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**Alex et al.**(10) **Patent No.: US 8,476,026 B2**  
(45) **Date of Patent: Jul. 2, 2013**(54) **BIOMARKERS OF OVARIAN CANCER**(75) Inventors: **Ng Alex**, Newton, MA (US); **Brian Liu**,  
Somerville, MA (US)(73) Assignee: **The Brigham and Women's Hospital,**  
**Inc.**, Boston, MA (US)(\*) Notice: Subject to any disclaimer, the term of this  
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U.S.C. 154(b) by 188 days.(21) Appl. No.: **12/935,210**(22) PCT Filed: **Mar. 20, 2009**(86) PCT No.: **PCT/US2009/001776**§ 371 (c)(1),  
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USPC ..... **435/7.1**(58) **Field of Classification Search**  
None  
See application file for complete search history.(56) **References Cited**

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Sanzo, LLC(57) **ABSTRACT**

The invention is directed to assays for biomarkers associated with ovarian cancer that can be used diagnostically. It includes glass or plastic plates or slides on which the biomarkers have been immobilized and kits containing these plates or slides.

**19 Claims, 1 Drawing Sheet**

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TABLE 1-continued

Biomarkers for Ovarian Cancer		
Biomarker	Accession No.	Level in Ovarian Cancer Patients Relative to Normal Levels
tripartite motif-containing 3	O75382	Down
protein kinase C, theta	Q04759	Down
syntaxin 8	Q9UNK0	Down
glutamate-ammonia ligase (glutamine synthase)	P15104	Down
protein kinase C, beta 1	P05771	Down
chromosome condensation 1	P18754	Down
DEAH (Asp-Glu-Ala-His) box polypeptide 16	O60231	Down
ribosomal protein L22	P35268	Down
caveolin 1, caveolae protein, 22 kDa	Q03135	Down
retinoblastoma-like 2 (p130)	Q08999	Down
cyclin-dependent kinase inhibitor 1A (p21, Cip1)	P38936	Down
protein tyrosine phosphatase, receptor-type, Z polypeptide 1	O76043	Down
general transcription factor II, i	O15359	Down
adaptor-related protein complex 2, alpha 1 subunit	O95782	Down
linker for activation of T cells	O43561	Down

TABLE 2

Biomarkers Whose Level Changes are Prominent in Patients with Mucinous, but not Serous, Ovarian Cancer		
Biomarker	Accession No.	Level in Ovarian Cancer Patients Relative to Normal Levels
non-metastatic cells 1, protein (NM23)	P15531	up
zeta-chain (TCR) associated protein kinase 70 kDa	P43403	up
TATA box binding protein	P20226	up
thyroid autoantigen 70 kDa (Ku antigen)	P12956	Down
5-hydroxytryptamine (serotonin) receptor 2A	P28223	Down

TABLE 3

Biomarkers Whose Levels are Lower in Samples from Patients with Mucinous Ovarian Cancer who Smoke Relative to Patients with Mucinous Ovarian Cancer who Don't Smoke		
Biomarker	Accession No.	Level in Smoking MOC <sup>a</sup> Patients Relative to Nonsmoking MOC Patients
survival of motor neuron protein interacting protein 1	O14893	Down
three prime repair exonuclease 1	Q9BPW1	Down
chromogranin B (secretogranin 1)	P05060	Down
solute carrier family 25 (mitochondrial carrier, Aralar), member 12	O75746	Down
cyclin-dependent kinase 4	P11802	Down
likely ortholog of rat F-actin binding protein nexilin	Q0ZGT2	Down

<sup>a</sup>MOC = mucinous ovarian cancer

All references cited herein are fully incorporated by reference. Having now fully described the invention, it will be understood by those of skill in the art that the invention may be practiced within a wide and equivalent range of conditions, parameters and the like, without affecting the spirit or scope of the invention or any embodiment thereof.

What is claimed is:

1. A method of diagnostically evaluating a female subject for ovarian cancer, comprising:

- a) obtaining a test biological sample of blood, plasma, or serum from said female subject;
- b) assaying said test biological sample for casein kinase 1, epsilon using an antibody profiling assay;

c) comparing the results obtained in step b) with the results of an assay of casein kinase 1, epsilon in a control sample;

wherein an elevated level of autoantibodies specific for casein kinase 1, epsilon in said test biological sample relative to said control sample, is an indication that said subject has ovarian cancer.

2. The method of claim 1, further comprising assaying said biological sample for one or more additional proteins using an antibody profiling assay, wherein an elevated level of autoantibodies specific for said one or more additional proteins is a further indication that said subject has ovarian cancer, and wherein said additional proteins are selected from the

group consisting of: CSE1 chromosome segregation 1-like (yeast) (UniProt Knowledgebase sequence P55060);

v-crk sarcoma virus CT10 oncogene homolog (avian) (UniProt Knowledgebase sequence P46108); WAS protein family, member 1 (UniProt Knowledgebase sequence Q92558); topoisomerase (DNA) II alpha 170kDa (UniProt Knowledgebase sequence P11388); and integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (UniProt Knowledgebase sequence P17301).

3. The method of claim 2, wherein a total of at least 5 proteins (including casein kinase 1, epsilon) are assayed.

4. The method of claim 3, wherein said female subject has symptoms suggesting that said female subject may have ovarian cancer.

5. The method of claim 1, further comprising assaying said biological sample for one or more additional proteins using an antibody profiling assay, wherein an elevated level of autoantibodies specific for said one or more additional proteins is a further indication that said subject has ovarian cancer, and wherein said additional proteins are selected from the group consisting of:

erythrocyte membrane protein band 4.9 (dematin) (UniProt Knowledgebase sequence Q08495); potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (UniProt Knowledgebase sequence Q12791); nuclear receptor coactivator 3 (UniProt Knowledgebase sequence Q9Y6Q9); TEA domain family member 1 (SV40 transcriptional enhancer factor) (UniProt Knowledgebase sequence P28347); peroxisome biogenesis factor 1 (UniProt Knowledgebase sequence O43933); translin-associated factor X (UniProt Knowledgebase sequence Q99598); G protein-coupled receptor 51 (UniProt Knowledgebase sequence O75899); solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter, NA<sup>+</sup>/H<sup>+</sup>, amiloride sensitive) (UniProt Knowledgebase sequence P19634); MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, *S. pombe*) (*S. cerevisiae*) (UniProt Knowledgebase sequence Q14566); syntaxin 6 (UniProt Knowledgebase sequence O43752); KH domain containing, RNA binding, signal transduction associated 1 (UniProt Knowledgebase sequence Q07666); dystrophia myotonica-protein kinase (UniProt Knowledgebase sequence Q09013); eukaryotic translation initiation factor 4 gamma, 1 (UniProt Knowledgebase sequence Q04637); Rho GDP dissociation inhibitor (GDI) beta (UniProt Knowledgebase sequence P52566);

endothelin receptor type A (UniProt Knowledgebase sequence P25101);

synaptophysin (UniProt Knowledgebase sequence P08247); transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) (UniProt Knowledgebase sequence P15923); fibronectin 1 (UniProt Knowledgebase sequence P02751); RAS p21 protein activator (GTPase activating protein) 1 (UniProt Knowledgebase sequence P20936); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 (UniProt Knowledgebase sequence P51531);

syntaxin binding protein 5 (tomosyn) (UniProt Knowledgebase sequence Q5T5C0);

