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Personal Statement

I am an endocrinologist with specialty training in reproductive endocrinology. I am also a translational researcher and my focus has been on the genetics of rare endocrine disorders. Presently, I am Head of Endocrinology, Diabetes & Metabolism and Pediatric Endocrinology at the CHUV and serve as the chair of a European consortium of clinicians, geneticists, basic scientists, and bioinformaticians focused on congenital GnRH deficiency.

Education and Positions

1990	MD, University of Geneva Medical School
1990-1994	Resident, Internal Medicine, Fribourg Hospital
1994	Resident, Metabolic Unit, Guys Hospital, London, UK
1995-1996	Chief Resident, Internal Medicine, Geneva University Hospital
1996-1997	Resident, Internal Medicine, Diabetes Unit, Geneva University Hospital
1997-1998	Chief Resident, Internal Medicine, Diabetes Unit, Geneva University Hospital
1998-1999	Clinical Fellow, Endocrinology & Diabetes, Massachusetts General Hospital (MGH), Boston, MA
1999-2002	Clinical & Research Fellow, Reproductive Endocrinology, MGH, Boston, MA
2002	Instructor in Medicine, Harvard Medical School, Boston, MA
2003	Assistant in Medicine, Massachusetts General Hospital, Boston, MA
2005	Assistant Professor in Harvard Medical School, Boston, MA
2007	Associate Member, MGH Center of Human Genetic Research, Boston, MA
2010	Associate Professor, Harvard Medical School, Boston, MA
2010	Chief, Endocrine Diabetes & Metabolism service, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne
2010	Chief, Pediatric Endocrinology Unit, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne
2010	Professor in Medicine, University of Lausanne, Faculty of Biology & Medicine

Awards and Honors:

1998	Denber Pinard Award
2000	Endocrine Fellows Foundation Award
2001	Endocrine Society MCR Travel Award
2001	Endocrine Society Merck Clinical Research Award
2004	Claflin Award, Massachusetts General Hospital (MGH)
2005	Poster of Distinction, MGH Clinical Research Day
2006	Poster of Distinction, MGH Clinical Research Day
2007	Poster of Distinction, MGH Clinical Research Day
2007	Best Abstract, European Pediatric Endocrine Society, Helsinki, FI

2009 Krane Award for Translational Research, Massachusetts General Hospital
2012 Best Abstract, European Pediatric Endocrine Society, Leipzig, DE
2012 Swiss National Science Foundation

Editorial Activities

American Journal of Human Genetics, Clinical Endocrinology, Endocrinology, European Journal of Human Genetics, International Journal of Andrology, Journal of Clinical Endocrinology & Metabolism, Journal of Clinical Investigation, Molecular Endocrinology, Swiss National Science Foundation grant reviewer, Nature

Professional Societies

College of Physicians of Switzerland, Swiss Internal Medicine Society, Swiss Society for Endocrinology and Diabetes, Massachusetts Medical Society, American Diabetes Association, Endocrine Society, European Society of Endocrinology, European Society of Paediatric Endocrinology, Fédération des Médecins Suisses, Société Vaudoise du diabète.

Current Research Support

SNF IZSTZ0_202612 (co-PI: Pitteloud) 499'059 CHF Apr 2022 - Mar 2026
The Genetics of Congenital Hypogonadotropic Hypogonadism in Pakistan
This project will focus on: (i) launching a collaboration with Pakistani medical doctors and geneticists to identify patients with a central defect of infertility, more specifically with CHH; (ii) training female Pakistani and Swiss scientists; iii) improving education, diagnosis and treatment of Pakistani patients with disorders of puberty and infertility; (iv) identifying novel CHH genes that will illuminate a greater biological understanding of reproduction.

SNF 310030B_201275 (PI: Pitteloud) 907'990 CHF Apr 2021 - Mar 2025
The Neuroendocrine Control of Human Reproduction
This project will focus on clinical, genetic and basic aspect of GnRH neuron biology, employing a multidisciplinary and translational approach to address the current challenges in the field: (1) We therefore propose to improve the early diagnosis of CHH by validating machine learning to distinguish CDGP from CHH. (2) We aim to promote personalized medicine by demonstrating the role of genetics in guiding clinical assessment. (3) We propose to combine WGS with transcriptomics to increase the yield of molecular diagnosis and translate these findings in clinical genetics. (4) Finally, we will use CHH patients-derived iPSC and genome editing technologies to functionally validate the genetic makeup of each patient, along the evaluation of potential individualized treatments.

Horizon 2020 Research and Innovation Action - #847941 (Co-PI: Pitteloud) Jan 2020 – Dec 2025
783’510 EUR
MiniNO - Associative mechanisms linking a defective minipuberty to the appearance of mental and non-mental disorders: infantile NO replenishment as a new therapeutic possibility
The miniNO project aims to identify the key causative mechanisms of the lifelong multimorbidity associated with preterm birth. Prematurity is associated with alterations in the maturation of the hypothalamic-pituitary-gonadal axis, and specifically with its transient activation during infancy, known as minipuberty. MiniNO will study for the first time the association between premature birth and alterations in minipuberty and infantile nitric oxide (NO) signaling in the brain, and comorbidities

that appear later on in life. MiniNO is expected to improve the quality of life of millions of prematurely born individuals and reduce the financial and societal burdens they impose.

SNF / Bridge “Discovery” 40B2-0_187153 (Co-PIs: Pitteloud) Dec 2020 – Mar 2024
848’176 CHF
SensoCort: A wearable device for real-time monitoring of cortisol in humans
Wearable devices permit the minimally invasive or non-invasive measurement of analytes in biofluids such as interstitial fluid, saliva, tears and sweat. Optimally, these measurements will serve as surrogates for analyte concentrations in blood. This project will develop and validate the first of its kind wearable medical companion device for real-time cortisol monitoring in human sweat, under medical specifications and medical hypothesis validations. If successful, such unique wearable technology, called Lab on Skin, will have a strong impact not only for the field of endocrinology but can be extended to obesity management, and other stress related disorders.

SNF IZCOZ0_182958 (PI: Pitteloud) 319'564 CHF Apr 2019 - Mar 2023
Improving Cleft Lip/Palate management of care through genomic medicine
Specific Aim 1: To identify novel genes implicated in syndromic and non–syndromic CLP. We propose to discovery novel gene using a combination of: (i) multi-plex families with CLP ; (ii) whole genome sequencing (WGS) to capture missing non-coding, regulatory, or variants impacting DNA structure/localization/folding; (iii) VariantMaster, a bioinformatic tool developed by one of our team member and employed successfully to discover the genetic causes of similar Mendelian disorders. Specific Aim 2: To elucidate the shared genetic basis between CLP and CHH. We aim to assess rare variants in CLP genes in a large CHH cohort by: (i) performing detailed phenotyping in a large CHH cohort with special attention on CLP; (ii) and assessing the enrichment of CLP associated genes in this large CHH cohort.

Past Support

SNF 310030 173260 (PI: Pitteloud) 1'098'212 CHF Apr 2017 - Mar 2021
The Neuroendocrine Control of Human Reproduction
This multi-disciplinary project will include clinical, human genetics, bioinformatics, and basic research and capitalize on cutting-edge technologies (next-generation sequencing, bioinformatics, mass spectrometry, and gene editing) and the established European network of experts in reproduction (COST Action BM1105, www.gnrhnetwork.eu) to achieve the following three aims: Aim 1: To enhance early diagnosis in patients with CHH by combining phenotypic, genetic, and molecular approaches. Aim 2: To further elucidate the genetic complexity of GnRH deficiency disorders. Aim 3: To validate the roles of cubilin (CUBN) and its co-receptor megalin (LRP2) in GnRH neuron biology.

