

## BIOGRAPHICAL SKETCH

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NAME Colin R. Jefcoate	POSITION TITLE Professor of Pharmacology		
eRA COMMONS USER NAME (credential, e.g., agency login) CJEFCOATE			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Oxford University, Oxford, England	B.A./B.S.	1963	Chemistry
Oxford University, Oxford, England	Ph.D.	1966	Chemistry
Basal University, Switzerland	Postdoctoral	1966-1967	
Cornell University, Ithaca, NY	Postdoctoral	1967-1969	
Edinburgh University, Edinburgh, Scotland	Postdoctoral	1969-1972-	
University of Wisconsin, Madison, WI	Postdoctoral	1972-1973	

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

### A. Personal Statement

The laboratory is interested in **P450 Cytochromes (CYPs)** function in both physiological and pathological processes. In the 1980's, we showed that the limiting step in **steroid biosynthesis** from cholesterol is the metabolism of cholesterol to pregnenolone in the inner membrane of specialized mitochondria, catalyzed by CYP11A1. Hormonal regulation occurs first at the level of cholesterol transport into the mitochondria. The mediator of this response is the steroidogenesis acute regulatory protein (StAR). We study how this protein directs cholesterol transfer into mitochondria and, more recently, the hormonal regulation of StAR expression. We have shown that **StAR mRNA** forms a second long transcript that is regulated through AU-rich elements by a PKA-induced phosphoprotein, TIS11b, and that PKA stimulates StAR transcription through suppression of the repressor kinase, SIK, which inhibits CREB and SF1 (R01 DK074819, with G.Hammer, U of Michigan). In 1990, we purified an unusual mouse CYP, subsequently called **Cyp1b1**, which we cloned from a mouse embryofibroblast line. We now study how Cyp1b1 mediates the rapid disruption of bone marrow lymphoid and myeloid progenitor cells by **polycyclic aromatic hydrocarbons** and associated injury repair processes in other exposed tissues (R01 DK072749, with C. Czuprynski). Cyp1b1 is also expressed in early embryo cells, where it appears to be a major contributor to **retinoic acid synthesis**. We find that embryogenesis and later development in Cyp1b1<sup>-/-</sup> mice is very sensitive to vitamin A depletion and that these mice exhibit a substantially decreased **obesity response** to high dietary fat, due to anomalies in the adipose tissue and to enhanced **hepatic fatty acid metabolism**. We are exploring how Cyp1b1-deficient **endothelial cells** exhibit impaired angiogenesis *in vivo*, due to increased oxidative stress (Nader Sheibani, PI; R01 EY018179). We suspect that the endothelial changes may affect the liver and adipose development. We have just developed **Floxed Cyp1b1** mES cells, which will allow us to explore these cell-type specific contributions of Cyp1b1.

### B. Positions and Honors

#### Positions and Employment

1966-1967	NATO Fellow with P. Hemmerich, Basal University, Switzerland
1967-1969	NIH and NATO Fellow with J.L. Gaylor, Cornell University, Ithaca, NY
1969-1972	MRC Fellow with G.S. Boyd, Edinburgh University, Edinburgh, Scotland
1972	Visiting Scientist with W.H. Orme-Johnson, Biochemistry, University of Wisconsin, Madison, WI
1972-1973	Research Associate with W.H. Orme-Johnson, Biochemistry, University of Wisconsin, Madison, WI
1973-1978	Assistant Professor, Pharmacology, University of Wisconsin, Madison, WI

1978-1982	Associate Professor, Pharmacology, University of Wisconsin, Madison, WI
1982-Present	Professor, Pharmacology, University of Wisconsin, Madison, WI
1983-1998	Director, Environmental Toxicology Center, University of Wisconsin, Madison, WI
1998-2003	Director, NIEHS Center for Developmental and Molecular Toxicology, University of Wisconsin, Madison, WI

### **Other Experience and Professional Memberships**

1995-1996	Editor of <i>Physiological Functions of Cytochrome P450</i> , published October, 1996.
2000-	National Cancer Institute Study Group for Research on Genotoxicity of Estrogens.
2000-2003	External Advisor University of New Mexico – NIEHS Center
2001	External Advisor University of California Santa Cruz Toxicology Program
2002	Society of Toxicology – President Molecular Biology Specialty Section
2003	Society of Toxicology Elections Committee
2003	External Advisor - University of Queensland School of Biomedical Sciences
2003	Georgetown University DOD Center of Excellence for Environmental Effects on Breast Cancer
2003-2006	Associate Editor, Toxicological Sciences
2004	Fox Chase Cancer Center NIEHS Center for Environmental and Developmental Effects on Breast Cancer
2004-Present	Associate Editor, Journal National Cancer Institute.
Present	Member of the Society of Toxicology
Present	Member of American Society for Pharmacology and Experimental Therapeutics (ASPET)

