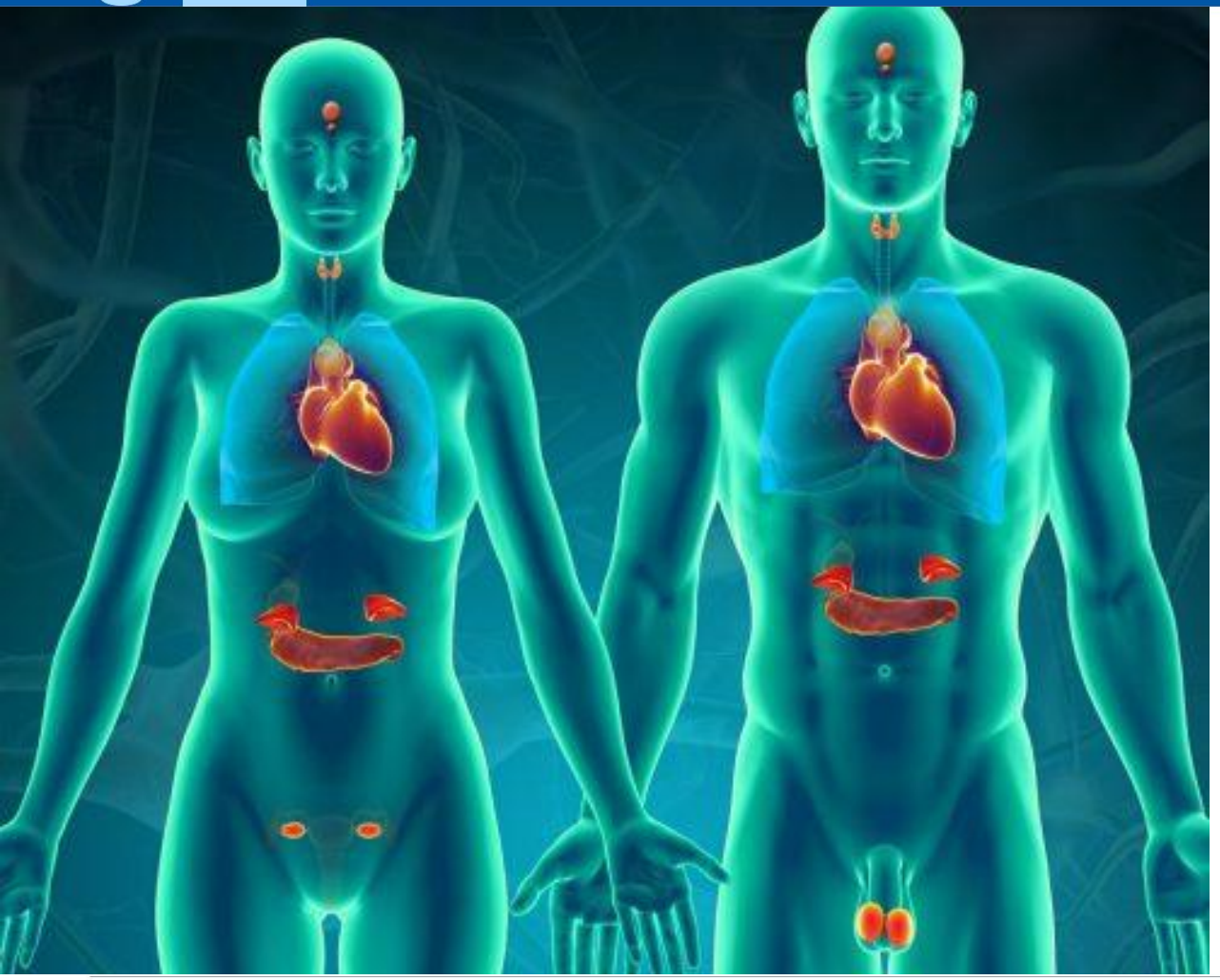
Advancement of Treatments
FOR RARE DISEASES



Developing Therapies for Rare Paediatric Endocrine Disorders

Nicolas C. Nicolaides MD, PhD
Paediatrician - Paediatric Endocrinologist
Assistant Professor in Pediatrics

University of Cyprus
Medical School

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Advancement of Treatments FOR RARE DISEASES

1. Rare paediatric endocrine disorders
2. Novel therapeutic management
3. Future perspectives
4. Concluding remarks

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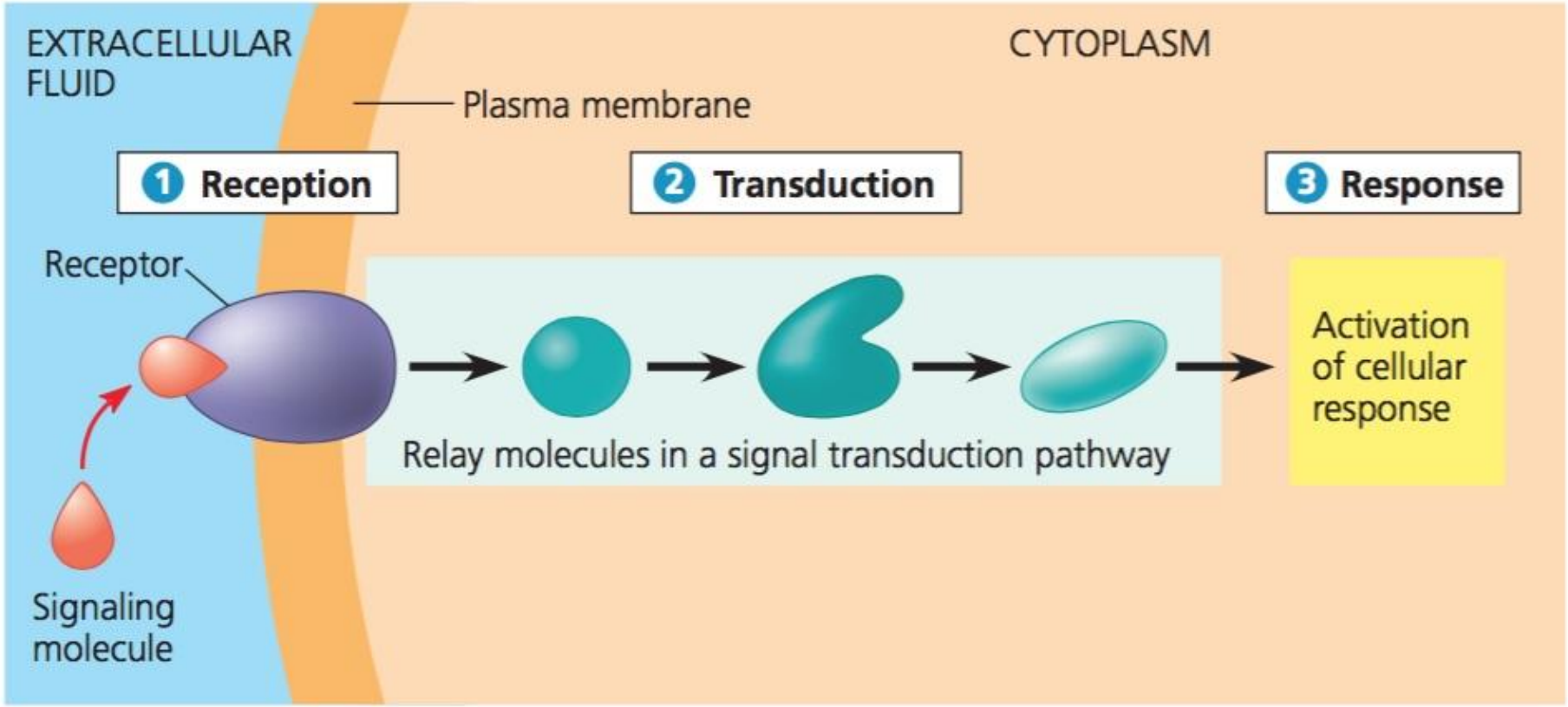
Doctor of Medicine MD (Hons)
Valedictorian of the class
University of Patras Medical School
Grade: 8,37/10

“Doctors need to understand one thing: put down the surgical scissors and delve into molecular medicine.”

