

WHAT IS CLAIMED IS:

1. Use of a kit comprising one or more reagents for the detection of nucleic acid encoding a modified AR polypeptide in the manufacture of a medicament for determining whether a subject is or will become less responsive to therapy with a first- or second-generation androgen receptor (AR) antagonist, wherein:
 - the one or more reagents are those for testing a sample containing a nucleic acid encoding an AR polypeptide from the subject to determine whether the encoded AR polypeptide is modified at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1; and
 - the subject is characterized as resistant or will become resistant to therapy with a first- or second-generation AR antagonist if the subject has the modification, optionally wherein the modification comprises a substitution or a deletion of the amino acid at amino acid position 876 in the AR polypeptide.
2. The use according to claim 1, wherein the subject has already been administered a first- or second-generation AR antagonist for the treatment of a cancer, optionally wherein the cancer is prostate cancer.
3. Use of a kit comprising one or more reagents for the detection of nucleic acid encoding a modified AR polypeptide in the manufacture of a medicament for optimizing the therapy of a subject receiving a first- or second-generation AR antagonist for treatment of a cancer, wherein:
 - the one or more reagents are those for testing a sample containing a nucleic acid encoding an AR polypeptide from the subject to determine whether the encoded AR polypeptide is modified at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1, optionally wherein the modification comprises a substitution or a deletion of the amino acid at amino acid position 876 in the AR polypeptide.
4. Use of a kit comprising one or more reagents for the detection of nucleic acid encoding a modified AR polypeptide in the manufacture of a medicament for selecting a subject for therapy with a third-generation AR antagonist, wherein:
 - the one or more reagents are those for testing a sample containing a nucleic acid encoding an AR polypeptide from the subject to determine whether the encoded AR polypeptide is modified at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1; and
 - the subject is characterized as a candidate for therapy with a third-generation AR antagonist if the subject has the modification, optionally wherein the modification comprises a substitution or a deletion of the amino acid at amino acid position 876 in the AR polypeptide.

5. The use according to any one of claims 1-4, wherein the modification is a substitution of phenylalanine to an amino acid selected from among leucine, isoleucine, valine, alanine, glycine, methionine, serine, threonine, cysteine, tryptophan, lysine, arginine, histidine, proline, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid at amino acid position 876 of the AR polypeptide.
6. The use according to any one of claims 1-4, wherein the modification is a substitution of phenylalanine to an amino acid selected from among glycine, alanine, valine, leucine, and isoleucine at amino acid position 876 of the AR polypeptide.
7. The use according to claim 6, wherein the modification is a substitution of phenylalanine to leucine at amino acid position 876 of the AR polypeptide.
8. The use according to any of claims 1-4, wherein the modification comprises a deletion of nucleic acid encoding amino acid position 876 of the AR polypeptide.
9. The use according to any of claims 1-8, wherein the nucleic acid encoding the modified AR polypeptide encodes leucine at amino acid position 876 of the AR polypeptide with a TTA, TTG, CTT or CTC codon.
10. The use according to any of claims 1-9, wherein the nucleic acid is RNA or DNA, optionally wherein the DNA is genomic DNA.
11. The use according to any of claims 1-9, wherein the method further comprises isolating mRNA from the RNA sample.
12. The use according to any of claims 1-11, wherein testing comprises amplifying the nucleic acid encoding amino acid position 876 of the AR polypeptide, optionally wherein amplification is by polymerase chain reaction (PCR), optionally wherein PCR amplification comprises using a pair of oligonucleotide primers that flank the region encoding amino acid position 876 of the AR polypeptide.
13. The use according to any of claims 1-12, comprising sequencing the amplified nucleic acid.
14. The use according to any of claims 1-13, wherein testing comprises contacting the nucleic acid with a sequence specific nucleic acid probe, wherein the sequence specific nucleic acid probe:
 - (a) binds to a nucleic acid encoding a modified receptor that is modified at amino acid position 876; and
 - (b) does not bind to a nucleic acid encoding the wild-type receptor having phenylalanine at amino acid position 876.

15. The use according to any of claims 1-14, wherein the sample is from a tumor cell sample from the subject, optionally wherein the sample contains circulating tumor cells (CTC) or disseminated tumor cells (DTC).
16. The use according to any of claims 1-14, wherein the sample is from a tumor biopsy sample, a blood sample, a serum sample, a lymph sample, or a bone marrow aspirate, optionally wherein the sample contains circulating tumor cells (CTC) or disseminated tumor cells (DTC).
17. The use according to any of claims 1-16, wherein the first- or second-generation AR antagonist inhibits a wild-type AR polypeptide by competitive antagonism.
18. The use according to any of claims 1-17, wherein the second-generation AR antagonist is selected from among ARN-509, enzalutamide (MDV3100), and RD162.
19. The use according to any of claims 1-18, wherein the subject has a disease or disorder selected from among cancer, an inflammatory disorder or a proliferative disorder.
20. The use according to claim 19, wherein the subject has cancer, optionally wherein the cancer is a prostate cancer, a breast cancer, a bladder cancer, or a hepatocellular cancer, optionally wherein the cancer is prostate cancer, optionally wherein the cancer is castration resistant prostate cancer.
21. The use according to any of claims 1-20, wherein the subject has a solid tumor.
22. The use according to any of claims 1-21, wherein the subject is treated with the first- or second-generation AR antagonist prior to obtaining the sample.
23. The use according to claim 22, wherein the sample is a sample obtained at 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 14 months, 16 months, 18 months, 20 months, 22 months, or 24 months following the first administration of with the first- or second-generation AR antagonist.
24. The use according to claim 22 or 23, wherein the sample is obtained 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times over the course of treatment with the first- or second-generation AR antagonist.
25. The use according to any of claims 1-24, wherein the subject is responsive to the treatment with the first- or second-generation AR antagonist when it is first administered.

