

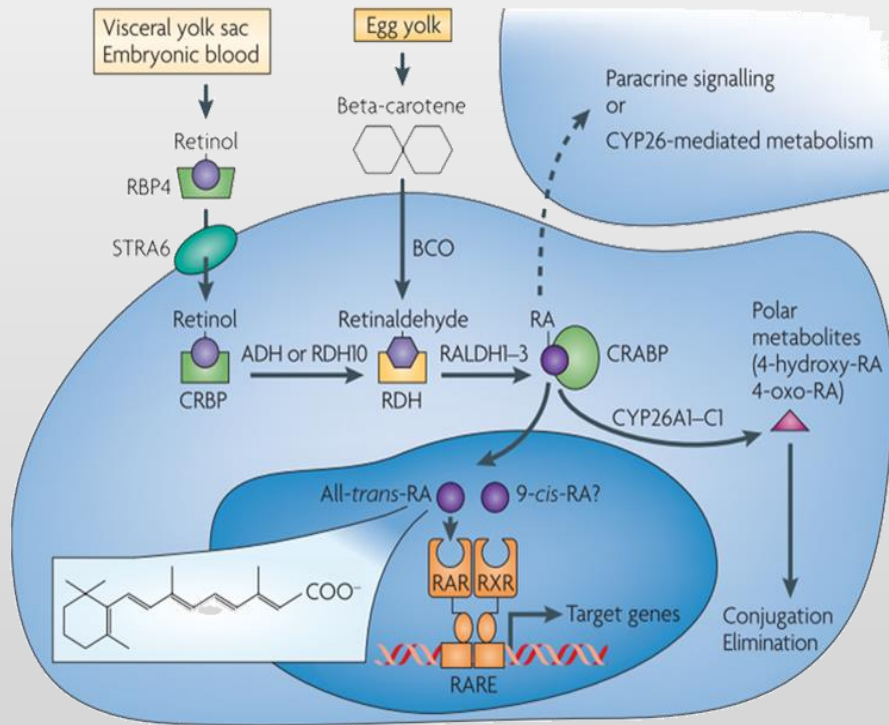
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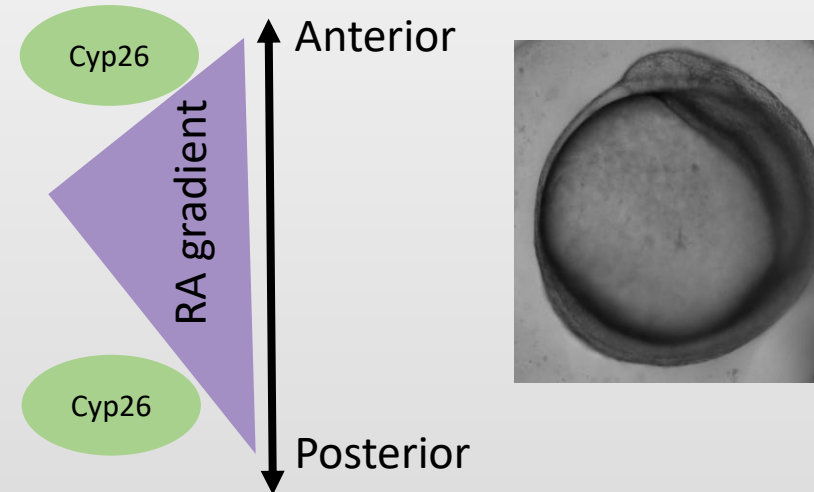
AOP linking RAR/RXR overactivation to feeding disruption

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Retinoic Acid (RA) signaling in early development



Reviewed by Niederreither and Dollé.
Nature Reviews Genetics. 2008.



- Highly Conserved receptor in vertebrates (RAR)
- Anteroposterior concentration gradient
- RA gradient is controlled by enzymatic mechanistic (cyp26)
- Positional and directional signalization

Growing interest in retinoid signaling disruption

Reproductive Toxicology 93 (2020) 250–258



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Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

Regulatory needs and activities to address the retinoid system in the context of endocrine disruption: The European viewpoint

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Reproductive Toxicology 96 (2020) 114–127

Contents lists available at ScienceDirect

Reproductive Toxicology

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Received: 5 November 2019 | Revised: 12 April 2020 | Accepted: 13 April 2020

