COLLOQUE SCIENTIFIQUE FIRENDO

2ème ÉDITION

« DIMORPHISME SEXUEL DANS LES MALADIES RARES ENDOCRINIENNES »

MARDI
11 DÉCEMBRE
2018

FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

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« DIMORPHISME SEXUEL DANS LES MALADIES RARES ENDOCRINIENNES »

DIMORPHISME SEXUEL DU RENOUVELLEMENT CELLULAIRE DE LA CORTICOSURRÉNALE

Anaëlle GRABEK
agrabek@unice.fr

Andreas SCHEDL Lab
Institut de Biologie Valrose, Nice

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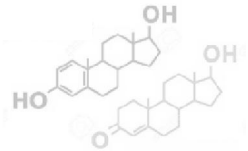
TABLE

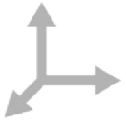
I INTRODUCTION

II SEX-SPECIFIC ADRENAL CORTEX HOMEOSTASIS

III ROLE OF THE SEX CHROMOSOMES



III ROLE OF THE SEX HORMONES



IV CONCLUSION & PERSPECTIVES

SEX SPECIFICITY OF THE ADRENAL CORTEX

DISEASE PREVALENCE

Cushing syndrome – Steffensen et al., 2010

Addison's disease – North American Survey of Individuals with Addison's disease, 1997

Adrenal cortical cancer – Audenet et al., 2013; Ayala-Ramirez et al., 2013; Scollo et al., 2016

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HISTOLOGY

X-zone regression – Hershkovitz et al. 2007
Cortex (zF) thickness – Bielohuby et al. 2007

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HISTOLOGY

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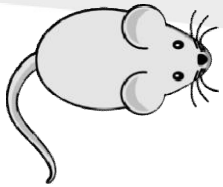
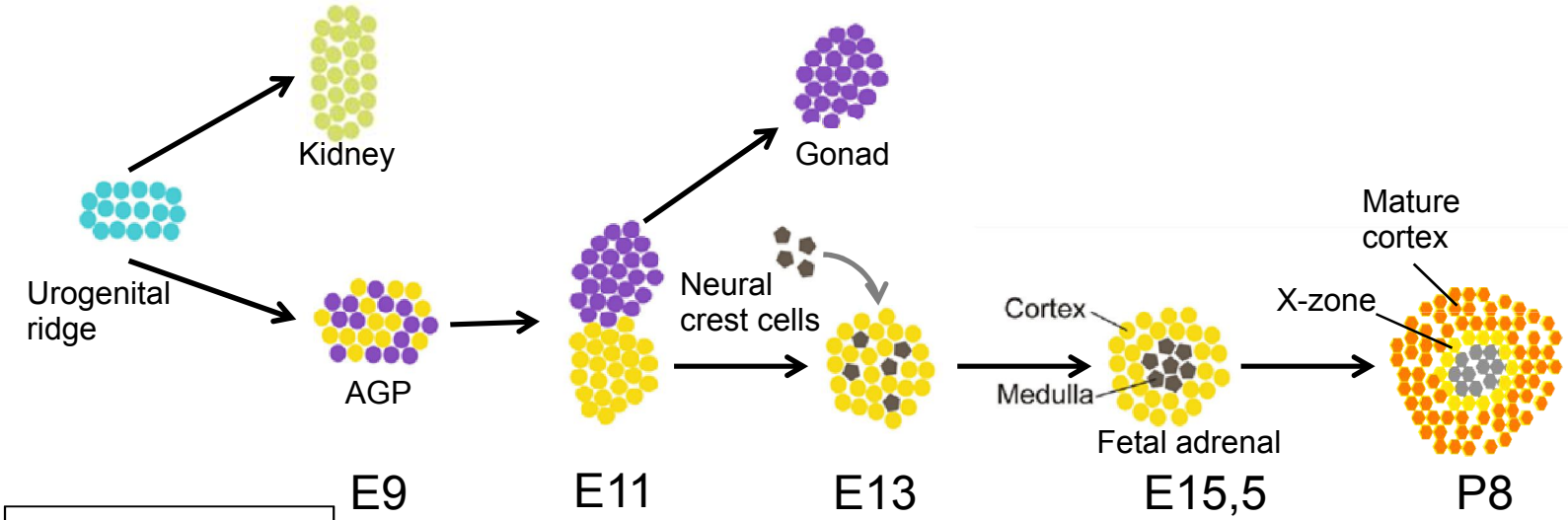
PHENOTYPE DEVELOPMENT

Constitutive activation of β-catenin – Berthon et al. 2012
RSPO1 gain of function – unpublished
YAP/TAZ knock out – Levasseur et al. 2017
RSPO3 knock out – Vidal et al. 2016

ADRENAL DEVELOPMENT

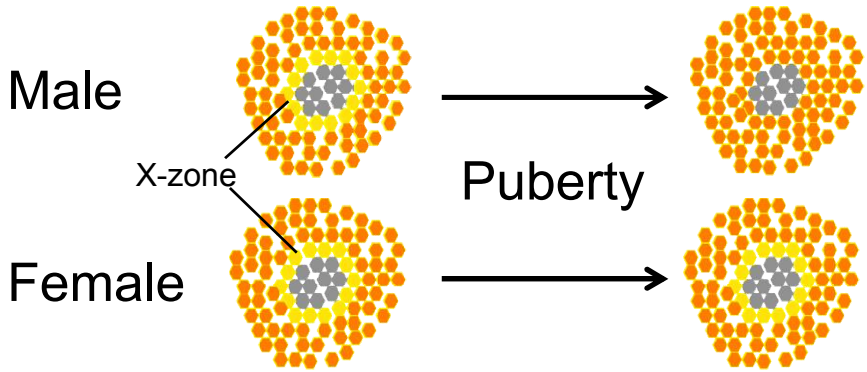


Development



At puberty

- Loss of the X-zone, remnant of the fetal adrenal, in the male



Modified from Pihlajoki et al. *Front Endocrinol* (2015)

