Characterization of human toxicodynamic variability using peripheral blood mononuclear cells from a large cohort of healthy volunteers

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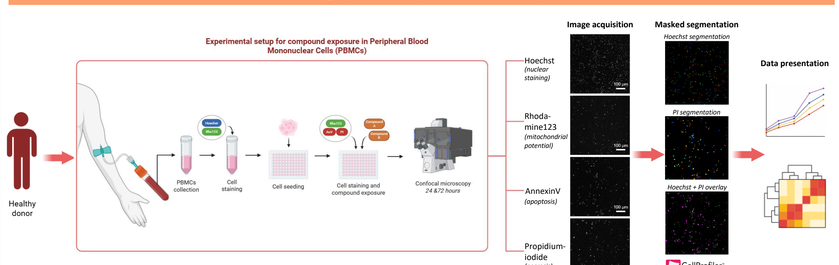
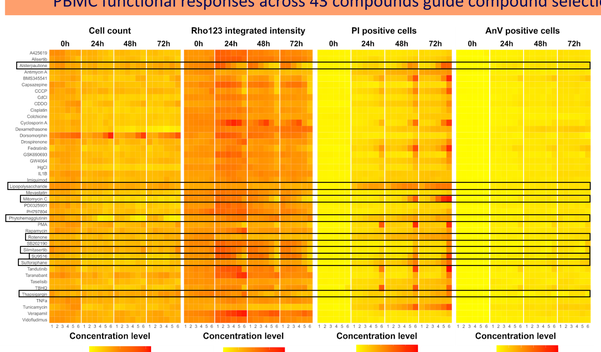
INTRODUCTION

Accurately characterizing interindividual variability in toxicodynamic responses is critical to improve chemical safety assessment. Freshly isolated peripheral blood mononuclear cells (PBMCs) provide a human-relevant platform to study variability in cytotoxicity, mitotoxicity and stress pathway activation. Using functional high-content imaging and transcriptomics, we screened 43 compounds across a wide concentration range to quantify donor-specific responses and identify key stress response mechanisms. These data inform the selection of compounds for a larger 200-donor cohort, enabling assessment of population-level differences in sex (male/female), age (20-29; 40-49; 60-69) and ethnicity (White, Asian, and Sub-Saharan African).

Workflow for assessing cytotoxicity and mitotoxicity in human PBMCs



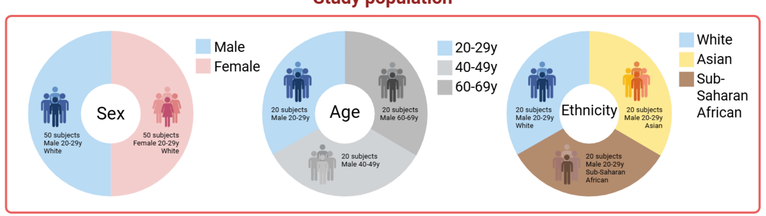
PBMC functional responses across 43 compounds guide compound selection for population studies



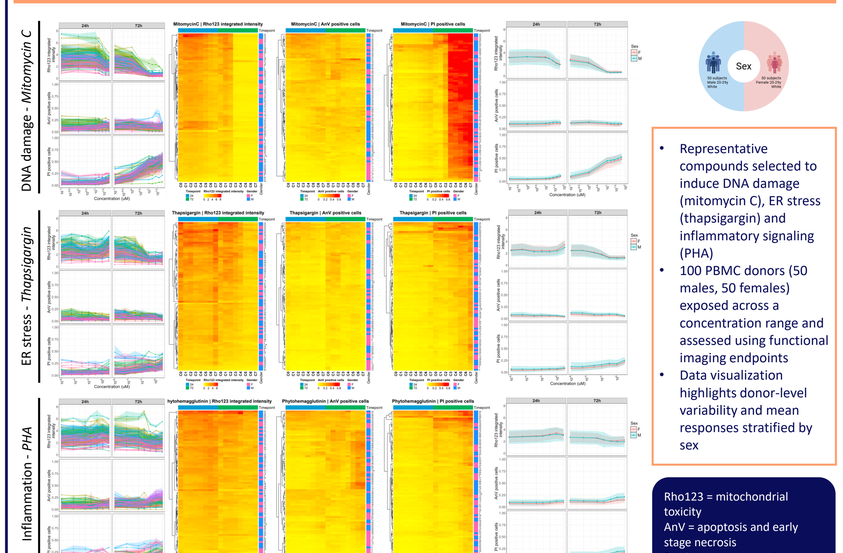
- PBMCs exposed to 43 mechanistically diverse compounds
- Functional endpoints measured at 24 and 72 h (cell count, rho123 for mitochondrial potential, PI for necrosis, and AnV for apoptosis)
- Heatmap shows concentration-dependent response for most compounds
- Data guided selection of 10 compounds for follow-up in the 200-donor study

