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PREDART: Prediction of human developmental and reproductive toxicity through non-mammalian assays

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Background

- Current regulatory assessment of fertility and potential effects of chemicals on the developing foetus

- Consequences if a compound is found to be toxic to reproduction and/or development

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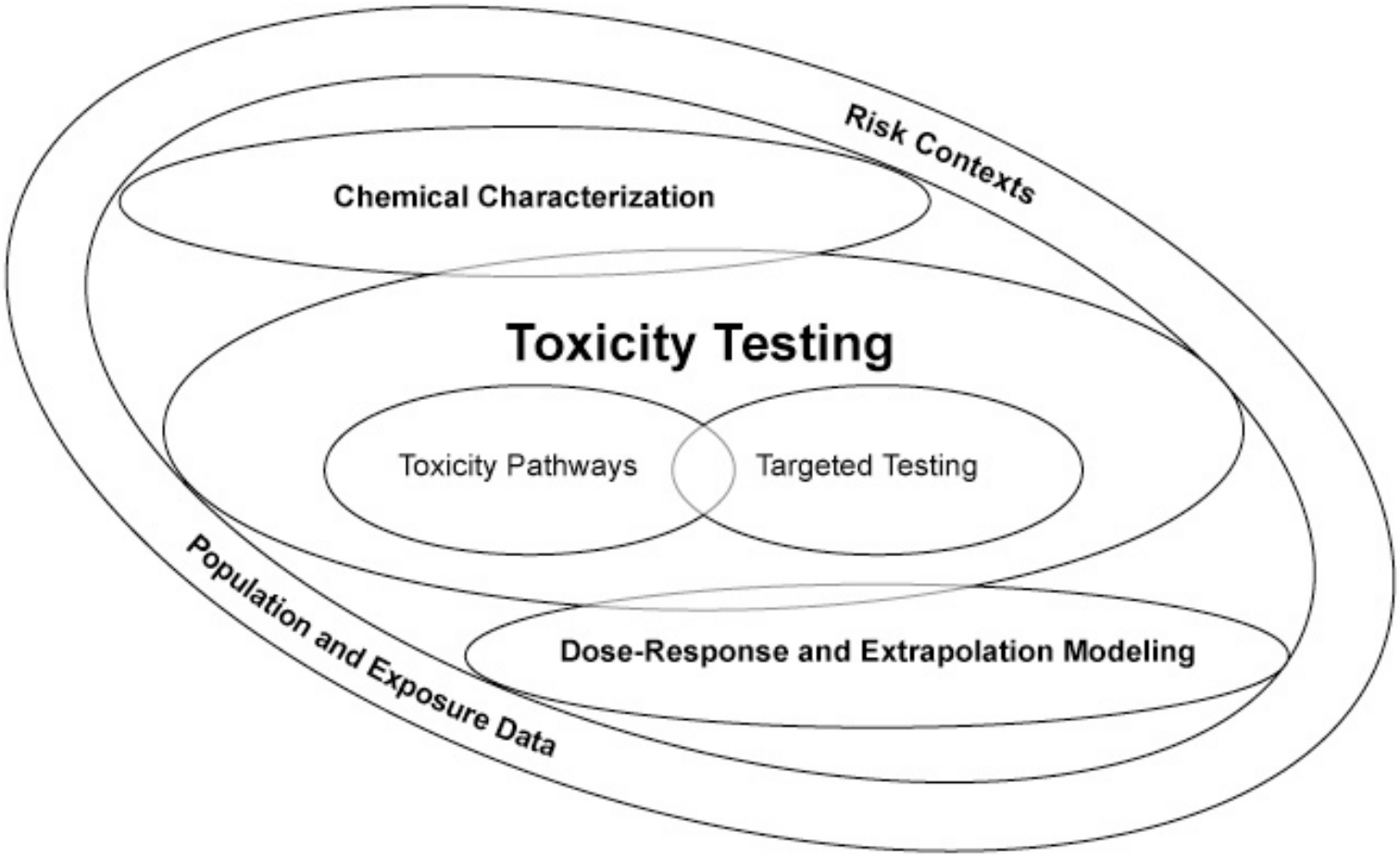
New Toxicology Paradigm



National Academy of Sciences – "Toxicity Testing in the 21st Century: A Vision and a Strategy"

