University of Dundee.
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Novel *in vivo* mechanistic toxicology approaches to inform regulatory testing.

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NERC SCIENCE OF THE ENVIRONMENT

Background

- The use of transgenic mouse models has transformed our knowledge of the pathogenesis of human disease.

- Mouse models have provided new avenues for the development and use of drugs.

- They provide information that can not be obtained from *in vitro* studies:

Disease models (e.g. degenerative diseases)
Metabolic pathways
Drug efficacy models
Regulatory networks
Embryonic development
Gene-environment interactions, etc…

Next generation of mouse models to inform toxicological studies.

- **Mouse models humanized for pathways of drug disposition: changing the paradigm for drug development and use.**

There are profound species differences in pathways of drug metabolism and disposition which can be a major confounding factor in drug development and in predicting human responses to drugs.

- **Mouse reporter models of cytoprotective pathways: *in vivo* identification of toxicity mechanisms.**

There is a need to understand the pathways intimately linked to the toxic effects of chemical agents.

➢ Mouse models humanized for pathways of drug disposition: changing the paradigm for drug development and use.

- **The models:**

8HUM: 33 murine P450s from 4 gene clusters have been deleted and replaced with the major P450s involved in drug disposition in man

- CYP1A1,CYP1A2, CYP2C9,CYP2D6,CYP3A4 and CYP3A7

- 8HUM mice have also been humanized for the transcription factors CAR & PXR

- P450 expression in 8HUM is regulatable and equivalent to the range of levels found in human liver

CypC4KO: 34 murine P450 genes from 4 gene clusters have been deleted creating a mouse with highly compromised P450 metabolism

- **Applications:**

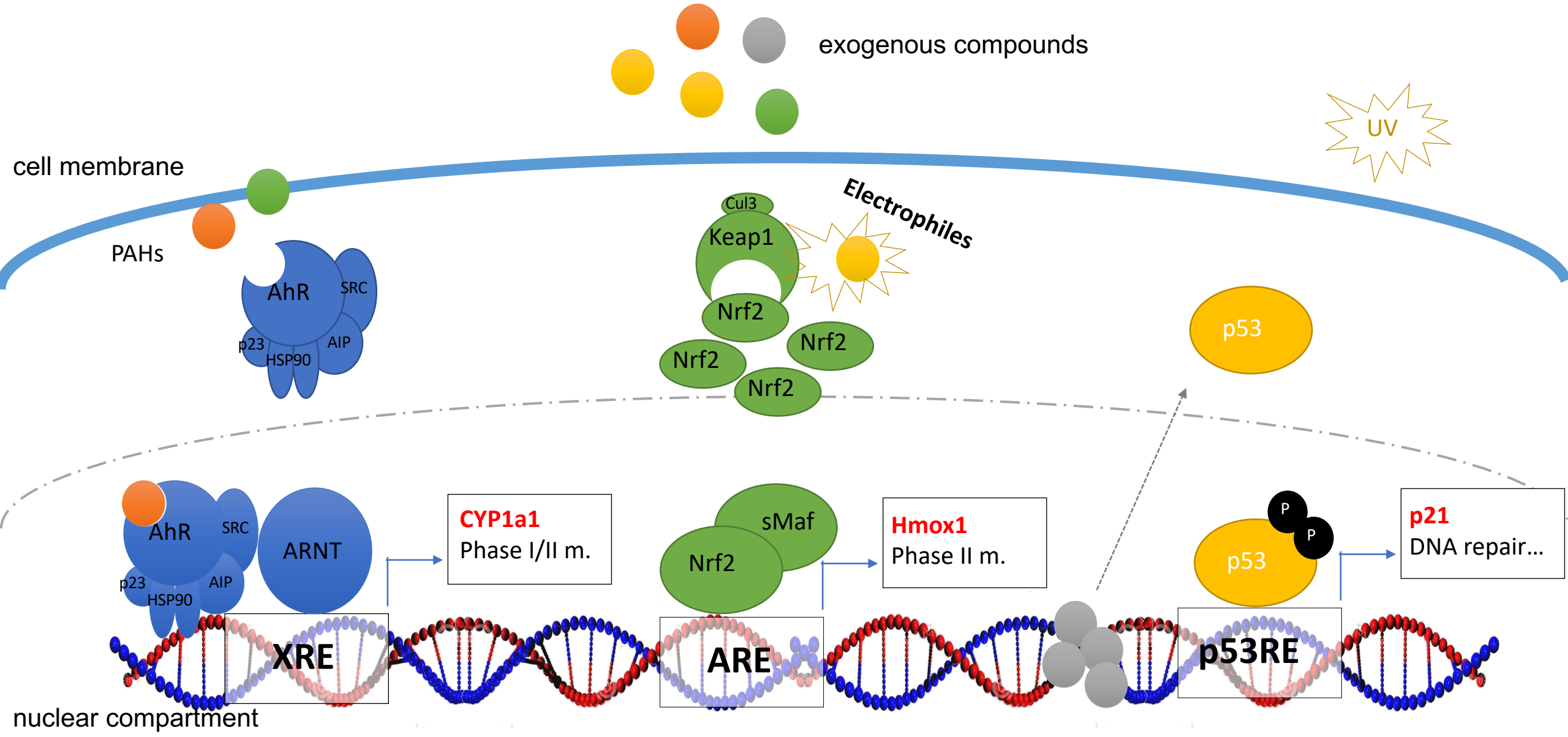
- Improve the predictive power of drug efficacy studies with more human-like PK and in vivo generation of human drug metabolites.

