An *In Vitro* Human Population Model for Screening Environmental Chemicals for the Cardiotoxicity Hazard

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MOLECULAR DEVICES

Cellular Dynamics International

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Why Are We Interested in Cardiotoxicity?

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- Cardiovascular disease remains the leading cause of morbidity and mortality in the United States – a complex interplay of genetic and environmental factors[1]

PHARMACEUTICALS

- Known major safety liability[2]
- Leading cause of drug failure and reported adverse events[2]
- Inter-individual variability is responsible for many AEs in susceptible individuals
  - Important but poorly predicted

ENVIRONMENTAL CHEMICALS

- Neglected phenotype – no cardiotoxicity tests required
- 35% ischaemic heart disease burden attributable to environmental risk[3]
- Environmental chemicals have demonstrated the potential to affect human cardiomyocytes *in vitro*[4]

[1]Bhatnagar, 2017 (PMID: 28684622); [2]Ferri *et al.*, 2013 (PMID: 23507039); [3]Prüss-Ustün *et al.*, 2017 (PMID: 27621336); [4]Sirenko *et al.*, 2017 (PMID: 28259702)

Research Objective

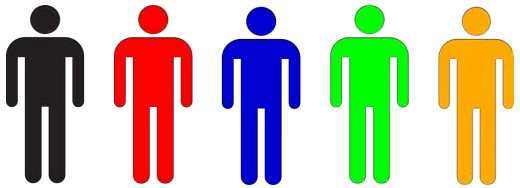
- There is a widespread lack of information regarding the human health cardiotoxicity hazard of environmental chemicals
  - Variability in cardiotoxicity hazard is another critical factor
- We need a biologically-relevant, high-throughput method for screening the potential cardiotoxicity hazard and variability of chemicals

Hypothesis:

A population of iPSC-derived cardiomyocytes can be used to assess the cardiotoxicity hazard of environmental chemicals.

Approach and Study Design

5 individual, “healthy” human donors



iPSC reprogramming and differentiation

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Screening of >1000 diverse chemicals

Pharmaceuticals

Pesticides

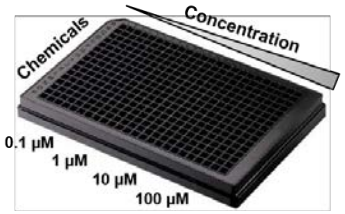
Industrial chemicals

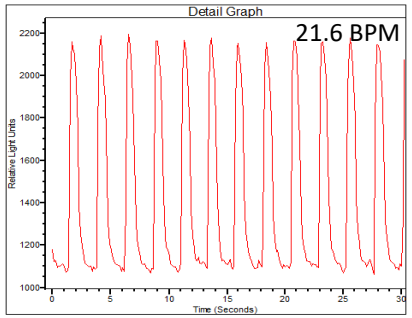
Flame retardants

Plastics, PAHs

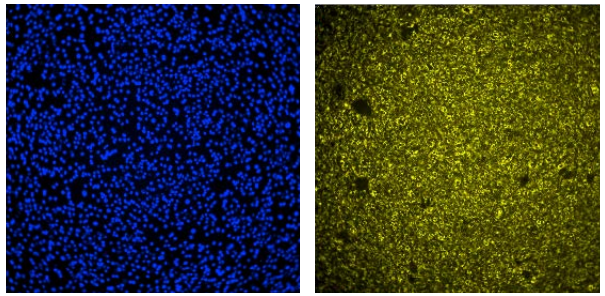
Food additives, dyes

Functional Cardiophysiology
[Ca^{2+} Flux Monitoring]



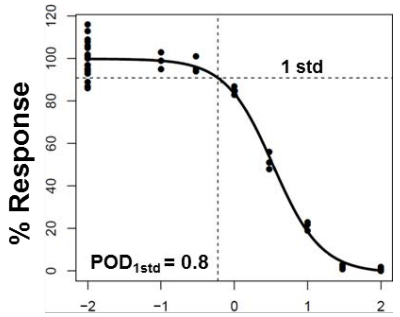


Cellular/Mitochondrial Toxicity
[High-Content Imaging]



