ΕΝΔΟΡΑΜΑ ’14

ΠΑΙΔΟΕΝΔΟΚΡΙΝΟΛΟΓΙΑ

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1. ΑΥΞΗΣΗ ΚΑΙ ΑΥΞΗΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

Mechanism of activation of protein kinase JAK2 by the growth hormone receptor.

Brooks AJ, Dai W, O'Mara ML, Abankwa D, Chhabra Y, Pelekanos RA, Gardon O, Tunny KA, Blucher KM, Morton CJ, Parker MW, Sierecki E, Gambin Y, Gomez GA, Alexandrov K, Wilson IA, Doxastakis M, Mark AE, Waters MJ.

Science. 2014; 344(6185): 1249783.

Abstract: Signaling from JAK (Janus kinase) protein kinases to STAT (signal transducers and activators of transcription) transcription factors is key to many aspects of biology and medicine, yet the mechanism by which cytokine receptors initiate signaling is enigmatic. We present a complete mechanistic model for activation of receptor-bound JAK2, based on an archetypal cytokine receptor, the growth hormone receptor. For this, we used fluorescence resonance energy transfer to monitor positioning of the JAK2 binding motif in the receptor dimer, substitution of the receptor extracellular domains with Jun zippers to control the position of its transmembrane (TM) helices, atomistic modeling of TM helix movements, and docking of the crystal structures of the JAK2 kinase and its inhibitory pseudokinase domain with an opposing kinase-pseudokinase domain pair. Activation of the receptor dimer induced a separation of its JAK2 binding motifs, driven by a ligand-induced transition from a parallel TM helix pair to a left-handed crossover arrangement. This separation leads to removal of the pseudokinase domain from the kinase domain of the partner JAK2 and pairing of the two kinase domains, facilitating trans-activation. This model may well generalize to other class I cytokine receptors.

24-month use of once-weekly GH, LB03002, in prepubertal children with GH deficiency.

Khadilkar V, Radjuk KA, Bolshova E, Khadgawat R, El Kholy M, Desai M, Peterkova V, Mericq V, Kratzsch J, Siepl EC, Martin D, Lopez P, Ji HJ, Bae YJ, Lee JH, Saenger PH.

J Clin Endocrinol Metab. 2014; 99(1): 126-32.

Background: Sustained-release GH formulations may provide a strategy for improving treatment compliance and persistence in GH-deficient patients.

Objective: The aim of the study was to examine efficacy and safety of LB03002, a sustained-release GH formulation for once-weekly administration.

Design: We conducted a phase III, 12-month, multinational, randomized, open-label, comparator-controlled trial with a 12-month uncontrolled extension.

Patients: Prepubertal GH treatment-naive GH-deficient children (mean age, 7.8 y) participated in the study.

Intervention: We administered once-weekly LB03002 (n=91) or daily GH (n=87) for 1 year, followed by once-weekly LB03002 for all patients for another year (LB03002 throughout, n=87; switched to LB03002, n=80).

Outcome Measures: Height, height velocity (HV), IGF-1, GH antibodies, and adverse events were determined throughout. Primary analysis was noninferiority of LB03002 *vs.* daily GH at 1 year by analysis of covariance.

Results: Mean±SD HV during year 1 was 11.63±2.60 cm/y with LB03002, and 11.97±3.09 cm/y with daily GH, with increases from baseline of 8.94±2.91 and 9.04±3.19 cm/y, respectively. The least square mean HV difference for LB03002 - daily GH was -0.43 cm/y (99% confidence interval, -1.45 to 0.60 cm/y). Mean HV also remained above baseline in year 2 (8.33±1.92 cm/y in the LB03002 throughout group, and 7.28±2.34 cm/y in the switched to LB03002 group). Injection site reactions occurred more frequently in LB03002-treated patients but were considered mild to moderate in >90% of cases.

Conclusions: Growth response with once-weekly LB03002 in GH-deficient children is comparable to that with daily GH, achieving expected growth rates for 24 months. Once-weekly LB03002 is a strong candidate for long-term GH replacement in GH-deficient children.

2. ΘΥΡΕΟΕΙΔΗΣ

European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism.

Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G; ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE; Congenital Hypothyroidism Consensus Conference Group.

J Clin Endocrinol Metab. 2014; 99(2): 363-84.

Objective: The aim was to formulate practice guidelines for the diagnosis and management of congenital hypothyroidism (CH).

Evidence: A systematic literature search was conducted to identify key articles relating to the screening, diagnosis, and management of CH. The evidence-based guidelines were developed with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, describing both the strength of recommendations and the quality of evidence. In the absence of sufficient evidence, conclusions were based on expert opinion.

Consensus Process: Thirty-two participants drawn from the European Society for Paediatric Endocrinology and five other major scientific societies in the field of pediatric endocrinology were allocated to working groups with assigned topics and specific questions. Each group searched the literature, evaluated the evidence, and developed a draft document. These papers were debated and finalized by each group before presentation to the full assembly for further discussion and agreement.

