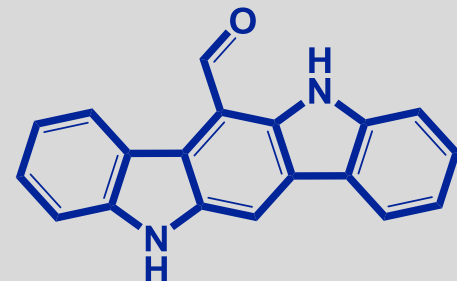


# Chemical and Physical Factors Influencing Skin Metabolism: Introducing the Bioactive Molecule FICZ

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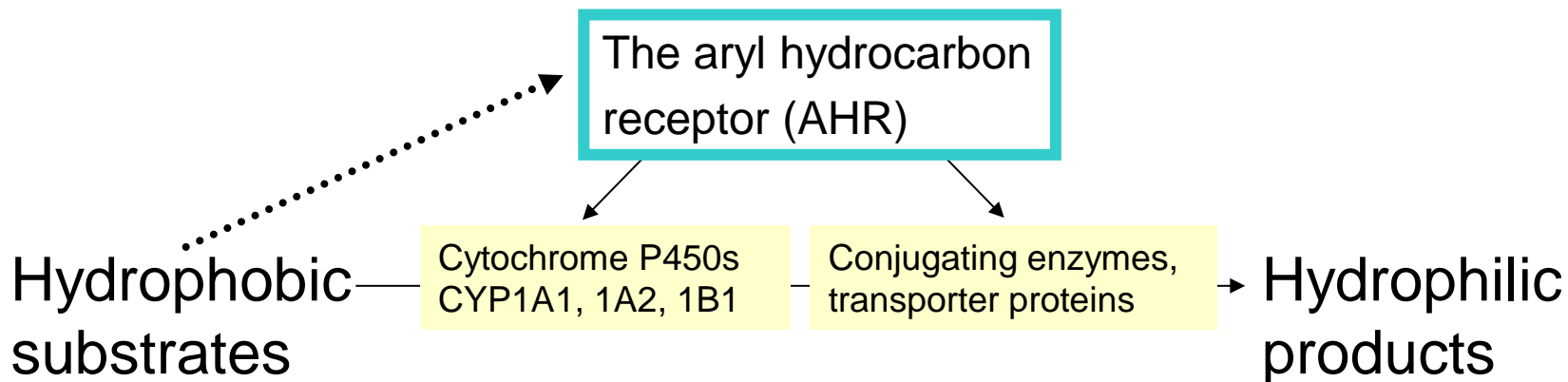
# Outline of presentation

- Part 1 Arylhydrocarbon receptor (AHR) - mediated regulation of CYP1 family of enzymes
- Part 2 AHR activation in skin

# Cytochrome P450 enzymes

Human CYP gene families <i>18</i>	Number of sub-families	Number of genes <i>57</i>	Transcription factors (receptor proteins)	Substrates or functions
CYP1	2	3	Aryl hydrocarbon receptor (AHR)	Xenobiotics/drugs, arachidonic acid, eicosanoids, retinoids, estrogens, melatonin, uroporphyrin ORPHAN
CYP2	13	16	Pregnane X receptor (PXR, NR1I2), Constitutive androstane receptor (CAR, NR1I3)	Xenobiotics, drugs, bilirubin, arachidonic acid, eicosanoids, steroids, 5-hydroxytryptamin
CYP3	1	4	Pregnane X receptor (PXR, NR1I2), Constitutive androstane receptor (CAR, NR1I3)	Xenobiotics, arachidonic acid, bilirubin, eicosanoids, steroids, cortisol, bile acids
CYP4	5	12	Peroxisome proliferator-activated receptors (PPARs, NR1C1/2/3)	Fatty acids, arachidonic acid, eicosanoids,
CYP5	1	1		Thromboxane A <sub>2</sub> synthase
CYP7	2	2	Farnesoid X receptor (FXR, NR1H4); liver X receptor (LXR, NR1H2/3)	22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 27-hydroxycholesterol, and cholestenic acid
CYP8	2	2		Prostacyclin synthase, bile acid synthesis
CYP11	2	3	(Multiple transactivating factors and cAMP responses)	Biosynthesis of all steroid hormones through cholesterol side chain cleavage
CYP17	1	1		Steroid 17 $\alpha$ -hydroxylase, 17/20-lyase
CYP19	1	1	Estrogen receptor (ER, NR3A1/2), Androgen receptor (AR, NR3C4)	Aromatization of estrogens and androgens
CYP20	1	1		Unknown
CYP21	1	1		Steroid 21-hydroxylase
CYP24	1	1	Vitamin D receptor (VDR, NR1I1)	Vitamin D <sub>3</sub> 24-hydroxylase
CYP26	3	3	Retinoic acid receptors (RAR, NR1B1/2/3, RXR, NR2B1/2/3)	Retinoic acid hydroxylation
CYP27	3	3		Bile acid biosynthesis, vitamin D <sub>3</sub> hydroxylations
CYP39	1	1		24-hydroxycholesterol 7 $\alpha$ -hydroxylase
CYP46	1	1		Cholesterol 24-hydroxylase in central nervous system
CYP51	1	1		Lanosterol 14 $\alpha$ -desmethylase

