

Gonadotrophin Actions Beyond Reproduction

Ilpo Huhtaniemi, MD, PhD

Department of Reproductive
Biology, Imperial College London

Topics:

- Non-reproductive effects of gonadotrophins
- Estragonadal actions of gonadotrophins
- Are gonadotrophins tumorigenic?

FSH Directly Regulates Bone Mass

Li Sun,¹ Yuanzhen Peng,¹ Allison C. Sharrow,^{2,3} Jameel Iqbal,¹ Zhiyuan Zhang,¹ Dionysios J. Papachristou,^{2,3} Samir Zaidi,¹ Ling-Ling Zhu,¹ Beatrice B. Yaroslavskiy,^{2,3} Hang Zhou,¹ Alberta Zallone,⁴ M. Ram Sairam,⁵ T. Rajendra Kumar,⁶ Wei Bo,⁷ Jonathan Braun,⁷ Luis Cardoso-Landa,¹ Mitchell B. Schaffler,¹ Baljit S. Moonga,¹ Harry C. Blair,^{2,3,*} and Mone Zaidi^{1,*}

¹Mount Sinai Bone Program, Department of Medicine and Department of Orthopedics, Mount Sinai School of Medicine, New York, NY 10029, USA

²Departments of Pathology and Cell Biology, University of Pittsburgh, Pittsburgh, PA 15261, USA

³VA Medical Center, Pittsburgh, PA 15261, USA

⁴Department of Anatomy and Histology, University of Bari, 70124 Bari, Italy

⁵Clinical Research Institute of Montreal, Montreal, QC H2W 1R7, Canada

⁶Department of Molecular and Integrative Physiology, University of Kansas, Kansas City, KS 66160, USA

⁷Department of Pathology, University of California, Los Angeles, Los Angeles, CA 90095, USA

*Contact: hcblair@imap.upitt.edu (H.C.B.); mone.zaidi@mssm.edu (M.Z.)

DOI 10.1016/j.cell.2006.01.051

Cell 2006; 125: 247-260.

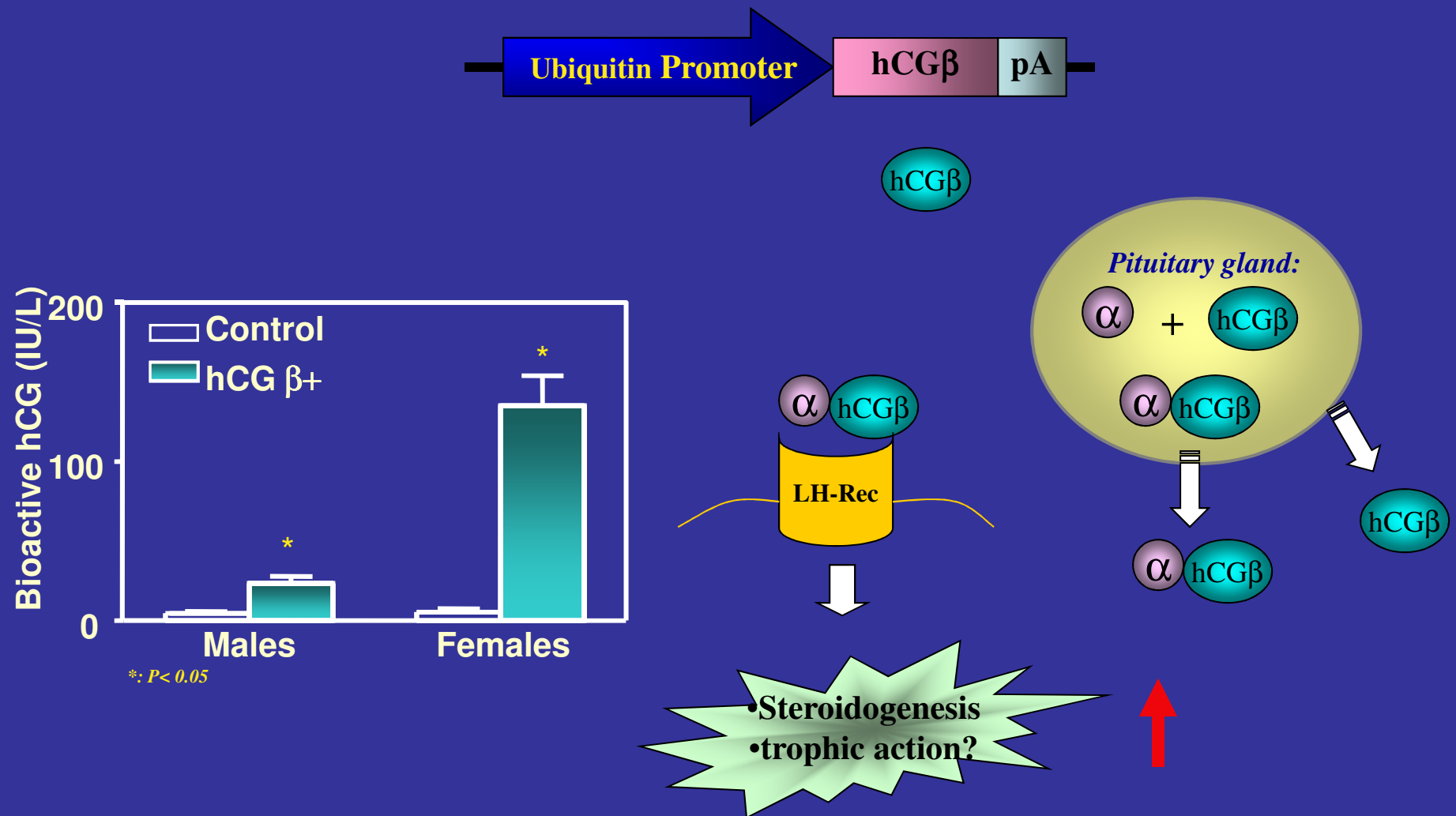
Expression of the LH/hCG receptor has been found in many extragonadal organs:

- Cervix
- Fallopian tubes
- Breast
- Myometrium
- Urinary bladder
- Prostate
- Uterine arteries
- Skin
- Adrenal gland
- Several fetal tissues
- Macrophages
- Sperm
- Trophoblast
- Lymphocytes
- Oocyte
- Early embryo
- Placenta
- Fetal membranes
- Umbilical cord
- Ovarian cancer
- Endometrial hyperpl.
- Prostatic hyperplasia
- Prostatic cancer
- Adrenal hyperplasia
- Leiomyomata
- Endometrial cancer
- Adenomyosis
- Trophoblastic neoplasms
- Epididymis
- Pineal glands

