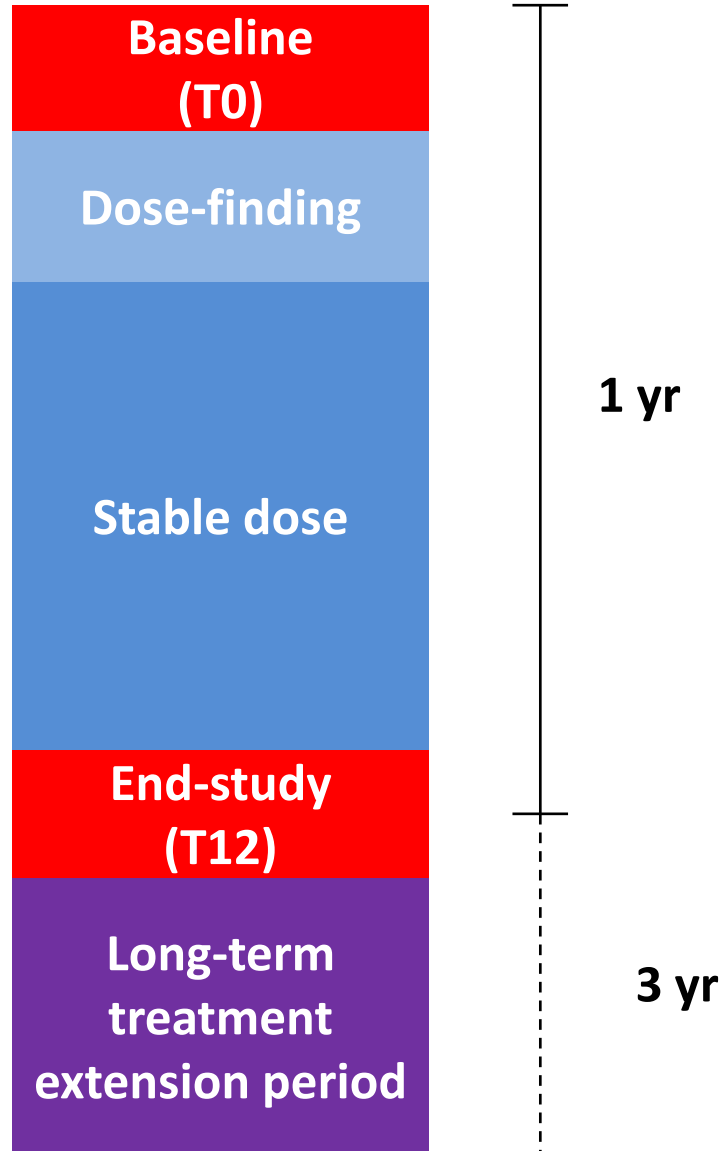


T3



Metabolic phenotype
Triac Trial I

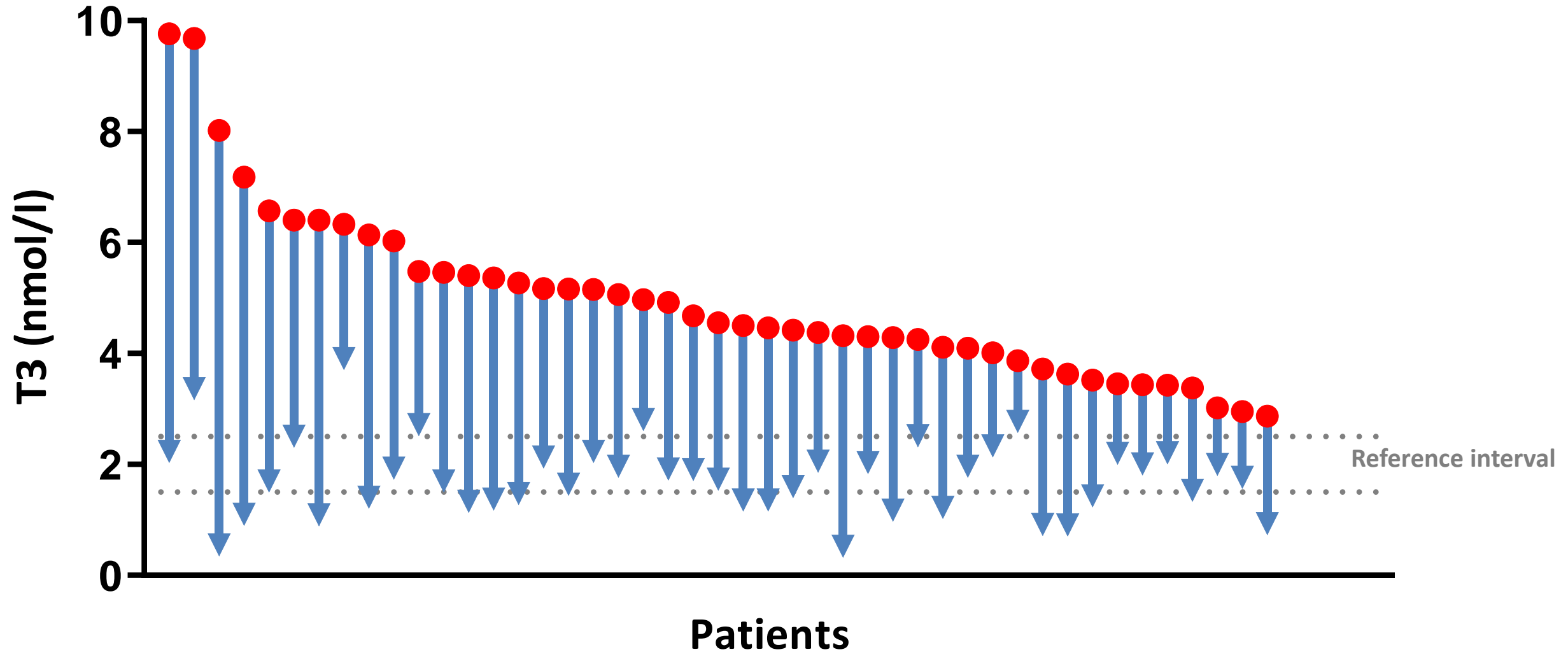
Triac Trial I: international phase 2 trial