- Athanasios G. Papavassiliou
Professor of Biochemistry
University of Athens

"Signalopathies"



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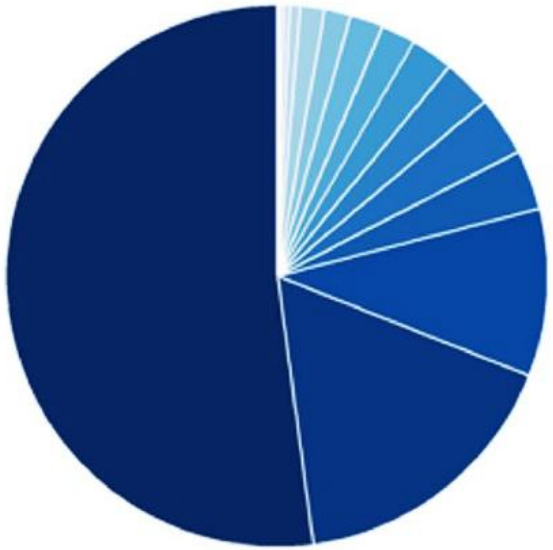
The changing landscape of Paediatric Endocrinology

- The landscape of paediatric endocrinology has changed considerably over the last decade
- The advances in genetics have resulted in a wave of molecular research in Paediatric Endocrinology
- Better understanding of genetic causes and the molecular basis of endocrine conditions
- Identification of molecular targets for treatment of paediatric endocrine disorders
- Development of therapies for rare paediatric endocrine disorders

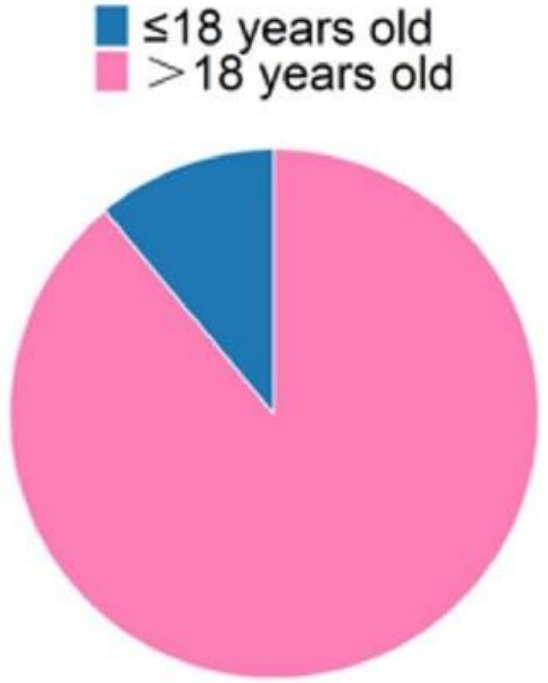
Gevers EF and de Winter JP. *Eur J Pediatr.* 2023; 182(4): 1439-1443

Rare paediatric endocrine disorders



Orphanet classification

- Rare neurologic disease
- Rare systemic and rheumatologic disease
- Rare neoplastic disease
- Rare respiratory disease
- Rare eye disease
- Rare hematologic disease
- Inborn errors of metabolism
- Rare circulatory system disease
- Rare gastroenterologic disease
- Rare hepatic disease
- Rare cardiac disease
- Rare renal disease
- Rare developmental defect during embryogenesis
- Rare bone disease
- Rare skin disease
- Rare endocrine disease
- Rare immune disease



Li MJ *et al. Orphanet J Rare Dis.* 2025; 20(1): 410

Advancement of Treatments FOR RARE DISEASES

Endo-ERN Main Thematic Groups (MTGs)

