ASPIS

Open Symposium 2-3 July 2026 Maastricht The Netherlands

Estimation of intra-specific ranges of genetic susceptibility to toxicity using genetically diverse populations of human lymphoblastoid cell lines

Konrad Patyra[1], Maria Adonay[2,3], Robert Anholt[2,3], Trudy Mackay[2,3], Pekka Kohonen[1,4], John Colbourne[5], Juha Rantala[1], Roland Grafström[1,4] and Vesa Hongisto[1]

1. Misvik Biology Oy, Turku, Finland, 2. Center for Human Genetics, Clemson University, Greenwood, SC, USA, 3. Department of Genetics and Biochemistry, Clemson University, Clemson, SC, USA , 4. Institute for Environmental Medicine, Karolinska Institutet, Solna, Sweden, 5. School of Biosciences, The University of Birmingham, Edgbaston, Birmingham, United Kingdom

Project: PrecisionTox

These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement
No. 963845 (ONTOX),
No. 965406 (PrecisionTox),
No. 964537 (RISK-HUNT3R)

aspis-cluster.eu

Intra-specific genetic susceptibility to chemical toxicity
Aims, material and methods

Open Symposium 2-3 July 2026 Maastricht The Netherlands

AIMS

- ✓ Assess the impact of genetic variation on toxicity using a genetically diverse panel of lymphoblastoid cell lines (LCLs)
- ✓ To identify genetic variants (SNPs) and affected cellular mechanisms associated with toxic responses.

SNP analysis, LCLs selection and ordering

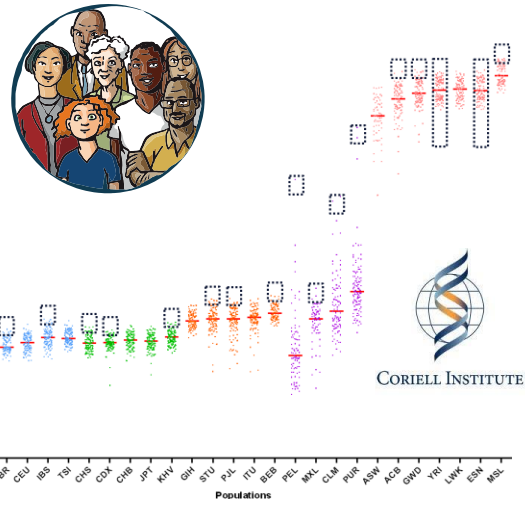
EUROPEAN
FIN – FINNISH
GBR – BRITISH
IBS – IBERIAN IN SPAIN

EAST ASIAN
CHS – HAN CHINESE SOUTH, CHINA
CDX – CHINESE DAI IN XISHUANGBANNA
KHV – KINH IN HO CHI MINH CITY, VIETNAM

SOUTH ASIAN
STU – SRI LANKAN TAMIL IN THE UK
PJL – PUNJABI IN LAHORE, PAKISTAN
BEB – BENGALI IN BANGLADESH

AMERICAN
PEL – PERUVIAN IN LIMA, PERU
MXL – MEXICAN ANCESTRY IN CALIFORNIA, USA
CLM – COLOMBIAN IN MEDELLIN
PUR – PUERTO RICAN IN PUERTO RICO

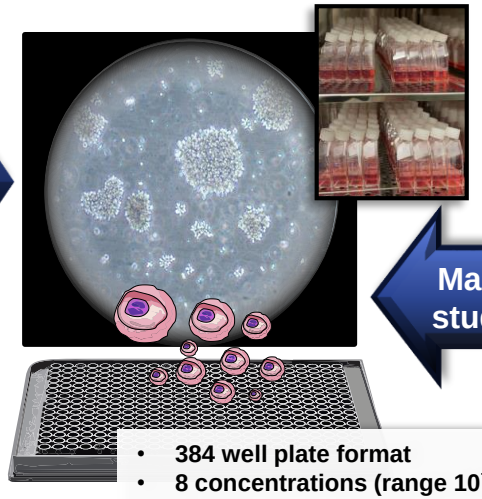
AFRICAN
ACB – AFRICAN CARIBBEAN IN BARBADOS
GWD – GAMBIAN IN WESTERN DIVISION - MANDINKA
YRI – YORUBA IN IBADAN, NIGERIA
ESN – ESAN IN NIGERIA
MSL – MENDE IN SIERRA LEONE