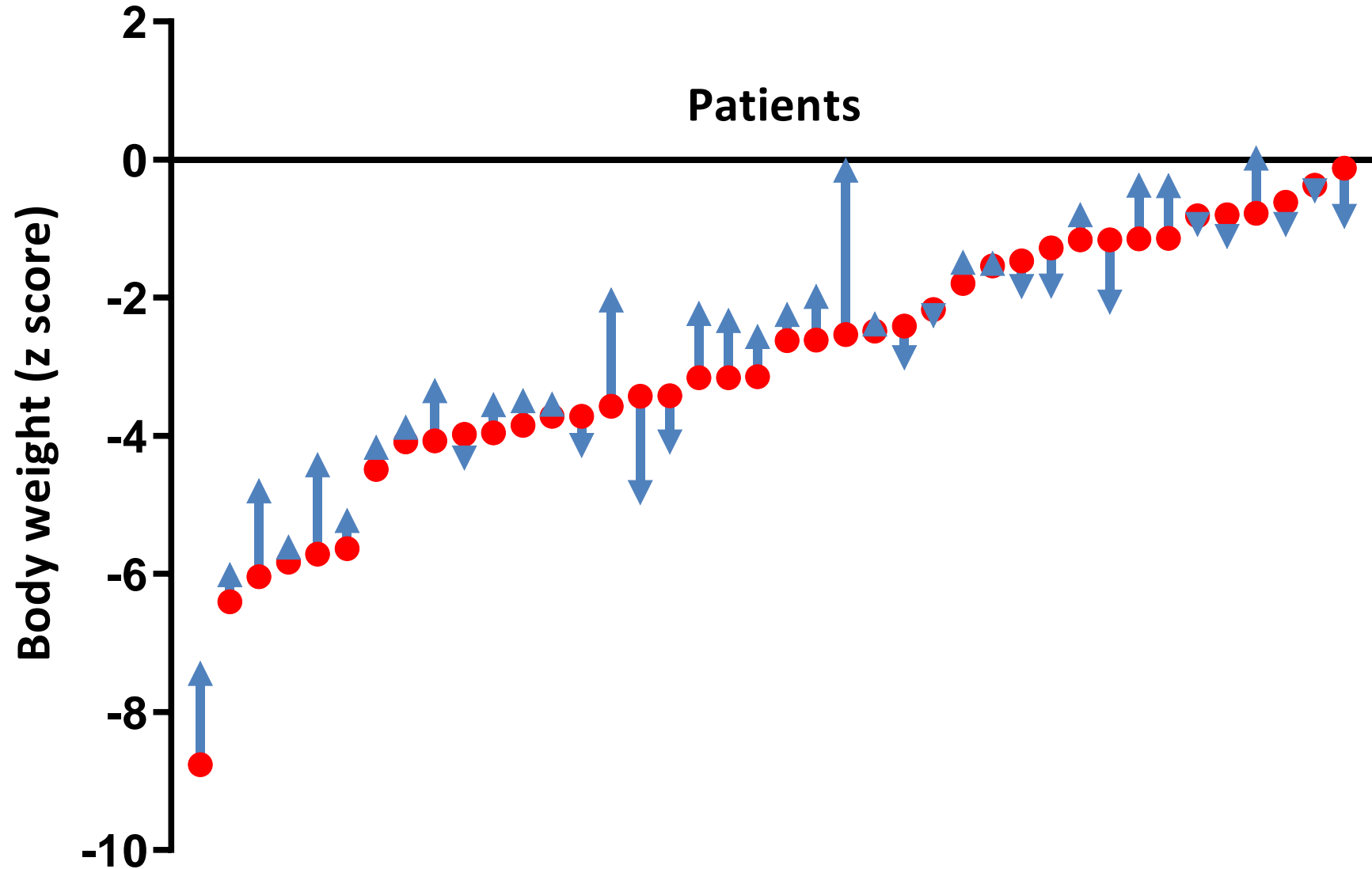
N=46
Median age 7.1 yrs
(range 0.8 – 66.8)

