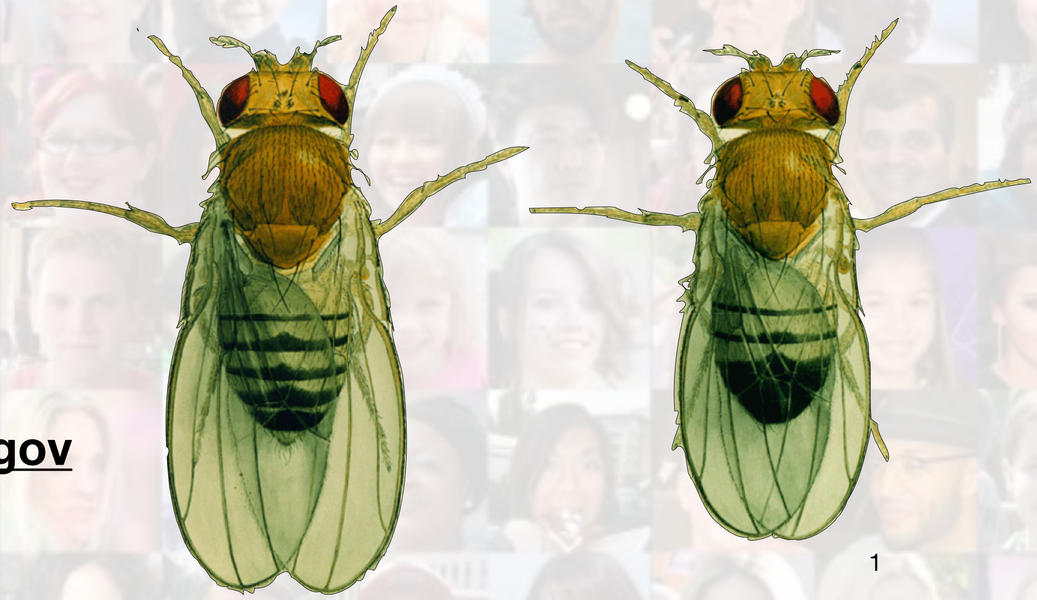
Comparative Genomics for Precision Toxicology

Brian Oliver
Intramural Research Program, NIH, Bethesda MD, USA



Disclaimer

briano@nih.gov

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

“No data, no market”

ASPIS: effects of chemicals on health

€60 million, 3 projects, 5 years

Prof. John Colbourne

Prof. Mathieu Vinken

Prof. Bob van de Water

PRECISION TOX

Comparative

Expression & Metabolite Profiling

Initiating events

Adverse outcome

ONTOX

Data mining

Artificial Intelligence

Adverse outcome pathways

Focused *in silico* & *in vitro* testing

RISK HUNT3R

Human Cell lines

Pluripotent Stem Cells

Organs on a chip

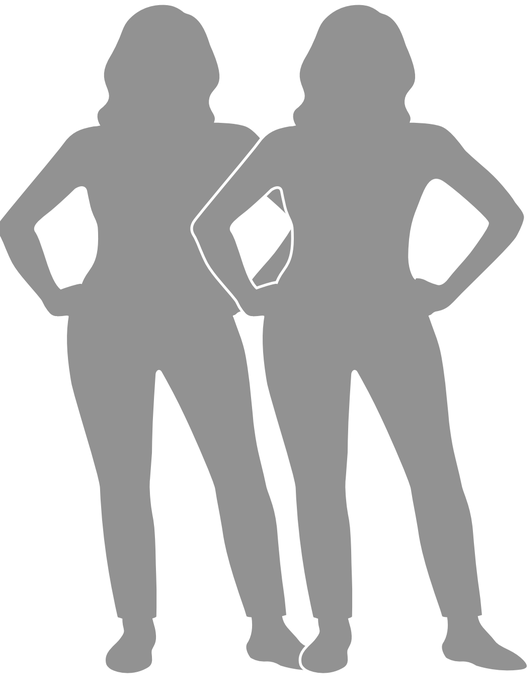
Metabolism, Distribution, & Excretion

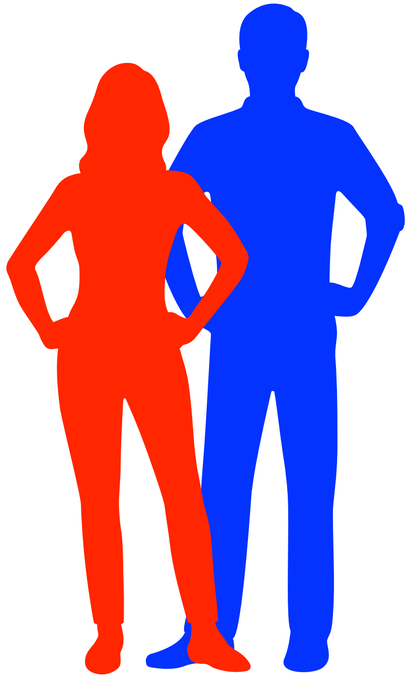
ASPIS covers the NAMs

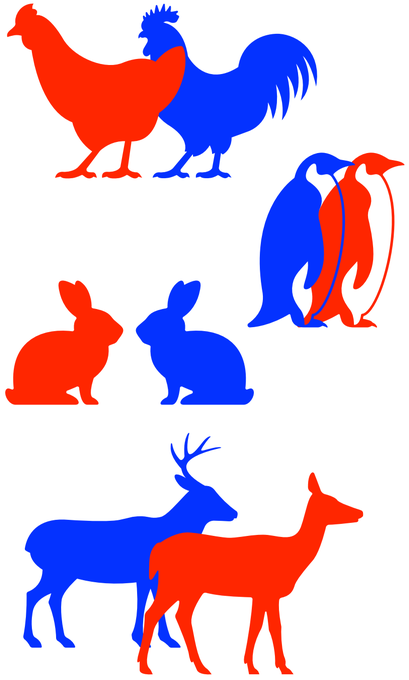
	Pathways	Tissues	Organs	Organ systems	Embryo > Adult	Complex behavior	Through-put	Expt. Control	Human Genetics	Ethics
Data Mining	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Low**	**Yes**	**Testing people retrospectively**
Cells	**Yes**	**No**	**No**	**No**	**No**	**No**	**Ultra**	**High**	**Yes**	**Origin of cells** **Reagents**
On a chip	**Yes**	**Yes**	**No**	**No**	**No**	**No**	**Yes**	**Can be Delicate**	**Yes**	**Origin of cells** **Reagents**
organoids et al.	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**Moderate**	**Can be Delicate**	**Human**	**Origin of cells** **Reagents**
Model Organisms	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Moderate**	**High**	**Orthologs** **Humanization**	**Sentience**

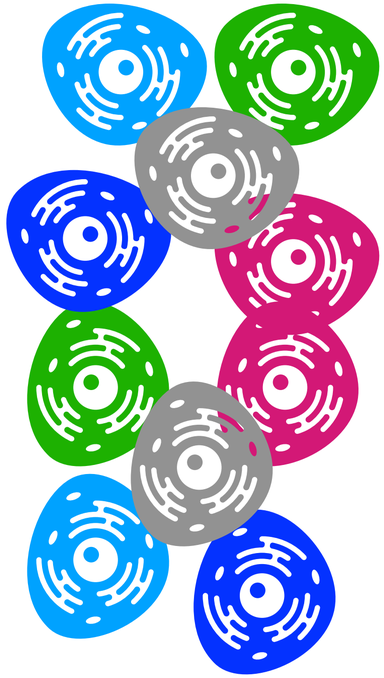
Functional Variance:

