



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)

This output reflects only the author's view and the Directorate-General for Research and Innovation (DG RTD) cannot be held responsible for any use that may be made of the information contained therein.

Open **2-3 July 2026** Symposium

Maastricht
The Netherlands

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

Konrad Patyra¹, Maria Adonay^{2,3}, Robert Anholt^{2,3}, Trudy Mackay^{2,3}, Pekka Kohonen^{1,4}, John Colbourne⁵, Juha Rantala¹, Roland Grafström^{1,4} and Vesa Hongisto¹

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

aspis-cluster.eu



Intra-specific genetic susceptibility to chemical toxicity

Aims, material and methods

Open **2-3 July 2026**
Symposium 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

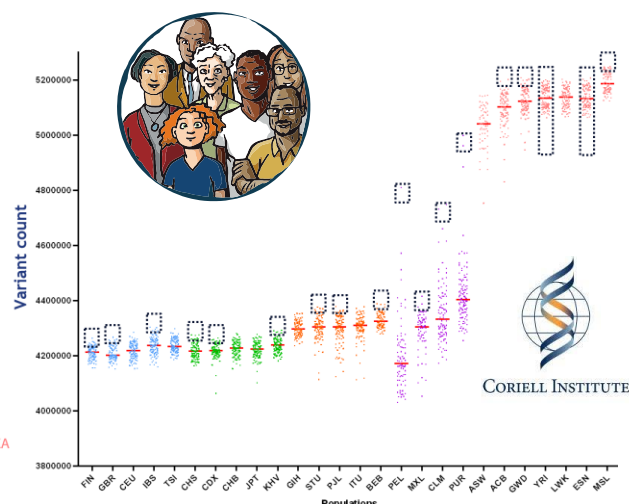
EUROPEAN
FIN – FINNISH
GBR – BRITISH
IBS – IBERIAN IN SPAIN

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

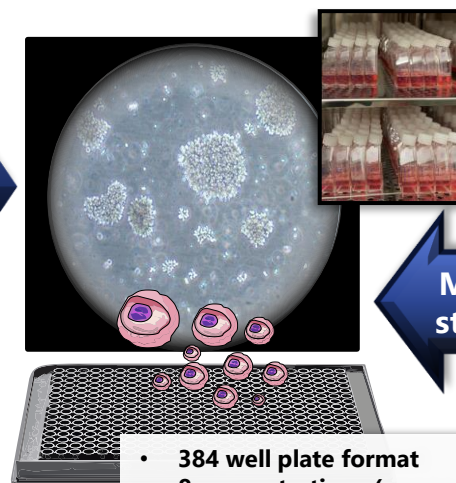
SOUTH ASIAN
STU – SRI LANKAN TAMIL IN THE UK
PJL – PUNJABI IN LAHORE, PAKISTAN
BEB – BENGALI IN BANGLADESH

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 – ESN IN NIGERIA
MSL – MENDE IN SIERRA LEONE



LCLs



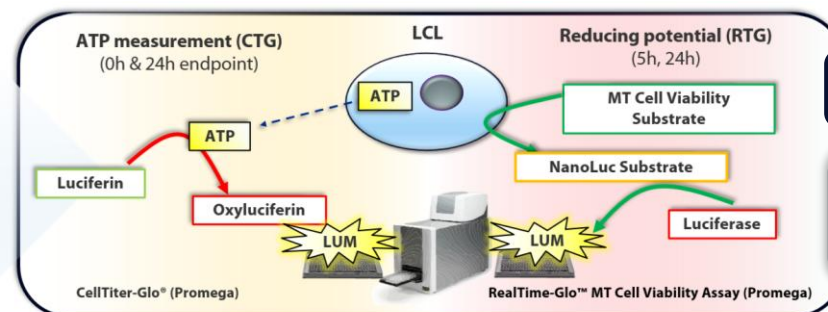
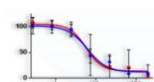
- 384 well plate format
- 8 concentrations (range 10^7)
- 4 biological replicates

