

METHODS AND COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BLADDER CANCER

Field of the Invention

[0001] The field of the invention relates to cancer and the diagnosis and treatment of cancer.

Background

[0002] Early detection of cancer can impact treatment outcomes and disease progression. Typically, cancer detection relies on diagnostic information obtained from biopsy, x-rays, CAT scans, NMR and the like. These procedures may be invasive, time consuming and expensive. Moreover, they have limitations with regard to sensitivity and specificity. There is a need in the field of cancer diagnostics for a highly specific, highly sensitive, rapid, inexpensive, and relatively non-invasive method of diagnosing cancer. Various embodiments of the invention described below meet this need as well as other needs existing in the field of diagnosing and treating cancer.

Summary of the Invention

[0003] Embodiments of the disclosure provide methods of diagnosis, prognosis and treatment of cancer, e.g. bladder cancer. Other embodiments provide compositions relating to the diagnosis, prognosis and treatment of cancer, such as bladder cancer.

[0004] In certain embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject; b) contacting the sample obtained from the subject with one or more agents that detect one or more markers expressed by a bladder cancer cell c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of the marker in the sample obtained from the subject with the expression level in the non-cancerous cell, wherein a higher level of expression of the marker in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer. Suitable markers include the genes encoded for by SEQ ID NOS: 1-41.

[0005] In some embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a plurality of genes including WDR72; c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of the plurality of genes including WDR72 in the non-cancerous cell with the sample, wherein a higher level of expression in the sample of the plurality of genes including WDR72 in the sample obtained from the subject compared to the non-cancerous cell indicates that the subject has bladder cancer. The marker encoded for by the

gene can be for example a nucleic acid such as an RNA molecule encoded for by the gene or a complement of an RNA molecule encoded for by the gene. The marker may be a protein encoded for by the gene.

[0006] In some embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72; c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72 in the non-cancerous cell, wherein a higher level of expression in the sample of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample obtained from the subject compared to the non-cancerous cell indicates that the subject has bladder cancer. The marker encoded for by the gene can be for example a nucleic acid such as an RNA molecule encoded for by the gene or a complement of an RNA molecule encoded for by the gene. The marker may be a protein encoded for by the gene.

[0007] In other embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a panel of markers encoded by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A,

CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72; c) contacting a non-cancerous cell, with the one or more agents from b); and d) comparing the expression level of the panel of markers encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample obtained from the subject with the expression level of the panel of markers encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72, in the non-cancerous cell, wherein a higher level of expression of the panel of markers encoded for by genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72, in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

[0008] In other embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a panel of markers encoded by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72; c) contacting a non-cancerous cell, with the one or more agents from b); and d) comparing the expression level of the panel of markers encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, FCRLB, SERPINB5, DSCR6, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample obtained from the subject with the expression level of the panel of markers encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72, in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

DSCR6, TOP2A, and WDR72, in the non-cancerous cell, wherein a higher level of expression of the panel of markers encoded for by genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COLO10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

[0009] In other embodiments the invention provides a method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a panel of markers encoded by the genes, UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72; c) contacting a non-cancerous cell, with the one or more agents from b); and d) comparing the expression level of the panel of markers encoded for by the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72 in the sample obtained from the subject with the expression level of the panel of markers encoded for by the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72, in the non-cancerous cell, wherein a higher level of expression of the panel of markers encoded for by genes, UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72 in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

[0010] In further embodiments the invention provides a method of detecting bladder cancer cells in a sample comprising a) obtaining a sample b) contacting the sample obtained in a) with one or more agents that detect expression of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72; c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample obtained in a) with the expression level of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6,

UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72, in the non-cancerous cell, wherein a higher level of expression of one or more of the markers encoded by genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72 in the sample compared to the non-cancerous cell indicates that the sample contains bladder cancer cells. The sample may be an in vitro sample or an in vivo sample, or derived from an in vivo sample.

[0011] With regard to the embodiments described in the preceding paragraphs, the sample may be any sample as described infra, for example, a bodily fluid, such as blood, serum or urine. The sample may be a cellular sample or the extract of a cellular sample. The sample may be a tissue sample. Nucleic acids and/or proteins may be isolated from the sample. Nucleic acids such as RNA may be transcribed into cDNA. The agent may be one or more molecules that bind specifically to one or more proteins expressed by the cancer cell or one or more nucleic acids expressed by the cell. For example, the agent may be a protein such as an antibody that binds specifically to the protein expressed by one of the marker genes identified infra. The agent may be one or more nucleic acids that hybridize to a nucleic acid expressed by the cancer cell. The nucleic acid expressed by the cancer cell may be an RNA molecule, e.g. an mRNA molecule. The nucleic acid molecule that hybridizes to the nucleic acid expressed by the cancer cell may be a DNA molecule, such as a DNA probe.

[0012] In still other embodiments the invention provides a composition of matter useful in distinguishing a bladder cancer cell from a non-cancerous cell comprising one or more molecules that specifically bind to a molecule expressed at higher levels by a bladder cancer cell compared to a non-cancer cell. As an example, the composition may comprise a protein, that binds to one or more molecules expressed by the bladder cancer cell at higher levels compared to the non-cancer cell. As another example, the composition may comprise a nucleic acid that binds to one or more molecules expressed by the bladder cancer cell at higher levels compared to the non-cancer cell.

[0013] In some embodiments the invention provides a composition of matter comprising one or more proteins, such as an antibody, that specifically binds to a molecule expressed by a

bladder cancer cell chosen from the markers encoded by the SEQ ID NOS: 1-41. The molecule expressed by the bladder cancer cell may be expressed by the cancer cell at a level that is higher than the level expressed by a non-cancerous cell.

[0014] In some embodiments the invention provides a composition of matter comprising one or more proteins, such as an antibody, that specifically binds to a molecule expressed by a bladder cancer cell chosen from the markers encoded by the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72. The molecule expressed by the bladder cancer cell may be expressed by the cancer cell at a level that is higher than the level expressed by a non-cancerous cell.

[0015] In some embodiments the invention provides a composition of matter comprising one or more proteins, such as an antibody, that specifically binds to a molecule expressed by a bladder cancer cell chosen from the markers encoded by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COLO10A1, SERPINB4, UBE2C, SFN, SERPINB5, DSCR6, TOP2A, and WDR72. The molecule expressed by the bladder cancer cell may be expressed by the cancer cell at a level that is higher than the level of the same marker expressed by a non-cancerous cell.

[0016] In further embodiments the invention provides a composition of matter comprising a plurality of proteins, such as a plurality antibodies, that specifically binds to a panel of molecules expressed by a bladder cancer cell wherein the panel of markers comprises molecule encoded by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72. The panel of markers may be expressed at a level that is higher than the level of the panel of markers in a non-cancerous cell.

[0017] In further embodiments the invention provides a composition of matter comprising a plurality of proteins, such as a plurality antibodies, that specifically binds to a panel of molecules expressed by a bladder cancer cell wherein the panel of markers comprises molecule encoded by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COLO10A1, SERPINB4, UBE2C, SFN, K SERPINB5, DSCR6

RT17P3, TOP2A, and WDR72. The panel of markers may be expressed at a level that is higher than the level of the panel of markers in a non-cancerous cell.

[0018] In certain embodiments the invention provides a composition of matter comprising a protein, such as an antibody, that specifically binds to a molecule expressed by a bladder cancer cell chosen from a molecule encoded by one or more of the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 TOP2A, and WDR72. The molecule expressed by the bladder cancer cell may be expressed by the bladder cancer cell at level that is higher than the level expressed by a non-cancerous cell.

[0019] In other embodiments the invention provides a composition of matter comprising a nucleic acid that specifically binds to a molecule, such as an mRNA molecule, expressed by a bladder cancer cell wherein the molecule is chosen from a marker encoded for by the genes listed in SEQ ID NOS: 1-40. The molecule expressed by the bladder cancer cell may be expressed by the bladder cancer cell at level that is higher than the level expressed by a non-cancerous cell.

[0020] [0018] In other embodiments the invention provides a composition of matter comprising a nucleic acid that specifically binds to a molecule, such as an mRNA molecule, expressed by a bladder cancer cell wherein the molecule is chosen from a marker encoded for by the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72. The molecule expressed by the bladder cancer cell may be expressed by the bladder cancer cell at level that is higher than the level expressed by a non-cancerous cell.

[0021] In other embodiments the invention provides a composition of matter comprising a nucleic acid that specifically binds to a molecule, such as an mRNA molecule, expressed by a bladder cancer cell wherein the molecule is chosen from a marker encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72. The molecule expressed by the bladder cancer cell may be expressed by the cancer cell at level that is higher than the level expressed by a non-cancerous cell.

[0022] In still further embodiments the invention provides a method of determining if a bladder cancer in a subject is advancing comprising a) measuring the expression level of one or

more markers associated with bladder cancer at a first time point; b) measuring the expression level of the one or more markers measured in a) at a second time point, wherein the second time point is subsequent to the first time point; and c) comparing the expression level measured in a) and b), wherein an increase in the expression level of the one or more markers in b) compared to a) indicates that the subject's bladder cancer is advancing. Suitable markers include those markers encoded for by the genes provided in SEQ ID NOS: 1-40 and/or SEQ ID NO 41. In some embodiments a suitable marker may be chosen from the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72.

[0023] In some embodiments the invention provides a method of determining if a bladder cancer in a subject is advancing comprising a) measuring the expression level of the panel of markers encoded for by the genes LOC650517, FCRLB, 1L1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COLO10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72 at a first time point; b) measuring the expression level of the markers measured in a) at a second time point, wherein the second time point is subsequent to the first time point; and c) comparing the expression level measured in a) and b), wherein an increase in the expression level of the markers at the second time point compared to the first time point indicates that the subject's bladder cancer is advancing.

[0024] In some embodiments the invention provides antigens (i.e. cancer-associated polypeptides) associated with bladder cancer as targets for diagnostic and/or therapeutic antibodies. In some embodiments, the antigen may be chosen from a protein encoded by, a gene listed in SEQ ID NOS: 1-40, a fragment thereof, or a combination of proteins encoded by a gene listed in SEQ ID NOS 1-40 and/or SEQ ID NO 41. In some embodiments the antigen may be chosen from a protein (or fragment thereof) encoded for by genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72.

[0025] In some embodiments the invention provides antigens (i.e. cancer-associated polypeptides) associated with bladder cancer as targets for diagnostic and/or therapeutic antibodies. In some embodiments, the antigen may include a panel of proteins encoded by the genes LOC650517, FCRLB, 1L1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COLO10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72 or a fragment thereof.

[0026] In yet other embodiments the invention provides a method of eliciting an immune response to a bladder cancer cell comprising contacting a subject with a protein or protein

fragment that is expressed by a bladder cancer cell thereby eliciting an immune response to the bladder cancer cell. As an example the subject may be contacted intravenously or intramuscularly with protein or protein fragment.

[0027] In further embodiments the invention provides a method of eliciting an immune response to a bladder cancer cell comprising contacting a subject with one or more proteins or protein fragments that is encoded by a gene chosen from the genes listed in SEQ ID NOS: 1-40, and/or SEQ ID NO: 41, thereby eliciting an immune response to a bladder cancer cell. As an example the subject may be contacted with the protein or the protein fragment intravenously or intramuscularly.

[0028] In further embodiments the invention provides a method of eliciting an immune response to a bladder cancer cell comprising contacting a subject with one or more proteins or protein fragments that is encoded by a gene chosen from the genes UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72, thereby eliciting an immune response to a bladder cancer cell. As an example the subject may be contacted with the protein or the protein fragment intravenously or intramuscularly.

[0029] In yet other embodiments the invention provides a kit for detecting bladder cancer cells in a sample. The kit may comprise one or more agents that detect expression of any the cancer associated sequences disclosed infra e.g. SEQ ID NOS 1-41. The agents may bind to one or more of the cancer associated sequences disclosed infra. The kit may include agents that are proteins and/or nucleic acids for example. In one embodiment the kit provides a plurality of agents. The agents may be able to detect the panel of markers encoded by the genes comprising LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 TOP2A, and WDR72, or a complement thereof. The agent may comprise a detectable substance.

[0030] In yet other embodiments the invention provides a kit for detecting bladder cancer cells in a sample. The kit may comprise one or more agents that detect expression of any the cancer associated sequences disclosed infra. The kit may include agents that are proteins and/or nucleic acids for example. In one embodiment the kit provides a plurality of agents. The agents may be able to detect the panel of markers encoded by the genes comprising LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH,

COL10A1, SERPINB4, UBE2C, SFN, KRT17P3, SERPINB5, DSCR6, TOP2A, and WDR72 or a complement thereof. The agent may comprise a detectable substance.

[0031] In still other embodiments the invention provides a kit for detecting bladder cancer in a sample comprising a plurality of agents that specifically bind to a molecule encoded for by the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72. The agent may comprise a detectable substance.

[0032] In other embodiments the invention provides a kit for detection of bladder cancer in a sample obtained from a subject. The kit may comprise one or more agents that bind specifically to a molecule expressed specifically by a bladder cancer cell, e.g. one or more of the markers encoded for by SEQ ID NOS; 1-41. The kit may comprise one or more containers and instructions for determining if the sample is positive for cancer. The kit may optionally contain one or more multiwell plates, a detectable substance such as a dye, a radioactively labeled molecule, a chemiluminescently labeled molecule and the like. The detectible substance may be linked the agent that specifically binds to a molecule expressed by a bladder cancer cell. The kit may further contain a positive control (e.g. one or more bladder cancer cells; or specific known quantities of the molecule expressed by the bladder cancer cell) and a negative control (e.g. a tissue or cell sample that is non-cancerous). The agent may comprise a detectable substance.

[0033] In certain embodiments the invention provides a kit comprising a plurality of antibodies. The plurality of antibodies may bind to one or more proteins encoded for by a gene chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72. The antibodies may comprise a detectable substance.

[0034] In certain embodiments the invention provides a kit comprising a plurality of antibodies. The plurality of antibodies may bind to one or more proteins encoded for by a gene chosen from UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72. The antibodies may comprise a detectable substance.

[0035] In certain embodiments the invention provides a kit comprising a plurality of oligonucleotides. The plurality of oligonucleotides may bind to one or more nucleic acids, e.g. RNA encoded for by a gene chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72. The oligonucleotides may comprise a detectable substance.

[0036] In certain embodiments the invention provides a kit comprising a plurality of oligonucleotides. The plurality of oligonucleotides may bind to one or more nucleic acids, e.g. RNA encoded for by a gene chosen from UBE2C, FCRLB, COL10A1, MMP11, TOP2A, and WDR72. The oligonucleotides may comprise a detectable substance.

[0037] In some embodiments the invention provides a kit for the detection of bladder cancer comprising one or more agents that specifically bind one or more markers encoded by genes chosen from a gene disclosed infra., e.g., LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72. The agent may be a protein, such as an antibody. Alternatively, the agent may be a nucleic acid such as a DNA molecule or an RNA molecule. The kit may comprise one or more containers and instructions for determining if the sample is positive for cancer. The kit may optionally contain one or more multiwell plates, a detectable substance such as a dye, a radioactively labeled molecule, a chemiluminescently labeled molecule and the like. The detectable substance may be linked to the agent that specifically binds the one or more markers disclosed infra. The kit may further contain a positive control (e.g. one or more bladder cancer cells; or specific known quantities of the molecule expressed by the bladder cancer cell) and a negative control (e.g. a tissue or cell sample that is non-cancerous). As an example the kit may take the form of an ELISA or a DNA microarray. In some embodiments the kit may include one or more antibodies suitable for use in a fluorescent activated cell sorter, e.g. use in flow cytometry.

[0038] Some embodiments are directed to a method of treating bladder cancer in a subject, the method comprising administering to a subject in need thereof a therapeutic agent modulating the activity of a bladder cancer associated protein, wherein the cancer associated protein is encoded by gene listed in SEQ ID NOS: 1-40 and/or SEQ ID NO 41, homologs

thereof, combinations thereof, or a fragment thereof. In some embodiments, the therapeutic agent binds to the cancer associated protein. In some embodiments, the therapeutic agent is an antibody. In some embodiments, the antibody may be a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody is a humanized or human antibody. In some embodiments the antibody may be conjugated with a drug or a toxin.

[0039] In some embodiments, a method of treating bladder cancer in a subject may comprise administering to a subject in need thereof a therapeutic agent that modulates the expression of one or more genes chosen from those listed in SEQ ID NOS: 1-40, and/or SEQ ID NO: 41, fragments thereof, homologs thereof, and/or complements thereof.

[0040] In further embodiments, the invention provides a method of treating bladder cancer may comprise a gene knockdown of one or more genes listed in SEQ ID NOS: 1-40, fragments thereof, homologs thereof, and or compliments thereof.

[0041] In still other embodiments, the present invention provides methods of screening a drug candidate for activity against bladder cancer, the method comprising: (a) contacting a cell that expresses one or more bladder cancer associated genes chosen from those listed in SEQ ID NOS: 1-40 and/or SEQ ID NO: 41 with a drug candidate; (b) detecting an effect of the drug candidate on expression of the one or more bladder cancer associated genes in the cell from a); and (c) comparing the level of expression of one or more of the genes recited in a) in the absence of the drug candidate to the level of expression of the one or more genes recited in a) in the presence of the drug candidate; wherein a decrease in the expression of the bladder cancer associated gene in the presence of the drug candidate indicates that the candidate has activity against bladder cancer.

[0042] In some embodiments, the present invention provides methods of visualizing a bladder cancer tumor comprising a) targeting one or more bladder cancer associated proteins with a labeled molecule that binds specifically to the cancer tumor, wherein the bladder cancer associated protein is selected from a protein encoded for by one or more genes chosen from those listed in SEQ ID NOS: 1-40 and/or SEQ ID NO: 41; and b) detecting the labeled molecule, wherein the labeled molecule visualizes the tumor. Visualization may be done in vivo, or in vitro.

[0043] In yet other embodiments the invention provides methods of visualizing a bladder cancer tumor comprising a) targeting one or more bladder cancer associated genes, e.g. one or more genes encoded for by SEQ ID NOS: 1-40, with a labeled molecule, such as a nucleic acid that binds specifically to the cancer tumor genes chosen from those listed in SEQ

ID NOS: 1-40; and b) detecting the labeled molecule, wherein the labeled molecule visualizes the tumor. Visualization may be done in vivo, or in vitro.

DESCRIPTION OF DRAWINGS

[0044] For a fuller understanding of the nature and advantages of the present invention, reference should be had to the following detailed description taken in connection with the accompanying drawings, in which:

[0045] FIG. 1 shows the expression of LOC650517 in bladder tumors v. normal tissues.

[0046] FIG. 2 shows the expression of FCRLB in bladder tumors v. normal tissues.

[0047] FIG. 3 shows the expression of IL1A in bladder tumors v. normal tissues.

[0048] FIG. 4 shows the expression of S100A2 in bladder tumors v. normal tissues.

[0049] FIG. 5 shows the expression of MMP11 in bladder tumors v. normal tissues.

[0050] FIG. 6 shows the expression of S100A7A in bladder tumors v. normal tissues.

[0051] FIG. 7 shows the expression of UGT1A6 in bladder tumors v. normal tissues.

[0052] FIG. 8 shows the expression of FAM83A in bladder tumors v. normal tissues.

[0053] FIG. 9 shows the expression of SLC1A6 in bladder tumors v. normal tissues.

[0054] FIG. 10 shows the expression of UPK3B in bladder tumors v. normal tissues.

[0055] FIG. 11 shows the expression of BX116033 in bladder tumors v. normal tissues.

[0056] FIG. 12 shows the expression of MMP12 in bladder tumors v. normal tissues.

[0057] FIG. 13 shows the expression of KRT16 in bladder tumors v. normal tissues.

[0058] FIG. 14 shows the expression of UBD in bladder tumors v. normal tissues.

[0059] FIG. 15 shows the expression of UGT1A6 in bladder tumors v. normal tissues.

[0060] FIG. 16 shows the expression of S100A7 in bladder tumors v. normal tissues.

[0061] FIG. 17 shows the expression of WISP3 in bladder tumors v. normal tissues.

[0062] FIG. 18 shows the expression of PTHLH in bladder tumors v. normal tissues.

[0063] FIG. 19 shows the expression of COLO10A1 in bladder tumors v. normal tissues.

[0064] FIG. 20 shows the expression of SERPINB4 in bladder tumors v. normal tissues.

[0065] FIG. 21 shows the expression of UBE2C in bladder tumors v. normal tissues.

[0066] FIG. 22 shows the expression of SFN in bladder tumors v. normal tissues.

[0067] FIG. 23 shows the expression of KRT17P3 in bladder tumors v. normal tissues.

[0068] FIG. 24 shows the expression of MMP11 in bladder tumors v. normal tissues.

[0069] FIG. 25 shows the expression of MMP12 in bladder tumors v. normal tissues.

[0070] FIG. 26 shows the expression of COL10A1 in bladder tumors v. normal tissues.

[0071] FIG. 27 shows the expression of KRT6A in bladder tumors v. normal tissues.

[0072] FIG. 28 shows the expression of SFN in bladder tumors v. normal tissues.

[0073] FIG. 29 shows the expression of FCRLB in bladder tumors v. normal tissues.

[0074] FIG. 30 shows the expression of SERPINB5 in bladder tumors v. normal tissues.

[0075] FIG. 31 shows the expression of IL1A in bladder tumors v. normal tissues.

[0076] FIG. 32 shows the expression of KRT16 in bladder tumors v. normal tissues.

[0077] FIG. 33 shows the expression of SLC1A6 in bladder tumors v. normal tissues.

[0078] FIG. 34 shows the expression of S100A2 in bladder tumors v. normal tissues.

[0079] FIG. 35 shows the expression of S100A7A in bladder tumors v. normal tissues.

[0080] FIG. 36 shows the expression of DSCR6 in bladder tumors v. normal tissues.

[0081] FIG. 37 shows the expression of UBE2C in bladder tumors v. normal tissues.

[0082] FIG. 38 shows the expression of MMP11 in bladder tumors v. normal tissues.

[0083] FIG. 39 shows the expression of COL10A1 in bladder tumors v. normal tissues.

[0084] FIG. 40 is an agarose gel showing expression of COL10A, MMP11, SFN, and FCRLB in the urine of bladder cancer patients.

[0085] FIG. 41 an immunofluorescent microscopy image and shows that MMP11 is detectable in bladder cancer samples, but not in normal bladder tissue.

[0086] FIG 42 shows WDR72 mRNA expression by Illumina microarray. Samples are MB_3946 (normal bladder tissue) and MB_3933 (bladder cancer tissue).

[0087] FIG 43 shows WDR72 mRNA expression by 1-step qRT-PCR. Samples are MB_3946 (normal bladder tissue) and MB_3933 (bladder cancer tissue).

[0088] FIG 44 shows WDR72 mRNA expression in normal and bladder cancer tissues measured by qRT-PCR. WDR72 expression levels of four histologically normal (N1-N4) and 20 bladder cancer tissues (C1-C20) were normalized to GAPDH expression levels, and are expressed as $2^{-(\Delta Ct)}$ values. Input cDNA samples were obtained as a TissueScan™ cDNA Array (Bladder Cancer, Panel I, Origene). WDR72: primers: MP3-F-WDR72, MP3-R-WDR72, and probe: MP3-P-WDR72-FAM. GAPDH: primers: MP4-F-GAPDH, MP4-R-GAPDH, and probe: MP4-P-GAPDH-Cy5.

[0089] FIG 45 shows WDR72 and TOP2A mRNA expression in human bladder cancer SCaBER cells spiked into 50 ml-aliquots of human urine from a healthy individual. A. Ct values for the WDR72 and GAPDH duplex assay. B. Ct values for the TOP2A and GAPDH duplex assay. C. GAPDH-normalized WDR72 and TOP2A expression levels. The WDR72-GAPDH assay may detect 100 SCaBER cells per 50 ml of urine. D. SCaBER detection by combining the WDR72-GAPDH and TOP2A-GAPDH assays.

[0090] FIG 46 shows Ct values of the WDR72-GAPDH assay with 100 ml of urine from a healthy individual using the ZR Urine RNA Isolation Kit method with substitution of the

syringe part (urine manually pressed through a filter attached to the syringe) by a 0.2 micron vacuum sterile filtration device step (Nalgene).

