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Retinoid Review Project
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High-throughput screening (HTS) and modeling of the retinoid system

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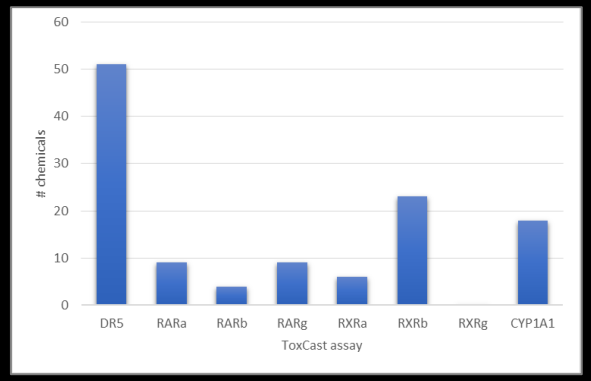
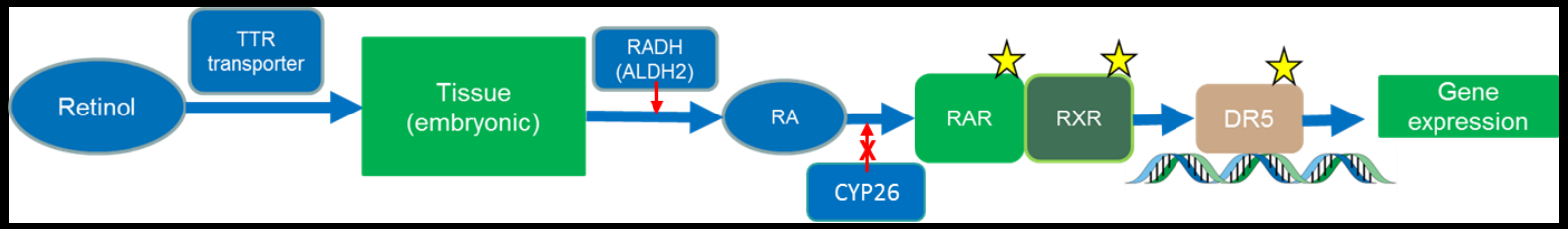
Retinoid system in ToxCast





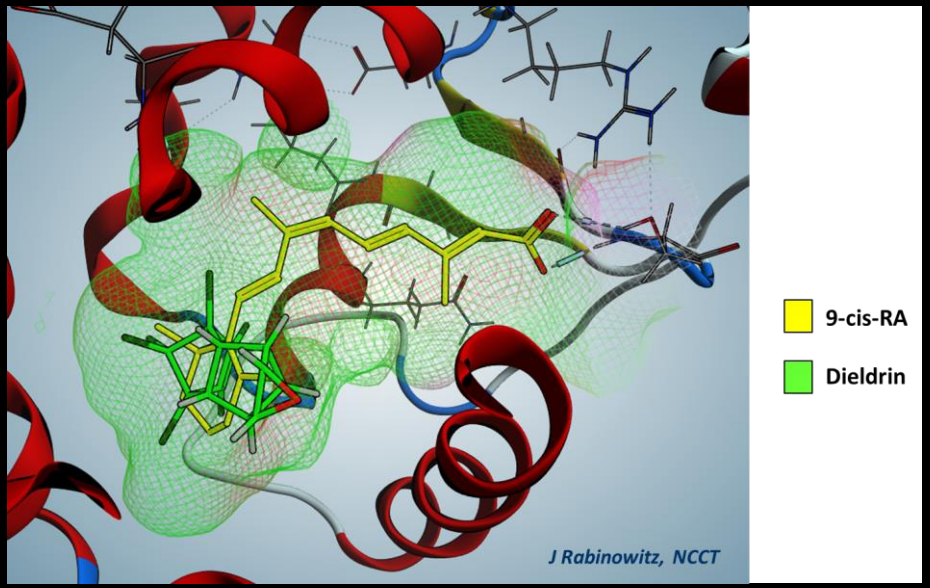
★ Rat DevTox models constructed from ToxCast-I [Sipes et al. 2011] and ToxCast-II models for male DevTox [Leung et al. 2016], cleft palate [Baker et al. in prep] and digital (paw) defects [Ahir et al. in prep].

★ ToxCast data available for 11 assays in the retinoid system for 1858 chemicals; lack HTS data on key enzymes for RA formation (EC: 1.2.1.36, RALDH) and breakdown (EC: 1.14.-.-, CYP26, but have CYP1A1 (EC:1.14.14.1)).

★ 89 chemicals tested (4.8%) registered an AC50 $\leq$ 2 µM in one or more of the 11 ToxCast assays interrogating the retinoid system.