DOI: 10.1002/dvdy.179

DISEASE CONNECTIONS

Developmental Dynamics WILEY



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Toxicology

Volume 458, 30 June 2021, 152843



An adverse outcome pathway on the disruption of retinoic acid metabolism leading to developmental craniofacial defects

Elena Menegola^a, Christina H.J. Veltman^b, Maria Battistoni^a, Francesca Di Renzo^a, Angelo Moretto^c, Francesca Metruccio^d, Anna Beronius^e, Johanna Zilliacus^e, Katerina Kyriakopoulou^f, Anastasia Spyropoulou^f, Kyriaki Machera^f, Leo T.M. van der Ven^b, Mirjam Luijten^b

Chemical-induced craniofacial anomalies caused by disruption of neural crest cell development in a zebrafish

frontiers
in Pharmacology

Front Pharmacol. 2022; 13: 971296.

Published online 2022 Sep 6. doi: [10.3389/fphar.2022.971296](https://doi.org/10.3389/fphar.2022.971296)

PMCID: PMC9511990

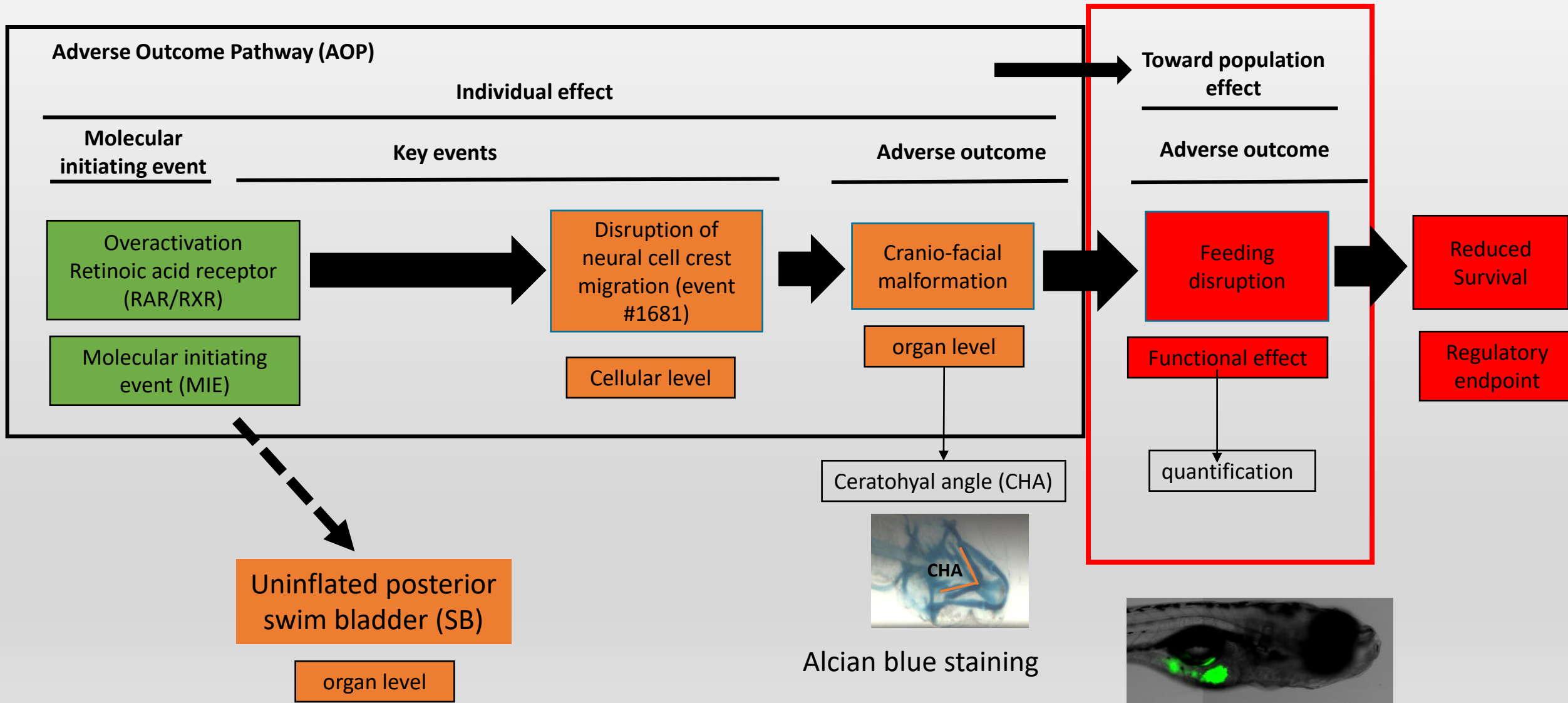
PMID: [36172177](https://pubmed.ncbi.nlm.nih.gov/36172177/)