[0091] FIG 47 demonstrates that WDR72 can be detected linearly by qRT-PCR using primers specific for WDR72.

[0092] FIG 48 shows that WDR72 is expressed at higher levels in bladder tumor tissue compared to normal bladder samples as measured by qRT-PCR.

[0093] FIG 49 shows that WDR72 is detected by qRT-PCR when human urine is spiked with RNA.

[0094] FIG 50 shows that WDR72 is expressed at higher levels in bladder tumor samples compared to normal bladder samples when measured by the commercially available Flexscript LDA assay.

DETAILED DESCRIPTION

[0095] Before the present compositions and methods are described, it is to be understood that this invention is not limited to the particular processes, compositions, or methodologies described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present disclosure, the preferred methods, devices, and materials are now described. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0096] As used herein, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a “therapeutic” is a reference to one or more therapeutics and equivalents thereof known to those skilled in the art, and so forth.

[0097] As used herein, the term “about” means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45% to 55%.

[0098] “Administering,” when used in conjunction with a therapeutic, means to administer a therapeutic directly into or onto a target tissue or to administer a therapeutic to a patient whereby the therapeutic treats the tissue to which it is targeted. Thus, as used herein, the term “administering,” when used in conjunction with a therapeutic, can include, but is not

limited to, providing the therapeutic into or onto the target tissue; providing the therapeutic systemically to a patient by, e.g., intravenous injection whereby the therapeutic reaches the target tissue; providing the therapeutic in the form of the encoding sequence thereof to the target tissue (e.g., by so-called gene-therapy techniques). “Administering” a composition may be accomplished by oral administration, intravenous injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, transdermal diffusion or electrophoresis, local injection, extended release delivery devices including locally implanted extended release devices such as bioerodible or reservoir-based implants, as protein therapeutics or as nucleic acid therapeutic via gene therapy vectors, topical administration, or by any of these methods in combination with other known techniques. Such combination techniques include, without limitation, heating, radiation and ultrasound.

[0099] “Agent” as used herein refers to a molecule that specifically binds to a cancer associated sequence or a molecule encoded for by a cancer associated sequence or a receptor that binds to a molecule encoded for by a cancer associated sequence. Examples of agents include nucleic acid molecules, such as DNA and proteins, such as antibodies. The agent may be linked with a label or detectible substance as described infra. The agent may be linked with a therapeutic agent or a toxin.

[00100] The term “amplify” as used herein means creating an amplification product which may include, for example, additional target molecules, or target-like molecules or molecules complementary to the target molecule, which molecules are created by virtue of the presence of the target molecule in the sample. In the situation where the target is a nucleic acid, an amplification product can be made enzymatically with DNA or RNA polymerases or reverse transcriptases, or any combination thereof.

[00101] The term “animal,” “patient” or “subject” as used herein includes, but is not limited to, humans, non-human primates and non-human vertebrates such as wild, domestic and farm animals including any mammal, such as cats, dogs, cows, sheep, pigs, horses, rabbits, rodents such as mice and rats. In some embodiments, the term “subject,” “patient” or “animal” refers to a male. In some embodiments, the term “subject,” “patient” or “animal” refers to a female.

[00102] The term “antibody”, as used herein, means an immunoglobulin or a part thereof, and encompasses any polypeptide comprising an antigen-binding site regardless of the source, method of production, or other characteristics. The term includes for example, polyclonal, monoclonal, monospecific, polyspecific, humanized, single-chain, chimeric,

synthetic, recombinant, hybrid, mutated, and CDR-grafted antibodies. A part of an antibody can include any fragment which can bind antigen, for example, an Fab, F(ab')₂, Fv, scFv.

[00103] The term “biological sources” as used herein refers to the sources from which the target polynucleotides or proteins or peptide fragments may be derived. The source can be of any form of “sample” as described infra, including but not limited to, cell, tissue or fluid. “Different biological sources” can refer to different cells/tissues/organs of the same individual, or cells/tissues/organs from different individuals of the same species, or cells/tissues/organs from different species.

[00104] The term “capture reagent” refers to a reagent, for example an antibody or antigen binding protein, capable of binding a target molecule or analyte to be detected in a sample.

[00105] The term “gene expression result” refers to a qualitative and/or quantitative result regarding the expression of a gene or gene product. Any method known in the art may be used to quantitate a gene expression result. The gene expression result can be an amount or copy number of the gene, the RNA encoded by the gene, the mRNA encoded by the gene, the protein product encoded by the gene, or any combination thereof. The gene expression result can also be normalized or compared to a standard. The gene expression result can be used, for example, to determine if a gene is expressed, overexpressed, or differentially expressed in two or more samples by comparing the gene expression results from 2 or more samples or one or more samples with a standard or a control.

[00106] The term “homology,” as used herein, refers to a degree of complementarity. There may be partial homology or complete homology. The word “identity” may substitute for the word “homology.” A partially complementary nucleic acid sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as “substantially homologous.” The inhibition of hybridization of the completely complementary nucleic acid sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially homologous sequence or hybridization probe will compete for and inhibit the binding of a completely homologous sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% homology or identity). In the

absence of non-specific binding, the substantially homologous sequence or probe will not hybridize to the second non-complementary target sequence.

[00107] As used herein, the term “hybridization” or “hybridizing” refers to hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding between complementary nucleoside or nucleotide bases. For example, adenine and thymine are complementary nucleobases which pair through the formation of hydrogen bonds. “Complementary,” as used herein in reference to nucleic acid molecules refers to the capacity for precise pairing between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the same position of a DNA or RNA molecule, then the oligonucleotide and the DNA or RNA are considered to be complementary to each other at that position. The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, “specifically hybridizable” and “complementary” are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that a nucleic acid sequence need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. A nucleic acid compound is specifically hybridizable when there is binding of the molecule to the target, and there is a sufficient degree of complementarity to avoid non-specific binding of the molecule to non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

[00108] The term “inhibiting” includes the administration of a compound of the present disclosure to prevent the onset of the symptoms, alleviating the symptoms, or eliminating the disease, condition or disorder. The term “inhibiting” may also refer to lowering the expression level of gene, such as a gene encoding a cancer associated sequence. Expression level of RNA and/or protein may be lowered.

[00109] The term “label” and/or detectible substance refer to a composition capable of producing a detectable signal indicative of the presence of the target polynucleotide or a polypeptide or protein in an assay sample. Suitable labels include radioisotopes, nucleotide chromophores, enzymes, substrates, fluorescent molecules, chemiluminescent moieties, magnetic particles, bioluminescent moieties, and the like. As such, a label is any composition detectable by a device or method, such as, but not limited to, a spectroscopic, photochemical,

biochemical, immunochemical, electrical, optical, chemical detection device or any other appropriate device. In some embodiments, the label may be detectable visually without the aid of a device. The term “label” is used to refer to any chemical group or moiety having a detectable physical property or any compound capable of causing a chemical group or moiety to exhibit a detectable physical property, such as an enzyme that catalyzes conversion of a substrate into a detectable product. The term “label” also encompasses compounds that inhibit the expression of a particular physical property. The label may also be a compound that is a member of a binding pair, the other member of which bears a detectable physical property.

[00110] A “microarray” is a linear or two-dimensional array of, for example, discrete regions, each having a defined area, formed on the surface of a solid support. The density of the discrete regions on a microarray is determined by the total numbers of target polynucleotides to be detected on the surface of a single solid phase support, preferably at least about 50/cm² more preferably at least about 100/cm², even more preferably at least about 500/cm², and still more preferably at least about 1,000/cm². As used herein, a DNA microarray is an array of oligonucleotide primers placed on a chip or other surfaces used to identify, amplify, detect, or clone target polynucleotides. Since the position of each particular group of primers in the array is known, the identities of the target polynucleotides can be determined based on their binding to a particular position in the microarray.

[00111] As used herein, the term “naturally occurring” refers to sequences or structures that may be in a form normally found in nature. “Naturally occurring” may include sequences in a form normally found in any animal.

[00112] The use of “nucleic acid,” “polynucleotide” or “oligonucleotide” or equivalents herein means at least two nucleotides covalently linked together. In some embodiments, an oligonucleotide is an oligomer of 6, 8, 10, 12, 20, 30 or up to 100 nucleotides. In some embodiments, an oligonucleotide is an oligomer of at least 6, 8, 10, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, or 500 nucleotides. A “polynucleotide” or “oligonucleotide” may comprise DNA, RNA, PNA or a polymer of nucleotides linked by phosphodiester and/or any alternate bonds.

[00113] As used herein, the term “optional” or “optionally” refers to embodiments where the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the event occurs and instances where it does not.

[00114] The phrases “percent homology,” “% homology,” “percent identity,” or “% identity” refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by

using the MEGALIGN program (LASERGENE software package, DNASTAR). The MEGALIGN program can create alignments between two or more sequences according to different methods, e.g., the Clustal Method. (Higgins, D. G. and P. M. Sharp (1988) *Gene* 73:237-244.) The Clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no homology between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be calculated by the Clustal Method, or by other methods known in the art, such as the Jotun Hein Method. (See, e.g., Hein, J. (1990) *Methods Enzymol.* 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

[00115] By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00116] “Recombinant protein,” as used herein, means a protein made using recombinant techniques, for example, but not limited to, through the expression of a recombinant nucleic acid as depicted infra. A recombinant protein may be distinguished from naturally occurring protein by at least one or more characteristics. For example, the protein may be isolated or purified away from some or all of the proteins and compounds with which it is normally associated in its wild type host, and thus may be substantially pure. For example, an isolated protein is unaccompanied by at least some of the material with which it is normally associated in its natural state, preferably constituting at least about 0.5%, more preferably at least about 5% by weight of the total protein in a given sample. A substantially pure protein comprises about 50-75%, about 80%, or about 90%. In some embodiments, a substantially pure protein comprises about 80-99%, 85-99%, 90-99%, 95-99%, or 97-99% by weight of the total protein. A recombinant protein can also include the production of a cancer associated protein from one organism (e.g. human) in a different organism (e.g. yeast, E. coli, or the like) or host cell. Alternatively, the protein may be made at a significantly higher concentration than is normally seen, through the use of an inducible promoter or high expression promoter, such that the protein is made at increased concentration levels. Alternatively, the protein may be in a

form not normally found in nature, as in the addition of an epitope tag or amino acid substitutions, insertions and deletions, as discussed herein.

[00117] As used herein, the term “sample” refers to composition that is being tested or treated with a reagent, agent, capture reagent, binding partner and the like. Samples may be obtained from subjects. In some embodiments, the sample may be blood, plasma, serum, or any combination thereof. A sample may be derived from blood, plasma, serum, or any combination thereof. Other typical samples include, but are not limited to, any bodily fluid obtained from a mammalian subject, tissue biopsy, sputum, lymphatic fluid, blood cells (e.g., peripheral blood mononuclear cells), tissue or fine needle biopsy samples, urine, peritoneal fluid, colostrums, breast milk, fetal fluid, fecal material, tears, pleural fluid, or cells therefrom. The sample may be processed in some manner before being used in a method described herein, for example a particular component to be analyzed or tested according to any of the methods described infra. One or more molecules may be isolated from a sample.

[00118] The terms “specific binding,” “specifically binds,” and the like, refer to instances where two or more molecules form a complex that is measurable under physiologic or assay conditions and is selective. An antibody or antigen binding protein or other molecule is said to “specifically bind” to a protein, antigen, or epitope if, under appropriately selected conditions, such binding is not substantially inhibited, while at the same time non-specific binding is inhibited. Specific binding is characterized by a high affinity and is selective for the compound, protein, epitope, or antigen. Nonspecific binding usually has a low affinity. Examples of specific binding include the binding of enzyme and substrate, an antibody and its antigenic epitope, a cellular signaling molecule and its respective cell receptor.

[00119] As used herein, a polynucleotide “derived from” a designated sequence refers to a polynucleotide sequence which is comprised of a sequence of approximately at least about 6 nucleotides, preferably at least about 8 nucleotides, more preferably at least about 10-12 nucleotides, and even more preferably at least about 15-20 nucleotides corresponding to a region of the designated nucleotide sequence. “Corresponding” means homologous to or complementary to the designated sequence. Preferably, the sequence of the region from which the polynucleotide is derived is homologous to or complementary to a sequence that is unique to a cancer associated gene.

[00120] As used herein, the term “tag,” “sequence tag” or “primer tag sequence” refers to an oligonucleotide with specific nucleic acid sequence that serves to identify a batch of polynucleotides bearing such tags therein. Polynucleotides from the same biological source are covalently tagged with a specific sequence tag so that in subsequent analysis the polynucleotide

can be identified according to its source of origin. The sequence tags also serve as primers for nucleic acid amplification reactions.

[00121] The term “support” refers to conventional supports such as beads, particles, dipsticks, fibers, filters, membranes, and silane or silicate supports such as glass slides.

[00122] As used herein, the term “therapeutic” or “therapeutic agent” means an agent that can be used to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In part, embodiments of the present disclosure are directed to the treatment of cancer or the decrease in proliferation of cells. In some embodiments, the term “therapeutic” or “therapeutic agent” may refer to any molecule that associates with or affects the target marker or cancer associated sequence disclosed *infra*, its expression or its function. In various embodiments, such therapeutics may include molecules such as, for example, a therapeutic cell, a therapeutic peptide, a therapeutic gene, a therapeutic compound, or the like, that associates with or affects the target marker or cancer associated sequence disclosed *infra*, its expression or its function.

[00123] A “therapeutically effective amount” or “effective amount” of a composition is a predetermined amount calculated to achieve the desired effect, *i.e.*, to inhibit, block, or reverse the activation, migration, metastasis, or proliferation of cells. In some embodiments, the effective amount is a prophylactic amount. In some embodiments, the effective amount is an amount used to medically treat the disease or condition. The specific dose of a composition administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the composition administered, the route of administration, and the condition being treated. It will be understood that the effective amount administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of composition to be administered, and the chosen route of administration. A therapeutically effective amount of composition of this invention is typically an amount such that when it is administered in a physiologically tolerable excipient composition, it is sufficient to achieve an effective systemic concentration or local concentration in the targeted tissue.

[00124] The terms “treat,” “treated,” or “treating” as used herein can refer to both therapeutic treatment or prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological condition, symptom, disorder or disease, or to obtain beneficial or desired clinical results. In some embodiments, the term may refer to both treating and preventing. For the purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the

condition, disorder or disease; stabilization (*i.e.*, not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

[00125] The term “tissue” refers to any aggregation of similarly specialized cells that are united in the performance of a particular function.

Cancer Associated Sequences

[00126] In some embodiments, the present disclosure provides for nucleic acid and protein sequences that are associated with cancer, herein termed “cancer associated” or “CA” sequences. In some embodiments, the present disclosure provides nucleic acid and protein sequences that are associated with bladder cancers or carcinomas such as, without limitation, urothelial carcinoma, transitional cell carcinoma, non-transitional cell carcinomas, such as, without limitation, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, neural cell tumors, cervical carcinoma, or lymphoma, recurrent and metastatic bladder cancer, or a combination thereof. The method of diagnosing may comprise measuring the level of expression of a cancer associated marker disclosed herein. The method may further comprise comparing the expression level of the cancer associated sequence with a standard and/or a control. The standard may be from a sample known to contain bladder cancer cells. The control may include known bladder cancer cells and/or non-cancerous cells, such as non-cancer cells derived from bladder tissue.

[00127] Cancer associated sequences may include those that are up-regulated (*i.e.* expressed at a higher level), as well as those that are down-regulated (*i.e.* expressed at a lower level), in cancers. Cancer associated sequences can also include sequences that have been altered (*i.e.*, translocations, truncated sequences or sequences with substitutions, deletions or insertions, including, but not limited to, point mutations) and show either the same expression profile or an altered profile. In some embodiments, the cancer associated sequences are from humans; however, as will be appreciated by those in the art, cancer associated sequences from other organisms may be useful in animal models of disease and drug evaluation; thus, other cancer associated sequences may be useful, including those obtained from any subject, such as, without limitation, sequences from vertebrates, including mammals, such as rodents (rats, mice, hamsters, guinea pigs, etc.), primates, and farm animals (including sheep, goats, pigs, cows,

horses, etc.). Cancer associated sequences from other organisms may be obtained using the techniques outlined herein.

[00128] Examples of cancer associated sequences include SEQ ID NOS: 1-41. Other examples of cancer associated sequences are the DNA sequences encoding the genes LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, TOP2A, and WDR72.

[00129] In some embodiments, the cancer associated sequences are nucleic acids. As will be appreciated by those skilled in the art and as described herein, cancer associated sequences of embodiments herein may be useful in a variety of applications including diagnostic applications to detect nucleic acids or their expression levels in a subject, therapeutic applications or a combination thereof. Further, the cancer associated sequences of embodiments herein may be used in screening applications; for example, generation of biochips comprising nucleic acid probes to the cancer associated sequences.

[00130] A nucleic acid of the present disclosure may include phosphodiester bonds, although in some cases, as outlined below (for example, in antisense applications or when a nucleic acid is a candidate drug agent), nucleic acid analogs may have alternate backbones, comprising, for example, phosphoramidate (Beaucage et al., *Tetrahedron* 49(10):1925 (1993) and references therein; Letsinger, *J. Org. Chem.* 35:3800 (1970); Sprinzl et al., *Eur. J. Biochem.* 81:579 (1977); Letsinger et al., *Nucl. Acids Res.* 14:3487 (1986); Sawai et al., *Chem. Lett.* 805 (1984), Letsinger et al., *J. Am. Chem. Soc.* 110:4470 (1988); and Pauwels et al., *Chemica Scripta* 26:141 (1986)), phosphorothioate (Mag et al., *Nucleic Acids Res.* 19:1437 (1991); and U.S. Pat. No. 5,644,048), phosphorodithioate (Briu et al., *J. Am. Chem. Soc.* 111:2321 (1989), O-methylphosphoroamidite linkages (see Eckstein, *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press), and peptide nucleic acid backbones and linkages (see Egholm, *J. Am. Chem. Soc.* 114:1895 (1992); Meier et al., *Chem. Int. Ed. Engl.* 31:1008 (1992); Nielsen, *Nature*, 365:566 (1993); Carlsson et al., *Nature* 380:207 (1996),). Other analog nucleic acids include those with positive backbones (Denpcy et al., *Proc. Natl. Acad. Sci. USA* 92:6097 (1995); non-ionic backbones (U.S. Pat. Nos. 5,386,023, 5,637,684, 5,602,240, 5,216,141 and 4,469,863; Kiedrowshi et al., *Angew. Chem. Intl. Ed. English* 30:423 (1991); Letsinger et al., *J. Am. Chem. Soc.* 110:4470 (1988); Letsinger et al., *Nucleoside & Nucleotide* 13:1597 (1994); Chapters 2 and 3, ASC Symposium Series 580,

“Carbohydrate Modifications in Antisense Research”, Ed. Y. S. Sanghui and P. Dan Cook; Mesmaeker et al., *Bioorganic & Medicinal Chem. Lett.* 4:395 (1994); Jeffs et al., *J. Biomolecular NMR* 34:17 (1994); *Tetrahedron Lett.* 37:743 (1996)) and non-ribose backbones, including those described in U.S. Pat. Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, “Carbohydrate Modifications in Antisense Research”, Ed. Y. S. Sanghui and P. Dan Cook. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids (see Jenkins et al., *Chem. Soc. Rev.* (1995) pp. 169-176). Several nucleic acid analogs are described in Rawls, *C & E News* Jun. 2, 1997 page 35. These modifications of the ribose-phosphate backbone may be done for a variety of reasons, for example to increase the stability and half-life of such molecules in physiological environments for use in anti-sense applications or as probes on a biochip.

[00131] As will be appreciated by those skilled in the art, such nucleic acid analogs may be used in some embodiments of the present disclosure. In addition, mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made.

[00132] In some embodiments, the nucleic acids may be single stranded or double stranded or may contain portions of both double stranded or single stranded sequence. As will be appreciated by those skilled in the art, the depiction of a single strand also defines the sequence of the other strand; thus the sequences described herein also includes the complement of the sequence. The nucleic acid may be DNA, both genomic and cDNA, RNA, or a hybrid, where the nucleic acid contains any combination of deoxyribo- and ribo-nucleotides, and any combination of bases, including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine, hypoxanthine, isocytosine, isoguanine, etc. As used herein, the term “nucleoside” includes nucleotides and nucleoside and nucleotide analogs, and modified nucleosides such as amino modified nucleosides. In addition, “nucleoside” includes non-naturally occurring analog structures. Thus, for example, the subject units of a peptide nucleic acid, each containing a base, are referred to herein as a nucleoside.

[00133] In some embodiments, cancer associated sequences may include both nucleic acid and amino acid sequences. In some embodiments, the cancer associated sequences may include sequences having at least about 60% homology with the disclosed sequences. In some embodiments, the cancer associated sequences may have at least about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, about 99%, about 99.8% homology with the disclosed sequences. In some embodiments, the cancer associated sequences

may be “mutant nucleic acids”. As used herein, “mutant nucleic acids” refers to deletion mutants, insertions, point mutations, substitutions, translocations.

[00134] In some embodiments, the cancer associated sequences may be recombinant nucleic acids. By the term “recombinant nucleic acid” herein refers to nucleic acid molecules, originally formed in vitro, in general, by the manipulation of nucleic acid by polymerases and endonucleases, in a form not normally found in nature. Thus a recombinant nucleic acid may also be an isolated nucleic acid, in a linear form, or cloned in a vector formed in vitro by ligating DNA molecules that are not normally joined, are both considered recombinant for the purposes of this invention. It is understood that once a recombinant nucleic acid is made and reintroduced into a host cell or organism, it can replicate using the in vivo cellular machinery of the host cell rather than in vitro manipulations; however, such nucleic acids, once produced recombinantly, although subsequently replicated in vivo, are still considered recombinant or isolated for the purposes of the invention. As used herein, a “polynucleotide” or “nucleic acid” is a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. This term includes double- and single-stranded DNA and RNA. It also includes known types of modifications, for example, labels which are known in the art, methylation, “caps”, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications-such as, for example, those with uncharged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example proteins (including e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide.

[00135] The use of microarray analysis of gene expression allows the identification of host sequences associated with bladder cancer. These sequences may then be used in a number of different ways, including diagnosis, prognosis, screening for modulators (including both agonists and antagonists), antibody generation (for immunotherapy and imaging), etc. However, as will be appreciated by those skilled in the art, sequences that are identified in one type of cancer may have a strong likelihood of being involved in other types of cancers as well. Thus, while the sequences outlined herein are initially identified as correlated with bladder cancers, they may also be found in other types of cancers as well.

[00136] Some embodiments described herein may be directed to the use of cancer associated sequences for diagnosis and treatment of bladder cancer. In some embodiments, the cancer associated sequence may be selected from: LOC650517, FCRLB, IL1A, S100A2,

MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a combination thereof. In some embodiments, these cancer associated sequences may be associated with bladder cancers including, without limitation, urothelial carcinoma, transitional cell carcinoma, non-transitional cell carcinomas, such as, without limitation, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, neural cell tumors, cervical carcinoma, or lymphoma, recurrent and metastatic bladder cancer, or a combination thereof.

[00137] In some embodiments, the cancer associated sequences may be DNA sequences encoding the above mRNA or the cancer associated protein or cancer associated polypeptide expressed by the above mRNA or homologs thereof. In some embodiments, the cancer associated sequence may be a mutant nucleic acid of the above disclosed sequences. In some embodiments, the homolog may have at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% identity with the disclosed polypeptide sequence.

[00138] In some embodiments, an isolated nucleic acid comprises at least 10, 12, 15, 20 or 30 contiguous nucleotides of a sequence selected from the group consisting of the cancer associated polynucleotide sequences disclosed in SEQ ID NOS 1-40.

[00139] In some embodiments, the polynucleotide, or its complement or a fragment thereof, further comprises a detectable label, is attached to a solid support, is prepared at least in part by chemical synthesis, is an antisense fragment, is single stranded, is double stranded or comprises a microarray.