MTG1 Adrenal

MTG2 Disorders of Calcium & Phosphate Homeostasis

MTG3 Genetic disorders of Glucose & Insulin Homeostasis

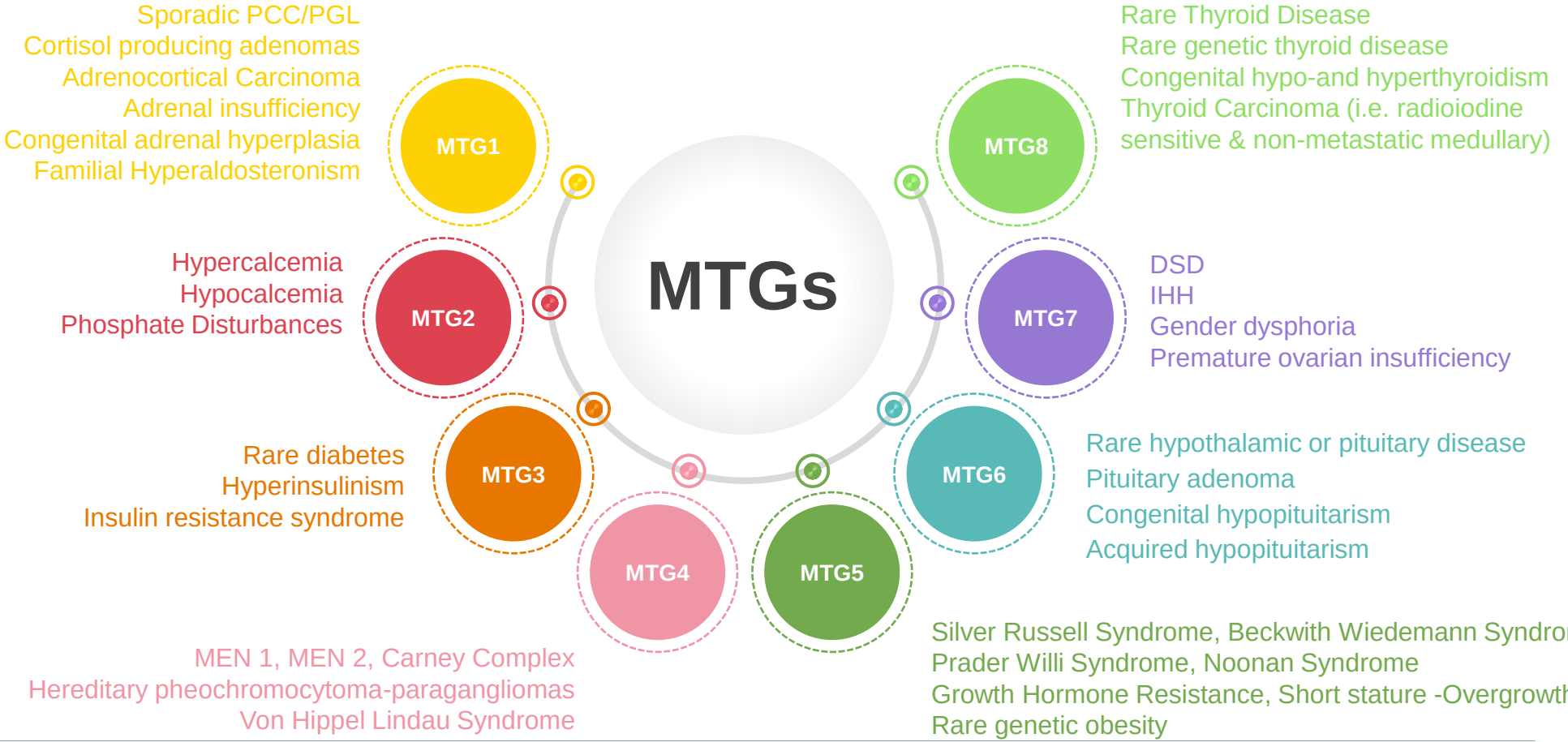
MTG4 Genetic Endocrine Tumour Syndromes

MTG5 Growth & Genetic Obesity Syndromes

MTG6 Hypothalamic and Pituitary Conditions

MTG7 Sex Development & Maturation

MTG8 Thyroid



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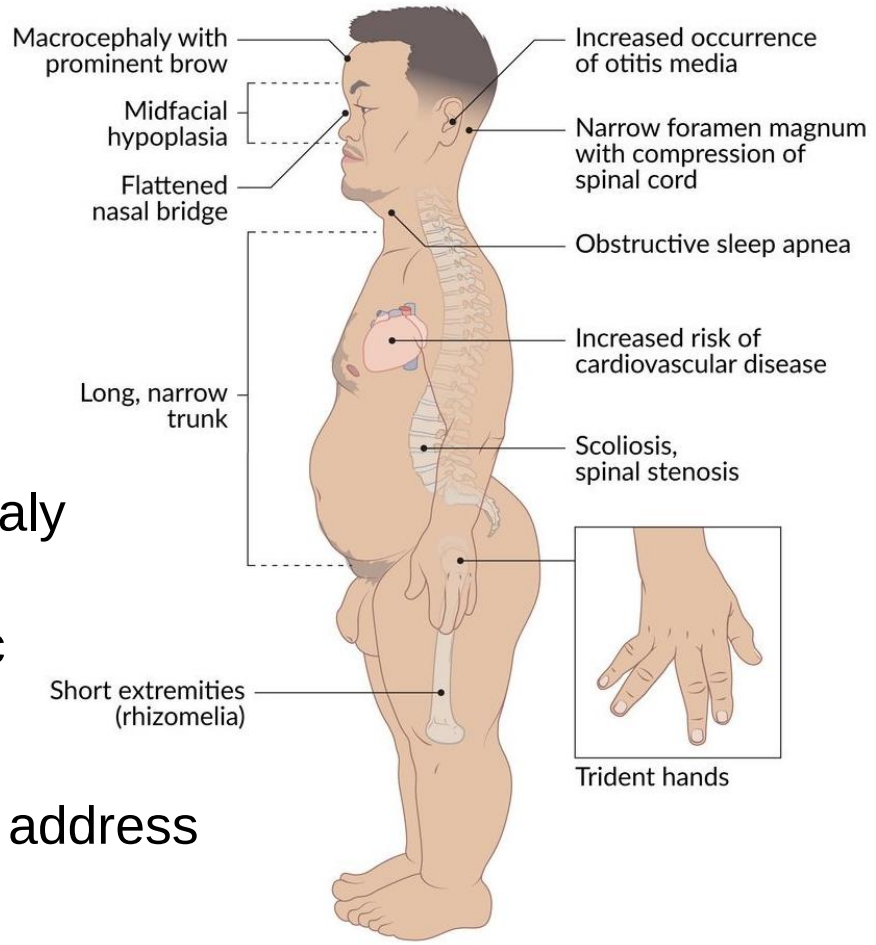
Achondroplasia

- Impaired longitudinal bone growth that results in disproportionate short stature
- The most common skeletal dysplasia (1:15 000 - 1:40 000 in US)
- Disproportionate short stature, rhizomelic shortening, macrocephaly
- The diagnosis is based upon clinical manifestations, radiographic findings, and genetic testing results
- The recommendations of the International Consensus Statement address optimal management across diverse medical specialty areas



Alves I *et al. Orphanet J Rare Dis.* 2026; 21(1): 34; Savarirayan R *et al. Nat Rev Endocrinol.* 2025; 21(5): 314-324

