

Antagonism of the Aryl Hydrocarbon Receptor

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2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)

- Shown to inhibit proliferation of estrogen-responsive breast cancer cells

- Problem: TCDD is toxic



- Both of these effects are mediated by the aryl hydrocarbon receptor (AHR)

- * Solution: A non-toxic AHR ligand that inhibits breast cancer proliferation

Aryl Hydrocarbon Receptor (AHR)

- Ligand activated transcription factor
- Increases expression of enzymes that metabolize foreign compounds
 - E.g. CYP1A1
- Expression of CYP1A1 is correlated with toxic effects

Research Aims

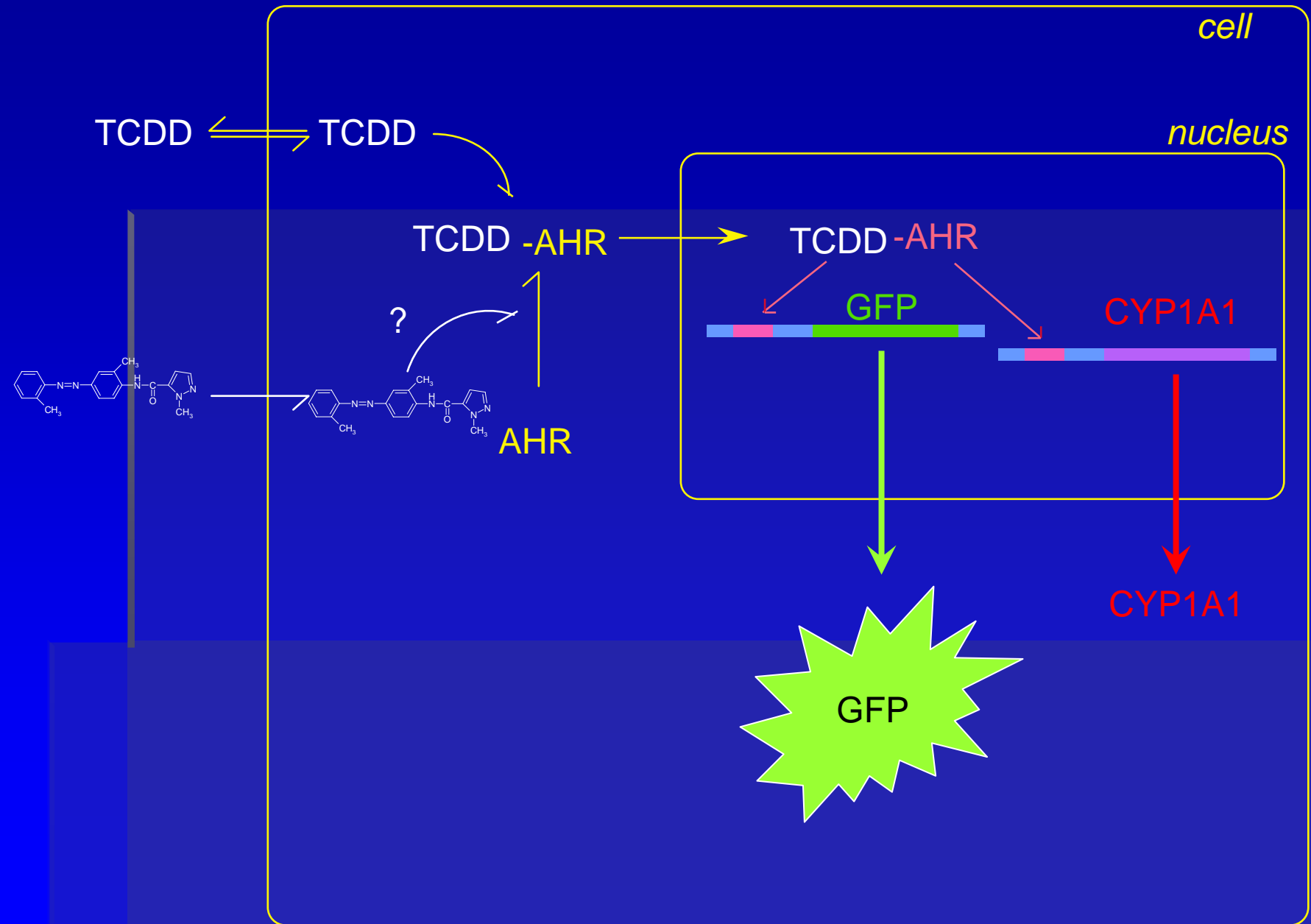
Find an AHR ligand:

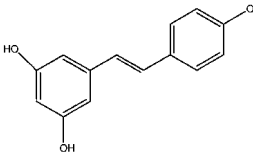

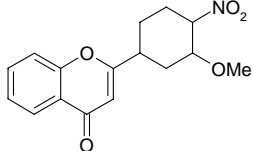

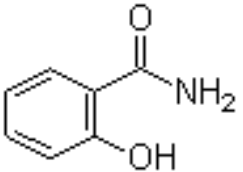

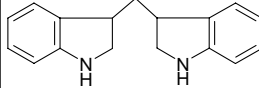

1. Does not increase AHR- dependent expression of CYP1A1
2. Inhibits proliferation of breast cancer cells

Reporter Gene

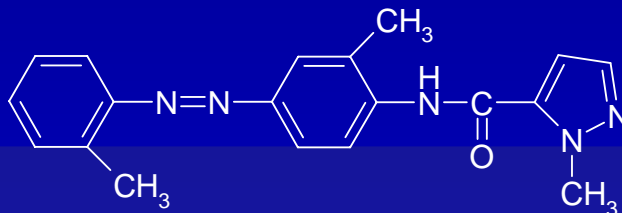
- Problem: It is time-consuming and expensive to measure CYP1A1 for all possible AHR ligands
- Solution: Reporter Gene
 1. Easy to measure
 2. Foreign to organism

*Mouse hepatoma cells transfected with green fluorescent protein (GFP) driven by CYP1A1 regulatory sequences



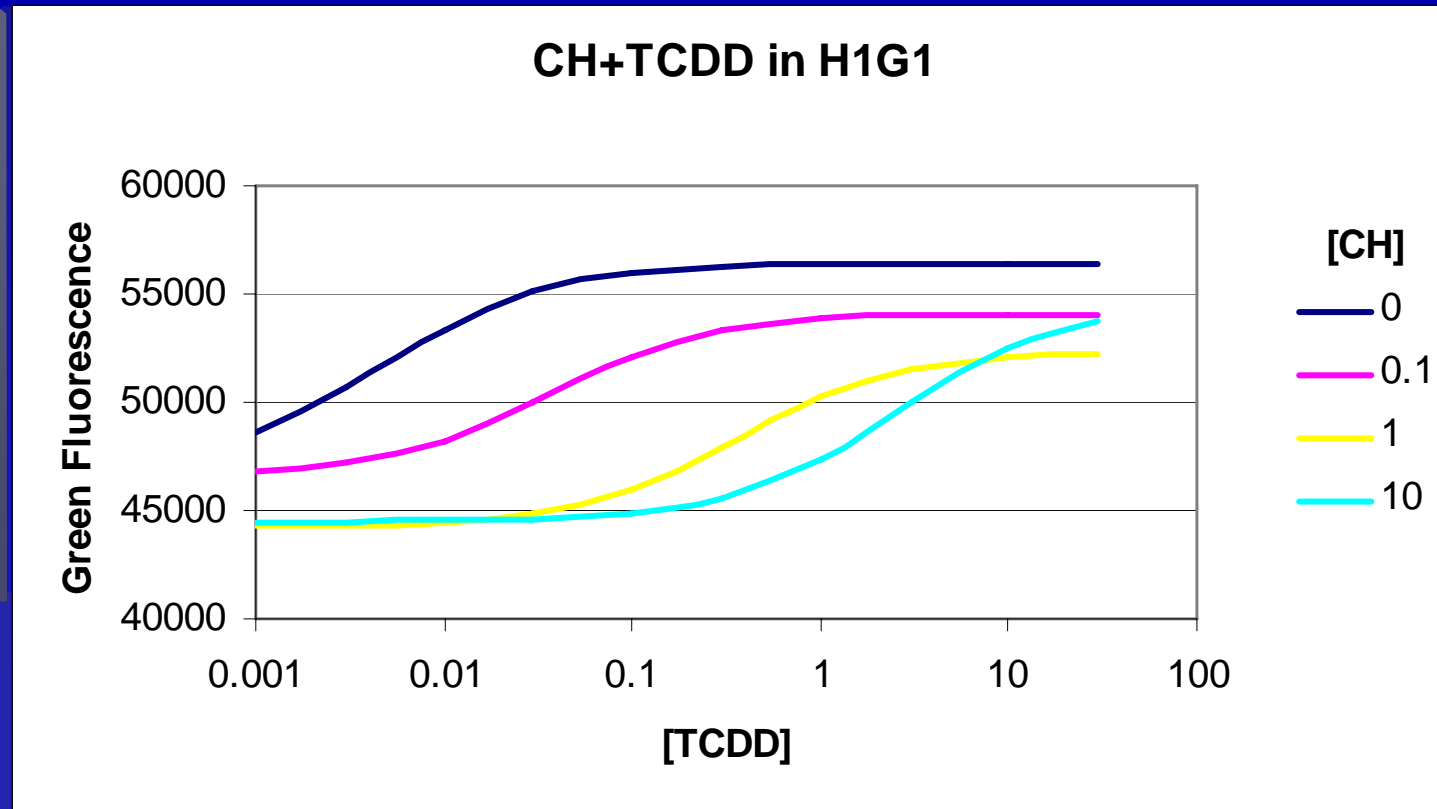
Compound	Source	GFP	GFP +dioxin	CYP +dioxin
RES				
MNF				
SAL				
DIM				

