Alteration of Renal Corticosteroid Signaling Pathways in Preterm Infants: Neonatal Adaptation and Developmental Programming of Hypertension

Laurence Dumeige[a], Melanie Nehlich[a], Christophe Lhadj[a], Say Viengchareun[a], Qiong-Yao Xue[a], Eric Pussard[a,b] , Marc Lombès[a,c,d], Laetitia Martinerie[a,d,e]

[a]Faculté de Médecine Paris-Sud, UMR-S INSERM 1185, Le Kremlin Bicêtre, France;
[b]Service de Génétique Moléculaire, Pharmacogénétique et Hormonologie, Hôpital de Bicêtre, APHP, Le Kremlin Bicêtre, France;
[c]Service d'Endocrinologie et Maladies de la reproduction, Hôpital de Bicêtre, APHP, Le Kremlin Bicêtre, France;
[d]PremUp Foundation, Paris, France;
[e]Service d'Endocrinologie et Diabétologie Pédiatrique, Hôpital Robert Debré, APHP, Paris, France

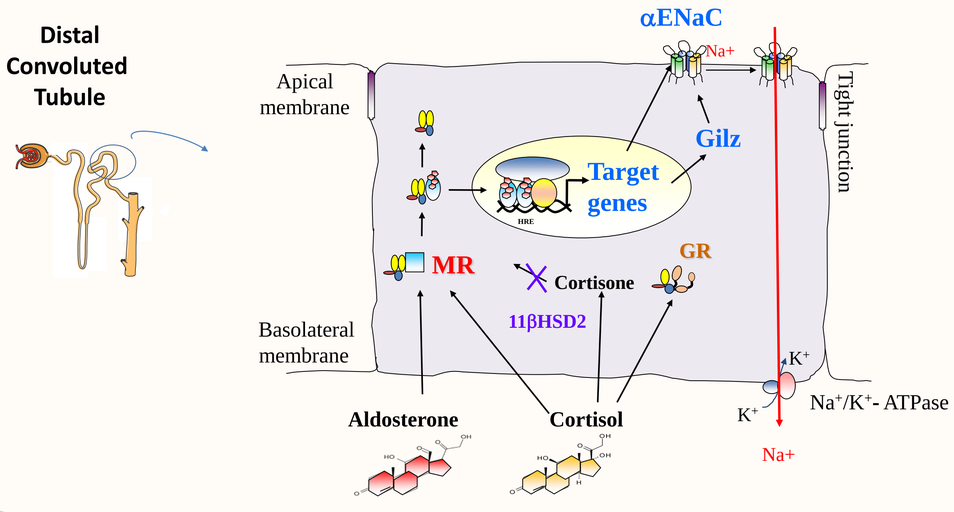
Introduction

Prematurity, a worldwide health issue, is often associated with renal tubular immaturity leading to major salt losses, whose mechanisms remain poorly understood [1].

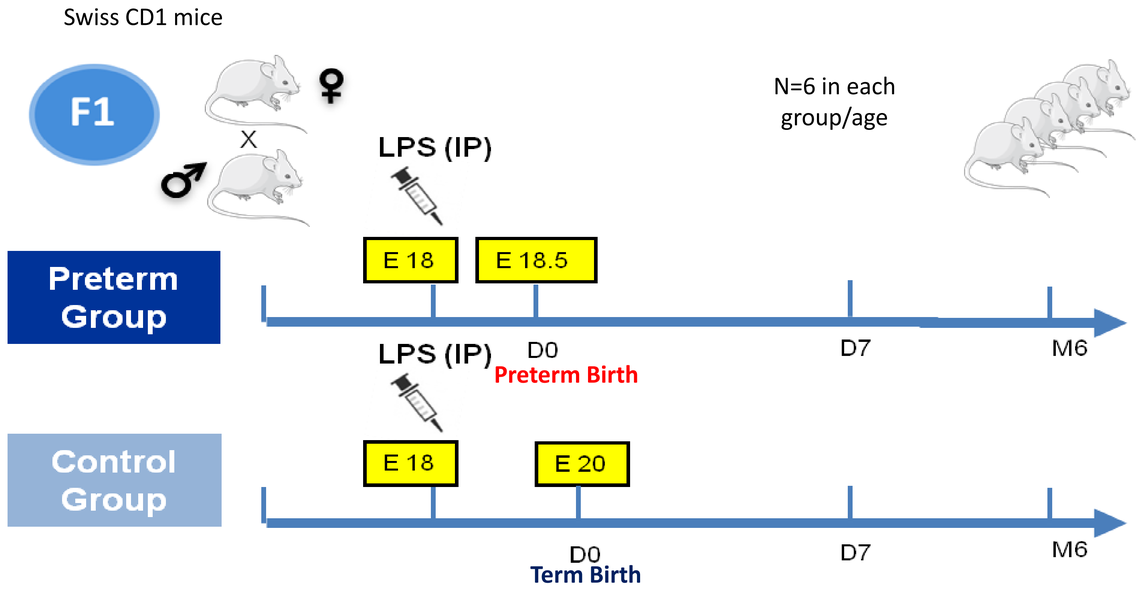
Moreover, these premature infants are prone to develop hypertension early in adulthood [2], with several lines of evidences in favor of a phenotypic transmission to the offspring[3].