Computational model for fetal skeletal defects potentially linked to disruption of retinoic acid signaling

Jocelyn D. Pierro,¹ Bhavesh K. Ahir,² Nancy C. Baker,³ Nicole C. Kleinstreuer,⁴ Menghang Xia,⁵ and Thomas B. Knudsen^{1,*†}

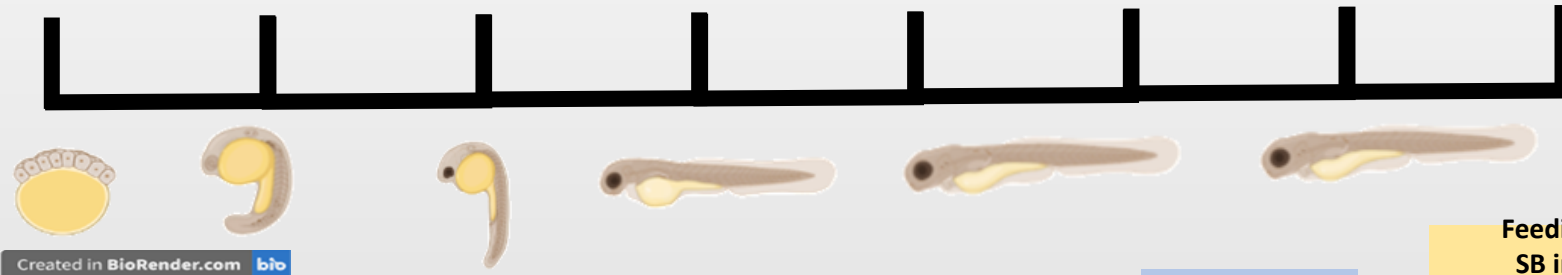
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Building link between early development malformation and population decline with quantitative data

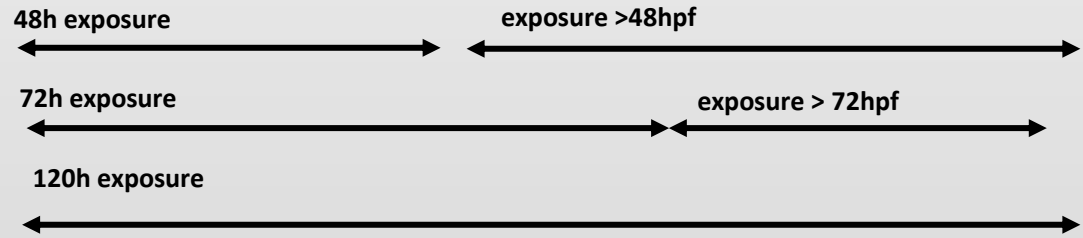


Experimental design

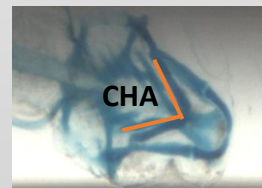
0-4 hpf 24 hpf 48 hpf 72 hpf 96 hpf 120 hpf 7dpf



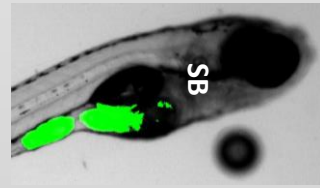
Created in BioRender.com bio



Craniofacial malformation (120hpf)
-alcian blue
-CHA angle



Feeding assay
SB inflation
168hpf
n=15-20 larvae/
condition
Posterior swim bladder inflation
168hpf



