Early life exposure to ultrafine particles from air pollution affects proximal tubular epithelial cells development

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UFPs conference, Bruxelles, 4th July 2024



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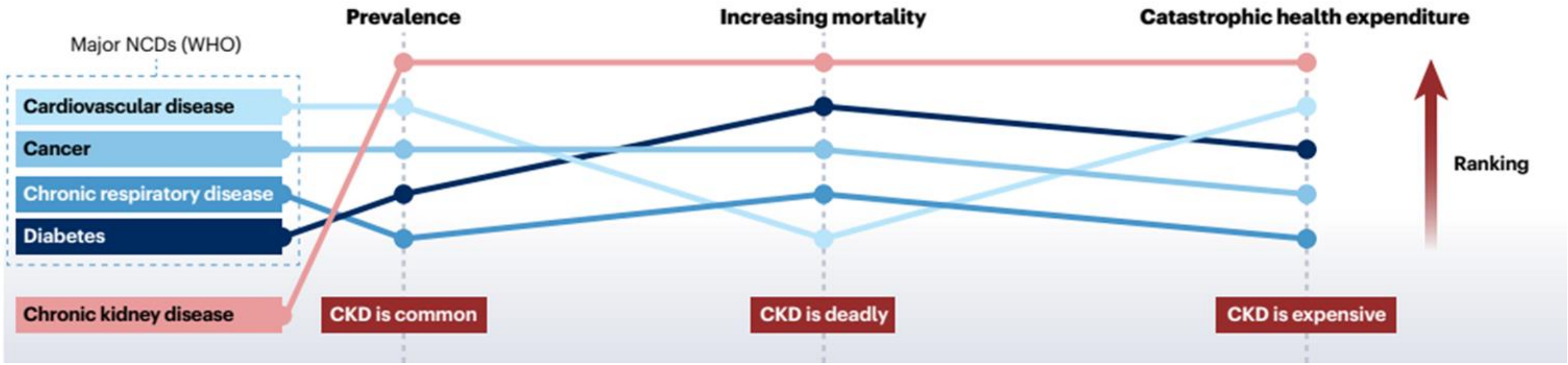
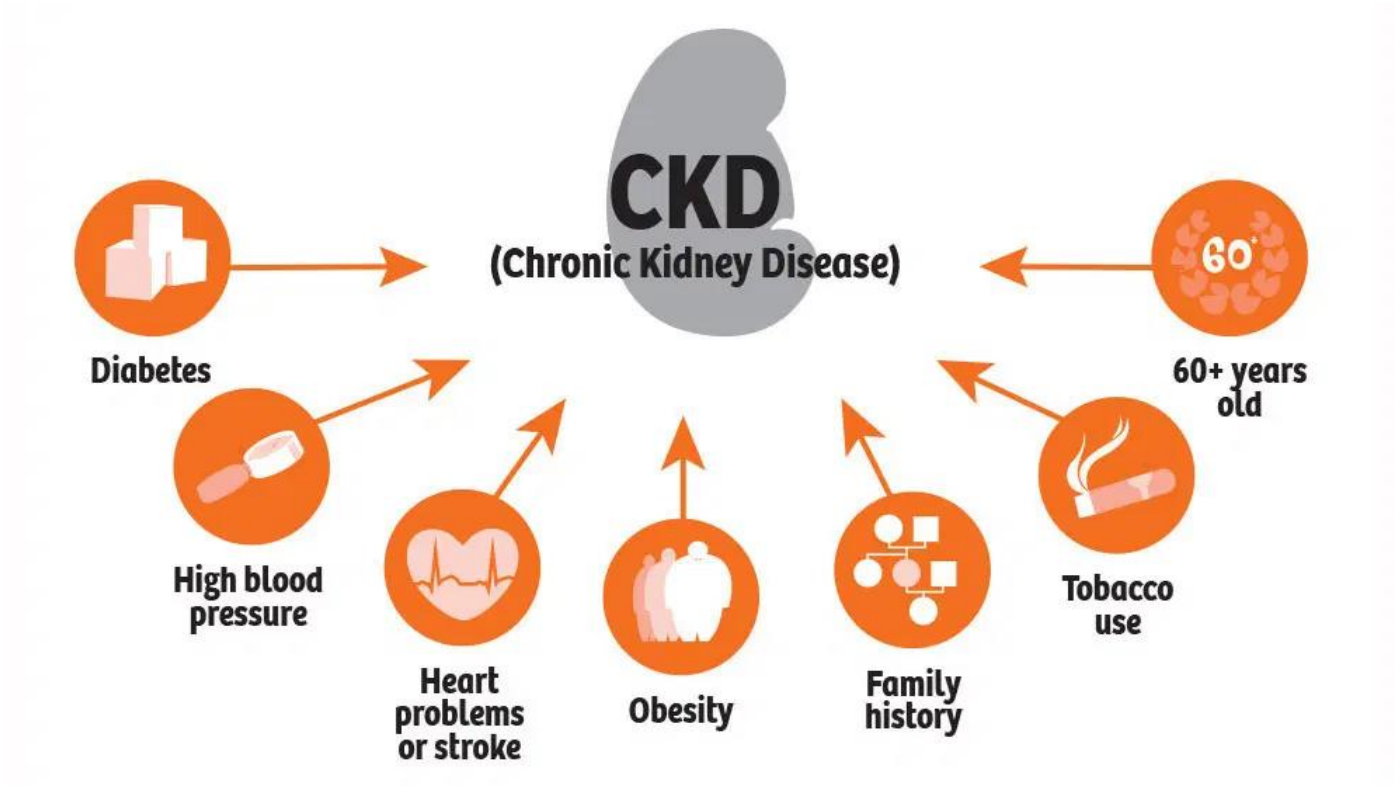
Chronic kidney disease (CKD) is a global health priority

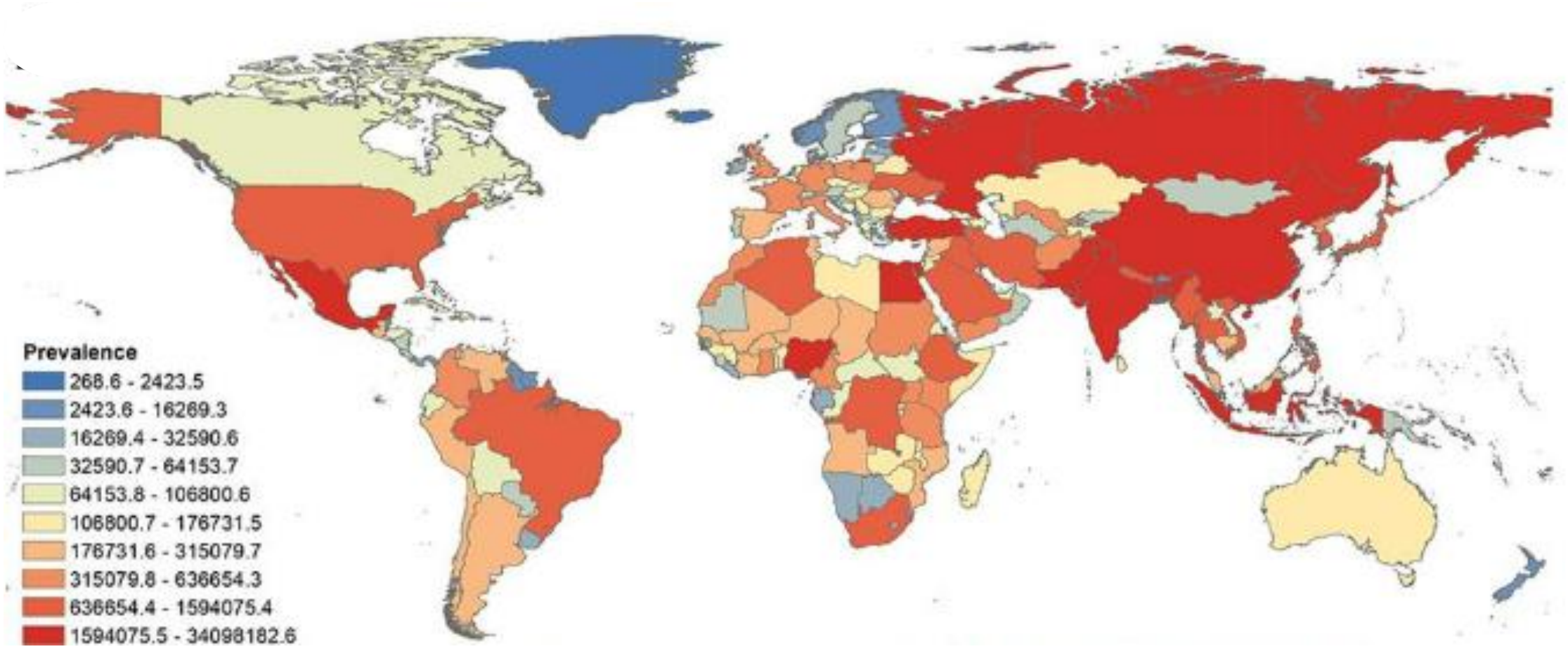


Traditional risk factors of CKD



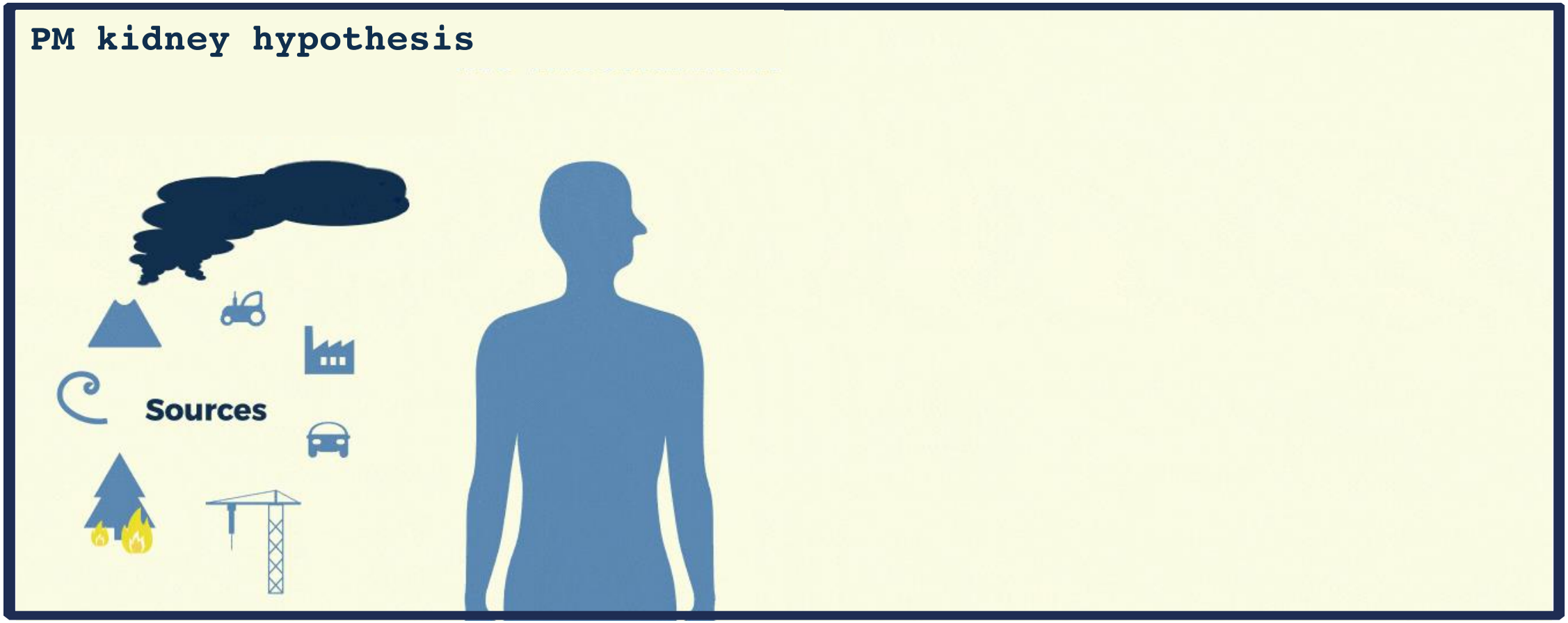
Air pollution is an overlooked contributor to CKD

