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(54) **USE OF MARKERS IN THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER**

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USPC **506/9**; 435/7.92; 506/18

(57) **ABSTRACT**

The invention provides method for diagnosis, monitoring, and prognosis of prostate cancer using one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, and LY9, and PSA. The invention provides kits for practicing the methods of the invention.

FIG. 1

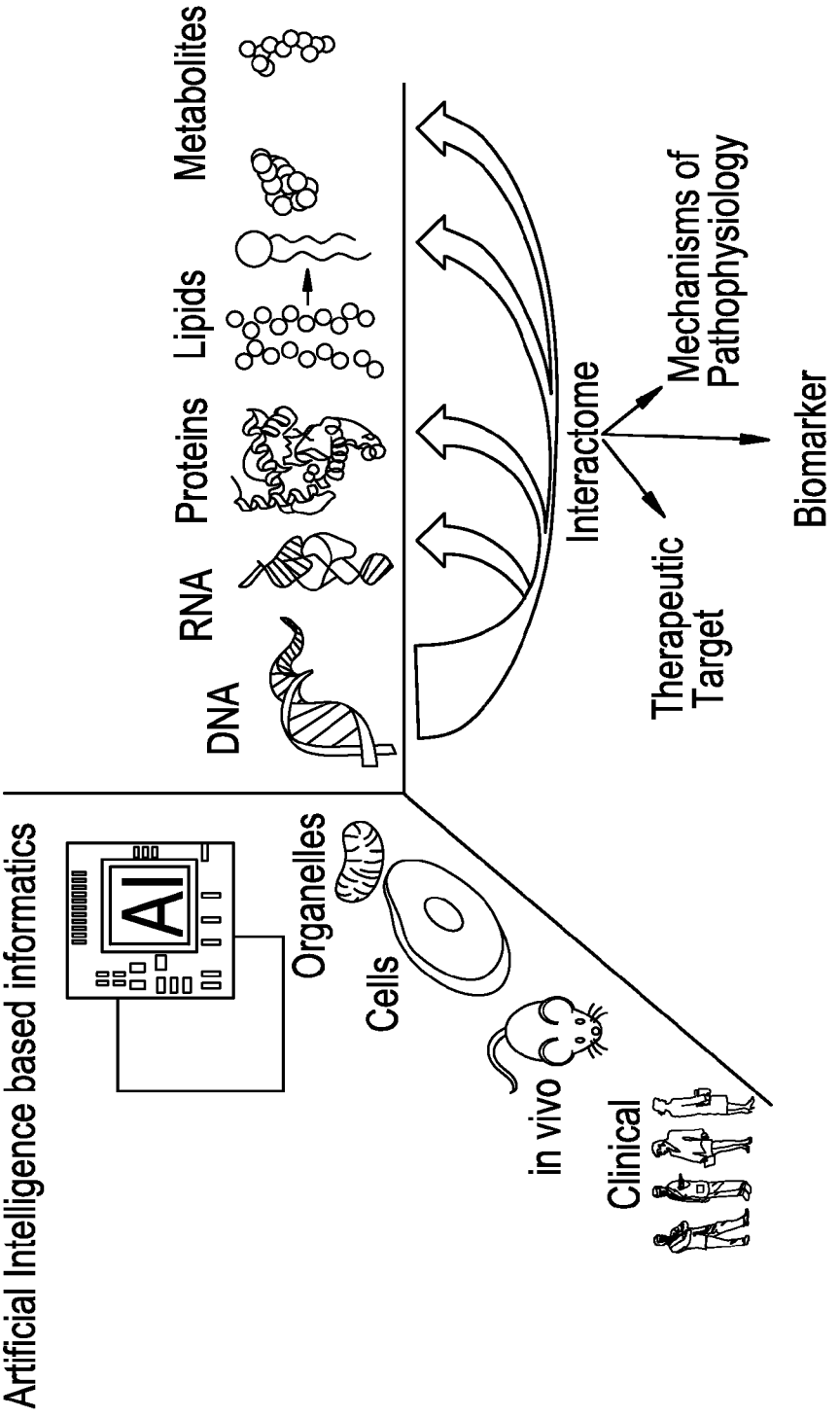

Artificial Intelligence based informatics
AI
Organelles
Cells
in vivo
Clinical
DNA
RNA
Proteins
Lipids
Metabolites
Interactome
Therapeutic Target
Mechanisms of Pathophysiology
Biomarker

FIG. 2A

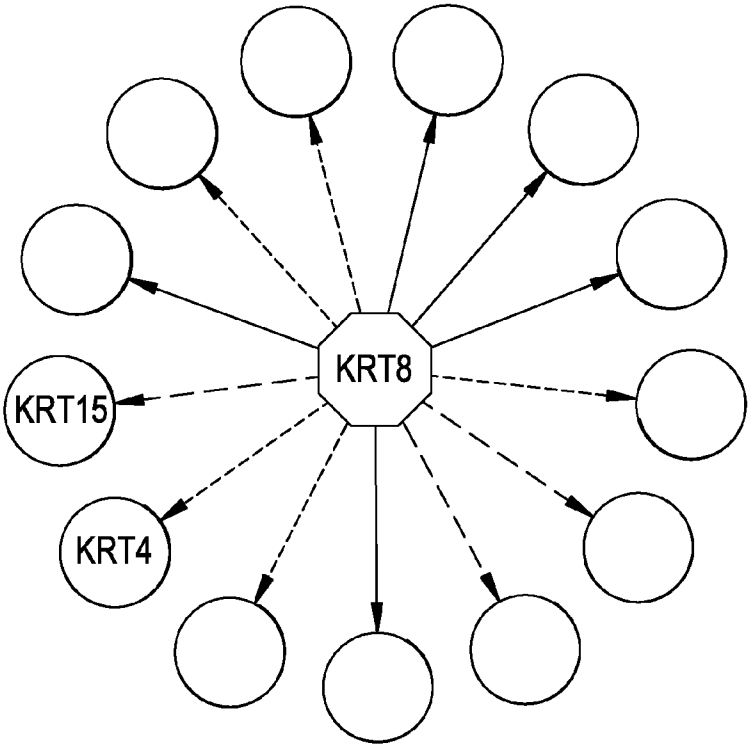


FIG. 2B

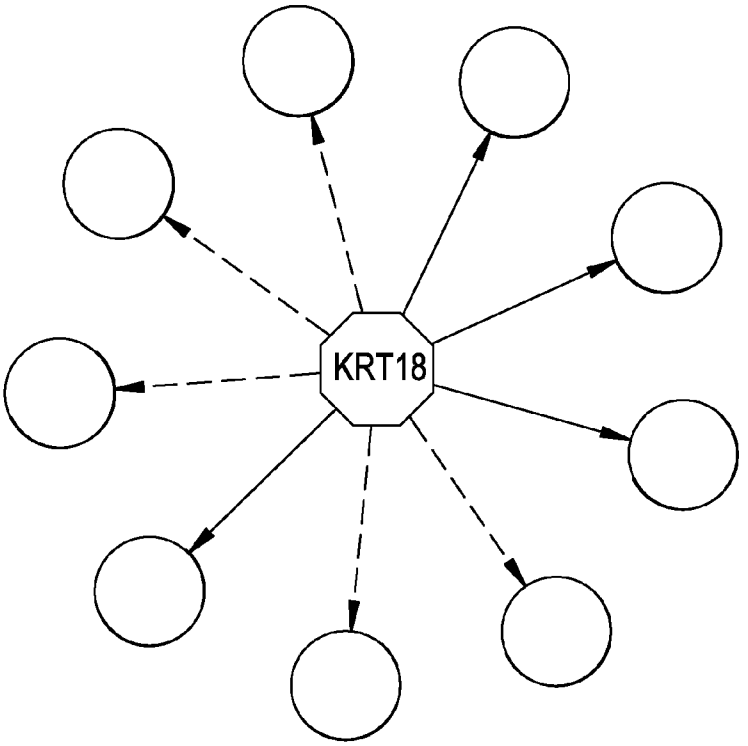


FIG. 2C

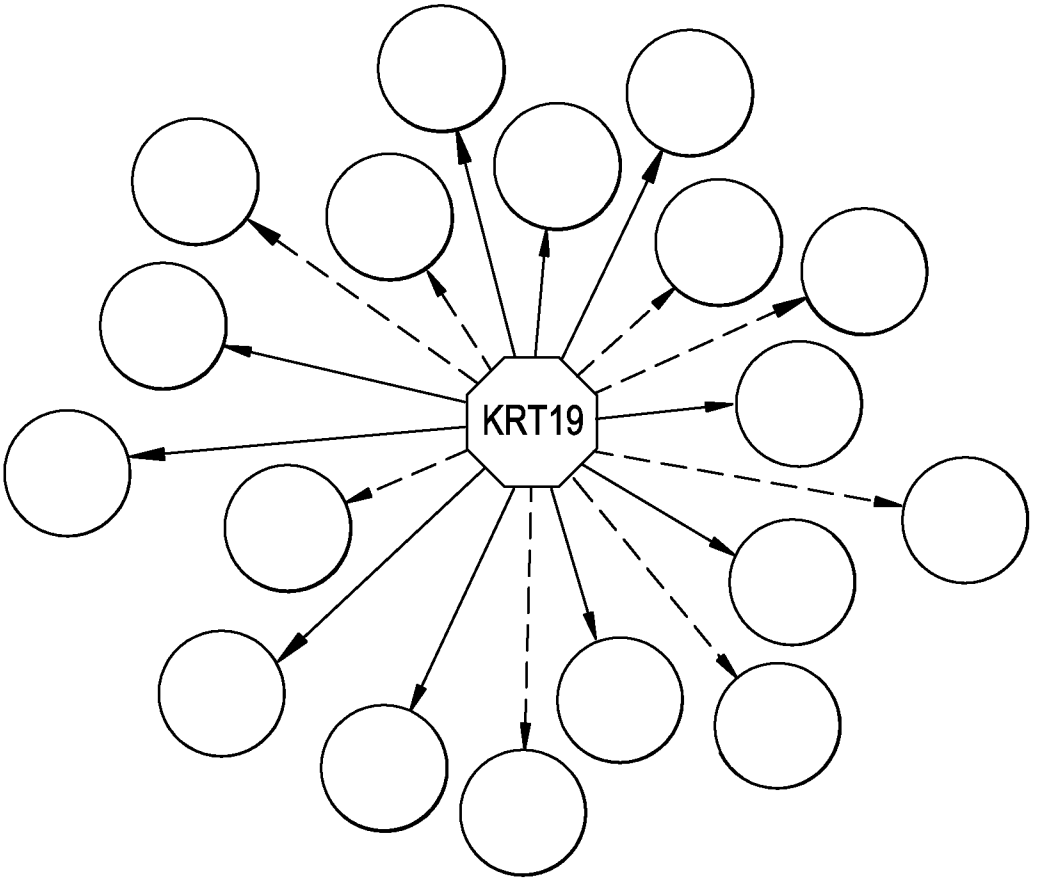


FIG. 3A

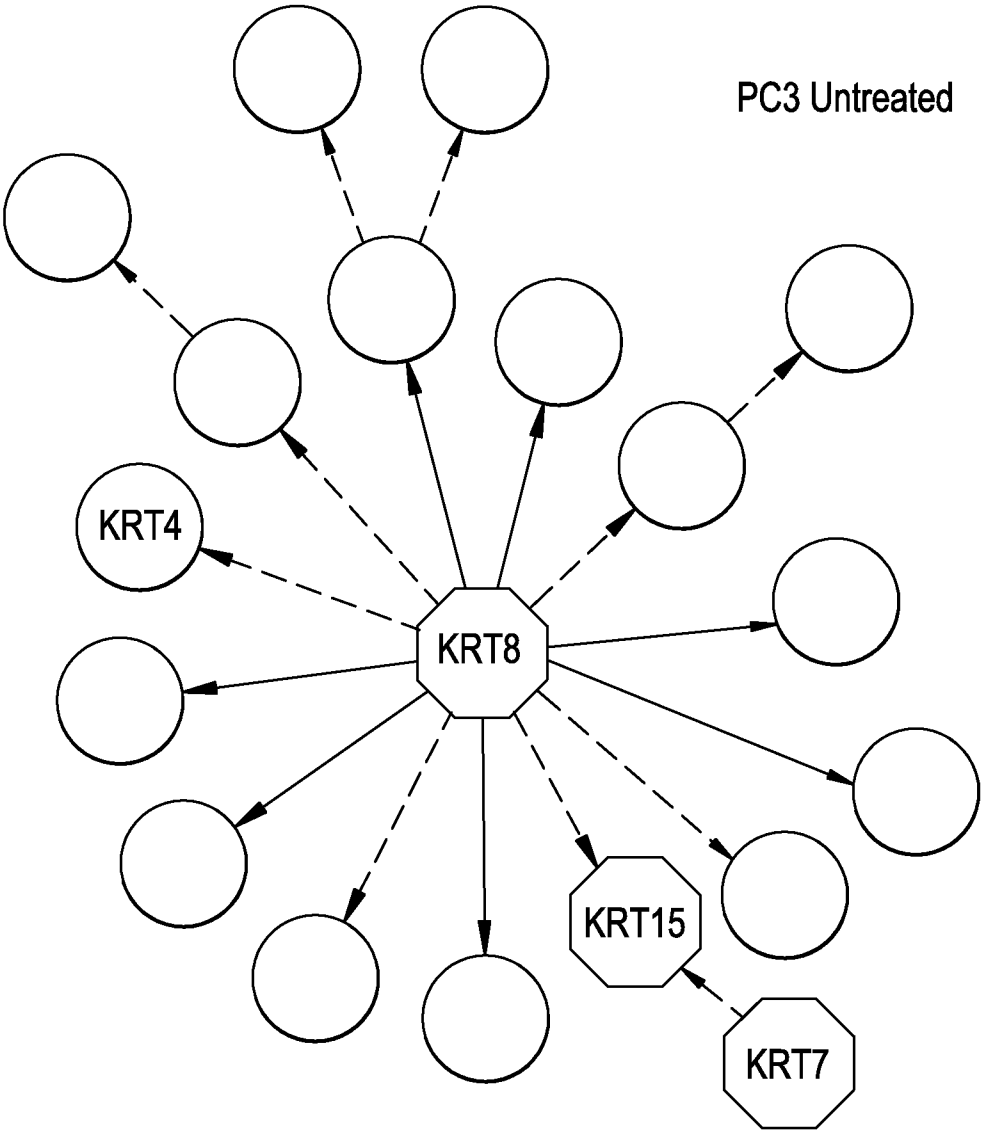


FIG. 3B

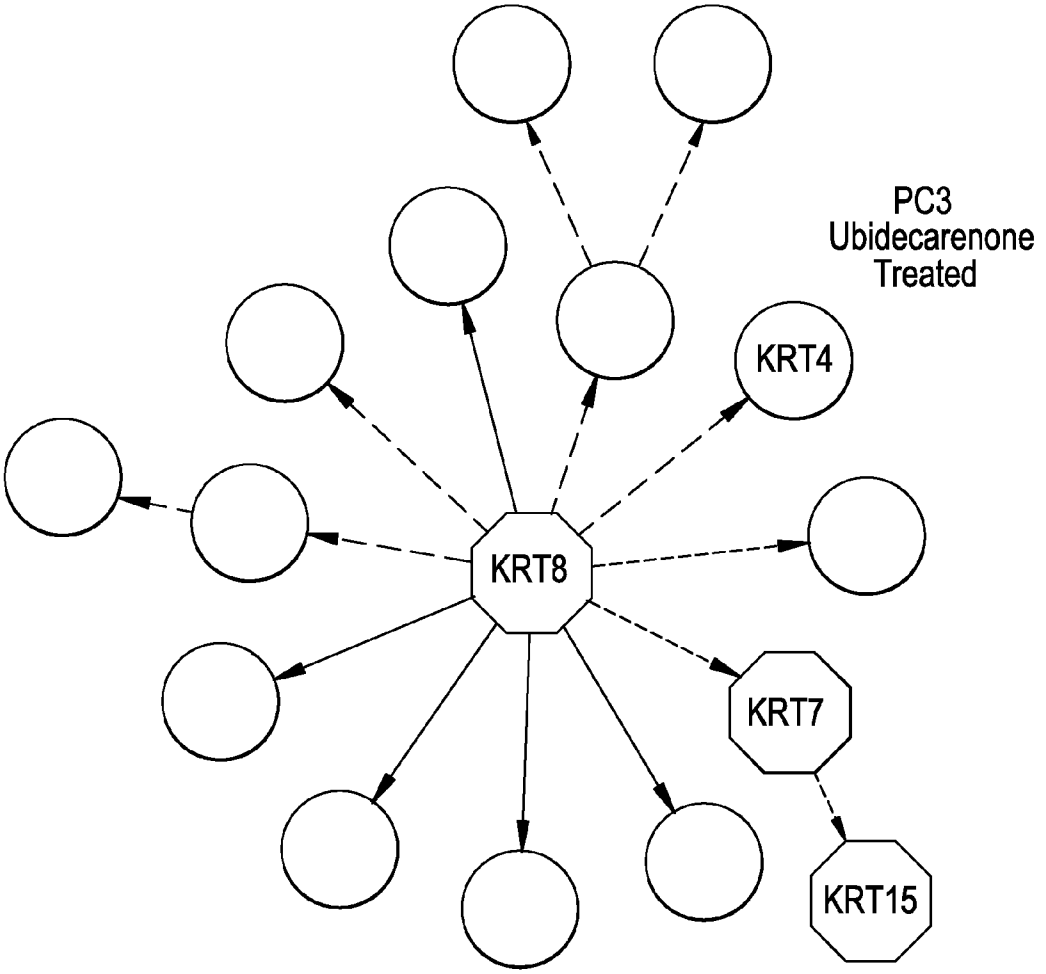


FIG. 3C

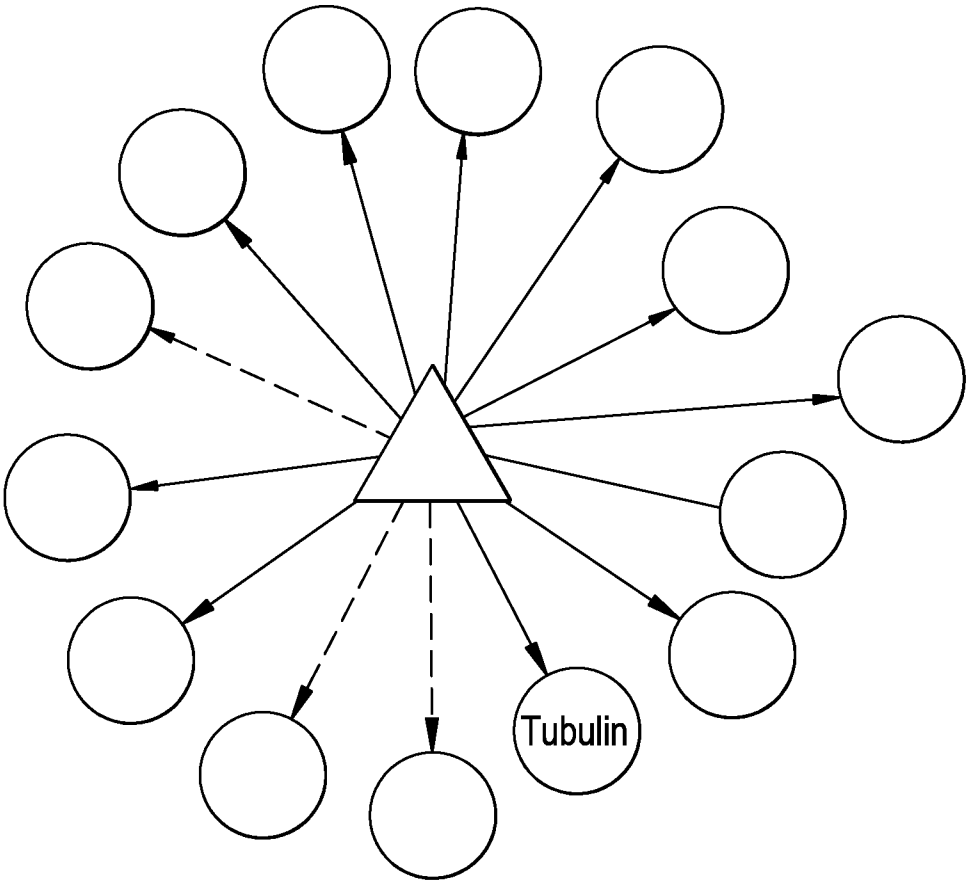


FIG. 3D

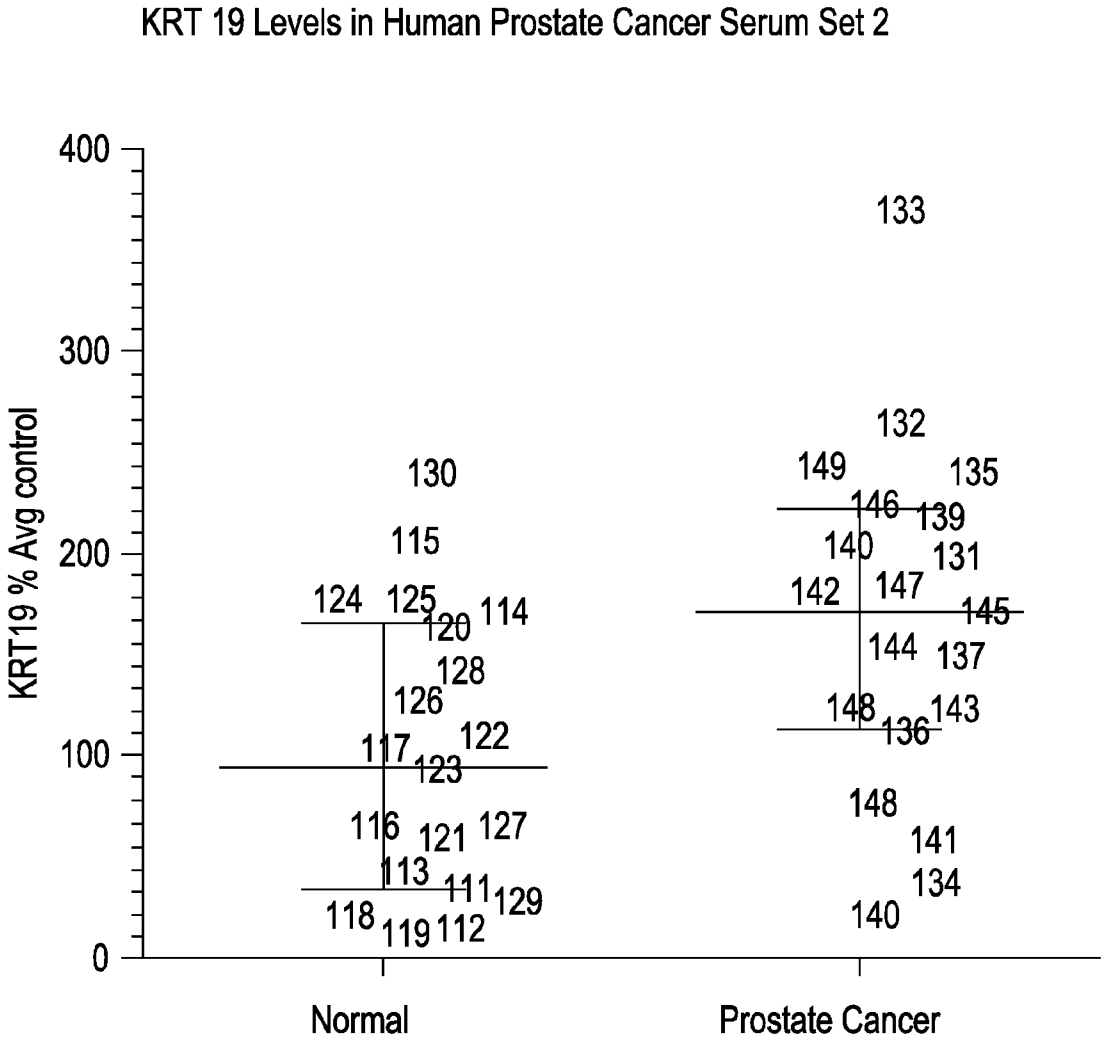

KRT 19 Levels in Human Prostate Cancer Serum Set 2
KRT19 % Avg control
400
300
200
100
0
130
115
124
125
120
114
128
126
117
122
123
116
121
127
113
111
129
118
119
112
133
132
149
135
146
139
140
131
142
147
145
144
137
148
143
136
148
141
134
140
Normal
Prostate Cancer
Bars represent median with interquartile range

FIG. 4

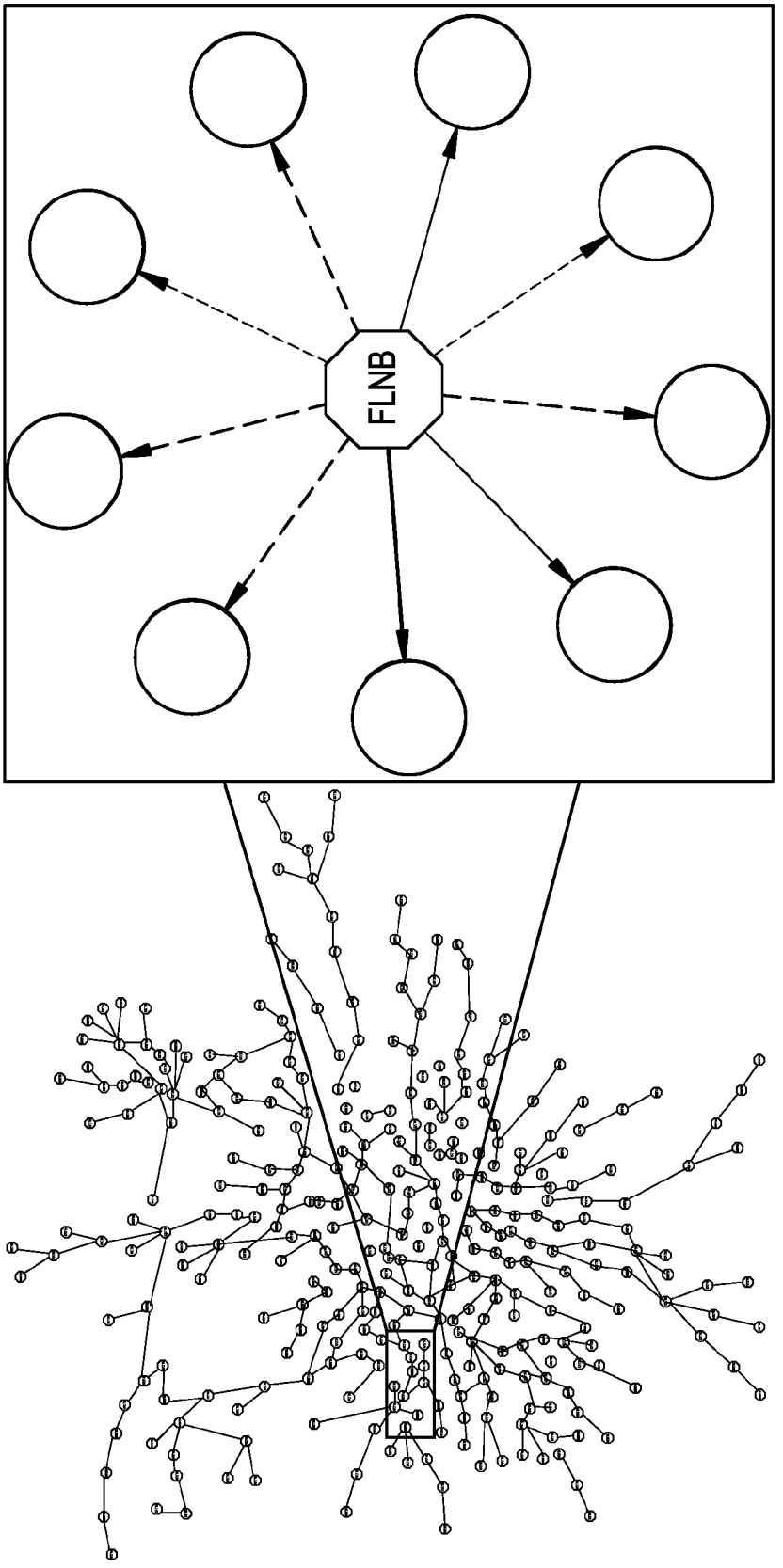


FIG. 5

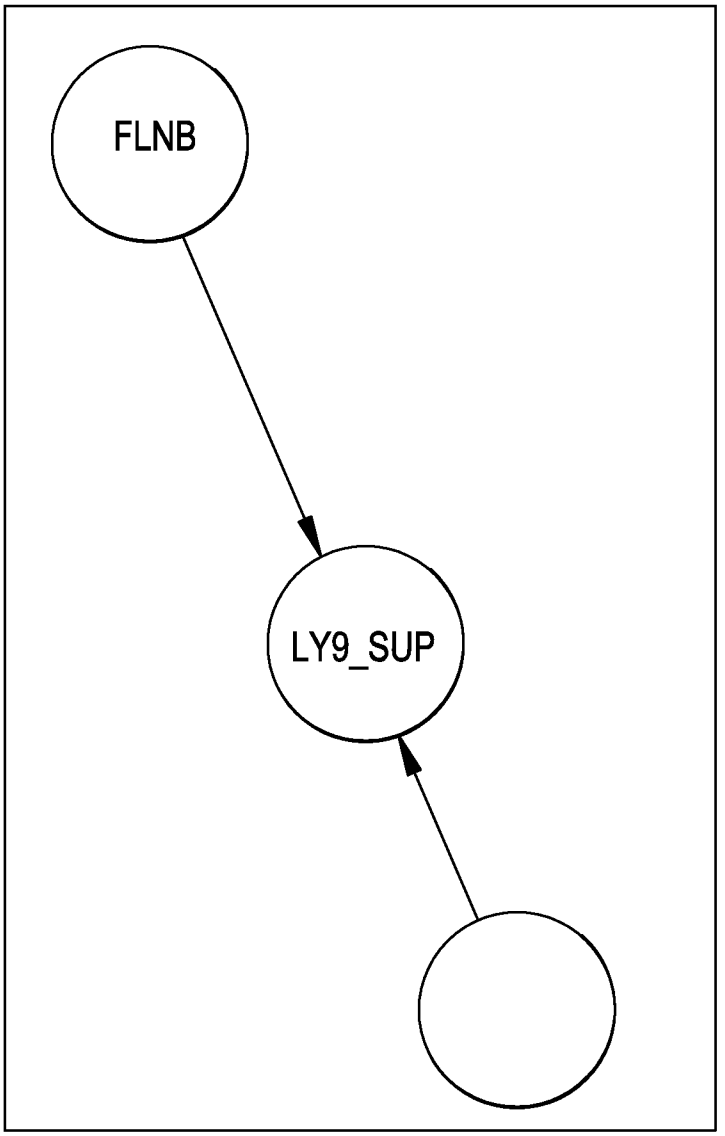


FIG. 6A

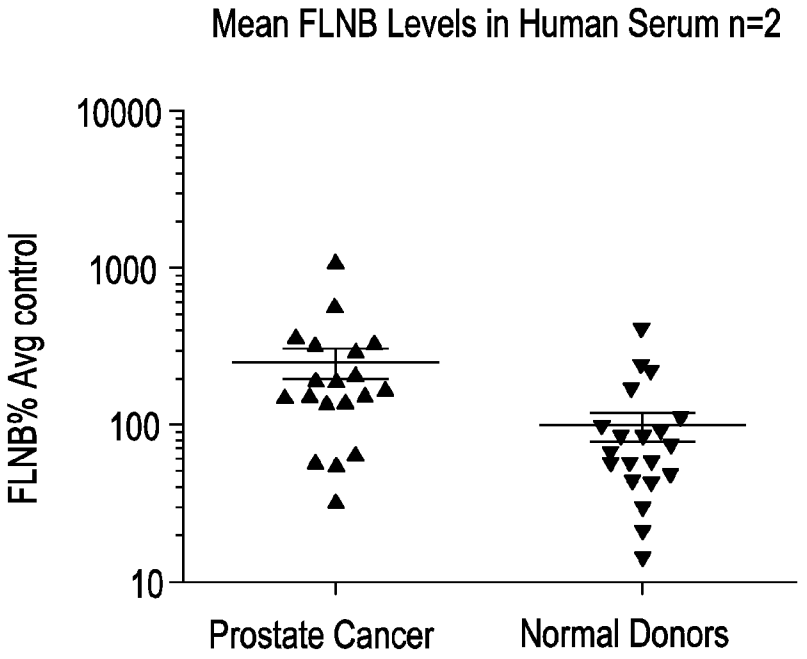

Mean FLNB Levels in Human Serum n=2
FLNB% Avg control
10000
1000
100
10
Prostate Cancer
Normal Donors

FIG. 6B

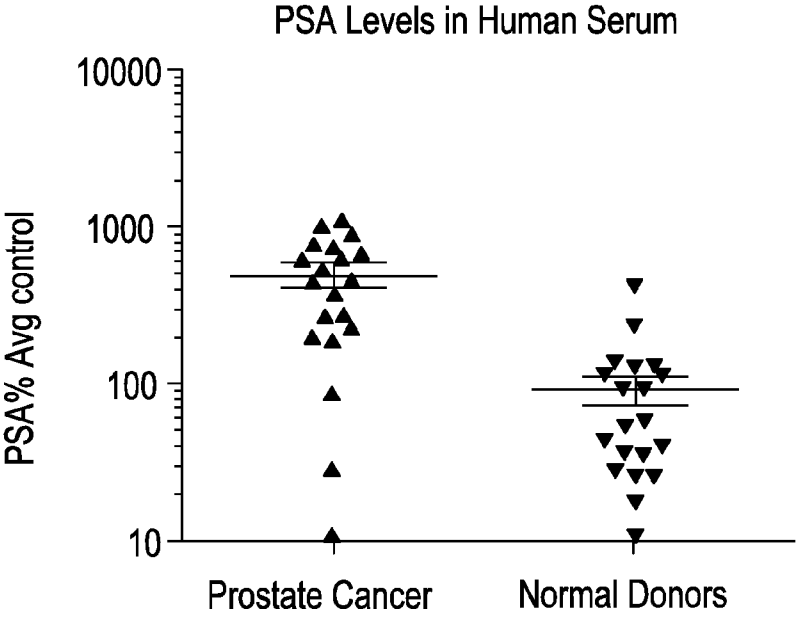

PSA Levels in Human Serum
PSA% Avg control
10000
1000
100
10
Prostate Cancer
Normal Donors

FIG. 7

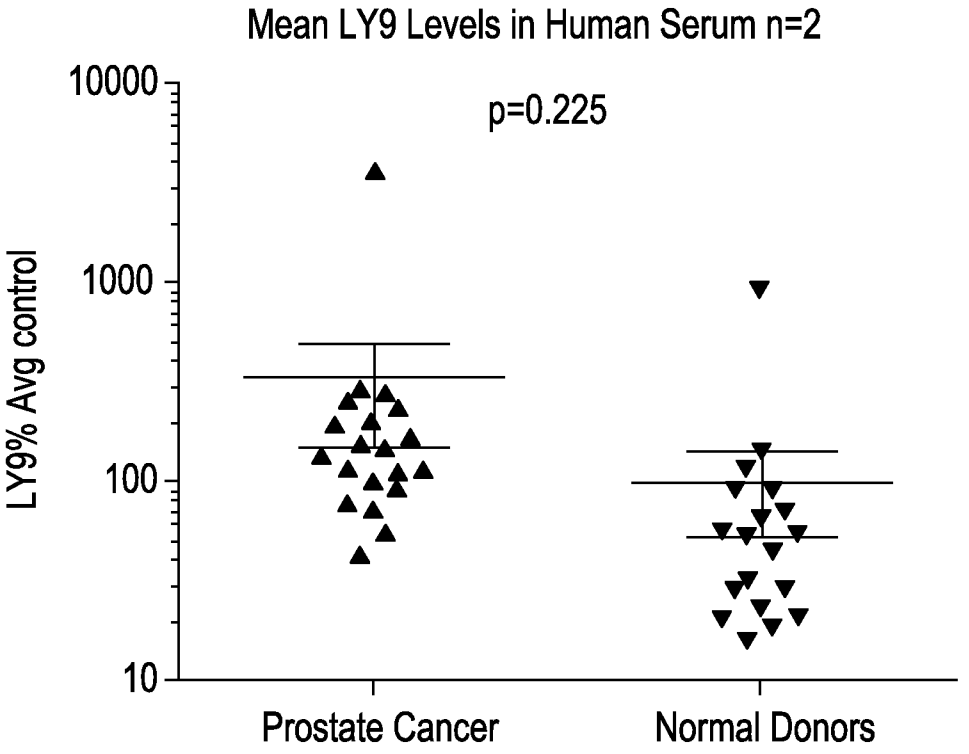

Mean LY9 Levels in Human Serum n=2
p=0.225
LY9% Avg control
10000
1000
100
10
Prostate Cancer
Normal Donors

FIG. 8A

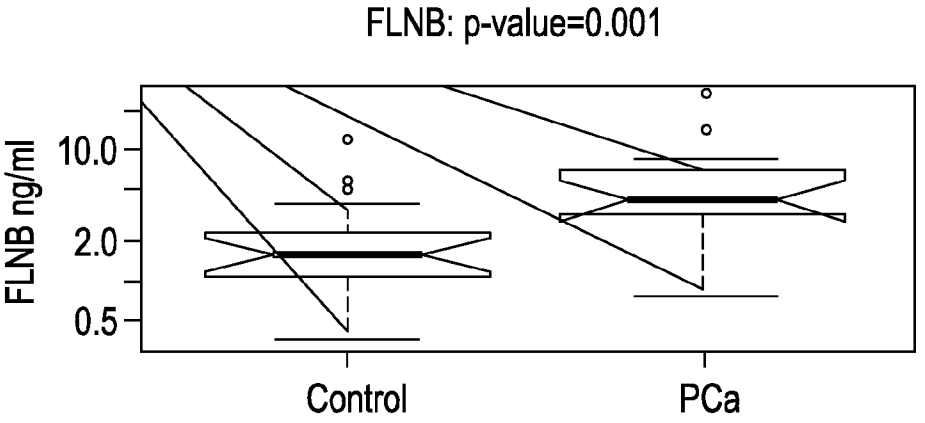


FIG. 8B

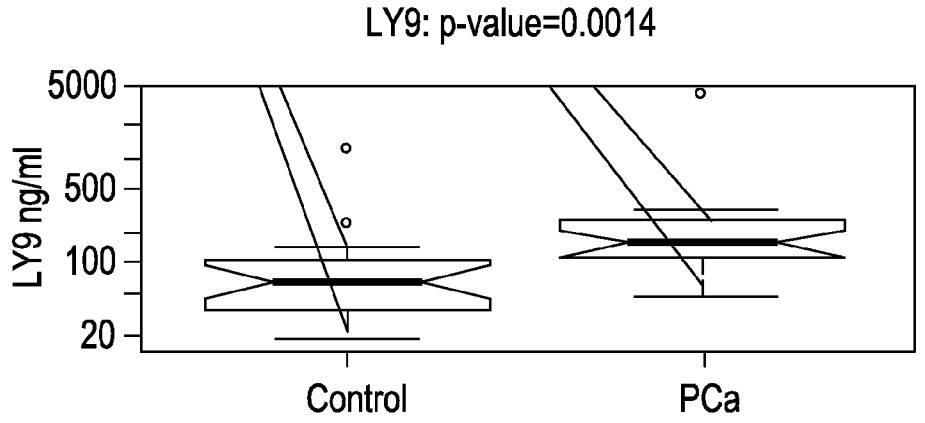


FIG. 8C

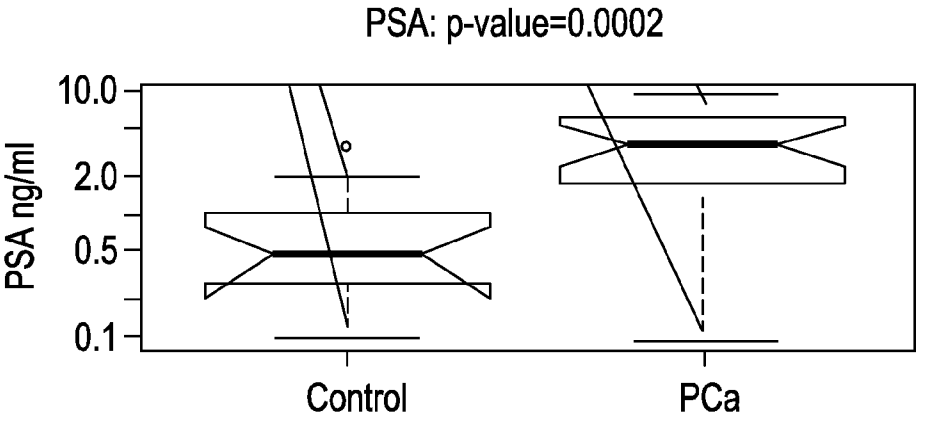


FIG. 9A

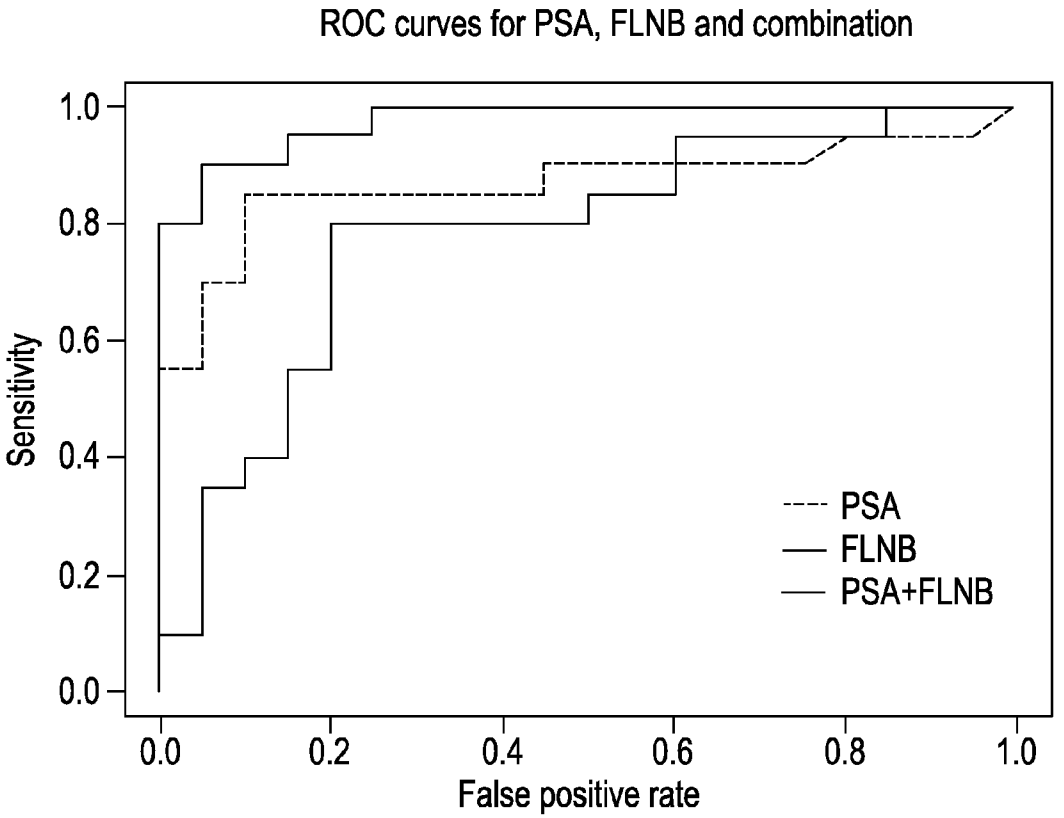


FIG. 9B

Marker	AUC
PSA	0.87
FLNB	0.78
PSA + FLNB	0.975

FIG. 10A

Linear scoring function

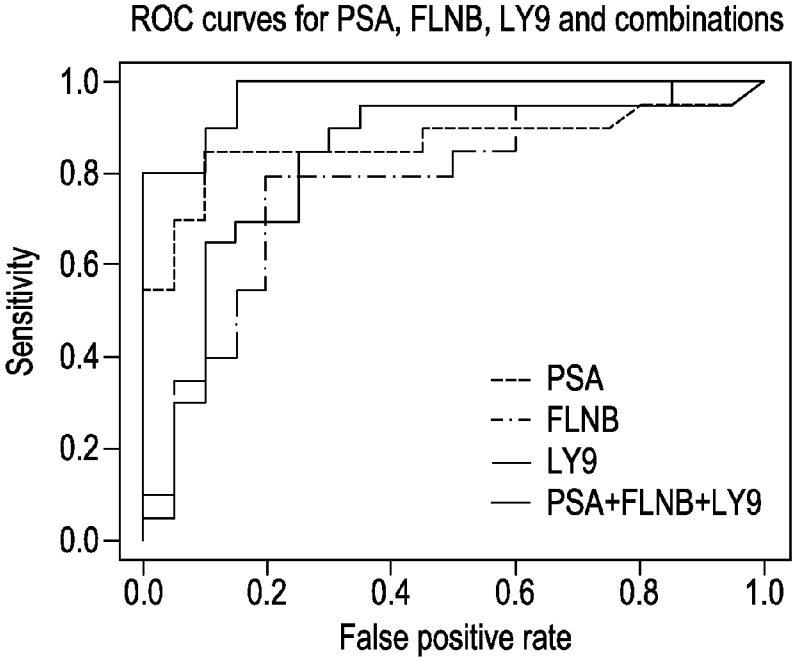
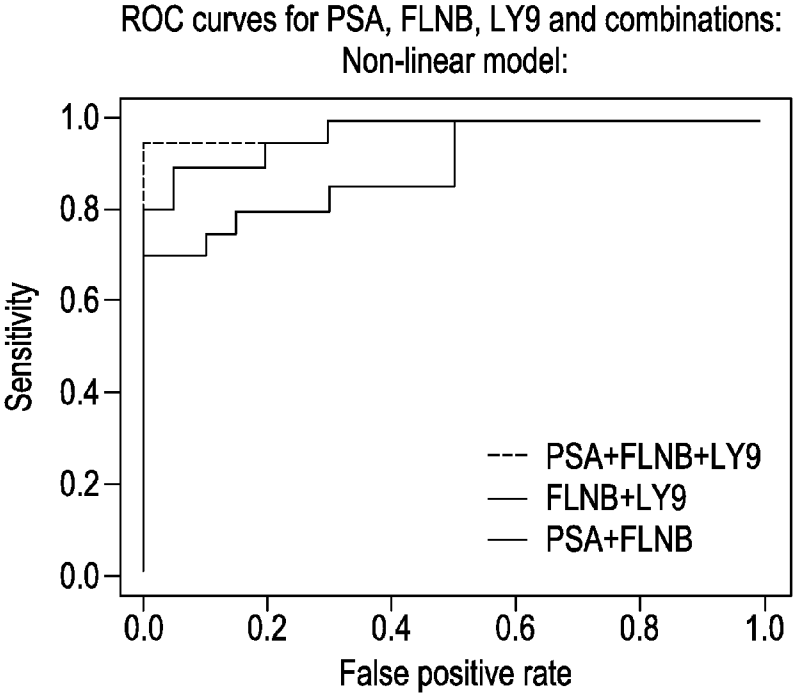


FIG. 10B

Non-Linear scoring function



USE OF MARKERS IN THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 61/665,201, filed Jun. 27, 2012; U.S. Provisional Application Ser. No. 61/672,090, filed Jul. 16, 2012; U.S. Provisional Application Ser. No. 61/673,094, filed Jul. 18, 2012; U.S. Provisional Application Ser. No. 61/702,523, filed Sep. 18, 2012, and U.S. Provisional Application Ser. Nos. 61/718,064, 61/718,080, and 61/718,081 all filed on Oct. 24, 2012. Each of the applications is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jun. 25, 2013, is named 119992-06604_SL.txt and is 461,537 bytes in size.