CTI (Co-PI: Pitteloud) 340’000 CHF Dec 2015 - Nov 2017
EndoSLims - Full cycle genomic data management and analysis routines for the genetics of diabetes and other endocrine disorders
This project links next-generation sequencing with bioinformatics pipelines and a tailored computerized laboratory information systems (SLiMS) to develop an integrated platform for molecular diagnostic testing of endocrine disorders
Role: Co-PI

SNF 31003A 153328 (PI: Pitteloud) 756’000 CHF Apr 2014 - Mar 2017
The neuroendocrine control of human reproduction
This project uses next-generation sequencing (NGS) technologies and functional genomics to identify novel genes underlying congenital GnRH deficiency and reveal genetic overlaps across

developmental disorders. Additionally, NGS results are analyzed along with data from genome-wide association studies to identify novel genes controlling pubertal timing.

SNF IZLSZ3 148908 (Co-PI: Pitteloud) 229'000 CHF Jan 2014 - Dec 2016

Exploring the molecular basis and phenotypic spectrum of reproductive disorders in South Africa
This project aims to investigate the genetic basis of reproductive disorders among a cohort of South African probands. Collaborative genotyping and phenotyping studies in concert with *in vitro* functionality studies are planned to elucidate the biology of novel genes identified in this unique population.

COST BM1105 (Chair & PI: Pitteloud) 180'000 CHF Apr 2012 - Mar 2016

European Collaboration in Science & Technology (COST)
GnRH deficiency: Elucidation of the neuroendocrine control of human reproduction
This project aims to create a European consortium of clinician investigators, basic scientists, geneticists, bioinformaticians, and genetic counselors interested in the study, diagnosis, treatment, and counseling of patients with delayed puberty and congenital GnRH deficiency.

CRSII3_141960 (Co-PI: Pitteloud) 1'500'000 CHF Dec 2012 - Nov 2015

SNF Sinergia: FGF21 is a link between reproduction and energy balance
This interdisciplinary translational research grant includes 4 sub-projects. The project brings together investigators with expertise in human genetics (Pitteloud), circadian clock (Albrecht), structural biology (Mohammadi), and astrocyte biology (Pellerin) to elucidate the central role of FGF21 in energy sensing and a link between metabolism and reproduction.

SERI C12.0106 (PI: Pitteloud) 180'000 CHF Dec 2012 - Nov 2015

Enhancing bioinformatic approaches for analysis of exome sequencing data generated form GnRH deficient patients
This project aims to develop a targeted bioinformatic filtering/prioritizing pipeline to identify high-quality candidate genes for congenital hypogonadotropic hypogonadism. The resulting deliverable will be distributed to other European investigators via the funded COST action BM1105

SNF 31003A 135648 (PI: Pitteloud) 537'000 CHF Apr 2011 - Mar 2014

The neuroendocrine control of human reproduction
This project examines the role of the fibroblast growth factor 8 (FGF8) gene network and bone morphogenic proteins (BMPs) in the neuroendocrine control of reproduction. Multidisciplinary approaches incorporating the complementary fields of human genetics, molecular biology, and structural biology are employed.

5R01 HD 056264 (PI: Pitteloud) 1'300'000 $ Jul 2008 - Jun 2013

NIH-NICHD: Role of FGF signaling in neuroendocrine control of reproduction
This translational research project aims to define the role of FGF8 signaling in GnRH development using an interdisciplinary approach including human genetics (and the human disease model of idiopathic hypogonadotropic hypogonadism [GnRH deficiency]), biochemistry, and structural biology.

RO1 DK 071168 (PI: Hayes/Pitteloud) 870'000 $ Jul 2006 - Jun 2011

NIH/NIDDK: Modulation of insulin action by testosterone in men
The goals of this grant were to examine the impact of testosterone on insulin sensitivity in men and to assess the differential effects of testosterone and estradiol in men with the metabolic syndrome. This grant involved physiologic investigation, human genetic studies, and detailed metabolic phenotyping studies.

Supervision of junior researchers

A. Master thesis

- Vanessa Héritier (Master thesis). 2013-2015
« Evaluation du rythme circadien du Fibroblast growth factor 21 (FGF21) chez les enfants pré-pubertaires obèses, avec un diabète de type 1 et normaux »

- Adelina Ameti (Master thesis). 2013-2015
« Le syndrome des ovaires polykystiques chez les adolescentes obèses »

- Isaline Francey (Master thesis). 2013-2015
« Hyperprolactinémie et désordres de la reproduction »

- Muriel Jeanmonod (Master thesis). 2013-2015
« Diabète et troubles de la production de testostérone chez l'homme »

- Sylvain Rossier (Master thesis). 2013-2015
« Caractéristiques cliniques et génétiques du syndrome de néoplasies endocriniennes multiples de type 1 »

- Lourenço Brian Lopes (Master thesis). 2016-2018
« Caractérisation des patients avec maladie de Cushing et évaluation de leur réponse thérapeutique »

- Stephen Adjahou (Master thesis). 2016-2018
« Etude rétrospective sur les patients atteints d'hypogonadisme hypogonadotrope au CHUV »

- Jean-David Muller (Master thesis). 2016-2018
« PCOS » chez les adolescents

- David Naef (Master thesis). 2018-2020
« Étude rétrospective sur les phénotypes des phéochromocytomes et demande prospective d'analyses génétiques B13 »

- Mathilde Sandmeier (Master thesis). 2018-2020
« Variabilité phénotypique du syndrome des ovaires polykystiques chez les patientes suivies au CHUV »

- Damien Choffat (Master thesis). 2018-2020
« Déficience en 21hydroxylase : de la génétique à la clinique »

B. Former MD or PhD students

- Andrew Dwyer (PhD). 2011-2014
« Needs assessment in male GnRH deficient patients: A fundamental step to develop targeted nursing interventions aimed at enhancing health promoting behaviors and developing patient-centered approaches to care»

- Daniele Cassatella (PhD). 2012-2017
« Bioinformatic approaches for analyzing exome sequencing data in patients with reproductive disorders »

- Cheng Xu (PhD). 2013-2017
« Phenotype-genotype correlation and novel gene discovery in congenital hypogonadotropic hypogonadism »

- Santini Sara (MD) 2015-17 – «CHH genes discovery»

- Zosia Kolesinska (MD/PhD) 2018-2020 – «Genetic etiologies of disorders of sex development»

- Jesse Rademaker (PhD) 2019-2021 – «High-throughput approaches for CHH genes discovery»

C. Present MD, Post-doc or PhD students

Adamo Michela (PhD) 2018 – «High-throughput approaches for CHH genes discovery»
Antoniou Maria-Christina (MD) 2019 - «Differentiating constitutional delay of puberty and CHH»
Yassine Zouaghi (PhD) 2020 – «Artificial Intelligence-based diagnostics and management of CHH»
Dassine Berdous (Post-doc) 2020 – "Patients-derived IPS cells for GnRH neurons development modeling"

