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(54) Biomarkers for cardiovascular side-effects induced by cox-2 inhibitory compounds

(57) Cardiovascular tissue mRNA expression profiles in monkeys treated with coxibs was analyzed. Genomic data indicated that the animals showing vasculitis exhibit a specific mRNA expression pattern. The pattern includes gene expression changes involved in blood and endothelial cell (EC) activation, interaction of blood cells with EC, activation of INFγ pathway, and release of pro-inflammatory cytokines and chemo-attractants. These results provide direct evidence of minimal vasculitis together with corresponding genomic signature and peripheral biomarkers for minimal vasculatis. These results also suggest that treatment might triggers/aggravate a clinically latent cardiovascular disorder in the context of an endothelium tropic viral infection and/or an autoimmune vascular disorder.

The histopathological examination revealed marginal vascular changes consistent with the genomic findings. Measurement of soluble proteins present in serum and plasma using a multiplex assay were in line with the genomic results, showing the increased level of INFγ inducible proteins. Increased expression of CXCL10 chemokine was confirmed by an ELISA both in serum and plasma. Use of these peripheral biomarkers allows a safe usage of cox-2 inhibitory compounds in clinics and selection of cox-2 inhibitory follow-up compounds with no cardiovascular toxicity. These data together with biochemical and histopathological findings suggest that the specific cox2 inhibitor may exaggerate host immune response during some specific viral infections with endothelial tropism, or subjacent vascular autoimmune disorders.

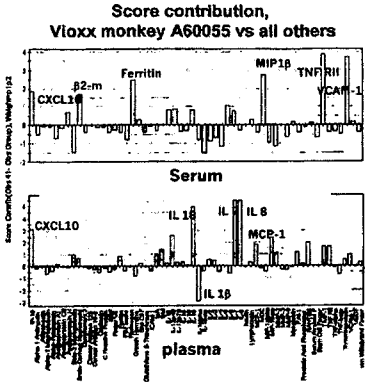

FIG. 5

Protein profiling in serum and plasma using RBM® multiplex assay.
The Monkey #A60055 exhibits a specific protein expression profile: soluble MHC molecules, b2-m, other chemokines, cytokines (INFγ, CXCL10, MCP-1, IL-18, TNF RII, IL1b), and soluble VCAM-1.

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EUROPEAN SEARCH REPORT

Application Number
EP 10 01 0203

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	SCHNEIDER F ET AL: "Fatal allergic vasculitis associated with celecoxib", LANCET THE, LANCET LIMITED. LONDON, GB, vol. 359, no. 9309, 9 March 2002 (2002-03-09), pages 852-853, XP004794659, ISSN: 0140-6736, DOI: DOI:10.1016/S0140-6736(02)07922-9 * the whole document *	1-3	INV. G01N33/53 A61K45/06 C12Q1/68
A	PALOP-LARREA VICENTE ET AL: "Leukocytoclastic vasculitis related to rofecoxib", ANNALS OF PHARMACOTHERAPY, HARVEY WHITNEY BOOKS COMPANY, vol. 37, no. 11, 1 November 2003 (2003-11-01), pages 1731-1732, XP009142039, ISSN: 1060-0280 * the whole document *	1-3	
A	STEFAN P BERGER ET AL: "Proteinase 3, the Major Autoantigen of Wegener s Granulomatosis, Enhances IL-8 Production by Endothelial Cells In Vitro1", JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 7, no. 5, 1 January 1996 (1996-01-01) , pages 694-701, XP007916368, ISSN: 1046-6673 * abstract *	1-3	TECHNICAL FIELDS SEARCHED (IPC) G01N

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~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
Munich	5 May 2011	Behrens, Ralf

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

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Application Number
EP 10 01 0203

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	MASARU TERAI ET AL: "Dramatic decrease of circulating levels of monocyte chemoattractant protein-1 in Kawasaki disease after gamma globulin treatment", JOURNAL OF LEUKOCYTE BIOLOGY, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, US, vol. 65, 1 May 1999 (1999-05-01), pages 566-572, XP007916366, ISSN: 0741-5400 * abstract * -----	1-3	
A	GUHER SARUHAN-DIRESKENELI ET AL: "Cytokines and chemokines in neuro-Behc et s disease compared to multiple sclerosis and other neurological diseases", JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 145, 1 December 2003 (2003-12-01), pages 127-134, XP007916367, ISSN: 0165-5728, DOI: DOI:10.1016/J.JNEUROIM.2003.08.040 [retrieved on 2003-10-27] * abstract * -----	1-3	TECHNICAL FIELDS SEARCHED (IPC)
L	GIANNITSIS EVANGELOS: "Rationale for testing the cardiovascular risk for patients with COX-2 inhibitors on the basis of biomarker NT-proBNP.", CLINICAL LABORATORY. 2005, vol. 51, no. 1-2, 2005, pages 63-72, XP008056286, ISSN: 1433-6510 * the whole document * -----		