FIELD OF THE INVENTION

[0003] The invention relates to treatment, prevention, reduction, diagnosis, monitoring, and prognosis of abnormal prostate states, including benign prostate hyperplasia and oncological disorders, especially prostate cancer, in humans using filamin B, lymphocyte antigen 9 (LY9), keratins and tubulin, specifically using keratins 4, 7, 8, 15, 18, and 19, and tubulin-beta 3, particularly keratins 7, 15, or 19. The filamin B, lymphocyte antigen 9 (LY9), keratins and tubulin can further be used in conjunction with prostate specific antigen (PSA) for the treatment, prevention, reduction, diagnosis, monitoring, and prognosis of abnormal prostate states, including benign prostate hyperplasia and oncological disorders, especially prostate cancer. The invention also relates to panels and kits for use in practicing the methods of the invention.

BACKGROUND OF THE INVENTION

[0004] Oncological disorders, such as cancer, are presently one of the leading causes of death in developed nations and is a serious threat to modern society. Cancer can develop in any tissue of any organ at any age. Worldwide, more than 10 million people are diagnosed with cancer every year and it is estimated that this number will grow to 15 million new cases every year by 2020. It is believed that cancer causes six million deaths every year or 12% of the deaths worldwide.

[0005] Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing. However, there are cases of aggressive prostate cancers. The cancer cells may metastasize from the prostate to other parts of the body, particularly to the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

[0006] Rates of detection of prostate cancers vary widely across the world, with detection rates in south and east Asia being lower than those in Europe, and especially in the United States. Prostate cancer tends to develop in men over the age of fifty and, although it is one of the most prevalent types of cancer in men, many never have symptoms or undergo therapy for prostate cancer, and eventually die of other causes. Further, treatment of prostate cancer may do more harm to the subject than the prostate cancer itself. Prostate specific antigen (PSA) screening has lead to a significant rise in the number of men diagnosed with prostate cancer with an associated increase in potentially unnecessary biopsies preformed. Despite its limitations, including a positive predictive value of only 25-40%, PSA remains the only generally accepted biomarker for prostate cancer.

[0007] Prostate cancer is, in most cases, slow-growing and symptom-free. Moreover, since men with the condition are typically older, they often die of causes unrelated to the prostate cancer, such as heart/circulatory disease, pneumonia, other unrelated cancers, or old age. On the other hand, the more aggressive prostate cancers account for more cancer-related deaths among men in the United States than any other cancer except lung cancer.

[0008] About two-thirds of prostate cancer cases are slow growing, whereas the other third are more aggressive and fast developing. It is important to be able to distinguish between aggressive and non-aggressive forms of the disease, and further, to distinguish prostate cancer from benign prostate hyperplasia (BPH). Commonly used screening tests, e.g., for prostate specific antigen (PSA) cannot distinguish between prostate cancer and BPH.

SUMMARY OF THE INVENTION

[0009] The present invention is based, at least in part, on Applicants' discovery that keratins 4, 7, 8, 15, 18, and 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) are differentially regulated in prostate cancer cells.

[0010] Accordingly, the invention provides methods for diagnosing, monitoring (e.g., of disease progression or treatment), prognosing, treating, alleviating symptoms of, inhibiting progression of, or preventing, an oncological disease state, e.g., prostate cancer, in a mammal. The invention further provides panels and kits for practicing the methods of the invention.

[0011] In one aspect, the invention provides methods for diagnosing an abnormal prostate state in a subject comprising:

[0012] (1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a biological sample from the subject; and

[0013] (2) comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a normal control sample, wherein an altered level of the one or more prostate cancer related markers in the biological sample relative to the normal control sample is indicative of an abnormal prostate state in the subject.

[0014] In certain embodiments, the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, an increased level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the subject.

[0015] In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin

B, LY9, and keratin 19 in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject. In such embodiments, levels of one, two, or all three of filamin B, LY9, and keratin 19 can be detected. For the marker levels detected, none of the markers have increased levels.

[0016] In certain embodiments, the method further comprises detecting the level of prostate specific antigen (PSA) in the biological sample and preferably further comprising comparing the level of PSA in the biological sample to the level of PSA in a normal control sample. In certain embodiments, an increase in the level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample has greater predictive value of the subject having an abnormal prostate state than the predictive value of a single marker alone. In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample has a greater predictive value of the subject having a normal prostate state than any single marker alone.

[0017] Throughout the methods, kits, and panels of the invention, one or more of filamin B, LY9 and keratin 19 is understood as any of filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

[0018] In certain embodiments of the invention, the abnormal prostate state is prostate cancer.

[0019] In certain embodiments of the invention, the prostate cancer is androgen-dependent prostate cancer. In certain embodiments of the invention, the prostate cancer is androgen-independent prostate cancer. In certain embodiments of the invention, the prostate cancer is aggressive prostate cancer. In certain embodiments of the invention, the prostate cancer is non-aggressive prostate cancer.

[0020] In certain embodiments of the invention, the abnormal prostate state is benign prostate hyperplasia.

[0021] In another aspect, the invention provides a method for identifying a subject as being at increased risk for developing prostate cancer, the method comprising:

[0022] (1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a biological sample from the subject; and

[0023] (2) comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a normal control sample, wherein an altered level of the one or more prostate cancer related markers in the biological sample relative to the control sample is indicative of an increased risk for developing prostate cancer in the subject.

[0024] In certain embodiments, the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, an increased level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of an increased risk for developing prostate cancer in the subject. In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of no increased risk for developing prostate cancer in the subject.

[0025] In certain embodiments, the method further comprises detecting the level of prostate specific antigen (PSA) in the biological sample and preferably further comprises comparing the level of PSA in the biological sample to the level of PSA in a normal control sample. In certain embodiments, an increase in the level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample has greater predictive value of an increased risk for developing prostate cancer in the subject than an increase in any of the individual markers alone. In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, has greater predictive value of no increased risk for developing prostate cancer in the subject than any single marker alone.

[0026] In the embodiments of the invention, one or more prostate cancer markers selected from the group consisting of filamin B, LY9 and keratin 19 is: filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

[0027] In certain embodiments of the diagnostic or prognostic methods of the invention, one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. In certain embodiments, one or more prostate cancer related markers is selected from the group consisting of keratin 7, keratin 8, and keratin 15. In certain embodiments, one or more prostate cancer related markers is selected from the group consisting of keratin 7 and keratin 15. In certain embodiments, one or more prostate cancer markers is selected from the group consisting of keratin 7, 15, and 19. In certain embodiments, the diagnostic and prognostic methods of the invention further comprise detecting the level of prostate specific antigen (PSA) in the biological sample, and preferably further comprise comparing the level of PSA in the biological sample to a level of PSA in a control sample.

[0028] In certain embodiments, the control sample for PSA is the same control sample as for the other prostate cancer related markers of the invention. In certain embodiments, the control sample for PSA is different from the control sample for the other prostate cancer related markers of the invention

[0029] In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the sub-

ject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject.

[0030] In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an increased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an increased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of no increased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of no increased risk of developing prostate cancer in the subject.

[0031] In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, the method further comprises detecting the level of prostate specific antigen (PSA) in the biological sample, and preferably further comprises comparing the level of PSA in the biological sample to the level of PSA in a normal control sample. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increase in the level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample is indicative of an abnormal prostate state in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an decrease in the level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample is indicative of an abnormal prostate state in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, is indicative of a normal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased or normal level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, is indicative of a normal prostate state in the subject.

[0032] In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, the method further comprises detecting the level of prostate specific antigen (PSA) in the biological sample, and preferably further comprises comparing the level of PSA in the biological sample to the level of PSA in a normal control sample. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increase in the level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample is indicative of an increased risk for the subject of developing prostate cancer wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an decrease in the level of one or more of the prostate cancer

related markers in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to the level of PSA in the normal control sample is indicative of an increased risk for the subject of developing prostate cancer wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, is indicative of an decreased risk or normal risk of developing prostate cancer in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the prognostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased or normal level of one or more of the prostate cancer related markers in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, is indicative of a decreased risk or normal risk of developing prostate cancer in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone.

[0033] In various embodiments of any of the diagnostic or prognostic methods of the invention, the method may further comprise comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a sample obtained from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer. In such embodiments, comparison with one or more additional control sample can facilitate differentiating between two prostate cancer states selected from the group consisting of: normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, and metastatic prostate cancer and non-metastatic prostate cancer; or differentiating between any two or more of normal prostate, prostate cancer, benign prostate hyperplasia, androgen dependent prostate cancer, androgen independent prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

[0034] In certain embodiments of the invention, when a tumor is present, the method further comprises detecting the size of the prostate tumor in the subject.

[0035] In certain embodiments of the diagnostic and prognostic methods the invention, the method further comprises obtaining a sample from a subject.

[0036] In certain embodiments of the diagnostic and prognostic methods the invention, the method further comprises selecting a subject who has or is suspected of having prostate cancer.

[0037] In certain embodiments of the invention, the method further comprises selecting a treatment regimen for the subject based on the level of the one or more prostate cancer markers. In certain embodiments of the invention, the method further comprises treating the subject with a a treatment regimen based on the level of the one or more prostate cancer markers. In certain embodiments, a treatment regimen comprises one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, growth factor therapy, cytokine therapy, and chemotherapy.

[0038] In yet another aspect, the invention provides methods for monitoring prostate cancer in a subject, the method comprising

[0039] (1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a first biological sample obtained at a first time from a subject having prostate cancer;

[0040] (2) determining a level of expression of the one or more prostate cancer related markers in a second biological sample obtained from the subject at a second time, wherein the second time is after or later than, the first time; and

[0041] (3) comparing the level of the one or more prostate cancer related markers in the second sample with the level of the one or more prostate cancer related markers in the first sample, wherein a change in the level of the one or more prostate cancer related markers in the second sample as compared to the first sample is indicative of a change in prostate cancer status in the subject.

[0042] In certain embodiments, the subject is actively treated for prostate cancer prior to obtaining the second sample. That is, the subject is undergoing active treatment for prostate cancer.

[0043] In certain embodiments, the subject is not actively treated for prostate cancer prior to obtaining the second sample. That is, the subject is being monitored using watchful waiting.

[0044] In certain embodiments, one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, an increased level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample as compared to the first biological sample is indicative of progression of the prostate cancer in the subject. In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample as compared to the first biological sample is indicative of non-progression of the prostate cancer in the subject.

[0045] In certain embodiments, the methods further comprise determining the level of prostate specific antigen (PSA) in the first biological sample and the second biological sample and preferably, further comprising comparing the

level of PSA in the second biological sample to the level of PSA in the first biological sample. In certain embodiments, an increased level of the one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample relative to the level of the one or more prostate cancer related markers in the first biological sample, in combination with an increase in the level of PSA in the second biological sample relative to the level of PSA in the first biological sample has greater predictive value of progression of the prostate cancer in the subject than any single marker alone. In certain embodiments, no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample relative to the level of the one or more prostate cancer related markers in the first biological sample, in combination with a decreased or same level of PSA in the second biological sample relative to the level of PSA in the first biological sample has greater predictive value of non-progression of the prostate cancer in the subject than any single marker alone.

[0046] In embodiments of the invention, the one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 is: filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

[0047] In certain embodiments of the monitoring methods of the invention, the one or more prostate cancer markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. In certain embodiments of the monitoring methods of the invention, the one or more prostate cancer related markers is selected from the group consisting of keratin 7, keratin 8, and keratin 15. In certain embodiments of the monitoring methods of the invention, the one or more prostate cancer related markers is selected from the group consisting of keratin 7, keratin 15, and keratin 19. In certain embodiments of the monitoring methods of the invention, the one or more prostate cancer related markers is selected from the group consisting of keratin 7 and keratin 15.

[0048] In certain embodiments of the monitoring methods of the invention, wherein the one or more prostate cancer markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, the methods further comprise determining the level of prostate specific antigen (PSA) in the first biological sample and the second biological sample, and preferably further comprise comparing the level of PSA in the second biological sample to the level of PSA in the first biological sample.

[0049] In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the second sample relative to a first sample is indicative of prostate tumor progression in the subject. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the second sample relative to a first sample is indicative of prostate tumor progression in the subject. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased level of one or more of the prostate cancer related markers in the second sample relative to a first sample is indicative of no prostate tumor progression in the subject. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the second sample relative to a first sample is indicative of no prostate tumor progression in the subject.

[0050] In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, the method further comprises detecting the level of prostate specific antigen (PSA) in the second sample, and preferably further comprises comparing the level of PSA in the second sample to the level of PSA in a first sample. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increase in the level of one or more of the prostate cancer related markers in the second sample relative to the first sample, in combination with an increase in the level of PSA in the second sample as compared to the level of PSA in the first sample is indicative of prostate tumor progression in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an decrease in the level of one or more of the prostate cancer related markers in the second sample relative to the first sample, in combination with an increase in the level of PSA in the second sample as compared to the level of PSA in the first sample is indicative of prostate tumor progression in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, a decreased or normal level of one or more of the prostate cancer related markers in the second sample relative to the first sample, in combination with a decreased or normal level of PSA in the second sample as compared to the level of PSA in the first sample, is indicative of no prostate tumor progression in the subject. In certain embodiments of the monitoring methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3, an increased or normal level of one or more of the prostate cancer related markers in the second sample relative to the first sample, in combination with a decreased or normal level of PSA in the second sample as compared to the level of PSA in the first sample, is indicative of no prostate

tumor progression in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone.

[0051] In certain embodiments of the monitoring methods of the invention, the methods further comprise comparing the level of the one or more prostate cancer related markers in the first biological sample or the second biological sample with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a normal control sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer.

[0052] In certain embodiments of the monitoring methods of the invention, the methods further comprise detecting the size of the prostate tumor in the subject.

[0053] In certain embodiments of the monitoring methods of the invention, the methods further comprise obtaining a first sample and a second sample from the subject.

[0054] In certain embodiments of the monitoring methods of the invention, the methods further comprise selecting and/or administering a different treatment regimen for the subject based on progression of the prostate cancer in the subject.

[0055] In certain embodiments of the monitoring methods of the invention, the methods further comprise comprises maintaining a treatment regimen for the subject based on non-progression of the prostate cancer in the subject.

[0056] In certain embodiments, the treatment regimens comprise one or more treatments selected from the group consisting of: surgery, radiation, hormone therapy, antibody therapy, growth factor therapy, cytokine therapy, and chemotherapy.

[0057] In certain embodiments of the monitoring methods of the invention, the methods further comprise withholding an active treatment of the prostate cancer in the subject based on non-progression of the prostate cancer in the subject. In certain embodiments, the active treatment is one or more treatments selected from the group consisting of: surgery, radiation, hormone therapy, antibody therapy, growth factor therapy, cytokine therapy, and chemotherapy.

[0058] In still another aspect, the invention provides methods for detecting a set of prostate cancer related markers, the method comprising:

[0059] (1) analyzing a biological sample from a subject for a level of two or more prostate cancer related markers of a set of prostate cancer related markers, wherein the set of prostate cancer related markers comprises filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0060] (2) detecting each of the two or more prostate specific makers in the biological sample, thereby detecting the set of prostate cancer related biomarkers.

[0061] In certain embodiments, the set of prostate cancer related markers comprises filamin B, LY9, and keratin 19. In certain embodiments, the two or more prostate cancer related markers are: filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19. In certain embodiments, the set of prostate cancer related markers comprises keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. In certain embodiments, the set of prostate cancer related markers comprises keratin 7, keratin 8, and keratin 15. In certain embodiments, the set of prostate cancer related markers comprises keratin 7, keratin 15, and keratin 19. In certain embodiments, the set of prostate cancer related markers comprises keratin 7 and keratin 15.

[0062] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises isolating a component of the biological sample.

[0063] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises labeling a component of the biological sample.

[0064] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises processing the biological sample.

[0065] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises contacting a prostate cancer related marker to be detected with a prostate cancer related marker binding agent.

[0066] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises forming a complex between a prostate cancer related marker to be detected and a prostate cancer related marker binding agent.

[0067] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises contacting each of the one or more prostate cancer related markers with a prostate cancer related marker binding agent.

[0068] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises forming a complex between each of the one or more prostate cancer related markers and a prostate cancer related marker binding agent.

[0069] In various embodiments of any of the methods of the invention, the step of detecting or determining a level of one or more prostate cancer related markers in a biological sample comprises attaching a prostate cancer related marker to be detected to a solid surface.

[0070] In yet another aspect, the invention provides a panel of reagents for use in a detection method, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer related marker of a set of prostate cancer related markers, wherein the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA.

[0071] In certain embodiments, the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, the two or more prostate cancer related markers is: filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

[0072] In certain embodiments, the set of prostate cancer specific markers comprises two or more prostate cancer

related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. In certain embodiments, the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of keratin 7, keratin 8, and keratin 15. In certain embodiments, the set of prostate cancer specific markers comprises keratin 7 and keratin 15.

[0073] In certain embodiments, the set of prostate cancer specific markers further comprises PSA. In certain embodiments, the panel of reagents comprises a detection reagent specific for the detection of PSA.

[0074] In yet another aspect, the invention provides for the use of any of the foregoing panels of the invention in any of the methods provided by the invention.

[0075] In still another aspect, the invention provides a kit for the diagnosis, monitoring, or characterization of an abnormal prostate state, comprising: at least one reagent specific for the detection of a level of at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9.

[0076] In certain embodiments, the kit further comprises instructions for the diagnosis, monitoring, or characterization of an abnormal prostate state based on the level of the at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 detected.

[0077] In certain embodiments, the kit further comprises instructions to detect the level of PSA in a sample in which the at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 is detected.

[0078] In certain embodiments, the kit further comprises at least one reagent specific for the detection of a level of PSA.

[0079] In one embodiment, the invention provides a kit comprising at least one reagent specific for the detection of a level of at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, and LY9 and at least one reagent specific for the detection of a level of PSA.

[0080] Further, the invention provides methods for diagnosing prostate cancer comprising determining a level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) in a biological sample obtained from a subject; and comparing the level of expression of the one or more markers in the biological sample obtained from the subject with the level of expression of the corresponding one or more markers in a control sample, wherein a modulation in the level of expression of the one or more markers in the biological sample is an indication that the subject is afflicted with prostate cancer. In certain embodiments, an increase in the level of expression of filamin B (FLNB), lymphocyte antigen 9 (LY9), or keratin 19 in the biological sample as compared to a normal control sample is an indication that the subject is afflicted with prostate cancer.

[0081] The invention further provides methods prognosing whether a subject is predisposed to developing prostate cancer, the method comprising determining the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) present in a biological sample obtained from the subject; and comparing the level of expression of the one or more markers present in the biological sample obtained from the subject with the level of expression of the corresponding markers in a control sample, wherein a modulation in the level of expression of the one or more markers in the biological sample obtained from the subject with the level of expression of the corresponding marker in a control sample is an indication that the subject is predisposed to developing prostate cancer. In certain embodiments, an increase in the level of expression of filamin B (FLNB), lymphocyte antigen 9 (LY9), or keratin 19 in the biological sample as compared to a normal control sample is an indication that the subject is predisposed to prostate cancer.

[0082] The invention further provides methods for monitoring the treatment of prostate cancer in a subject, the methods comprising determining a level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) present in a first sample obtained from the subject prior to administering at least a portion of a treatment regimen to the subject; determining a level of expression of a corresponding one or more markers in a second sample obtained from the subject following administration of at least a portion of the treatment regimen to the subject; and comparing the level of expression of the one or more markers in the first sample with the expression level of the corresponding one or more markers in the second sample, wherein a modulation in the level of expression of the one or more in the second sample as compared to the one or more markers in the first sample is an indication of a modulation in prostate cancer status in the subject. In certain embodiments, an decrease in the level of expression of filamin B (FLNB), lymphocyte antigen 9 (LY9), or keratin 19 in the biological sample as compared to the control sample is an indication that the subject is responding to treatment for prostate cancer.

[0083] In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) further include detection of prostate specific antigen (PSA) for the diagnosing, prognosing, and monitoring the treatment of prostate cancer.

[0084] The invention also provides methods for diagnosing prostate cancer comprising determining a level of expression of keratin 7 or keratin 15 in a biological sample obtained from a subject; and comparing the level of expression of keratin 7 or keratin 15 in the biological sample obtained from the subject with the level of expression of keratin 7 or keratin 15 in a control sample, wherein an modulation in the level of expression of keratin 7 or keratin 15 in the biological sample as compared to the control sample is an indication that the subject is afflicted with prostate cancer.

[0085] The invention provides methods of prognosing whether a subject is predisposed to developing prostate cancer, the method comprising determining the level of expression of keratin 7 or keratin 15 present in a biological sample

obtained from the subject; and comparing the level of expression of keratin 7 or keratin 15 present in the biological sample obtained from the subject with the level of expression of keratin 7 or keratin 15 in a control sample, wherein a modulation in the level of expression of keratin 7 or keratin 15 in the biological sample obtained from the subject with the level of expression of keratin 7 or keratin 15 in a control sample is an indication that the subject is predisposed to developing prostate cancer.

[0086] The invention provides methods for monitoring the treatment of prostate cancer in a subject, the methods comprising determining a level of expression of keratin 7 or keratin 15 present in a first sample obtained from the subject prior to administering at least a portion of a treatment regimen to the subject; determining a level of expression of keratin 7 or keratin 15 in a second sample obtained from the subject following administration of at least a portion of the treatment regimen to the subject; and comparing the level of expression of keratin 7 or keratin 15 in the first sample with the expression level of keratin 7 or keratin 15 in the second sample, wherein a modulation in the level of expression of keratin 7 or keratin 15 in the second sample as compared to keratin 7 or keratin 15 in the first sample is an indication that the therapy is modulating prostate cancer in the subject.

[0087] The invention also provides methods for diagnosing prostate cancer comprising determining a level of expression of keratin 19 in a biological sample obtained from a subject; and comparing the level of expression of keratin 19 in the biological sample obtained from the subject with the level of expression of keratin 19 in a control sample, wherein an increase in the level of expression of keratin 19 in the biological sample as compared to a normal control sample is an indication that the subject is afflicted with prostate cancer.

[0088] The invention provides methods prognosing whether a subject is predisposed to developing prostate cancer, the method comprising determining the level of expression of keratin 19 present in a biological sample obtained from the subject; and comparing the level of expression of keratin 19 present in the biological sample obtained from the subject with the level of expression of keratin 19 in a control sample, wherein a modulation in the level of expression of keratin 19 in the biological sample obtained from the subject with the level of expression of keratin 19 in a normal control sample is an indication that the subject is predisposed to developing prostate cancer.

[0089] The invention provides methods for monitoring the treatment of prostate cancer in a subject, the methods comprising determining a level of expression of keratin 19 present in a first sample obtained from the subject prior to administering at least a portion of a treatment regimen to the subject; determining a level of expression of keratin 19 in a second sample obtained from the subject following administration of at least a portion of the treatment regimen to the subject; and comparing the level of expression of keratin 19 in the first sample with the expression level of keratin 19 in the second sample, wherein a decrease in the level of expression of keratin 19 in the second sample as compared to keratin 19 in the first sample is an indication that the subject is responding to treatment for prostate cancer.

[0090] In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of filamin B for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of LY9 for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of PSA for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of filamin B for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of keratin 4 for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of keratin 8 for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of keratin 18 for the diagnosing, prognosing, and monitoring the treatment of prostate cancer. In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level of keratin 7, 15, or 19 further include detection of tubulin-beta 3 for the diagnosing, prognosing, and monitoring the treatment of prostate cancer.

[0091] In certain embodiments, keratin 7, 15, or 19 is keratin 7. In certain embodiments, keratin 7, 15, or 19 is keratin 15. In certain embodiments, keratin 7, 15, or 19 is keratin 19. In certain embodiments, keratin 7, 15, or 19 is keratin 7 and 15. In certain embodiments, keratin 7, 15, or 19 is keratin 7 and 19. In certain embodiments, keratin 7, 15, or 19 is keratin 15 and 19. In certain embodiments, keratin 7, 15, or 19 is keratin 7, 15, and 19.

[0092] In certain embodiments, filamin B, LY9, or keratin 19 is filamin B. In certain embodiments, filamin B, LY9, or keratin 19 is LY9. In certain embodiments, filamin B, LY9, or keratin 19 is keratin 19. In certain embodiments, filamin B, LY9, or keratin 19 is filamin B and LY9. In certain embodiments, filamin B, LY9, or keratin 19 is filamin B and keratin 19. In certain embodiments, filamin B, LY9, or keratin 19 is LY9, and keratin 19. In certain embodiments, filamin B, LY9, or keratin 19 is filamin B, LY9, and keratin 19.

[0093] In certain embodiments, the control sample is a sample from a normal subject or normal tissue. In certain embodiments, the control sample is a sample from the same subject from an earlier time point than the biological sample. In certain embodiments, the control sample is a sample from a subject with benign prostatic hyperplasia (BPH).

[0094] In certain embodiments, diagnosing includes differentiating between normal prostate and prostate cancer. In certain embodiments, diagnosing includes differentiating between benign prostate hyperplasia and prostate cancer.

[0095] The invention provides methods of characterizing prostate cancer status in a subject, the method comprising determining the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18,

keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) present in a biological sample obtained from the subject; and comparing the level of expression of the one or more markers present in the biological sample obtained from the subject with the level of expression of the one or more markers in a control sample, wherein the level of expression of the one or more markers in the biological sample obtained from the subject compared to the level of expression of the corresponding marker in a control sample is an indication of the prostate cancer status in the subject.

[0096] The invention provides methods of characterizing prostate cancer status in a subject, the method comprising determining the level of expression of keratin 7, 15, or 19 present in a biological sample obtained from the subject; and comparing the level of expression of keratin 7, 15, or 19 present in the biological sample obtained from the subject with the level of expression of keratin 7, 15, or 19 in a control sample, wherein the level of expression of keratin 7, 15, or 19 in the biological sample obtained from the subject compared to the level of expression of keratin 7, 15, or 19 in a control sample is an indication of the prostate cancer status in the subject.

[0097] In certain embodiments, the methods further comprises detection of the level of expression of prostate specific antigen (PSA) in the biological sample in which the expression level of filamin B or LY9 is detected in the methods of characterization of prostate cancer. In certain embodiments, the method further includes comparing the level of expression of PSA in the biological sample with the level of PSA in a control sample. In certain embodiments, the results from the detection of the expression level of PSA is used in conjunction with the results from detection of the level of one or more (e.g., 1, 2, 3, 4, 5, 6, or 7) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the methods of characterization of prostate cancer.

[0098] In certain embodiments, the control sample is a sample from a normal subject or normal tissue. In certain embodiments, the control sample is a sample from the same subject from an earlier time point than the biological sample. In certain embodiments, the control sample is a sample from a subject with benign prostatic hyperplasia (BPH). In certain embodiments, the control sample is a sample from a subject with androgen dependent prostate cancer. In certain embodiments, the control sample is a sample from a subject with androgen independent prostate cancer. In certain embodiments, the control sample is a sample from a subject with an aggressive prostate cancer. In certain embodiments, the control sample is a sample from a subject with a non-aggressive prostate cancer.

[0099] In certain embodiments of the invention, characterizing includes differentiating between normal prostate and prostate cancer. In certain embodiments, characterizing includes differentiating between benign prostate hyperplasia and prostate cancer. In certain embodiments, characterizing includes differentiating between androgen sensitive and androgen insensitive prostate cancer. In certain embodiments, characterizing includes differentiating between aggressive prostate cancer and non-aggressive prostate cancer. In certain embodiments, characterizing includes differentiating between any two or more of normal prostate, prostate cancer, benign prostate hyperplasia, androgen sensitive prostate cancer, androgen insensitive prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer and non-metastatic prostate cancer. In certain embodiments, characterizing includes detecting a change in status from androgen independent prostate cancer to androgen dependent prostate cancer. In certain embodiments, characterizing includes detecting a change in status from androgen independent prostate cancer to androgen dependent prostate cancer in response prior to a change in response to treatment. In certain embodiments, characterizing includes detecting a change in the size or relative aggressiveness of the prostate cancer. In certain embodiments, characterizing includes detecting a change from non-metastatic to metastatic prostate cancer.

[0100] In certain embodiments of the invention, an increase in the expression level of keratin 19 is an indication of increased pathology of prostate cancer or increased likelihood of developing prostate cancer. In certain embodiments of the invention, a decrease in the expression level of keratin 19 is an indication of decreased pathology of prostate cancer or decreased likelihood of developing prostate cancer. In certain embodiments of the invention, no significant change in the expression level of keratin 19 is an indication of no significant change in prostate cancer status.

[0101] In certain embodiments of the invention, an increase in the expression level of filamin B or LY9 is an indication of increased pathology of prostate cancer or increased likelihood of developing prostate cancer. In certain embodiments of the invention, an decrease in the expression level of filamin B or LY9 is an indication of decreased pathology of prostate cancer or decreased likelihood of developing prostate cancer. In certain embodiments of the invention, no significant change in the expression level of filamin B or LY9 is an indication of no significant change in prostate cancer status.

[0102] In certain embodiments, methods of the invention further comprise obtaining a biological sample from a subject.

[0103] In certain embodiments, methods of the invention further comprise selecting a subject for having or being suspected of having prostate cancer.

[0104] In certain embodiments, methods of the invention further comprise selection of a regimen for treatment of the subject including one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, and chemotherapy.

[0105] In certain embodiments, the method further comprises selection of the one ore more specific treatment regimens for the subject based on the results of the methods.

[0106] In certain embodiments, the method further comprises changing the treatment regimen of the subject based on the results of the methods.

[0107] In certain embodiments, the method further comprises a change in hormone based therapy based on monitoring of the subject based on the results of the methods.

[0108] In certain embodiments, the method further comprises not treating the subject with one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, or chemotherapy for an interval prior to performing a subsequent diagnostic, prognostic, or monitoring method provided herein.

[0109] The invention provides methods of treating a subject with prostate cancer by determining a level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8,

keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), present in a first sample obtained from the subject having prostate cancer; determining a level of expression of the one or more markers in a second sample obtained from the subject after administration of at least a portion of a treatment for prostate cancer; comparing the level of expression of the one or more markers in the first sample with the expression level of the one or more markers in the second sample, wherein a modulated level of expression of the one or more markers in the second sample as compared to the one or more markers in the first sample is an indication that the subject is an indication of modulation of prostate cancer in the subject; and selecting a treatment for the subject based on the expression level of the one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9). For example, a decrease in the level of filamin B, LY9, or keratin 19 is an indication that the subject is responding to treatment. An increase in the level of filamin B, LY9, or keratin 19 is an indication that the subject is not responding to treatment.

[0110] As used herein, modulation is understood as a change in an expression level of a marker, particularly a statistically significant change in an expression level of a marker as compared to an appropriate control. The meaning of an increase or a decrease in an expression level of the marker as compared to a control depends, at least, on the specific identity of the marker and the control used. Such considerations are well understood by those of skill in the art. The meaning of the modulation in the expression level(s) of markers can be determined based on the teachings provided herein.

[0111] In certain embodiments, the treatment method further comprises determining a level of expression of PSA in the first sample and determining a level of expression of PSA in the second sample. In certain embodiments, the treatment of the subject is maintained upon detection of a decrease in the expression level of at least one of filamin B, LY9, keratin 19, or PSA in the second sample, indicating that the subject was responsive to the treatment. In certain embodiments, the treatment of the subject is discontinued upon detection of a decrease in the expression level of at least one of filamin B, LY9, keratin 19, or PSA in the second sample, indicating that disease is no longer present or minimized such that treatment is no longer required. In certain embodiments, a new treatment of the subject is initiated upon detection of a decrease in the expression level of at least one of filamin B, LY9, keratin 19, or PSA in the second sample, e.g., resection after shrinkage of the tumor. In certain embodiments, the treatment of the subject is discontinued upon detection of an increase in the expression level of at least one of filamin B, LY9, keratin 19, or PSA in the second sample, indication of a lack of response or discontinuation of response to the treatment. In certain embodiments, a new treatment of the subject is initiated upon detection of an increase in the expression level of at least one of filamin B, LY9, keratin 19, or PSA in the second sample, e.g., due to lack of response or discontinuation of response to treatment. One of skill in the art can select appropriate methods of treatment of a subject based, at least in part, on his response, or non-response, to treatments being used as determined by the expression level of the markers.

[0112] The invention provides method of selecting a subject with prostate cancer for administration of active treatment, rather than watchful waiting, by determining a level of expression of filamin B, LY9, or keratin 19, present in a first sample obtained from the subject having prostate cancer wherein the subject has not been actively treated for prostate cancer; determining a level of expression of filamin B, LY9, or keratin 19 in a second sample obtained from the subject; comparing the level of expression of filamin B, LY9, or keratin 19 in the first sample obtained at an earlier time point with the expression level of filamin B, LY9, or keratin 19 in the second sample; wherein a decreased level of expression of filamin B, LY9, or keratin 19 in the second sample as compared to filamin B, LY9, or keratin 19 in the first sample is an indication that the subject should not be administered active treatment for prostate cancer; and selecting against active treatment of a subject for prostate cancer.

[0113] The invention also provides methods of selecting a subject with prostate cancer for administration of active treatment by determining a level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), present in a first sample obtained from the subject having prostate cancer wherein the subject has not been actively treated for prostate cancer; determining a level of expression of the corresponding one or more markers in a second sample obtained from the subject; comparing the level of expression of the one or more markers in the first sample obtained at an earlier time point with the expression level of the one or more markers in the second sample; wherein an modulated level of expression of the one or more markers in the second sample as compared to the one or more markers in the first sample is considered in determining if a subject should be actively treated for prostate cancer.

[0114] In certain embodiments, actively treating the subject for prostate cancer comprises treating the subject with one or more therapies such as hormone therapy, chemotherapy, radiation therapy, and surgery.

[0115] In certain embodiments, methods of subject selection further comprise determining a level of expression of PSA in the first sample and determining a level of expression of PSA in the second sample. In certain embodiments, a decreased level of expression of PSA in the second sample as compared to the level of expression of PSA in the first sample is an indication that the subject should not be administered active treatment for prostate cancer. In certain embodiments, an increased level of expression of PSA in the second sample as compared to the level of expression of PSA in the first sample is an indication that the subject should be administered active treatment for prostate cancer.

[0116] In certain embodiments of any of the methods provided herein, filamin B or LY9 is understood as filamin B and LY9. In certain embodiments of any of the methods provided herein, filamin B or LY9 is understood as filamin B. In certain embodiments of any of the methods provided herein, filamin B or LY9 is understood as LY9.

[0117] In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 7. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 15. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 19. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 7 and 15. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is

understood as keratin 15 and 19. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 7 and 19. In certain embodiments of any of the methods provided herein, keratin 7, 15, or 19 is understood as keratin 7, 15, and 19.

[0118] In certain embodiments, one or more markers selected from any group provided herein does not include keratin 4. In certain embodiments, one or more markers selected from any group provided herein does not include keratin 7. In certain embodiments, one or more markers selected from any group provided herein does not include keratin 8. In certain embodiments, one or more markers selected from any group provided herein does not include keratin 15. In certain embodiments, one or more markers selected from any group provided herein does not include keratin 18. In certain embodiments, one or more markers selected from any group provided herein does not include keratin 19. In certain embodiments, one or more markers selected from any group provided herein does not include tubulin-beta 3. In certain embodiments, one or more markers selected from any group provided herein does not include filamin B. In certain embodiments, one or more markers selected from any group provided herein does not include LY9. In certain embodiments, one or more markers selected from any group provided herein does not include PSA.

[0119] In certain embodiments of any of the methods provided herein, the methods further comprising obtaining a biological sample from the subject.

[0120] The invention provides methods of identifying a compound for treating prostate cancer comprising obtaining a test cell; contacting the test cell with a test compound; determining the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) in the test cell; comparing the level of expression of the one or more markers in the test cell with a control cell not contacted by the test compound; and selecting a test compound that modulates the level of expression of the one or more markers in the test cell, thereby identifying a compound for treating a disorder in a subject. In certain embodiments, the methods further include identifying a compound that modulates the level of expression of PSA.

[0121] The invention provides methods of identifying a compound for treating prostate cancer comprising obtaining a test cell; contacting the test cell with a test compound; determining the level of expression of keratin 7, 15, or 19 in the test cell; comparing the level of expression of keratin 7, 15, or 19 in the test cell with a control cell not contacted by the test compound; and selecting a test compound that modulates the level of expression of keratin 7, 15, or 19 in the test cell, thereby identifying a compound for treating a disorder in a subject.

[0122] The invention provides methods of identifying a compound for treating prostate cancer comprising obtaining a test cell; contacting the test cell with a test compound; determining the level of expression of filamin B or LY9 in the test cell; comparing the level of expression of filamin B or LY9 in the test cell with a control cell not contacted by the test compound; and selecting a test compound that modulates the level of expression of filamin B or LY9 in the test cell, thereby identifying a compound for treating a disorder in a subject.

[0123] In certain embodiments, the methods of identifying a compound for treating prostate cancer further include identifying a compound that modulates the level of expression of PSA.

[0124] In certain embodiments, the test cell is contacted with the agent in vitro.

[0125] In certain embodiments, the test cell is contacted with the agent in vivo. In certain embodiments, the test cell is present in a xenogenic model of cancer. In certain embodiments, the test cell is present in an animal model of prostate cancer. In certain embodiments, the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) is detected in the test cell by detection of the expression level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) in a biological sample in the organism containing the test cell.

[0126] The invention provides kits for the diagnosis, monitoring, or characterization of prostate cancer comprising at least one reagent specific for the detection of the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) in a sample.

[0127] In certain embodiments, the kit further comprises instructions for the diagnosis, monitoring, or characterization of prostate cancer based on the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9). In certain embodiments, the kit includes instructions to detect the level of expression of PSA in the same sample in which the level of expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) is detected. In certain embodiments, the kit includes at least one reagent specific for the detection of the level of expression of PSA. In certain embodiments, the kits include at least one antibody or nucleic acid for binding to f one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) for use in the methods provided herein. In certain embodiments, the kit includes at least one antibody or nucleic acid for binding to keratin 7 and one antibody or nucleic acid for binding to keratin 15. In certain embodiments, the kits further include at least one antibody or nucleic acid for binding to PSA for use in the methods provided herein. The kits may further provide instructions for practicing the methods provided herein.

[0128] Where applicable or not specifically disclaimed, any one of the embodiments described herein are contemplated to be able to combine with any other one or more embodiments, even though the embodiments are described under different aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0129] FIG. **1**: Schematic representing the underlying principles of the Interrogative Platform Technology provided in WO2012119129.

[0130] FIGS. **2**A-C: Causal associations of Keratins, including (A-B) KRT8, KRT18 and (C) KRT19 in human prostate cancer cells as inferred by the Interrogative Platform Technology.

[0131] FIGS. **3**A-D: Mechanistic insight into regulation of keratins by mitochondrial function inferred by the Interrogative Platform Technology. (A-B) KRT8-KRT15 association is abolished upon ubidecaronone treatment. Note change of direction of arrow between and positions of KRT7 and KRT15 before treatment (A) and after treatment (B). (C) Tubulin-beta 3 interacts with a number of proteins. (D) Expression levels of keratin 19 in biological samples from subjects with prostate cancer or control samples.

[0132] FIG. **4**: Inference of filamin B (FLNB) as a hub of activity in prostate cancer and as a biomarker using the Interrogative Platform Technology provided in WO2012119129.

[0133] FIG. **5**: Portion of an inference map showing filamin B is connected directly to LY9, which is, in turn, connected to at least one other marker.

[0134] FIGS. **6**A-B: Validation of filamin B levels in human serum samples. Levels of (A) filamin B and (B) PSA were elevated in prostate cancer samples when compared to normal serum. Data represents percent average change, with normal donors set to 100% on a log scale.

[0135] FIG. **7**: Validation of LY9 levels in human serum samples. Levels of LY9 were elevated in prostate cancer samples when compared to normal serum. Data represents percent average change, with normal donors set to 100% on a log scale.

[0136] FIGS. **8**A-C: Validation of (A) filamin B, (B) LY9, and (C) PSA levels in human serum samples. Data are shown as ng/ml of the marker in serum.