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

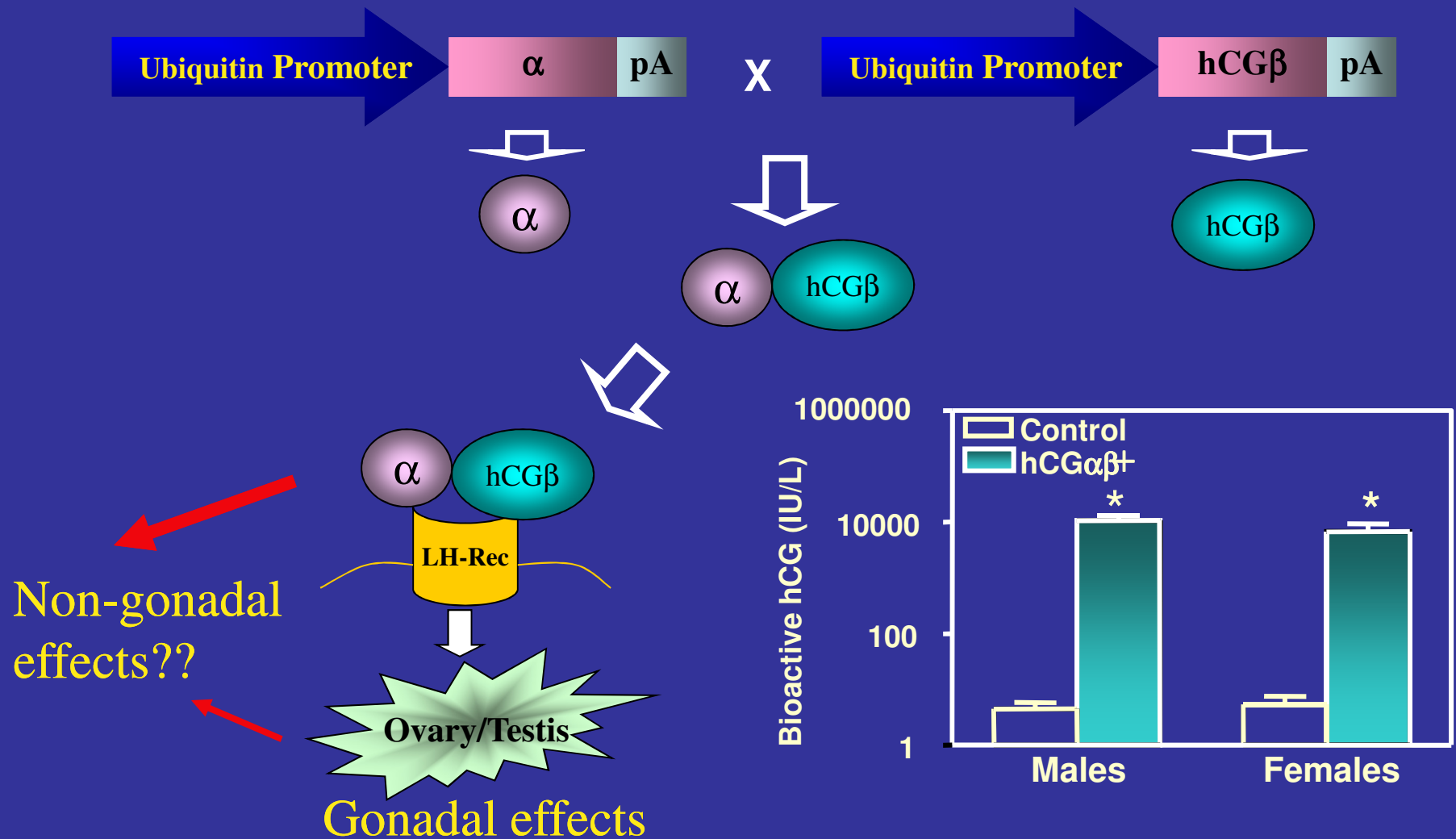
Transgenic Model for High hCG Overexpression

hCG β - subunit under universal ubiquitin promoter (hCG β + mice):



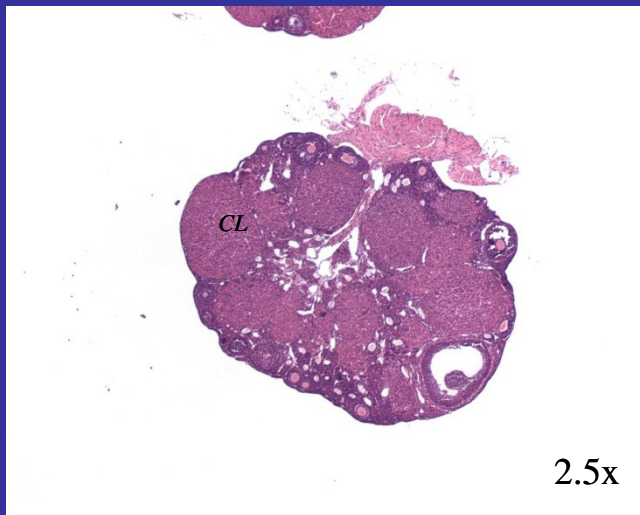
Transgenic Model for High hCG Expression

Common α and hCG β - subunit under ubiquitin promoter
(*hCG $\alpha\beta$ ⁺* mice):

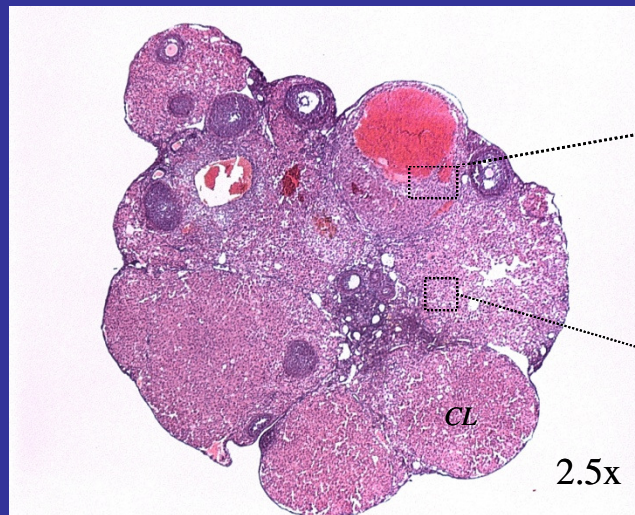


hCG β + female mice: luteinized and cystic ovaries

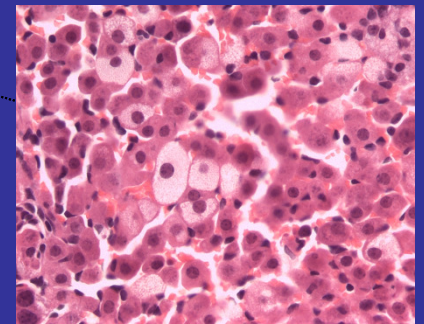
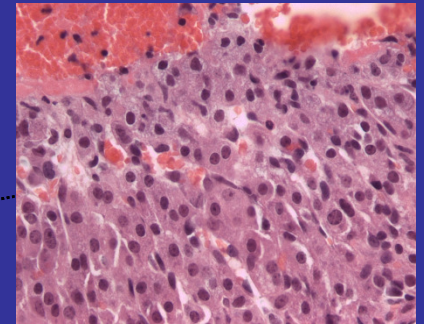
6 month old:



Adult control

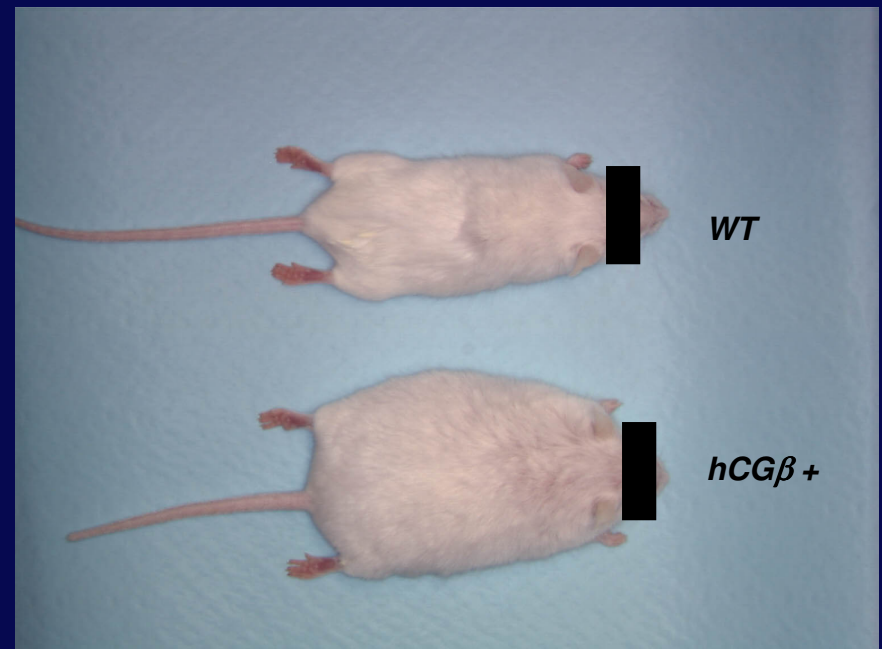
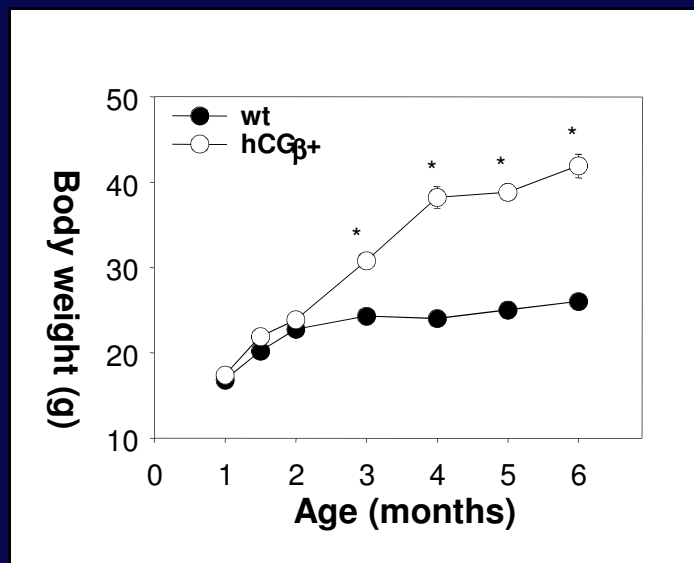