**Rotterdam, Berlin, Paris, Toulouse are
part of Endo-ERN**

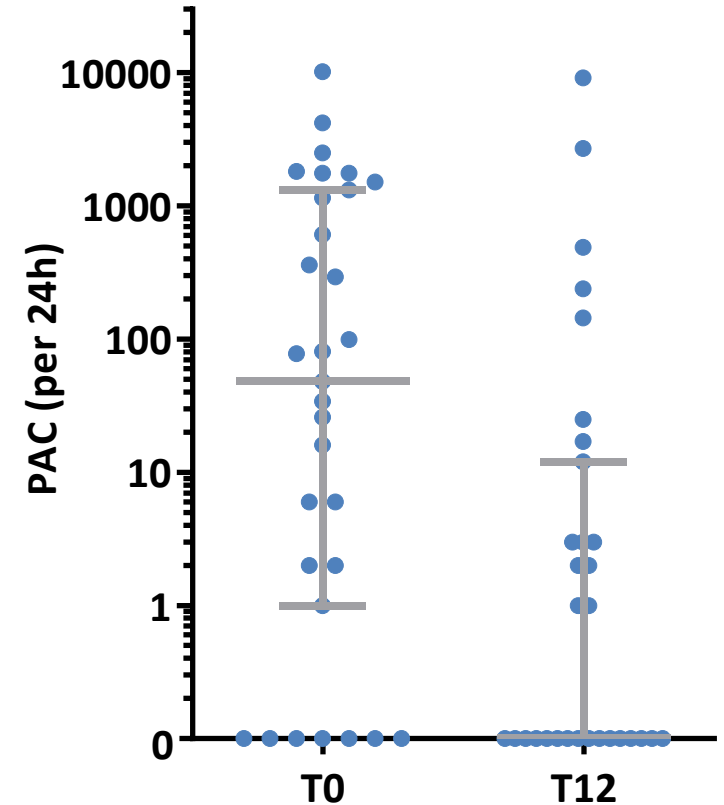
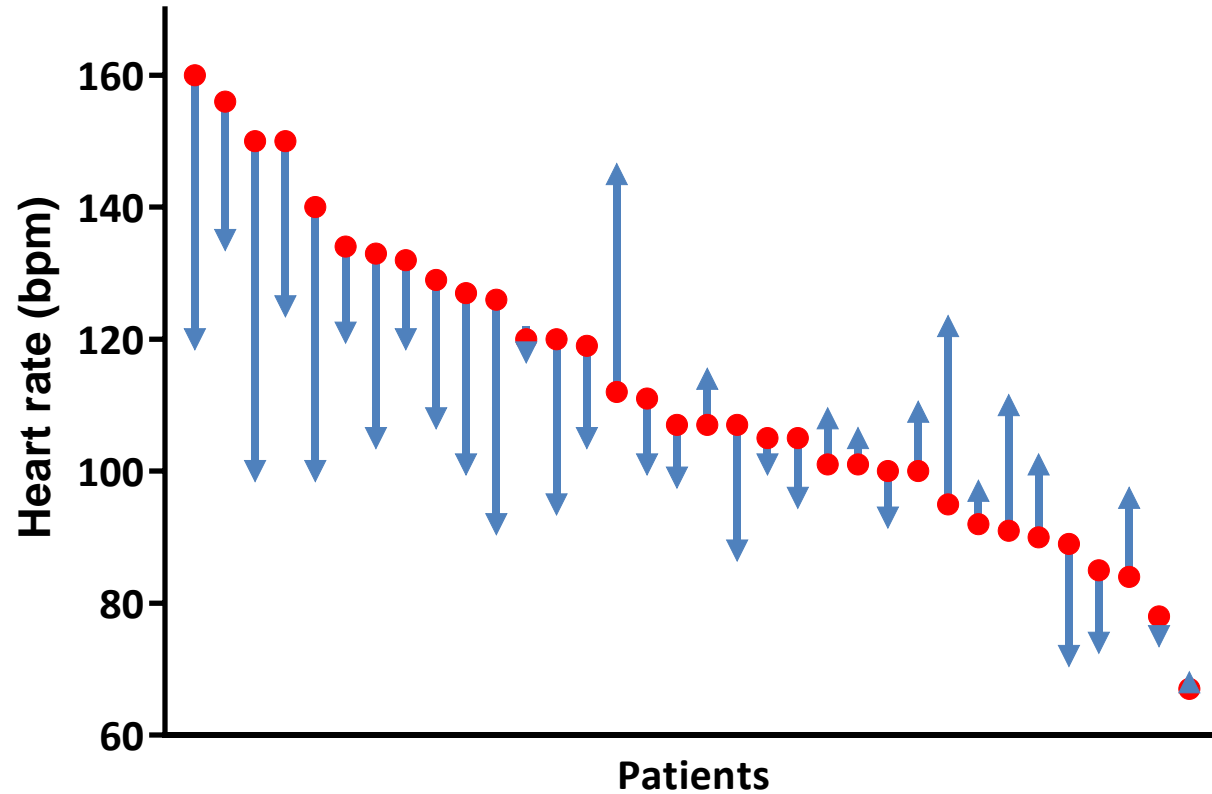
Primary outcome: T3 concentrations normalize



Secondary outcomes: body weight improves



Secondary outcomes: heart rate improve & PACs subside



Triac: effects on mortality

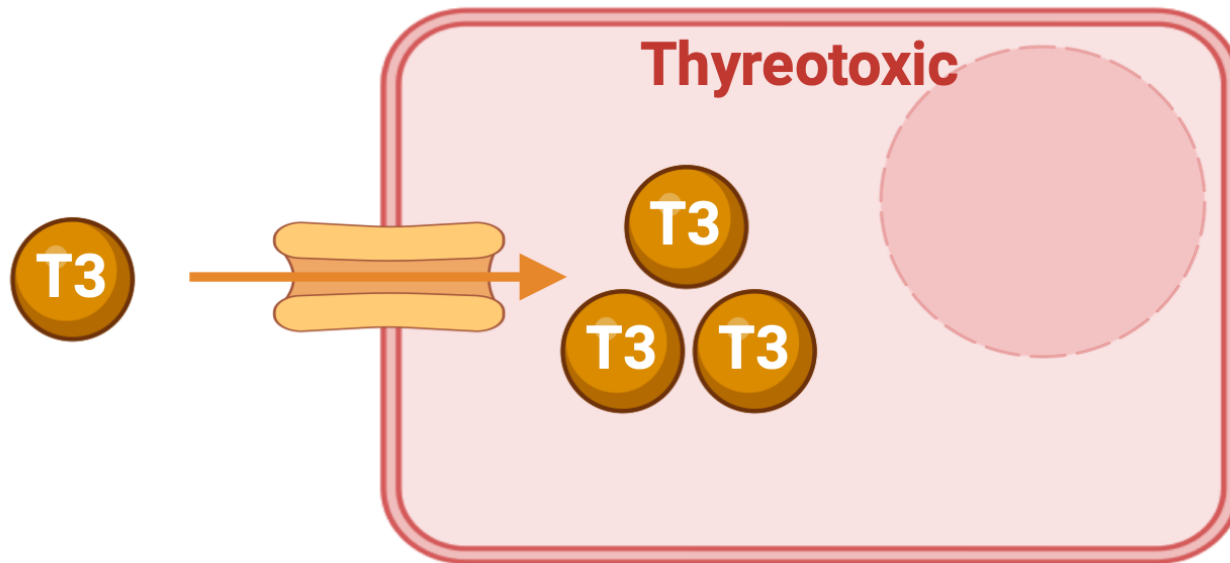
Triac: effects on mortality

Unpublished data removed

Is Triac effective in patients with MCT8 deficiency?