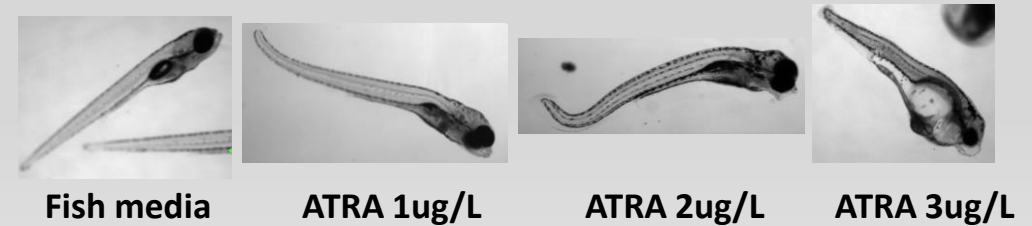
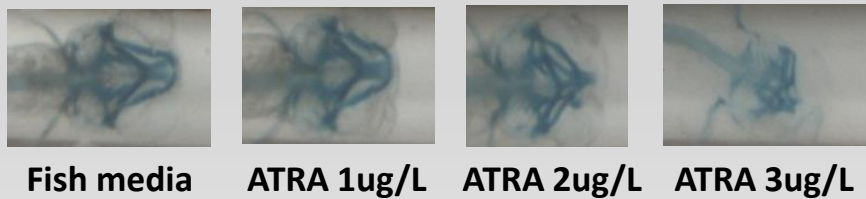