Global burden of CKD attributable to PM2.5 in 194 countries and territories

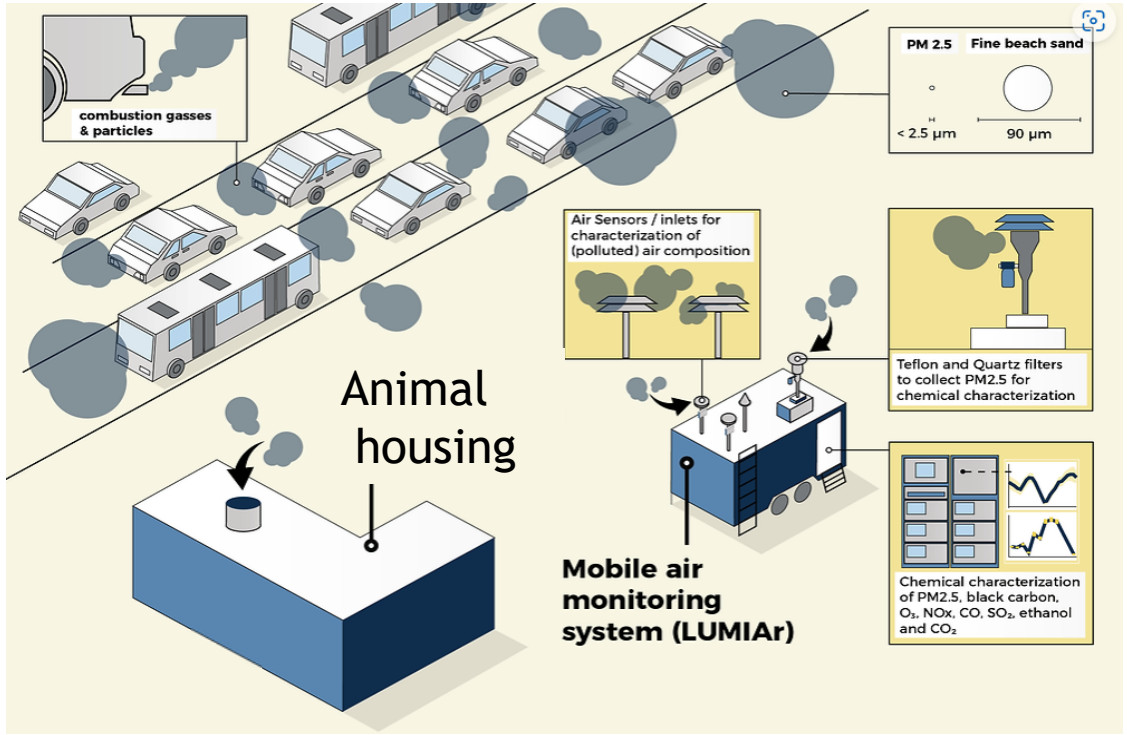


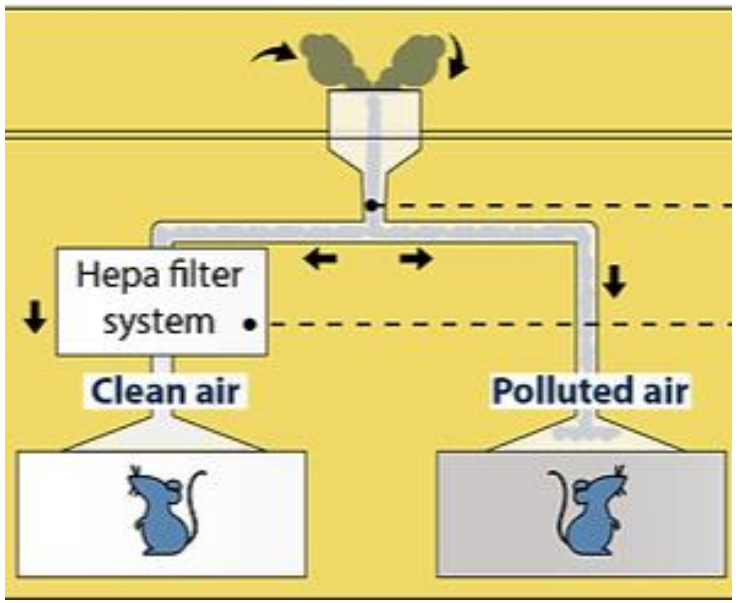
Cumulative exposure to PM2.5 is associated with the decline in renal function in elderly people, renal transplant recipients, and patients with diabetes.

PM kidney: Pollution is the motor of premature aging of the kidney



Exposome chamber to study the biological mechanisms by which PM2.5 affects kidney health





PM2.5 cut off

Garden Medical Faculty University of São Paulo (Brazil)

PM2.5 and acute kidney injury lead to premature renal aging and high risk to develop CKD

Journal of Pathology
J Pathol 2024
Published online 00 Month 0000 in Wiley Online Library
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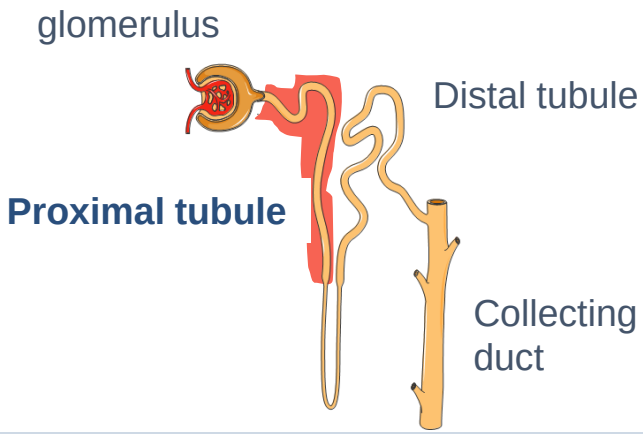
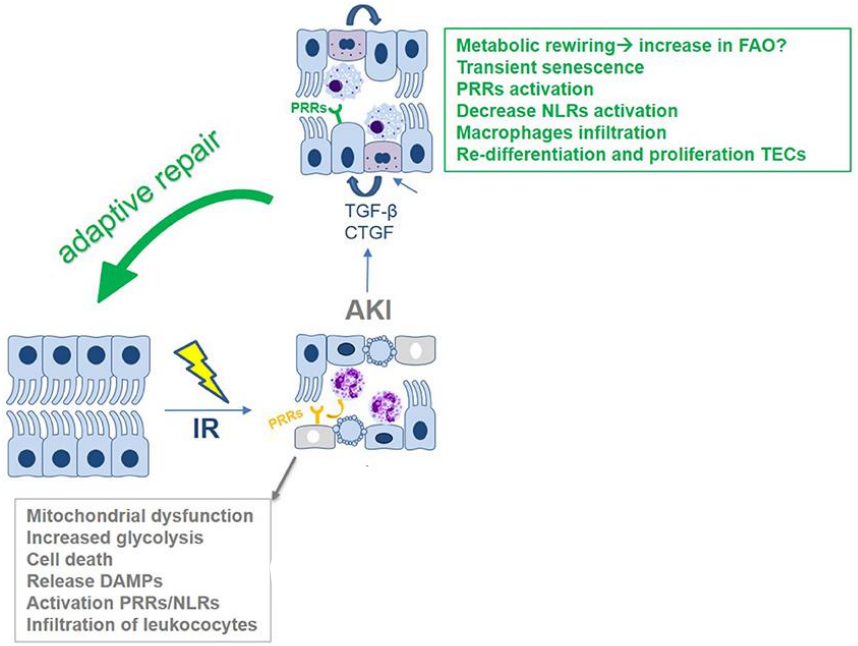
ORIGINAL ARTICLE

Air pollution aggravates renal ischaemia–reperfusion–induced acute kidney injury

Talita Rojas Sanches[1], Antonio Carlos Parra[1], Peiqi Sun[2], Mariana Pereira Graner[1], Lucas Yuji Umesaki Itto[1], Loes Maria Butter[2], Nike Claessen[2], Joris JTH Roelofs[2,3], Sandrine Florquin[2,3], Mariana Matera Veras[4], Maria de Fatima Andrade[5], Paulo Hilário Nascimento Saldiva[2,3,6], Jesper Kers[2,3,6], Lucia Andrade[1]* and Alessandra Tammaro[2]*





Tammaro et al Frontiers in immunology 2019
Sanches et al Journal of pathology 2024

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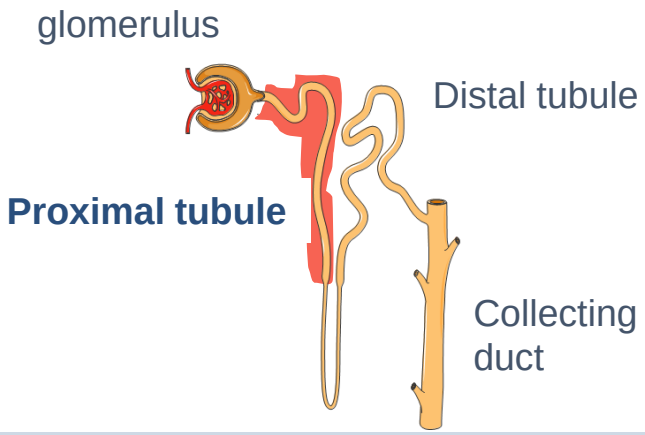

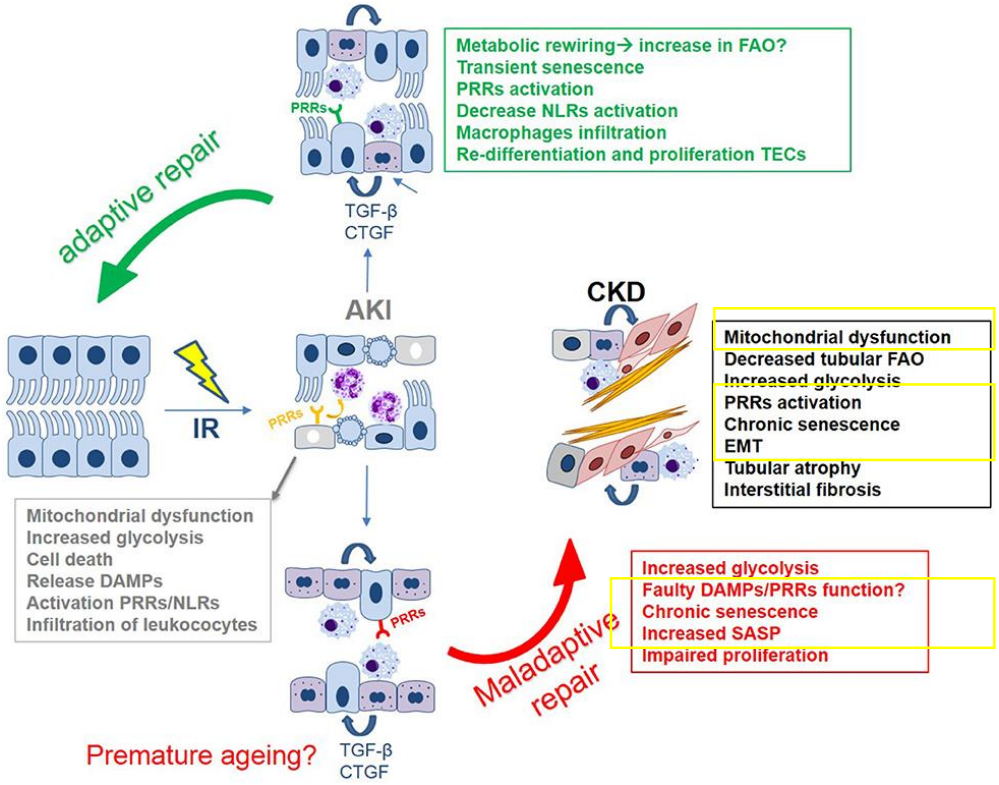

Tammaro et al Frontiers in immunology 2019
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Nanoparticles are cleared from the body through the kidneys

ACS NANO

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Inhaled Nanoparticles Accumulate at Sites of Vascular Disease

