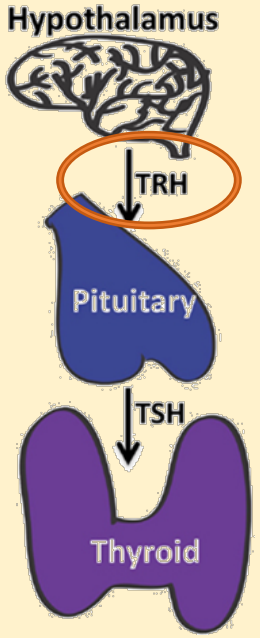
Integrating *in silico* and *in vitro* Data for New Approach Methods Evaluation: Application to Tox21 TRHR Assay Results

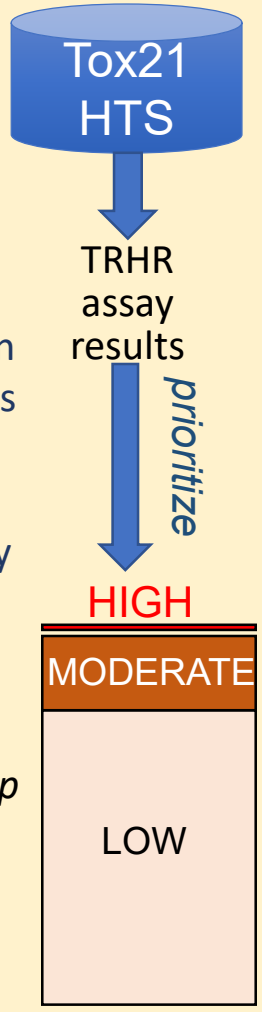
Mahmoud Shobair[1], Christopher Grulke[1], Daniel Chang[1], Ryan Lougee[2], Katie Paul Friedman[1] , Ann Richard[1]

[1]Center for Computational Toxicology & Exposure, Office of Research & Development, U.S. Environmental Protection Agency, RTP, NC, USA. [2]Oak Ridge Institute for Science and Education, U.S. Environmental Protection Agency, RTP, NC, USA

OBJECTIVES



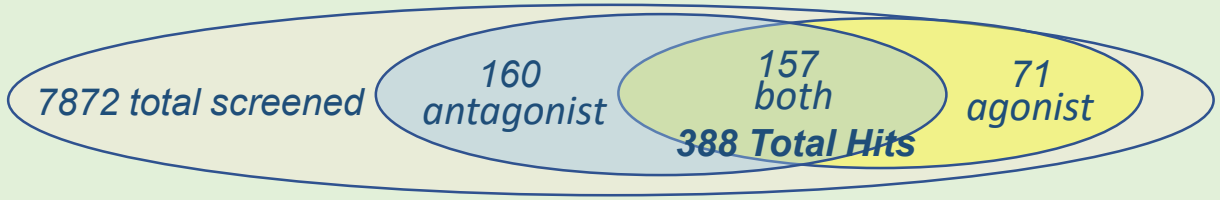
- Evaluate environmental chemicals for potential to interact with the thyrotropin-releasing hormone receptor (TRHR)
- Large number of diverse environmental chemicals screened in Tox21 TRHR assay, yet false negatives and positives expected
- Goal is to identify subset of likeliest true actives from the full set of assay results



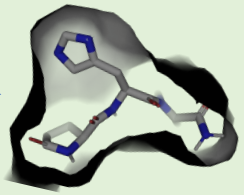
- *Prioritize subset of actives (true hits) and inactives (potential false negatives) for follow-up testing using:*
  - *domain knowledge*
  - *chemotype enrichments*
  - *in silico computational chemistry models*

APPROACH

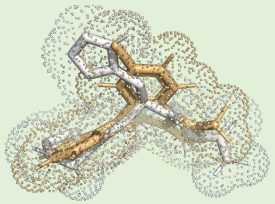
- Cheminformatics analysis of *in vitro* assay data [**Tox21_TRHR**[1]]

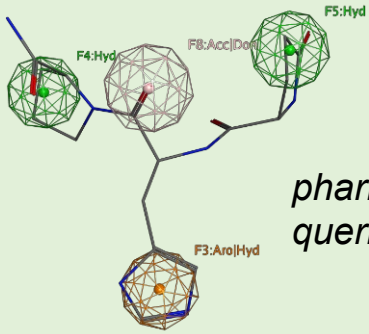


- Building reference dataset [**research articles**[2]]

primary literature BindingDB → *data curation mining* →  *receptor binding features*

- 2D Filters/3D modeling [**MOE**[3]]
  - chemotype enrichments & heuristics

 *molecular alignment*



pharmacophore queries

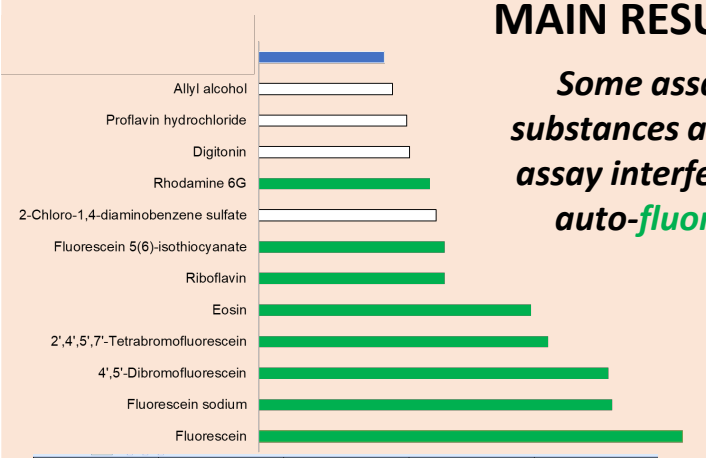
1. https://comptox.epa.gov/dashboard
2. PMID: 8648595, 17035026 , 16162016
3. MOE (The Molecular Operating Environment), software available from Chemical Computing Group Inc., 1010 Sherbrooke Street West, Suite 910, Montreal, Canada H3A 2R7 (http://www.chemcomp.com