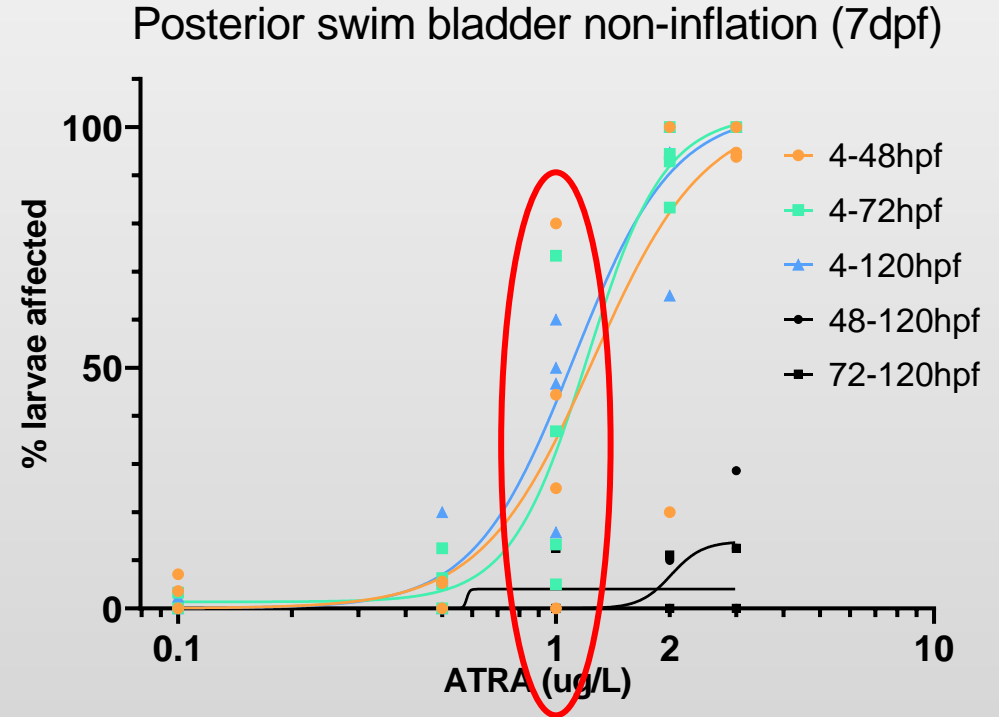
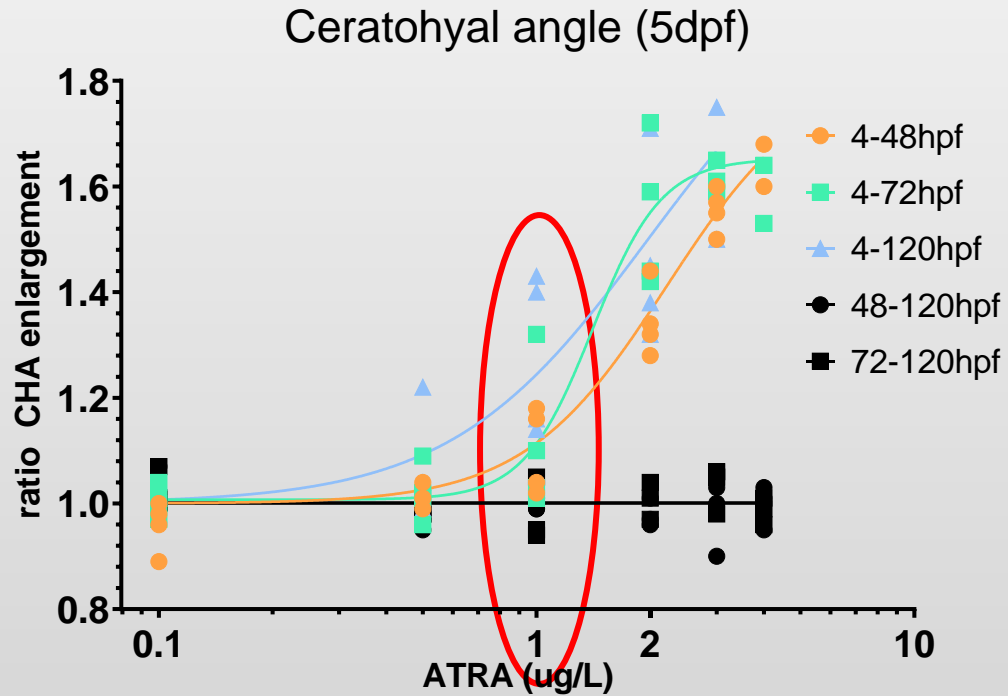
Survival at 14dpf

