Metabolic communication in kidney disease

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Conflicts of interest

- Research grant, Novo Nordisk A/S

Cagrilintide’s actions in the kidney

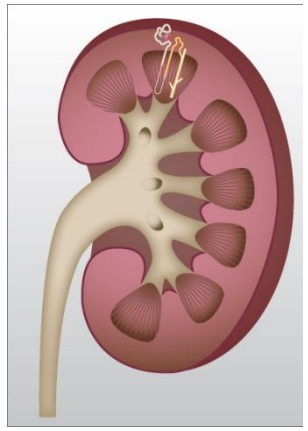
- Research grant, Novo Nordisk A/S

Mechanisms of Glp1a in the kidney

- Patent: Endogenous complement inhibitor

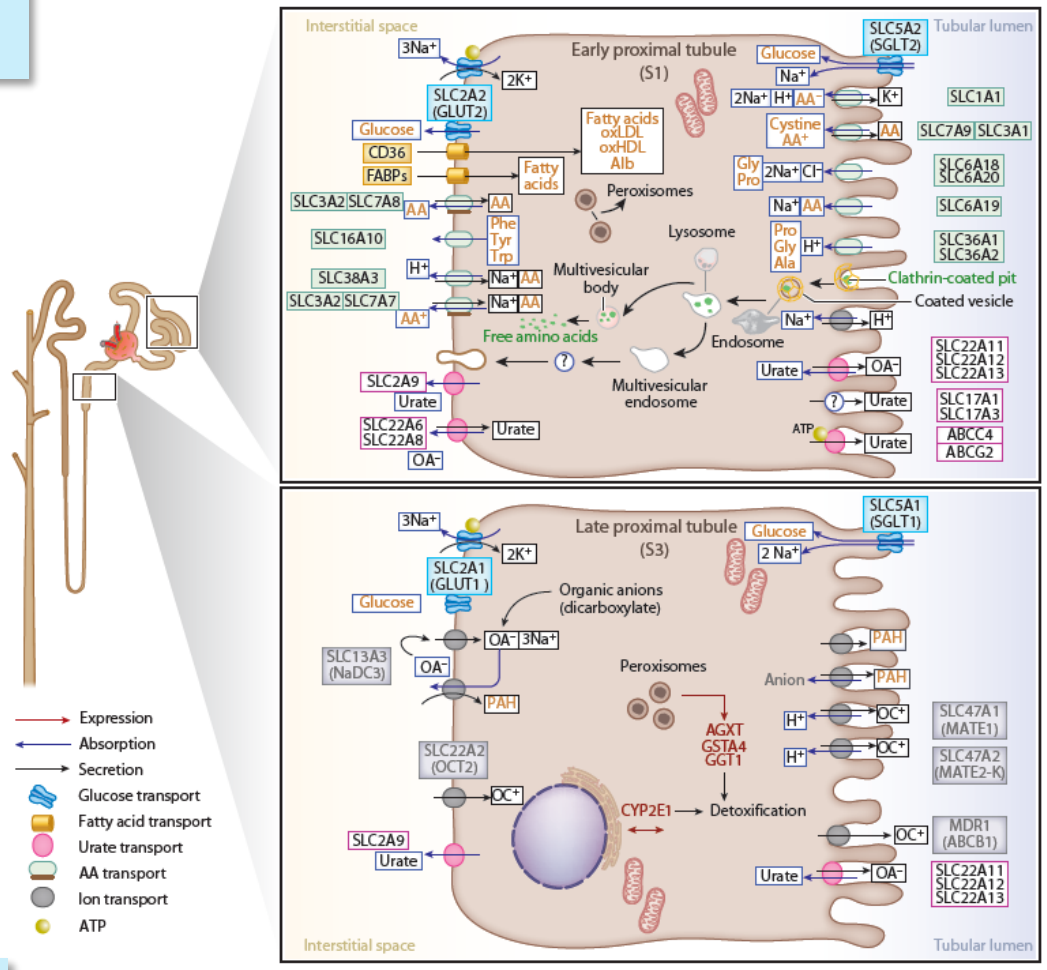
The proximal tubule – a hub of metabolism

180l of primary urine



20% of every heart beat

0.5% of body weight



Reabsorbs nutrients:
180g of glucose
50g of amino acids

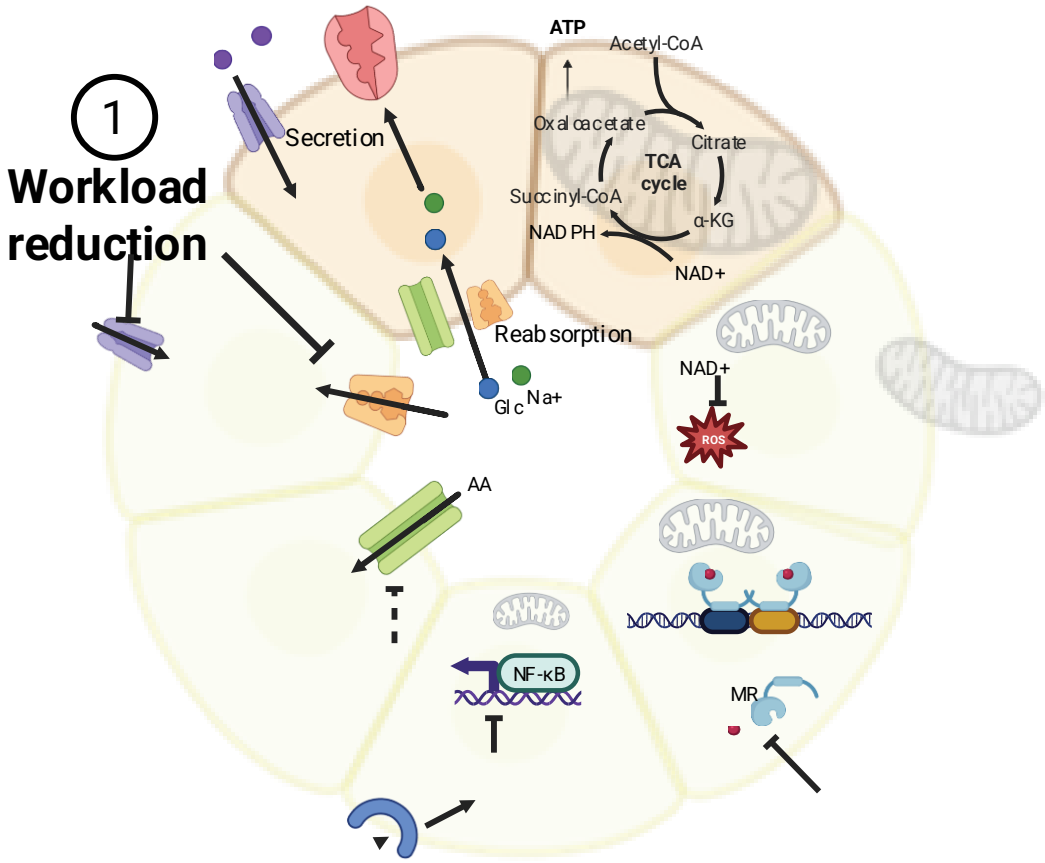
Secrets toxins /Organic Anions (from the gut)