CORIELL INSTITUTE

LCLs

selection



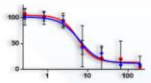
Main study

- 384 well plate format
- 8 concentrations (range 10^7)
- 4 biological replicates

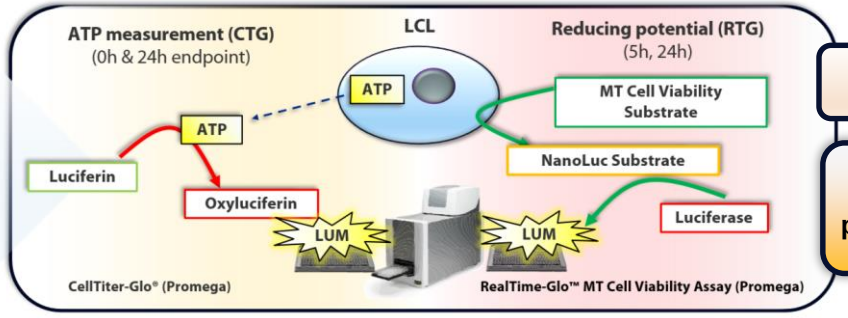
PILOT SCREENING
91 chemicals

20 LCLs

CHEMICALS — Selected chemicals — DRUGS



METHOD SELECTION AND OPTIMIZATION



Luminescence measurements

Viability

Cellular reducing potential & ATP

0h

24h

DATA ANALYSIS
(Dose-response and IC_{50} value analysis, statistical analysis)

~ 1 billion cells grown !

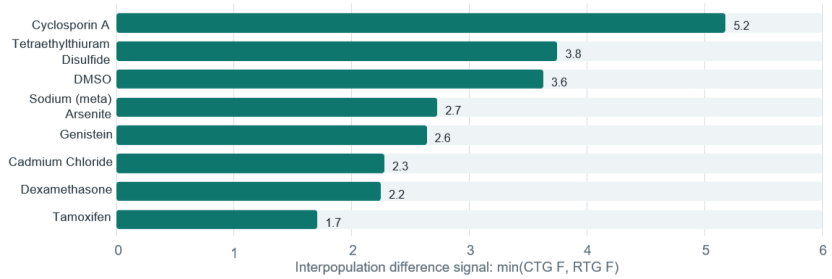
Intra-specific genetic susceptibility to chemical toxicity
Results

Open Symposium 2-3 July 2026 Maastricht The Netherlands

ANOVA analysis: Inter-, and Intrapopulation Cell-Line Variation in Chemical Response

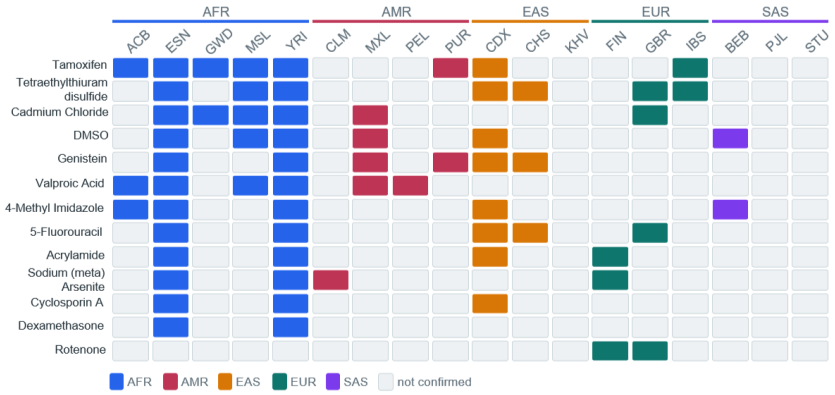
A Interpopulation Variability

Chemicals where response differs between populations; bar shows min (CTG F, RTG F).

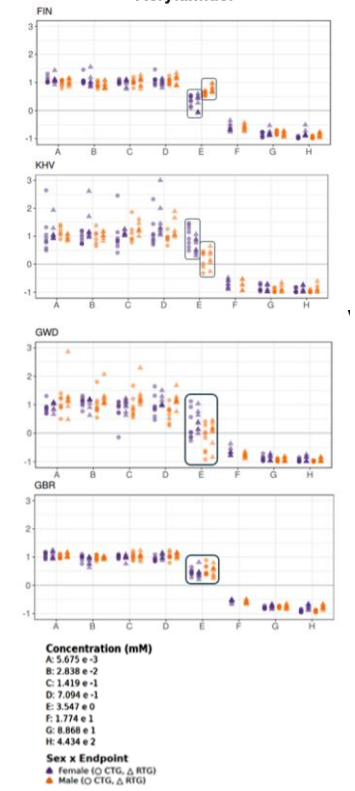


B Intrapopulation Cell-Line Variability

Chemical-level variation among cell lines within each population.