Ras-GTPase-activating protein SH3-domain-binding protein (UniProt Knowledgebase sequence Q13283); glutamate receptor, ionotropic, N-methyl D-aspartate 2B (UniProt Knowledgebase sequence Q13224); zeta-chain (TCR) associated protein kinase 70kDa (UniProt

Knowledgebase sequence P43403); and TATA box binding protein (UniProt Knowledgebase sequence P20226).

6. The method of claim 5, wherein a total of at least 10 proteins (including casein kinase 1, epsilon) are assayed.

7. The method of claim 6, wherein said female subject has symptoms suggesting that said female subject may have ovarian cancer.

8. The method of claim 5, wherein said female subject has symptoms suggesting that said female subject may have ovarian cancer.

9. The method of claim 1, further comprising assaying said biological sample for one or more further proteins using an antibody profiling assay, wherein a reduced level of autoantibodies specific for said one or more further proteins is a further indication that said subject has ovarian cancer, and wherein said further proteins are selected from the group consisting of: synapsin II (UniProt Knowledgebase sequence Q92777); sortilin-related receptor, L (DLR class) A repeats-containing (UniProt Knowledgebase sequence Q92673); excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D) (UniProt Knowledgebase sequence P18074); and signal transducer and activator of transcription 6, interleukin-4 induced (UniProt Knowledgebase sequence P42226).

10. The method of claim 9, wherein a total of at least 5 proteins (including casein kinase 1, epsilon) are assayed.

11. The method of claim 10, wherein said female subject has symptoms suggesting that said female subject may have ovarian cancer.

12. The method of claim 9, wherein said female subject has symptoms suggesting that said female subject may have ovarian cancer.

13. The method of claim 1, further comprising assaying said biological sample for one or more further proteins using an antibody profiling assay, wherein a reduced level of autoantibodies specific for said one or more further proteins is a further indication that said subject has ovarian cancer, and wherein said further proteins are selected from the group consisting of: tripartite motif containing 3 (UniProt Knowledgebase sequence O75382); protein kinase C, theta (UniProt Knowledgebase sequence Q04759); syntaxin 8 (UniProt Knowledgebase sequence Q9UNK0); glutamate-ammonia ligase (glutamine synthase) (UniProt Knowledgebase sequence P15104); protein kinase C, beta 1 (UniProt Knowledgebase sequence P05771); chromosome condensation 1 (UniProt Knowledgebase sequence P18754); DEAH (Asp-Glu-Ala-His) box polypeptide 16 (UniProt Knowledgebase sequence O60231); ribosomal protein L22 (UniProt Knowledgebase sequence P35268); caveolin 1, caveolae protein, 22kDa (UniProt Knowledgebase sequence Q03135); retinoblastoma-like 2 (p130) (UniProt Knowledgebase sequence Q08999);

cyclin-dependent kinase inhibitor 1A (p21, Cip 1) (UniProt Knowledgebase sequence P38936); protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (UniProt Knowledgebase sequence O76043); general transcription factor II, i (UniProt Knowledgebase sequence O15359); adaptor-related protein complex 2, alpha 1 subunit (UniProt Knowledgebase sequence O95782); linker for activation of T cells (UniProt Knowledgebase sequence O43561); thyroid autoantigen 70kDa (Ku antigen) (UniProt Knowledgebase sequence P12956); and 5-hydroxytryptamine (serotonin) receptor 2A (UniProt Knowledgebase sequence P28223).

14. The method of claim 13, wherein a total of at least 10 proteins (including casein kinase 1, epsilon) are assayed.

15. The method of claim 14, wherein said female subject has been diagnosed as having ovarian cancer or has symptoms suggesting that said female subject may have ovarian cancer.

16. The method of claim 13, wherein said female subject has been diagnosed as having ovarian cancer or has symptoms suggesting that said female subject may have ovarian cancer.

17. The method of claim 1, wherein said female subject has been diagnosed as having ovarian cancer or has symptoms suggesting that said female subject may have ovarian cancer.

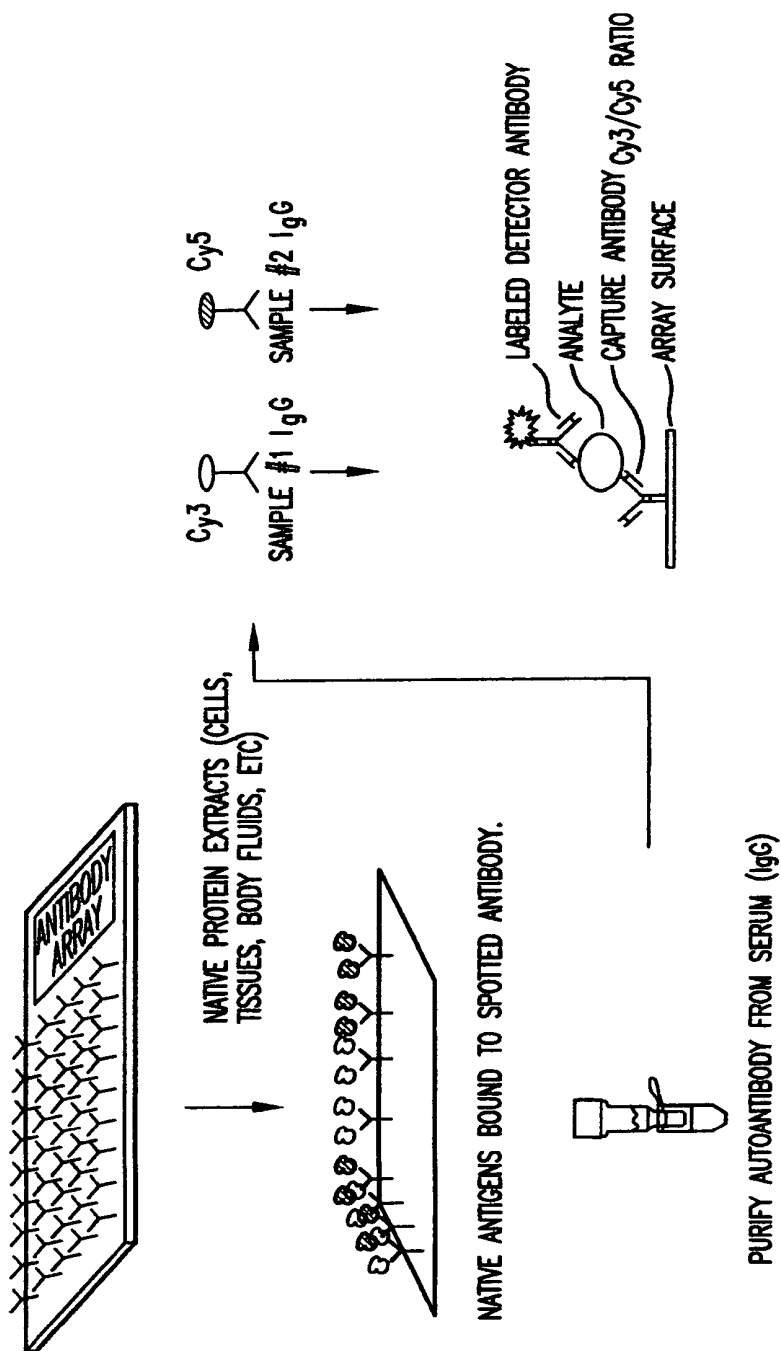
18. The method of claim 1, wherein a single autoantibody assay is used to assay said test biological sample and said control sample.