[0137] FIGS. **9**A-B: ROC curve analysis of sensitivity and false positive rate (FPR) of PSA, FLNB and the combination of PSA and FLNB (A) and area under the curve values (AUC) calculated (B) based on the analysis. The combination of PSA and FLNB was more sensitive than either marker alone.

[0138] FIGS. **10**A-B: ROC curve analysis of PSA, FLNB, LY9 and combinations of PSA, FLNB, and LY9 using linear (A) and non-linear (B) scoring functions. The combination of PSA, LY9, and FLNB was more sensitive than any marker alone.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0139] As used herein, each of the following terms has the meaning associated with it in this section.

[0140] A "patient" or "subject" to be treated by the method of the invention can mean either a human or non-human animal, preferably a mammal. By "subject" is meant any animal, including horses, dogs, cats, pigs, goats, rabbits, hamsters, monkeys, guinea pigs, rats, mice, lizards, snakes, sheep, cattle, fish, and birds. A human subject may be referred to as a patient. It should be noted that clinical observations described herein were made with human subjects and, in at least some embodiments, the subjects are human.

[0141] "Therapeutically effective amount" means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease, e.g., the amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment, e.g., is sufficient to ameliorate at least one sign or symptom of the disease, e.g., to prevent progression of the disease or condition, e.g., prevent tumor growth, decrease tumor size, induce tumor cell apoptosis, reduce tumor angiogenesis, prevent metastasis. When administered for preventing a disease, the amount is sufficient to avoid or delay onset of the disease. The "therapeutically effective amount" will vary depending on the compound, its therapeutic index, solubility, the disease and its severity and the age, weight, etc., of the patient to be treated, and the like. For example, certain compounds discovered by the methods of the present invention may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment. Administration of a therapeutically effective amount of a compound may require the administration of more than one dose of the compound.

[0142] "Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). Prevention does not require that the disease or condition never occurs in the subject. Prevention includes delaying the onset or severity of the disease or condition.

[0143] The term "prophylactic" or "therapeutic" treatment refers to administration to the subject of one or more agents or interventions to provide the desired clinical effect. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing at least one sign or symptom of the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate, or maintain at least one sign or symptom of the existing unwanted condition or side effects therefrom).

[0144] As used herein, "treatment", particularly "active treatment" refers to performing an intervention to treat prostate cancer in a subject, e.g., reduce at least one of the growth rate, reduction of tumor burden, reduce or maintain the tumor size, or the malignancy (e.g., likelihood of metastasis) of the tumor; or to increase apoptosis in the tumor by one or more of administration of a therapeutic agent, e.g., chemotherapy or hormone therapy; administration of radiation therapy (e.g., pellet implantation, brachytherapy), or surgical resection of the tumor, or any combination thereof appropriate for treatment of the subject based on grade and stage of the tumor and other routine considerations. Active treatment is distinguished from "watchful waiting" (i.e., not active treatment) in which the subject and tumor are monitored, but no interventions are performed to affect the tumor. Watchful waiting can include administration of agents that alter effects caused by the tumor (e.g., incontinence, erectile dysfunction) that are not administered to alter the growth or pathology of the tumor itself.

[0145] The term "therapeutic effect" refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or in the enhancement of desirable physical or

mental development and conditions in an animal or human. A therapeutic effect can be understood as a decrease in tumor growth, decrease in tumor growth rate, stabilization or decrease in tumor burden, stabilization or reduction in tumor size, stabilization or decrease in tumor malignancy, increase in tumor apoptosis, and/or a decrease in tumor angiogenesis.

[0146] The terms "disorders", "diseases", and "abnormal state" are used inclusively and refer to any deviation from the normal structure or function of any part, organ, or system of the body (or any combination thereof). A specific disease is manifested by characteristic symptoms and signs, including biological, chemical, and physical changes, and is often associated with a variety of other factors including, but not limited to, demographic, environmental, employment, genetic, and medically historical factors. Certain characteristic signs, symptoms, and related factors can be quantitated through a variety of methods to yield important diagnostic information. As used herein the disorder, disease, or abnormal state is an abnormal prostate state, including benign prostate hyperplasia and cancer, particularly prostate cancer. The abnormal prostate state of prostate cancer can be further subdivided into stages and grades of prostate cancer as provided, for example in Prostate. In: Edge S B, Byrd D R, Compton C C, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, N.Y.: Springer, 2010, pp 457-68 (incorporated herein by reference). Further, abnormal prostate states can be classified as one or more of benign prostate hyperplasia (BPH), androgen sensitive prostate cancer, androgen insensitive or resistant prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

[0147] A subject at "increased risk for developing prostate cancer" may or may not develop prostate cancer. Identification of a subject at increased risk for developing prostate cancer should be monitored for additional signs or symptoms of prostate cancer. The methods provided herein for identifying a subject with increased risk for developing prostate cancer can be used in combination with assessment of other known risk factors or signs of prostate cancer including, but not limited to decreased urinary stream, urgency, hesitancy, nocturia, incomplete bladder emptying, and age.

[0148] The term "expression" is used herein to mean the process by which a polypeptide is produced from DNA. The process involves the transcription of the gene into mRNA and the translation of this mRNA into a polypeptide. Depending on the context in which used, "expression" may refer to the production of RNA, or protein, or both.

[0149] The terms "level of expression of a gene", "gene expression level", "level of a marker", and the like refer to the level of mRNA, as well as pre-mRNA nascent transcript(s), transcript processing intermediates, mature mRNA(s) and degradation products, or the level of protein, encoded by the gene in the cell.

[0150] The term "specific identification" is understood as detection of a marker of interest with sufficiently low background of the assay and cross-reactivity of the reagents used such that the detection method is diagnostically useful. In certain embodiments, reagents for specific identification of a marker bind to only one isoform of the marker. In certain embodiments, reagents for specific identification of a marker bind to more than one isoform of the marker. In certain embodiments, reagents for specific identification of a marker bind to all known isoforms of the marker.

[0151] The term "modulation" refers to upregulation (i.e., activation or stimulation), down-regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart. A "modulator" is a compound or molecule that modulates, and may be, e.g., an agonist, antagonist, activator, stimulator, suppressor, or inhibitor.

[0152] The term "control sample," as used herein, refers to any clinically relevant comparative sample, including, for example, a sample from a healthy subject not afflicted with an oncological disorder, e.g., prostate cancer, or a sample from a subject from an earlier time point, e.g., prior to treatment, an earlier tumor assessment time point, at an earlier stage of treatment. A control sample can be a purified sample, protein, and/or nucleic acid provided with a kit. Such control samples can be diluted, for example, in a dilution series to allow for quantitative measurement of levels of analytes, e.g., markers, in test samples. A control sample may include a sample derived from one or more subjects. A control sample may also be a sample made at an earlier time point from the subject to be assessed. For example, the control sample could be a sample taken from the subject to be assessed before the onset of an oncological disorder, e.g., prostate cancer, at an earlier stage of disease, or before the administration of treatment or of a portion of treatment. The control sample may also be a sample from an animal model, or from a tissue or cell lines derived from the animal model of oncological disorder, e.g., prostate cancer. The level of activity or expression of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), lymphocyte antigen 9 (LY9), and PSA in a control sample consists of a group of measurements may be determined, e.g., based on any appropriate statistical measure, such as, for example, measures of central tendency including average, median, or modal values. Different from a control is preferably statistically significantly different from a control.

[0153] The term "control level" refers to an accepted or pre-determined level of a marker in a subject sample. A control level can be a range of values. Marker levels can be compared to a single control value, to a range of control values, to the upper level of normal, or to the lower level of normal as appropriate for the assay.

[0154] In one embodiment, the control is a standardized control, such as, for example, a control which is predetermined using an average of the levels of expression of one or more markers from a population of subjects having no cancer, especially subjects having no prostate cancer. In still other embodiments of the invention, a control level of a marker in a non-cancerous sample(s) derived from the subject having cancer. For example, when a biopsy or other medical procedure reveals the presence of cancer in one portion of the tissue, the control level of a marker may be determined using the non-affected portion of the tissue, and this control level may be compared with the level of the marker in an affected portion of the tissue.

[0155] In certain embodiments, the control can be from a subject, or a population of subject, having an abnormal prostate state. For example, the control can be from a subject suffering from benign prostate hyperplasia (BPH), androgen sensitive prostate cancer, androgen insensitive or resistant prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, or non-metastatic prostate cancer. It is understood that not all markers will have different levels for each of the abnormal prostate states listed.

It is understood that a combination of maker levels may be most useful to distinguish between abnormal prostate states, possibly in combination with other diagnostic methods. Further, marker levels in biological samples can be compared to more than one control sample (e.g., normal, abnormal, from the same subject, from a population control). Marker levels can be used in combination with other signs or symptoms of an abnormal prostate state to provide a diagnosis for the subject.

[0156] A control can also be a sample from a subject at an earlier time point, e.g., a baseline level prior to suspected presence of disease, before the diagnosis of a disease, at an earlier assessment time point during watchful waiting, before the treatment with a specific agent (e.g., chemotherapy, hormone therapy) or intervention (e.g., radiation, surgery). In certain embodiments, a change in the level of the marker in a subject can be more significant than the absolute level of a marker, e.g., as compared to control.

[0157] As used herein, a sample obtained at an "earlier time point" is a sample that was obtained at a sufficient time in the past such that clinically relevant information could be obtained in the sample from the earlier time point as compared to the later time point. In certain embodiments, an earlier time point is at least four weeks earlier. In certain embodiments, an earlier time point is at least six weeks earlier. In certain embodiments, an earlier time point is at least two months earlier. In certain embodiments, an earlier time point is at least three months earlier. In certain embodiments, an earlier time point is at least six months earlier. In certain embodiments, an earlier time point is at least nine months earlier. In certain embodiments, an earlier time point is at least one year earlier. Multiple subject samples (e.g., 3, 4, 5, 6, 7, or more) can be obtained at regular or irregular intervals over time and analyzed for trends in changes in marker levels. Appropriate intervals for testing for a particular subject can be determined by one of skill in the art based on ordinary considerations.

[0158] As used herein, "changed as compared to a control" sample or subject is understood as having a level of the analyte or diagnostic or therapeutic indicator (e.g., marker) to be detected at a level that is statistically different than a sample from a normal, untreated, or abnormal state control sample. Changed as compared to control can also include a difference in the rate of change of the level of one or more markers obtained in a series of at least two subject samples obtained over time. Determination of statistical significance is within the ability of those skilled in the art, e.g., the number of standard deviations from the mean that constitute a positive or negative result.

[0159] As used herein, the term "obtaining" is understood herein as manufacturing, purchasing, or otherwise coming into possession of.

[0160] As used herein, "detecting", "detection", "determining", and the like are understood that an assay performed for identification of a specific marker in a sample, e.g., one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), lymphocyte antigen 9 (LY9), and PSA. The amount of marker expression or activity detected in the sample can be none or below the level of detection of the assay or method.

[0161] As used herein, "greater predictive value" is understood as an assay that has significantly greater sensitivity and/or specificity, preferably greater sensitivity and specificity, than the test to which it is compared. The predictive value of a test can be determined using an ROC analysis. In an ROC analysis a test that provides perfect discrimination or accuracy between normal and disease states would have an area under the curve (AUC)=1, whereas a very poor test that provides no better discrimination than random chance would have AUC=0.5. As used herein, a test with a greater predictive value will have a statistically improved AUC as compared to another assay. The assays are preformed in an appropriate subject population.

[0162] The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0163] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to."

[0164] The term "or" is used inclusively herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise. For example, as used herein, filamin B or LY9 is understood to include filamin B alone, LY9 alone, and the combination of filamin B and LY9.

[0165] The term "such as" is used herein to mean, and is used interchangeably, with the phrase "such as but not limited to."

[0166] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[0167] The recitation of a listing of chemical group(s) in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0168] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

[0169] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

[0170] As used herein, "one or more" is understood as each value 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and any value greater than 10.

[0171] Reference will now be made in detail to exemplary embodiments of the invention. While the invention will be described in conjunction with the exemplary embodiments, it will be understood that it is not intended to limit the invention to those embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

Keratins

[0172] Keratin 4

[0173] Keratin 4, also known as as K4; CK4; CK-4; CYK4, is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains coexpressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in differentiated layers of the mucosal and esophageal epithelia with family member KRT13. Mutations in these genes have been associated with White Sponge Nevus, characterized by oral, esophageal, and anal leukoplakia. The type II cytokeratins are clustered in a region of chromosome 12q12-q13.

[0174] As used herein, keratin 4 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 4 is 3851 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3851 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 4, GenBank Accession No. NM_002272 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 1 and 2. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0175] It is understood that the invention includes the use of any fragments of keratin 4 sequences as long as the fragment can allow for the specific identification of keratin 4. Moreover, it is understood that there are naturally occurring variants of keratin 4 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Keratin 7

[0176] Keratin 7, also known as as CK7, K2C7, K7, SCL, CK-7; cytokeratin 7; cytokeratin-7; keratin, 55K type II cytoskeletal; keratin, simple epithelial type I, K7; keratin, type II cytoskeletal 7; keratin-7; sarcolectin; type II mesothelial keratin K7; and type-II keratin Kb7, is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains coexpressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in the simple epithelia lining the cavities of the internal organs and in the gland ducts and blood vessels. The genes encoding the type II cytokeratins are clustered in a region of chromosome 12q12-q13. Alternative splicing may result in several transcript variants; however, not all variants have been fully described.

[0177] As used herein, keratin 7 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 7 is 3855 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3855 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 7, GenBank Accession No. NM_005556 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 3 and 4. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0178] It is understood that the invention includes the use of any fragments of keratin 7 sequences as long as the fragment can allow for the specific identification of keratin 7. Moreover, it is understood that there are naturally occurring variants of keratin 7 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Keratin 8

[0179] Keratin 8, also known as K8; KO; CK8; CK-8; CYK8; K2C8; CARD2 is a member of the type II keratin family clustered on the long arm of chromosome 12. Type I and type II keratins heteropolymerize to form intermediate-sized filaments in the cytoplasm of epithelial cells. The product of this gene typically dimerizes with keratin 18 to form an intermediate filament in simple single-layered epithelial cells. This protein plays a role in maintaining cellular structural integrity and also functions in signal transduction and cellular differentiation. Mutations in this gene cause cryptogenic cirrhosis. Alternatively spliced transcript variants have been found for this gene.

[0180] As used herein, keratin 8 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 8 is 3856 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3856 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 8, variant 1, GenBank Accession No. NM_001256282 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 5 and 6; and *homo sapiens* keratin 8, variant 3, GenBank Acession No. NM_001256293 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 7 and 8. (The GenBank numbers are incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0181] It is understood that the invention includes the use of either on of or both of the variants of keratin 8 provided in the sequence listing and any fragments of keratin 8 sequences as long as the fragment can allow for the specific identification of keratin 8. Moreover, it is understood that there are naturally occurring variants of keratin 8 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Keratin 15

[0182] Keratin 15, also known as as K15; CK15; K1CO, is a member of the keratin gene family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. Most of the type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains and are clustered in a region on chromosome 17q21.2.

[0183] As used herein, keratin 15 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 15 is 3866 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3866 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 15, GenBank Accession No. NM_002275 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 9 and 10. (The GenBank number is incorporated herein by refer-

ence in the version available on the filing date of the application to which this application claims priority.)

[0184] It is understood that the invention includes the use of any fragments of keratin 15 sequences as long as the fragment can allow for the specific identification of keratin 15. Moreover, it is understood that there are naturally occurring variants of keratin 15 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Keratin 18

[0185] Keratin 18, also known as as K18; CYK18, encodes the type I intermediate filament chain keratin 18. Keratin 18, together with its filament partner keratin 8, are perhaps the most commonly found members of the intermediate filament gene family. They are expressed in single layer epithelial tissues of the body. Mutations in this gene have been linked to cryptogenic cirrhosis. Two transcript variants encoding the same protein have been found for this gene.

[0186] As used herein, keratin 15 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 18 is 3875 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3875 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 18, variant 1, GenBank Accession No. NM_000224 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 11 and 12, and *homo sapiens* keratin 18, variant 2, GenBank Accession No. 199187 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 13 and 14. (The GenBank numbers are incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0187] It is understood that the invention includes the use of either on of or both of the variants of keratin 18 provided in the sequence listing and any fragments of keratin 18 sequences as long as the fragment can allow for the specific identification of keratin 18. Moreover, it is understood that there are naturally occurring variants of keratin 18 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Keratin 19

[0188] Keratin 19, also known as K19; CK19; K1CS, is a member of the keratin gene family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. The type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains. Unlike its related family members, this smallest known acidic cytokeratin is not paired with a basic cytokeratin in epithelial cells. It is specifically expressed in the periderm, the transiently superficial layer that envelopes the developing epidermis. The type I cytokeratins are clustered in a region of chromosome 17q12-q21.

[0189] As used herein, keratin 19 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 19 is 3880 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/3880 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* keratin 19, GenBank Accession No. NM_002276 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 15 and 16. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0190] It is understood that the invention includes the use of any fragments of keratin 19 sequences as long as the fragment can allow for the specific identification of keratin 19. Moreover, it is understood that there are naturally occurring variants of keratin 19 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Tubulin-Beta 3

[0191] Tubulin-beta 3, also known as CDCBM; TUBB4; beta-4; CFEOM3A, is a class III member of the beta tubulin protein family. Beta tubulins are one of two core protein families (alpha and beta tubulins) that heterodimerize and assemble to form microtubules. This protein is primarily expressed in neurons and may be involved in neurogenesis and axon guidance and maintenance. Mutations in this gene are the cause of congenital fibrosis of the extraocular muscles type 3. Alternate splicing results in multiple transcript variants. A pseudogene of this gene is found on chromosome 6.

[0192] As used herein, Tubulin-beta 3 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human Tubulin-beta 3 is 10381 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/10381 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). *Homo sapiens* Tubulin-beta 3, variant 2, GenBank Accession No. NM_001197181 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 17 and 18. *Homo sapiens* Tubulin-beta 3, variant 1, GenBank Accession No. NM_006086 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 19 and 20. (The GenBank numbers are incorporated herein by reference in the versions available on the filing date of the application to which this application claims priority.)

[0193] It is understood that the invention includes the use of any fragments of Tubulin-beta 3 sequences as long as the fragment can allow for the specific identification of Tubulin-beta 3. Moreover, it is understood that there are naturally occurring variants of Tubulin-beta 3 which may or may not be associated with a specific disease state, the use of which are also included in this application.

Filamin B

[0194] Filamin B is also known as filamin-3, beta-filamin, ABP-280 homolog, filamin homolog 1, thyroid autoantigen, actin binding protein 278, actin-binding-like protein, Larsen syndrome 1 (autosomal dominant), AOI; FH1; SCT; TAP; LRS1; TABP; FLN-B; FLN1L; ABP-278; and ABP-280. The gene encodes a member of the filamin family. The encoded protein interacts with glycoprotein Ib alpha as part of the process to repair vascular injuries. The platelet glycoprotein Ib complex includes glycoprotein Ib alpha, and it binds the actin cytoskeleton. Mutations in this gene have been found in several conditions: atelosteogenesis type 1 and type 3; boomerang dysplasia; autosomal dominant Larsen syndrome; and spondylocarpotarsal synostosis syndrome. Multiple

alternatively spliced transcript variants that encode different protein isoforms have been described for this gene.

[0195] As used herein, filamin B refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI gene ID for filamin B is 2317 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/2317 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

[0196] *Homo sapiens* filamin B, beta (FLNB), RefSeqGene on chromosome 3, locus NG_012801 is shown in SEQ ID NO: 21. *Homo sapiens* filamin B, beta (FLNB), transcript variant 1, GenBank Accession No. NM_001164317.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 22 and 23. *Homo sapiens* filamin B, beta (FLNB), transcript variant 3, GenBank Accession No. NM_001164318.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 24 and 25. *Homo sapiens* filamin B, beta (FLNB), transcript variant 4, GenBank Accession No. NM_001164319.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 26 and 27. *Homo sapiens* filamin B, beta (FLNB), transcript variant 2, GenBank Accession No. NM_001457.3 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 28 and 29. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0197] It is understood that the invention includes the use of any combination of one or more of the filamin B sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of filamin B. Methods of the invention and reagents can be used to detect single isoforms of filamin B, combinations of filamin β isoforms, or all of the filamin B isoforms simultaneously. Unless specified, filamin B can be considered to refer to one or more isoforms of filamin B, including total filamin B. Moreover, it is understood that there are naturally occurring variants of filamin B, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

Lymphocyte Antigen 9

[0198] Lymphocyte antigen 9 (LY9) is also known as RP11-312J18.1, CD229, SLAMF3, hly9, mLY9, T-lymphocyte surface antigen Ly-9; and cell surface molecule Ly-9. LY9 belongs to the SLAM family of immunomodulatory receptors (see SLAMF1; MIM 603492) and interacts with the adaptor molecule SAP (SH2D1A; MIM 300490) (Graham et al., 2006).

[0199] As used herein, LY9 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI gene ID for LY9 is 4063 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/4063 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

[0200] *Homo sapiens* lymphocyte antigen 9 (LY9), transcript variant 2, GenBank Accession No. NM_001033667 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 30 and 31. *Homo sapiens* lymphocyte antigen 9 (LY9), transcript variant 3, GenBank Accession No. NM_001261456 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 32 and 33. *Homo sapiens* lymphocyte antigen 9 (LY9), transcript variant 4, GenBank Accession No. NM_001261457 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 34 and 35. *Homo sapiens* lymphocyte antigen 9 (LY9), transcript variant 1, GenBank Accession No. NM_002348 is shown amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 36 and 37. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

[0201] It is understood that the invention includes the use of any combination of one or more of the LY9 sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of LY9. Methods of the invention and reagents can be used to detect single isoforms of LY9, combinations of LY9 isoforms, or all of the LY9 isoforms simultaneously. Unless specified, LY9 can be considered to refer to one or more isoforms of LY9, including total LY9. Moreover, it is understood that there are naturally occurring variants of LY9, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

Prostate Specific Antigen

[0202] Prostate-specific antigen (PSA) is also known as kallikrein-3, seminin, P-30 antigen, semenogelase, gamma-seminoprotein, APS, hK3, and KLK2A1. Kallikreins are a subgroup of serine proteases having diverse physiological functions. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. This gene is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19. Its protein product is a protease present in seminal plasma. It is thought to function normally in the liquefaction of seminal coagulum, presumably by hydrolysis of the high molecular mass seminal vesicle protein. Serum level of this protein, called PSA in the clinical setting, is useful in the diagnosis and monitoring of prostatic carcinoma. Alternate splicing of this gene generates several transcript variants encoding different isoforms.

[0203] As used herein, PSA refers to both the gene and the protein, in both processed and unprocessed forms, unless clearly indicated otherwise by context. The NCBI gene ID for PSA is 354 and detailed information can be found at www.ncbi.nlm.nih.gov/gene/354 (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

[0204] *Homo sapiens* PSA is located on chromosome 19 at 19q13.41Sequence: NC_000019.9 (51358171.51364020). Four splice variants of human PSA are known: Prostate-specific antigen isoform 3 preproprotein, NM_001030047.1; Prostate-specific antigen isoform 4 preproprotein, NM_001030048.1; Prostate-specific antigen isoform 6 preproprotein, NM_001030050.1; and Prostate-specific antigen isoform 1 preproprotein, NM_001648.2. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

[0205] It is understood that the invention includes the use of any combination of one or more of the PSA sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of PSA. Methods of the invention and reagents can be used to detect single isoforms of PSA, combinations of PSA isoforms, or all of the PSA isoforms simultaneously. Unless

specified, PSA can be considered to refer to one or more isoforms of PSA, including total PSA. Moreover, it is understood that there are naturally occurring variants of PSA, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

Treatment of Disease States

[0206] The present invention provides methods for use of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) to treat disease states in a subject, e.g., a mammal, e.g., a human.

[0207] The present invention also provides methods for treatment of a subject with prostate cancer with a therapeutic, e.g., a nucleic acid based therapeutic, that modulates the expression or activity of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9).

[0208] The invention also provides methods for selection and/or administration of known treatment agents, especially hormone based therapies vs. non-hormone based therapies, and aggressive or active treatment vs. "watchful waiting", depending on the detection of a change in the level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), as compared to a control. The selection of treatment regimens can further include the detection of PSA to assist in selection of the therapeutic methods. Selection of treatment methods can also include other diagnostic considerations and patient characteristics including results from imaging studies, tumor size or growth rates, risk of poor outcomes, disruption of daily activities, and age.

[0209] As used herein, the term "aggressive oncological disorder", such as aggressive prostate cancer, refers to an oncological disorder involving a fast-growing tumor. An aggressive oncological disorder typically does not respond, responds poorly, or loses response to therapeutic treatment. For example, an prostate cancer may be considered to become an aggressive prostate cancer upon loss of response to hormone therapy, necessitating treatment with chemotherapy, surgery, and/or radiation. As used herein, an aggressive prostate cancer, for example, is one that will likely or has metastasized. As used herein, an aggressive prostate cancer is one that will result in significant changes in quality of life as the tumor grows. Active treatment is therapeutically indicated for an aggressive oncological disorder, e.g., aggressive prostate cancer.

[0210] As used herein, the term "non-aggressive oncological disorder" such as a non-aggressive prostate cancer, refers to an oncological disorder involving a slow-growing tumor. A non-aggressive oncological disorder typically responds favorably or moderately to therapeutic treatment or grows so slowly that immediate treatment is not warranted. A non-aggressive prostate tumor is one that a person skilled in the art, e.g., an oncologist, may decide to not actively treat with routine interventions for the treatment of cancer, e.g., chemotherapy, radiation, surgery, as the active treatment may do more harm than the disease, particularly in an older subject. A non-aggressive prostate tumor is one that a person skilled in the art may decide to monitor with "watchful waiting" rather than subjecting the person to any active therapeutic interventions to alter the presence or growth of the tumor (e.g., radiation, surgery, chemotherapy, hormone therapy).

Diagnostic/Prognostic Uses of the Invention

[0211] The invention provides methods for diagnosing an abnormal prostate state, e.g., BPH or an oncological disease state, e.g., prostate cancer, in a subject. The invention further provides methods for prognosing or monitoring progression or monitoring response of an abnormal prostate state, e.g., BPH or prostate cancer, to a therapeutic treatment during active treatment or watchful waiting.

[0212] The invention provides, in one embodiment, methods for diagnosing an oncological disorder, e.g., prostate cancer. The methods of the present invention can be practiced in conjunction with any other method used by the skilled practitioner to prognose the occurrence or recurrence of an oncologic disorder and/or the survival of a subject being treated for an oncologic disorder. The diagnostic and prognostic methods provided herein can be used to determine if additional and/or more invasive tests or monitoring should be performed on a subject. It is understood that a disease as complex as an oncological disorder is rarely diagnosed using a single test. Therefore, it is understood that the diagnostic, prognostic, and monitoring methods provided herein are typically used in conjunction with other methods known in the art. For example, the methods of the invention may be performed in conjunction with a morphological or cytological analysis of the sample obtained from the subject, imaging analysis, and/or physical exam. Cytological methods would include immunohistochemical or immunofluorescence detection (and quantitation if appropriate) of any other molecular marker either by itself, in conjunction with other markers. Other methods would include detection of other markers by in situ PCR, or by extracting tissue and quantitating other markers by real time PCR. PCR is defined as polymerase chain reaction.

[0213] Methods for assessing tumor progression during watchful waiting or the efficacy of a treatment regimen, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, or any other therapeutic approach useful for treating an oncologic disorder in a subject are also provided. In these methods the amount of marker in a pair of samples (a first sample obtained from the subject at an earlier time point or prior to the treatment regimen and a second sample obtained from the subject at a later time point, e.g., at a later time point when the subject has undergone at least a portion of the treatment regimen) is assessed. It is understood that the methods of the invention include obtaining and analyzing more than two samples (e.g., 3, 4, 5, 6, 7, 8, 9, or more samples) at regular or irregular intervals for assessment of marker levels. Pairwise comparisons can be made between consecutive or non-consecutive subject samples. Trends of marker levels and rates of change of marker levels can be analyzed for any two or more consecutive or non-consecutive subject samples.

[0214] The invention also provides a method for determining whether an oncologic disorder, e.g., prostate cancer, is aggressive. The method comprises determining the amount of a marker present in a sample and comparing the amount to a control amount of the marker present in one or more control samples, as defined in Definitions, thereby determining whether an oncologic disorder is aggressive. Marker levels can be compared to marker levels in samples obtained at

different times from the same subject or marker levels from normal or abnormal prostate state subjects. A rapid increase in the level of marker may be indicative of a more aggressive cancer than a slow increase or no increase or change in the marker level.

[0215] The methods of the invention may also be used to select a compound that is capable of modulating, i.e., decreasing, the aggressiveness of an oncologic disorder, e.g., prostate cancer. In this method, a cancer cell is contacted with a test compound, and the ability of the test compound to modulate the expression and/or activity of a marker in the invention in the cancer cell is determined, thereby selecting a compound that is capable of modulating aggressiveness of an oncologic disorder.

[0216] Using the methods described herein, a variety of molecules, may be screened in order to identify molecules which modulate, e.g., increase or decrease the expression and/or activity of a marker of the invention, i.e., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), optionally in combination with PSA. Compounds so identified can be provided to a subject in order to inhibit the aggressiveness of an oncologic disorder in the subject, to prevent the recurrence of an oncologic disorder in the subject, or to treat an oncologic disorder in the subject.

Markers of the Invention

[0217] The invention relates to markers (hereinafter "biomarkers", "markers" or "markers of the invention"). The preferred markers of the invention are one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9). Methods of the invention also include use of the marker PSA in conjunction with one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9).

[0218] The invention provides nucleic acids and proteins (e.g., isolated nucleic acids and isolated proteins or fragments thereof) that are encoded by, or correspond to, the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). These markers are particularly useful in screening for the presence of an altered prostate state, e.g., BPH or prostate cancer, in assessing aggressiveness and metastatic potential of an oncologic disorder, assessing the androgen dependent status of an oncological disorder, assessing whether a subject is afflicted with an oncological disorder, identifying a composition for treating an oncological disorder, assessing the efficacy of a compound for treating an oncological disorder, monitoring the progression of an oncological disorder, prognosing the aggressiveness of an oncological disorder, prognosing the survival of a subject with an oncological disorder, prognosing the recurrence of an oncological disorder, and prognosing whether a subject is predisposed to developing an oncological disorder.

[0219] In some embodiments of the present invention, other biomarkers can be used in connection with the methods of the present invention. As used herein, the term "one or more biomarkers" is intended to mean that one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), are assayed, optionally in combination with PSA, and, in various embodiments, more than one other biomarker may be assayed, such as two, three, four, five, six, seven, eight, nine, or more biomarkers in the list may be assayed. One or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and keratin 19 can be assayed in combination with one or more of filamin B, LY9, and PSA. Filamin B can be used in conjunction with one or more other biomarkers, e.g., LY9 or PSA, known to be associated with prostate cancer. LY9 can be used in conjunction with one or more other biomarkers, e.g., filamin B or PSA, known to be associated with prostate cancer. That is, any combination of the filamin B and LY9 biomarkers, optionally with PSA can be used, e.g., filamin B; LY9; filamin B and PSA; filamin B and LY9; LY9 and PSA; filamin B, LY9, and PSA; all of which can optionally be combined with other markers, e.g., one or more of keratins 4, 7, 8, 15, 18, 19, or tubulin-beta 3.

[0220] Methods, kits, and panels provided herein include any combination of 1, 2, 3, 4, 5, 6, 7, 8, or 9 markers of the set filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. Such combinations include any of the following marker sets:

[0221] Marker sets with one member: filamin B; LY9; keratin 4; keratin 7; keratin 8; keratin 15; keratin 18; keratin 19; and tubulin-beta 3. Any single marker can be used in combination with PSA.

[0222] Marker sets with two members: filamin B, LY9; filamin B, keratin 4; filamin B, keratin 7; filamin B, keratin 8; filamin B, keratin 15; filamin B, keratin 18; filamin B, keratin 19; filamin B, tubulin-beta 3; LY9, keratin 4; LY9, keratin 7; LY9, keratin 8; LY9, keratin 15; LY9, keratin 18; LY9, keratin 19; LY9, tubulin-beta 3; keratin 4, keratin 7; keratin 4, keratin 8; keratin 4, keratin 15; keratin 4, keratin 18; keratin 4, keratin 19; keratin 4, tubulin-beta 3; keratin 7, keratin 8; keratin 7, keratin 15; keratin 7, keratin 18; keratin 7, keratin 19; keratin 7, tubulin-beta 3; keratin 8, keratin 15; keratin 8, keratin 18; keratin 8, keratin 19; keratin 8, tubulin-beta 3; keratin 15, keratin 18; keratin 15, keratin 19; keratin 15, tubulin-beta 3; keratin 18, tubulin-beta 3; keratin 18, keratin 19; and keratin 19, tubulin-beta 3. Any marker set can be used in combination with PSA.

[0223] Marker sets with three members: filamin B, LY9, keratin 4; filamin B, LY9, keratin 7; filamin B, LY9, keratin 8; filamin B, LY9, keratin 15; filamin B, LY9, keratin 18; filamin B, LY9, keratin 19; filamin B, LY9, tubulin-beta 3; filamin B, keratin 4, keratin 7; filamin B, keratin 4, keratin 8; filamin B, keratin 4, keratin 15; filamin B, keratin 4, keratin 18; filamin B, keratin 4, keratin 19; filamin B, keratin 4, tubulin-beta 3; filamin B, keratin 7, keratin 8; filamin B, keratin 7, keratin 15; filamin B, keratin 7, keratin 18; filamin B, keratin 7, keratin 19; filamin B, keratin 7, tubulin-beta 3; filamin B, keratin 8, keratin 15; filamin B, keratin 8, keratin 18; filamin B, keratin 8, keratin 19; filamin B, keratin 8, tubulin-beta 3; filamin B, keratin 15, keratin 18; filamin B, keratin 15, keratin 19; filamin B, keratin 15, tubulin-beta 3; filamin B, keratin 18, keratin 19; filamin B, keratin 18, tubulin-beta 3; filamin B, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7; LY9, keratin 4, keratin 8; LY9, keratin 4, keratin 15; LY9, keratin 4, keratin 18; LY9, keratin 4, keratin 19; LY9, keratin 4, tubulin-beta 3; LY9, keratin 7, keratin 8; LY9, keratin 7, keratin 15; LY9, keratin 7, keratin 18; LY9, keratin 7, keratin 19; LY9, keratin 7, tubulin-beta 3; LY9, keratin 8, keratin 15; LY9, keratin 8, keratin 18; LY9, keratin 8, keratin 19; LY9, keratin 8, tubulin-beta 3; LY9, keratin 15, keratin 18; LY9, keratin 15,

keratin 19; LY9, keratin 15, tubulin-beta 3; LY9, keratin 18, keratin 19; LY9, keratin 18, tubulin-beta 3; LY9, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8; keratin 4, keratin 7, keratin 15; keratin 4, keratin 7, keratin 18; keratin 4, keratin 7, keratin 19; keratin 4, keratin 7, tubulin-beta 3; keratin 4, keratin 8, keratin 15; keratin 4, keratin 8, keratin 18; keratin 4, keratin 8, keratin 19; keratin 4, keratin 8, tubulin-beta 3; keratin 4, keratin 15, keratin 18; keratin 4, keratin 15, keratin 19; keratin 4, keratin 15, tubulin-beta 3; keratin 4, keratin 18, keratin 19; keratin 4, keratin 19, tubulin-beta 3; keratin 7, keratin 8, keratin 15; keratin 7, keratin 8, keratin 18; keratin 7, keratin 8, keratin 19; keratin 7, keratin 8, tubulin-beta 3; keratin 7, keratin 8, tubulin-beta 3; keratin 7, keratin 15, keratin 18; keratin 7, keratin 15, keratin 19; keratin 7, keratin 15, tubulin-beta 3; keratin 7, keratin 18, keratin 19; keratin 7, keratin 18, tubulin-beta 3; keratin 15, keratin 18, keratin 19; keratin 15, keratin 18, tubulin-beta 3; and keratin 18, keratin 19, tubulin-beta 3. Any marker set can be used in combination with PSA.

[0224] Marker sets with four members: filamin B, LY9, keratin 4, keratin 7; filamin B, LY9, keratin 4, keratin 8; filamin B, LY9, keratin 4, keratin 15; filamin B, LY9, keratin 4, keratin 18; filamin B, LY9, keratin 4, keratin 19; filamin B, LY9, keratin 4, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8; filamin B, keratin 4, keratin 7, keratin 15; filamin B, keratin 4, keratin 7, keratin 18; filamin B, keratin 4, keratin 7, tubulin-beta 3; filamin B, keratin 4, keratin 7, tubulin-beta 3; filamin B, keratin 7, keratin 8, keratin 15; filamin B, keratin 7, keratin 8, keratin 18; filamin B, keratin 7, keratin 8, keratin 19; filamin B, keratin 7, keratin 8, tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18; filamin B, keratin 8, keratin 15, keratin 19; filamin B, keratin 8, keratin 15, tubulin-beta 3; filamin B, keratin 15, keratin 18, keratin 19; filamin B, keratin 15, keratin 18, tubulin-beta 3; filamin B, keratin 18, keratin 19, and tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8; LY9, keratin 4, keratin 7, keratin 15; LY9, keratin 4, keratin 7, keratin 18; LY9, keratin 4, keratin 7, keratin 19; LY9, keratin 4, keratin 7, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15; LY9, keratin 7, keratin 8, keratin 18; LY9, keratin 7, keratin 8, keratin 19; LY9, keratin 7, keratin 8, tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18; LY9, keratin 8, keratin 15, keratin 19; LY9, keratin 8, keratin 15, tubulin-beta 3; LY9, keratin 15, keratin 18, keratin 19; LY9, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15; keratin 4, keratin 7, keratin 8, keratin 18; keratin 4, keratin 7, keratin 8, keratin 19; keratin 4, keratin 7, keratin 8, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18; keratin 4, keratin 8, keratin 15, keratin 19; keratin 4, keratin 8, keratin 15, tubulin-beta 3; keratin 4, keratin 15, keratin 18, keratin 19; keratin 4, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 18, keratin 19, tubulin-beta 3; keratin 8, keratin 15, keratin 18, keratin 19; keratin 8, keratin 15, keratin 18, tubulin-beta 3; and keratin 15, keratin 18, keratin 19, tubulin-beta 3. Any marker set can be used in combination with PSA.

[0225] Marker sets with five members: keratin 8, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 8, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, keratin 15, keratin 18, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 18, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18, keratin 19; filamen B, LY9, keratin 18, keratin 19 tubulin-beta 3; filamen B, LY9, keratin 15, keratin 19 tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, keratin 19; filamen B, keratin 4, keratin 18, keratin 19 tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 19 tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, keratin 19; filamen B keratin 7, keratin 18, keratin 19 tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 19, tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 18, tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 18, keratin 19; filamen B, keratin 8, keratin 18, keratin 19 tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 19 tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18 tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 18, keratin 19 and tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, keratin 19; LY9, keratin 7, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 7, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, and tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; keratin 4, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; keratin 7, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamen B, LY9, keratin 4, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 4, keratin 18, ubulin-beta 3; filamen B, LY9, keratin 4, keratin 18, keratin 19; filamen B, LY9, keratin 7, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 7, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 7, keratin 18, keratin 19; filamen B, LY9, keratin 8, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 8, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 8, keratin 18, keratin 19; filamen B, LY9, keratin 15, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, keratin 19; filamen B, keratin 4, keratin 7, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 7, keratin 18, tubulin-beta 3; filamen B, keratin 4, keratin 7, keratin 18, keratin 19; filamen B, keratin 4, keratin 8, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 8, keratin 18, tubulin-beta 3;

filamen B, keratin 4, keratin 8, keratin 18, keratin 19; filamen B, keratin 4, keratin 15, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, keratin 19; filamen B, keratin 7, keratin 8, keratin 19, tubulin-beta 3; filamen B, keratin 7, keratin 8, keratin 18, tubulin-beta 3; filamen B, keratin 7, keratin 8, keratin 18, keratin 19; filamen B, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 18, keratin 19; LY9, keratin 4, keratin 8, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, keratin 19; LY9, keratin 4, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, keratin 19; LY9, keratin 7, keratin 8, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 18, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 18, keratin 19; LY9, keratin 7, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 7, keratin 8, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; keratin 4, keratin 7, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; and keratin 7, keratin 8, keratin 15, keratin 18, keratin 19. Any marker set can be used in combination with PSA.

[0226] Marker sets with six members: keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 18, keratin 19, and tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 19, and tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 8, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 8, keratin 15, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19; and LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18. Any marker set can be used in combination with PSA.

[0227] Marker sets with seven members: keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 18, keratin 19, and tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 19, and tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19; and filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18. Any marker set can be used in combination with PSA.

[0228] Marker sets with eight members: LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3;

and filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19. Any marker set can be used in combination with PSA.

[0229] Marker sets with nine members: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3.

[0230] Any marker set can be used in combination with PSA.

[0231] The invention provides for the use of various combinations and sub-combinations of markers. It is understood that any single marker or combination of the markers provided herein can be used in the invention unless clearly indicated otherwise. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0232] Throughout the application, one or more of filamin B, LY9 and keratin 19 is understood as any of: filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0233] Throughout the application, combination of the filamin B and LY9 with PSA is understood as any of filamin B; LY9; filamin B and PSA; filamin B and LY9; LY9 and PSA; filamin B, LY9, and PSA.

[0234] Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 is understood as any of keratin 4; keratin 7; keratin 8; keratin 15; keratin 18; tubulin beta-3; keratin 4 and keratin 7; keratin 4 and keratin 8; keratin 4 and keratin 15; keratin 4 and keratin 18; keratin 4 and tubulin beta-3; keratin 7 and keratin 8; keratin 7 and keratin 15; keratin 7 and keratin 18; keratin and tubulin beta-3; keratin 8 and keratin 15; keratin 8 and keratin 18; keratin 8 and tubulin beta-3; keratin 15 and keratin 18; keratin 15 and tubulin beta-3; keratin 18 and tubulin beta-3; keratin 4, keratin 7 and keratin 8; keratin 4, keratin 7 and keratin 15; keratin 4, keratin 7 and keratin 18; keratin 4, keratin 7 and tubulin beta-3; keratin 4, keratin 8 and keratin 15; keratin 4, keratin 8 and keratin 18; keratin 4, keratin 8 and tubulin beta-e; keratin 4, keratin 15 and keratin 18; keratin 4, keratin 15 and tubulin beta-e; keratin 4, keratin 18 and tubulin beta-3; kertin 4, keratin 7, keratin 8 and keratin 15; keratin 4, keratin 7, keratin 8 and keratin 18; keratin 4, keratin 7, keratin 8 and tubulin beta-3; keratin 4, keratin 8, keratin 15 and keratin 18; keratin 4, keratin 8, keratin 15 and tubulin beta-3; keratin 4, keratin 15, keratin 18 and tubulin beta-3; keratin 4, keratin 7, keratin 8, keratin 15 and keratin 18; keratin 4, keratin 7, keratin 8, keratin 15, and tubulin beta-3; keratin 4, keratin 7, keratin 8, keratin 18, and tubulin beta-3; keratin 4, keratin 7, keratin 15, keratin 18, and tubulin beta-3; keratin 4, keratin 8, keratin 15, keratin 18, and tubulin beta-3; or keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0235] Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7, 15, and 19 is understood as any of keratin 7; keratin 15; keratin 19; keratin 7 and 15; keratin 7 and 19; keratin 15 and 19; and keratin 7, 15, and 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0236] Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7, 8, and 15 is understood as any of keratin 7; keratin 8; keratin 15; keratin 7 and 8; keratin 7 and 15; keratin 8 and 15; and keratin 7, 8, and 15. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0237] Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7 and 15 is understood as any of keratin 7; keratin 15; or keratin 7 and 15. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0238] Throughout the application, one or more prostate cancer markers selected from the group consisting filamin B, LY9, or keratin 19 is understood as any of filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9, and keratin 19; and filamin B, LY9, and keratin 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA.