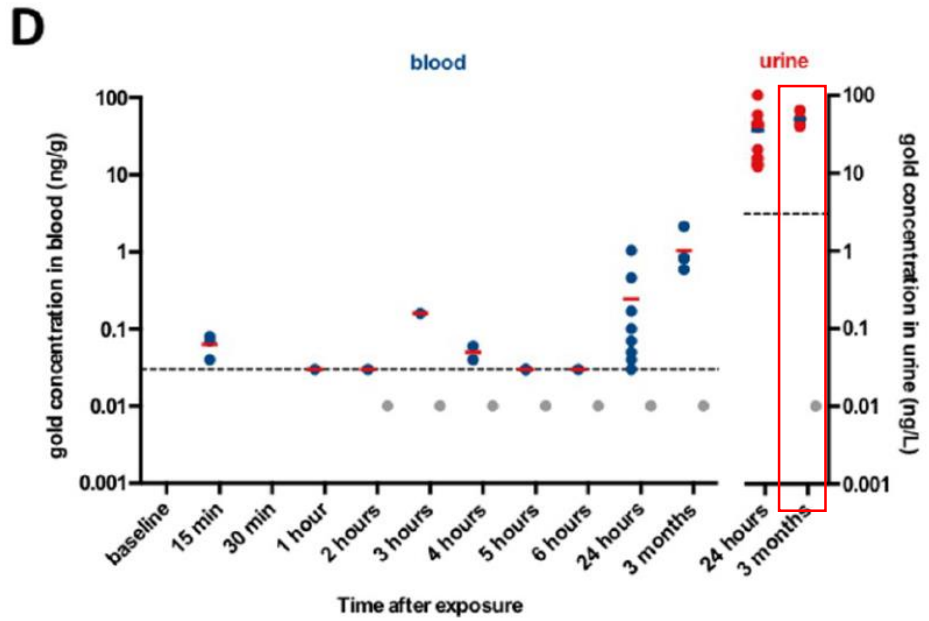
Mark R. Miller,[*,†,∞,▽] Jennifer B. Raftis,[‡,∞,▽] Jeremy P. Langrish,[†] Steven G. McLean,[†] Pawitrabhorn Samutrtai,[§] Shea P. Connell,[†] Simon Wilson,[†] Alex T. Vesey,[†] Paul H. B. Fokkens,[∥] A. John F. Boere,[∥] Petra Krystek,[⊥] Colin J. Campbell,[§] Patrick W. F. Hadoke,[†] Ken Donaldson,[‡] Flemming R. Cassee,[∥,#] David E. Newby,[†] Rodger Duffin,[‡,▽] and Nicholas L. Mills[†,▽]

[†]BHF Centre for Cardiovascular Science, [‡]MRC Centre for Inflammation Research, and [§]EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH16 4TJ, United Kingdom

[∥]National Institute for Public Health and the Environment (RIVM), 3721 MA Bilthoven, The Netherlands

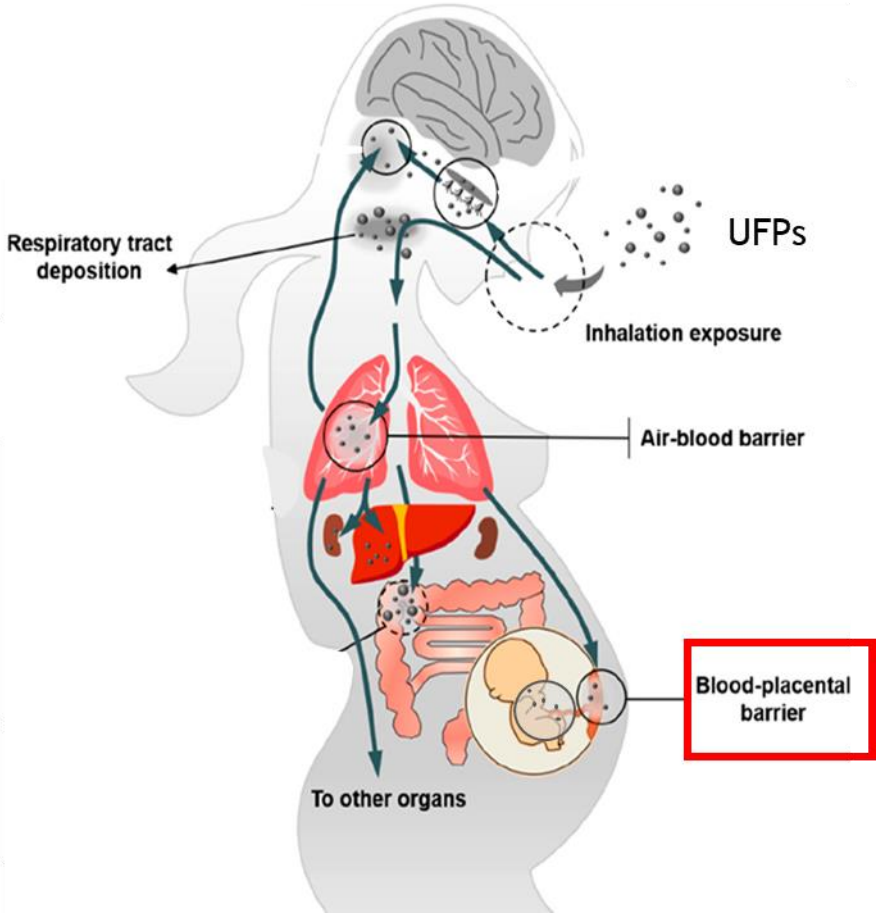
[⊥]Department of Environment and Health, VU University, 1081 HV Amsterdam, The Netherlands

[#]Institute for Risk Assessment Sciences, Utrecht University, 3512 JE Utrecht, The Netherlands



Suggesting slow release from the kidney and that nanoparticles may accumulate in the kidney before being excreted

UFPs reach fetal organs including the kidney



THE LANCET
Planetary Health

ARTICLES | VOLUME 6, ISSUE 10, E804-E811, OCTOBER 2022

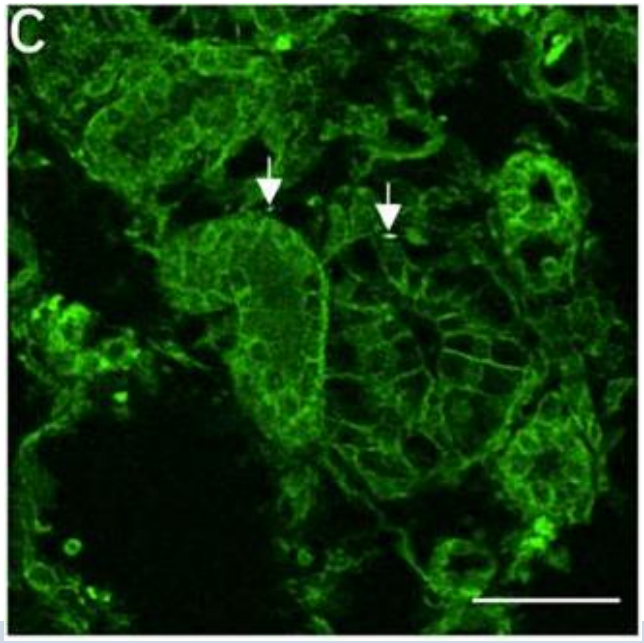
Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies

Eva Bongaerts, MSc • Laetitia L Lecante, PhD • Hannelore Bové, PhD • Prof Maarten B J Roeffaers, PhD • Prof Marcel Ameloot, PhD • Prof Paul A Fowler, PhD • et al. Show all authors

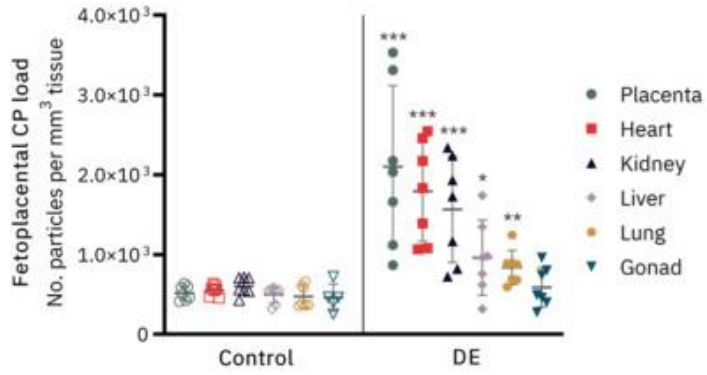
Open Access • Published: October, 2022 • DOI: https://doi.org/10.1016/S2542-5196(22)00200-5 •

Check for updates

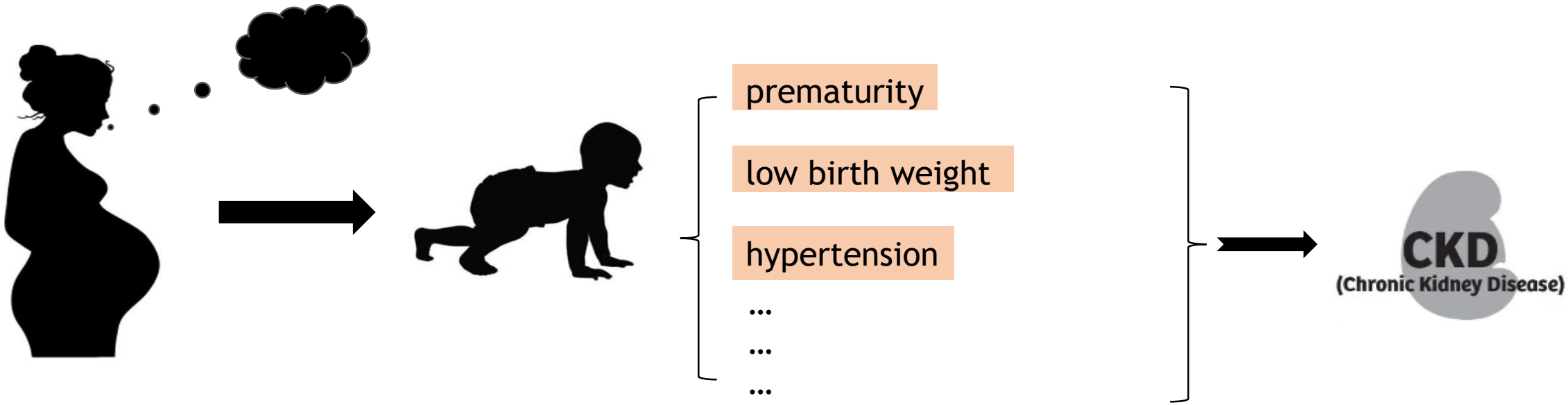
Human



Rabbits

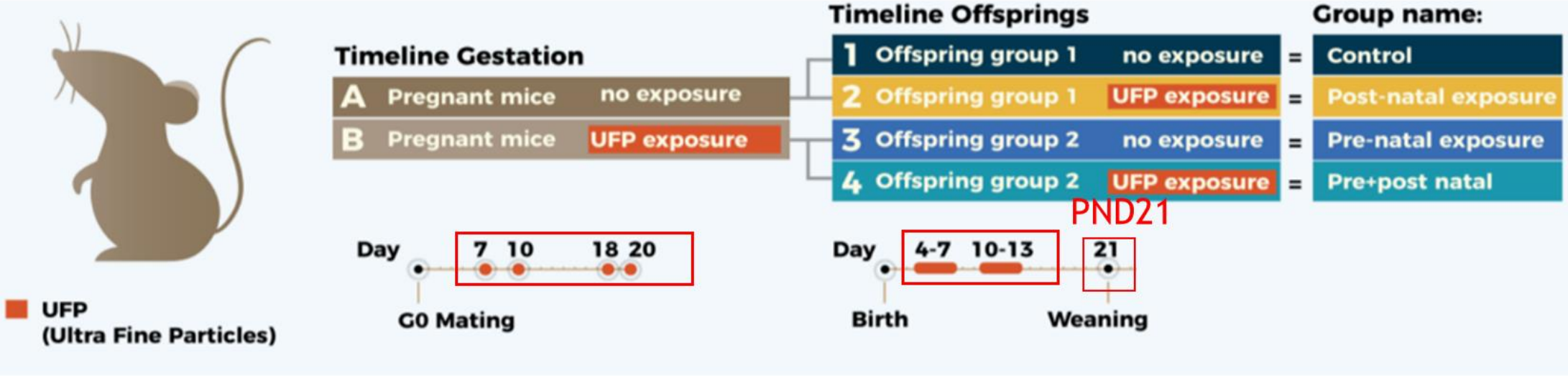


PM2.5 can affect kidney development but we don't know how....