D. Contributions to early careers of researchers

2005-2007	Taneli Raivio, MD, PhD (post-doc) currently: Professor, University of Helsinki, Finland
2005-2007	Elka Jacobson-Dickman, MD (post-doc) currently: Fellowship Program Director & Associate - Director, Pediatric Endocrinology, Maimonides Medical Center, Brooklyn, USA
2008-2010	Cecilia Martin, PhD (post-doc) currently: Post-doc, Brigham & Womens Hospital, Boston, USA
2009-2010	Magdalena Avbelj, MD (post-doc) currently: Faculty, Pediatric endocrinology, University Medical Center Ljubljana, SL
2009-2010	Gerasimos Sykiotis, MD, PhD (post-doc) currently: Privat Docent & Faculty, Endocrinology, Diabetes & Metabolism, CHUV, Lausanne, CH
2010-2012	Hichem Miraoui, PhD (post-doc) currently: Post-doc, Harvard Medical School Dept. of Genetics, Boston, MA, USA
2011-2014	Andrew Dwyer (PhD student) currently: Assistant Professor, Boston College, Connell School of Nursing, Chestnut Hill, MA, USA
2013-2017	Emmanuel Somm PhD (Post-doc) currently: Research Associate, University of Geneva, CH
2013-2017	Cheng Xu MD-PhD (PhD) currently: Research associate, CHUV, Lausanne, CH
2014-2016	Sara Santini (MD) currently: Clinical fellow, CHUV, Lausanne, CH
2015-2017	Justine Bouilly (Post-Doc) currently: Biologist, CHUV, Lausanne, CH
2013-2018	Daniele Cassatella (PhD) currently: Bioinformatician, Synlab, Lausanne, CH
2017-2020	James Acierno Jr. (PhD) currently: Consultant in Genetics, Boston, USA & Lausanne, CH

Teaching activities

Faculty of Biology and Medicine (UNIL/CHUV – Lausanne)

- B2.6. - Endocrinology of reproduction / neuroendocrinology
  (7h/year - since 2010)

- B3.5 - Growth and development: Puberty
  (1h/year - since 2013)

- B3.9 – Cours à option “Ni fille ni garçon - DSD à l’âge adulte »
  (3h/year - since 2015)

- M1.9 – Cours à option « L’hypophyse reine des glandes- introduction à la neuroendocrinologie, prolactinomes, acromégalie»
  (10h/year - since 2019)

- M2.2 - Chronic and complex diseases – Adrenal disease
  (3h/year - since 2011)

- Bachelor es Science en Biologie “Physiology of Complex Systems - Endocrinologie de la reproduction et métabolisme du glucose”
  (4h/year – Since 2014)

- Master of Science in Medical Biology (MSc) – Metabolism, diabetes and metabolic syndrome – glucose metabolism and diabetes
  (4h/year – since 2017)

Publications

Web of science: 146 entries, H-index: 44, total 6597 citations (without self-citations), 66.3 per item.
Google Scholar: H-index 56 (43 since 2017), total 12070 citations.

Publication List accessible at:
http://www.ncbi.nlm.nih.gov/pubmed/?term=pitteloud+n

Original Peer-Reviewed Articles

1. **Pitteloud N**, Binz K, Caulfield A, Philippe J. Ketoacidosis during gestational diabetes. Case report. Diabetes Care. 1998. 21(6):1031-2.
2. **Pitteloud N**, Philippe J. Characteristics of Caucasian type 2 diabetic patients during ketoacidosis and at follow-up. Schweiz Med Wochenschr. 2000. 130(16):576-82.
3. Beranova M, Oliveira LM, Bédécarrats GY, Schipani E, Vallejo M, Ammini AC, Quintos JB, Hall JE, Martin KA, Hayes FJ, **Pitteloud N**, Kaiser UB, Crowley WF, Seminara SB. Prevalence, phenotypic spectrum, and modes of inheritance of gonadotropin-releasing hormone receptor mutations in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2001. 86(4):1580-8.
4. **Pitteloud N**, Boepple PA, DeCruz S, Valkenburgh SB, Crowley WF, Hayes FJ. The fertile eunuch variant of idiopathic hypogonadotropic hypogonadism: spontaneous reversal associated with a homozygous mutation in the gonadotropin-releasing hormone receptor. J Clin Endocrinol Metab. 2001. 86(6):2470-5.

5. Hayes FJ, **Pitteloud N**, DeCruz S, Crowley WF, Boepple PA. Importance of inhibin B in the regulation of FSH secretion in the human male. J Clin Endocrinol Metab. 2001. 86(11):5541-6.
6. **Pitteloud N**, Hayes FJ, Boepple PA, DeCruz S, Seminara SB, MacLaughlin DT, Crowley WF. The role of prior pubertal development, biochemical markers of testicular maturation, and genetics in elucidating the phenotypic heterogeneity of idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002. 87(1):152-60.
7. **Pitteloud N**, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002. 87:4128-36.
8. **Pitteloud N**, Villegas J, Dwyer AA, Crowley WF, McPhaul MJ, Hayes FJ. Acute stress masking the biochemical phenotype of partial androgen insensitivity syndrome in a patient with a novel mutation in the androgen receptor. J Clin Endocrinol Metab. 2004. 89(3):1053-8.
9. **Pitteloud N**, Acierno JS, Meysing AU, Dwyer AA, Hayes FJ, Crowley WF. Reversible Kallmann Syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the FGFR1 gene. J Clin Endocrinol Metab. 2005. 90(3):1317-22.
10. **Pitteloud N**, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005. 90(5):2636-41.
11. **Pitteloud N**, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson K-F, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity and mitochondrial function in men. Diabetes Care. 2005. 28(7):1636-42.
12. Corssmit EPM, Seminara SB, **Pitteloud N**, Fliers E. Kallmann syndrome in a 47,XXX patient. Am J Med Genet A. 2005. 39(1):52-3. PMID: 16222664
13. Kumar, PA*, **Pitteloud N***, Andrews PA, Dwyer AA, Hayes F, Crowley WF, Dym M. Testis morphology in patients with idiopathic hypogonadotropic hypogonadism. Hum Reprod. 2006. 21:1033-40.(* denotes co-first authors)
14. **Pitteloud N**, Acierno J.S, jr., Meysing A., Eliseenkova A.V., Ma J., Ibrahimi O.A., Metzger D., Hayes F.J., Dwyer A.A., Hughes V.A., Yialamas, M., Hall J.E., Grant E., Mohammadi M., Crowley W.F.Jr. 2006. Mutations in FGFR1 cause both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. Proc Natl Acad Sci USA. 2006. 103:6281-6.
15. **Pitteloud N**, Meysing A, Quinton R, Acierno JS, Dwyer AA, Plummer L, Fliers E, Boepple PA, Hayes FJ, Seminara SB, Bouloux P, Mohammadi M, Crowley WF, Jr. . Mutations in Fibroblast Growth Factor Receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. Mol Cell Endocrinol. 2006. 254-255:60-9.
16. Pallais JC, Bo-Abbas Y, **Pitteloud N**, Crowley WF Jr, Seminara SB. . Neuroendocrine, gonadal, placental, and obstetric phenotypes in patients with IHH and mutations in the G-protein coupled receptor, GPR54. Mol Cell Endocrinol. 2006. 254-255:70-7.
17. Cerrato F, Shagoury J, Kralickova M, Dwyer A, Falardeau J, Ozata M, Van Vliet G, Bouloux P, Hall JE, Hayes FJ, **Pitteloud N**, Martin KA, Welt C, Seminara SB. Coding sequence analysis of GNRHR and GPR54 in patients with congenital and adult-onset forms of hypogonadotropic hypogonadism. Eur J Endocrinol. 2006. 155:Suppl 1:S3-S10.
18. **Pitteloud N**, Quinton R, Pearce S, Raivio T, Acierno J, Dwyer A, Plummer L, Hughes V, Seminara S, Cheng YZ, Li WP, Maccoll G, Eliseenkova AV, Olsen SK, Ibrahimi OA, Hayes FJ, Boepple P, Hall JE, Bouloux P, Mohammadi M, Crowley W. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. J Clin Invest. 2007. 117:457-63.
19. Yialamas MA, Dwyer AA, Hanley E, Lee H, **Pitteloud N**, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2007. 92:4254-4259.
20. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, Cole LW, Pearce SH, Lee H, Boepple P, Crowley WF, **Pitteloud N**. Reversal of idiopathic hypogonadotropic hypogonadism. N Engl J Med. 2007. 357:863-73.
21. **Pitteloud N**, Zhang C, Pignatelli D, Li JD, Raivio T, Cole LW, Plummer L, Jacobson-Dickman EE, Mellon PL, Zhou QY, Crowley WF Jr. Loss-of-function mutation in the prokineticin 2 gene