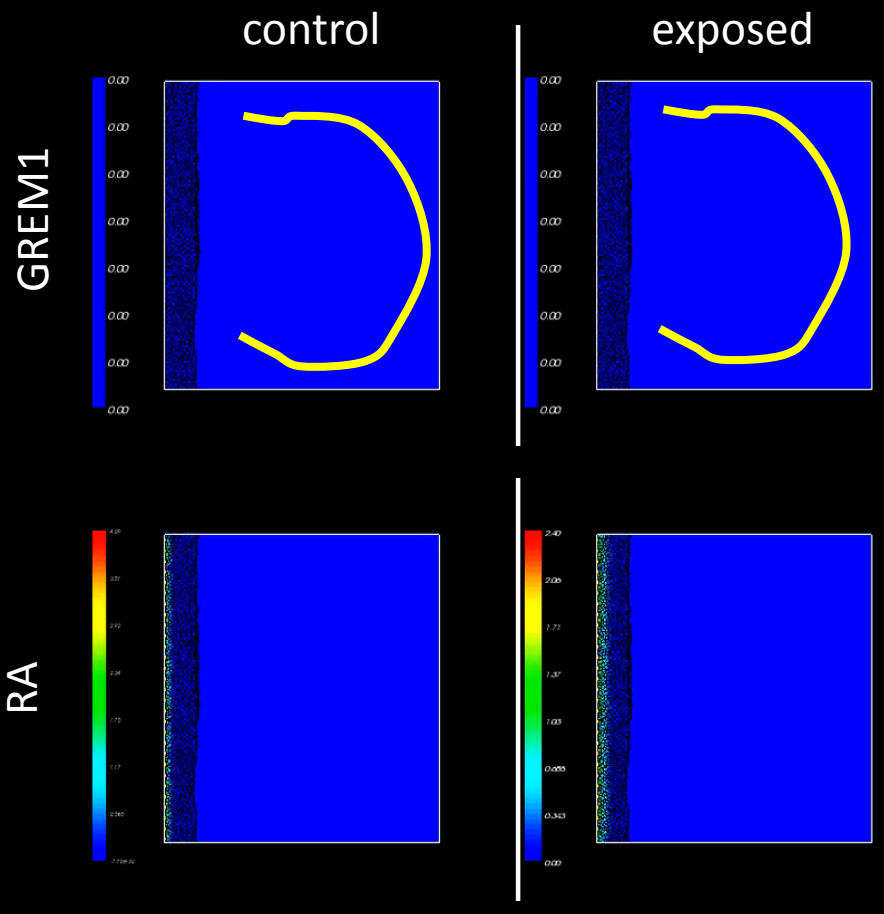
Dieldrin: weak activation of the retinoid system

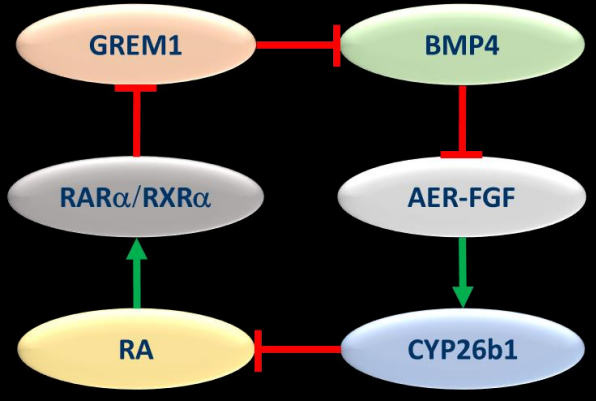
Assay Name	Hit Call	Top	Scaled Top	AC50	log AC50	Intended Target Family
BSK_CASM3C_SAA_up	ACTIVE	0.153	1.52	0.0406	-1.39	cell adhesion molecules
ATG_DR5_CIS_up	ACTIVE	0.690	1.17	0.579	-0.237	nuclear receptor
ATG_RARa_TRANS_up	ACTIVE	1.31	1.13	0.770	-0.113	nuclear receptor
ATG_ERE_CIS_up	ACTIVE	0.956	1.95	1.00	0.00200	nuclear receptor
ATG_M_19_TRANS_dn	ACTIVE	0.439	1.20	1.01	0.00626	background measurement
ATG_RARg_TRANS_up	ACTIVE	1.62	1.36	1.68	0.225	nuclear receptor
ATG_PXRE_CIS_up	ACTIVE	2.18	3.23		0.282	nuclear receptor
ATG_PXR_TRANS_up	ACTIVE	2.11	1.60	2.55	0.407	nuclear receptor



