

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/067766 A2

- (51) International Patent Classification⁷: **A61B** L. [US/US]; 1905 11th Street S.W., Rochester, MN 55902 (US).
- (21) International Application Number: PCT/US02/05760
- (22) International Filing Date: 20 February 2002 (20.02.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/792,686 23 February 2001 (23.02.2001) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/792,686 (CON)
Filed on 23 February 2001 (23.02.2001)
- (71) Applicant (*for all designated States except US*): **MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH** [US/US]; 200 First Street S.W., Rochester, MN 55905 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **GORONZY, Jorg, J.** [DE/US]; 1804 Spel Lane S.W., Rochester, MN 55902 (US). **WEYAND, Cornelia, M.** [DE/US]; 1804 Spel Lane S.W., Rochester, MN 55902 (US). **KOPECKY, Stephen,**
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *without international search report and to be republished upon receipt of that report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHODS AND MATERIAL FOR EVALUATING CARDIOVASCULAR CONDITIONS

(57) Abstract: The invention provides methods and materials for evaluating cardiovascular conditions (e.g., angina conditions). Specifically, the invention provides methods and materials related to determining whether or not a mammal has at least one unstable plaque. The invention also provides kits for assessing cardiovascular conditions, substantially pure populations of cells, and methods of identifying compounds to treat life-threatening cardiovascular conditions (e.g., unstable angina).



WO 02/067766 A2

METHODS AND MATERIALS FOR EVALUATING CARDIOVASCULAR CONDITIONS

5

BACKGROUND

1. Technical Field

The invention relates to methods and materials involved in evaluating cardiovascular conditions. Specifically, the invention relates to methods and materials involved in determining whether or not a mammal has an unstable plaque.

10

2. Background Information

Coronary artery disease is characterized by long periods of clinical stability with few or no symptoms. In addition, classical pathologic studies have demonstrated that the disease is commonly far advanced anatomically before any symptoms are reported (Blumgart HL *et al.*, *Am. Heart Journal*, 19:1 (1940)). An additional characteristic of coronary artery disease is a propensity to an abrupt, sometimes catastrophic, change in a previous stable or silent clinical course leading to a variety of acute coronary syndromes (Fuster V *et al.*, *N. Engl. J. Med.* 326:310-318 (1992)).

15

20

SUMMARY

The invention involves evaluating cardiovascular conditions. Specifically, the invention provides methods and materials related to determining whether or not a mammal has an unstable plaque. In addition, the invention provides methods and materials related to determining whether or not a mammal is at risk for developing an unstable plaque. The invention also provides kits for assessing cardiovascular conditions, substantially pure populations of cells, and methods of identifying compounds that can be used to treat a life-threatening cardiovascular condition (e.g., unstable angina) or reduce the risk of developing a life-threatening cardiovascular condition (e.g., the presence of unstable plaques).

25

30

The term “cardiovascular condition” as used herein refers to symptomatic (e.g., angina conditions) and asymptomatic coronary artery disease. The term “angina condition” as used herein refers to a cardiovascular condition where the mammal experiences chest pain resulting from an inadequate delivery of oxygen to the heart muscle. Typically, this chest pain is characterized as a heavy or squeezing pain in the midsternal area of the chest. Angina conditions can be either stable or unstable. In general, stable angina refers to an angina condition that is not changing in severity, duration, or frequency, while unstable angina refers to an angina condition that is increasing in severity, duration, or frequency. Typically, unstable angina patients are at an increased risk of having a myocardial infarction as compared to stable angina patients.

The term “unstable plaque” as used herein refers to an inflamed plaque that can rupture at any time possibly leading to a thrombotic event and/or myocardial infarction. Typically, inflamed plaques are small plaques. The term “stable plaque” as used herein refers to a plaque that is not inflamed. Plaques that are not inflamed typically do not rupture.