19. The method of claim 18, wherein, in said autoantibody assay, antibodies from said test biological sample are labeled with a first detectable label and antibodies from said control sample are labeled with a second detectable label; wherein said first detectable label and said second detectable labels are dyes or fluorescent labels that absorb or fluoresce at a different wavelengths from one another.

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## BIOMARKERS OF OVARIAN CANCER

## CROSS REFERENCE TO RELATED APPLICATIONS

The present application is US national stage of international application PCT/US2009/001776, which had an international filing date of Mar. 20, 2009, and claims priority to, and the benefit of, United States provisional application 61/064,894 filed on Apr. 1, 2008 incorporated herein by reference in its entirety. The international application was published in English under PCT Article 21(2) on Dec. 3, 2009.

## FIELD OF THE INVENTION

The present invention is directed to biomarkers that can be used in the diagnosis of ovarian cancer. The invention also includes assays in which the biomarkers are immobilized on plates or slides by monoclonal antibodies and then used in determining the antibody profile of a subject.

## BACKGROUND OF THE INVENTION

Ovarian cancer is the fifth leading cause of death from cancer in U.S. women. In most instances, a diagnosis is not made until the cancer is in an advanced state; at a time when the five-year survival rate of patients is only about 28% (Ries, et al., SEERC Cancer Stat. Rev. 1973-1995 (1998)). In contrast, the five year survival rate for women diagnosed with localized disease is about 95%. These statistics provide an incentive to search for tests that can be used to identify ovarian cancer at an early stage.

Proteins preferentially expressed by ovarian cancer cells but not by normal cells may elicit a host immune response that will be reflected in the antibodies present in a host. For example, Zheng et al. demonstrated the presence of serum autoantibodies to a panel of known antigens in various human cancers (Zhang, et al., *Cancer Epidemiol Biomarkers Prev.* 12:136-143 (2003); Zhang, *Cancer Detect. Prev.* 28(2):114-118 (2004)). The results strongly suggest that uniquely constituted antigen panels or protein microarrays may provide an approach for discriminating autoantibody reactivity between cancer patients and control individuals.

One disadvantage with many assays that look at the array of antibodies present in a patient is that they use antigens that are denatured due to having been directly bound to a microtiter plate and which lack posttranslational modifications due to their having been either chemically synthesized or recombinantly produced in bacteria. As a result, the ability of antibodies to recognize and bind antigens is impaired and a distorted profile is obtained. Recently, an improved assay has been developed in which antigens are bound to a plate or slide by a monoclonal antibody (WO 2006/119155; Qin, et al., *Proteomics* 6:3199-209 (2006)). This preserves the normal conformation of the antigens. In addition, the antigens are derived from native cells rather than being synthesized or recombinantly produced in bacteria. Thus, they also retain posttranslational modifications that may affect the binding of antibodies. Once an appropriately prepared plate is available, it is used to compare the binding of antibodies from patients with a particular disease or condition with those derived from subjects known to be disease free. In this manner, it is possible to identify a set of antigenic differences that are characteristic of a disease and that have the potential of being used diagnostically.

## SUMMARY OF THE INVENTION

## General Summary

5 Previous reports have described in detail a microarray assay for examining the antibody profile of a sample of blood, plasma or serum (WO 2006/119155; Qin, et al., *Proteomics* 6:3199-209 (2006); Ehrlich, et al., *Nat. Protocols* 1:452-60 (2006); Liu, et al., *Expert Rev. Proteomics* 3:283-96 (2006), all incorporated herein by reference in their entirety). The main characteristic of this assay is that monoclonal antibodies, each recognizing a single known antigen, are bound to a solid support, such as a glass slide, with each antibody at a separate location. The corresponding antigens are then bound to the immobilized monoclonal antibodies, e.g., by incubating a crude cell lysate with the prepared support. In this way, a microarray is formed in which antigens maintaining their native structural characteristics are immobilized, each antigen at a unique site on the assay support.

10 In the next step, the IgG fraction is isolated from a "test sample" of blood, plasma or serum and the "test antibodies" thus obtained are detectably labeled with a fluorescent dye. These labeled antibodies are then combined with an equal amount of "control antibodies" that have been isolated from a second sample of blood, serum or plasma (e.g., from a subject known to be disease free). The control antibodies are attached to a second fluorescent label that is different than, and distinguishable from, the label used for the test antibodies. The mixture of labeled test and control antibodies is incubated with the immobilized antigens and the relative amount of binding is determined based upon the detectable labels. The assay procedure can be used to compare the antibodies present in patients having a disease such as cancer to the antibodies in samples from normal individuals. Results have indicated that the procedure can be used to identify antigens that are characteristic of, inter alia, prostate cancer (see WO 2006/119155).