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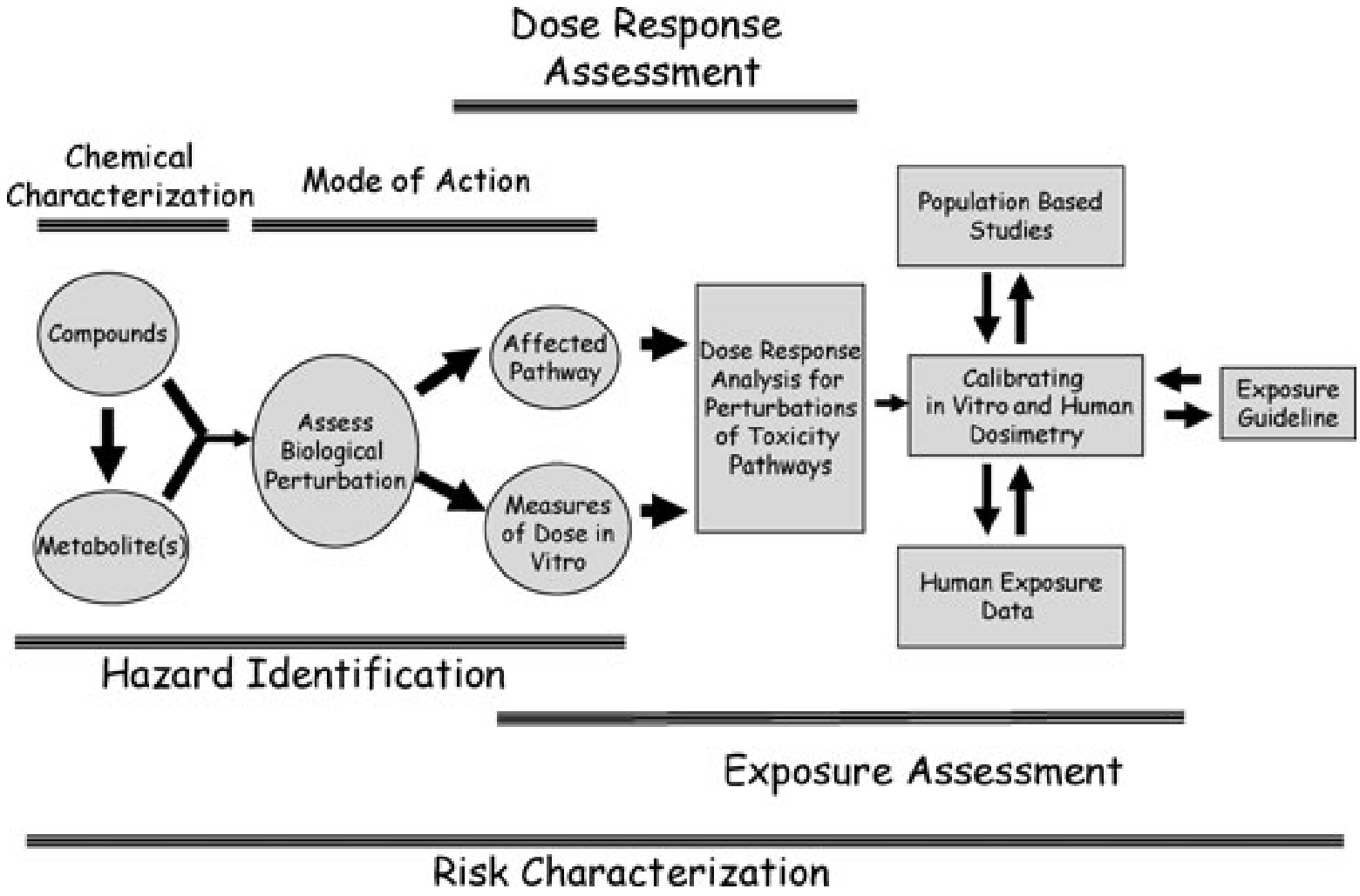
TOX21 for Risk Assessment