Triac

Yes



Metabolic phenotype

Triac Trial I

Real world data

reTRIACt study

CHMP (EMA) meeting right now!!

CHMP (EMA) meeting right now!!



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 December 2024

EMA/CHMP/539348/2024

Human Medicines Division

Committee for medicinal products for human use (CHMP)

Draft agenda for the meeting on 09-12 December 2024

2.1.2. Tiratricol - Orphan - EMEA/H/C/005220

Rare Thyroid Therapeutics International AB; treatment of monocarboxylate transporter 8 (MCT8) deficiency

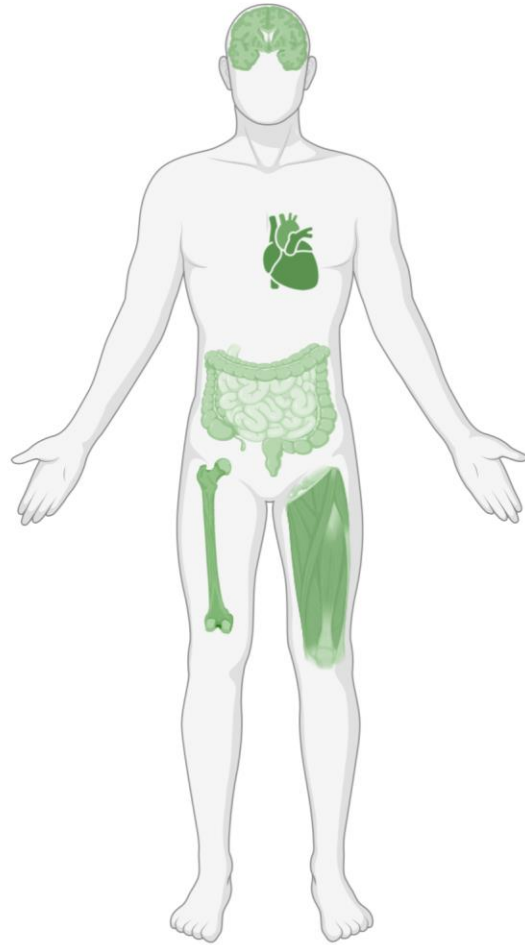
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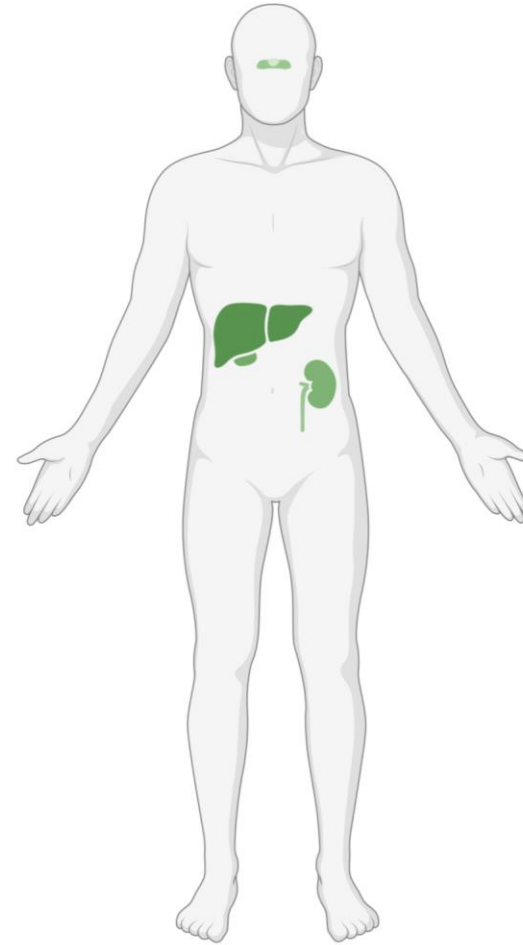
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Thyroid hormone receptor TR α and TR β



TR α



TR β

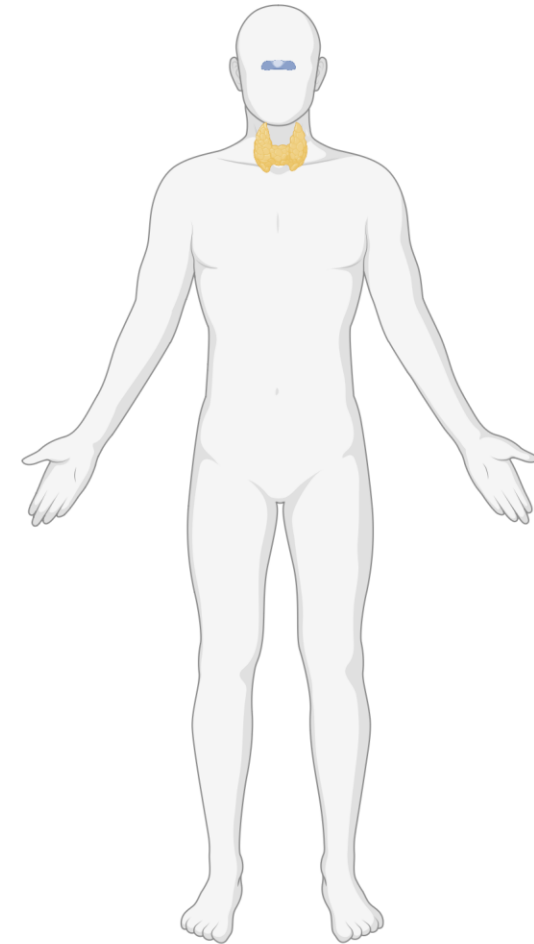
RTH β – tissue specific disordered thyroid state