We aim to determine the impact of UFPs during early life on kidney development

Research framework



Carbonaceous UFPs (450µg/m^3) generated by a spark generator for 4hours/day (mean particle size ~ 55nm)

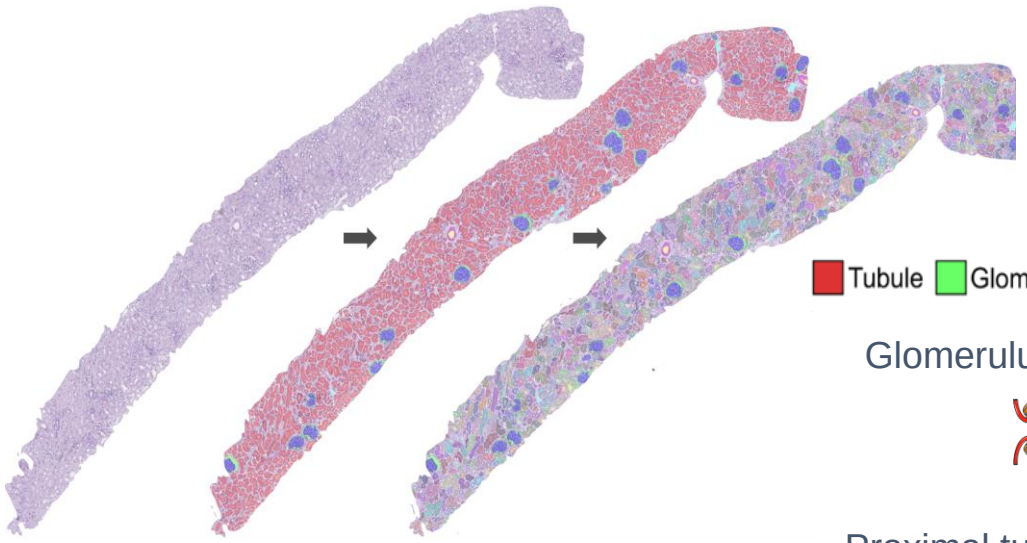
- Experiments carried out at RIVM (Dutch institute of health) from Prof. Flemming Cassee group

FLASH analysis to study kidney morphometric changes …

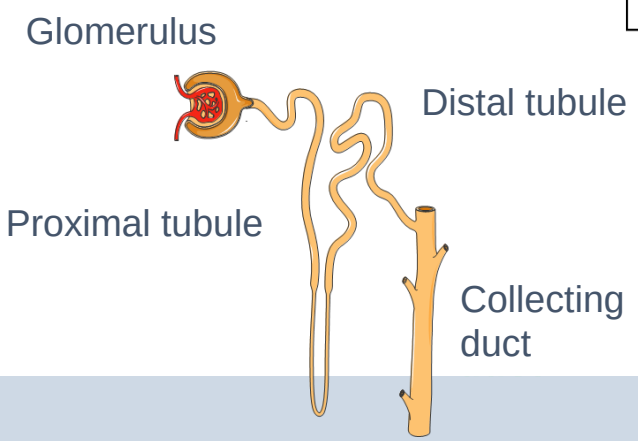
offspring kidney ⇨ PAS-D ⇨ FLASH

➢ FLASH is an innovative deep-learning algorithm that measures morphometric changes in each kidney segments.

Framework for Large-scale Histomorphometry (FLASH)



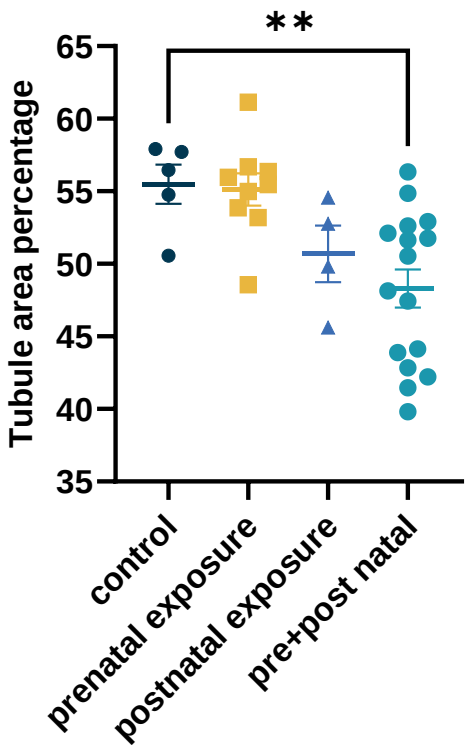
Features

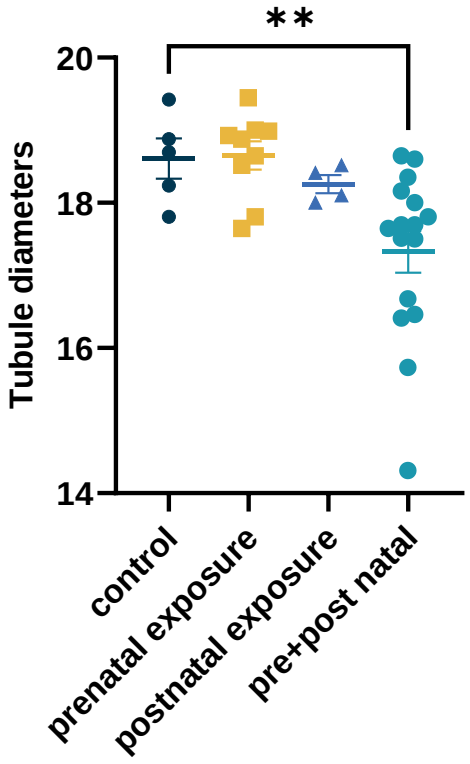


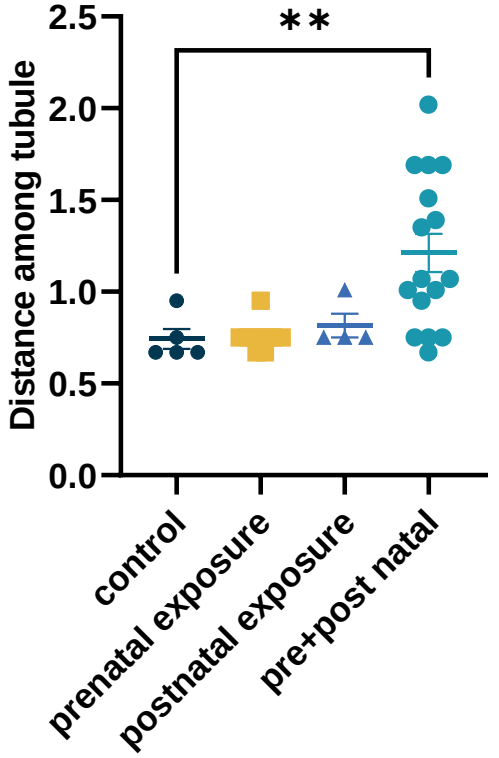
Feature	Description
Area A	Area of the segmented structure [µm²]
Diameter $dmax$	Diameter of the largest circle fully fitting inside the structure [µm]
Distance $distmin$	Closest distance between structures of the same class [µm]
Circularity C	Measures how circular the structure is using the ratio of its area (A) multiplied by 4*π to its squared perimeter (P). The circularity of a circle equals 1. $C = \frac{4 * \pi * A}{P^2}$
Elongation Elo	Function of the length of the structure's minor and major axis. The elongation of a circle is 0 and gets higher the more elongated the structure is. $Elo = 1 - \frac{minor\_axis\_length}{major\_axis\_length}$
Eccentricity Ecc	Ratio of the distance between the structure's focal points over the major axis' length. The eccentricity equals 0 for a circle and 1 for ellipses. $Ecc = \frac{\sqrt{(major\_axis\_length^2 - minor\_axis\_length^2)}}{major\_axis\_length}$
Solidity S	Measures the density of the structure by taking the ratio of its area to the area of its convex hull H $S = \frac{A}{H}$
Area Percentage	Proportion of a class' total area from the overall tissue area [%]
Count	Number of instances of a particular class present in one WSI or specimen

Hölscher et.al, Nat Commun, 2023

Pre-postnatal group showed PT dysgenesis: a condition characterized by poor development of the proximal tubule

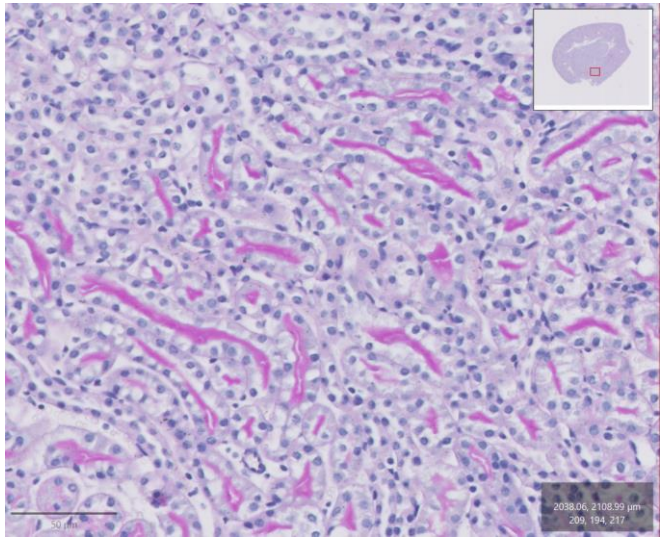




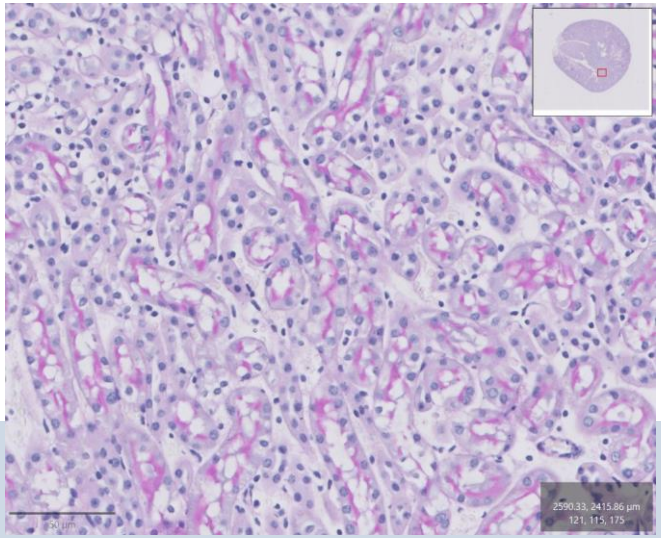


UFPs group showed a disorganized brush border(BB) in proximal tubule

Control group :

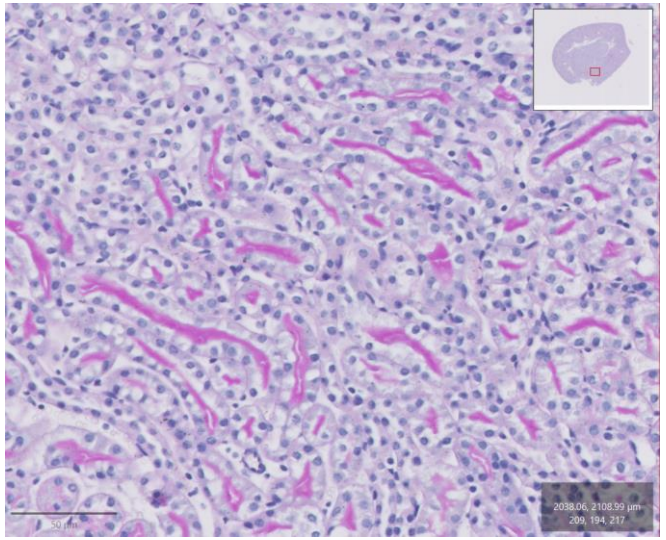


UFPs group :