causes Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. Proc Natl Acad Sci USA. 2007. 104:17447-52.
22. **Pitteloud N**, Dwyer AA, Decruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of LH Secretion by Testosterone in Men Requires Aromatization for its Pituitary but not its Hypothalamic Effects: Evidence from the Tandem Study of Normal and Gonadotropin-Releasing Hormone-Deficient Men. J Clin Endocrinol Metab. 2008. 93:784-91.
23. **Pitteloud N**, Dwyer AA, Decruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. The Relative Role of Gonadal Sex Steroids and Gonadotropin-Releasing Hormone Pulse Frequency in the Regulation of FSH Secretion in Men. J Clin Endocrinol Metab. 2008. 93:2686-92.
24. Boepple PA, Hayes FJ, Dwyer AA, Raivio T, Lee H, Crowley WF Jr, **Pitteloud N**. Relative roles of inhibin B and sex steroids in the negative feedback regulation of follicle-stimulating hormone in men across the full spectrum of seminiferous epithelium function. Journal of Endocrinology and Metabolism. 2008. 93:1809-14.
25. Cole LW, Sidis Y, Zhang C, Quinton R, Plummer L, Pignatelli D, Hughes VA, Dwyer AA, Raivio T, Hayes FJ, Seminara SB, Huot C, Alos N, Speiser P, Takeshita A, Van Vliet G, Pearce S, Crowley WF Jr, Zhou QY, **Pitteloud N**. Mutations in Prokineticin 2 (PROK2) and PROK2 Receptor (PROKR2) in Human Gonadotrophin-Releasing Hormone Deficiency: Molecular Genetics and Clinical Spectrum. J Clin Endocrinol Metab. 2008. 93:3551-59.
26. Falardeau J, Chung WC, Beenken A, Raivio T, Plummer L, Sidis Y, Jacobson-Dickman EE, Eliseenkova AV, Ma J, Dwyer A, Quinton R, Na S, Hall JE, Huot C, Alois N, Pearce SH, Cole LW, Hughes V, Mohammadi M, Tsai P, **Pitteloud N**. Decreased FGF8 signaling causes deficiency of gonadotropin-releasing hormone in humans and mice. J. Clin. Invest. 2008. 118:2822-31.
27. Chen H, Xu CF, Ma J, Eliseenkova AV, Li W, Pollock PM, **Pitteloud N**, Miller WT, Neubert TA, Mohammadi M. A crystallographic snapshot of tyrosine trans-phosphorylation in action. Proc Natl Acad Sci USA. 2008. 105:19660-5.
28. Jongmans MC, van Ravenswaaij-Arts CM, **Pitteloud N**, Ogata T, Sato N, Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman JE, Brunner HG, Crowley WF Jr, Hoefsloot LH. . CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. Clin Genet. 2009. 75:65-71.
29. **Pitteloud N**, Thambundit A, Dwyer AA, Falardeau JL, Plummer L, Caronia LM, Hayes FJ, Lee H, Boepple PA, Crowley WF Jr. Role of seminiferous tubular development in determining the FSH versus LH responsiveness to GnRH in early sexual maturation. Neuroendocrinology. 2009. 90(3):260-8.
30. Raivio T, Sidis Y, Plummer L, Chen H, Ma J, Mukherjee A, Jacobson-Dickman E, Quinton R, Van Vliet G, Lavoie H, Hughes VA, Dwyer A, Hayes FJ, Xu S, Sparks S, Kaiser UB, Mohammadi M, **Pitteloud N**. Impaired fibroblast growth factor receptor 1 signaling as a cause of normosmic idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2009. 94(11):4380-90.
31. Chan YM, de Guillebon A, Lang-Muritano M, Plummer L, Cerrato F, Tsiaras S, Gaspert A, Lavoie HB, Wu CH, Crowley WF Jr, Amory JK, **Pitteloud N**, Seminara SB. GNRH1 mutations in patients with idiopathic hypogonadotropic hypogonadism. Proc Natl Acad Sci USA. 2009. 106(28):11703-8.
32. Sykiotis GP, Plummer L, Hughes VA, Au M, Durrani S, Nayak-Young S, Dwyer AA, Quinton R, Hall JE, Gusella JF, Seminara SB, Crowley WF Jr, **Pitteloud N**. Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. Proc Natl Acad Sci USA. 2010. 107(34):15140-4. PMID:20696889
33. Dwyer AA, Hayes FJ, Plummer L, **Pitteloud N**, Crowley WF Jr. The long-term clinical follow-up and natural history of men with adult-onset idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2010. 95(9):4235-43. PMID :20591981
34. Trarbach EB, Abreu AP, Silveira LF, Garmes HM, Baptista MT, Teles MG, Costa EM, Mohammadi M, **Pitteloud N**, Mendonca BB, Latronico AC. Nonsense mutations in FGF8 gene causing different degrees of human gonadotropin-releasing deficiency. J Clin Endocrinol Metab. 2010. 95(7):3491-6. PMID :20463092
35. Sykiotis GP, Hoang XH, Avbelj M, Hayes FJ, Thambundit A, Dwyer A, Au M, Plummer L, Crowley WF Jr, **Pitteloud N**. Congenital idiopathic hypogonadotropic hypogonadism: evidence

of defects in the hypothalamus, pituitary, and testes. J Clin Endocrinol Metab. 2010. 95(6):3019-27. PMID: 20382682
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Reviews/Chapters/Editorials

1. **Pitteloud N**, Philippe J. Risque Coronarien chez les Diabétiques: effets préventifs des statines. Médecine et Hygiène. 1998. 56:529-36.
2. Hayes FJ, **Pitteloud N**. Hypogonadotropic Hypogonadism and Gonadotropin Therapy. In: The Endocrinology of the Male (McLachlan R ed.) www@endotext.org; 2001.
3. **Pitteloud N**, Crowley WFJr. Congenital Hypogonadotropic Hypogonadism: Clinical Features and Pathophysiology. Endocrinology Series: Hypogonadism: Basic, Clinical, and Therapeutic Principles. 2005.
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5. Pallais JC, Caudill M, **Pitteloud N**, Seminara S, Crowley, Jr WF. Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency Overview). In: Pagon RA, Adam MP, Bird TC, Dolan CR, Fong CT, Stephens K, editors. Gene Reviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. 2007 May 23 [updated 2010 Oct 14]. PMID: 20301455
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32. Cossu G, Daniel RT, Pierzchala K, Berhouma M, **Pitteloud N**, Lamine F, Colao A, Messerer M. Thyrotropin-secreting pituitary adenomas: a systematic review and meta-analysis of postoperative outcomes and management. Pituitary. 2019. Nov 2. PMID: 30390277
33. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, Raivio T, **Pitteloud N.** Clinical Management of Congenital Hypogonadotropic Hypogonadism. Endocr Rev. 2019. 40(2):669-710. PMID: 306986717
34. Subramanian M, Wojtusciszyn A, Favre L, Boughorbel S, Shan J, Letaief KB, **Pitteloud N**, Chouchane L. Precision medicine in the era of artificial intelligence: implications in chronic disease management. J Transl Med. 2020. 18(1):472. PMID: 33298113
35.