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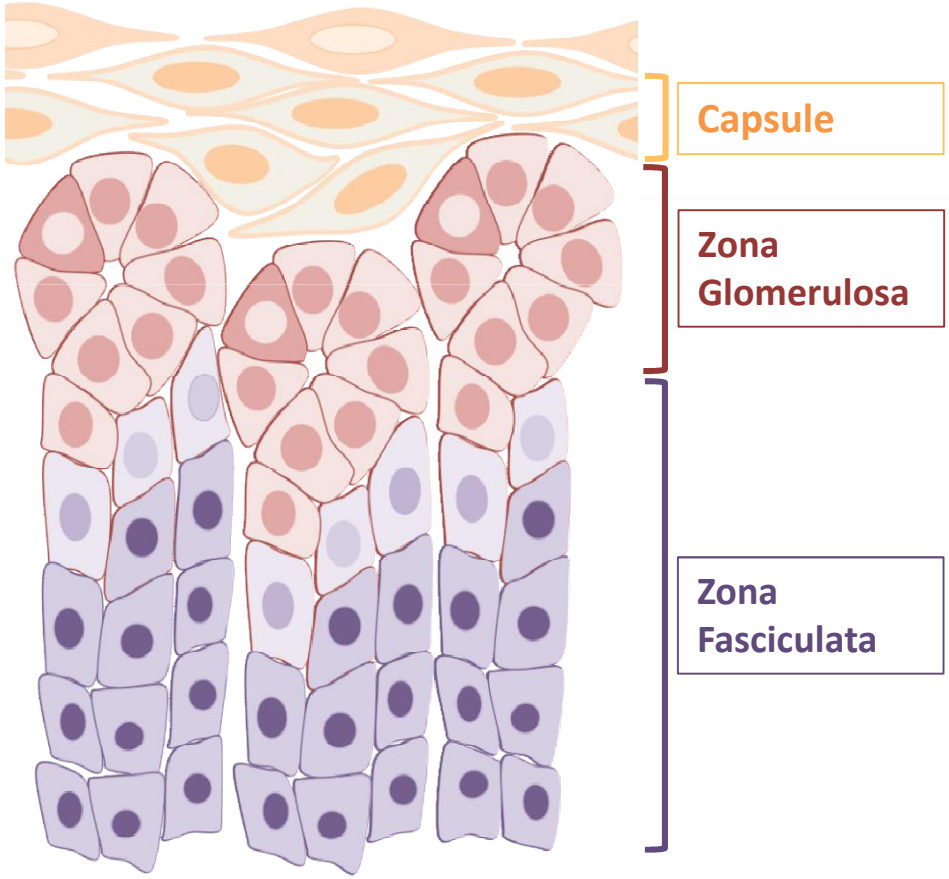
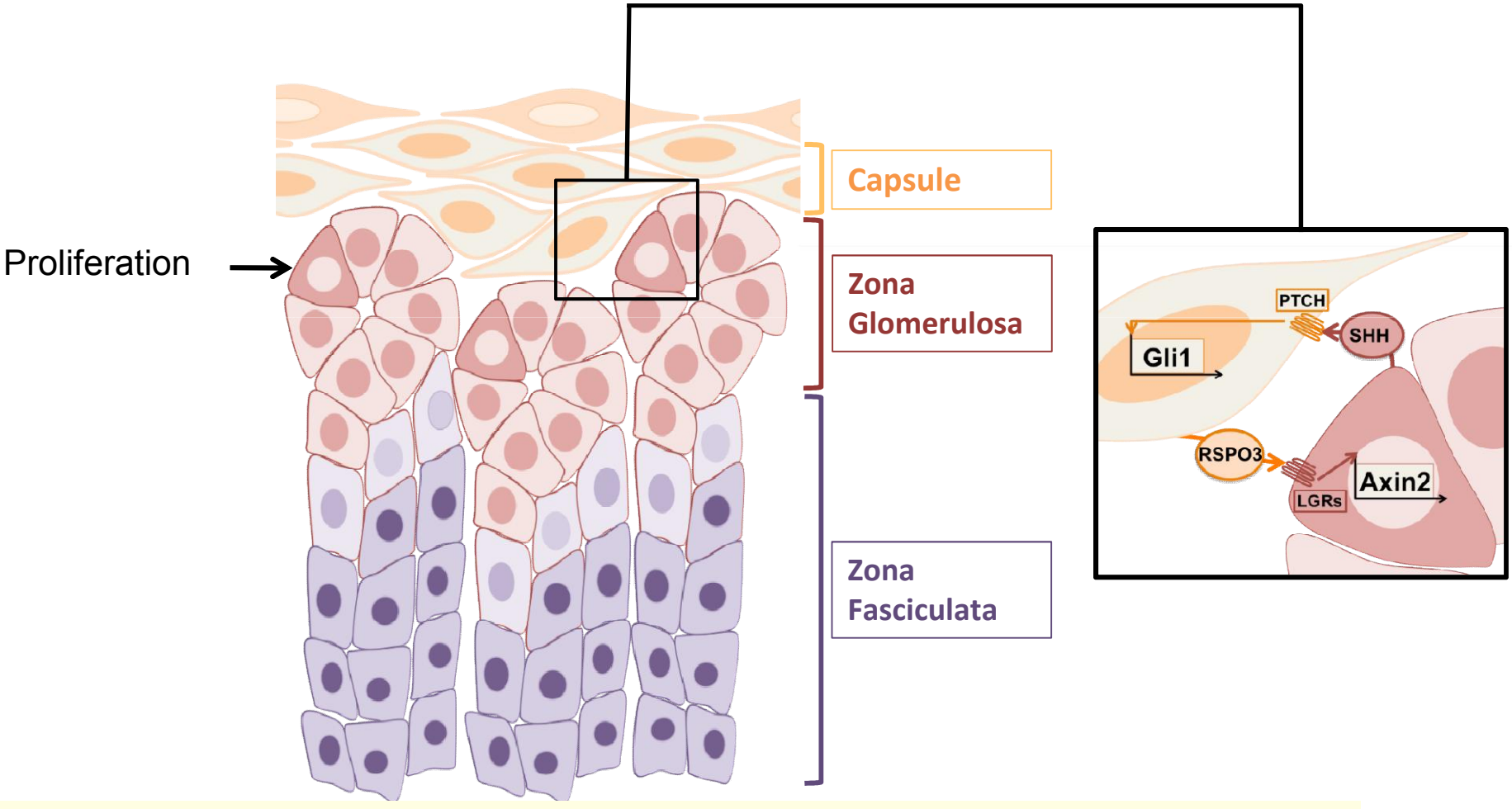
ADRENAL CORTEX HOMEOSTASIS

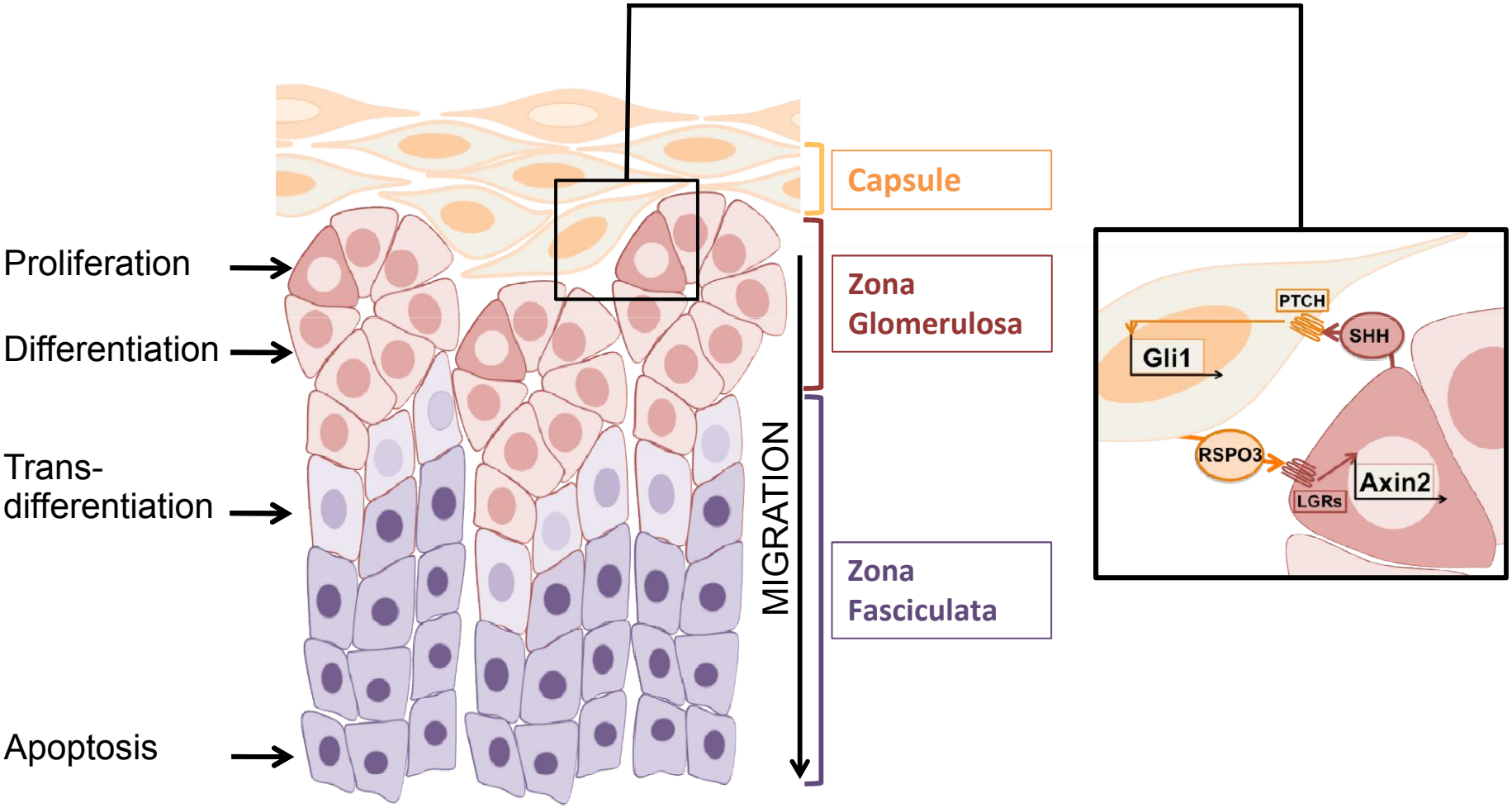


ADRENAL CORTEX HOMEOSTASIS



- SHH mark a progenitor cell population
- Rspo3 is required to maintain proliferation and zonation of the adrenal cortex