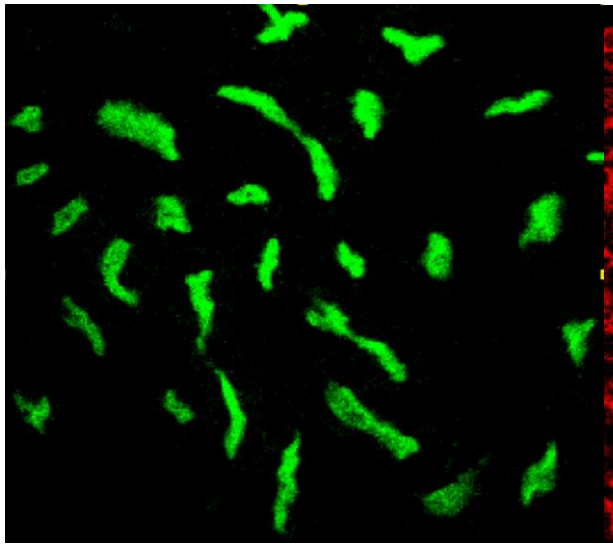


…and loss of actin cytoskeleton organization in proximal tubule

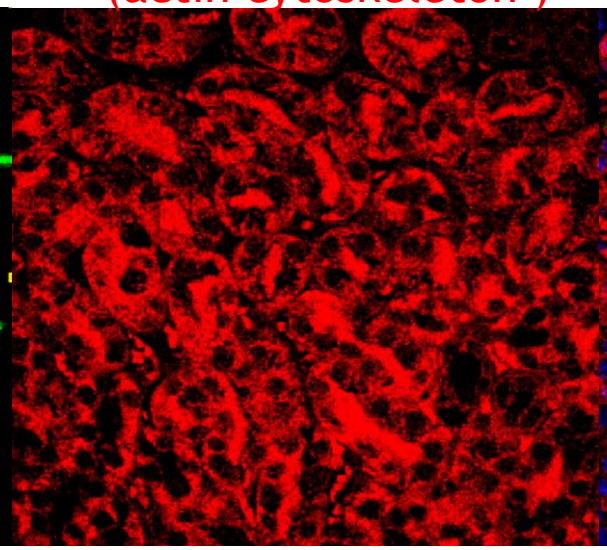
Control group :



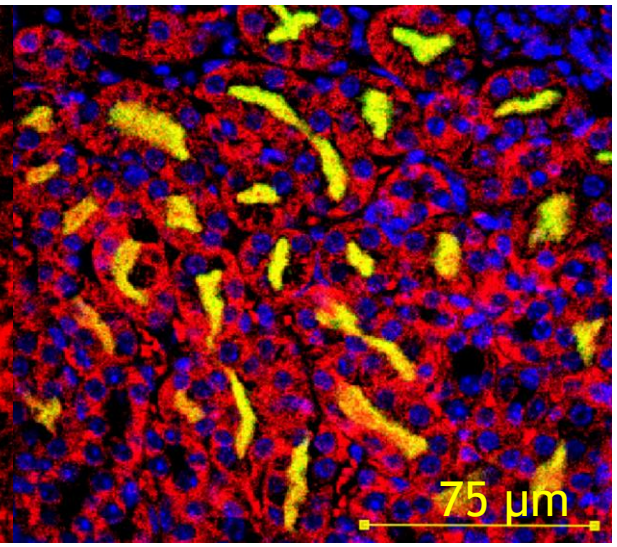
LTL-FITC(BB)



Phalloidin
(actin cytoskeleton)



Merge



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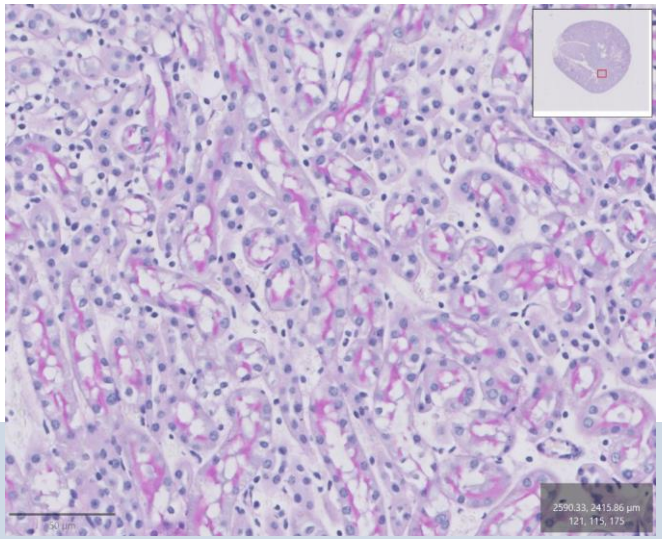
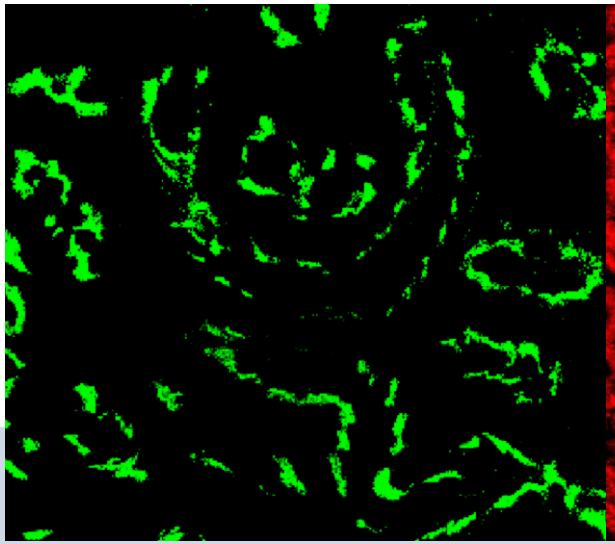
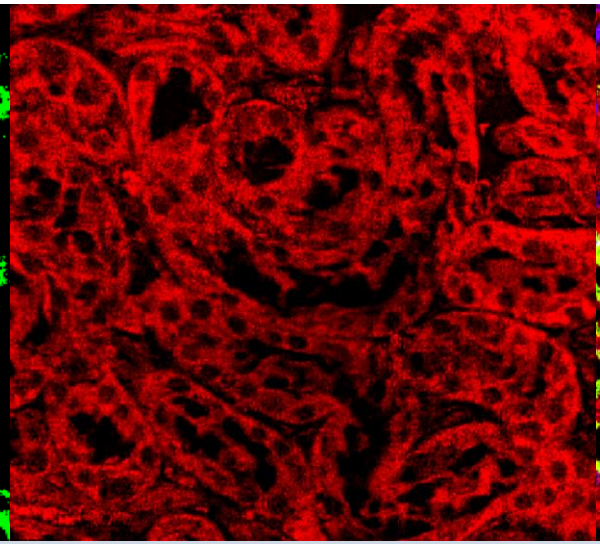
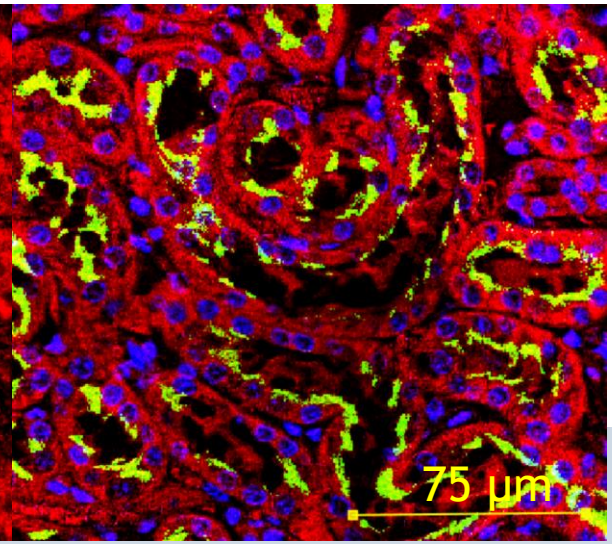
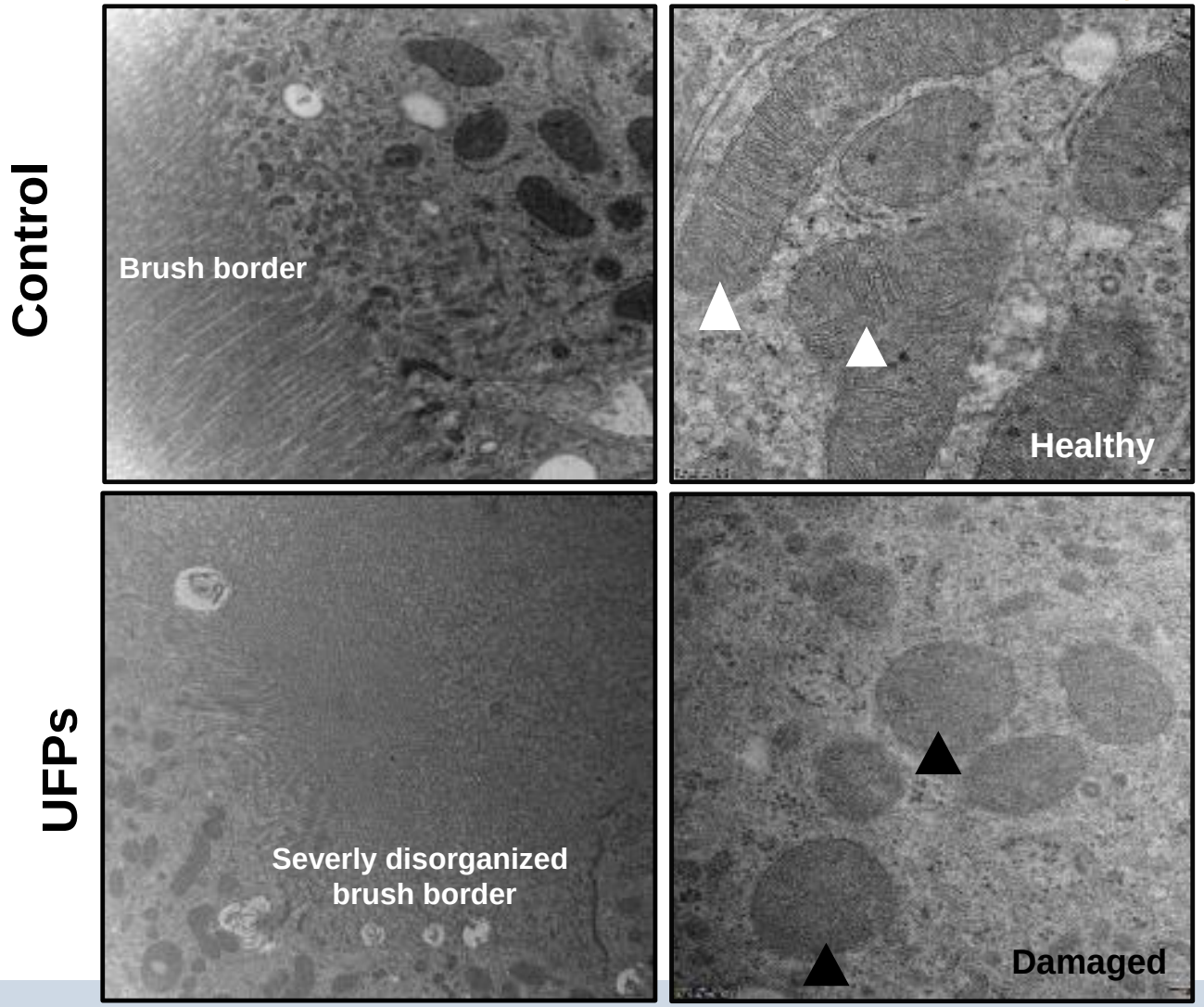








BB and mitochondrial abnormalities observed by TEM in UFPs group

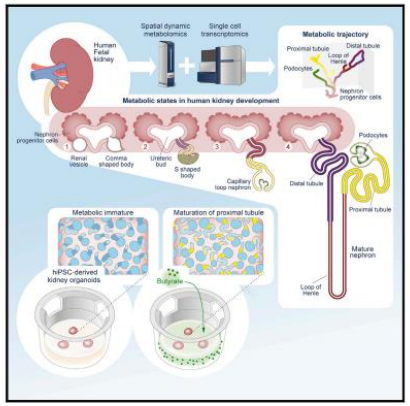


UFPs group display decreased mitochondrial metabolism…

Cell Stem Cell

Spatial dynamic metabolomics identifies metabolic cell fate trajectories in human kidney differentiation

Graphical abstract



Authors

Gangqi Wang, Bram Heijs, Sarantos Kostidis, ..., Cathelijne W. van den Berg, Bernard M. van den Berg, Ton J. Rabelink

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a.j.rabelink@lumc.nl

In brief

In this study, Wang et al. report metabolic trajectories during human kidney epithelium development using spatial dynamic metabolomics. This knowledge can be used to enhance proximal tubule differentiation and maturation in hiPSC-derived kidney organoids.