Invited Lectures: National (2010-present)

30.09.2010 Diagnosis and genetic of hypogonadism. 4ème Journée d'Endocrinologie Vaud-Genève, Morges (invited lecture)

16.11.2010 What is new in GnRH. Visiting Professor. Service Endocrinology & Pediatric Endocrinology, University Inselspital. Bern (invited lecture)

09.12.2010 Percer les mystères de la puberté. Leçon inaugurale. CHUV

17.12.2010 Des nouveaux gènes contrôlant la reproduction humaine et leur identification. Colloque scientifique de l'Unité de Médecine de la Reproduction. Maternité, CHUV (invited lecture)

14.01.2011 Role of FGF signaling in the neuroendocrine control of reproduction. Faber Foundation. Lausanne (invited lecture)

20.01.2011 Prolactinome. Colloque cas Clinique. CHUV

31.01.2011 Role of FGF signaling in the neuroendocrine control of reproduction. Visiting professor seminar. Center for Integrative Genomics. Lausanne (invited lecture)

15.02.2011 Ménopause. Colloque cas Clinique. CHUV

19.03.2011 La transition de la pédiatrie vers les adultes. Conférence Turner Syndrome, Bussigny-sur-Lausanne (invited lecture)

01.04.2011 Diabétologie:Traitement basé sur les valeurs de laboratoire. Primary Care Academy. Montreux (invited lecture)

14.04.2011 Puberté tardive : clinique et génétique. Colloque d'endocrinologie pédiatrique. Lausanne (invited lecture)

18.04.2011 Hyperfonction et hypofonction surrénaliennes. Colloque PG du Dépt de Médecine. CHUV

19.05.2011 Genetics basis of hypogonadotrophic hypogonadism. Service d'endocrinologie, Hôpitaux Universitaires de Genève. Genève (visiting professor et invited lecture)

26.05.2011 Le principe d'action des incrétines et leur rôle dans le traitement du diabète de type 2. Symposia Novo Nordisk. Lausanne (invited lecture et moderator)

21.06.2011 Gynécomastie. Colloque vignette. CHUV

07.07.2011 Les diabètes avec accent sur MODY. Colloque cas clinique. CHUV

22.09.2011 L'obésité chez l'enfant et adolescent. Colloque d'endocrinologie pédiatrique, CHUV (co-organisator et moderator)

03.10.2011 Progress in the understanding of hypogonadotropic hypogonadism. Kinderspital Zürich, Zürich (visiting professor and invited lecture)

06.10.2011 Endocrinologie de la grossesse. Endocrinologie et grossesse. 5ème Réunion Vaud-Genève d'endocrinologie, Morges (invited lecture and co-organizer)

13.10.2011 Traitement des aspects métaboliques du syndrome des ovaires polykystiques. Polycystic Ovarian Syndrome (PCOS) Symposia. CHUV (invited lecture, moderator and organizer)

25.10.2011 Human GnRH deficiency: Deciphering molecular pathogenesis. Advanced cell culture techniques for tissue engineering and drug discovery and development. XXII. BD-STCS Workshop 2011, Bâle (invited lecture)

03.11.2011 Syndrome des ovaires polykystiques : identification, investigation et suivi. Colloques de l'Unité Multidisciplinaire de Santé des Adolescents (UMSA), CHUV (invited lecture)

08.11.2011 Discussion: importance and implications for daily practice. Advisory Brd Meeting "Degludec The future of insulin therapy, Morges

01.12.2011 Aspects cliniques du syndrome des ovaires polykystiques. Les rencontres de Prangins, Prangins, Suisse (invited lecture)

06.12.2011 Retard pubertaire et prise en charge. Vidéoconférence des hôpitaux de Suisse romande. Colloque de Pédiatrie, CHUV (invited lecture)

02.12.2011 Male hypogonadism. Session: Continuous Medical Education. Annual SGED Meeting, Berne (invited lecture)

19.01.2012 Puberté tardive – Kallmann – Projet Européen, Réunion annuelle SSEDP /SGPED, St-Sulpice

08.03.2012 Troubles du cycle chez la jeune femme. Place et importance du syndrome des ovaires polykystiques. Colloque de formation de la Sté Neuchâteloise de Médecine, Hôpital de Neuchâtel (invited lecture)

08.03.2012 Diabète et hypogonadisme : prise en charge. Journée Vaud-Genève de diabétologie 2012, Morges (invited lecture and co-organizer)

29.03.2012 Hypogonadisme chez l'homme. Sessions interactives avec cas pratiques. Symposium Médical de l'Institut Central (ICHV) 2012 : L'endocrinologie dans tous ses états. Clinique Romande de Réadaptation SUVA, Sion (invited lecture)

03.05.2012 Progrès récents dans la recherche des incrétines. Nouveautés dans le traitement du diabète de type 2. CHUV (invited lecture)

18.05.2012 FGF21 a link between metabolism and reproduction. Session: Human genetics and models. FGF Gordon Conference 2012, Les Diablerets (invited lecture)

07.06.2012 Registre européen – déficience en GnRH. Colloque cas clinique, CHUV

14.06.2012 Suivi Basedow en âge adulte. Colloque d'endocrinologie pédiatrique « Les troubles thyroïdiens ». CHUV (invited lecture)

30.07.2012 Pathologies hypophysaires et médecine interne. Colloque PG du Département de Médecine, CHUV

31.10.2012 Acromégalie. Colloque hebdomadaire du Service de Neurologie. CHUV

07.11.2012 Morbus Cushing : Statu quo et Prise en charge. Atelier Novartis Consultant Network « Syndrome de Cushing ». Lausanne (chair)

16.11.2012 PCO et syndrome métabolique. Les Journées NETTER de la Sté Européenne de Gynécologie, Montreux (invited lecture)

13.12.2012 Apport du diagnostic génétique pour les pathologies surrénaliennes. Pathologies surrénaliennes. 6ème Journée VD-GE Endocrinologie, La Longeraie, Morges (invited lecture et co-organizer)

04.09.2013 Role of FGF signaling in the neuroendocrine control of reproduction. Séminaire endocrinologie et Diabète Hôpital Universitaire de Bâle (invited lecture)

21.11.2013 Redefining syndromes in the era of exomes. Annual Symposium of the Swiss Endocrine society, Bern

12.12.2013 Fertilité : Evaluation et traitement de l'infertilité chez l'homme : le point de vue de l'endocrinologue. 7ème Journée VD-GE Endocrinologie, La Longeraie, Morges (invited lecture et co-organizer)

23.04.2015 Hirsutismus. Formation pour spécialistes FMH Endocrinologie / Diabétologie (FOSPED), Bienne, Switzerland

04.06.2015 Nouvelles stratégies thérapeutiques dans l'œdème maculaire diabétique. Hôpital ophtalmique Jules-Gonin, Lausanne (invited lecture)

23.06.2015 Traitement de fertilité dans l'hypogonadisme hypogonadotrope masculin. Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

27.10.2015 Déficit en testostérone et troubles métaboliques**.** Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

29.10.2015 Syndrome des ovaires polykystiques, entrave à la fertilité et haut risque cardiovasculaire sur la durée. 6ème Journée jurassienne d'endocrinologie et de diabétologie, Delémont

03.12.2015 Variations de la différenciation sexuelle (VDS) /Disorders of Sex Development (DSD): un challenge pour la transition (symposium, invited lecture and co-organizer)

14.01.2016 Diagnosis and treatment of hypogonadotropic hypogonadism. Women's Health Congress 2016, University Hospital, Basel (invited lecture)

02.02.2016 Acromégalie: nouveautés. Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

12.01.2017 Detection of polycystic ovaries early in puberty - does it make any difference? Women's Health Congress 2017, CHUV (Symposium)