[00140] In some embodiments, the invention provides an isolated polypeptide, encoded within an open reading frame of a cancer associated sequence selected from the polynucleotide sequences shown in SEQ ID NOS 1-40, or its complement. In some embodiments, the invention provides an isolated polypeptide, wherein said polypeptide comprises the amino acid sequence encoded by a polynucleotide selected from the group consisting of sequences disclosed in SEQ ID NOS 1-40. In some embodiments, the invention provides an isolated polypeptide, wherein said polypeptide comprises the amino acid sequence encoded by a cancer associated polypeptide as described infra.

[00141] In some embodiments, the invention further provides an isolated polypeptide, comprising the amino acid sequence of an epitope of the amino acid sequence of a

cancer associated polypeptide disclosed infra. The polypeptide or fragment thereof may be attached to a solid support. In some embodiments the invention provides an isolated antibody (monoclonal or polyclonal) or antigen binding fragment thereof, that binds to such a polypeptide. The isolated antibody or antigen binding fragment thereof may be attached to a solid support. The isolated antibody or antigen binding fragment thereof may further comprise a detectable substance.

[00142] Some embodiments also provide for antigens (e.g., cancer-associated polypeptides) associated with a variety of cancers as targets for diagnostic and/or therapeutic antibodies, e.g. bladder cancer. These antigens may also be useful for drug discovery (e.g., small molecules) and for further characterization of cellular regulation, growth, and differentiation.

Methods of Detecting and Diagnosing Bladder Cancer

[00143] In some embodiments, the method of detecting or diagnosing bladder cancer may comprise assaying gene expression of a subject in need thereof. Any method known in the art may be used to assay gene expression of one or more markers disclosed infra. In some embodiments, detecting a level of a cancer associated sequence may comprise techniques such as, but not limited to, PCR, mass spectroscopy, microarray, gel electrophoresis, hybridization using one or more probes that specifically bind a nucleic acid encoding a cancer associated sequence disclosed infra. Information relating to expression of the receptor can also be useful in determining therapies aimed at up or down-regulating the cancer associated sequence's signaling using agonists or antagonists.

[00144] In some embodiments, a method of diagnosing bladder cancer may comprise detecting a level of the cancer associated protein in a subject. In some embodiments, a method of screening for cancer may comprise detecting a level of the cancer associated protein. In some embodiments, the cancer associated protein is encoded by a nucleotide sequence selected from a sequence disclosed in SEQ ID NOS 1-40, a fragment thereof or a complementary sequence thereof. In some embodiments, a method of detecting cancer in a sample may comprise contacting the sample obtained from a subject with an antibody that specifically binds the protein. In some embodiments, the antibody may be a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody may be a humanized or a recombinant antibody. Antibodies can be made that specifically bind to this region using known methods and any method is suitable. In some embodiments, the antibody specifically binds to one or more of a molecule, such as protein or peptide, encoded for by one or more cancer associated sequences disclosed infra.

[00145] In some embodiments, the antibody binds to an epitope from a protein encoded by the nucleotide sequence disclosed in SEQ ID NOS: 1-40 with an antibody against the protein. In some embodiments, the epitope is a fragment of the protein sequence encoded by the nucleotide sequence of any of the cancer associated sequences disclosed infra. In some embodiments, the epitope comprises about 1-10, 1-20, 1-30, 3-10, or 3-15 residues of the cancer associated sequence. In some embodiments, the epitope is not linear.

[00146] In some embodiments, the antibody binds to the regions described herein or a peptide with at least 90, 95, or 99% homology or identity to the region. In some embodiments, the fragment of the regions described herein is 5-10 residues in length. In some embodiments, the fragment of the regions (e.g. epitope) described herein are 3-5 residues in length. The fragments are described based upon the length provided. In some embodiments, the epitope is about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 20 residues in length.

[00147] In some embodiments, the sequence to which the antibody binds may include both nucleic acid and amino acid sequences. In some embodiments, the sequence to which the antibody binds may include sequences having at least about 60% homology with the disclosed sequences. In some embodiments, the sequence to which the antibody binds may have at least about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, about 99%, about 99.8% homology with the disclosed sequences. In some embodiments, the sequences may be referred to as “mutant nucleic acids” or “mutant peptide sequences.”

[00148] In some embodiments, a subject can be diagnosed with bladder cancer by detecting the presence of a cancer associated sequence (e.g. SEQ ID NOS: 1-40) in a sample obtained from a subject. In some embodiments, the method comprises detecting the presence or absence of a cancer associated sequence selected from sequences disclosed in SEQ ID NOS 1-40, wherein the absence of the cancer associated sequence indicates that absence of bladder cancer. In some embodiments, the method further comprises treating the subject diagnosed with bladder cancer with an antibody that binds to a cancer associated sequence disclosed infra and inhibits the growth or progression of the bladder cancer. As discussed, bladder cancer may be detected in any type of sample, including, but not limited to, serum, blood, tumor and the like. The sample may be any type of sample as it is described herein.

[00149] Any assay known in the art may be used to screen for the presence, absence or expression level of one or more proteins encoded for by a cancer associated sequence described infra. In some embodiments the assay may be for example an ELISA, a radio-immuno assay, a western blot, a flow cytometry assay and the like.

[00150] In some embodiments, the method of diagnosing a subject with bladder cancer comprises obtaining a sample and detecting the presence of a cancer associated sequence selected from sequences disclosed in SEQ ID NOS: 1-41, wherein the presence of the cancer associated sequence indicates the subject has bladder cancer. In some embodiments, detecting the presence of a cancer associated sequence selected from sequences disclosed infra comprises contacting the sample with an antibody or other type of capture reagent or specific binding partner that specifically binds to the cancer associated sequence's protein and detecting the presence or absence of the binding to the cancer associated sequence's protein in the sample.

[00151] In some embodiments, the present disclosure provides a method of diagnosing bladder cancer, or a neoplastic condition in a subject, the method comprising obtaining a cancer associated sequence gene expression result of a cancer associated sequence selected from sequences disclosed infra from a sample derived from a subject; and diagnosing bladder cancer or a neoplastic condition in the subject based on the cancer associated sequence gene expression result, wherein the subject is diagnosed as having bladder cancer or a neoplastic condition if the cancer associated sequence is expressed at a level that is 1) higher than a negative control such a non-cancerous bladder tissue or cell sample and/or 2) higher than or equivalent to the expression level of the cancer associated sequence in a standard or positive control wherein the standard or positive control is known to contain bladder cancer cells.

[00152] Some embodiments are directed to a biochip comprising one or more nucleic acid sequences which encode one or more cancer associated proteins. In some embodiments, a biochip comprises a nucleic acid molecule which encodes at least a portion of a cancer associated protein. In some embodiments, the cancer associated protein is encoded by a sequence selected from SEQ ID NOS 1-40, homologs thereof, combinations thereof, or a fragment thereof. In some embodiments, the nucleic acid molecule specifically hybridizes with a nucleic acid sequence selected from SEQ ID NOS 1-40. In some embodiments, the biochip comprises a first and second nucleic molecule wherein the first nucleic acid molecule specifically hybridizes with a first sequence selected from cancer associated sequences disclosed infra and the second nucleic acid molecule specifically hybridizes with a second sequence selected from cancer associated sequences disclosed infra, wherein the first and second sequences are not the same sequence. In some embodiments, the present invention provides methods of detecting or diagnosing cancer, such as bladder cancer, comprising detecting the expression of a nucleic acid sequence selected from a sequence disclosed in SEQ ID NOS: 1-40, wherein a sample is contacted with a biochip comprising a sequence selected from sequences disclosed in SEQ ID NOS: 1-40, homologs thereof, combinations thereof, or a fragment thereof.

[00153] Also provided herein is a method for diagnosing or determining the propensity to cancers, for example bladder cancer, by measuring the expression level of one or more of the cancer associated sequences disclosed infra in a sample and comparing the expression level of the one or more cancer associated sequences in the sample with expression level of the same cancer associated sequences in a non-cancerous cell. A higher level of expression of one or more of the cancer associated sequences disclosed infra compared to the non-cancerous cell indicates a propensity for the development of cancer, e.g., bladder cancer.

[00154] In some embodiments, the invention provides a method for detecting a cancer associated sequence with the expression of a polypeptide in a test sample, comprising detecting a level of expression of at least one polypeptide such as, without limitation, a cancer associated protein encoded for by a sequence disclosed infra, or a fragment thereof. In some embodiments, the method comprises comparing the level of expression of the polypeptide in the test sample with a level of expression of polypeptide in a normal sample, i.e. a non-cancerous sample, wherein an altered level of expression of the polypeptide in the test sample relative to the level of polypeptide expression in the normal sample is indicative of the presence of cancer in the test sample. In some embodiments, the polypeptide expression is compared to a cancer sample, wherein the level of expression is at least the same as the cancer is indicative of the presence of cancer in the test sample. In some embodiments the test sample is compared to a normal, e.g. a non-cancerous sample where an expression level in the test sample that is greater than that found in the normal sample indicates the presence of cancer in the test sample. In some embodiments, the sample is a cell sample. In some embodiments the sample is a tissue sample. In some embodiments the sample is a bodily fluid. Examples of suitable bodily fluids, include, but are not limited to, blood, serum, saliva or urine. In some embodiments the sample is a blood sample. In some embodiments the sample is a serum sample. In some embodiments the sample is a urine sample.

[00155] In some embodiments, the invention provides a method for detecting cancer by detecting the presence of an antibody in a test serum sample. In some embodiments, the antibody recognizes a polypeptide or an epitope of a cancer associated sequence disclosed herein. In some embodiments, the method comprises detecting a level of an antibody against an antigenic polypeptide such as, without limitation, a cancer associated protein such as a protein encoded for by a cancer associated sequence disclosed infra, or an antigenic fragment thereof. In some embodiments, the method comprises comparing the level of the antibody in the test sample with a level of the antibody in the control sample, wherein an altered level of antibody in said test sample relative to the level of antibody in the control sample is indicative of the

presence of cancer in the test sample. In some embodiments, the control sample is a sample derived from a non-cancerous sample e.g. blood or serum obtained from a subject that is cancer free. In some embodiments, the control is derived from a cancer sample, and, therefore, in some embodiments, the method comprises comparing the levels of binding and/or the amount of antibody in the sample, wherein when the levels or amount are the same as the cancer control sample is indicative of the presence of cancer in the test sample.

[00156] In some embodiments, a method for diagnosing cancer or a neoplastic condition comprises a) determining the expression of one or more genes comprising a nucleic acid sequence selected from the group consisting of the human genomic and mRNA sequences described in SEQ ID NOS: 1-40, in a first sample type (*e.g.* tissue, bodily fluid, etc.) of a first individual; and b) comparing said expression of said gene(s) from a second normal sample type from said first individual or a second unaffected individual; wherein a difference in said expression indicates that the first individual has cancer. In some embodiments, the expression is increased as compared to the normal sample.

[00157] In some embodiments, the invention also provides a method for detecting presence or absence of cancer cells in a subject. In some embodiments, the method comprises contacting one or more cells from the subject with an antibody as described herein. The antibody may be conjugated to a detectable substance. In some embodiments the antibody that binds to a protein encoded for by a cancer associated sequence disclosed *infra* may bind to a second antibody wherein the second antibody is conjugated to a detectable substance. In some embodiments the antibody that binds to a protein encoded for by a cancer associated sequence disclosed *infra* is bound to a solid support. In some embodiments, the method comprises detecting a complex of a cancer associated protein and the antibody, wherein detection of the complex indicates with the presence of cancer cells in the subject. The complex may include a detectable substance as described *infra*. The complex may include a solid support, such as bead, a chip, a magnet, a multiwell plate and the like.

[00158] In some embodiments, the present disclosure provides methods of detecting cancer in a test sample, comprising: (i) detecting a level of activity of at least one polypeptide that is a gene product; and (ii) comparing the level of activity of the polypeptide in the test sample with a level of activity of polypeptide in a normal sample, wherein an altered level of activity of the polypeptide in the test sample relative to the level of polypeptide activity in the normal sample is indicative of the presence of cancer in the test sample, wherein said gene product is a product of a gene selected from one or more of the cancer associated sequences provided *infra*.

Capture Reagents and Specific Binding Partners

[00159] The invention provides for specific binding partners and capture reagents that bind specifically to cancer associated sequences disclosed infra and the polypeptides or proteins encoded for by those sequences. The capture reagents and specific binding partners may be used in diagnostic assays as disclosed infra and/or in therapeutic methods described infra as well as in drug screening assays disclosed infra. Capture reagents include for example nucleic acids and proteins. Suitable proteins include antibodies.

[00160] As used herein, the term "specifically binds" or "specifically binding" means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding is indicated if the molecule has measurably higher affinity for cells expressing a protein encoded for by a cancer associated sequence disclosed infra than for cells that do not express the same protein encoded for by the cancer associated sequences disclosed infra. Specificity of binding can be determined, for example, by competitive inhibition of a known binding molecule.

[00161] The term "specifically binding," as used herein, includes both low and high affinity specific binding. Specific binding can be exhibited, for example, by a low affinity homing molecule having a K_d of at least about 10^{-4} M. Specific binding also can be exhibited by a high affinity homing molecule, for example, a homing molecule having a K_d of at least about 10^{-5} M. Such a molecule can have, for example, a K_d of at least about 10^{-6} M, at least about 10^{-7} M, at least about 10^{-8} M, at least about 10^{-9} M, at least about 10^{-10} M, or can have a K_d of at least about 10^{-11} M or 10^{-12} M or greater. Both low and high affinity homing molecules are useful and are encompassed by the invention. Low affinity homing molecules are useful in targeting, for example, multivalent conjugates. High affinity homing molecules are useful in targeting, for example, multivalent and univalent conjugates.

[00162] In some embodiments the specific binding partner or capture reagent is an antibody. Binding in IgG antibodies, for example, is generally characterized by an affinity of at least about 10^{-7} M or higher, such as at least about 10^{-8} M or higher, or at least about 10^{-9} M or higher, or at least about 10^{-10} or higher, or at least about 10^{-11} M or higher, or at least about 10^{-12} M or higher. The term is also applicable where, e.g., an antigen-binding domain is specific for a particular epitope that is not carried by numerous antigens, in which case the antibody or antigen binding protein carrying the antigen-binding domain will generally not bind other antigens. In some embodiments, the capture reagent has a K_d equal or less than 10^{-9} M, 10^{-10} M, or 10^{-11} M

for its binding partner (e.g. antigen). In some embodiments, the capture reagent has a K_a greater than or equal to 10^9 M^{-1} for its binding partner. Capture reagent can also refer to, for example, antibodies. Intact antibodies, also known as immunoglobulins, are typically tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each, and two heavy (H) chains of approximately 50 kDa each. Two types of light chain, termed lambda and kappa, exist in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins are assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. Each light chain is composed of an N-terminal variable (V) domain (VL) and a constant (C) domain (CL). Each heavy chain is composed of an N-terminal V domain (VH), three or four C domains (CHs), and a hinge region. The CH domain most proximal to VH is designated CH1. The VH and VL domains consist of four regions of relatively conserved sequences named framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequences (complementarity determining regions, CDRs). The CDRs contain most of the residues responsible for specific interactions of the antibody or antigen binding protein with the antigen. CDRs are referred to as CDR1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain are referred to as H1, H2, and H3, while CDR constituents on the light chain are referred to as L1, L2, and L3. CDR3 is the greatest source of molecular diversity within the antibody or antigen binding protein-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Eds. Harlow et al., 1988. One of skill in the art will recognize that each subunit structure, e.g., a CH, VH, CL, VL, CDR, and/or FR structure, comprises active fragments. For example, active fragments may consist of the portion of the VH, VL, or CDR subunit that binds the antigen, i.e., the antigen-binding fragment, or the portion of the CH subunit that binds to and/or activates an Fc receptor and/or complement.

[00163] Non-limiting examples of binding fragments encompassed within the term “antigen-specific antibody” used herein include: (i) an Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) an F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) an Fd fragment consisting of the VH and CH1 domains; (iv) an Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment, which consists of a VH domain; and (vi) an isolated CDR. Furthermore, although the two domains of the Fv fragment,

VL and VH, are coded for by separate genes, they may be recombinantly joined by a synthetic linker, creating a single protein chain in which the VL and VH domains pair to form monovalent molecules (known as single chain Fv (scFv)). The most commonly used linker is a 15-residue (Gly₄Ser)₃ peptide, but other linkers are also known in the art. Single chain antibodies are also intended to be encompassed within the terms “antibody or antigen binding protein,” or “antigen-binding fragment” of an antibody. The antibody can also be a polyclonal antibody, monoclonal antibody, chimeric antibody, antigen-binding fragment, Fc fragment, single chain antibodies, or any derivatives thereof.

[00164] Antibodies can be obtained using conventional techniques known to those skilled in the art, and the fragments are screened for utility in the same manner as intact antibodies. Antibody diversity is created by multiple germline genes encoding variable domains and a variety of somatic events. The somatic events include recombination of variable gene segments with diversity (D) and joining (J) gene segments to make a complete VH domain, and the recombination of variable and joining gene segments to make a complete VL domain. The recombination process itself is imprecise, resulting in the loss or addition of amino acids at the V (D) J junctions. These mechanisms of diversity occur in the developing B cell prior to antigen exposure. After antigenic stimulation, the expressed antibody genes in B cells undergo somatic mutation. Based on the estimated number of germline gene segments, the random recombination of these segments, and random VH-VL pairing, up to 1.6×10^7 different antibodies may be produced (Fundamental Immunology, 3rd ed. (1993), ed. Paul, Raven Press, New York, N.Y.). When other processes that contribute to antibody diversity (such as somatic mutation) are taken into account, it is thought that upwards of 1×10^{10} different antibodies may be generated (Immunoglobulin Genes, 2nd ed. (1995), eds. Jonio et al., Academic Press, San Diego, Calif.). Because of the many processes involved in generating antibody diversity, it is unlikely that independently derived monoclonal antibodies with the same antigen specificity will have identical amino acid sequences.

[00165] Antibody or antigen binding protein molecules capable of specifically interacting with the antigens, epitopes, or other molecules described herein may be produced by methods well known to those skilled in the art. For example, monoclonal antibodies can be produced by generation of hybridomas in accordance with known methods. Hybridomas formed in this manner can then be screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and Biacore analysis, to identify one or more hybridomas that produce an antibody that specifically interacts with a molecule or compound of interest. As an alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a

polypeptide of the present disclosure may be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with a polypeptide of the present disclosure to thereby isolate immunoglobulin library members that bind to the polypeptide. Techniques and commercially available kits for generating and screening phage display libraries are well known to those skilled in the art. Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody or antigen binding protein display libraries can be found in the literature.

[00166] Examples of chimeric antibodies include, but are not limited to, humanized antibodies. The antibodies described herein can also be human antibodies. In some embodiments, the capture reagent comprises a detection reagent. The detection reagent can be any reagent that can be used to detect the presence of the capture reagent binding to its specific binding partner. The capture reagent can comprise a detection reagent directly or the capture reagent can comprise a particle that comprises the detection reagent. In some embodiments, the capture reagent and/or particle comprises a color, colloidal gold, radioactive tag, fluorescent tag, or a chemiluminescent substrate. The particle can be, for example, a viral particle, a latex particle, a lipid particle, or a fluorescent particle.

[00167] The capture reagents (e.g. antibody) of the present disclosure can also include an anti-antibody, i.e. an antibody that recognizes another antibody but is not specific to an antigen, such as, but not limited to, anti-IgG, anti-IgM, or anti-IgE antibody. This non-specific antibody can be used as a positive control to detect whether the antigen specific antibody is present in a sample.

[00168] Nucleic acid capture reagents include DNA, RNA and PNA molecules for example. The nucleic acid may be about 5 nucleotides long, about 10 nucleotides long, about 15 nucleotides long, about 20 nucleotides long, about 25 nucleotides long, about 30 nucleotides long, about 35 nucleotides long about 40 nucleotides long. The nucleic acid may be greater than 30 nucleotides long. The nucleic acid may be less than 30 nucleotides long.

Treatment of Bladder Cancer

[00169] In some embodiments, bladder cancers expressing one of the cancer associated sequences disclosed infra may be treated by antagonizing the cancer associated sequence's activity. In some embodiments, a method of treating bladder cancer may comprise administering a therapeutic such as, without limitation, antibodies that antagonize the ligand binding to the cancer associated sequence, small molecules that inhibit the cancer associated sequence's expression or activity, siRNAs directed towards the cancer associated sequence, or the like.

[00170] In some embodiments, a method of treating cancer (*e.g.* bladder or other types of cancer) comprises detecting the presence of a cancer associated sequence's receptor and administering a cancer treatment. The treatment may specifically bind to the cancer associated sequence's receptor. The cancer treatment may be any cancer treatment or one that is specific to the inhibiting the action of a cancer associated sequence. For example, various cancers are tested to determine if a specific molecule is present before giving a cancer treatment. In some embodiments, therefore, a sample would be obtained from the patient and tested for the presence of a cancer associated sequence or the overexpression of a cancer associated sequence as described herein. In some embodiments, if a cancer associated sequence is found to be overexpressed then a bladder cancer treatment or therapeutic is administered to the subject. The bladder cancer treatment may be a conventional non-specific treatment, such as chemotherapy, or the treatment may comprise a specific treatment that only targets the activity of the cancer associated sequence or the receptor to which the cancer associated sequence binds. These treatments can be, for example, an antibody that specifically binds to the cancer associated sequence and inhibits its activity. The treatment may be a nucleic acid that downregulates or silences the expression of the cancer associated sequence.

[00171] Some embodiments herein describe method of treating cancer or a neoplastic condition comprising administering an antibody against the cancer associated sequence to a subject. In some embodiments, the antibody may be monoclonal or polyclonal. In some embodiments, the antibody may be humanized or recombinant. In some embodiments, the antibody may neutralize biological activity of the cancer associated sequence by binding to and/or interfering with the cancer associated sequence's receptor. In some embodiments the antibody may bind to site on the protein encoded for by the cancer associated DNA sequence that is not the receptor. In some embodiments, administering the antibody may be to a biological fluid or tissue, such as, without limitation, blood, urine, serum, tumor tissue, or the like.

[00172] In some embodiments, a method of treating cancer may comprise administering an agent that interferes with the synthesis, secretion, receptor binding or receptor signaling of cancer associated proteins or its receptors. In some embodiments, the cancer may be selected from, including, without limitation, urothelial carcinoma, transitional cell carcinoma, non-transitional cell carcinomas, such as, without limitation, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, neural cell tumors, cervical carcinoma, or lymphoma, recurrent and metastatic bladder cancer, or a combination thereof.

[00173] In some embodiments, the cancer cell may be targeted specifically with a therapeutic based upon the differentially expressed gene or gene product. For example, in some embodiments, the differentially expressed gene product may be an enzyme, which can convert an anti-cancer prodrug into its active form. Therefore, in normal cells, where the differentially expressed gene product is not expressed or expressed at significantly lower levels, the prodrug may be either not activated or activated in a lesser amount, and may be, therefore less toxic to normal cells. Therefore, the cancer prodrug may, in some embodiments, be given in a higher dosage so that the cancer cells can metabolize the prodrug, which will, for example, kill the cancer cell, and the normal cells will not metabolize the prodrug or not as well, and, therefore, be less toxic to the patient. An example of this is where tumor cells overexpress a metalloprotease, which is described in Atkinson *et al.*, British Journal of Pharmacology (2008) 153, 1344–1352,. Using proteases to target cancer cells is also described in Carl *et al.*, PNAS, Vol. 77, No. 4, pp. 2224-2228, April 1980. For example, doxorubicin or other type of chemotherapeutic can be linked to a peptide sequence that is specifically cleaved or recognized by the differentially expressed gene product. The doxorubicin or other type of chemotherapeutic is then cleaved from the peptide sequence and is activated such that it can kill or inhibit the growth of the cancer cell whereas in the normal cell the chemotherapeutic is never internalized into the cell or is not metabolized as efficiently, and is, therefore, less toxic.