Recommendations: The recommendations include: worldwide neonatal screening, approaches to assess the cause (including genotyping) and the severity of the disorder, the immediate initiation of appropriate L-T4 supplementation and frequent monitoring to ensure dose adjustments to keep thyroid hormone levels in the target ranges, a trial of treatment in patients suspected of transient CH, regular assessments of developmental and neurosensory functions, consulting health professionals as appropriate, and education about CH. The harmonization of diagnosis, management, and routine health surveillance would not only optimize patient outcomes, but should also facilitate epidemiological studies of the disorder.

Individuals with CH require monitoring throughout their lives, particularly during early childhood and pregnancy.

Direct iodine supplementation of infants versus supplementation of their breastfeeding mothers: a double-blind, randomised, placebo-controlled trial.

Bouhouch RR, Bouhouch S, Cherkaoui M, Aboussad A, Stinca S, Haldimann M, Andersson M, Zimmermann MB.

Lancet Diabetes Endocrinol. 2014; 2(3): 197-209.

Background: Iodine deficiency in infants can damage the developing brain and increase mortality. Present recommendations state that oral iodised oil should be given to breastfeeding mothers to correct iodine deficiency in infancy when iodised salt is not available, and that direct supplementation should be given to infants who are not being breastfed or receiving iodine-fortified complimentary foods. However, there is little evidence for these recommendations. We aimed to assess the safety and efficacy of direct versus indirect supplementation of the infant.

Methods: We did this double blind, randomised, placebo-controlled trial in Morocco. Healthy breastfeeding mothers and their term newborn babies (aged ≤8 weeks) were block randomised by clinic day to receive either: one dose of 400 mg iodine to the mother and placebo to the infant (indirect infant supplementation), or one dose of about 100 mg iodine to the infant and placebo to the mother (direct infant supplementation). Randomisation was masked to participants and investigators. Coprimary outcomes were: maternal and infant urinary iodine concentrations, breastmilk iodine concentration, maternal and infant thyroid-stimulating hormone (TSH) concentrations, maternal and infant thyroxine (T4) concentrations, and infant growth. These outcomes were measured at baseline, and when infants were aged about 3 months, 6 months, and 9 months, and the two groups were compared using mixed effects models. This study is registered with ClinicalTrials.gov, number NCT01126125.

Findings: We recruited 241 mother-infant pairs between Feb 25, and Aug 10, 2010, and completed data collection by Aug 6, 2011. At baseline, median urinary iodine concentration was 35 μg/L (IQR 29-40) in mothers and 73 μg/L (29-237) in infants, suggesting iodine deficiency. During the study, maternal urinary iodine concentration (p=0.011), breastmilk iodine concentration (p<0.0001), and infant urinary iodine concentration (p=0.042) were higher in the indirect infant supplementation group than in the direct supplementation group. Maternal TSH (p=0.276) and T4 (p=0.074) concentrations did not differ between the groups over the course of the study, nor did infant TSH (p=0.597) and T4 (p=0.184) concentrations, but the number of infants with thyroid hypofunction was lower (p=0.023) in the indirect supplementation group than the direct supplementation group. The infant groups did not differ in anthropomorphic measures, except that length-for-age Z score was slightly greater in the direct infant supplementation group (p=0.032). At 3 months and 6 months of age, median infant urinary iodine concentration in the indirect infant supplementation group was sufficient (>100 μg/L), whereas infant urinary iodine concentration was sufficient only at 6 months in the direct supplementation group. There were no serious adverse events in either group.

Interpretation: In regions of moderate-to-severe iodine deficiency without effective salt iodisation, lactating women who receive one dose of 400 mg iodine as oral iodised oil soon after delivery can provide adequate iodine to their infants through breastmilk for at least 6 months, enabling the infants to achieve euthyroidism. Direct supplementation is less effective in improving infant iodine status.

3. ΕΠΙΝΕΦΡΙΔΙΑ

An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure.

Whitaker MJ, Debono M, Huatan H, Merke DP, Arlt W, Ross RJ.

Clin Endocrinol (Oxf). 2014; 80(4): 554-61

Objective: It is not possible with current hydrocortisone replacement to mimic the diurnal cortisol profile in patients with adrenal insufficiency. Previous attempts with modified-release technology were unsuccessful. Our objective was to develop hydrocortisone formulations that recreate the diurnal cortisol profile using multiparticulate technology.

Design and Measurements: Screening by *in vitro* dissolution profiles, pharmacokinetic (PK) testing in dexamethasone-suppressed dogs and humans, and comparison with a reference population.

Setting: Field laboratories and clinical research facility.

Results: Formulations were generated using an enteric (delayed release) design configuration with an extended (sustained release) dissolution profile. In vitro dissolution confirmed delayed and sustained hydrocortisone release. However, in dogs and humans, sustained release resulted in reduced bioavailability. A formulation, DIURF-006, was developed that maintained delayed release but omitted the sustained-release functionality. PK characterization of DIURF-006 showed that, despite absence of a sustained-release component, absorption was sufficiently sustained to deliver extended hydrocortisone absorption. In dexamethasone-suppressed volunteers (n = 16) receiving a twice-daily 'toothbrush' regimen (20 mg at 23:00 h and 10 mg at 07:00 h), DIURF-006 gave a similar cortisol profile to physiological cortisol levels: DIURF-006 *vs.* physiological, Geomean AUC 5610 *vs.* 4706 h * nmol/l, Geomean Cmax 665 *vs.* 594 nmol/l and Median Tmax 8·5 h *vs.* clock time 08:12 h for peak cortisol. The relative bioavailability of DIURF-006 *vs.* hydrocortisone was 89%, and cortisol levels increased linearly with doses between 5 and 30 mg.