Regulates electrolytes And blood pressure

Chrysopoulou and Rinschen, Ann Rev Physiol 2024

Kidney metabolism as a therapeutic strategy

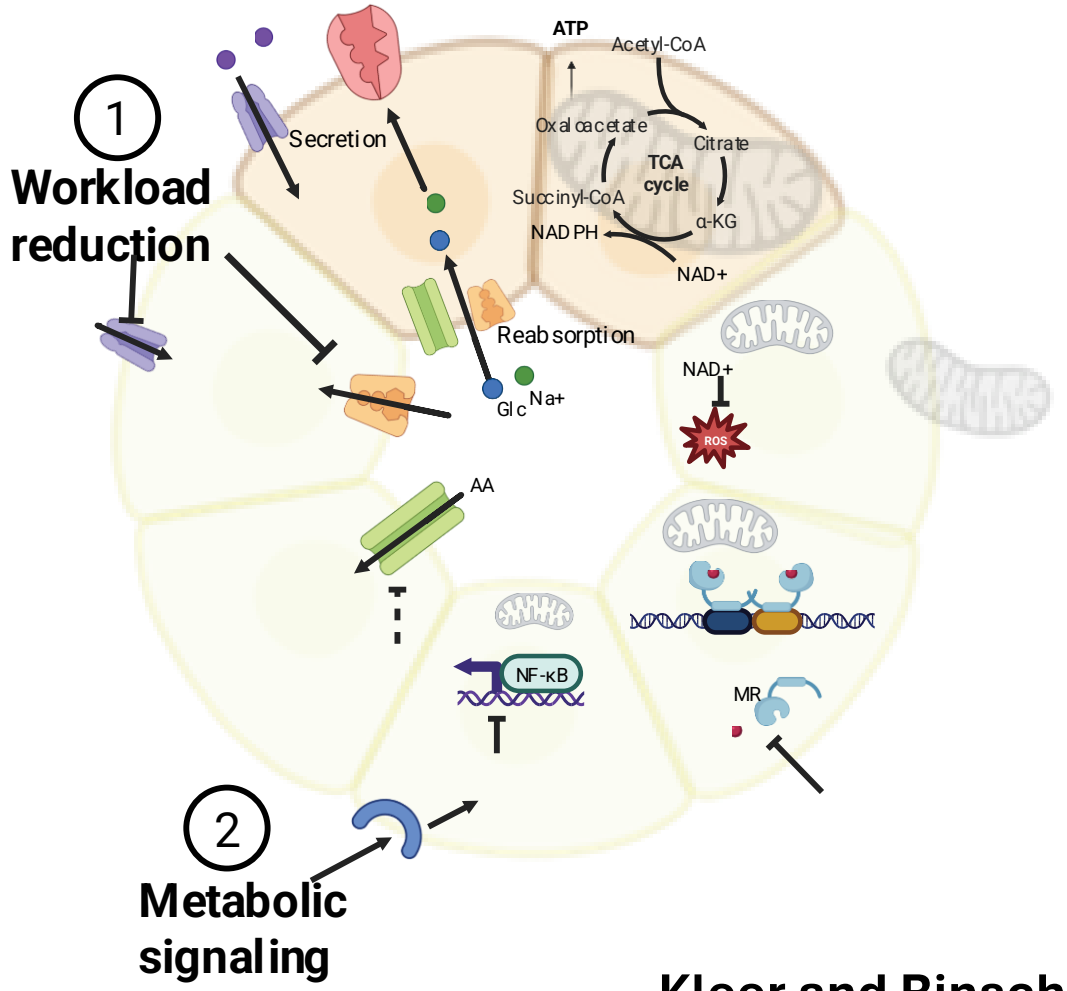
1. Workload reduction



Kleer and Rinschen, NDT 2025

Kidney metabolism as a therapeutic strategy

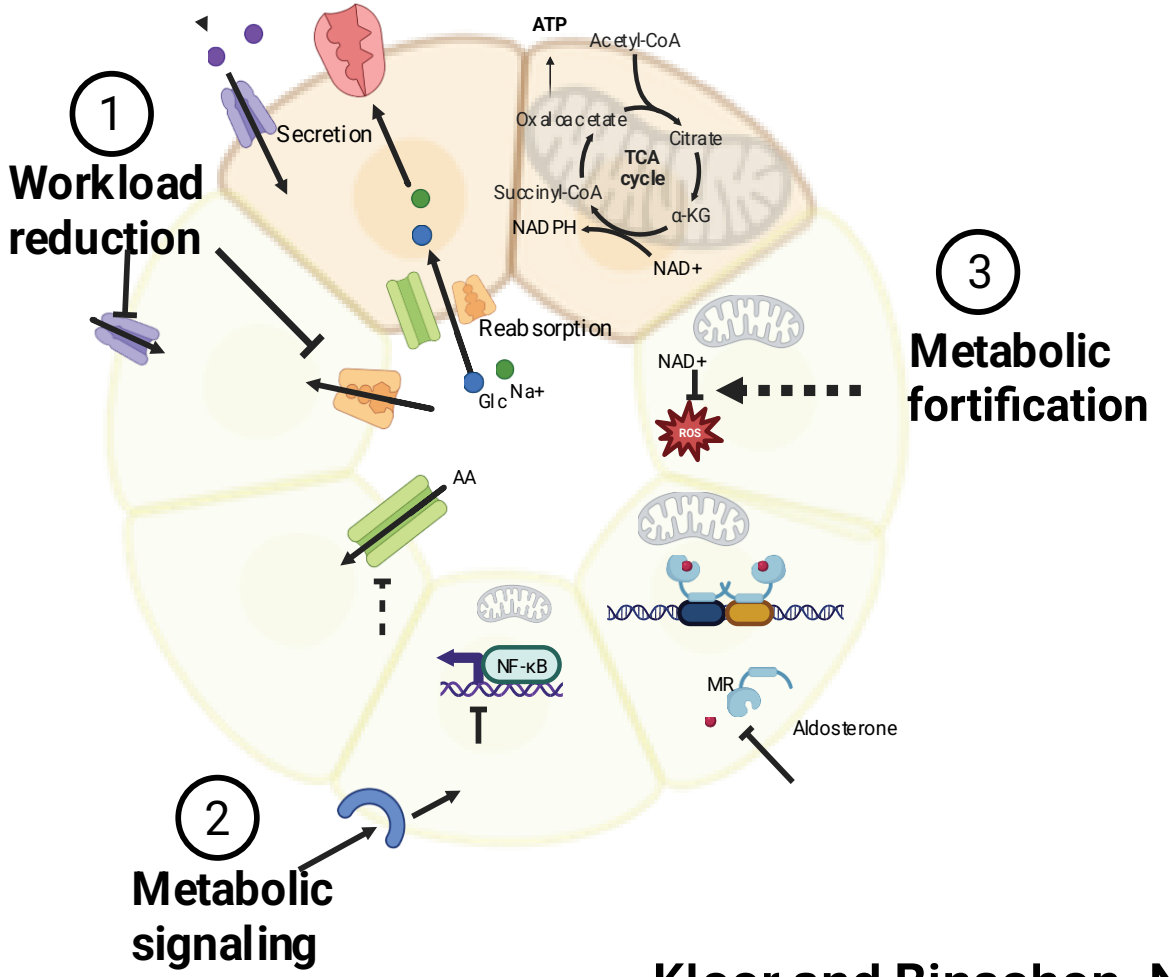
1. Workload reduction
2. Metabolic signaling



Kleer and Rinschen, NDT 2025

Kidney metabolism as a therapeutic strategy

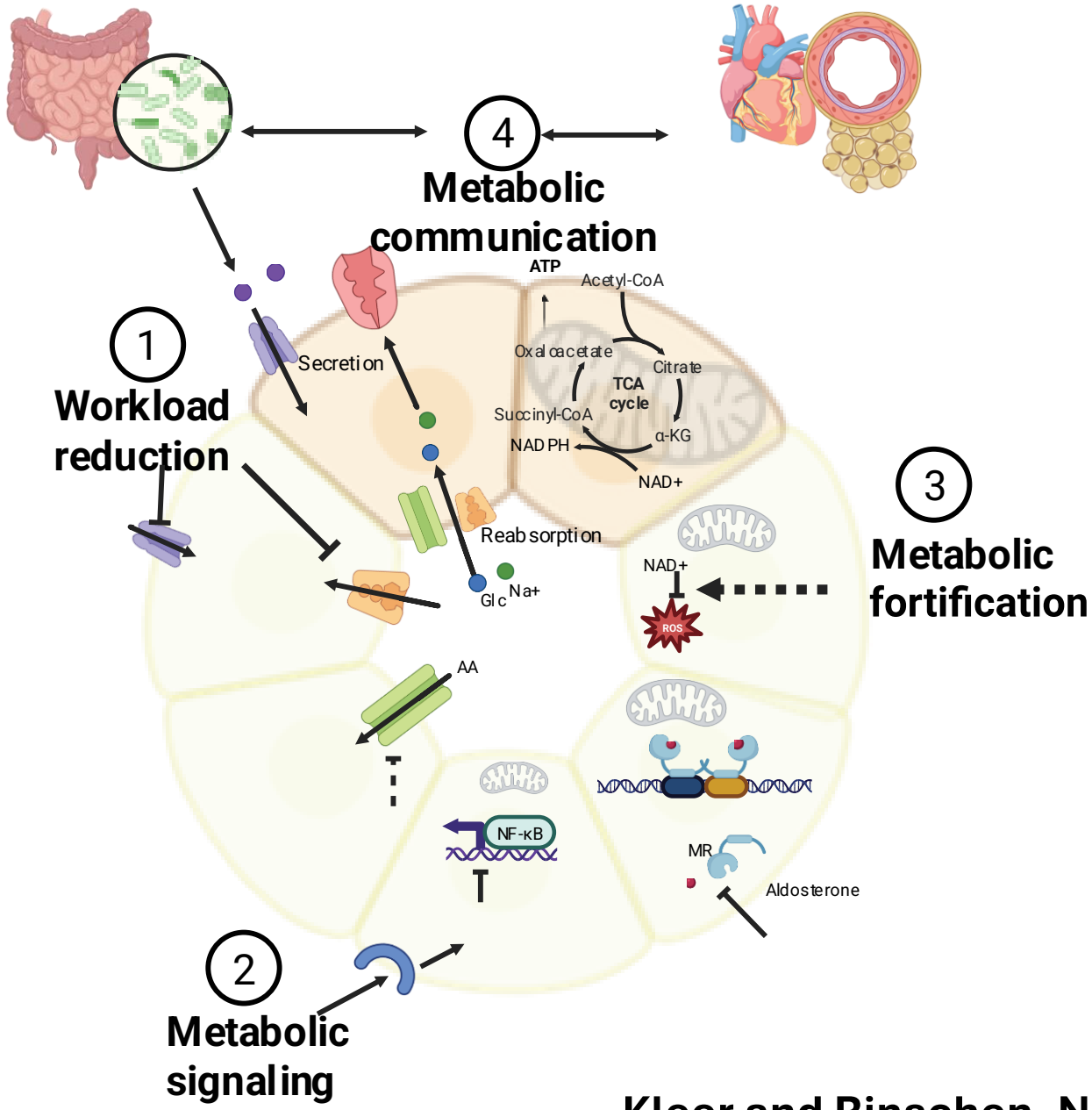
1. Workload reduction
2. Metabolic signaling
3. Metabolic fortification