Genotype < Genotypes < Sexes < Species < Cell type



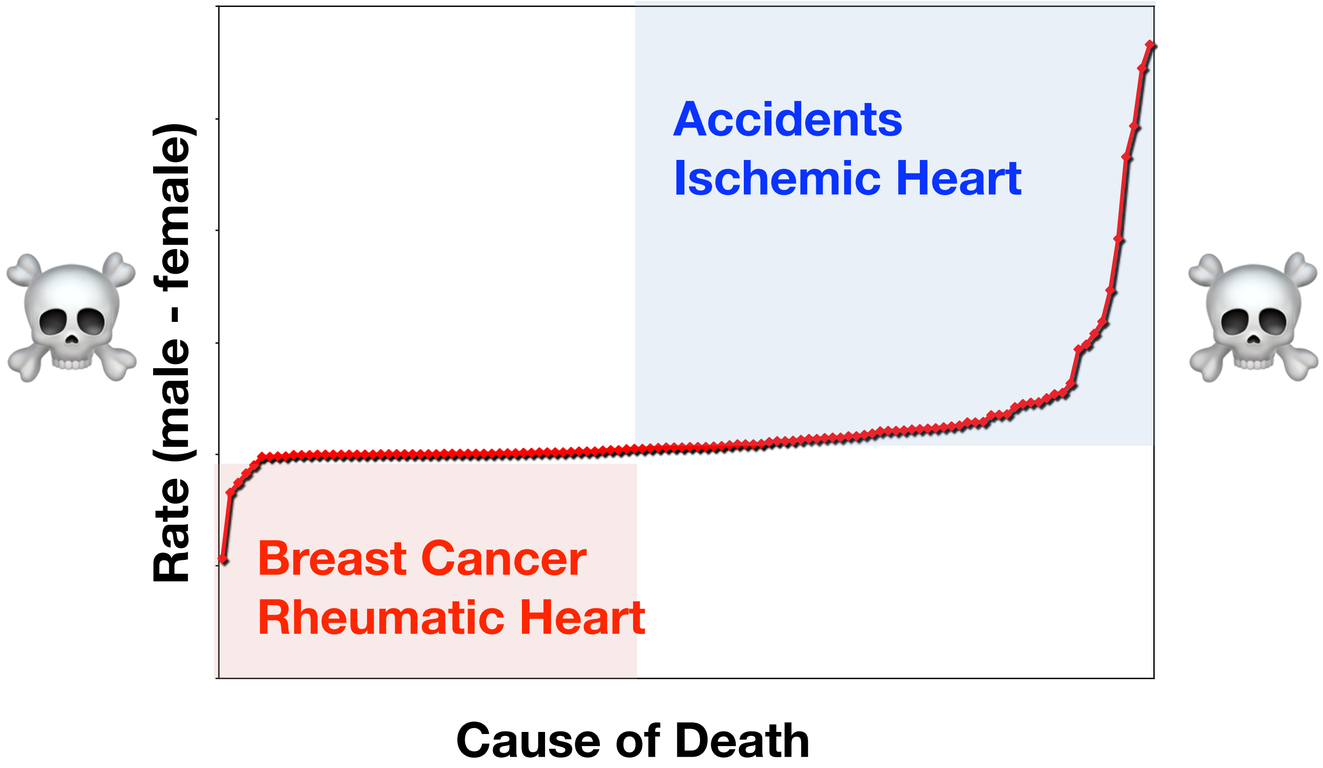


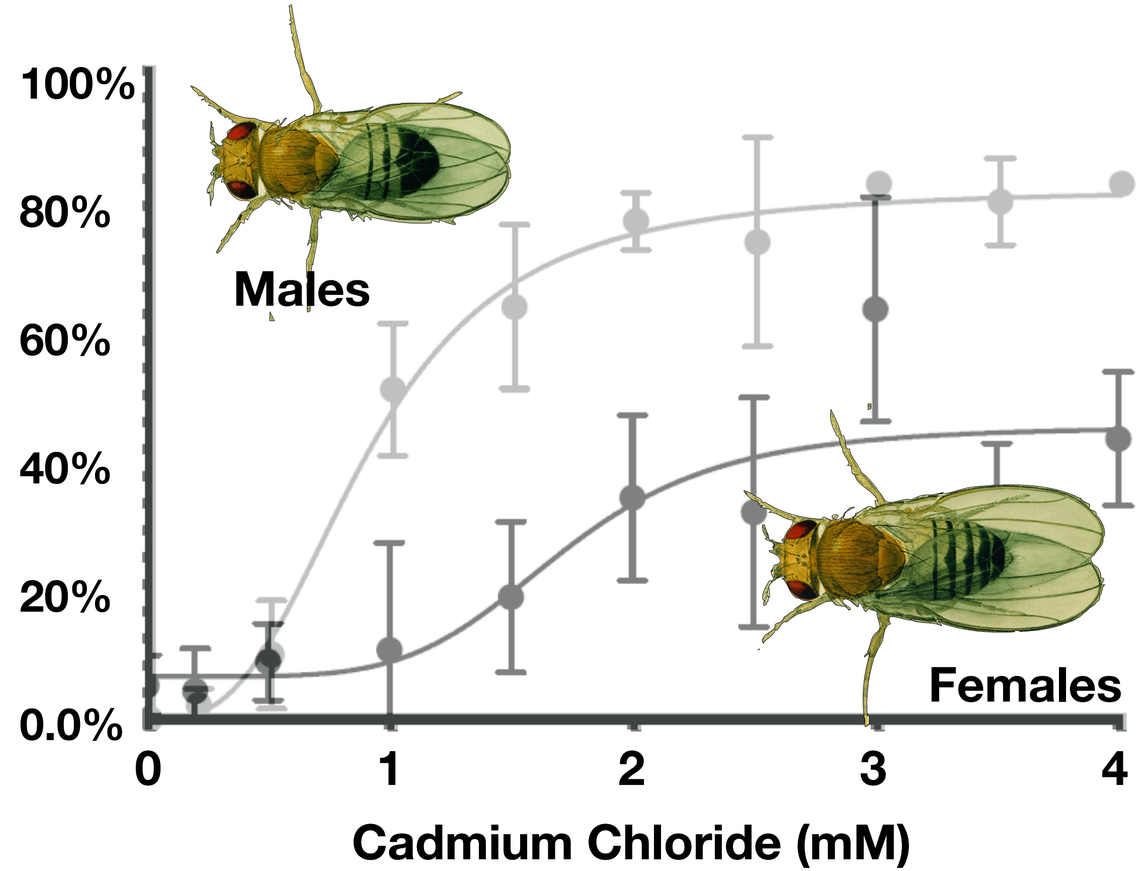




Stratify by sex. Please…

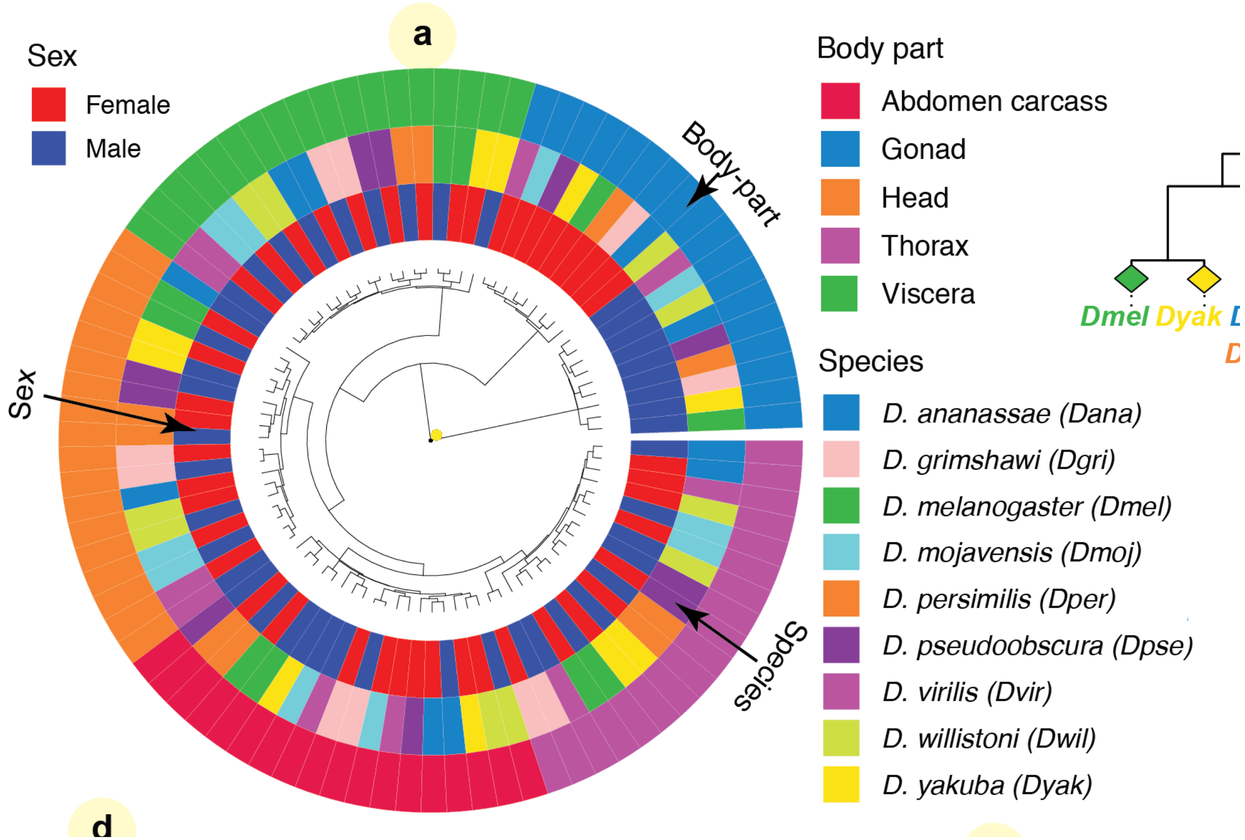
USA Mortality 2006

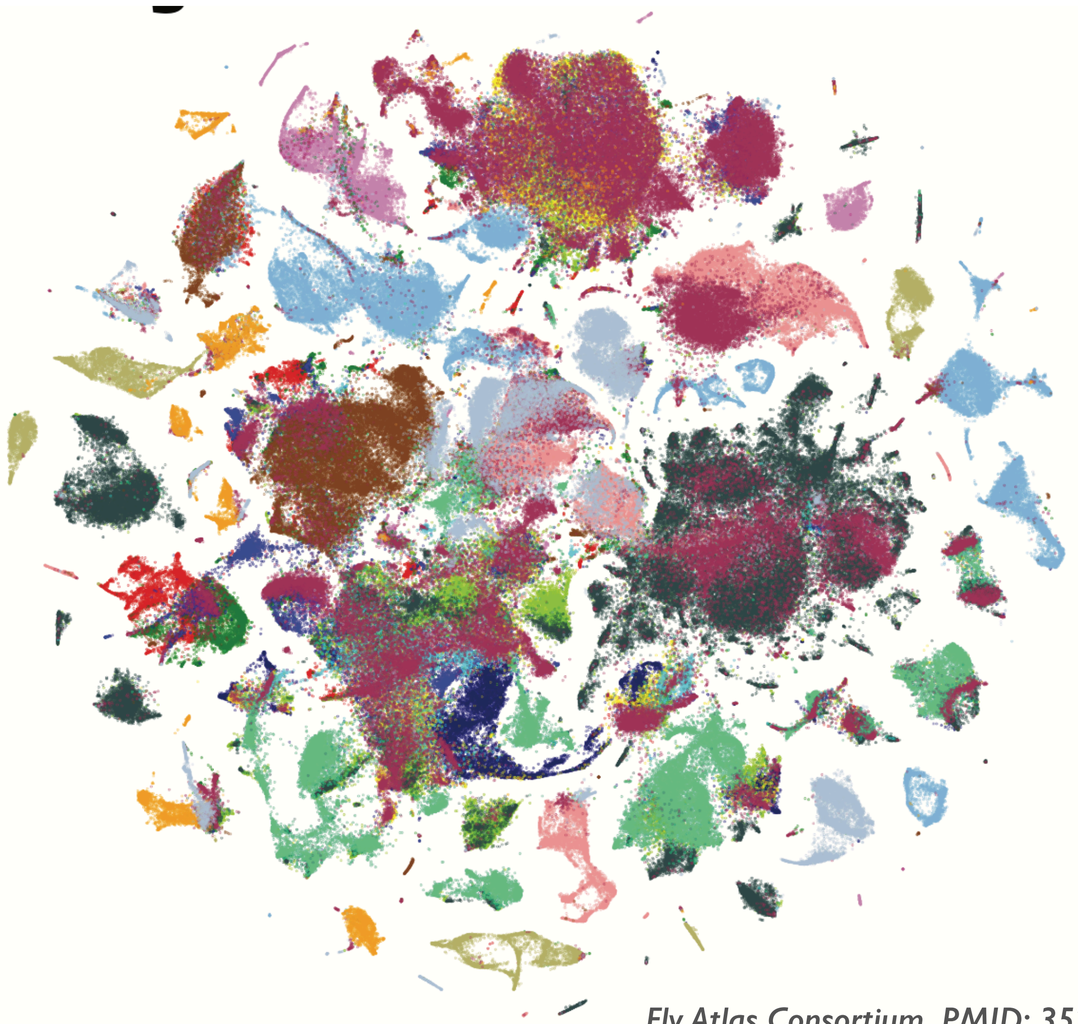