Conclusion: A multiparticulate oral hydrocortisone formulation with only an enteric coat provides delayed and sustained absorption and when given in a 'toothbrush' regimen provides physiological cortisol exposure.

A Phase 2 Study of Chronocort®, a Modified-release Formulation of Hydrocortisone, in the Treatment of Adults with Classic Congenital Adrenal Hyperplasia.

Mallappa A, Sinaii N, Kumar P, Whitaker MJ, Daley LA, Digweed D, Eckland DJ, VanRyzin C, Nieman LK, Arlt W, Ross RJ, Merke DP.

J Clin Endocrinol Metab. 2014; [Epub ahead of print]

Context: Treatment of congenital adrenal hyperplasia (CAH) is suboptimal. Inadequate suppression of androgens and glucocorticoid excess are common and current glucocorticoid formulations cannot replace the cortisol circadian rhythm.

Objectives: The primary objective was to characterize the pharmacokinetic profile of Chronocort®, a modified-release hydrocortisone formulation, in adults with CAH. Secondary objectives included examining disease control following 6 months of Chronocort® with dose titration.

Design, Setting and Patients: Sixteen adults (8 females) with classic CAH participated in an open label, non-randomized, Phase 2 study at the National Institutes of Health Clinical Center. 24-hour blood sampling was performed on conventional glucocorticoids and

following 6 months of Chronocort®. Chronocort® was initiated at 10mg (0700h) and 20mg (2300h). Dose titration was performed based on androstenedione and 17-hydroxyprogresterone (17-OHP) levels and clinical symptomatology.

Main Outcome Measures: Cortisol pharmacokinetics of Chronocort® and biomarkers of CAH control (androstenedione and 17-OHP).

Results: In CAH patients, Chronocort® cortisol profiles were similar to physiologic cortisol secretion. Compared to conventional therapy, 6 months of Chronocort® resulted in a decrease in hydrocortisone dose equivalent (28 ± 11.8 *vs.* 25.9 ± 7.1mg/day), with lower 24-hour (P = 0.004), morning (0700h - 1500h; P = 0.002), and afternoon (1500h - 2300h; P = 0.011) androstenedione area under the curve (AUC) and lower 24-hour (P = 0.023) and morning (0700h - 1500h; P = 0.02) 17-OHP AUC.

Conclusions: Twice daily Chronocort® approximates physiologic cortisol secretion, and was well tolerated and effective in controlling androgen excess in adults with CAH. This novel hydrocortisone formulation represents a new treatment approach for patients with CAH.

Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial.

Oksnes M, Björnsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM, Broman JE, Triebner K, Kämpe O, Hulting AL, Bensing S, Husebye ES, Løvås K.

J Clin Endocrinol Metab. 2014; 99(5): 1665-74.

Context: Conventional glucocorticoid replacement therapy fails to mimic the physiological cortisol rhythm, which may have implications for morbidity and mortality in patients with Addison's disease.

Objective: The objective of the study was to compare the effects of continuous sc hydrocortisone infusion (CSHI) with conventional oral hydrocortisone (OHC) replacement therapy.

Design, Patients and Interventions: This was a prospective crossover, randomized, multicenter clinical trial comparing 3 months of treatment with thrice-daily OHC vs CSHI. From Norway and Sweden, 33 patients were enrolled from registries and clinics. All patients were assessed at baseline and after 8 and 12 weeks in each treatment arm.

Main Outcome Measures: The morning ACTH level was the primary outcome measure. Secondary outcome measures were effects on metabolism, health-related quality of life (HRQoL), sleep, and safety.

Results: CSHI yielded normalization of morning ACTH and cortisol levels, and 24-hour salivary cortisol curves resembled the normal circadian variation. Urinary concentrations of glucocorticoid metabolites displayed a normal pattern with CSHI but were clearly altered with OHC. Several HRQoL indices in the vitality domain improved over time with CSHI. No benefit was found for either treatments for any subjective (Pittsburgh Sleep Quality Index questionnaire) or objective (actigraphy) sleep parameters.

Conclusion: CSHI safely brought ACTH and cortisol toward normal circadian levels without adversely affecting glucocorticoid metabolism in the way that OHC did. Positive effects on HRQoL were noted with CSHI, indicating that physiological glucocorticoid replacement therapy may be beneficial and that CSHI might become a treatment option for patients poorly controlled on conventional therapy.

New management strategy of pregnancies at risk of congenital adrenal hyperplasia using fetal sex determination in maternal serum: French cohort of 258 cases (2002-2011).

Tardy-Guidollet V, Menassa R, Costa JM, David M, Bouvattier-Morel C, Baumann C, Houang M, Lorenzini F, Philip N, Odent S, Guichet A, Morel Y.

J Clin Endocrinol Metab. 2014; 99(4): 1180-8.

Context: Prenatal dexamethasone (DEX) treatment has been proposed since 1984 to prevent genital virilization in girls with congenital adrenal hyperplasia (CAH). DEX is effective in CAH females if initiated before the sixth week of gestation, but its safety in children treated in utero remains controversial regarding cognitive functions.