Kleer and Rinschen, NDT 2025

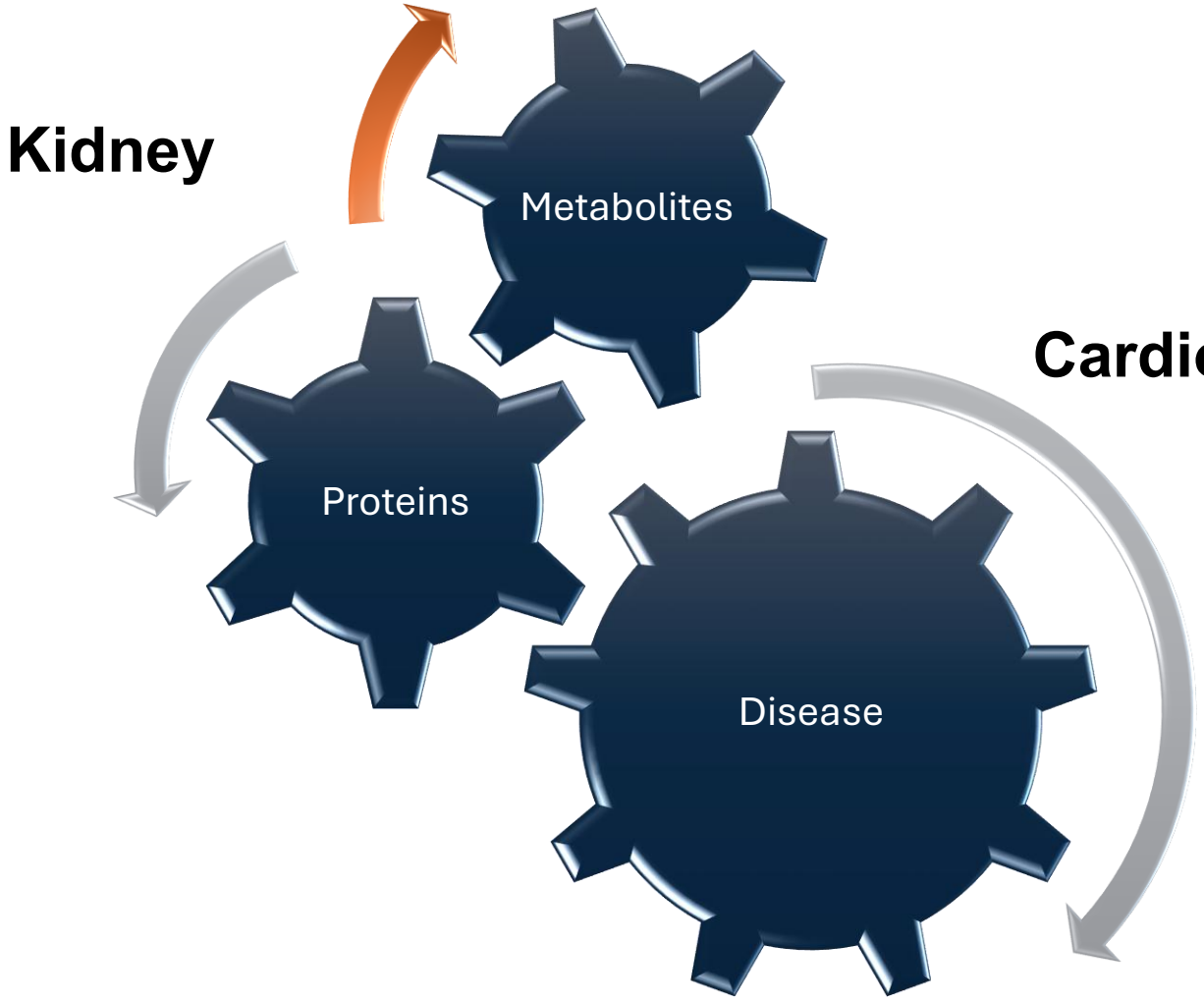
Kidney metabolism as a therapeutic strategy

1. Workload reduction
2. Metabolic signaling
3. Metabolic fortification
4. Metabolic communication



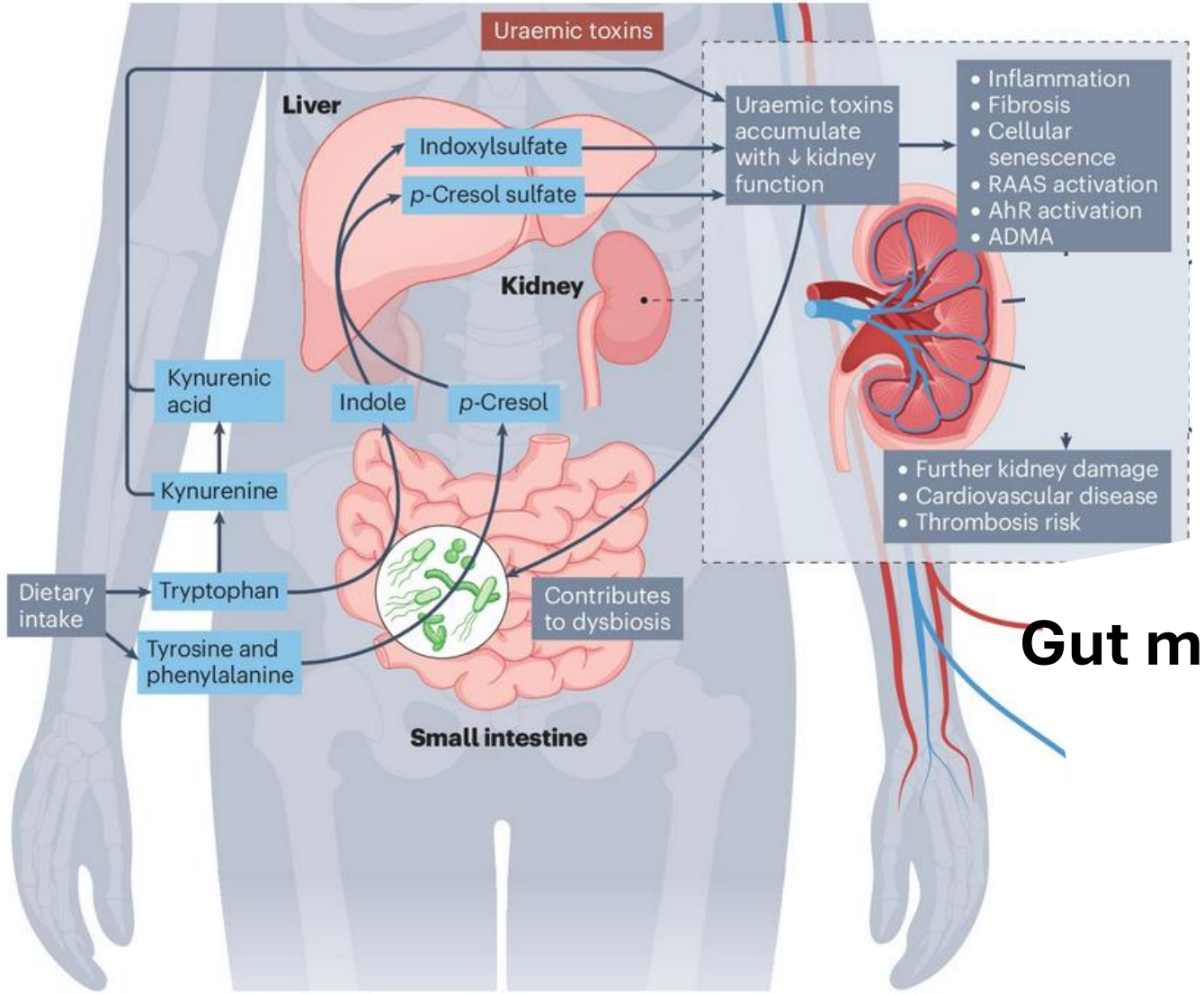
Kleer and Rinschen, NDT 2025

Use large-scale pathophysiology to provide new targets to chronic kidney disease, and by extension, cardiovascular disease.



Späth et al. Kidney International 2018, Rinschen et al. Nat Rev Mol Cell Biol 2019, Sci Signal 2019, 2022; Nat Comm 2022; Hatje JASN 2022, Hutzfeldt et al. AJP renal 2022; Lassé et al, Nat. Comm 2023, Billing et al. Circulation 2024, Knol et al. Nat Rev Nephrology 2024, Demir et al. EMBO J 2025, Jaschke et al. Cell 2025

Metabolites actively secreted by the kidney



Kidneys fail:

Gut metabolites with cardiovascular bioactivity increase

“Toxicity by association”

Knol MGE, Wulfmeyer V, Mueller RU, Rinschen MM. Nat Rev Nephrology 2024

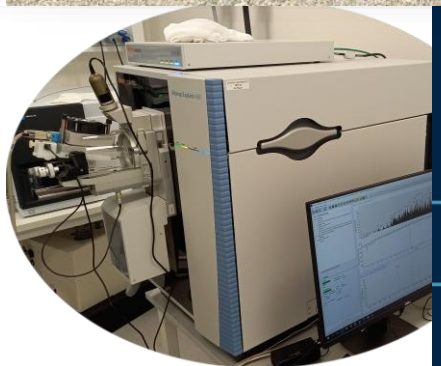
Todays goal:

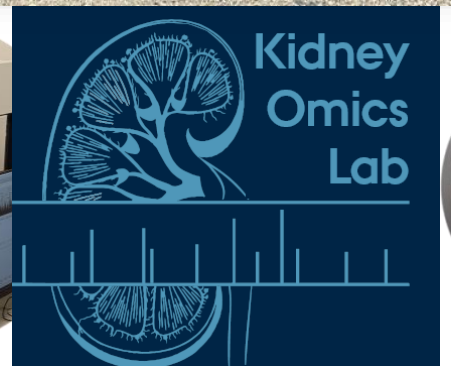
#1 Introduction of the concept of metabolic communication in kidney disease, using SGLT2 inhibitors as an example

#2 New approaches to understand the metabolite language by systems-level bioactivity determination