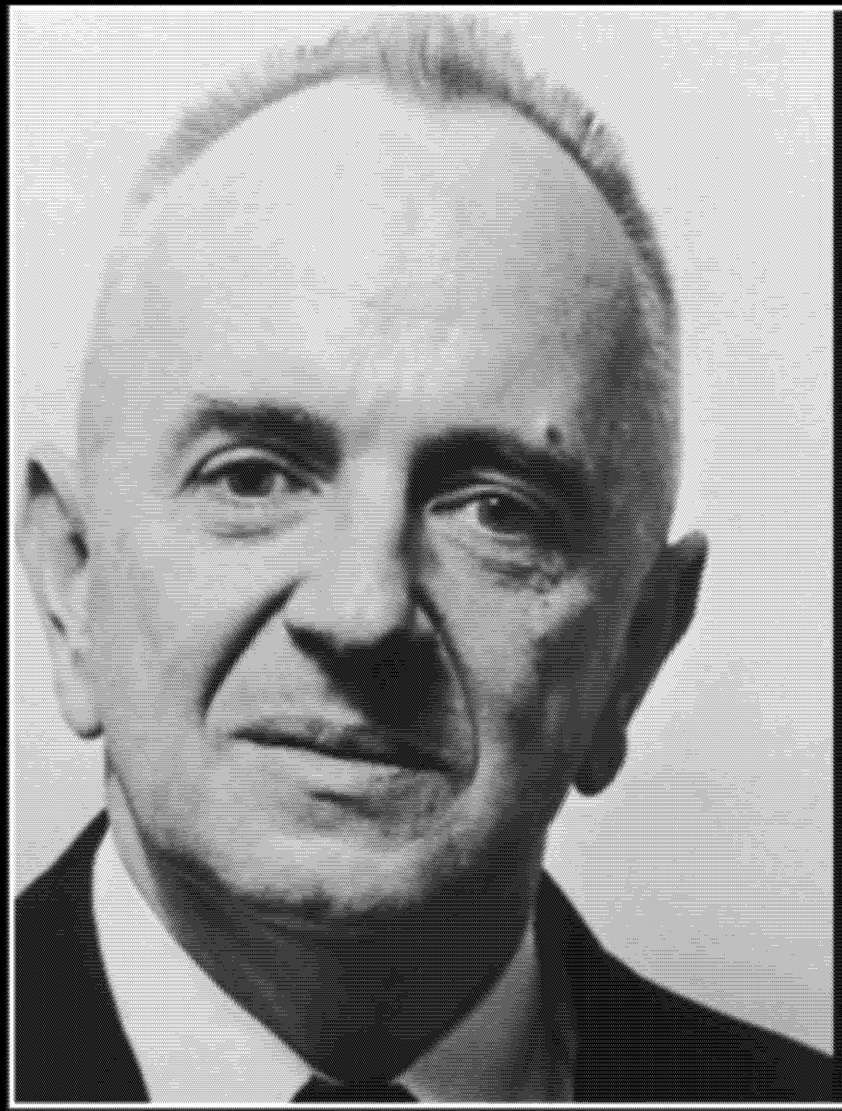


Precision Toxicology, unpublished

Organ/Cell expression differences are greater than those based on genetic diversity.







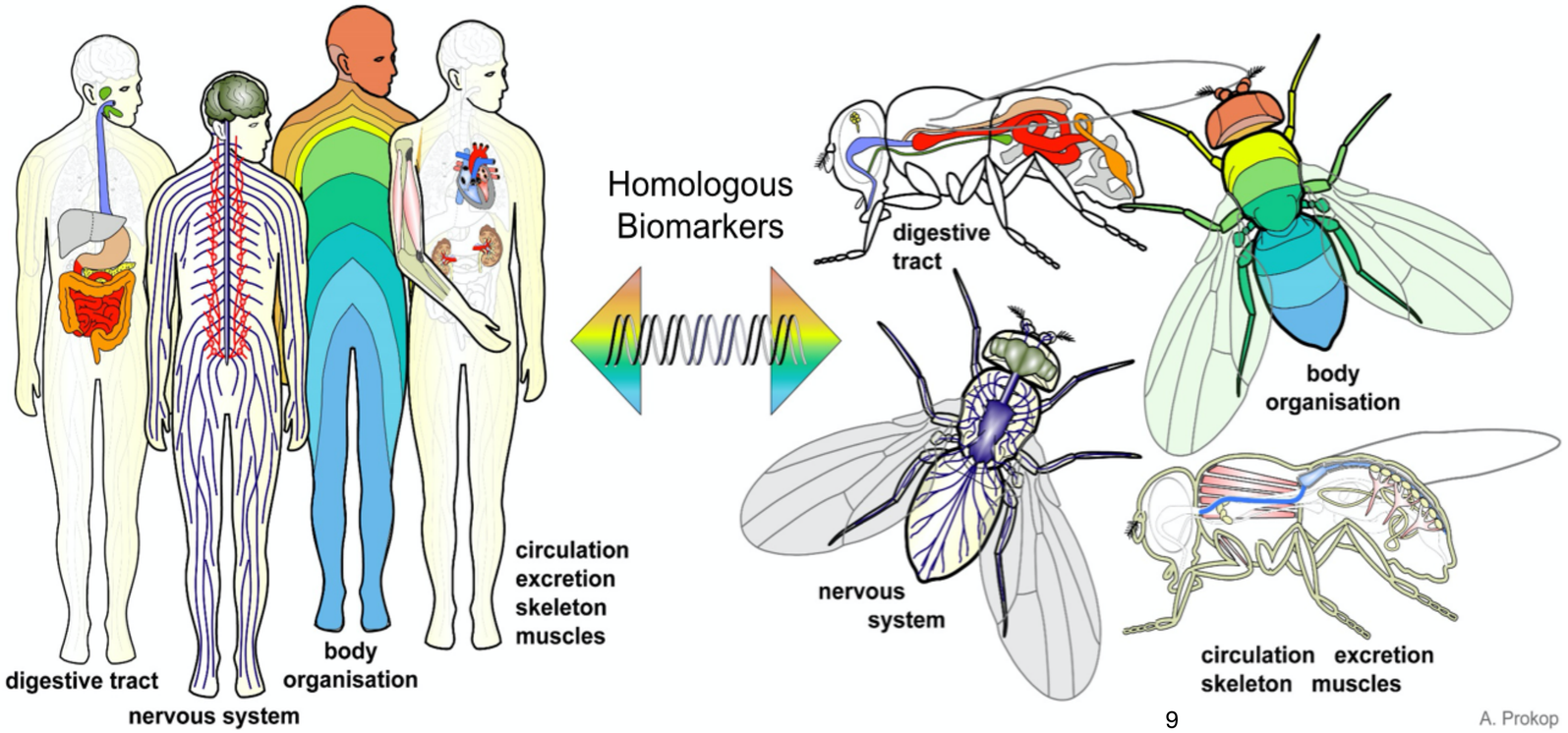
Nothing in biology makes sense except in the light of evolution.