ADRENAL CORTEX HOMEOSTASIS



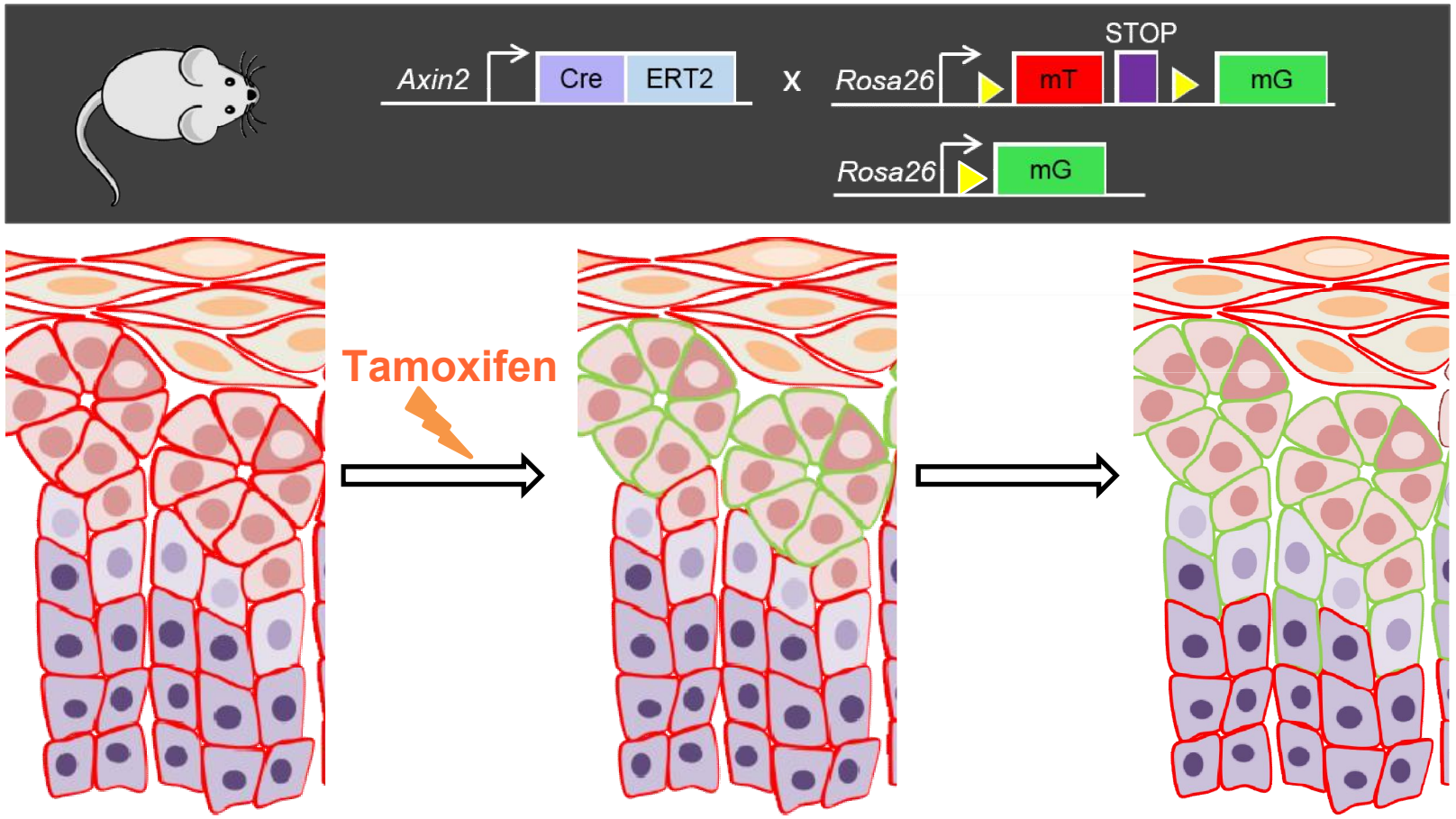
- Cells from the zG transdifferentiate into zF as they centripetally migrate
- Equilibrium between proliferation and apoptosis to maintain the cortex

STUDY AIM

Is adrenal cortex homeostasis sexually dimorphic?

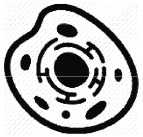
What is driving the sexual dirmorphism?

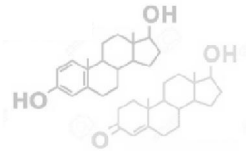
LINEAGE TRACING EXPERIMENT

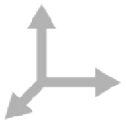


- Label a specific cell population
- Follow the fate of the cells and their descendants

