



COLLOQUE SCIENTIFIQUE FIRENDO

2^{ème} ÉDITION

« DIMORPHISME SEXUEL
DANS LES MALADIES RARES
ENDOCRINIENNES »

MARDI
11 DÉCEMBRE
2018

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A ROAD MAP TO SEX-SPECIFIC ADRENAL DISORDERS

Marie-Christine Chaboissier (Nice),

Antoine Martinez (Clermont Ferrand)

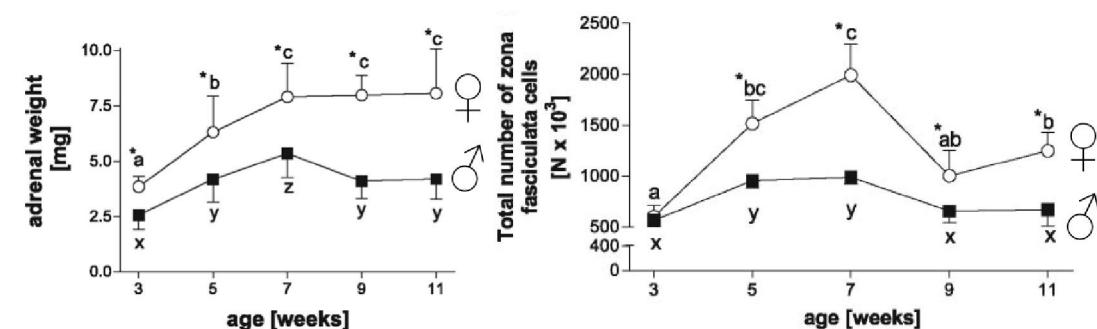
Andreas Schedl (Nice)

SEXUAL DIMORPHISM OF THE ADRENAL CORTEX

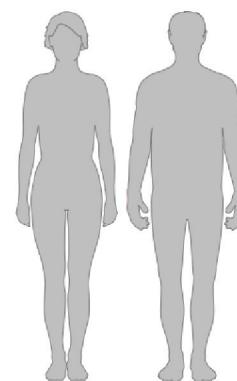
- Adrenal gland in mice: bigger in ♀



Bielohuby, AJPEM 2007



- Adrenocortical diseases are more frequent in ♀ :