15 Applying the assay described above to patients with ovarian cancer, a set of antigenic markers have been identified that are consistently altered in patients with this disease and which may be used diagnostically. Some of these biomarkers are elevated in ovarian cancer patients relative to normal controls whereas others are decreased. The biomarkers are shown in Tables 1-3 along with its UniProt Knowledgebase accession number. Each accession number is associated with a unique amino acid sequence that unambiguously defines the protein and which is readily accessible to the public. It will be understood that, for the purposes of the present application, reference to a particular biomarker in Tables 1-3 means the marker defined by the accession number provided.

20 Most of the markers do not appear to have been previously associated with ovarian cancer. Assays for these markers (e.g., ELISA assays or radioimmunoassays) can be used on samples derived from patients that have symptoms suggesting that they may have ovarian cancer to help make a diagnosis. Alternatively a multiplex platform consisting of 5 or more selected antigens could be used in an antibody profiling assay. Assays may also be used on patients already known to have ovarian cancer to assess whether the disease is progressing and whether it is responding to therapy. The markers shown in Tables 2 and 3 are associated with specific subgroups of ovarian cancer patients. The markers shown in Table 2 are altered in patients with mucinous ovarian cancer but not in patients with serous ovarian cancer. The markers in Table 3 are decreased in mucinous ovarian cancer patients that smoke relative to mucinous ovarian cancer patients that do not smoke.

A few of the cancer associated markers (CAMs) identified appear to have been previously implicated in ovarian cancer. These include: topoisomerase II alpha; c-src tyrosine kinase; catechol-O-methyltransferase; nuclear receptor coactivator 3; NM23; and cyclin-dependent kinase 4. However, it does not appear that autoantibody assays of the type discussed herein have been used to evaluate these markers in the past. Since antibodies to markers will be amplified as the result of natural immunological processes, these assays are, in effect, increased in sensitivity. In addition, the IgG fraction can be precipitated from serum using routine techniques and this reduces the likelihood of distorted assay results due to other serum components.

#### Detailed Summary

In its first aspect, the invention is directed to a method of diagnostically evaluating a subject for ovarian cancer by obtaining a "test" biological sample from the subject and assaying the sample for one or more of the following cancer associated markers (CAMs): CSE1 chromosome segregation 1-like (yeast) (UniProt Knowledgebase sequence P55060); casein kinase 1, epsilon (UniProt Knowledgebase sequence P49674); v-crk sarcoma virus CT 10 oncogene homolog (avian) (UniProt Knowledgebase sequence P46108); WAS protein family, member 1 (UniProt Knowledgebase sequence Q92558); erythrocyte membrane protein band 4.9 (dematin) (UniProt Knowledgebase sequence Q08495); potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (UniProt Knowledgebase sequence Q12791); nuclear receptor coactivator 3 (UniProt Knowledgebase sequence Q9Y6Q9); TEA domain family member 1 (SV40 transcriptional enhancer factor) (UniProt Knowledgebase sequence P28347); peroxisome biogenesis factor 1 (UniProt Knowledgebase sequence O43933); translin-associated factor X (UniProt Knowledgebase sequence Q99598); G protein-coupled receptor 51 (UniProt Knowledgebase sequence O75899); solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter,  $\text{Na}^+/\text{H}^+$ , amiloride sensitive) (UniProt Knowledgebase sequence P19634); integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (UniProt Knowledgebase sequence P17301); MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, *S. pombe*) (*S. cerevisiae*) (UniProt Knowledgebase sequence Q14566); syntaxin 6 (UniProt Knowledgebase sequence O43752); KH domain containing, RNA binding, signal transduction associated 1 (UniProt Knowledgebase sequence Q07666); dystrophin myotonic-protein kinase (UniProt Knowledgebase sequence Q09013); eukaryotic translation initiation factor 4 gamma, 1 (UniProt Knowledgebase sequence Q04637); Rho GDP dissociation inhibitor (GDI) beta (UniProt Knowledgebase sequence P52566); endothelin receptor type A (UniProt Knowledgebase sequence P25101); synaptophysin (UniProt Knowledgebase sequence P08247); transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) (UniProt Knowledgebase sequence P15923); fibronectin 1 (UniProt Knowledgebase sequence P02751); RAS p21 protein activator (GTPase activating protein) 1 (UniProt Knowledgebase sequence P20936); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 (UniProt Knowledgebase sequence P51531); syntaxin binding protein 5 (tomosyn) (UniProt Knowledgebase sequence Q5T5C0); Ras-GTPase-activating protein SH3-domain-binding protein (UniProt Knowledgebase sequence Q13283); glutamate receptor, ionotropic, N-methyl D-aspartate 2B (UniProt Knowledgebase sequence Q13224); zeta-chain (TCR) associated protein kinase 70 kDa (UniProt

Knowledgebase sequence P43403); TATA box binding protein (UniProt Knowledgebase sequence P20226). The results from the test biological sample are compared to those from one or more similar "control samples" obtained from subjects known to be disease free or from the general population. If the comparison indicates that the test sample has a higher amount of one or more CAMs, this is an indication that the test subject has ovarian cancer. As the number of elevated CAMs increases, so does the probability that ovarian cancer is present and progressing.

The term "diagnostically evaluating a subject for ovarian cancer" means that a sample from the subject is tested to determine if it has the abnormalities described herein as being characteristic of samples derived from ovarian cancer patients. As discussed above, the abnormalities may be an indication that a woman not previously diagnosed as having ovarian cancer does, in fact, have the disease. However, it will be understood that these assays may be used in other contexts as well. For example, they may be used to determine whether a patient with a disease in remission is having a relapse or whether a treatment regimen is effective in returning a patient to a more normal profile. In cases where, a patient shows an elevation in only one, or a few markers, and further examination fails to reveal overt ovarian disease, the patient should be followed closely to see if abnormalities in additional CAMs develop and whether ovarian tumors become detectable.