- Mitochondrial metabolism is very important for proximal tubular development

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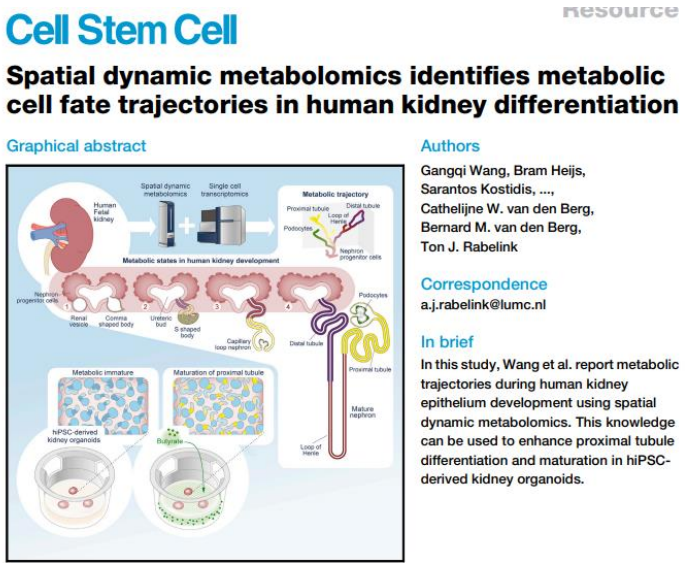

Cell Stem Cell

Resource

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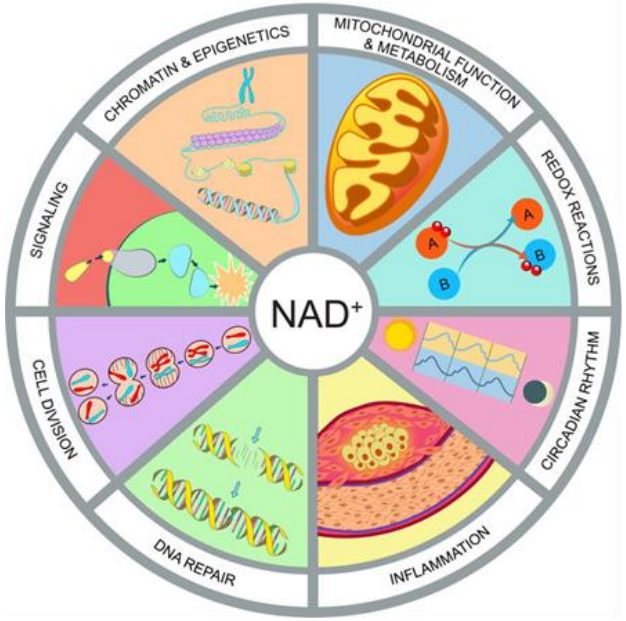
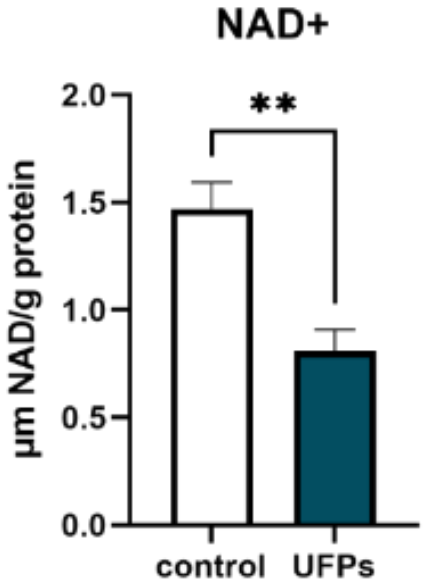


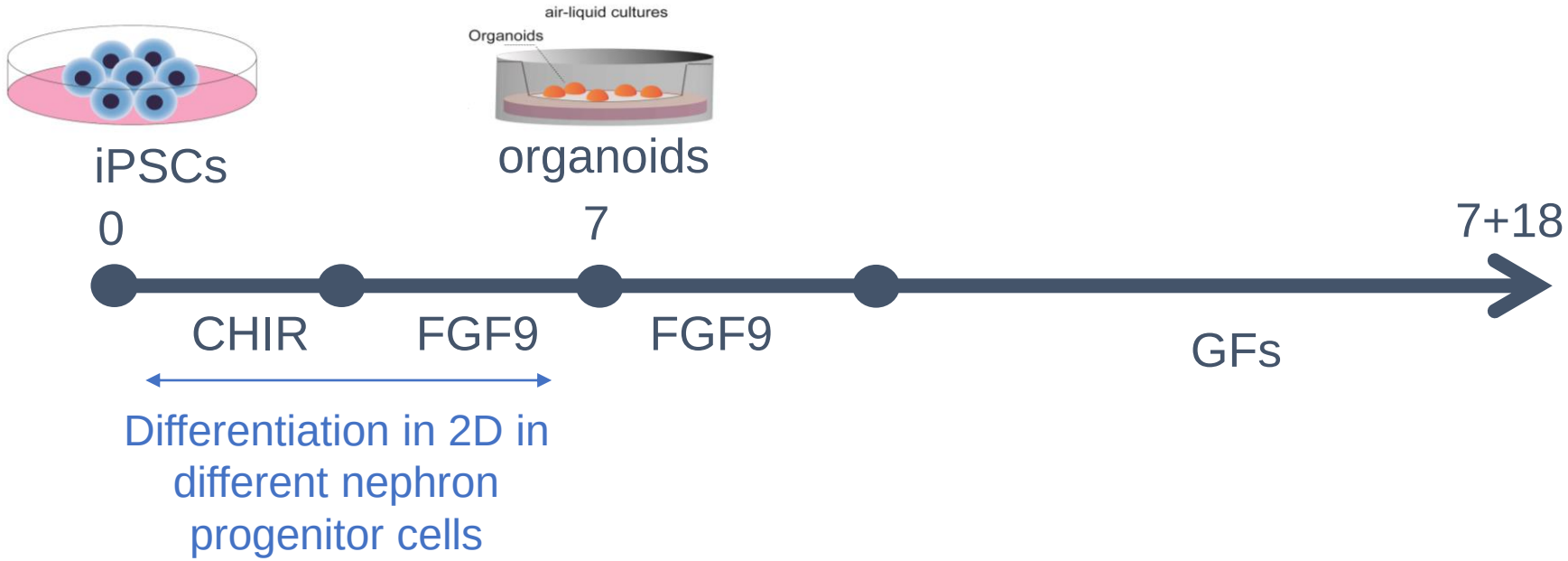
Nicotinamide-adenine-dinucleotide

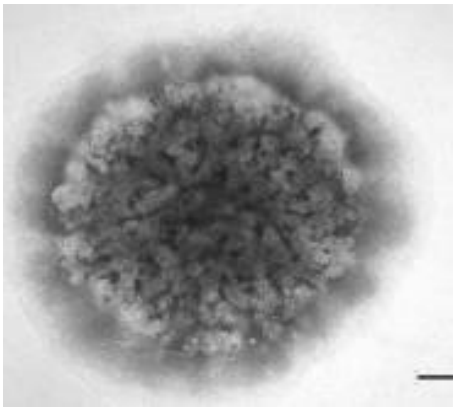
(Rajman et al., 2018)



- Nicotinamide-adenine-dinucleotide (NAD+), a critical coenzyme involved in mitochondrial metabolism, playing a significant role in mitochondrial function and maintaining mitochondrial health.

Can I model PT dysgenesis in kidney organoids?





(iPSC-derived organoids culture protocol described in Jansen et al. Development 2022 based on Melissa Little's protocol)

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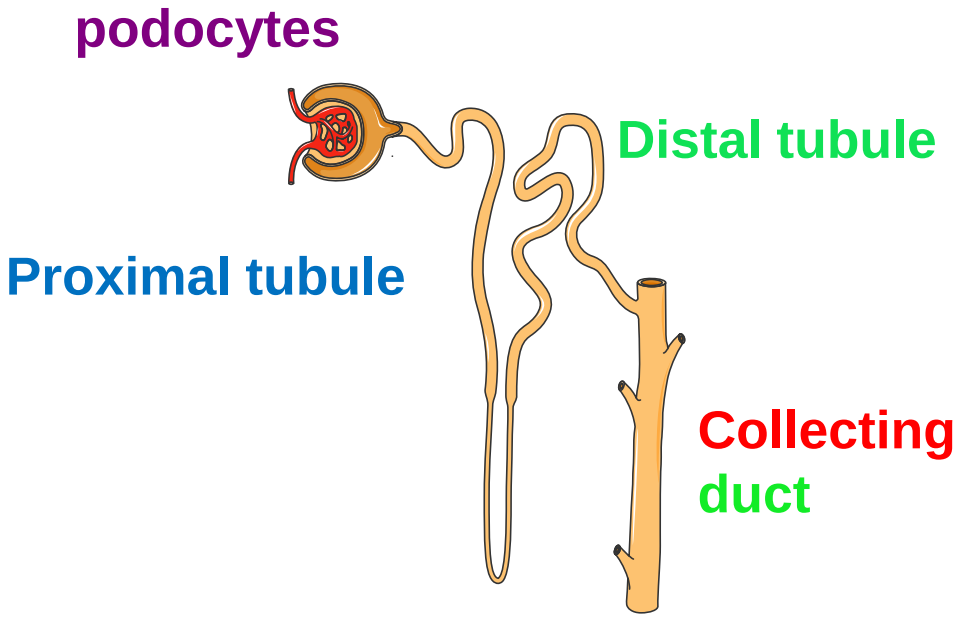
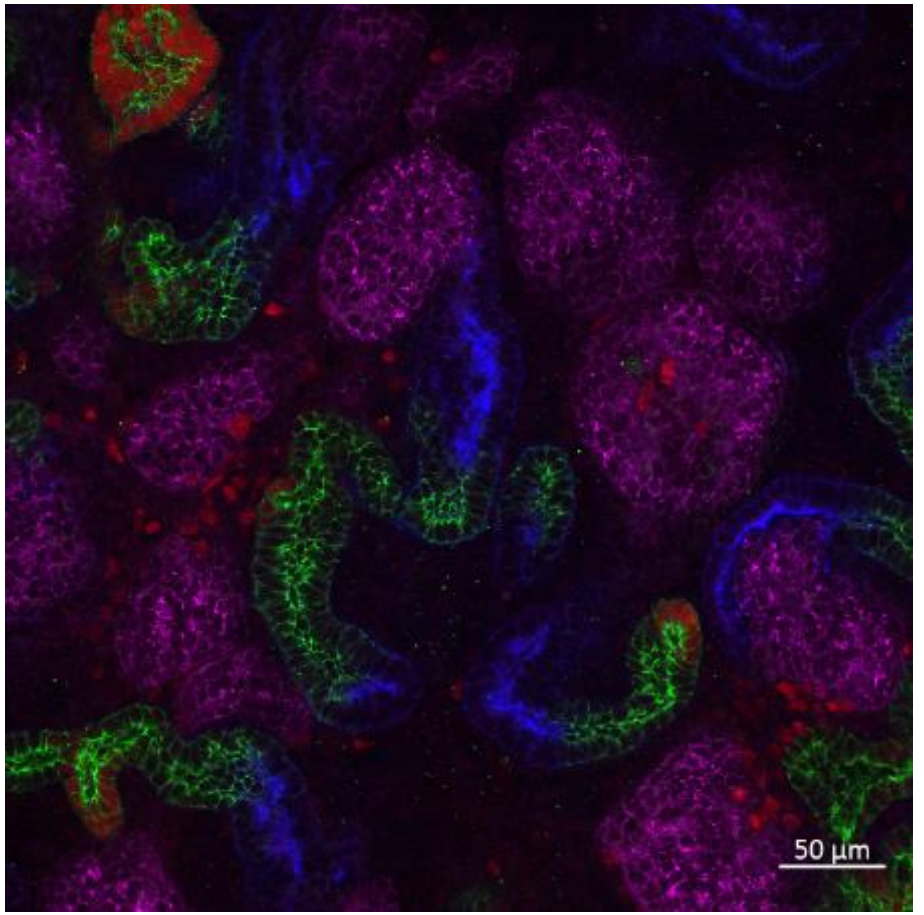
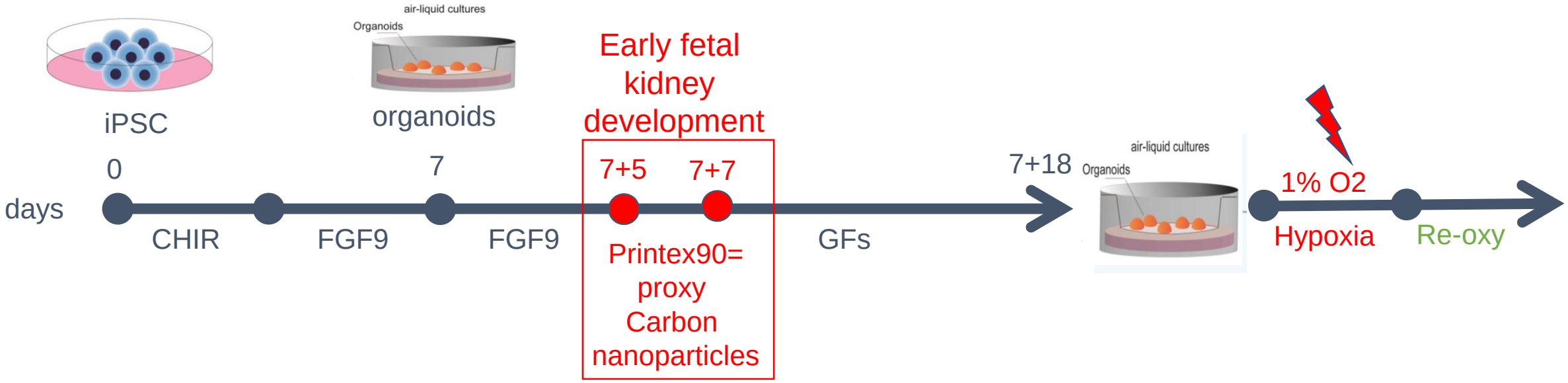