Lacroix, The Lancet 2015

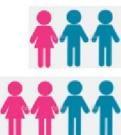
-unilateral adenomas: 4-8/1

-unilateral carcinomas: 1.5-3/1

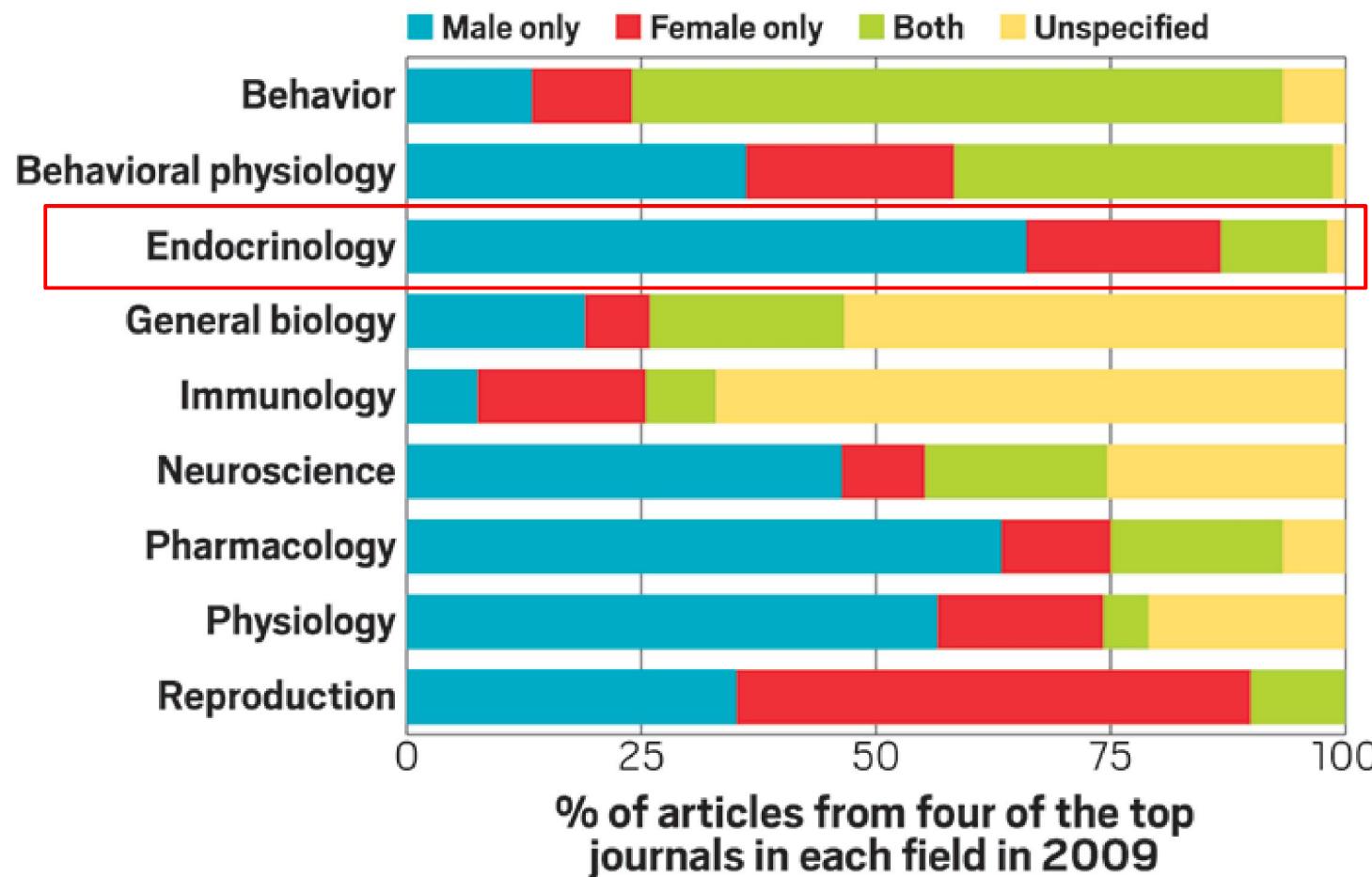
-bilateral hyperplasia macro: 2-3/1

-bilateral hyperplasia micro: 0.5/1 < 12 years
2.5/1 > 12 years

-bilateral adenomas or carcinomas: 2-4/1



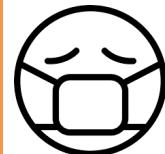
SEXUAL DIMORPHISM OF THE ADRENAL CORTEX



(2001 report from the Government Accounting Office).