TABLE

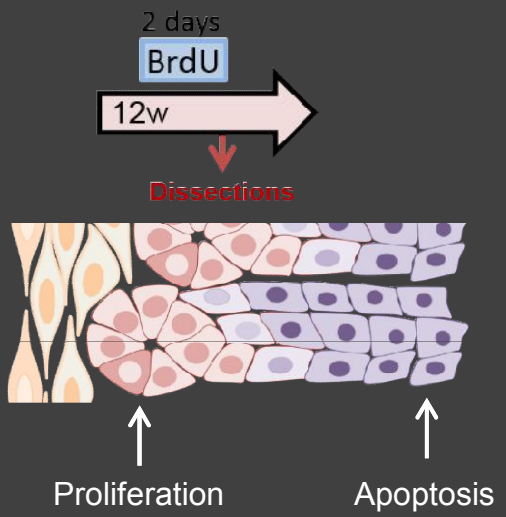


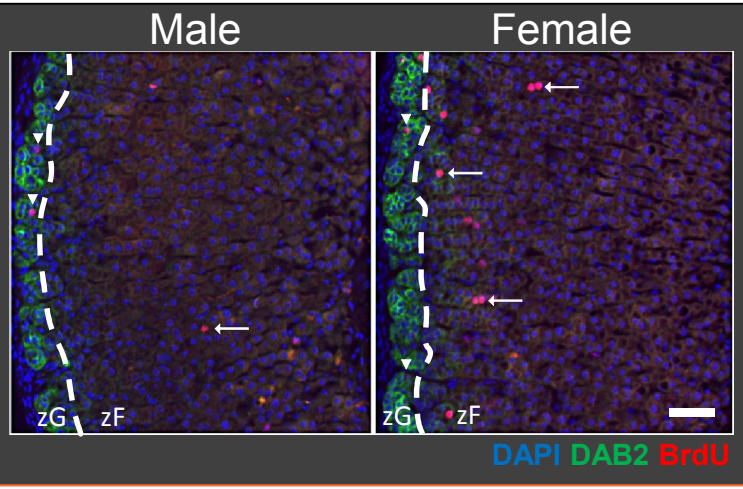


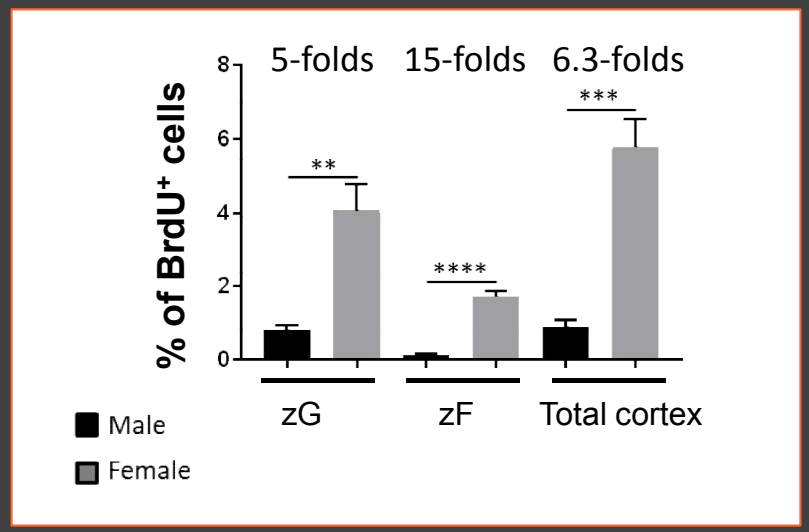


PROLIFERATION ANALYSIS

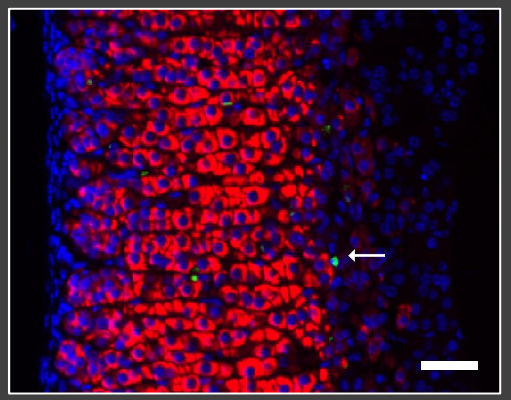
Poliferation

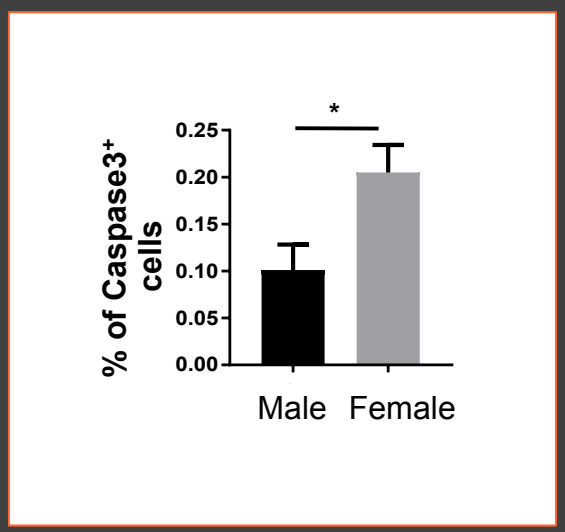






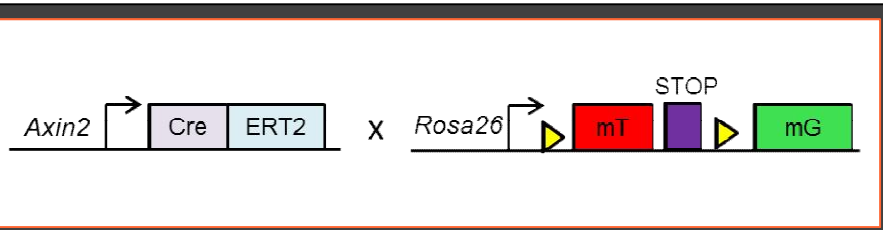
Apoptosis

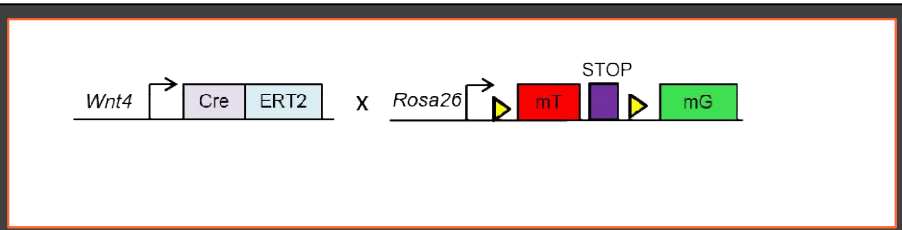


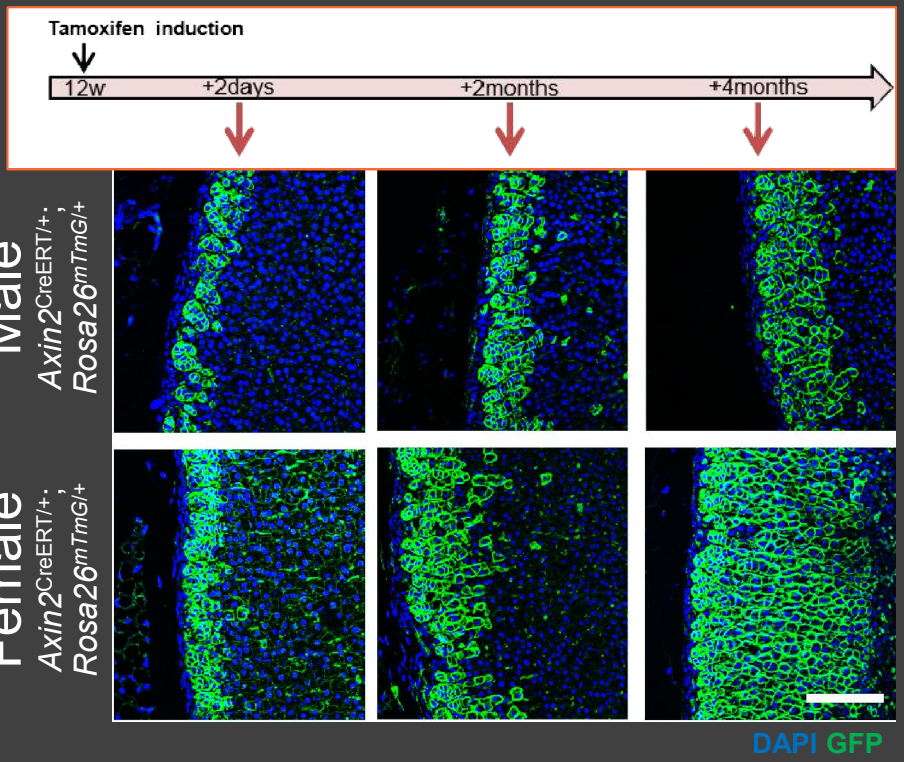


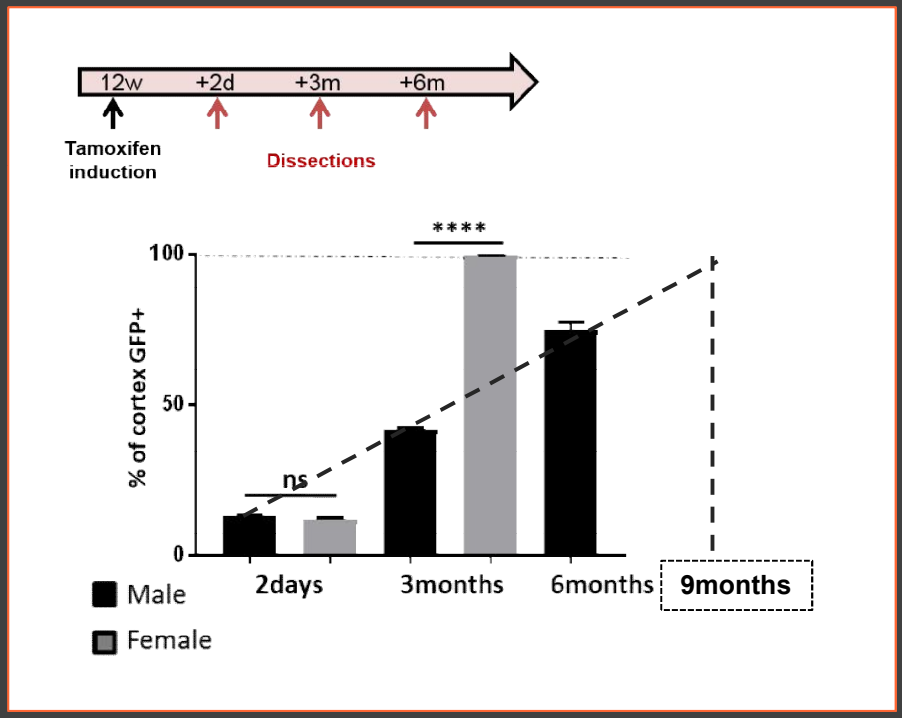
- Proliferation and apoptosis are increased in the female cortex