Alternative assays for reproductive/developmental toxicity

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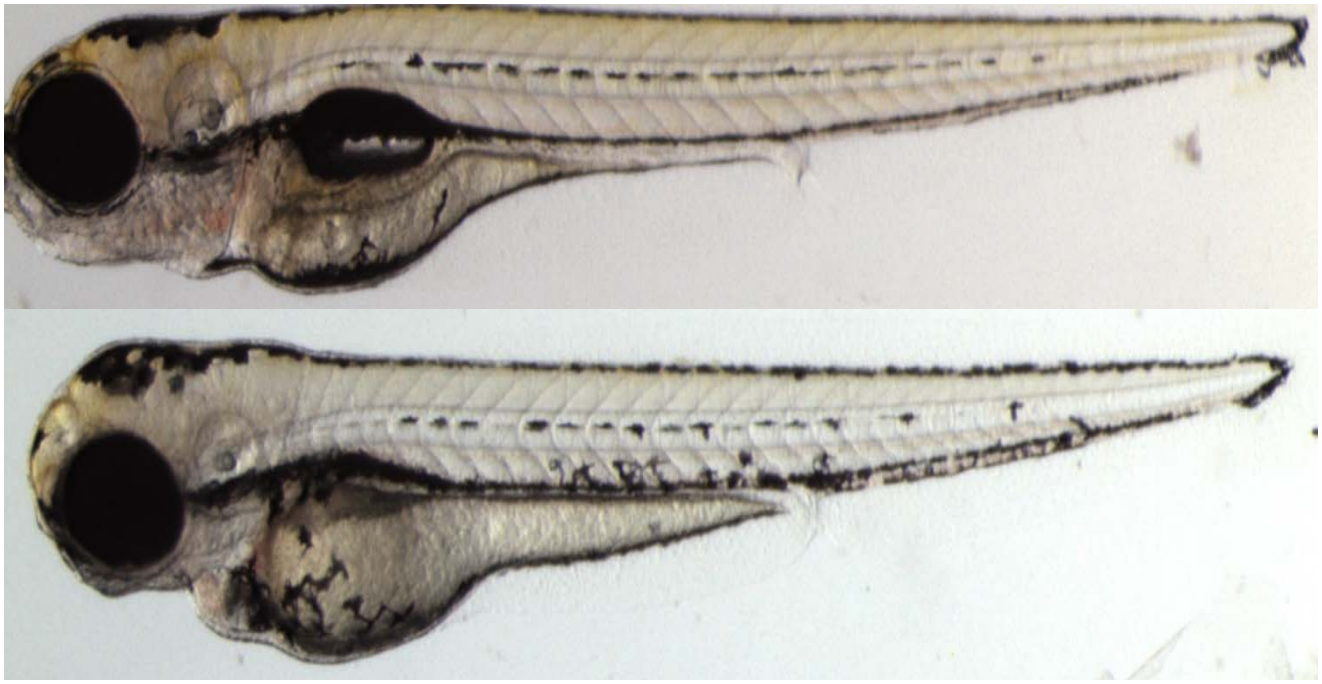
Zebra fish



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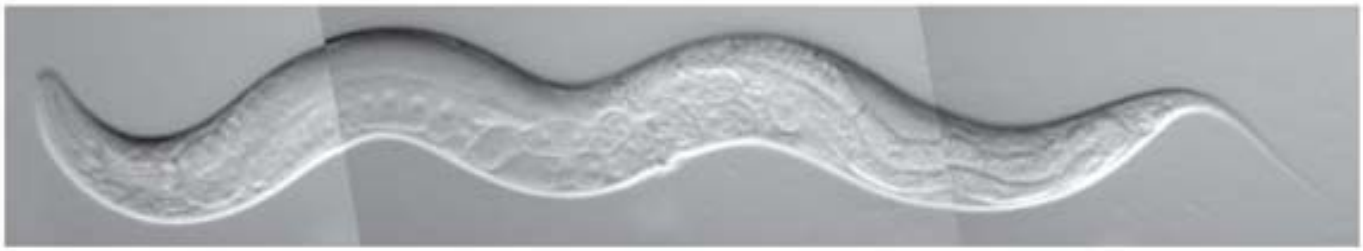
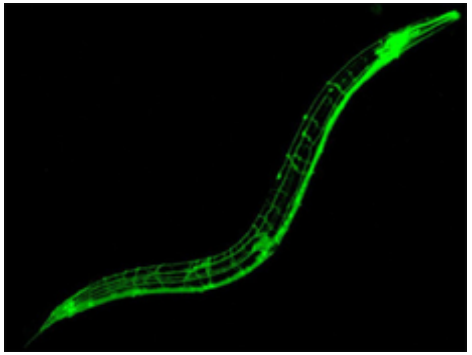
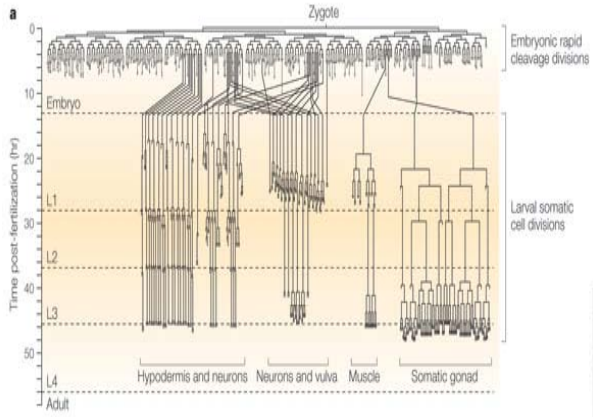
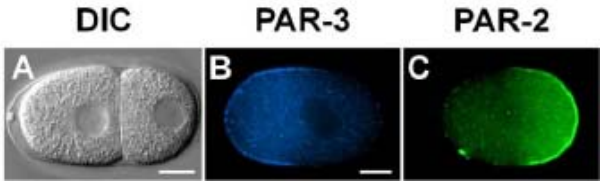
Caenorhabditis elegans