— Theodosius Dobzhansky —

AZ QUOTES

Studying human variants in flies

- 85% of OMIM genes have fly homologs
- Genes and variants function cross-species in patient studies

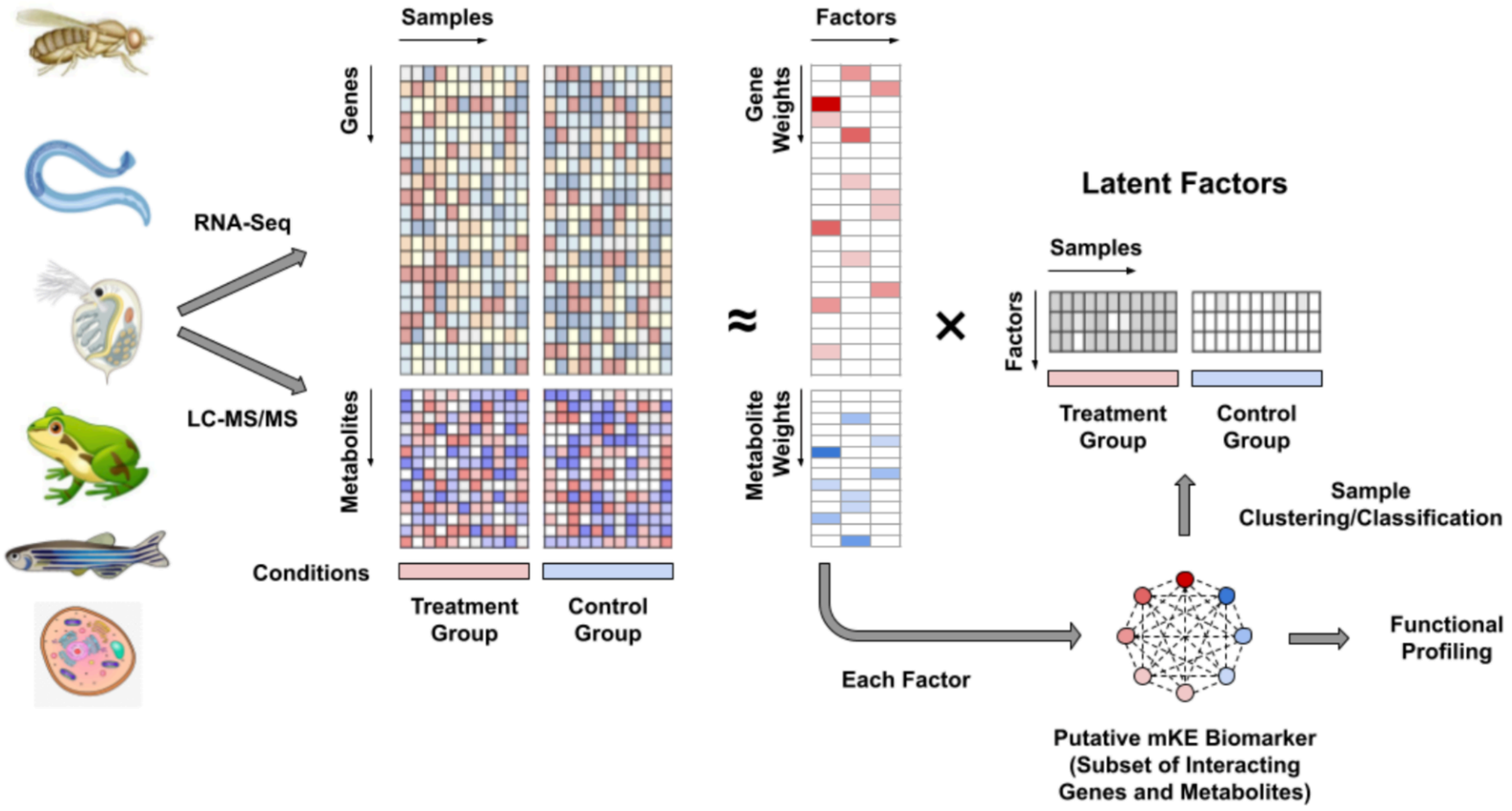


ATAD3A (Harel et al. 2016)
TM2D3 (Jakobsdottir et al. 2016)
EBF3 (Chao et al. 2017)
OGDHL (Yoon et al. 2017)
CACNA1A (Luo et al 2017)
ARIH1 (Tan et al. 2018)
ATP5F1D (Oláhová et al. 2018)
WDR37 (Kanca et al. 2018)
MARK3 (Ansar et al. 2018)
DNM1L (Assia Batzir et al. 2019)
DROSHA (Barish & Senturk et al. 2022)
IQSEC1 (Chung et al. 2019)
OXR1 (Wang et al. 2019)
ACOX1 (Chung et al. 2020)
TOMM70 (Dutta et al. 2020)
CDK19 (Chung et al. 2020)
CAPZA2 (Huang et al. 2021)
RNF2 (Luo et al. 2021)
GBA1 (Wang et al. 2022)
TIAM1 (Lu et al. 2022)
FRMD5 (Lu et al. 2022)
SPTSSA (Srivastava et al. 2022)

A. Prokop

Bellen et al., 2019; Baldridge et al. 2021

Comparative Strategy

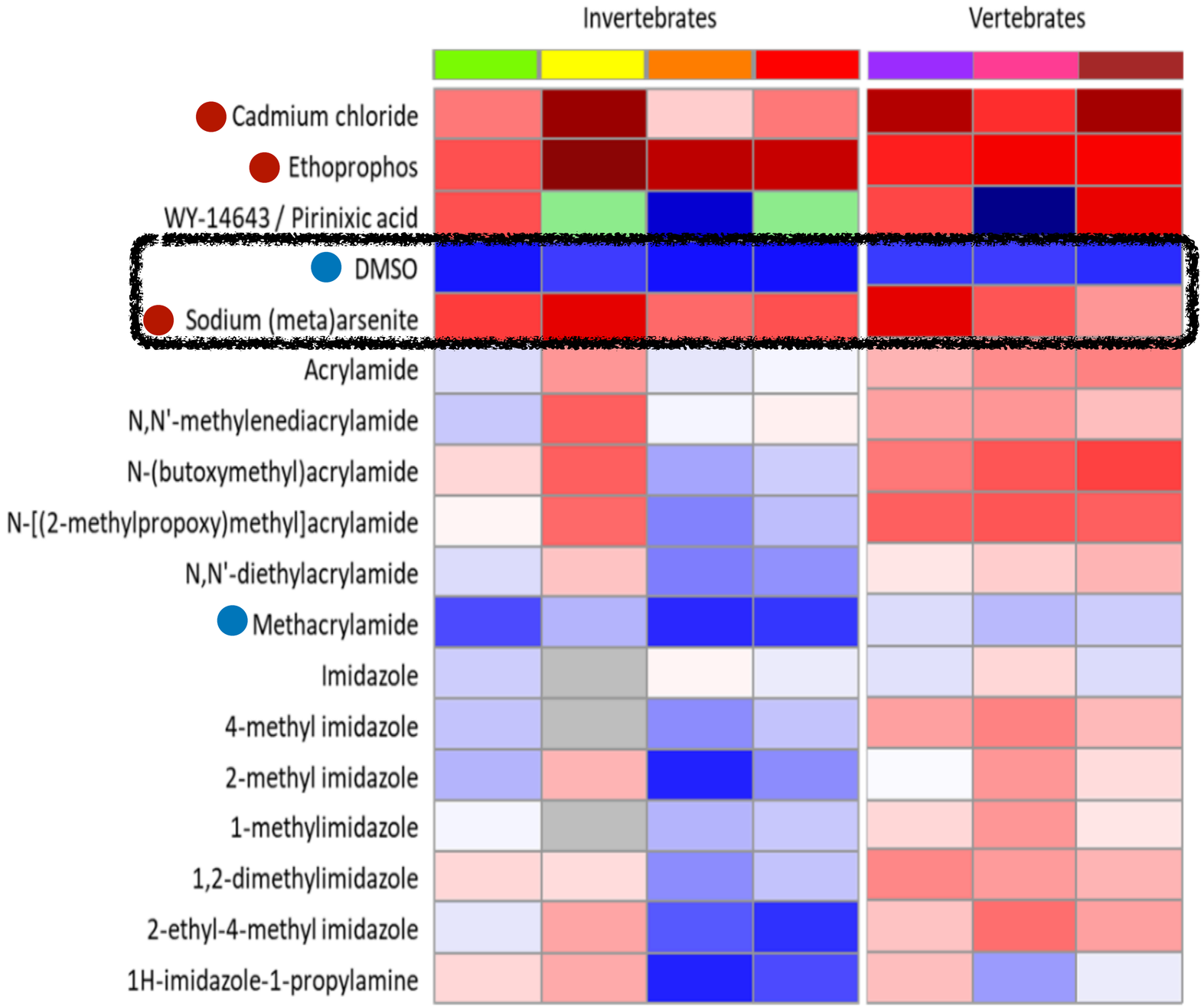


- Range finding to determine phenotypic dose responses (lethality & behavior differences)
- Time and dose normalized across species based on range finding
- Perform gene expression and metabolite profiling time-course
- Identify early, potentially initiating events, pathway modeling
- Testing models using directed genetics and populations

Precision Toxicology, unpublished

Pilot Range Finding

- Already encouraging
- Consistent high toxicity
- Consistent low toxicity
- Next steps:
  - normalize response cross-species
  - RNAseq
  - Metabolomics