Experimental conditions

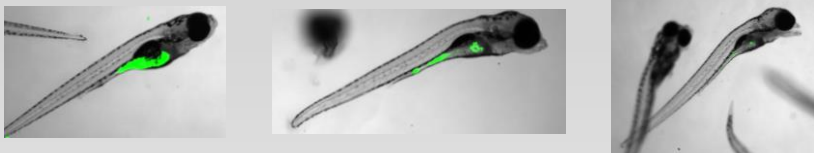
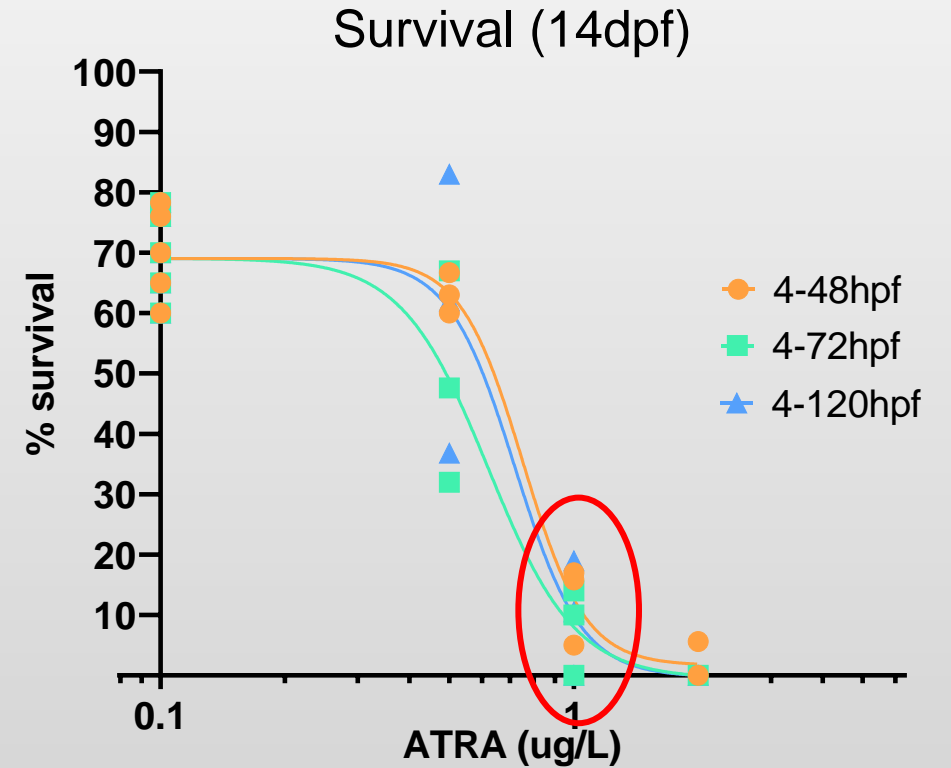
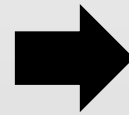
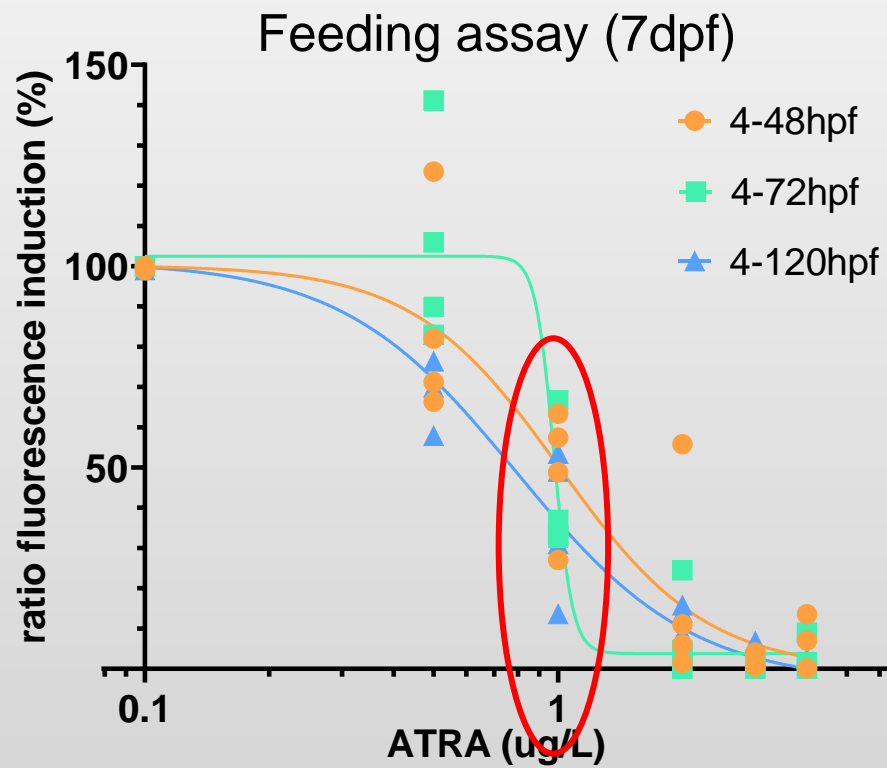
- Fish media
- DMSO 0.04%
- ATRA 0.5; 1; 2; 3 µg/L