Developmental fate of
every cell mapped out







Transparent body and egg assist imaging

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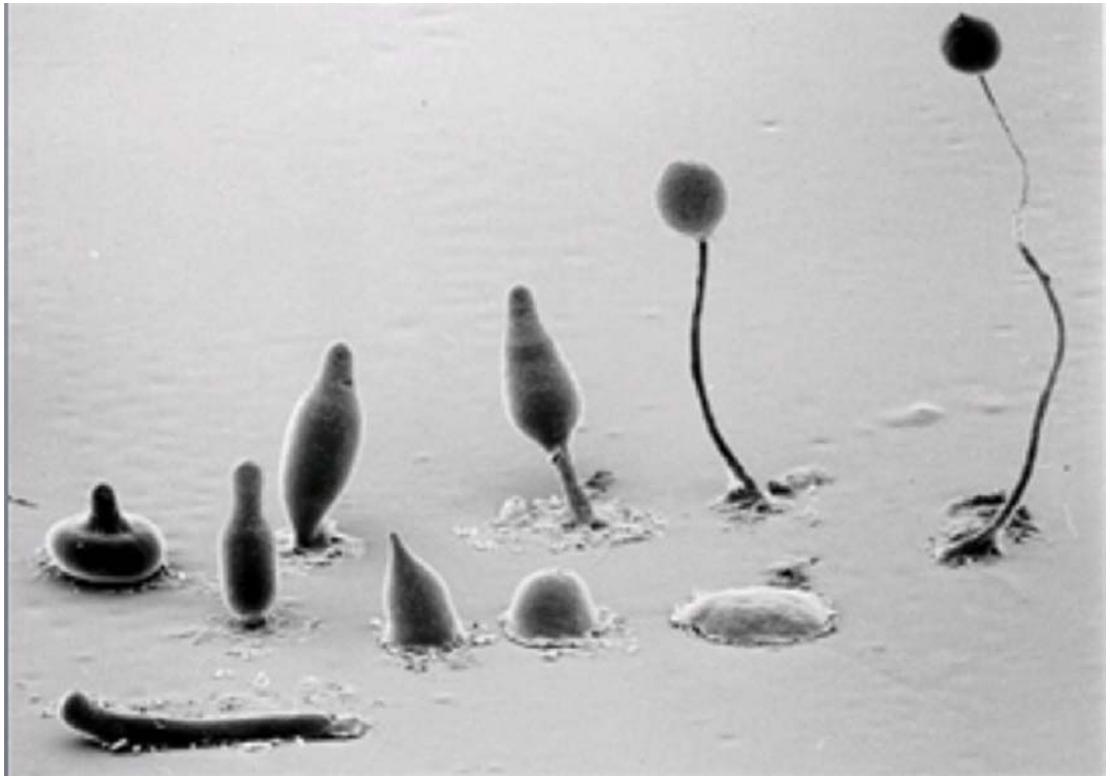
Dictyostelium (slime mold)