Objective: To avoid prenatal DEX in males and initiate DEX in due time in CAH females, we proposed in 2002 a protocol for fetal sex determination in the maternal serum (SRY test).

Design and Setting: We conducted a retrospective study of the management of 258 fetuses in the period 2002 through 2011 in pregnancies managed in referent medical centers with an institutional practice.

Patients: A total of 258 fetuses at risk of CAH (134 males and 124 females) were included.

Intervention: DEX was offered after informed consent to pregnant women.

Main Outcome Measure: The sensitivity of an early SRY test was evaluated after data collection.

Results: The SRY test is sensitive from 4 weeks and 5 days of gestation. It avoided prenatal DEX in 68% of males, and this percentage increased over the years. DEX was maintained until prenatal diagnosis in non-CAH females. Virilization was prevented in 12 CAH girls treated at the latest at 6 weeks gestation and minimized in 3 girls treated between 6 and 7 weeks gestation. Maternal tolerance was correct. No fetal malformations were noted in the 154 children treated in utero.

Conclusions: The SRY test is reliable to avoid prenatal DEX in males, but its application must be improved. Prenatal DEX should be maintained to prevent virilization and traumatic surgery in CAH girls after informed consent and information provided to families about the benefit to risk ratio in limiting hyperandrogenism during fetal life. Our large multicentric French cohort has helped to better assess the risks previously reported.

Noninvasive prenatal diagnosis of congenital adrenal hyperplasia using cell-free fetal DNA in maternal plasma.

New MI, Tong YK, Yuen T, Jiang P, Pina C, Chan KC, Khattab A, Liao GJ, Yau M, Kim SM, Chiu RW, Sun L, Zaidi M, Lo YM.

J Clin Endocrinol Metab. 2014; 99(6): E1022-30.

Context: Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition that arises from mutations in CYP21A2 gene, which encodes for the steroidogenic enzyme 21-hydroxylase. To prevent genital ambiguity in affected female fetuses, prenatal treatment with dexamethasone must begin on or before gestational week 9. Currently used chorionic villus sampling and amniocentesis provide genetic results at approximately 14 weeks of gestation at the earliest. This means that mothers who want to undergo prenatal dexamethasone treatment will be unnecessarily treating seven of eight fetuses (males and three of four unaffected females), emphasizing the desirability of earlier genetic diagnosis in utero.

Objective: The objective of the study was to develop a noninvasive method for early prenatal diagnosis of fetuses at risk for CAH.

Patients: Fourteen families, each with a proband affected by phenotypically classical CAH, were recruited.

Design: Cell-free fetal DNA was obtained from 3.6 mL of maternal plasma. Using hybridization probes designed to capture a 6-Mb region flanking CYP21A2, targeted massively parallel sequencing (MPS) was performed to analyze genomic DNA samples from parents and proband to determine parental haplotypes. Plasma DNA from pregnant mothers also underwent targeted MPS to deduce fetal inheritance of parental haplotypes.

Results: In all 14 families, the fetal CAH status was correctly deduced by targeted MPS of DNA in maternal plasma, as early as 5 weeks 6 days of gestation.

Conclusions: MPS on 3.6 mL plasma from pregnant mothers could potentially provide the diagnosis of CAH, noninvasively, before the ninth week of gestation. Only affected female fetuses will thus be treated. Our strategy represents a generic approach for noninvasive prenatal testing for an array of autosomal recessive disorders.

Treatment and health outcomes in adults with congenital adrenal hyperplasia.

Han TS, Walker BR, Arlt W, Ross RJ.

Nat Rev Endocrinol. 2014; 10(2): 115-24.

Abstract: Congenital adrenal hyperplasia (CAH) is a genetic disorder caused by defective steroidogenesis that results in glucocorticoid deficiency; the most common underlying mutation is in the gene that encodes 21-hydroxylase. Life-saving glucocorticoid treatment was introduced in the 1950s, and the number of adult patients is now growing; however, no consensus has been reached on the management of CAH beyond childhood. Adult patients are prescribed a variety of glucocorticoids, including hydrocortisone, prednisone, prednisolone, dexamethasone and combinations of these drugs taken in either a circadian or reverse circadian regimen. Despite these personalized treatments, biochemical control of CAH is only achieved in approximately one-third of patients. Some patients have a poor health status, with an increased incidence of obesity and osteoporosis, and impaired fertility and quality of life. The majority of poor health outcomes seem to relate to inadequate treatment rather than the genotype of the patient. Patients receiving high doses of glucocorticoids and the more potent synthetic long-acting glucocorticoids are at an increased risk of obesity, insulin resistance and a reduced quality of life. Further research is required to optimize the treatment of adult patients with CAH and improve health outcomes.

The 'omics' of adrenocortical tumours for personalized medicine.

Assié G, Jouinot A, Bertherat J.

Nat Rev Endocrinol. 2014; 10(4): 215-28.