SEXUALLY DIMORPHIC RENEWAL





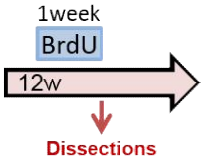


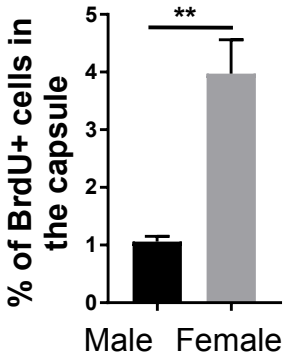


- Cellular renewal of the adrenal cortex is increased in females

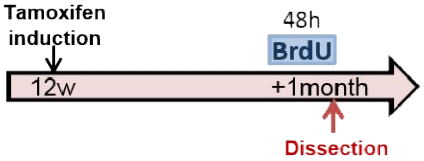
ACTIVITY OF THE CAPSULAR COMPARTMENT

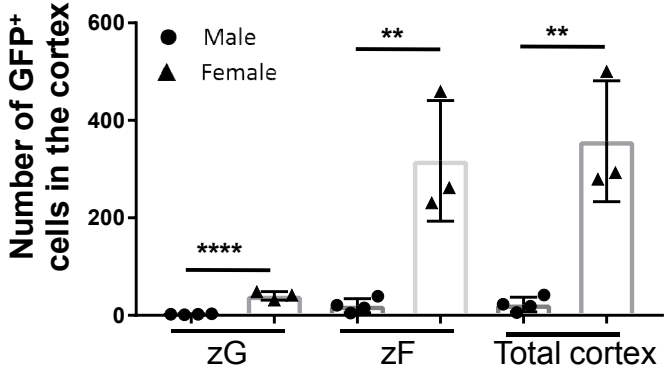
Proliferation

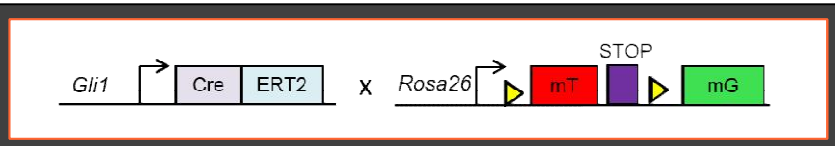


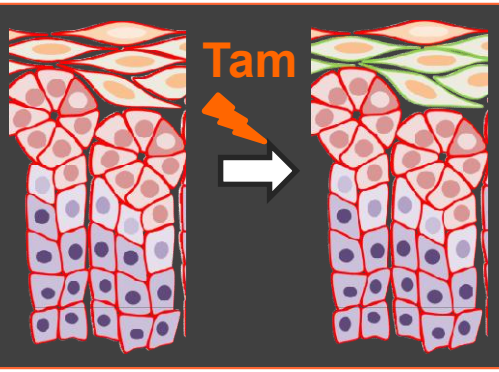


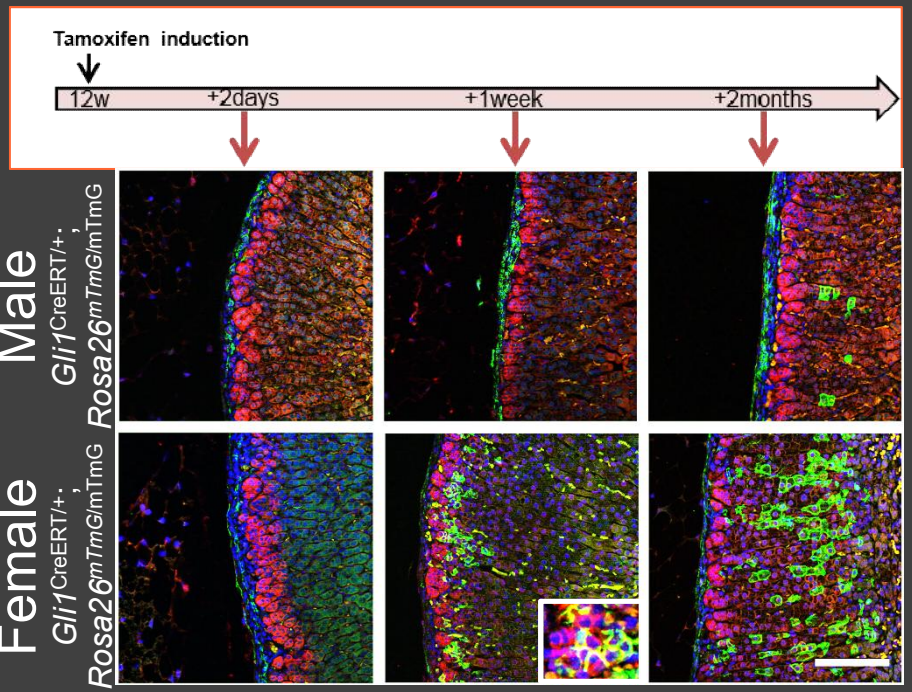
Recruitment











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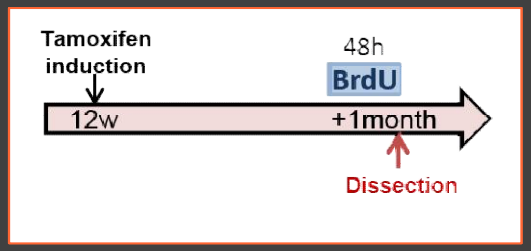
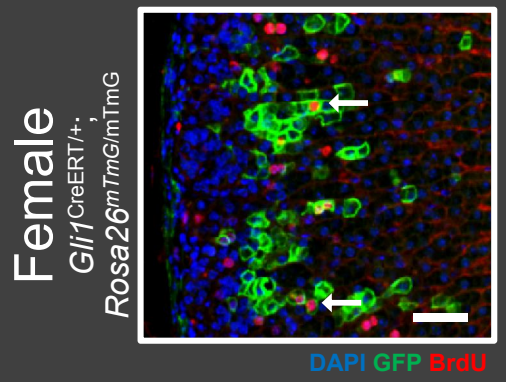
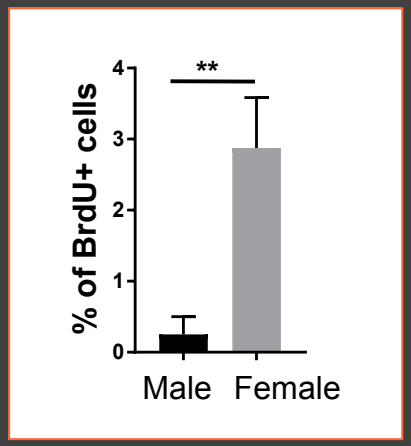


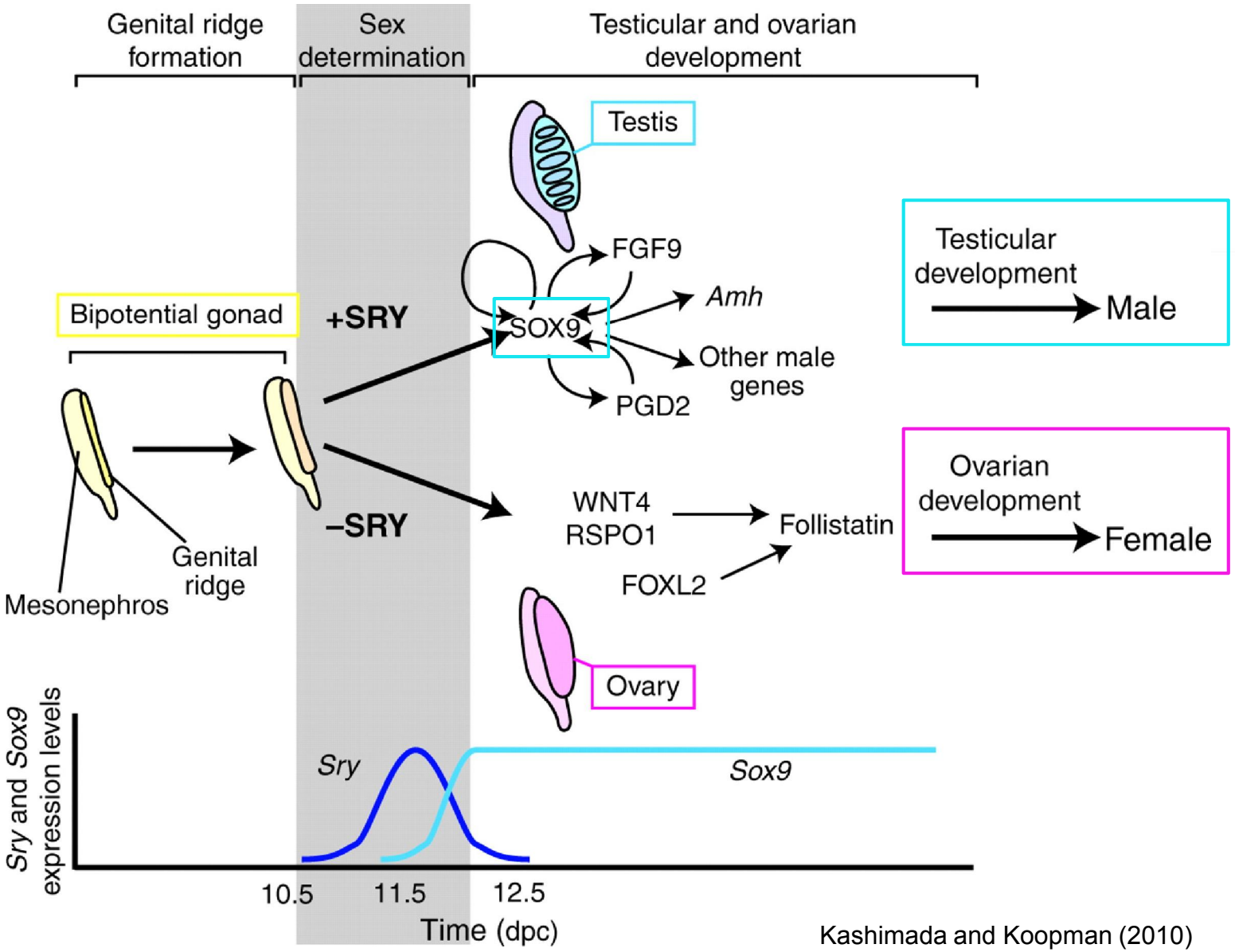




- Females show an increased proliferation in the capsule (4x)
- During adrenal homeostasis, capsular cells are recruited to replenish the female cortex
- Once they have reached the zF, the capsular cells can re-enter the cell cycle and proliferate.

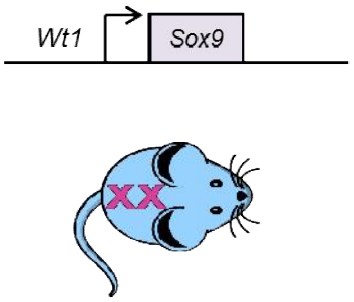
TABLE

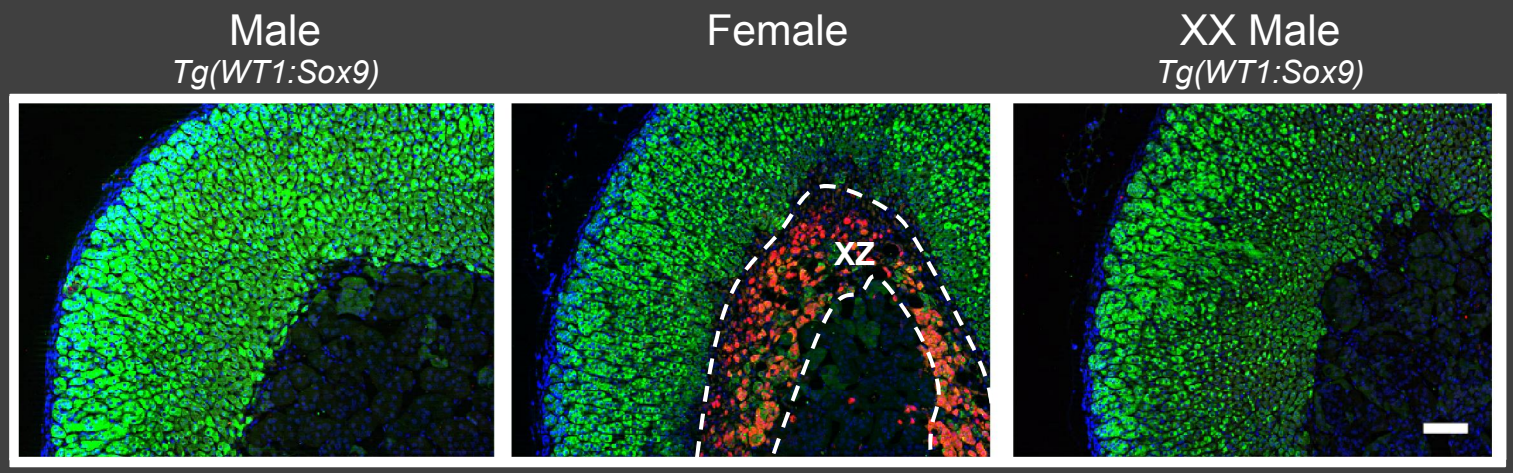
SEX DETERMINATION



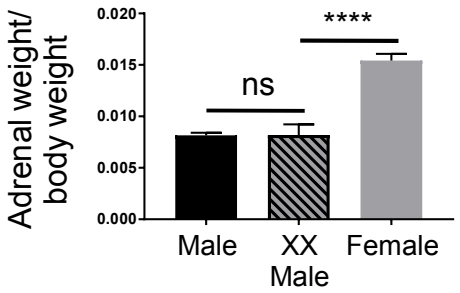
Kashimada and Koopman (2010)