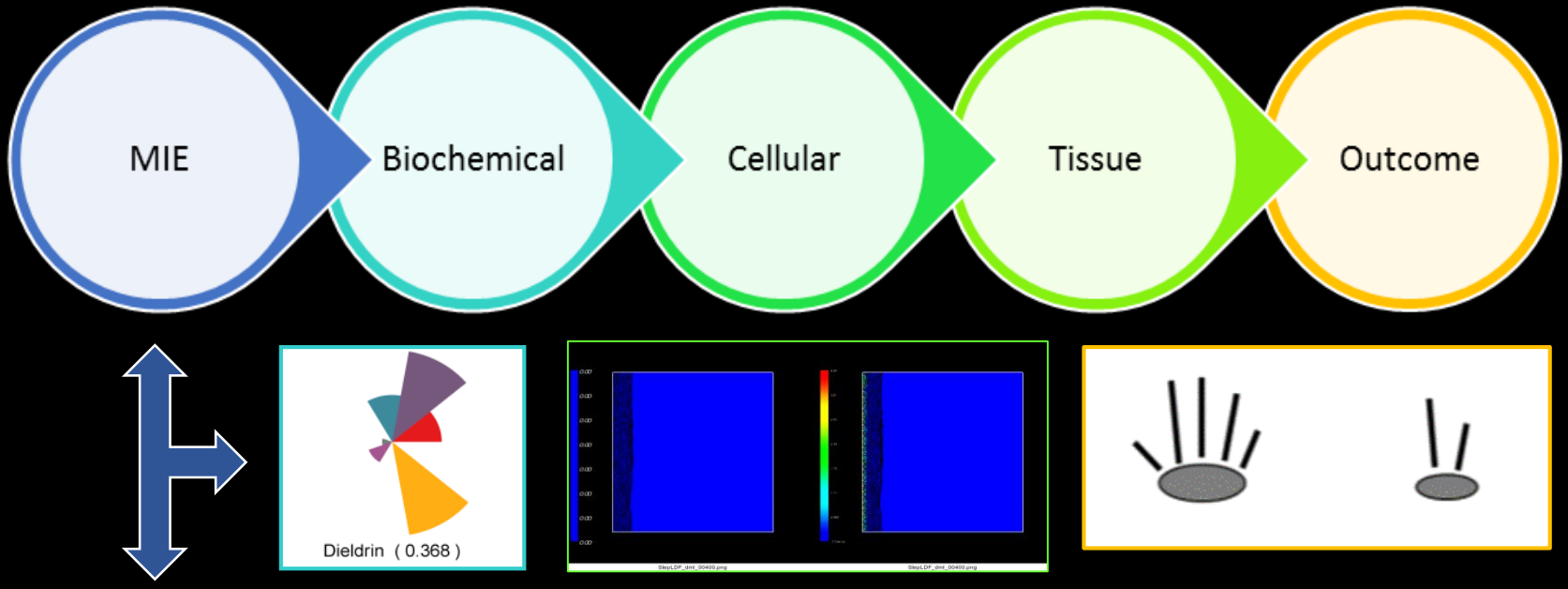
https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=Dieldrin