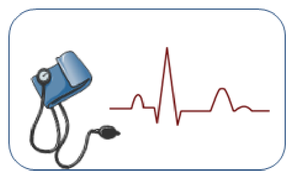
Objectives

To study the role of renal corticosteroid signaling pathways [4] in the development of renal and cardio-vascular complications in preterms infants

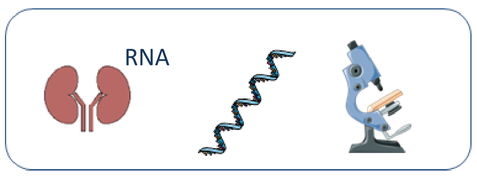


Generation of premature newborn mice

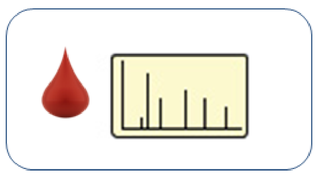




Cardiovascular investigation (M6)

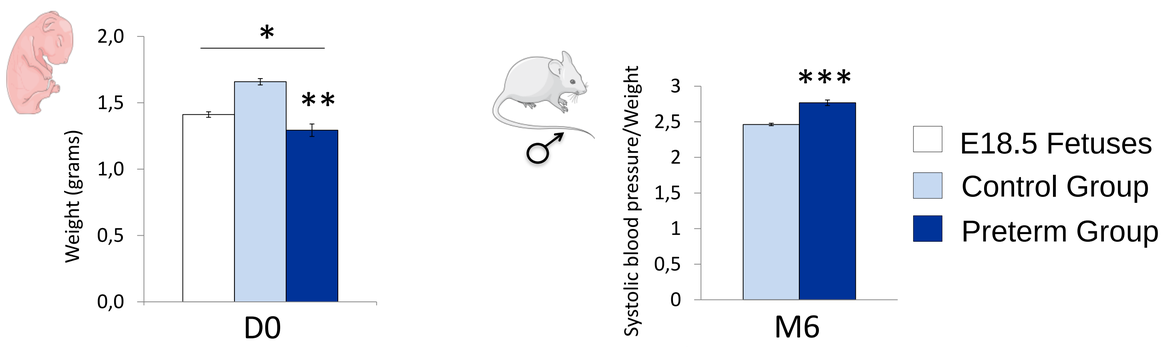


Study of *MR*, *GR*, *αENaC* and *Gilz* expression by RT-qPCR and glomeruli density on HES histological section (M6)



Steroid assays by mass spectrometry (M6)

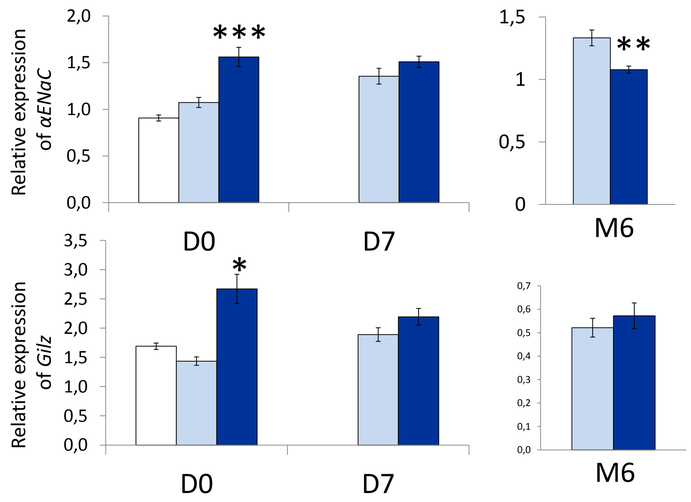
1 Clinical characteristics of preterm mice



Optimal model of preterm birth:

✓Preterm neonates presented with maladaptation : Growth retardation, 70% of live births and 35% of long term survival.
✓Significant early-onset hypertension in males

2 Impact of prematurity on renal corticosteroid pathways



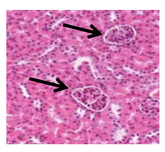
Strong activation of renal corticosteroid target gene transcription at birth in premature mice

Independently of *MR* and *GR* expression and plasma steroid levels

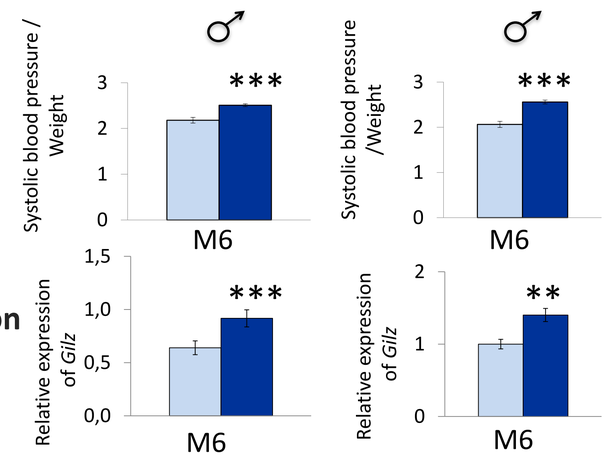
Not sustained in adulthood

3 Is there a dysregulation of blood pressure in the offspring ?

Dysregulation of blood pressure at M6 in F2 and F3 males



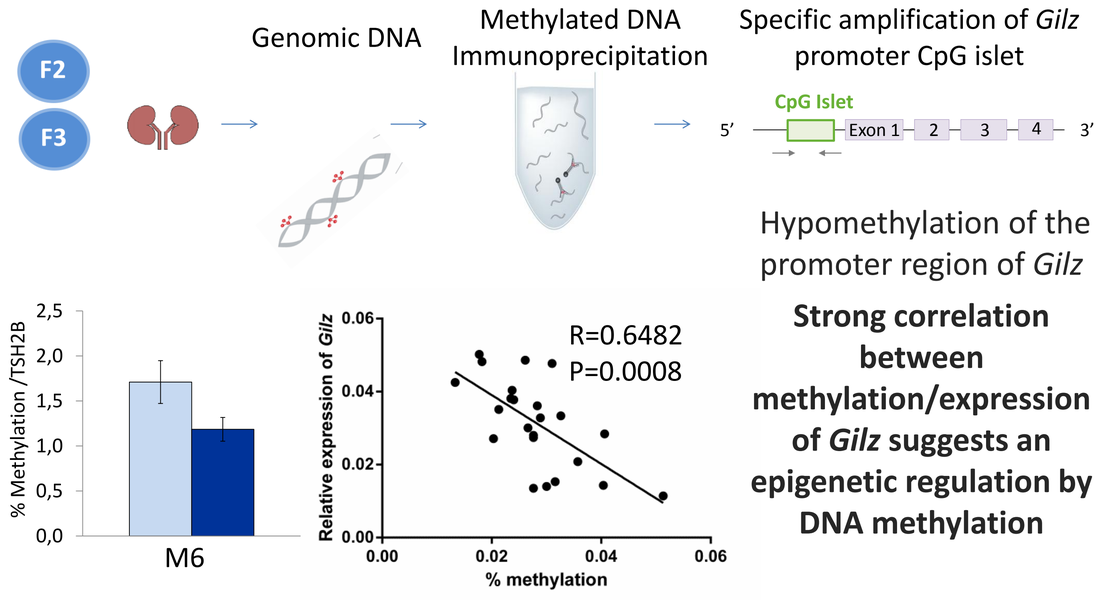
Independently of glomeruli density



But with **persistent increased renal *Gilz* expression**

✓ independently of *MR* or *GR* expression
✓Independently of plasma aldosterone or corticosteroid levels.

4 Is an epigenetic mechanism implicated?



Hypomethylation of the promoter region of *Gilz*

Strong correlation between methylation/expression of *Gilz* suggests an epigenetic regulation by DNA methylation

Conclusion:

We provide evidence for transgenerational dysregulation of blood pressure, induced by prematurity , associated with persistent increased expression of *Gilz* which could partly be in relation with an hypomethylation of its promoter.

→ Better understanding of developmental programming of cardiovascular diseases

→ Better management of premature infants from birth to adulthood

References

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Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

Laurence Dumeige

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