hCG β +, line 24 - 212

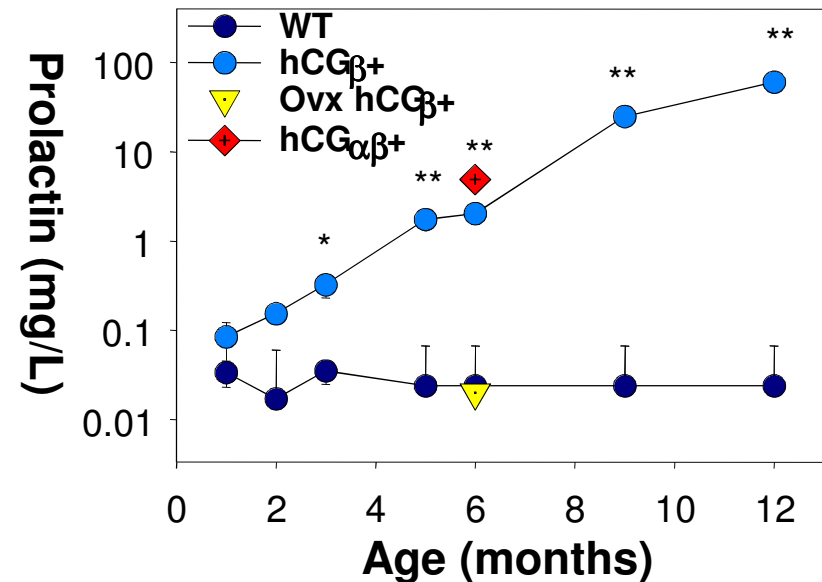
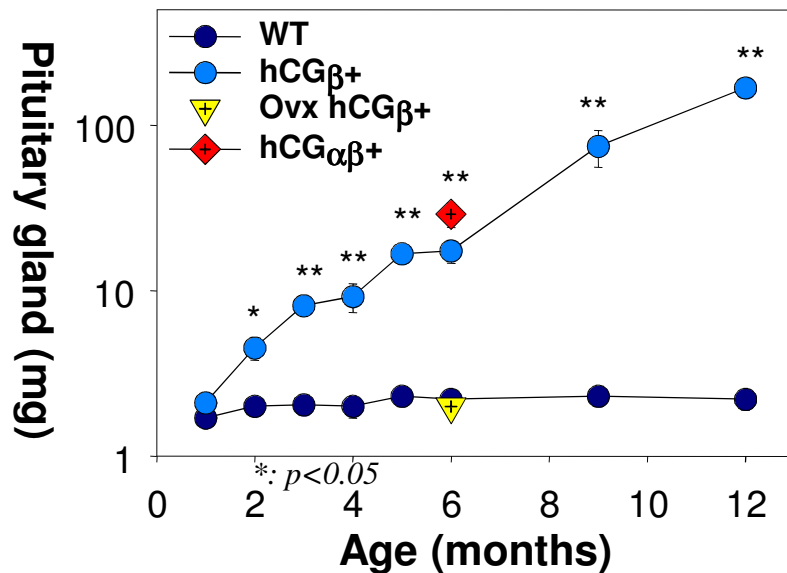


Rulli et al. Endocrinology 2002

TG Female Mice Overexpressing hCG Are Obese

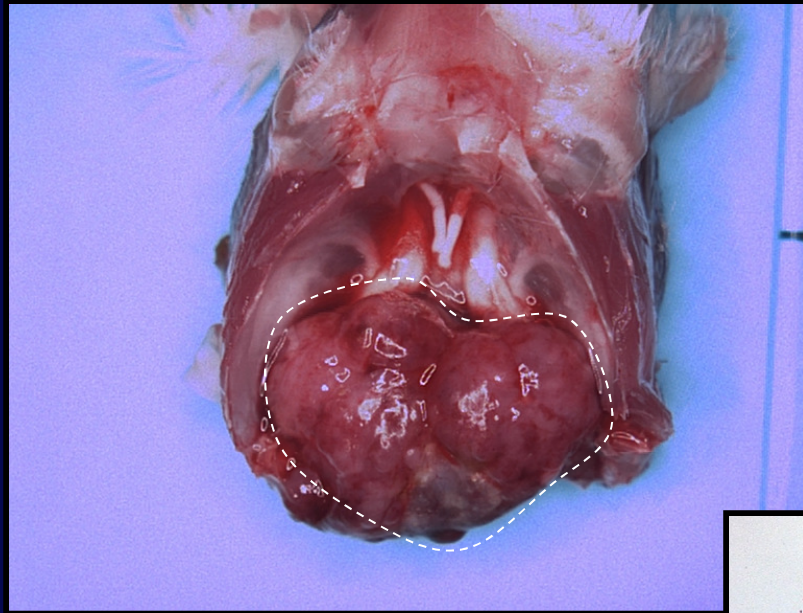


Pituitary Gland Hyperplasia and Adenomas, Associated with Hyperprolactinaemia



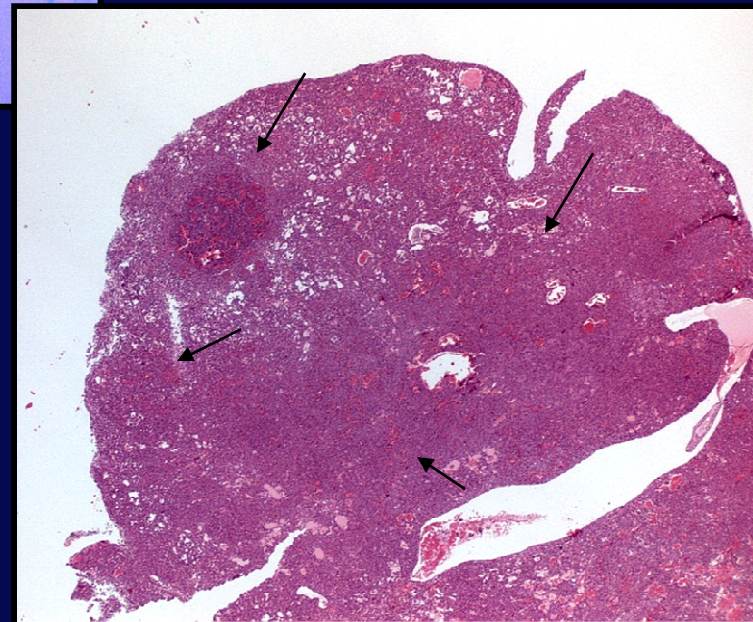
The Pituitary phenotype is prevented by ovariectomy, suggesting the involvement of ovarian steroids or other gonadal factors