[0239] In certain embodiments, methods of diagnosing, prognosing, and monitoring the treatment of prostate cancer by detecting the level sets of markers including of keratin 7, 15, or 19 and filamin B; keratin 7, 15, 19 or LY9; keratin 7, 15, 19, or PSA; keratin 4, 7, 15, or 19; keratin 7, 8, 15, or 19; keratin 7, 15, 18, or 19; and keratin 7, 15, 19, or tubulin-beta 3.

[0240] A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as an abnormal prostate state. In a preferred embodiment, the marker is detected in a blood sample, e.g., serum or plasma. In one embodiment, the marker is detected in serum. In one embodiment, the marker is detected in plasma. In certain embodiments, the serum or plasma can be further processed to remove abundant blood proteins (e.g., albumin) or proteins that are not marker proteins prior to analysis. A "marker nucleic acid" is a nucleic acid (e.g., mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (e.g., cDNA) comprising the entire or a partial sequence of any of the nucleic acid sequences provided herein or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences provided herein or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the entire or a partial sequence of any of the amino acid sequences provided herein. The terms "protein" and "polypeptide" are used interchangeably.

[0241] A "biological sample" or a "subject sample" is a body fluid or tissue in which a prostate cancer related marker may be present. In certain embodiments the sample is blood or a blood product (e.g., serum or plasma). In certain embodiments, the sample is a tissue sample, e.g., a tissue sample from at or near the site of the prostate hyperplasia or tumor, or the suspected prostate hyperplasia or tumor. A tissue sample can be obtained, for example, during biopsy or surgical resection of the prostate. A tissue sample can include one or more of normal tissue, hyperplasia, and cancerous tissue. Methods of distinguishing between such tissue types are known, e.g., histological analysis, immunohistochemical analysis. In certain embodiments, the control sample can be a normal portion of sample tissue removed from a subject.

[0242] An "oncological disorder-associated" body fluid is a fluid which, when in the body of a subject, contacts, or passes through oncological cells or into which cells or proteins shed from oncological cells are capable of passing. Exemplary oncological disorder-associated body fluids include blood fluids (e.g. whole blood, blood serum, blood having platelets removed therefrom), and are described in more detail below. Many oncological disorder-associated body fluids can have oncological cells therein, particularly when the cells are metastasizing. Cell-containing fluids which can contain oncological cells include, but are not limited to, whole blood, blood having platelets removed therefrom, lymph, prostatic fluid, urine, and semen.

[0243] The "normal" level of expression of a marker is the level of expression of the marker in cells of a human subject or patient or a population of subjects not afflicted with an oncological disorder or an abnormal prostate state, e.g., BPH or prostate cancer.

[0244] An "over-expression", "higher level of expression", "higher level", and the like of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least 25% more, at least 50% more, at least 75% more, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten times the expression level of the marker in a control sample (e.g., sample from a healthy subject not having the marker associated disease, i.e., an abnormal prostate state) and preferably, the average expression level of the marker or markers in several control samples.

[0245] A "lower level of expression" or "lower level" of a marker refers to an expression level in a test sample that is less than 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% of the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease, i.e., an abnormal prostate state) and preferably, the average expression level of the marker in several control samples.

[0246] A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (e.g. an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or having a high percentage of identity (e.g., at least 80% identity) with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (e.g. splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

[0247] "Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

[0248] "Identical" or "identity" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are identical at that position. A first region is identical to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Identity between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% identity. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

[0249] "Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least a 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least a 15 amino acid segment of a marker or variant marker protein. In certain embodiments, a protein of the invention is a peptide sequence or epitope large enough to permit the specific binding of an antibody to the marker.

[0250] The invention further provides antibodies, antibody derivatives and antibody fragments which specifically bind with the marker proteins and fragments of the marker proteins of the present invention. Unless otherwise specified herewithin, the terms "antibody" and "antibodies" broadly encompass naturally-occurring forms of antibodies (e.g., IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

[0251] In certain embodiments, the positive or negative fold change refers to that of any gene described herein.

[0252] As used herein, "positive fold change" refers to "up-regulation" or "increase (of expression)" of a gene that is listed herein.

[0253] As used herein, "negative fold change" refers to "down-regulation" or "decrease (of expression)" of a gene that is listed herein.

[0254] Various aspects of the invention are described in further detail in the following subsections.

Isolated Nucleic Acid Molecules

[0255] One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode

a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, e.g., those suitable for use as PCR primers for the amplification of a specific product or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

[0256] An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. In one embodiment, an "isolated" nucleic acid molecule (preferably a protein-encoding sequences) is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. In another embodiment, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. A nucleic acid molecule that is substantially free of cellular material includes preparations having less than about 30%, 20%, 10%, or 5% of heterologous nucleic acid (also referred to herein as a "contaminating nucleic acid").

[0257] A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., ed., *Molecular Cloning: A Laboratory Manual,* 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989).

[0258] A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

[0259] In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

[0260] Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 15, more preferably at least about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

[0261] Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. In certain embodiments, the probes hybridize to nucleic acid sequences that traverse splice junctions. The probe comprises a label group attached thereto, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit or panel for identifying cells or tissues which express or mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, e.g., detecting mRNA levels or determining whether a gene encoding the protein or its translational control sequences have been mutated or deleted.

[0262] The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (e.g., protein having the sequence provided in the sequence listing), and thus encode the same protein.

[0263] It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (e.g., the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation and changes known to occur in cancer. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

[0264] As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

[0265] As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

[0266] In another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is

intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6× sodium chloride/sodium citrate (SSC) at about 45° C., followed by one or more washes in 0.2×SSC, 0.1% SDS at 50-65° C.

Nucleic Acid Therapeutics

[0267] Nucleic acid therapeutics are well known in the art. Nucleic acid therapeutics include both single stranded and double stranded (i.e., nucleic acid therapeutics having a complementary region of at least 15 nucleotides in length that may be one or two nucleic acid strands) nucleic acids that are complementary to a target sequence in a cell. Nucleic acid therapeutics can be delivered to a cell in culture, e.g., by adding the nucleic acid to culture media either alone or with an agent to promote uptake of the nucleic acid into the cell. Nucleic acid therapeutics can be delivered to a cell in a subject, i.e., in vivo, by any route of administration. The specific formulation will depend on the route of administration.

[0268] As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions may include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50° C. or 70° C. for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

[0269] Sequences can be "fully complementary" with respect to each when there is base-pairing of the nucleotides of the first nucleotide sequence with the nucleotides of the second nucleotide sequence over the entire length of the first and second nucleotide sequences. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 4, 3 or 2 mismatched base pairs upon hybridization, while retaining the ability to hybridize under the conditions most relevant to their ultimate application. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs as is common in double stranded nucleic acid therapeutics, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as "fully complementary" for the purposes described herein.

[0270] "Complementary" sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but not limited to, G:U Wobble or Hoogstein base pairing.

[0271] The terms "complementary," "fully complementary", and "substantially complementary" herein may be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between an antisense nucleic acid or the antisense strand of dsRNA and a target sequence, as will be understood from the context of their use.

[0272] As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (e.g., an mRNA encoding filamin B, LY9, a keratin, tubulin-beta 3, or PSA) including a 5' UTR, an open reading frame (ORF), or a 3' UTR. For example, a polynucleotide is complementary to at least a part of filamin B, LY9, a keratin, tubulin-beta 3, or PSA mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding filamin B, LY9, a keratin, tubulin-beta 3, or PSA.

[0273] Nucleic acid therapeutics typically include chemical modifications to improve their stability and to modulate their pharmacokinetic and pharmacodynamic properties. For example, the modifications on the nucleotides can include, but are not limited to, LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C— allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof.

[0274] Nucleic acid therapeutics may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both (in nucleic acid therapeutics including a sense strand) in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand may contain both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

Single Stranded Nucleic Acid Therapeutics

[0275] Antisense nucleic acid therapeutic agent single stranded nucleic acid therapeutics, typically about 16 to 30 nucleotides in length and are complementary to a target nucleic acid sequence in the target cell, either in culture or in an organism. Patents directed to antisense nucleic acids, chemical modifications, and therapeutic uses are provided, for example, in U.S. Pat. No. 5,898,031 related to chemically modified RNA-containing therapeutic compounds, and U.S. Pat. No. 6,107,094 related methods of using these compounds as therapeutic agent. U.S. Pat. No. 7,432,250 related to methods of treating patients by administering single-stranded

chemically modified RNA-like compounds; and U.S. Pat. No. 7,432,249 related to pharmaceutical compositions containing single-stranded chemically modified RNA-like compounds. U.S. Pat. No. 7,629,321 is related to methods of cleaving target mRNA using a single-stranded oligonucleotide having a plurality RNA nucleosides and at least one chemical modification. Each of the patents listed in the paragraph are incorporated herein by reference.

Double Stranded Nucleic Acid Therapeutics

[0276] In many embodiments, the duplex region is 15-30 nucleotide pairs in length. In some embodiments, the duplex region is 17-23 nucleotide pairs in length, 17-25 nucleotide pairs in length, 23-27 nucleotide pairs in length, 19-21 nucleotide pairs in length, or 21-23 nucleotide pairs in length.

[0277] In certain embodiments, each strand has 15-30 nucleotides.

[0278] The RNAi agents that are used in the methods of the invention include agents with chemical modifications as disclosed, for example, in Publications WO 2009/073809 and WO/2012/037254, the entire contents of each of which are incorporated herein by reference.

[0279] An "RNAi agent," "double stranded RNAi agent," double-stranded RNA (dsRNA) molecule, also referred to as "dsRNA agent," "dsRNA", "siRNA", "iRNA agent," as used interchangeably herein, refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary, as defined below, nucleic acid strands. As used herein, an RNAi agent can also include dsiRNA (see, e.g., US Patent publication 20070104688, incorporated herein by reference). In general, the majority of nucleotides of each strand are ribonucleotides, but as described herein, each or both strands can also include one or more non-ribonucleotides, e.g., a deoxyribonucleotide and/or a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "RNAi agent" for the purposes of this specification and claims.

[0280] The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi agent may comprise one or more nucleotide overhangs. The term "siRNA" is also used herein to refer to an RNAi agent as described above.

[0281] In another aspect, the agent is a single-stranded antisense RNA molecule. An antisense RNA molecule is complementary to a sequence within the target mRNA. Antisense RNA can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. et al., (2002) *Mol Cancer Ther* 1:347-355. The antisense RNA molecule may have about 15-30 nucleotides that are complementary to the target mRNA. For example, the antisense RNA molecule may have a sequence of at least 15, 16, 17, 18, 19, 20 or more contiguous nucleotides complementary to the filamin B or LY9 sequences provided herein.

[0282] The term "antisense strand" refers to the strand of a double stranded RNAi agent which includes a region that is substantially complementary to a target sequence (e.g., a human TTR mRNA). As used herein, the term "region complementary to part of an mRNA encoding transthyretin" refers to a region on the antisense strand that is substantially complementary to part of a TTR mRNA sequence. Where the region of complementarity is not fully complementary to the target sequence, the mismatches are most tolerated in the terminal regions and, if present, are generally in a terminal region or regions, e.g., within 6, 5, 4, 3, or 2 nucleotides of the 5' and/or 3' terminus.

[0283] The term "sense strand," as used herein, refers to the strand of a dsRNA that includes a region that is substantially complementary to a region of the antisense strand.

[0284] The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Pat. No. 5,876,930.

Isolated Proteins and Antibodies

[0285] One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

[0286] An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is

substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

[0287] Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

[0288] Preferred marker proteins are encoded by nucleotide sequences provided in the sequence listing. Other useful proteins are substantially identical (e.g., at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

[0289] To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. Preferably, the percent identity between the two sequences is calculated using a global alignment. Alternatively, the percent identity between the two sequences is calculated using a local alignment. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=# of identical positions/total # of positions (e.g., overlapping positions)×100). In one embodiment the two sequences are the same length. In another embodiment, the two sequences are not the same length.

[0290] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., BLASTX and BLASTN) can be used. See http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a k-tuple value of 2.

[0291] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

[0292] Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (i.e., such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, e.g., an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, e.g., a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and $F(ab')_2$ fragments.

[0293] An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the proteins of the invention, and encompasses at least one

epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, e.g., hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

[0294] The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof. Methods of making polyclonal, monoclonal, and recombinant antibody and antibody fragments are well known in the art.

Predictive Medicine

[0295] The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing a disease or disorder, such as, without limitation, an oncological disorder, e.g., prostate cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the disorder.

[0296] Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit an oncological disorder, e.g., prostate cancer, or to treat or prevent any other disorder (i.e. in order to understand any carcinogenic effects that such treatment may have)) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

[0297] A. Diagnostic Assays

[0298] An exemplary method for detecting the presence or absence or change of expression level of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (e.g. an oncological disorder-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo.

[0299] Methods provided herein for detecting the presence, absence, change of expression level of a marker protein or nucleic acid in a biological sample include obtaining a biological sample from a subject that may or may not contain the marker protein or nucleic acid to be detected, contacting the sample with a marker-specific binding agent (i.e., one or more marker-specific binding agents) that is capable of forming a complex with the marker protein or nucleic acid to be detected, and contacting the sample with a detection reagent for detection of the marker—marker-specific binding agent complex, if formed. It is understood that the methods provided herein for detecting an expression level of a marker in a biological sample includes the steps to perform the assay. In certain embodiments of the detection methods, the level of the marker protein or nucleic acid in the sample is none or below the threshold for detection.

[0300] The methods include formation of either a transient or stable complex between the marker and the marker-specific binding agent. The methods require that the complex, if formed, be formed for sufficient time to allow a detection reagent to bind the complex and produce a detectable signal (e.g., fluorescent signal, a signal from a product of an enzymatic reaction, e.g., a peroxidase reaction, a phosphatase reaction, a beta-galactosidase reaction, or a polymerase reaction).

[0301] In certain embodiments, all markers are detected using the same method. In certain embodiments, all markers are detected using the same biological sample (e.g., same body fluid or tissue). In certain embodiments, different markers are detected using various methods. In certain embodiments, markers are detected in different biological samples.

[0302] 1. Protein Detection

[0303] In certain embodiments of the invention, the marker to be detected is a protein. Proteins are detected using a number of assays in which a complex between the marker protein to be detected and the marker specific binding agent would not occur naturally, for example, because one of the components is not a naturally occurring compound or the marker for detection and the marker specific binding agent are not from the same organism (e.g., human marker proteins detected using marker-specific binding antibodies from mouse, rat, or goat). In a preferred embodiment of the invention, the marker protein for detection is a human marker protein. In certain detection assays, the human markers for detection are bound by marker-specific, non-human antibodies, thus, the complex would not be formed in nature. The complex of the marker protein can be detected directly, e.g., by use of a labeled marker-specific antibody that binds directly to the marker, or by binding a further component to the marker-marker-specific antibody complex. In certain embodiments, the further component is a second marker-specific antibody capable of binding the marker at the same time as the first marker-specific antibody. In certain embodiments, the further component is a secondary antibody that binds to a marker-specific antibody, wherein the secondary antibody preferably linked to a detectable label (e.g., fluorescent label, enzymatic label, biotin). When the secondary antibody is linked to an enzymatic detectable label (e.g., a peroxidase, a phosphatase, a beta-galactosidase), the secondary antibody is detected by contacting the enzymatic detectable label with an appropriate substrate to produce a colorimetric, fluorescent, or other detectable, preferably quantitatively detectable, product. Antibodies for use in the methods of the invention can be polyclonal, however, in a preferred embodiment monoclonal antibodies are used. An intact antibody, or a fragment or derivative thereof (e.g., Fab or $F(ab')_2$) can be used in the methods of the invention. Such strategies of marker protein detection are used, for example, in ELISA, RIA, western blot, and immunofluorescence assay methods.

[0304] In certain detection assays, the marker present in the biological sample for detection is an enzyme and the detection reagent is an enzyme substrate. For example, the enzyme

can be a protease and the substrate can be any protein that includes an appropriate protease cleavage site. Alternatively, the enzyme can be a kinase and the substrate can be any substrate for the kinase. In preferred embodiments, the substrate which forms a complex with the marker enzyme to be detected is not the substrate for the enzyme in a human subject.

[0305] In certain embodiments, the marker-marker-specific binding agent complex is attached to a solid support for detection of the marker. The complex can be formed on the substrate or formed prior to capture on the substrate. For example, in an ELISA, RIA, immunoprecipitation assay, western blot, immunofluorescence assay, in gel enzymatic assay the marker for detection is attached to a solid support, either directly or indirectly. In an ELISA, RIA, or immunofluorescence assay, the marker is typically attached indirectly to a solid support through an antibody or binding protein. In a western blot or immunofluorescence assay, the marker is typically attached directly to the solid support. For in-gel enzyme assays, the marker is resolved in a gel, typically an acrylamide gel, in which a substrate for the enzyme is integrated.

[0306] 2. Nucleic Acid Detection

[0307] In certain embodiments of the invention, the marker is a nucleic acid. Nucleic acids are detected using a number of assays in which a complex between the marker nucleic acid to be detected and a marker-specific probe would not occur naturally, for example, because one of the components is not a naturally occurring compound. In certain embodiments, the analyte comprises a nucleic acid and the probe comprises one or more synthetic single stranded nucleic acid molecules, e.g., a DNA molecule, a DNA-RNA hybrid, a PNA, or a modified nucleic acid molecule containing one or more artificial bases, sugars, or backbone moieties. In certain embodiments, the synthetic nucleic acid is a single stranded is a DNA molecule that includes a fluorescent label. In certain embodiments, the synthetic nucleic acid is a single stranded oligonucleotide molecule of about 12 to about 50 nucleotides in length. In certain embodiments, the nucleic acid to be detected is an mRNA and the complex formed is an mRNA hybridized to a single stranded DNA molecule that is complementary to the mRNA. In certain embodiments, an RNA is detected by generation of a DNA molecule (i.e., a cDNA molecule) first from the RNA template using the single stranded DNA that hybridizes to the RNA as a primer, e.g., a general poly-T primer to transcribe poly-A RNA. The cDNA can then be used as a template for an amplification reaction, e.g., PCR, primer extension assay, using a marker-specific probe. In certain embodiments, a labeled single stranded DNA can be hybridized to the RNA present in the sample for detection of the RNA by fluorescence in situ hybridization (FISH) or for detection of the RNA by northern blot.

[0308] For example, in vitro techniques for detection of mRNA include northern hybridizations, in situ hybridizations, and rtPCR. In vitro techniques for detection of genomic DNA include Southern hybridizations. Techniques for detection of mRNA include PCR, northern hybridizations and in situ hybridizations. Methods include both qualitative and quantitative methods.

[0309] A general principle of such diagnostic, prognostic, and monitoring assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways known in the art, e.g., ELISA assay, PCR, FISH.

[0310] 3. Detection of Expression Levels

[0311] Marker levels can be detected based on the absolute expression level or a normalized or relative expression level. Detection of absolute marker levels may be preferable when monitoring the treatment of a subject or in determining if there is a change in the prostate cancer status of a subject. For example, the expression level of one or more markers can be monitored in a subject undergoing treatment for prostate cancer, e.g., at regular intervals, such a monthly intervals. A modulation in the level of one or more markers can be monitored over time to observe trends in changes in marker levels. Expression levels of one or more of filamin B, LY9, or keratin 19 in the subject may be higher than the expression level of those markers in a normal sample, but may be lower than the prior expression level, thus indicating a benefit of the treatment regimen for the subject. Similarly, rates of change of marker levels can be important in a subject who is not subject to active treatment for prostate cancer (e.g., watchful waiting). Changes, or not, in marker levels may be more relevant to treatment decisions for the subject than marker levels present in the population. Rapid changes in marker levels in a subject who otherwise appears to have a normal prostate may be indicative of an abnormal prostate state, even if the markers are within normal ranges for the population.

[0312] As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, e.g., a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, e.g., a non-cancer sample, or between samples from different sources.

[0313] Alternatively, the expression level can be provided as a relative expression level as compared to an appropriate control, e.g., population control, adjacent normal tissue control, earlier time point control, etc. Preferably, the samples used in the baseline determination will be from non-cancer cells. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is cancer specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cancer cells provides a means for grading the severity of the cancer state.

Diagnostic, Prognostic, and Treatment Methods

[0314] The invention provides methods for detecting an abnormal prostate state in a subject by

[0315] (1) contacting a biological sample from a subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate-cancer related protein set as fol-

lows: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0316] (2) measuring the amount of each prostate-cancer related marker detected in the biological sample by each detection reagent; and

[0317] (3) comparing the level of expression of the one or more prostate-cancer related protein in the biological sample obtained from the subject with a level of expression of the one or more prostate-cancer related protein in a normal control sample, thereby detecting an abnormal prostate state.

[0318] In certain embodiments, detecting an abnormal prostate state comprises diagnosing prostate cancer status in a subject. In certain embodiments, an abnormal prostate state comprises identifying a predisposed to developing prostate cancer.

[0319] The invention provides methods for monitoring the treatment of prostate cancer in a subject by

[0320] (1) contacting a first biological sample obtained from the subject prior to administering at least a portion of a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0321] (2) contacting a second biological sample obtained from the subject after administering at least a portion of a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0322] (3) measuring the amount of prostate-cancer related marker detected in each the first biological sample and the second biological sample by each detection reagent; and

[0323] (4) comparing the level of expression of the one or more prostate-cancer related markers in the first sample with the expression level of the one or more prostate-cancer related markers in the second sample, thereby monitoring the treatment of prostate cancer in the subject.

[0324] The invention provides method of selecting for administration of active treatment or against administration of active treatment of prostate cancer in a subject by

[0325] (1) contacting a first biological sample obtained from the subject prior to administering a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0326] (2) contacting a second biological sample obtained from the subject prior to administering a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

[0327] (3) measuring the amount of prostate-cancer related marker detected in each the first biological sample and the second biological sample by each detection reagent; and

[0328] (4) comparing the level of expression of the one or more prostate-cancer related markers in the first sample with the expression level of the one or more prostate-cancer related markers in the second sample, wherein selecting for administration of active treatment or against administration of active treatment of prostate cancer is based on the presence or absence of changes in the level of expression of one or more markers between the first sample and the second sample.

[0329] In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is two or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is three or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is four or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is five or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is six or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is seven or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is eight or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is nine or more markers.

[0330] In certain embodiments of the diagnostic methods provided herein, an increase in the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample as compared to the level of expression of the one or more prostate-cancer related markers in a normal control sample is an indication that the subject is afflicted with prostate cancer. In certain embodiments of the diagnostic methods provided herein, no increase in the detected expression level of one or more of filamin B, LY9, and keratin 19 in the biological sample as compared to the expression level in a normal control sample is an indication that the subject is not afflicted with prostate cancer or not predisposed to developing prostate cancer.

[0331] In certain embodiments of the diagnostic methods provided herein, an increase in the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample as compared to the level of expression of the one or more prostate-cancer related markers in a normal control sample is an indication that the subject is predisposed to developing prostate cancer.

[0332] In certain embodiments of the monitoring methods provided herein, no increase in the detected level of expression of any of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers in the first sample is an indication that the therapy is efficacious for treating prostate cancer in the subject. In certain embodiments the monitoring methods provided herein, further comprise comparing the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the first sample or the level of expression of one or more prostate-cancer

related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second sample with the expression of the one or more prostate-cancer related markers in a control sample.

[0333] In certain embodiments of the monitoring methods provided herein, an increase in the level of expression of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers in the first sample is an indication for selection of active treatment of prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, no increase in the detected level of expression of any of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers in the first sample is an indication against selection of active treatment of prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, wherein an increased expression level of one or more of filamin B, LY9, and keratin 19 in the second sample as compared to the expression level in the first sample is an indication that the therapy is not efficacious in the treatment of prostate cancer.

[0334] In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is selected from the group of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is selected from the group of keratin 7, keratin 8, and keratin 15. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is selected from the group of keratin 7, keratin 15, and keratin 19. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is keratin 7 or keratin 15. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the biological sample is compared to the level of the one or more prostate-cancer related markers in a normal control sample is indicative of a modulation in prostate cancer status.

[0335] In certain embodiments of the monitoring methods provided herein, modulation of the level of expression of the one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample is indicative of a change in prostate cancer status in response to treatment of the prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, the methods further comprise comparing the level of expression of one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample; or the level of expression of one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample to the level of expression of one or more prostate-cancer related markers in a normal control sample.

[0336] In certain embodiments the diagnostic methods provided herein further comprise detecting the level of expression of prostate specific antigen (PSA) in the biological sample and preferably further comprise comparing the level of expression of PSA in the biological sample to a PSA expression level in a normal control sample. In certain embodiments, the combination of PSA level with one or more of the prostate-cancer maker levels increases the predictive value of the method.

[0337] In certain embodiments the monitoring methods provided herein further comprise detecting the level of expression of prostate specific antigen (PSA) in the first sample and the second sample, and preferably further comprising comparing the level of expression of PSA in the first sample with the level of expression of PSA in the second sample. In certain monitoring methods, the change in PSA level in combination with the change in prostate-cancer maker level increases the predictive value of the method.

[0338] In certain embodiments the diagnostic and monitoring methods provided herein further comprise comparing the detected level of the one or more prostate markers in the biological samples with one or more control samples wherein the control sample is one or more of a sample from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and sample obtained from a subject with non-aggressive prostate cancer. Comparison of the marker levels in the biological samples with control samples from subjects with various normal and abnormal prostate states facilitates the differentiation between various prostate states including normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, or between any two or more prostate states including normal prostate, prostate cancer, benign prostate hyperplasia, androgen dependent prostate cancer, androgen independent prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

[0339] In certain embodiments the diagnostic and monitoring methods provided herein further comprising detecting the size of the prostate tumor in the subject. In certain embodiments the monitoring methods provided herein further comprise detecting a change in the size or relative aggressiveness of the tumor. In certain embodiments, the size of the prostate tumor in the subject is detected prior to administering the at least a portion of a treatment regimen to the subject. In certain embodiments, the size of the prostate tumor in the subject is detected after administering the at least a portion of a treatment regimen to the subject. Certain monitoring methods, further comprise comparing the size of the prostate tumor in the subject prior to administering the at least a portion of a treatment regimen to the subject to the size of the prostate

tumor in the subject after administering the at least a portion of a treatment regimen to the subject.

[0340] In certain embodiments the diagnostic and monitoring methods provided herein further comprising obtaining a subject sample.

[0341] In certain embodiments the diagnostic and monitoring methods provided herein further comprising selecting a treatment regimen for the subject based on the level expression of one or more of the prostate-cancer related markers provided in claims **1**.

[0342] In certain embodiments the diagnostic and monitoring methods provided herein further comprising selecting a subject for having or being suspected of having prostate cancer.

[0343] In certain embodiments the diagnostic and monitoring methods provided herein further comprising treating the subject with a regimen including one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, and chemotherapy.

[0344] In certain embodiments the diagnostic and monitoring methods provided herein further comprising selecting the one or more specific treatment regimens for the subject based on the results of the diagnostic and monitoring methods provided herein. In certain embodiments, the treatment method is maintained based on the results from the diagnostic or prognostic methods. n certain embodiments, the treatment method is changed based on the results from the diagnostic or prognostic methods.

[0345] In certain embodiments, a change the treatment regimen comprises changing a hormone based therapy treatment. In certain embodiments, treatments for prostate cancer include one or more of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, or chemotherapy based on the results of a method of any one of claims **1-64** for an interval prior to performing a subsequent diagnostic, prognostic, or monitoring method provided herein.

[0346] In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises isolating a component of the biological sample.

[0347] In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises labeling a component of the biological sample.

[0348] In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises amplifying a component of a biological sample.

[0349] In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises forming a complex with a probe and a component of a biological sample. In certain embodiments, forming a complex with a probe comprises forming a complex with at least one non-naturally occurring reagent. In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises processing the biological sample. In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level of at least two markers comprises a panel of markers. In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises attaching the marker to be detected to a solid surface.

[0350] The invention provides methods of selecting for administration of active treatment or against administration of active treatment of prostate cancer in a subject comprising:

[0351] (1) detecting a level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta in a first sample obtained from the subject having prostate cancer wherein the subject has not been actively treated for prostate cancer;

[0352] (2) detecting a level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a second sample from the subject;

[0353] (3) comparing the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the first sample with the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the second sample;

[0354] wherein selecting for administration of active treatment or against administration of active treatment of prostate cancer is based on the presence or absence of changes in the level of expression of one or more markers between the first sample and the second sample.

[0355] In certain embodiments, the method further comprising obtaining a third sample obtained from the subject, detecting a level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the third sample, and comparing the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the third sample with the level of the one or more markers in the first sample or the one or more markers in the second sample.

[0356] In certain embodiments, an increased level of one or more of filamin B, LY9, and keratin 19 in the second sample as compared to the level of one or more of filamin B, LY9, and keratin 19 in the first sample is an indication that the therapy is not efficacious in the treatment of prostate cancer.

[0357] In certain embodiments, an increased of one or more of filamin B, LY9, and keratin 19 in the second sample as compared to the level of one or more of filamin B, LY9, and keratin 19 in the first sample is an indication for selecting active treatment for prostate cancer.

[0358] In certain embodiments, the method further comprises comparing the level of one or more markers selected from the group consisting of filamin B, LY9, and keratin 19 in the first sample or the level of one or more markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second sample with the level of one or more of filamin B, LY9, and keratin 19 in a control sample. In certain embodiments, the method comprises detecting the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample; detecting the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample; and comparing the level of the one or more of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample with the one or more of

the level of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample. In certain embodiments, the method comprises detection of a subset of keratins such as keratin 7, keratin 8, and keratin 15; keratin 7, 15, and 19; and keratin 7 or keratin 15. In certain embodiments, the method further comprises comparing the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample; or the level of expression of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample to the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in a control sample.

[0359] In certain embodiments, no change in the level of expression of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 between the first sample and the second sample is an indication for selecting against active treatment for prostate cancer.

[0360] In certain embodiments, the methods further comprise detecting the level of prostate specific antigen (PSA) in the first sample and the second sample, and then preferably further comprising comparing the level of PSA in the first sample with the level of PSA in the second sample.

[0361] In certain embodiments, a decrease in the level of one or more of filamin B, LY9, and keratin 19 in the second sample as compared to the level of one or more of filamin B, LY9, and keratin 19 in the first sample in combination with a decrease in the level of PSA in the second sample as compared to the level of PSA in the first sample has greater predictive value that the therapy is efficacious in treating prostate cancer in the subject than analysis of a single marker alone.

[0362] In certain embodiments, a decrease in the level of one or more of filamin B, LY9, and keratin 19 in the second sample as compared to the level of one or more of filamin B, LY9, and keratin 19 in the first sample in combination with a decrease in the level of expression of PSA in the second sample as compared to the level of PSA in the first sample has greater predictive value that for selecting against active treatment for prostate cancer than analysis of a single marker alone.

Monitoring Clinical Trials

[0363] Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening or monitoring the treatment of a single subject, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for an oncological disorder. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention (e.g., filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, optionally in combination with PSA) in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker (s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene (s) may indicate efficacious treatment and no need to change dosage.

Kits

[0364] The invention also provides compositions and kits for diagnosing, prognosing, or monitoring a disease or disorder, recurrence of a disorder, or survival of a subject being treated for a disorder (e.g., an abnormal prostate state, BPH, an oncologic disorder, e.g., prostate cancer). These kits include one or more of the following: a detectable antibody that specifically binds to a marker of the invention, a detectable antibody that specifically binds to a marker of the invention, reagents for obtaining and/or preparing subject tissue samples for staining, and instructions for use.

[0365] The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample. Such kits can be used to determine if a subject is suffering from or is at increased risk of developing an abnormal prostate state. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (e.g., an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for use of the kit for practicing any of the methods provided herein or interpreting the results obtained using the kit based on the teachings provided herein. The kits can also include reagents for detection of a control protein in the sample not related to the abnormal prostate state, e.g., actin for tissue samples, albumin in blood or blood derived samples for normalization of the amount of the marker present in the sample. The kit can also include the purified marker for detection for use as a control or for quantitation of the assay performed with the kit.

[0366] Kits include panel of reagents for use in a method to diagnose prostate cancer in a subject (or to identify a subject predisposed to developing prostate cancer, etc.), the panel comprising at least two detection reagents, wherein each detection reagent is specific for one prostate cancer-specific protein, wherein said prostate cancer-specific proteins are selected from the prostate cancer-specific protein sets provided herein.

[0367] For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a first marker protein; and, optionally, (2) a second, different antibody which binds to either the first marker protein or the first antibody and is conjugated to a detectable label. In certain embodiments, the kit includes (1) a second antibody (e.g., attached to a solid support) which binds to a second marker protein; and, optionally, (2) a second, different antibody which binds to either the second marker protein or the second antibody and is conjugated to a detectable label. The first and second marker proteins are different. In an embodiment, the first and second markers are markers of the invention, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and PSA. In certain embodiments, neither the first

marker nor the second marker is PSA. In certain embodiments, the kit comprises a third antibody which binds to a third marker protein which is different from the first and second marker proteins, and a second different antibody that binds to either the third marker protein or the antibody that binds the third marker protein wherein the third marker protein is different from the first and second marker proteins.

[0368] For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. In certain embodiments, the kit can further include, for example: (1) an oligonucleotide, e.g., a second detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a second marker protein or (2) a pair of primers useful for amplifying the second marker nucleic acid molecule. The first and second markers are different. In an embodiment, the first and second markers are markers of the invention, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and PSA. In certain embodiments, neither the first marker nor the second marker is PSA. In certain embodiments, the kit can further include, for example: (1) an oligonucleotide, e.g., a third detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a third marker protein or (2) a pair of primers useful for amplifying the third marker nucleic acid molecule wherein the third marker is different from the first and second markers. In certain embodiments, the kit includes a third primer specific for each nucleic acid marker to allow for detection using quantitative PCR methods.

[0369] For chromatography methods, the kit can include markers, including labeled markers, to permit detection and identification of one or more markers of the invention, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and optionally PSA, by chromatography. In certain embodiments, kits for chromatography methods include compounds for derivatization of one or more markers of the invention. In certain embodiments, kits for chromatography methods include columns for resolving the markers of the method.

[0370] Reagents specific for detection of a marker of the invention, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and PSA, allow for detection and quantitation of the marker in a complex mixture, e.g., serum, tissue sample. In certain embodiments, the reagents are species specific. In certain embodiments, the reagents are not species specific. In certain embodiments, the reagents are isoform specific. In certain embodiments, the reagents are not isoform specific. In certain embodiments, the reagents detect total keratin 8, keratin 18, filamin B, PSA, or LY9.

[0371] In certain embodiments, the kits for the diagnosis, monitoring, or characterization of prostate cancer comprise at least one reagent specific for the detection of the level of expression of at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9. In certain embodiments, the kits further comprise instructions for the diagnosis, monitoring, or characterization of prostate cancer based on the level of expression of the at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9. In certain embodiments, the kits further comprise instructions to detect the level of PSA in a sample in which the at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 is detected. In certain embodiments, the kits further comprise at least one reagent for the specific detection of PSA.

[0372] The invention provides kits comprising at least one reagent specific for the detection of a level of expression of at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 and at least one reagent specific for the detection of a level of expression of PSA.

[0373] In certain embodiments, the kits can also comprise, e.g., a buffering agents, a preservative, a protein stabilizing agent, reaction buffers. The kit can further comprise components necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. The controls can be control serum samples or control samples of purified proteins or nucleic acids, as appropriate, with known levels of target markers. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

[0374] The kits of the invention may optionally comprise additional components useful for performing the methods of the invention.

Panels

[0375] The invention provides panels of reagents for detection of one or more prostate-related marker in a subject sample and at least one control reagent. In certain embodiments, the control reagent is to detect the marker for detection in the biological sample wherein the panel is provided with a control sample containing the marker for use as a positive control and optionally to quantitate the amount of marker present in the biological sample. In certain embodiments, the panel includes a detection reagent for a maker not related to an abnormal prostate state that is known to be present or absent in the biological sample to provide a positive or negative control, respectively. The panel can be provided with reagents for detection of a control protein in the sample not related to the abnormal prostate state, e.g., actin for tissue samples, albumin in blood or blood derived samples for normalization of the amount of the marker present in the sample. The panel can be provided with a purified marker for detection for use as a control or for quantitation of the assay performed with the panel.

[0376] In a preferred embodiment, the panel includes reagents for detection of two or more markers of the invention (e.g., 2, 3, 4, 5, 6, 7, 8, 9), preferably in conjunction with a control reagent. In the panel, each marker is detected by a reagent specific for that marker. In certain embodiments, the panel further includes a reagent for the detection of PSA. In certain embodiments, the panel includes replicate wells, spots, or portions to allow for analysis of various dilutions (e.g., serial dilutions) of biological samples and control samples. In a preferred embodiment, the panel allows for quantitative detection of one or more markers of the invention.

[0377] In certain embodiments, the panel is a protein chip for detection of one or more markers. In certain embodiments,

the panel is an ELISA plate for detection of one or more markers. In certain embodiments, the panel is a plate for quantitative PCR for detection of one or more markers.

[0378] In certain embodiments, the panel of detection reagents is provided on a single device including a detection reagent for one or more markers of the invention and at least one control sample. In certain embodiments, the panel of detection reagents is provided on a single device including a detection reagent for two or more markers of the invention and at least one control sample. In certain embodiments, multiple panels for the detection of different markers of the invention are provided with at least one uniform control sample to facilitate comparison of results between panels.

Screening Assays

[0379] The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, i.e., candidate or test compounds or agents (e.g., proteins, peptides, peptidomimetics, peptoids, small molecules or other drugs), which modulate the state of the diseased cell by modulating the expression and/or activity of a marker of the invention, i.e., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, or LY9; optionally in combination with PSA. Such assays typically comprise a reaction between a marker of the invention and one or more assay components. The other components may be either the test compound itself, or a combination of test compounds and a natural binding partner of a marker of the invention. Compounds identified via assays such as those described herein may be useful, for example, for modulating, e.g., inhibiting, ameliorating, treating, or preventing the disease. Compounds identified for modulating the expression level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, or LY9; optionally in combination with PSA, are preferably further tested for activity useful in the treatment of cancer, preferably prostate cancer, e.g., inhibiting tumor cell growth, inhibiting tumor angiogenesis, inducing tumor cell apoptosis, etc.

[0380] The test compounds used in the screening assays of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, e.g., Zuckermann et al., 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

[0381] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop et al. (1994) *J. Med. Chem.* 37:1233.

[0382] Libraries of compounds may be presented in solution (e.g., Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, U.S. Pat. No. 5,223,409), plasmids (Cull et al, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* **249**:**386**-390; Devlin, 1990, *Science* 249:404-406; Cwirla et al, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, supra.).

[0383] The screening methods of the invention comprise contacting a cell, e.g., a diseased cell, especially a prostate cancer cell, with a test compound and determining the ability of the test compound to modulate the expression and/or activity of filamin B, LY9, or keratin 19, optionally in combination with PSA, in the cell. The expression and/or activity of filamin B, LY9, or keratin 19; optionally in combination with PSA, can be determined using any methods known in the art, such as those described herein.

[0384] In another embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a marker of the invention or biologically active portions thereof. In yet another embodiment, the invention provides assays for screening candidate or test compounds which bind to a marker of the invention or biologically active portions thereof. Determining the ability of the test compound to directly bind to a marker can be accomplished, for example, by any method known in the art.

[0385] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent capable of modulating the expression and/or activity of a marker of the invention identified as described herein can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment as described above.

[0386] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references and published patents and patent applications cited throughout the application are hereby incorporated by reference.

Exemplification of the Invention

[0387] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, GenBank Accession and Gene numbers, and published patents and patent applications cited throughout the application are hereby incorporated by reference.

Example 1

Identification of Keratins and Tubulin as Prostate Cancer Markers

[0388] Extracellular Keratins are known to influence the cell proliferation and metastasis of epithelial derived prostate cancers. Androgen refractory prostate cancers exhibit differ-

ential expression keratin 8 (K8) when compared to normal tissue. Modulation and degradation of keratins is in turn mediated by mitochondrial generation of Reactive Oxygen Species (ROS). Despite these advances a systematic approach to understanding of keratins and other EC proteins in prostate cancer metastasis and proliferation is lacking. An interrogative systems biology based discovery platform disclosed in WO2012119129 (incorporated herein by reference), and shown schematically in FIG. **1**, provides new mechanistic insights into understanding mitochondrial role in behavior of prostate cancer cells. The discovery platform involves discovery across a hierarchy of systems including in vitro human cell based models and human serum samples from prostate cancer patients and downstream data integration and mathematical modeling employing an Artificial Intelligence (AI) based informatic module. For cellular models, androgen sensitive LnCAP cell line and metastatic, androgen refractory PC3 cell line were treated with ubidecarenone (coenzyme Q10) in order to engage the mitochondrial machinery. Proteomic signatures were captured using a 2D LC-MS orbitrap technology. Total protein signatures were input to an AI based informatics module to generate causal protein networks (FIGS. **2**A-C). Wet lab assays that specifically measure mitochondrial ROS, ATP and caspase 3 activation confirmed changes in intracellular levels of these markers. Several novel protein causal interactions that govern induction of mitochondrial machinery by ubidecarenone in PC3 cells were observed. Causal protein maps revealed association of keratins 8 and 15 in PC3 models and not LnCAP. The keratin 8/15 association was lost upon treatment with ubidecarenone, and a direct association of keratins 7 and 15 was established (FIGS. **3**A-D). These results suggest that a change in the interaction among keratins 7, 8, and 15 is particularly useful in demonstrating a response to treatment or a change in prostate cancer status in a subject. Further, keratins 8 and 15 were differentially associated in the androgen refractory, metastatic PC3 cell line and the androgen sensitive LnCAP cell line. This indicates that keratins 8 and 15 could be useful do differentiate between prostate cancer states, e.g., between androgen sensitive and metastatic, androgen refractory prostate cancer.

[0389] An increase in the expression of keratin 19 in relation to prostate cancer was confirmed using a panel of serum samples from subjects suffering from prostate cancer as compared to an appropriate matched control population.

[0390] Thus novel mechanistic insight into prostate cancer proliferation and mitochondrial role in modulating metastasis was gained with a novel chemical systems biology approach.

[0391] The results provided herein demonstrate that modulation of keratin and potential causal association in androgen refractory prostate cancer was inferred by the Platform technology. This provides a potential mechanisms of keratin regulation in response to modulation of mitochondrial function was deciphered by the Platform technology. Thus, novel drivers of cancer pathophysiology were validated in patient serum samples.

Example 2

Identification of Filamin B as a Prostate Cancer Marker

[0392] An interrogative systems biology based discovery platform was used to obtain mechanistic insights into understanding mitochondrial role in behavior of prostate cancer cells. The Platform technology, which is described in detail in WO2012119129, involves discovery across a hierarchy of systems including in vitro human cell based models and human serum samples from prostate cancer patients and downstream data integration and mathematical modeling employing an Artificial Intelligence (AI) based informatics module.

[0393] The results provided herein demonstrate the modulation of filamin B and LY9, and potential causal association in androgen refractory prostate cancer that was inferred using the Platform technology. The application provides potential mechanisms of filamin B and LY9 regulation in response to modulation of mitochondrial function was deciphered by the Platform technology and provides validation of the markers in patient serum samples.

[0394] Using the Platform methods, human prostate cancer cells PC3 (androgen insensitive, metastatic) and LnCap (androgen sensitive) were modeled in cancer microenvironments including hypoxia, reduced environments, and hyperglycemia and in presence of coenzyme Q10. Normal cells (human dermal fibroblasts (HDFa) and SV40 transformed human liver cells (THLE2)) were modeled under similar conditions mentioned above. Proteomics of cellular proteins and proteins secreted in the supernatant were carried out by LCMS. Data were input into the Bayesian Network Inference (BNI) algorithms REFS™.

[0395] Causal associations between proteins were derived by the BNI. Differential network analysis was employed to tease out the hubs of activity in prostate cancer when compared to normal cells in normal microenviroments. Filamin B was identified as differential hub of activity in PC3 and not in LnCap and normal cells. That is, Filamin B was found to differ between androgen sensitive LnCAP cell line and metastatic, androgen refractory PC3 cell line. This indicates that Filamin B could be useful do differentiate between prostate cancer states, e.g., between androgen sensitive and metastatic, androgen refractory prostate cancer. The interaction matrix placing filamin B at the center of an interaction hub is shown in FIG. **4**. The interaction of LY9 with filamin B is shown in FIG. **5**.