Simulation of RA fields: virtual dysmorphogenesis



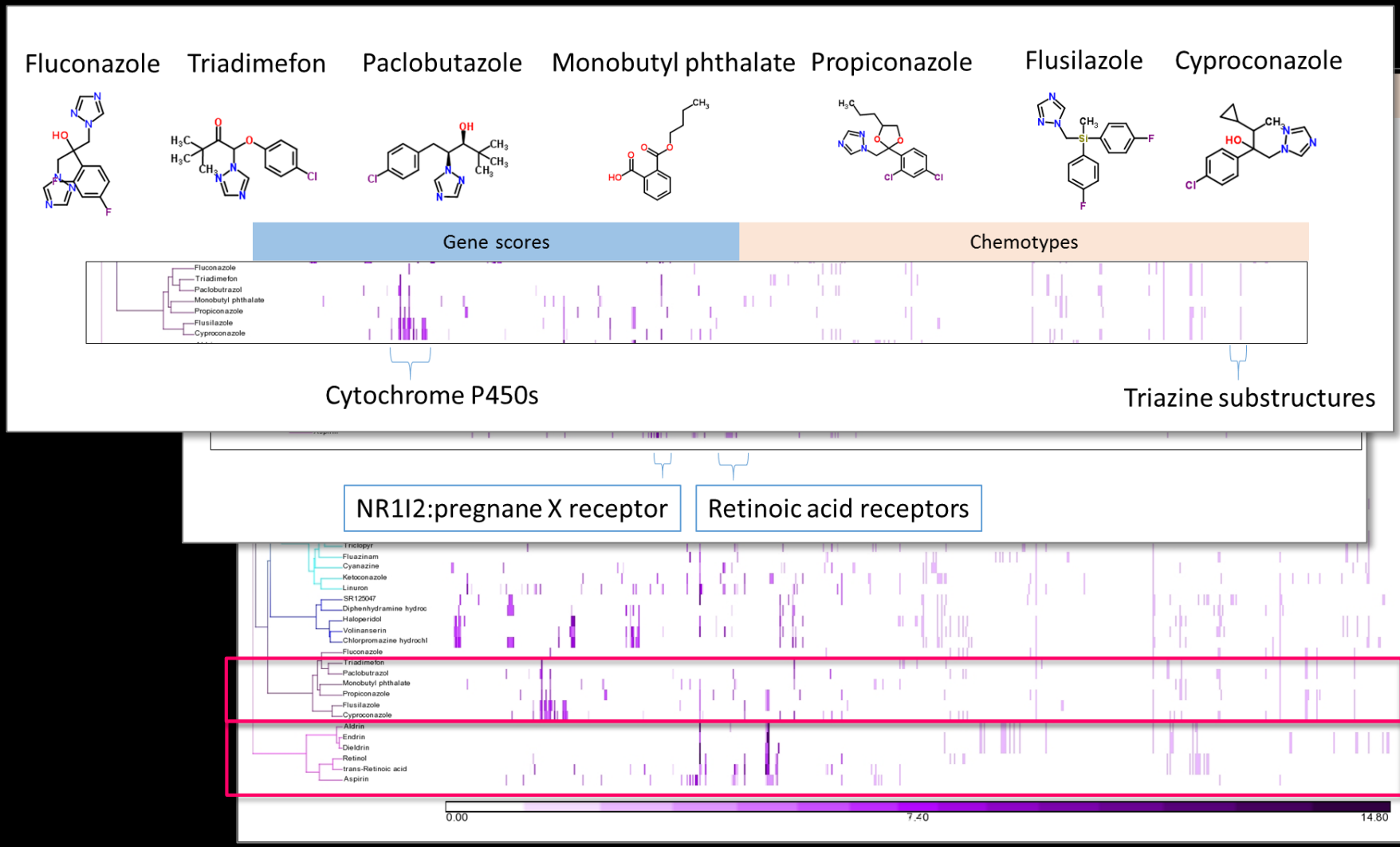


Thinking about AOPs …



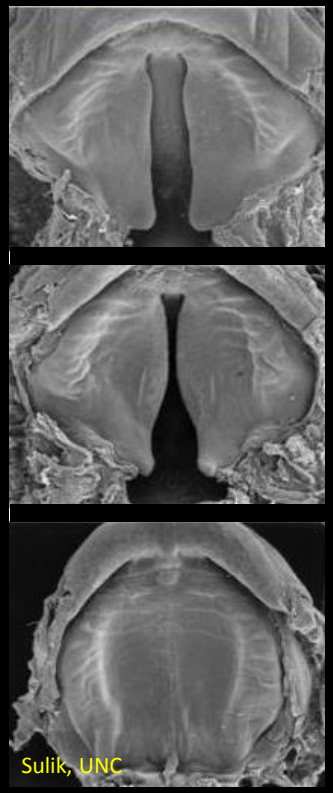
ToxCast bioactivity signature	integrated and coordinated cell signaling	tissue dynamics in computer simulation	AOP-based hazard prediction model

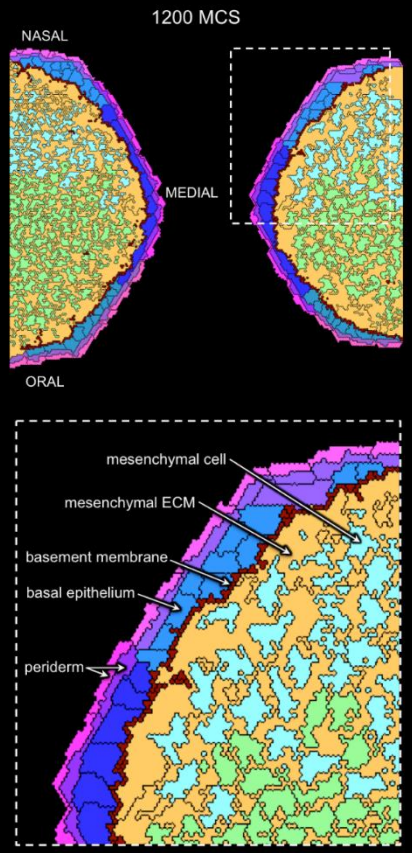
Cleft Palate: chemotype-bioactivity clusters for 63 chemicals