Pituitary adenoma



Age: 12 months old
Weight: 205 mg
Size: 1x0.7x0.5 cm

- **Suprasellar expansion**
- **Fragile and hemorrhagic**
- **Irregular shape and distorted architecture**
- **Multifocal nodules**

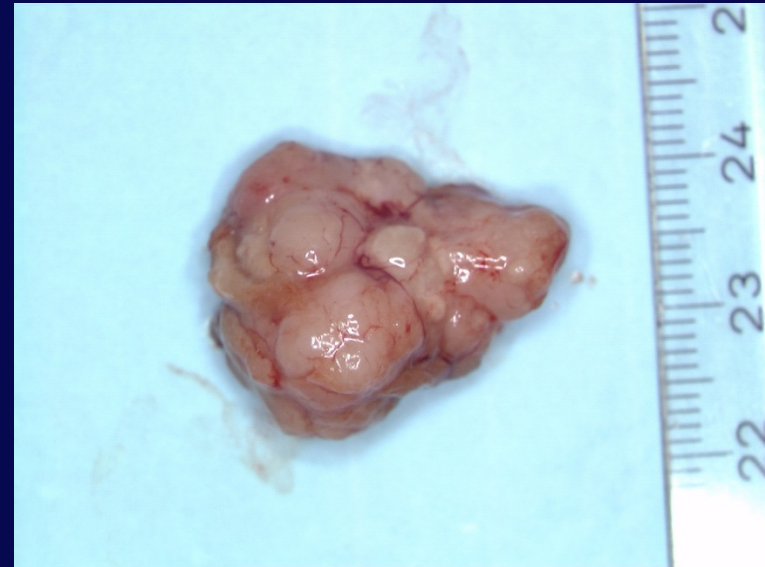
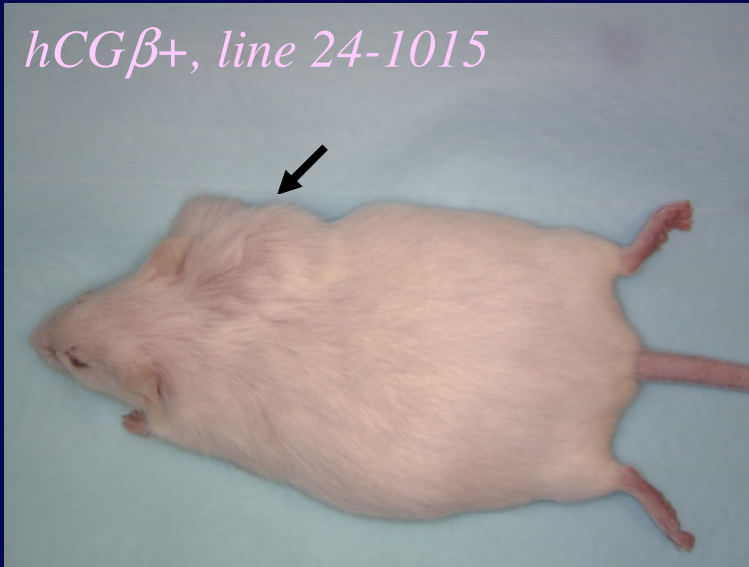


QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

hCG β + female mice: mammary tumors

10 month old:

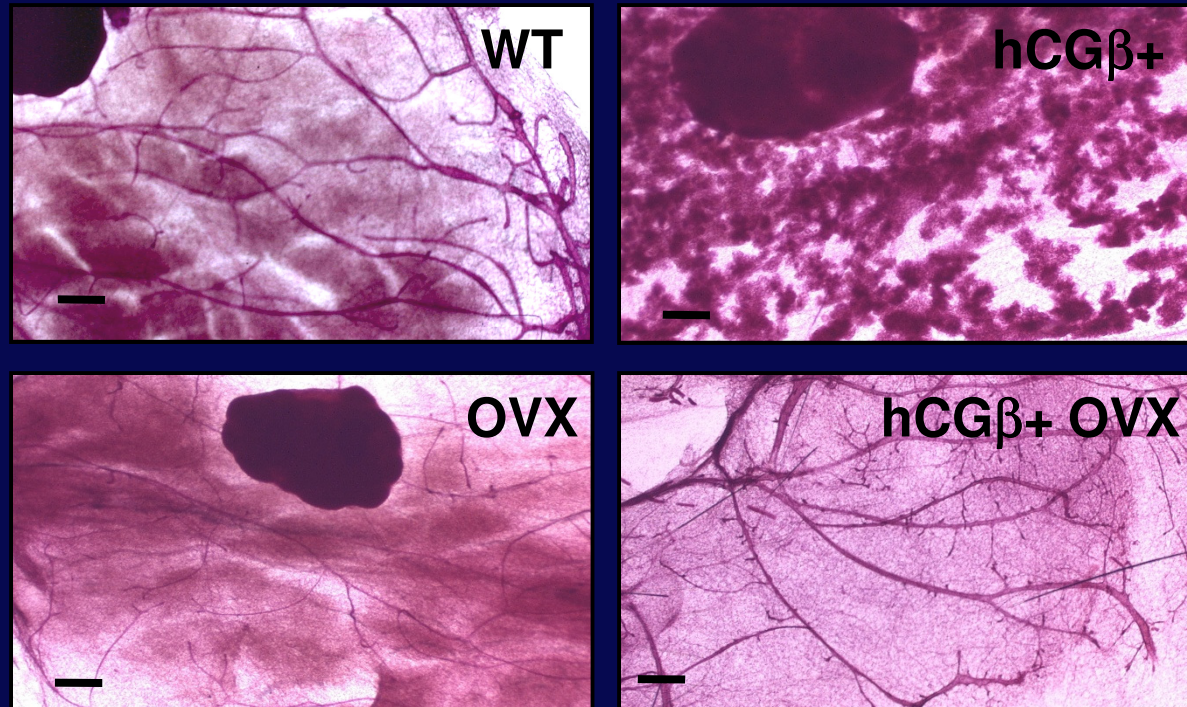
hCG β +, line 24-1015



Weight: 3.2 g

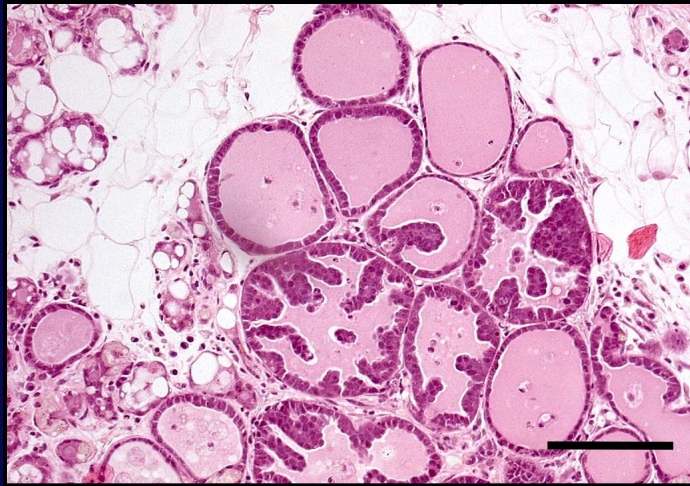
Size: 2x2.5x1.4 cm

Lobuloalveolar development of the mammary gland: Secondary effects of ovarian hyperstimulation



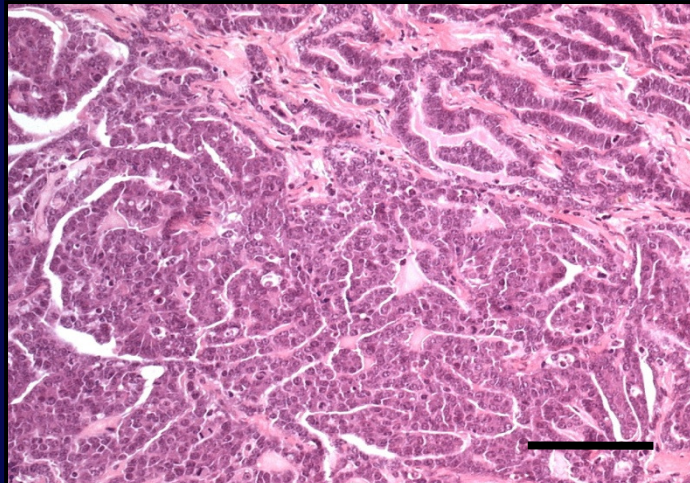
Mice ovariectomized at 6 weeks-old, and analyzed at 6 months of age.