SEXUAL DIMORPHISM OF THE ADRENAL CORTEX



DISEASE PREVALENCE

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

Cushing syndrome – Steffensen et al., 2010

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



HISTOLOGY

X-zone regression – Hershkovitz et al. 2007

Cortex (zF) thickness – Bielohuby et al. 2007



PHENOTYPE DEVELOPMENT

YAP/TAZ knock out – Levasseur et al. 2017

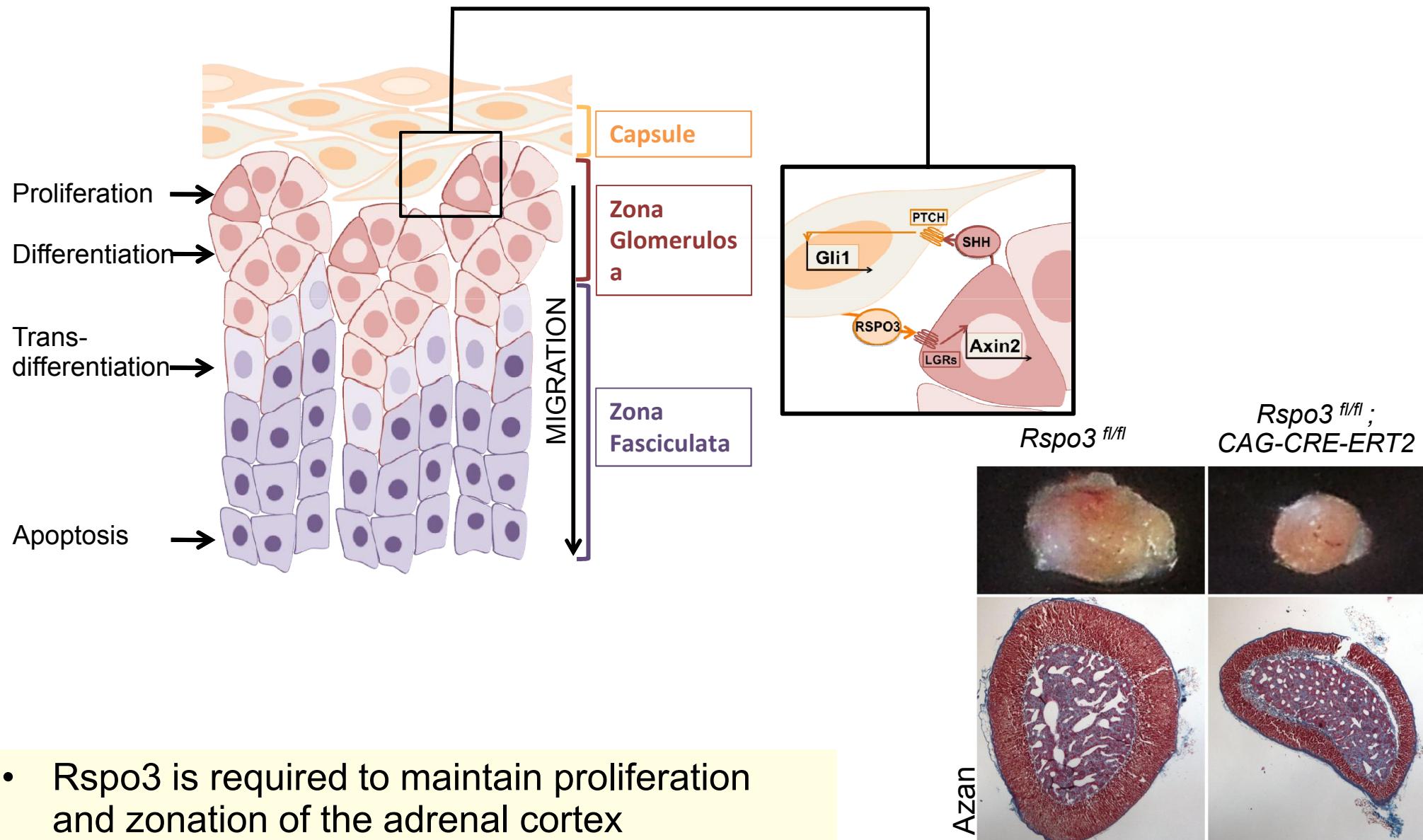
Constitutive activation of β -catenin – Berthon et al. 2012