Putative AHR antagonist



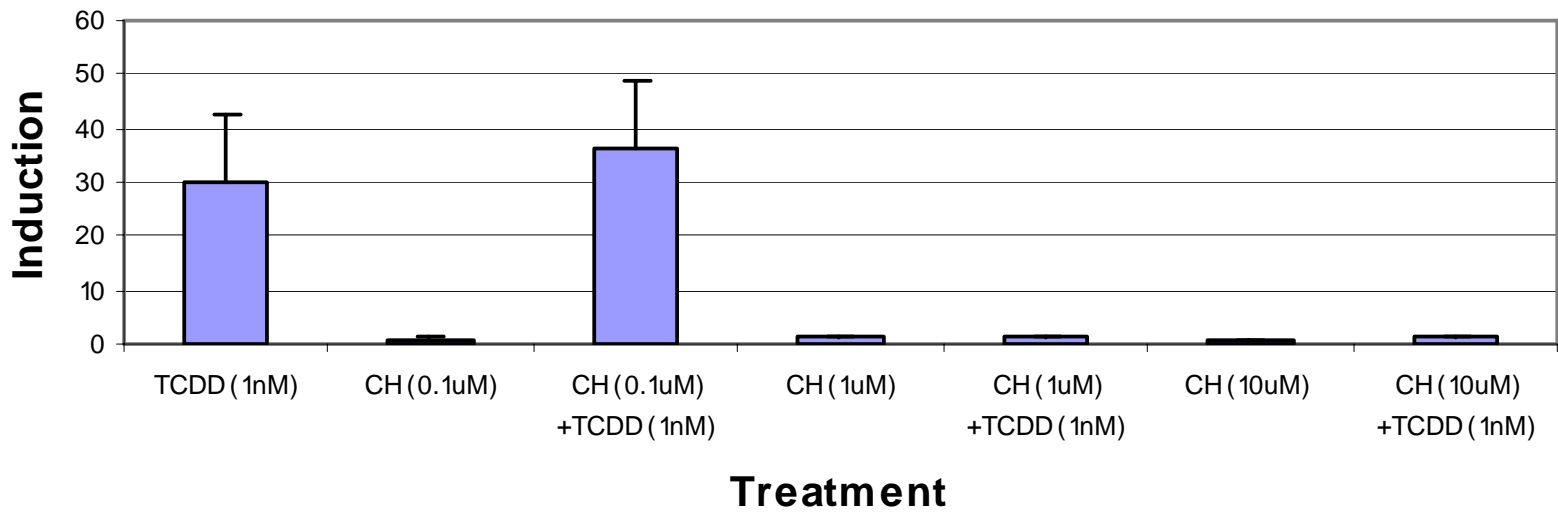
- 2-Methyl-2*H*-pyrazole-3-carboxylic Acid (2-methyl-4-*o*-tolylazo-phenyl)-amide
→ CH-223191
- Inhibits TCDD-induced CYP1A1 transcription
- No estrogenic effect