ADRENAL CORTEX IN SEX REVERSAL MOUSE MODEL

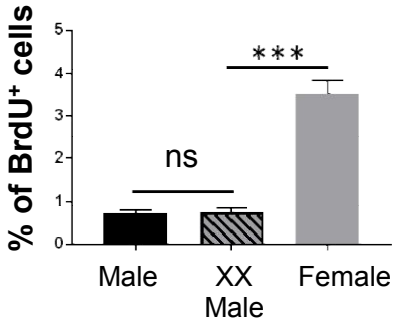




Weight



Proliferation



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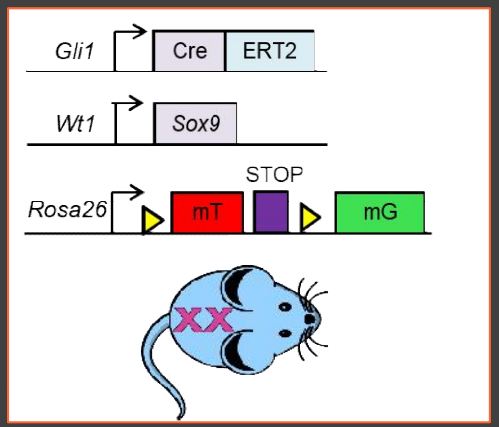
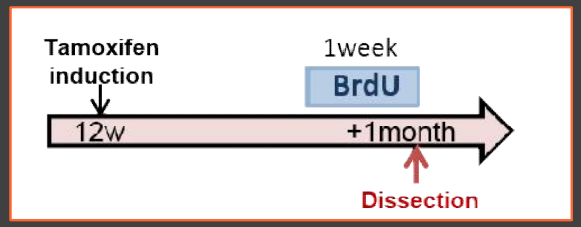
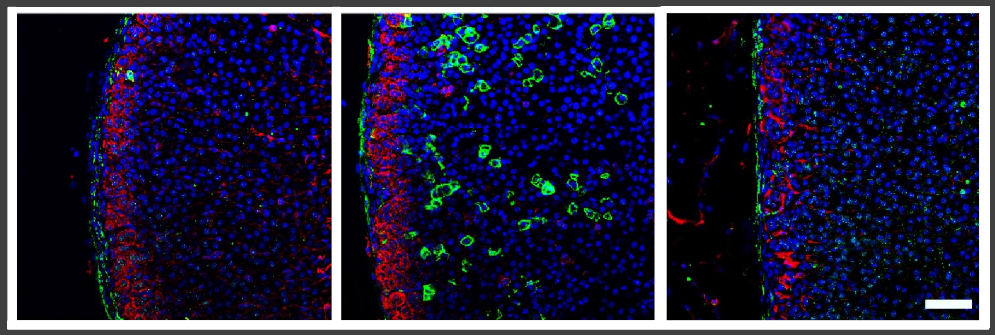
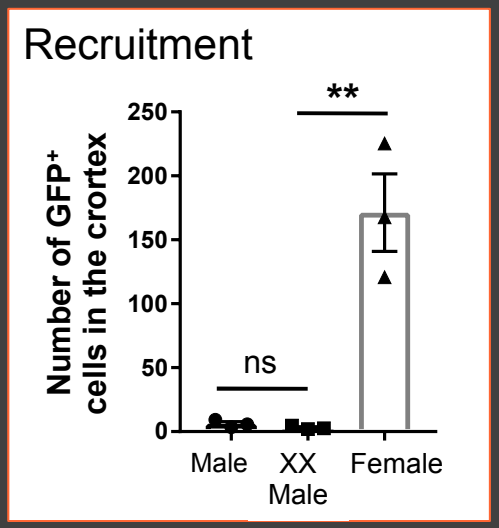




DAPI GFP DAB2



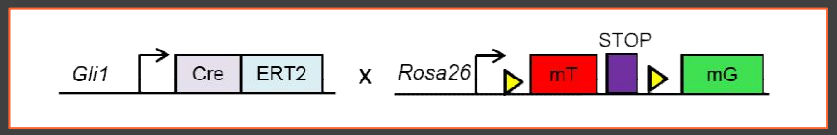
XY Male	XX Female	XX Male
Gli1$^{CreERT/+}$; *Tg(WT1:Sox9)* *Rosa26*$^{mTmG/mTmG}$;	*Gli1*$^{CreERT/+}$; *Rosa26*$^{mTmG/mTmG}$	*Gli1*$^{CreERT/+}$; *Tg(WT1:Sox9)* *Rosa26*$^{mTmG/mTmG}$;

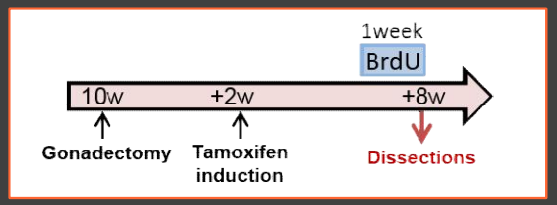


- Capsular stem cell activity follows the gonadal rather than the chromosomic sex