In addition to assays for CAMs that are elevated in samples derived from patients with ovarian cancer, the invention is directed to diagnostic assays for CAMs that have been found to be characteristically lower in ovarian cancer patients. Thus, in another aspect, the invention is directed to a method of diagnostically evaluating a subject using essentially the procedure described above but in which disease presence or progression is indicated by one or more CAMs in test biological samples being lower than in the control samples. CAMs characteristically reduced are: synapsin II (UniProt Knowledgebase sequence Q92777); sortilin-related receptor, L (DLR class) A repeats-containing (UniProt Knowledgebase sequence Q92673); excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D) (UniProt Knowledgebase sequence P18074); signal transducer and activator of transcription 6, interleukin-4 induced (UniProt Knowledgebase sequence P42226); tripartite motif-containing 3 (UniProt Knowledgebase sequence O75382); protein kinase C, theta (UniProt Knowledgebase sequence Q04759); syntaxin 8 (UniProt Knowledgebase sequence Q9UNK0); glutamate-ammonia ligase (glutamine synthase) (UniProt Knowledgebase sequence P15104); protein kinase C, beta 1 (UniProt Knowledgebase sequence P05771); chromosome condensation 1 (UniProt Knowledgebase sequence P18754); DEAH (Asp-Glu-Ala-His) box polypeptide 16 (UniProt Knowledgebase sequence O60231); ribosomal protein L22 (UniProt Knowledgebase sequence P35268); caveolin 1, caveolae protein, 22 kDa (UniProt Knowledgebase sequence Q03135); retinoblastoma-like 2 (p130) (UniProt Knowledgebase sequence Q08999); cyclin-dependent kinase inhibitor 1A (p21, Cip1) (UniProt Knowledgebase sequence P38936); protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (UniProt Knowledgebase sequence O76043); general transcription factor II, i (UniProt Knowledgebase sequence O15359); adaptor-related protein complex 2, alpha 1 subunit (UniProt Knowledgebase sequence O95782); linker for activation of T cells (UniProt Knowledgebase sequence O43561); thyroid autoantigen 70 kDa (Ku antigen) (UniProt Knowledgebase sequence P12956); 5-hydroxytryptamine (serotonin) receptor 2A (UniProt Knowledgebase sequence P28223).

As recognized in the art the amount of CAM present in normal individuals will typically be expressed as a range. The amount of a CAM in a test biological sample is "higher than" or "lower than" the control amount if it falls outside of this range, with greater variation more strongly suggesting disease presence. For example if a CAM was found to be present in serum at  $20 \pm 6$  ug/ml in normal subjects, an assay indicating a concentration of 25 ug/ml would not be indicative of disease presence, whereas a concentration of 40 ug/ml would be considered high and, depending on the CAM, may be an indication of cancer. A concentration of 80 ug/ml would be even more suggestive.

Examples of test biological samples that can be used include blood, plasma, serum, urine, and ovarian fluid (i.e., fluid immediately surrounding the ovary). The most preferred of these is blood, plasma or serum. The amount of CAM present in the biological sample can be determined by any method known in the art, e.g. by ELISA, radioimmunoassay or radioreceptor assay. The most preferred method however is by an antibody profiling assay. For the purposes of the present application, this is defined as assessing the amount CAM present indirectly by examining the amount of antibody against the CAM in the biological sample. Specific examples are provided herein and are described in WO 2006/119155 (incorporated herein by reference in its entirety). Preferably at least 7 different CAMs should be examined and more preferably, 20, 40 or all CAMs.

Certain of the CAMs are characteristic not only of the presence of ovarian cancer but also of a particular type of cancer. For example, mucinous (as opposed to serous) ovarian cancer is suggested by increased levels of one or more of the following markers: non-metastatic cells 1, protein (NM23) (UniProt Knowledgebase sequence P15531); zeta-chain (TCR) associated protein kinase 70 kDa (UniProt Knowledgebase sequence P43403); TATA box binding protein (UniProt Knowledgebase sequence P20226); and/or a decreased level of one or more of: thyroid autoantigen 70 kDa (Ku antigen) (UniProt Knowledgebase sequence P12956); and 5-hydroxytryptamine (serotonin) receptor 2A (UniProt Knowledgebase sequence P28223). In addition, there are certain CAMs that are found to be decreased in mucinous cancer patients that smoke relative to nonsmoking patients. These CAMs are: survival of motor neuron protein interacting protein 1 (UniProt Knowledgebase sequence O14893); three prime repair exonuclease 1 (UniProt Knowledgebase sequence Q9BPW1); chromogranin B (secretogranin 1) (UniProt Knowledgebase sequence P05060); solute carrier family 25 (mitochondrial carrier, Aralar), member 12 (UniProt Knowledgebase sequence O75746); cyclin-dependent kinase 4 (UniProt Knowledgebase sequence P11802); and likely ortholog of rat F-actin binding protein nexilin (UniProt Knowledgebase sequence Q0ZGT2).

In another aspect, the invention includes a solid support (e.g. a glass or plastic plate or slide) having at least 7 different CAMs, each attached at a different position. The CAMs are selected from: CSE1 chromosome segregation 1-like (yeast) (UniProt Knowledgebase sequence P55060); casein kinase 1, epsilon (UniProt Knowledgebase sequence P49674); v-crk sarcoma virus CT10 oncogene homolog (avian) (UniProt Knowledgebase sequence P46108); topoisomerase (DNA) II alpha 170 kDa (UniProt Knowledgebase sequence P11388); c-src tyrosine kinase (UniProt Knowledgebase sequence P41240); catechol-O-methyltransferase (UniProt Knowledgebase sequence P21964); WAS protein family, member 1 (UniProt Knowledgebase sequence Q92558); erythrocyte membrane protein band 4.9 (dematin) (UniProt Knowledgebase sequence Q08495); potassium large conductance cal-