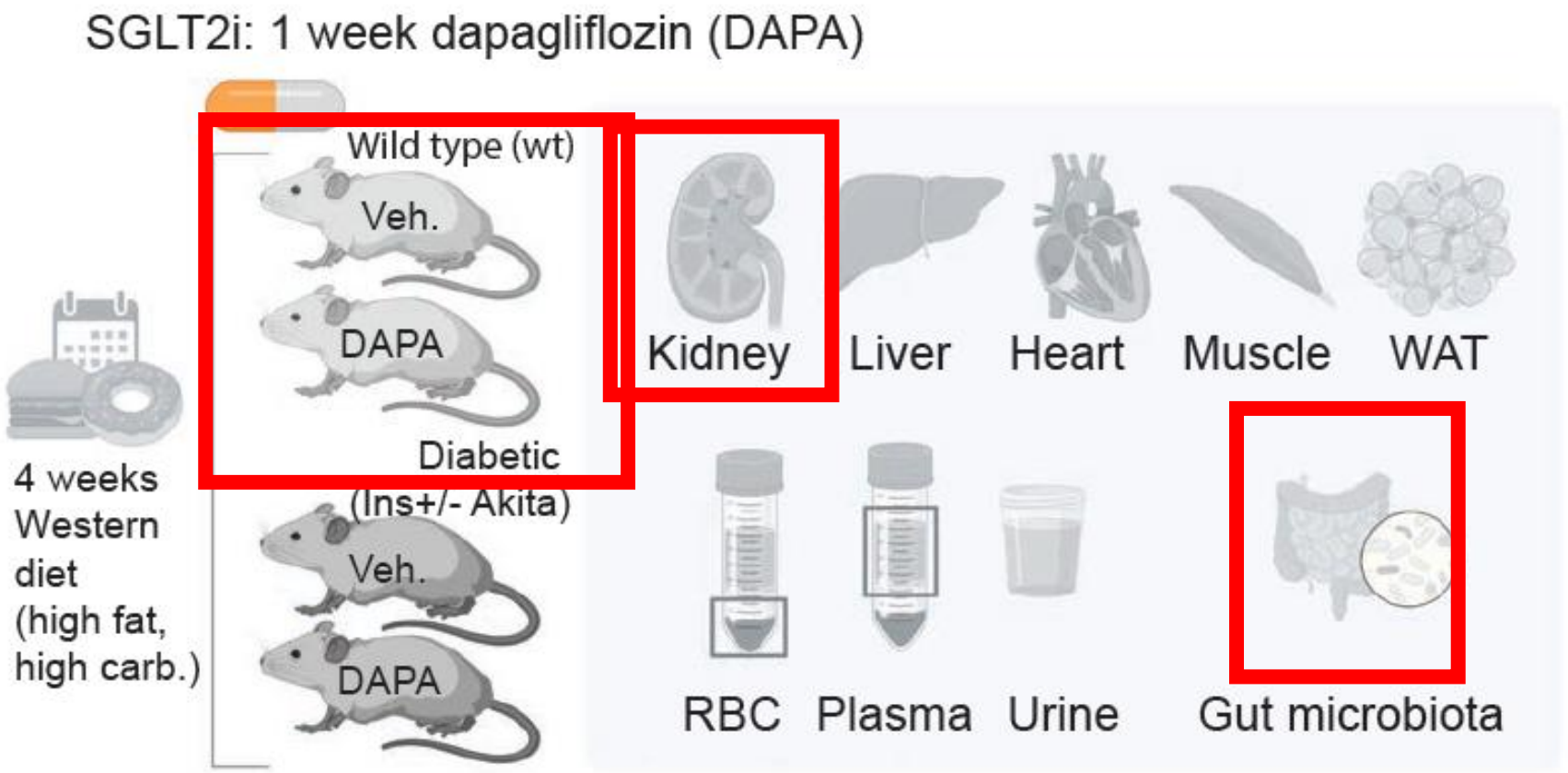
Thank you to the team!

Dybbøl Mølle/Dybbeler Schanzen





Strategy to study SGLT2i: 1 week of Dapagliflozin (DAPA)