[00174] In some embodiments, a method of treating bladder cancer may comprise gene knockdown of one or more cancer associated sequences described herein. Gene knockdown refers to techniques by which the expression of one or more of an organism's genes is reduced, either through genetic modification (a change in the DNA of one of the organism's chromosomes such as, without limitation, chromosomes encoding cancer associated sequences) or by treatment with a reagent such as a short DNA or RNA oligonucleotide with a sequence complementary to either an mRNA transcript or a gene. In some embodiments, the oligonucleotide used may be selected from RNase-H competent antisense, such as, without limitation, ssDNA oligonucleotides, ssRNA oligonucleotides, phosphorothioate oligonucleotides, or chimeric oligonucleotides; RNase-independent antisense, such as morpholino oligonucleotides, 2'-O-methyl phosphorothioate oligonucleotides, locked nucleic acid oligonucleotides, or peptide nucleic acid oligonucleotides; RNAi oligonucleotides, such as, without limitation, siRNA duplex oligonucleotides, or shRNA oligonucleotides; or any combination thereof. In some embodiments, a plasmid may be introduced into a cell, wherein the plasmid expresses either an antisense RNA transcript or an shRNA transcript. The oligo

introduced or transcript expressed may interact with the target mRNA (ex. sequences disclosed in Table 1) by complementary base pairing (a sense-antisense interaction).

[00175] The specific mechanism of silencing may vary with the oligo chemistry. In some embodiments, the binding of a oligonucleotide described herein to the active gene or its transcripts may cause decreased expression through blocking of transcription, degradation of the mRNA transcript (e.g. by small interfering RNA (siRNA) or RNase-H dependent antisense) or blocking either mRNA translation, pre-mRNA splicing sites or nuclease cleavage sites used for maturation of other functional RNAs such as miRNA (e.g. by Morpholino oligonucleotides or other RNase-H independent antisense). For example, RNase-H competent antisense oligonucleotides (and antisense RNA transcripts) may form duplexes with RNA that are recognized by the enzyme RNase-H, which cleaves the RNA strand. As another example, RNase-independent oligonucleotides may bind to the mRNA and block the translation process. In some embodiments, the oligonucleotides may bind in the 5'-UTR and halt the initiation complex as it travels from the 5'-cap to the start codon, preventing ribosome assembly. A single strand of RNAi oligonucleotides may be loaded into the RISC complex, which catalytically cleaves complementary sequences and inhibits translation of some mRNAs bearing partially-complementary sequences. The oligonucleotides may be introduced into a cell by any technique including, without limitation, electroporation, microinjection, salt-shock methods such as, for example, CaCl₂ shock; transfection of anionic oligo by cationic lipids such as, for example, Lipofectamine; transfection of uncharged oligonucleotides by endosomal release agents such as, for example, Endo-Porter; or any combination thereof. In some embodiments, the oligonucleotides may be delivered from the blood to the cytosol using techniques selected from nanoparticle complexes, virally-mediated transfection, oligonucleotides linked to octaguanidinium dendrimers (Morpholino oligonucleotides), or any combination thereof.

[00176] In some embodiments, a method of treating bladder cancer may comprise treating a subject with a suitable reagent to knockdown or inhibit expression of a gene encoding the mRNA disclosed in SEQ ID NOS: 1-40 or the protein disclosed in SEQ ID NO: 41, or a combination thereof. In other embodiments the invention provides for the in vitro knockdown of the expression of one or more of the genes disclosed in SEQ ID NOS: 1-40 or the gene encoding the protein disclosed in SEQ ID NO: 41, for example in an in vitro culture of cells or cells obtained from a sample obtained from a subject.

[00177] The method may comprise culturing hES cell-derived clonal embryonic progenitor cell lines CM02 and EN13 (see U.S. Patent Publication 2008/0070303, entitled "Methods to accelerate the isolation of novel cell strains from pluripotent stem cells and cells

obtained thereby”; and U.S. patent application Ser. No. 12/504,630 filed on July 16, 2009 and titled “Methods to Accelerate the Isolation of Novel Cell Strains from Pluripotent Stem Cells and Cells Obtained Thereby”) with a retrovirus expressing silencing RNA directed to a cancer-associated sequence. In some embodiments, the method may further comprise confirming down-regulation by qPCR. In some embodiments, the method further comprises cryopreserving the cells. In some embodiments, the method further comprises reprogramming the cells. In some embodiments, the method comprises cryopreserving or reprogramming the cells within two days by the exogenous administration of OCT4, MYC, KLF4, and SOX2 (see Takahashi and Yamanaka 2006 Aug 25;126(4):663-76; U.S. Patent Application Serial No. 12/086,479, published as US2009/0068742 and entitled “Nuclear Reprogramming Factor”) and by the method described in PCT/US06/30632, published as WO/2007/019398 and entitled “Improved Methods of Reprogramming Animal Somatic Cells”,. In some embodiments, the method may comprise culturing mammalian differentiated cells under conditions that promote the propagation of ES cells. In some embodiments, any convenient ES cell propagation condition may be used, e.g., on feeders or in feeder free media capable of propagating ES cells. In some embodiments, the method comprises identifying cells from ES colonies in the culture. Cells from the identified ES colony may then be evaluated for ES markers, e.g., Oct4, TRA 1-60, TRA 1-81, SSEA4, etc., and those having ES cell phenotype may be expanded. Control lines that have not been preconditioned by the knockdown may be reprogrammed in parallel to demonstrate the effectiveness of the preconditioning.

[00178] In some embodiments, the cancers treated by modulating the activity or expression of sequences disclosed in Table 1 and or SEQ ID NOS: 1-41 or the gene product thereof.

[00179] In some embodiments, a method of treating cancer comprises administering an antibody (*e.g.* monoclonal antibody, human antibody, humanized antibody, recombinant antibody, chimeric antibody, and the like) that specifically binds to a cancer associated protein that is expressed on a cell surface. In some embodiments, the antibody binds to an extracellular domain of the cancer associated protein. In some embodiments, the antibody binds to a cancer associated protein differentially expressed on a cancer cell surface relative to a normal cell surface, or, in some embodiments, to at least one human cancer cell line. In some embodiments, the antibody is linked to a therapeutic agent or a toxin.

[00180] In some embodiments, implementation of an immunotherapy strategy for treating, reducing the symptoms of, or preventing cancer or neoplasms, (*e.g.*, a vaccine) may be achieved using many different techniques available to the skilled artisan.

[00181] Immunotherapy or the use of antibodies for therapeutic purposes has been used in recent years to treat cancer. Passive immunotherapy involves the use of monoclonal antibodies in cancer treatments. See, for example, *Cancer: Principles and Practice of Oncology*, 6 Th Edition (2001) Chapt. 20 pp. 495-508. Inherent therapeutic biological activity of these antibodies include direct inhibition of tumor cell growth or survival, and the ability to recruit the natural cell killing activity of the body's immune system. These agents may be administered alone or in conjunction with radiation or chemotherapeutic agents. Alternatively, antibodies may be used to make antibody conjugates where the antibody is linked to a toxic agent and directs that agent to the tumor by specifically binding to the tumor.

Screening for Cancer Therapeutics

[00182] The invention provides for screening assays to determine if a candidate molecule has an inhibitory effect on the growth and or metastasis of bladder cancer cells. Suitable candidates include proteins, peptides, nucleic acids such as DNA, RNA shRNA smRNA and the like, small molecules including small organic molecules and small inorganic molecules. A small molecule may include molecules less than 50kd.

[00183] In some embodiments, a method of identifying an anti-cancer agent is provided, wherein the method comprises contacting a candidate agent to a sample; and determining the cancer associated sequence's activity in the sample. In some embodiments, the candidate agent is identified as an anti-cancer agent if the cancer associated sequence's activity is reduced in the sample after the contacting. In other embodiments the candidate agent reduces the expression level of one or more cancer associated sequences disclosed infra.

[00184] In some embodiments, the candidate agent is an antibody. In some embodiments, the method comprises contacting a candidate antibody that binds to the cancer associated sequence with a sample, and assaying for the cancer associated sequence's activity, wherein the candidate antibody is identified as an anti-cancer agent if the cancer associated sequence activity is reduced in the sample after the contacting. A cancer associated sequence's activity can be any activity of the cancer associated sequence. An example of an activity may include inhibiting enzymatic activity either of the cancer associated sequence itself or of an enzyme that interacts with or is modulated by the cancer associated sequence either at the nucleic acid level or the protein level.

[00185] In some embodiments, the present disclosure provides methods of identifying an anti-cancer (*e.g.* bladder cancer) agent comprising contacting a candidate agent to a cell sample; and determining activity of a cancer associated sequence, wherein the candidate agent is identified as an anti-cancer agent if the cancer associated sequence's activity is reduced

in the cell sample after the contacting. In some embodiments, the present disclosure provides methods of identifying an anti-cancer agent, the method comprising contacting a candidate agent that binds to a cancer associated sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, WDR72 and TOP2A or a combination thereof with a cell sample, and assaying for the cancer associated sequence's activity or expression level, wherein the candidate antibody is identified as an anti-cancer agent if the cancer associated sequence's activity is reduced in the cell sample after the contacting.

[00186] In some embodiments, a method of screening drug candidates includes comparing the level of expression of the cancer-associated sequence in the absence of the drug candidate to the level of expression in the presence of the drug candidate.

[00187] Some embodiments are directed to a method of screening for a therapeutic agent capable of binding to a cancer-associated sequence (nucleic acid or protein), the method comprising combining the cancer-associated sequence and a candidate therapeutic agent, and determining the binding of the candidate agent to the cancer-associated sequence.

[00188] Further provided herein is a method for screening for a therapeutic agent capable of modulating the activity of a cancer-associated sequence. In some embodiments, the method comprises combining the cancer-associated sequence and a candidate therapeutic agent, and determining the effect of the candidate agent on the bioactivity of the cancer-associated sequence. An agent that modulates the bioactivity of a cancer associated sequence may be used as a therapeutic agent capable of modulating the activity of a cancer-associated sequence.

[00189] In certain embodiments the invention provides a method of screening for anticancer activity comprising: (a) contacting a cell that expresses a cancer associated gene selected from one or more cancer associated sequences disclosed infra, homologs thereof, combinations thereof, or fragments thereof with an anticancer drug candidate; (b) detecting an effect of the anticancer drug candidate on an expression of the cancer associated sequence in the cell (either at the nucleic acid or protein level); and (c) comparing the level of expression in the absence of the drug candidate to the level of expression in the presence of the drug candidate; wherein an effect on the expression of the cancer associate polynucleotide indicates that the candidate has anticancer activity. For example the drug candidate may lower the expression level of the cancer associated sequence in the cell.

[00190] In some embodiments, a method of evaluating the effect of a candidate cancer drug may comprise administering the drug to a patient and removing a cell sample from the patient. The expression profile of the cell is then determined. In some embodiments, the method may further comprise comparing the expression profile of the patient to an expression profile of a healthy individual. In some embodiments, the expression profile comprises measuring the expression of one or more or any combination thereof of the sequences disclosed herein. In some embodiments, where the expression profile of one or more or any combination thereof of the sequences disclosed herein is modified (increased or decreased) the candidate cancer drug is said to be effective.

[00191] In some embodiments, the invention provides a method of screening for anticancer activity comprising: (a) providing a cell that expresses a cancer associated gene that encodes a nucleic acid sequence selected from the group consisting of the cancer associated sequences shown in SEQ ID NOS 1-40 or the gene encoding SEQ ID NO: 41, or fragment thereof, (b) contacting the cell, which can be derived from a cancer cell with an anticancer drug candidate; (c) monitoring an effect of the anticancer drug candidate on an expression of the cancer associated sequence in the cell sample, and optionally (d) comparing the level of expression in the absence of said drug candidate to the level of expression in the presence of the drug candidate.

[00192] Suitable drug candidates include, but are not limited to an inhibitor of transcription, a G-protein coupled receptor antagonist, a growth factor antagonist, a serine-threonine kinase antagonist, a tyrosine kinase antagonist. In some embodiments, where the candidate modulates the expression of the cancer associated sequence the candidate is said to have anticancer activity. In some embodiments, the anticancer activity is determined by measuring cell growth. In some embodiments, the candidate inhibits or retards cell growth and is said to have anticancer activity. In some embodiments, the candidate causes the cell to die, and thus, the candidate is said to have anticancer activity.

[00193] In some embodiments, the present invention provides a method of screening for activity against bladder cancer. In some embodiments, the method comprises contacting a cell that overexpresses a cancer associated gene which is complementary to a cancer associated sequence selected from cancer associated sequences disclosed infra, homologs thereof, combinations thereof, or fragments thereof with a bladder cancer drug candidate. In some embodiments, the method comprises detecting an effect of the bladder cancer drug candidate on an expression of the cancer associated polynucleotide in the cell or an effect on the cell's growth or viability. In some embodiments, the method comprises comparing the level of expression,

cell growth, or viability in the absence of the drug candidate to the level of expression, cell growth, or viability in the presence of the drug candidate; wherein an effect on the expression of the cancer associated polynucleotide, cell growth, or viability indicates that the candidate has activity against a bladder cancer cell that overexpresses a cancer associated gene, wherein said gene comprises a sequence that is a sequence selected from sequences disclosed in SEQ ID NOS: 1-40 or the gene encoding SEQ ID NO: 41, or complementary thereto, homologs thereof, combinations thereof, or fragments thereof. In some embodiments, the drug candidate may include, for example, a transcription inhibitor, a G-protein coupled receptor antagonist, a growth factor antagonist, a serine-threonine kinase antagonist, or a tyrosine kinase antagonist.

Methods of Identifying Bladder Cancer Markers

[00194] The pattern of gene expression in a particular living cell may be characteristic of its current state. Nearly all differences in the state or type of a cell are reflected in the differences in RNA levels of one or more genes. Comparing expression patterns of uncharacterized genes may provide clues to their function. High throughput analysis of expression of hundreds or thousands of genes can help in (a) identification of complex genetic diseases, (b) analysis of differential gene expression over time, between tissues and disease states, and (c) drug discovery and toxicology studies. Increase or decrease in the levels of expression of certain genes correlate with cancer biology. For example, oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis. (Marshall, *Cell*, 64: 313-406 (1991); Weinberg, *Science*, 254: 1138-1146 (1991)). Accordingly, some embodiments herein provide for polynucleotide and polypeptide sequences involved in cancer and, in particular, in oncogenesis.

[00195] Oncogenes are genes that can cause cancer. Carcinogenesis can occur by a wide variety of mechanisms, including infection of cells by viruses containing oncogenes, activation of protooncogenes in the host genome, and mutations of protooncogenes and tumor suppressor genes. Carcinogenesis is fundamentally driven by somatic cell evolution (i.e. mutation and natural selection of variants with progressive loss of growth control). The genes that serve as targets for these somatic mutations are classified as either protooncogenes or tumor suppressor genes, depending on whether their mutant phenotypes are dominant or recessive, respectively.

[00196] Some embodiments of the invention are directed to cancer associated sequences ("target markers"). Some embodiments are directed to methods of identifying novel target markers useful in the diagnosis and treatment of cancer wherein expression levels of mRNAs, miRNAs, proteins, or protein post translational modifications including but not limited

to phosphorylation and sumoylation are compared between five categories of cell types: (1) immortal pluripotent stem cells (such as embryonic stem (“ES”) cells, induced pluripotent stem (“iPS”) cells, and germ-line cells such as embryonal carcinoma (“EC”) cells) or gonadal tissues; (2) ES, iPS, or EC-derived clonal embryonic progenitor (“EP”) cell lines, (3) nucleated blood cells including but not limited to CD34+ cells and CD133+ cells; (4) normal mortal somatic adult-derived tissues and cultured cells including: skin fibroblasts, vascular endothelial cells, normal non-lymphoid and non-cancerous tissues, and the like, and (5) malignant cancer cells including cultured cancer cell lines or human tumor tissue. mRNAs, miRNAs, or proteins that are generally expressed (or not expressed) in categories 1, 3, and 5, or categories 1 and 5 but not expressed (or expressed) in categories 2 and 4 are candidate targets for cancer diagnosis and therapy. Some embodiments herein are directed to human applications, non-human veterinary applications, or a combination thereof.

[00197] In some embodiments, a method of identifying a target marker comprises the steps of: 1) obtaining a molecular profile of the mRNAs, miRNAs, proteins, or protein modifications of immortal pluripotent stem cells (such as embryonic stem (“ES”) cells, induced pluripotent stem (“iPS”) cells, and germ-line cells such as embryonal carcinoma (“EC”) cells); 2) ES, iPS, or EC-derived clonal embryonic progenitor (“EP”) cell lines malignant cancer cells including cultured cancer cell lines or human tumor tissues, and comparing those molecules to those present in mortal somatic cell types such as cultured clonal human embryonic progenitors, cultured somatic cells from fetal or adult sources, or normal tissue counterparts to malignant cancer cells. Target markers that are shared between pluripotent stem cells such as hES cells and malignant cancer cells, but are not present in a majority of somatic cell types may be candidate diagnostic markers and therapeutic targets.

[00198] Cancer associated sequences of embodiments herein are disclosed, for example, in SEQ ID NOS 1-41. These sequences were extracted from fold-change and filter analysis. Expression of cancer associated sequences in normal and bladder tumor tissues is disclosed infra.

[00199] Once expression is determined, the gene sequence results may be further filtered by considering fold-change in cancer cell lines vs. normal tissue; general specificity; secreted or not, level of expression in cancer cell lines; and signal to noise ratio.

[00200] It will be appreciated that there are various methods of obtaining expression data and uses of the expression data. For example, the expression data that can be used to detect or diagnose a subject with cancer can be obtained experimentally. In some embodiments, obtaining the expression data comprises obtaining the sample and processing the sample to

experimentally determine the expression data. The expression data can comprise expression data for one or more of the cancer associated sequences described herein. The expression data can be experimentally determined by, for example, using a microarray or quantitative amplification method such as, but not limited to, those described herein. In some embodiments, obtaining expression data associated with a sample comprises receiving the expression data from a third party that has processed the sample to experimentally determine the expression data.

[00201] Detecting a level of expression or similar steps that are described herein may be done experimentally or provided by a third-party as is described herein. Therefore, for example, “detecting a level of expression” may refer to experimentally measuring the data and/or having the data provided by another party who has processed a sample to determine and detect a level of expression data.

[00202] The comparison of gene expression on an mRNA level using Illumina gene expression microarrays hybridized to RNA probe sequences may be used. For example samples may be prepared from diverse categories of cell types: 1) human embryonic stem (“ES”) cells, or gonadal tissues 2) ES, iPS, or EC-derived clonal embryonic progenitor (“EP”) cell lines, 3) nucleated blood cells including but not limited to CD34+ cells and CD133+ cells; 4) Normal mortal somatic adult-derived tissues and cultured cells including: skin fibroblasts, vascular endothelial cells, normal non-lymphoid and non-cancerous tissues, and the like, and 5) malignant cancer cells including cultured cancer cell lines or human tumor tissue and filters was performed to detect genes that are generally expressed (or not expressed) in categories 1, 3, and 5, or categories 1 and 5 but not expressed (or expressed) in categories 2 and 4. Therapies in these cancers based on this observation would be based on reducing the expression of the above referenced transcripts up-regulated in cancer, or otherwise reducing the expression of the gene products.

Techniques for Analyzing Samples

[00203] Any technique known in the art may be used to analyze a sample according to the methods disclosed infra such as methods of detecting or diagnosing cancer in a sample or identifying a new cancer associated sequence. Exemplary techniques are provided below.

[00204] Gene Expression Assays: Measurement of the gene expression levels may be performed by any known methods in the art, including but not limited to quantitative PCR, or microarray gene expression analysis, bead array gene expression analysis and Northern analysis. The gene expression levels may be represented as relative expression normalized to the *ADPRT* (Accession number NM_001618.2), *GAPD* (Accession number NM_002046.2), or other

housekeeping genes known in the art. In the case of microarrayed probes of mRNA expression, the gene expression data may also be normalized by a median of medians method. In this method, each array gives a different total intensity. Using the median value is a robust way of comparing cell lines (arrays) in an experiment. As an example, the median was found for each cell line and then the median of those medians became the value for normalization. The signal from the each cell line was made relative to each of the other cell lines.

[00205] RNA extraction: Cells of the present disclosure may be incubated with 0.05% trypsin and 0.5 mM EDTA, followed by collecting in DMEM (Gibco, Gaithersburg, MD) with 0.5% BSA. Total RNA may be purified from cells using the RNeasy Mini kit (Qiagen, Hilden, Germany).

[00206] Isolation of total RNA and miRNA from cells: Total RNA or samples enriched for small RNA species may be isolated from cell cultures that undergo serum starvation prior to harvesting RNA to approximate cellular growth arrest observed in many mature tissues. Cellular growth arrest may be performed by changing to medium containing 0.5% serum for 5 days, with one medium change 2-3 days after the first addition of low serum medium. RNA may be harvested according to the vendor's instructions for Qiagen RNeasy kits to isolate total RNA or Ambion mirVana kits to isolate RNA enriched for small RNA species. The RNA concentrations may be determined by spectrophotometry and RNA quality may be determined by denaturing agarose gel electrophoresis to visualize 28S and 18S RNA. Samples with clearly visible 28S and 18S bands without signs of degradation and at a ratio of approximately 2:1, 28S:18S may be used for subsequent miRNA analysis.

[00207] Assay for miRNA in samples isolated from human cells: The miRNAs may be quantitated using a Human Panel TaqMan MicroRNA Assay from Applied Biosystems, Inc. This is a two-step assay that uses stem-loop primers for reverse transcription (RT) followed by real-time TaqMan®. The assay includes two steps, reverse transcription (RT) and quantitative PCR. Real-time PCR may be performed on an Applied Biosystems 7500 Real-Time PCR System. The copy number per cell may be estimated based on the standard curve of synthetic mir-16 miRNA and assuming a total RNA mass of approximately 15pg/cell.

[00208] The reverse transcription reaction may be performed using 1x cDNA archiving buffer, 3.35 units MMLV reverse transcriptase, 5mM each dNTP, 1.3 units AB RNase inhibitor, 2.5 nM 330-plex reverse primer (RP), 3 ng of cellular RNA in a final volume of 5 µl. The reverse transcription reaction may be performed on a BioRad or MJ thermocycler with a cycling profile of 20 °C for 30 sec; 42 °C for 30 sec; 50 °C for 1 sec, for 60 cycles followed by one cycle of 85 °C for 5 min.

[00209] Real-time PCR. Two microlitres of 1:400 diluted Pre-PCR product may be used for a 20 ul reaction. All reactions may be duplicated. Because the method is very robust, duplicate samples may be sufficient and accurate enough to obtain values for miRNA expression levels. TaqMan universal PCR master mix of ABI may be used according to manufacturer's suggestion. Briefly, 1x TaqMan Universal Master Mix (ABI), 1 uM Forward Primer, 1 uM Universal Reverse Primer and 0.2 uM TaqMan Probe may be used for each real-time PCR. The conditions used may be as follows: 95°C for 10 min, followed by 40 cycles at 95°C for 15 s, and 60°C for 1 min. All the reactions may be run on ABI Prism 7000 Sequence Detection System.

[00210] Microarray hybridization and data processing. cDNA samples and cellular total RNA (5 µg in each of eight individual tubes) may be subjected to the One-Cycle Target Labeling procedure for biotin labeling by in vitro transcription (IVT) (Affymetrix, Santa Clara, CA) or using the Illumina Total Prep RNA Labelling kit. For analysis on Affymetrix gene chips, the cRNA may be subsequently fragmented and hybridized to the Human Genome U133 Plus 2.0 Array (Affymetrix) according to the manufacturer's instructions. The microarray image data may be processed with the GeneChip Scanner 3000 (Affymetrix) to generate CEL data. The CEL data may be then subjected to analysis with dChip software, which has the advantage of normalizing and processing multiple datasets simultaneously. Data obtained from the eight nonamplified controls from cells, from the eight independently amplified samples from the diluted cellular RNA, and from the amplified cDNA samples from 20 single cells may be normalized separately within the respective groups, according to the program's default setting. The model based expression indices (MBEI) may be calculated using the PM/MM difference mode with log-2 transformation of signal intensity and truncation of low values to zero. The absolute calls (Present, Marginal and Absent) may be calculated by the Affymetrix Microarray Software 5.0 (MAS 5.0) algorithm using the dChip default setting. The expression levels of only the Present probes may be considered for all quantitative analyses described below. The GEO accession number for the microarray data is GSE4309. For analysis on Illumina Human HT-12 v4 Expression Bead Chips, labeled cRNA may be hybridized according to the manufacturer's instructions.