- More accurate predictions of individual patient responses to targeted anticancer drugs

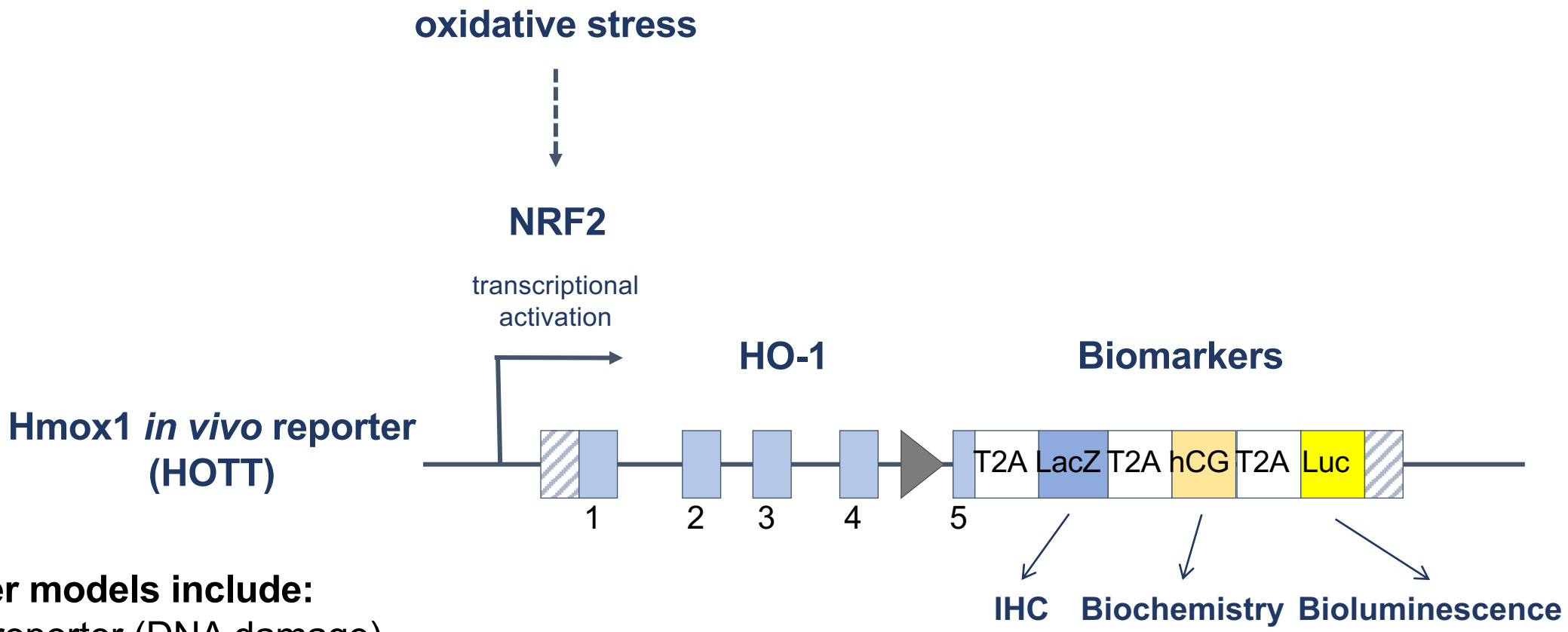
- Understanding how variability in P450 isozymes affects drug efficacy. Potential application in the study of drug-induced toxicity