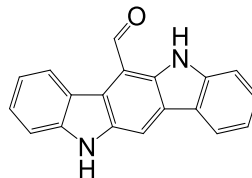
# Biotransformation



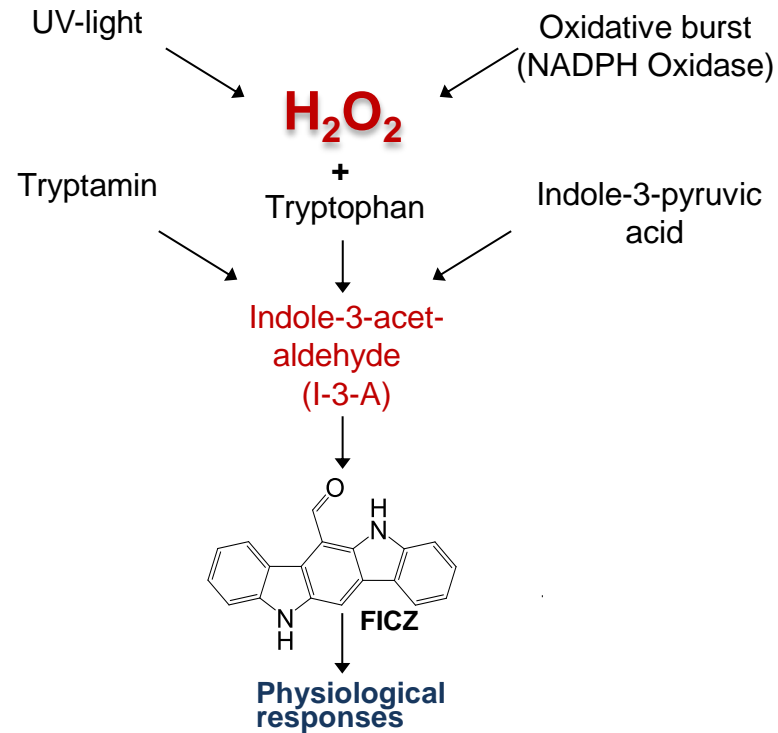
- Some xenobiotic CYP1 substrates/inducers
  - Polycyclic aromatic hydrocarbons (PAHs)
  - Dioxin-like substances
  - Drugs (e.g. omeprazol, ketoconazol, leflunomide...)
  - Natural polyphenols (quercetin, resveratrol, curcumin.....)
  - Metals (arsenic, mercury, nickel, cadmium...)