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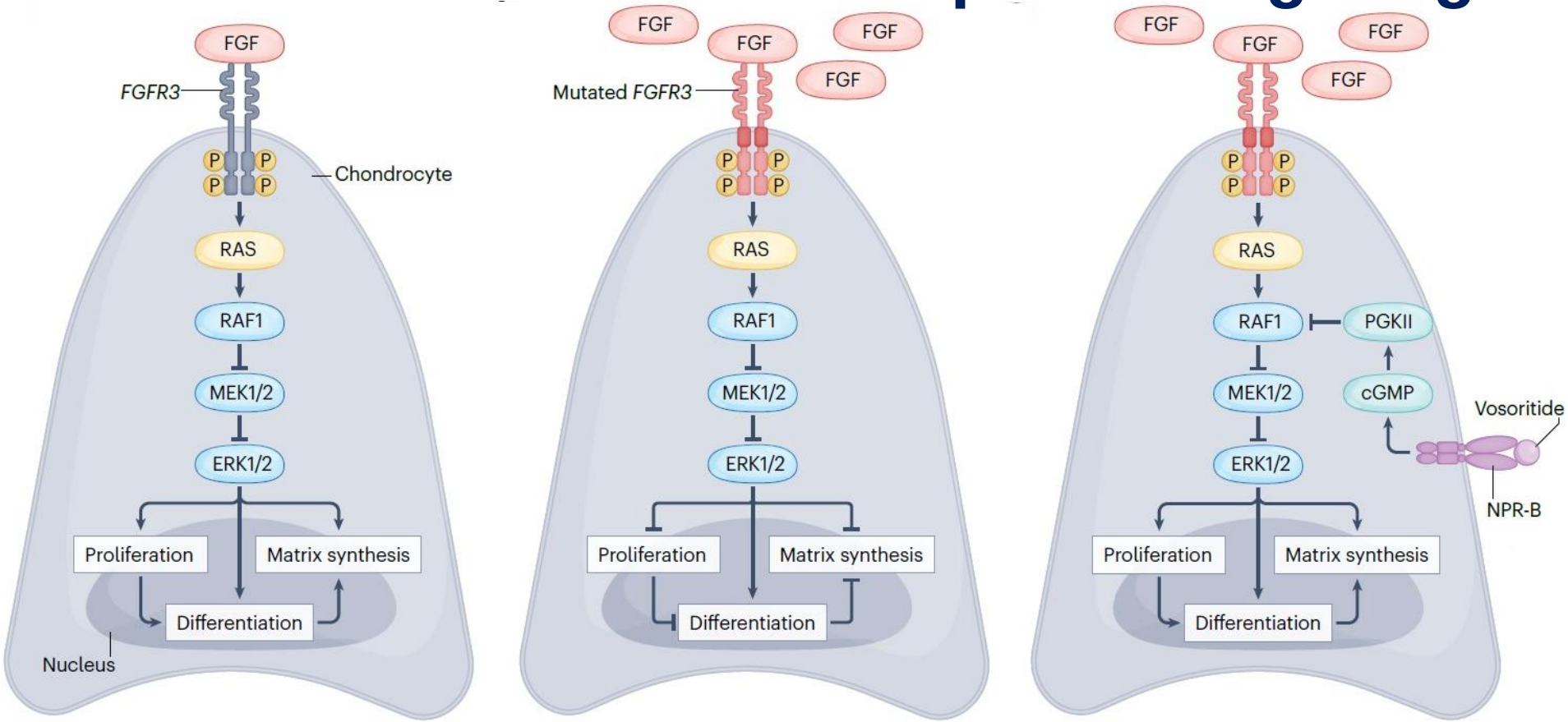
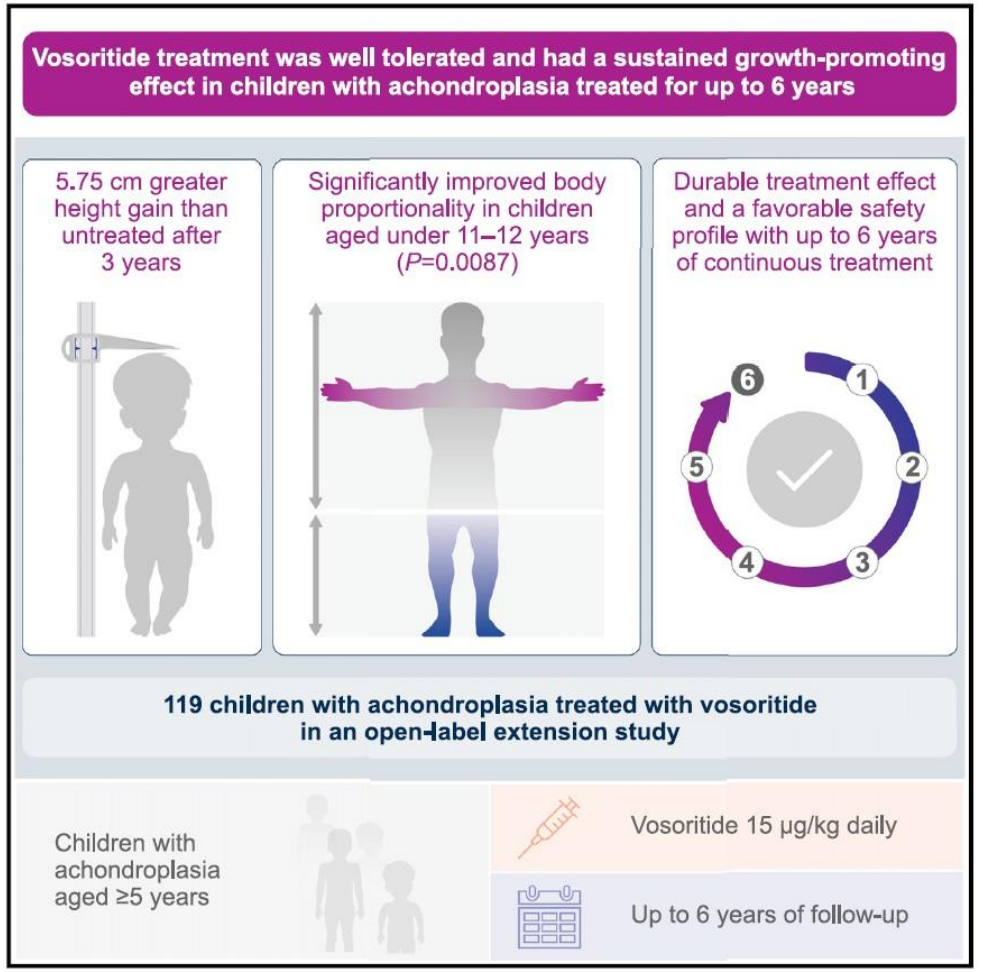
Molecular basis and therapeutic targeting



Savarirayan R *et al. Nat Rev Endocrinol.* 2025; 21(5): 314-324

Vosoritide

- Vosoritide: recombinant C-type natriuretic peptide analog that stimulates endochondral ossification
- Approved by the FDA to promote linear growth in children with achondroplasia whose epiphyses are still open
- In a phase 2 study, treatment resulted in an increase in the annualized growth velocity for up to 42 months *(NEJM 2019)*
- In a phase 3 study, patients showed a greater increase in mean annualized growth velocity up to 52 weeks *(Lancet 2020)*
- The least-squares mean difference for change from baseline in height Z score was 0·25 *(Lancet Child Adolesc 2024)*



Savarirayan R *et al. Med.* 2025; 6(5): 100566

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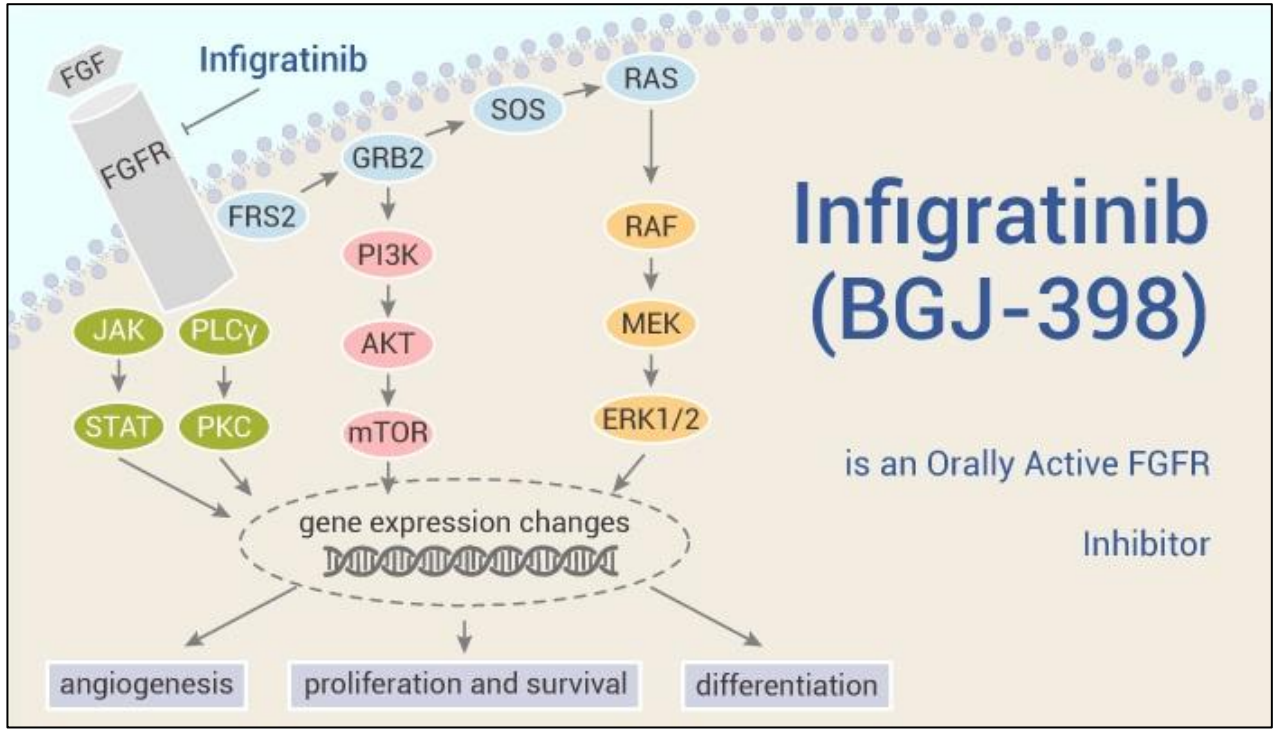
Infigratinib