[00211] Calculation of coverage and accuracy. A true positive is defined as probes called Present in at least six of the eight nonamplified controls, and the true expression levels are defined as the log-averaged expression levels of the Present probes. The definition of coverage is (the number of truly positive probes detected in amplified samples)/(the number of truly positive probes). The definition of accuracy is (the number of truly positive probes

detected in amplified samples)/(the number of probes detected in amplified samples). The expression levels of the amplified and nonamplified samples may be divided by the class interval of 20.5 (20, 20.5, 21, 21.5...), where accuracy and coverage are calculated. These expression level bins may be also used to analyze the frequency distribution of the detected probes.

[00212] Analysis of gene expression profiles of cells: The unsupervised clustering and class neighbor analyses of the microarray data from cells may be performed using GenePattern software (<http://www.broad.mit.edu/cancer/software/genepattern/>), which performs the signal-to-noise ratio analysis/T-test in conjunction with the permutation test to preclude the contribution of any sample variability, including those from methodology and/or biopsy, at high confidence. The analyses may be conducted on the 14,128 probes for which at least 6 out of 20 single cells provided Present calls and at least 1 out of 20 samples provided expression levels >20 copies per cell. The expression levels calculated for probes with Absent/Marginal calls may be truncated to zero. To calculate relative gene expression levels, the Ct values obtained with Q-PCR analyses may be corrected using the efficiencies of the individual primer pairs quantified either with whole human genome (BD Biosciences) or plasmids that contain gene fragments. The relative expression levels may be further transformed into copy numbers with a calibration line calculated using the spike RNAs included in the reaction mixture ($\log_{10}[\text{expression level}] = 1.05 \times \log_{10}[\text{copy number}] + 4.65$). The Chi-square test for independence may be performed to evaluate the association of gene expressions with Gata4, which represents the difference between cluster 1 and cluster 2 determined by the unsupervised clustering and which is restricted to PE at later stages. The expression levels of individual genes measured with Q-PCR may be classified into three categories: high (>100 copies per cell), middle (10–100 copies per cell), and low (<10 copies per cell). The Chi-square and P-values for independence from Gata4 expression may be calculated based on this classification. Chi squared is defined as follows: $\chi^2 = \sum \sum (n_{ij} - f_i f_j)^2 / n f_i f_j$, where i and j represent expression level categories (high, middle or low) of the reference (Gata4) and the target gene, respectively; f_i , f_j , and f_{ij} represent the observed frequency of categories i, j and ij, respectively; and n represents the sample number (n = 24). The degrees of freedom may be defined as (r - 1) x (c - 1), where r and c represent available numbers of expression level categories of Gata4 and of the target gene, respectively.

Generating an Immune Response Against Bladder Cancer

[00213] In some embodiments, antigen presenting cells (APCs) may be used to activate T lymphocytes in vivo or ex vivo, to elicit an immune response against cells expressing

a cancer associated sequence. APCs are highly specialized cells and may include, without limitation, macrophages, monocytes, and dendritic cells (DCs). APCs may process antigens and display their peptide fragments on the cell surface together with molecules required for lymphocyte activation. In some embodiments, the APCs may be dendritic cells. DCs may be classified into subgroups, including, e.g., follicular dendritic cells, Langerhans dendritic cells, and epidermal dendritic cells. In other embodiments the invention provides a method of eliciting an antibody response to one or more of the cancer associated sequences disclosed infra. The method may comprise administering a protein or a peptide fragment encoded by one or more of the cancer associated sequences disclosed infra to a subject.

[00214] Some embodiments are directed to the use of cancer associated polypeptides and polynucleotides encoding a cancer associated sequence, a fragment thereof, or a mutant thereof, and antigen presenting cells (such as, without limitation, dendritic cells), to elicit an immune response against cells expressing a cancer-associated polypeptide sequence, such as, without limitation, cancer cells, in a subject. In some embodiments, the method of eliciting an immune response against cells expressing a cancer associated sequence comprises (1) isolating a hematopoietic stem cell, (2) genetically modifying the cell to express a cancer associated sequence, (3) differentiating the cell into DCs; and (4) administering the DCs to the subject (e.g., human patient). In some embodiments, the method of eliciting an immune response includes (1) isolating DCs (or isolation and differentiation of DC precursor cells), (2) pulsing the cells with a cancer associated sequence, and; (3) administering the DCs to the subject. These approaches are discussed in greater detail, infra. In some embodiments, the pulsed or expressing DCs may be used to activate T lymphocytes ex vivo. These general techniques and variations thereof may be within the skill of those in the art (see, e.g., WO97/29182; WO 97/04802; WO 97/22349; WO 96/23060; WO 98/01538; Hsu et al., 1996, *Nature Med.* 2:52-58), and that still other variations may be discovered in the future. In some embodiments, the cancer associated sequence is contacted with a subject to stimulate an immune response. In some embodiments, the immune response is a therapeutic immune response so as to treat a subject as described infra. In some embodiments, the immune response is a prophylactic immune response. For example, the cancer associated sequence can be contacted with a subject under conditions effective to stimulate an immune response. The cancer associated sequence can be administered as, for example, a DNA molecule (e.g. DNA vaccine), RNA molecule, or polypeptide, or any combination thereof. Administering a sequence to stimulate an immune response was known, but the identity of which sequences to use was not known prior to the

present disclosure. Any sequence or combination of sequences disclosed herein or a homolog thereof can be administered to a subject to stimulate an immune response.

[00215] In some embodiments, dendritic cell precursor cells are isolated for transduction with a cancer associated sequence, and induced to differentiate into dendritic cells. The genetically modified DCs express the cancer associated sequence, and may display peptide fragments on the cell surface.

[00216] In some embodiments, the cancer associated sequence expressed comprises a sequence of a naturally occurring protein. In some embodiments, the cancer associated sequence does not comprise a naturally occurring sequence. As already noted, fragments of naturally occurring proteins may be used; in addition, the expressed polypeptide may comprise mutations such as deletions, insertions, or amino acid substitutions when compared to a naturally occurring polypeptide, so long as at least one peptide epitope can be processed by the DC and presented on a MHC class I or II surface molecule. In some embodiments, it may be desirable to use sequences other than “wild type,” in order to, for example, increase antigenicity of the peptide or to increase peptide expression levels. In some embodiments, the introduced cancer associated sequences may encode variants such as polymorphic variants (e.g., a variant expressed by a particular human patient) or variants characteristic of a particular cancer (e.g., a cancer in a particular subject).

[00217] In some embodiments, a cancer associated sequence may be introduced (transduced) into DCs or stem cells in any of a variety of standard methods, including transfection, recombinant vaccinia viruses, adeno-associated viruses (AAVs), retroviruses, etc.

[00218] In some embodiments, the transformed DCs of the invention may be introduced into the subject (e.g., without limitation, a human patient) where the DCs may induce an immune response. Typically, the immune response includes a cytotoxic T-lymphocyte (CTL) response against target cells bearing antigenic peptides (e.g., in a MHC class I/peptide complex). These target cells are typically cancer cells.

[00219] In some embodiments, when the DCs are to be administered to a subject, they may preferably be isolated from, or derived from precursor cells from, that subject (i.e., the DCs may be administered to an autologous subject). However, the cells may be infused into HLA-matched allogeneic or HLA-mismatched allogeneic subject. In the latter case, immunosuppressive drugs may be administered to the subject.

[00220] In some embodiments, the cells may be administered in any suitable manner. In some embodiments, the cell may be administered with a pharmaceutically acceptable carrier (e.g., saline). In some embodiments, the cells may be administered through intravenous, intra-

articular, intramuscular, intradermal, intraperitoneal, or subcutaneous routes. Administration (i.e., immunization) may be repeated at time intervals. Infusions of DC may be combined with administration of cytokines that act to maintain DC number and activity (e.g., GM-CSF, IL-12).

[00221] In some embodiments, the dose administered to a subject may be a dose sufficient to induce an immune response as detected by assays which measure T cell proliferation, T lymphocyte cytotoxicity, and/or effect a beneficial therapeutic response in the patient over time, e.g., to inhibit growth of cancer cells or result in reduction in the number of cancer cells or the size of a tumor.

[00222] In some embodiments, DCs are obtained (either from a patient or by in vitro differentiation of precursor cells) and pulsed with antigenic peptides having a cancer associated sequence. The pulsing results in the presentation of peptides onto the surface MHC molecules of the cells. The peptide/MHC complexes displayed on the cell surface may be capable of inducing a MHC-restricted cytotoxic T-lymphocyte response against target cells expressing cancer associated polypeptides (e.g., without limitations, cancer cells).

[00223] In some embodiments, cancer associated sequences used for pulsing may have at least about 6 or 8 amino acids and fewer than about 30 amino acids or fewer than about 50 amino acid residues in length. In some embodiments, an immunogenic peptide sequence may have from about 8 to about 12 amino acids. In some embodiments, a mixture of human protein fragments may be used; alternatively a particular peptide of defined sequence may be used. The peptide antigens may be produced by de novo peptide synthesis, enzymatic digestion of purified or recombinant human peptides, by purification of the peptide sequence from a natural source (e.g., a subject or tumor cells from a subject), or expression of a recombinant polynucleotide encoding a human peptide fragment.

[00224] In some embodiments, the amount of peptide used for pulsing DC may depend on the nature, size and purity of the peptide or polypeptide. In some embodiments, an amount of from about 0.05 ug/ml to about 1 mg/ml, from about 0.05 ug/ml to about 500 ug/ml, from about 0.05 ug/ml to about 250 ug/ml, from about 0.5 ug/ml to about 1 mg/ml, from about 0.5 ug/ml to about 500 ug/ml, from about 0.5 ug/ml to about 250 ug/ml, or from about 1 ug/ml to about 100 ug/ml of peptide may be used. After adding the peptide antigen(s) to the cultured DC, the cells may then be allowed sufficient time to take up and process the antigen and express antigen peptides on the cell surface in association with either class I or class II MHC. In some embodiments, the time to take up and process the antigen may be about 18 to about 30 hours, about 20 to about 30 hours, or about 24 hours.

[00225] Numerous examples of systems and methods for predicting peptide binding motifs for different MHC Class I and II molecules have been described. Such prediction could be used for predicting peptide motifs that will bind to the desired MHC Class I or II molecules. Examples of such methods, systems, and databases that those of ordinary skill in the art might consult for such purpose include:

1. Peptide Binding Motifs for MHC Class I and II Molecules; William E. Biddison, Roland Martin, *Current Protocols in Immunology*, Unit 11 (DOI: 10.1002/0471142735.ima01is36; Online Posting Date: May, 2001).

[00226] Reference 1 above, provides an overview of the use of peptide-binding motifs to predict interaction with a specific MHC class I or II allele, and gives examples for the use of MHC binding motifs to predict T-cell recognition.

[00227] Table 3 provides an exemplary result for a HLA peptide motif search at the NIH Center for Information Technology website, BioInformatics and Molecular Analysis Section.

TABLE 3: exemplary result for HLA peptide motif search

User Parameter and Scoring Information: Explicit number

Method selected to mimic the number of results

Number of results requested 20

HLA molecule type selected A_0201

Length selected for subsequences to be scored 9

Echoing mode selected for input sequence Y

Echoing format Numbered lines

Length of user's input peptide sequence 369

Number of subsequence scores calculated 361

Number of top-scoring subsequences 20

reported back in scoring output table

Scoring Results

Rank	Start Position	Subsequence residue listing	Score (estimate of half time of disassociation of a molecule containing this subsequence)
1	310	SLLKFLAKV (SEQ ID NO: 42)	2249.173
2	183	MLLVFGIDV (SEQ ID NO: 43)	1662.432
3	137	KVTDLVQFL (SEQ ID NO: 44)	339.313
4	254	GLYDGMMEHL (SEQ ID NO: 45)	315.870
5	228	ILILSIIFI (SEQ ID NO: 46)	224.357
6	296	FLWGPRAHA (SEQ ID NO: 47)	189.678
7	245	VIWEALNMM (SEQ ID NO: 48)	90.891

8	308	KMSILKFLA (SEQ ID NO: 49)	72.836
9	166	KNYEDHFPL (SEQ ID NO: 50)	37.140
10	201	FVLVTSI GL (SEQ ID NO: 51)	31.814
11	174	ILFSEASEC (SEQ ID NO: 52)	31.249
12	213	GMLSDVQSM (SEQ ID NO: 53)	30.534
13	226	ILILILSI (SEQ ID NO: 54)	16.725
14	225	GILILISI (SEQ ID NO: 55)	12.208
15	251	NMMGLYDGM (SEQ ID NO: 56)	9.758
16	88	QIACSSPSV (SEQ ID NO: 57)	9.563
17	66	LIPSTPEEV (SEQ ID NO: 58)	7.966
18	220	SMPKTGILI (SEQ ID NO: 59)	7.535
19	233	IIFIEGYCT (SEQ ID NO: 60)	6.445
20	247	WEALNMGL (SEQ ID NO: 61)	4.395

[00228] One skilled in the art of peptide-based vaccination may determine which peptides would work best in individuals based on their HLA alleles (e.g., due to “MHC restriction”). Different HLA alleles will bind particular peptide motifs (usually 2 or 3 highly conserved positions out of 8-10) with different energies which can be predicted theoretically or measured as dissociation rates. Thus, a skilled artisan may be able to tailor the peptides to a subject’s HLA profile.

[00229] In some embodiments, the present disclosure provides methods of eliciting an immune response against cells expressing a cancer associated sequence comprising contacting a subject with a cancer associated sequence under conditions effective to elicit an immune response in the subject, wherein said cancer associated sequence comprises a sequence or fragment thereof a gene selected from one or more of the cancer associated sequences provided infra.

Transfecting Cells With Cancer Associated Sequences

[00230] Cells may be transfected with one or more of the cancer associated sequences disclosed infra. Transfected cells may be useful in screening assays, diagnosis and detection assays. Transfected cells expressing one or more cancer associated sequence disclosed herein may be used to obtain isolated nucleic acids encoding cancer associated sequences and/or isolated proteins or peptide fragments encoded by one or more cancer associated sequences.

[00231] Electroporation may be used to introduce the cancer associated nucleic acids described herein into mammalian cells (Neumann, E. et al. (1982) *EMBO J.* 1, 841-845), plant and bacterial cells, and may also be used to introduce proteins (Marrero, M.B. et al. (1995) *J. Biol. Chem.* 270, 15734-15738; Nolkrantz, K. et al. (2002) *Anal. Chem.* 74, 4300-4305; Rui, M. et al. (2002) *Life Sci.* 71, 1771-1778). Cells (such as the cells of this invention) suspended in a buffered solution of the purified protein of interest are placed in a pulsed electrical field. Briefly, high-voltage electric pulses result in the formation of small (nanometer-sized) pores in the cell membrane. Proteins enter the cell via these small pores or during the process of membrane reorganization as the pores close and the cell returns to its normal state. The efficiency of delivery may be dependent upon the strength of the applied electrical field, the length of the pulses, temperature and the composition of the buffered medium. Electroporation is successful with a variety of cell types, even some cell lines that are resistant to other delivery methods, although the overall efficiency is often quite low. Some cell lines may remain refractory even to electroporation unless partially activated.

[00232] Microinjection may be used to introduce femtoliter volumes of DNA directly into the nucleus of a cell (Capecchi, M.R. (1980) *Cell* 22, 470-488) where it can be integrated directly into the host cell genome, thus creating an established cell line bearing the sequence of interest. Proteins such as antibodies (Abarzua, P. et al. (1995) *Cancer Res.* 55, 3490-3494; Theiss, C. and Meller, K. (2002) *Exp. Cell Res.* 281, 197-204) and mutant proteins (Naryanan, A. et al. (2003) *J. Cell Sci.* 116, 177-186) can also be directly delivered into cells via microinjection to determine their effects on cellular processes firsthand. Microinjection has the

advantage of introducing macromolecules directly into the cell, thereby bypassing exposure to potentially undesirable cellular compartments such as low-pH endosomes.

[00233] Several proteins and small peptides have the ability to transduce or travel through biological membranes independent of classical receptor-mediated or endocytosis-mediated pathways. Examples of these proteins include the HIV-1 TAT protein, the herpes simplex virus 1 (HSV-1) DNA-binding protein VP22, and the *Drosophila* Antennapedia (Antp) homeotic transcription factor. In some embodiments, protein transduction domains (PTDs) from these proteins may be fused to other macromolecules, peptides or proteins such as, without limitation, a cancer associated polypeptide to successfully transport the polypeptide into a cell (Schwarze, S.R. et al. (2000) *Trends Cell Biol.* 10, 290-295). Exemplary advantages of using fusions of these transduction domains is that protein entry is rapid, concentration-dependent and appears to work with difficult cell types (Fenton, M. et al. (1998) *J. Immunol. Methods* 212, 41-48).

[00234] In some embodiments, liposomes may be used as vehicles to deliver oligonucleotides, DNA (gene) constructs and small drug molecules into cells (Zabner, J. et al. (1995) *J. Biol. Chem.* 270, 18997-19007; Felgner, P.L. et al. (1987) *Proc. Natl. Acad. Sci. USA* 84, 7413-7417). Certain lipids, when placed in an aqueous solution and sonicated, form closed vesicles consisting of a circularized lipid bilayer surrounding an aqueous compartment. The vesicles or liposomes of embodiments herein may be formed in a solution containing the molecule to be delivered. In addition to encapsulating DNA in an aqueous solution, cationic liposomes may spontaneously and efficiently form complexes with DNA, with the positively charged head groups on the lipids interacting with the negatively charged backbone of the DNA. The exact composition and/or mixture of cationic lipids used can be altered, depending upon the macromolecule of interest and the cell type used (Felgner, J.H. et al. (1994) *J. Biol. Chem.* 269, 2550-2561). The cationic liposome strategy has also been applied successfully to protein delivery (Zelphati, O. et al. (2001) *J. Biol. Chem.* 276, 35103-35110). Because proteins are more heterogeneous than DNA, the physical characteristics of the protein, such as its charge and hydrophobicity, may influence the extent of its interaction with the cationic lipids.

Pharmaceutical Compositions and Modes of Administration

[00235] Modes of administration for a therapeutic (either alone or in combination with other pharmaceuticals) can be, but are not limited to, sublingual, injectable (including short-acting, depot, implant and pellet forms injected subcutaneously or intramuscularly), or by use of vaginal creams, suppositories, pessaries, vaginal rings, rectal suppositories, intrauterine devices, and transdermal forms such as patches and creams.

[00236] Specific modes of administration will depend on the indication. The selection of the specific route of administration and the dose regimen is to be adjusted or titrated by the clinician according to methods known to the clinician in order to obtain the optimal clinical response. The amount of therapeutic to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, *e.g.*, the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (*e.g.*, by the clinician).

[00237] Pharmaceutical formulations containing the therapeutic of the present disclosure and a suitable carrier can be solid dosage forms which include, but are not limited to, tablets, capsules, cachets, pellets, pills, powders and granules; topical dosage forms which include, but are not limited to, solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels and jellies, and foams; and parenteral dosage forms which include, but are not limited to, solutions, suspensions, emulsions, and dry powder; comprising an effective amount of a polymer or copolymer of the present disclosure. It is also known in the art that the active ingredients can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, *Modern Pharmaceutics*, Banker & Rhodes, Marcel Dekker, Inc. (1979); and *Goodman & Gilman's The Pharmaceutical Basis of Therapeutics*, 6th Edition, MacMillan Publishing Co., New York (1980) can be consulted.

[00238] The compositions of the present disclosure can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. The compositions can be administered by continuous infusion subcutaneously over a period of about 15 minutes to about 24 hours. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[00239] For oral administration, the compositions can be formulated readily by combining the therapeutic with pharmaceutically acceptable carriers well known in the art. Such carriers enable the therapeutic of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient

to be treated. Pharmaceutical preparations for oral use can be obtained by adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not limited to, the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00240] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active therapeutic doses.

[00241] Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, e.g., lactose, binders such as, e.g., starches, and/or lubricants such as, e.g., talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active therapeutic can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

[00242] For buccal administration, the pharmaceutical compositions can take the form of, e.g., tablets or lozenges formulated in a conventional manner.

[00243] For administration by inhalation, the therapeutic for use according to the present disclosure is conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the therapeutic and a suitable powder base such as lactose or starch.

[00244] The compositions of the present disclosure can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[00245] In addition to the formulations described previously, the therapeutic of the present disclosure can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection.

[00246] Depot injections can be administered at about 1 to about 6 months or longer intervals. Thus, for example, the compositions can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00247] In transdermal administration, the compositions of the present disclosure, for example, can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism.

[00248] Pharmaceutical compositions can include suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as, e.g., polyethylene glycols.

[00249] The compositions of the present disclosure can also be administered in combination with other active ingredients, such as, for example, adjuvants, protease inhibitors, or other compatible drugs or compounds where such combination is seen to be desirable or advantageous in achieving the desired effects of the methods described herein.

[00250] In some embodiments, the disintegrant component comprises one or more of croscarmellose sodium, carmellose calcium, crospovidone, alginic acid, sodium alginate, potassium alginate, calcium alginate, an ion exchange resin, an effervescent system based on food acids and an alkaline carbonate component, clay, talc, starch, pregelatinized starch, sodium starch glycolate, cellulose floc, carboxymethylcellulose, hydroxypropylcellulose, calcium silicate, a metal carbonate, sodium bicarbonate, calcium citrate, or calcium phosphate.

[00251] In some embodiments, the diluent component may include one or more of mannitol, lactose, sucrose, maltodextrin, sorbitol, xylitol, powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, carboxyethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, starch, sodium starch glycolate, pregelatinized starch, a calcium phosphate, a metal carbonate, a metal oxide, or a metal aluminosilicate.

[00252] In some embodiments, the optional lubricant component, when present, comprises one or more of stearic acid, metallic stearate, sodium stearyl fumarate, fatty acid, fatty alcohol, fatty acid ester, glyceryl behenate, mineral oil, vegetable oil, paraffin, leucine, silica, silicic acid, talc, propylene glycol fatty acid ester, polyethoxylated castor oil, polyethylene glycol, polypropylene glycol, polyalkylene glycol, polyoxyethylene-glycerol fatty ester, polyoxyethylene fatty alcohol ether, polyethoxylated sterol, polyethoxylated castor oil, polyethoxylated vegetable oil, or sodium chloride.

Kits

[00253] Also provided by the invention are kits and systems for practicing the subject methods, as described above, such components configured to diagnose cancer in a subject, treat cancer in a subject, detect cancer in a sample, or perform basic research experiments on cancer cells (e.g., either derived directly from a subject, grown in vitro or ex vivo, or from an animal model of cancer). The various components of the kits may be present in separate containers or certain compatible components may be pre-combined into a single container, as desired.

[00254] In some embodiments, the invention provides a kit for diagnosing the presence of cancer in a test sample, said kit comprising at least one polynucleotide that selectively hybridizes to a cancer associated polynucleotide sequence shown in SEQ ID NOS 1-40 and/or a nucleic acid encoding SEQ ID NO: 41, or its complement. In another embodiment the invention provides an electronic library comprising a cancer associated polynucleotide, a cancer associated polypeptide, or fragment thereof, disclosed infra. In some embodiments the kit may include one or more capture reagents or specific binding partners of one or more cancer associated sequences disclosed infra.

[00255] The subject systems and kits may also include one or more other reagents for performing any of the subject methods. The reagents may include one or more matrices, solvents, sample preparation reagents, buffers, desalting reagents, enzymatic reagents, denaturing reagents, probes, polynucleotides, vectors (e.g., plasmid or viral vectors), etc., where calibration standards such as positive and negative controls may be provided as well. As such, the kits may include one or more containers such as vials or bottles, with each container containing a separate component for carrying out a sample processing or preparing step and/or for carrying out one or more steps for producing a normalized sample according to the present disclosure.

[00256] In addition to above-mentioned components, the subject kits typically further include instructions for using the components of the kit to practice the subject methods. The instructions for practicing the subject methods are generally recorded on a suitable recording

medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or sub-packaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

[00257] In addition to the subject database, programming and instructions, the kits may also include one or more control samples and reagents, e.g., two or more control samples for use in testing the kit.

