Liver-kidney organs-on-a-chip reveal distant site for bioactivation of human carcinogen

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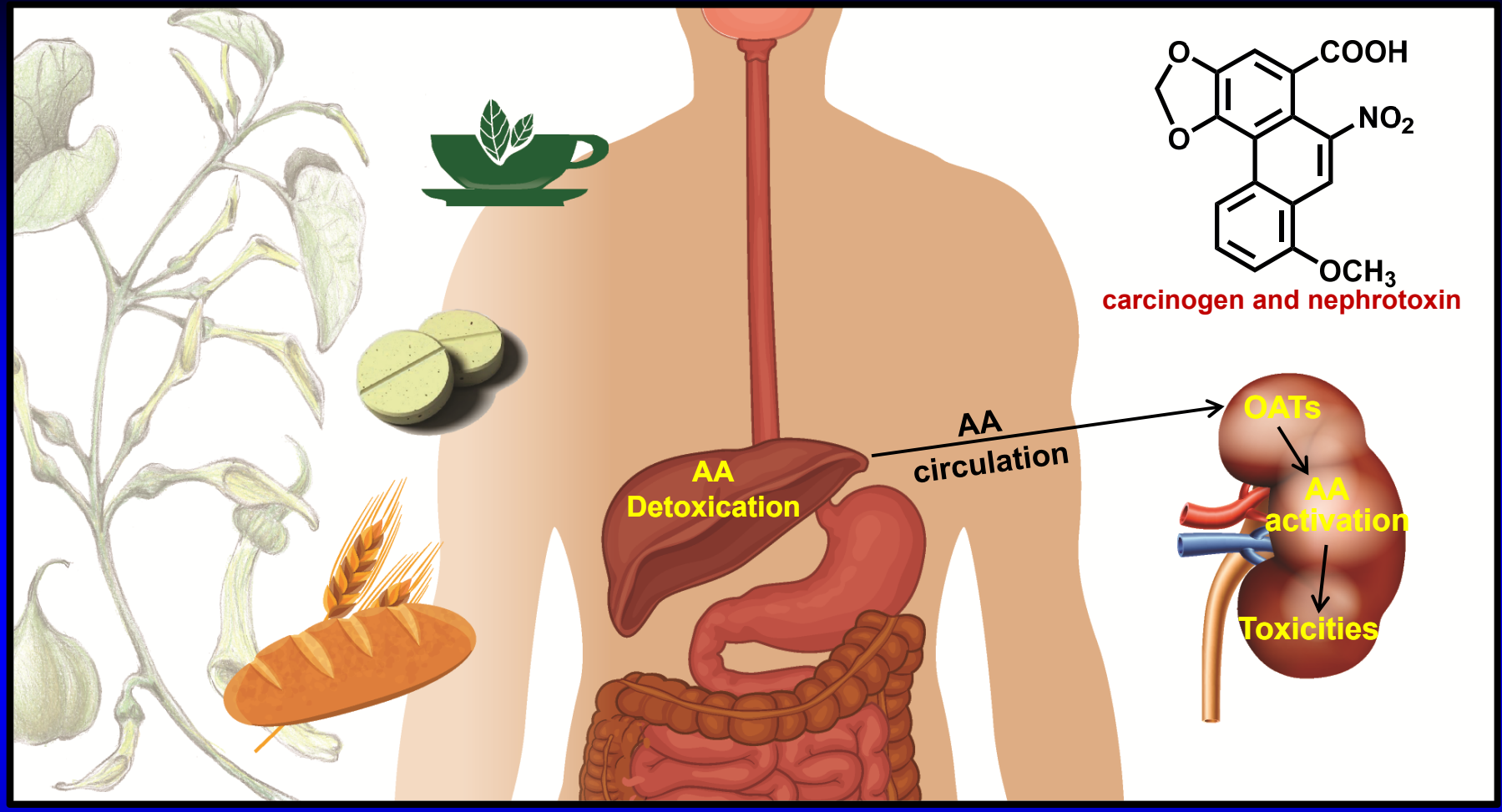
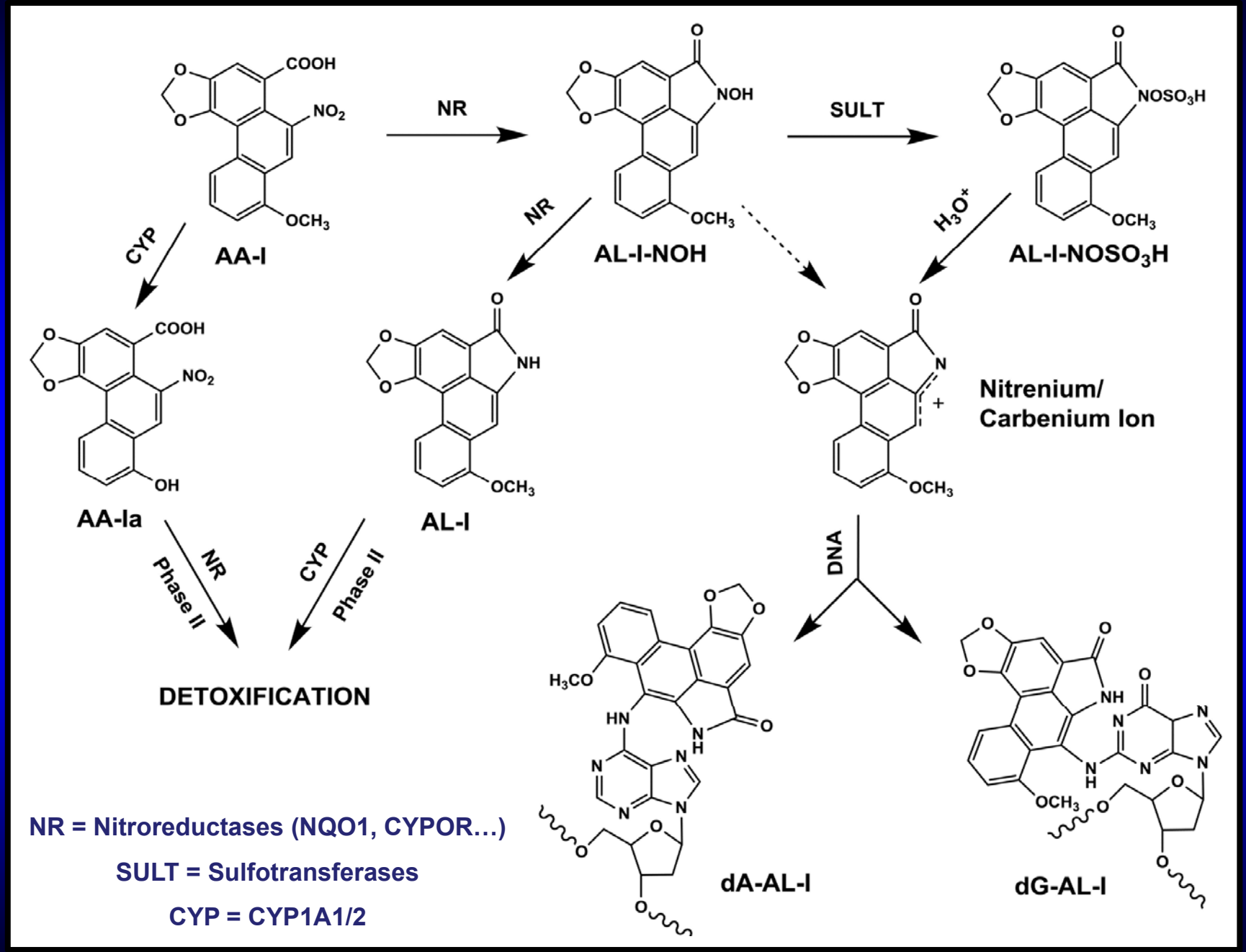