FGFR1–3 selective tyrosine kinase inhibitor



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Infigratinib Therapy in Children with Achondroplasia

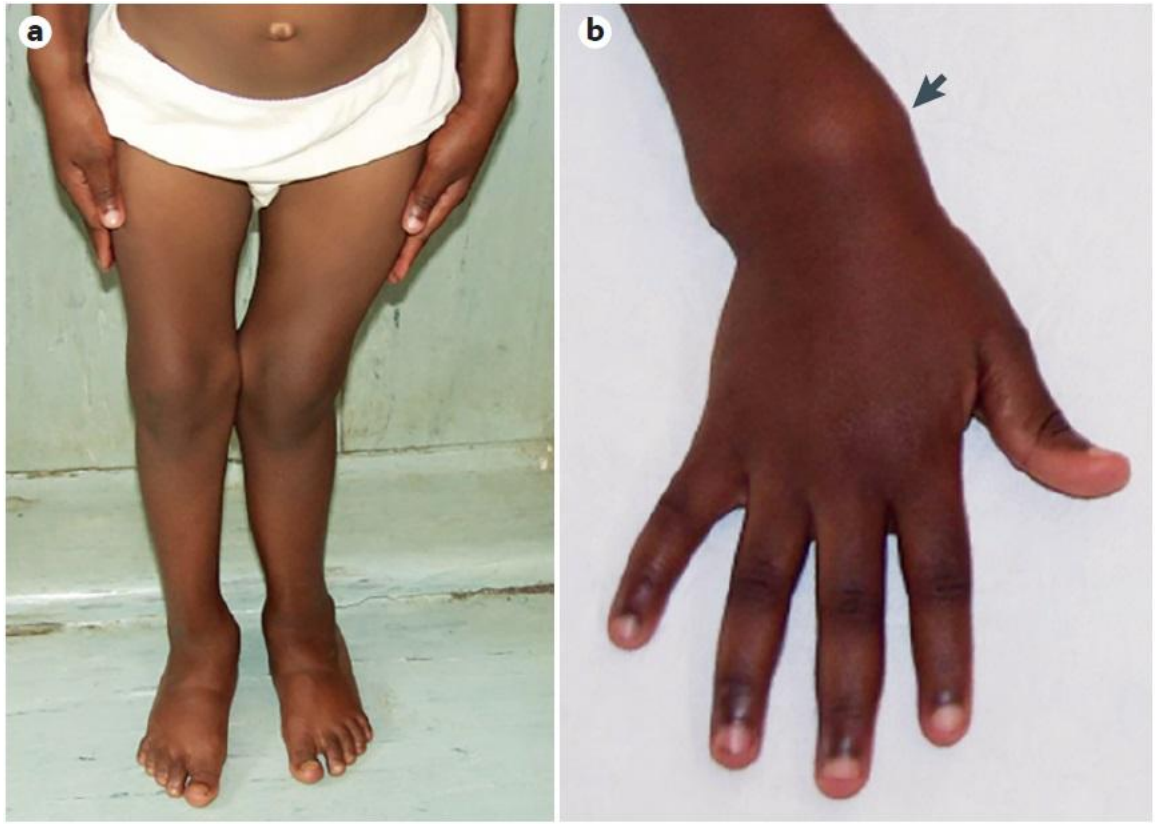
R. Savarirayan,[1] J.M. De Bergua,[2] P. Arundel,[3] J.P. Salles,[4] V. Saraff,[5] B. Delgado,[6] A. Leiva-Gea,[6] H. McDevitt,[7] M. Nicolino,[8] M. Rossi,[8] M. Salcedo,[9] V. Cormier-Daire,[10] M. Skae,[11] P. Kannu,[12] J. Phillips III,[13] H. Saal,[14] P. Harmatz,[15] T. Candler,[16] D. Hill,[17] E. Muslimova,[17] R. Weng,[17] Y. Bai,[17] S. Raj,[1]

CONCLUSIONS

The administration of oral infigratinib did not result in any apparent major safety signal and increased the annualized height velocity and z score and decreased the upper-to-lower body segment ratio at 18 months of treatment in cohort 5. (Funded by BridgeBio Pharma; PROPEL2 ClinicalTrials.gov number, NCT04265651.)