Example 3

Validation of Filamin B as a Prostate Cancer Marker in Human Samples

[0396] Having identified filamin B as a prostate cancer marker using the platform technology, human serum samples from normal subjects and subjects with prostate cancer were used to confirm filamin B as a prostate cancer marker.

[0397] Specifically, human serum samples were procured from a commercial vendor that sources human serum. Twenty samples were from normal donors and 20 samples were from patients diagnosed with prostate cancer. Prostate cancer samples were from patients with different prognosis and aggressiveness of cancers reported. Clinical characteristics of the subjects are provided in the table.

	Prostate Cancer	Control Group
Median Age	61 (47-86)	58 (45-72)
Ethnicity		
Caucasian	75%	85%
African American	15%	10%
Hispanic	10%	5%

-continued

	Prostate Cancer	Control Group
Tumor Stage		
Stage I	20%	
Stage II	35%	
Stage III	5%	
Stage IV	40%	

[0398] Commercially available ELISA tests for filamin B and PSA were procured from commercial source. The assays were performed using the manufactures' instructions. The results from the assay are shown in FIGS. **6**A-B. The results show the differential levels of FlnB and PSA in patients with a diagnosis for prostate cancer as compared to control subjects without prostate cancer.

[0399] As shown, both filamin B and PSA levels were elevated in serum samples from patients diagnosed with prostate cancer. The correlation between PSA and FlnB expression in serum samples is 0.20075, indicating a relatively low correlation between the variables. This demonstrates that filamin B and PSA are useful for the detection of prostate cancer in different subjects. These results demonstrate that filamin B is useful for the diagnosis of prostate cancer, and that filamin B is useful for improving the detection of prostate cancer by PSA. Additional samples can be analyzed to further refine the results.

Example 4

Stratification of Subjects with Prostate Cancer using LY9

[0400] The same human serum samples used in Example 4 were further tested to detect the presence of LY9. A commercially available ELISA test for LY9 was procured from commercial source. The assay was performed using the manufactures' instructions. The results from the assay are shown in FIG. **7**. The results show the differential levels of LY9 in patients with a diagnosis for prostate cancer as compared to control subjects without prostate cancer. As shown, samples from subjects with prostate cancer were found to have higher levels of LY9 as compared to normal subjects. Results from assays of expression levels of both filamin B and LY9 in human serum with results expressed as ng/ml of protein are shown in FIGS. **8**A-C. Additional samples can be analyzed to further refine the results.

Example 5

Analysis of Filamin B Levels Improves the Detection of Prostate Cancer as Compared to PSA Alone

[0401] Having demonstrated that level of filamin B is increased in the serum of subjects with prostate cancer, the results were analyzed in conjunction with the study of PSA levels in the same samples to determine the predictive value of filamin B and PSA together was better than either of the markers alone. Receiver operating characteristic (ROC) curve analysis of sensitivity and false positive rate (FPR) of PSA, filamin B, and the combination of PSA and filamin B was generated. The curves and the area under the curve (AUC) values are shown in FIGS. **9**A and B. The goal of this analysis is to gauge the predictive power of the test independent of a specific cut-off. When using an ROC analysis, a test that provides perfect discrimination or accuracy between normal and disease states would have AUC=1, whereas a very poor test that provides no better discrimination than random chance would have AUC=0.5

[0402] As demonstrated by the analysis, filamin B alone performs very well and most importantly somewhat orthogonal to PSA. PSA is reported to have a very high false positive rate, e.g., about 75% (as reported in, Gilligan, The new data on prostate cancer screening: What should we do now? Cleveland Clin. J. Med. 76: 446-448, 2009, incorporated herein by reference). That is, it has a high sensitivity and low specificity. In the specific study presented, the AUC for FLNB is lower than that for PSA. However, the correlation level of 0.20075 determined in Example 3, indicates a relatively low correlation between the variables. That is, subjects identified as having an elevated filamin B level did not necessarily have a high PSA level, and the reverse was also true, suggesting that the markers in combination can provide a predictive test than either marker alone.

[0403] This was confirmed in the ROC analysis. As shown, the combination of PSA and filamin B was found to have a higher AUC indicating better discrimination of the test than PSA alone, and to be more predictive than either of the markers alone. The combination of PSA and filamin B is very good and provides a drastic increase PSA test specificity, which is the main problem with the test.

Example 6

Analysis of Filamin B, LY9, and PSA Levels Together Improves the Detection of Prostate Cancer as Compared to any Marker Alone

[0404] Having demonstrated that each filamin B, LY9, and PSA are all elevated in serum samples from subjects with prostate cancer, the ROC curve analysis was performed comparing each of the three markers individually to the combination of all three markers using a linear scoring function, and comparing the combination of filamin B and LY9, and the combination of filamin B and PSA, against the combination of all three markers using a non-linear scoring function to determine which combinations of the markers were more effective than each single marker for the detection of prostate cancer in a subject. As shown, the combination of all three markers was more predictive than any of the markers alone (FIG. **10**A). The combination of filamin B with PSA, either with or without LY9, was more predictive than the combination of filamin B with LY9 (FIG. **10**B). Additional samples can be analyzed to further refine the results. The AUC results are summarized in the table.

Marker	AUC
LY9	0.85
FLNB	0.78
PSA	0.87
LY9 + FLNB + PSA	0.98

Example 7

Stratification of Subjects with Prostate Cancer using Keratin 4, Keratin 7, Keratin 8, Keratin 15, Keratin 18, Keratin 19, Tubulin-beta 3

[0405] As demonstrated in Examples 3 and 4 respectively, filamin B levels and LY9 levels can be used to distinguish

subjects who are or are not suffering from prostate cancer. Further, as demonstrated in Examples 6 and 7, the analysis of both filamin B and PSA, optionally further in combination with LY9, is more sensitive than an analysis based on either marker alone.

[0406] A series of subject samples are obtained from an appropriate source, e.g., a commercial source, wherein the samples were obtained from subjects with different stages of prostate cancer, e.g., aggressive prostate cancer, androgen sensitive, androgen insensitive, metastatic; or from subjects not suffering from prostate cancer, e.g., subjects with normal prostate or subjects with BPH. The samples are analyzed for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. The level of the expression of the makers, alone and in various combinations, correlate with the presence or absence of disease, and with the severity of prostate cancer. For example, an increase in the expression level of one or more of keratin 19, filamin B, LY9, and PSA, as compared to a normal sample from a subject not suffering from prostate cancer, is indicative of prostate cancer in the subject. Expression levels of keratins 7, 8, and 15 may also be particularly useful in the stratification of subjects with prostate cancer.

Example 8

Monitoring of Prostate Cancer Treatment using Keratin 4, Keratin 7, Keratin 8, Keratin 15, Keratin 18, Keratin 19, Tubulin-beta 3

[0407] At the time of diagnosis with prostate cancer, subjects are invited to participate in a trial. A subject sample, e.g., blood, is obtained. Periodically, throughout the monitoring, watchful waiting, or active treatment of the subject, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, a new subject sample is obtained. At the end of the study, all subject samples are tested for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. The subject samples are matched to the medical records of the subjects to correlate marker levels with prostate cancer status at the time of diagnosis, rate of progression of disease, response of subjects to one or more interventions, and transitions between androgen dependent and independent status. An increase in the expression level of one or more of keratin 19, filamin B, LY9, and PSA, as compared to a normal sample from a subject not suffering from prostate cancer, is indicative of prostate cancer in the subject. Expression levels of keratins 7, 8, and 15 may also be particularly useful in the diagnosis and monitoring of subjects with prostate cancer.

Example 9

Detection and Monitoring of Prostate Cancer using keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3

[0408] Despite its limitations, including a positive predictive value of only 25-40%, PSA remains the only generally accepted biomarker for prostate cancer. Moreover, as prostate cancer is most commonly a slow growing tumor in men of advanced age, treatment of the cancer may do more harm to the subject than the tumor itself would. Therefore, the tests together for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA are used for the detection an monitoring of prostate cancer. The level of the expression of the makers, alone and in various combinations are used in detection, including in routine, preventative, screening methods in men having an increased risk of prostate cancer (e.g., increased age, family history, race, etc.) or in monitoring of subjects diagnosed with prostate cancer prior to or during treatment may be useful to better identify subjects in need of further, potentially more invasive, diagnostic tests, e.g., prostate exam or biopsy, digital rectal exam; or more aggressive treatment. Detection of levels of expression of the markers, or various combinations thereof, may also be indicative of a good or poor response to a specific treatment regimen prior to changes in other signs or symptoms, e.g., loss of tumor response to hormone therapy.

[0409] In routine screening methods for prostate cancer, a serum sample from a subject is tested for the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. The levels are compared to one or more appropriate controls, e.g., other normal subjects, subjects with prostate cancer. Detection of an abnormal level of one or more of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19; indicates that the subject should be considered for further tests for the presence of prostate cancer. Changes in the level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19, in the subject may be more indicative of a change in prostate cancer status than comparison to a population control.

[0410] In determining a therapeutic regimen for a subject with prostate cancer not yet being actively treated for prostate cancer (i.e., watchful waiting) can be tested at regular intervals to determine if there is a change in the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. An modulation in the level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA indicates that the subject should be considered for further tests to monitor the prostate cancer and more active therapeutic interventions should be considered.

[0411] In a subject undergoing treatment for prostate cancer (e.g., hormone therapy, chemotherapy, radiation therapy, surgery) is tested prior to the initiation of the treatment and during and/or after the treatment to determine if the treatment results in a decrease in the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. A decrease in the level of keratin 19, filamin B, LY9, or PSA is indicative of response to treatment.

Expression levels of keratins 7, 8, and 15 may also be particularly useful in the diagnosis and monitoring of subjects with prostate cancer.

Example 10

Stratification of Subjects with Prostate Cancer using Filamin B, PSA, or LY9

[0412] As demonstrated in Examples 3 and 4 respectively, filamin B levels and LY9 levels can be used to distinguish subjects who are or are not suffering from prostate cancer. Further, as demonstrated in Examples 6 and 7, the analysis of both filamin B and PSA, optionally further in combination with LY9, is more sensitive than an analysis based on either marker alone.

[0413] A series of subject samples are obtained from an appropriate source, e.g., a commercial source, wherein the samples were obtained from subjects with different stages of prostate cancer, e.g., aggressive prostate cancer, androgen sensitive, androgen insensitive, metastatic; or from subjects not suffering from prostate cancer, e.g., subjects with normal prostate or subjects with BPH. The samples are analyzed for the expression level of filamin B and PSA, and optionally the level of LY9, and further with one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19. The level of filamin B, LY9, and PSA, alone and in various combinations, optionally with other markers, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, correlate with the presence or absence of disease, and with the severity of prostate cancer.

Example 11

Monitoring of Prostate Cancer Treatment using Filamin B, PSA, or LY9

[0414] At the time of diagnosis with prostate cancer, subjects are invited to participate in a trial. A subject sample, e.g., blood, is obtained. Periodically, throughout the monitoring, watchful waiting, or active treatment of the subject, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, a new subject sample is obtained. At the end of the study, all subject samples are tested for the level of filamin B, PSA, and optionally in further combination with one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. The subject samples are matched to the medical records of the subjects to correlate filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, or tubulin-beta 3 levels, as appropriate, with prostate cancer status at the time of diagnosis, rate of progression of disease, response of subjects to one or more interventions, and transitions between androgen dependent and independent status.

Example 12

Detection and Monitoring of Prostate Cancer using Filamin B, PSA, or LY9

[0415] Despite its limitations, including a positive predictive value of only 25-40%, PSA remains the only generally accepted biomarker for prostate cancer. Moreover, as prostate cancer is most commonly a slow growing tumor in men of advanced age, treatment of the cancer may do more harm to the subject than the tumor itself would. As demonstrated herein, there is a low correlation between elevated levels of filamin B and PSA in subjects with prostate cancer. Further, elevated levels of LY9 have been demonstrated to be associated with prostate cancer. Therefore, the tests together, particularly filamin B and PSA, optionally in combination with one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, in detection, including in routine, preventative, screening methods in men having an increased risk of prostate cancer (e.g., increased age, family history, race, etc.) or in monitoring of subjects diagnosed with prostate cancer prior to or during treatment may be useful to better identify subjects in need of further, potentially more invasive, diagnostic tests, e.g., prostate exam or biopsy, digital rectal exam; or more aggressive treatment. Detection of levels of expression of filamin B, PSA, LY9 keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, may also be indicative of a good or poor response to a specific treatment regimen prior to changes in other signs or symptoms, e.g., loss of tumor response to hormone therapy.

[0416] In routine screening methods for prostate cancer, a serum sample from a subject is tested for the level of expression of both filamin B and PSA, and optionally one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19. The levels are compared to one or more appropriate controls, e.g., other normal subjects, subjects with prostate cancer. Detection of an abnormal level of one or more of filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19 indicates that the subject should be considered for further tests for the presence of prostate cancer. Changes in the level of filamin B, optionally in combination with one or more of PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, or tubulin-beta 3, especially keratin 19 with PSA in the subject may be more indicative of a change in prostate cancer status than comparison to a population control.

[0417] In determining a therapeutic regimen for a subject with prostate cancer not yet being actively treated for prostate cancer (i.e., watchful waiting) can be tested at regular intervals to determine if there is a change in the level of expression of filamin B, PSA, LY9 keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. An increase in the level of filamin B, PSA, keratin 19, or LY9 indicates that the subject should be considered for further tests to monitor the prostate cancer and more active therapeutic interventions should be considered.

[0418] In a subject undergoing treatment for prostate cancer (e.g., hormone therapy, chemotherapy, radiation therapy, surgery) is tested prior to the initiation of the treatment and during and/or after the treatment to determine if the treatment results in a change in the level of expression of one or more of filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. A decrease in the level of filamin B, PSA, keratin 19, or LY9 is indicative of response to treatment.

EQUIVALENTS

[0419] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

SEQUENCE LISTING

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Val Ser Met Ser Gly Gly Ala Gly Arg Cys Ser Ser Gly Gly Phe Gly
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Ser Arg Ser Leu Tyr Asn Leu Arg Gly Asn Lys Ser Ile Ser Met Ser
    50                  55                  60

Val Ala Gly Ser Arg Gln Gly Ala Cys Phe Gly Gly Ala Gly Gly Phe
65                  70                  75                  80

Gly Thr Gly Gly Phe Gly Gly Gly Phe Gly Gly Ser Phe Ser Gly Lys
                85                  90                  95

Gly Gly Pro Gly Phe Pro Val Cys Pro Ala Gly Gly Ile Gln Glu Val
            100                 105                 110

Thr Ile Asn Gln Ser Leu Leu Thr Pro Leu His Val Glu Ile Asp Pro
        115                 120                 125

Glu Ile Gln Lys Val Arg Thr Glu Glu Arg Glu Gln Ile Lys Leu Leu
    130                 135                 140

Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Gln Phe Leu Glu Gln
145                 150                 155                 160

Gln Asn Lys Val Leu Glu Thr Lys Trp Asn Leu Leu Gln Gln Gln Thr
                165                 170                 175

Thr Thr Thr Ser Ser Lys Asn Leu Glu Pro Leu Phe Glu Thr Tyr Leu
            180                 185                 190

Ser Val Leu Arg Lys Gln Leu Asp Thr Leu Gly Asn Asp Lys Gly Arg
        195                 200                 205

Leu Gln Ser Glu Leu Lys Thr Met Gln Asp Ser Val Glu Asp Phe Lys
    210                 215                 220

Thr Lys Tyr Glu Glu Glu Ile Asn Lys Arg Thr Ala Ala Glu Asn Asp
225                 230                 235                 240

Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Leu Asn Lys Val
                245                 250                 255

Glu Leu Glu Ala Lys Val Asp Ser Leu Asn Asp Glu Ile Asn Phe Leu
            260                 265                 270

Lys Val Leu Tyr Asp Ala Glu Leu Ser Gln Met Gln Thr His Val Ser
        275                 280                 285

Asp Thr Ser Val Val Leu Ser Met Asp Asn Asn Arg Asn Leu Asp Leu
    290                 295                 300

Asp Ser Ile Ile Ala Glu Val Arg Ala Gln Tyr Glu Glu Ile Ala Gln
305                 310                 315                 320

Arg Ser Lys Ala Glu Ala Glu Ala Leu Tyr Gln Thr Lys Val Gln Gln
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Leu Gln Ile Ser Val Asp Gln His Gly Asp Asn Leu Lys Asn Thr Lys
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Ser Glu Ile Ala Glu Leu Asn Arg Met Ile Gln Arg Leu Arg Ala Glu
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Ile Glu Asn Ile Lys Lys Gln Cys Gln Thr Leu Gln Val Ser Val Ala
    370                 375                 380

Asp Ala Glu Gln Arg Gly Glu Asn Ala Leu Lys Asp Ala His Ser Lys
385                 390                 395                 400

Arg Val Glu Leu Glu Ala Ala Leu Gln Gln Ala Lys Glu Glu Leu Ala
                405                 410                 415

Arg Met Leu Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala Leu
            420                 425                 430

Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Tyr
        435                 440                 445

Arg Met Ser Gly Glu Cys Gln Ser Ala Val Ser Ile Ser Val Val Ser
    450                 455                 460

Gly Ser Thr Ser Thr Gly Gly Ile Ser Gly Gly Leu Gly Ser Gly Ser
465                 470                 475                 480

Gly Phe Gly Leu Ser Ser Gly Phe Gly Ser Gly Ser Gly Ser Gly Phe
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Gly Leu Gly Ser Ser Ser Leu Tyr Gly Leu Gly Ala Ser Arg Pro Arg
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Val Ala Val Arg Ser Ala Tyr Gly Gly Pro Val Gly Ala Gly Ile Arg
    50                  55                  60

Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala
65                  70                  75                  80

Asp Pro Ser Leu Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys
                85                  90                  95

Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
            100                 105                 110

Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu
        115                 120                 125

Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln
    130                 135                 140

Ile Ala Gly Leu Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly
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Arg Leu Glu Ala Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe
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Glu Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys
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Val Glu Leu Glu Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe
    210                 215                 220

Leu Arg Thr Leu Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile
225                 230                 235                 240

Ser Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp
                245                 250                 255

Leu Asp Gly Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala
            260                 265                 270

Lys Cys Ser Arg Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu
        275                 280                 285

Thr Leu Gln Ala Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr
    290                 295                 300

Arg Asn Glu Ile Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala
305                 310                 315                 320

Glu Ile Asp Asn Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile
                325                 330                 335

Ala Glu Ala Glu Glu Arg Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala
            340                 345                 350

Lys Gln Glu Glu Leu Glu Ala Ala Leu Gln Arg Gly Lys Gln Asp Met
        355                 360                 365

Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala
    370                 375                 380

Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu
385                 390                 395                 400

Ser Arg Leu Ala Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met
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Asn Ser Thr Gly Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu
            420                 425                 430

Gly Gly Thr Met Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly
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Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly Gly Leu Gly Gly
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Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr Ala Val Thr Val
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Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val Asp Pro Asn Ile
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Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln Gln Lys Thr Ala
145                 150                 155                 160

Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile Asn Asn Leu Arg
                165                 170                 175

Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys Leu Glu Ala Glu
            180                 185                 190

Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys Asn Lys Tyr Glu
        195                 200                 205

Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu Phe Val Leu Ile
    210                 215                 220

Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val Glu Leu Glu Ser
225                 230                 235                 240

Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu Arg Gln Leu Tyr
                245                 250                 255

Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser Asp Thr Ser Val
            260                 265                 270

Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met Asp Ser Ile Ile
        275                 280                 285

Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn Arg Ser Arg Ala
    290                 295                 300

Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu Leu Gln Ser Leu
305                 310                 315                 320

Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys Thr Glu Ile Ser
                325                 330                 335

Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu Ile Glu Gly Leu
            340                 345                 350

Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala Asp Ala Glu Gln
        355                 360                 365

Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys Leu Ser Glu Leu
    370                 375                 380

Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala Arg Gln Leu Arg
385                 390                 395                 400

Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu Asp Ile Glu Ile
                405                 410                 415

Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser Arg Leu Glu Ser
            420                 425                 430

Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr Ser Gly Tyr Ala
        435                 440                 445

Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser Pro Gly Leu Ser
    450                 455                 460

Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly Ser Ser Ser Phe
465                 470                 475                 480

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tctccgcctg gttcggcccg cctgcctcca ctcctgcctc taccatgtcc atcagggtga 120

cccagaagtc ctacaaggtg tccacctctg gcccccgggc cttcagcagc cgctcctaca 180

cgagtgggcc cggttcccgc atcagctcct cgagcttctc ccgagtgggc agcagcaact 240

ttcgcggtgg cctgggcggc ggctatggtg gggccagcgg catgggaggc atcaccgcag 300

ttacggtcaa ccagagcctg ctgagccccc ttgtcctgga ggtggacccc aacatccagg 360

ccgtgcgcac ccaggagaag gagcagatca agaccctcaa caacaagttt gcctccttca 420

tagacaaggt acggttcctg gagcagcaga acaagatgct ggagaccaag tggagcctcc 480

tgcagcagca gaagacggct cgaagcaaca tggacaacat gttcgagagc tacatcaaca 540

accttaggcg gcagctggag actctgggcc aggagaagct gaagctggag gcggagcttg 600

gcaacatgca ggggctggtg gaggacttca agaacaagta tgaggatgag atcaataagc 660

gtacagagat ggagaacgaa tttgtcctca tcaagaagga tgtggatgaa gcttacatga 720

acaaggtaga gctggagtct cgcctggaag ggctgaccga cgagatcaac ttcctcaggc 780

agctatatga agaggagatc cgggagctgc agtcccagat ctcggacaca tctgtggtgc 840

tgtccatgga caacagccgc tccctggaca tggacagcat cattgctgag gtcaaggcac 900

agtacgagga tattgccaac cgcagccggg ctgaggctga gagcatgtac cagatcaagt 960

atgaggagct gcagagcctg gctgggaagc acggggatga cctgcggcgc acaaagactg 1020

agatctctga gatgaaccgg aacatcagcc ggctccaggc tgagattgag ggcctcaaag 1080

gccagagggc ttccctggag gccgccattg cagatgccga gcagcgtgga gagctggcca 1140

ttaaggatgc caacgccaag ttgtccgagc tggaggccgc cctgcagcgg gccaagcagg 1200

acatggcgcg gcagctgcgt gagtaccagg agctgatgaa cgtcaagctg gccctggaca 1260

tcgagatcgc cacctacagg aagctgctgg agggcgagga gagccggctg gagtctggga 1320

tgcagaacat gagtattcat acgaagacca ccagcggcta tgcaggtggt ctgagctcgg 1380

cctatggggg cctcacaagc cccggcctca gctacagcct gggctccagc tttggctctg 1440

gcgcgggctc cagctccttc agccgcacca gctcctccag ggccgtggtt gtgaagaaga 1500

tcgagacacg tgatgggaag ctggtgtctg agtcctctga cgtcctgccc aagtgaacag 1560

ctgcggcagc ccctcccagc ctacccctcc tgcgctgccc cagagcctgg gaaggaggcc 1620

gctatgcagg gtagcactgg gaacaggaga cccacctgag gctcagccct agccctcagc 1680

ccacctgggg agtttactac ctggggaccc cccttgccca tgcctccagc tacaaaacaa 1740

ttcaattgct ttttttttttt ggtccaaaat aaaacctcag ctagctctgc caatgtcaaa 1800

aaaaaaa 1807

<210> SEQ ID NO 7
<211> LENGTH: 483
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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Met Ser Ile Arg Val Thr Gln Lys Ser Tyr Lys Val Ser Thr Ser Gly
1               5                  10                  15

Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg
            20                  25                  30

Ile Ser Ser Ser Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly
        35                  40                  45

Gly Leu Gly Gly Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr
    50                  55                  60

Ala Val Thr Val Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val
65                  70                  75                  80

Asp Pro Asn Ile Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys
                85                  90                  95

Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
            100                 105                 110

Glu Gln Gln Asn Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln
        115                 120                 125

Gln Lys Thr Ala Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile
    130                 135                 140

Asn Asn Leu Arg Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys
145                 150                 155                 160

Leu Glu Ala Glu Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys
                165                 170                 175

Asn Lys Tyr Glu Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu
            180                 185                 190

Phe Val Leu Ile Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val
        195                 200                 205

Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu
    210                 215                 220

Arg Gln Leu Tyr Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser
225                 230                 235                 240

Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met
                245                 250                 255

Asp Ser Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn
            260                 265                 270

Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu
        275                 280                 285

Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys
    290                 295                 300

Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu
305                 310                 315                 320

Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala
                325                 330                 335

Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys
            340                 345                 350

Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala
        355                 360                 365

Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu
    370                 375                 380

Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser
385                 390                 395                 400

Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr
                405                 410                 415
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Ser Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser
            420                 425                 430

Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly
        435                 440                 445

Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys
    450                 455                 460

Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val
465                 470                 475                 480

Leu Pro Lys


<210> SEQ ID NO 8
<211> LENGTH: 1901
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

acaggccttt ccttacctcc ctccatgctg tccacttcct ctgtaaagct ctcaaccctg     60

tcccccttccc cctctctcct gggaaagagc cctcccatgc ctagctgctg ctcttaggga    120

ccctgtggct aggtgcgcgg atggaaatcc aggatctccg cctggttcgg cccgcctgcc    180

tccactcctg cctctaccat gtccatcagg gtgacccaga agtcctacaa ggtgtccacc    240

tctggccccc gggccttcag cagccgctcc tacacgagtg ggcccggttc ccgcatcagc    300

tcctcgagct tctcccgagt gggcagcagc aactttcgcg gtggcctggg cggcggctat    360

ggtggggcca gcggcatggg aggcatcacc gcagttacgg tcaaccagag cctgctgagc    420

ccccttgtcc tggaggtgga ccccaacatc caggccgtgc gcacccagga gaaggagcag    480

atcaagaccc tcaacaacaa gtttgcctcc ttcatagaca aggtacggtt cctggagcag    540

cagaacaaga tgctggagac caagtggagc ctcctgcagc agcagaagac ggctcgaagc    600

aacatggaca acatgttcga gagctacatc aacaacctta ggcggcagct ggagactctg    660

ggccaggaga agctgaagct ggaggcggag cttggcaaca tgcaggggct ggtggaggac    720

ttcaagaaca agtatgagga tgagatcaat aagcgtacag agatggagaa cgaatttgtc    780

ctcatcaaga aggatgtgga tgaagcttac atgaacaagg tagagctgga gtctcgcctg    840

gaagggctga ccgacgagat caacttcctc aggcagctat atgaagagga gatccgggag    900

ctgcagtccc agatctcgga cacatctgtg gtgctgtcca tggacaacag ccgctccctg    960

gacatggaca gcatcattgc tgaggtcaag gcacagtacg aggatattgc caaccgcagc   1020

cgggctgagg ctgagagcat gtaccagatc aagtatgagg agctgcagag cctggctggg   1080

aagcacgggg atgacctgcg gcgcacaaag actgagatct ctgagatgaa ccggaacatc   1140

agccggctcc aggctgagat tgagggcctc aaaggccaga gggcttccct ggaggccgcc   1200

attgcagatg ccgagcagcg tggagagctg gccattaagg atgccaacgc caagttgtcc   1260

gagctggagg ccgccctgca gcgggccaag caggacatgg cgcggcagct gcgtgagtac   1320

caggagctga tgaacgtcaa gctggccctg gacatcgaga tcgccaccta caggaagctg   1380

ctggagggcg aggagagccg gctggagtct gggatgcaga acatgagtat tcatacgaag   1440

accaccagcg gctatgcagg tggtctgagc tcggcctatg ggggcctcac aagccccggc   1500

ctcagctaca gcctgggctc cagctttggc tctggcgcgg gctccagctc cttcagccgc   1560

accagctcct ccagggccgt ggttgtgaag aagatcgaga cacgtgatgg gaagctggtg   1620
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tctgagtcct ctgacgtcct gcccaagtga acagctgcgg cagcccctcc cagcctaccc 1680

ctcctgcgct gccccagagc ctgggaagga ggccgctatg cagggtagca ctgggaacag 1740

gagacccacc tgaggctcag ccctagccct cagcccacct ggggagttta ctacctgggg 1800

acccccccttg cccatgcctc cagctacaaa acaattcaat tgctttttt ttttggtcca 1860

aaataaaacc tcagctagct ctgccaatgt caaaaaaaaa a 1901

<210> SEQ ID NO 9
<211> LENGTH: 456
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Thr Thr Thr Phe Leu Gln Thr Ser Ser Ser Thr Phe Gly Gly Gly
1 5 10 15

Ser Thr Arg Gly Gly Ser Leu Leu Ala Gly Gly Gly Gly Phe Gly Gly
20 25 30

Gly Ser Leu Ser Gly Gly Gly Gly Ser Arg Ser Ile Ser Ala Ser Ser
35 40 45

Ala Arg Phe Val Ser Ser Gly Ser Gly Gly Gly Tyr Gly Gly Gly Met
50 55 60

Arg Val Cys Gly Phe Gly Gly Gly Ala Gly Ser Val Phe Gly Gly Gly
65 70 75 80

Phe Gly Gly Gly Val Gly Gly Gly Phe Gly Gly Gly Phe Gly Gly Gly
85 90 95

Asp Gly Gly Leu Leu Ser Gly Asn Glu Lys Ile Thr Met Gln Asn Leu
100 105 110

Asn Asp Arg Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Glu
115 120 125

Ala Asn Ala Asp Leu Glu Val Lys Ile His Asp Trp Tyr Gln Lys Gln
130 135 140

Thr Pro Thr Ser Pro Glu Cys Asp Tyr Ser Gln Tyr Phe Lys Thr Ile
145 150 155 160

Glu Glu Leu Arg Asp Lys Ile Met Ala Thr Thr Ile Asp Asn Ser Arg
165 170 175

Val Ile Leu Glu Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg
180 185 190

Leu Lys Tyr Glu Asn Glu Leu Ala Leu Arg Gln Gly Val Glu Ala Asp
195 200 205

Ile Asn Gly Leu Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr
210 215 220

Asp Leu Glu Met Gln Ile Glu Gly Leu Asn Glu Glu Leu Ala Tyr Leu
225 230 235 240

Lys Lys Asn His Glu Glu Glu Met Lys Glu Phe Ser Ser Gln Leu Ala
245 250 255

Gly Gln Val Asn Val Glu Met Asp Ala Ala Pro Gly Val Asp Leu Thr
260 265 270

Arg Val Leu Ala Glu Met Arg Glu Gln Tyr Glu Ala Met Ala Glu Lys
275 280 285

Asn Arg Arg Asp Val Glu Ala Trp Phe Phe Ser Lys Thr Glu Glu Leu
290 295 300

Asn Lys Glu Val Ala Ser Asn Thr Glu Met Ile Gln Thr Ser Lys Thr
305 310 315 320

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Glu Ile Thr Asp Leu Arg Arg Thr Met Gln Glu Leu Glu Ile Glu Leu
                325                 330                 335

Gln Ser Gln Leu Ser Met Lys Ala Gly Leu Glu Asn Ser Leu Ala Glu
            340                 345                 350

Thr Glu Cys Arg Tyr Ala Thr Gln Leu Gln Gln Ile Gln Gly Leu Ile
        355                 360                 365

Gly Gly Leu Glu Ala Gln Leu Ser Glu Leu Arg Cys Glu Met Glu Ala
    370                 375                 380

Gln Asn Gln Glu Tyr Lys Met Leu Leu Asp Ile Lys Thr Arg Leu Glu
385                 390                 395                 400

Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu Glu Gly Gln Asp Ala Lys
                405                 410                 415

Met Ala Gly Ile Gly Ile Arg Glu Ala Ser Ser Gly Gly Gly Gly Ser
            420                 425                 430

Ser Ser Asn Phe His Ile Asn Val Glu Glu Ser Val Asp Gly Gln Val
        435                 440                 445

Val Ser Ser His Lys Arg Glu Ile
    450                 455


<210> SEQ ID NO 10
<211> LENGTH: 1861
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

cactcaaggt gtgcaggcag ctgtgtttgt caggaaggca gaaggagttg gctttgcttt     60

aggggaggag acgaggtccc acaacaccct ctgaagggta tataaggagc cccagcgtgc    120

agcctggcct ggtacctcct gccagcatct cttgggtttg ctgagaactc acgggctcca    180

gctacctggc catgaccacc acatttctgc aaacttcttc ctccaccttt gggggtggct    240

caacccgagg gggttccctc ctggctgggg gaggtggctt tggtgggggg agtctctctg    300

ggggaggtgg aagccgaagt atctcagctt cttctgctag gtttgtctct tcagggtcag    360

gaggaggata tgggggtggc atgagggtct gtggctttgg tggaggggct ggtagtgttt    420

tcggtggagg ctttggaggg ggcgttggtg ggggttttgg tggtggcttt ggtggtggcg    480

atggtggtct cctctctggc aatgagaaaa ttaccatgca gaacctcaat gaccgcctgg    540

cctcctacct ggacaaggta cgtgccctgg aggaggccaa tgctgacctg gaggtgaaga    600

tccatgactg gtaccagaag cagaccccaa ccagcccaga atgcgactac agccaatact    660

tcaagaccat tgaagagctc cgggacaaga tcatggccac caccatcgac aactcccggg    720

tcatcctgga gatcgacaat gccaggctgg ctgcggacga cttcaggctc aagtatgaga    780

atgagctggc cctgcgccag ggcgttgagg ctgacatcaa cggcttgcgc cgagtcctgg    840

atgagctgac cctggccagg actgacctgg agatgcagat cgagggcctg aatgaggagc    900

tagcctacct gaagaagaac cacgaagagg agatgaagga gttcagcagc cagctggccg    960

gccaggtcaa tgtggagatg gacgcagcac cgggtgtgga cctgacccgt gtgctggcag   1020

agatgaggga gcagtacgag gccatggcgg agaagaaccg ccgggatgtc gaggcctggt   1080

tcttcagcaa gactgaggag ctgaacaaag aggtggcctc caacacagaa atgatccaga   1140

ccagcaagac ggagatcaca gacctgagac gcacgatgca ggagctggag atcgagctgc   1200

agtcccagct cagcatgaaa gctgggctgg agaactcact ggccgagaca gagtgccgct   1260
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atgccacgca gctgcagcag atccaggggc tcattggtgg cctggaggcc cagctgagtg 1320

agctccgatg cgagatggag gctcagaacc aggagtacaa gatgctgctt gacataaaga 1380

cacggctgga gcaggagatc gctacttacc gcagcctgct cgagggccag gatgccaaga 1440

tggctggcat tggcatcagg gaagcctctt caggaggtgg tggtagcagc agcaatttcc 1500

acatcaatgt agaagagtca gtggatggac aggtggtttc ttcccacaag agagaaatct 1560

aagtgtctat tgcaggagaa acgtcccttg ccactcccca ctctcatcag gccaagtgga 1620

ggactggcca gagggcctgc acatgcaaac tccagtccct gccttcagag agctgaaaag 1680

ggtccctcgg tcttttattt cagggctttg catgcgctct attccccctc tgcctctccc 1740

caccttcttt ggagcaagga gatgcagctg tattgtgtaa caagctcatt tgtacagtgt 1800

ctgttcatgt aataaagaat tacttttcct tttgcaaata aaaaaaaaaa aaaaaaaaaa 1860

a 1861

<210> SEQ ID NO 11
<211> LENGTH: 430
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu
1 5 10 15

Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala
20 25 30

Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val
35 40 45

Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
50 55 60

Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
65 70 75 80

Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
100 105 110

Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His
115 120 125

Tyr Phe Lys Ile Ile Glu Asp Leu Arg Ala Gln Ile Phe Ala Asn Thr
130 135 140

Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala
145 150 155 160

Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln
165 170 175

Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr
180 185 190

Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu
195 200 205

Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu
210 215 220

Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro
225 230 235 240

Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr

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               245                 250                 255

Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser
            260                 265                 270

Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu
        275                 280                 285

Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln
    290                 295                 300

Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu
305                 310                 315                 320

Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu
                325                 330                 335

Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr
            340                 345                 350

Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn
        355                 360                 365

Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu
    370                 375                 380

Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn
385                 390                 395                 400

Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly
                405                 410                 415

Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His
            420                 425                 430


<210> SEQ ID NO 12
<211> LENGTH: 1485
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

tccggggcgg gggcggggcc tcactctgcg atataactcg ggtcgcgcgg ctcgcgcagg     60

ccgccaccgt cgtccgcaaa gcctgagtcc tgtcctttct ctctccccgg acagcatgag    120

cttcaccact cgctccacct tctccaccaa ctaccggtcc ctgggctctg tccaggcgcc    180

cagctacggc gcccggccgg tcagcagcgc ggccagcgtc tatgcaggcg ctgggggctc    240

tggttcccgg atctccgtgt cccgctccac cagcttcagg ggcggcatgg ggtccggggg    300

cctggccacc gggatagccg ggggtctggc aggaatggga ggcatccaga acgagaagga    360

gaccatgcaa agcctgaacg accgcctggc ctcttacctg gacagagtga ggagcctgga    420

gaccgagaac cggaggctgg agagcaaaat ccgggagcac ttggagaaga agggacccca    480

ggtcagagac tggagccatt acttcaagat catcgaggac ctgagggctc agatcttcgc    540

aaatactgtg gacaatgccc gcatcgttct gcagattgac aatgcccgtc ttgctgctga    600

tgactttaga gtcaagtatg agacagagct ggccatgcgc cagtctgtgg agaacgacat    660

ccatgggctc cgcaaggtca ttgatgacac caatatcaca cgactgcagc tggagacaga    720

gatcgaggct ctcaaggagg agctgctctt catgaagaag aaccacgaag aggaagtaaa    780

aggcctacaa gcccagattg ccagctctgg gttgaccgtg gaggtagatg cccccaaatc    840

tcaggacctc gccaagatca tggcagacat ccgggcccaa tatgacgagc tggctcggaa    900

gaaccgagag gagctagaca agtactggtc tcagcagatt gaggagagca ccacagtggt    960

caccacacag tctgctgagg ttggagctgc tgagacgacg ctcacagagc tgagacgtac   1020
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agtccagtcc ttggagatcg acctggactc catgagaaat ctgaaggcca gcttggagaa 1080

cagcctgagg gaggtggagg cccgctacgc cctacagatg gagcagctca acgggatcct 1140

gctgcacctt gagtcagagc tggcacagac ccgggcagag ggacagcgcc aggcccagga 1200

gtatgaggcc ctgctgaaca tcaaggtcaa gctggaggct gagatcgcca cctaccgccg 1260

cctgctggaa gatggcgagg actttaatct tggtgatgcc ttggacagca gcaactccat 1320

gcaaaccatc caaaagacca ccacccgccg gatagtggat ggcaaagtgg tgtctgagac 1380

caatgacacc aaagttctga ggcattaagc cagcagaagc agggtaccct ttggggagca 1440

ggaggccaat aaaaagttca gagttcaaaa aaaaaaaaaa aaaaa 1485

<210> SEQ ID NO 13
<211> LENGTH: 430
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu
1 5 10 15

Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala
20 25 30

Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val
35 40 45

Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
50 55 60

Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
65 70 75 80

Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
100 105 110

Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His
115 120 125

Tyr Phe Lys Ile Ile Glu Asp Leu Arg Ala Gln Ile Phe Ala Asn Thr
130 135 140

Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala
145 150 155 160

Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln
165 170 175

Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr
180 185 190

Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu
195 200 205

Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu
210 215 220

Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro
225 230 235 240

Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr
245 250 255

Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser
260 265 270

Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu
275 280 285

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Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln
    290                 295                 300

Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu
305                 310                 315                 320

Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu
                325                 330                 335

Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr
            340                 345                 350

Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn
        355                 360                 365

Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu
    370                 375                 380

Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn
385                 390                 395                 400

Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly
                405                 410                 415

Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His
            420                 425                 430


<210> SEQ ID NO 14
<211> LENGTH: 1439
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

gcagcctcga gggccaacaa cacctgctgt ccgtgtccat gcccggttgg ccaccccgtt     60

tctgggggca tgagcttcac cactcgctcc accttctcca ccaactaccg gtccctgggc    120

tctgtccagg cgcccagcta cggcgcccgg ccggtcagca gcgcggccag cgtctatgca    180

ggcgctgggg gctctggttc ccggatctcc gtgtcccgct ccaccagctt caggggcggc    240

atggggtccg ggggcctggc caccgggata gccgggggtc tggcaggaat gggaggcatc    300

cagaacgaga aggagaccat gcaaagcctg aacgaccgcc tggcctctta cctggacaga    360

gtgaggagcc tggagaccga gaaccggagg ctggagagca aaatccggga gcacttggag    420

aagaagggac cccaggtcag agactggagc cattacttca agatcatcga ggacctgagg    480

gctcagatct tcgcaaatac tgtggacaat gcccgcatcg ttctgcagat tgacaatgcc    540

cgtcttgctg ctgatgactt tagagtcaag tatgagacag agctggccat gcgccagtct    600

gtggagaacg acatccatgg gctccgcaag gtcattgatg acaccaatat cacacgactg    660

cagctggaga cagagatcga ggctctcaag gaggagctgc tcttcatgaa gaagaaccac    720

gaagaggaag taaaaggcct acaagcccag attgccagct ctgggttgac cgtggaggta    780

gatgccccca aatctcagga cctcgccaag atcatggcag acatccgggc ccaatatgac    840

gagctggctc ggaagaaccg agaggagcta gacaagtact ggtctcagca gattgaggag    900

agcaccacag tggtcaccac acagtctgct gaggttggag ctgctgagac gacgctcaca    960

gagctgagac gtacagtcca gtccttggag atcgacctgg actccatgag aaatctgaag   1020

gccagcttgg agaacagcct gagggaggtg gaggcccgct acgccctaca gatggagcag   1080

ctcaacggga tcctgctgca ccttgagtca gagctggcac agacccgggc agagggacag   1140

cgccaggccc aggagtatga ggccctgctg aacatcaagg tcaagctgga ggctgagatc   1200

gccacctacc gccgcctgct ggaagatggc gaggacttta atcttggtga tgccttggac   1260
```

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agcagcaact ccatgcaaac catccaaaag accaccaccc gccggatagt ggatggcaaa 1320

gtggtgtctg agaccaatga caccaaagtt ctgaggcatt aagccagcag aagcagggta 1380

ccctttgggg agcaggaggc caataaaaag ttcagagttc aaaaaaaaaa aaaaaaaaa 1439

<210> SEQ ID NO 15
<211> LENGTH: 400
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly
1 5 10 15

Gly Leu Gly Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg
20 25 30

Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser
35 40 45

Ser Ala Arg Phe Val Ser Ser Ser Ser Ser Gly Ala Tyr Gly Gly Gly
50 55 60

Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu
65 70 75 80

Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile
100 105 110

Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser
115 120 125

His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala
130 135 140

Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu
145 150 155 160

Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg
165 170 175

Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu
180 185 190

Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys
195 200 205

Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr
210 215 220

Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala
225 230 235 240

Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr
245 250 255

Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr
260 265 270

Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr Glu Gln
275 280 285

Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr Leu Gln
290 295 300

Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ala Leu
305 310 315 320

Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln Leu Ala
325 330 335

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```
His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly Asp Val
            340                 345                 350

Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu Met Asp
        355                 360                 365

Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu
    370                 375                 380

Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys Val Leu
385                 390                 395                 400
```