26.01.2017 Endocrinologie de la reproduction. The Year in Endocrinology / Publications incontournables de l'année 2016 (symposium, invited lecture and co-organizer)

16.02.2017 Hypogonadisme chez l'homme (quand faut-il le chercher et qui substituer en testostérone?) Société vaudoise de médecine (Symposium)

02.03.2017 The Year in Diabetes / Publications incontournables de l'année 2016 (symposium, co-organizer)

06.04.2017 The Year in Obesity / Publications incontournables de l'année 2016 (symposium, co-organizer)

07.12.2017 Prolactinome: quand arrêter le traitement d'agonistes dopaminergiques. Rencontre endocrinologie-neurochirurgie (symposium lecture and co-organizer)

18.01.2018 Reproduction. The Year in Endocrinology / Publications incontournables de l'année 2017 (symposium lecture and organizer)

15.02.2018 The Year in Diabetes / Publications incontournables de l'année 2017 (symposium, co-organizer)

15.03.2018 The Year in Obesity / Publications incontournables de l'année 2017 (symposium, co-organizer)

13.09.2018 Infertilité dans les hypogonadismes hypogonadotropes : usage de la pompe à GnRH et des gonadotropines. Symposium Endocrinologie de la reproduction (lecture and co-organizer)

04.10.2018 Différences physiologiques entre hommes et femmes liées aux hormones et à l'activité physique, Réseau Romand de Médecine de l'Exercice et du Sport (RRMES) Symposium d'automne, Yverdon-les-Bains (invited lecture)

31.10.2018 Différences physiologiques entre hommes et femmes liées aux hormones : implication pour l'activité, CHUV, Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

13.11.2018 Progrès en endocrinologie. Forum pour la formation médicale FomF, Update Refresher en Médecine Interne, Beaulieu, Lausanne (invited lecture)

10.01.2019 Reproduction & pathologies hypophysaires. The Year in Endocrinology / Publications incontournables de l'année 2018 (symposium lecture and organizer)

16.01.2019 Syndrome des ovaires polykystiques. Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

14.02.2019 The Year in Diabetes / Publications incontournables de l'année 2018 (symposium, co-organizer)

14.03.2019 Obésité et hypogonadisme. The Year in Obesity / Publications incontournables de l'année 2018 (symposium lecture, co-organizer)

03.05.2019 Aménorrhée hypothalamique. 2ème Journée Update en PMA, Endocrinologie, Gynécologie et Ménopause, Lausanne (invited lecture)

19.06.2019 Endocrinologie pratique au moyen d'exemples de cas. Forum pour la formation médicale FomF, Update Refresher en Médecine Interne, Beaulieu, Lausanne (invited lecture)

04.07.2019 Perturbateurs endocriniens. Centre Universitaire de médecine générale et santé publique (Unisanté) Lausanne (invited lecture)

15.11.2019 Gynecomastia and puberty. Annual SGED Meeting, Bern (invited lecture)

30.01.2020 Reproduction & pathologies hypophysaires. The Year in Endocrinology / Publications incontournables de l'année 2019 (symposium lecture and co-organizer)

04.03.2020 Traitement de la ménopause. Séminaires hebdomadaires du Service d'Endocrinologie, Diabétologie et Métabolisme, CHUV

19.11.2020 La prise en charge endocrinologique I, Programme Dysphorie de genre et prise en charge des demandes de réassignation sexuelle. CHUV (invited lecture)

04.02.2021 La prise en charge endocrinologique II, Programme Dysphorie de genre et prise en charge des demandes de réassignation sexuelle. CHUV (invited lecture)

12.02.2021 Maladies de l'hypophyse et des glandes surrénales. Forum pour la formation médicale FomF, Update Refresher en Médecine Interne, Livestream, Hôtel de la Paix, Lausanne (invited lecture)

19.03.2021 Régulation de l'axe hypothalamo-hypophyso-gonadique et aspects génétiques. CAS en gynécologie médicale et endocrinologie gynécologique, Université de Genève en visioconférence

09.12.2021 La prise en charge endocrinologique, Programme Dysphorie de genre et prise en charge des demandes de réassignation sexuelle. CHUV (invited lecture)

09.12.2021 Hirsutisme, Symposium d'endocrinologie, Morges (invited lecture)

11.12.2021 Cas d'exemple d'affections des glandes surrénales, FomF Update Refresher en Médecine Interne, Livestream, SwissTech Convention Center, Lausanne (invited lecture)

11.05.2022 L'endocrinologie en pratique à partir d'exemple de cas, FomF Update Refresher en Médecine Interne, Livestream, SwissTech Convention Center, Lausanne (invited lecture)

13.05.2022 Hypogonadisme chez l'homme : quel bilan et prise en charge ? FomF Endocrinologie – Diabétologie Update Refresher, Livestream, SwissTech Convention Center, Lausanne (invited lecture)

Invited Lectures: International (2010-present)

22.09.2010 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), 49th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), Prague, Czech Republic (invited lecture)

01.03.2011 Role of FSH in human gonadal development: clinical implications for male fertility. University Tokyo, Japan (symposium)

20.05.2011 Gonadotropin sensitivity. 43rd International Symposia on GH and Growth Factors in Endocrinology and Metabolism (KICGS). Rome, Italy (invited lecture)

4-7.06.2011 Management of hypogonadism through puberty. Meet the Professor Lecture. 93rd Annual Meeting of the Endocrine Society. Boston, USA (invited lecture)

4-7.06.2011 Genetic susceptibility to hypothalamic amenorrhea. 93rd Annual Meeting of the Endocrine Society. Boston, USA (symposium)

27.09.2011 Monogenic disorders behind hypogonadotropic hypogonadism. Sandoz International Satellite Symposium, 50th annual meeting of the European Society for Paediatric Endocrinology ESPE 2011, Glasgow, UK (symposium)

20.10.2011 Complex genetics of human GnRH deficiency. Institute of Metabolic Science Seminar Series. Cambridge, UK (visiting professor)

29.10.2011 Hypogonadotropic hypogonadism. Panel discussion: Treatment of hypogonadotropic hypogonadism in male from childhood. 43rd International Symposium on Endocrinology and Metabolism, Tokyo, Japan (invited lecture)

10.11.2011 Novel insights into hypogonadotropic hypogonadism. 39th Meeting of the British Society for Paediatric Endocrinology and Diabetes. London, England (symposium)

25.02.2012 GnRH deficiency: clinical and genetic aspects. Assir Central Hospital, Abha, Arabia Saudia (visiting professor)

22.03.2012 Novel mutations causing infertility. Session: Clinical Management Workshop 3: Advances in assessment and management of infertility. Society for Endocrinology

BES 2012, Harrogate, UK (symposium)

27.04.2012 Chez qui dépister un diabète ? 10th Swiss-Russian General Practitioners Conference 2012, St-Petersbourg, Russia (symposium)

05.05.2012 New mechanisms of hypothalamic amenorrhea. Symposium 49: Genetic breakthroughs in reproductive pathology and physiology. 15th International Congress of Endocrinology & 14th European Congress of Endocrinology. Florence, Italy (symposium)

20.05.2012 Genetics of idiopathic hypogonadotropic hypogonadism. Neuroendocrine Symposium, Shanghai, China (symposium)

12.09.2012 Functional Hypothalamic Amenorrhea: genetic basis. European NeuroEndocrine Association (ENEA). Vienna, Austria (invited lecture)

28.09.2012 Clinical and genetic aspects of hypogonadotropic hypogonadism. 46th Annual Scientific Meeting of the Japanese Society for Pediatric Endocrinology, Osaka, Japan (symposium)

