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(54) **METHODS AND SYSTEMS FOR PHARMACOGENOMIC TREATMENT OF CARDIOVASCULAR CONDITIONS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,591,734	A	1/1997	Bianchi et al.	
5,632,276	A	5/1997	Eidelberg et al.	
5,981,174	A	11/1999	Wolf et al.	
6,114,128	A	9/2000	Håkansson et al.	
6,399,310	B1	6/2002	Murphy, Jr. et al.	
6,610,489	B2	8/2003	Wolffe et al.	
2002/0037849	A1*	3/2002	Fruebis et al.	514/12
2002/0132234	A1*	9/2002	Moskowitz	435/6
2003/0092620	A1*	5/2003	Lucas et al.	514/12
2004/0166491	A1*	8/2004	Henderson	435/6
2005/0065079	A1*	3/2005	Scalia et al.	514/12
2006/0058507	A1*	3/2006	Briggs et al.	530/350
2006/0177838	A1	8/2006	Ligget et al.	
2008/0096982	A1	4/2008	Liggett et al.	
2008/0248476	A1	10/2008	Cargill et al.	
2008/0300228	A1*	12/2008	Cerri et al.	514/172

FOREIGN PATENT DOCUMENTS

WO	03/018745	3/2003
WO	2006/031955	6/2006
WO	2007/060206	5/2007
WO	2010/018855	9/2010

OTHER PUBLICATIONS

NCBI website dbSNP database ss85330593 Submitted date Dec. 4, 2007.*
Ferrandi. Journal of Cardiovascular Pharmacology. 2002. 40: 881-889.*
Wall. Nature Reviews—Genetics. 2002. 4: 587-59.*
Pal. The Prostate. 2009. 69:1548-1556.*
Zill. Molecular Psychiatry. 2004. 9: 1030-1036.*
Furstenwerth. Critical Care Medicine. 2013. 41(7): e140.*
Takahashi (Hypertension Research. 2011. 34: 1147-1160.*
Cluster Report for rs2345088 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2345088>).*
Cluster Report for rs16877182 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=16877182>).*
Cluster Report for rs1689522 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=16893522>).*
Cluster Report for rs2461911 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2461911>).*
Cluster Report for rs5013093 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=5013093>).*
Cluster Report for rs12513375 (retrieved on Nov. 21, 2013 from: < http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=12513375>).*
Winnicka. Acta Poloniae Pharmaceutica—Drug Research. 2005. 62(1): 75-79.*
Clinical Trial NCT00415038. Retrieved on May 13, 2015 from the internet: https://clinicaltrials.gov/ct2/show/record/NCT00415038.*
PCT International Search Report for PCT/EP2010/065589 in the name of Rostaquo S.p.A. et al. Mail Date: May 24, 2011.
PCT Written Opinion for PCT/EP2010/065589 in the name of Rostaquo S.p.A. et al. Mail Date: Feb. 9, 2012.
PCT International Preliminary Report on Patentability for PCT/EP2010/065589 in the name of Rostaquo S.p.A. et al. Mail Date: Mar. 14, 2012.
European Search Report for 09177111.3-1216 in the name of Rostaquo S.p.A. et al. completed on Jul. 16, 2010.
Ferrari, P. et al. "Rostafuroxin: an ouabain antagonist that corrects renal and vascular Na^+—K^+—ATPase alterations in ouabain and adducin-dependent hypertension", *Am J Physiol Regulatory Integrative Comp Physiol*, 290:529-535, Mar. 1, 2006.

(Continued)

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(57) **ABSTRACT**

Methods and systems are provided herein that are based on the effects of genetic variations on the biological activities associated to rostafuroxin in an individual. In particular, compositions, methods and systems are herein described that are based on an indentified influence on an individual response to rostafuroxin of one or more polymorphisms in an intergenic or intragenic region of a gene selected from the group consisting of KCNS3, THSD7A, FAM46A, LOC389970, HLA-G, and TTC29, and/or a genetic variation in linkage disequilibrium therewith.

25 Claims, 10 Drawing Sheets