- Improve *in silico* algorithms for extrapolating laboratory data to the clinic

➢ Mouse reporter models of cytoprotective pathways: *in vivo* identification of toxicity mechanisms.



➢ Mouse reporter models of cytoprotective pathways: *in vivo* identification of toxicity mechanisms.



Other models include:
p21 reporter (DNA damage)
IL6 reporter (Inflammation)
GSTP1 reporter (AP1 signaling)
CYP1a1 reporter (AhR signaling)
CAR/PXR reporter

Robust quantitative (early) biomarkers.
Real time measurements.
Tissue and cellular resolution.

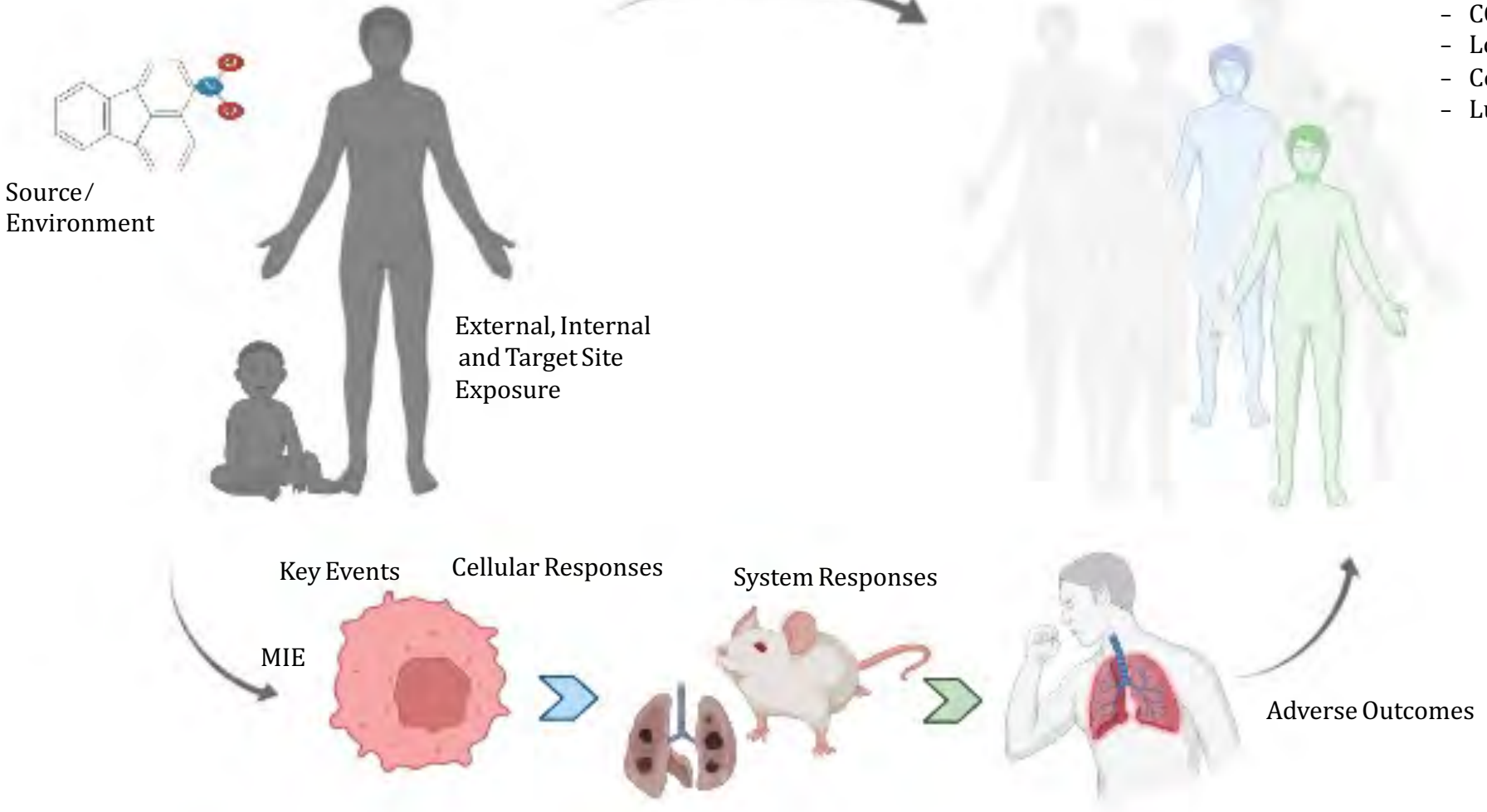
➢ Mouse reporter models of cytoprotective pathways: *in vivo* identification of toxicity mechanisms.

