

# Global Gene Expression Profiling in Neonatal Rat Myocardium in Response to the Anti-diabetic Drug Rosiglitazone

Chao-Jen Wong<sup>1,\*</sup>, Elliot Kleiman<sup>1</sup>, Frank Gonzales<sup>3</sup>, Paul Paolini<sup>1,2</sup>,  
Gary Hardiman<sup>4</sup>, and Roman Šášik<sup>5</sup>

1. Computational Science Research Center, San Diego State University, San Diego, CA, USA
  2. Department of Biology, San Diego State University, San Diego, CA, USA
  3. School of Public Health, San Diego State University, San Diego, CA, USA
  4. Department of Medicine, University of California San Diego, La Jolla, CA, USA
  5. University of California San Diego Cancer Center, La Jolla, CA, USA
- \*E-mail: [cjwong@myth.sdsu.edu](mailto:cjwong@myth.sdsu.edu)

A recent meta-analysis on the relationship between the anti-diabetic drug rosiglitazone (Avandia) and cardiovascular death has created public concern and controversy regarding the drug's safety. An alternative meta-analysis approach using clinical data and continuity corrections concludes that the link between rosiglitazone and its risk is not statistically significant [1], while RT-PCR studies suggest a possible enhancement in cardioprotective mechanisms over a forty-eight hour time frame [2].

In this work, we utilize microarray technology to advance our understanding of the biological influences of rosiglitazone in heart cells. We have employed Illumina's BeadChip<sup>TM</sup> technology to examine the time course gene expression of ventricular myocytes under the treatment of the drug in neonatal rats (*Rattus norvegicus*). We report the general expression profiling and, most importantly, interpret the data to determine if the drug significantly affects the regulatory networks and pathways that are directly involved in the contractile response of heart cells via the calcium signaling pathway that plays a pivotal role in regulating myocyte contraction. In implementing these objectives, we have: (i) identified differentially expressed genes using conservative statistical analysis and bioinformatic methods that limit Type I errors [3]; (ii) delineated biological processes and molecular functions that may be overrepresented; and (iii) recognized gene expression patterns based on a subset of genes exhibiting significantly differential expression values.

Our preliminary results show that monocarboxylic acid metabolic, fatty acid metabolic, lipid metabolic, and cellular lipid metabolic processes are overrepresented by differentially expressed genes under the drug treatment, as shown in Table 1. The up- and down-regulated genes are listed in Table 2; out of these thirty-two genes, there is no gene directly involved in the the calcium signaling pathway, which suggests rosiglitazone does not dramatically alter cardiac contractility. Further work to identify gene regulatory networks from time course expression data will provide a global view of transcriptional network of heart cell responses to rosiglitazone, which may also demonstrate any connection between the drug and heart failure.

GO ID	GO Term	<i>p</i> -value	Count	Size
GO:0032787	monocarboxylic acid metabolic process	0.00038	5	170
GO:0006631	fatty acid metabolic process	0.00092	4	118
GO:0006629	lipid metabolic process	0.00209	6	368
GO:0044255	cellular lipid metabolic process	0.00493	5	303

Table 1: Biological process ontology terms overrepresented by genes differentially expressed in cardiac myocytes under the treatment of rosiglitazone. The *size* value represents the number of genes associated with that particular biological process. The *count* value represents the number of genes in a particular biological process that are significantly regulated.

## References

- [1] G. A. Diamond, L. Bax, and S. Kaul, Uncertain Effects of Rosiglitazone on the Risk for Myocardial Infarction and Cardiovascular Death, *Annals of Internal Medicine* 147(8), 12 October 2007.
- [2] R. Shah, F. Gonzales, E. Golez, D. Augustin, S. Caudillo, A. Abbott, J. Morello, P. McDonough, P. Paolini, and H. Shubeita, The Anti-diabetic Agent Rosiglitazone Upregulates SERCA2 and Enhances TNF- $\alpha$  and LPS-Induced NF- $\kappa$ B-Dependent Transcription and TNF- $\alpha$ -Induced IL-6 Secretion in Ventricular Myocytes, *Cellular Physiology and Biochemistry* 15:41-50, 2004.
- [3] R. Gentleman, V. Carey, W. Huber, R. Irizarry, and S. Duoit, *Bioinformatics and Computational Biology Solutions Using R and Bioconductor*, Springer (2005).

Symbol	Gene Name	<i>p</i> -value	
△	adipose	differentiation related protein	6.01e-9
△	Retsat	all-trans-13,14-dihydroretinol saturase	2.79e-9
△	Ccl6	chemokine (C-C motif) ligand 6	4.55e-7
△	Acbal	ATP-binding cassette, sub-family A (ABC1)	4.44e-6
△	Etfdh	electron-transferring-flavoprotein dehydrogenase	7.54e-6
△	Decr1	2,4-dienoyl CoA reductase 1, mitochondrial	1.74e-5
▽	RGD1564665*	similar to RIKEN cDNA 4930555G01	2.89e-5
△	Olr472*	olfactory receptor 472	4.29e-5
△	Acot7	acyl-CoA thioesterase 7	5.26e-5
▽	Gusb	glucuronidase, beta	9.54e-5
△	Srebfl	sterol regulatory element binding factor 1	1.15e-4
▽	Cd83*	CD83 antigen	5.84e-4
▽	Entpd2	ectonucleoside triphosphate diphosphohydrolase 2	0.0005
△	Mgst2*	microsomal glutathione S-transferase 2	0.0006
▽	RGD1562868*	similar to squamous cell carcinoma antigen 2	0.0007
△	Tiparp*	TCDD-inducible poly(ADP-ribose) polymerase	0.0008
△	Prg4*	proteoglycan 4, (megakaryocyte stimulating factor)	0.0008
▽	Map2k6	mitogen-activated protein kinase kinase 6	0.0011
△	Gpd1	glycerol-3-phosphate dehydrogenase 1 (soluble)	0.0011
▽	Coro1a	coronin, actin binding protein 1A	0.0015
▽	Ppt1	palmitoyl-protein thioesterase 1	0.0015
△	Hccs*	holocytochrome c synthetase	0.0017
△	Lpl	lipoprotein lipase	0.0020
△	Csrp1	cysteine and glycine-rich protein 1	0.0024
▽	Aif1	allograft inflammatory factor 1	0.0024
▽	Gbp1*	guanylate binding protein 1, interferon-inducible	0.0028
△	Dpep1	dipeptidase 1 (renal)	0.0030
△	Acta1	actin, alpha 1, skeletal muscle	0.0031
△	Grip2	glutamate receptor interacting protein 2	0.0033
▽	Ceacam10	CEA-related cell adhesion molecule 10	0.0033
▽	Tbc1d7*	TBC1 domain family, member 7	0.0035
▽	Ncstn	nicastrin	0.0038
▽	LOC501250	hypothetical LOC501250	0.0038
△	Cpt1a	carnitine palmitoyltransferase 1a, liver	0.0041
▽	mrpl9	mitochondrial ribosomal protein L9	0.0044
△	Ptgis	prostaglandin I2 (prostacyclin) synthase	0.0048
▽	Pink1*	PTEN induced putative kinase 1	0.0050

Table 2: Differentially expressed genes in response to rosiglitazone. The symbols △ and ▽ represent up- and down-regulation, respectively. The symbol \* indicates predicted gene.