Additional Embodiments of the Invention

[00258] Embodiments of the disclosure provide methods of diagnosis and/or treatment of cancer, including, but not limited to, bladder cancer. The methods may be used for diagnosing and/or treating bladder cancers such as, for example, urothelial carcinoma, transitional cell carcinoma, non-transitional cell carcinomas, such as, without limitation, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, neural cell tumors, cervical carcinoma, or lymphoma, recurrent and metastatic bladder cancer, or a combination thereof.

[00259] In some embodiments, the methods comprise targeting a marker that is expressed at abnormal levels in bladder tumor tissue in comparison to normal somatic tissue. In some embodiments, the marker may comprise a sequence selected from sequences encoding LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof, or a combination thereof. In some embodiments, the marker may comprise a sequence selected from SEQ ID NOs: 1-38, a complement thereof or a combination thereof or is encoded by the same. In some embodiments, the methods for the treatment of bladder cancer and related pharmaceutical preparations and kits are provided.

[00260] Some embodiments provide methods of treating bladder cancer comprising administering a composition including a therapeutic that affects the expression, abundance or activity of a target marker. In some embodiments, the target marker may be selected from:

LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof or a combination thereof. In some embodiments, the target marker may be selected from SEQ ID NOs: 1-38, a complement thereof or a combination thereof.

[00261] Some embodiments provide methods of detecting bladder cancer comprising detecting a level of a target marker associated with the bladder cancer. In some embodiments, the target marker may include LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof or any combination thereof. In some embodiments, the target marker may be selected from SEQ ID NOs: 1-41, a complement thereof or a combination thereof or is encoded by the same.

[00262] Some embodiments herein provide antigens (i.e. cancer-associated polypeptides) associated with bladder cancer as targets for diagnostic and/or therapeutic antibodies. In some embodiments, these antigens can be used for drug discovery (e.g., small molecules) and/or for further characterization of cellular regulation, growth, and differentiation.

[00263] Some embodiments provide methods of diagnosing bladder cancer in a subject, the method comprising: (a) determining the expression of one or more genes or gene products or homologs thereof; and (b) comparing the expression of the one or more nucleic acid sequences from a second normal sample from the first subject or a second unaffected subject, wherein a difference in the expression indicates that the first subject has bladder cancer, wherein the gene or the gene product is referred to as a gene selected from: LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a combination thereof. In some embodiments, the gene or the gene product may be a gene encoding a sequence selected from SEQ ID NOs: 1-40, a complement thereof or a combination thereof.

[00264] Some embodiments provide methods of eliciting an immune response against cells expressing a cancer associated sequence comprising contacting a subject with a cancer associated sequence under conditions effective to elicit an immune response in the subject, wherein the cancer associated sequence comprises a gene selected from: LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a fragment thereof or a combination thereof. In some embodiments, the gene may be a gene encoding a sequence selected from SEQ ID NOs: 1-40, a complement thereof or a combination thereof.

[00265] Some embodiments provide methods of detecting bladder cancer in a test sample, comprising: (i) detecting a level of activity of at least one polypeptide that is a gene product; and (ii) comparing the level of activity of the polypeptide in the test sample with a level of activity of polypeptide in a normal sample, wherein an altered level of activity of the polypeptide in the test sample relative to the level of polypeptide activity in the normal sample is indicative of the presence of cancer in the test sample, wherein the gene product is a product of a gene selected from: LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a combination thereof. In some embodiments, the gene product may be a product of a gene encoding a sequence selected from SEQ ID NOs: 1-40, a complement thereof or a combination thereof.

[00266] Some embodiments herein provide methods of treating bladder cancer in a subject, the method comprising administering to a subject in need thereof a therapeutic agent modulating the activity of a cancer associated protein, wherein the cancer associated protein is encoded by a nucleic acid comprising a nucleic acid sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 homologs thereof, combinations thereof, or a fragment thereof. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-40, a complement thereof or a

combination thereof. In some embodiments, the therapeutic agent binds to the cancer associated protein. In some embodiments, the therapeutic agent is an antibody. In some embodiments, wherein the antibody may be a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody is a humanized or human antibody. In some embodiments, a method of treating cancer may comprise gene knockdown of a gene such as, without limitation, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a combination thereof. In some embodiments, the gene may be a gene encoding a sequence selected from SEQ ID NOs: 1-40, a complement thereof or a combination thereof. In some embodiments, a method of treating cancer may comprise treating cells to knockdown or inhibit expression of a gene encoding mRNA including, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a combination thereof. In some embodiments, the gene may be a gene encoding mRNA, wherein said mRNA is selected from SEQ ID NOs: 1-40, a complement thereof or a combination thereof. In some embodiments, the bladder cancer is selected from urothelial carcinoma, transitional cell carcinoma, non-transitional cell carcinomas, such as, without limitation, squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, neural cell tumors, cervical carcinoma, or lymphoma, recurrent and metastatic bladder cancer, or a combination thereof.

[00267] In some embodiments, a method of diagnosing a subject with bladder cancer comprises obtaining a sample and detecting the presence of a cancer associated sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof, or a combination thereof, wherein the presence of the cancer associated sequence indicates the subject has bladder cancer. In some embodiments, the cancer associated sequence may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof, a combination thereof or is encoded by the same. In some embodiments, detecting the presence of the cancer associated sequence comprises contacting the sample with

an antibody or other type of capture reagent that specifically binds to the cancer associated sequence's protein and detecting the presence or absence of the binding to the cancer associated sequence's protein in the sample.

[00268] In some embodiments, the present invention provides methods of treating bladder cancer in a subject, the method comprising administering to a subject in need thereof a therapeutic agent that modulates the activity of a marker selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof or homologs thereof, wherein the therapeutic agent treats the cancer in the subject. In some embodiments, the marker may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00269] In some embodiments, the present invention provides methods of diagnosing bladder cancer in a subject, the method comprising determining the expression of a marker selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof or a combination thereof from a sample; and diagnosing cancer in the subject based on expression of the marker, wherein the subject is diagnosed as having cancer if the marker is overexpressed. In some embodiments, the marker may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00270] In some embodiments, the present invention provides methods of detecting cancer in a test sample, the method comprising: (i) detecting a level of an antibody, wherein the antibody binds to an antigenic polypeptide encoded by a nucleic acid sequence comprising a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or a fragment thereof; and (ii) comparing the level of the antibody in the test sample with a level of the antibody in a control sample, wherein an altered level of antibody in the test sample relative

to the level of antibody in the control sample is indicative of the presence of cancer in the test sample. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00271] In some embodiments, the present invention provides methods of detecting cancer in a test sample, comprising: (i) detecting a level of activity of at least one polypeptide that is encoded by a nucleic acid comprising a nucleic acid sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or a fragment thereof; and (ii) comparing the level of activity of the polypeptide in the test sample with a level of activity of polypeptide in a normal sample, wherein an altered level of activity of the polypeptide in the test sample relative to the level of polypeptide activity in the normal sample is indicative of the presence of cancer in the test sample. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00272] In some embodiments, the present invention provides methods of detecting bladder cancer in a test sample, the method comprising: (i) detecting a level of expression of at least one polypeptide that is encoded by a nucleic acid comprising a nucleic acid sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or a fragment thereof; and (ii) comparing the level of expression of the polypeptide in the test sample with a level of expression of polypeptide in a normal sample, wherein an altered level of expression of the polypeptide in the test sample relative to the level of polypeptide expression in the normal sample is indicative of the presence of cancer in the test sample. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-41, a fragment thereof, a complement thereof or a combination thereof.

[00273] In some embodiments, the present invention provides methods of detecting bladder cancer in a test sample, the method comprising: (i) detecting a level of expression of a nucleic acid sequence comprising a sequence selected from LOC650517, FCRLB, IL1A,

S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, mutant nucleic acids thereof, combinations thereof, or a fragment thereof; and (ii) comparing the level of expression of the nucleic acid sequence in the test sample with a level of expression of nucleic acid sequence in a normal sample, wherein an altered level of expression of the nucleic acid sequence in the test sample relative to the level of nucleic acid sequence expression in the normal sample is indicative of the presence of cancer in the test sample. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00274] In some embodiments, the present invention provides methods of screening for activity against cancer, the method comprising: (a) contacting a cell that expresses a cancer associated gene comprising a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or fragments thereof with a cancer drug candidate; (b) detecting an effect of the cancer drug candidate on an expression of the cancer associated polynucleotide in the cell; and (c) comparing the level of expression in the absence of the drug candidate to the level of expression in the presence of the drug candidate; wherein an effect on the expression of the cancer associate polynucleotide indicates that the candidate has activity against cancer. In some embodiments, the cancer associated gene comprises a sequence selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof or encodes the same.

[00275] In some embodiments, the present invention provides methods of screening for activity against bladder cancer, the method comprising: (a) contacting a cell that overexpresses a cancer associated gene comprising a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or fragments thereof

with a cancer drug candidate; (b) detecting an effect of the cancer drug candidate on an expression of the cancer associated polynucleotide in the cell or an effect on cell growth or viability; and (c) comparing the level of expression, cell growth, or viability in the absence of the drug candidate to the level of expression, cell growth, or viability in the presence of the drug candidate; wherein an effect on the expression of the cancer associated polynucleotide, cell growth, or viability indicates that the candidate has activity against cancer cell that overexpresses the cancer associated gene. In some embodiments, the cancer associated gene comprises a sequence selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof or encodes the same.

[00276] In some embodiments, the present invention provides methods of diagnosing bladder cancer in a subject, the method comprising: a) determining the expression of one or more nucleic acid sequences, wherein the one or more nucleic acid sequences comprises a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof, combinations thereof, or fragments thereof in a first sample of a first subject; and b) comparing the expression of the one or more nucleic acid sequences from a second normal sample from the first subject or a second unaffected subject, wherein a difference in the expression of nucleic acid sequences indicates that the first subject has cancer. In some embodiments, the nucleic acid sequence may be selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00277] In some embodiments, the present invention provides methods of diagnosing bladder cancer in a subject, the method comprising: a) determining the expression of one or more genes or gene products or homologs thereof in a subject; and b) comparing the expression of the one or more genes or gene products or homologs thereof in the subject to the expression of one or more genes or gene products or homologs thereof from a normal sample from the subject or a normal sample from an unaffected subject, wherein a difference in the expression indicates that the subject has bladder cancer, wherein the one or more genes or gene products comprises a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8,

GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof, homologs thereof or combinations thereof. In some embodiments, the gene or gene product encodes a sequence selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof or a combination thereof.

[00278] In some embodiments, the present invention provides methods of detecting bladder cancer in a test sample, comprising: (i) detecting a level of activity of at least one polypeptide; and (ii) comparing the level of activity of the polypeptide in the test sample with a level of activity of polypeptide in a normal sample, wherein an altered level of activity of the polypeptide in the test sample relative to the level of polypeptide activity in the normal sample is indicative of the presence of cancer in the test sample, wherein the polypeptide is a gene product of a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 complements thereof. In some embodiments, the polypeptide comprises a sequence selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof and combinations thereof.

[00279] In some embodiments, the present invention provides methods of diagnosing bladder cancer in a subject, the method comprising: obtaining one or more gene expression results for one or more sequences, wherein the one or more sequences comprises a sequence selected from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 a complement thereof, or a combination thereof, from a sample derived from a subject; and diagnosing cancer in the subject based on the one or more gene expression results, wherein the subject is diagnosed as having cancer if one or more genes is overexpressed. In some embodiments, the one or more sequences comprises a sequence selected from SEQ ID NOs: 1-40, a fragment thereof, a complement thereof, or a combination thereof.

1. A method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a panel of markers encoded by the gene WDR72 and one or more genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A,

UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, or a complement thereof; c) contacting a non-cancerous cell, with the one or more agents from b); and d) comparing the expression level of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, or a complement thereof in the sample obtained from the subject with the expression level of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from OC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof, in the non-cancerous cell, wherein a higher level of expression of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

2. The method of 1, wherein the subject is a human.
3. The method of 1, wherein the sample is a bodily fluid.
4. The method of 3, wherein the bodily fluid is blood.
5. The method of 3, wherein the bodily fluid is serum.
6. The method of 3, wherein the bodily fluid is urine.

7. The method of 1, wherein the sample is a tissue sample.
8. The method of 1, wherein the sample is comprised of cells.
9. The method of 1, wherein the one or more agents is a nucleic acid.
10. The method of 1, wherein the one or more agents is a protein.
11. The method of 10, wherein the protein is an antibody.

12. A method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of one or more of the markers encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof; c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of one or more of the markers encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the non-cancerous cell, wherein a higher level of expression in the sample of one or more of the markers encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the sample obtained from the subject compared to the non-cancerous cell indicates that the subject has bladder cancer.

13. The method of 12, wherein the subject is a human.
14. The method of 12, wherein the sample is a bodily fluid.
15. The method of 14, wherein the bodily fluid is blood.

16. The method of 14, wherein the bodily fluid is serum.
17. The method of 14, wherein the bodily fluid is urine.
18. The method of 12, wherein the sample is a tissue sample.
19. The method of 12, wherein the sample is comprised of cells.
20. The method of 12, wherein the one or more agents is a nucleic acid.
21. The method of 12, wherein the one or more agents is a protein.
22. The method of 21, wherein the protein is an antibody.
23. A kit for detecting bladder cancer in sample comprising one or more agents that bind to a marker encoded for by one or more genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6.
24. The kit of 23, wherein the one or more agents is a nucleic acid.
25. The kit of 23, wherein the one or more agents is a protein.
26. The kit of 23, wherein the protein is an antibody.
27. The kit of 23, wherein the sample is obtained from a human.
28. The kit of 23, wherein the sample is a bodily fluid.
29. The kit of 23, wherein the bodily fluid is blood.
30. The kit of 23, wherein the bodily fluid is serum.
31. The kit of 23, wherein the sample is tissue.
32. The kit of 23, wherein the sample is comprised of cells.

EXAMPLE 1

[00280] LOC650517: LOC650517 (Accession number XR_019109.1) encodes Keratin 17 pseudogene 3. It is disclosed here that LOC650517 is a novel marker for bladder tumors. As shown in Figure 1, LOC650517 expression was assayed by Illumina microarray, a probe specific for LOC650517 (probe sequence AAGAACCGCAAGGATGCCAAGGATTGGTTCTTCAGCAAGACAGAGGAACT; (SEQ ID NO: 62) Illumina probe ID ILMN_1653934) detected strong gene expression (>200 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of LOC650517 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<200 RFUs). The specificity of elevated LOC650517 expression in malignant tumors of bladder origin shown herein demonstrates that LOC650517 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00281] Therapeutics that target LOC650517 can be identified using the methods described herein and therapeutics that target LOC650517 include, but are not limited to, antibodies that modulate the activity of LOC650517. The manufacture and use of antibodies are described herein.

EXAMPLE 2

[00282] FCRLB: FCRLB (Accession number NM_001002901.2) encodes Homo sapiens Fc receptor-like B. It is disclosed here that FCRLB is a novel marker for bladder tumors. As shown in Figure 2, FCRLB expression was assayed by Illumina microarray, a probe specific for FCRLB (probe sequence CACCCTTAGCCCTTCAGATAAGCCTAGCCAGTACATATTTTCAGCACAGGC; (SEQ ID NO: 63) Illumina probe ID ILMN_1782015) detected strong gene expression (>170 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of FCRLB in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung,

kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<170 RFUs). The specificity of elevated FCRLB expression in malignant tumors of bladder origin shown herein demonstrates that FCRLB is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00283] Therapeutics that target FCRLB can be identified using the methods described herein and therapeutics that target FCRLB include, but are not limited to, antibodies that modulate the activity of FCRLB. The manufacture and use of antibodies are described herein.

EXAMPLE 3

[00284] IL1A: IL1A (Accession number NM_000575.3) encodes Homo sapiens interleukin 1, alpha. It is disclosed here that IL1A is a novel marker for bladder tumors. As shown in Figure 3, IL1A expression was assayed by Illumina microarray, a probe specific for IL1A (probe sequence CAGGGCATT TTTGGTCCAAGTTGTGCTTATCCCATAGCCAGGAAACTCTGC; (SEQ ID NO: 64) Illumina probe ID ILMN_1658483) detected strong gene expression (>260 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of IL1A in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<260 RFUs). The specificity of elevated IL1A expression in malignant tumors of bladder origin shown herein demonstrates that IL1A is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00285] Therapeutics that target IL1A can be identified using the methods described herein and therapeutics that target IL1A include, but are not limited to, antibodies that modulate the activity of IL1A. The manufacture and use of antibodies are described herein.

EXAMPLE 4

[00286] S100A2: S100A2 (Accession number NM_005978.3) encodes Homo sapiens S100 calcium binding protein A2. It is disclosed here that S100A2 is a novel marker for bladder tumors. As shown in Figure 4, S100A2 expression was assayed by Illumina microarray, a probe specific for S100A2 (probe sequence CTCAGCTGGAGTGCTGGGAGATGAGGGCCTCCTGGATCCTGCTCCCTTCT; (SEQ ID NO: 65) Illumina probe ID ILMN_1725852) detected strong gene expression (>1000 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of S100A2 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<1000 RFUs). The specificity of elevated S100A2 expression in malignant tumors of bladder origin shown herein demonstrates that S100A2 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00287] Therapeutics that target S100A2 can be identified using the methods described herein and therapeutics that target S100A2 include, but are not limited to, antibodies that modulate the activity of S100A2. The manufacture and use of antibodies are described herein.

EXAMPLE 5

[00288] MMP11: MMP11 (Accession number NM_005940.3) encodes Homo sapiens matrix metalloproteinase 11 (stromelysin 3). It is disclosed here that MMP11 is a novel marker for bladder tumors. As shown in Figure 5, MMP11 expression was assayed by Illumina microarray, a probe specific for MMP11 (probe sequence CAGGTCTTGGTAGGTGCCTGCATCTGTCTGCCTTCTGGCTGACAATCCTG; (SEQ ID NO: 66) Illumina probe ID ILMN_1655915) detected strong gene expression (>1600 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of MMP11 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<1600

RFUs). The specificity of elevated MMP11 expression in malignant tumors of bladder origin shown herein demonstrates that MMP11 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00289] Therapeutics that target MMP11 can be identified using the methods described herein and therapeutics that target MMP11 include, but are not limited to, antibodies that modulate the activity of MMP11. The manufacture and use of antibodies are described herein.

EXAMPLE 6

[00290] S100A7A: S100A7A (Accession number NM_176823.3) encodes Homo sapiens S100 calcium binding protein A7A. It is disclosed here that S100A7A is a novel marker for bladder tumors. As shown in Figure 6, S100A7A expression was assayed by Illumina microarray, a probe specific for S100A7A (probe sequence AGAGTTCTGACCAGCACCAGATAAGCTTCAGTGCTCTCCTTTCTTTGGCC; (SEQ ID NO: 67) Illumina probe ID ILMN_1673191) detected strong gene expression (>100 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of S100A7A in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<100 RFUs). The specificity of elevated S100A7A expression in malignant tumors of bladder origin shown herein demonstrates that S100A7A is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00291] Therapeutics that target S100A7A can be identified using the methods described herein and therapeutics that target S100A7A include, but are not limited to, antibodies that modulate the activity of S100A7A. The manufacture and use of antibodies are described herein.

EXAMPLE 7

[00292] UGT1A6: UGT1A6 (Accession number NM_205862.1) encodes Homo sapiens UDP glucuronosyltransferase 1 family, polypeptide A6. It is disclosed here that

UGT1A6 is a novel marker for bladder tumors. As shown in Figure 7, UGT1A6 expression was assayed by Illumina microarray, a probe specific for UGT1A6 (probe sequence TACCAGGCTTTCTGACTCCTGCTCTAGGATTCTCACCCACGTACTGGCTAG; (SEQ ID NO: 68) Illumina probe ID ILMN_1752813) detected strong gene expression (>300 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of UGT1A6 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<300 RFUs). The specificity of elevated UGT1A6 expression in malignant tumors of bladder origin shown herein demonstrates that UGT1A6 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00293] Therapeutics that target UGT1A6 can be identified using the methods described herein and therapeutics that target UGT1A6 include, but are not limited to, antibodies that modulate the activity of UGT1A6. The manufacture and use of antibodies are described herein.

EXAMPLE 8

[00294] FAM83A: FAM83A (Accession number NM_032899.4) encodes Homo sapiens family with sequence similarity 83, member A. It is disclosed here that FAM83A is a novel marker for bladder tumors. As shown in Figure 8, FAM83A expression was assayed by Illumina microarray, a probe specific for FAM83A (probe sequence CAGCCTGGTCACCTCCTGAGGAATAAATGCTGAACCTCACAAGCCCCATC; (SEQ ID NO: 69) Illumina probe ID ILMN_2239774) detected strong gene expression (>800 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of FAM83A in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<800 RFUs). The specificity of elevated FAM83A expression in malignant tumors of bladder origin shown herein demonstrates that FAM83A is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder

tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00295] Therapeutics that target FAM83A can be identified using the methods described herein and therapeutics that target FAM83A include, but are not limited to, antibodies that modulate the activity of FAM83A. The manufacture and use of antibodies are described herein.

EXAMPLE 9

[00296] SLC1A6: SLC1A6 (Accession number NM_005071.1) encodes Homo sapiens solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6. It is disclosed here that SLC1A6 is a novel marker for bladder tumors. As shown in Figure 9, SLC1A6 expression was assayed by Illumina microarray, a probe specific for SLC1A6 (probe sequence TGACCGGCTTCGCACAATGACCAACGTACTGGGGGACTCAATTGGAGCGG; (SEQ ID NO: 70) Illumina probe ID ILMN_2171471) detected strong gene expression (>120 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of SLC1A6 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<120 RFUs). The specificity of elevated SLC1A6 expression in malignant tumors of bladder origin shown herein demonstrates that SLC1A6 is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00297] Therapeutics that target SLC1A6 can be identified using the methods described herein and therapeutics that target SLC1A6 include, but are not limited to, antibodies that modulate the activity of SLC1A6. The manufacture and use of antibodies are described herein.

EXAMPLE 10

[00298] UPK3B: UPK3B (Accession number NM_182684.1) encodes Homo sapiens uropod 3B (UPK3B), transcript variant 2. It is disclosed here that UPK3B is a novel marker for bladder tumors. As shown in Figure 10, UPK3B expression was assayed by Illumina microarray, a probe specific for UPK3B (probe sequence GCTCACCCAGGGCTGAGACCAAGTGGTCAGACCCCATCACTCTCCACCAA; (SEQ ID

NO: 71) Illumina probe ID ILMN_2264177) detected strong gene expression (>220 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of UPK3B in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<220 RFUs). The specificity of elevated UPK3B expression in malignant tumors of bladder origin shown herein demonstrates that UPK3B is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00299] Therapeutics that target UPK3B can be identified using the methods described herein and therapeutics that target UPK3B include, but are not limited to, antibodies that modulate the activity of UPK3B. The manufacture and use of antibodies are described herein.

EXAMPLE 11

[00300] BX116033: BX116033 (Accession number BX116033) encodes BX116033 NCI_CGAP_Lu24 Homo sapiens cDNA clone IMAGp998A155622, mRNA sequence. It is disclosed here that BX116033 is a novel marker for bladder tumors. As shown in Figure 11, BX116033 expression was assayed by Illumina microarray, a probe specific for BX116033 (probe sequence TGCCGTATTCTTGGTGTCTGGAGCAGTGCCTGACCTGTGGCGGGTGCTTA; (SEQ ID NO: 72) Illumina probe ID ILMN_1863962) detected strong gene expression (>200 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of BX116033 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<200 RFUs). The specificity of elevated BX116033 expression in malignant tumors of bladder origin shown herein demonstrates that BX116033 is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00301] Therapeutics that target BX116033 can be identified using the methods described herein and therapeutics that target BX116033 include, but are not limited to, antibodies that modulate the activity of BX116033. The manufacture and use of antibodies are described herein.