- Aristolochic acid (AA) is a nitrophenanthrene carboxylic acid and a natural product of *Aristolochia* plants

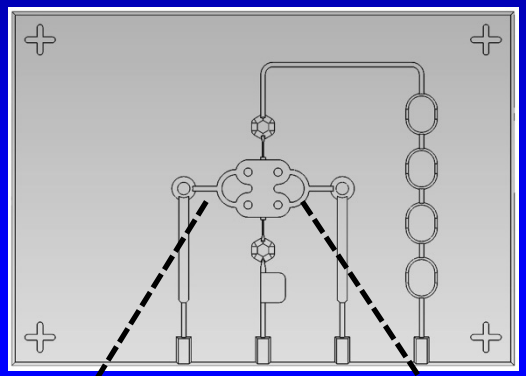
- *Aristolochia* plants used in traditional Chinese medicine and in Western folk medicine for centuries. In case of Balkan endemic nephropathy exposure to AA occurs through bread contaminated with *Aristolochia clematitis* seeds.


AA-I
NR
AL-I-NOH
SULT
AL-I-NOSO3H
CYP
NR
H3O+
AA-Ia
AL-I
Nitrenium/
Carbenium Ion
NR
Phase II
CYP
Phase II
DNA
DETOXIFICATION
dA-AL-I
dG-AL-I
NR = Nitroreductases (NQO1, CYPOR…)
SULT = Sulfotransferases
CYP = CYP1A1/2

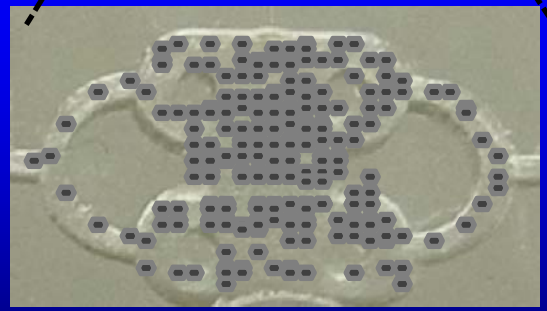
Liver and Kidney in Nortis MPS device
MPS = Microfluidic Physiological System

Diameter of “tubule”: ~120 µm
Internal volume: ~70 nL
Flow rate: 0.5-1.0 µL/min
~5000 kidney cells