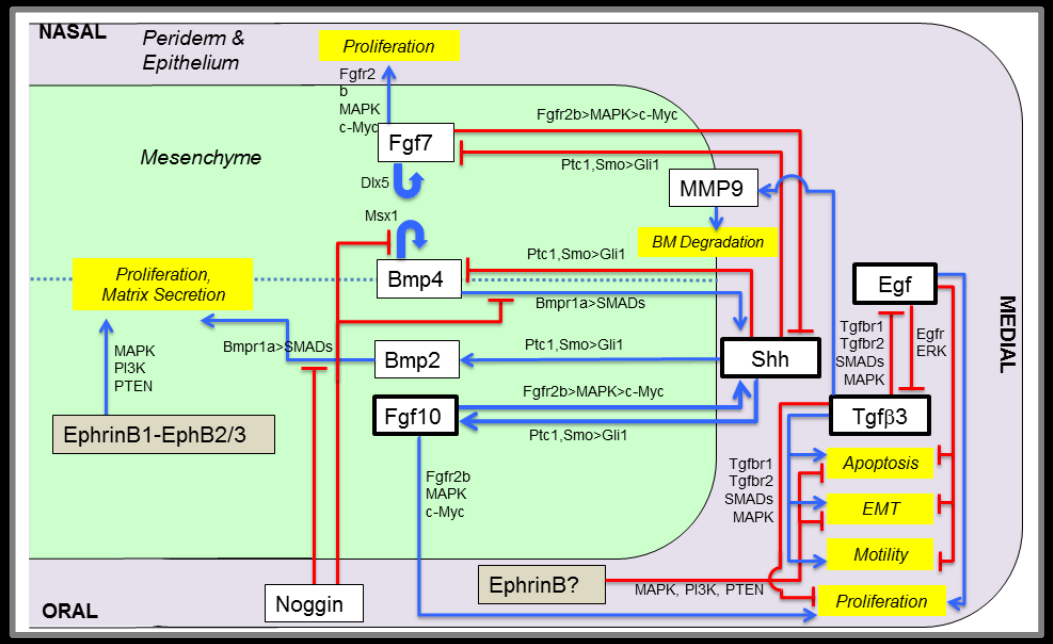


Baker et al. (unpublished)