Mammary gland tumours: malignant adenocarcinoma

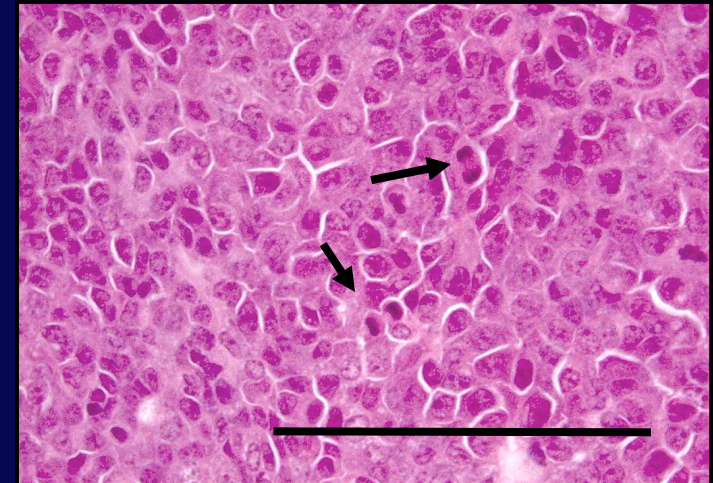


**Epithelial proliferation
forming papillary
projections penetrating into
the alveolar lumen**

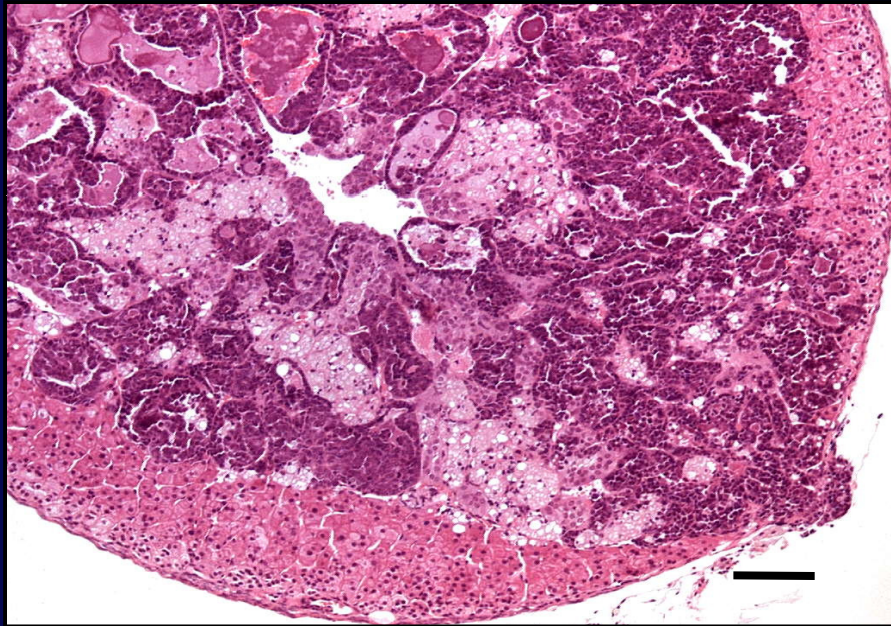
Papillary adenocarcinoma



Areas of solid tumour



Mammary gland tumors: high frequency of metastasis



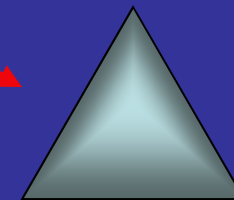
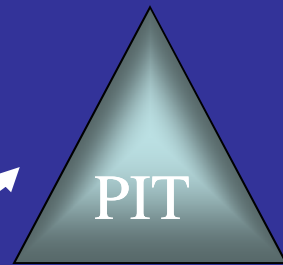
**Mammary tumours
metastasize to the adrenal
gland
(papillary pattern)**

Prolactinomas



Hyperprolactinaemia

Ubiquitin/hCG
TG mice

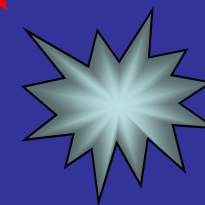
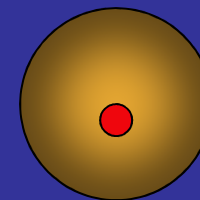