Fruiting bodies

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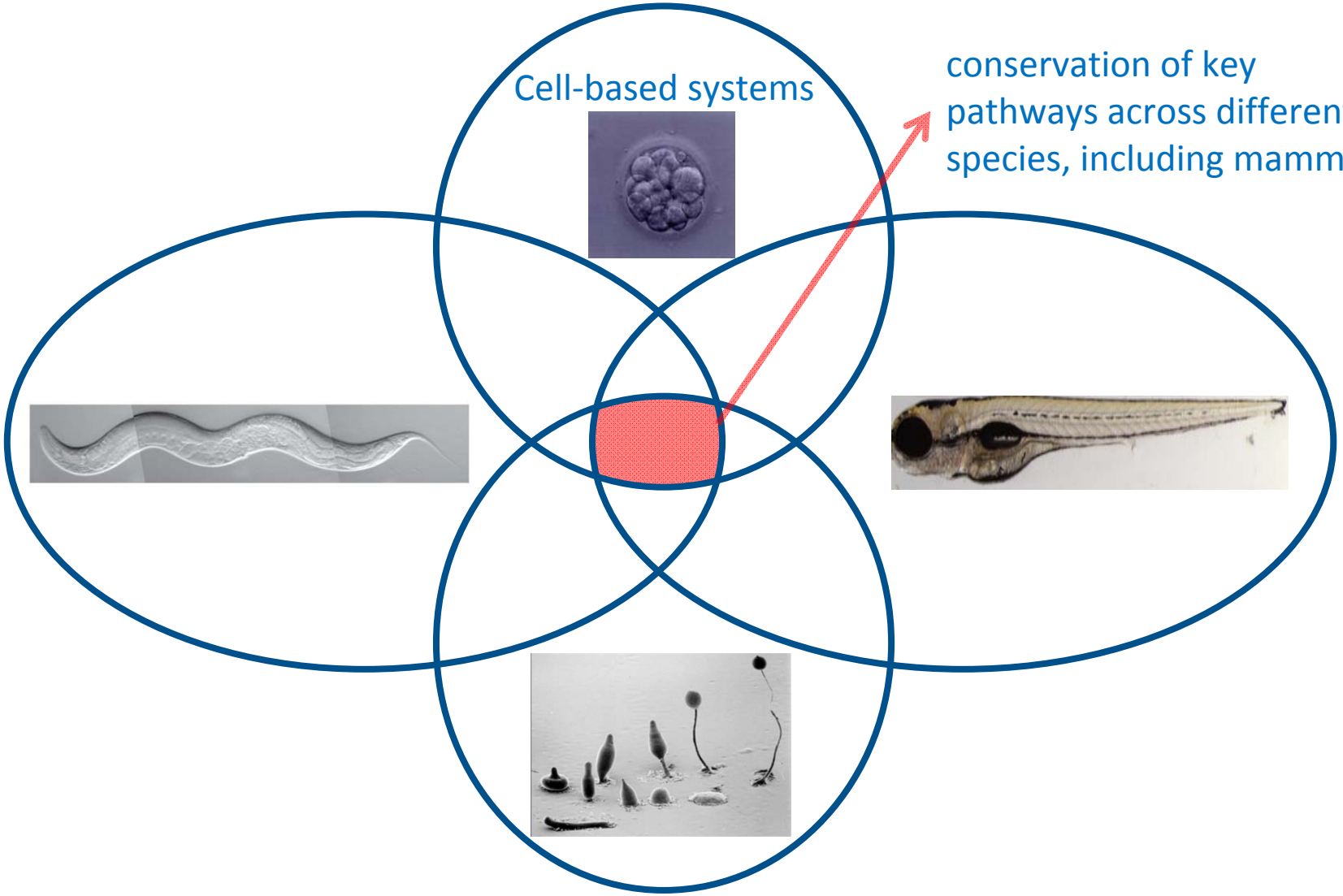
Key to Success



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Ultimate goal

- Practical, commercial solutions, including an integration of the available systems
- Understanding of exposure concentrations in the test systems versus those in rats/rabbits and humans
- Adequate assessment of dose-response to enable the integrated test system to be used for risk assessment

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Phase 1

- Exploration of key developmental pathways
- Overlay the information on key developmental pathways from the different test systems and identify common denominators
- Identify conserved pathways across the phyla which could be exploited as surrogate markers for mammalian developmental toxicity potential

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Our contribution to Phase 1

- Knowledge sharing on experiences with non-mammalian assays and substance-testing
- Discussion on an initial compound set and appropriate existing in vivo data for comparison
- Guidance on key industry requirements for model development and incorporation into existing testing strategies

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Phase 2

- Using the knowledge gained from Phase 1, begin to explore perturbations of these key conserved pathways, and their association with developmental perturbations
- Comparison of findings with genomic and other data from existing mammalian studies
- Assessment of compound uptake by non-mammalian systems in relation to physico-chemical properties;
- Determination of the applicability domain (i.e. the types of chemical structures, physicochemical properties and mechanisms of action for which the model can make reliable predictions).
- For physico-chemical properties Lipinski and Tice rules need to apply (Delaney *et al*. 2006; Lipinski 1997, Tice 2001)
- Transfer to a stable medium-throughput system with commercial potential
- **Key success criteria are reproducibility, robustness and reliability**

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Our contribution to Phase 2

- Provision of compounds
- Continued knowledge sharing, including outputs from test systems

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Hints and tips

- Focus on the abilities of your test system
- Find partners with supplemental expertise
- Focus on commercial application as the ultimate goal: KIS (KEEP IT SIMPLE!)