Proteome

Phosphoproteome

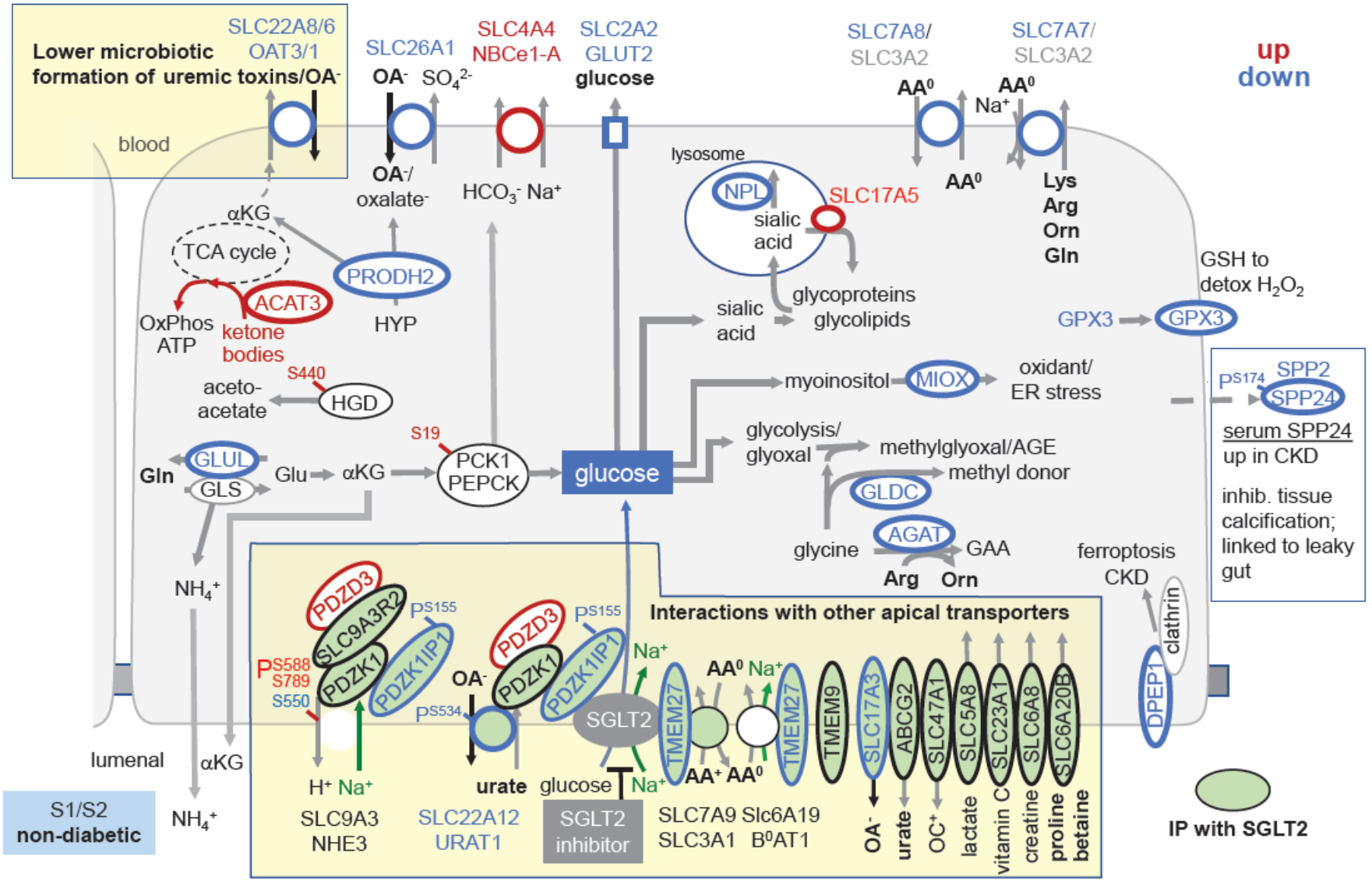
(Un)targeted Metabolome

SGLT2 interactome

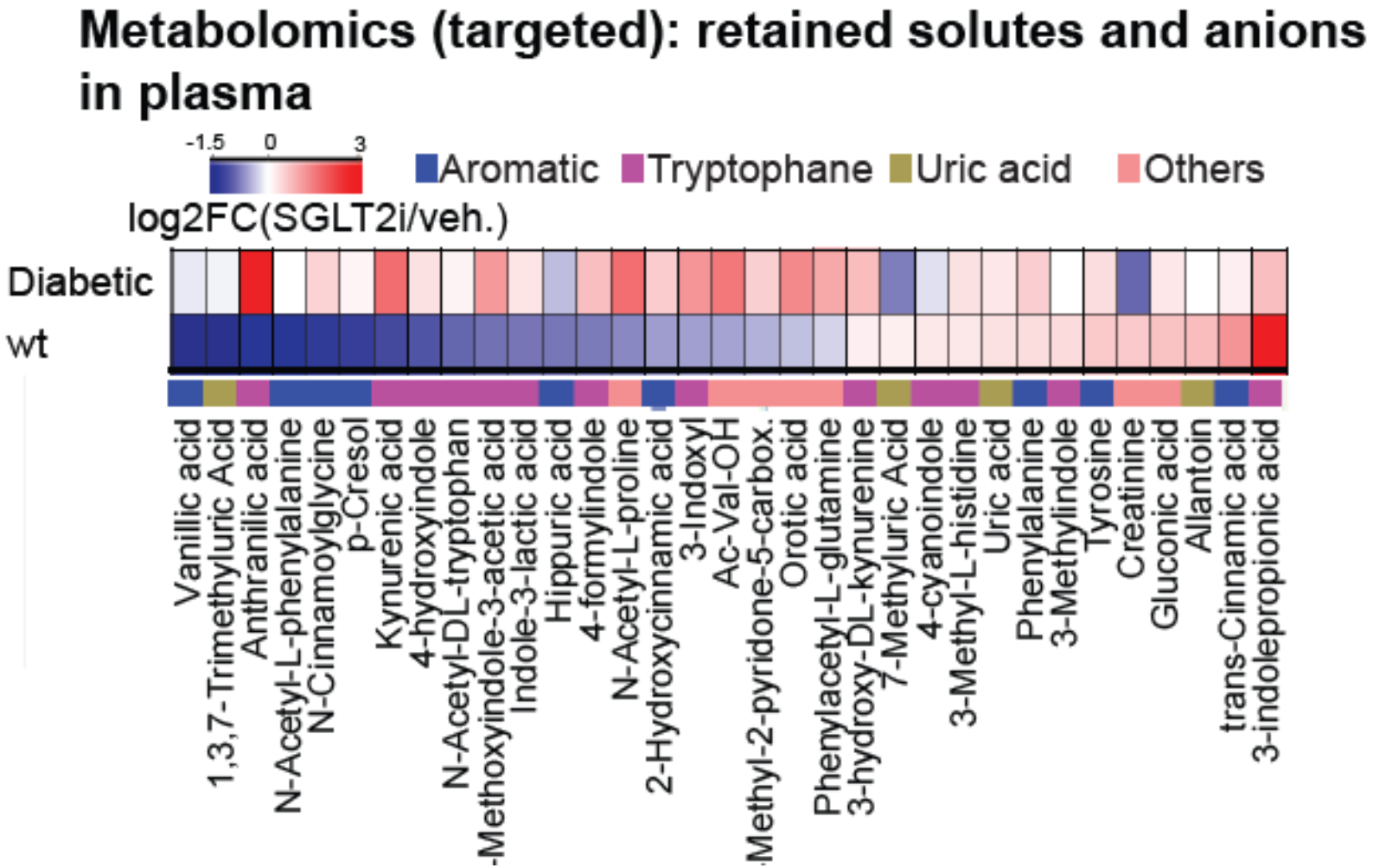
Metaproteome

Billing et al. Circulation 2024

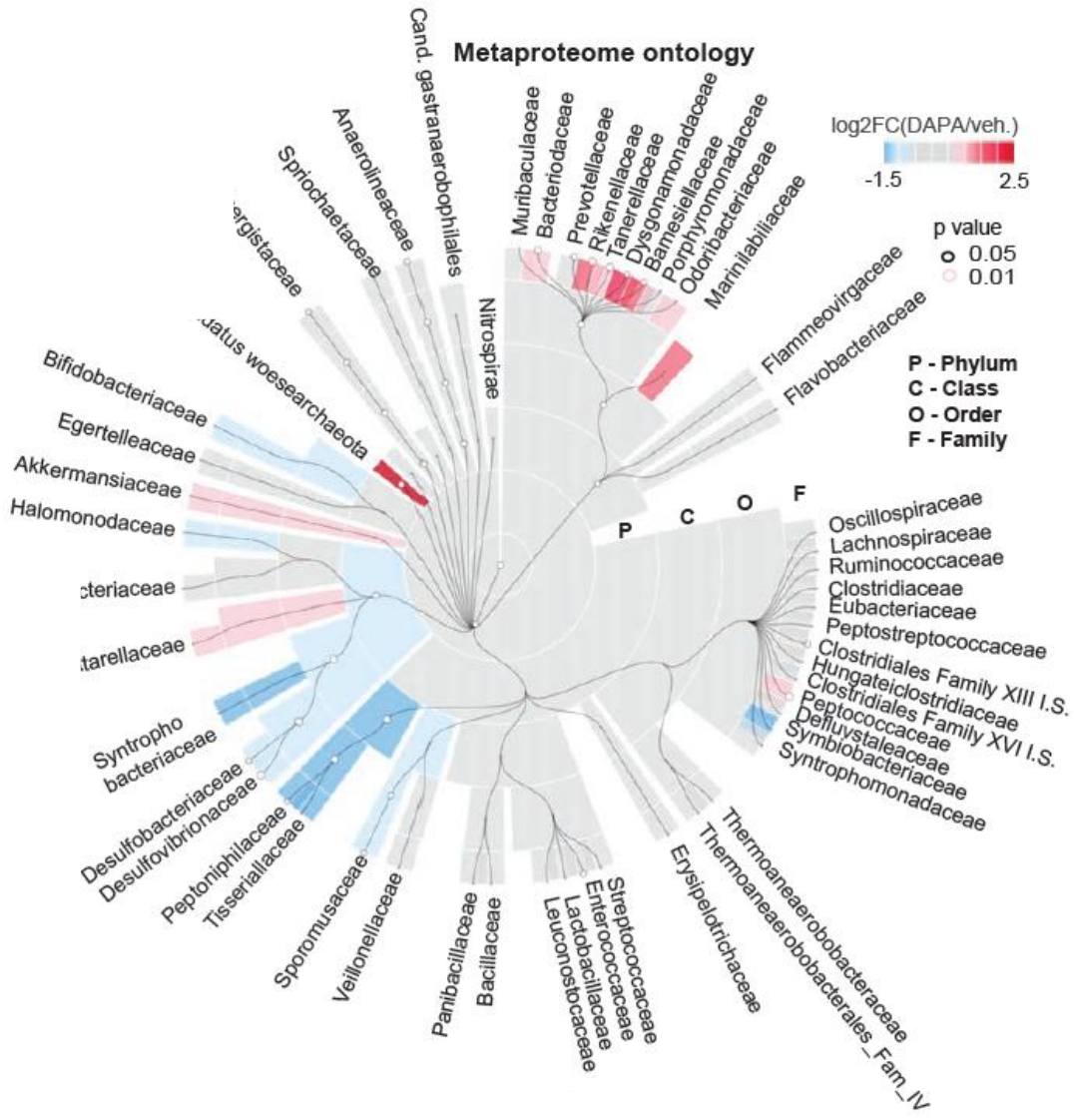
Potential mechanism: Kidney protection



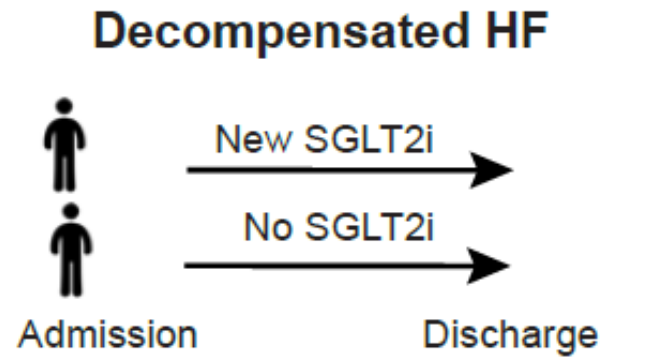
Decreased organic anions with SGLT2i

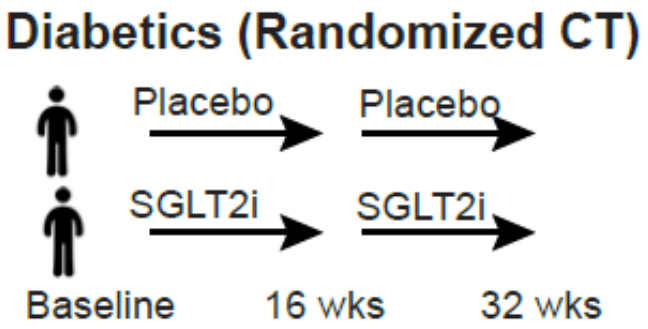


Gut microbiome proteome reveals beneficial taxa

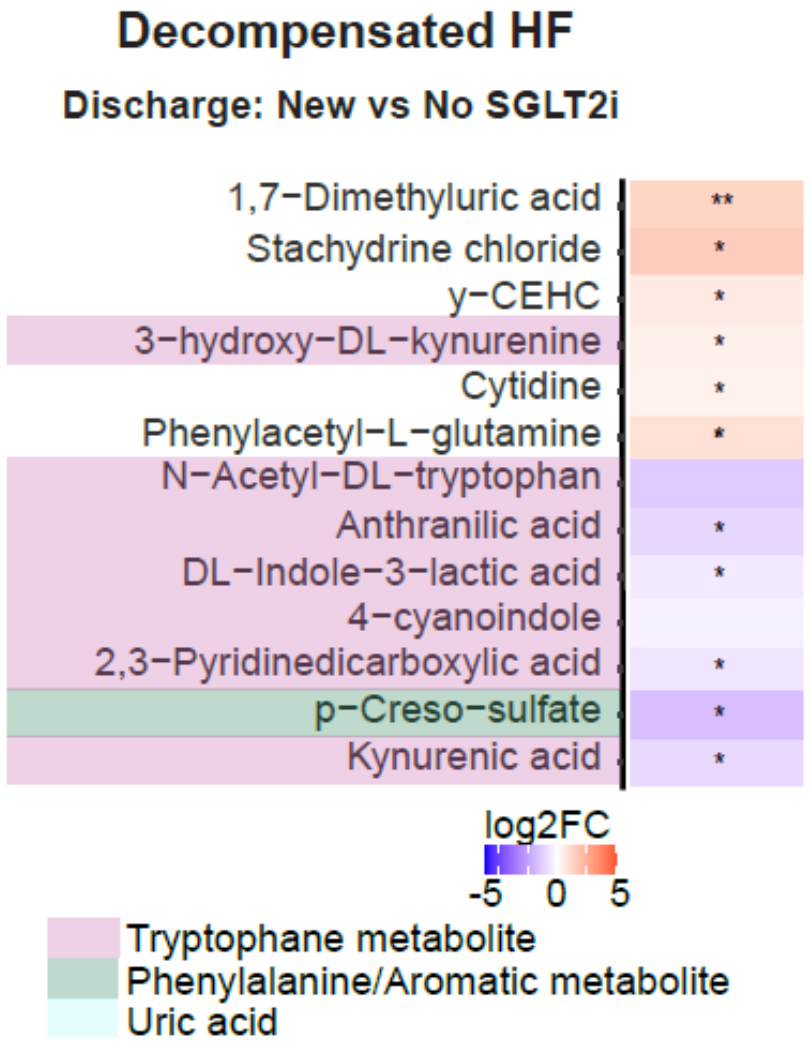


Analysis of plasma in two patient groups

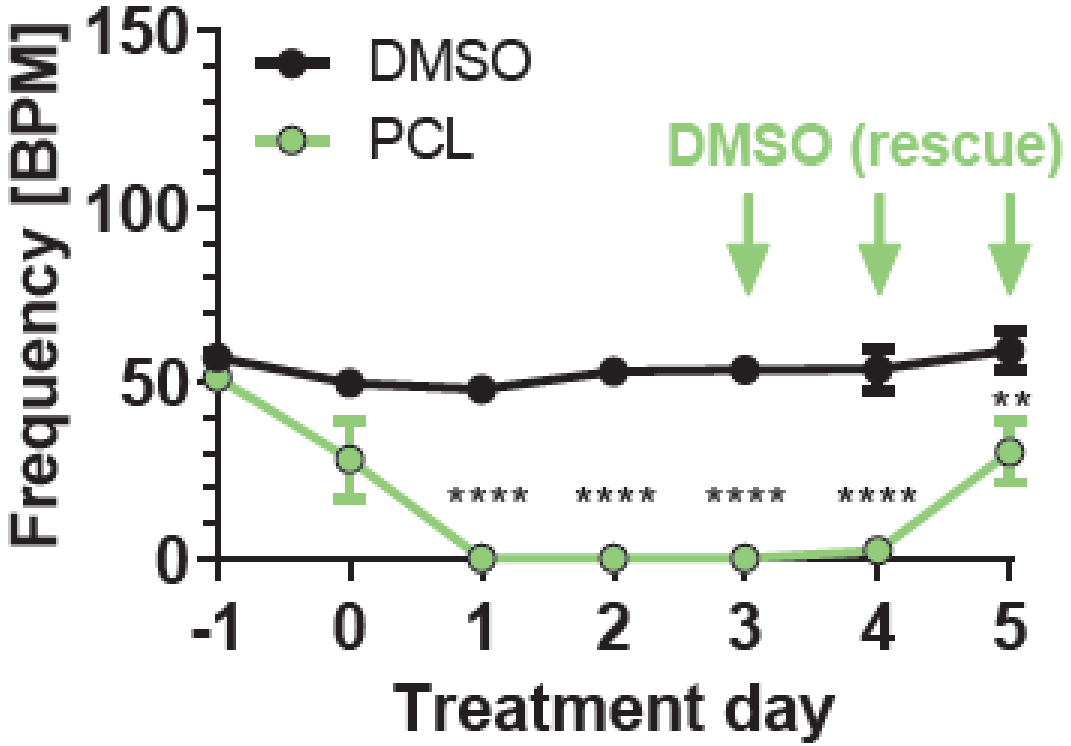




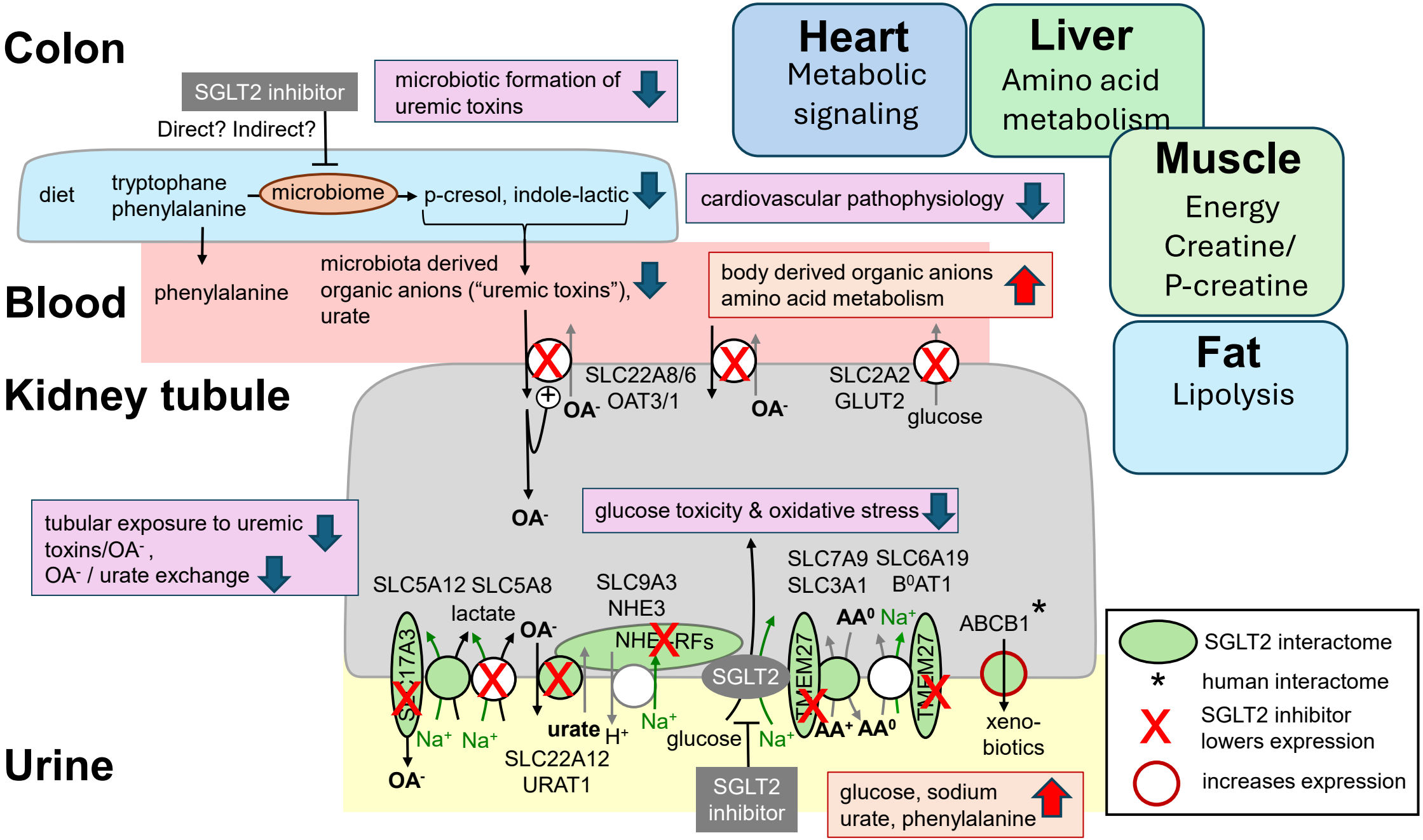