Liver – on-a-chip
Chamber

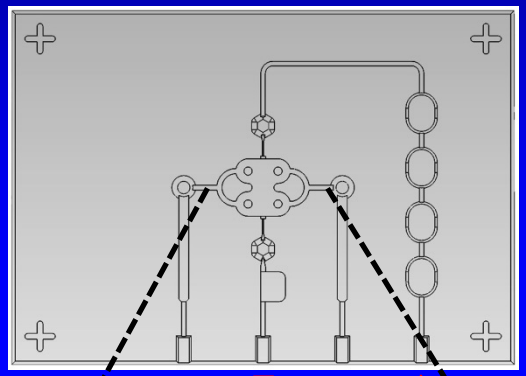


Flow in Flow out

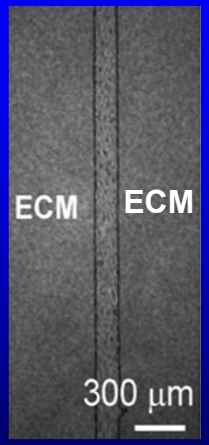


Collagen type I- base matrix or
Matrigel™ overlaid layer

Kidney – on-a-chip
Channel



Flow out Flow in

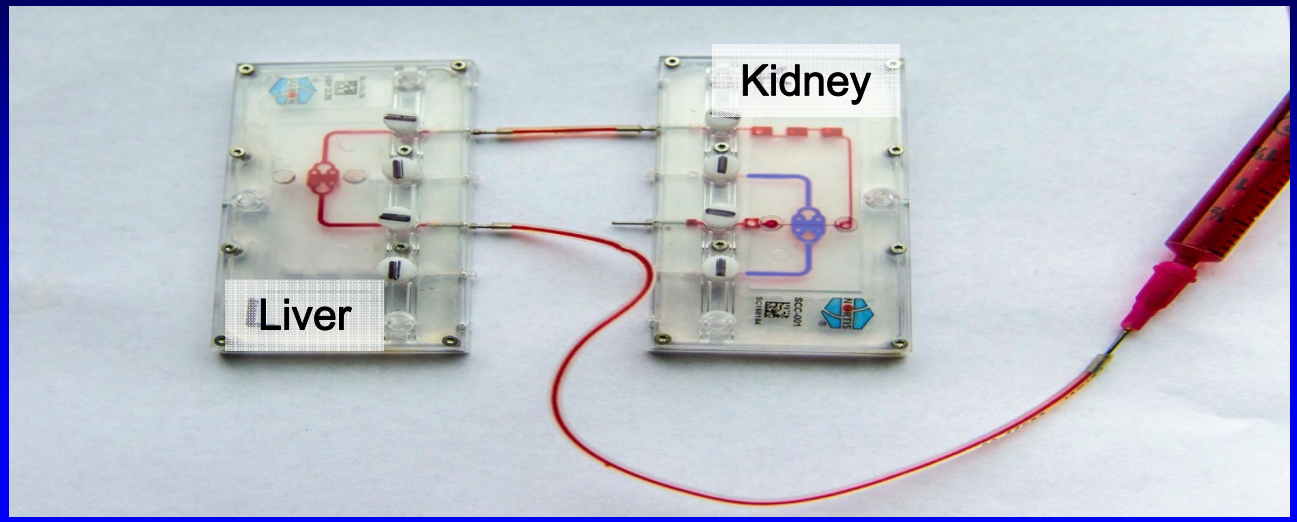


ECM: Type I Collagen (6 mg/mL)

David Eaton, Jonathan Himmelfarb, Ed Kelly

‘Liver-on-a-chip’ + ‘Kidney-on-a-chip’

Shi-Yu (Shirley) Chang **PhD project**

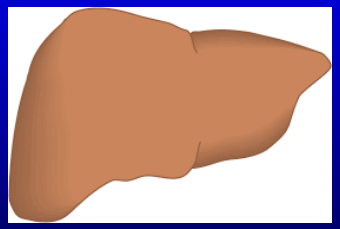


HYPOTHESIS

Hepatic biotransformation of AA-I will modify its nephrotoxicity, and this can be identified in an integrated MPS model