- Some endogenous CYP1 substrates/inducers

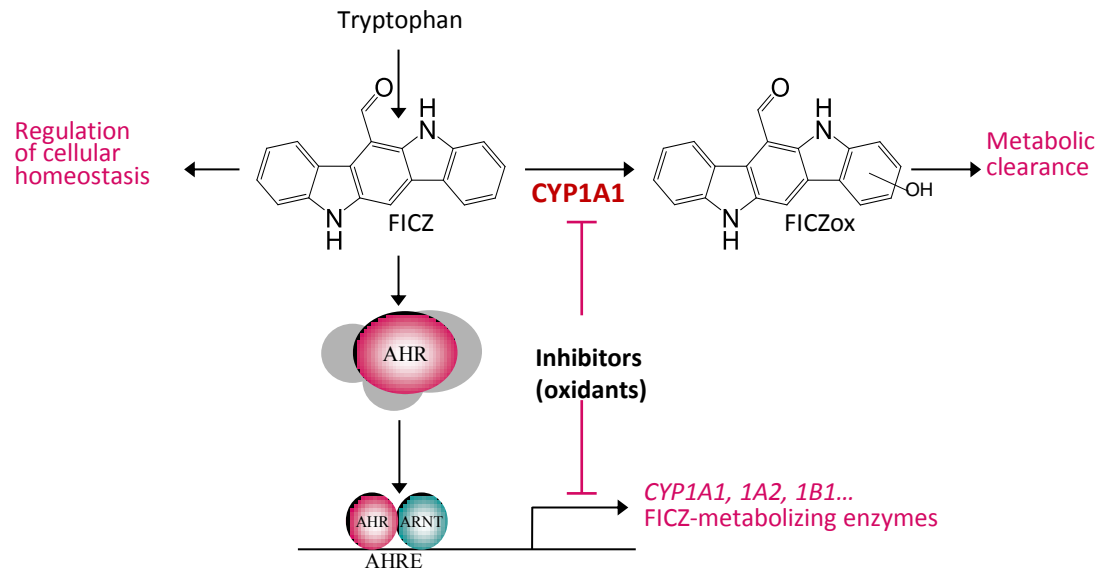
- 6-formylindolo[3,2-*b*]carbazole, FICZ
- Estradiol
- Arachidonic acids
- Melatonin



# Formation of FICZ



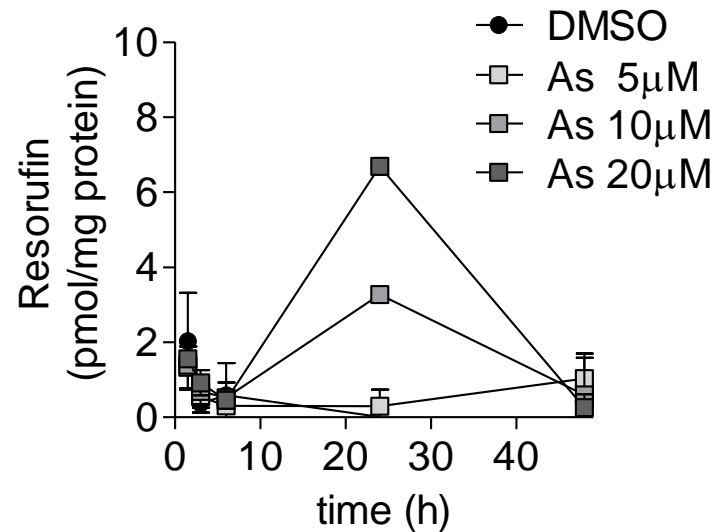
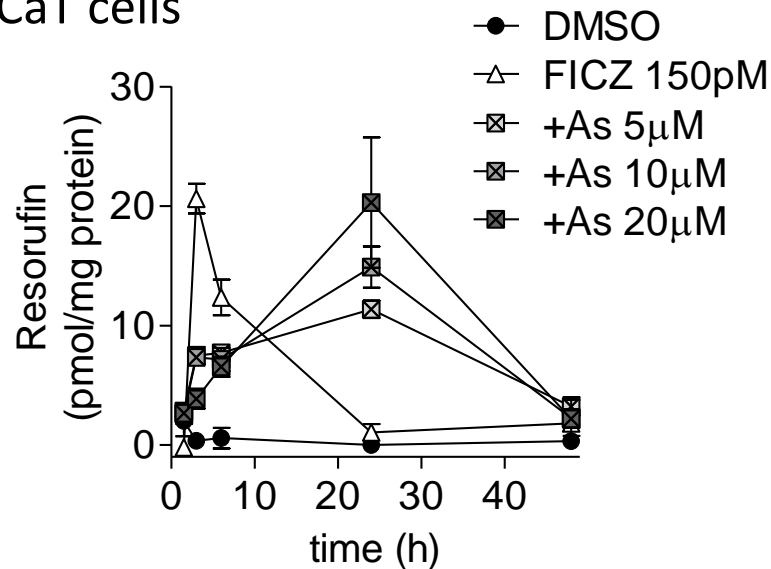
# CYP1 inhibitors are indirect AHR activators