Savarirayan R *et al. N Engl J Med.* 2025; 392(9): 865-874

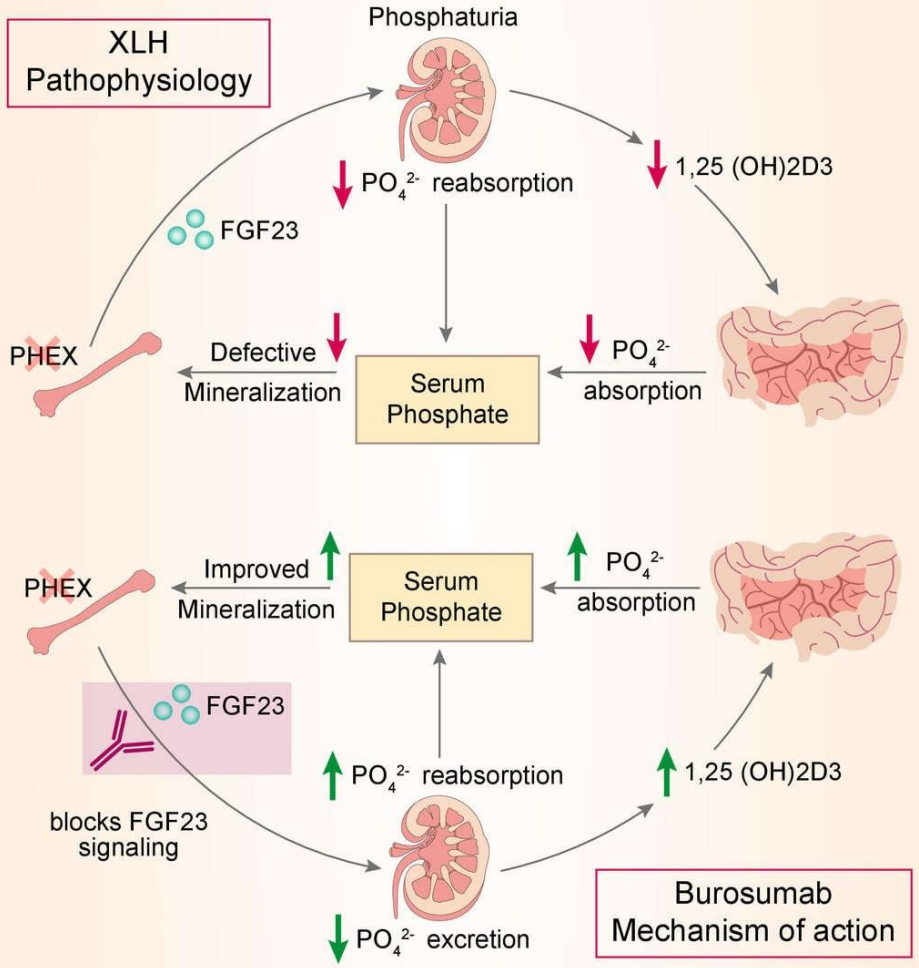
X-linked hypophosphataemic rickets



- Inherited disease of phosphate metabolism
- Inactivating mutations of the Phosphate Regulating Endopeptidase Homolog (*PHEX*), X-linked
- 1:20 000 individuals
- Impaired growth, rickets, osteomalacia, bone pain, hearing difficulties, enthesopathy and osteoarthritis
- Treatment of XLH with phosphate and vitamin D supplementation leads to increased FGF23 levels

Carpenter TO *et al. Nat Rev Dis Primers.* 2017; 3: 17101

Beck-Nielsen SS *et al. Orphanet J Rare Dis.* 2019; 14(1): 58



Burosumab

- Investigational recombinant fully human monoclonal IgG1κ antibody against the FGF23
- First approved in European Union on February 19, 2018
  Approved by the FDA in patients aged 1 year and older
- Subcutaneously every two weeks
- Subjects treated with burosumab were more likely to achieve substantial healing of rickets compared with phosphate and calcitriol therapy
- Side effects: injection site reactions, dental abscesses and caries

Brandi ML *et al. Orphanet J Rare Dis.* 2025; 20(1): 505

Hypoparathyroidism

The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 2810–2817
https://doi.org/10.1210/clinem/dgaf065
Advance access publication 30 January 2025
Clinical Research Article

Bone Health and Linear Growth in Children With Familial Hypoparathyroidism Treated With Human Parathyroid Hormone 1-34

Karen K. Winer,[1,2] Babette S. Zemel,[3] Andrea Kelly,[4] James C. Reynolds,[5] Taura Webb,[2] Didier Hans,[6] Michail S. Lionakis,[2] and Heidi J. Kalkwarf[7]

Abstract

Context: Our study explores the impact of human parathyroid hormone (PTH) 1-34 injections (PTH therapy) on growth, areal bone mineral density (BMD), and bone quality (measured by trabecular bone score, TBS) in hypoparathyroidism due to autoimmune polyendocrine syndrome type 1 (APS-1) or an activating variant of the calcium sensing receptor (CaR).

Objective: To assess associations of (1) age and PTH therapy duration with age-standardized Z-scores for height (HAZ), BMD (BMD-Z), and TBS (TBS-Z) in CaR or APS-1, and (2) APS-1 disease severity with BMD-Z and TBS-Z.

Methods: This secondary analysis pooled linear growth and lumbar spine (LS) dual-energy x-ray absorptiometry data from studies of hypoparathyroidism with mean baseline age of 13.7 ± 5.5 years. Comparing the 2 diagnostic etiologies (18 APS-1 and 9 CaR), we examined the impact of age and PTH duration on HAZ, LS-BMD-Z, and LS-TBS-Z using longitudinal mixed-effects modeling.

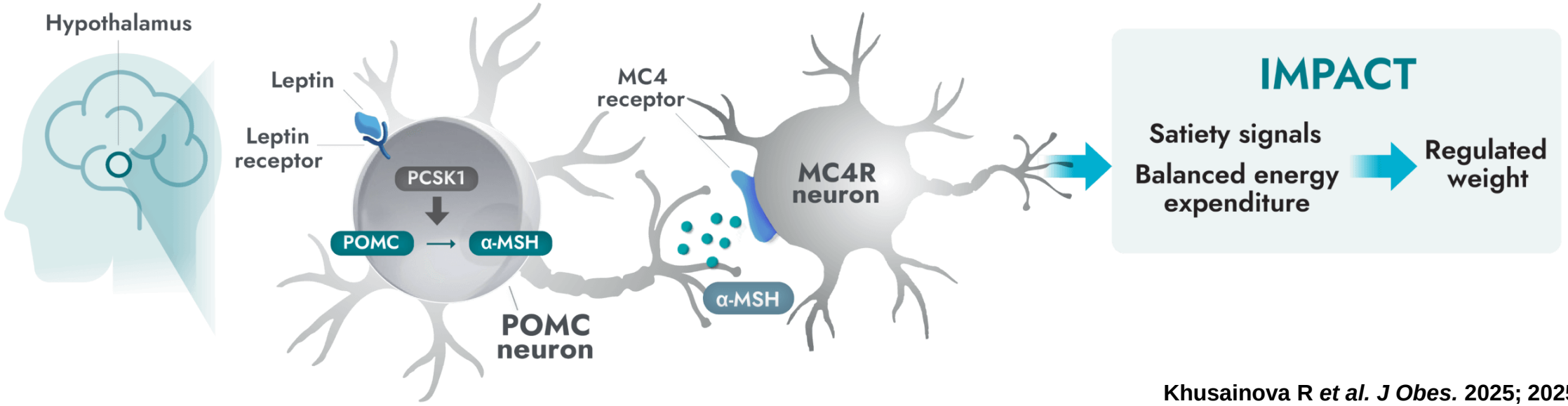
Results: During PTH therapy, mean HAZ remained below 0 in the APS-1 group at all ages, whereas HAZ increased in the CaR group (age by group interaction $P < .0001$). Mean LS-BMD-Z were normal (BMD-Z: 0 ± 1) for both groups. Mean LS-TBS-Z were near or above 0 and differed by group; CaR showed an upward trajectory according to time on PTH whereas the APS-1 group maintained a LS-TBS-Z of approximately 0 (time by group interaction $P = .02$). The APS-1 group with greater disease severity (≥7 manifestations) had lower LS-BMD-Z and LS-TBS-Z than the less severe APS-1 or CaR groups.

Conclusion: Our study highlights distinct growth and BMD patterns in APS-1 and CaR and underscores the need for careful monitoring and tailored treatment strategies to optimize growth and bone health.