Computer simulation: medial edge fusion

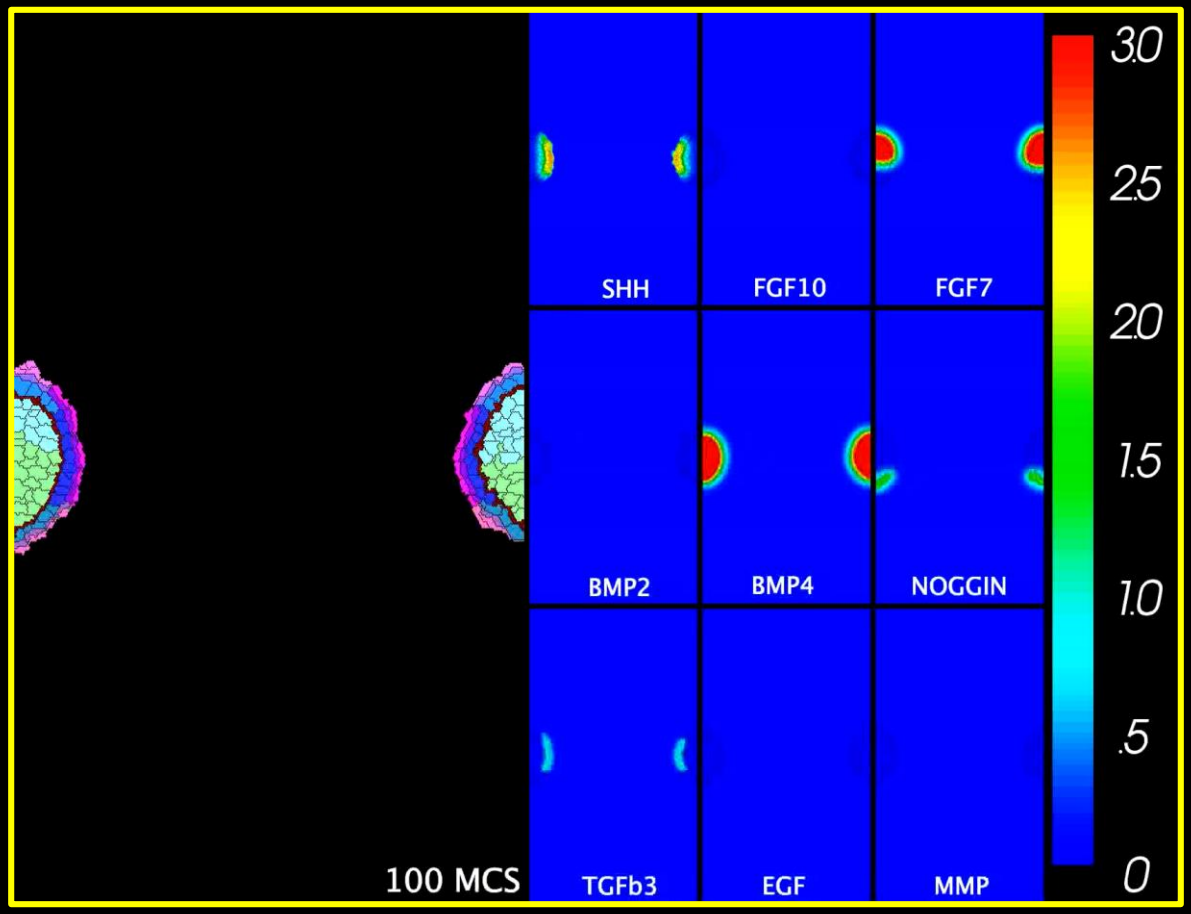




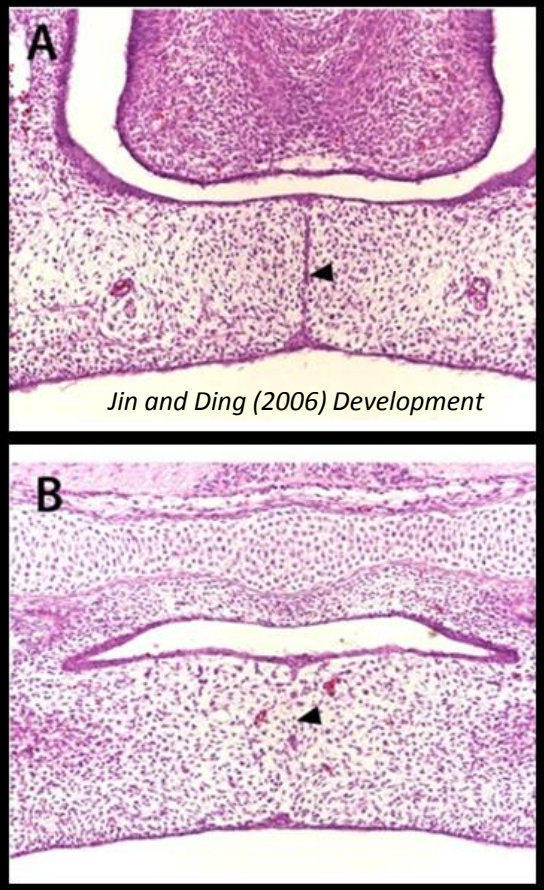


Hutson et al. (2016) submitted

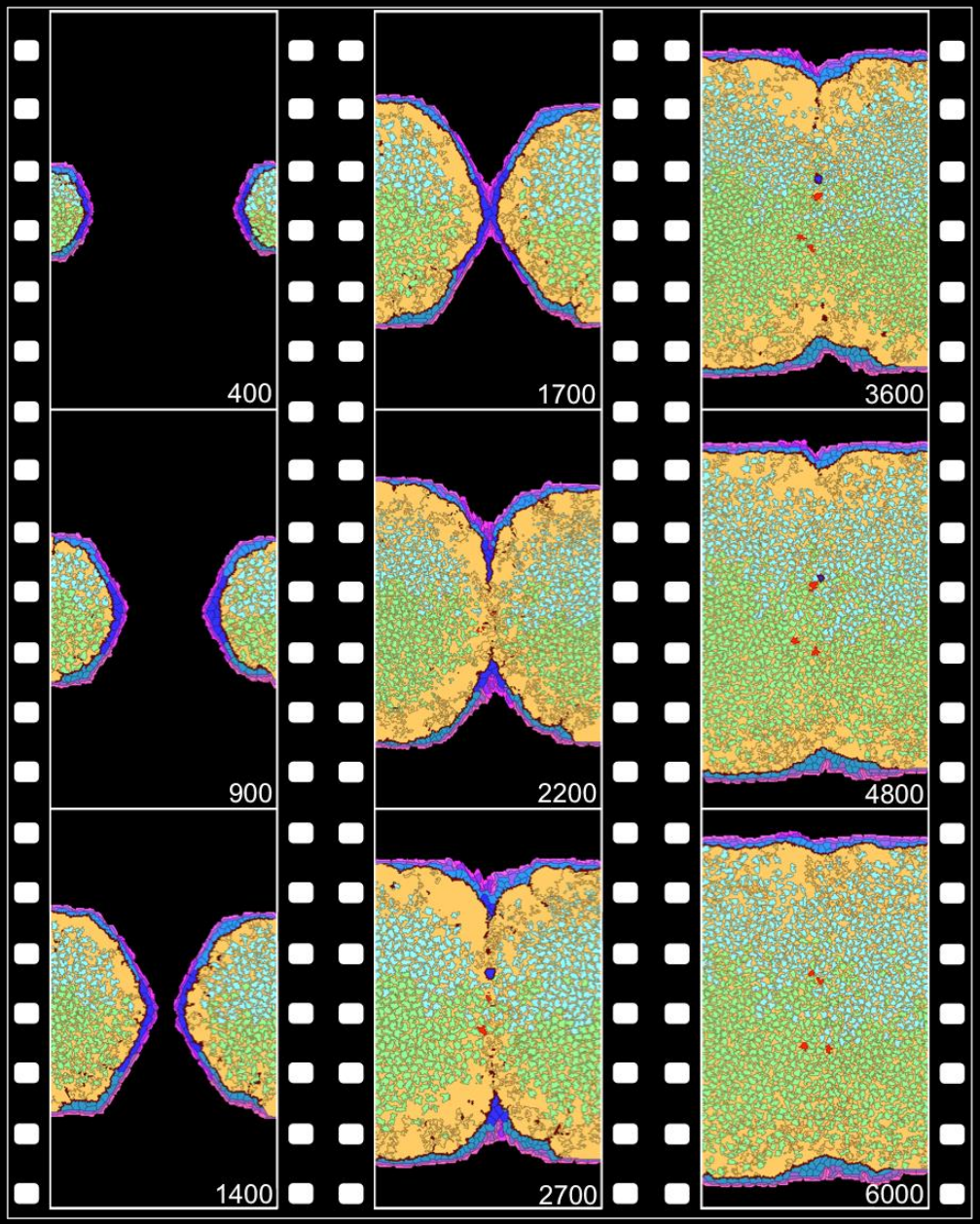