PILOT SCREENING 91 chemicals

20 LCLs

CHEMICALS	Selected chemicals	DRUGS	
CADMIUM CHLORIDE <chem>Cl-[Cd]-Cl</chem> Utilized in dyeing, pigments, photocopying and electroplating of cadmium	SODIUM (META)ARSENITE <chem>[O-]As(=O)([O-])[O-].[Na+]</chem> Pesticide, but also used as hide preservative, antiseptic, dyeing, and soaps	ACRYLAMIDE <chem>CC=CC(=O)N</chem> Chemical formed in some foods during high-temperature cooking processes	4-METHYLIMIDAZOLE <chem>CN1CN=CN=C1</chem> Chemical formed during cooking of foods, production of flavors and coloring substances
GENISTEIN <chem>Oc1c(O)c2c(c1)oc3cc(O)c(O)cc3c2</chem> Phytoestrogenic isoflavone	DEXAMETHASONE <chem>CC12CCC3=C1C(=C(C=C3)C(=O)OC4C(C=CC24)C</chem> Glucocorticoid medication (anti-inflammation)	VALPROIC ACID <chem>CCC(=O)O</chem> Anticonvulsant/ bipolar disorder/ migraine medication	TAMOXIFEN <chem>Cc1ccc(cc1C2=CC=CC=C2)C3=CC=CC=C3</chem> Selective estrogen receptor modulator (breast cancer)
CYCLOSPORIN A <chem>C1CC2C(C3CC4C(C2)C(C1)C(C3)C4)C5=CC=CC=C5</chem> Calcineurin inhibitor (immunosuppressive medication)	ROTENONE <chem>O=C1C=CC(=C2C(=C1)C(=C(C=C2)O)O)O</chem> Naturally occurring botanical pesticide and mitochondrial complex I inhibitor	TETRAETHYLTHIAM DISULFIDE <chem>CCCCSCSCCCCC</chem> Medication used for support treatment of chronic alcoholism	5-FLUOROURACIL <chem>C1=CN=C(C(=O)NC1=O)F</chem> Cytotoxic chemotherapy medication (various cancers)

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 !