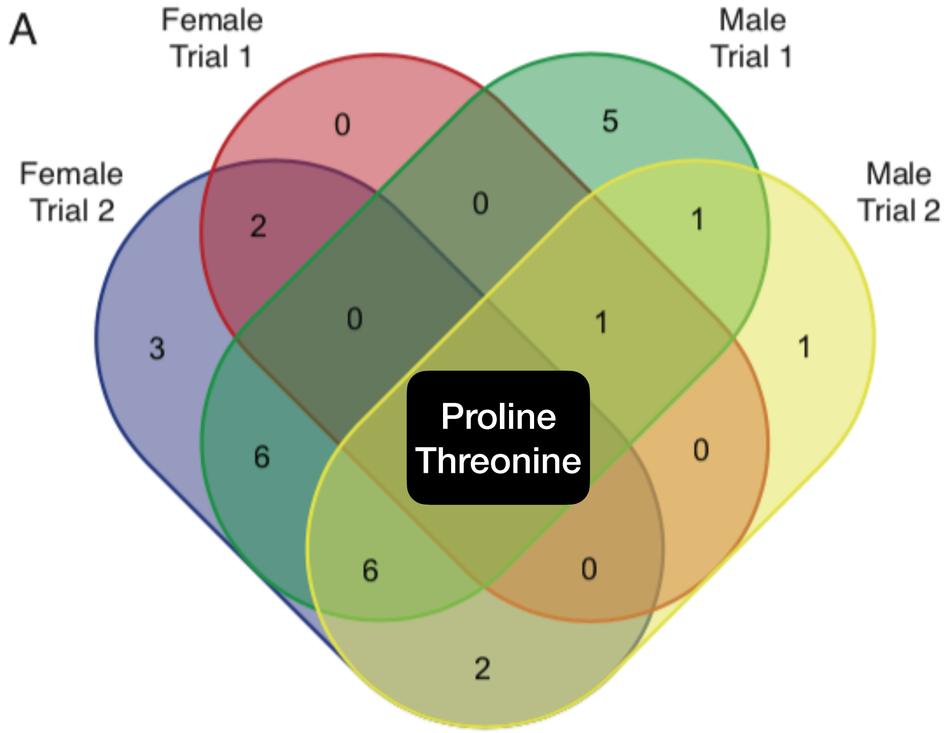


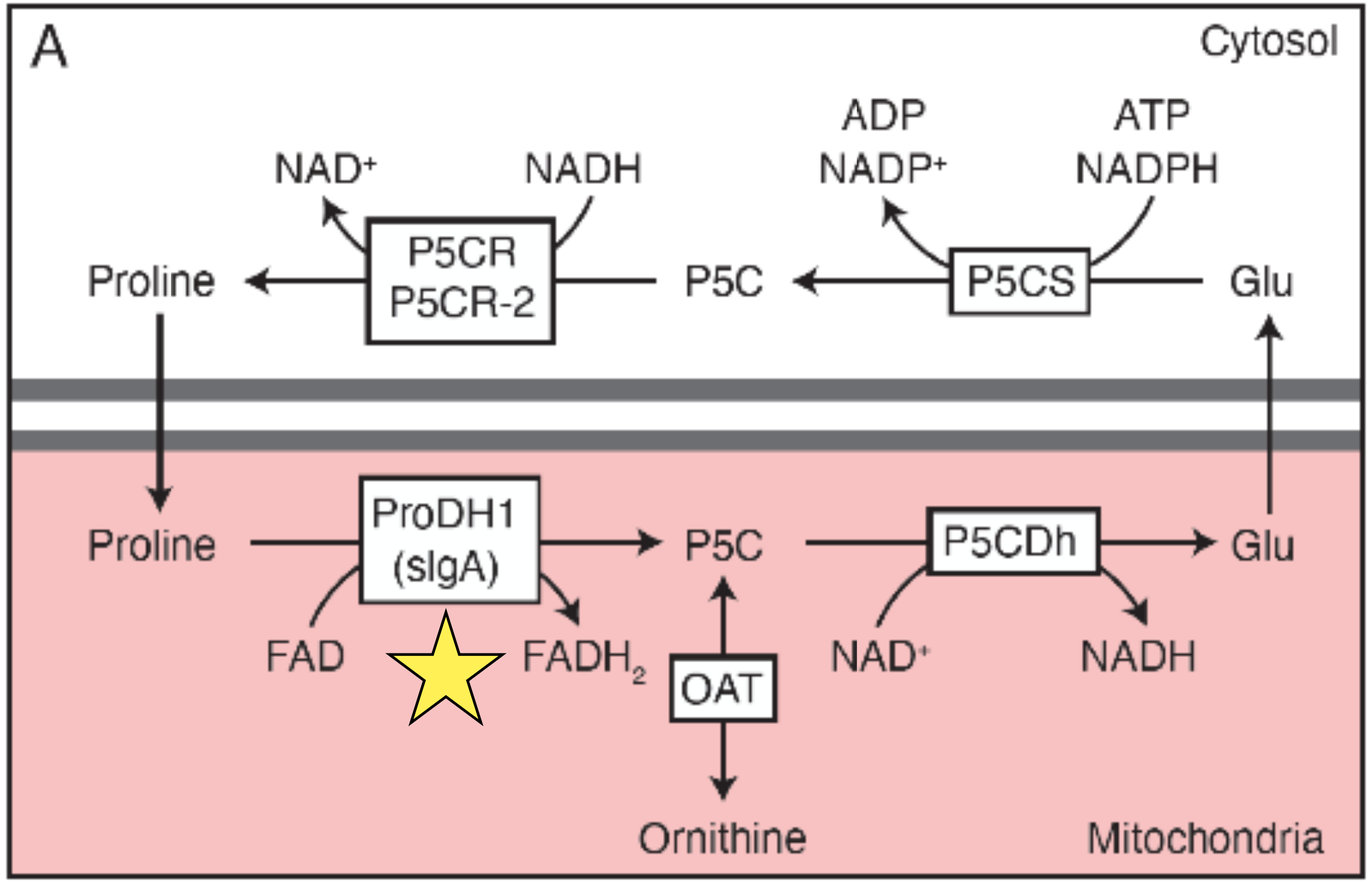
Precision Toxicology, unpublished

Proline levels are up after arsenic exposure

Adverse or protective effect?

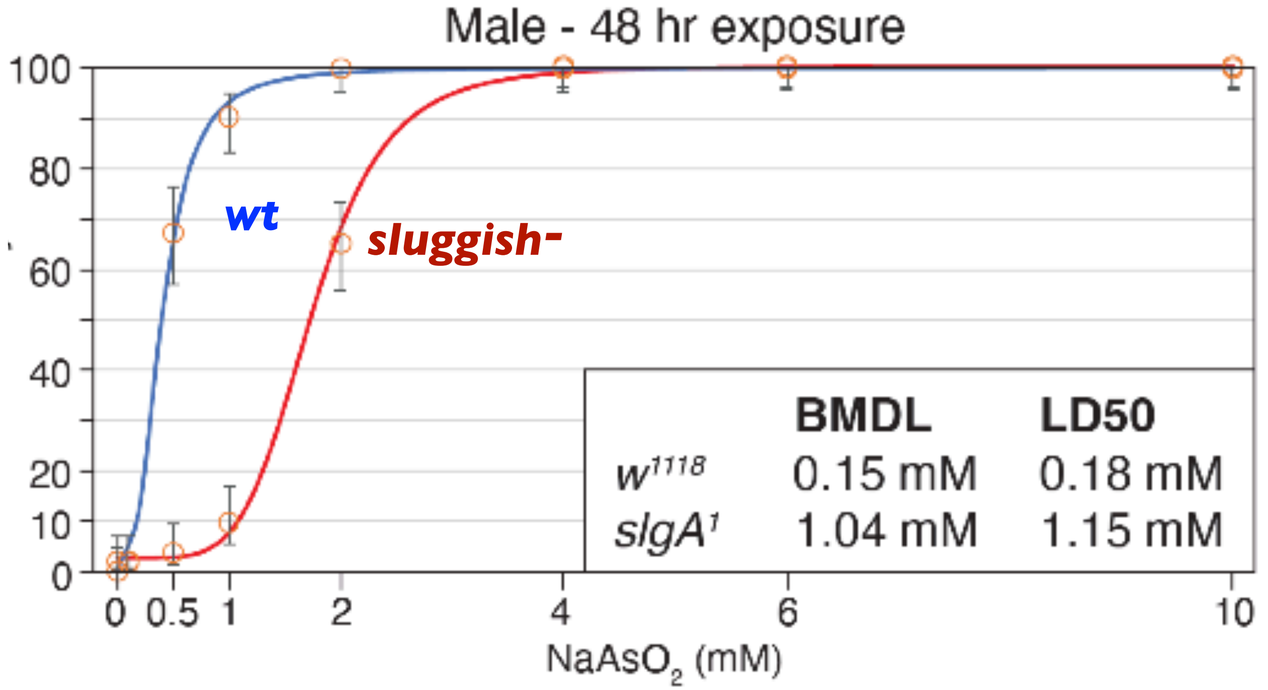
Mass Spec Results

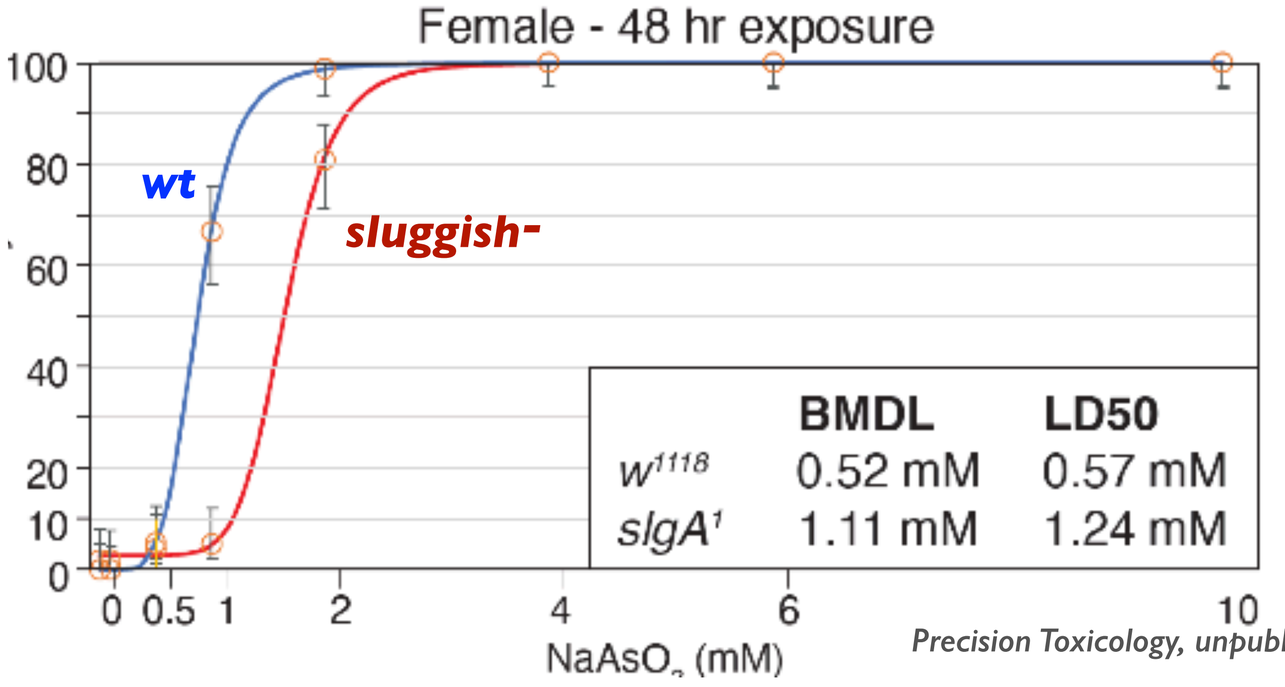




Precision Toxicology, unpublished

- ***sluggish*** **suppresses toxicity.**
- ***sluggish*** **further increases Proline levels**
- **Consistent with Proline being protective against stress in plants**
- **Diminished sex-bias in *sluggish* mutants**
- **Sex-biased Proline levels?**