Dose Response Curve



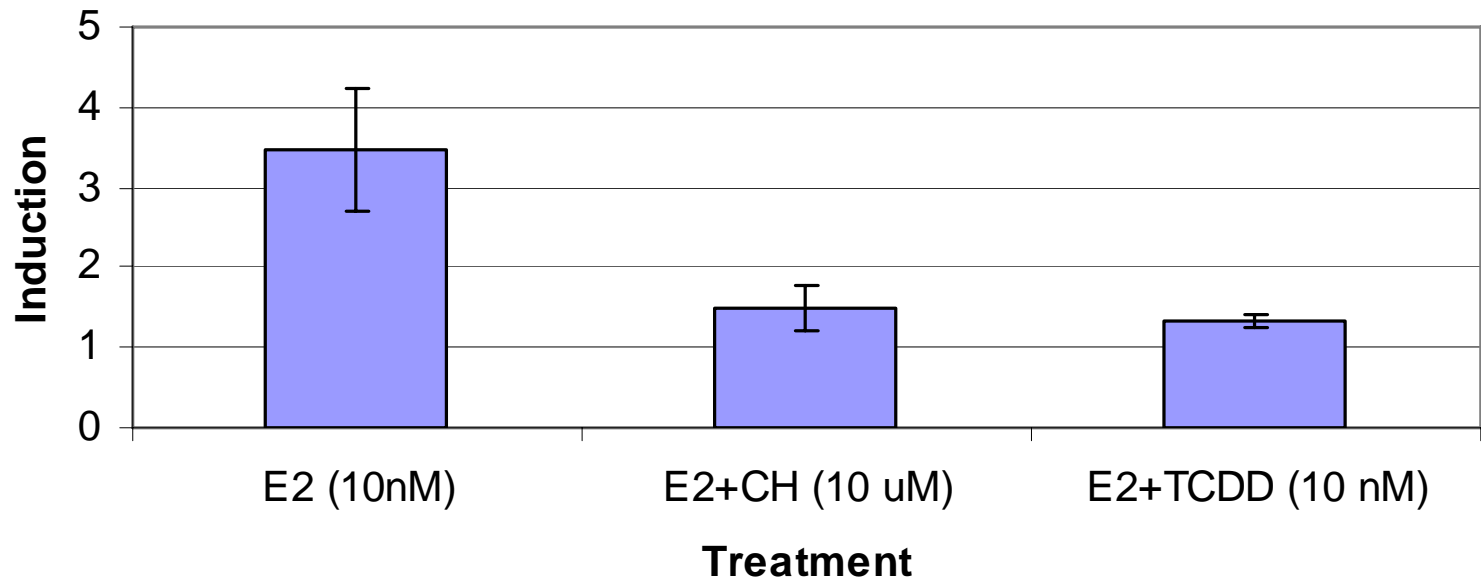
CH+TCDD

CH +TCDD in MCF-7
CYP1A1 (24 Hr.)



E2+CH+TCDD

**E2+CH+TCDD in MCF-7
CyclinD1 (3 Hr.)**



Conclusions

- CH blocks induction of CYP1A1 by TCDD
- CH also blocks induction of cyclin D1 by estrogen
- Ongoing studies will determine whether CH inhibits the proliferation of breast cancer cells

Acknowledgements

INBRE

Moses Lee

Merck/AAAS