Wincent et al., PNAS, 2012

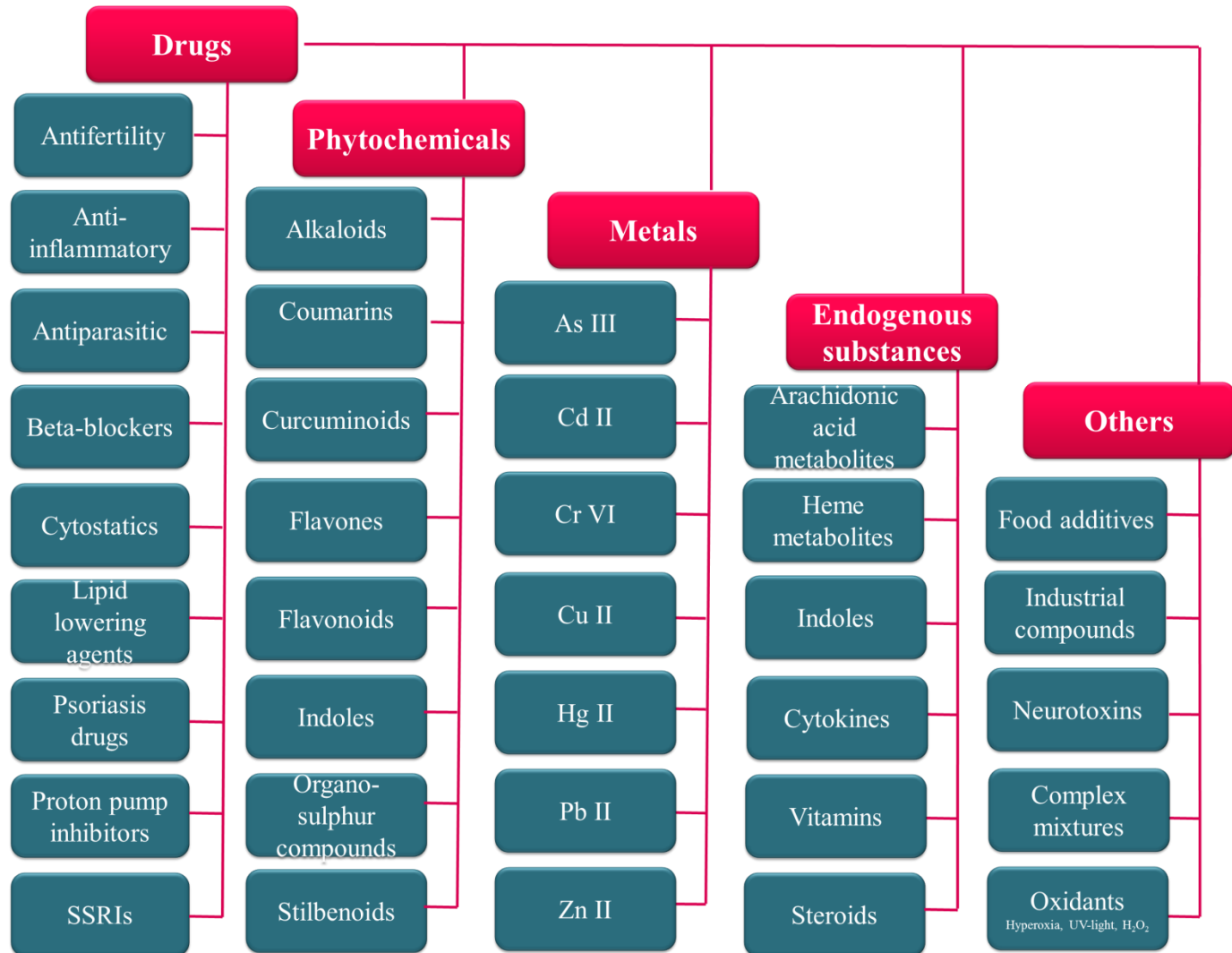
# Sodium arsenic initially represses CYP1A1 activity