Thyroid function tests

T4 ↑

T3 ↑

TSH =



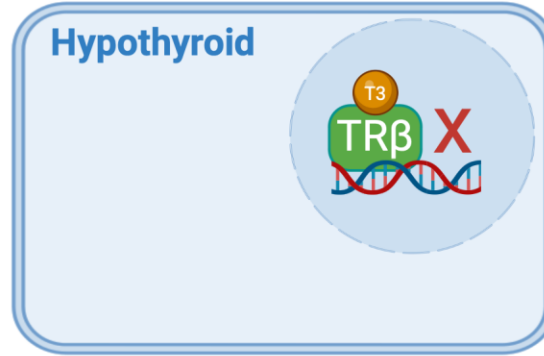
RTH β – tissue specific disordered thyroid state

Thyroid
function
tests

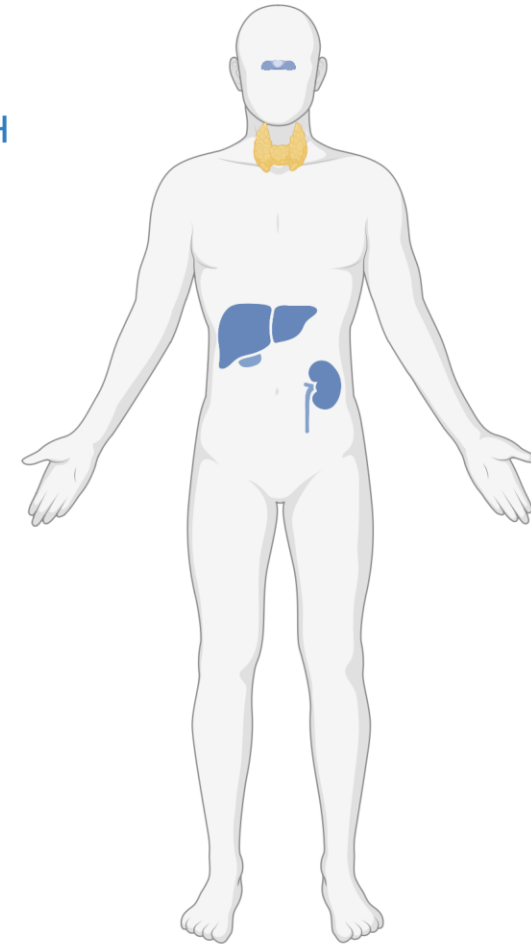
T4 ↑

T3 ↑

TSH =



Pituitary
Enhanced bioactive TSH
Liver
Dyslipidemia, NAFLD
Kidney



TR = Thyroid hormone receptor

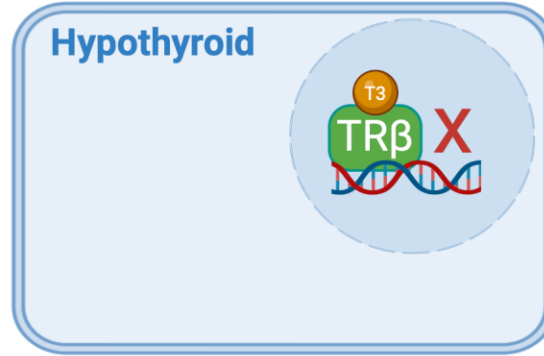
RTH β – tissue specific disordered thyroid state