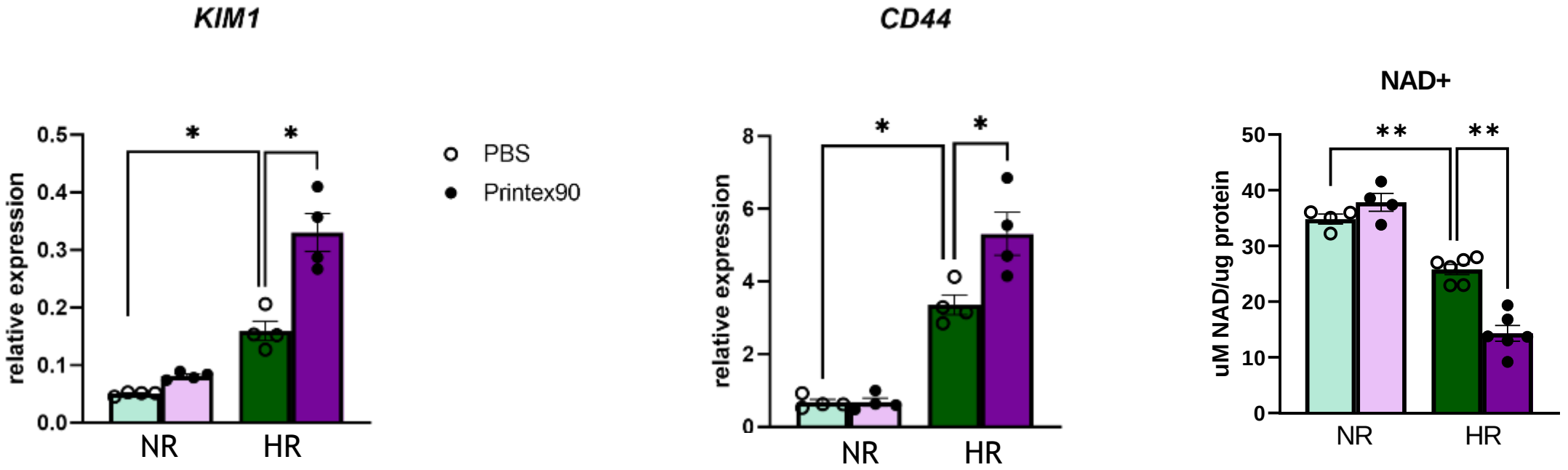
Nephrin LTL ECAD GATA3

(iPSC-derived organoids culture protocol described in Jansen et al. Development 2022 based on Melissa Little's protocol)

Hypoxia helps to reveal PT dysgenesis in organoids



Enhanced tubular damage and decreased NAD+ pool also in organoids

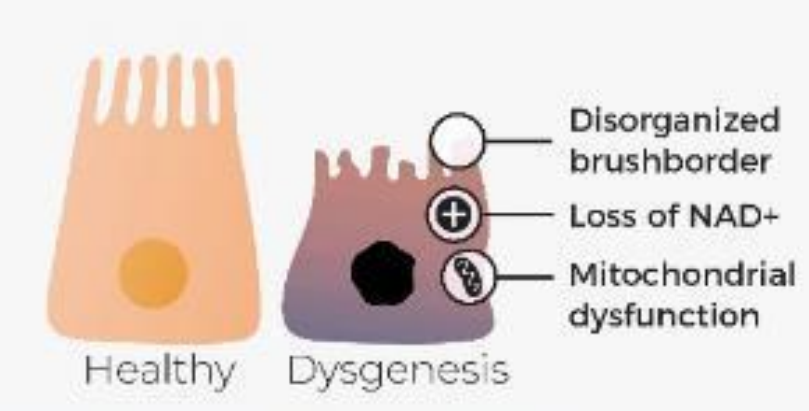


Tubular damage markers

NR: Normoxia
HR: Hypoxia

Summary and conclusion

The kidneys from the UFPs-exposed group, displayed PT dysgenesis, a condition characterized by poor PT development.



Similar to observation in vivo, exposing organoids to Printex90 (a proxy for UFPs), followed by a hypoxic injury, resulted in decreased NAD+ and increase in the PT damage marker KIM-1 and CD44

Early life exposure to UFPs may induce developmental programming of kidney disease.
We should protect mothers and their unborn children to prevent the growing burden of CKD in future generations

"The early environment in which human beings grow shapes growth and development and lays the foundations for later health and wellbeing"

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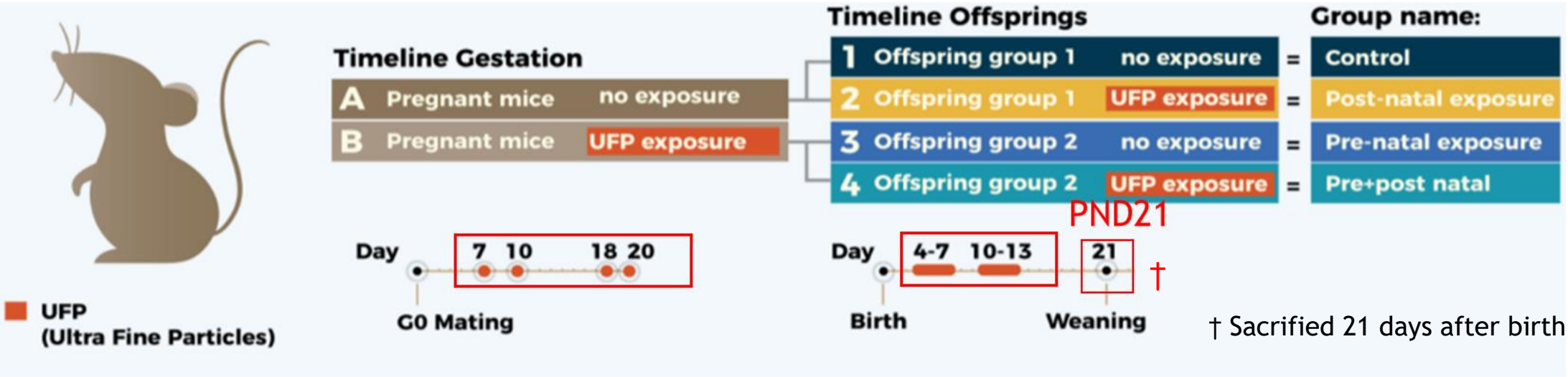
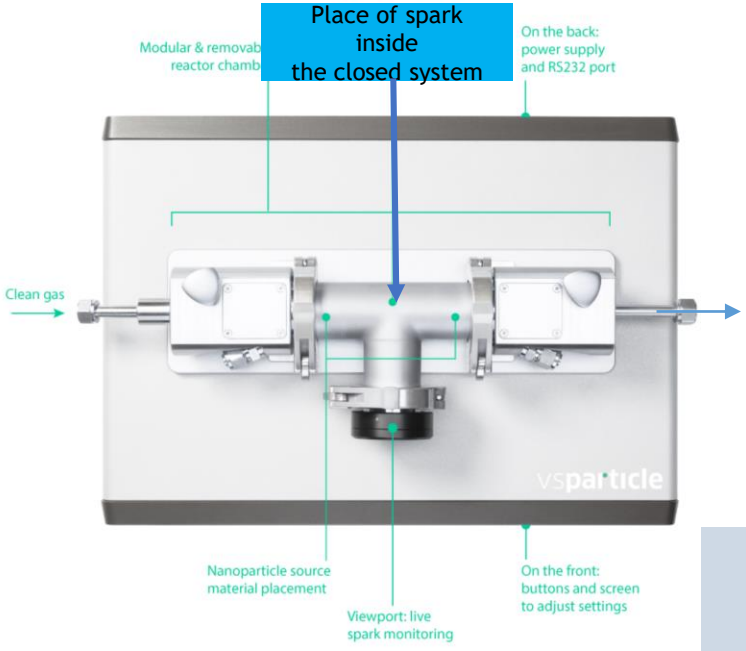
ANY QUESTIONS?

Research framework…





Aerosolized carbon UFPs ($450 \mu g/m^3$)

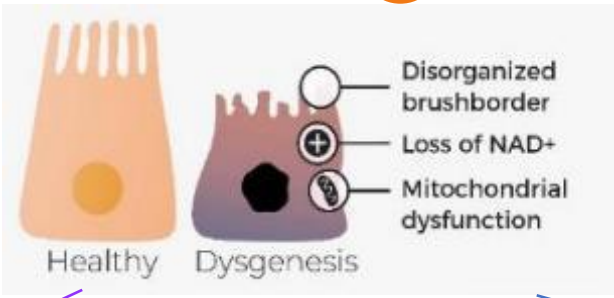
(mean particle size ~ 55nm)

||

Individuals are exposed during increased breathing or traffic in a tunnel

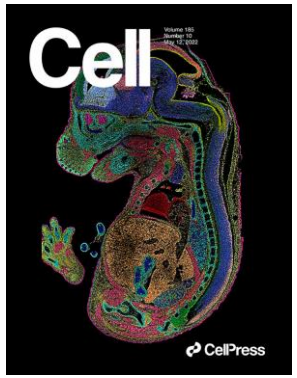
- Experiments carried out at RIVM.

