**ETS Symposium – Molecular aspects of embryology and teratology**

**Gene regulatory networks and the underlying biology of developmental toxicity**

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Embryonic cells are specified by large-scale networks of functionally linked regulatory genes. Knowledge of the relevant gene regulatory networks is essential for understanding phenotypic heterogeneity that emerges from disruption of molecular functions, cellular processes or signaling pathways. Cell-based screening assays and genomic technologies have now produced extensive amounts of molecular and cellular data that capture pathway-level responses to chemical perturbation. A compendium of biological signatures mined from US EPA's ToxCast™ *in vitro* assay collection has been mapped to specific endpoints of *in vivo* prenatal developmental toxicity studies using EPA's Toxicity Reference Database (ToxRefDB). An initial evaluation of ~300 environmental chemicals across ~500 *in vitro* assays returned well-over 400 significant associations to developmental endpoints. These associations included 75-80 biological pathways, posing the challenge of fitting together genes, proteins, and metabolites in these pathways into cellular networks. EPA's new Virtual Embryo project (v-Embryo™) is providing a framework to build and analyze network-level inferences using cell-based computational models of morphogenesis that accept data on biological pathways, together with relevant knowledge of developing systems. By simulating dysmorphogenesis *in silico*, these models may be used in future efforts to sweep diverse biological pathways, signaling networks, and morphogenetic processes to understand mechanisms and predict developmental toxicities. [*This work has been reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy*].