# Multiscale Systems Modeling of Male Reproductive Tract Defects: From Genes to Populations


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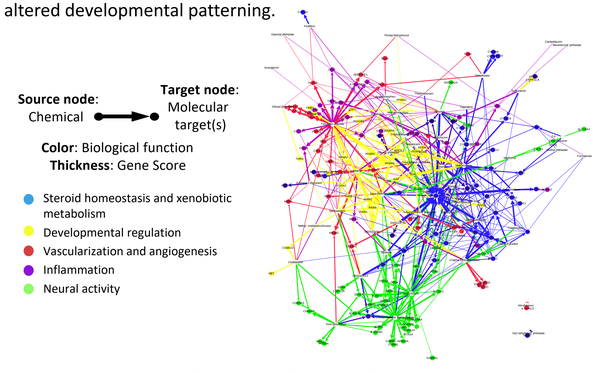
## Background

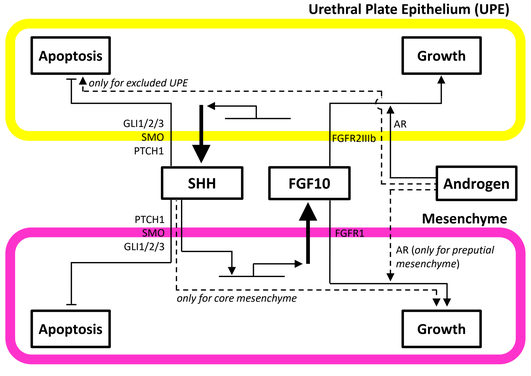
Experimental evidence and epidemiological findings suggest a common origin for several disorders of the male reproductive tract (hypogonadism, cryptorchidism, hypospadias, and germline cancers; *1*). The male developmental toxicity of 54 chemicals are reported in ToxRefDB, which is associated with 156 out of a total of 293 (53%) molecular targets in the ToxCastDB based on the screening results of 541 biochemical and cellular high-throughput assays (*2*). Such complexity calls for a computational approach to study embryogenesis as a system and the consequences of altered developmental patterning.

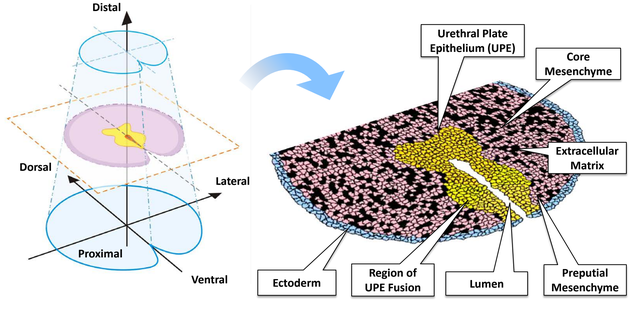



**GOAL**: The objective of this study is to build a multicellular agent-based model of genital tubercle (GT) development that simulates urethrogenesis from the sexually-indifferent urethral plate stage to urethral tube closure.

## Modeling genital tubercle (GT) development

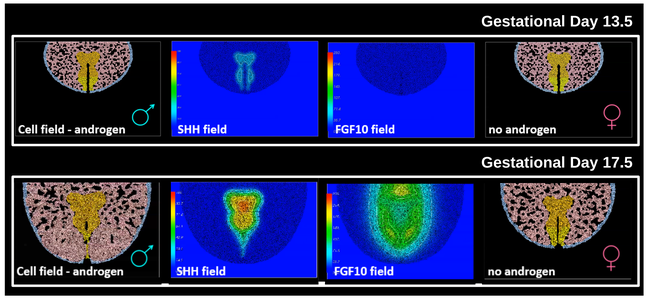
- GT development is Initially indifferent in male and female embryos (SHH, FGF10)
- Androgen signaling drives subsequent growth and development of the male GT
- Sensitive to genetic (e.g., SHH, FGFs, EHPB, TGFB pathways) and chemical (e.g., estrogenic or anti-androgenic) perturbation
- Ventral midline fusion is a critical event, leading to urethral closure in male fetuses
- Multicellular agent-based models provide the cell-level decision making in addition to patterning systems and extracellular gradients that drive individual cell behaviors and integrate them into a coordinated multicellular response (*3*).
- Spatially dynamic signals (e.g., SHH, FGF10, and androgen) were implemented in the model to address differential adhesion, cell motility, proliferation, and apoptosis.



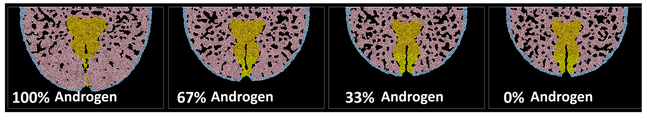




## Results of the modeling

- Urethral tube closure was the emergent property of the model that was linked to gender-specific rates of ventral mesenchymal proliferation and urethral plate endodermal apoptosis, both under control of androgen signaling.



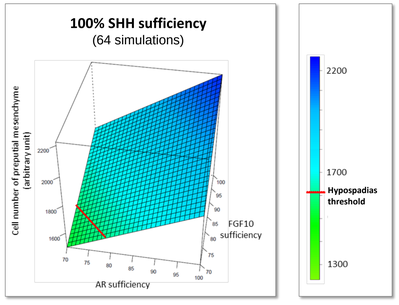

- Disruption of SHH, FGF10, or androgen signaling leads to urethral closure defects (e.g., hypospadias).




- Urethral tube closure was a stochastic event driven by UPE (contact, fusion apoptosis) and preputial mesenchyme (proliferation, condensation, migration).

| *Androgenization* (*n = 10 sims*) | *Phenotype (MCS 4000)* Septation | Fusion | Conden. | Closure Index |
|---|---|---|---|---|
| 100% | 6/10 | 8/10 | 10/10 | 0.80 |
| 67% | 2/10 | 5/10 | 10/10 | 0.57 |
| 33% | 0/10 | 4/10 | 0/10 | 0.13 |
| 0% | 0/10 | 2/10 | 0/10 | 0.07 |

## Model predictions




- Probability of urethral closure defects was predicted on minimal disruption of cell signaling pathways in combination
- The model predicted hypospadias could occur at 70% SHH, 70% FGF10 sufficiency, and a ≥5% reduction in AR sufficiency.

## Conclusion

- A multicellular agent-based model successfully simulated the interactions between some morphoregulatory, endocrine, and chemical influences during GT development.
- Further studies will simulate (a) additional dynamic signals identified in the chemical-target network (*2*), including estrogen and retinoic acid; and (b) population-level responses to reveal critical thresholds in teratogenesis for complex interactions between genetic (e.g., FGF10 polymorphism), environmental (e.g., androgen receptor disruption), and lifestyle (e.g., cholesterol deficiency for SHH) factors (*1*, *4*, *5*).

## References


(*1*) Skakkebæk *et al*., 2016, *Physiol. Rev.* 96:55-97; (*2*) Leung *et al*., 2015, *Environ. Health Perspect.* (advanced publication); (*3*) Leung *et al*. (submitted); (*4*) Carmichael *et al*., 2013, *J. Urol.* 190:1884-1892; (*5*) Jeong and McMahon, 2002, *J. Clin. Invest.* 110:591-596.