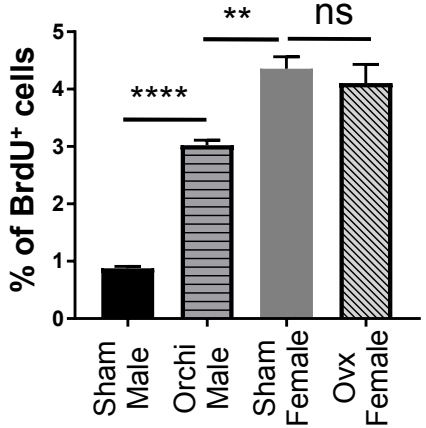
TABLE

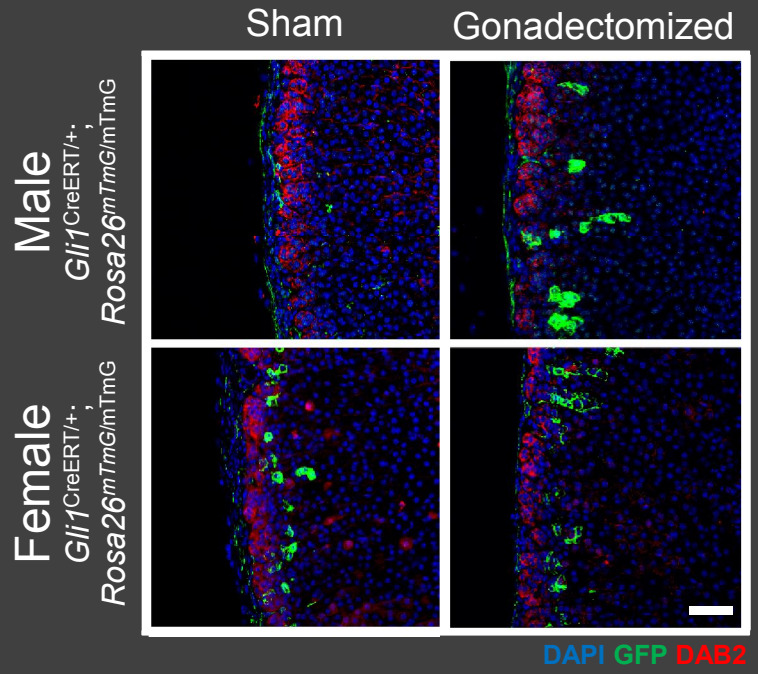
GONADECTOMY IN ADULT MALES AND FEMALES



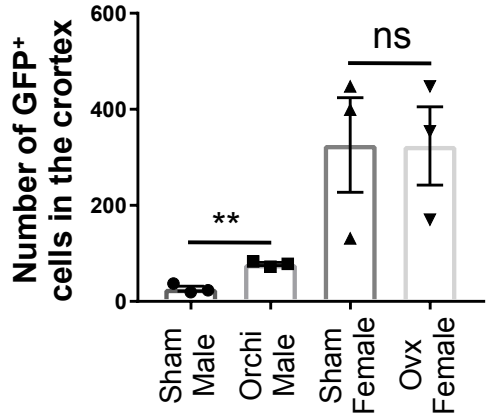


Proliferation



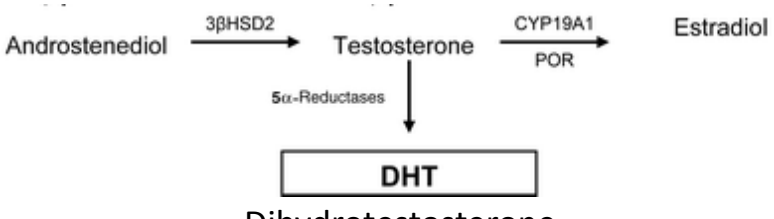


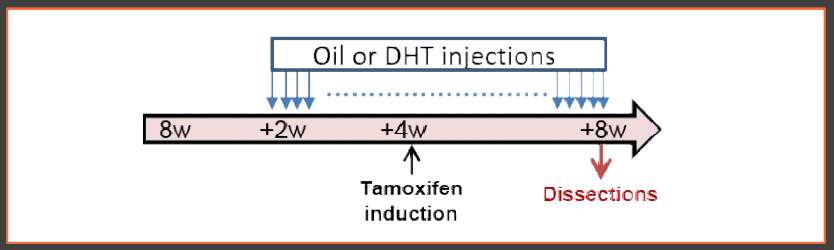
Recruitment

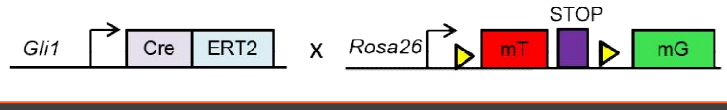


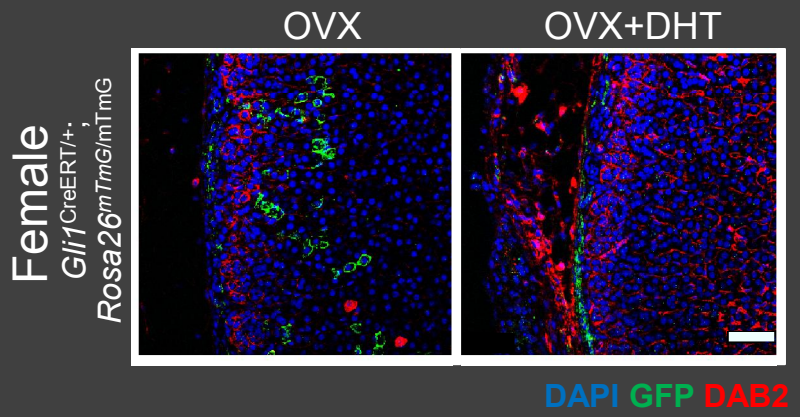
- Testis removal induce increased proliferation and recruitment of capsular cells

DHT TREATMENT IN ADULTS

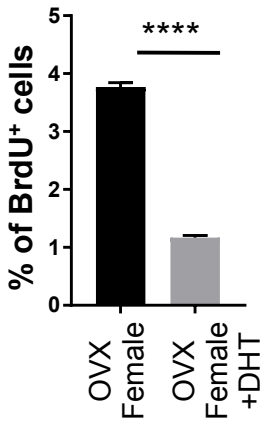




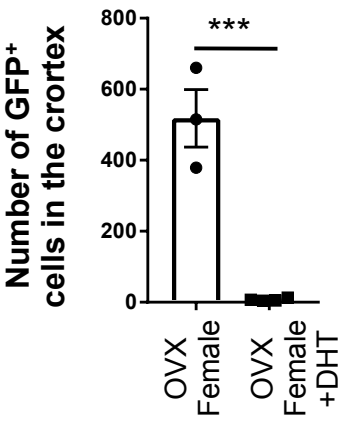




Proliferation

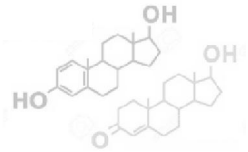


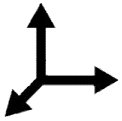
Recruitment



- DHT treatment in gonadectomized females inhibits capsular cell proliferation and recruitment

TABLE

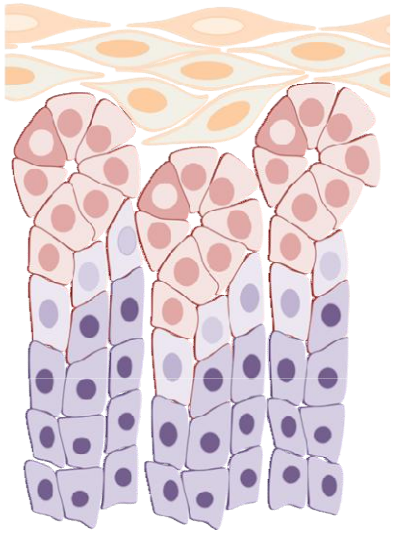




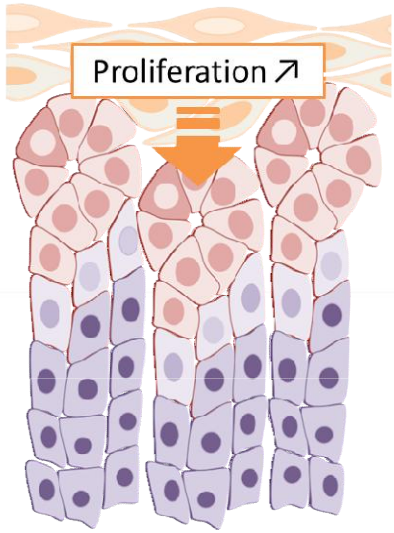
CONCLUSIONS

MALE

Proliferation →
Differentiation →
Trans-differentiation →
→
Apoptosis →

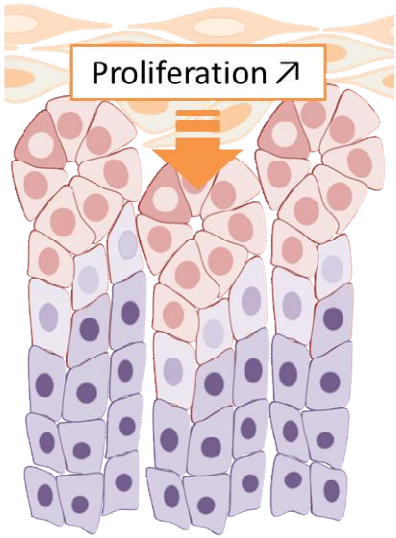


Proliferation →
Differentiation →
Trans-differentiation →
→
Apoptosis →

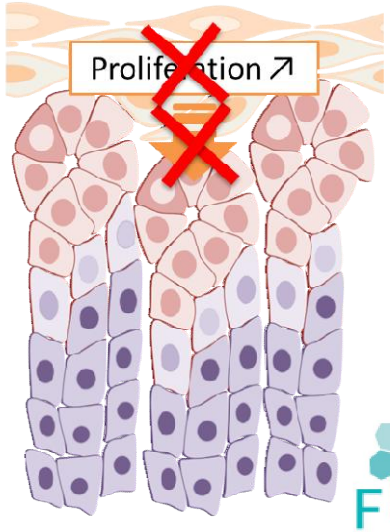


FEMALE

Proliferation ↗ →
Differentiation →
Trans-differentiation →
Proliferation ↗ →
Apoptosis ↗ →



Proliferation ↗ →
Differentiation →
Trans-differentiation →
Proliferation ↗ →
Apoptosis ↗ →



FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

CONCLUSIONS

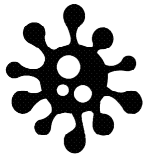
- HIGH CELLULAR TURN OVER IN THE ADRENAL CORTEX
- INCREASED CELLULAR RENEWAL IN FEMALES
- PROLIFERATION AND CONTRIBUTION OF CAPSULAR CELLS TO THE FEMALE CORTEX
- DHT INHIBITS CAPSULAR CELLS ACTIVITY

PERSPECTIVES

- MECHANISTIC UNDERSTANDING OF THE SEXUAL DIMORPHISM

- APPLY TO HUMAN

- PHYSIOLOGICAL IMPLICATIONS



- APPLY TO DISEASE MODEL

COLLOQUE SCIENTIFIQUE FIRENDO
2ème ÉDITION

« DIMORPHISME SEXUEL DANS LES MALADIES RARES ENDOCRINIENNES »

11 DECEMBRE 2018

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CONTRE LE CANCER
LA LIGUE
101 comités