HaCaT cells



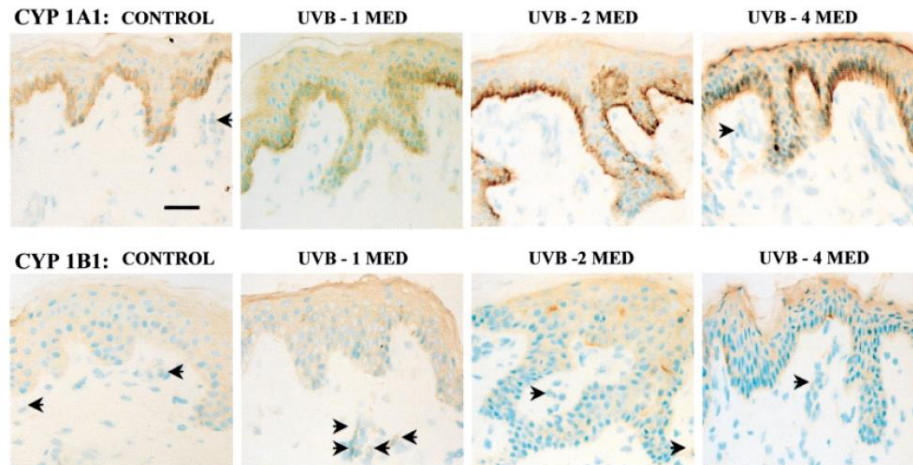
Mohammadi Bardbori, in manuscript

# Non-classical AHR activators



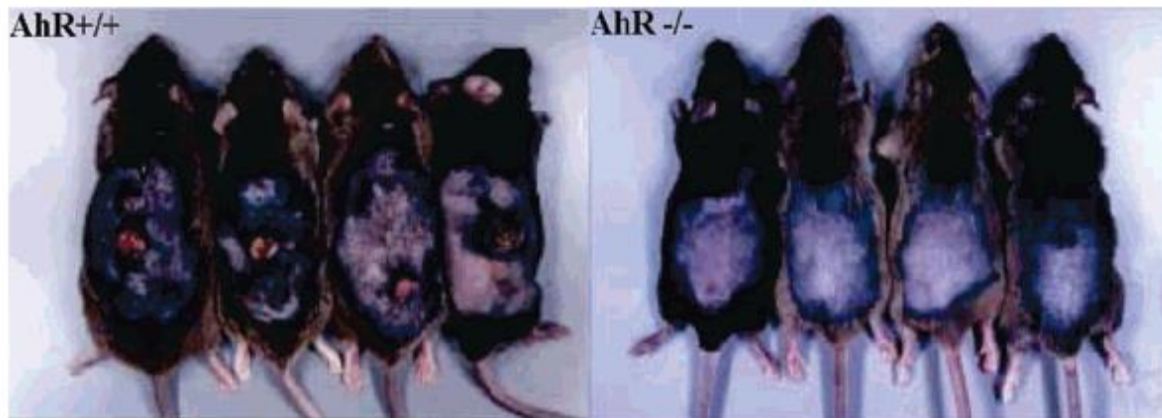


# AHR and skin



- FICZ is formed?