Aristolochic acid

Metabolism



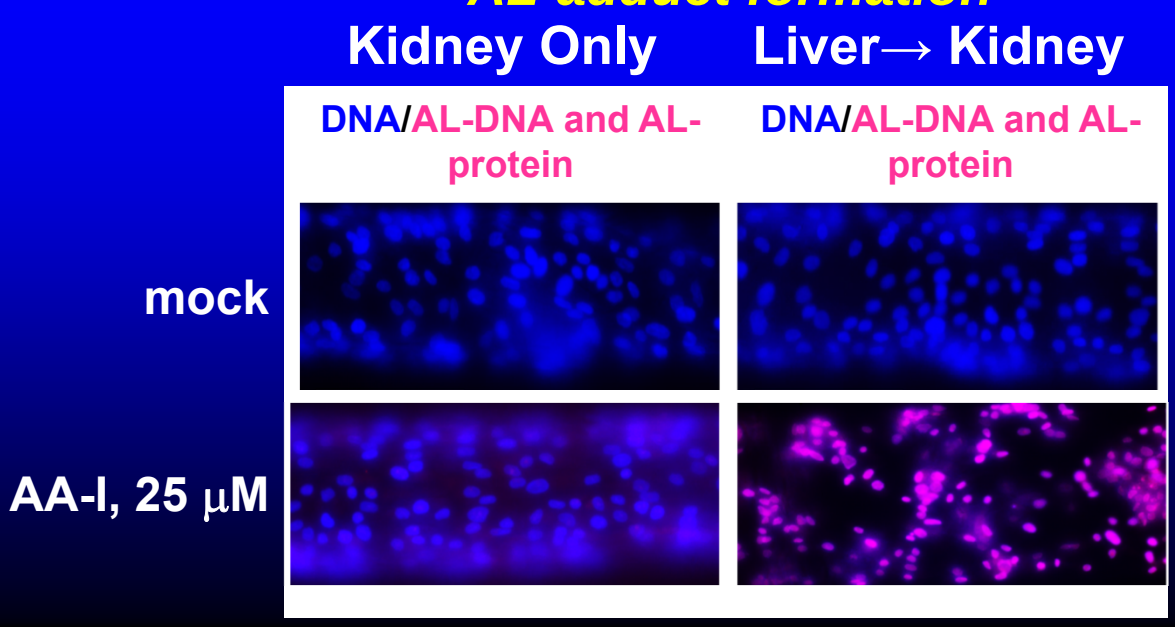
Bioactivation

Detoxification

Hepatic metabolism enhances AA-I toxicities in the kidney

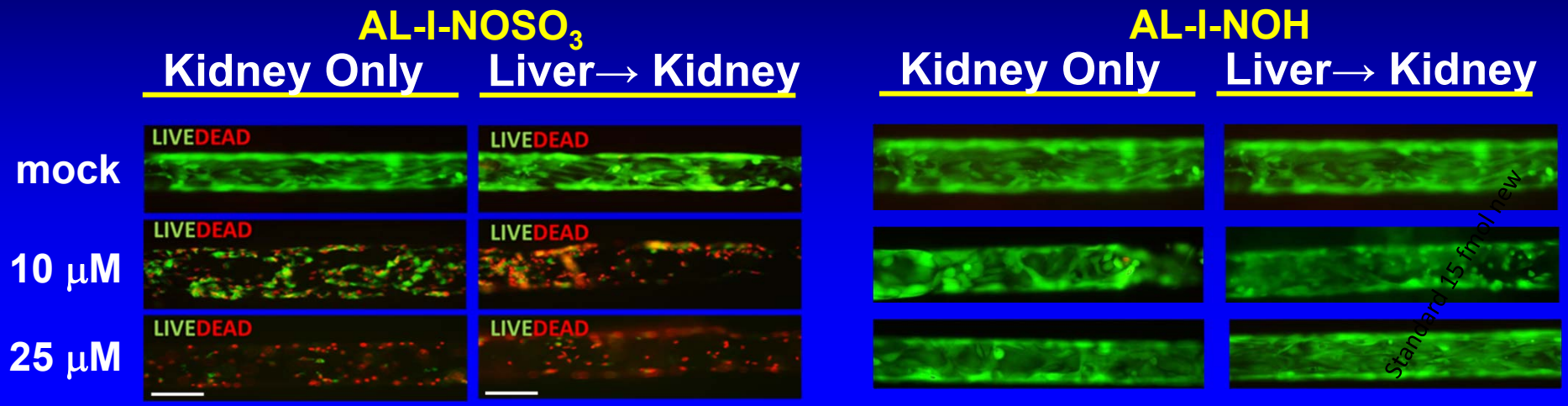
Cell viability

AL-adduct formation

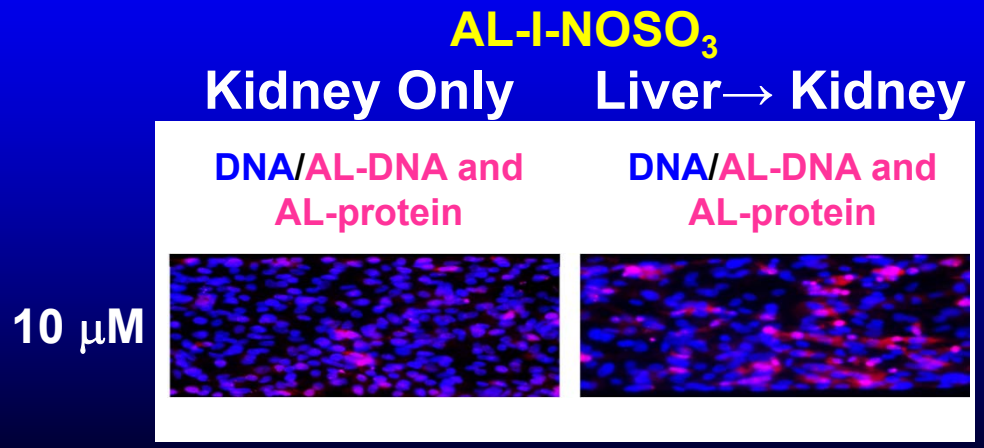


N-sulfonyloxyaristolactam, but not its precursor, is toxic to kidneys