cium-activated channel, subfamily M, alpha member 1 (UniProt Knowledgebase sequence Q12791); nuclear receptor coactivator 3 (UniProt Knowledgebase sequence Q9Y6Q9); TEA domain family member 1 (SV40 transcriptional enhancer factor) (UniProt Knowledgebase sequence P28347); peroxisome biogenesis factor 1 (UniProt Knowledgebase sequence O43933); translin-associated factor X (UniProt Knowledgebase sequence Q99598); G protein-coupled receptor 51 (UniProt Knowledgebase sequence O75899); solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter,  $\text{Na}^+/\text{H}^+$ , amiloride sensitive) (UniProt Knowledgebase sequence P19634); integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (UniProt Knowledgebase sequence P17301); MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, *S. pombe*) (*S. cerevisiae*) (UniProt Knowledgebase sequence Q14566); syntaxin 6 (UniProt Knowledgebase sequence O43752); KH domain containing, RNA binding, signal transduction associated 1 (UniProt Knowledgebase sequence Q07666); dystrophin myotonic-protein kinase (UniProt Knowledgebase sequence Q09013); eukaryotic translation initiation factor 4 gamma, 1 (UniProt Knowledgebase sequence Q04637); Rho GDP dissociation inhibitor (GDI) beta (UniProt Knowledgebase sequence P52566); endothelin receptor type A (UniProt Knowledgebase sequence P25101); synaptophysin (UniProt Knowledgebase sequence P08247); transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) (UniProt Knowledgebase sequence P15923); fibronectin 1 (UniProt Knowledgebase sequence P02751); RAS p21 protein activator (GTPase activating protein) 1 (UniProt Knowledgebase sequence P20936); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 (UniProt Knowledgebase sequence P51531); syntaxin binding protein 5 (tomosyn) (UniProt Knowledgebase sequence Q5T5C0); Ras-GTPase-activating protein SH3-domain-binding protein (UniProt Knowledgebase sequence Q13283); glutamate receptor, ionotropic, N-methyl D-aspartate 2B (UniProt Knowledgebase sequence Q13224); synapsin II (UniProt Knowledgebase sequence Q92777); sortilin-related receptor, L (DLR class) A repeats-containing (UniProt Knowledgebase sequence Q92673); excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D) (UniProt Knowledgebase sequence P18074); signal transducer and activator of transcription 6, interleukin-4 induced (UniProt Knowledgebase sequence P42226); tripartite motif-containing 3 (UniProt Knowledgebase sequence O75382); protein kinase C, theta (UniProt Knowledgebase sequence Q04759); syntaxin 8 (UniProt Knowledgebase sequence Q9UNK0); glutamate-ammonia ligase (glutamine synthase) (UniProt Knowledgebase sequence P15104); protein kinase C, beta 1 (UniProt Knowledgebase sequence P05771); chromosome condensation 1 (UniProt Knowledgebase sequence P18754); DEAH (Asp-Glu-Ala-His) box polypeptide 16 (UniProt Knowledgebase sequence O60231); ribosomal protein L22 (UniProt Knowledgebase sequence P35268); caveolin 1, caveolae protein, 22 kDa (UniProt Knowledgebase sequence Q03135); retinoblastoma-like 2 (p130) (UniProt Knowledgebase sequence Q08999); cyclin-dependent kinase inhibitor 1A (p21, Cip 1) (UniProt Knowledgebase sequence P38936); protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (UniProt Knowledgebase sequence O76043); general transcription factor II, i (UniProt Knowledgebase sequence O15359); adaptor-related protein complex 2, alpha 1 subunit (UniProt Knowledgebase sequence O95782); linker for activation of T cells (UniProt Knowledgebase sequence O43561); non-metastatic cells 1, protein (NM23) (UniProt

Knowledgebase sequence P15531); zeta-chain (TCR) associated protein kinase 70 kDa (UniProt Knowledgebase sequence P43403); TATA box binding protein (UniProt Knowledgebase sequence P20226); thyroid autoantigen 70 kDa (Ku antigen) (UniProt Knowledgebase sequence P12956); 5-hydroxytryptamine (serotonin) receptor 2A (UniProt Knowledgebase sequence P28223); survival of motor neuron protein interacting protein 1 (UniProt Knowledgebase sequence O14893); three prime repair exonuclease 1 (UniProt Knowledgebase sequence Q9BPW1); chromogranin B (secretogranin 1) (UniProt Knowledgebase sequence P05060); solute carrier family 25 (mitochondrial carrier, Aralar), member 12 (UniProt Knowledgebase sequence O75746); cyclin-dependent kinase 4 (UniProt Knowledgebase sequence P11802); likely ortholog of rat F-actin binding protein nexilin (UniProt Knowledgebase sequence Q0ZGT2). Preferably each CAM is attached to the plate or slide by a monoclonal antibody that specifically recognizes it. In a preferred embodiment at least 20 CAMs are attached to the plate or slide, more preferably, at least 40 CAMs and, most preferably, all of the above CAMs. In general, there should not be a total of more than 100 different antigens of any type (and preferably no more than 65, 70 or 75) bound to the solid support. However, if desired, a single type of antigen may be bound to more than one site in order to provide a verification of the accuracy of results. For example, an array may have 30 or 40 different CAMs in triplicate, i.e., bound at three different sites. The array may, if desired, include only the CAMs shown herein and no other antigens, or a few (e.g., 1-5) additional antigens to serve as positive or negative controls, i.e., antigens that would be expected not to change as long as samples were being properly collected and assays properly run. The use of positive and negative controls in this manner is well known in the art.

The plate or slide with attached CAMs may be included as part of a kit along with instructions concerning its use in performing a diagnostic assay for ovarian cancer. Optionally, the kit may also include a control sample derived from one or more individuals known not to have ovarian disease or from the general population and/or other components that may be needed to perform assays such as buffers, fluorescent labeling reagents, antibodies that serve as standards, etc.

The invention also includes an assay for comparing the autoantibodies present in a subject. The assay involves obtaining an immobilized array of CAMs, each CAM being attached to the surface of a solid support by an antibody, especially a monoclonal antibody, that specifically recognizes it. The CAMs are selected from the group consisting of: CSE1 chromosome segregation 1-like (yeast) (UniProt Knowledgebase sequence P55060); casein kinase 1, epsilon (UniProt Knowledgebase sequence P49674); v-crk sarcoma virus CT10 oncogene homolog (avian) (UniProt Knowledgebase sequence P46108); topoisomerase (DNA) II alpha 170 kDa (UniProt Knowledgebase sequence P11388); c-src tyrosine kinase (UniProt Knowledgebase sequence P41240); catechol-O-methyltransferase (UniProt Knowledgebase sequence P21964); WAS protein family, member 1 (UniProt Knowledgebase sequence Q92558); erythrocyte membrane protein band 4.9 (dematin) (UniProt Knowledgebase sequence Q08495); potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (UniProt Knowledgebase sequence Q12791); nuclear receptor coactivator 3 (UniProt Knowledgebase sequence Q9Y6Q9); TEA domain family member 1 (SV40 transcriptional enhancer factor) (UniProt Knowledgebase sequence P28347); peroxisome biogenesis factor 1 (UniProt Knowledgebase sequence O43933); translin-associated factor X (UniProt Knowledge-