Adrenal hyperplasia

Obesity

Mammary gland
tumours

Metastases



hCG



LH
+

FSH

LHR

FSHR

OVARY

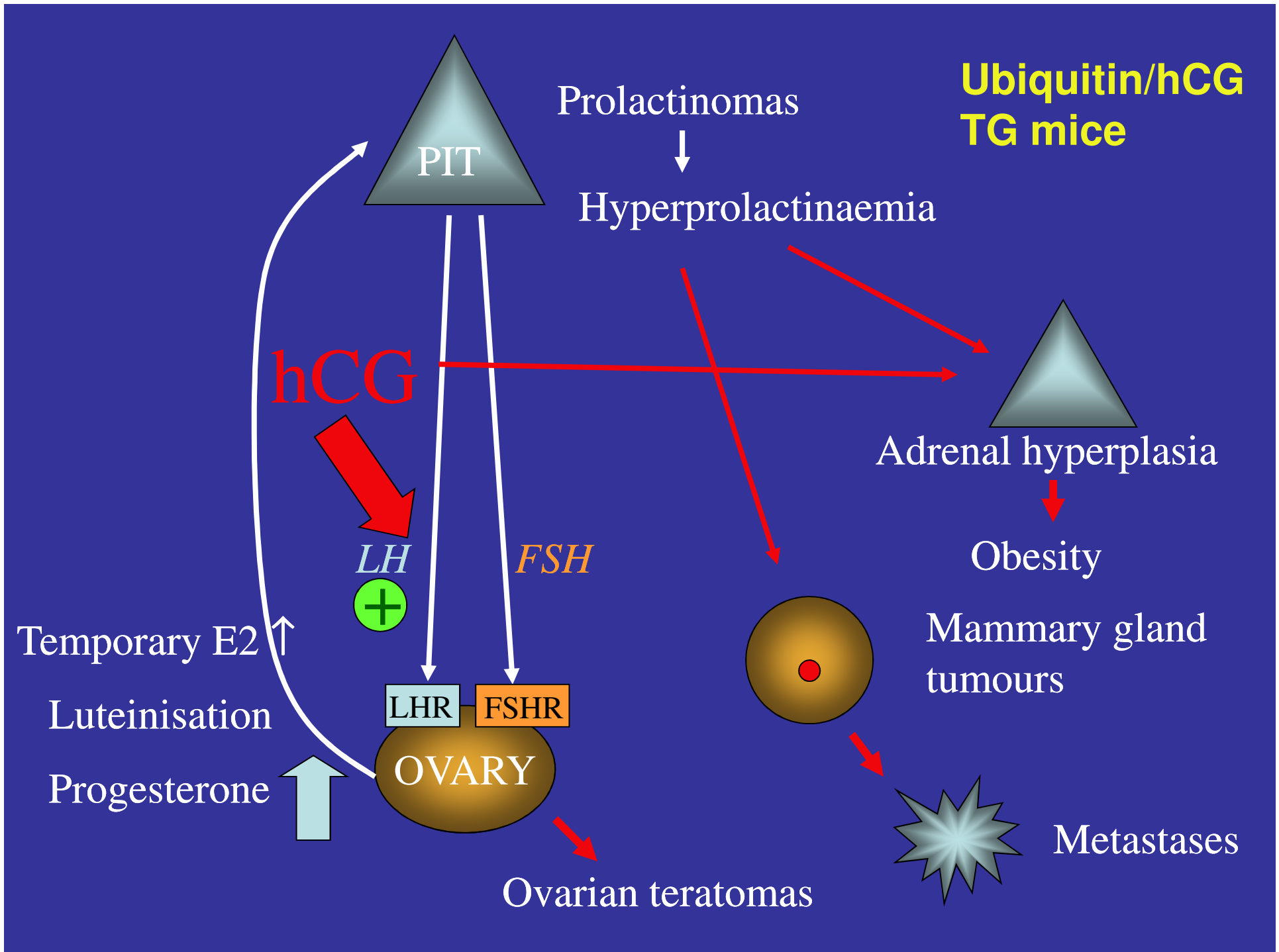
Temporary E2 ↑

Luteinisation

Progesterone ↑



Ovarian teratomas



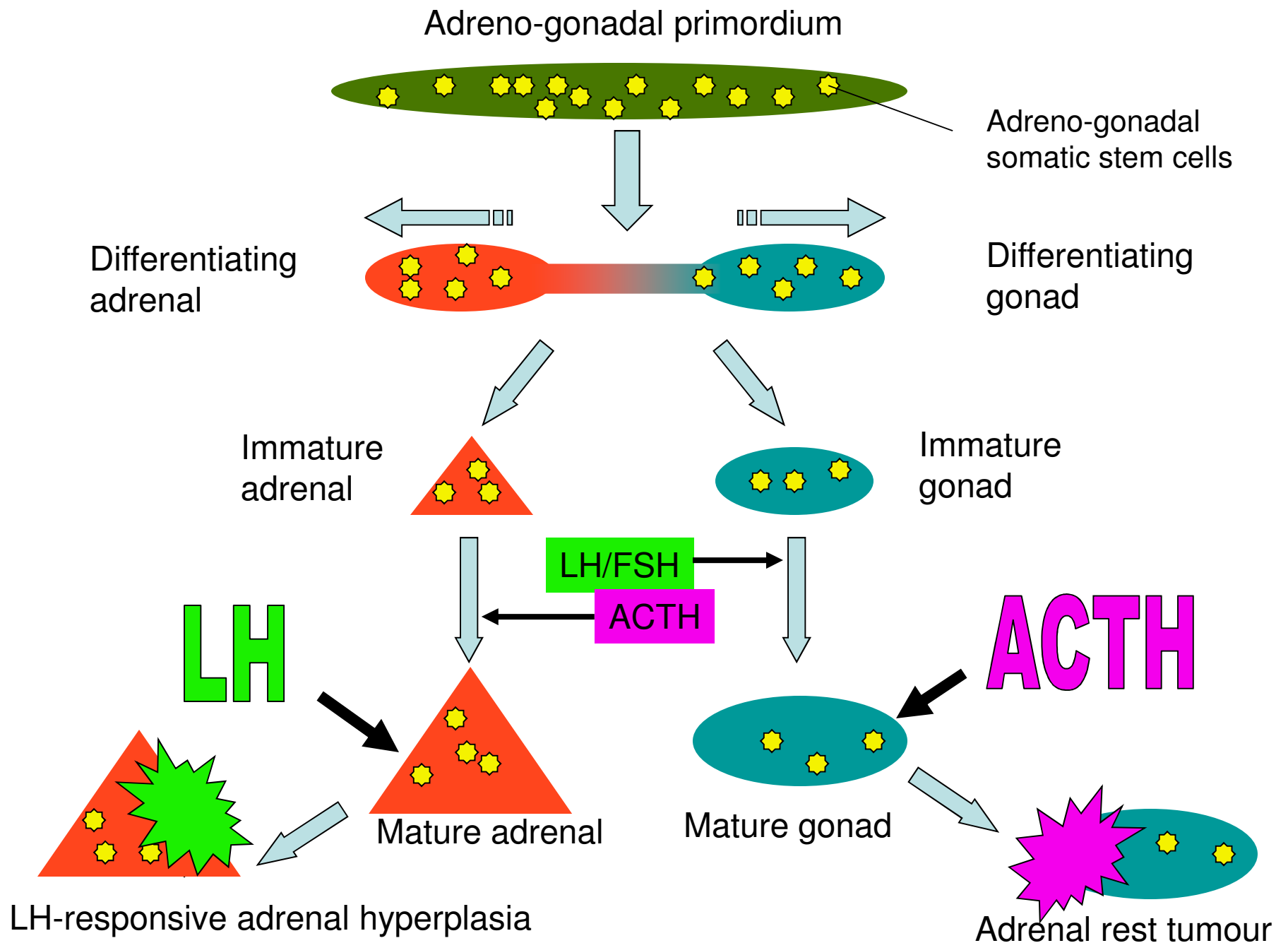
Are gonadotrophins tumorigenic?

It is well documented both clinically and experimentally that gonadotrophin-stimulated gonadal sex hormone production can promote hormone-dependent tumours. In contrast, the evidence for direct tumorigenic effects of gonadotrophins relies mainly on *in vitro* studies, and the clinical and experimental evidence *in vivo* is still fragmentary, weak and controversial.

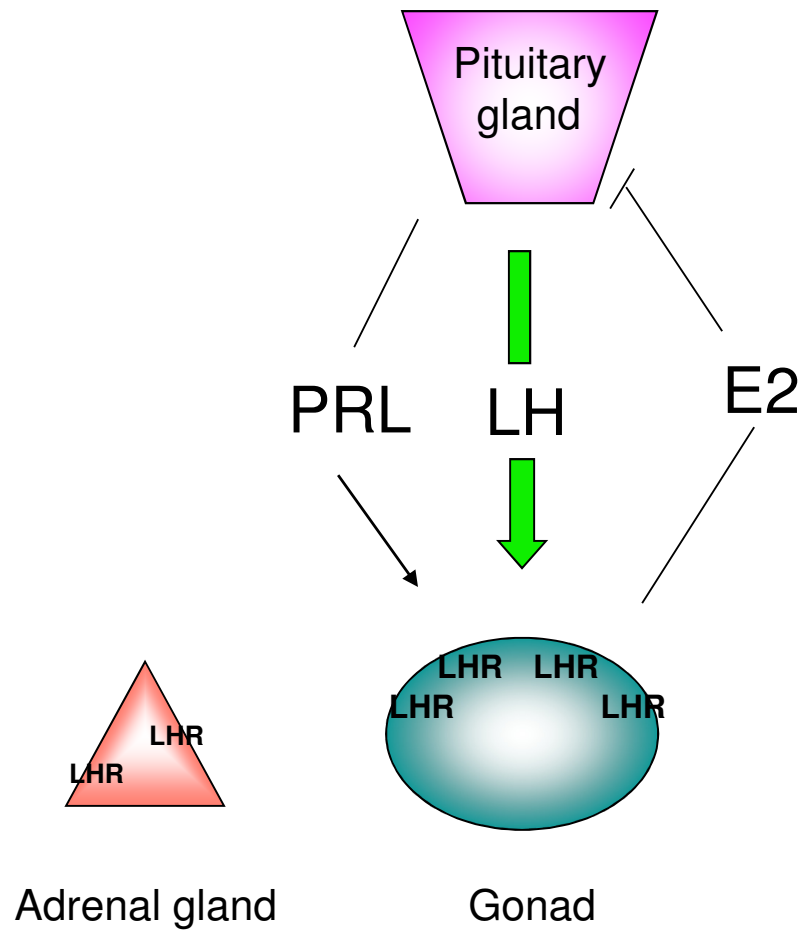
- Studies from 1940's demonstrate that certain strains of mice develop adrenal tumours after gonadectomy
- Susceptible strains e.g. DBA/2J and CE/J
- Non-susceptible strains e.g. C57Bl and FVB/N
- Can we identify the genetic polymorphism(s) responsible for the post-gonadectomy tumorigenesis in susceptible strains?
- Genetic linkage study in DBA/2J and C57/6J strains