Thyroid
function
tests

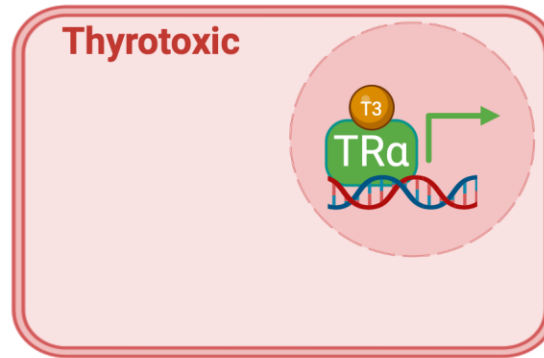
T4 \uparrow

T3 \uparrow

TSH =

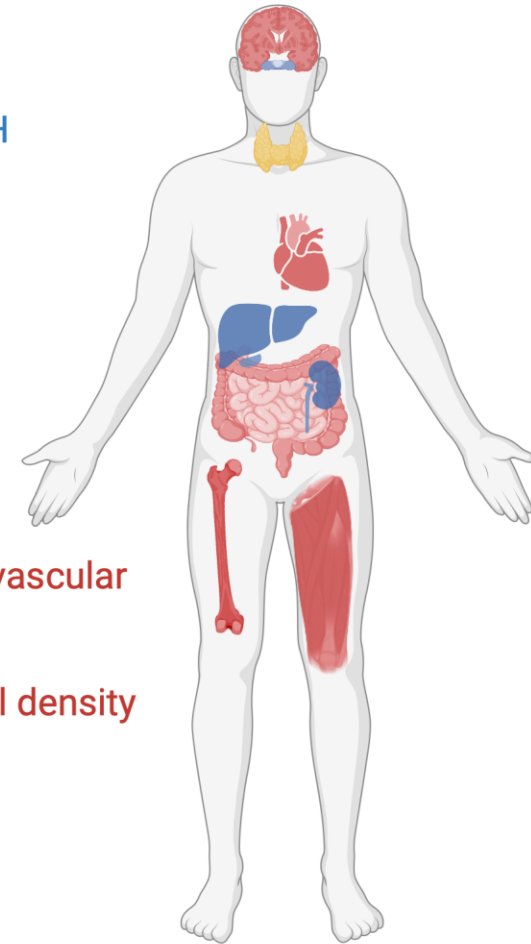


Pituitary
Enhanced bioactive TSH
Liver
Dyslipidemia, NAFLD
Kidney

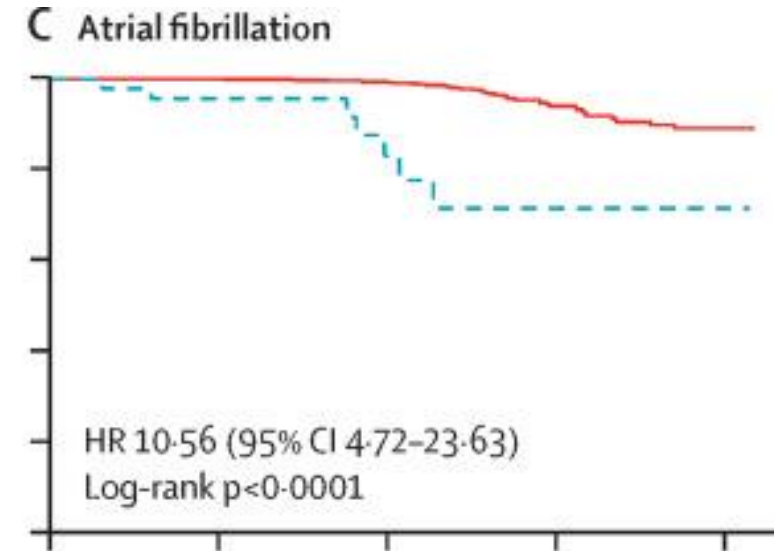
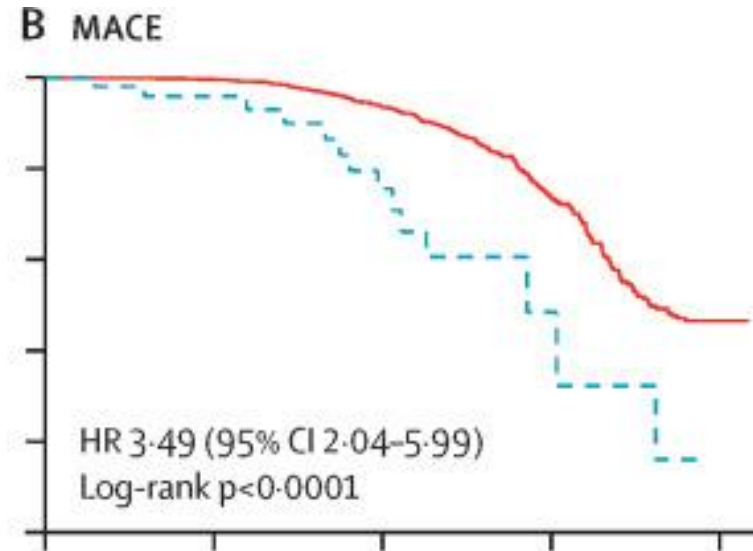
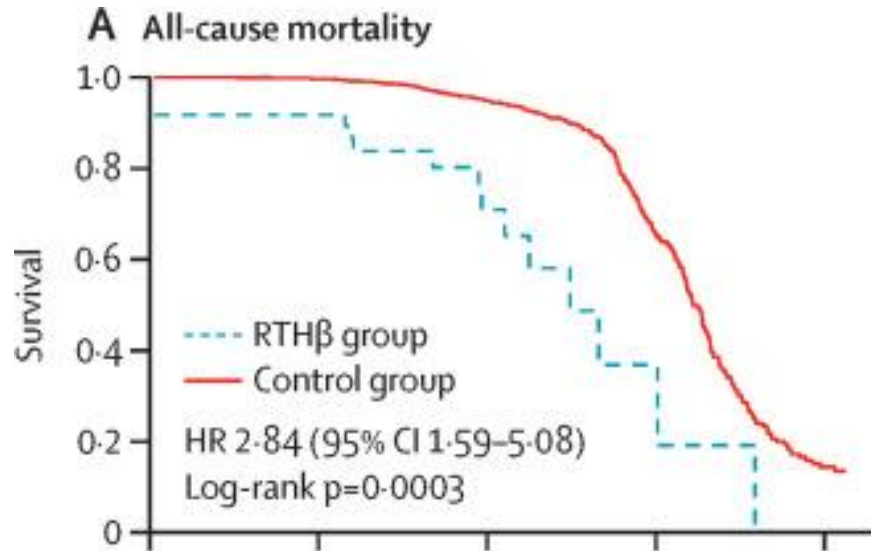


Brain
ADHD
Heart
Atrial fibrillation, cardiovascular
mortality
Bone
Decreased bone mineral density
Muscle
Gut