Cell viability

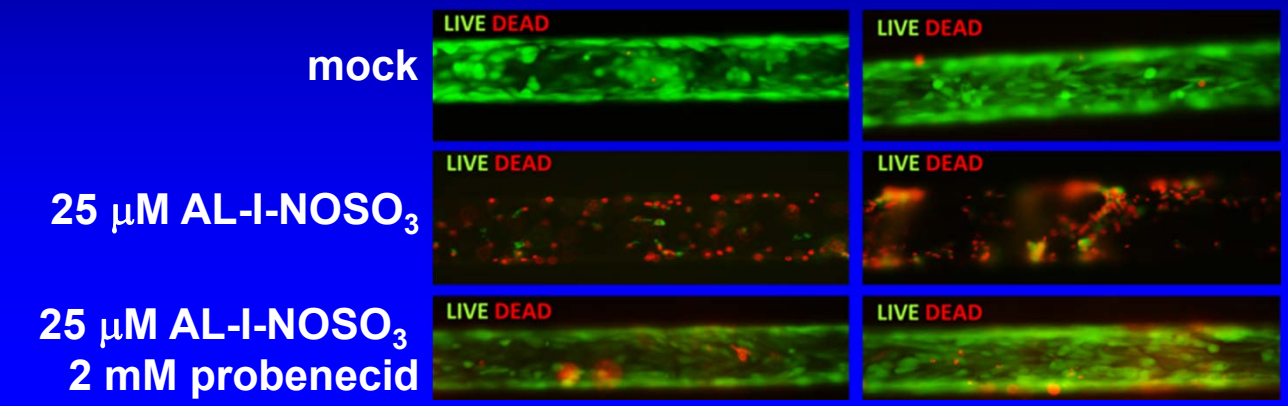


AL-adduct formation

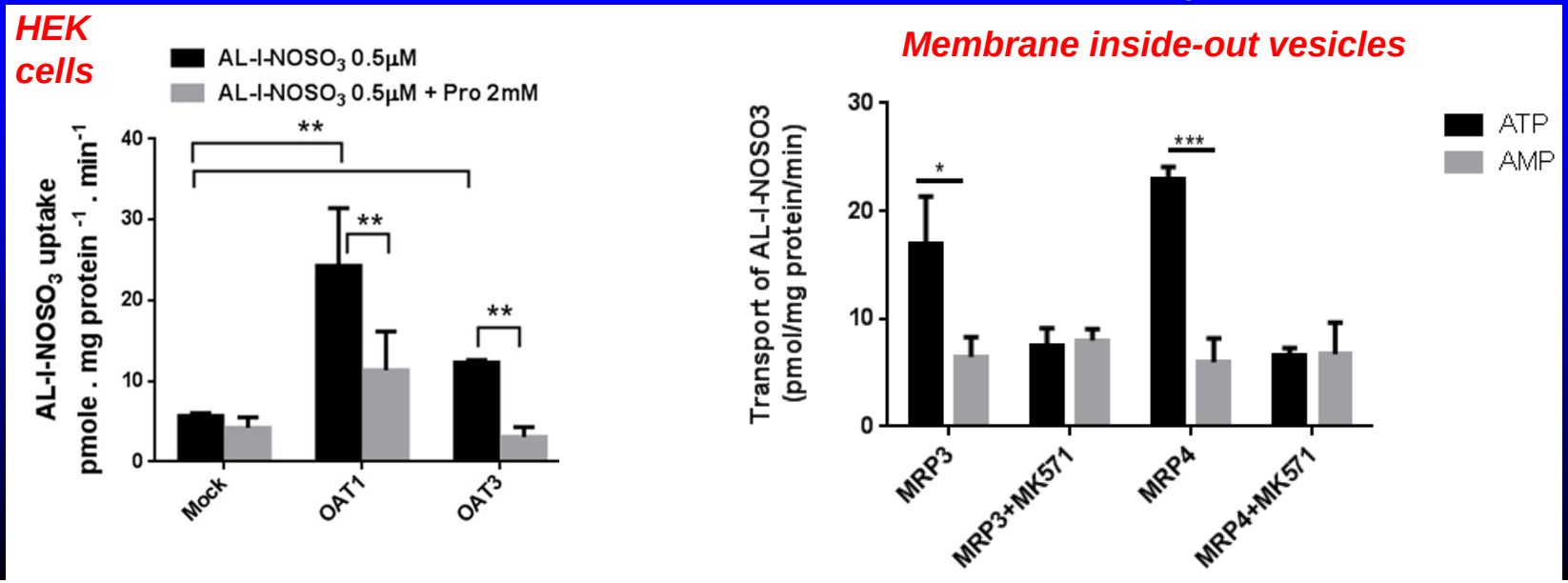


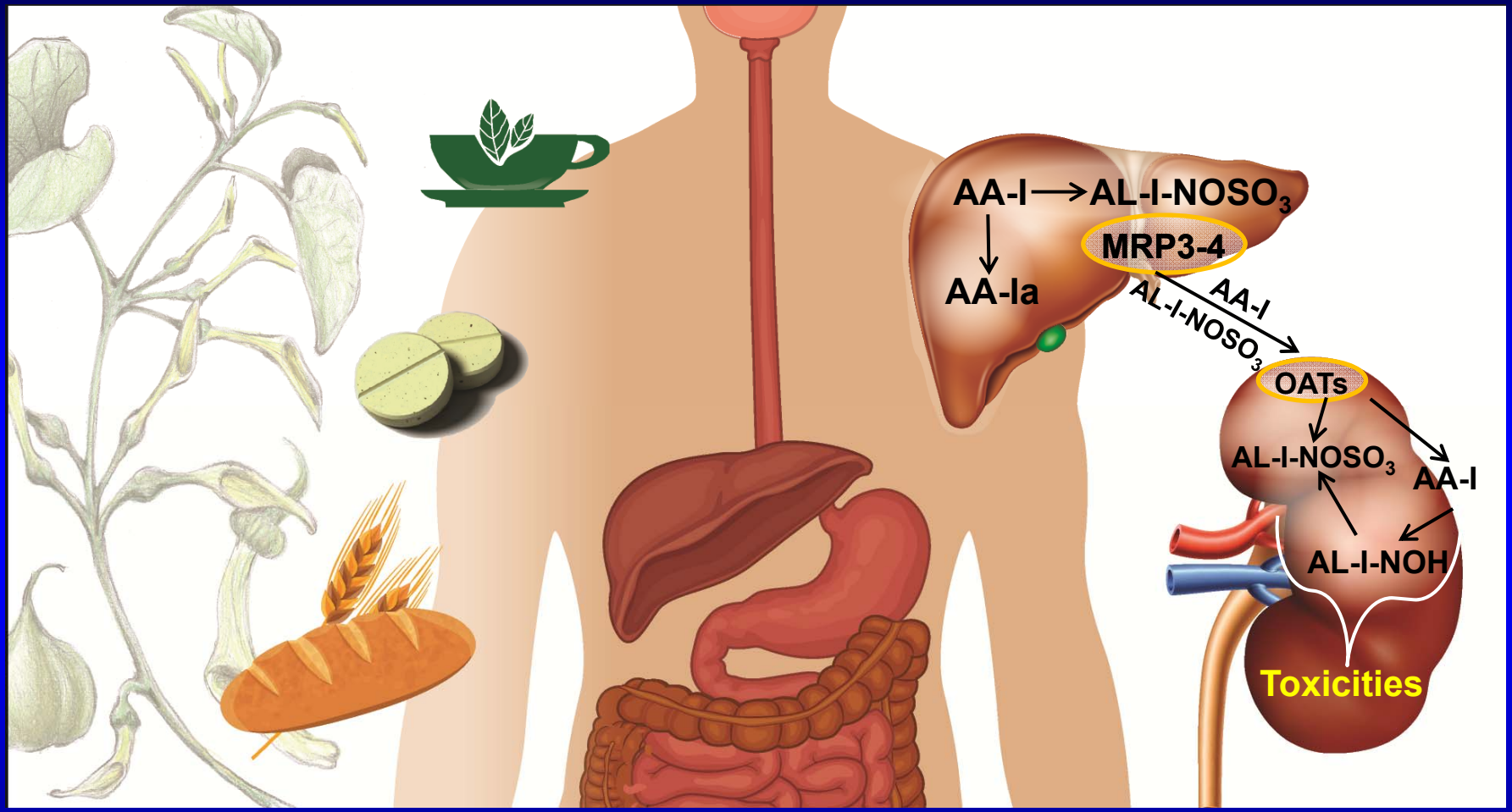
Organic anion transporters (OATs) and MRP3-4 are responsible for the transport of AL-I-NOSO$_3$ in the kidney and liver

Toxicity of AL-I-NOSO$_3$ in MPS



Membrane transport of AL-I-NOSO$_3$




AA-I → AL-I-NOSO3
MRP3-4
AA-Ia
AL-I-NOSO3
AA-I
OATs
AL-I-NOSO3
AA-I
AL-I-NOH
Toxicities

Laboratory of Chemical Biology

Arthur Grollman
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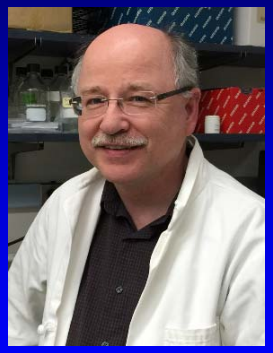
Kathleen Dickman
(cell biology)



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