RSPO3 knock out – Vidal et al. 2016 (and unpublished data)

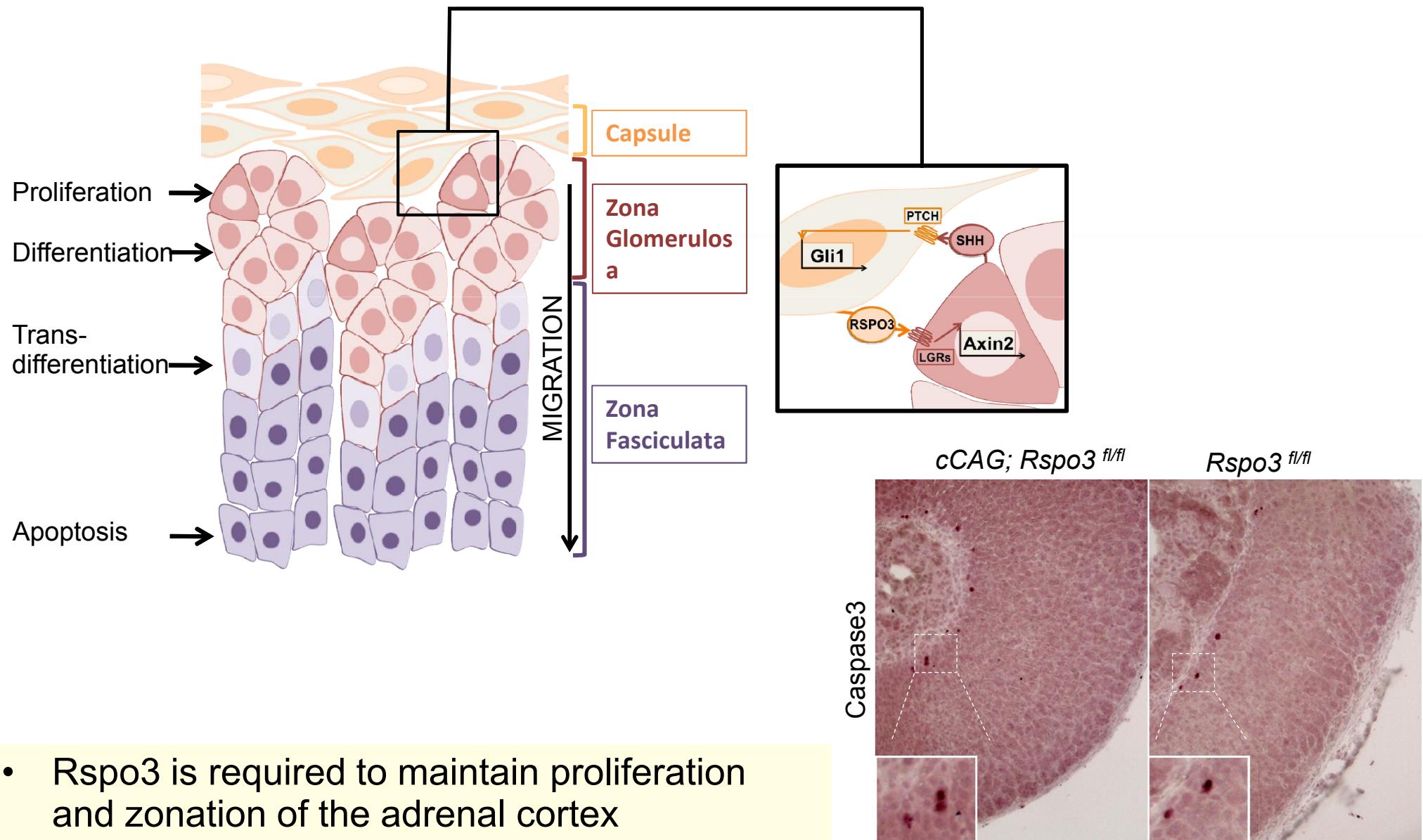
RSPO1 gain of function – unpublished

PKA signaling - Dumontet et al., 2018

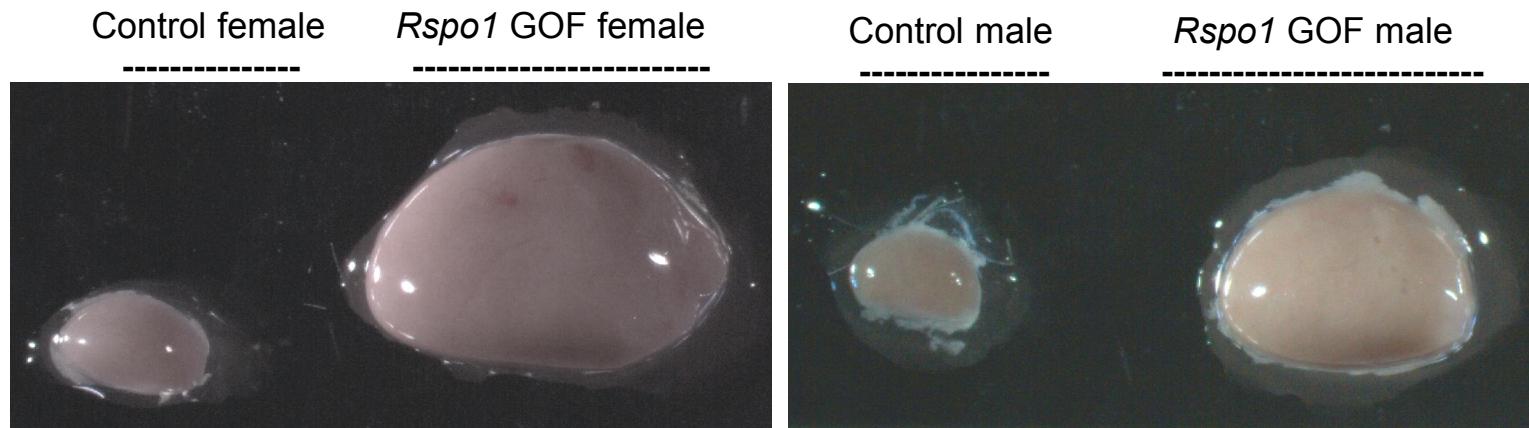
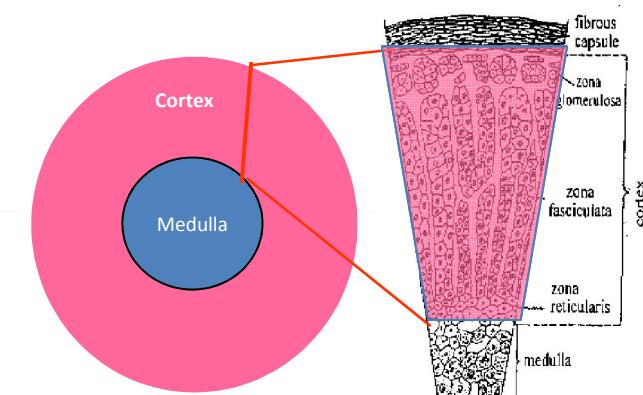
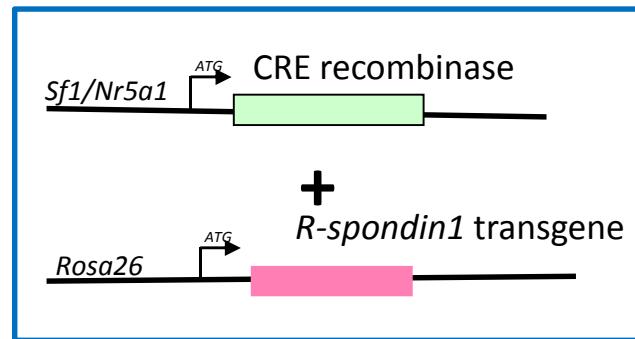
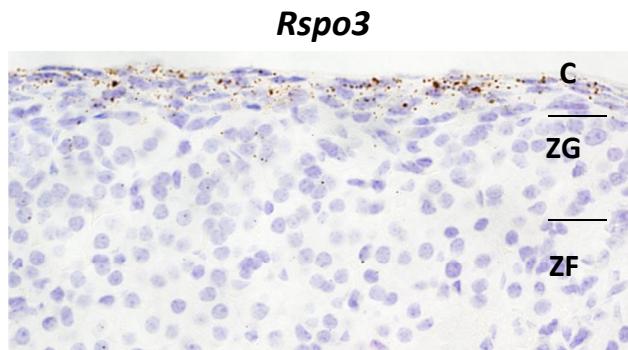
ADRENAL CORTEX HOMEOSTASIS