Mechanistic studies carried out using stress reporter models in our lab	PMID
Mechanisms of drug induced toxicity (e.g. acetaminophen)	29086419, 24934809, 25690736
Mechanisms of drug-induced radiation sensitivity	27604276
Identification of toxicity associated to food safety / consumer products	31139862, 32474023
Role of AhR activation in the regulation of the immune system	28146477, 27875245
Regulation of gene expression through nuclear receptors (CAR/PXR/AhR)	9680065

Application of mouse reporter models to understand the toxicity of environmental chemicals.	PMID
Mechanisms of action of non-genotoxic carcinogens (e.g. iAs)	33213951; In progress
Identification of toxic components of complex mixtures (e.g. DEPs)	Manuscript
Toxicity of man-made environmental chemicals (e.g. Aroclor 1254)	In progress
Cellular susceptibility to endogenous toxicants (e.g. progerin)	Manuscript

Env. pollution: Knowledge and experimental gaps

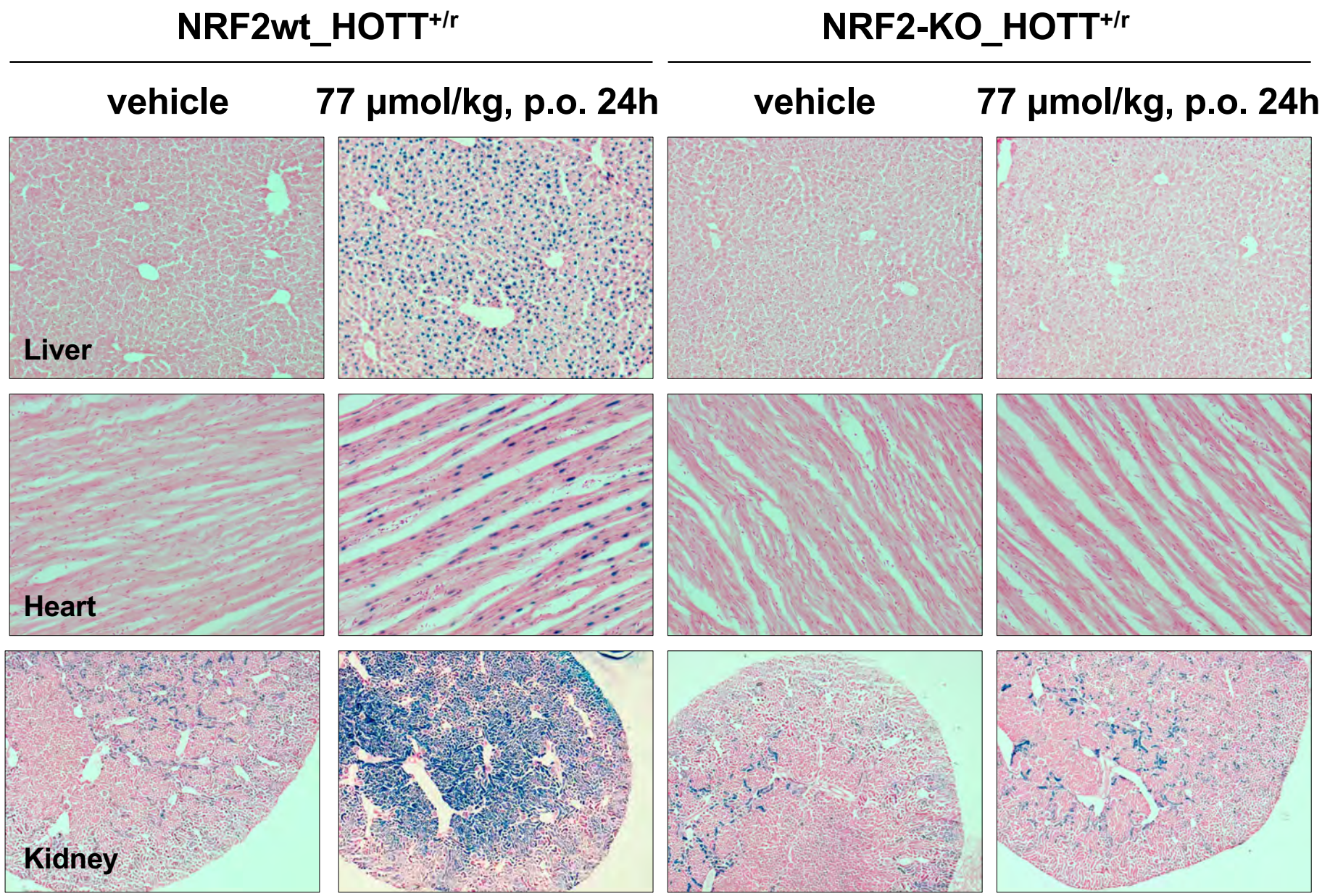