The methods and materials described herein can be used to identify mammals having at least one unstable plaque or mammals having an increased risk of developing at least one unstable plaque. Thus, the invention provides methods and materials that can be used to inform medical professionals about the risk a patient faces with respect to experiencing a myocardial infarction. In other words, the methods and materials described herein can be used to screen patients (e.g., patients with angina, patients that smoke, and patients that are overweight) such that those patients with at least one unstable plaque and, therefore, at an increased risk for myocardial infarction are identified and appropriately treated. For example, patients presenting an angina condition can be screened using the methods and materials described herein to identify those patients having unstable plaques. When it is determined that a patient has an unstable plaque, then that patient can be further evaluated by, for example, angiography. Since angiography is typically used to evaluate patients suspected to have unstable angina, the methods and materials provided herein can allow medical professionals reliably determine which patients need further evaluation and which patients do not. In addition, methods and materials described herein can provide important information about a

patient's cardiovascular condition (e.g., angina condition) in both an efficient and objective manner.

In general, the invention features a method for determining whether or not a mammal (e.g., human) has an unstable plaque. The method includes determining whether or not a sample from the mammal contains an elevated level of an interferon- γ -activated transcription factor, where the elevated level indicates that the mammal contains the unstable plaque. The sample can be a blood sample and can contain mononuclear cells. The sample can be a nuclear extract. The interferon- γ -activated transcription factor can be a phosphorylated transcriptional factor. The interferon- γ -activated transcription factor can be phosphorylated STAT-1.

In another embodiment, the invention features a method of assisting a person in determining whether or not a mammal has an unstable plaque. The method includes (a) determining the level of an interferon- γ -activated transcription factor in a sample from the mammal, and (b) communicating information about the level to the person, where an elevated level of the interferon- γ -activated transcription factor in the sample indicates that the mammal contains the unstable plaque. The person can be a medical professional (e.g., a doctor, a nurse practitioner, a scientist, and a technician). The communication can include sending the information directly to the person. The communication can include sending the information indirectly to the person. The communication can include making the information electronically available to the person. The interferon- γ -activated transcription factor can be STAT-1.

Another embodiment of the invention features a method for determining whether or not a mammal has an unstable plaque. The method includes determining whether or not a sample from the mammal contains an elevated level of a polypeptide, where the polypeptide is encoded by DNA responsive to an interferon- γ -activated transcription factor, and where the level indicates that the mammal contains the unstable plaque. The sample can contain mononuclear cells. The polypeptide can be CD64 or IP-10. The interferon- γ -activated transcription factor can be STAT-1.

Another embodiment of the invention features a method of assisting a person in determining whether or not a mammal has an unstable plaque. The method includes (a) determining the level of a polypeptide in a sample from the mammal, where the

专利名称(译)	评估心血管疾病的方法和材料		
公开(公告)号	EP1368651A2	公开(公告)日	2003-12-10
申请号	EP2002709690	申请日	2002-02-21
[标]申请(专利权)人(译)	梅约医学教育与研究基金会		
申请(专利权)人(译)	梅奥基金会MEDICALEDUCATION和研究		
当前申请(专利权)人(译)	梅奥基金会MEDICALEDUCATION和研究		
[标]发明人	GORONZY JORG J WEYAND CORNELIA M KOPECKY STEPHEN L		
发明人	GORONZY, JORG, J. WEYAND, CORNELIA, M. KOPECKY, STEPHEN, L.		
IPC分类号	G01N33/68 G01N33/53 G01N33/566 G01N33/50		
CPC分类号	G01N33/6863 G01N33/6893 G01N2333/57 G01N2333/70596 G01N2800/32 G01N2800/324 G06Q50/24 G16H50/30		
优先权	09/792686 2001-02-23 US		
其他公开文献	EP1368651A4		
外部链接	Espacenet		

摘要(译)

本发明提供了用于评估心血管病症（例如心绞痛病症）的方法和材料。具体地，本发明提供了与确定哺乳动物是否具有至少一种不稳定斑块有关的方法和材料。本发明还提供了用于评估心血管病症，基本上纯的细胞群的试剂盒，以及鉴定治疗威胁生命的心血管病症（例如，不稳定性心绞痛）的化合物的方法。