### **Honors and Awards**

1964	2 <sup>nd</sup> class Honors in Natural Science (Chemistry)
1966	D. Phil. (Chemistry) under R.O.C. Norman, Oxford (including one year at York University)
1998-2003	WARF Mid-Career Faculty Researcher Award

## **C. Selected Peer-reviewed Publications (Selected from 191 peer-reviewed publications)**

### **Most relevant to the current application**

1. Cho, Y.C., Zheng, W.C., Yamamoto, M., Liu, X., Hanlon, P.R., and Jefcoate C.R. (2005) Differentiation of pluripotent C3H10T1/2 cells rapidly elevates CYP1B1 through a novel process that overcomes a loss of Ah receptor. *Arch. Biochem. Biophys.* **439**, 139-153. PMID: 15967407.
2. Hanlon, P.R., Cimafranca, M.A., Liu, X., Cho, Y.C., and Jefcoate C.R. (2005) Microarray analysis of early adipogenesis in C3H10T1/2 cells: Cooperative inhibitory effects of growth factors and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicol. Appl. Pharmacol.* **207**, 39-58. PMID: 16054899.
3. Liu, X. and Jefcoate, C.R. (2006) 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and epidermal growth factor cooperatively suppress peroxisome proliferator-activated receptor- $\gamma$ 1 stimulation and restore focal adhesion complexes during adipogenesis: selective contributions of Src, Rho, and Erk distinguish these overlapping processes in C3H10T1/2 cells. *Mol. Pharmacol.* **70**, 1902-1915.
4. Tang, Y., Scheef, E.A., Wang, S., Sorenson, C.M., Marcus, C.B., Jefcoate, C.R., and Sheibani, N. (2009) Cyp1b1 expression promotes the proangiogenic phenotype of endothelium through decreased intracellular oxidative stress and thrombospondin-2 expression. *Blood* **113**, 744-754. PMID: 19005183.
5. Tang, Y., Scheef, E.A., Gurel, Z., Sorenson, C.M., Jefcoate, C.R., and Sheibani, N. (2009) Cyp1b1 and endothelial nitric oxide synthase combine to sustain proangiogenic functions of endothelial cells under hyperoxic stress. *Am J Physiol Cell Physiol* **298**, C665-678. PMID: 20032512.

### **Additional recent publications of importance to the field (in chronological order)**

1. Ganem, L.G., Trottier, E., Anderson, A., and Jefcoate, C.R. (1999) Phenobarbital induction of CYP1B1/2 in primary hepatocytes: endocrine regulation and evidence for a single pathway for multiple inducers. *Toxicol. Appl. Pharmacol.* **155**, 32-42. PMID: 10036216.
2. Hanlon, P.R., Ganem, L.G., Cho, Y.C., Yamamoto, M., and Jefcoate, C.R. (2003) AhR- and ERK-dependent pathways function synergistically to mediate 2,3,7,8-tetrachlorodibenzo-*p*-dioxin suppression of peroxisome proliferator-activated receptor- $\gamma$ 1 expression and subsequent adipocyte differentiation. *Toxicol. Appl. Pharmacol.* **189**, 11-27. PMID: 12758056.

3. Zheng, W., Brake, P.B., Bhattacharyya, K.K., Zhang, L., Zhao, D., and Jefcoate, C.R. (2003) Cell selective cAMP induction of rat CYP1B1 in adrenal and testis cells. Identification of a novel cAMP-responsive far upstream enhancer and a second AhR receptor-dependent mechanism. *Arch. Biochem. Biophys.* **416**, 53-67. PMID: 12859982.
4. Zhang, L., Zheng, W., and Jefcoate, C.R. (2003) Ah receptor regulation of mouse *Cyp1B1* is additionally modulated by a second novel complex that forms at two AhR response elements. *Toxicol. Appl. Pharmacol.* **192**, 174-190. PMID: 14550751.
5. Zheng, W. and Jefcoate, C.R. (2005) Steroidogenic factor-1 interacts with cAMP response element-binding protein to mediate cAMP stimulation of CYP1B1 via a far upstream enhancer. *Mol. Pharmacol.* **67**, 499-512. PMID: 15523052.
6. Hanlon, P.R., Zheng, W., Ko, A.Y., and Jefcoate, C.R. (2005) Identification of novel TCDD-regulated genes by microarray analysis. *Toxicol. Appl. Pharmacol.* **202**, 215-228. PMID: 15667827.
7. Jefcoate C.R. (2006) Liver X receptor opens a new gateway to StAR and to steroid hormones. *J. Clin. Invest.* **116**, 1832-1835. PMID: 16823483.
8. Duan, H. and Jefcoate C.R. (2007) The predominant cAMP-stimulated 3.5 kb StAR mRNA contains specific sequence elements in the extended 3'UTR that confer high basal instability. *J. Mol. Endocrinol.* **38**, 159-179. PMID: 17242178.
9. Jefcoate CR, Wang S, Liu X. (2008) Methods That Resolve Different Contributions of Clonal Expansion to Adipogenesis in 3T3-L1 and C3H10T1/2 Cells. *Methods Mol Biol.* **456**, 173-193.
10. Halberg, R.B., Larsen, M.C., Elmergreen, T.L., Ko, A.Y., Irving, A.A., Clipson, L., and Jefcoate, C.R. (2008) *Cyp1b1* exerts opposing effects on intestinal tumorigenesis via exogenous and endogenous substrates. *Cancer Res.* **68**, 7394-7402. PMID: 18794127.