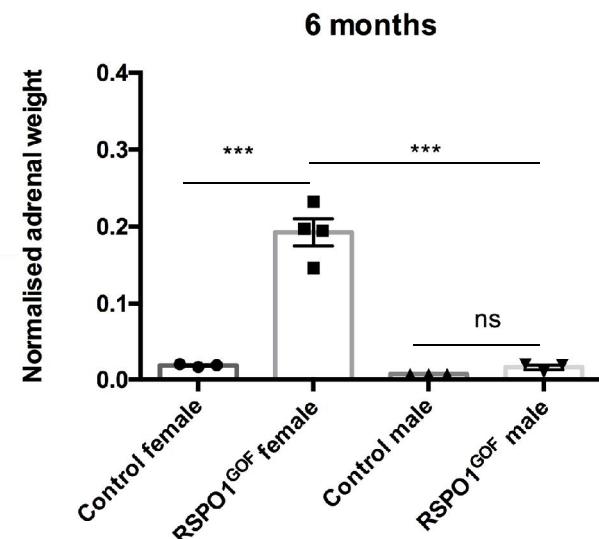
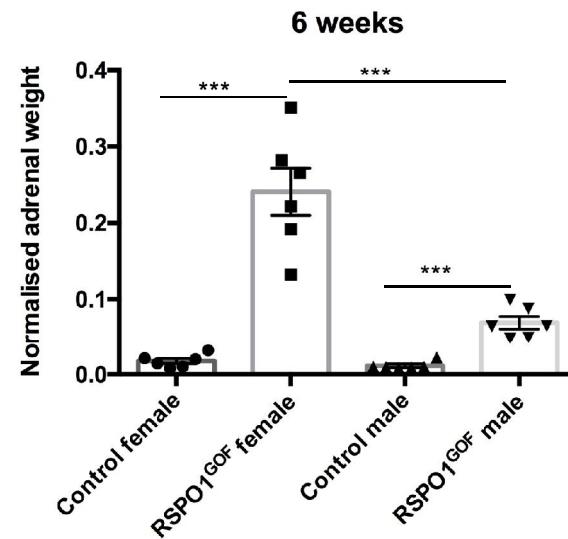
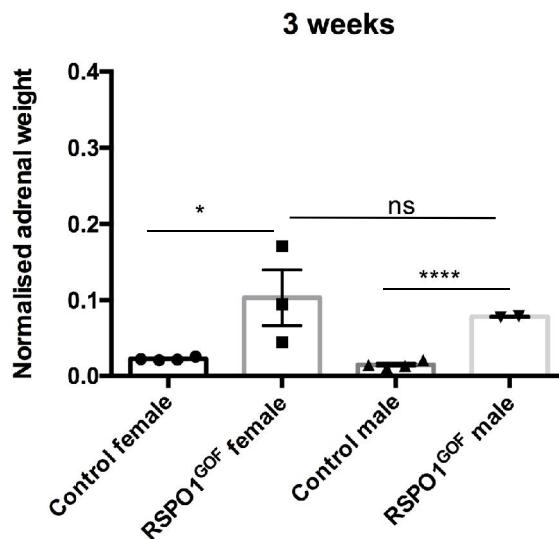
ADRENAL CORTEX HOMEOSTASIS



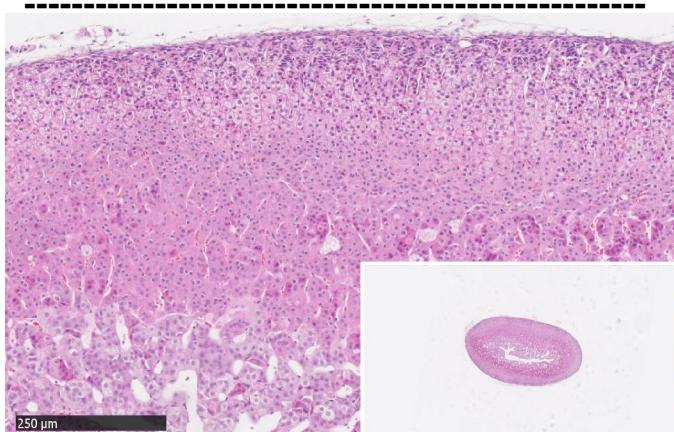
Ectopic expression of *R-spondin* results in a sexually dimorphic phenotype