Targeted metabolite panel
- Microbial compounds and anions
- Amino acids
- Purines/Urates



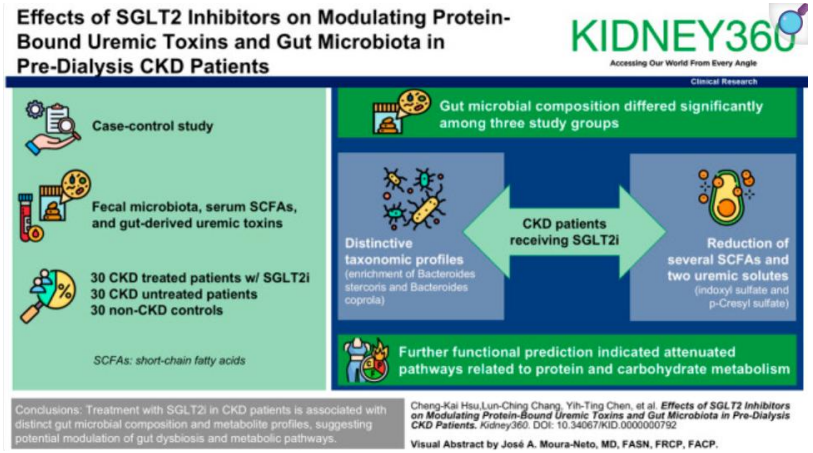
The most extreme effect: p-cresol



.. But also lower concentrations induced changes in heart rhythm....

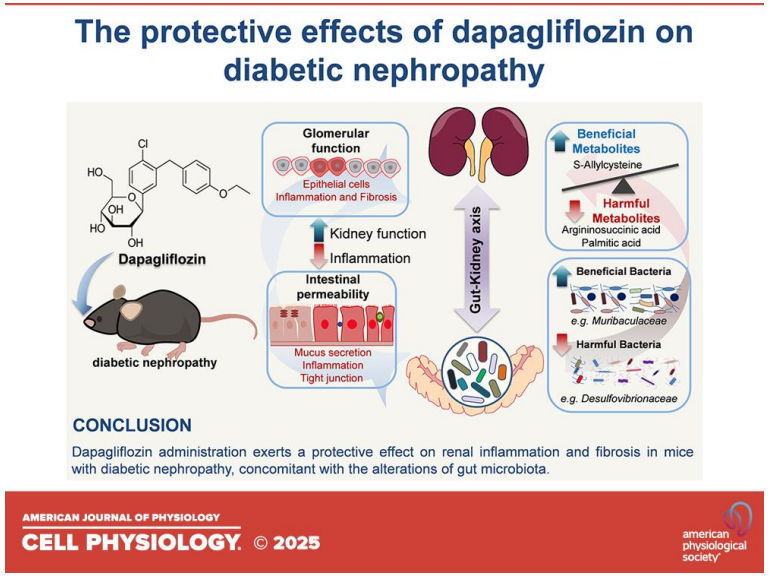


Billing et al. Circulation 2024



Reduction of p-cresol sulfate and indoxylsulfate in pre-dialysis patients

Hsu et al. Kidney360 2025



Reduction of desulfovibrionaceae bacteria in mouse gut microbiota

Ni et al. AJP Cell 2025

Description of perturbed microbiome in patients treated with EMPA (Ng et al., Liver int.)