EXPOSOME



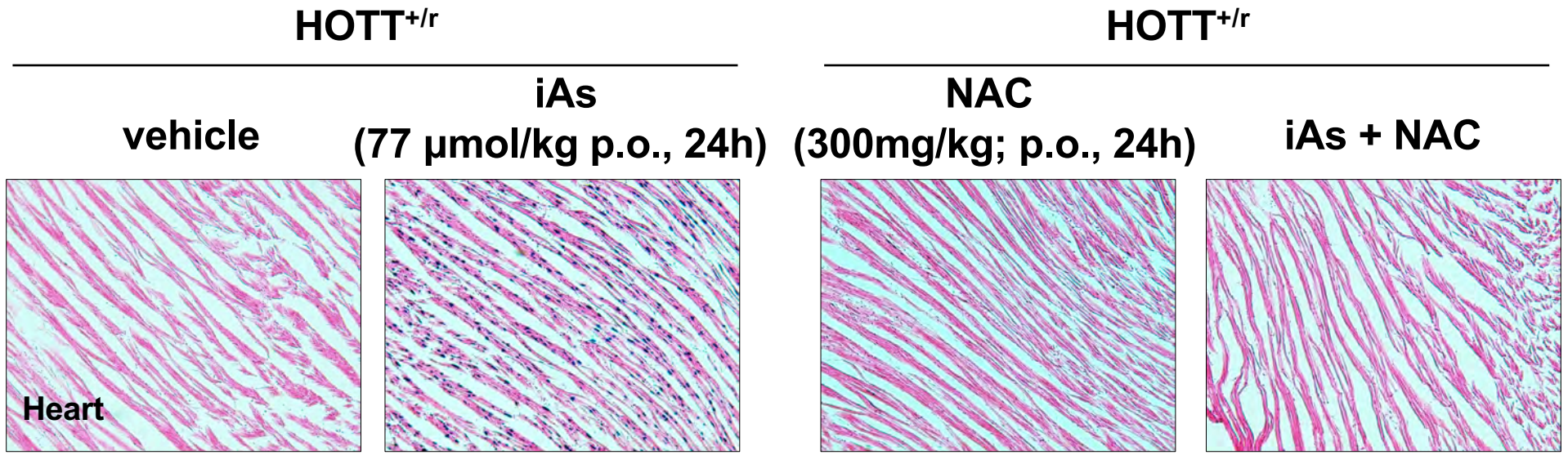
Diseases:
- Ischaemic heart disease.
- Cerebrovascular disease.
- COPD
- Lower respiratory infection.
- Cognitive function.
- Lung cancer.

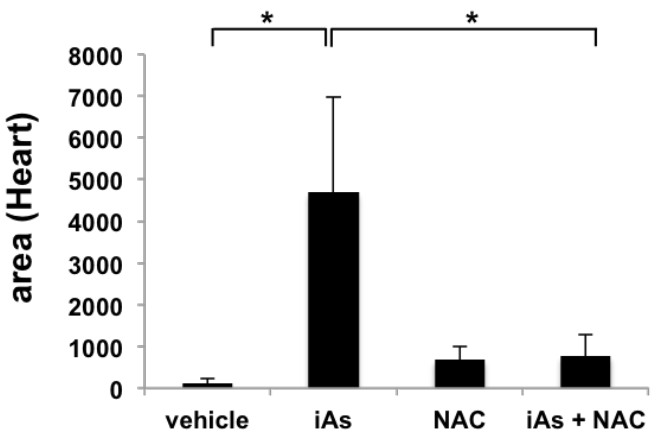
Adverse Outcome Pathway

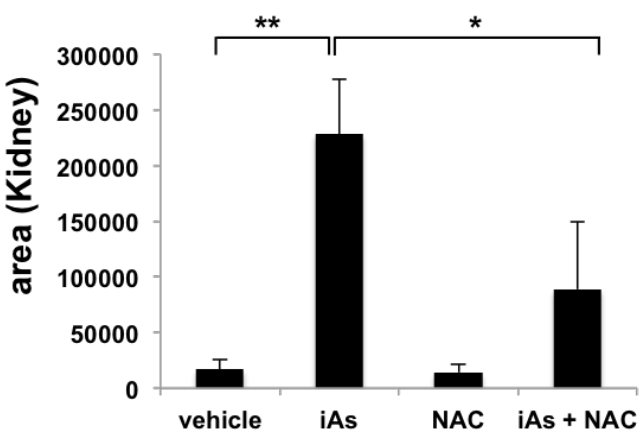
Identification of *in vivo* mechanisms of toxicity.

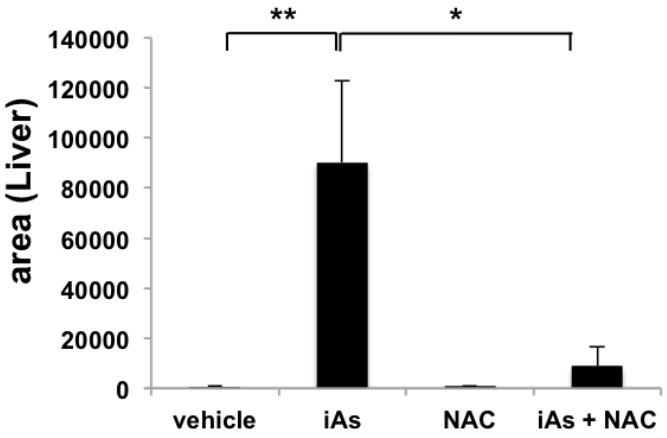


Use of cytoprotective agents to understand toxicity mechanisms.