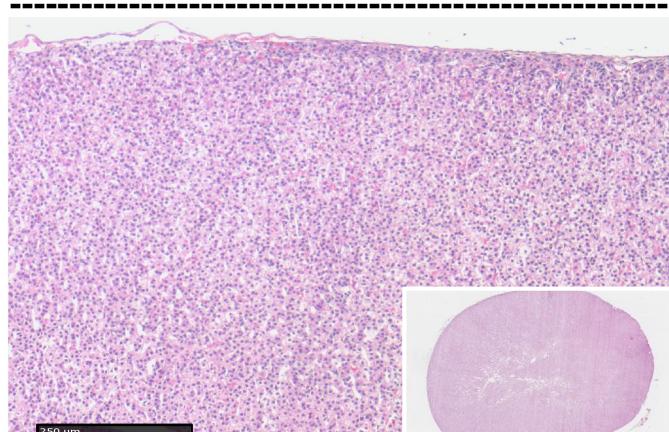
Ectopic expression of a *Rspo1* results in a sexually dimorphic phenotype



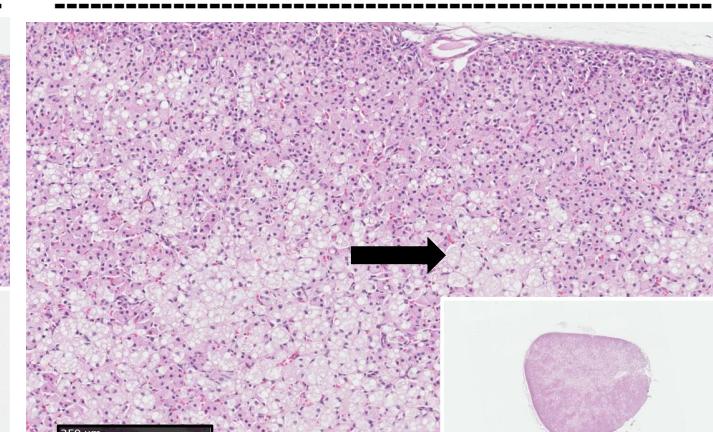
Control female 6 weeks



Rspo1 GOF female 6 weeks



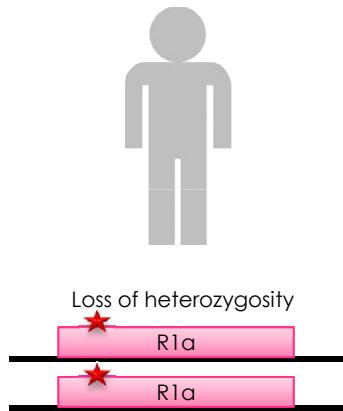
Rspo1 GOF male 6 weeks



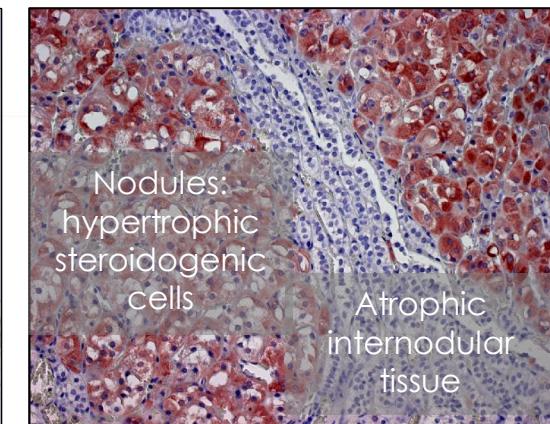
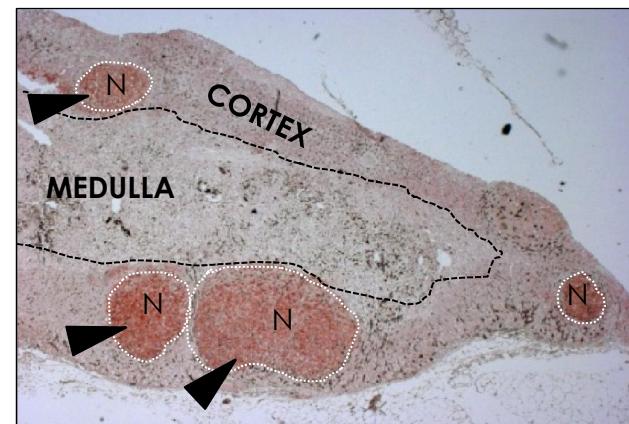
Cushing's syndrome due to loss of R1a in the adult cortex develops in a sex-dependent manner.