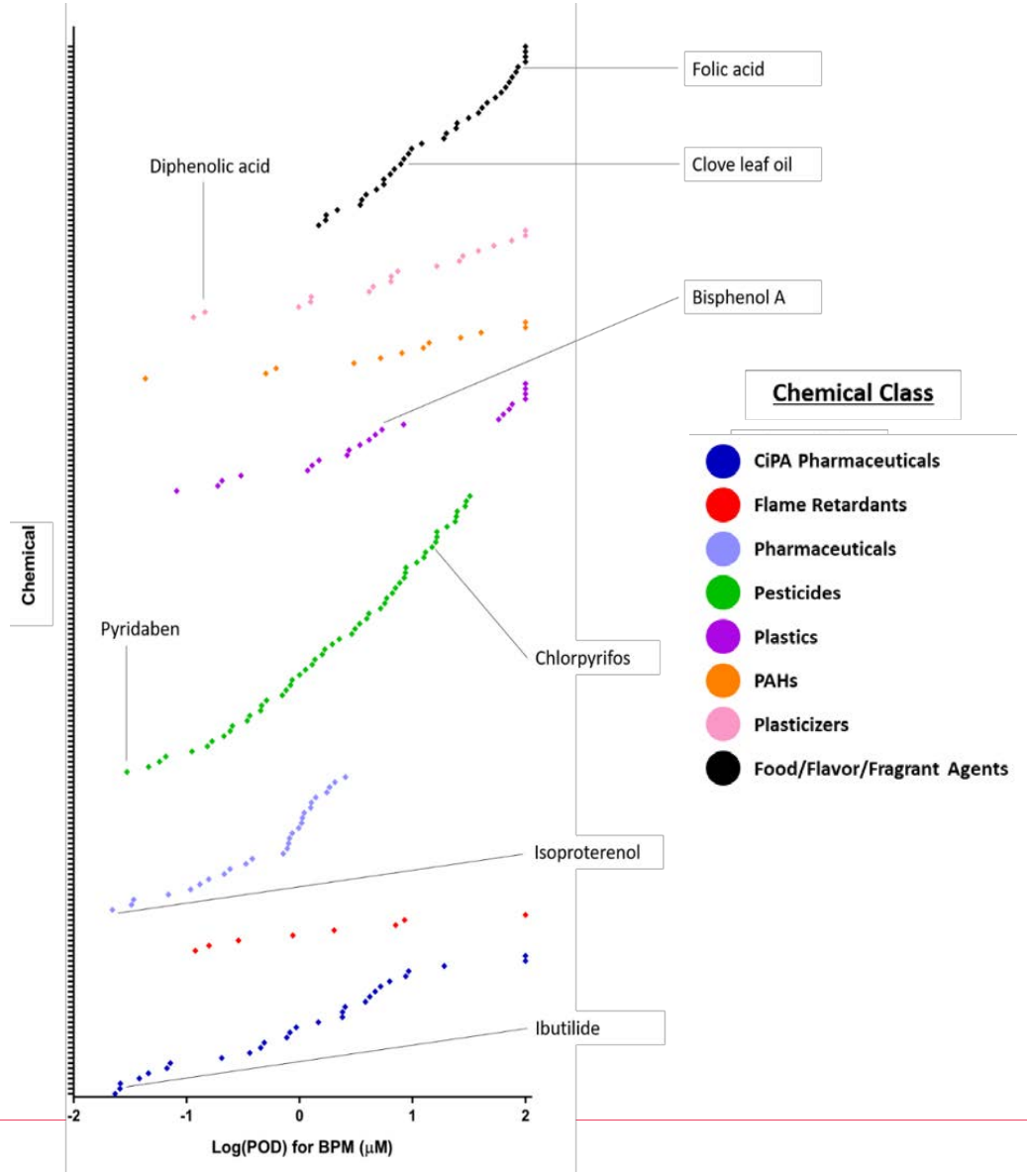
9 cardiophysiologic and cytotoxicity phenotypes

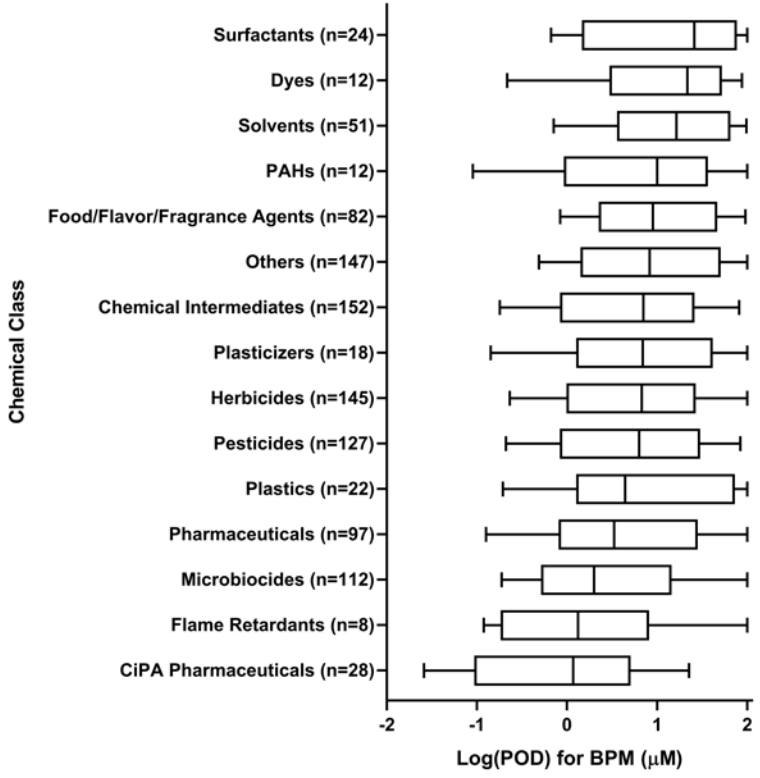
Dose-Response Profiling
[Quantitative POD values]



- **Characterize both the cardiotoxicity hazard and variability of environmental chemicals**
- Rank and group chemicals based on their bioactivity profiles using ToxPi
- Synthesize *in vitro*-derived toxicity values with *in vivo* exposure estimates to calculate MOEs

Variability in Cardiotoxicity Hazard





- Observable chemical-to-chemical variation in potency (and degree of population variability)
- Various environmental chemicals affect beating parameters

Conclusions

- Various environmental chemicals affect the beating parameters of iPSC-derived cardiomyocytes, with varied potencies and degrees of population variability

- This research demonstrates the feasibility of using an *in vitro* human population model to quantitatively assess both potential cardiotoxicity hazard and variability

  - Attractive for performing rapid, high-throughput screening of chemicals lacking adequate cardiotoxicity data

Ultimately, this research provides an innovative way to characterize the human health cardiotoxicity hazard of environmental chemicals.