Winer KK *et al. J Clin Endocrinol Metab.* 2025; 110(10): 2810-2817

Monogenic obesity

- A very rare, genetically determined form of extreme obesity in early childhood (less than 5 years). BMI > 99.5kg/m^2 of the age- and sex-specific percentiles
- Causative variants in the five genes *MC4R*, *LEP*, *LEPR*, *PCSK1*, and *POMC*.
  MC4R gene (autosomal dominant inheritance)



Khusainova R *et al. J Obes.* 2025; 2025: 9186826

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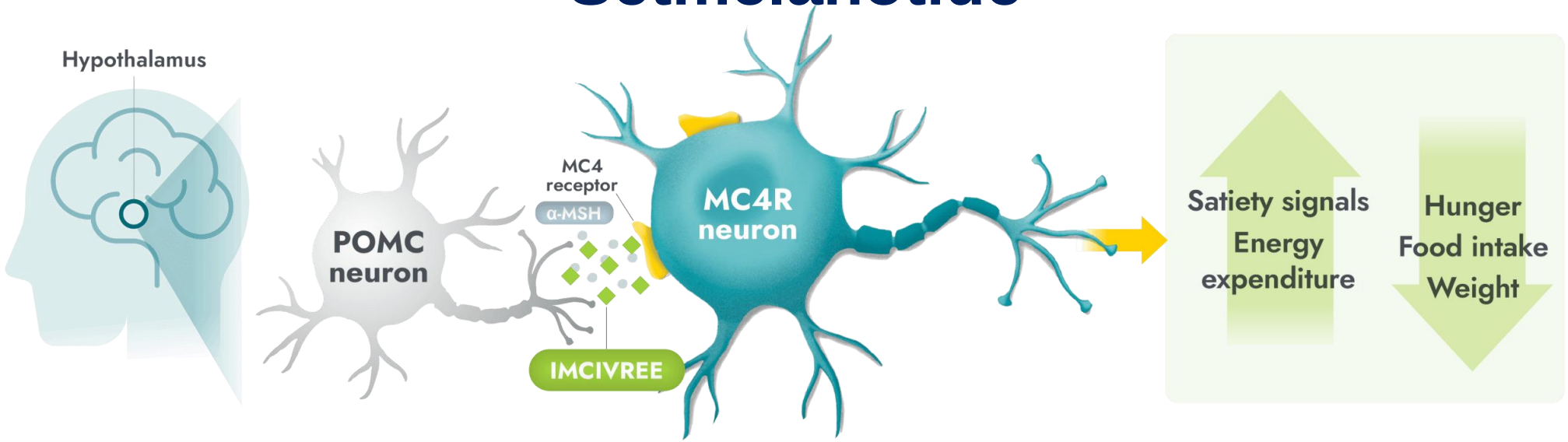
Setmelanotide



- MC4R agonist that can effectively “rescue” downstream signaling, even without upstream LEPR, PCSK1, or POMC activity
- The therapeutic goals of setmelanotide for treating obesity linked to POMC, PCSK1, or LEPR deficiencies and BBS include weight stabilization, hyperphagia control and quality of life improvement

Collet TH and Schwitzgebel V. *Front Nutr.* 2024; 11: 1509994

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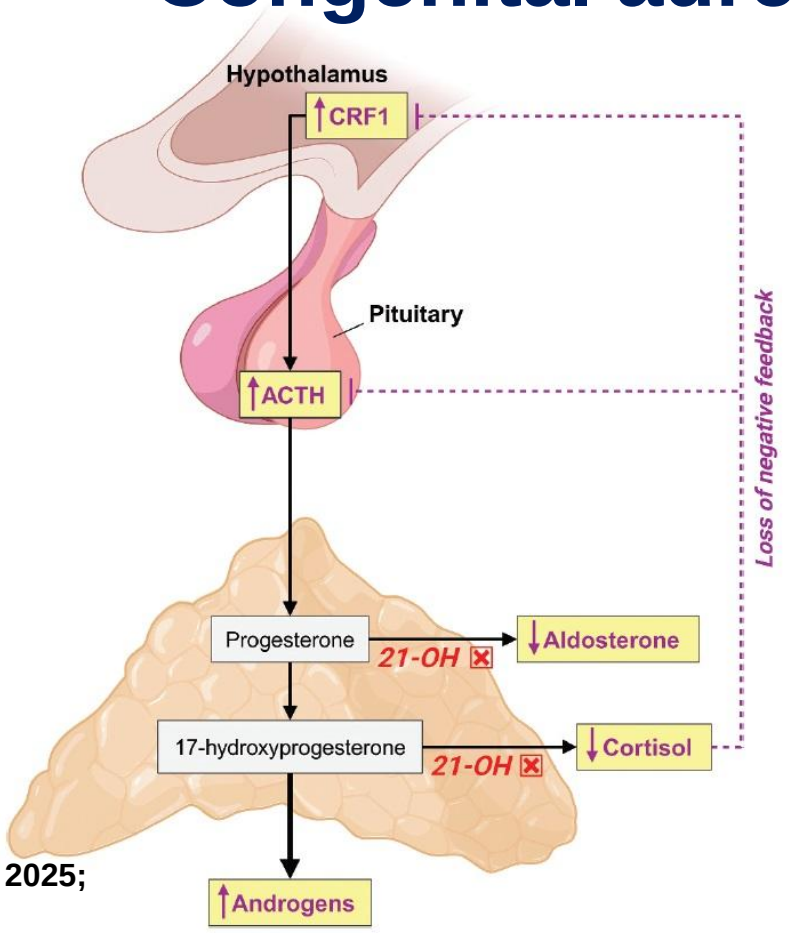
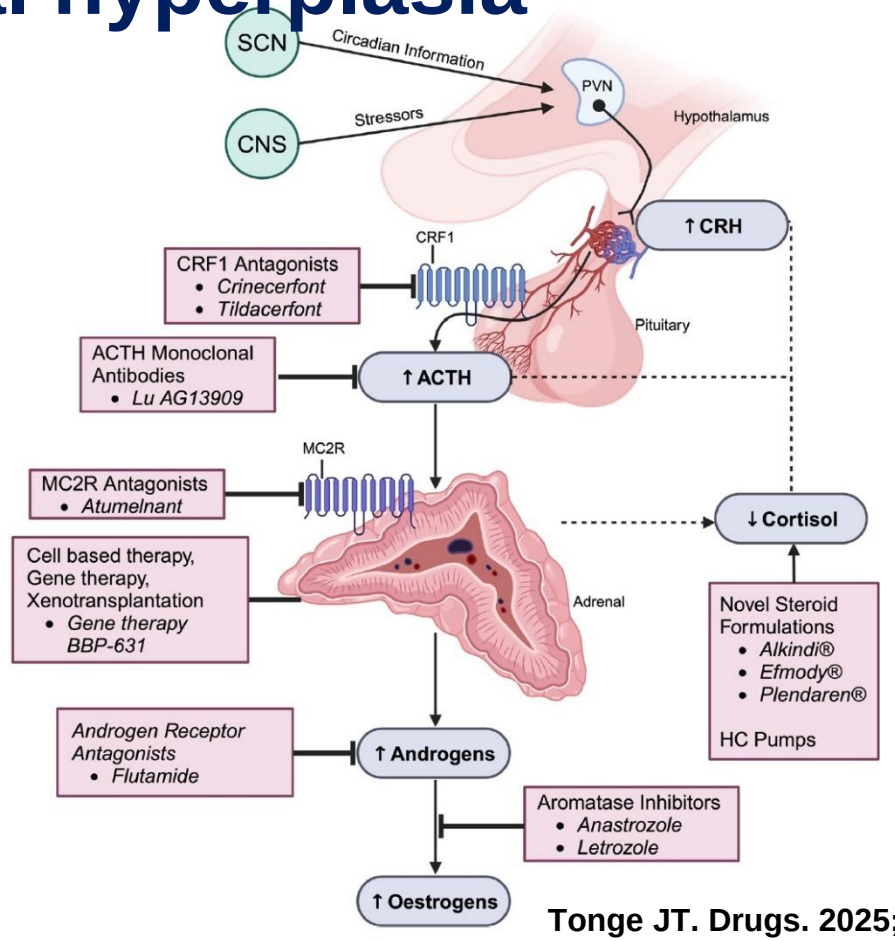
Congenital adrenal hyperplasia