base sequence Q99598); G protein-coupled receptor 51 (UniProt Knowledgebase sequence O75899); solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter,  $\text{Na}^+/\text{H}^+$ , amiloride sensitive) (UniProt Knowledgebase sequence P19634); integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (UniProt Knowledgebase sequence P17301); MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, *S. pombe*) (*S. cerevisiae*) (UniProt Knowledgebase sequence Q14566); syntaxin 6 (UniProt Knowledgebase sequence O43752); KH domain containing, RNA binding, signal transduction associated 1 (UniProt Knowledgebase sequence Q07666); dystrophin myotonic-protein kinase (UniProt Knowledgebase sequence Q09013); eukaryotic translation initiation factor 4 gamma, 1 (UniProt Knowledgebase sequence Q04637); Rho GDP dissociation inhibitor (GDI) beta (UniProt Knowledgebase sequence P52566); endothelin receptor type A (UniProt Knowledgebase sequence P25101); synaptophysin (UniProt Knowledgebase sequence P08247); transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) (UniProt Knowledgebase sequence P15923); fibronectin 1 (UniProt Knowledgebase sequence P02751); RAS p21 protein activator (GTPase activating protein) 1 (UniProt Knowledgebase sequence P20936); SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 (UniProt Knowledgebase sequence P51531); syntaxin binding protein 5 (tomosyn) (UniProt Knowledgebase sequence Q5T5C0); Ras-GTPase-activating protein SH3-domain-binding protein (UniProt Knowledgebase sequence Q13283); glutamate receptor, ionotropic, N-methyl D-aspartate 2B (UniProt Knowledgebase sequence Q13224); syntaxin II (UniProt Knowledgebase sequence Q92777); sortilin-related receptor, L (DLR class) A repeats-containing (UniProt Knowledgebase sequence Q92673); excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D) (UniProt Knowledgebase sequence P18074); signal transducer and activator of transcription 6, interleukin-4 induced (UniProt Knowledgebase sequence P42226); tripartite motif-containing 3 (UniProt Knowledgebase sequence O75382); protein kinase C, theta (UniProt Knowledgebase sequence Q04759); syntaxin 8 (UniProt Knowledgebase sequence Q9UNK0); glutamate-ammonia ligase (glutamine synthase) (UniProt Knowledgebase sequence P15104); protein kinase C, beta 1 (UniProt Knowledgebase sequence P05771); chromosome condensation 1 (UniProt Knowledgebase sequence P18754); DEAH (Asp-Glu-Ala-His) box polypeptide 16 (UniProt Knowledgebase sequence O60231); ribosomal protein L22 (UniProt Knowledgebase sequence P35268); caveolin 1, caveolae protein, 22 kDa (UniProt Knowledgebase sequence Q03135); retinoblastoma-like 2 (p130) (UniProt Knowledgebase sequence Q08999); cyclin-dependent kinase inhibitor 1A (p21, Cip 1) (UniProt Knowledgebase sequence P38936); protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (UniProt Knowledgebase sequence O76043); general transcription factor II, i (UniProt Knowledgebase sequence O15359); adaptor-related protein complex 2, alpha 1 subunit (UniProt Knowledgebase sequence O95782); linker for activation of T cells (UniProt Knowledgebase sequence O43561); non-metastatic cells 1, protein (NM23) (UniProt Knowledgebase sequence P15531); zeta-chain (TCR) associated protein kinase 70 kDa (UniProt Knowledgebase sequence P43403); TATA box binding protein (UniProt Knowledgebase sequence P20226); thyroid autoantigen 70 kDa (Ku antigen) (UniProt Knowledgebase sequence P12956); 5-hydroxytryptamine (serotonin) receptor 2A (UniProt Knowledgebase sequence P28223); survival of motor

neuron protein interacting protein 1 (UniProt Knowledgebase sequence O14893); three prime repair exonuclease 1 (UniProt Knowledgebase sequence Q9BPW1); chromogranin B (secretogranin 1) (UniProt Knowledgebase sequence P05060); solute carrier family 25 (mitochondrial carrier, Aralar), member 12 (UniProt Knowledgebase sequence O75746); cyclin-dependent kinase 4 (UniProt Knowledgebase sequence P11802); and likely ortholog of rat F-actin binding protein nexilin (UniProt Knowledgebase sequence Q0ZGT2). Test antibodies are then derived from a first sample of blood, serum or plasma and attached to a first detectable label. Control antibodies derived from a second sample of blood, serum or plasma are also obtained and are attached to a second detectable label that can be distinguished from the first detectable label after incubation with the immobilized CAMs. In the next step, the labeled test antibodies and labeled control antibodies are incubated with the array of immobilized CAMs. Unbound labeled antibodies are then removed and the amount of the first and second detectable labels associated with each CAM is determined.

In a preferred embodiment, the first and said second detectable labels are dyes or fluorescent labels chosen so that the first detectable label absorbs or fluoresces at a different wavelength than the second detectable label, e.g., Cy3 and Cy5 fluorescent dyes may be used. Preferably, the test antibodies are from a subject that is known to have, or is suspected of having, ovarian cancer and the control antibodies are from a subject that does not have this disease.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 represents a schematic of a "reverse capture" microarray assay. Highly specific monoclonal antibodies are spotted on an array surface and antigens from cell extracts are then bound to each. Test and control autoantibodies are then labeled with different CyDyes, and incubated with the array of immobilized antigens. After incubation, the ratio of the fluors present at each site on the array surface reflects the relative abundance of the autoantibodies in the samples.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is based upon the identification of antigens that are altered in subjects with ovarian cancer relative to subjects that do not have ovarian cancer. These antigens are shown in Tables 1-3, are all well known in the art and are unambiguously identified by the UniProt Knowledgebase sequence accession numbers also provided in the Tables. Although a difference in any of these CAMs in a subject is suggestive of the presence of ovarian cancer, a better assessment can be made by examining many, preferably all, of the antigens.

One way of assaying individual markers is to use an ELISA, radioimmuno- or radioreceptor assay. Alternatively, microarray plates can be used to examine multiple antigens at once. The most preferred method of doing this is to immobilize an array of monoclonal antibodies, each recognizing a specific antigen, to an inert solid surface. Many plastic, glass or nylon surfaces are known in the art and can be used for this purpose. Monoclonal antibodies appropriate for attachment are commercially available, e.g., from Clontech Inc. and other manufacturers, and in some cases it may be possible to purchase arrays already attached to a surface. If desired, fragments derived from the monoclonal antibodies that maintain the ability to specifically recognize antigen may also be used.

The next step in the procedure is to attach the antigens to the immobilized antibodies. This may be accomplished by lysing cells derived from culture or in vivo, removing cellular debris and then incubating the crude antigen solution with the array of immobilized antibodies. At the end of the incubation, unattached materials and antigens are removed, thereby leaving behind an array of antigens attached to slides or plates by the immobilized monoclonal antibodies. The identity of each of the attached antigens is known from the specificity of the antibody to which it is attached. In other words, each antibody is at a specific location on the slide or plate and recognizes only one particular type of antigen.

Once the array of immobilized antigens has been prepared, the next step is to prepare the antibody samples that will undergo testing. A sample is removed from a subject being tested for ovarian cancer. A second "control" sample is then obtained from one or more other individuals that do not have the disease. The IgG fraction present in the samples is then isolated using any method known in the art and the resulting antibodies are labeled. Any type of label that can be detected using a microarray assay is compatible with the present invention, with fluorescent dyes such as Cy3 and Cy5 being preferred. The main requirement for labeling is that the label attached to the antibodies derived from the test subject must be distinguishable from those derived from the control subject after binding has occurred. Thus, the absorption or emission wavelengths of the dyes should be sufficiently different to allow them to be readily distinguished.