Min. 3 replica

For ATRA induced malformation, the first 48 hours are critical for craniofacial malformation and swim bladder inflation



At 7dpf, IC50 = ATRA 1ug/L and is translated to survival rate of average ~10-15 % at 14dpf

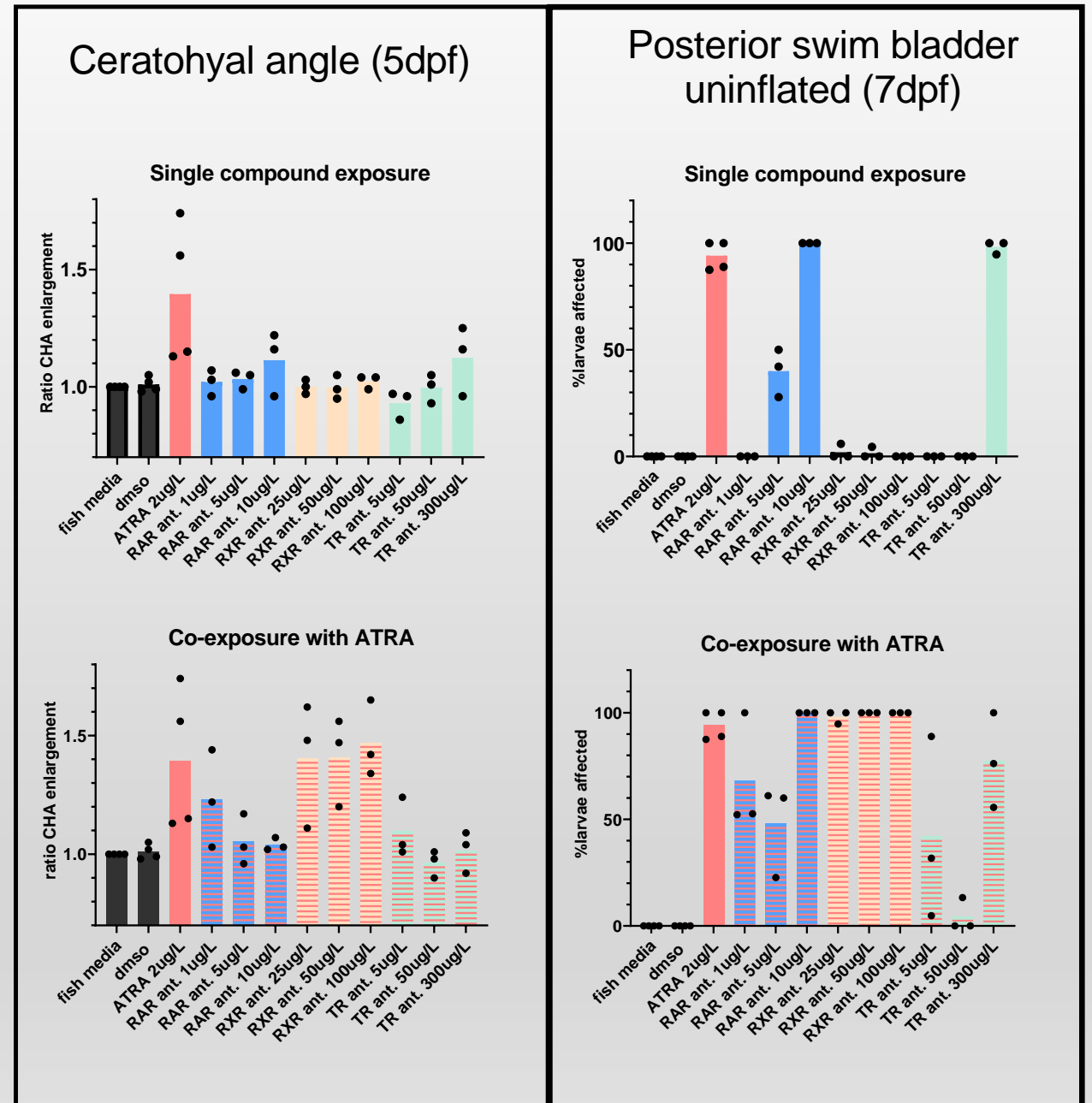
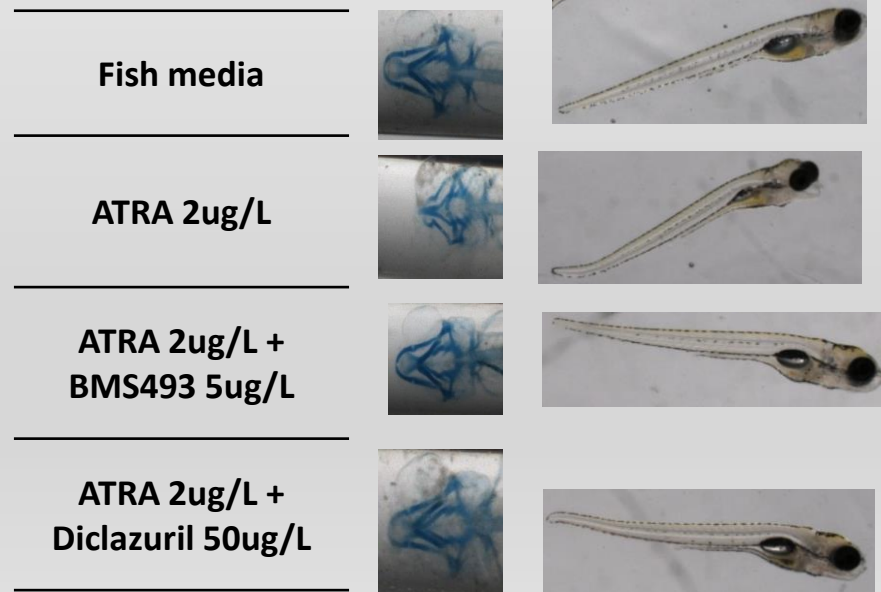


Craniofacial malformation and posterior swim bladder non-inflation are rescued by RAR and TR antagonist