<210> SEQ ID NO 16
<211> LENGTH: 1490
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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agatatccgc ccctgacacc attcctccct tccccctcc accggccgcg ggcataaaag     60

gcgccaggtg agggcctcgc cgctcctccc gcgaatcgca gcttctgaga ccagggttgc    120

tccgtccgtg ctccgcctcg ccatgacttc ctacagctat cgccagtcgt cggccacgtc    180

gtccttcgga ggcctgggcg gcggctccgt gcgttttggg ccgggggtcg cctttcgcgc    240

gcccagcatt cacgggggct ccggcggccg cggcgtatcc gtgtcctccg cccgctttgt    300

gtcctcgtcc tcctcggggg cctacggcgg cggctacggc ggcgtcctga ccgcgtccga    360

cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc    420

ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg    480

cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac    540

catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct    600

gcagatcgac aatgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca    660

ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct    720

gaccctggcc aggaccgacc tggagatgca gatcgaaggc ctgaaggaag agctggccta    780

cctgaagaag aaccatgagg aggaaatcag tacgctgagg ggccaagtgg gaggccaggt    840

cagtgtggag gtggattccg ctccgggcac cgatctcgcc aagatcctga gtgacatgcg    900

aagccaatat gaggtcatgg ccgagcagaa ccggaaggat gctgaagcct ggttcaccag    960

ccggactgaa gaattgaacc gggaggtcgc tggccacacg gagcagctcc agatgagcag   1020

gtccgaggtt actgacctgc ggcgcaccct tcagggtctt gagattgagc tgcagtcaca   1080

gctgagcatg aaagctgcct tggaagacac actggcagaa acggaggcgc gctttggagc   1140

ccagctggcg catatccagg cgctgatcag cggtattgaa gcccagctgg gcgatgtgcg   1200

agctgatagt gagcggcaga atcaggagta ccagcggctc atggacatca agtcgcggct   1260

ggagcaggag attgccacct accgcagcct gctcgaggga caggaagatc actacaacaa   1320

tttgtctgcc tccaaggtcc tctgaggcag caggctctgg ggcttctgct gtcctttgga   1380

gggtgtcttc tgggtagagg gatgggaagg aagggaccct taccccggc tcttctcctg   1440

acctgccaat aaaaatttat ggtccaaggg aaaaaaaaaa aaaaaaaaaa              1490
```

<210> SEQ ID NO 17
<211> LENGTH: 378
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 17

Met Asp Ser Val Arg Ser Gly Ala Phe Gly His Leu Phe Arg Pro Asp
1 5 10 15

Asn Phe Ile Phe Gly Gln Ser Gly Ala Gly Asn Asn Trp Ala Lys Gly
            20 25 30

His Tyr Thr Glu Gly Ala Glu Leu Val Asp Ser Val Leu Asp Val Val
        35 40 45

Arg Lys Glu Cys Glu Asn Cys Asp Cys Leu Gln Gly Phe Gln Leu Thr
    50 55 60

His Ser Leu Gly Gly Gly Thr Gly Ser Gly Met Gly Thr Leu Leu Ile
65 70 75 80

Ser Lys Val Arg Glu Glu Tyr Pro Asp Arg Ile Met Asn Thr Phe Ser
                85 90 95

Val Val Pro Ser Pro Lys Val Ser Asp Thr Val Val Glu Pro Tyr Asn
            100 105 110

Ala Thr Leu Ser Ile His Gln Leu Val Glu Asn Thr Asp Glu Thr Tyr
        115 120 125

Cys Ile Asp Asn Glu Ala Leu Tyr Asp Ile Cys Phe Arg Thr Leu Lys
    130 135 140

Leu Ala Thr Pro Thr Tyr Gly Asp Leu Asn His Leu Val Ser Ala Thr
145 150 155 160

Met Ser Gly Val Thr Thr Ser Leu Arg Phe Pro Gly Gln Leu Asn Ala
                165 170 175

Asp Leu Arg Lys Leu Ala Val Asn Met Val Pro Phe Pro Arg Leu His
            180 185 190

Phe Phe Met Pro Gly Phe Ala Pro Leu Thr Ala Arg Gly Ser Gln Gln
        195 200 205

Tyr Arg Ala Leu Thr Val Pro Glu Leu Thr Gln Gln Met Phe Asp Ala
    210 215 220

Lys Asn Met Met Ala Ala Cys Asp Pro Arg His Gly Arg Tyr Leu Thr
225 230 235 240

Val Ala Thr Val Phe Arg Gly Arg Met Ser Met Lys Glu Val Asp Glu
                245 250 255

Gln Met Leu Ala Ile Gln Ser Lys Asn Ser Ser Tyr Phe Val Glu Trp
            260 265 270

Ile Pro Asn Asn Val Lys Val Ala Val Cys Asp Ile Pro Pro Arg Gly
        275 280 285

Leu Lys Met Ser Ser Thr Phe Ile Gly Asn Ser Thr Ala Ile Gln Glu
    290 295 300

Leu Phe Lys Arg Ile Ser Glu Gln Phe Thr Ala Met Phe Arg Arg Lys
305 310 315 320

Ala Phe Leu His Trp Tyr Thr Gly Glu Gly Met Asp Glu Met Glu Phe
                325 330 335

Thr Glu Ala Glu Ser Asn Met Asn Asp Leu Val Ser Glu Tyr Gln Gln
            340 345 350

Tyr Gln Asp Ala Thr Ala Glu Glu Glu Gly Glu Met Tyr Glu Asp Asp
        355 360 365

Glu Glu Glu Ser Glu Ala Gln Gly Pro Lys
    370 375

<210> SEQ ID NO 18
<211> LENGTH: 1851

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

agacactcac cccggactcc cttgaacagg gacagggagg aaccccaggc agctagaccc 60

cagcagcagc cacacgagca cactgtgggg cagggagggg catctcttga gaacaaaaga 120

tccatttctc gactttccaa actggagagc ttcttgagag aaaagagaga gacaggtaca 180

ggtccacgcc acccacacac agccctgtgc acacagaccg gacacaggcg tccacagttc 240

tgggaagtca tcagtgatga gcatggcatc gaccccagcg gcaactacgt gggcgactcg 300

gacttgcagc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg 360

cctcgagcca ttctggtgga cctggaaccc ggaaccatgg acagtgtccg ctcaggggcc 420

tttggacatc tcttcaggcc tgacaatttc atctttggtc agagtggggc cggcaacaac 480

tgggccaagg gtcactacac ggaggggggcg gagctggtgg attcggtcct ggatgtggtg 540

cggaaggagt gtgaaaactg cgactgcctg cagggcttcc agctgaccca ctcgctgggg 600

ggcggcacgg gctccggcat gggcacgttg ctcatcagca aggtgcgtga ggagtatccc 660

gaccgcatca tgaacacctt cagcgtcgtg ccctcaccca aggtgtcaga cacggtggtg 720

gagccctaca acgccacgct gtccatccac cagctggtgg agaacacgga tgagacctac 780

tgcatcgaca acgaggcgct ctacgacatc tgcttccgca ccctcaagct ggccacgccc 840

acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cacctccttg 900

cgcttcccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc 960

ccgcgcctgc acttcttcat gcccggcttc gccccctca cagcccgggg cagccagcag 1020

taccgggccc tgaccgtgcc cgagctcacc cagcagatgt tcgatgccaa gaacatgatg 1080

gccgcctgcg acccgcgcca cggccgctac ctgacggtgg ccaccgtgtt ccggggccgc 1140

atgtccatga aggaggtgga cgagcagatg ctggccatcc agagcaagaa cagcagctac 1200

ttcgtggagt ggatccccaa caacgtgaag gtggccgtgt gtgacatccc gccccgcggc 1260

ctcaagatgt cctccacctt catcgggaac agcacggcca tccaggagct gttcaagcgc 1320

atctccgagc agttcacggc catgttccgg cgcaaggcct tcctgcactg gtacacgggc 1380

gagggcatgg acgagatgga gttcaccgag gccgagagca acatgaacga cctggtgtcc 1440

gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgta cgaagacgac 1500

gaggaggagt cggaggccca gggccccaag tgaagctgct cgcagctgga gtgagaggca 1560

ggtggcggcc ggggccgaag ccagcagtgt ctaaaccccc ggagccatct tgctgccgac 1620

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cctgacgttt tacggttttg ttttttactg gtttgtgttt atattttcgg ggatacttaa 1800

taaatctatt gctgtcagat acccttaaaa aaaaaaaaaa aaaaaaaaaa a 1851

<210> SEQ ID NO 19
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Arg Glu Ile Val His Ile Gln Ala Gly Gln Cys Gly Asn Gln Ile
1 5 10 15

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```
Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
            20                  25                  30

Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
        35                  40                  45

Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
    50                  55                  60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
65                  70                  75                  80

Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
                85                  90                  95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
            100                 105                 110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
        115                 120                 125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
    130                 135                 140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
145                 150                 155                 160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
                165                 170                 175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
            180                 185                 190

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
        195                 200                 205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
    210                 215                 220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
225                 230                 235                 240

Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
                245                 250                 255

Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
            260                 265                 270

Leu Thr Ala Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
        275                 280                 285

Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
    290                 295                 300

Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Arg
305                 310                 315                 320

Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Ser Lys
                325                 330                 335

Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
            340                 345                 350

Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ser Thr Phe Ile
        355                 360                 365

Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
    370                 375                 380

Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
385                 390                 395                 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
                405                 410                 415

Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
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420 425 430

Glu Gly Glu Met Tyr Glu Asp Asp Glu Glu Glu Ser Glu Ala Gln Gly
435 440 445

Pro Lys
450

<210> SEQ ID NO 20
<211> LENGTH: 1794
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

gacatcagcc gatgcgaagg gcggggccgc ggctataaga gcgcgcggcc gcggtccccg 60

accctcagca gccagcccgg cccgcccgcg cccgtccgca gccgcccgcc agacgcgccc 120

agtatgaggg agatcgtgca catccaggcc ggccagtgcg gcaaccagat cggggccaag 180

ttctgggaag tcatcagtga tgagcatggc atcgacccca gcggcaacta cgtgggcgac 240

tcggacttgc agctggagcg gatcagcgtc tactacaacg aggcctcttc tcacaagtac 300

gtgcctcgag ccattctggt ggacctggaa cccggaacca tggacagtgt ccgctcaggg 360

gcctttggac atctcttcag gcctgacaat ttcatctttg gtcagagtgg ggccggcaac 420

aactgggcca agggtcacta cacggagggg gcggagctgg tggattcggt cctggatgtg 480

gtgcggaagg agtgtgaaaa ctgcgactgc ctgcagggct tccagctgac ccactcgctg 540

gggggcggca cgggctccgg catgggcacg ttgctcatca gcaaggtgcg tgaggagtat 600

cccgaccgca tcatgaacac cttcagcgtc gtgccctcac ccaaggtgtc agacacggtg 660

gtggagccct acaacgccac gctgtccatc caccagctgg tggagaacac ggatgagacc 720

tactgcatcg acaacgaggc gctctacgac atctgcttcc gcaccctcaa gctggccacg 780

cccacctacg gggacctcaa ccacctggta tcggccacca tgagcggagt caccacctcc 840

ttgcgcttcc cgggccagct caacgctgac ctgcgcaagc tggccgtcaa catggtgccc 900

ttcccgcgcc tgcacttctt catgcccggc ttcgcccccc tcacagcccg gggcagccag 960

cagtaccggg ccctgaccgt gcccgagctc acccagcaga tgttcgatgc caagaacatg 1020

atggccgcct gcgacccgcg ccacggccgc tacctgacgg tggccaccgt gttccggggc 1080

cgcatgtcca tgaaggaggt ggacgagcag atgctggcca tccagagcaa gaacagcagc 1140

tacttcgtgg agtggatccc caacaacgtg aaggtggccg tgtgtgacat cccgccccgc 1200

ggcctcaaga tgtcctccac cttcatcggg aacagcacgg ccatccagga gctgttcaag 1260

cgcatctccg agcagttcac ggccatgttc cggcgcaagg ccttcctgca ctggtacacg 1320

ggcgagggca tggacgagat ggagttcacc gaggccgaga gcaacatgaa cgacctggtg 1380

tccgagtacc agcagtacca ggacgccacg gccgaggaag agggcgagat gtacgaagac 1440

gacgaggagg agtcggaggc ccagggcccc aagtgaagct gctcgcagct ggagtgagag 1500

gcaggtggcg gccggggccg aagccagcag tgtctaaacc cccggagcca tcttgctgcc 1560

gacaccctgc tttcccctcg ccctagggct cccttgccgc cctcctgcag tatttatggc 1620

ctcgtcctcc ccacctaggc cacgtgtgag ctgctcctgt ctctgtctta ttgcagctcc 1680

aggcctgacg ttttacggtt ttgtttttta ctggtttgtg tttatatttt cggggatact 1740

taataaatct attgctgtca gataccctta aaaaaaaaaa aaaaaaaaaa aaaa 1794

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<210> SEQ ID NO 21
<211> LENGTH: 163856
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

gcggccaggg gcgggcggcc gcagagcagc accggccgtg gctccggtag cagcaagttc 60

gaaccccgct cccgctccgc ttcggttctc gctccttcgg cccttgggcc tccaaacacc 120

agtccccggc agctcgttgc gcattgcgct ctccccgcca ccaggatgcc ggtaaccgag 180

aaggatctag ctgaggacgc gccttggaag aagatccagc agaacacgtt cacacgctgg 240

tgcaacgagc acctcaagtg cgtgaacaaa cgcatcggca acctgcagac cgacctgagc 300

gacgggctgc ggctcatcgc gctgctcgag gtgctcagcc agaagcgcat gtaccgcaag 360

taccatcagc ggcccacctt tcgccagatg cagctcgaga atgtgtccgt ggcgctcgag 420

ttcctggacc gtgagagcat caagctcgtg tccatcggtg agttctctgg ccgggcccag 480

gcgcccactg tggtgccgac ccgcccccgc gcgtgcaccc ctgcggaggg cgaggatttc 540

ccgcagcgcg cccccacctc ggagataagg gggagtcgtc cccaggggtg ggttataggg 600

ggcctagacc ccctccccgg tgtcttcccc tgggatggga cctgttgtga tcgctccccg 660

ccatccgccc cagcagtgca cctttggctg gctaagggtt gagggtttgg gctggggtca 720

caggaggaga ggtggagttg ttgcatttct ctacacctgg ggcgccccta tgggagctag 780

gggactagaa accctcgttc gctgtccccg ggggcgggcc ctagggtcag atgctccgcg 840

gagtgctctc cctgctgcgc ccaggttggt gctctcagag gcagctgaat gggcgttggc 900

tcggaggccg ggccgtgaga cctgaggagg aaccgttctc tgcgcctggg gcctccctgc 960

ccaggtggag acagagacct ggtaccttcc cctgccgtcg ctggaatggg tgtgggcccc 1020

gaggttgcaa gggtaggcgc gggtgtgtgt cctcgctctc tctgctccca gctcagctct 1080

ggccgcgcgc cgcaggttga acccactcct tgctgccgaa gttataattt agagatggtg 1140

gtggtaacag taattgctgt cttgtaggga gcccaactag cgtccactgt gtaccgtcag 1200

ccttctaagt tatctccgtc cctacgcatc ctgccatctg gggtgaggct agacccattt 1260

tacagataag ggggtccgga gggttaattg acctgtccaa ggtcagcaag tagggcccag 1320

ctgagaactg aaggaagtgg gcaacagtta gaaggaggct ttgttttcct ctcctctccc 1380

aaacctacac cagggtcttc ctgaaaggag ggagggaatt ggtgtctctt gctggactgg 1440

gccttctggt ctggggagga agaataagga tgaagtctcc cttgtggtct gagatagttg 1500

gaggcttccc agagggccac aaggctactg atagtgtggg ctgtgatggt aggggctgtg 1560

atgtgtgtgt gcatgtgggc gtttgtgcag agaacgtgtg tacacacata gcatgtgtgt 1620

atagcatgtg catatgcaaa gagtttgcat gtacacggaa tgtatgcaga gaatgtgtat 1680

ccacctacac gtgtgtatgg gtgtgtgtat gtgtgtgtgt gtatgtgggt gggtgggtgt 1740

gggttggggc agaggagggt tctgggtctg gatctcttcc taaggagaac cagggactgg 1800

ccctggcctg tgatttgggt ctcttcctga ggaaaccagg tcactatagt gaccctagtg 1860

acaggaagaa agggagatgg gtgtggctgc caggactttc tccagtggaa aagggattcc 1920

ctctaggctg agcctcccct gggccttagg gcctcaccct tcccttcccc cacacctgtc 1980

ctggcaggta aggctgcttc ctgcttcctg ggcccagatg gcagccgcac cacccagctg 2040

atctccagca gccctccccc tccccaaggg tggcttccct gcagaagaat ctgcatggca 2100

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cgctgttgtc ttctttctgg ggtccatctc ctgtactggg gagggagaac ctcagaatct 2160

cctggaattc tttaccattc agaaaccagc ctcccctctg aagaatccca aggcccagct 2220

gggctcaatt tggatctgtt ctttgtttta aaaatgtgta tttatttaat taactgaata 2280

aagaaactta aagtaaacca gaagtatcca aatacgacat gaaatctcta aaacaacaac 2340

aaaaccaaac caaaccgcag cactagcaaa tcacagactg cctgatctac ccactgttta 2400

cagaggcagc agctacttcc agcactgtct ctcatcagtg cccggggctg tgggtctcat 2460

tctagatttt gtctacattt ttttacatgg ttctcctgat tccctgctcc ccctccccac 2520

caccgccccg cctggagatg gagccttgct ctgtctccag gctggagtac aatggtgcca 2580

tctctgctca ctgcaacctc cacctcccgg gttcaagcga ttcttctgcc tcagcctcct 2640

gagtagctag aattacaggc acatgccacc acgcccggct aatttttgta ttcttagtag 2700

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cttattggtg gtcttttcac cattggcaga aacagtgaga gctgtgtggt gcagaaatcc 163500

agaaatgagg tgtagggaat tttgcctgcc ttcctgcaga cctgagctgg ctttggaatg 163560

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acctttaggt tttgctgctt agtcctgagg aagtggccac tcttgtggca ggtgtagtat 163680

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<211> LENGTH: 2633
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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Ile Gln Gln Asn Thr Phe Thr Arg Trp Cys Asn Glu His Leu Lys Cys
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Val Asn Lys Arg Ile Gly Asn Leu Gln Thr Asp Leu Ser Asp Gly Leu
35 40 45

Arg Leu Ile Ala Leu Leu Glu Val Leu Ser Gln Lys Arg Met Tyr Arg
50 55 60

Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
65 70 75 80

Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
85 90 95

Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
100 105 110

Leu Val Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Val Trp
115 120 125

Glu Asp Glu Gly Asp Asp Asp Ala Lys Lys Gln Thr Pro Lys Gln Arg
130 135 140

Leu Leu Gly Trp Ile Gln Asn Lys Ile Pro Tyr Leu Pro Ile Thr Asn
145 150 155 160

Phe Asn Gln Asn Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp
165 170 175

Ser Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ser Trp Asp Pro Gln
180 185 190

Lys Pro Val Asp Asn Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp
195 200 205

Leu Gly Val Pro Gln Val Ile Thr Pro Glu Glu Ile Ile His Pro Asp
210 215 220

Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala
225 230 235 240

Lys Leu Lys Pro Gly Ala Pro Leu Lys Pro Lys Leu Asn Pro Lys Lys
245 250 255

Ala Arg Ala Tyr Gly Arg Gly Ile Glu Pro Thr Gly Asn Met Val Lys
260 265 270

Gln Pro Ala Lys Phe Thr Val Asp Thr Ile Ser Ala Gly Gln Gly Asp
275 280 285

Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
290 295 300

Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
305 310 315 320

Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
325 330 335

His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
340 345 350

Asp Ala Ser Lys Val Thr Ala Lys Gly Pro Gly Leu Glu Ala Val Gly

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        355                 360                 365

Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala
    370                 375                 380

Gly Val Gly Asp Ile Gly Val Glu Val Glu Asp Pro Gln Gly Lys Asn
385                 390                 395                 400

Thr Val Glu Leu Leu Val Glu Asp Lys Gly Asn Gln Val Tyr Arg Cys
                405                 410                 415

Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
            420                 425                 430

Ala Gly Asp Thr Ile Pro Lys Ser Pro Phe Val Val Gln Val Gly Glu
        435                 440                 445

Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu Gln Pro
    450                 455                 460

Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
465                 470                 475                 480

Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
                485                 490                 495

Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
            500                 505                 510

Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
        515                 520                 525

Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
    530                 535                 540

Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
545                 550                 555                 560

Gly Gly Ile Val Gly Arg Ser Ala Asp Phe Val Val Glu Ser Ile Gly
                565                 570                 575

Ser Glu Val Gly Ser Leu Gly Phe Ala Ile Glu Gly Pro Ser Gln Ala
            580                 585                 590

Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
        595                 600                 605

Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
    610                 615                 620

Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
625                 630                 635                 640

Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
                645                 650                 655

Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
            660                 665                 670

Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
        675                 680                 685

Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
    690                 695                 700

Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
705                 710                 715                 720

Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
                725                 730                 735

Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
            740                 745                 750

Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
        755                 760                 765
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Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
    770                 775                 780

Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
785                 790                 795                 800

His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
                805                 810                 815

Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
            820                 825                 830

Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
        835                 840                 845

Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
    850                 855                 860

Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
865                 870                 875                 880

Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
                885                 890                 895

Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
            900                 905                 910

Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
        915                 920                 925

Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
    930                 935                 940

Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
945                 950                 955                 960

Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
                965                 970                 975

Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
            980                 985                 990

Val Thr Pro Val Thr Gly Arg Glu  Asn Ser Thr Ala Lys  Phe Ile Pro
        995                 1000                1005

Arg Glu  Glu Gly Leu Tyr Ala  Val Asp Val Thr Tyr  Asp Gly His
    1010                1015                1020

Pro Val  Pro Gly Ser Pro Tyr  Thr Val Glu Ala Ser  Leu Pro Pro
    1025                1030                1035

Asp Pro  Ser Lys Val Lys Ala  His Gly Pro Gly Leu  Glu Gly Gly
    1040                1045                1050

Leu Val  Gly Lys Pro Ala Glu  Phe Thr Ile Asp Thr  Lys Gly Ala
    1055                1060                1065

Gly Thr  Gly Gly Leu Gly Leu  Thr Val Glu Gly Pro  Cys Glu Ala
    1070                1075                1080

Lys Ile  Glu Cys Ser Asp Asn  Gly Asp Gly Thr Cys  Ser Val Ser
    1085                1090                1095

Tyr Leu  Pro Thr Lys Pro Gly  Glu Tyr Phe Val Asn  Ile Leu Phe
    1100                1105                1110

Glu Glu  Val His Ile Pro Gly  Ser Pro Phe Lys Ala  Asp Ile Glu
    1115                1120                1125

Met Pro  Phe Asp Pro Ser Lys  Val Val Ala Ser Gly  Pro Gly Leu
    1130                1135                1140

Glu His  Gly Lys Val Gly Glu  Ala Gly Leu Leu Ser  Val Asp Cys
    1145                1150                1155

Ser Glu  Ala Gly Pro Gly Ala  Leu Gly Leu Glu Ala  Val Ser Asp
    1160                1165                1170
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Ser Gly  Thr Lys Ala Glu Val  Ser Ile Gln Asn Asn  Lys Asp Gly
    1175                1180                1185

Thr Tyr  Ala Val Thr Tyr Val  Pro Leu Thr Ala Gly  Met Tyr Thr
    1190                1195                1200

Leu Thr  Met Lys Tyr Gly Gly  Glu Leu Val Pro His  Phe Pro Ala
    1205                1210                1215

Arg Val  Lys Val Glu Pro Ala  Val Asp Thr Ser Arg  Ile Lys Val
    1220                1225                1230

Phe Gly  Pro Gly Ile Glu Gly  Lys Asp Val Phe Arg  Glu Ala Thr
    1235                1240                1245

Thr Asp  Phe Thr Val Asp Ser  Arg Pro Leu Thr Gln  Val Gly Gly
    1250                1255                1260

Asp His  Ile Lys Ala His Ile  Ala Asn Pro Ser Gly  Ala Ser Thr
    1265                1270                1275

Glu Cys  Phe Val Thr Asp Asn  Ala Asp Gly Thr Tyr  Gln Val Glu
    1280                1285                1290

Tyr Thr  Pro Phe Glu Lys Gly  Leu His Val Val Glu  Val Thr Tyr
    1295                1300                1305

Asp Asp  Val Pro Ile Pro Asn  Ser Pro Phe Lys Val  Ala Val Thr
    1310                1315                1320

Glu Gly  Cys Gln Pro Ser Arg  Val Gln Ala Gln Gly  Pro Gly Leu
    1325                1330                1335

Lys Glu  Ala Phe Thr Asn Lys  Pro Asn Val Phe Thr  Val Val Thr
    1340                1345                1350

Arg Gly  Ala Gly Ile Gly Gly  Leu Gly Ile Thr Val  Glu Gly Pro
    1355                1360                1365

Ser Glu  Ser Lys Ile Asn Cys  Arg Asp Asn Lys Asp  Gly Ser Cys
    1370                1375                1380

Ser Ala  Glu Tyr Ile Pro Phe  Ala Pro Gly Asp Tyr  Asp Val Asn
    1385                1390                1395

Ile Thr  Tyr Gly Gly Ala His  Ile Pro Gly Ser Pro  Phe Arg Val
    1400                1405                1410

Pro Val  Lys Asp Val Val Asp  Pro Ser Lys Val Lys  Ile Ala Gly
    1415                1420                1425

Pro Gly  Leu Gly Ser Gly Val  Arg Ala Arg Val Leu  Gln Ser Phe
    1430                1435                1440

Thr Val  Asp Ser Ser Lys Ala  Gly Leu Ala Pro Leu  Glu Val Arg
    1445                1450                1455

Val Leu  Gly Pro Arg Ala Asp  Asp Thr Asp Ser Gln  Ser Trp Arg
    1460                1465                1470

Ser Pro  Leu Lys Ala Leu Ser  Glu Phe Phe Lys Gly  Asp Pro Lys
    1475                1480                1485

Gly Asp  Phe Asn Lys Thr Gly  Leu Val Glu Pro Val  Asn Val Val
    1490                1495                1500

Asp Asn  Gly Asp Gly Thr His  Thr Val Thr Tyr Thr  Pro Ser Gln
    1505                1510                1515

Glu Gly  Pro Tyr Met Val Ser  Val Lys Tyr Ala Asp  Glu Glu Ile
    1520                1525                1530

Pro Arg  Ser Pro Phe Lys Val  Lys Val Leu Pro Thr  Tyr Asp Ala
    1535                1540                1545

Ser Lys  Val Thr Ala Ser Gly  Pro Gly Leu Ser Ser  Tyr Gly Val
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    1550                1555                1560

Pro Ala  Ser Leu Pro Val Asp  Phe Ala Ile Asp Ala  Arg Asp Ala
    1565                1570                1575

Gly Glu  Gly Leu Leu Ala Val  Gln Ile Thr Asp Gln  Glu Gly Lys
    1580                1585                1590

Pro Lys  Arg Ala Ile Val His  Asp Asn Lys Asp Gly  Thr Tyr Ala
    1595                1600                1605

Val Thr  Tyr Ile Pro Asp Lys  Thr Gly Arg Tyr Met  Ile Gly Val
    1610                1615                1620

Thr Tyr  Gly Gly Asp Asp Ile  Pro Leu Ser Pro Tyr  Arg Ile Arg
    1625                1630                1635

Ala Thr  Gln Thr Gly Asp Ala  Ser Lys Cys Leu Ala  Thr Gly Pro
    1640                1645                1650

Gly Ile  Ala Ser Thr Val Lys  Thr Gly Glu Glu Val  Gly Phe Val
    1655                1660                1665

Val Asp  Ala Lys Thr Ala Gly  Lys Gly Lys Val Thr  Cys Thr Val
    1670                1675                1680

Leu Thr  Pro Asp Gly Thr Glu  Ala Glu Ala Asp Val  Ile Glu Asn
    1685                1690                1695

Glu Asp  Gly Thr Tyr Asp Ile  Phe Tyr Thr Ala Ala  Lys Pro Gly
    1700                1705                1710

Thr Tyr  Val Ile Tyr Val Arg  Phe Gly Gly Val Asp  Ile Pro Asn
    1715                1720                1725

Ser Pro  Phe Thr Val Met Ala  Thr Asp Gly Glu Val  Thr Ala Val
    1730                1735                1740

Glu Glu  Ala Pro Val Asn Ala  Cys Pro Pro Gly Phe  Arg Pro Trp
    1745                1750                1755

Val Thr  Glu Glu Ala Tyr Val  Pro Val Ser Asp Met  Asn Gly Leu
    1760                1765                1770

Gly Phe  Lys Pro Phe Asp Leu  Val Ile Pro Phe Ala  Val Arg Lys
    1775                1780                1785

Gly Glu  Ile Thr Gly Glu Val  His Met Pro Ser Gly  Lys Thr Ala
    1790                1795                1800

Thr Pro  Glu Ile Val Asp Asn  Lys Asp Gly Thr Val  Thr Val Arg
    1805                1810                1815

Tyr Ala  Pro Thr Glu Val Gly  Leu His Glu Met His  Ile Lys Tyr
    1820                1825                1830

Met Gly  Ser His Ile Pro Glu  Ser Pro Leu Gln Phe  Tyr Val Asn
    1835                1840                1845

Tyr Pro  Asn Ser Gly Ser Val  Ser Ala Tyr Gly Pro  Gly Leu Val
    1850                1855                1860

Tyr Gly  Val Ala Asn Lys Thr  Ala Thr Phe Thr Ile  Val Thr Glu
    1865                1870                1875

Asp Ala  Gly Glu Gly Gly Leu  Asp Leu Ala Ile Glu  Gly Pro Ser
    1880                1885                1890

Lys Ala  Glu Ile Ser Cys Ile  Asp Asn Lys Asp Gly  Thr Cys Thr
    1895                1900                1905

Val Thr  Tyr Leu Pro Thr Leu  Pro Gly Asp Tyr Ser  Ile Leu Val
    1910                1915                1920

Lys Tyr  Asn Asp Lys His Ile  Pro Gly Ser Pro Phe  Thr Ala Lys
    1925                1930                1935
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Ile Thr  Asp Asp Ser Arg Arg  Cys Ser Gln Val Lys  Leu Gly Ser
    1940                1945                1950

Ala Ala  Asp Phe Leu Leu Asp  Ile Ser Glu Thr Asp  Leu Ser Ser
    1955                1960                1965

Leu Thr  Ala Ser Ile Lys Ala  Pro Ser Gly Arg Asp  Glu Pro Cys
    1970                1975                1980

Leu Leu  Lys Arg Leu Pro Asn  Asn His Ile Gly Ile  Ser Phe Ile
    1985                1990                1995

Pro Arg  Glu Val Gly Glu His  Leu Val Ser Ile Lys  Lys Asn Gly
    2000                2005                2010

Asn His  Val Ala Asn Ser Pro  Val Ser Ile Met Val  Val Gln Ser
    2015                2020                2025

Glu Ile  Gly Asp Ala Arg Arg  Ala Lys Val Tyr Gly  Arg Gly Leu
    2030                2035                2040

Ser Glu  Gly Arg Thr Phe Glu  Met Ser Asp Phe Ile  Val Asp Thr
    2045                2050                2055

Arg Asp  Ala Gly Tyr Gly Gly  Ile Ser Leu Ala Val  Glu Gly Pro
    2060                2065                2070

Ser Lys  Val Asp Ile Gln Thr  Glu Asp Leu Glu Asp  Gly Thr Cys
    2075                2080                2085

Lys Val  Ser Tyr Phe Pro Thr  Val Pro Gly Val Tyr  Ile Val Ser
    2090                2095                2100

Thr Lys  Phe Ala Asp Glu His  Val Pro Gly Ser Pro  Phe Thr Val
    2105                2110                2115

Lys Ile  Ser Gly Glu Gly Arg  Val Lys Glu Ser Ile  Thr Arg Thr
    2120                2125                2130

Ser Arg  Ala Pro Ser Val Ala  Thr Val Gly Ser Ile  Cys Asp Leu
    2135                2140                2145

Asn Leu  Lys Ile Pro Glu Ile  Asn Ser Ser Asp Met  Ser Ala His
    2150                2155                2160

Val Thr  Ser Pro Ser Gly Arg  Val Thr Glu Ala Glu  Ile Val Pro
    2165                2170                2175

Met Gly  Lys Asn Ser His Cys  Val Arg Phe Val Pro  Gln Glu Met
    2180                2185                2190

Gly Val  His Thr Val Ser Val  Lys Tyr Arg Gly Gln  His Val Thr
    2195                2200                2205

Gly Ser  Pro Phe Gln Phe Thr  Val Gly Pro Leu Gly  Glu Gly Gly
    2210                2215                2220

Ala His  Lys Val Arg Ala Gly  Gly Pro Gly Leu Glu  Arg Gly Glu
    2225                2230                2235

Ala Gly  Val Pro Ala Glu Phe  Ser Ile Trp Thr Arg  Glu Ala Gly
    2240                2245                2250

Ala Gly  Gly Leu Ser Ile Ala  Val Glu Gly Pro Ser  Lys Ala Glu
    2255                2260                2265

Ile Thr  Phe Asp Asp His Lys  Asn Gly Ser Cys Gly  Val Ser Tyr
    2270                2275                2280

Ile Ala  Gln Glu Pro Gly Asn  Tyr Glu Val Ser Ile  Lys Phe Asn
    2285                2290                2295

Asp Glu  His Ile Pro Glu Ser  Pro Tyr Leu Val Pro  Val Ile Ala
    2300                2305                2310

Pro Ser  Asp Asp Ala Arg Arg  Leu Thr Val Met Ser  Leu Gln Glu
    2315                2320                2325
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Ser Gly  Leu Lys Val Asn Gln  Pro Ala Ser Phe Ala  Ile Arg Leu
    2330                 2335                 2340

Asn Gly  Ala Lys Gly Lys Ile  Asp Ala Lys Val His  Ser Pro Ser
    2345                 2350                 2355

Gly Ala  Val Glu Glu Cys His  Val Ser Glu Leu Glu  Pro Asp Lys
    2360                 2365                 2370

Tyr Ala  Val Arg Phe Ile Pro  His Glu Asn Gly Val  His Thr Ile
    2375                 2380                 2385

Asp Val  Lys Phe Asn Gly Ser  His Val Val Gly Ser  Pro Phe Lys
    2390                 2395                 2400

Val Arg  Val Gly Glu Pro Gly  Gln Ala Gly Asn Pro  Ala Leu Val
    2405                 2410                 2415

Ser Ala  Tyr Gly Thr Gly Leu  Glu Gly Gly Thr Thr  Gly Ile Gln
    2420                 2425                 2430

Ser Glu  Phe Phe Ile Asn Thr  Thr Arg Ala Gly Pro  Gly Thr Leu
    2435                 2440                 2445

Ser Val  Thr Ile Glu Gly Pro  Ser Lys Val Lys Met  Asp Cys Gln
    2450                 2455                 2460

Glu Thr  Pro Glu Gly Tyr Lys  Val Met Tyr Thr Pro  Met Ala Pro
    2465                 2470                 2475

Gly Asn  Tyr Leu Ile Ser Val  Lys Tyr Gly Gly Pro  Asn His Ile
    2480                 2485                 2490

Val Gly  Ser Pro Phe Lys Ala  Lys Val Thr Gly Gln  Arg Leu Val
    2495                 2500                 2505

Ser Pro  Gly Ser Ala Asn Glu  Thr Ser Ser Ile Leu  Val Glu Ser
    2510                 2515                 2520

Val Thr  Arg Ser Ser Thr Glu  Thr Cys Tyr Ser Ala  Ile Pro Lys
    2525                 2530                 2535

Ala Ser  Ser Asp Ala Ser Lys  Val Thr Ser Lys Gly  Ala Gly Leu
    2540                 2545                 2550

Ser Lys  Ala Phe Val Gly Gln  Lys Ser Ser Phe Leu  Val Asp Cys
    2555                 2560                 2565

Ser Lys  Ala Gly Ser Asn Met  Leu Leu Ile Gly Val  His Gly Pro
    2570                 2575                 2580

Thr Thr  Pro Cys Glu Glu Val  Ser Met Lys His Val  Gly Asn Gln
    2585                 2590                 2595

Gln Tyr  Asn Val Thr Tyr Val  Val Lys Glu Arg Gly  Asp Tyr Val
    2600                 2605                 2610

Leu Ala  Val Lys Trp Gly Glu  Glu His Ile Pro Gly  Ser Pro Phe
    2615                 2620                 2625

His Val  Thr Val Pro
    2630


<210> SEQ ID NO 23
<211> LENGTH: 9560
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<213> ORGANISM: Homo sapiens

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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Val Asn Lys Arg Ile Gly Asn Leu Gln Thr Asp Leu Ser Asp Gly Leu
35 40 45

Arg Leu Ile Ala Leu Leu Glu Val Leu Ser Gln Lys Arg Met Tyr Arg
50 55 60

Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
65 70 75 80

Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
85 90 95

Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
100 105 110

Leu Val Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Val Trp
115 120 125

Glu Asp Glu Gly Asp Asp Asp Ala Lys Lys Gln Thr Pro Lys Gln Arg
130 135 140

Leu Leu Gly Trp Ile Gln Asn Lys Ile Pro Tyr Leu Pro Ile Thr Asn
145 150 155 160

Phe Asn Gln Asn Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp
165 170 175

Ser Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ser Trp Asp Pro Gln
180 185 190

Lys Pro Val Asp Asn Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp
195 200 205

Leu Gly Val Pro Gln Val Ile Thr Pro Glu Glu Ile Ile His Pro Asp
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Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala
225 230 235 240

Lys Leu Lys Pro Gly Ala Pro Leu Lys Pro Lys Leu Asn Pro Lys Lys
245 250 255

Ala Arg Ala Tyr Gly Arg Gly Ile Glu Pro Thr Gly Asn Met Val Lys
260 265 270

Gln Pro Ala Lys Phe Thr Val Asp Thr Ile Ser Ala Gly Gln Gly Asp
275 280 285

Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
290 295 300

Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
305 310 315 320

Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
325 330 335

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His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
            340                 345                 350

Asp Ala Ser Lys Val Thr Ala Lys Gly Pro Gly Leu Glu Ala Val Gly
        355                 360                 365

Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala
    370                 375                 380

Gly Val Gly Asp Ile Gly Val Glu Val Glu Asp Pro Gln Gly Lys Asn
385                 390                 395                 400

Thr Val Glu Leu Leu Val Glu Asp Lys Gly Asn Gln Val Tyr Arg Cys
                405                 410                 415

Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
            420                 425                 430

Ala Gly Asp Thr Ile Pro Lys Ser Pro Phe Val Val Gln Val Gly Glu
        435                 440                 445

Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu Gln Pro
    450                 455                 460

Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
465                 470                 475                 480

Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
                485                 490                 495

Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
            500                 505                 510

Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
        515                 520                 525

Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
    530                 535                 540

Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
545                 550                 555                 560

Gly Gly Ile Val Gly Arg Ser Ala Asp Phe Val Val Glu Ser Ile Gly
                565                 570                 575

Ser Glu Val Gly Ser Leu Gly Phe Ala Ile Glu Gly Pro Ser Gln Ala
            580                 585                 590

Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
        595                 600                 605

Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
    610                 615                 620

Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
625                 630                 635                 640

Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
                645                 650                 655

Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
            660                 665                 670

Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
        675                 680                 685

Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
    690                 695                 700

Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
705                 710                 715                 720

Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
                725                 730                 735

Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
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Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
        755                 760                 765

Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
    770                 775                 780

Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
785                 790                 795                 800

His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
                805                 810                 815

Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
            820                 825                 830

Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
        835                 840                 845

Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
    850                 855                 860

Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
865                 870                 875                 880

Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
                885                 890                 895

Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
            900                 905                 910

Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
        915                 920                 925

Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
    930                 935                 940

Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
945                 950                 955                 960

Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
                965                 970                 975

Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
            980                 985                 990

Val Thr Pro Val Thr Gly Arg Glu  Asn Ser Thr Ala Lys  Phe Ile Pro
        995                 1000                1005

Arg Glu  Glu Gly Leu Tyr Ala  Val Asp Val Thr Tyr  Asp Gly His
    1010                1015                1020

Pro Val  Pro Gly Ser Pro Tyr  Thr Val Glu Ala Ser  Leu Pro Pro
    1025                1030                1035

Asp Pro  Ser Lys Val Lys Ala  His Gly Pro Gly Leu  Glu Gly Gly
    1040                1045                1050

Leu Val  Gly Lys Pro Ala Glu  Phe Thr Ile Asp Thr  Lys Gly Ala
    1055                1060                1065

Gly Thr  Gly Gly Leu Gly Leu  Thr Val Glu Gly Pro  Cys Glu Ala
    1070                1075                1080

Lys Ile  Glu Cys Ser Asp Asn  Gly Asp Gly Thr Cys  Ser Val Ser
    1085                1090                1095

Tyr Leu  Pro Thr Lys Pro Gly  Glu Tyr Phe Val Asn  Ile Leu Phe
    1100                1105                1110

Glu Glu  Val His Ile Pro Gly  Ser Pro Phe Lys Ala  Asp Ile Glu
    1115                1120                1125

Met Pro  Phe Asp Pro Ser Lys  Val Val Ala Ser Gly  Pro Gly Leu
    1130                1135                1140
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Glu His  Gly Lys Val Gly Glu  Ala Gly Leu Leu Ser  Val Asp Cys
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Ser Glu  Ala Gly Pro Gly Ala  Leu Gly Leu Glu Ala  Val Ser Asp
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Ser Gly  Thr Lys Ala Glu Val  Ser Ile Gln Asn Asn  Lys Asp Gly
    1175                1180                1185

Thr Tyr  Ala Val Thr Tyr Val  Pro Leu Thr Ala Gly  Met Tyr Thr
    1190                1195                1200

Leu Thr  Met Lys Tyr Gly Gly  Glu Leu Val Pro His  Phe Pro Ala
    1205                1210                1215

Arg Val  Lys Val Glu Pro Ala  Val Asp Thr Ser Arg  Ile Lys Val
    1220                1225                1230

Phe Gly  Pro Gly Ile Glu Gly  Lys Asp Val Phe Arg  Glu Ala Thr
    1235                1240                1245

Thr Asp  Phe Thr Val Asp Ser  Arg Pro Leu Thr Gln  Val Gly Gly
    1250                1255                1260

Asp His  Ile Lys Ala His Ile  Ala Asn Pro Ser Gly  Ala Ser Thr
    1265                1270                1275

Glu Cys  Phe Val Thr Asp Asn  Ala Asp Gly Thr Tyr  Gln Val Glu
    1280                1285                1290

Tyr Thr  Pro Phe Glu Lys Gly  Leu His Val Val Glu  Val Thr Tyr
    1295                1300                1305

Asp Asp  Val Pro Ile Pro Asn  Ser Pro Phe Lys Val  Ala Val Thr
    1310                1315                1320

Glu Gly  Cys Gln Pro Ser Arg  Val Gln Ala Gln Gly  Pro Gly Leu
    1325                1330                1335

Lys Glu  Ala Phe Thr Asn Lys  Pro Asn Val Phe Thr  Val Val Thr
    1340                1345                1350

Arg Gly  Ala Gly Ile Gly Gly  Leu Gly Ile Thr Val  Glu Gly Pro
    1355                1360                1365

Ser Glu  Ser Lys Ile Asn Cys  Arg Asp Asn Lys Asp  Gly Ser Cys
    1370                1375                1380

Ser Ala  Glu Tyr Ile Pro Phe  Ala Pro Gly Asp Tyr  Asp Val Asn
    1385                1390                1395

Ile Thr  Tyr Gly Gly Ala His  Ile Pro Gly Ser Pro  Phe Arg Val
    1400                1405                1410

Pro Val  Lys Asp Val Val Asp  Pro Ser Lys Val Lys  Ile Ala Gly
    1415                1420                1425

Pro Gly  Leu Gly Ser Gly Val  Arg Ala Arg Val Leu  Gln Ser Phe
    1430                1435                1440

Thr Val  Asp Ser Ser Lys Ala  Gly Leu Ala Pro Leu  Glu Val Arg
    1445                1450                1455

Val Leu  Gly Pro Arg Gly Leu  Val Glu Pro Val Asn  Val Val Asp
    1460                1465                1470

Asn Gly  Asp Gly Thr His Thr  Val Thr Tyr Thr Pro  Ser Gln Glu
    1475                1480                1485

Gly Pro  Tyr Met Val Ser Val  Lys Tyr Ala Asp Glu  Glu Ile Pro
    1490                1495                1500

Arg Ser  Pro Phe Lys Val Lys  Val Leu Pro Thr Tyr  Asp Ala Ser
    1505                1510                1515

Lys Val  Thr Ala Ser Gly Pro  Gly Leu Ser Ser Tyr  Gly Val Pro
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Ala Ser  Leu Pro Val Asp Phe  Ala Ile Asp Ala Arg  Asp Ala Gly
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Glu Gly  Leu Leu Ala Val Gln  Ile Thr Asp Gln Glu  Gly Lys Pro
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Lys Arg  Ala Ile Val His Asp  Asn Lys Asp Gly Thr  Tyr Ala Val
    1565                1570                1575

Thr Tyr  Ile Pro Asp Lys Thr  Gly Arg Tyr Met Ile  Gly Val Thr
    1580                1585                1590

Tyr Gly  Gly Asp Asp Ile Pro  Leu Ser Pro Tyr Arg  Ile Arg Ala
    1595                1600                1605

Thr Gln  Thr Gly Asp Ala Ser  Lys Cys Leu Ala Thr  Gly Pro Gly
    1610                1615                1620

Ile Ala  Ser Thr Val Lys Thr  Gly Glu Glu Val Gly  Phe Val Val
    1625                1630                1635

Asp Ala  Lys Thr Ala Gly Lys  Gly Lys Val Thr Cys  Thr Val Leu
    1640                1645                1650

Thr Pro  Asp Gly Thr Glu Ala  Glu Ala Asp Val Ile  Glu Asn Glu
    1655                1660                1665

Asp Gly  Thr Tyr Asp Ile Phe  Tyr Thr Ala Ala Lys  Pro Gly Thr
    1670                1675                1680

Tyr Val  Ile Tyr Val Arg Phe  Gly Gly Val Asp Ile  Pro Asn Ser
    1685                1690                1695

Pro Phe  Thr Val Met Ala Thr  Asp Gly Glu Val Thr  Ala Val Glu
    1700                1705                1710

Glu Ala  Pro Val Thr Glu Glu  Ala Tyr Val Pro Val  Ser Asp Met
    1715                1720                1725

Asn Gly  Leu Gly Phe Lys Pro  Phe Asp Leu Val Ile  Pro Phe Ala
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Val Arg  Lys Gly Glu Ile Thr  Gly Glu Val His Met  Pro Ser Gly
    1745                1750                1755

Lys Thr  Ala Thr Pro Glu Ile  Val Asp Asn Lys Asp  Gly Thr Val
    1760                1765                1770

Thr Val  Arg Tyr Ala Pro Thr  Glu Val Gly Leu His  Glu Met His
    1775                1780                1785

Ile Lys  Tyr Met Gly Ser His  Ile Pro Glu Ser Pro  Leu Gln Phe
    1790                1795                1800

Tyr Val  Asn Tyr Pro Asn Ser  Gly Ser Val Ser Ala  Tyr Gly Pro
    1805                1810                1815

Gly Leu  Val Tyr Gly Val Ala  Asn Lys Thr Ala Thr  Phe Thr Ile
    1820                1825                1830

Val Thr  Glu Asp Ala Gly Glu  Gly Gly Leu Asp Leu  Ala Ile Glu
    1835                1840                1845

Gly Pro  Ser Lys Ala Glu Ile  Ser Cys Ile Asp Asn  Lys Asp Gly
    1850                1855                1860

Thr Cys  Thr Val Thr Tyr Leu  Pro Thr Leu Pro Gly  Asp Tyr Ser
    1865                1870                1875

Ile Leu  Val Lys Tyr Asn Asp  Lys His Ile Pro Gly  Ser Pro Phe
    1880                1885                1890

Thr Ala  Lys Ile Thr Asp Asp  Ser Arg Arg Cys Ser  Gln Val Lys
    1895                1900                1905

Leu Gly  Ser Ala Ala Asp Phe  Leu Leu Asp Ile Ser  Glu Thr Asp
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Leu Ser  Ser Leu Thr Ala Ser  Ile Lys Ala Pro Ser  Gly Arg Asp
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Glu Pro  Cys Leu Leu Lys Arg  Leu Pro Asn Asn His  Ile Gly Ile
    1940                1945                1950

Ser Phe  Ile Pro Arg Glu Val  Gly Glu His Leu Val  Ser Ile Lys
    1955                1960                1965

Lys Asn  Gly Asn His Val Ala  Asn Ser Pro Val Ser  Ile Met Val
    1970                1975                1980

Val Gln  Ser Glu Ile Gly Asp  Ala Arg Arg Ala Lys  Val Tyr Gly
    1985                1990                1995

Arg Gly  Leu Ser Glu Gly Arg  Thr Phe Glu Met Ser  Asp Phe Ile
    2000                2005                2010

Val Asp  Thr Arg Asp Ala Gly  Tyr Gly Gly Ile Ser  Leu Ala Val
    2015                2020                2025

Glu Gly  Pro Ser Lys Val Asp  Ile Gln Thr Glu Asp  Leu Glu Asp
    2030                2035                2040

Gly Thr  Cys Lys Val Ser Tyr  Phe Pro Thr Val Pro  Gly Val Tyr
    2045                2050                2055