13.10.2012 Symposium on 'New Genetics of Familial Endocrinopathies' and Symposium on "Male infertility". 15th Annual Meeting of the Canadian Society of Endocrinology and Metabolism & the Canadian Diabetes Association, Vancouver, CAN (symposium)

28.11.2012 Delayed puberty. Symposium on Normal and abnormal development of the male reproductive tract. 7th European Congress of Andrology, Berlin (symposium)

19.01.2013 Hypogonadisme et diabète. Session on Diabetes and sexuality. Les XIV Rencontres Franco-Suisse (Sanofi-Aventis), Evian, France (symposium)

24.04.2013 Genetic basis of congenital hypogonadotropic hypogonadism. German Annual Meeting for Paediatric Endocrinology. Muenster, Germany (symposium)

25.05.2013 Hypogonadisme à l'âge adulte: Flashback sur la puberté. 5ème Symposium francophone (Novo Nordisk). Marseille, France (symposium)

30.08.2013 Oligogenicity in Congenital Hypogonadotropic Hypogonadism. European Joint Scientific Training School COST-FENS-IBRO, Prato, Italy (symposium)

21.09.2013 Genetic aspects of central hypogonadism in the male: The missing genotype-phenotype correlation. 5th International Symposium on Genetics of Male Infertility, Florence, Italy (symposium)

22.09.2013 Redefining syndromes in the era of exomes. 9th Joint Meeting of Paediatric Endocrinology, Milan, Italy (symposium)

06.10.2013 Congenital hypogonadotropic hypogonadism. British Society for Endocrinology Clinical Updates Course, Bristol, UK

22.11.2013 Histoire naturelle de pubertés retardées. 34ème Journées Guéritée, Paris, France (symposium)

06.06.2014 Hormonal control of spermatogenesis in men: Therapeutic aspects in hypogonadotropic hypogonadism. Les 57èmes Journées Internationales d'Endocrinologie Clinique H.P. Klotz, Paris, France (symposium)

08.07.2014 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH). 9th Annual Meeting of the European Neuroscience, Milan, Italy (symposium)

20.09.2014 Lessons drawn from gynaecological disorders in relation with hypothalamic-pituitary malfunction. 53rd Annual Meeting of the Society of Paediatric Endocrinology, Dublin, Ireland (symposium)

08.10.2014 FGF21: un lien entre reproduction et métabolisme. 31ème Congrès de la Société Française d'Endocrinologie, Lyon, France (symposium)

22.11.2014 Male hypogonadism: Pubertal development & fertility. 1st Sandoz Endocrinology Debate and Global Exchange, Vienna, Austria (symposium)

12.12.2014 Induction of spermatogenesis in men with hypogonadism. 9th Hammersmith Multidisciplinary Endocrinology Symposium. Hammersmith, UK (symposium)

18.02.2015 The genetics of hypogonadotropic hypogonadism in males and females. ESE Basic Endocrinology Course in Reproductive Endocrinology 2015. Edinburgh, UK.

03.02.2015 Use of Genomics in Elucidating Puberty. 14th International Pituitary Congress, San Diego, USA (symposium)

05.03.2015 FGF21: Metabolism and Reproduction. The Endocrine Society's 97th Annual Meeting and Expo (Endo 2015), San Diego, USA (symposium)

27.04.2015 NGS in the molecular diagnostic of CHH - exome vs targeted genes:
What is the best strategy? COST Action BM1105 Joint Scientific Meeting & Training School, Monash University Prato Center, Prato, Italy (symposium)

02.10.2015 Pubertal Induction and Fertility Prospects in Males. 54th Annual Meeting of European Society for Pediatric Endocrinology, Barcelona, Spain (symposium)

03.11.2015 FGF's and Hypogonadism. Society for Endocrinology British Endocrine Society 2015, Edinburgh, UK (symposium)

11.11.2015 Hypogonadotropic hypogonadism: Etiology and treatment. Global Excellence Symposium in Growth and Reproduction, Copenhagen, Denmark (symposium)

27.01.2016 GnRH: An overview of its critical role in puberty and reproductive development. Royal Society of Medicine, London, UK (symposium)

04.09.2016 FGFR mutations in congenital hypogonadotropic hypogonadism. Joint meeting of the International Congress of Endocrinology (ICE) and the China Society of Endocrinology (CSE), Beijing, China (symposium)

23.09.2016 Gonadotrophin replacement for induction of fertility in hypogonadal men. 9th European Congress of Andrology (ECA2016) (Symposium)

28.01.2017 FGF21: a link between metabolism and reproduction. Matajc Day International Second Annual Meeting in Pediatric endocrinology, Bled, Slovenia (Symposium)

17.03.2017 Lecture 1: Hypogonadotropic hypogonadism. Finnish society for pediatric Endocrinology, Rovaniemi, Finland (Symposium)

17.03.2017 Lecture 2: Transition Clinic – Our experience. Finnish society for pediatric Endocrinology, Rovaniemi, Finland (Symposium)

21.05.2017 Pubertal induction and hormone replacement in young males. 19th European Congress of Endocrinology (ECE), Lisbon, Portugal (Symposium)

21.09.2017 FGF21: a peripheral hormone linking metabolism with reproduction in humans? 42ème Colloque de la Société de Neuroendocrinologie (SNE), Dijon, France (Symposium)

25.11.2017 Fertility and pregnancy in relation to hypogonadotropic hypogonadism. European Society of Endocrinology (ESE), Krakow, Poland (Symposium)

14.12.2017 Treatment of congenital hypogonadotropic hypogonadism. Masterclass fertility and pediatric endocrinology, Utrecht, The Netherlands (invited lecture)

06.03.2018 FN3 domain in the pathogenicity of CHH, 1st European Center for Reproductive Endocrinology (EUCRE) Conference, Monash University, Prato, Italy (invited lecture and co-organizer)

12.06.2018 Hypogonadotropic hypogonadism in adolescents. European masterclass on hypogonadotropic hypogonadism, Hoofddorp, The Netherlands (invited lecture)

29.11.2018 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), CNE, Pretoria, South of Africa (visiting professor)

30.03.2019 Les hypogonadismes hypogonadotropes réversibles. Les Chemins de Paris, Les Hormones de la puberté, Hôtel Pullman Tour Eiffel, Paris (invited lecture)

18.07.2019 Redefining syndromes at the era of whole genome sequencing. Pediatrics Grand Rounds Madison University Hospital, Madison Wisconsin, USA (visiting professor)

18.07.2019 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH). Primate Center Madison University, Madison Wisconsin, USA

17.08.2019 KS Patients information day. UCL Medical School Library, Royal Free Hospital, Hampstead, London (visiting professor)

02.09.2019 Overlap between CHH and Cornelia de Lange syndrome, 2nd European Center for Reproductive Endocrinology (EUCRE) Conference, Monash University, Prato, Italy (invited lecture and co-organizer)

19.10.2019 Hypogonadotropic hypogonadism from causes to treatment. Combined Endocrinology-Gynecology seminar, Porto, Portugal (visiting professor)

02.03.2020 Mini-Puberty. Horizon 2020, Lille, France (invited lecture)

09.10.2020 New genes involved in the hypogonadotropic hypogonadism, 36ème Congrès de la Société Française d'Endocrinologie (SFE), Marseille (invited lecture – virtual)

15.02.2021 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH). Postgraduated School of Endocrinology, University of Milano (invited lecture – virtual)

02.05.2022 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), Gordon Research Conference, Ciocco in Lucca (Italy)

21.05.2022 Decrease FGF signaling in human reproduction, European Congress of Endocrinology (ECE) Milano (invited lecture)