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

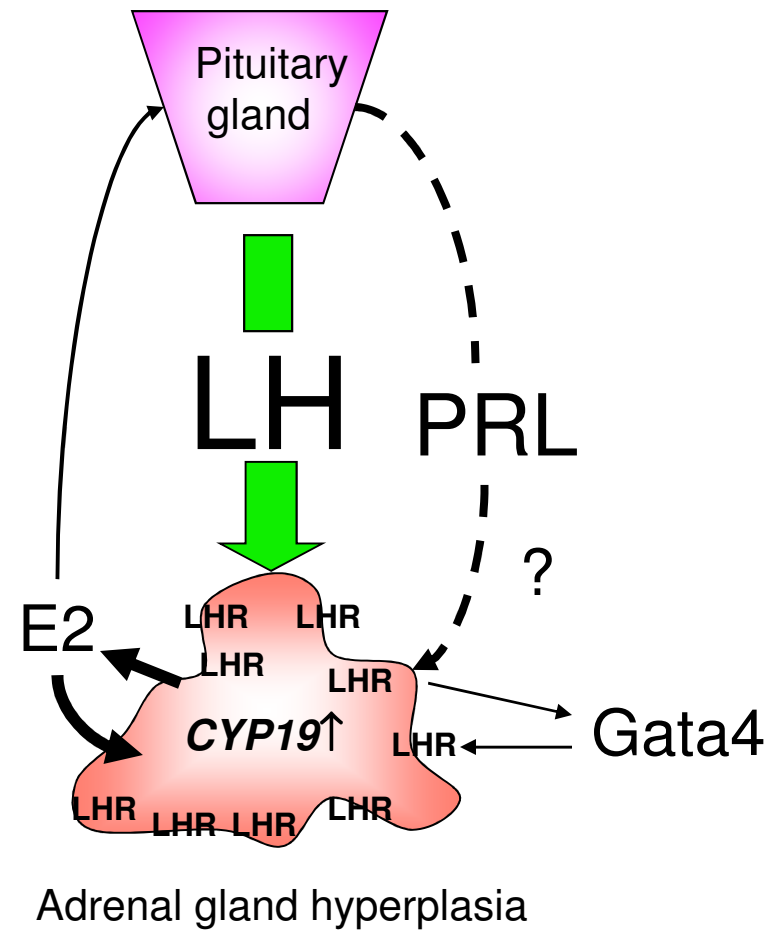
Endocrinology 2008; 1249; 651-661.



A) Intact

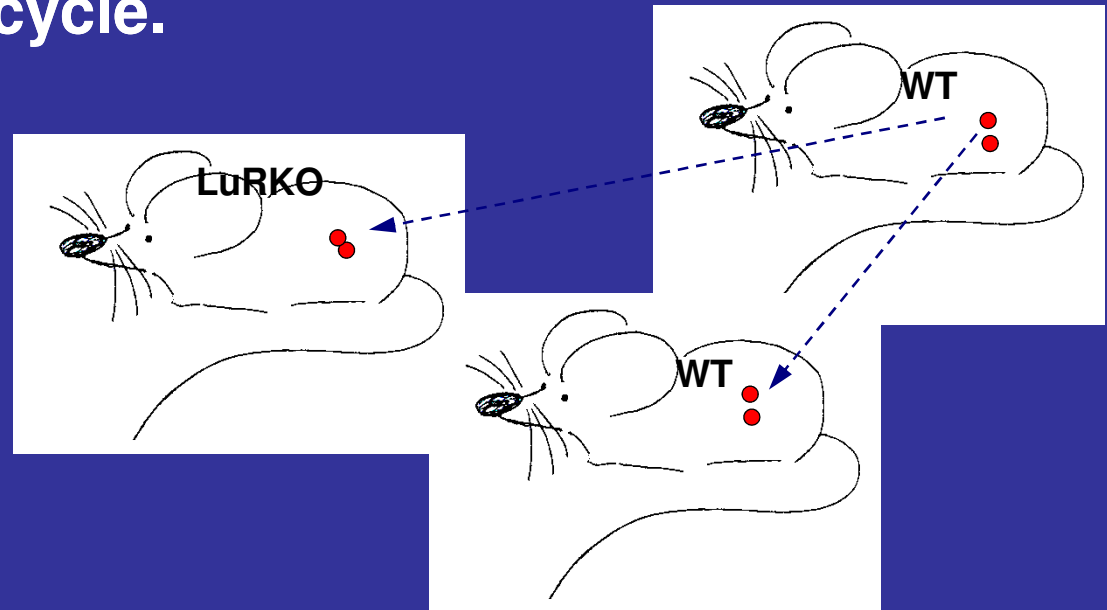


B) After gonadectomy



Are extragonadal LH receptors important for mouse reproductive function? - Ovarian transplantation in LH receptor knockout (LuRKO) mice?

- Ovaries from prepubertal WT mice were orthotopically transplanted to 21 d-old LuRKO mice.
- Function of transplants was monitored by vaginal opening and oestrous cycle.
- Mice with successful transplantation were mated with WT males.

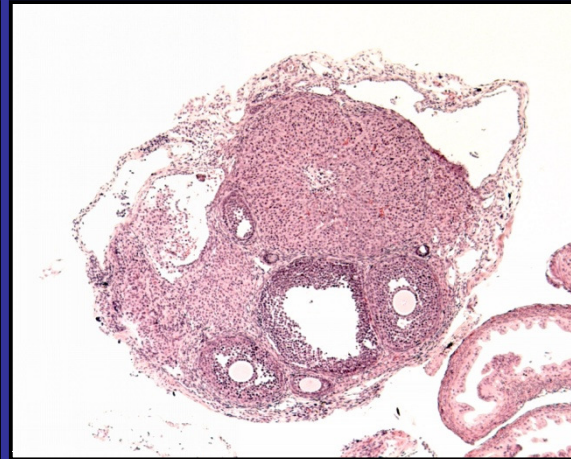


Onset of Ovulation in Orthotopically Transplanted WT Ovaries in LuRKO and WT Mice