PPNAD R1a mutations

Kirschner et al. 2000



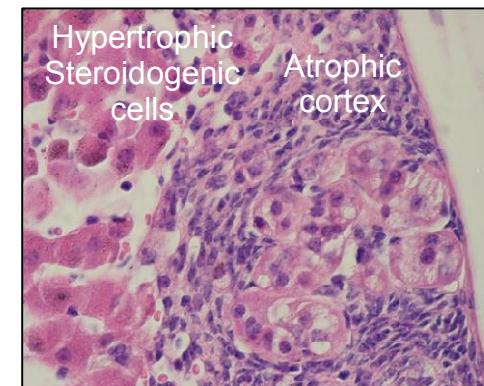
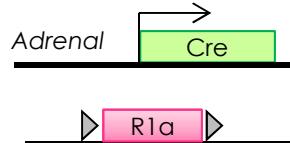
Sahut-Barnola et al. 2010



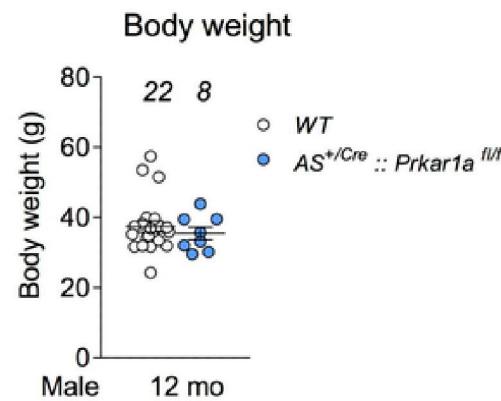
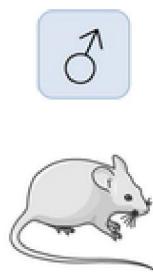
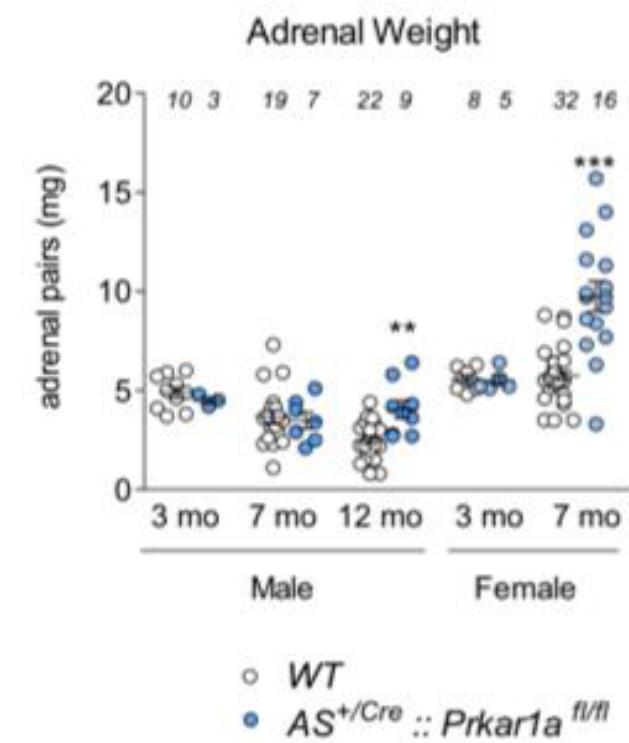
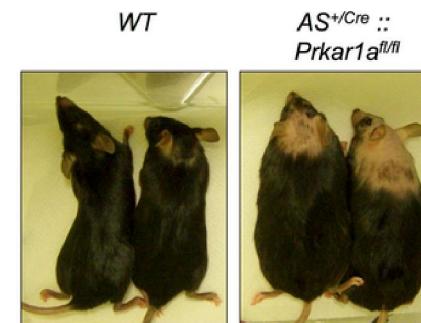
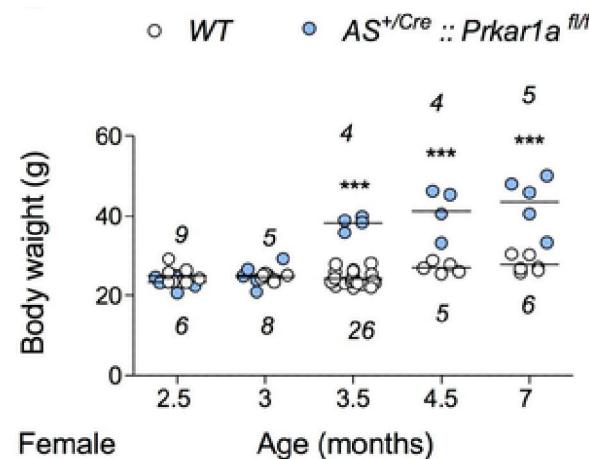
Cushing syndrome