25.07.2022 Clinical spectrum of congenital hypogonadotropic hypogonadism, Lahore Children Hospital, Pakistan (visiting professor)

26.07.2022 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), CREM Center of Research in Excell in molecular biology, Lahore Pakistan (visiting professor)

27.07.2022 Clinical spectrum of congenital hypogonadotropic hypogonadism, Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), University of Islamabad, Pakistan (visiting professor)

29.07.2022 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), Aga Khan Medical Institute, Karachi, Pakistan (visiting professor)

30.07.2022 Genetic of Congenital Hypogonadotropic Hypogonadism (CHH), Dow Medical Center, Karachi, Pakistan (visiting professor)

07.08.2022 New genes controlling fertility, International Congress of Neuroendocrinology (ICN), Glasgow, UK (invited lecture)

Major scientific achievements of Nelly Pitteloud

Prof. Pitteloud's major contributions to the field of reproductive endocrinology span the following areas:
i) Elucidating the genetic control of puberty and reproduction in humans, ii) redefining the genetic architecture of congenital hypogonadotropic hypogonadism (CHH), iii) transforming our understanding of the spectrum of human GnRH deficiency, iv) identifying predictors of outcome and testing novel therapies to treat infertility, v) discovering a novel link between reproduction and metabolism, vi) Defining a novel gatekeeper involved in the crosstalk between liver, microbiota, and brown adipose tissue and vii) international recognition and diffusion.

i) Elucidating the genetic control of puberty and reproduction in humans
The human disease model of patients with CHH has been a unique source of insight into the genetic control of puberty and reproduction in humans. The study of patients with rare mutations in genes regulating GnRH secretion and action has led to major insights into the physiology of reproduction with potential for the treatment of infertility. Over the last 25 years, genetic studies using cytogenetics, linkage analysis or candidate gene approaches have identified >25 loci comprising rare, high-impact variants underlying CHH. Prof. Pitteloud has been a leader in a number of these important gene discoveries. Notably, her work has deepened our understanding of the critical role of the FGF signaling pathway in reproduction (i.e. FGF8/FGFR1 signaling pathway with mutations in *FGFR1, FGF8, FGF17, HS6ST1*, the *FGF8* synexpression group (1,2,3,4)). More recently, Pr. Pitteloud' laboratory has discovered mutations in genes encoding fibronectin-3 (FN3) domains (*DCC*, *NTN1*, *NDNF*, *PLXNA1*) (22,23,24) in CHH, with a crucial role of these genes in GnRH neuron migration.

ii) Redefining the architecture of CHH
Observations of low penetrance and variable expressivity have long puzzled investigators examining the genetics of CHH. Prof. Pitteloud introduced the innovative notion of digenicity and oligogenicity as an explanation hypothesizing then demonstrating that CHH is not strictly a monogenic disorder (5,6,7). Indeed her lab and others have shown that the genetic architecture of CHH is complex, implicating multiple gene defects in each patient (i.e. oligogenicity) (5,6). Further, CHH presents with several associated phenotypes such as anosmia, cleft palate, hearing loss (8). Recently, we and others have shown that the disease subphenotypes can guide targeted gene identification (1,5,8) with implications for genetic testing and counseling. Our reports of phenotypic and genetic overlap between CHH and other syndromes such as CHARGE syndrome (14), septo-optic dysplasia, combined pituitary hormone deficiency (10), holoprosencephaly (2) and split hand-foot malformation (1) challenge current disease nosology.

iii) Transforming our understanding of the spectrum of GnRH deficiency
Prof. Pitteloud's work has helped elucidate the phenotypic spectrum of CHH (9) as well as work demonstrating that CHH and KS are not distinct clinical entities as previously thought (10). Further, her work has expanded the view for GnRH deficiency with the notion that milder forms of GnRH deficiency can manifest as constitutional delay of growth and puberty (CDGP); adult onset hypogonadotropic hypogonadism (AHH) in men (11) and hypothalamic amenorrhea (HA) in women (12). Indeed the Pitteloud team and others have shown these disorders to be variants across a spectrum of GnRH deficiency. Moroever, Prof Pitteloud's 2007 New England Journal of Medicine article demonstrating CHH reversal in adult life in 10% of patients (13) has completely transformed

the view of CHH from a lifelong disease to a plastic phenotype depending on environmental exposures; this is also supported by our discovery of genetic susceptibility to HA (12).

iv) Identifying predictors of outcome and testing novel therapies to treat infertility

Even though GnRH deficiency is a treatable form of infertility, Prof. Pitteloud identified that 30% of CHH patients remain infertile (9). Moreover, she identified critical predictors of outcome that help guide therapeutic management in the field. By deepening her investigation she used pulsatile GnRH therapy to unmask additional defects in the hypothalamic-pituitary-gonadal axis (15). These additional pituitary and gonadal defects account for some of these treatment failures, unmasked by GnRH treatment. Subsequently, she developed a novel approach to maximize fertility in the most severe cases of GnRH deficiency using a sequential approach (pre-treatment with rFSH) (16). She tested this innovative strategy in a pilot study that showed promising results (17). She led the international group in drafting and publishing the Nature Reviews Endocrinology Consensus Statement on approach to Diagnosis and treatment of CHH that was published in 2015 (18).

v) Discovering a novel link between reproduction and metabolism

Reproductive fitness is known to be tightly linked to energy availability, although the exact molecular mechanisms are still unknown. Through human genetics, we discovered mutations in *KLB* encoding β-Klotho, the obligate co-receptor mediating FGF21 signaling, in patients with CHH and a high frequency of associated metabolic defects. These mutations are loss-of-function and impair FGF21 signaling (19). Further, we reported that *Klb*-deficient mice also exhibit delayed puberty and subfertility partly due to a hypothalamic defect, and that FGF21 reach the hypothalamus through the fenestrated capillaries of the median eminence. Thus, the hepatokine FGF21, a key central metabolic regulator, appears to constitute another critical link between metabolism and reproduction.

vi) Defining a novel gatekeeper involved in the crosstalk between liver, microbiota, and brown adipose tissue

The study of the metabolic phenotype of β-Klotho deficient mice led to an expected finding; these mice were resistant to diet-induced obesity (DIO), although they lack FGF21 signaling pathway. These mice exhibited enhanced energy expenditure and BAT activity. Further they show not only an increase but also a shift in bile acid (BA) composition featured by activation of the classical (neutral) BA synthesis pathway at the expense of the alternative (acidic) pathway. High hepatic production of cholic acid (CA) results in a large excess of microbiota-derived deoxycholic acid (DCA). DCA is specifically responsible for activating the TGR5 receptor that stimulates BAT thermogenic activity. In fact, combined gene deletion of Klb and Tgr5 or antibiotic treatment abrogating bacterial conversion of CA into DCA both abolish DIO resistance in $Klb^{-/-}$ mice (20,21). These data demonstrated that gut microbiota can regulate host thermogenesis via conversion of primary into secondary BA and have critical impact on metabolic phenotypes. Pharmacological or nutritional approaches to selectively modulate gut microbiota may have critical impact on metabolic disorders.

vii) International recognition and diffusion

In 2012, in recognition of her research accomplishments, Prof. Pitteloud was nominated in the Swiss Academy of Science. In parallel, she initiated (and chairs) a European consortium to study GnRH biology (COST Action BM1105) that includes >150 investigators spanning 28 countries. This Action has: i) established a European patient registry for GnRH deficiency; ii) received external funding for new research collaborations; iii) held three training schools and iv) produced a consensus statement on the diagnosis and treatment of GnRH deficiency (18). Recently, she is a founding member for the European Center for Reproductive Endocrinology.

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