Ile Val  Ser Thr Lys Phe Ala  Asp Glu His Val Pro  Gly Ser Pro
    2060                2065                2070

Phe Thr  Val Lys Ile Ser Gly  Glu Gly Arg Val Lys  Glu Ser Ile
    2075                2080                2085

Thr Arg  Thr Ser Arg Ala Pro  Ser Val Ala Thr Val  Gly Ser Ile
    2090                2095                2100

Cys Asp  Leu Asn Leu Lys Ile  Pro Glu Ile Asn Ser  Ser Asp Met
    2105                2110                2115

Ser Ala  His Val Thr Ser Pro  Ser Gly Arg Val Thr  Glu Ala Glu
    2120                2125                2130

Ile Val  Pro Met Gly Lys Asn  Ser His Cys Val Arg  Phe Val Pro
    2135                2140                2145

Gln Glu  Met Gly Val His Thr  Val Ser Val Lys Tyr  Arg Gly Gln
    2150                2155                2160

His Val  Thr Gly Ser Pro Phe  Gln Phe Thr Val Gly  Pro Leu Gly
    2165                2170                2175

Glu Gly  Gly Ala His Lys Val  Arg Ala Gly Gly Pro  Gly Leu Glu
    2180                2185                2190

Arg Gly  Glu Ala Gly Val Pro  Ala Glu Phe Ser Ile  Trp Thr Arg
    2195                2200                2205

Glu Ala  Gly Ala Gly Gly Leu  Ser Ile Ala Val Glu  Gly Pro Ser
    2210                2215                2220

Lys Ala  Glu Ile Thr Phe Asp  Asp His Lys Asn Gly  Ser Cys Gly
    2225                2230                2235

Val Ser  Tyr Ile Ala Gln Glu  Pro Gly Asn Tyr Glu  Val Ser Ile
    2240                2245                2250

Lys Phe  Asn Asp Glu His Ile  Pro Glu Ser Pro Tyr  Leu Val Pro
    2255                2260                2265

Val Ile  Ala Pro Ser Asp Asp  Ala Arg Arg Leu Thr  Val Met Ser
    2270                2275                2280

Leu Gln  Glu Ser Gly Leu Lys  Val Asn Gln Pro Ala  Ser Phe Ala
    2285                2290                2295
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Ile Arg  Leu Asn Gly Ala Lys  Gly Lys Ile Asp Ala  Lys Val His
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Ser Pro  Ser Gly Ala Val Glu  Glu Cys His Val Ser  Glu Leu Glu
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Pro Asp  Lys Tyr Ala Val Arg  Phe Ile Pro His Glu  Asn Gly Val
    2330                2335                2340

His Thr  Ile Asp Val Lys Phe  Asn Gly Ser His Val  Val Gly Ser
    2345                2350                2355

Pro Phe  Lys Val Arg Val Gly  Glu Pro Gly Gln Ala  Gly Asn Pro
    2360                2365                2370

Ala Leu  Val Ser Ala Tyr Gly  Thr Gly Leu Glu Gly  Gly Thr Thr
    2375                2380                2385

Gly Ile  Gln Ser Glu Phe Phe  Ile Asn Thr Thr Arg  Ala Gly Pro
    2390                2395                2400

Gly Thr  Leu Ser Val Thr Ile  Glu Gly Pro Ser Lys  Val Lys Met
    2405                2410                2415

Asp Cys  Gln Glu Thr Pro Glu  Gly Tyr Lys Val Met  Tyr Thr Pro
    2420                2425                2430

Met Ala  Pro Gly Asn Tyr Leu  Ile Ser Val Lys Tyr  Gly Gly Pro
    2435                2440                2445

Asn His  Ile Val Gly Ser Pro  Phe Lys Ala Lys Val  Thr Gly Gln
    2450                2455                2460

Arg Leu  Val Ser Pro Gly Ser  Ala Asn Glu Thr Ser  Ser Ile Leu
    2465                2470                2475

Val Glu  Ser Val Thr Arg Ser  Ser Thr Glu Thr Cys  Tyr Ser Ala
    2480                2485                2490

Ile Pro  Lys Ala Ser Ser Asp  Ala Ser Lys Val Thr  Ser Lys Gly
    2495                2500                2505

Ala Gly  Leu Ser Lys Ala Phe  Val Gly Gln Lys Ser  Ser Phe Leu
    2510                2515                2520

Val Asp  Cys Ser Lys Ala Gly  Ser Asn Met Leu Leu  Ile Gly Val
    2525                2530                2535

His Gly  Pro Thr Thr Pro Cys  Glu Glu Val Ser Met  Lys His Val
    2540                2545                2550

Gly Asn  Gln Gln Tyr Asn Val  Thr Tyr Val Val Lys  Glu Arg Gly
    2555                2560                2565

Asp Tyr  Val Leu Ala Val Lys  Trp Gly Glu Glu His  Ile Pro Gly
    2570                2575                2580

Ser Pro  Phe His Val Thr Val  Pro
    2585                2590


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<211> LENGTH: 9434
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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aaggatctag ctgaggacgc gccttggaag aagatccagc agaacacgtt cacacgctgg    240

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        35 40 45

Arg Leu Ile Ala Leu Leu Glu Val Leu Ser Gln Lys Arg Met Tyr Arg
    50 55 60

Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
65 70 75 80

Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
                85 90 95

Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
            100 105 110

Leu Val Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Val Trp
        115 120 125

Glu Asp Glu Gly Asp Asp Asp Ala Lys Lys Gln Thr Pro Lys Gln Arg
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Leu Leu Gly Trp Ile Gln Asn Lys Ile Pro Tyr Leu Pro Ile Thr Asn
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Phe Asn Gln Asn Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp
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Ser Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ser Trp Asp Pro Gln
            180 185 190

Lys Pro Val Asp Asn Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp
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Leu Gly Val Pro Gln Val Ile Thr Pro Glu Glu Ile Ile His Pro Asp
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Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala
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Lys Leu Lys Pro Gly Ala Pro Leu Lys Pro Lys Leu Asn Pro Lys Lys
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Ala Arg Ala Tyr Gly Arg Gly Ile Glu Pro Thr Gly Asn Met Val Lys
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Gln Pro Ala Lys Phe Thr Val Asp Thr Ile Ser Ala Gly Gln Gly Asp
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Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
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Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
305 310 315 320

Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
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His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
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Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala

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Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
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Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
465                 470                 475                 480

Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
                485                 490                 495

Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
            500                 505                 510

Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
        515                 520                 525

Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
    530                 535                 540

Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
545                 550                 555                 560

Gly Gly Ile Val Gly Arg Ser Ala Asp Phe Val Val Glu Ser Ile Gly
                565                 570                 575

Ser Glu Val Gly Ser Leu Gly Phe Ala Ile Glu Gly Pro Ser Gln Ala
            580                 585                 590

Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
        595                 600                 605

Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
    610                 615                 620

Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
625                 630                 635                 640

Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
                645                 650                 655

Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
            660                 665                 670

Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
        675                 680                 685

Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
    690                 695                 700

Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
705                 710                 715                 720

Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
                725                 730                 735

Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
            740                 745                 750

Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
        755                 760                 765

Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
    770                 775                 780
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Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
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His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
                805                 810                 815

Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
            820                 825                 830

Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
        835                 840                 845

Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
    850                 855                 860

Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
865                 870                 875                 880

Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
                885                 890                 895

Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
            900                 905                 910

Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
        915                 920                 925

Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
    930                 935                 940

Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
945                 950                 955                 960

Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
                965                 970                 975

Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
            980                 985                 990

Val Thr Pro Val Thr Gly Arg Glu  Asn Ser Thr Ala Lys  Phe Ile Pro
        995                 1000                1005

Arg Glu  Glu Gly Leu Tyr Ala  Val Asp Val Thr Tyr  Asp Gly His
    1010                1015                1020

Pro Val  Pro Gly Ser Pro Tyr  Thr Val Glu Ala Ser  Leu Pro Pro
    1025                1030                1035

Asp Pro  Ser Lys Val Lys Ala  His Gly Pro Gly Leu  Glu Gly Gly
    1040                1045                1050

Leu Val  Gly Lys Pro Ala Glu  Phe Thr Ile Asp Thr  Lys Gly Ala
    1055                1060                1065

Gly Thr  Gly Gly Leu Gly Leu  Thr Val Glu Gly Pro  Cys Glu Ala
    1070                1075                1080

Lys Ile  Glu Cys Ser Asp Asn  Gly Asp Gly Thr Cys  Ser Val Ser
    1085                1090                1095

Tyr Leu  Pro Thr Lys Pro Gly  Glu Tyr Phe Val Asn  Ile Leu Phe
    1100                1105                1110

Glu Glu  Val His Ile Pro Gly  Ser Pro Phe Lys Ala  Asp Ile Glu
    1115                1120                1125

Met Pro  Phe Asp Pro Ser Lys  Val Val Ala Ser Gly  Pro Gly Leu
    1130                1135                1140

Glu His  Gly Lys Val Gly Glu  Ala Gly Leu Leu Ser  Val Asp Cys
    1145                1150                1155

Ser Glu  Ala Gly Pro Gly Ala  Leu Gly Leu Glu Ala  Val Ser Asp
    1160                1165                1170

Ser Gly  Thr Lys Ala Glu Val  Ser Ile Gln Asn Asn  Lys Asp Gly
    1175                1180                1185
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Thr Tyr  Ala Val Thr Tyr Val  Pro Leu Thr Ala Gly  Met Tyr Thr
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Leu Thr  Met Lys Tyr Gly Gly  Glu Leu Val Pro His  Phe Pro Ala
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Arg Val  Lys Val Glu Pro Ala  Val Asp Thr Ser Arg  Ile Lys Val
    1220                1225                1230

Phe Gly  Pro Gly Ile Glu Gly  Lys Asp Val Phe Arg  Glu Ala Thr
    1235                1240                1245

Thr Asp  Phe Thr Val Asp Ser  Arg Pro Leu Thr Gln  Val Gly Gly
    1250                1255                1260

Asp His  Ile Lys Ala His Ile  Ala Asn Pro Ser Gly  Ala Ser Thr
    1265                1270                1275

Glu Cys  Phe Val Thr Asp Asn  Ala Asp Gly Thr Tyr  Gln Val Glu
    1280                1285                1290

Tyr Thr  Pro Phe Glu Lys Gly  Leu His Val Val Glu  Val Thr Tyr
    1295                1300                1305

Asp Asp  Val Pro Ile Pro Asn  Ser Pro Phe Lys Val  Ala Val Thr
    1310                1315                1320

Glu Gly  Cys Gln Pro Ser Arg  Val Gln Ala Gln Gly  Pro Gly Leu
    1325                1330                1335

Lys Glu  Ala Phe Thr Asn Lys  Pro Asn Val Phe Thr  Val Val Thr
    1340                1345                1350

Arg Gly  Ala Gly Ile Gly Gly  Leu Gly Ile Thr Val  Glu Gly Pro
    1355                1360                1365

Ser Glu  Ser Lys Ile Asn Cys  Arg Asp Asn Lys Asp  Gly Ser Cys
    1370                1375                1380

Ser Ala  Glu Tyr Ile Pro Phe  Ala Pro Gly Asp Tyr  Asp Val Asn
    1385                1390                1395

Ile Thr  Tyr Gly Gly Ala His  Ile Pro Gly Ser Pro  Phe Arg Val
    1400                1405                1410

Pro Val  Lys Asp Val Val Asp  Pro Ser Lys Val Lys  Ile Ala Gly
    1415                1420                1425

Pro Gly  Leu Gly Ser Gly Val  Arg Ala Arg Val Leu  Gln Ser Phe
    1430                1435                1440

Thr Val  Asp Ser Ser Lys Ala  Gly Leu Ala Pro Leu  Glu Val Arg
    1445                1450                1455

Val Leu  Gly Pro Arg Gly Leu  Val Glu Pro Val Asn  Val Val Asp
    1460                1465                1470

Asn Gly  Asp Gly Thr His Thr  Val Thr Tyr Thr Pro  Ser Gln Glu
    1475                1480                1485

Gly Pro  Tyr Met Val Ser Val  Lys Tyr Ala Asp Glu  Glu Ile Pro
    1490                1495                1500

Arg Ser  Pro Phe Lys Val Lys  Val Leu Pro Thr Tyr  Asp Ala Ser
    1505                1510                1515

Lys Val  Thr Ala Ser Gly Pro  Gly Leu Ser Ser Tyr  Gly Val Pro
    1520                1525                1530

Ala Ser  Leu Pro Val Asp Phe  Ala Ile Asp Ala Arg  Asp Ala Gly
    1535                1540                1545

Glu Gly  Leu Leu Ala Val Gln  Ile Thr Asp Gln Glu  Gly Lys Pro
    1550                1555                1560

Lys Arg  Ala Ile Val His Asp  Asn Lys Asp Gly Thr  Tyr Ala Val
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    1565                1570                1575

Thr Tyr  Ile Pro Asp Lys Thr  Gly Arg Tyr Met Ile  Gly Val Thr
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Tyr Gly  Gly Asp Asp Ile Pro  Leu Ser Pro Tyr Arg  Ile Arg Ala
    1595                1600                1605

Thr Gln  Thr Gly Asp Ala Ser  Lys Cys Leu Ala Thr  Gly Pro Gly
    1610                1615                1620

Ile Ala  Ser Thr Val Lys Thr  Gly Glu Glu Val Gly  Phe Val Val
    1625                1630                1635

Asp Ala  Lys Thr Ala Gly Lys  Gly Lys Val Thr Cys  Thr Val Leu
    1640                1645                1650

Thr Pro  Asp Gly Thr Glu Ala  Glu Ala Asp Val Ile  Glu Asn Glu
    1655                1660                1665

Asp Gly  Thr Tyr Asp Ile Phe  Tyr Thr Ala Ala Lys  Pro Gly Thr
    1670                1675                1680

Tyr Val  Ile Tyr Val Arg Phe  Gly Gly Val Asp Ile  Pro Asn Ser
    1685                1690                1695

Pro Phe  Thr Val Met Val Thr  Glu Glu Ala Tyr Val  Pro Val Ser
    1700                1705                1710

Asp Met  Asn Gly Leu Gly Phe  Lys Pro Phe Asp Leu  Val Ile Pro
    1715                1720                1725

Phe Ala  Val Arg Lys Gly Glu  Ile Thr Gly Glu Val  His Met Pro
    1730                1735                1740

Ser Gly  Lys Thr Ala Thr Pro  Glu Ile Val Asp Asn  Lys Asp Gly
    1745                1750                1755

Thr Val  Thr Val Arg Tyr Ala  Pro Thr Glu Val Gly  Leu His Glu
    1760                1765                1770

Met His  Ile Lys Tyr Met Gly  Ser His Ile Pro Glu  Ser Pro Leu
    1775                1780                1785

Gln Phe  Tyr Val Asn Tyr Pro  Asn Ser Gly Ser Val  Ser Ala Tyr
    1790                1795                1800

Gly Pro  Gly Leu Val Tyr Gly  Val Ala Asn Lys Thr  Ala Thr Phe
    1805                1810                1815

Thr Ile  Val Thr Glu Asp Ala  Gly Glu Gly Gly Leu  Asp Leu Ala
    1820                1825                1830

Ile Glu  Gly Pro Ser Lys Ala  Glu Ile Ser Cys Ile  Asp Asn Lys
    1835                1840                1845

Asp Gly  Thr Cys Thr Val Thr  Tyr Leu Pro Thr Leu  Pro Gly Asp
    1850                1855                1860

Tyr Ser  Ile Leu Val Lys Tyr  Asn Asp Lys His Ile  Pro Gly Ser
    1865                1870                1875

Pro Phe  Thr Ala Lys Ile Thr  Asp Asp Ser Arg Arg  Cys Ser Gln
    1880                1885                1890

Val Lys  Leu Gly Ser Ala Ala  Asp Phe Leu Leu Asp  Ile Ser Glu
    1895                1900                1905

Thr Asp  Leu Ser Ser Leu Thr  Ala Ser Ile Lys Ala  Pro Ser Gly
    1910                1915                1920

Arg Asp  Glu Pro Cys Leu Leu  Lys Arg Leu Pro Asn  Asn His Ile
    1925                1930                1935

Gly Ile  Ser Phe Ile Pro Arg  Glu Val Gly Glu His  Leu Val Ser
    1940                1945                1950
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Ile Lys  Lys Asn Gly Asn His  Val Ala Asn Ser Pro  Val Ser Ile
    1955                1960                1965

Met Val  Val Gln Ser Glu Ile  Gly Asp Ala Arg Arg  Ala Lys Val
    1970                1975                1980

Tyr Gly  Arg Gly Leu Ser Glu  Gly Arg Thr Phe Glu  Met Ser Asp
    1985                1990                1995

Phe Ile  Val Asp Thr Arg Asp  Ala Gly Tyr Gly Gly  Ile Ser Leu
    2000                2005                2010

Ala Val  Glu Gly Pro Ser Lys  Val Asp Ile Gln Thr  Glu Asp Leu
    2015                2020                2025

Glu Asp  Gly Thr Cys Lys Val  Ser Tyr Phe Pro Thr  Val Pro Gly
    2030                2035                2040

Val Tyr  Ile Val Ser Thr Lys  Phe Ala Asp Glu His  Val Pro Gly
    2045                2050                2055

Ser Pro  Phe Thr Val Lys Ile  Ser Gly Glu Gly Arg  Val Lys Glu
    2060                2065                2070

Ser Ile  Thr Arg Thr Ser Arg  Ala Pro Ser Val Ala  Thr Val Gly
    2075                2080                2085

Ser Ile  Cys Asp Leu Asn Leu  Lys Ile Pro Glu Ile  Asn Ser Ser
    2090                2095                2100

Asp Met  Ser Ala His Val Thr  Ser Pro Ser Gly Arg  Val Thr Glu
    2105                2110                2115

Ala Glu  Ile Val Pro Met Gly  Lys Asn Ser His Cys  Val Arg Phe
    2120                2125                2130

Val Pro  Gln Glu Met Gly Val  His Thr Val Ser Val  Lys Tyr Arg
    2135                2140                2145

Gly Gln  His Val Thr Gly Ser  Pro Phe Gln Phe Thr  Val Gly Pro
    2150                2155                2160

Leu Gly  Glu Gly Gly Ala His  Lys Val Arg Ala Gly  Gly Pro Gly
    2165                2170                2175

Leu Glu  Arg Gly Glu Ala Gly  Val Pro Ala Glu Phe  Ser Ile Trp
    2180                2185                2190

Thr Arg  Glu Ala Gly Ala Gly  Gly Leu Ser Ile Ala  Val Glu Gly
    2195                2200                2205

Pro Ser  Lys Ala Glu Ile Thr  Phe Asp Asp His Lys  Asn Gly Ser
    2210                2215                2220

Cys Gly  Val Ser Tyr Ile Ala  Gln Glu Pro Gly Asn  Tyr Glu Val
    2225                2230                2235

Ser Ile  Lys Phe Asn Asp Glu  His Ile Pro Glu Ser  Pro Tyr Leu
    2240                2245                2250

Val Pro  Val Ile Ala Pro Ser  Asp Asp Ala Arg Arg  Leu Thr Val
    2255                2260                2265

Met Ser  Leu Gln Glu Ser Gly  Leu Lys Val Asn Gln  Pro Ala Ser
    2270                2275                2280

Phe Ala  Ile Arg Leu Asn Gly  Ala Lys Gly Lys Ile  Asp Ala Lys
    2285                2290                2295

Val His  Ser Pro Ser Gly Ala  Val Glu Glu Cys His  Val Ser Glu
    2300                2305                2310

Leu Glu  Pro Asp Lys Tyr Ala  Val Arg Phe Ile Pro  His Glu Asn
    2315                2320                2325

Gly Val  His Thr Ile Asp Val  Lys Phe Asn Gly Ser  His Val Val
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Gly Ser  Pro Phe Lys Val Arg  Val Gly Glu Pro Gly  Gln Ala Gly
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Asn Pro  Ala Leu Val Ser Ala  Tyr Gly Thr Gly Leu  Glu Gly Gly
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Thr Thr  Gly Ile Gln Ser Glu  Phe Phe Ile Asn Thr  Thr Arg Ala
    2375                 2380                 2385

Gly Pro  Gly Thr Leu Ser Val  Thr Ile Glu Gly Pro  Ser Lys Val
    2390                 2395                 2400

Lys Met  Asp Cys Gln Glu Thr  Pro Glu Gly Tyr Lys  Val Met Tyr
    2405                 2410                 2415

Thr Pro  Met Ala Pro Gly Asn  Tyr Leu Ile Ser Val  Lys Tyr Gly
    2420                 2425                 2430

Gly Pro  Asn His Ile Val Gly  Ser Pro Phe Lys Ala  Lys Val Thr
    2435                 2440                 2445

Gly Gln  Arg Leu Val Ser Pro  Gly Ser Ala Asn Glu  Thr Ser Ser
    2450                 2455                 2460

Ile Leu  Val Glu Ser Val Thr  Arg Ser Ser Thr Glu  Thr Cys Tyr
    2465                 2470                 2475

Ser Ala  Ile Pro Lys Ala Ser  Ser Asp Ala Ser Lys  Val Thr Ser
    2480                 2485                 2490

Lys Gly  Ala Gly Leu Ser Lys  Ala Phe Val Gly Gln  Lys Ser Ser
    2495                 2500                 2505

Phe Leu  Val Asp Cys Ser Lys  Ala Gly Ser Asn Met  Leu Leu Ile
    2510                 2515                 2520

Gly Val  His Gly Pro Thr Thr  Pro Cys Glu Glu Val  Ser Met Lys
    2525                 2530                 2535

His Val  Gly Asn Gln Gln Tyr  Asn Val Thr Tyr Val  Val Lys Glu
    2540                 2545                 2550

Arg Gly  Asp Tyr Val Leu Ala  Val Lys Trp Gly Glu  Glu His Ile
    2555                 2560                 2565

Pro Gly  Ser Pro Phe His Val  Thr Val Pro
    2570                 2575
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<211> LENGTH: 2602
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Ile Gln Gln Asn Thr Phe Thr Arg Trp Cys Asn Glu His Leu Lys Cys
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Val Asn Lys Arg Ile Gly Asn Leu Gln Thr Asp Leu Ser Asp Gly Leu
        35                  40                  45

Arg Leu Ile Ala Leu Leu Glu Val Leu Ser Gln Lys Arg Met Tyr Arg
    50                  55                  60

Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
65                  70                  75                  80

Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
                85                  90                  95

Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
            100                 105                 110

Leu Val Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Val Trp
        115                 120                 125

Glu Asp Glu Gly Asp Asp Asp Ala Lys Lys Gln Thr Pro Lys Gln Arg
    130                 135                 140

Leu Leu Gly Trp Ile Gln Asn Lys Ile Pro Tyr Leu Pro Ile Thr Asn
145                 150                 155                 160

Phe Asn Gln Asn Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp
                165                 170                 175

Ser Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ser Trp Asp Pro Gln
            180                 185                 190

Lys Pro Val Asp Asn Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp
        195                 200                 205

Leu Gly Val Pro Gln Val Ile Thr Pro Glu Glu Ile Ile His Pro Asp
    210                 215                 220

Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala
225                 230                 235                 240

Lys Leu Lys Pro Gly Ala Pro Leu Lys Pro Lys Leu Asn Pro Lys Lys
                245                 250                 255

Ala Arg Ala Tyr Gly Arg Gly Ile Glu Pro Thr Gly Asn Met Val Lys
            260                 265                 270

Gln Pro Ala Lys Phe Thr Val Asp Thr Ile Ser Ala Gly Gln Gly Asp
        275                 280                 285

Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
    290                 295                 300

Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
305                 310                 315                 320

Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
                325                 330                 335

His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
            340                 345                 350

Asp Ala Ser Lys Val Thr Ala Lys Gly Pro Gly Leu Glu Ala Val Gly
        355                 360                 365

Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala
    370                 375                 380

Gly Val Gly Asp Ile Gly Val Glu Val Glu Asp Pro Gln Gly Lys Asn
385                 390                 395                 400

Thr Val Glu Leu Leu Val Glu Asp Lys Gly Asn Gln Val Tyr Arg Cys
                405                 410                 415

Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
            420                 425                 430

Ala Gly Asp Thr Ile Pro Lys Ser Pro Phe Val Val Gln Val Gly Glu
        435                 440                 445
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Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu Gln Pro
    450                 455                 460

Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
465                 470                 475                 480

Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
                485                 490                 495

Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
            500                 505                 510

Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
        515                 520                 525

Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
    530                 535                 540

Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
545                 550                 555                 560

Gly Gly Ile Val Gly Arg Ser Ala Asp Phe Val Val Glu Ser Ile Gly
                565                 570                 575

Ser Glu Val Gly Ser Leu Gly Phe Ala Ile Glu Gly Pro Ser Gln Ala
            580                 585                 590

Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
        595                 600                 605

Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
    610                 615                 620

Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
625                 630                 635                 640

Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
                645                 650                 655

Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
            660                 665                 670

Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
        675                 680                 685

Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
    690                 695                 700

Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
705                 710                 715                 720

Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
                725                 730                 735

Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
            740                 745                 750

Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
        755                 760                 765

Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
    770                 775                 780

Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
785                 790                 795                 800

His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
                805                 810                 815

Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
            820                 825                 830

Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
        835                 840                 845

Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
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    850                 855                 860

Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
865                 870                 875                 880

Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
                885                 890                 895

Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
            900                 905                 910

Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
        915                 920                 925

Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
    930                 935                 940

Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
945                 950                 955                 960

Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
                965                 970                 975

Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
            980                 985                 990

Val Thr Pro Val Thr Gly Arg Glu  Asn Ser Thr Ala Lys  Phe Ile Pro
        995                 1000                1005

Arg Glu  Glu Gly Leu Tyr Ala  Val Asp Val Thr Tyr  Asp Gly His
    1010                1015                1020

Pro Val  Pro Gly Ser Pro Tyr  Thr Val Glu Ala Ser  Leu Pro Pro
    1025                1030                1035

Asp Pro  Ser Lys Val Lys Ala  His Gly Pro Gly Leu  Glu Gly Gly
    1040                1045                1050

Leu Val  Gly Lys Pro Ala Glu  Phe Thr Ile Asp Thr  Lys Gly Ala
    1055                1060                1065

Gly Thr  Gly Gly Leu Gly Leu  Thr Val Glu Gly Pro  Cys Glu Ala
    1070                1075                1080

Lys Ile  Glu Cys Ser Asp Asn  Gly Asp Gly Thr Cys  Ser Val Ser
    1085                1090                1095

Tyr Leu  Pro Thr Lys Pro Gly  Glu Tyr Phe Val Asn  Ile Leu Phe
    1100                1105                1110

Glu Glu  Val His Ile Pro Gly  Ser Pro Phe Lys Ala  Asp Ile Glu
    1115                1120                1125

Met Pro  Phe Asp Pro Ser Lys  Val Val Ala Ser Gly  Pro Gly Leu
    1130                1135                1140

Glu His  Gly Lys Val Gly Glu  Ala Gly Leu Leu Ser  Val Asp Cys
    1145                1150                1155

Ser Glu  Ala Gly Pro Gly Ala  Leu Gly Leu Glu Ala  Val Ser Asp
    1160                1165                1170

Ser Gly  Thr Lys Ala Glu Val  Ser Ile Gln Asn Asn  Lys Asp Gly
    1175                1180                1185

Thr Tyr  Ala Val Thr Tyr Val  Pro Leu Thr Ala Gly  Met Tyr Thr
    1190                1195                1200

Leu Thr  Met Lys Tyr Gly Gly  Glu Leu Val Pro His  Phe Pro Ala
    1205                1210                1215

Arg Val  Lys Val Glu Pro Ala  Val Asp Thr Ser Arg  Ile Lys Val
    1220                1225                1230

Phe Gly  Pro Gly Ile Glu Gly  Lys Asp Val Phe Arg  Glu Ala Thr
    1235                1240                1245
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Thr Asp  Phe Thr Val Asp Ser  Arg Pro Leu Thr Gln  Val Gly Gly
    1250                1255                1260

Asp His  Ile Lys Ala His Ile  Ala Asn Pro Ser Gly  Ala Ser Thr
    1265                1270                1275

Glu Cys  Phe Val Thr Asp Asn  Ala Asp Gly Thr Tyr  Gln Val Glu
    1280                1285                1290

Tyr Thr  Pro Phe Glu Lys Gly  Leu His Val Val Glu  Val Thr Tyr
    1295                1300                1305

Asp Asp  Val Pro Ile Pro Asn  Ser Pro Phe Lys Val  Ala Val Thr
    1310                1315                1320

Glu Gly  Cys Gln Pro Ser Arg  Val Gln Ala Gln Gly  Pro Gly Leu
    1325                1330                1335

Lys Glu  Ala Phe Thr Asn Lys  Pro Asn Val Phe Thr  Val Val Thr
    1340                1345                1350

Arg Gly  Ala Gly Ile Gly Gly  Leu Gly Ile Thr Val  Glu Gly Pro
    1355                1360                1365

Ser Glu  Ser Lys Ile Asn Cys  Arg Asp Asn Lys Asp  Gly Ser Cys
    1370                1375                1380

Ser Ala  Glu Tyr Ile Pro Phe  Ala Pro Gly Asp Tyr  Asp Val Asn
    1385                1390                1395

Ile Thr  Tyr Gly Gly Ala His  Ile Pro Gly Ser Pro  Phe Arg Val
    1400                1405                1410

Pro Val  Lys Asp Val Val Asp  Pro Ser Lys Val Lys  Ile Ala Gly
    1415                1420                1425

Pro Gly  Leu Gly Ser Gly Val  Arg Ala Arg Val Leu  Gln Ser Phe
    1430                1435                1440

Thr Val  Asp Ser Ser Lys Ala  Gly Leu Ala Pro Leu  Glu Val Arg
    1445                1450                1455

Val Leu  Gly Pro Arg Gly Leu  Val Glu Pro Val Asn  Val Val Asp
    1460                1465                1470

Asn Gly  Asp Gly Thr His Thr  Val Thr Tyr Thr Pro  Ser Gln Glu
    1475                1480                1485

Gly Pro  Tyr Met Val Ser Val  Lys Tyr Ala Asp Glu  Glu Ile Pro
    1490                1495                1500

Arg Ser  Pro Phe Lys Val Lys  Val Leu Pro Thr Tyr  Asp Ala Ser
    1505                1510                1515

Lys Val  Thr Ala Ser Gly Pro  Gly Leu Ser Ser Tyr  Gly Val Pro
    1520                1525                1530

Ala Ser  Leu Pro Val Asp Phe  Ala Ile Asp Ala Arg  Asp Ala Gly
    1535                1540                1545

Glu Gly  Leu Leu Ala Val Gln  Ile Thr Asp Gln Glu  Gly Lys Pro
    1550                1555                1560

Lys Arg  Ala Ile Val His Asp  Asn Lys Asp Gly Thr  Tyr Ala Val
    1565                1570                1575

Thr Tyr  Ile Pro Asp Lys Thr  Gly Arg Tyr Met Ile  Gly Val Thr
    1580                1585                1590

Tyr Gly  Gly Asp Asp Ile Pro  Leu Ser Pro Tyr Arg  Ile Arg Ala
    1595                1600                1605

Thr Gln  Thr Gly Asp Ala Ser  Lys Cys Leu Ala Thr  Gly Pro Gly
    1610                1615                1620

Ile Ala  Ser Thr Val Lys Thr  Gly Glu Glu Val Gly  Phe Val Val
    1625                1630                1635
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Asp Ala  Lys Thr Ala Gly Lys  Gly Lys Val Thr Cys  Thr Val Leu
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Thr Pro  Asp Gly Thr Glu Ala  Glu Ala Asp Val Ile  Glu Asn Glu
    1655                 1660                 1665

Asp Gly  Thr Tyr Asp Ile Phe  Tyr Thr Ala Ala Lys  Pro Gly Thr
    1670                 1675                 1680

Tyr Val  Ile Tyr Val Arg Phe  Gly Gly Val Asp Ile  Pro Asn Ser
    1685                 1690                 1695

Pro Phe  Thr Val Met Ala Thr  Asp Gly Glu Val Thr  Ala Val Glu
    1700                 1705                 1710

Glu Ala  Pro Val Asn Ala Cys  Pro Pro Gly Phe Arg  Pro Trp Val
    1715                 1720                 1725

Thr Glu  Glu Ala Tyr Val Pro  Val Ser Asp Met Asn  Gly Leu Gly
    1730                 1735                 1740

Phe Lys  Pro Phe Asp Leu Val  Ile Pro Phe Ala Val  Arg Lys Gly
    1745                 1750                 1755

Glu Ile  Thr Gly Glu Val His  Met Pro Ser Gly Lys  Thr Ala Thr
    1760                 1765                 1770

Pro Glu  Ile Val Asp Asn Lys  Asp Gly Thr Val Thr  Val Arg Tyr
    1775                 1780                 1785

Ala Pro  Thr Glu Val Gly Leu  His Glu Met His Ile  Lys Tyr Met
    1790                 1795                 1800

Gly Ser  His Ile Pro Glu Ser  Pro Leu Gln Phe Tyr  Val Asn Tyr
    1805                 1810                 1815

Pro Asn  Ser Gly Ser Val Ser  Ala Tyr Gly Pro Gly  Leu Val Tyr
    1820                 1825                 1830

Gly Val  Ala Asn Lys Thr Ala  Thr Phe Thr Ile Val  Thr Glu Asp
    1835                 1840                 1845

Ala Gly  Glu Gly Gly Leu Asp  Leu Ala Ile Glu Gly  Pro Ser Lys
    1850                 1855                 1860

Ala Glu  Ile Ser Cys Ile Asp  Asn Lys Asp Gly Thr  Cys Thr Val
    1865                 1870                 1875

Thr Tyr  Leu Pro Thr Leu Pro  Gly Asp Tyr Ser Ile  Leu Val Lys
    1880                 1885                 1890

Tyr Asn  Asp Lys His Ile Pro  Gly Ser Pro Phe Thr  Ala Lys Ile
    1895                 1900                 1905

Thr Asp  Asp Ser Arg Arg Cys  Ser Gln Val Lys Leu  Gly Ser Ala
    1910                 1915                 1920

Ala Asp  Phe Leu Leu Asp Ile  Ser Glu Thr Asp Leu  Ser Ser Leu
    1925                 1930                 1935

Thr Ala  Ser Ile Lys Ala Pro  Ser Gly Arg Asp Glu  Pro Cys Leu
    1940                 1945                 1950

Leu Lys  Arg Leu Pro Asn Asn  His Ile Gly Ile Ser  Phe Ile Pro
    1955                 1960                 1965

Arg Glu  Val Gly Glu His Leu  Val Ser Ile Lys Lys  Asn Gly Asn
    1970                 1975                 1980

His Val  Ala Asn Ser Pro Val  Ser Ile Met Val Val  Gln Ser Glu
    1985                 1990                 1995

Ile Gly  Asp Ala Arg Arg Ala  Lys Val Tyr Gly Arg  Gly Leu Ser
    2000                 2005                 2010

Glu Gly  Arg Thr Phe Glu Met  Ser Asp Phe Ile Val  Asp Thr Arg
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    2015                2020                2025

Asp Ala  Gly Tyr Gly Gly Ile  Ser Leu Ala Val Glu  Gly Pro Ser
    2030                2035                2040

Lys Val  Asp Ile Gln Thr Glu  Asp Leu Glu Asp Gly  Thr Cys Lys
    2045                2050                2055

Val Ser  Tyr Phe Pro Thr Val  Pro Gly Val Tyr Ile  Val Ser Thr
    2060                2065                2070

Lys Phe  Ala Asp Glu His Val  Pro Gly Ser Pro Phe  Thr Val Lys
    2075                2080                2085

Ile Ser  Gly Glu Gly Arg Val  Lys Glu Ser Ile Thr  Arg Thr Ser
    2090                2095                2100

Arg Ala  Pro Ser Val Ala Thr  Val Gly Ser Ile Cys  Asp Leu Asn
    2105                2110                2115

Leu Lys  Ile Pro Glu Ile Asn  Ser Ser Asp Met Ser  Ala His Val
    2120                2125                2130

Thr Ser  Pro Ser Gly Arg Val  Thr Glu Ala Glu Ile  Val Pro Met
    2135                2140                2145

Gly Lys  Asn Ser His Cys Val  Arg Phe Val Pro Gln  Glu Met Gly
    2150                2155                2160

Val His  Thr Val Ser Val Lys  Tyr Arg Gly Gln His  Val Thr Gly
    2165                2170                2175

Ser Pro  Phe Gln Phe Thr Val  Gly Pro Leu Gly Glu  Gly Gly Ala
    2180                2185                2190

His Lys  Val Arg Ala Gly Gly  Pro Gly Leu Glu Arg  Gly Glu Ala
    2195                2200                2205

Gly Val  Pro Ala Glu Phe Ser  Ile Trp Thr Arg Glu  Ala Gly Ala
    2210                2215                2220

Gly Gly  Leu Ser Ile Ala Val  Glu Gly Pro Ser Lys  Ala Glu Ile
    2225                2230                2235

Thr Phe  Asp Asp His Lys Asn  Gly Ser Cys Gly Val  Ser Tyr Ile
    2240                2245                2250

Ala Gln  Glu Pro Gly Asn Tyr  Glu Val Ser Ile Lys  Phe Asn Asp
    2255                2260                2265

Glu His  Ile Pro Glu Ser Pro  Tyr Leu Val Pro Val  Ile Ala Pro
    2270                2275                2280

Ser Asp  Asp Ala Arg Arg Leu  Thr Val Met Ser Leu  Gln Glu Ser
    2285                2290                2295

Gly Leu  Lys Val Asn Gln Pro  Ala Ser Phe Ala Ile  Arg Leu Asn
    2300                2305                2310

Gly Ala  Lys Gly Lys Ile Asp  Ala Lys Val His Ser  Pro Ser Gly
    2315                2320                2325

Ala Val  Glu Glu Cys His Val  Ser Glu Leu Glu Pro  Asp Lys Tyr
    2330                2335                2340

Ala Val  Arg Phe Ile Pro His  Glu Asn Gly Val His  Thr Ile Asp
    2345                2350                2355

Val Lys  Phe Asn Gly Ser His  Val Val Gly Ser Pro  Phe Lys Val
    2360                2365                2370

Arg Val  Gly Glu Pro Gly Gln  Ala Gly Asn Pro Ala  Leu Val Ser
    2375                2380                2385

Ala Tyr  Gly Thr Gly Leu Glu  Gly Gly Thr Thr Gly  Ile Gln Ser
    2390                2395                2400
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Glu Phe  Phe Ile Asn Thr Thr  Arg Ala Gly Pro Gly  Thr Leu Ser
    2405                2410                2415

Val Thr  Ile Glu Gly Pro Ser  Lys Val Lys Met Asp  Cys Gln Glu
    2420                2425                2430

Thr Pro  Glu Gly Tyr Lys Val  Met Tyr Thr Pro Met  Ala Pro Gly
    2435                2440                2445

Asn Tyr  Leu Ile Ser Val Lys  Tyr Gly Gly Pro Asn  His Ile Val
    2450                2455                2460

Gly Ser  Pro Phe Lys Ala Lys  Val Thr Gly Gln Arg  Leu Val Ser
    2465                2470                2475

Pro Gly  Ser Ala Asn Glu Thr  Ser Ser Ile Leu Val  Glu Ser Val
    2480                2485                2490

Thr Arg  Ser Ser Thr Glu Thr  Cys Tyr Ser Ala Ile  Pro Lys Ala
    2495                2500                2505

Ser Ser  Asp Ala Ser Lys Val  Thr Ser Lys Gly Ala  Gly Leu Ser
    2510                2515                2520

Lys Ala  Phe Val Gly Gln Lys  Ser Ser Phe Leu Val  Asp Cys Ser
    2525                2530                2535

Lys Ala  Gly Ser Asn Met Leu  Leu Ile Gly Val His  Gly Pro Thr
    2540                2545                2550

Thr Pro  Cys Glu Glu Val Ser  Met Lys His Val Gly  Asn Gln Gln
    2555                2560                2565

Tyr Asn  Val Thr Tyr Val Val  Lys Glu Arg Gly Asp  Tyr Val Leu
    2570                2575                2580

Ala Val  Lys Trp Gly Glu Glu  His Ile Pro Gly Ser  Pro Phe His
    2585                2590                2595

Val Thr  Val Pro
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<210> SEQ ID NO 29
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<213> ORGANISM: Homo sapiens

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agtccccggc agctcgttgc gcattgcgct ctccccgcca ccaggatgcc ggtaaccgag    180

aaggatctag ctgaggacgc gccttggaag aagatccagc agaacacgtt cacacgctgg    240

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tgggaatcct gggacccgca gaagcctgtg gataatgcac gagaagccat gcagcaggca    780

gatgactggc tgggtgtccc acaggtcatc actcctgaag aaatcattca cccggatgtg    840
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gcaaaggaga tgacttaaaa tccgcttaat ctcttccagt gtccgtgtta atgtatttgg   8460

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gaccacgggt gttgtaagct gggacacgga agccaaactg gaatcaaacg ccgactgtaa   9420

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<210> SEQ ID NO 30
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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Met Val Ala Pro Lys Ser His Thr Asp Asp Trp Ala Pro Gly Pro Phe
1               5                  10                  15

Ser Ser Lys Pro Gln Arg Ser Gln Leu Gln Ile Phe Ser Ser Val Leu
            20                  25                  30

Gln Thr Ser Leu Leu Phe Leu Leu Met Gly Leu Arg Ala Ser Gly Lys
        35                  40                  45

Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
    50                  55                  60
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Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
65                  70                  75                  80

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
                85                  90                  95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
            100                 105                 110

Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser
        115                 120                 125

Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
    130                 135                 140

Glu Phe Thr Leu Phe Val Tyr Ala Pro Phe Ile Glu Lys Leu Ser Val
145                 150                 155                 160

His Val Ile Glu Gly Asp His Arg Thr Leu Leu Glu Gly Ser Gly Leu
                165                 170                 175

Glu Ser Ile Ile Ser Thr Leu Ala Glu Pro Arg Val Ser Val Arg Glu
            180                 185                 190

Gly
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<210> SEQ ID NO 31
<211> LENGTH: 1525
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

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acacgtgtgg accccatttt atttttacac caatttggtg aaaatgctgc tttcctcagc 1440

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aaataaaaag tatcttttct cccca 1525

<210> SEQ ID NO 32
<211> LENGTH: 641
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Met Val Ala Pro Lys Ser His Thr Asp Asp Trp Ala Pro Gly Pro Phe
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Ser Ser Lys Pro Gln Arg Ser Gln Leu Gln Ile Phe Ser Ser Val Leu
20 25 30

Gln Thr Ser Leu Leu Phe Leu Leu Met Gly Leu Arg Ala Ser Gly Lys
35 40 45

Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
50 55 60

Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
65 70 75 80

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
85 90 95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
100 105 110

Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser
115 120 125

Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
130 135 140

Glu Phe Thr Leu Phe Val Tyr Glu Gln Leu Gln Glu Pro Gln Val Thr
145 150 155 160

Met Lys Ser Val Lys Val Ser Glu Asn Phe Ser Cys Asn Ile Thr Leu
165 170 175

Met Cys Ser Val Lys Gly Ala Glu Lys Ser Val Leu Tyr Ser Trp Thr
180 185 190

Pro Arg Glu Pro His Ala Ser Glu Ser Asn Gly Gly Ser Ile Leu Thr
195 200 205

Val Ser Arg Thr Pro Cys Asp Pro Asp Leu Pro Tyr Ile Cys Thr Ala
210 215 220

Gln Asn Pro Val Ser Gln Arg Ser Ser Leu Pro Val His Val Gly Gln
225 230 235 240

Phe Cys Thr Asp Pro Gly Ala Ser Arg Gly Gly Thr Thr Gly Glu Thr
245 250 255

Val Val Gly Val Leu Gly Glu Pro Val Thr Leu Pro Leu Ala Leu Pro
260 265 270

Ala Cys Arg Asp Thr Glu Lys Val Val Trp Leu Phe Asn Thr Ser Ile
275 280 285

Ile Ser Lys Glu Arg Glu Glu Ala Ala Thr Ala Asp Pro Leu Ile Lys
290 295 300

Ser Arg Asp Pro Tyr Lys Asn Arg Val Trp Val Ser Ser Gln Asp Cys
305 310 315 320

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Ser Leu Lys Ile Ser Gln Leu Lys Ile Glu Asp Ala Gly Pro Tyr His
                325                 330                 335

Ala Tyr Val Cys Ser Glu Ala Ser Ser Val Thr Ser Met Thr His Val
            340                 345                 350

Thr Leu Leu Ile Tyr Arg Arg Leu Arg Lys Pro Lys Ile Thr Trp Ser
        355                 360                 365

Leu Arg His Ser Glu Asp Gly Ile Cys Arg Ile Ser Leu Thr Cys Ser
    370                 375                 380

Val Glu Asp Gly Gly Asn Thr Val Met Tyr Thr Trp Thr Pro Leu Gln
385                 390                 395                 400

Lys Glu Ala Val Val Ser Gln Gly Glu Ser His Leu Asn Val Ser Trp
                405                 410                 415

Arg Ser Ser Glu Asn His Pro Asn Leu Thr Cys Thr Ala Ser Asn Pro
            420                 425                 430

Val Ser Arg Ser Ser His Gln Phe Leu Ser Glu Asn Ile Cys Ser Gly
        435                 440                 445

Pro Glu Arg Asn Thr Lys Leu Trp Ile Gly Leu Phe Leu Met Val Cys
    450                 455                 460

Leu Leu Cys Val Gly Ile Phe Ser Trp Cys Ile Trp Lys Arg Lys Gly
465                 470                 475                 480

Arg Cys Ser Val Pro Ala Phe Cys Ser Ser Gln Ala Glu Ala Pro Ala
                485                 490                 495

Asp Thr Pro Gly Tyr Glu Lys Leu Asp Thr Pro Leu Arg Pro Ala Arg
            500                 505                 510

Gln Gln Pro Thr Pro Thr Ser Asp Ser Ser Ser Asp Ser Asn Leu Thr
        515                 520                 525

Thr Glu Glu Asp Glu Asp Arg Pro Glu Val His Lys Pro Ile Ser Gly
    530                 535                 540

Arg Tyr Glu Val Phe Asp Gln Val Thr Gln Glu Gly Ala Gly His Asp
545                 550                 555                 560

Pro Ala Pro Glu Gly Gln Ala Asp Tyr Asp Pro Val Thr Pro Tyr Val
                565                 570                 575

Thr Glu Val Glu Ser Val Val Gly Glu Asn Thr Met Tyr Ala Gln Val
            580                 585                 590

Phe Asn Leu Gln Gly Lys Thr Pro Val Ser Gln Lys Glu Glu Ser Ser
        595                 600                 605

Ala Thr Ile Tyr Cys Ser Ile Arg Lys Pro Gln Val Val Pro Pro Pro
    610                 615                 620

Gln Gln Asn Asp Leu Glu Ile Pro Glu Ser Pro Thr Tyr Glu Asn Phe
625                 630                 635                 640

Thr
```