Experimental condition

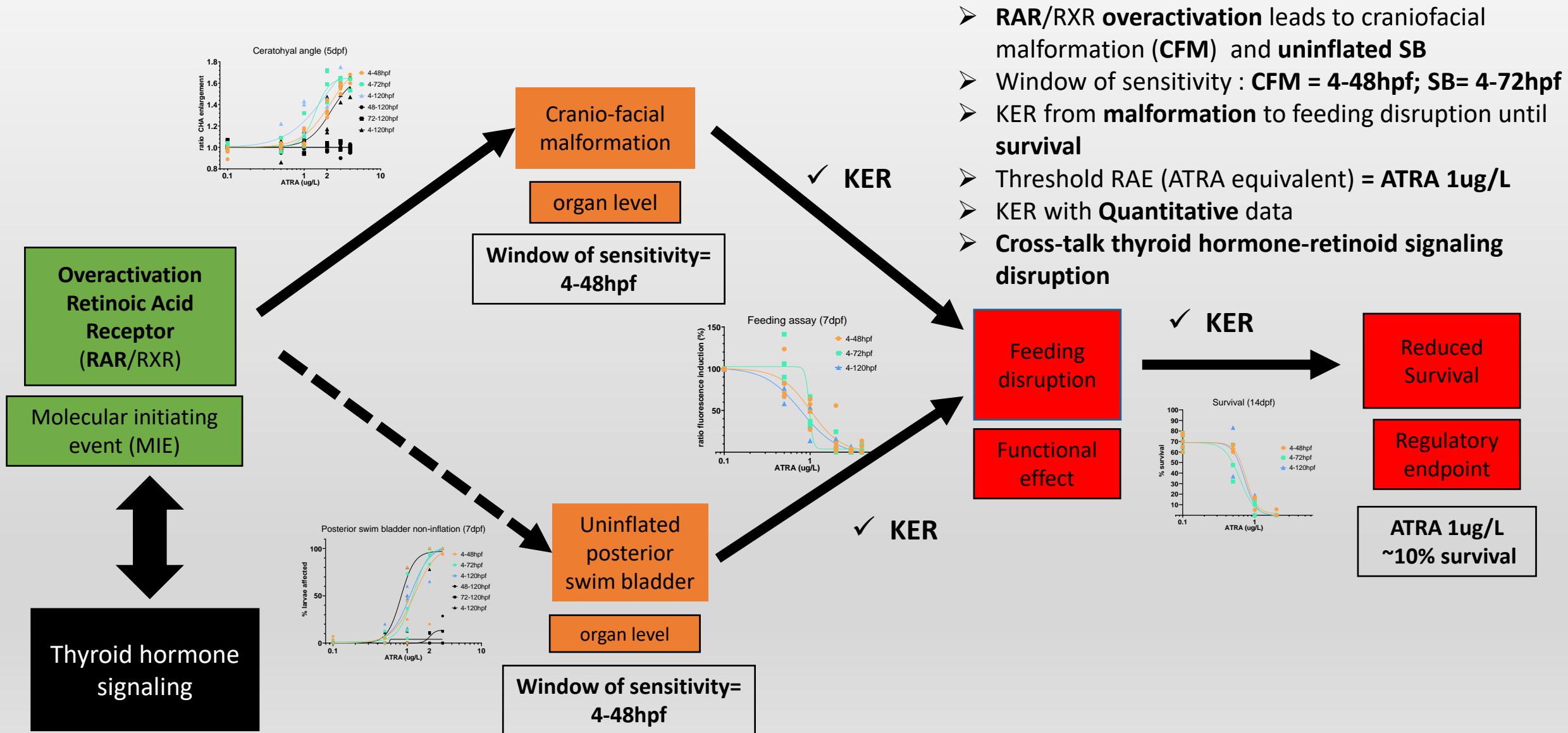
Exposure time = 4-120hpf; 3 Replica per compounds; N=17-20

- RAR antagonist = BMS493
- RXR antagonist = UVI3003
- TR antagonist = Diclazuril



Conclusion:

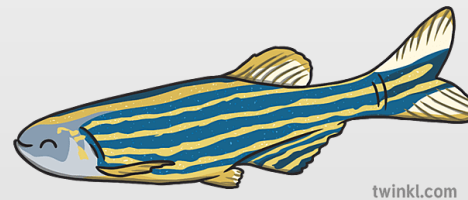
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Thank you for your attention !



QR code

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More about my project: <https://www.recetox.muni.cz/prorisk/phd-fellows/esr-8-audrey-phan>

Linkedin: <https://www.linkedin.com/in/audrey-phan-0bb456105/>