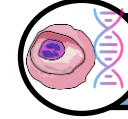
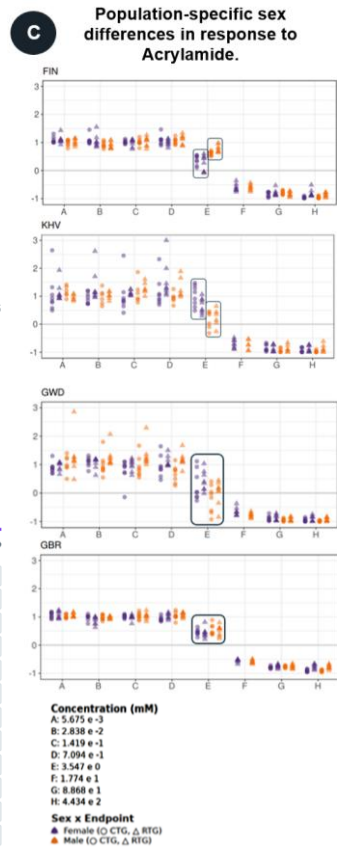
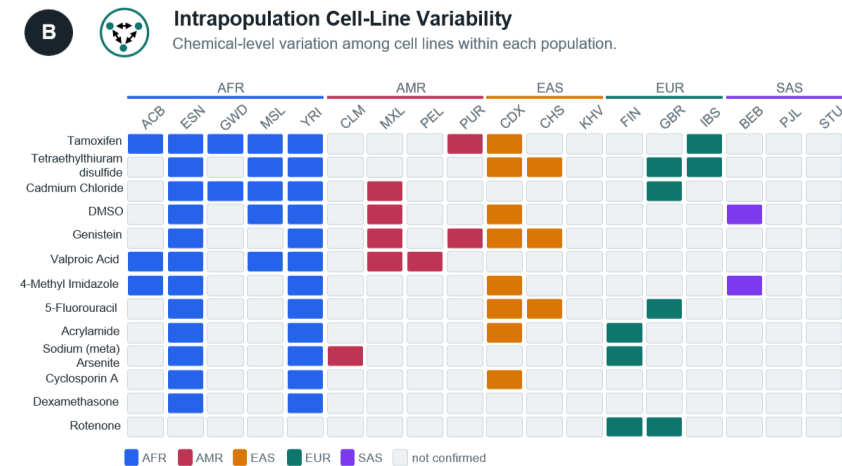
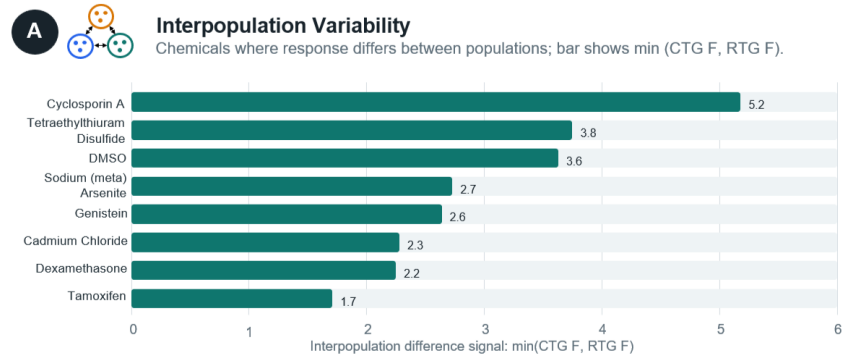
Intra-specific genetic susceptibility to chemical toxicity

Results

Open 2-3 July 2026
Symposium Maastricht
The Netherlands



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



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



Metal handling

transport and detoxification capacity
SLC30A10, ABCB11



YORUBA IN IBADAN, NIGERIA



ESAN FROM NIGERIA

Metabolic survival

energy rewiring and stress-adaptive signaling
PFKFB3, RAPGEF4, NR5A2



Oxidative damage control

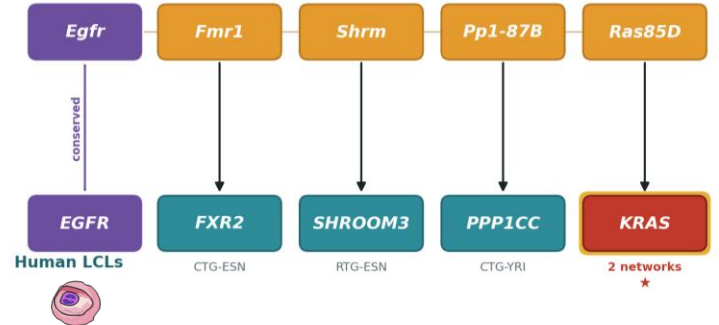
buffering reactive oxygen stress and damaged proteins
BACH1, TALDO1, UBE2Q2



Connecting the fly and human results through Egfr/EGFR



Drosophila





Intra-specific genetic susceptibility to chemical toxicity

Conclusions and acknowledgements

Open 2-3 July 2026
Symposium 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 Oy · Finland

Vesa Hongisto, Juha Rantala, Pekka Kohonen, Roland Grafström



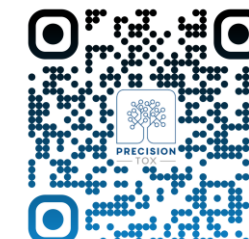
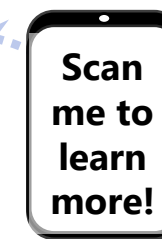
Clemson University · USA

Trudy Mackay, Robert Anholt, Maria E. Adonay, Elisa Howansky, Katelynne Collins



University of Birmingham · UK

John Colbourne



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