26. A method for screening compounds that antagonize a modified AR, comprising:
- (a) expressing a modified AR in a cell, wherein the modified AR is modified at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1;
 - (b) contacting the cell with a test compound being screened; and
 - (c) detecting the level of AR activity in the cell, wherein a decrease in activity relative to the activity of SEQ ID NO: 1 indicates that the compound antagonizes the modified AR receptor.
27. The method of claim 26, wherein the test compound exhibits full antagonist activity toward the modified AR receptor.
28. The method of claim 26 or 27, wherein the test compound does not exhibit agonist activity toward the modified AR receptor.
29. The method of any of claims 26-28, wherein the modification is a substitution or deletion of the amino acid at position 876 of the AR polypeptide.
30. The method of claim 36, wherein the modification is a substitution of phenylalanine to an amino acid selected from among leucine, isoleucine, valine, alanine, glycine, methionine, serine, threonine, cysteine, tryptophan, lysine, arginine, histidine, proline, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid at amino acid position 876 of the AR polypeptide.
32. The method of claim 30, wherein the modification is a substitution of phenylalanine to an amino acid selected from among glycine, alanine, valine, leucine, and isoleucine at amino acid position 876 of the AR polypeptide.
33. The method of claim 32, wherein the modification is a substitution of phenylalanine to leucine at amino acid position 876 of the AR polypeptide.
34. The method of any of claims 26-32, wherein the cell is deficient for the expression of wild-type AR, expresses a low level of wild-type AR, or expresses a modified AR receptor.
35. The method of any of claims 26-34, wherein the cell is a selected from among HeLa, CV1, COS7, HepG2, HEK-293, DU145, PC3, TSY-PR1, LNCaP, CWR, VCaP and LAPC4, optionally wherein the cell is a selected from among CWR, LNCaP, VCaP and LAPC4.
36. The method of any of claims 26-35, wherein the cell comprises a reporter gene operably linked to an androgen responsive promoter.

37. The method of claim 36, wherein activity is determined by analyzing the expression of the reporter gene.
38. The method of claim 36 or claim 37, wherein the promoter comprises androgen response element, optionally wherein the androgen response element is 4xARE or a probasin element.
39. The method of any of claims 26-38, wherein the promoter is a probasin, a prostate specific antigen, MMTV LTR, FASN, STEAP4, TMPRSS2, ORM1, or NKX3.1 promoter.
40. The method of any of claims 26-39, wherein the reporter gene encodes a protein selected from among a luciferase, a fluorescent protein, a bioluminescent protein, or an enzyme.
41. A kit comprising a carrier or package that is compartmentalized to receive one or more containers, each container comprising (a) one or more reagents for the detection of nucleic acid encoding a modified AR polypeptide comprising a modification at amino acid position 876 or a modified AR polypeptide comprising a modification at amino acid position 876; (b) optionally one or more buffer, PCR reagent, antibody, substrate for enzymatic staining, chromagen, or protein control sample; and (c) optionally labeled with a listing of contents and/or instructions for use, and/or containing a package insert with instructions for use.
42. The kit of claim 41, wherein the modified AR polypeptide comprises an amino acid substitution that is F876L.
43. The kit of claim 41 or 42, comprising a pair oligonucleotide primers that flank the nucleic acid region encoding amino acid 876 of a AR polypeptide.
44. The kit of claim 41 or 42, comprising an oligonucleotide primer that
(a) binds to a nucleic acid encoding a modified AR that is modified at amino acid position 876;
and
(b) does not bind to a nucleic acid encoding the wild-type AR having phenylalanine at amino acid position 876.
45. The kit of claim 41 or 42, comprising a microchip comprising
(a) a modified AR polypeptide having a modification that is F876L, or a portion thereof comprising a modification that is F876L; or
(b) a nucleic acid encoding a mutant AR polypeptide having a modification that is F876L, or a portion thereof comprising a modification that is F876L.

46. The kit of claim 45, wherein the nucleic acid is a deoxyribonucleotide, deoxyribonucleoside, ribonucleoside, or ribonucleotide or polymer thereof, in either single- or double-stranded form, wherein the nucleic acid encoding the modified AR polypeptide encodes leucine at amino acid position 876 of the AR polypeptide with a TTA, TTG, CTT or CTC codon; and wherein:

the AR polypeptide comprises a modification at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1, the modification comprising a deletion of the amino acid at position 876 of the AR polypeptide or a substitution of phenylalanine to an amino acid selected from a group consisting of leucine, isoleucine, valine, alanine, glycine, methionine, serine, threonine, cysteine, tryptophan, lysine, arginine, histidine, proline, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid at amino acid position 876 of the AR polypeptide.

47. An isolated antibody that binds to an isolated AR polypeptide or variant thereof having AR activity comprising a modification at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1, wherein the modification confers resistance to an AR antagonist on the modified AR polypeptide or variant, and wherein the antibody does not bind to or binds with lower affinity to a wild-type AR polypeptide having the sequence of amino acids set forth in SEQ ID NO: 1.

48. The antibody of claim 47, wherein the isolated AR polypeptide comprises an amino acid substitution that is F876L.

49. The isolated antibody of claim 47, wherein the isolated AR polypeptide comprises a modification at an amino acid position corresponding to amino acid position 876 of the amino acid sequence set forth in SEQ ID NO: 1, the modification comprising a deletion of the amino acid at position 876 of the AR polypeptide or a substitution of phenylalanine to an amino acid selected from a group consisting of leucine, isoleucine, valine, alanine, glycine, methionine, serine, threonine, cysteine, tryptophan, lysine, arginine, histidine, proline, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid at amino acid position 876 of the AR polypeptide.