## D. Research Support

### Ongoing Research Support

#### ACTIVE

R01 DK072749 Jefcoate (PI)

03/01/07-02/29/12

NIH

Liver Vs Bone PAH Metabolism: Synergy with TNF in Bone

Major goal: To determine the mechanism of generation of reactive polycyclic aromatic hydrocarbon metabolites in bone marrow and how this alters hematopoiesis.

R01 DK074819 Jefcoate (PI)

07/01/08-06/30/13

NIH

StAR Expression: Integration of Transcription with Regulation via the mRNA 3'UTR

Major goal: (1) Explore the hypothesis that protein kinase C-initiated stimulation of StAR transcription is synergistically enhanced by low levels of cAMP/PKA; (2) Further develop our finding that Br-cAMP, but not PKC, rapidly stimulates TIS11b, a newly identified regulator of post-transcriptional regulation; (3) Address the hypothesis that hormonal regulation (particularly by ACTH) initiates signaling through both cAMP/PKA and Ca/PKC pathways that can potentially utilize both synergy in transcription and TIS11b modulation of post-transcriptional processes.

R01 EY018179 Sheibani (PI), Jefcoate (Co-PI)

08/01/09-07/31/11

NIH

CYP1B1 and Retinopathy of Prematurity

Major goal: Delineate the physiological role of CYP1B1 in the modulation of retinal vascular oxidative stress and its impact on expression and activity of eNOS and TSP2, and the role of NF- $\kappa$ B in modulation of these genes.

## Completed Research Support

- R01 DK55302                      Jefcoate (PI)    03/15/99-02/28/03  
NIH/NIDDK  
Mechanism of TCDD Suppression of Adipogenesis  
The major goals of this project were: (1) to elucidate the mechanism of suppression of differentiation of mouse embryo fibroblasts to adipocytes; (2) to evaluate the possible role of Cyp1b1.
- R01 CA81493                      Czuprynski (PI) Jefcoate (Co-PI)    05/01/99-02/28/04  
NIH/NCI  
Mechanisms of DMBA-Induced Bone Marrow Toxicity  
The major goal of this project was to examine the role of Cyp1b1 in the ability of DMBA-treated bone marrow stromal cells to cause apoptosis in developing B lymphocytes.
- R01 ES09827                      Jefcoate (PI)    02/01/00-01/31/05  
NIH/NIEHS  
Disruption of Steroidogenesis by Arsenite  
The major goal of this project was to study the inhibitory effects of arsenite on cholesterol metabolism.
- R01 CA87609                      Jefcoate (PI)    04/01/01-03/31/06  
NIH/NCI  
Polycyclic Hydrocarbons and CYP1B1 in Breast Cancer  
The major goals of this project are: (1) to test the hypothesis that CYP1B1 in human breast epithelial cells is a major contributor to carcinogenic activity of PAHs in this tissue; (2) to show that the expression is substantially dependent on mammary development.
- W81XWH-06-1-2005                      Jefcoate (PI)    12/15/05-04/14/07  
Department of Defense  
Regulation of Tumor Cell Growth by the Mesenchymal Environment of the Bone Marrow is Enhanced by a High Fat Diet  
Major goals: (1) Characterize how *in vivo* adipogenesis in bone marrow stromal cells (BMS) affects the growth of LnCAP prostate cell lines; (2) Identify how BMS adipogenesis *in vivo* changes the growth support for LnCAP cells; (3) Identify growth stimulatory factors released from BMS under conditions that optimally stimulate LnCAP cell growth.
- P50 DK065303                      Bushman (PI); Jefcoate (Project Leader)    09/01/05-08/31/07  
NIH  
Mechanisms for Acquired Changes in Prostate Growth Regulation: Development – Project 1  
Major goals: (1) Examine the impact of bone stromal cell differentiation on prostate cancer cell growth