EXAMPLE 12

[00302] MMP12: MMP12 (Accession number NM_002426.2) encodes Homo sapiens matrix metalloproteinase 12 (macrophage elastase). It is disclosed here that MMP12 is a novel marker for bladder tumors. As shown in Figure 12, MMP12 expression was assayed by Illumina microarray, a probe specific for MMP12 (probe sequence TCTATTTGAAGCATGCTCTGTAAGTTGCTTCCTAACATCCTTGGACTGAG; (SEQ ID NO: 73) Illumina probe ID ILMN_2073758) detected strong gene expression (>120 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of MMP12 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<120 RFUs). The specificity of elevated MMP12 expression in malignant tumors of bladder origin shown herein demonstrates that MMP12 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00303] Therapeutics that target MMP12 can be identified using the methods described herein and therapeutics that target MMP12 include, but are not limited to, antibodies that modulate the activity of MMP12. The manufacture and use of antibodies are described herein.

EXAMPLE 13

[00304] KRT16: KRT16 (Accession number NM_005557.2) encodes Homo sapiens keratin 16 (focal non-epidermolytic palmoplantar keratoderma). It is disclosed here that KRT16 is a novel marker for bladder tumors. As shown in Figure 13, KRT16 expression was assayed by Illumina microarray, a probe specific for KRT16 (probe sequence AGGAGTACCAGATCTTGCTGGATGTGAAGACGCGGCTGGAGCAGGAGATT; (SEQ ID NO: 74) Illumina probe ID ILMN_2228162) detected strong gene expression (>520 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of KRT16 in a wide variety of

normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<520 RFUs). The specificity of elevated KRT16 expression in malignant tumors of bladder origin shown herein demonstrates that KRT16 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00305] Therapeutics that target KRT16 can be identified using the methods described herein and therapeutics that target KRT16 include, but are not limited to, antibodies that modulate the activity of KRT16. The manufacture and use of antibodies are described herein.

EXAMPLE 14

[00306] UBD: UBD (Accession number NM_006398.2) encodes Homo sapiens ubiquitin D. It is disclosed here that UBD is a novel marker for bladder tumors. As shown in Figure 1, UBD expression was assayed by Illumina microarray, a probe specific for UBD (probe sequence CCTCCTCCAGGTGCGAAGGTCCAGCTCAGTGGCACAAGTGAAAGCAATGA; (SEQ ID NO: 75) Illumina probe ID ILMN_1678841) detected strong gene expression (>170 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of UBD in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<170 RFUs), with the exception of lymph node (1076 RFUs). The specificity of elevated UBD expression in malignant tumors of bladder origin shown herein demonstrates that UBD is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00307] Therapeutics that target UBD can be identified using the methods described herein and therapeutics that target UBD include, but are not limited to, antibodies that modulate the activity of UBD. The manufacture and use of antibodies are described herein.

EXAMPLE 15

[00308] UGT1A6: UGT1A6 (Accession number NM_001072.3) encodes Homo sapiens UDP glucuronosyltransferase 1 family, polypeptide A6. It is disclosed here that UGT1A6 is a novel marker for bladder tumors. As shown in Figure 15, UGT1A6 expression was assayed by Illumina microarray, a probe specific for UGT1A6 (probe sequence GGCCGGTCATGCCCAACATGGTCTTCATTGGAGGTATCAACTGTAAGAAG; (SEQ ID NO: 76) Illumina probe ID ILMN_1706390) detected strong gene expression (>200 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of UGT1A6 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<200 RFUs). The specificity of elevated UGT1A6 expression in malignant tumors of bladder origin shown herein demonstrates that UGT1A6 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00309] Therapeutics that target UGT1A6 can be identified using the methods described herein and therapeutics that target UGT1A6 include, but are not limited to, antibodies that modulate the activity of UGT1A6. The manufacture and use of antibodies are described herein.

EXAMPLE 16

[00310] S100A7: S100A7 (Accession number NM_002963.3) encodes Homo sapiens S100 calcium binding protein A7. It is disclosed here that S100A7 is a novel marker for bladder tumors. As shown in Figure 16, S100A7 expression was assayed by Illumina microarray, a probe specific for S100A7 (probe sequence GCTGAGAGGTCCATAATAGGCATGATCGACATGTTTCACAAATACACCAG; (SEQ ID NO: 77) Illumina probe ID ILMN_1757351) detected strong gene expression (>420 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of S100A7 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<420

RFUs). The specificity of elevated S100A7 expression in malignant tumors of bladder origin shown herein demonstrates that S100A7 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00311] Therapeutics that target S100A7 can be identified using the methods described herein and therapeutics that target S100A7 include, but are not limited to, antibodies that modulate the activity of S100A7. The manufacture and use of antibodies are described herein.

EXAMPLE 17

[00312] WISP3: WISP3 (Accession number NM_003880.2) encodes Homo sapiens WNT1 inducible signaling pathway protein 3. It is disclosed here that WISP3 is a novel marker for bladder tumors. As shown in Figure 17, WISP3 expression was assayed by Illumina microarray, a probe specific for WISP3 (probe sequence GCTGTGGATTACATCTTGTGTGTGTCAGAGAACTGCAGAGAACCTGGAG; (SEQ ID NO: 78) Illumina probe ID ILMN_1712360) detected strong gene expression (>170 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of WISP3 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<170 RFUs). The specificity of elevated WISP3 expression in malignant tumors of bladder origin shown herein demonstrates that WISP3 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00313] Therapeutics that target WISP3 can be identified using the methods described herein and therapeutics that target WISP3 include, but are not limited to, antibodies that modulate the activity of WISP3. The manufacture and use of antibodies are described herein.

EXAMPLE 18

[00314] PTH1H: PTH1H (Accession number NM_198964.1) encodes Homo sapiens parathyroid hormone-like hormone. It is disclosed here that PTH1H is a novel marker for

bladder tumors. As shown in Figure 18, PTHLH expression was assayed by Illumina microarray, a probe specific for PTHLH (probe sequence TGGTTAGACTCTGGAGTGACTGGGAGTGGGCTAGAAGGGGACCACCTGTC; (SEQ ID NO: 79) Illumina probe ID ILMN_1785699) detected strong gene expression (>900 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of PTHLH in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<900 RFUs). The specificity of elevated PTHLH expression in malignant tumors of bladder origin shown herein demonstrates that PTHLH is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00315] Therapeutics that target PTHLH can be identified using the methods described herein and therapeutics that target PTHLH include, but are not limited to, antibodies that modulate the activity of PTHLH. The manufacture and use of antibodies are described herein.

EXAMPLE 19

[00316] COL10A1: COL10A1 (Accession number NM_000493.3) encodes Homo sapiens collagen, type X, alpha 1. It is disclosed here that COL10A1 is a novel marker for bladder tumors. As shown in Figure 19, COL10A1 expression was assayed by Illumina microarray, a probe specific for COL10A1 (probe sequence CCCCTAAAATATTTCTGATGGTGCCTACTCTGAGGCCTGTATGGCCCCT; (SEQ ID NO: 80) Illumina probe ID ILMN_1672776) detected strong gene expression (>100 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of COL10A1 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<100 RFUs), with the exception of bone (477 RFUs). The specificity of elevated COL10A1 expression in malignant tumors of bladder origin shown herein demonstrates that COL10A1 is a marker for the diagnosis of bladder cancer (*e.g.* including but not limited to bladder tumor

transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00317] Therapeutics that target COL10A1 can be identified using the methods described herein and therapeutics that target COL10A1 include, but are not limited to, antibodies that modulate the activity of COL10A1. The manufacture and use of antibodies are described herein.

EXAMPLE 20

[00318] SERPINB4: SERPINB4 (Accession number NM_002974.2) encodes Homo sapiens serpin peptidase inhibitor, clade B (ovalbumin), member 4. It is disclosed here that SERPINB4 is a novel marker for bladder tumors. As shown in Figure 20, SERPINB4 expression was assayed by Illumina microarray, a probe specific for SERPINB4 (probe sequence GCATGACCTGGAGCCACGGTCTCTCAGTATCTAAAGTCCTACACAAGGCC; (SEQ ID NO: 81) Illumina probe ID ILMN_1782716) detected strong gene expression (>2000 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of SERPINB4 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<2000 RFUs). The specificity of elevated SERPINB4 expression in malignant tumors of bladder origin shown herein demonstrates that SERPINB4 is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00319] Therapeutics that target SERPINB4 can be identified using the methods described herein and therapeutics that target SERPINB4 include, but are not limited to, antibodies that modulate the activity of SERPINB4. The manufacture and use of antibodies are described herein.

EXAMPLE 21

[00320] UBE2C: UBE2C (Accession number NM_181803.1) encodes Homo sapiens ubiquitin-conjugating enzyme E2C. It is disclosed here that UBE2C is a novel marker for bladder tumors. As shown in Figure 21, UBE2C expression was assayed by Illumina microarray, a probe specific for UBE2C (probe sequence CCCTCATGAACCCAACATTGATAGTCCCTTGAACACACATGCTGCCGAGC; (SEQ ID

NO: 82) Illumina probe ID ILMN_1714730) detected strong gene expression (>500 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of UBE2C in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<500 RFUs). The specificity of elevated UBE2C expression in malignant tumors of bladder origin shown herein demonstrates that UBE2C is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00321] Therapeutics that target UBE2C can be identified using the methods described herein and therapeutics that target UBE2C include, but are not limited to, antibodies that modulate the activity of UBE2C. The manufacture and use of antibodies are described herein.

EXAMPLE 22

[00322] SFN: SFN (Accession number NM_006142.3) encodes Homo sapiens stratifin. It is disclosed here that SFN is a novel marker for bladder tumors. As shown in Figure 22, SFN expression was assayed by Illumina microarray, a probe specific for SFN (probe sequence CTCTGATCGTAGGAATTGAGGAGTGTCCTCGCCTTGTGGCTGAGAACTGGA; (SEQ ID NO: 83) Illumina probe ID ILMN_1806607) detected strong gene expression (>3000 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of SFN in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<3000 RFUs). The specificity of elevated SFN expression in malignant tumors of bladder origin shown herein demonstrates that SFN is a marker for the diagnosis of bladder cancer (*e.g.*, including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00323] Therapeutics that target SFN can be identified using the methods described herein and therapeutics that target SFN include, but are not limited to, antibodies that modulate the activity of SFN. The manufacture and use of antibodies are described herein.

EXAMPLE 23

- **KRT17P3:** KRT17P3 (Accession number XR 015626.2) encodes Homo sapiens. It is disclosed here that KRT17P3 is a novel marker for bladder tumors. As shown in Figure 23, KRT17P3 expression was assayed by Illumina microarray, a probe specific for KRT17P (probe sequence TGGGCTGACCTTGGCCAGAGCCGACCTGGAGATGCAGATTGAGAACCTCA ; (SEQ ID NO: 84) Illumina probe ID ILMN_3195198) detected strong gene expression (>3000 RFUs) in bladder tumor transitional cell carcinoma. In contrast, expression of KRT17P3 in a wide variety of normal tissues including normal bladder, colon, rectum, cervix, endometrium, uterus myometrium, ovary, fallopian tube, bone, skeletal muscle, skin, adipose tissue, soft tissue, lung, kidney, esophagus, lymph node, thyroid, urinary bladder, pancreas, prostate, rectum, liver, spleen, stomach, spinal cord, brain, testis, thyroid, and salivary gland was generally low (<3000 RFUs). The specificity of elevated KRT17P3 expression in malignant tumors of bladder origin shown herein demonstrates that is KRT17P3 a marker for the diagnosis of bladder cancer (e.g., including but not limited to bladder tumor transitional cell carcinoma and metastatic bladder tumors), and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00324] Therapeutics that target KRT17P3 can be identified using the methods described herein and therapeutics that target KRT17P3 include, but are not limited to, antibodies that modulate the activity of KRT17P3. The manufacture and use of antibodies are described herein.

EXAMPLE 24

[00325] qRT PCR was performed on normal bladder tissue and bladder tumors. Total RNA was extracted (RNeasy, Qiagen), then cDNA generated using the SuperScript III reverse transcriptase in combination with random hexamer primers alone or in combination with oligo-dT primers (all reverse transcription components from Invitrogen/Life Technologies). PCRs were carried out on a 7900HT Sequence Detection System or a 7500 Real Time PCR System (Applied Biosystems/Life Technologies) utilizing SYBR® Green I (Applied Biosystems/Life Technologies) or TaqMan chemistries. TaqMan PCR was conducted with probes from the Universal Probe Library (UPL) (Roche) in combination with correspondingly designed primers.

Background: The UPL System contains a relatively small number of short hydrolysis probes that cover an extensive proportion of the human mRNA transcriptome. UPL probes contain locked nucleic acids (LNAs) which increase the probes' melting temperatures. This allows the probe and the longer, unmodified, primers to anneal at the same temperature.

[00326] Primers for each of the genes studied are provided below.

Gene	primer sequence1
MMP11	ACCGCTGGAGCCAGACGCC (SEQ ID NO: 85)
MMP12	TCTGGACTACACATTCAGGAGGCAC (SEQ ID NO:86)
COL10A1	GGGCCTCAATGGACCCACCG (SEQ ID NO: 87)
KRT6A	TGAGGAGTGCAGGCTGAATGGC (SEQ ID NO:88)
SFN	GTGGAGAGGGACTGGCAGAGC (SEQ ID NO: 89)
FCRLB	GCCAGGCCGTGCGCTACTTCC (SEQ ID NO:90)
SERPINB5	ACTGGTGGCAGGGGCTTCTAGC (SEQ ID NO:91)
IL1A	GGTTGAGTTTAAGCCAATCCA (SEQ ID NO:92)
KRT16	ATCGAGGACCTGAGGAACAA (SEQ ID NO: 93)
SLC1A6	CTATGGGCACGTCTTCCAG (SEQ ID NO:94)
S100A2	TCTGCCACCTGGTCTGCCACA (SEQ ID NO:95)
S100A7A	AAGCCTGCTGACGATGATG (SEQ ID NO: 96)
DSCR6	ATCCAGACACCTGGAGATGCTG (SEQ ID NO: 97)
UBE2C	GATAGTCCCTTGAACACACATGCTG (SEQ ID NO: 98)

Gene	primer sequence 2
MMP11	CGAGAGGCCAATGCTGGGTAGC (SEQ ID NO: 99)
MMP12	GTCACAGAGAGCTGGTTCTGAATTGTC (SEQ ID NO:100)
COL10A1	CTGGGCCTTTGGCCTGCCTT (SEQ ID NO: 101)
KRT6A	CAATGGCTCTGCCACTGCTGGAAC (SEQ ID NO: 102)
SFN	GGGACACTCCTCAATTCCTACGATC (SEQ ID NO: 103)
FCRLB	CTTGCACTGTCACAGCCACCTTAGC (SEQ ID NO: 104)
SERPINB5	GCCATCTAAAGTAACTAAACCCATAGAC (SEQ ID NO:105
IL1A	TGCTGACCTAGGCTTGATGA (SEQ ID NO:106)
KRT16	GGGCCAGTTCATGCTCATAC (SEQ ID NO:107)
SLC1A6	GGACGAACCTGGTGATGC (SEQ ID NO: 108)
S100A2	AGTGACCAGCACAGCCAGCG (SEQ ID NO: 109)
S100A7A	GCGAGGTAATGTATGCCCTTT (SEQ ID NO: 110)
DSCR6	ACTCCGCAGGTATTCTTGACGC (SEQ ID NO: 111)
UBE2C	CCGAGCTCTGGAAAAACCCACAGC (SEQ ID NO: 112)

[00327] The results are presented in Figures 24-36 and show that expression of MMP11, MMP12, COL10A1, KRT6A, SFN, FCRLB, SERPINB5, IL1A, KRT16, SLC1A6,

S100A2, S100A7A, and DSCR6 are all elevated in bladder tumor samples compared to normal bladder tissue.

EXAMPLE 25

[00328] LIGATION-DEPENDENT AMPLIFICATION (LDA) FLEXSCRIPT ASSAY (Luminex Corporation). LDA was used to analyze expression of the gene UBE2C in normal bladder tissue and bladder tumors using primers for UBE2C disclosed in the table contained in the previous example.

[00329] The LDA FlexScript assay is based on a multiplex real-time Reverse Transcription-Polymerase Chain Reaction (qRT-PCR), followed by the hybridization of the different types of PCR products to different types of beads, and finally the detection and quantification of the bead-bound PCR products. In short, RNA is reverse-transcribed. Then, two probes per target are hybridized to adjacent regions on the complementary DNA (cDNA), and ligated with a thermostable ligase. Probe-probe pairs are PCR-amplified using universal primers binding to 5' extensions of the probes (choosing a cycle number at which reactions are expected to be in the dynamic range, i.e. in the exponential amplification phase), and treated with lambda exonuclease to remove one of the strands. The remaining (biotinylated) strands are then hybridized to unique oligonucleotides attached to Luminex microspheres, incubated with streptavidin-phycoerythrin (PE), and quantified based on PE fluorescence.

[00330] The results presented in Figure 37 show that UBE2C expression is elevated in bladder tumors compared to normal bladder tissue.

EXAMPLE 26

[00331] Example 26 provides ELISA data for MMP11 and COL10A1, (Figs 38-39).

[00332] Levels of the two protein markers were assayed in serum using a USCEN ELISA kit (USCEN) according to the manufacturer's instructions. In brief, 100 μ L of the blank, standards, and samples with specified dilutions were added to the appropriate wells of a 96 well plate followed by 2 hours of incubation at 37°C. After removal of the liquid, 100ul of Detection Reagent A was added to each well and incubated for 1 hour at 37°C. After removal of Reagent A, each well was washed 3 times with 350 uL of wash solution. 100 uL of Detection Reagent B was added to each well and then incubated for 30 minutes at 37°C. After removal of Reagent B, each well was washed 5 times with 350 uL of wash solution. 90 uL of Substrate solution was added to each well and incubated for 15-25 minutes at 37°C. 50 uL of Stop Solution was added to each well. The plate was read either on the Molecular Devices SpectraMax250 or the BioTek Synergy H1 plate reader at 450nm. A standard curve was derived from the standards supplied in the kit and the sample values were extrapolated from this curve.

[00333] The results are shown in Figures 38-39 and indicate that MMP11 and COL10A are elevated in serum from bladder cancer patients.

EXAMPLE 27

[00334] Agarose gel analysis of markers COL10A, MMP11, SFN and FCRLB in voided urine. RNA was extracted from cells in voided urine with the ZR Urine RNA Isolation KitTM (Zymo Research) then reverse-transcribed using SuperScript III reverse transcriptase in the presence of random hexamer and oligo-dT primers (Invitrogen/Life Technologies). Following PCR with 50 cycles, products were analyzed on pre-cast 4% Agarose (HR) gels containing ethidium bromide (E-Gel®, Invitrogen/Life Technologies). Urine specimens: all from male individuals, three with bladder cancer (1-3), and three healthy controls (A-C). GAPDH serves as loading and/or positive control.

	Forward primer	Reverse primer
<i>COL10A1</i>	GGGCCTCAATGGACCCACCG (SEQ ID NO: 113)	CTGGGCCTTTGGCCTGCCTT (SEQ ID NO: 118)
<i>MMP11</i>	ACCGCTGGAGCCAGACGCC (SEQ ID NO: 114)	CGAGAGGCCAATGCTGGGTAGC (SEQ ID NO: 119)
<i>SFN</i>	GTGGAGAGGGACTGGCAGAGC (SEQ ID NO: 115)	GGGACACTCCTCAATTCCTACGATC (SEQ ID NO: 120)
<i>FCRLB</i>	GCCAGGCCGTGCGCTACTTCC (SEQ ID NO: 116)	CTTGCACTGTACAGCCACCTTAGC (SEQ ID NO: 121)
<i>GAPDH</i>	GGCCTCCAAGGAGTAAGACC (SEQ ID NO: 117)	AGGGGTCTACATGGCAACTG (SEQ ID NO: 122)

[00335] The results are presented in Figure 40 and show that detectable levels of the markers COL10A, MMP11, SFN, and FCRLB can be found in the urine of bladder cancer patients.

EXAMPLE 28

[00336] Immunofluorescence microscopy

[00337] Paraffin embedded tissue sections were obtained from Asterand (Detroit, MI). These specimens included: Normal bladder tissue (donors with no history of cancer) and bladder cancer tissue. Prior to the staining with antibodies, the sections were dewaxed in xylene and rehydrated in cycles of ethanol (100%, 95%, 70%) followed by a wash in distilled water. Antigen retrieval was performed in epitope retrieval buffer (IHC World #IW-1100) by incubating the slides at 95 °C 40 minutes using an IHC-Steamer Set (IHC World #IW-1102). Immunostaining was performed using a polyclonal rabbit anti-human MMP11 antibody (Abcam #ab52904) at a 1:100 dilution. The primary antibody was detected using an Alexa Fluor 594 Donkey anti-rabbit IgG (Life Sciences #A21207) at a 1:200 dilution.

[00338] Vectashield mounting medium with DAPI was used to preserve the stained samples (Vector Laboratories #H-1200). Images were taken with an exposure time of 400 milliseconds using a Nikon Eclipse TE2000-U at a magnification of 10,000 and an X-Cite 120 fluorescence illumination system (Lumen Dynamics).

[00339] The results are shown in Figure 41 and demonstrate that MMP11 is detected in bladder cancer samples, but not in normal bladder tissue. Blue staining represents DAPI detection; red staining represents MMP11 detection.

EXAMPLE 29

[00340] WDR72: WDR72 (Accession number NM_182758.1) is a novel marker for bladder tumors. As shown in Figure 42, WDR72 expression was assayed by Illumina microarray, a probe specific for WDR72 (probe sequence GAGATATGGGTGCCCTTTTGTACGTCTAGGCCTAGGTAACCAGTGGAGTG; (SEQ ID NO: 123) Illumina probe ID ILMN_1782716) detected strong gene expression (>2000 RFUs) in bladder cancer tissue. In contrast, expression of WDR72 in normal bladder tissue was generally low. The specificity of elevated WDR72 expression in malignant tumors of bladder origin shown herein demonstrates that WDR72 is a marker for the diagnosis of bladder cancer, and is a target for therapeutic intervention in bladder cancer. The marker may be detected in urine and/or sera.

[00341] Therapeutics that target WDR72 can be identified using the methods described herein and therapeutics that target WDR72 include, but are not limited to, antibodies that modulate the activity of WDR72. The manufacture and use of antibodies are described herein.

EXAMPLE 30

[00342] Commercially available bladder and bladder tumor tissue RNA samples were serially diluted in water, then subjected to 1-step qRT-PCR amplification. mRNA was reverse-transcribed and cDNA amplified in reaction volumes of 30 microliter using the Path-IDTM Multiplex One-Step RT-PCR Kit (Life Technologies) with the following primers and probes mixed together (multiplexed): 300 nM of MP3-F-WDR72, 400 nM of MP3-R-WDR72, 250 nM of MP3-P-WDR72-FAM, 20 nM of MP4-F-GAPDH, 400 nM of MP4-R-GAPDH, 250 nM of MP4-P-GAPDH-Cy5, 100 nM of MP2-F-UBE2C, 400 nM of MP2-R-UBE2C, 500 nM MP1-F-TOP2A, 400 nM of MP1-R-TOP2A, and 250 nM of MP1-P-TOP2A-JOE (Primers and probes are provided in the Table below).

[00343] (qRT-)PCRs were carried out on the ABI 7500 Real Time PCR System employing 7500 System SDS v2.0.5 software (Life Technologies) with the thermoprogram set

for 48°C for 10 minutes, then 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 seconds and 60°C for 2.5 minutes.

[00344] Results are shown in Figure 43 and demonstrate that expression of WDR72 is elevated in bladder cancer tissue relative to normal tissue.

[00345] cDNA was amplified using the Path-IDTM Multiplex One-Step RT-PCR Kit (Life Technologies) with the following primers and probes mixed together (multiplexed): MP3-F-WDR72, MP3-R-WDR72, MP3-P-WDR72-FAM, MP4-F-GAPDH, MP4-R-GAPDH, and MP4-P-GAPDH-Cy5 (Primers and probes are provided in the Table below).

[00346] (qRT-)PCRs were carried out on the ABI 7500 Real Time PCR System employing 7500 System SDS v2.0.5 software (Life Technologies) with the thermoprogram set for 48°C for 10 minutes, then 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 seconds and 60°C for 2.5 minutes.