Future plans

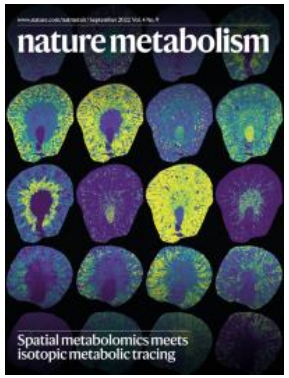


- Further unravel the mechanism leading to pTECs changes;
- Subject mice exposed to UFPs during early life to a model of renal ischemia reperfusion injury.

How different?

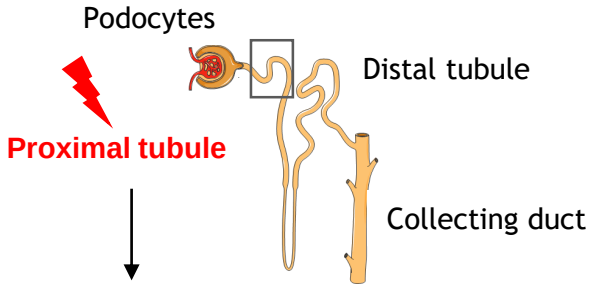


Sc spatial transcriptomics by StereoSeq



Sc Spatial metabolomics by MALDI MSI

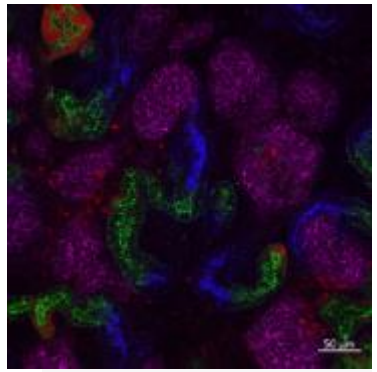
Consequence?



Renal ischemia/reperfusion-induced acute kidney injury

Possible intervention?

iPSCs-derived kidney organoids

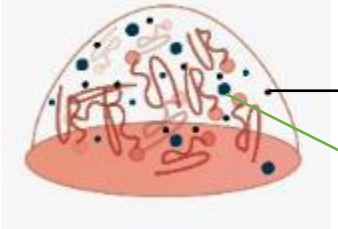


Nephrin: podocytes

LTL: proximal tubule

ECAD: distal tubule

GATA3: collecting duct



UFPs

NAD+ boosters and other targets

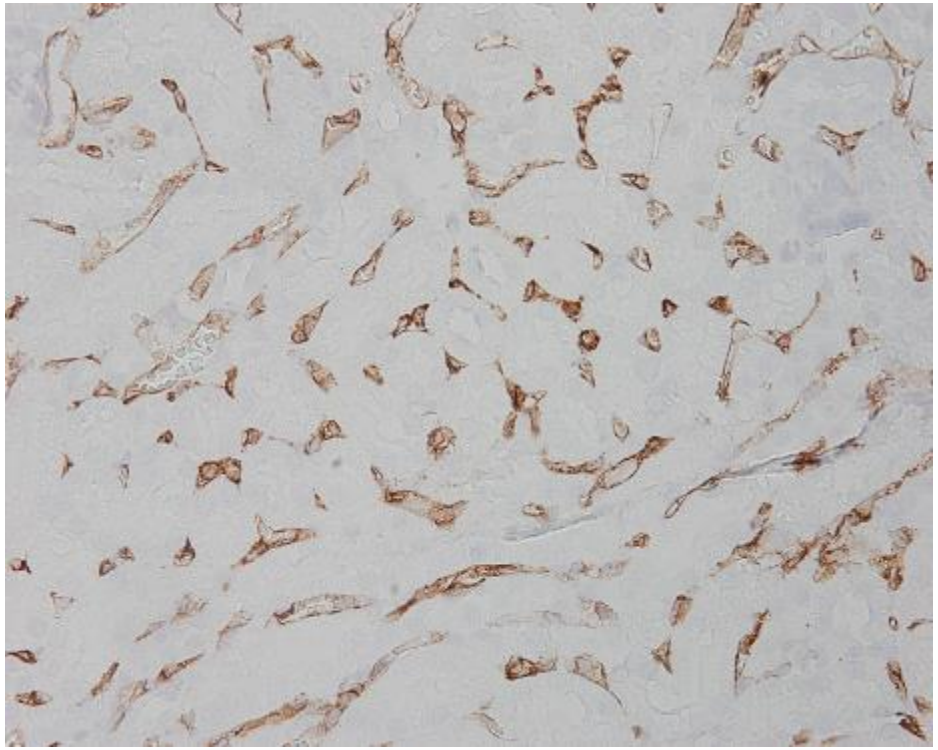
Objective 1

Objective 2

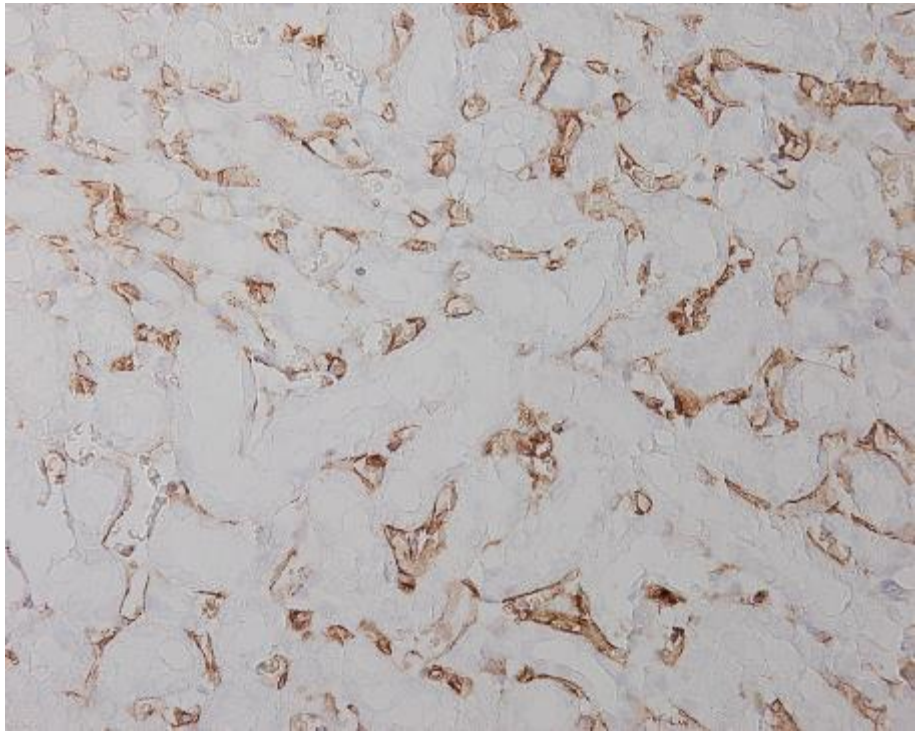
Objective 3

Undergoing experiment...

CD34 staining to understand the capillary network surrounding the Proximal tubular ….



Control group



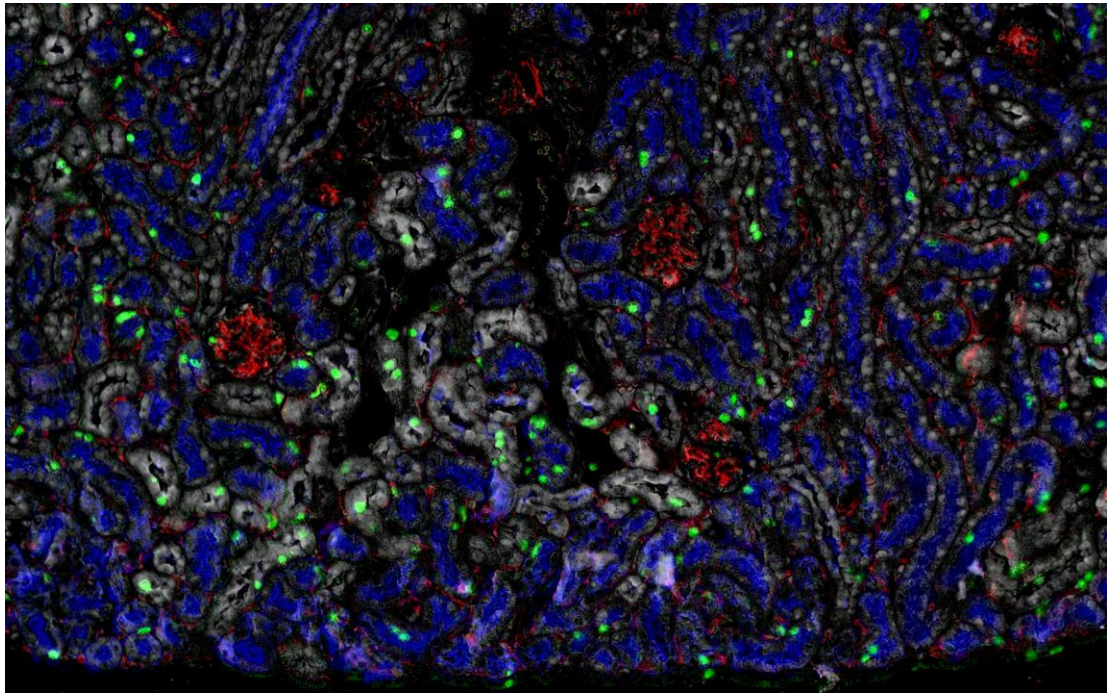
Prepost-natal group

Quantification in progress

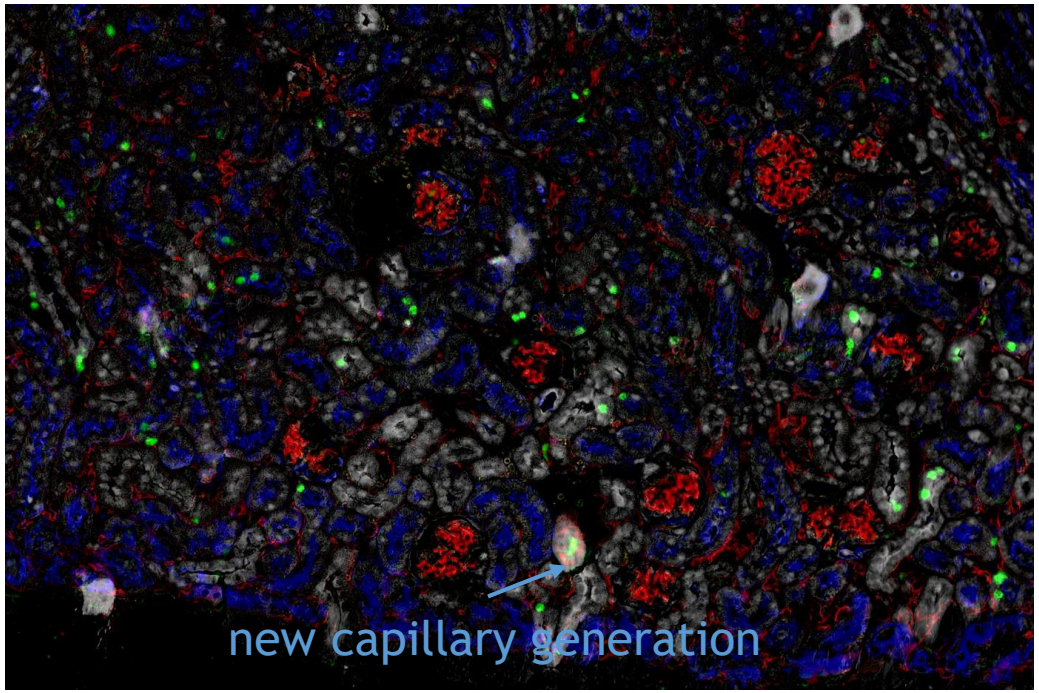
Undergoing experiment...

In prepostanal group, Ki67, VEGF, CD34 staining may show

1. Reduced proliferation cells in the cortex....
2. Generated new capillaries...



Control group



Prepost-natal group

- LTL
- VEGF
- Ki67
- CD34

Quantification in progress

Pre-postnatal group showed interstitium area increase by FLASH anlysis ...