C Population-specific sex differences in response to Acrylamide.



Cadmium Chloride: Candidate biology from gene-level GWAS hits in LCLs

Endpoint	Population	Unique SNPs – p < 0.001	Unique SNPs – p < 0.00001	Unique Genes – p < 0.001	Unique Genes – p < 0.00001	Unique Genes – Network Input Set	Total Genes In Network
CTG	ESN	10,671	85	2,180	21	12	17
CTG	YRI	12,206	219	2,464	65	43	106
RTG	ESN	10,437	182	2,216	55	33	101
RTG	YRI	9,240	109	2,049	32	14	128

Cadmium Chloride

Gene lists are mapped candidates, not proven causal variants

Mitochondria + structure

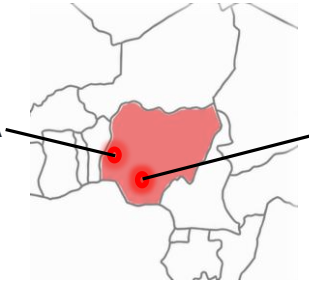
mitochondrial quality control and cell architecture

PARK2, EGFR, ENAH

Metabolic survival

energy rewiring and stress-adaptive signaling

PFKFB3, RAPGEF4, NR5A2



Metal handling

transport and detoxification capacity

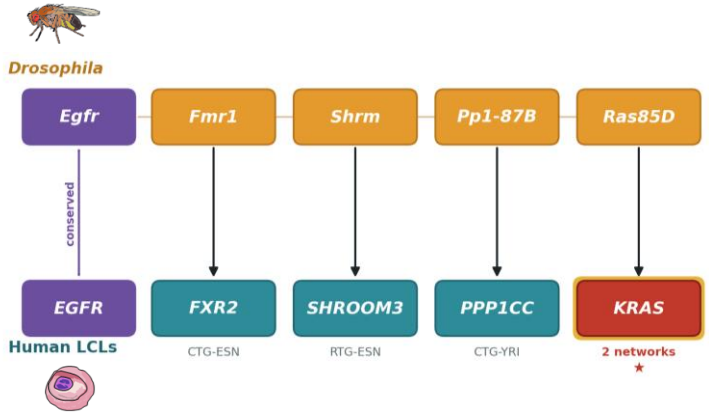
SLC30A10, ABCB11

Oxidative damage control

buffering reactive oxygen stress and damaged proteins

BACH1, TALDO1, UBE2Q2

Connecting the fly and human results through Egfr/EGFR



Intra-specific genetic susceptibility to chemical toxicity
Conclusions and acknowledgements

Open Symposium 2-3 July 2026 Maastricht The Netherlands

Conclusions

- **People differ** — a cell line's population and individual donor are the biggest drivers of chemical response — seen in both CTG and RTG assays.
- **Population differences are real** — confirmed for 8 chemicals, including cadmium; sex has little effect (~6%).
- **Cadmium makes biological sense** — candidate genes cluster in metal handling & oxidative defence (ESN) and metabolic / mitochondrial survival (YRI).
- **The fly agrees** — conserved Egfr/EGFR networks recover the same human genes (e.g. KRAS) — independent cross-species support.

Take-home: genetic background shapes toxicity — and should be considered in chemical safety assessment.

Preliminary & hypothesis-generating — GWAS / eQTL ongoing.

Acknowledgements

misvik biology

Misvik Biology Oy · Finland
Vesa Hongisto, Juha Rantala, Pekka Kohonen, Roland Grafström

CLEMSON UNIVERSITY

Clemson University · USA
Trudy Mackay, Robert Anholt, Maria E. Adonay, Elisa Howansky, Katelynne Collins

UNIVERSITY OF BIRMINGHAM

University of Birmingham · UK
John Colbourne

Scan me to learn more!

Cell lines: Coriell Institute, USA.
Funded by EU H2020 — PrecisionTox (GA 965406).