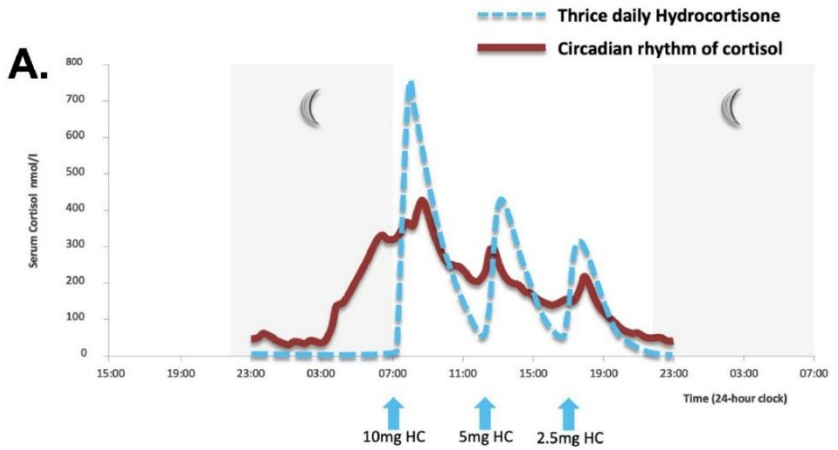


Bancos I *et al.*
Expert Rev Endocrinol Metab. 2025;
20(1): 33-49

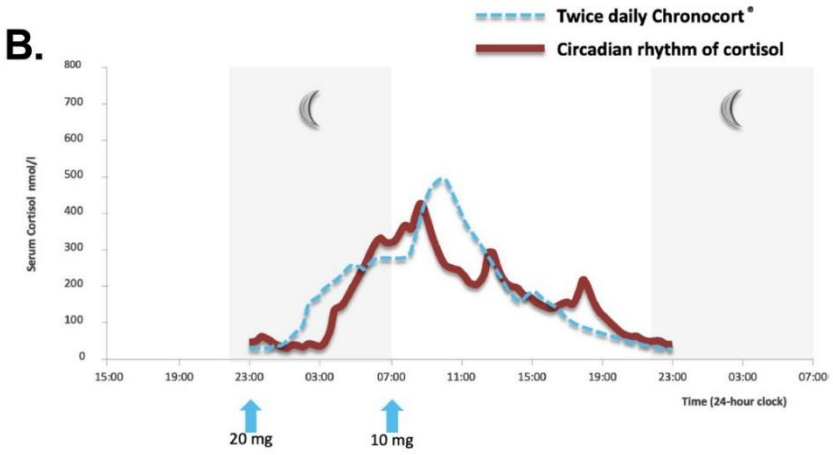


Tonge JT. Drugs. 2025; 85(12): 1551-1563

Hydrocortisone

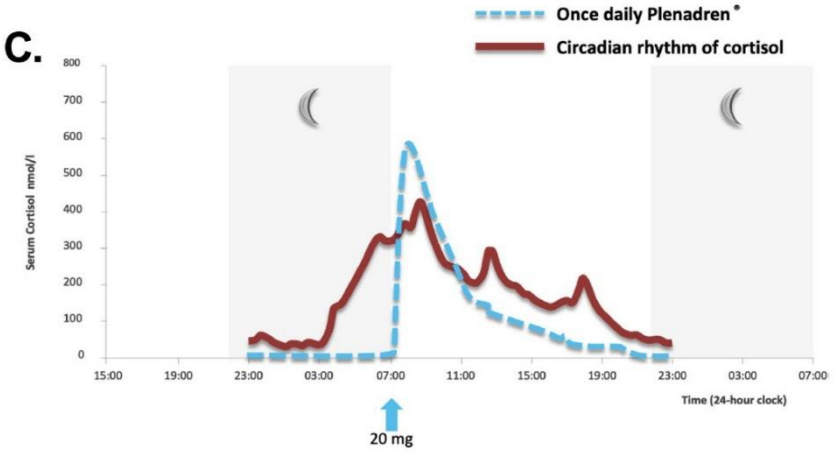


Chronocort ®



C

Plenadren ®



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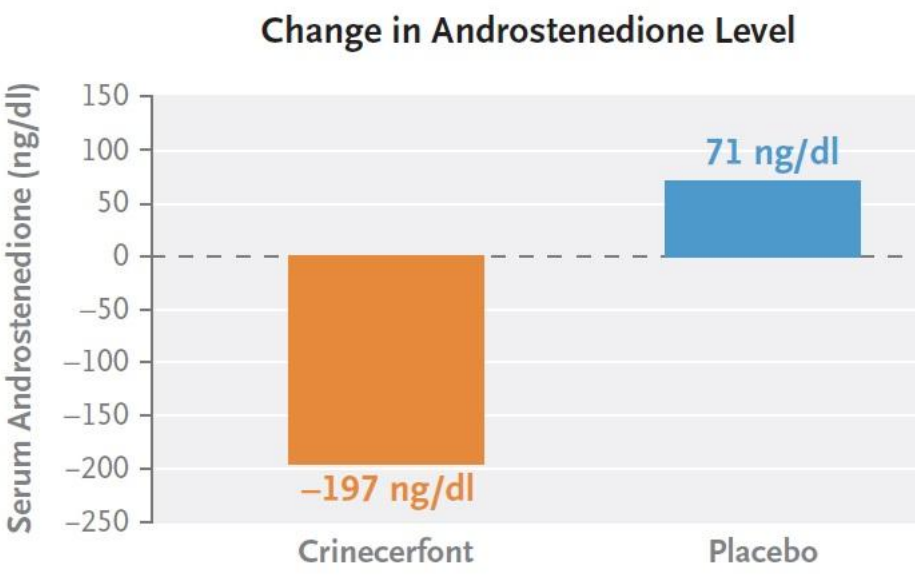
CRH antagonists - Crinecerfont

WHO	103 children Mean age, 12.1 years
CLINICAL STATUS	Total glucocorticoid dose of more than 12 mg/m² per day (in hydrocortisone equivalents) Androstenedione level greater than the midpoint of the reference range 17-hydroxyprogesterone level more than two times the upper limit of normal No other condition requiring long-term glucocorticoid therapy



The most common adverse events overall were headache, pyrexia, and vomiting

Sarafoglou K *et al. N Engl J Med.* 2024; 391(6): 493-503

Future perspectives

1. Gene therapy using a viral vector
2. Small interfering ribonucleic acid (siRNA)
3. Antisense oligonucleotides (ASO)

Baylot V *et al. Commun Biol.* 2024; 7(1): 489

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Conclusions

- The landscape of paediatric endocrinology has changed considerably over the last decade
- The tremendous progress in genetics and biology have resulted in a wave of molecular research in Paediatric Endocrinology
- Endo-ERN has provided access to clinical experts for patients with rare endocrine conditions and the opportunity to collaborate at the clinical and translational research level
- Achondroplasia, X-Linked Hypophosphataemic rickets, Hypoparathyroidism, Monogenic Obesity and Congenital Adrenal Hyperplasia
- “The future holds promises” through the application of novel molecular biology methods in clinical practice

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