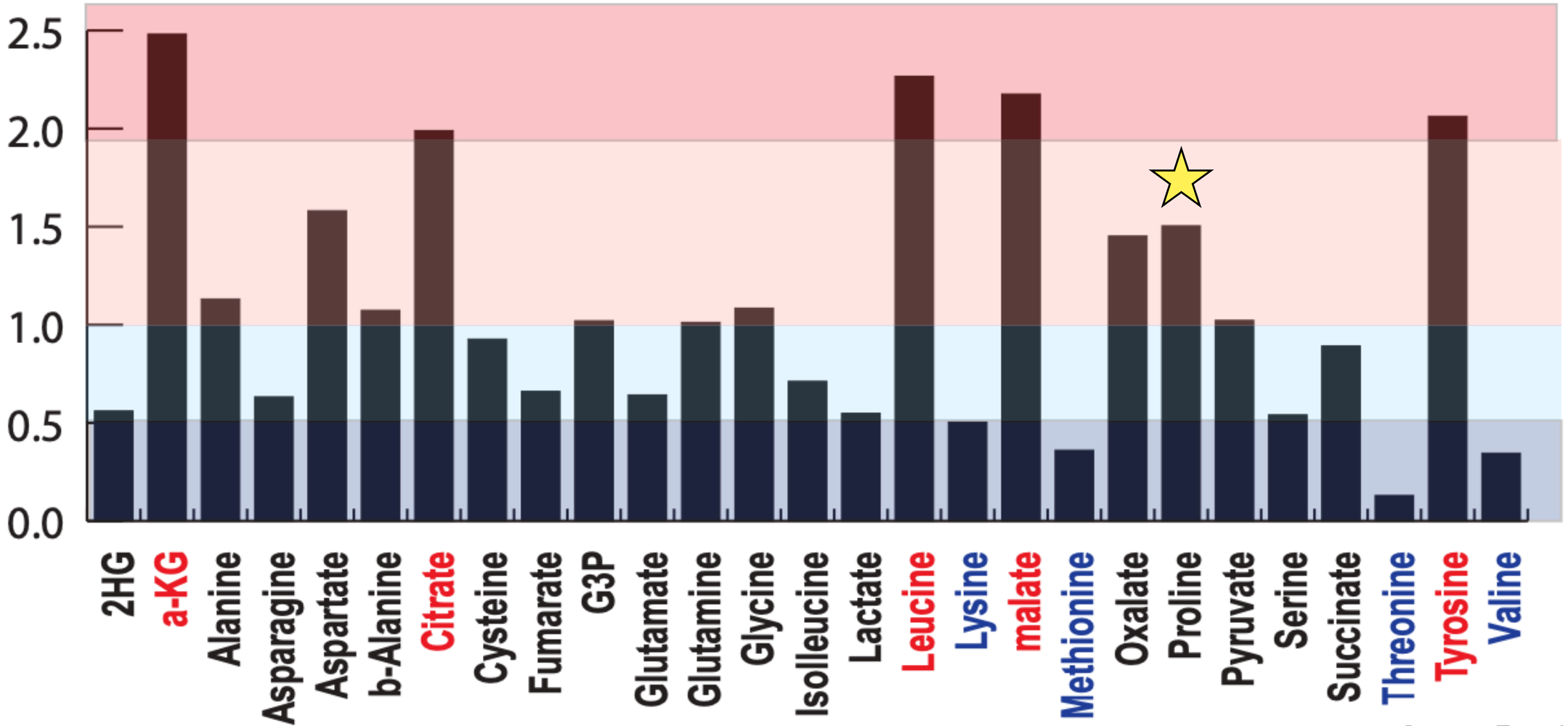


Liang et al., 2013; Zarattini & Forlani 2017

Precision Toxicology, unpublished

Metabolites show sex-bias

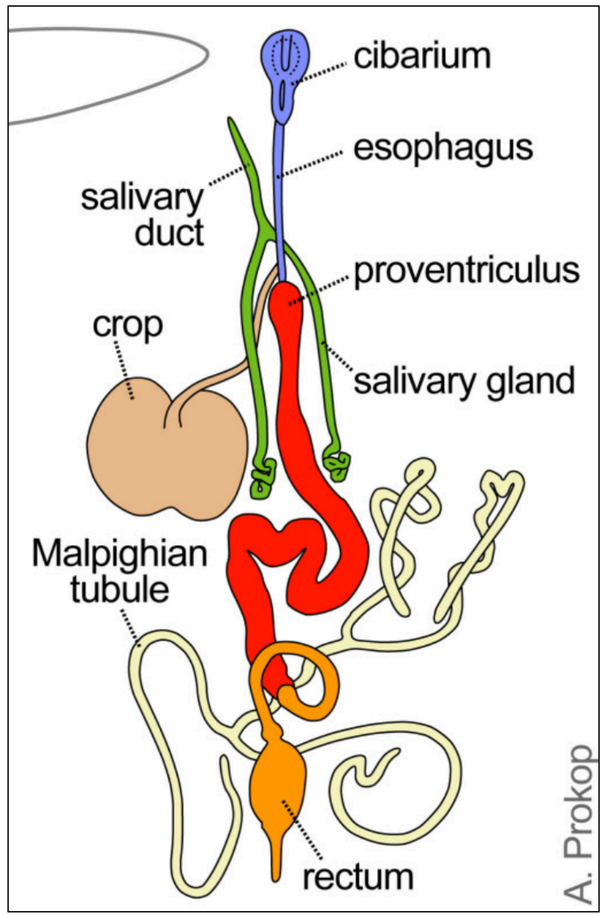
Including 50% more Proline in females (preliminary)

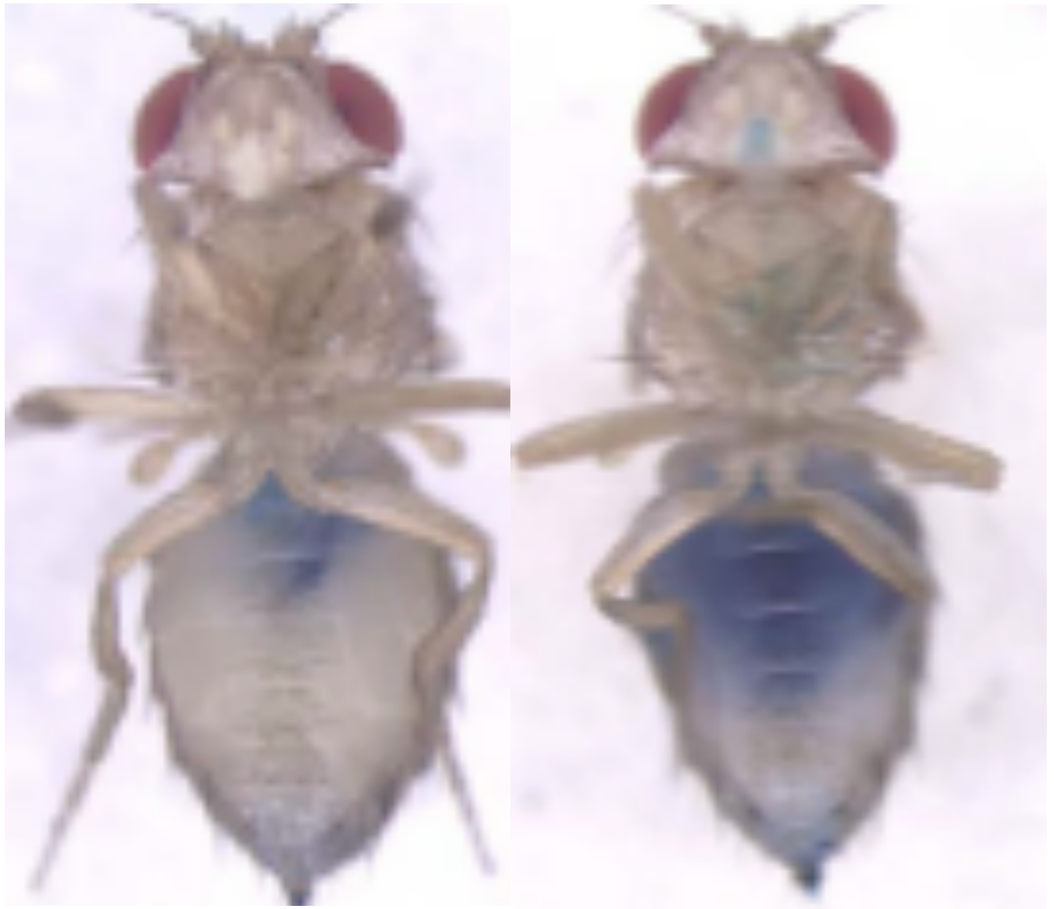


Precision Toxicology, unpublished

Even if they don’t die, there’s a phenotype

Retained food in stomach (crop). then vomit (regurgitate).