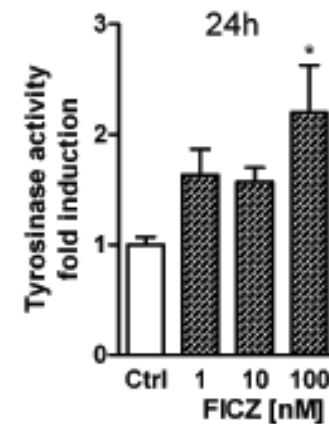
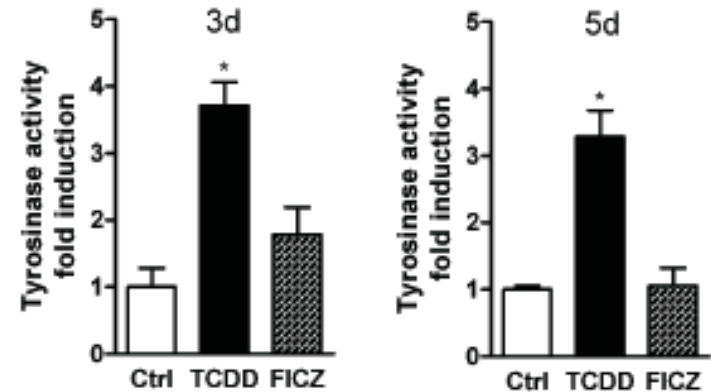
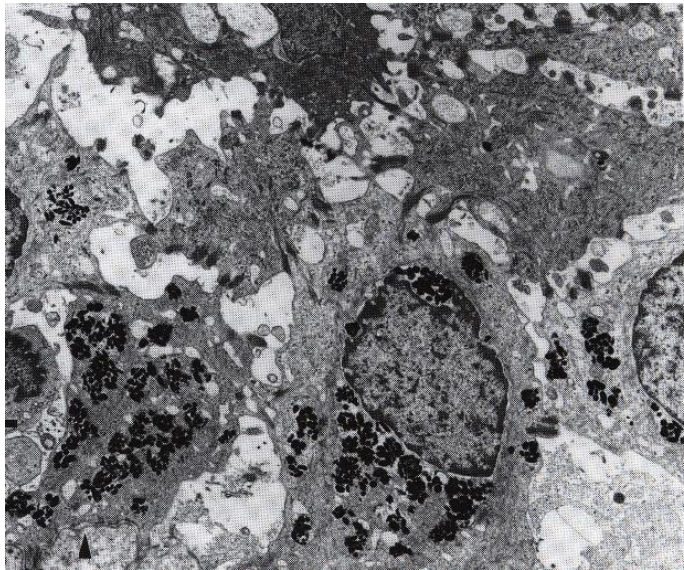
Katiyar et al., JID, 2000



Gross appearance of skin tumors in AhR+/+ and AhR-/- mice after repeated application of airborne particulate extract (APE)