JEDNs 85

Inserm
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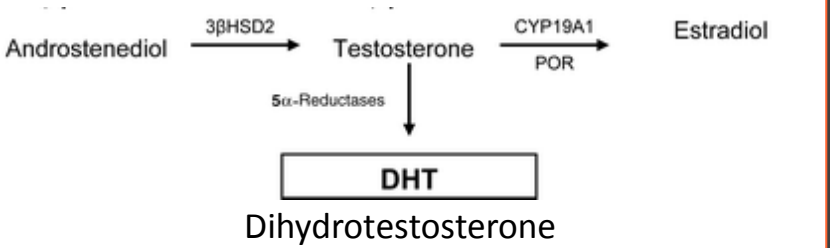
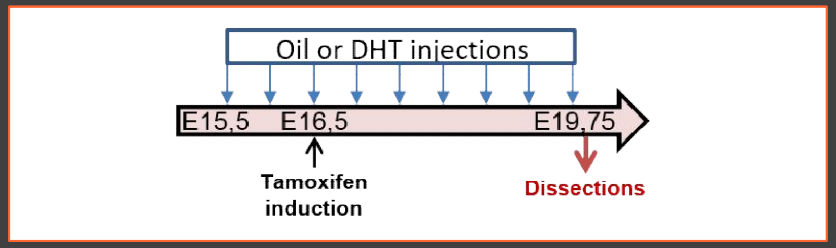
UNIVERSITÉ CÔTE D'AZUR

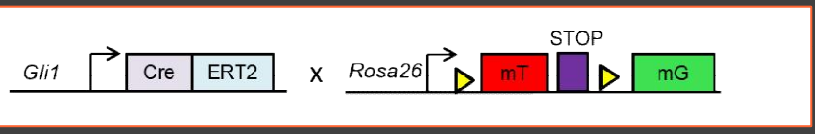
FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

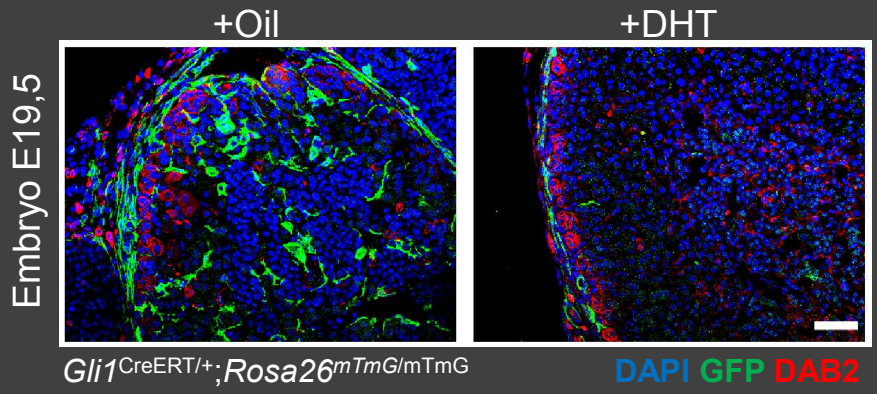
FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

DHT TREATMENT IN ADULTS

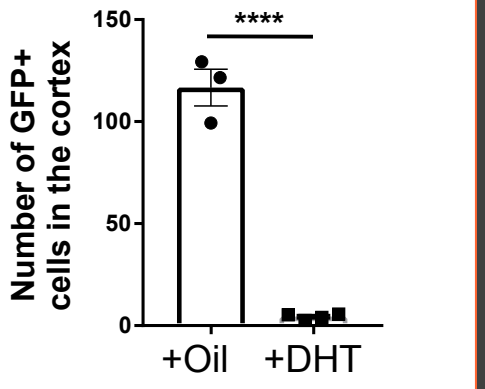








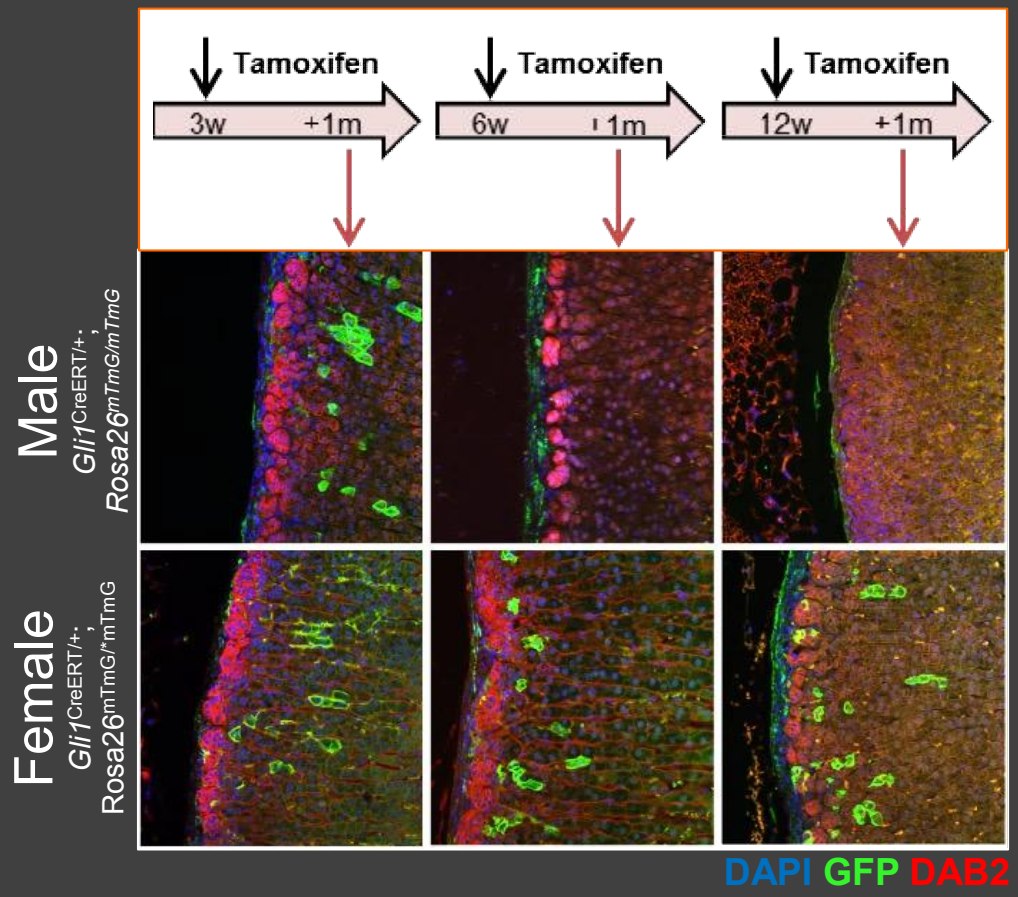
Recruitment



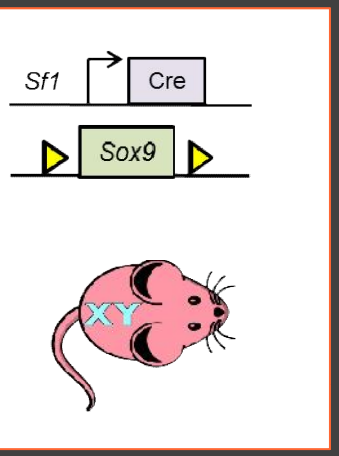
- DHT treatment in embryos inhibits capsular cell proliferation and recruitment

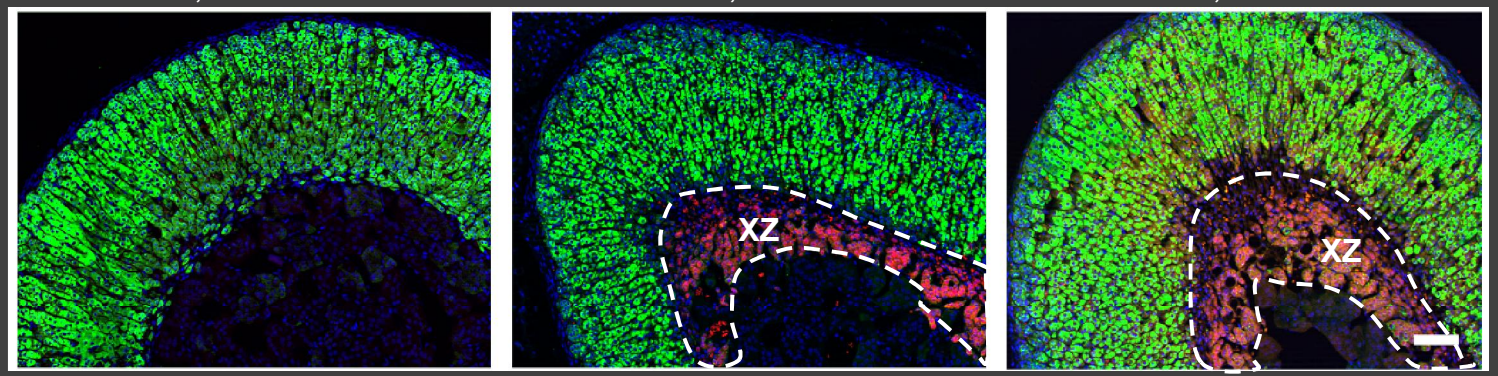
TIMING OF PUBERTY

- Recruitment of capsular stem cell is lost at puberty in males



ADRENAL CORTEX IN SEX REVERSAL MOUSE MODEL





Adults

DAPI 3β-HSD α20-HSD