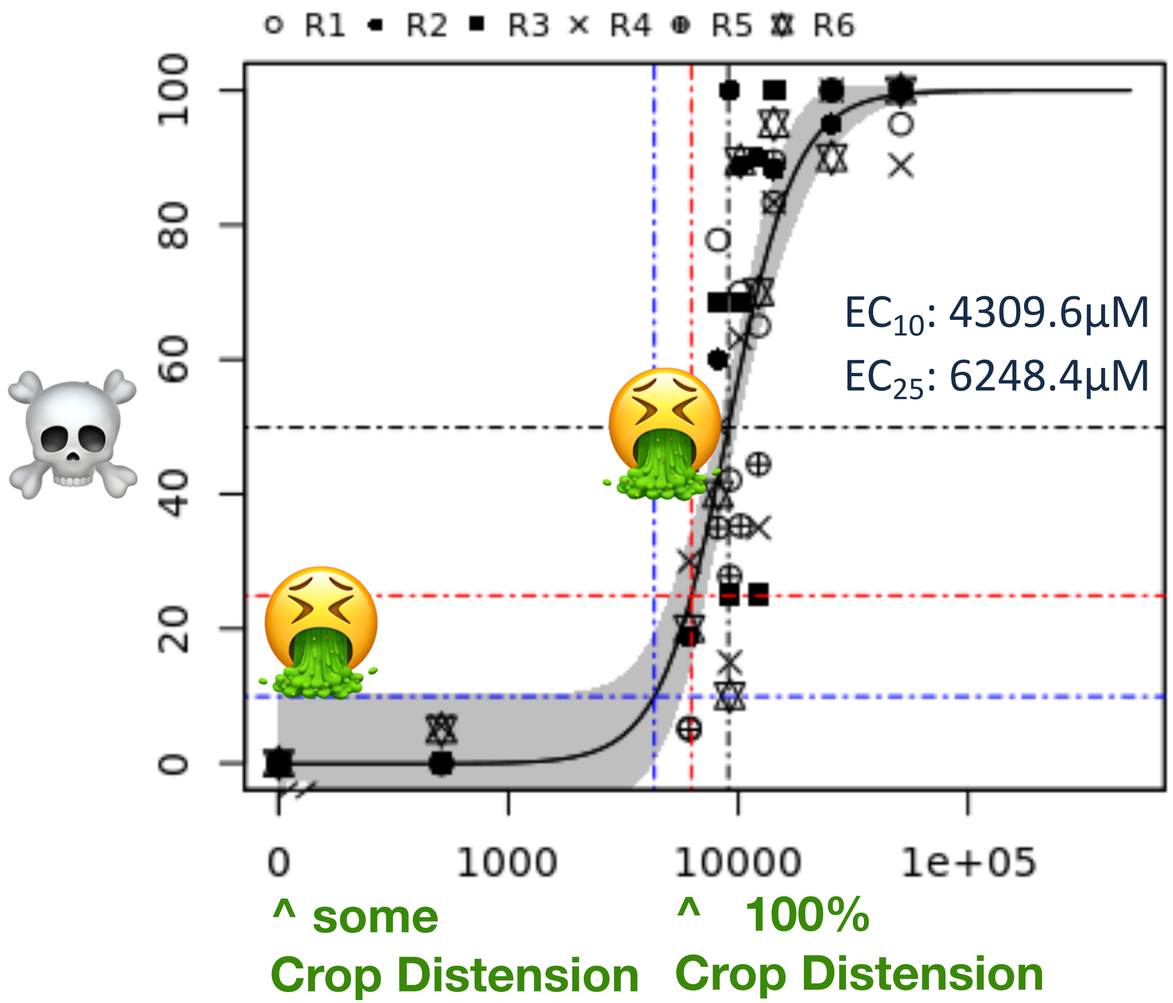


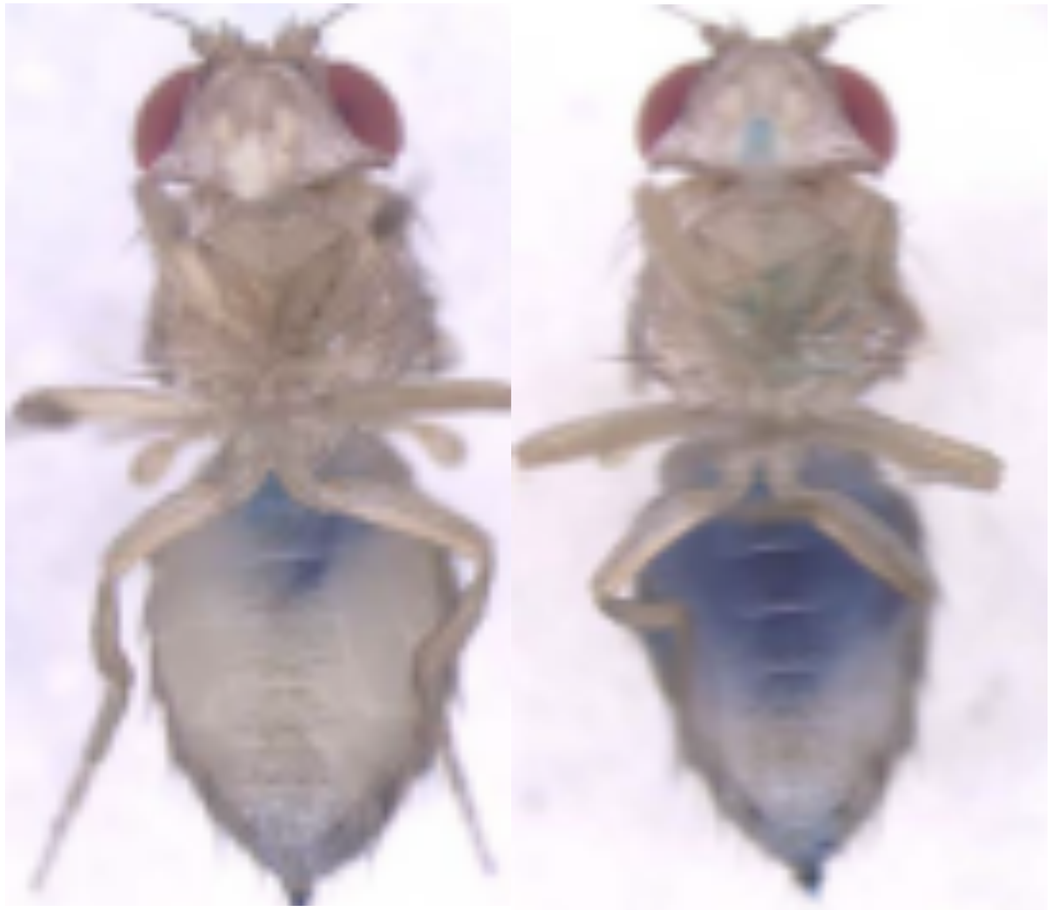


Blue food, 0% DMSO **Blue food, 2% DMSO**

Precision Toxicology, unpublished

Crop retention response often precedes death

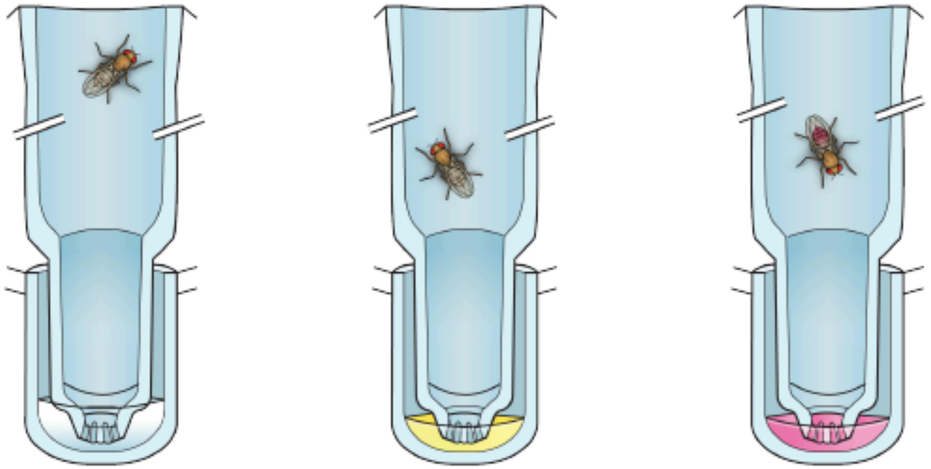




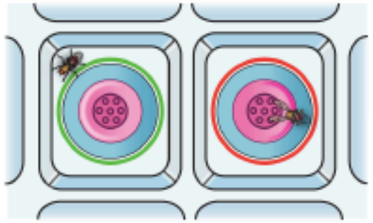
Precision Toxicology, unpublished

Ministration and Industrialization
Designing Flexible Plate Based Systems

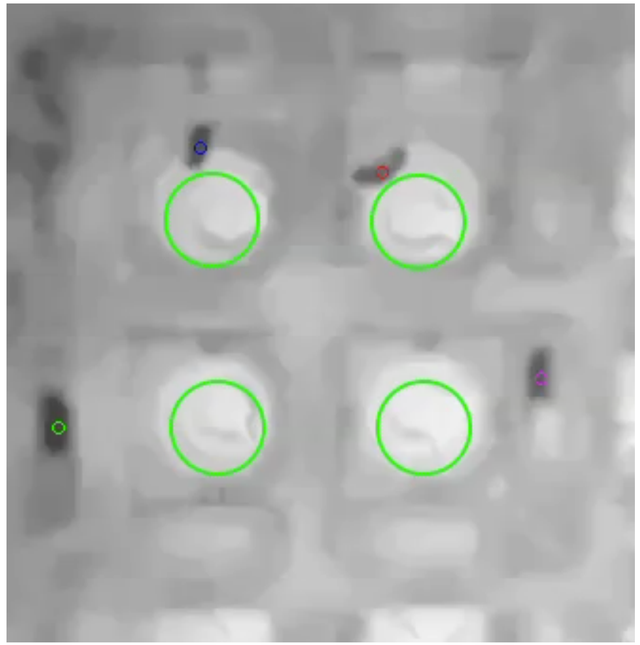
A. Treatment (acute bolus, chronic exposure, combinations)