After test and control antibodies have been labeled, an equal amount of each (e.g., 100 microgram) is placed in a buffer solution and incubated with the array of immobilized antigens. The incubation buffer may consist of any type of standard buffer used in handling antibodies, e.g., PBS. The incubations may be carried out at about room temperature for a period ranging from 15 minutes to 2 hours with about 45 minutes being generally preferred. At the end of this time, unbound labeled antibody is removed and plates or slides are then analyzed to determine the amount of fluorescence or light absorption associated with each immobilized antigen. By comparing the results obtained using wavelengths characteristic of the dye attached to the test antibodies with those characteristic of the dye attached to the control antibodies, a profile can be obtained in which antibodies preferentially present in the test sample are identified. The presence of such antibodies is an indication that the antigens that they recognize are produced to a greater extent in the test subject.

Microarray plates or slides containing an array of the CAMs (or a subset of the CAMs) may be prepared and included as part of a kit. The kit will also include instructions describing how the plates or slides can be used in diagnostic assays for ovarian cancer. In addition, it may include other components needed in assays such as buffers or a "control" preparation of antibodies.

Although the antigens that have been identified herein are characteristic of ovarian cancer, it is expected that some of the antigens, or combinations of antigens will also be useful in diagnosing other types of disease as well. Assays utilizing arrays of the markers in Tables 1-3 may also be combined with assays of other factors of diagnostic value.

#### EXAMPLES

We have applied an innovative reverse-capture antibody array assay (described in WO 2006/119155), to profile the autoantibodies in eleven mucinous and five serous ovarian cancer plasma samples. Briefly, immunoglobulin G antibodies (IgG) were isolated from patient and normal control

plasma samples. Individual patient IgG was labeled with a fluorescent fluor and combined with an equal amount of normal control IgG, which was pooled from a group of 20 healthy female donors and labeled with another color fluorescent fluor. The combined IgGs were then hybridized to an antibody array, which had been precoated with antigens extracted from tumor tissues. After hybridization, the array was washed and scanned by a fluorescence scanner. The intensities of the two-color fluorescent fluors at each antibody spot represented the competitive binding of patient and normal IgGs to the antigen at that spot.

To account for any labeling and binding artifacts, another antibody array hybridization experiment was conducted using the same IgGs but for which the fluor labels for the patient and normal IgGs were reversed. The array data were normalized and analyzed by open-source microarray software MeV 4.0 to identify significant autoantibody biomarkers.

By clustering analysis of the microarray data, we have identified a group of autoantibody biomarkers whose titers were significantly different (up or down) in the plasma samples of cancer patients relative to that of the normal control sample (see Table 1). We also noted that there are some

autoantibody biomarkers that are more prominent in plasma of patients with mucinous ovarian cancer (see Table 2). In this regard, it should be noted that mucinous ovarian cancers are clinically and morphologically distinct from other histopathologic subtypes of ovarian cancer. Studies have suggested that patients with mucinous histologic subtypes of tumors respond poorly to standard platinum-taxane chemotherapy. More studies may reveal if these mucinous-specific biomarkers are derived from mucinous tumor-specific pathogenesis pathways.

In addition, epidemiologic studies have shown that smoking is a risk factor for developing mucinous ovarian tumors, with an adjusted odds ratio of smoking exposure to mucinous cancer development ranging from 1.5 to 3.2. By analyzing within the mucinous group, we identified autoantibody biomarkers whose titers in the smoking samples are significantly lower than the titers in nonsmoking samples (see Table 3).

Many of the antigens recognized by these biomarkers are involved in signaling pathways that regulate cytoskeleton remodeling, cell migration, growth and survival of cancer cells, suggesting that elevated plasma autoantibodies from ovarian cancer patients might have heightened reactivities with epitopes presented by these antigens.

TABLE 1

Biomarkers for Ovarian Cancer		
Biomarker	Accession No.	Level in Ovarian Cancer Patients Relative to Normal Levels
CSE1 chromosome segregation 1-like (yeast)	P55060	up
casein kinase 1, epsilon	P49674	up
v-crk sarcoma virus CT10 oncogene homolog (avian)	P46108	up
topoisomerase (DNA) II alpha. 170 kDa	P11388	up
c-src tyrosine kinase	P41240	up
catechol-O-methyltransferase	P21964	up
WAS protein family, member 1	Q92558	up
erythrocyte membrane protein band 4.9 (dematin)	Q08495	up
potassium large conductance calcium-activated channel, subfamily M, alpha member 1	Q12791	up
nuclear receptor coactivator 3	Q9Y6Q9	up
TEA domain family member 1 (SV40 transcriptional enhancer factor)	P28347	up
peroxisome biogenesis factor 1	O43933	up
translin-associated factor X	Q99598	up
G protein-coupled receptor 51	O75899	up
solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter, NA <sup>+</sup> /H <sup>+</sup> , amiloride sensitive)	P19634	up
integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	P17301	up
MCM6 minichromosome maintenance deficient 6 (MIS5 homolog, <i>S. pombe</i> ) ( <i>S. cerevisiae</i> )	Q14566	up
syntaxin 6	O43752	up
KH domain containing, RNA binding, signal transduction associated 1	Q07666	up
dystrophia myotonica-protein kinase	Q09013	up
eukaryotic translation initiation factor 4 gamma, 1	Q04637	up
Rho GDP dissociation inhibitor (GDI) beta	P52566	up
endothelin receptor type A	P25101	up
synaptophysin	P08247	up
transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	P15923	up
fibronectin 1	P02751	up
RAS p21 protein activator (GTPase activating protein) 1	P20936	up
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	P51531	up
syntaxin binding protein 5 (tomosyn)	Q5T5C0	up
Ras-GTPase-activating protein SH3-domain-binding protein	Q13283	up
glutamate receptor, ionotropic, N-methyl D-aspartate 2B	Q13224	up
synapsin II	Q92777	Down
sortilin-related receptor, L (DLR class) A repeats-containing	Q92673	Down
excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D)	P18074	Down
signal transducer and activator of transcription 6, interleukin-4 induced	P42226	Down

专利名称(译)	卵巢癌的生物标志物		
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申请(专利权)人(译)	布里格姆妇女医院, INC.		
当前申请(专利权)人(译)	布里格姆妇女医院, INC.		
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摘要(译)

本发明涉及可用于诊断的与卵巢癌相关的生物标志物的测定。它包括固定有生物标记物的玻璃或塑料板或载玻片以及含有这些板或载玻片的试剂盒。