TR = Thyroid hormone receptor



RTH β : increased cardiovascular morbidity and mortality



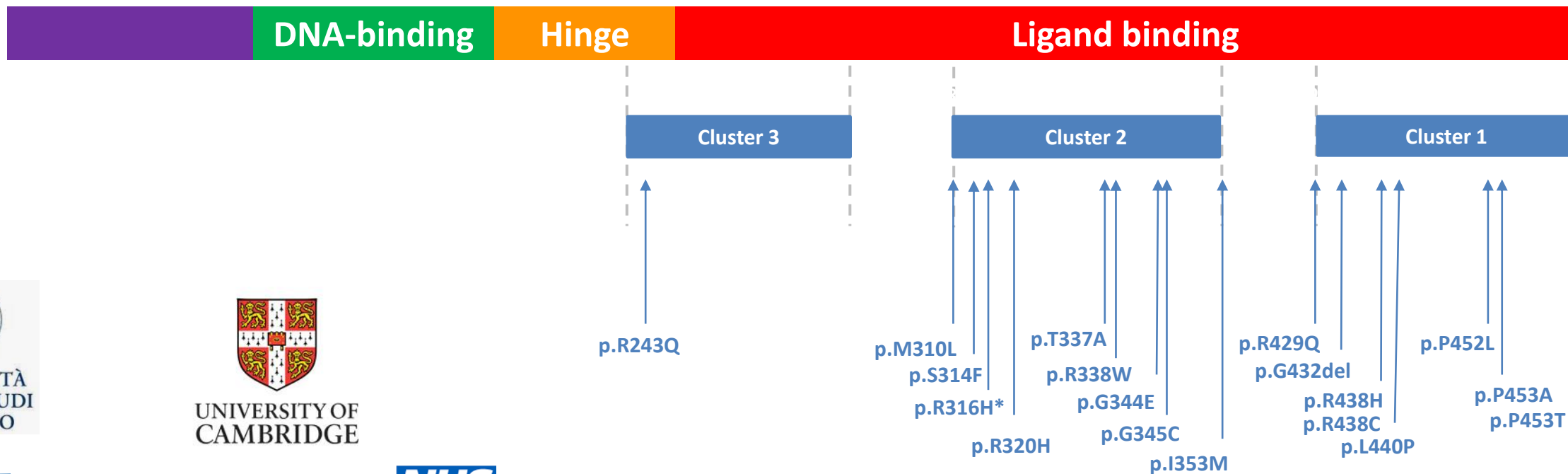
RTH β : therapies

Symptomatic (beta-blockers)

Anecdotal reports on Triac

No clinical trials available

RTH β : collaborative effort



Manchester University
NHS Foundation Trust



Birmingham Women's
and Children's
NHS Foundation Trust

23 patients with 18 mutations

*heterozygous and homozygous

Hallands sjukhus Kungsbacka



Preliminary real-world data: Triac reduces FT4 into normal range in RTH β

Unpublished data removed

Triac Trial III – Outcomes (1)

Primary	Normalization of serum thyroid hormones	(Blood)
Secondary	Reduction in heart rate	(Holter)
	Normalization of energy expenditure	(Hood)
	Reduction of anxiety, ADHD	(neurocognitive/ psychological tests)

Triac Trial III – Outcomes (2)

Other	Occurrence of atrial fibrillation, PVC, PACs	(Holter)
	Moving	(Patch)
	Improvement of bone mineral density	(DEXA scans)
	School performance	(?? Diary??)
	QoL	(Questionnaire)
	Stool frequency and diarrhea	(Questionnaire)
	Reduced perspiration	(Questionnaire)
	Improvement of body weight	(Examination)
	Tissue markers (SHBG, CK, lipids etc)	(Blood)
	Scans (brain/heart/liver): harvest vs burden??	(MRI/echo)
Safety	signs of thyrotoxicosis; cardiac	

Triac Trial III - Design

Who	paediatric patients (align with UK-initiative for adult RTH β)
Duration	12 or 24 months (??)
Placebo	?? (or cross-over) (fill-it-up design?)*
Other medication	allow b-blockers or ATD?
Mutations	all?

Triac Trial III – next steps

Further share institutional data

Set up RTH β registry (EuRREB)

(Time)

(Money)



Identify relevant & specific outcomes

Triac Trial III – next steps

Partners

UK (Rees, Chatterjee)

Dublin, Ireland (Moran)

Milan, Italy (Persani, Campi)

Leuven, Belgium (Rochtus, Decalonne)

Philadelphia, USA (Bauer)

(others)

Funding

ERDERA (?)

Egetis (?)

Eurostars (?)

Acknowledgements



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Rotterdam, Netherlands

Carolina Medina-Gomez

Fernando Rivadeneira

Rosalie Sterenberg

Marco Medici

Thyroid group

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Peter Simm

Tony Huynh

Belgium

Linda De Meirleir †

Silvia Depoorter

Brasil

Felipe Monti Lora

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Jill Hamilton

Alexander Chesover

Nina Lenherr

Jacqueline Curtis

Czech Republic

Jan Lebl

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Israel

Amnon Zung

Poland

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Iuliu Bacos

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The Netherlands

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Stan Nowak

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Nitash Zwaveling

Anne-Marie van

Wermeskerken

Jet van der Spek

David Koolen

South Africa

Adri van der Walt

Turkey

Serap Turan

United Kingdom

Krishna Chatterjee

Carla Moran

Greta Lyons

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Belgium

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USA

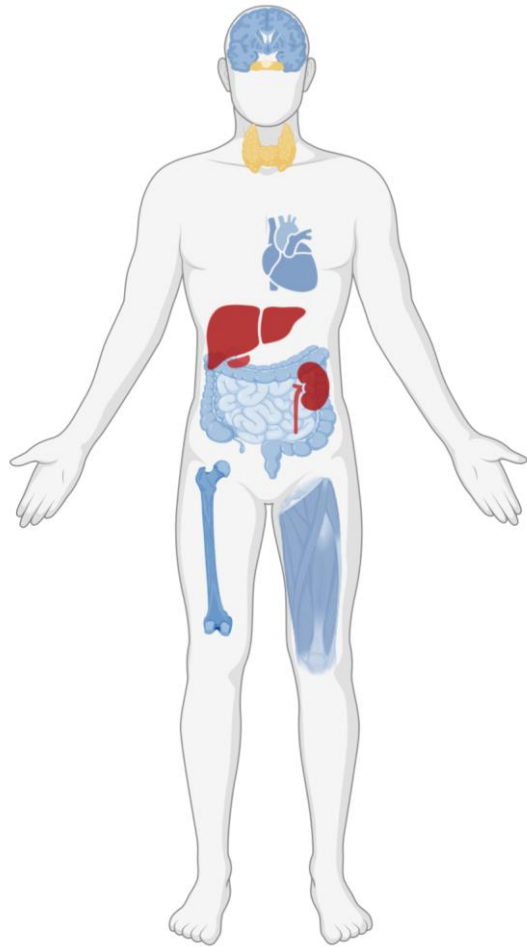
Philadelphia: Andrew Bauer

Questions:

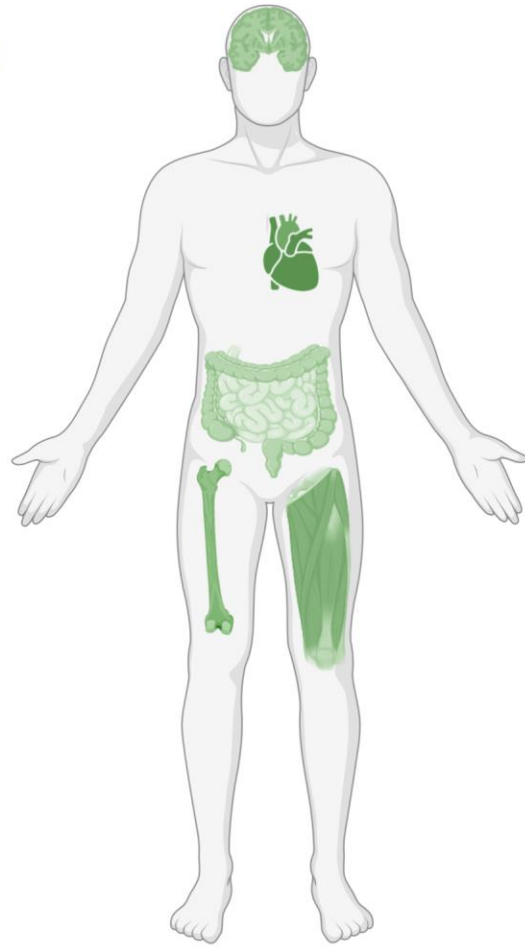
Edward Visser

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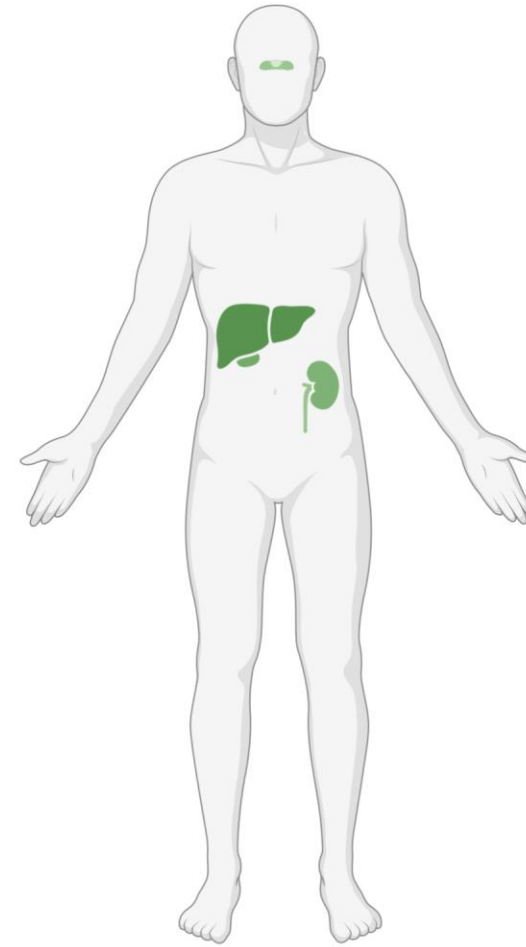
Thyroid hormone receptor TR α or TR β



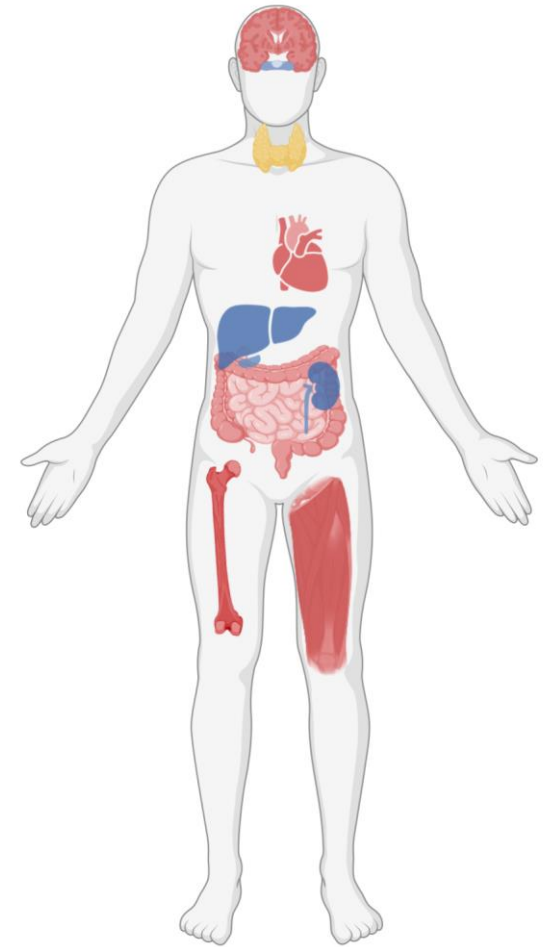
defect in TR α



TR α



TR β



defect in TR β

RTH β : clinical characteristics

Thyroid gland

Goitre 66 – 95%

Heart

Tachycardia (atrial fibrillation) 33 – 75%

Nervous system

Emotional disturbances 60%

Hyperkinetic behaviour 33 – 68%

ADHD 40 – 60%

Learning disability 30%

Intellectual disability (IQ<70) 6 – 16%

Hearing loss 10 – 22%

Growth and development

Short stature (< 5th percentile) 18 – 25%

Delayed bone age (> 2SD) 29 – 47%

Low BMI (children) 33%