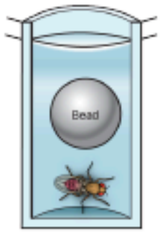
B. Monitoring



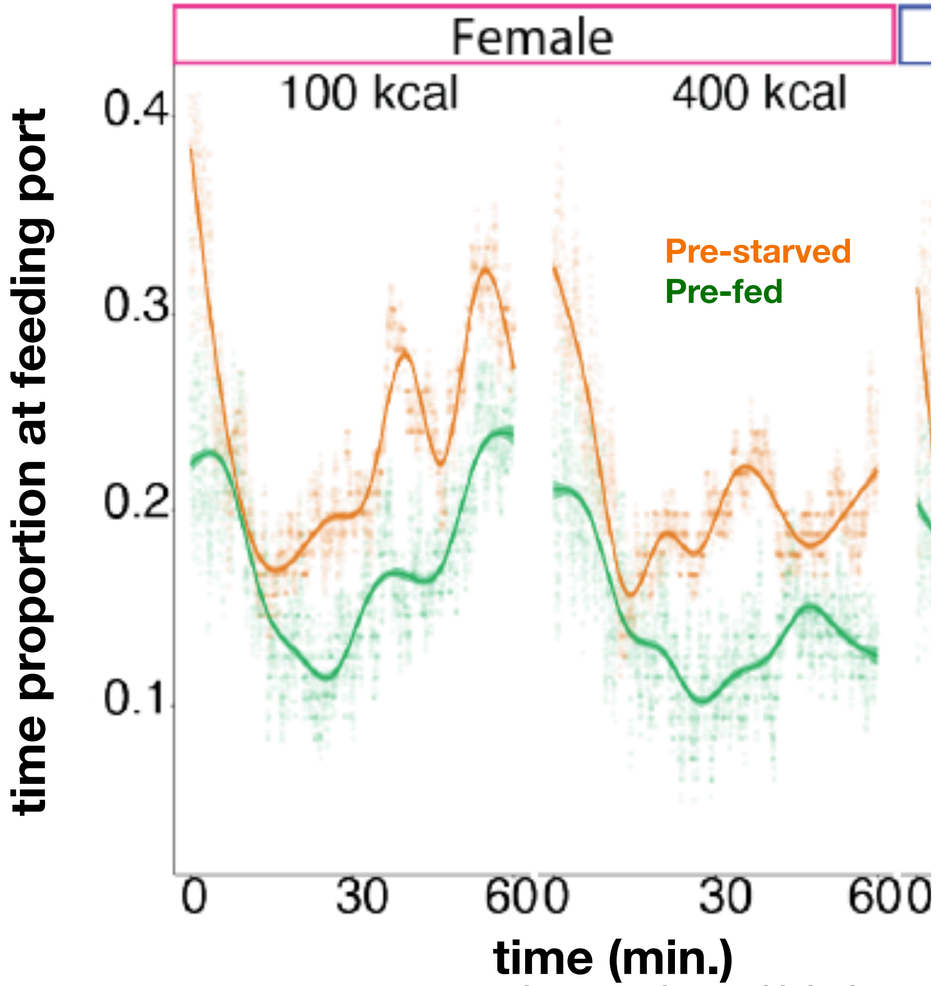
- Distance travel
- Food interactions
- Fly activity



C. Maceration



- Biochemical assays
- Transcriptomics
- Proteomics
- Microbiome
- Metabolism...



Jaime et al., unpublished

My Discussion Points

- Genetic and Biochemical Pathways cut across the NAMs. Make sure to capitalize.
- Data mining requires data. Lot's of data. Lot's of organized data.

  FAIR (find, access, interoperate, and reuse).
- More diversity of cell types and organoids. More single cell genomics.
- Physiology and complex behavior requires whole organisms. Full stop.
- NAMs must scale. This needs to be an industry, not a research program.

Sharvani Mahadevaraju

Leif Benner

Pradeep Bhaskar

Teresa Przytycka

Soumitra Pal

Jillian Gomez

Ibraheem Farooq

Sex in the FCA: Michelle Arbeitman, Michelle Bland, **Sumatra Pal**, **Teresa Przytycka**, **Liz Rideout, Geo Vogler,** Marianna Wolfner

Hongjie Li [#1,2,3], Jasper Janssens [#4,5], Maxime De Waegeneer [4,5], Sai Saroja Kolluru [6,7,8], Kristofer Davie [4], Vincent Gardeux [9,10], Wouter Saelens [9,10], Fabrice P A David [9,10,11], Maria Brbić [8,12], Katina Spanier [4,5], Jure Leskovec [8,12], Colleen N McLaughlin [1], Qijing Xie [1], Robert C Jones [6,7,8], Katja Brueckner [13], Jiwon Shim [14], Sudhir Gopal Tattikota [15,16], Frank Schnorrer [17], Katja Rust [18,19], Todd G Nystul [19], Zita Carvalho-Santos [20], Carlos Ribeiro [20], Soumitra Pal [21], Sharvani Mahadevaraju [22], Teresa M Przytycka [21], Aaron M Allen [23], Stephen F Goodwin [23], Cameron W Berry [24], Margaret T Fuller [24], Helen White-Cooper [25], Erika L Matunis [26], Stephen DiNardo [27,28], Anthony Gaienza [29], Lucy Erin O'Brien [29], Julian A T Dow [30], FCA Consortium§; Heinrich Jasper [31], Brian Oliver [22], Norbert Perrimon [15,16], Bart Deplancke [9,10], Stephen R Quake [6,7,8], Liqun Luo [1], Stein Aerts [4,5], Devika Agarwal [32], Yasir Ahmed-Braimah [33], Michelle Arbeitman [34], Majd M Ariss [35], Jordan Augsburger [13], Kumar Ayush [12], Catherine C Baker [36], Torsten Banisch [37], Katja Birker [38], Rolf Bodmer [38], Benjamin Bolival [36], Susanna E Brantley [36], Julie A Brill [39,40], Nora C Brown [41], Norene A Buehner [41], Xiaoyu Tracy Cai [31], Rita Cardoso-Figueiredo [20], Fernando Casares [42], Amy Chang [43], Thomas R Clandinin [44], Sheela Crasta [6,7,8], Claude Desplan [45], Angela M Detweiler [8], Darshan B Dhakan [20], Erika Donà [46], Stefanie Engert [43], Swann Floc'hlay [4,5], Nancy George [47], Amanda J González-Segarra [43], Andrew K Groves [3,48], Samantha Gumbin [29], Yanmeng Guo [49,50], Devon E Harris [36], Yael Heifetz [51], Stephen L Holtz [52], Felix Horns [53], Bruno Hudry [54], Ruei-Jiun Hung [15], Yuh Nung Jan [49,50], Jacob S Jaszczak [49,50], Gregory S X E Jefferis [46], Jim Karkanias [8], Timothy L Karr [55], Nadja Sandra Katheder [31], James Kezos [38], Anna A Kim [29,56,57], Seung K Kim [24,58], Lutz Kockel [24], Nikolaos Konstantinides [59], Thomas B Kornberg [60], Henry M Krause [61], Andrew Thomas Labott [29], Meghan Laturney [43], Ruth Lehmann [62], Sarah Leinwand [43], Jiefu Li [1], Joshua Shing Shun Li [15], Kai Li [49,50], Ke Li [49,50], Liying Li [49,50], Tun Li [49,50], Maria Litovchenko [9,10], Han-Hsuan Liu [49,50], Yifang Liu [15], Tzu-Chiao Lu [2], Jonathan Manning [47], Anjeli Mase [13], Mikaela Matera-Vatnick [41], Neuza Reis Matias [36], Caitlin E McDonough-Goldstein [63,64], Aaron McGeever [8], Alex D McLachlan [65], Paola Moreno-Roman [29], Norma Neff [8], Megan Neville [23], Sang Ngo [29], Tanja Nielsen [38], Caitlin E O'Brien [49,50], David Osumi-Sutherland [66], Mehmet Neset Özel [67], Irene Papatheodorou [47], Maja Petkovic [49,50], Clare Pilgrim [68], Angela Oliveira Pisco [8], Carolina Reisenman [43], Erin Nicole Sanders [29], Gilberto Dos Santos [69], Kristin Scott [43], Aparna Sherlekar [29], Philip Shiu [43], David Sims [32], Rene V Sit [8], Maija Slaidina [70], Harold E Smith [71], Gabriella Sterne [43], Yu-Han Su [29], Daniel Sutton [72], Marco Tamayo [38], Michelle Tan [8], Ibrahim Tastekin [20], Christoph Treiber [73], David Vacek [1], Georg Vogler [38], Scott Waddell [73], Wanpeng Wang [60], Rachel I Wilson [52], Mariana F Wolfner [41], Yiu-Cheung E Wong [36], Anthony Xie [1], Jun Xu [15], Shinya Yamamoto [3,74], Jia Yan [8], Zepeng Yao [43], Kazuki Yoda [29], Ruijun Zhu [49,50], Robert P Zinzen [75]

Fly Cell Atlas

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	Marina RUIZ	Aurelia BOIGE	Renpeng DING
	Giovanni ASOLE	Leonie MUELLER	Filips OLESKOVS
			Nadezda CISTJAKOVA

Flies & Toxicology: Sarah Anderson, Pradeep Bhaskar, Jesse Cushman, **Ibraheem Farooq**, Alejandra Flores, Marcial Garmendia-Cedillos, Susan Harbison, **Jessica Holsopple**, **Maria Jaime**, **Sean Karott**, **Thom Kaufman**, Jonathan Krynitsky, **Will Ludington**, Sharvani Mahadevaraju, Daniel Martinez, Tom Pohida, **Ghadi Salem**, **Shannon Smoot**, **Jason Tennessen**

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