LuRKO



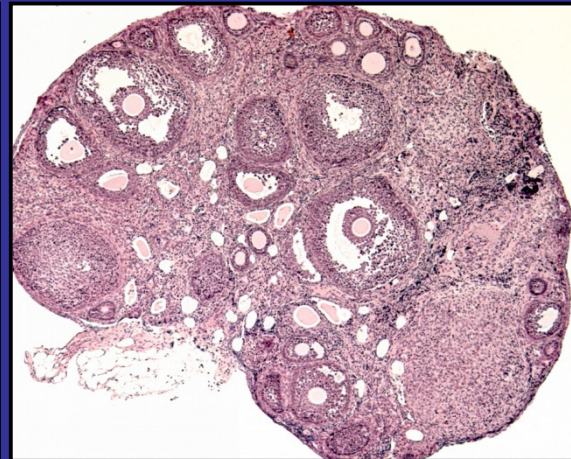
LuRKO
+ WT



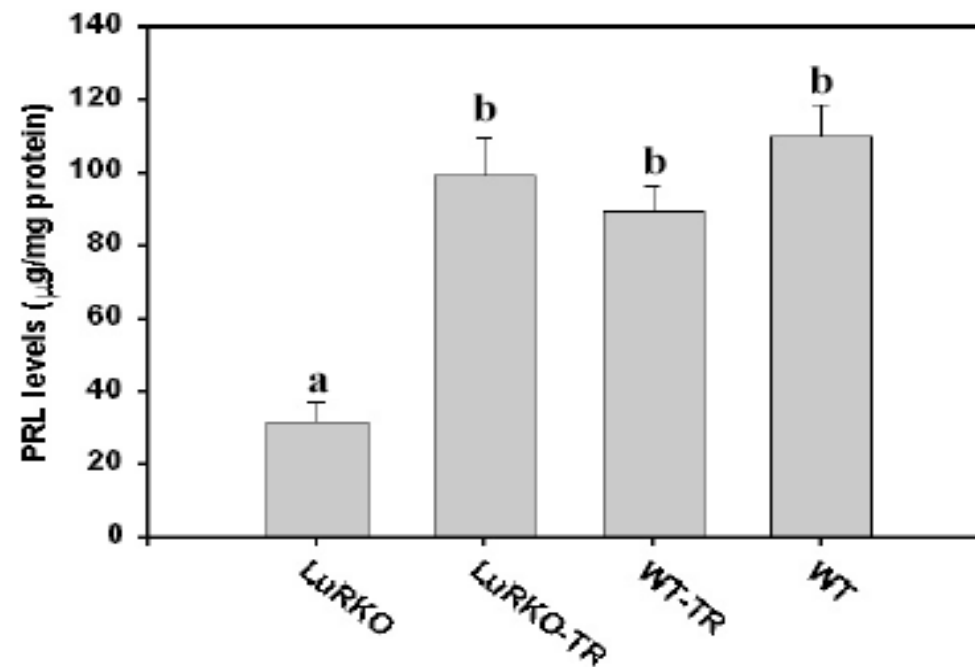
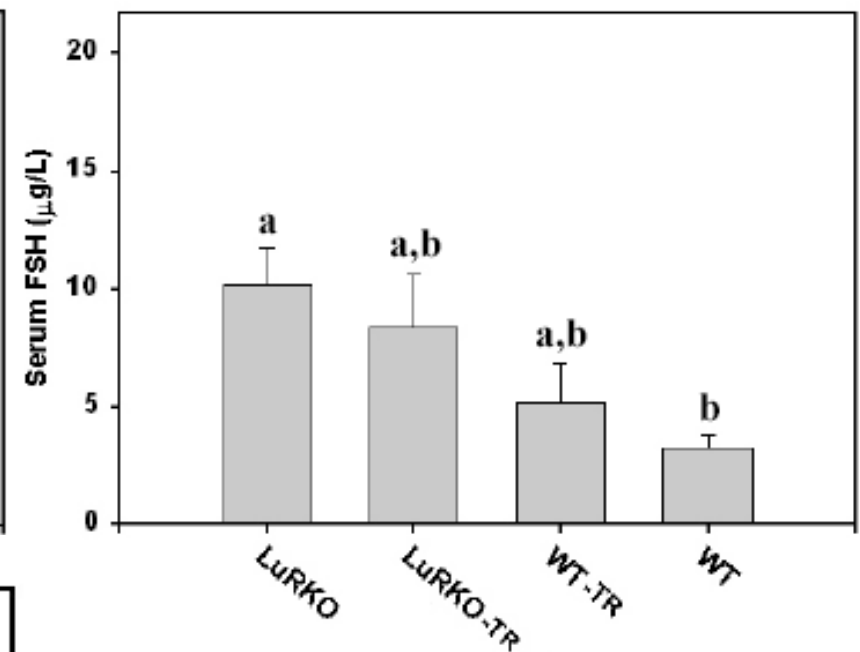
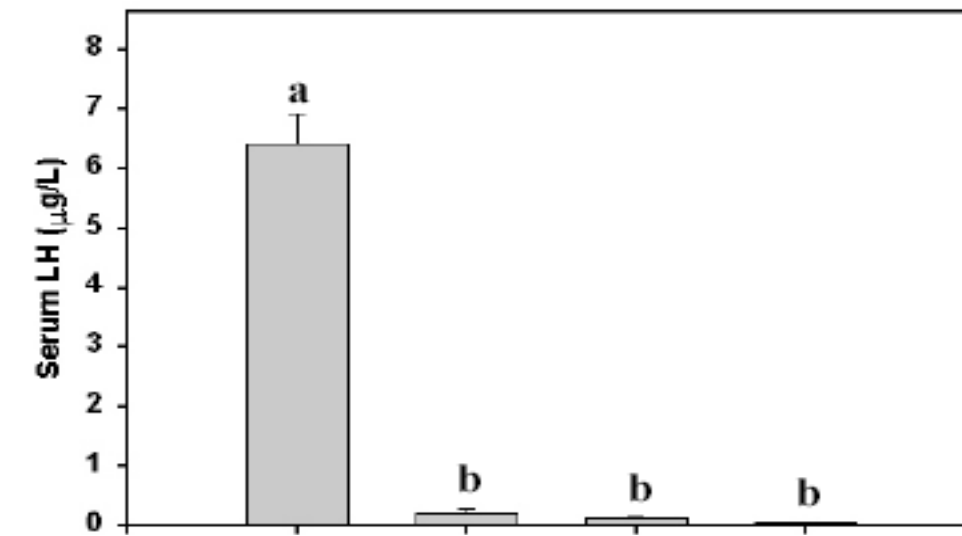
WT + WT



WT



Serum LH, FSH and PRL in Ovary-Transplanted LuRKO and WT Mice



Pakarainen et al. JCI 2005.

LuRKO females show wild-type phenotype after ovary transplantation and become fertile

	No. of mice bred	Vaginal plugs	Litters born	No. of pups/litter
LuRKO + WT ovaries	20	95 %	9 (56 %)	4.2 ± 2.4
WT + WT ovaries	22	95 %	16 (80 %)	4.4 ± 2.3
WT, without operation	10	100 %	10 (100 %)	6.0 ± 2.4

N.S.

→ Extragonadal LHR have no effect on sexual behavior and fertility of female mice.

LuRKO + WT ov.



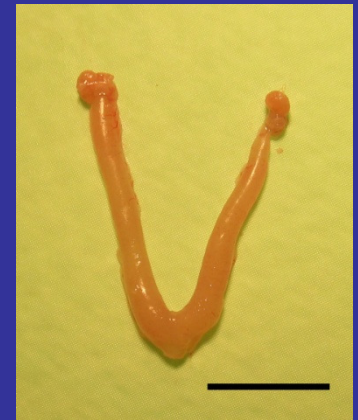
1 cm

LuRKO



1 cm

WT



1 cm

Conclusions: Extragonadal actions of gonadotrophins

- The effect on FSH on osteoclast function needs independent verification
- Mouse data demonstrate direct LH/hCG effects on adrenal and mammary glands
- Extragonadal LHR expression is not needed for female mouse fertility
- Mouse data demonstrate extragonadal tumorigenic effects of LH/hCG
- In humans, the best evidence for extragonadal gonadotrophin action is on adrenal cortex

Department of Physiology, University of Turku, Finland

- Tomi Pakarainen
- Fuping Zhang
- Petteri Ahtiainen
- Susana Rulli
- Matti Poutanen



Grants

- The Academy of Finland
- Sigrid Jusélius Foundation
- Medical Research Council UK
- The Wellcome Trust
- European Union