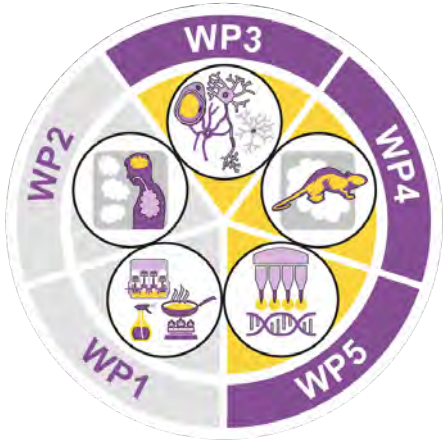


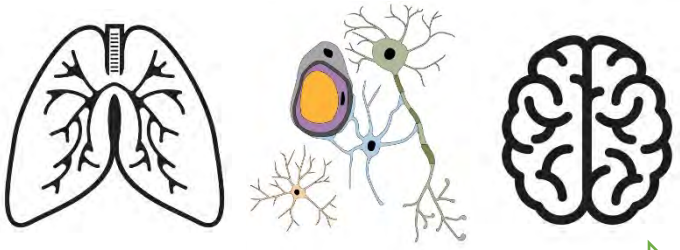


Inesta et al., 2021

Hazard Identification Platform – Indoor/Outdoor air pollution

HIP
Hazard Identification Platform





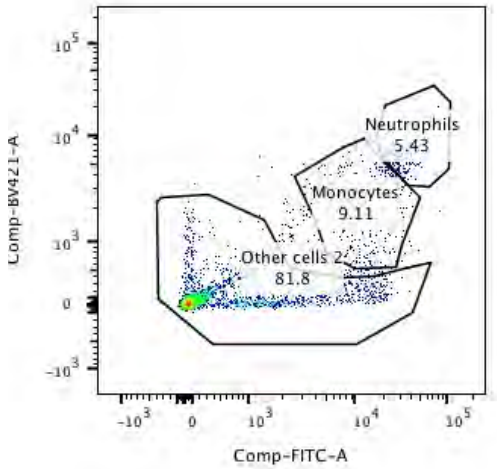
Lung to brain axis

Permeability; stress responses, inflammation, glial cell activation

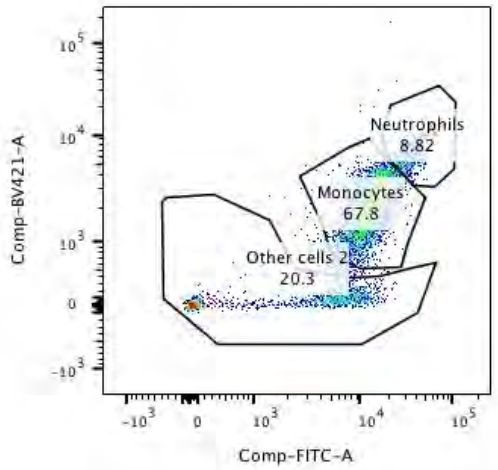
Single vs. repeat dosing

Inhalation toxicology

Untreated



Treated



Next generation of mouse models to inform toxicological studies.

Summary:

Humanized and reporter mouse models are a relevant approach to the NC3R remits: **r**educe, **r**efine.

Novel and powerful approach methdos to define drug deposition and generation of human metabolites *in vivo* and evaluate toxic mechanisms.

They have superior predictive capacity than current *in vivo* approaches to extrapolate toxicity observations from animals to man.

Thank you!

(questions?!)

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bts
driving excellence in toxicology

BTS ambassador for the University of Dundee

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