<210> SEQ ID NO 33
<211> LENGTH: 2508
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

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acatacacat acacatgcac acacacactc atatacacat gcagaagctg tgacacgtgc     60

ggaagctgtg gtaagtgcat cctccttcag tctcagttct gaaaatagat catcatggtg    120

gcaccaaaga gtcacacaga tgactgggct cctgggcctt tctccagtaa gccacagagg    180
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agtcagctgc aaatattctc ttctgttcta cagacctctc tcctcttcct gctcatggga 240

ctaagagcct ctggaaagga ctcagcccca acagtggtgt cagggatcct agggggttcc 300

gtgactctcc ccctaaacat ctcagtagac acagagattg agaacgtcat ctggattggt 360

cccaaaaatg ctcttgcttt cgcacgtccc aaagaaaatg taaccattat ggtcaaaagc 420

tacctgggcc gactagacat caccaagtgg agttactccc tgtgcatcag caatctgact 480

ctgaatgatg caggatccta caaagcccag ataaaccaaa ggaattttga agtcaccact 540

gaggaggaat tcaccctgtt cgtctatgag cagctgcagg agccccaagt caccatgaag 600

tctgtgaagg tgtctgagaa cttctcctgt aacatcactc taatgtgctc cgtgaagggg 660

gcagagaaaa gtgttctgta cagctggacc ccaagggaac cccatgcttc tgagtccaat 720

ggaggctcca ttcttaccgt ctcccgaaca ccatgtgacc cagacctgcc atacatctgc 780

acagcccaga accccgtcag ccagagaagc tccctccctg tccatgttgg gcagttctgt 840

acagatccag gagcctccag aggaggaaca acgggggaga ctgtggtagg ggtcctggga 900

gagccagtca ccctgccact tgcactccca gcctgccggg acacagagaa ggttgtctgg 960

ttgtttaaca catccatcat tagcaaagag agggaagaag cagcaacggc agatccactc 1020

attaaatcca gggatcctta caagaacagg gtgtgggtct ccagccagga ctgctccctg 1080

aagatcagcc agctgaagat agaggacgcc ggcccctacc atgcctacgt gtgctcagag 1140

gcctccagcg tcaccagcat gacacatgtc accctgctca tctaccgcag gctgaggaag 1200

cccaaaatca cgtggagcct caggcacagt gaggatggca tctgcaggat cagcctgacc 1260

tgctccgtgg aggacggggg aaacactgtc atgtacacat ggaccccgct gcagaaggaa 1320

gctgttgtgt cccaagggga atcacacctc aatgtctcat ggagaagcag tgaaaatcac 1380

cccaacctca catgcacagc cagcaaccct gtcagcagga gttcccacca gtttctttct 1440

gagaacatct gttcaggacc tgagagaaac acaaagcttt ggattgggtt gttcctgatg 1500

gtttgccttc tgtgcgttgg gatcttcagc tggtgcattt ggaagcgaaa aggacggtgt 1560

tcagtcccag ccttctgttc cagccaagct gaggccccag cggatacacc aggatatgag 1620

aagctggaca ctcccctcag gcctgccagg caacagccta cacccacctc agacagcagc 1680

tctgacagca acctcacaac tgaggaggat gaggacaggc ctgaggtgca caagcccatc 1740

agtggaagat atgaggtatt tgaccaggtc actcaggagg gcgctggaca tgacccagcc 1800

cctgagggcc aagcagacta tgatcccgtc actccatatg tcacggaagt tgagtctgtg 1860

gttggagaga acaccatgta tgcacaagtg ttcaacttac agggaaagac cccagtttct 1920

cagaaggaag agagctcagc cacaatctac tgctccatac ggaaacctca ggtggtgcca 1980

ccaccacaac agaatgatct tgagattcct gaaagtccta cctatgaaaa tttcacctga 2040

aaggaaaagc agctgctgcc tctctcctgg gaccgtgggg ttggaaagtc agctggacct 2100

catggggcct ggggctcaca gacagaagca cctcagaatt tccttcagtg cctcagagat 2160

gcctggatgt ggcccctccc cctccttctc acccttaagg actcccaaac ccattaatag 2220

ttcagacaca ggctccttct tggagcctat gggcttcaga tgtctttgcc ccatttgtca 2280

cctcgcacac ttatagcgtt tcctcctcga aattctacca agactggtca aatgttgctg 2340

aggggcctgg accagctgtc ctttacacca ccttctcaac actgctgaaa agaacccaag 2400

agaattgtca cacatgacac aagatgtaca taatatcatg ctcactgcag tgttatttaa 2460

aataaaaggc aggaaataaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2508

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<210> SEQ ID NO 34
<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Val Ala Pro Lys Ser His Thr Asp Asp Trp Ala Pro Gly Pro Phe
1 5 10 15

Ser Ser Lys Pro Gln Arg Ser Gln Leu Gln Ile Phe Ser Ser Val Leu
20 25 30

Gln Thr Ser Leu Leu Phe Leu Leu Met Gly Leu Arg Ala Ser Gly Lys
35 40 45

Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
50 55 60

Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
65 70 75 80

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
85 90 95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
100 105 110

Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser
115 120 125

Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
130 135 140

Glu Phe Thr Leu Phe Val Tyr Glu Gln Leu Gln Glu Pro Gln Val Thr
145 150 155 160

Met Lys Ser Val Lys Val Ser Glu Asn Phe Ser Cys Asn Ile Thr Leu
165 170 175

Met Cys Ser Val Lys Gly Ala Glu Lys Ser Val Leu Tyr Ser Trp Thr
180 185 190

Pro Arg Glu Pro His Ala Ser Glu Ser Asn Gly Gly Ser Ile Leu Thr
195 200 205

Val Ser Arg Thr Pro Cys Asp Pro Asp Leu Pro Tyr Ile Cys Thr Ala
210 215 220

Gln Asn Pro Val Ser Gln Arg Ser Ser Leu Pro Val His Val Gly Gln
225 230 235 240

Phe Cys Thr Asp Pro Gly Ala Ser Arg Gly Gly Thr Thr Gly Glu Thr
245 250 255

Val Val Gly Val Leu Gly Glu Pro Val Thr Leu Pro Leu Ala Leu Pro
260 265 270

Ala Cys Arg Asp Thr Glu Lys Val Val Trp Leu Phe Asn Thr Ser Ile
275 280 285

Ile Ser Lys Glu Arg Glu Glu Ala Ala Thr Ala Asp Pro Leu Ile Lys
290 295 300

Ser Arg Asp Pro Tyr Lys Asn Arg Val Trp Val Ser Ser Gln Asp Cys
305 310 315 320

Ser Leu Lys Ile Ser Gln Leu Lys Ile Glu Asp Ala Gly Pro Tyr His
325 330 335

Ala Tyr Val Cys Ser Glu Ala Ser Ser Val Thr Ser Met Thr His Val
340 345 350

Thr Leu Leu Ile Tyr Arg Pro Glu Arg Asn Thr Lys Leu Trp Ile Gly
355 360 365

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Leu Phe Leu Met Val Cys Leu Leu Cys Val Gly Ile Phe Ser Trp Cys
    370                 375                 380

Ile Trp Lys Arg Lys Gly Arg Cys Ser Val Pro Ala Phe Cys Ser Ser
385                 390                 395                 400

Gln Ala Glu Ala Pro Ala Asp Thr Pro Glu Pro Thr Ala Gly His Thr
                405                 410                 415

Leu Tyr Ser Val Leu Ser Gln Gly Tyr Glu Lys Leu Asp Thr Pro Leu
            420                 425                 430

Arg Pro Ala Arg Gln Gln Pro Thr Pro Thr Ser Asp Ser Ser Ser Asp
        435                 440                 445

Ser Asn Leu Thr Thr Glu Glu Asp Glu Asp Arg Pro Glu Val His Lys
    450                 455                 460

Pro Ile Ser Gly Arg Tyr Glu Val Phe Asp Gln Val Thr Gln Glu Gly
465                 470                 475                 480

Ala Gly His Asp Pro Ala Pro Glu Gly Gln Ala Asp Tyr Asp Pro Val
                485                 490                 495

Thr Pro Tyr Val Thr Glu Val Glu Ser Val Val Gly Glu Asn Thr Met
            500                 505                 510

Tyr Ala Gln Val Phe Asn Leu Gln Gly Lys Thr Pro Val Ser Gln Lys
        515                 520                 525

Glu Glu Ser Ser Ala Thr Ile Tyr Cys Ser Ile Arg Lys Pro Gln Val
    530                 535                 540

Val Pro Pro Pro Gln Gln Asn Asp Leu Glu Ile Pro Glu Ser Pro Thr
545                 550                 555                 560

Tyr Glu Asn Phe Thr
                565
```

<210> SEQ ID NO 35
<211> LENGTH: 2280
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

```
acatacacat acacatgcac acacacactc atatacacat gcagaagctg tgacacgtgc     60

ggaagctgtg gtaagtgcat cctccttcag tctcagttct gaaaatagat catcatggtg    120

gcaccaaaga gtcacacaga tgactgggct cctgggcctt tctccagtaa gccacagagg    180

agtcagctgc aaatattctc ttctgttcta cagacctctc tcctcttcct gctcatggga    240

ctaagagcct ctggaaagga ctcagcccca acagtggtgt cagggatcct agggggttcc    300

gtgactctcc ccctaaacat ctcagtagac acagagattg agaacgtcat ctggattggt    360

cccaaaaatg ctcttgcttt cgcacgtccc aaagaaaatg taaccattat ggtcaaaagc    420

tacctgggcc gactagacat caccaagtgg agttactccc tgtgcatcag caatctgact    480

ctgaatgatg caggatccta caaagcccag ataaaccaaa ggaattttga agtcaccact    540

gaggaggaat tcaccctgtt cgtctatgag cagctgcagg agccccaagt caccatgaag    600

tctgtgaagg tgtctgagaa cttctcctgt aacatcactc taatgtgctc cgtgaagggg    660

gcagagaaaa gtgttctgta cagctggacc ccaagggaac cccatgcttc tgagtccaat    720

ggaggctcca ttcttaccgt ctcccgaaca ccatgtgacc cagacctgcc atacatctgc    780

acagcccaga accccgtcag ccagagaagc tccctccctg tccatgttgg gcagttctgt    840

acagatccag gagcctccag aggaggaaca acgggggaga ctgtggtagg ggtcctggga    900
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gagccagtca ccctgccact tgcactccca gcctgccggg acacagagaa ggttgtctgg 960

ttgtttaaca catccatcat tagcaaagag agggaagaag cagcaacggc agatccactc 1020

attaaatcca gggatcctta caagaacagg gtgtgggtct ccagccagga ctgctccctg 1080

aagatcagcc agctgaagat agaggacgcc ggcccctacc atgcctacgt gtgctcagag 1140

gcctccagcg tcaccagcat gacacatgtc accctgctca tctaccgacc tgagagaaac 1200

acaaagcttt ggattgggtt gttcctgatg gtttgccttc tgtgcgttgg gatcttcagc 1260

tggtgcattt ggaagcgaaa aggacggtgt tcagtcccag ccttctgttc cagccaagct 1320

gaggccccag cggatacacc agaacccaca gctggccaca cgctatactc tgtgctctcc 1380

caaggatatg agaagctgga cactcccctc aggcctgcca ggcaacagcc tacacccacc 1440

tcagacagca gctctgacag caacctcaca actgaggagg atgaggacag gcctgaggtg 1500

cacaagccca tcagtggaag atatgaggta tttgaccagg tcactcagga gggcgctgga 1560

catgacccag cccctgaggg ccaagcagac tatgatcccg tcactccata tgtcacggaa 1620

gttgagtctg tggttggaga gaacaccatg tatgcacaag tgttcaactt acagggaaag 1680

accccagttt ctcagaagga agagagctca gccacaatct actgctccat acggaaacct 1740

caggtggtgc caccaccaca acagaatgat cttgagattc ctgaaagtcc tacctatgaa 1800

aatttcacct gaaaggaaaa gcagctgctg cctctctcct gggaccgtgg ggttggaaag 1860

tcagctggac ctcatggggc ctggggctca cagacagaag cacctcagaa tttccttcag 1920

tgcctcagag atgcctggat gtggcccctc cccctccttc tcaccccttaa ggactcccaa 1980

acccattaat agttcagaca caggctcctt cttggagcct atgggcttca gatgtctttg 2040

ccccatttgt cacctcgcac acttatagcg tttcctcctc gaaattctac caagactggt 2100

caaatgttgc tgaggggcct ggaccagctg tcctttacac caccttctca acactgctga 2160

aaagaaccca agagaattgt cacacatgac acaagatgta cataatatca tgctcactgc 2220

agtgttattt aaaataaaag gcaggaaata aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2280

<210> SEQ ID NO 36
<211> LENGTH: 655
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Met Val Ala Pro Lys Ser His Thr Asp Asp Trp Ala Pro Gly Pro Phe
1 5 10 15

Ser Ser Lys Pro Gln Arg Ser Gln Leu Gln Ile Phe Ser Ser Val Leu
20 25 30

Gln Thr Ser Leu Leu Phe Leu Leu Met Gly Leu Arg Ala Ser Gly Lys
35 40 45

Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
50 55 60

Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
65 70 75 80

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
85 90 95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
100 105 110

Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser

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        115                 120                 125

Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
    130                 135                 140

Glu Phe Thr Leu Phe Val Tyr Glu Gln Leu Gln Glu Pro Gln Val Thr
145                 150                 155                 160

Met Lys Ser Val Lys Val Ser Glu Asn Phe Ser Cys Asn Ile Thr Leu
                165                 170                 175

Met Cys Ser Val Lys Gly Ala Glu Lys Ser Val Leu Tyr Ser Trp Thr
            180                 185                 190

Pro Arg Glu Pro His Ala Ser Glu Ser Asn Gly Gly Ser Ile Leu Thr
        195                 200                 205

Val Ser Arg Thr Pro Cys Asp Pro Asp Leu Pro Tyr Ile Cys Thr Ala
    210                 215                 220

Gln Asn Pro Val Ser Gln Arg Ser Ser Leu Pro Val His Val Gly Gln
225                 230                 235                 240

Phe Cys Thr Asp Pro Gly Ala Ser Arg Gly Gly Thr Thr Gly Glu Thr
                245                 250                 255

Val Val Gly Val Leu Gly Glu Pro Val Thr Leu Pro Leu Ala Leu Pro
            260                 265                 270

Ala Cys Arg Asp Thr Glu Lys Val Val Trp Leu Phe Asn Thr Ser Ile
        275                 280                 285

Ile Ser Lys Glu Arg Glu Glu Ala Ala Thr Ala Asp Pro Leu Ile Lys
    290                 295                 300

Ser Arg Asp Pro Tyr Lys Asn Arg Val Trp Val Ser Ser Gln Asp Cys
305                 310                 315                 320

Ser Leu Lys Ile Ser Gln Leu Lys Ile Glu Asp Ala Gly Pro Tyr His
                325                 330                 335

Ala Tyr Val Cys Ser Glu Ala Ser Ser Val Thr Ser Met Thr His Val
            340                 345                 350

Thr Leu Leu Ile Tyr Arg Arg Leu Arg Lys Pro Lys Ile Thr Trp Ser
        355                 360                 365

Leu Arg His Ser Glu Asp Gly Ile Cys Arg Ile Ser Leu Thr Cys Ser
    370                 375                 380

Val Glu Asp Gly Gly Asn Thr Val Met Tyr Thr Trp Thr Pro Leu Gln
385                 390                 395                 400

Lys Glu Ala Val Val Ser Gln Gly Glu Ser His Leu Asn Val Ser Trp
                405                 410                 415

Arg Ser Ser Glu Asn His Pro Asn Leu Thr Cys Thr Ala Ser Asn Pro
            420                 425                 430

Val Ser Arg Ser Ser His Gln Phe Leu Ser Glu Asn Ile Cys Ser Gly
        435                 440                 445

Pro Glu Arg Asn Thr Lys Leu Trp Ile Gly Leu Phe Leu Met Val Cys
    450                 455                 460

Leu Leu Cys Val Gly Ile Phe Ser Trp Cys Ile Trp Lys Arg Lys Gly
465                 470                 475                 480

Arg Cys Ser Val Pro Ala Phe Cys Ser Ser Gln Ala Glu Ala Pro Ala
                485                 490                 495

Asp Thr Pro Glu Pro Thr Ala Gly His Thr Leu Tyr Ser Val Leu Ser
            500                 505                 510

Gln Gly Tyr Glu Lys Leu Asp Thr Pro Leu Arg Pro Ala Arg Gln Gln
        515                 520                 525
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Pro Thr Pro Thr Ser Asp Ser Ser Ser Asp Ser Asn Leu Thr Thr Glu
    530                 535                 540

Glu Asp Glu Asp Arg Pro Glu Val His Lys Pro Ile Ser Gly Arg Tyr
545                 550                 555                 560

Glu Val Phe Asp Gln Val Thr Gln Glu Gly Ala Gly His Asp Pro Ala
                565                 570                 575

Pro Glu Gly Gln Ala Asp Tyr Asp Pro Val Thr Pro Tyr Val Thr Glu
            580                 585                 590

Val Glu Ser Val Val Gly Glu Asn Thr Met Tyr Ala Gln Val Phe Asn
        595                 600                 605

Leu Gln Gly Lys Thr Pro Val Ser Gln Lys Glu Glu Ser Ser Ala Thr
    610                 615                 620

Ile Tyr Cys Ser Ile Arg Lys Pro Gln Val Val Pro Pro Pro Gln Gln
625                 630                 635                 640

Asn Asp Leu Glu Ile Pro Glu Ser Pro Thr Tyr Glu Asn Phe Thr
                645                 650                 655


<210> SEQ ID NO 37
<211> LENGTH: 2550
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

acatacacat acacatgcac acacacactc atatacacat gcagaagctg tgacacgtgc     60

ggaagctgtg gtaagtgcat cctccttcag tctcagttct gaaaatagat catcatggtg    120

gcaccaaaga gtcacacaga tgactgggct cctgggcctt tctccagtaa gccacagagg    180

agtcagctgc aaatattctc ttctgttcta cagacctctc tcctcttcct gctcatggga    240

ctaagagcct ctggaaagga ctcagcccca acagtggtgt cagggatcct agggggttcc    300

gtgactctcc ccctaaacat ctcagtagac acagagattg agaacgtcat ctggattggt    360

cccaaaaatg ctcttgcttt cgcacgtccc aaagaaaatg taaccattat ggtcaaaagc    420

tacctgggcc gactagacat caccaagtgg agttactccc tgtgcatcag caatctgact    480

ctgaatgatg caggatccta caaagcccag ataaaccaaa ggaattttga agtcaccact    540

gaggaggaat tcaccctgtt cgtctatgag cagctgcagg agccccaagt caccatgaag    600

tctgtgaagg tgtctgagaa cttctcctgt aacatcactc taatgtgctc cgtgaagggg    660

gcagagaaaa gtgttctgta cagctggacc ccaagggaac cccatgcttc tgagtccaat    720

ggaggctcca ttcttaccgt ctcccgaaca ccatgtgacc cagacctgcc atacatctgc    780

acagcccaga accccgtcag ccagagaagc tccctccctg tccatgttgg gcagttctgt    840

acagatccag gagcctccag aggaggaaca acgggggaga ctgtggtagg ggtcctggga    900

gagccagtca ccctgccact tgcactccca gcctgccggg acacagagaa ggttgtctgg    960

ttgtttaaca catccatcat tagcaaagag agggaagaag cagcaacggc agatccactc   1020

attaaatcca gggatcctta caagaacagg gtgtgggtct ccagccagga ctgctccctg   1080

aagatcagcc agctgaagat agaggacgcc ggcccctacc atgcctacgt gtgctcagag   1140

gcctccagcg tcaccagcat gacacatgtc accctgctca tctaccgcag gctgaggaag   1200

cccaaaatca cgtggagcct caggcacagt gaggatggca tctgcaggat cagcctgacc   1260

tgctccgtgg aggacggggg aaacactgtc atgtacacat ggaccccgct gcagaaggaa   1320

gctgttgtgt cccaagggga atcacacctc aatgtctcat ggagaagcag tgaaaatcac   1380
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cccaacctca catgcacagc cagcaaccct gtcagcagga gttcccacca gtttctttct 1440

gagaacatct gttcaggacc tgagagaaac acaaagcttt ggattgggtt gttcctgatg 1500

gtttgccttc tgtgcgttgg gatcttcagc tggtgcattt ggaagcgaaa aggacggtgt 1560

tcagtcccag ccttctgttc cagccaagct gaggccccag cggatacacc agaacccaca 1620

gctggccaca cgctatactc tgtgctctcc caaggatatg agaagctgga cactcccctc 1680

aggcctgcca ggcaacagcc tacacccacc tcagacagca gctctgacag caacctcaca 1740

actgaggagg atgaggacag gcctgaggtg cacaagccca tcagtggaag atatgaggta 1800

tttgaccagg tcactcagga gggcgctgga catgacccag cccctgaggg ccaagcagac 1860

tatgatcccg tcactccata tgtcacggaa gttgagtctg tggttggaga gaacaccatg 1920

tatgcacaag tgttcaactt acagggaaag accccagttt ctcagaagga agagagctca 1980

gccacaatct actgctccat acggaaacct caggtggtgc caccaccaca acagaatgat 2040

cttgagattc ctgaaagtcc tacctatgaa aatttcacct gaaaggaaaa gcagctgctg 2100

cctctctcct gggaccgtgg ggttggaaag tcagctggac ctcatggggc ctggggctca 2160

cagacagaag cacctcagaa tttccttcag tgcctcagag atgcctggat gtggcccctc 2220

cccctccttc tcacccttaa ggactcccaa acccattaat agttcagaca caggctcctt 2280

cttggagcct atgggcttca gatgtctttg ccccatttgt cacctcgcac acttatagcg 2340

tttcctcctc gaaattctac caagactggt caaatgttgc tgaggggcct ggaccagctg 2400

tcctttacac caccttctca acactgctga aaagaaccca agagaattgt cacacatgac 2460

acaagatgta cataatatca tgctcactgc agtgttattt aaaataaaag gcaggaaata 2520

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2550

<210> SEQ ID NO 38
<211> LENGTH: 238
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
1 5 10 15

Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
20 25 30

Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
35 40 45

Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
50 55 60

His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65 70 75 80

Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
85 90 95

Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
100 105 110

Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
115 120 125

Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
130 135 140

Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile

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145                 150                 155                 160

Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
                165                 170                 175

His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
            180                 185                 190

Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
        195                 200                 205

Cys Ser Trp Val Ile Leu Ile Thr Glu Leu Thr Met Pro Ala Leu Pro
    210                 215                 220

Met Val Leu His Gly Ser Leu Val Pro Trp Arg Gly Gly Val
225                 230                 235


<210> SEQ ID NO 39
<211> LENGTH: 1906
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct     60

tcctcaccct gtccgtgacg tggattggtg ctgcacccct catcctgtct cggattgtgg    120

gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca    180

gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca    240

tcaggaacaa aagcgtgatc ttgctgggtc ggcacagcct gtttcatcct gaagacacag    300

gccaggtatt tcaggtcagc cacagcttcc cacacccgct ctacgatatg agcctcctga    360

agaatcgatt cctcaggcca ggtgatgact ccagccacga cctcatgctg ctccgcctgt    420

cagagcctgc cgagctcacg gatgctgtga aggtcatgga cctgcccacc caggagccag    480

cactggggac cacctgctac gcctcaggct ggggcagcat tgaaccagag gagttcttga    540

ccccaaagaa acttcagtgt gtggacctcc atgttatttc caatgacgtg tgtgcgcaag    600

ttcaccctca gaaggtgacc aagttcatgc tgtgtgctgg acgctggaca gggggcaaaa    660

gcacctgctc gtgggtcatt ctgatcaccg aactgaccat gccagccctg ccgatggtcc    720

tccatggctc cctagtgccc tggagaggag gtgtctagtc agagagtagt cctggaaggt    780

ggcctctgtg aggagccacg gggacagcat cctgcagatg gtcctggccc ttgtcccacc    840

gacctgtcta caaggactgt cctcgtggac cctcccctct gcacaggagc tggaccctga    900

agtcccttcc ccaccggcca ggactggagc ccctaccct ctgttggaat ccctgcccac    960

cttcttctgg aagtcggctc tggagacatt tctctcttct tccaaagctg ggaactgcta   1020

tctgttatct gcctgtccag gtctgaaaga taggattgcc caggcagaaa ctgggactga   1080

cctatctcac tctctccctg cttttaccct tagggtgatt ctgggggccc acttgtctgt   1140

aatggtgtgc ttcaaggtat cacgtcatgg ggcagtgaac catgtgccct gcccgaaagg   1200

ccttccctgt acaccaaggt ggtgcattac cggaagtgga tcaaggacac catcgtggcc   1260

aacccctgag cacccctatc aacccccctat tgtagtaaac ttggaacctt ggaaatgacc   1320

aggccaagac tcaagcctcc ccagttctac tgacctttgt ccttaggtgt gaggtccagg   1380

gttgctagga aaagaaatca gcagacacag gtgtagacca gagtgtttct taaatggtgt   1440

aattttgtcc tctctgtgtc ctggggaata ctggccatgc ctggagacat atcactcaat   1500

ttctctgagg acacagatag gatggggtgt ctgtgttatt tgtggggtac agagatgaaa   1560
```

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gaggggtggg atccacactg agagagtgga gagtgacatg tgctggacac tgtccatgaa 1620

gcactgagca gaagctggag gcacaacgca ccagacactc acagcaagga tggagctgaa 1680

aacataaccc actctgtcct ggaggcactg ggaagcctag agaaggctgt gagccaagga 1740

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gaagctgatt cactatgggg ggaggtgtat tgaagtcctc cagacaaccc tcagatttga 1860

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<210> SEQ ID NO 40
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

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Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
20 25 30

Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
35 40 45

Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
50 55 60

His Cys Ile Arg Lys Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu
65 70 75 80

Leu Arg Leu Ser Glu Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met
85 90 95

Asp Leu Pro Thr Gln Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser
100 105 110

Gly Trp Gly Ser Ile Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu
115 120 125

Gln Cys Val Asp Leu His Val Ile Ser Asn Asp Val Cys Ala Gln Val
130 135 140

His Pro Gln Lys Val Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr
145 150 155 160

Gly Gly Lys Ser Thr Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys
165 170 175

Asn Gly Val Leu Gln Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala
180 185 190

Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys
195 200 205

Trp Ile Lys Asp Thr Ile Val Ala Asn Pro
210 215

<210> SEQ ID NO 41
<211> LENGTH: 1335
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

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gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240

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tcaggaagcc aggtgatgac tccagccacg acctcatgct gctccgcctg tcagagcctg 300

ccgagctcac ggatgctgtg aaggtcatgg acctgcccac ccaggagcca gcactgggga 360

ccacctgcta cgcctcaggc tggggcagca ttgaaccaga ggagttcttg accccaaaga 420

aacttcagtg tgtggacctc catgttattt ccaatgacgt gtgtgcgcaa gttcaccctc 480

agaaggtgac caagttcatg ctgtgtgctg gacgctggac agggggcaaa agcacctgct 540

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gcagtgaacc atgtgccctg cccgaaaggc cttccctgta caccaaggtg gtgcattacc 660

ggaagtggat caaggacacc atcgtggcca acccctgagc acccctatca acccccтatt 720

gtagtaaact tggaaccttg gaaatgacca ggccaagact caagcctccc cagttctact 780

gacctttgtc cttaggtgtg aggtccaggg ttgctaggaa aagaaatcag cagacacagg 840

tgtagaccag agtgtttctt aaatggtgta attttgtcct ctctgtgtcc tggggaatac 900

tggccatgcc tggagacata tcactcaatt tctctgagga cacagatagg atggggtgtc 960

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agtgacatgt gctggacact gtccatgaag cactgagcag aagctggagg cacaacgcac 1080

cagacactca cagcaaggat ggagctgaaa acataaccca ctctgtcctg gaggcactgg 1140

gaagcctaga gaaggctgtg agccaaggag ggagggtctt cctttggcat gggatgggga 1200

tgaagtaagg agagggactg gacccccтgg aagctgattc actatggggg gaggtgtatt 1260

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agctgttata ctgtg 1335

<210> SEQ ID NO 42
<211> LENGTH: 69
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
20 25 30

Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
35 40 45

Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
50 55 60

His Cys Ile Arg Lys
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<210> SEQ ID NO 43
<211> LENGTH: 555
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

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gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240

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tcaggaagtg agtaggggcc tggggtctgg ggagcaggtg tctgtgtccc agaggaataa 300

cagctgggca ttttccccag gataacctct aaggccagcc ttgggactgg gggagagagg 360

gaaagttctg gttcaggtca catggggagg cagggttggg gctggaccac cctccccatg 420

gctgcctggg tctccatctg tgttcctcta tgtctctttg tgtcgctttc attatgtctc 480

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<210> SEQ ID NO 44
<211> LENGTH: 261
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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1 5 10 15

Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
20 25 30

Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
35 40 45

Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
50 55 60

His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65 70 75 80

Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
85 90 95

Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
100 105 110

Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
115 120 125

Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
130 135 140

Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145 150 155 160

Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
165 170 175

His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
180 185 190

Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
195 200 205

Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
210 215 220

Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
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Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
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Ile Val Ala Asn Pro
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<210> SEQ ID NO 45
<211> LENGTH: 1464
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 45

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gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240

tcaggaacaa aagcgtgatc ttgctgggtc ggcacagcct gtttcatcct gaagacacag 300

gccaggtatt tcaggtcagc cacagcttcc cacacccgct ctacgatatg agcctcctga 360

agaatcgatt cctcaggcca ggtgatgact ccagccacga cctcatgctg ctccgcctgt 420

cagagcctgc cgagctcacg gatgctgtga aggtcatgga cctgcccacc caggagccag 480

cactggggac cacctgctac gcctcaggct ggggcagcat tgaaccagag gagttcttga 540

ccccaaagaa acttcagtgt gtggacctcc atgttatttc caatgacgtg tgtgcgcaag 600

ttcaccctca gaaggtgacc aagttcatgc tgtgtgctgg acgctggaca gggggcaaaa 660

gcacctgctc gggtgattct gggggcccac ttgtctgtaa tggtgtgctt caaggtatca 720

cgtcatgggg cagtgaacca tgtgccctgc ccgaaaggcc ttccctgtac accaaggtgg 780

tgcattaccg gaagtggatc aaggacacca tcgtggccaa cccctgagca cccctatcaa 840

ccccctattg tagtaaactt ggaaccttgg aaatgaccag gccaagactc aagcctcccc 900

agttctactg acctttgtcc ttaggtgtga ggtccagggt tgctaggaaa agaaatcagc 960

agacacaggt gtagaccaga gtgtttctta aatggtgtaa ttttgtcctc tctgtgtcct 1020

ggggaatact ggccatgcct ggagacatat cactcaattt ctctgaggac acagatagga 1080

tggggtgtct gtgttatttg tggggtacag agatgaaaga ggggtgggat ccacactgag 1140

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ggatggggat gaagtaagga gagggactgg acccccctgga agctgattca ctatgggggg 1380

aggtgtattg aagtcctcca gacaaccctc agatttgatg atttcctagt agaactcaca 1440

gaaataaaga gctgttatac tgtg 1464

1. A method for diagnosing an abnormal prostate state in a subject comprising:

(1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a biological sample from the subject; and

(2) comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a normal control sample, wherein an altered level of the one or more prostate cancer related markers in the biological sample relative to the normal control sample is indicative of an abnormal prostate state in the subject.

2. The method of claim 1, wherein the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19.

3. The method of claim 1, wherein an increased level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of an abnormal prostate state in the subject.

4. The method of claim 1, wherein no increase in the detected level of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of a normal prostate state in the subject.

5. The method of claim 1, further comprising detecting the level of prostate specific antigen (PSA) in the biological sample.

6. The method of claim 5, further comprising comparing the level of PSA in the biological sample to the level of PSA in a normal control sample.

7. The method of claim 6, wherein an increase in the level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample relative to the level of PSA in the normal control sample is indicative of an abnormal prostate state in the subject.

8. The method of claim 7, wherein no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample, is indicative of a normal prostate state in the subject.

9. The method of claim 2, wherein the one or more prostate cancer markers selected from the group consisting of filamin B, LY9 and keratin 19 is: filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

10. The method of claim 1, wherein the abnormal prostate state is prostate cancer.

11-15. (canceled)

16. A method for identifying a subject as being at increased risk for developing prostate cancer, the method comprising:

(1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a biological sample from the subject; and

(2) comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a normal control sample, wherein an altered level of the one or more prostate cancer related markers in the biological sample relative to the normal control sample is indicative of an increased risk for developing prostate cancer in the subject.

17. The method of claim 16, wherein the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19.

18-37. (canceled)

38. A method for monitoring prostate cancer in a subject, the method comprising

(1) determining a level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a first biological sample obtained at a first time from a subject having prostate cancer;

(2) determining a level of expression of the one or more prostate cancer related markers in a second biological sample obtained from the subject at a second time, wherein the second time is later than the first time; and

(3) comparing the level of the one or more prostate cancer related markers in the second sample with the level of the one or more prostate cancer related markers in the first sample, wherein a change in the level of the one or more prostate cancer related markers in the second sample as compared to the first sample is indicative of a change in prostate cancer status in the subject.

39. The method of claim 38, wherein the subject is actively treated for prostate cancer prior to obtaining the second sample.

40. The method of claim 38, wherein the subject is not actively treated for prostate cancer prior to obtaining the second sample.

41. The method of claim 38, wherein the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19.

42. The method of claim 38, wherein an increased level of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample as compared to the first biological sample is indicative of progression of the prostate cancer in the subject.

43. The method of claim 38, wherein no increase in the detected level of expression of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the second biological sample as compared to the first biological sample is indicative of non-progression of the prostate cancer in the subject.

44. The method of claim 38, further comprising determining the level of prostate specific antigen (PSA) in the first biological sample and the second biological sample.

45. The method of claim 44, further comprising comparing the level of PSA in the second biological sample to the level of PSA in the first biological sample.

46-61. (canceled)

62. A method for detecting a set of prostate cancer related markers, the method comprising:

(1) analyzing a biological sample from a subject for a level of two or more prostate cancer related markers of a set of prostate cancer related markers, wherein the set of prostate cancer related markers comprises filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3;

(2) detecting each of the two or more prostate specific makers in the biological sample, thereby detecting the set of prostate cancer related biomarkers.

63. The method of claim 62, wherein the set of prostate cancer related markers comprises filamin B, LY9, and keratin 19.

64. The method of claim 63, wherein the two or more prostate cancer related markers of the set of prostate cancer related markers is: filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

65. The method of claim 62, wherein the set of prostate cancer related markers comprises keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3.

66. The method of claim 62, wherein the set of prostate cancer related markers comprises keratin 7, keratin 8, and keratin 15.

67. The method of claim 62, wherein the set of prostate cancer related markers comprises keratin 7 and keratin 15.

68-75. (canceled)

76. A panel of reagents for use in a detection method, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer related marker of a set of prostate cancer related markers, wherein the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA.

77. The panel of claim **76**, wherein the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19.

78. The panel of claim **77**, wherein the two or more prostate cancer related markers is: filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19.

79. The panel of claim **76**, wherein the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3.

80. The panel of claim **76**, wherein the set of prostate cancer specific markers comprises two or more prostate cancer related markers selected from the group consisting of keratin 7, keratin 8, and keratin 15.

81. The panel of claim **76**, wherein the set of prostate cancer specific markers comprises keratin 7 and keratin 15.

82. The panel of claim **76**, wherein the set of prostate cancer specific markers further comprises PSA.

83. The panel of claim **82**, wherein the panel of reagents comprises a detection reagent specific for the detection of PSA.

84. (canceled)

85. A kit for the diagnosis, monitoring, or characterization of an abnormal prostate state, comprising:

at least one reagent specific for the detection of a level of at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9.

86. The kit of claim **85**, wherein the kit further comprises instructions for the diagnosis, monitoring, or characterization of an abnormal prostate state based on the level of the at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 detected.

87. The kit of claim **85**, wherein the kit further comprises instructions to detect the level of PSA in a sample in which the at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 is detected.

88. The kit of claim **85**, further comprising at least one reagent specific for the detection of a level of PSA.

89. A kit comprising at least one reagent specific for the detection of a level of at least one prostate cancer related marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, and LY9 and at least one reagent specific for the detection of a level of PSA.

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