Population-based study to assess interindividual variability in functional stress responses

Study population



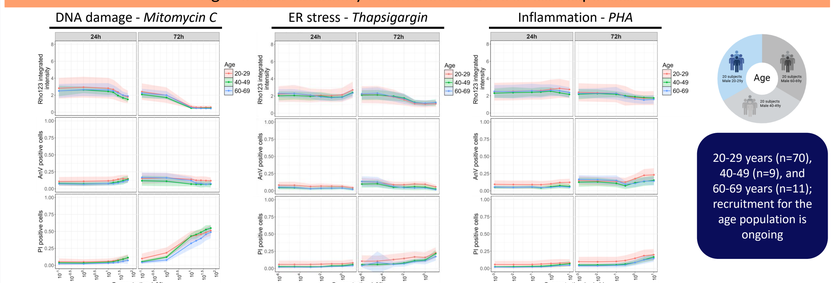
Functional PBMC responses reveal donor variability but comparable sensitivity between males and females



- Representative compounds selected to induce DNA damage (mitomycin C), ER stress (thapsigargin) and inflammatory signaling (PHA)
- 100 PBMC donors (50 males, 50 females) exposed across a concentration range and assessed using functional imaging endpoints
- Data visualization highlights donor-level variability and mean responses stratified by sex

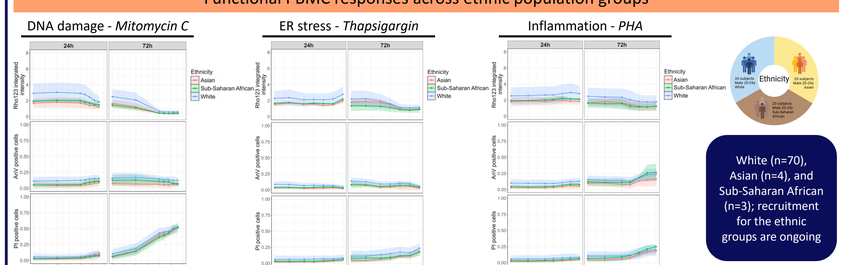
Rho123 = mitochondrial toxicity
AnV = apoptosis and early stage necrosis
PI = late stage necrosis

Age-related variability in functional PBMC stress responses



20-29 years (n=70), 40-49 (n=9), and 60-69 years (n=11); recruitment for the age population is ongoing

Functional PBMC responses across ethnic population groups



White (n=70), Asian (n=4), and Sub-Saharan African (n=3); recruitment for the ethnic groups are ongoing

CONCLUSION

- Functional imaging of PBMCs reveals concentration-dependent mitotoxic and cytotoxic responses across mechanistically diverse compounds, with variability primarily observed at the individual donor level.
- Despite donor-level variability in response magnitude and onset concentration, average responses were comparable across male and female donors, indicating similar sensitivity within this initial cohort.

FUTURE PERSPECTIVES

- Completion of transcriptomic profiling and expansion to 200-donor cohort across sex, age and ethnic groups will enable integration of functional and molecular responses to support population-based modeling and data-driven toxicodynamic variability factors for chemical risk assessment.

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