Computational Embryology and Predictive Toxicology of Hypospadias

M.C.K. Leung[1], N.S. Sipes[1], N.C. Baker[2], B.K. Ahir[1], C.J. Wolf[3], A.W. Seifert[4], M.S. Hutson[5], S.D. Perreault[3], R.M. Spencer[2], T.B. Knudsen[1]

[1] National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States; [2] Lockheed Martin, Research Triangle Park, NC, United States; [3] Reproductive Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States; [4] Department of Biology, University of Kentucky, Lexington, KY, United States; [5] Departments of Physics and Biological Sciences, Vanderbilt University, Nashville, United States

Hypospadias, one of the most common birth defects in human male infants, is a condition in which the urethral opening is misplaced along ventral aspect of the penis. We developed an Adverse Outcome Pathway (AOP) framework and computer simulation that describes the pathogenesis of hypospadias commencing with disruption of cell signaling and structural targets of the fetal testis and genital tubercle (GT) and followed by critical changes in cellular patterning during GT morphogenesis. We first utilized semi-automated literature mining to identify 511 PubMed hypospadias articles based on MeSH annotations with 'chemicals' (312 co-annotations with hypospadias, 157 of which were associated with toxicity or adverse effects) and 'proteins' (293 co-annotations with hypospadias). This information was used to develop an AOP framework linking potential molecular initiating events, altered cellular behaviors (proliferation, apoptosis, adhesion, differentiation, signaling protein elaboration, steroid hormone synthesis, tissue morphogenesis (invasion of preputial mesenchyme, septation of urethral plate endoderm, and integrity of cloacal ectoderm) and abnormal organogenesis (incomplete urethral tubulogenesis). We selected vinclozolin (hypospadias in rats at 96 mg/kg/day in ToxRefDB, AC50 = 0.307 µM for inhibition of the human androgen receptor binding in ToxCast) as a reference for proof-of-concept. A multicellular computer simulation model capable of rendering key events in GT development was built in CellDesigner for simulation using a cellular agent-based model (CompuCell3D.org) by incorporating key signals (e.g., SHH, FGF10, EphB2, and androgen) and cellular behaviors (e.g., selective adhesion, motility) to control urethral tubulogenesis. Overall, the AOP approach and computer simulation: 1) provided a platform for integrating available biological information to predictively model the complex pathogenesis of hypospadias; 2) enabled the generation of new research hypotheses; and, 3) contributed to better mechanistic understanding of this adverse developmental outcome. [*This abstract does not necessarily reflect official Agency policy*].