Abstract: Pan-genomic analyses of genetic and epigenetic alterations and gene expression profiles are providing important new insights into the pathogenesis and molecular classification of cancers. The technologies and methods used for these studies are rapidly diversifying and improving. The use of such methodologies for the analysis of adrenocortical tumours has revealed clear transcriptomic (mRNA and microRNA expression profiles), epigenomic (DNA methylation profiles) and genomic (DNA mutations and chromosomal alterations) differences between benign and malignant tumours. Interestingly, genomic studies of adrenal cancers have also identified subtypes of malignant tumours, which demonstrate distinct patterns of molecular alterations and are associated with different clinical outcomes. These discoveries have created the opportunity for classifying adrenocortical tumours on the

basis of molecular analyses. Following these genomic studies, efforts to develop new molecular tools that improve diagnosis and prognostication of patients with adrenocortical tumours have also been made. This Review describes the progress that has been made towards classification of adrenocortical tumours to date based on key genomic approaches. In addition, the potential for the development and use of various molecular tools to personalize the management of patients with adrenocortical tumours is discussed.

4. ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ ΑΝΑΠΑΡΑΓΩΓΗΣ

Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades.

Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y.

Clin Endocrinol (Oxf). 2014; 80(4): 570-6.

Context: Central precocious puberty (CPP), treated or untreated, may have implications in adulthood.

Objective: To assess the reproductive outcome and social adjustment of former CPP women between the 3rd and 5th decades of life.

Design: Cross-sectional study of an historical cohort.

Methods: Demographic data and gynaecological history of 214 CPP women aged 25-56 years [135 GnRH analogue (GnRHa)-treated, 18 cyproterone acetate (CyA)-treated, 61 untreated] and of 446 controls with normal puberty, matched for age and year of birth, were recorded in a structured interview.

Results: Marital status, education and number of children were similar in CPP women and controls. Clinical hyperandrogenism (acne/hirsutism with oligomenorrhoea) was more frequently reported in CPP women than in controls: GnRHa-treated 29·6% *vs.* 17·4% (P = 0·006), CyA-treated 50% *vs.* 20·4% (P = 0·04), untreated 34·4% *vs.* 17·2% (P = 0·003), with no significant difference between CPP groups. Spontaneous pregnancy was similarly achieved by treated CPP and controls: GnRHa-treated 90·4% *vs.* 93·4%, CyA-treated 86·7% *vs.* 90·2%. Assisted fertilization rate was higher in untreated CPP than treated CPP groups (P = 0·006) and controls (P = 0·03). Untreated CPP was the only parameter associated with clinical hyperandrogenism (OR=2·04, 95% CI, 1·0-4·16, P = 0·07) and fertility problems (OR=3·40, 95% CI, 1·15-10·0, P = 0·047). Course of pregnancy was uneventful in 90·2% of CPP women and 90·9% of controls.

Conclusions: The increased rate of clinical hyperandrogenism among CPP women implies that the underlying neuroendocrine dysfunction persists into adult life. Pubertal suppression treatment may have a protective effect as fertility problems were more prevalent only among untreated CPP women. Educational achievements and marital status were unaffected by CPP.

Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/Kallmann syndrome and effects of different modalities of hormonal treatment: a single-center study of 281 patients.

Trabado S, Maione L, Bry-Gauillard H, Affres H, Salenave S, Sarfati J, Bouvattier C, Delemer B, Chanson P, Le Bouc Y, Brailly-Tabard S, Young J.

J Clin Endocrinol Metab. 2014; 99(2): E268-75.

Context: Insulin-like factor 3 (INSL3) is a testicular hormone secreted during fetal life, the neonatal period, and after puberty.

Objective: To measure INSL3 levels in a large series of men with congenital hypogonadotropic hypogonadism (CHH)/ Kallmann syndrome (KS), in order to assess its diagnostic value and to investigate its regulation.

Patients: We studied 281 CHH/KS patients (91 untreated, 96 receiving T, and 94 receiving combined gonadotropin therapy [human chorionic gonadotropin, hCG, and FSH]) and 72 age-matched healthy men.

Methods: Serum INSL3 was immunoassayed with a validated RIA.

Results: Mean (±SD) INSL3 levels (pg/mL) were 659 ± 279 in controls and lower (60 ± 43; $P < .001$) in untreated CHH/KS patients, with no overlap between the two groups, when the threshold of 250 pg/mL was used. Basal INSL3 levels were lower in both untreated CHH/KS men with cryptorchidism than in those with intrascrotal testes and in patients with testicular volumes below 4 mL. Significant positive correlations between INSL3 and both serum total T and LH levels were observed in untreated CHH/KS. Mean INSL3 levels remained low in T-treated CHH/KS patients and were significantly higher in men receiving combined hCG-FSH therapy ($P < .001$), but the increase was lower cryptorchid patients. FSH-hCG combination therapy or hCG monotherapy, contrary to T and FSH monotherapies, significantly increased INSL3 levels in CHH/KS.

Conclusions: INSL3 is as sensitive a marker as T for the evaluation of altered Leydig cell function in CHH/KS patients. INSL3 levels correlate with LH levels in CHH/KS men showing, together with the rise in INSL3 levels during hCG therapy, that INSL3 secretion seems not constitutively secreted during adulthood but is dependence on pituitary LH.

5. ΠΑΧΥΣΑΡΚΙΑ ΚΑΙ ΜΕΤΑΒΟΛΙΚΟ ΣΥΝΔΡΟΜΟ

Obesity-associated variants within FTO form long-range functional connections with IRX3.

Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gómez-Marín C, Aneas I, Credidio FL, Sobreira DR, Wasserman NF, Lee JH, Puviindran V, Tam D, Shen M, Son JE, Vakili NA, Sung HK, Naranjo S, Acemel RD, Manzanares M, Nagy A, Cox NJ, Hui CC, Gomez-Skarmeta JL, Nóbrega MA.

Nature. 2014; 507(7492): 371-5.

Abstract: Genome-wide association studies (GWAS) have reproducibly associated variants within introns of FTO with increased risk for obesity and type 2 diabetes (T2D). Although the molecular mechanisms linking these noncoding variants with obesity are not immediately obvious, subsequent studies in mice demonstrated that FTO expression levels influence body mass and composition phenotypes. However, no direct connection between the obesity-associated variants and FTO expression or function has been made. Here we show that the obesity-associated noncoding sequences within FTO are functionally connected, at megabase distances, with the homeobox gene IRX3. The obesity-associated FTO region directly interacts with the promoters of IRX3 as well as FTO in the human, mouse and zebrafish genomes. Furthermore, long-range enhancers within this region recapitulate aspects of IRX3 expression, suggesting that the obesity-associated interval belongs to the regulatory landscape of IRX3. Consistent with this, obesity-associated single nucleotide polymorphisms are associated with expression of IRX3, but not FTO, in human brains. A direct link between IRX3 expression and regulation of body mass and composition is demonstrated by a reduction in body weight of 25 to 30% in Irx3-deficient mice, primarily through the loss of fat mass and

increase in basal metabolic rate with browning of white adipose tissue. Finally, hypothalamic expression of a dominant-negative form of Irx3 reproduces the metabolic phenotypes of Irx3-deficient mice. Our data suggest that IRX3 is a functional long-range target of obesity-associated variants within FTO and represents a novel determinant of body mass and composition.

A form of the metabolic syndrome associated with mutations in DYRK1B.

Keramati AR, Fathzadeh M, Go GW, Singh R, Choi M, Faramarzi S, Mane S, Kasaei M, Sarajzadeh-Fard K, Hwa J, Kidd KK, Babaee Bigi MA, Malekzadeh R, Hosseinian A, Babaei M, Lifton RP, Mani A.

N Engl J Med. 2014; 370(20): 1909-19.

Background: Genetic analysis has been successful in identifying causative mutations for individual cardiovascular risk factors. Success has been more limited in mapping susceptibility genes for clusters of cardiovascular risk traits, such as those in the metabolic syndrome.

Methods: We identified three large families with coinheritance of early-onset coronary artery disease, central obesity, hypertension, and diabetes. We used linkage analysis and whole-exome sequencing to identify the disease-causing gene.

Results: A founder mutation was identified in DYRK1B, substituting cysteine for arginine at position 102 in the highly conserved kinase-like domain. The mutation precisely cosegregated with the clinical syndrome in all the affected family members and was absent in unaffected family members and unrelated controls. Functional characterization of the disease gene revealed that nonmutant protein encoded by DYRK1B inhibits the SHH (sonic hedgehog) and Wnt signaling pathways and consequently enhances adipogenesis. Furthermore, DYRK1B promoted the expression of the key gluconeogenic enzyme glucose-6-phosphatase. The R102C allele showed gain-of-function activities by potentiating these effects. A second mutation, substituting proline for histidine 90, was found to cosegregate with a similar clinical syndrome in an ethnically distinct family.

Conclusions: These findings indicate a role for DYRK1B in adipogenesis and glucose homeostasis and associate its altered function with an inherited form of the metabolic syndrome.

Bone-specific insulin resistance disrupts whole-body glucose homeostasis via decreased osteocalcin activation.

Wei J, Ferron M, Clarke CJ, Hannun YA, Jiang H, Blaner WS, Karsenty G.

J Clin Invest. 2014; 124(4): 1-13.

Abstract: Insulin signaling in osteoblasts has been shown recently to contribute to whole-body glucose homeostasis in animals fed a normal diet; however, it is unknown whether bone contributes to the insulin resistance that develops in animals challenged by a high-fat diet (HFD). Here, we evaluated the consequences of osteoblast-specific overexpression of or loss of insulin receptor in HFD-fed mice. We determined that the severity of glucose intolerance and insulin resistance that mice develop when fed a HFD is in part a consequence of osteoblast-dependent insulin resistance. Insulin resistance in osteoblasts led to a decrease in circulating levels of the active form of osteocalcin, thereby decreasing insulin sensitivity in skeletal muscle. Insulin resistance developed in osteoblasts as the result of increased levels of free saturated fatty acids, which promote insulin receptor ubiquitination and subsequent

degradation. Together, these results underscore the involvement of bone, among other tissues, in the disruption of whole-body glucose homeostasis resulting from a HFD and the involvement of insulin and osteocalcin cross-talk in glucose intolerance. Furthermore, our data indicate that insulin resistance develops in bone as the result of lipotoxicity-associated loss of insulin receptors.

6. ΟΓΚΟΛΟΓΙΑ ΚΑΙ ΧΡΟΝΙΑ ΝΟΣΗΜΑΤΑ

Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study.

de Fine Licht S, Winther JF, Gudmundsdottir T, Holmqvist AS, Bonnesen TG, Asdahl PH, Tryggvadottir L, Anderson H, Wesenberg F, Malila N, Holm K, Hasle H, Olsen JH; ALiCCS study group.