Cell Agent-Based Model for Fusion



ABM for Fusion

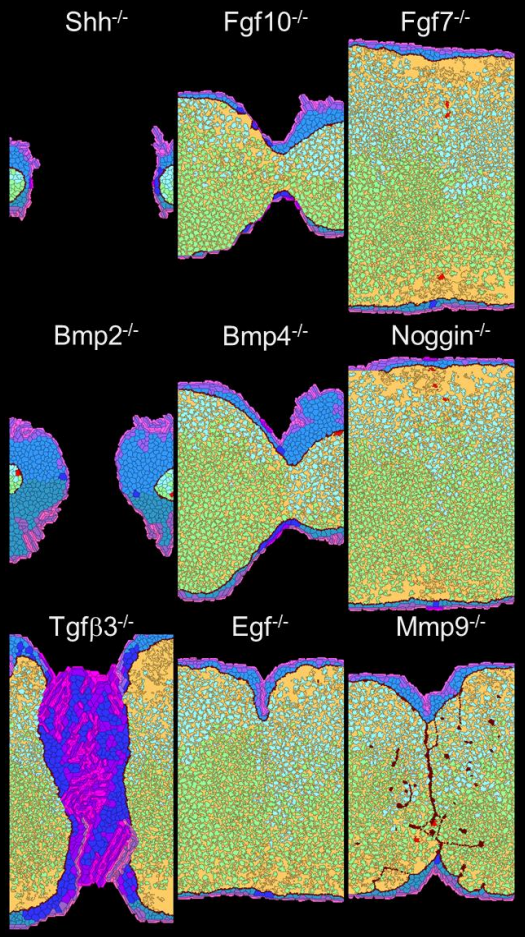


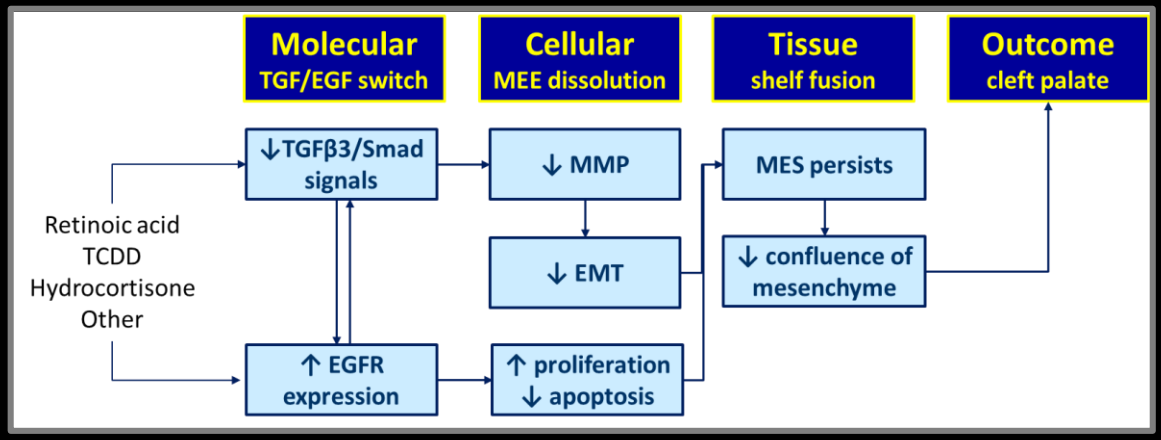
Jin and Ding (2006) Development



Hacking the Control Network:

in silico knockouts → Cybermorphs



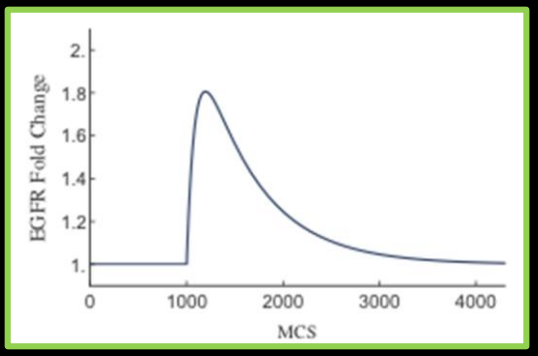


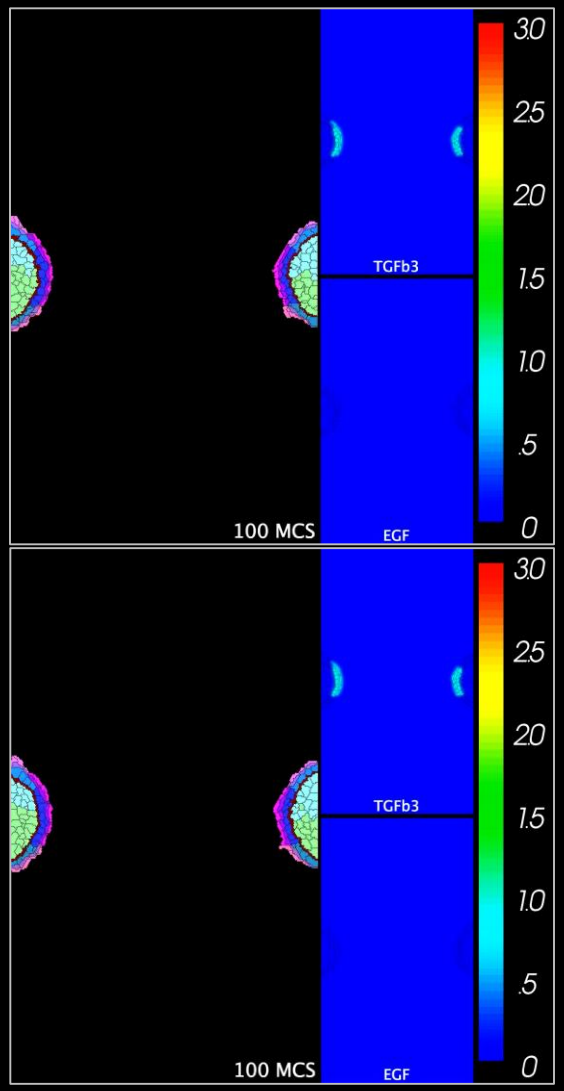
Fusion Switch

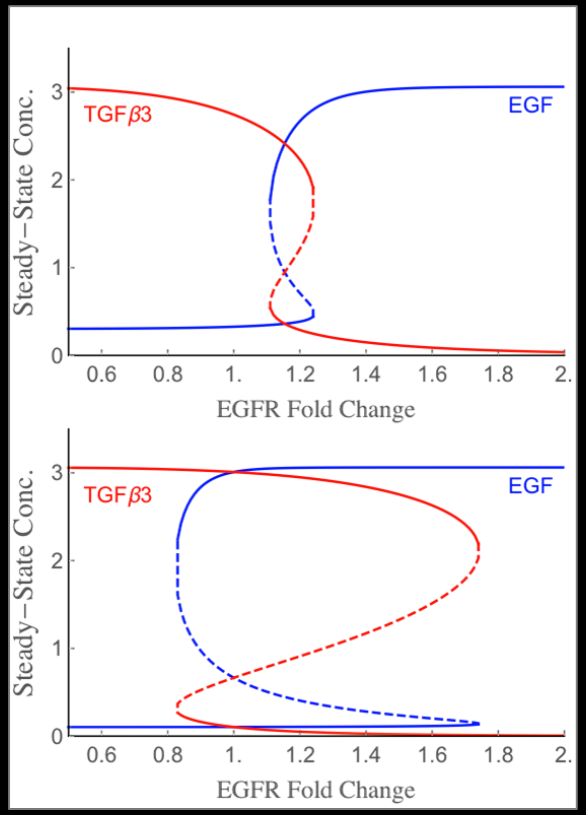
- TGFβ3 triggers apoptosis, epithelial-mesenchymal transition, and retraction to break down the midline seam.
- EGF has the opposite effect, maintaining epithelial proliferation and survival.
- ToxCast profiling for 63 cleft palate teratogens pointed to ~10 bioactivity clusters (eg, retinoid, glucocorticoid, GPCR, …).

TGF-EGF circuit dynamics:

modeling acute exposure to retinoic acid



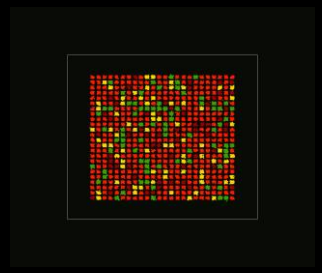


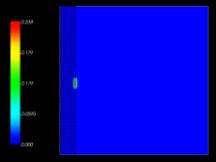


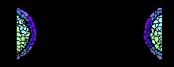
tipping point >1.8x (n=24)
(reversible)

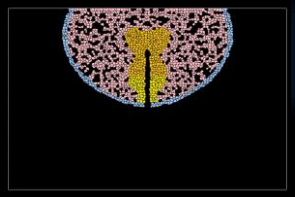
tipping point ~1.5x (n=16)
(non-reversible)

Toward a Virtual Embryo









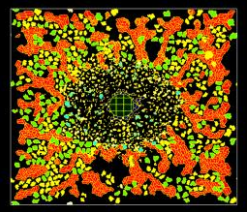
Vasculature

Limb-bud

Palate

Genital Tubercle

NVU/BBB



Heart

v-Embryo™

Neural Tube

Liver / GI

Testis / BTB

Renal

Underway

Planned

Future

Special Thanks

- Sid Hunter – NHEERL / ISTD
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- Imran Shah – NCCT
- RS Thomas – Director, NCCT
- Kevin Crofton – NCCT
- John Cowden – NCCT/CSS
- Tina Bahadori – CSS
- Jill Franzosa - CSS

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