Integrating *in silico* and *in vitro* Data for New Approach Methods Evaluation: Application to Tox21 TRHR Assay Results

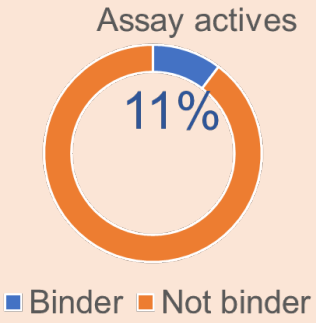
Mahmoud Shobair[1], Christopher Grulke[1], Daniel Chang[1], Katie Paul Friedman[1], Ryan Lougee[2], Ann Richard[1]

[1]Center for Computational Toxicology & Exposure, Office of Research & Development, U.S. Environmental Protection Agency, RTP, NC, USA. [2]Oak Ridge Institute for Science and Education, U.S. Environmental Protection Agency, RTP, NC, USA

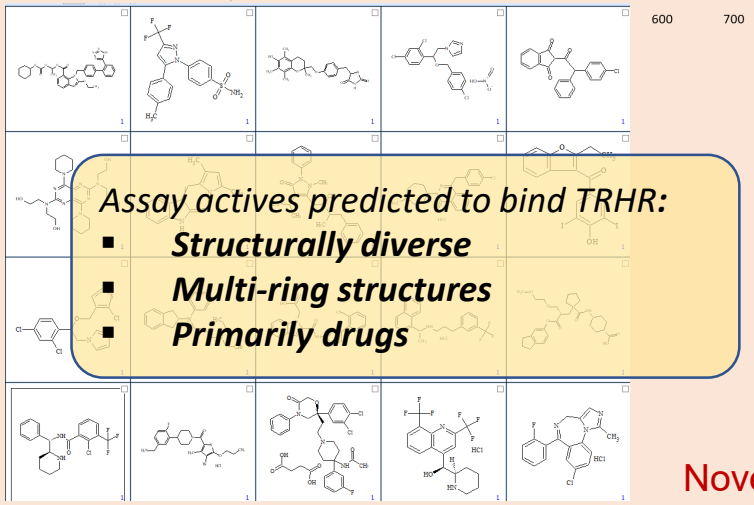
MAIN RESULTS



Some assay active substances attributed to assay interference from auto-fluorescence

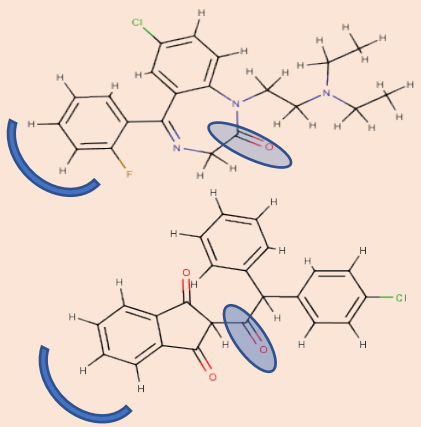


Most assay actives are unlikely to bind in TRH pocket



Assay actives predicted to bind TRHR:

- ***Structurally diverse***
- ***Multi-ring structures***
- ***Primarily drugs***

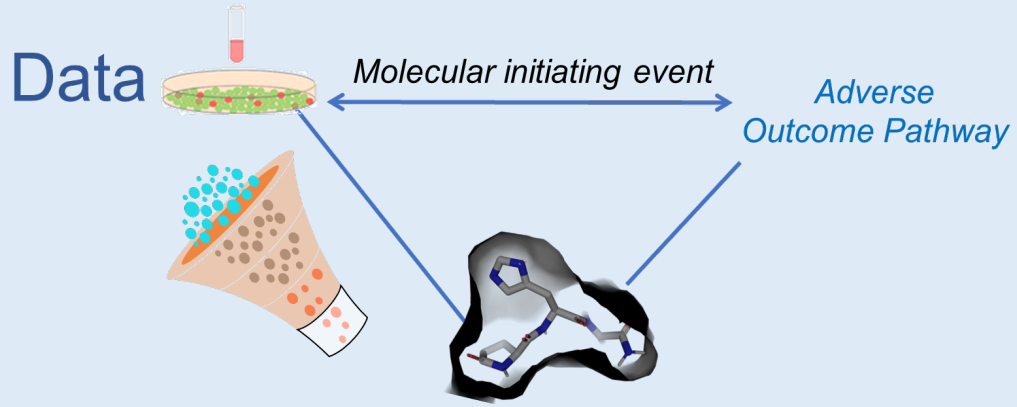


Novel Result: ***Chlorophacinone*** ***has structural features associated with Benzodiazepine inhibition of TRHR [hit in 5 models]***

- 40/7872 chemicals from Tox21 library are prioritized for further

IMPACT

- Environmental risk assessment of TRHR warrants further inquiry
- Combining structure-based methods and data enrichment analysis can increase confidence in HTS results and define a scope of prediction for risk
- Approach is generalizable to other Tox21 HTS assays



For more information, contact: Mahmoud Shobair, PhD e-mail: shobair.mahmoud@epa.gov