Lancet. 2014; 383(9933): 1981-9.

Background: The pattern of endocrine disorders in long-term survivors of childhood cancer has not been investigated comprehensively. Here, we aimed to assess the lifetime risk of these disorders in Nordic survivors of childhood cancer.

Methods: From the national cancer registries of Denmark, Finland, Iceland, Norway, and Sweden, we identified 31,723 1-year survivors of childhood cancer, notified since the start of registration in the 1940s and 1950s. From the national population registries, we randomly selected a comparison cohort of people matched by age, sex, and country. Study participants were linked to the national hospital registries, and observed numbers of first-time hospital contacts for endocrine disorders in survivors of childhood cancer were compared with the expected numbers derived from the population comparison cohort. We calculated the absolute excess risks attributable to status as a childhood cancer survivor and standardised hospitalisation rate ratios (SHRRs).

Findings: Of the childhood cancer survivors, 3292 had contact with a hospital for an endocrine disorder, yielding a SHRR of 4·8 (95% CI 4·6-5·0); the highest risks were in survivors of leukaemia (SHRR 7·3 [95% CI 6·7-7·9]), CNS tumours (6·6 [6·2-7·0]), and Hodgkin's lymphoma (6·2 [5·6-7·0]). The absolute excess risk for endocrine disorders was roughly 1000 per 100,000 person-years before 20 years of age, and 400 per 100,000 person-years during the remaining lifetime. For children with cancer diagnosed at 5-9 years of age, the cumulative risk for endocrine disorders was highest, and reached 43% at the age of 60 years. Diagnoses of pituitary hypofunction (SHRR 88·0), hypothyroidism (9·9), and testicular and ovarian dysfunction (42·5 and 4·7, respectively) together constituted 61% (655 of 1078) of all excess disease-induced and treatment-induced endocrine disorders in survivors of childhood cancer.

Interpretation: A cumulative risk for endocrine disorders at 60 years of age of above 40% in survivors of childhood cancer emphasises the importance of minimisation of damaging treatment, intensification of secondary prevention, and targeting of survivor follow-up throughout life. Since most long-term childhood cancer survivors are not followed in a specialised late-effect clinic, they are a growing challenge for the primary care physician and medical specialists working outside the late-effect area.

Update on endocrine and metabolic therapy-related late effects observed in survivors of childhood neoplasia.

Chemaitilly W, Hudson MM.

Curr Opin Endocrinol Diabetes Obes. 2014; 21(1): 71-6.

Purpose of Review: To provide a summary of the most recent research pertaining to the endocrine and metabolic complications observed in childhood cancer survivors.

Recent Findings: Data on prevalence and risk associations are increasingly available from large cohorts of childhood cancer survivors. New directions in research include novel risk-prediction strategies and the study of genetic predisposition.

Summary: Endocrine complications are observed in more than 50% of adult childhood cancer survivors. Some continue to develop decades following cancer treatment exposures. The present review provides a summary of the most recent outcomes research pertaining to growth, thyroid, gonadal-reproductive, bone and body composition with emphasis on new directions and challenges in each area.

7. ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ ΚΑΙ ΥΠΟΓΛΥΚΑΙΜΙΑ

Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength.

Elleri D, Allen JM, Tauschmann M, El-Khairi R, Benitez-Aguirre P, Acerini CL, Dunger DB, Hovorka R.

BMJ Open Diabetes Res Care. 2014; 2(1): e000040.

Objective: To assess feasibility of overnight closed-loop therapy in young children with type 1 diabetes and contrast closed loop using diluted versus standard insulin strength.

Research Design and Methods: Eleven children (male 6; age range 3.75-6.96 years; glycated hemoglobin 60 (14) mmol/mol; body mass index SD score 1.0 (0.8); diabetes duration 2.2 (1.0) years, mean (SD); total daily dose 12.9 (10.6, 16.5) IU/day, median (IQR)) were studied at a clinical research facility on two occasions. In random order, participants received closed loop with diluted insulin aspart (CL_Dil; 20 IU/mL) or closed loop with standard aspart (CL_Std; 100 IU/mL) from 17:00 until 8:00 the following morning. Children consumed an evening meal at 17:00 (44 (12) gCHO) and an optional bedtime snack (6 (7) gCHO) identical on both occasions. Meal insulin boluses were calculated by standard pump bolus calculators. Basal rates on insulin pump were adjusted every 15 min as directed by a model-predictive-control algorithm informed by a real-time glucose sensor values.

Results: Mean plasma glucose was 122 (24) mg/dL during CL_Dil vs 122 (23) mg/dL during CL_Std (p=0.993). The time spent in the target glucose range 70-145 mg/dL was 83 (70, 100)% vs 72 (54, 81)% (p=0.328). Time above 145 mg/dL was 13 (0, 27)% vs 19 (10, 45)% (p=0.477) and time spent below 70 mg/dL was 0.0 (0.0, 1.4)% vs 1.4 (0.0, 11.6)% (p=0.161). One asymptomatic hypoglycemia below 63 mg/dL occurred in one participant during CL_Dil versus six episodes in five participants during CL_Std (p=0.09). Glucose variability measured by CV of plasma glucose tended to be reduced during CL_Dil (20% (13, 31) vs 32% (24, 42), p=0.075).