ORIGINAL ARTICLE | Open Access

Gut Microbiota Predicts Treatment Response to Empagliflozin Among MASLD Patients Without Diabetes Mellitus

This article relates to:

Ho Yu Ng, Lina Zhang, Jing Tong Tan, Rex Wan Hin Hui, Man Fung Yuen, Wai Kay Seto, Wai K. Leu Ka Shing Cheung

First published: 14 February 2025 | https://doi.org/10.1111/liv.70023 | Citations: 10

RENAL FAILURE
2024, VOL. 46, NO. 1, 2300314
https://doi.org/10.1080/0886022X.2023.2300314
Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Canagliflozin attenuates kidney injury, gut-derived toxins, and gut microbiota imbalance in high-salt diet-fed Dahl salt-sensitive rats

Lili He[a], Qingjuan Zuo[a], Sai Ma[b], Guorui Zhang[c], Zhongli Wang[d], Tingting Zhang[a], Jianlong Zhai[e] and Yifang Guo[a]

[a]Department of Geriatric Cardiology, Hebei General Hospital, Shijiazhuang, China; [b]Department of Internal Medicine, Hebei General Hospital, Shijiazhuang, China; [c]Department of Cardiology, The Third Hospital of Shijiazhuang City Affiliated to Hebei Medical University, Shijiazhuang, China; [d]Department of Physical Examination Center, Hebei General Hospital, Shijiazhuang, China; [e]Department of Cardiology, Hebei General Hospital, Shijiazhuang, China

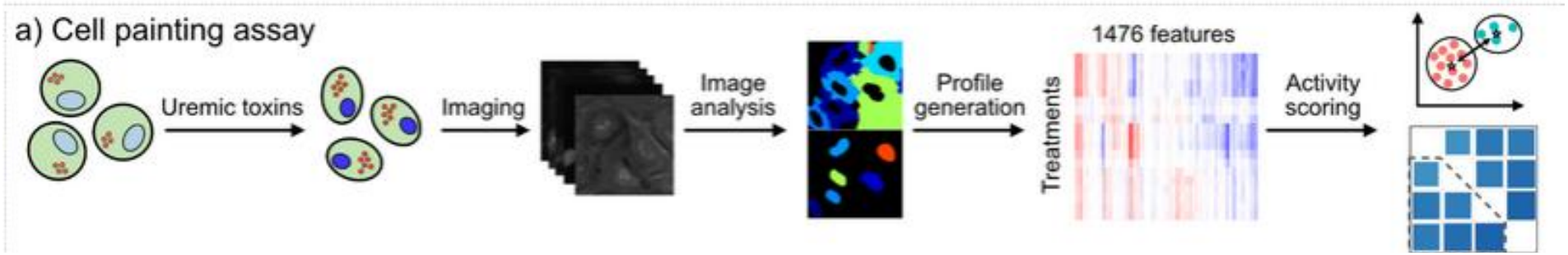
#2

Metabolic communication….

Which retained solutes („uremic toxins“) are actually bioactive?

Head-to-head comparison of 93 metabolites

Which retained solutes („uremic toxins“) are actually bioactive?



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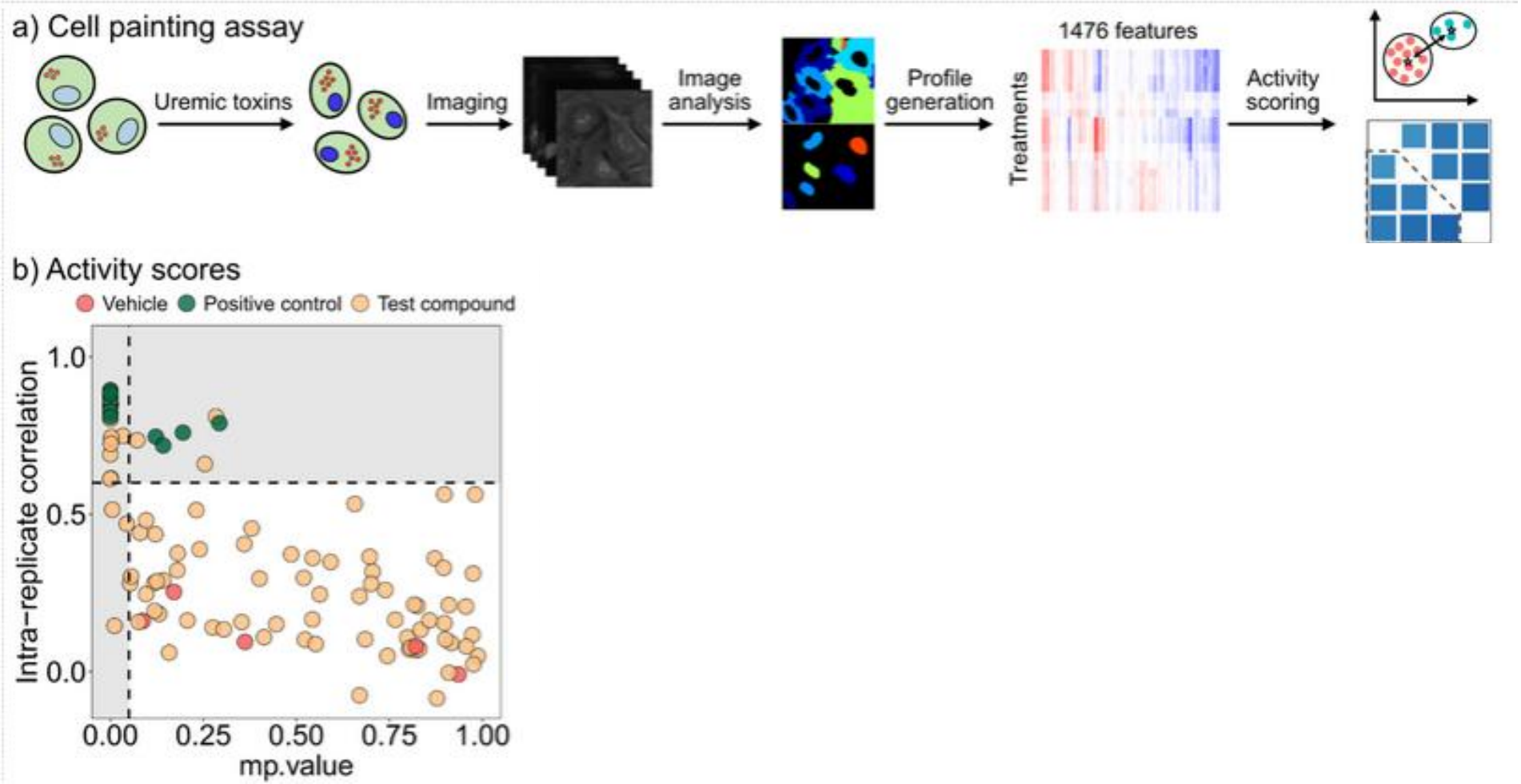