Inhibin alpha

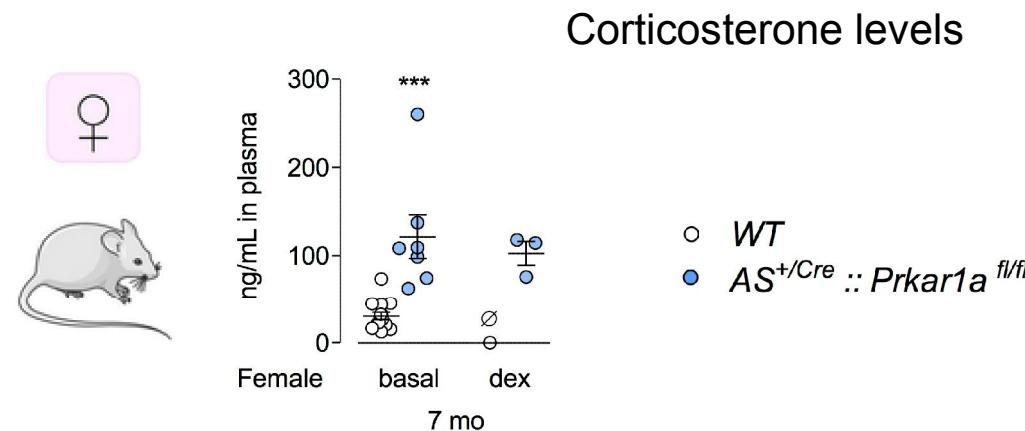
Modèle R1a AdKO



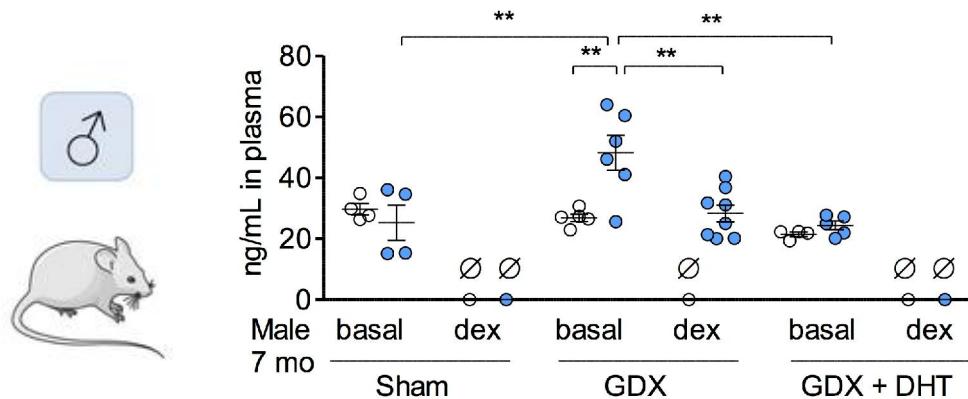
Cushing's syndrome due to loss of R1 α in the adult cortex develops in a sex-dependent manner.



Cushing's syndrome due to loss of R1α in the adult cortex develops in a sex-dependent manner.



Androgenic milieu delays the onset of Cushing's syndrome



FACTORS POTENTIALLY INFLUENCING SEXUAL DIMORPHISM

- genetic (sex chromosomes)
- hormonal
- epigenetic
- microbiota

ANR-funded project: Sex-Specs

1. Stem cell dynamics

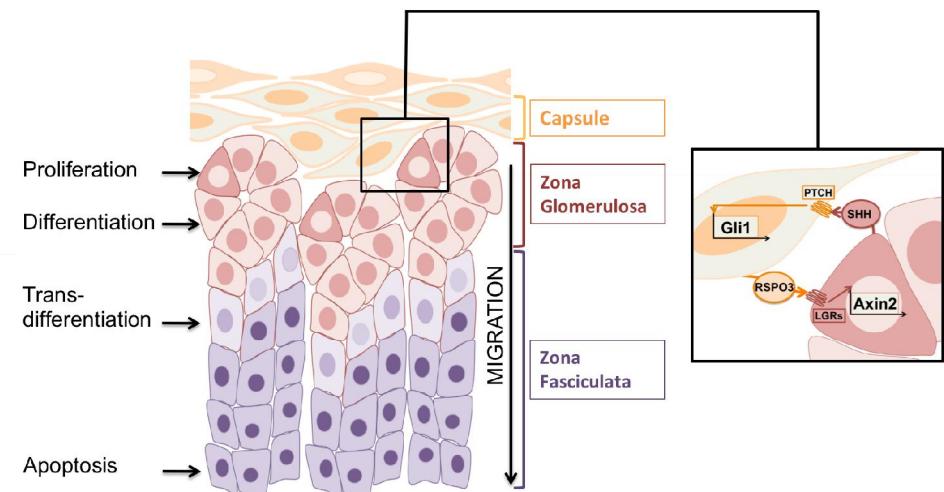
- *proliferation*
- *cell death*
- *physiology*

2. Hormonal control

- *influence on transcription*
- *epigenetic component?*

3. Influence of sex on phenotype

- Overactivation of PKA signaling (*model for Cushing syndrome*)
- Overactivation of beta-catenin signaling



ANR-funded project: Sex-Specs