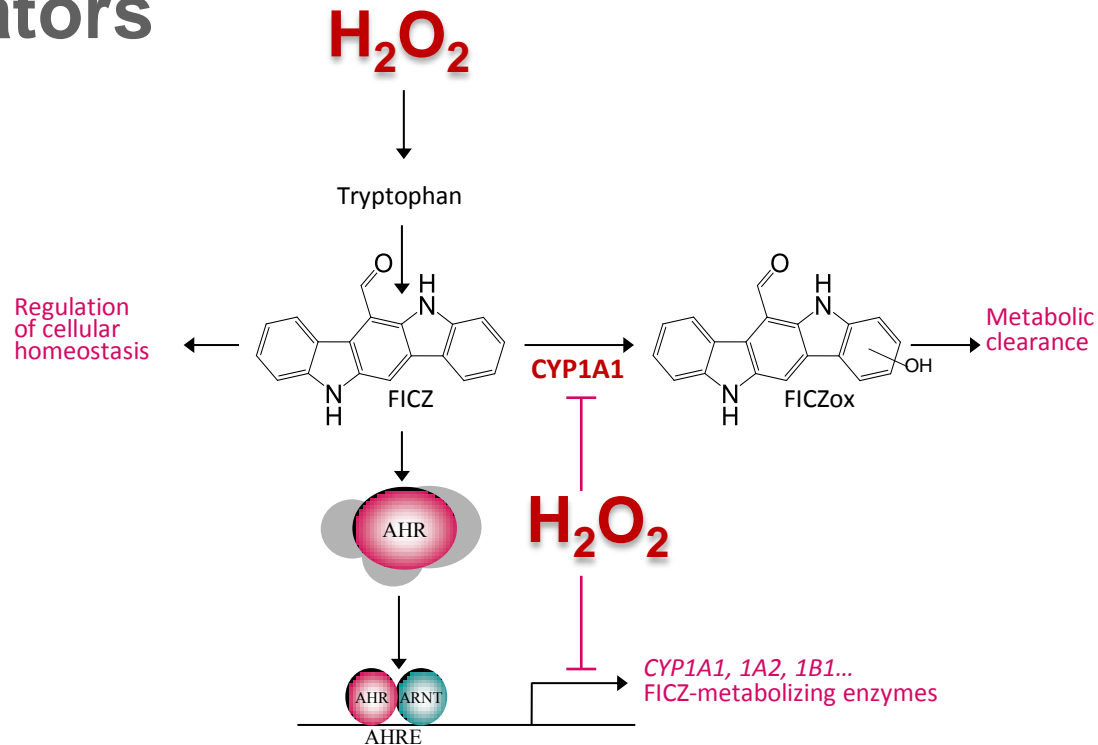
Matsumoto et al., Env Sci Tech, 2000

# FICZ stimulates pigmentation in normal human melanocytes



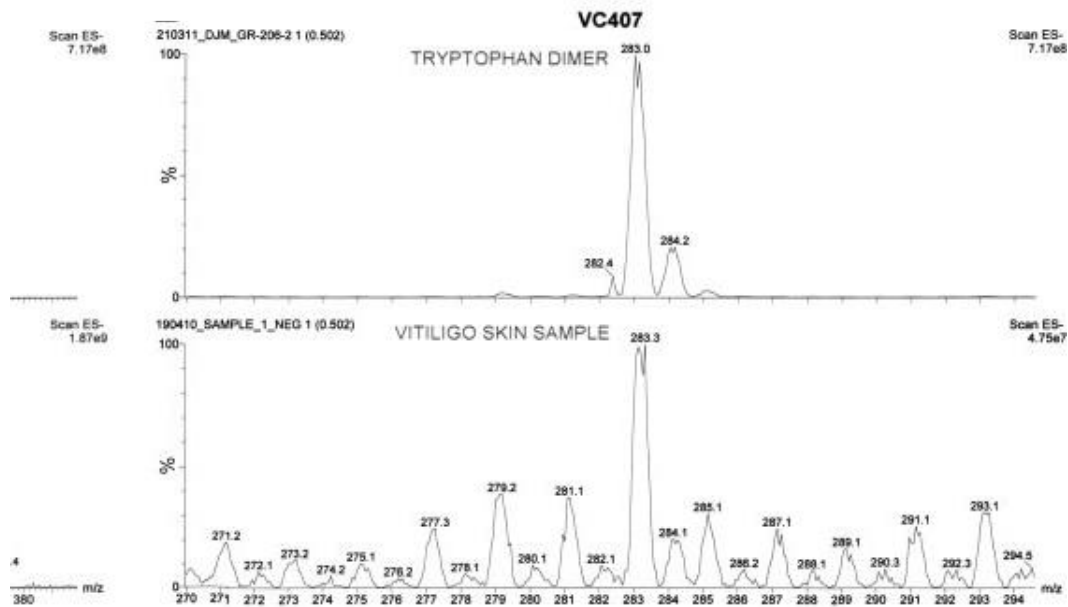
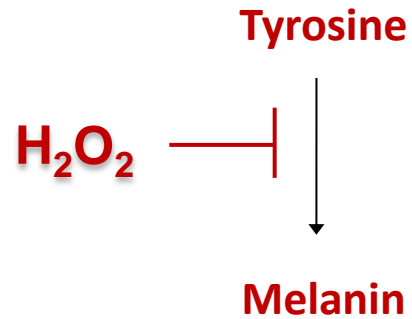
Luecke et al., 2011

# CYP1 inhibitors are indirect AHR activators



Wincent et al., PNAS, 2012

# FICZ is formed in vitiligo skin



# Take home messages

- The AHR is an important sensor of light and oxidants in skin
- CYP1 enzymes are constitutively expressed in skin and induced by UV-light and many chemical substances
- Oxidants may inhibit CYP1 enzymes and block metabolic degradation of FICZ.
  - Effects on T-cell regulation (inflammation, autoimmunity, allergy?)
  - Effects on cell proliferation (carcinogenesis?)

**Thank you!**

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