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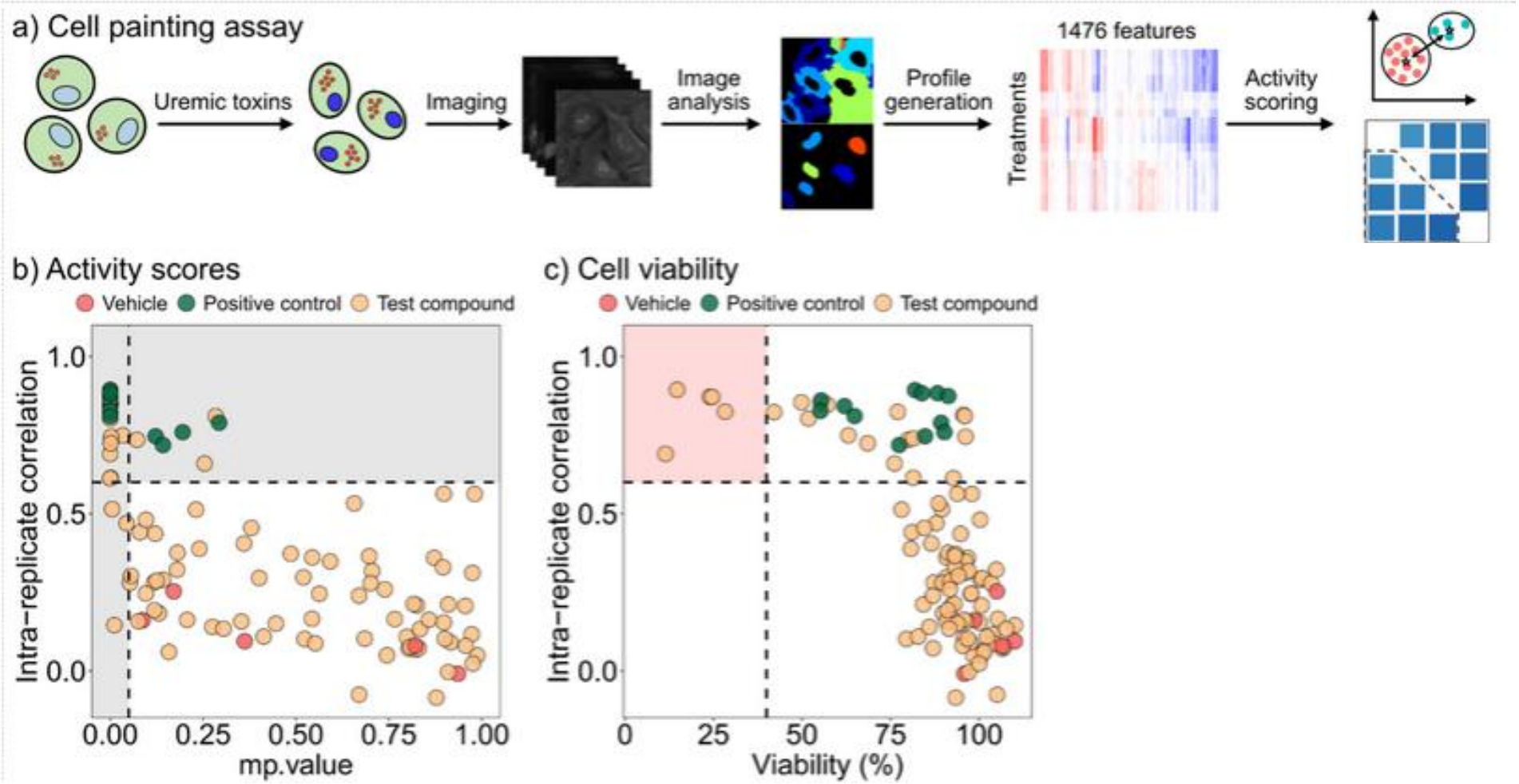
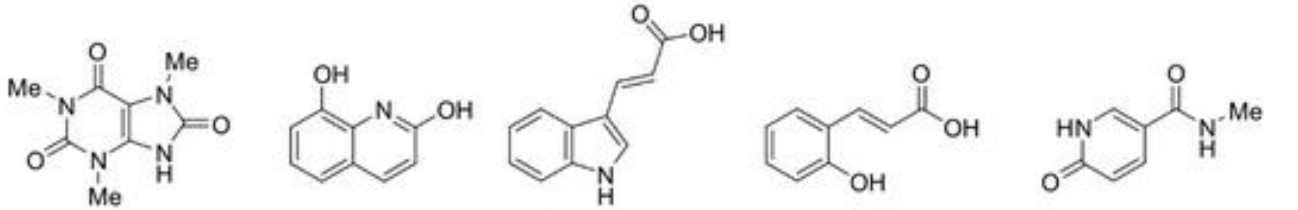
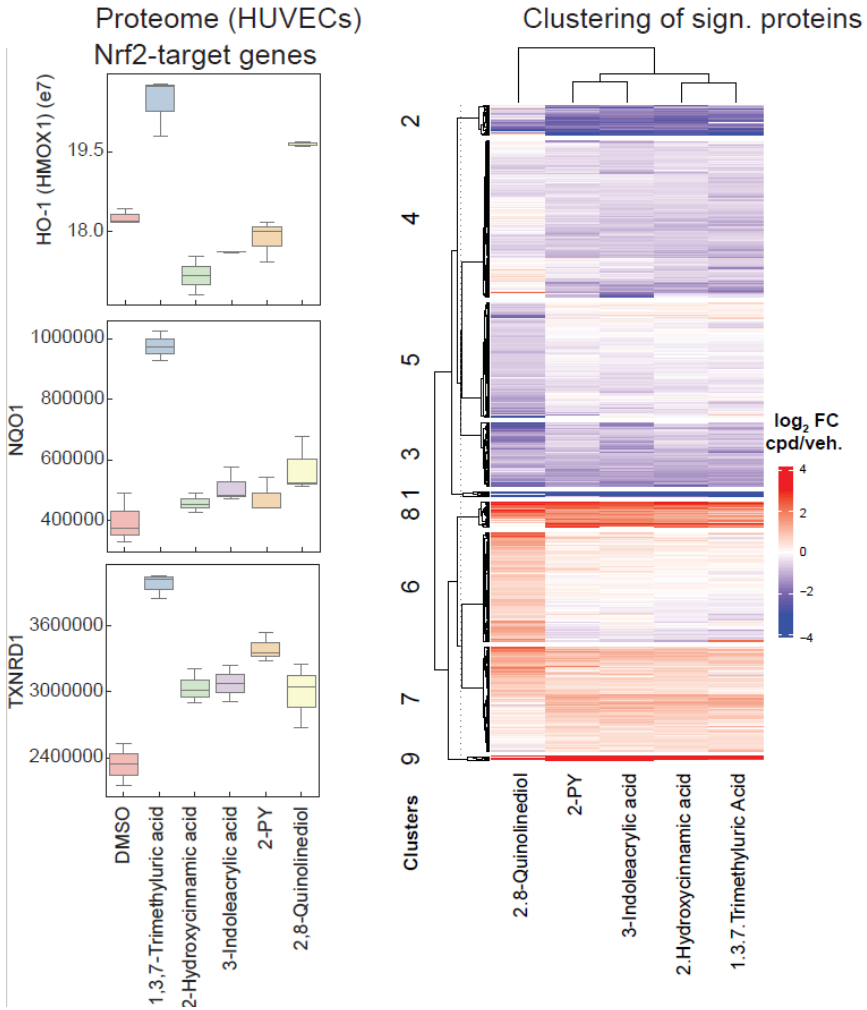


Compounds activating NRF2

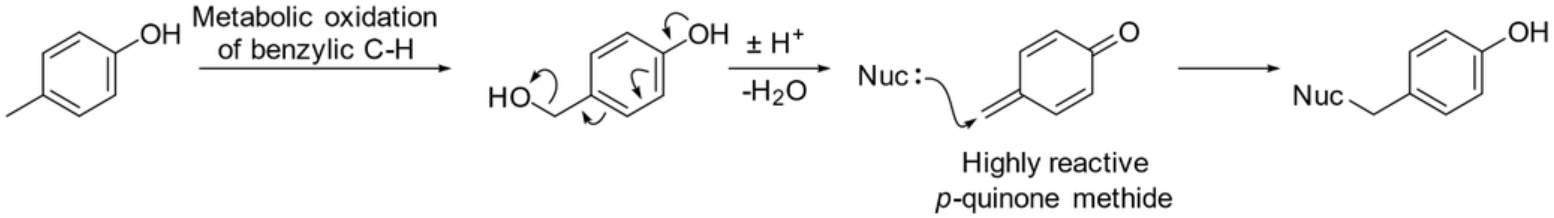
a) Group 1 compounds and CDDOs





Protein conjugation by p-Cresol and 4-hydroxyindole after metabolic activation

a) Covalent adduct formation by p-cresol



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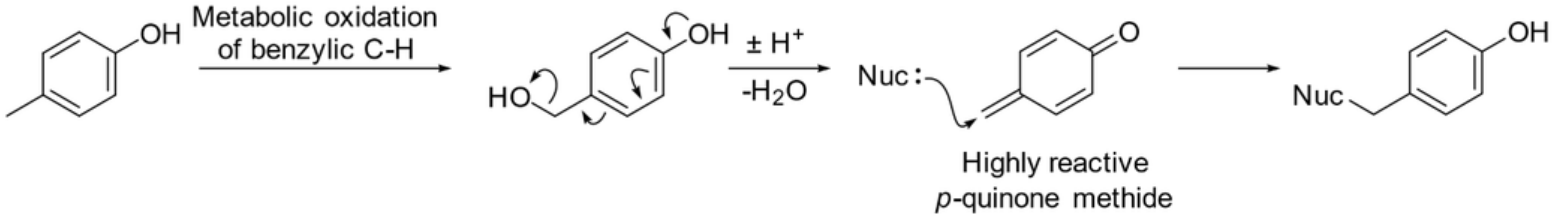
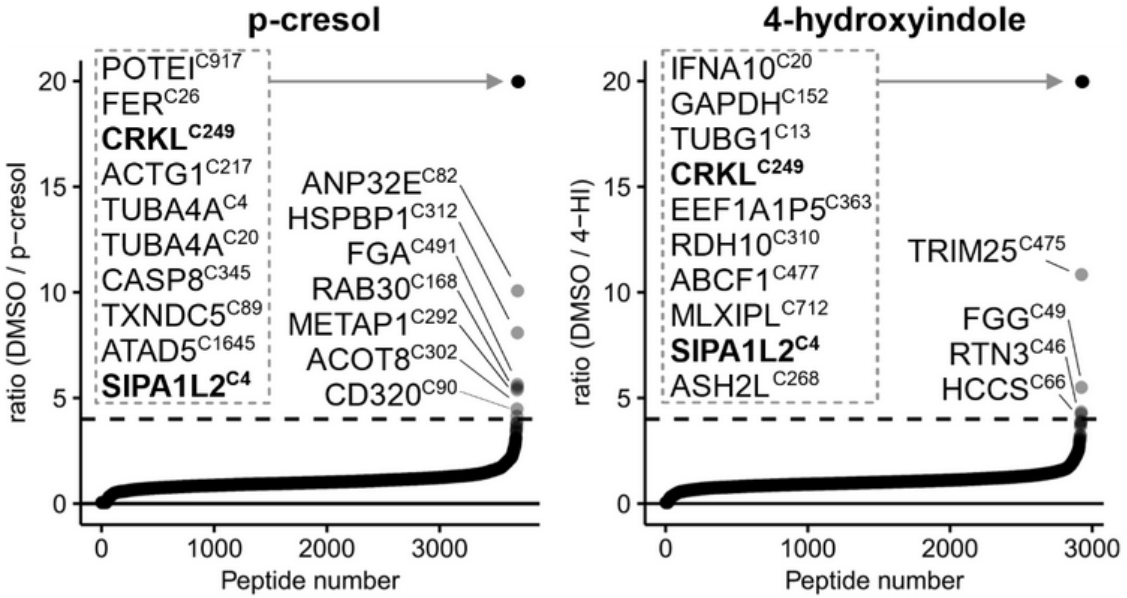


b) ABPP to identify cysteines bound by p-cresol and 4-hydroxyindole



Summary: Metabolic communication in kidney disease

- Kidney metabolism is providing new strategies to treat kidney disease
- SGLT2 inhibitors modulate metabolic communication involving gut-derived metabolites (in addition to other mechanisms)
- *In vitro* bioactivity profiling reveals mechanistic classes and synergies of gut-derived metabolites

Thank you!

Metabolic communication in SGLT2 inhibition
Volker Vallon, Young Chul Kim (UCSD), Friederike Cuello,
Thomas Eschenhagen (Hamburg), Per Løgstrup Poulsen,
Søren Gullaksen (Aarhus), Alexander Staruschenko (USF), Chih-Chien Sung (Taipei)

Cell painting
Thomas Poulsen, Esben Svenningsen, Ander Kiib (Aarhus)

Is this a relevant protein modification in patients?