Conclusions: In this feasibility study, closed-loop therapy maintained good overnight glucose control with tendency towards reduced hypoglycemia and reduced glucose variability using diluted insulin.

Prevention or early cure of type 1 diabetes by intranasal administration of gliadin in NOD mice.

Funda DP, Fundova P, Hansen AK, Buschard K.

PLoS One. 2014; 9(4): e94530.

Abstract: Induction of long-term tolerance to β-cell autoantigens has been investigated both in animal models and in human type 1 diabetes (T1D) in order to prevent the disease. As regards external compounds, the dietary plant protein fraction has been associated with high penetrance of the disease, whereas gluten-free diets prevent T1D in animal models. Herewith we investigated whether intranasal (i.n.) administration of gliadin or gluten may arrest the diabetogenic process. I.n. administration of gliadin to 4-week-old NOD mice significantly reduced the diabetes incidence. Similarly, the insulitis was lowered. Intranasal gliadin also rescued a fraction of prediabetic 13-week-old NOD mice from progressing to clinical onset of diabetes compared to OVA-treated controls. Vaccination with i.n. gliadin led to an induction of CD4(+)Foxp3(+) T cells and even more significant induction of γδ T cells in mucosal, but not in non-mucosal lymphoid compartments. This prevention strategy was characterized by an increased proportion of IL-10 and a decreased proportion of IL-2, IL-4 and IFN-γ-positive CD4(+)Foxp3(+) T cells, and IFN-γ-positive γδ T cells, preferentially in mucosal lymphoid organs. In conclusion, i.n. vaccination with gliadin, an environmental antigen with possible etiological influence in T1D, may represent a novel, safer strategy for prevention or even early cure of T1D.

Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia.

Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, Ellard S, Rampling D, Ashworth M, Brown RE, Hussain K.

N Engl J Med. 2014; 370(12): 1131-7.

Abstract: Hyperinsulinemic hypoglycemia is the most common cause of severe, persistent neonatal hypoglycemia. The treatment of hyperinsulinemic hypoglycemia that is unresponsive to diazoxide is subtotal pancreatectomy. We examined the effectiveness of the mammalian target of rapamycin (mTOR) inhibitor sirolimus in four infants with severe hyperinsulinemic hypoglycemia that had been unresponsive to maximal doses of diazoxide (20 mg per kilogram of body weight per day) and octreotide (35 μg per kilogram per day). All the patients had a clear glycemic response to sirolimus, although one patient required a small dose of octreotide to maintain normoglycemia. There were no major adverse events during 1 year of follow-up.

8. ΟΣΤΑ

Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone.

Kusumbe AP, Ramasamy SK, Adams RH.

Nature. 2014; 507(7492): 323-8.

Abstract: The mammalian skeletal system harbours a hierarchical system of mesenchymal stem cells, osteoprogenitors and osteoblasts sustaining lifelong bone formation. Osteogenesis is indispensable for the homeostatic renewal of bone as well as regenerative fracture healing, but these processes frequently decline in ageing organisms, leading to loss of bone mass and

increased fracture incidence. Evidence indicates that the growth of blood vessels in bone and osteogenesis are coupled, but relatively little is known about the underlying cellular and molecular mechanisms. Here we identify a new capillary subtype in the murine skeletal system with distinct morphological, molecular and functional properties. These vessels are found in specific locations, mediate growth of the bone vasculature, generate distinct metabolic and molecular microenvironments, maintain perivascular osteoprogenitors and couple angiogenesis to osteogenesis. The abundance of these vessels and associated osteoprogenitors was strongly reduced in bone from aged animals, and pharmacological reversal of this decline allowed the restoration of bone mass.

Endothelial Notch activity promotes angiogenesis and osteogenesis in bone.

Ramasamy SK, Kusumbe AP, Wang L, Adams RH.

Nature. 2014; 507(7492): 376-80.

Abstract: Blood vessel growth in the skeletal system and osteogenesis seem to be coupled, suggesting the existence of molecular crosstalk between endothelial and osteoblastic cells. Understanding the nature of the mechanisms linking angiogenesis and bone formation should be of great relevance for improved fracture healing or prevention of bone mass loss. Here we show that vascular growth in bone involves a specialized, tissue-specific form of angiogenesis. Notch signalling promotes endothelial cell proliferation and vessel growth in postnatal long bone, which is the opposite of the well-established function of Notch and its ligand Dll4 in the endothelium of other organs and tumours. Endothelial-cell-specific and inducible genetic disruption of Notch signalling in mice not only impaired bone vessel morphology and growth, but also led to reduced osteogenesis, shortening of long bones, chondrocyte defects, loss of trabeculae and decreased bone mass. On the basis of a series of genetic experiments, we conclude that skeletal defects in these mutants involved defective angiocrine release of Noggin from endothelial cells, which is positively regulated by Notch. Administration of recombinant Noggin, a secreted antagonist of bone morphogenetic proteins, restored bone growth and mineralization, chondrocyte maturation, the formation of trabeculae and osteoprogenitor numbers in endothelial-cell-specific Notch pathway mutants. These findings establish a molecular framework coupling angiogenesis, angiocrine signals and osteogenesis, which may prove significant for the development of future therapeutic applications.