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DOCUMENTS CONSIDERED TO BE RELEVANT

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A	SARI SUOMELA ET AL: "Interferon alpha-Inducible Protein 27 (IFI27) is Upregulated in Psoriatic Skin and Certain Epithelial Cancers", JOURNAL OF INVESTIGATIVE DERMATOLOGY, NATURE PUBLISHING GROUP, GB, vol. 122, no. 3, 1 March 2004 (2004-03-01) , pages 717-721, XP007918474, ISSN: 0022-202X -----	1-3	

TECHNICAL FIELDS SEARCHED (IPC)

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Application Number
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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

1-3(partially)

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 10 01 0203

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-3(partially)

Use of a member of the family of chemokines as biomarker for predicting cardiovascular side effects induced by a cox-2 inhibitor (eg CCL2, CXCL-10).

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2. claims: 1-3(partially)

Use of interferon, alpha-inducible protein 27 as biomarker for predicting cardiovascular side effects induced by a cox-2 inhibitor.

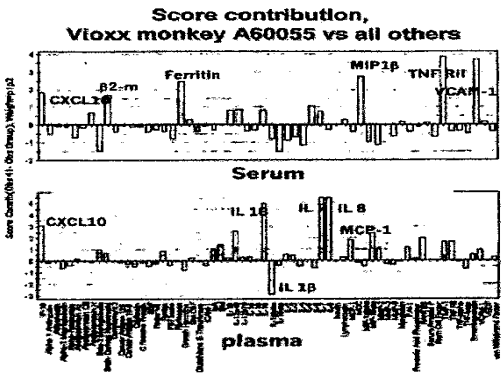
3-100. claims: 1-3(partially)

Use of other genes, or gene families, of table 1, or combinations thereof, for predicting cardiovascular side effects induced by a specific cox-2 inhibitor.

专利名称(译)	由cox-2抑制性化合物诱导的心血管副作用的生物标志物		
公开(公告)号	EP2287608A3	公开(公告)日	2011-06-15
申请号	EP2010010203	申请日	2006-03-10
[标]申请(专利权)人(译)	FIRALIS		
申请(专利权)人(译)	FIRALIS SAS		
当前申请(专利权)人(译)	FIRALIS SAS		
[标]发明人	FIRAT HUESEYIN BOISCLAIR JULIE GRENET OLIVIER PERENTES ELIAS SCHUMACHER MARTIN M		
发明人	FIRAT, HUESEYIN BOISCLAIR, JULIE GRENET, OLIVIER PERENTES, ELIAS SCHUMACHER, MARTIN, M.		
IPC分类号	G01N33/53 A61K45/06 C12Q1/68		
CPC分类号	C12Q1/6883 A61K31/00 C12Q2600/106 C12Q2600/142 C12Q2600/158 G01N33/68 G01N2800/328		
代理机构(译)	布鲁尔MARKUS		
优先权	60/661192 2005-03-11 US		
其他公开文献	EP2287608A2 EP2287608B1		
外部链接	Espacenet		

摘要(译)

分析了用coxibs处理的猴子中的心血管组织mRNA表达谱。基因组数据表明显示血管炎的动物表现出特异性mRNA表达模式。该模式包括涉及血液和内皮细胞（EC）活化的基因表达变化，血细胞与EC的相互作用，INFγ途径的激活，以及促炎细胞因子和化学引诱剂的释放。这些结果提供了最小血管炎的直接证据以及相应的基因组特征和用于最小血管的外周生物标志物。这些结果还表明，在内皮向性病毒感染和/或自身免疫性血管疾病的情况下，治疗可能触发/加重临床潜伏性心血管疾病。该组织病理学检查显示边缘血管变化与基因组结果一致。使用多重测定法测量血清和血浆中存在的可溶性蛋白质与基因组结果一致，显示INFγ诱导蛋白质的水平增加。通过ELISA在血清和血浆中证实CXCL10趋化因子的表达增加。使用这些外周生物标志物可以在临床中安全使用cox-2抑制性化合物，并选择无心血管毒性的cox-2抑制性随访化合物。这些数据以及生化和组织病理学研究结果表明，特定的cox2抑制剂可能在某些特定的病毒感染过程中夸大宿主的免疫反应，这些感染伴有内皮向性或下方的血管自身免疫障碍。



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Protein profiling in serum and plasma using RBM® multiplex assay.
The Monkey #A60055 exhibits a specific protein expression profile: soluble MHC molecules, b2-m, other chemokines, cytokines (INFγ, CXCL10, MCP-1, IL-18, TNF RII, IL1b), and soluble VCAM-1.