[00347] The results shown in Figure 44 demonstrate that expression levels of WDR72 was elevated in cancer samples compared to the histologically normal bladder tissue.

[00348] Human bladder cancer SCaBER cells (ATCC cat. no. HTB-3) were spiked into 50 ml aliquots of fresh urine from a healthy individual. Urine samples were processed via the ZR Urine RNA Isolation Kit (Zymo Research) and the resulting RNA was subjected to 1-step qRT-PCR. In short, mRNA was reverse-transcribed and cDNA amplified in reaction volumes of 30 microliter using the Path-IDTM Multiplex One-Step RT-PCR Kit (Life Technologies). For the WDR72 and GAPDH multiplex reactions, the following primers and probes were mixed together: 300 nM of MP3-F-WDR72, 400 nM of MP3-R-WDR72, 250 nM of MP3-P-WDR72-FAM, 20 nM of MP4-F-GAPDH, 400 nM of MP4-R-GAPDH, and 250 nM of MP4-P-GAPDH-Cy5 (Table below). For the TOP2A and GAPDH multiplex reactions, the following primers and probes were mixed together: 500 nM of TOP2A-MP-F, 500 nM of TOP2A-MP-R, 250 nM of TOP2A-FAM, 20 nM of GAPDH-MP-F, 400 nM of GAPDH-MP-R, and 250 nM of GAPDH-CY5 (Primers and Probes are provided in the Table below).

[00349] (qRT-)PCRs were carried out on the ABI 7500 Real Time PCR System employing 7500 System SDS v2.0.5 software (Life Technologies) with the thermoprogram set for 48°C for 10 minutes, then 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 seconds and 60°C for 2.5 minutes.

[00350] The results are shown in Figure 45 and demonstrate that WDR72 and TOP2A expression was detected in bladder carcinoma cells spiked into normal human urine.

[00351] The SurePrep™ Urine Exfoliated Cell RNA Purification Kit (Fisher Scientific) method was compared to a modified version of the ZR Urine RNA Isolation Kit

(Zymo Research) method on 100 milliliter aliquots of fresh urine from a healthy individual. For the ZR Urine RNA Isolation method, the step at which urine is manually pressed through a filter attached to a syringe was substituted by a vacuum filtration step using a Nalgene 0.2 micron vacuum sterile filtration device (Nalgene Rapid-Flow Sterile Disposable Filter Units with PES Membrane, catalogue numbers 564-0020 or 568-0020). RNA obtained from the SurePrep™ and the modified ZR Urine RNA Isolation methods was reverse-transcribed and cDNA amplified in reaction volumes of 30 microliter using the Path-ID™ Multiplex One-Step RT-PCR Kit (Life Technologies) with the following primers and probes mixed together (multiplexed): 300 nM of MP3-F-WDR72, 400 nM of MP3-R-WDR72, 250 nM of MP3-P-WDR72-FAM, 20 nM of MP4-F-GAPDH, 400 nM of MP4-R-GAPDH, and 250 nM of MP4-P-GAPDH-Cy5 (Primers and Probes are provided in the table below).

[00352] (qRT-)PCRs were carried out on the ABI 7500 Real Time PCR System employing 7500 System SDS v2.0.5 software (Life Technologies) with the thermoprogram set for 48°C for 10 minutes, then 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 seconds and 60°C for 2.5 minutes.

[00353] The results are shown in Figure 46 and demonstrated better results using the ZR Urine RNA isolation kit.

Gene Symbol	Accession No. (NCBI)	Label	Sequence (5' to 3')
MP3-F-WDR72	NM_182758.3		AAG GTC TGC CCC TGC AAG GTG T (SEQ ID NO:124)
MP3-R-WDR72	NM_182758.3		TGT GGA CTG GCA TTC CCT GTT GG (SEQ ID NO:125)
MP3-P-WDR72-FAM	NM_182758.3	6-FAM (5'), BHQ1 (3')	AGGCTGTAGTGGATTTGCTA (SEQ ID NO:126)
TOP2A-MP-F	NM_001067.3		ACA GAG CCA CGG AGA GCA GCA A (SEQ ID NO:127)
TOP2A-MP-R	NM_001067.3		GGA TGG CTT CCT TTT GCG GCG A (SEQ ID NO:128)
TOP2A-FAM	NM_001067.3	6-FAM (5'), BHQ1 (3')	TCTTCAAGCCCTCCTGCTAC (SEQ ID NO:129)
MP4-F-GAPDH	NM_002046.4		AATCAAGTGGGGCGATGCTGGC (SEQ ID NO:130)
MP4-R-GAPDH	NM_002046.4		TGACCTTGCCAGGGGTGCTAA (SEQ ID NO:131)
MP4-P-GAPDH-Cy5	NM_002046.4	Cy5 (5'), BHQ3 (3')	GTTTCGTCATGGGTGTGAACC (SEQ ID NO:132)

Primers and probes for multiplex qRT-PCR.

Illumina Probe:
Gene Symbol
WDR72
NM_182758.3

Accession No. (NCBI)
NM_182758.1

GAGATATGGGTGCCCTTTTGTACGTCTAGGCCTAGGTAACCAGTGGAGTG (SEQ ID NO: 133)

EXAMPLE 31

[00354] Multiplex 1-step quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed on various samples using Path-ID™ Multiplex One-Step RT-PCR Kit (Life Technologies) according to the manufacturer's instructions.

[00355] Primers used in qPCR were designed using OligoCalc 1-2 (Northwestern Univ, Northwestern, IL USA) Primer3 (NCBI, Bethesda, MD USA) and for multiplex PCR primers, MPprimer (Beijing Institute, Beijing China). Criteria for primer design was to have similar Tms for forward and reverse primers, to be specific for the gene of interest and to have unfavorable self-annealing thermodynamics. TaqMan® probes were designed using Primer Express® Software v2.0 (Life Technologies, Grand Island, NY USA) to have Tms approximately 10°C higher than for primers and whenever possible, to be specific for the gene of interest. Primers demonstrating good correlation and specificity for cancer, as well as exhibiting robustness and linear dose response to sample input proceeded for further testing.

[00356] WDR72 expression was studied using the following primers: JK1395-WDR72-F AATGCTGCCAAAGCAAGACTTC (SEQ ID NO:133); JK1416-WDR72-R CAGGTCCCCAGACAACATCC (SEQ ID NO: 134) and the following probe: [5HEX]CTCCCCCTCATAAAGTTCTTAAAGGCCACCA[BHQ1a-Q] (SEQ ID NO: 135) .

[00357] Commercially available qPCR Human Reference Total RNA (Clontech, Mountain View, CA USA) was diluted in sterile water and serial dilutions used to validate the linearity of WDR72 primers (Fig.47). RNA was reverse-transcribed and amplified using the Path-ID™ Multiplex One-Step RT-PCR Kit (Life Technologies,) per the manufacturer's instructions in a reaction volume of 20µL and the following primer and probe concentrations: 800nM forward primer, 1200nM reverse primer and 135nM of TaqMan® probe. Results shown in Figure 47 demonstrate linearity of the PCR result using the primers for WDR72.

[00358] PCR was carried out on the ABI 7500 Real Time PCR System employing 7500 System SDS v2.0.5 software (Life Technologies) with the thermoprogram set for 48°C for 15 minutes, then 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Expression levels were normalized to GAPDH.

[00359] TissueScan Bladder Panel I cDNA arrays (OriGene) from normal bladder and bladder cancer samples were tested for WDR72 expression using the Path-ID™ Multiplex One-Step RT-PCR Kit (Life Technologies) per the manufacturer's instructions with reaction volumes, primer and probe concentrations equivalent to conditions used in initial primer validation. PCR was carried out on

the ABI 7500 Real Time PCR System using the same thermoprogram used for primer validation experiments. Expression levels were normalized to β -actin. Results are shown in Figure 48 and demonstrate elevated expression of WDR72 in bladder tumor samples compared to normal bladder samples.

[00360] Urine was collected from normal healthy donors and RNA was extracted using the SurePrep™ Urine Exfoliated Cell Purification Kit (Fisher, Waltham, MA USA) per the manufacturer's instructions. To compare PCR performance within the urine matrix, dilutions of qPCR Human Reference Total RNA (Clontech) were spiked into the urine after the cell lysis stage. PCR was run as previously described for WDR72 primer validation using the Path-ID™ Multiplex One-Step RT-PCR Kit (Life Technologies). Expression levels were normalized to GAPDH. The results shown in Figure 49 demonstrate that PCR can detect WDR72 found in human urine.

EXAMPLE 32

[00361] RNA commercially available from OriGene (Rockville, MD USA), Asterand (Detroit, MI USA) or Clontech was amplified in the FlexScript LDA Gene Expression Assay (Luminex, Austin, TX USA). RNA, 25ng of sample RNA or 2ng of qPCR Human Reference Total RNA (Clontech) was ligated to common linkers and amplified in LDA-PCR Primer Mix (Luminex) with EagleTaq® 2X PCR Master Mix (Roche Applied Biosystems, Indianapolis, IN USA) in 35 μ L reaction volumes. PCR was carried out on a DNA Engine thermocycler (MJ Research, Watertown, MA USA) set for 40°C for 10 minutes, then 95°C for 10 minutes, followed by 28 cycles of 95°C for 15 seconds, 60°C for 30 seconds and 72°C for 15 seconds, followed by a final extension hold at 72°C for 5 minutes. Products were hybridized to LDA-Microspheres in LDA Hybridization Buffer (Luminex) before incubation with streptavidin phycoerythrin (LDA-SAPE) in SAPE Buffer (Luminex). Fluorescence measurements were run on the MagPix instrument equipped with xPonent software. Fluorescent values from two runs were averaged to determine expression of RNA complementary to WDR72-specific probes.

[00362] The results shown in Figure 50 demonstrate that WDR72 is expressed at higher levels in Bladder Tumor samples compared to Normal Bladder samples.

SEQUENCES

SEQ ID NO. 1

Homo sapiens hypothetical LOC650517 (LOC650517), XR_019109.1

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SEQ ID NO. 2

Homo sapiens Fc receptor-like B (FCRLB), NM_001002901.2

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SEQ ID NO. 3

Homo sapiens interleukin 1, alpha (IL1A), NM_000575.3

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 2941 aaa

SEQ ID NO. 4

Homo sapiens S100 calcium binding protein A2 (S100A2), NM_005978.3

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SEQ ID NO. 5

Homo sapiens matrix metalloproteinase 11 (stromelysin 3) (MMP11), NM_005940.3

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SEQ ID NO. 6

Homo sapiens S100 calcium binding protein A7A (S100A7A), NM_176823.3

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 4201 attactgcct ctcaactagga gcatcattta tttaccatta ttttcaattt catattaaaa
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SEQ ID NO. 7

Homo sapiens UDP glucuronosyltransferase 1 family, polypeptide A6 (UGT1A6), transcript variant 2, NM_205862.1

1 agaaacctga agctcaggag aggagtcaact cccctggcag atgggtgggt gggccagaag
 61 cagataccag gctttctgac tcctgctcta ggattctcac cacgtactgg ctagacttat
 121 acttctcaaa tcttaatttc ctaaaaggccg gtcattgcca acatgggtctt cattggagggt
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SEQ ID NO. 8

Homo sapiens family with sequence similarity 83, member A (FAM83A), transcript variant 1, NM_032899.4

1 ggaaagccgg ctcaccttcg cctccccctg cggctgggag gagaggaaat atcccatggc
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 421 agggctgact ttagtgacaa cgagagtgcc cggctggcca cggacgccct cttggatggg
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 541 gtggaggccc agtacatcca ggcccaggcc agggagcccc cgtgtccccc agacacctg
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 661 ttccctgtgg cctcagaggg cagcgagccg gccctactgc acagctgggc ctgagctgag
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 781 aacatcagag acctcgcccg ccgctgcac acccggaata gccaggctct ggtcatcctg
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2701 taatcccaga actttgggat gccagggtgg ttggattacc tgagatcagg tggattacct
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2881 gcatcactgc actccagcat gggcaacaaa gcaagactcc gtcacagaaa aaaaaaaaaa
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SEQ ID NO. 9

Homo sapiens solute carrier family 1 (high affinity aspartate/glutamate transporter),
member 6 (SLC1A6), NM_005071.1

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1 gatagaccat gagcagccat ggcaacagcc tgttccttcg ggagagcggc cagcggctgg
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SEQ ID NO. 10

Homo sapiens uroplakin 3B (UPK3B), transcript variant 2, NM_182684.1

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481 ccggagacac tgggtgacat tccggcctcc ccacagctgc tgaccgatgg ccactacatg
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SEQ ID NO. 11

BX116033 NCI_CGAP_Lu24 Homo sapiens cDNA clone IMAGp998A155622, BX116033

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SEQ ID NO. 12

Homo sapiens matrix metalloproteinase 12 (macrophage elastase) (MMP12), NM_002426.2

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 1741 ttggactgag aaattatact tacttctggc ataactaaaa ttaagtatat atattttggc
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SEQ ID NO. 13

Homo sapiens keratin 16 (focal non-epidermolytic palmoplantar keratoderma) (KRT16),
 NM_005557.2

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 121 gaagggtccc tgccgcatcg gaggcggcat cgggggcggc tccagccgca tctcctccgt
 181 cctggccgga gggctcctgc gtgccccag cacctacggg ggcggcctgt ctgtctcctc
 241 tcgcttctcc tctgggggag cctgcgggct gggggcggc tatggcggtg gcttcagcag
 301 cagcagcagc tttggtagtg gcttcggggg aggatatggt ggtggccttg gtgctggctt
 361 cggtggtggc ttgggtgctg gctttggtgg tggttttgct ggtggtgatg ggcttctggt
 421 gggcagtgag aaggtgacca tgagaacct caatgaccgc ctggcctcct acctggacaa
 481 ggtgcgtgct ctggaggagg ccaacgccga cctggaagtg aagatccgtg actggtacca
 541 gaggcagcgg ccagtgaga tcaaagacta cagtccctac ttcaagacca tcgaggacct
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 1201 gatccaggga ctgattggca gtgtggagga gcagctggcc cagctacgct gtgagatgga
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 1501 gaactgagct gcctctacca cagcctcctg cccaccagct ggctcactt cctgaaggcc

1561 cgggtcagga cctgtctctc ctggcgcagt tcccagctat cccccctgct cctctgctgg
1621 tgggtgggcta ataaagctga ctttctgggt gatgcaaaaa aaaaaaaaaa aaaaaaaaaa
1681 aaaaaaaaa

SEQ ID NO. 14

Homo sapiens ubiquitin D (UBD), NM_006398.2

1 gattgcttga ggagagaagt atgtgatcag aaagcattct ttgtctatta actcctgccc
61 agcaaaagtg aaagaaaatt catgggagca tgcaagaaca aagagcacag caaagctgga
121 caaacacagc aatccaggca ggggatttcc aactcaactc tggtagtaa gctgcatgca
181 aagtcctttt tctgtctctg gtttctggcc ccttgtctgc agagatggct cccaatgctt
241 cctgcctctg tgtgcatgtc cgttccgagg aatgggattt aatgaccttt gatgccaaacc
301 catatgacag cgtgaaaaaa atcaaaagac atgtccggtc taagaccaag gttcctgtgc
361 aggaccaggt tcttttgctg ggctccaaga tcttaaagcc acggagaagc ctctcatctt
421 acggcattga caaagagaag accatccacc ttaccctgaa agtggtgaag cccagtgatg
481 aggagctgcc cttgtttctt gtggagtcag gtgatgaggc aaagaggcac ctccctcagg
541 tgcgaaggtc cagctcagtg gcacaagtga aagcaatgat cgagactaag acgggtataa
601 tccctgagac ccagattgtg acttgcaatg gaaagagact ggaagatggg aagatgatgg
661 cagattacgg catcagaaag ggcaacttac tcttcctggc atcttattgt attggagggg
721 gaccaccctg ggcattgggt gttggcaggg gtcaaaaagc ttatttcttt taatctctta
781 ctcaacgaac acatcttctg atgatttccc aaaattaatg agaatgagat gagtagagta
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901 aacacaatta attaagtgac atgattttta ctaatgtatt actgagacta gtaaataaat
961 ttttaagcca a

SEQ ID NO. 15

Homo sapiens UDP glucuronosyltransferase 1 family, polypeptide A6 (UGT1A6), transcript variant 1, NM_001072.3

1 aaagggtaaa attcagagca agggagaggt agacaggacc tgtgaaaagc agtggttagt
61 ttagggaaaa tacctaggag ccctgtgatt tggagagtga aaactcttta ttaccgttgt
121 tactttaact ctttccagga tggcctgcct ccttcgctca tttcagagaa tttctgcagg
181 ggttttcttc ttagcacttt ggggcatggg tgtagggtgac aagctgctgg tggctccctca
241 ggacggaagc cactggctta gtatgaagga tatagttgag gttctcagtg accgggggtca
301 tgagattgta gtggtggtgc ctgaagttaa tttgcttttg aaagaatcca aatactacac
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421 tggaaacaat cactttgctg agcgatcatt cctaactgct cctcagacag agtacaggaa
481 taacatgatt gttattggcc tgtacttcat caactgccag agcctcctgc aggacaggga
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601 ctgtgggggtg atcctggctg agtatttggg cctaccatct gtgtacctct tcaggggttt
661 tccgtgttcc ctggagcata cattcagcag aagcccagac cctgtgtcct acattcccag
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901 gttaagatat gactttgtgc ttgaatatcc taggccgggc atgcccacaa tgggtcttcat

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 1861 gccccagagt gctttaaaaa attctcttaa ataaaaataa tagactcgct agtcagtaaa
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 2341 gaagataatc attgcttatg tcaaattggag ctgaatttga taaaaacca aaatacagct
 2401 atgaagtgct gggcaagttt acttttttct tgatgtttcc tacaactaaa aataaattaa
 2461 taaatttata taaattctat ttaaaaaaaaa aaaaa

SEQ ID NO. 16

Homo sapiens S100 calcium binding protein A7 (S100A7), NM_002963.3

1 gtccaaacac acacatctca ctcatccttc tactcgtgac gcttcccagc tctggctttt
 61 tgaaagcaaa gatgagcaac actcaagctg agagggtccat aataggcatg atcgacatgt
 121 ttcacaaata caccagacgt gatgacaaga ttgagaagcc aagcctgctg acgatgatga
 181 aggagaactt ccccaacttc cttagtgccct gtgacaaaaa gggcacaaat tacctcgccg
 241 atgtctttga gaaaaaggac aagaatgagg ataagaagat tgatttttct gagtttctgt
 301 ccttgcctgg agacatagcc acagactacc acaagcagag ccatggagca gcgccctgtt
 361 ccgggggcag ccagtgacct agccccacca atgggcctcc agagacccca ggaacaataa
 421 aatgtcttct cccaccagaa aaaaaaaaaa

SEQ ID NO. 17

Homo sapiens WNT1 inducible signaling pathway protein 3 (WISP3), transcript variant 1, NM_003880.2

1 cctgagtccc gggaggaaaag tgctcgccca ttcttgacct gtgacacgct cactgcgaag
 61 gcaggttatt agaagagtcc catgaaagggt ggctccacgg tcccagcgac atgcaggggg

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121 tcctcttctc cactcttctg cttgctggcc tggcacagtt ctgctgcagg gtacagggca
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241 gtaaacagtt ttgtcactgg ccctgcaa at gccctcagca gaagccccgt tgcctcctg
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361 aaatctgcaa tgaagctgac ctctgtgacc cacacaaagg gctgtattgt gactactcag
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1141 ctggagatat attttctgag ctcaagattc tgtaaaacca agcaaagg ggaaggtta
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1261 aaaaaaaaaa aaaaaaaaaa aaaaaagaaa aaaaaaaaaa aaaaaaa

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SEQ ID NO. 18

Homo sapiens parathyroid hormone-like hormone (PTH LH), transcript variant 3,
NM_198964.1

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121 cgtgtaaca cactacttat cattgatgca tatataaaac cattttat ttgcattat
181 ttcagaggaa ggcctctga tttgtttctt tttcccttt ttgctctttc tggctgtgtg
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421 gaacatcagc tctccatga caaggggaag tccatccaag atttacggcg acgattcttc
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541 cctaactcca agcctctctc caacacaaag aaccaccccg tccgatttgg gtctgatgat
601 gagggcagat acctaaactc ggaaactaac aagggtggaga cgtacaaaga gcagccgctc
661 aagacacctg ggaagaaaaa gaaaggcaag cccgggaaac gcaaggagca ggaaaagaaa
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 1861 aa

SEQ ID NO. 19

Homo sapiens collagen, type X, alpha 1 (COL10A1), NM_000493.3

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3301 aaaaaaa

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SEQ ID NO. 20

Homo sapiens serpin peptidase inhibitor, clade B (ovalbumin), member 4 (SERPINB4),
NM_002974.2

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1 ccttcattcc acagacacac acagcctctc tgcccacctc tgcttctctt aggaacacag
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1321 ttgctggcaa  caacagattc  tcttggtcca  tatttctttt  ctatctcatc  ttgatgatga
1381 tagtcatcat  caagaattta  atgattaaaa  tagcatgcct  ttctctcttt  ctcttaataa
1441 gccacatat  aaatgtactt  ttccttccag  aaaaatttcc  cttgaggaaa  aatgtccaag
1501 ataagatgaa  tcatttaata  ccgtgtcttc  taaatttgaa  atataattct  gtttctgacc
1561 tgttttaaat  gaaccaaacc  aaatcatact  ttctcttcaa  atttagcaac  ctagaaacac
1621 acatttcttt  gaatttaggt  gatacctaaa  tccttcttat  gtttctaaat  tttgtgattc
1681 tataaaacac  atcatcaata  aaataatgac  ataaaatcaa  aaaaaaaaaa  aaaaaa

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SEQ ID NO. 21

Homo sapiens ubiquitin-conjugating enzyme E2C (UBE2C), transcript variant 6,
NM_181803.1

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1  aaacgcgggc  gggcgggccc  gcagtcctgc  agttgcagtc  gtgttctccg  agttcctgtc
61  tctctgccaa  cgccgcccgg  atggcttccc  aaaaccgcga  ccagccgcc  actagcgtcg
121  ccgccgcccg  taaaggagct  gagccgagcg  ggggcgccgc  ccggggtccg  gtgggcaaaa
181  ggctacagca  ggagctgatg  accctcatga  acccaacatt  gatagtcctt  tgaacacaca
241  tgctgccgag  ctctggaaaa  accccacagc  ttttaagaag  tacctgcaag  aaacctactc
301  aaagcaggtc  accagccagg  agccctgacc  caggctgccc  agcctgtcct  tgtgtcgtct
361  ttttaatttt  tccttagatg  gtctgtcctt  tttgtgattt  ctgtatagga  ctctttatct
421  tgagctgtgg  tatttttgtt  ttgtttttgt  cttttaaaat  aagcctcggt  tgagcccttg
481  tatattaaat  aaatgcattt  ttgtcctttt  ttagacaaaa

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SEQ ID NO. 22

Homo sapiens BTB (POZ) domain containing 16 (BTBD16), NM_144587.2

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1  aggaaaccaa  ggcaagctcc  cctgtcaaaa  gcaccttggc  ccataagaag  aaaaggggga
61  gccccagatg  tgatgagcgc  ttccaggctt  caggctcaga  aggcgcccc  agctctcctg
121  taactcagag  gccagtgtga  tgggagttcc  tccactcagc  acacttcccc  tgtaaacacg
181  cctgtggtgg  gcaaaagggc  tttggaacgg  ttgcttgtct  tttctctcct  gcgtaatttc
241  cactttcatt  catgataatg  tcgaacacgc  acaaagctcg  gctggaacgc  cgggtcactg
301  gctcaaccaa  ccggtggcgt  ttgcccacac  agcctttctc  tggggacctg  ctctcacttt
361  cccagatgtg  caaggctctg  agcatagact  ttgaggaagc  tttgaggaac  ccagacaggt
421  tatgcatttc  acaaatccag  aagtttttct  ttgagaattt  caagaacaag  gacatccaaa
481  gtggggaagc  agatgtgatt  ctcgagtgcc  tgggcttcaa  atgggagctc  catcagcccc
541  agctttttca  gtctgagacc  ttggccaagc  tctacctgaa  agccctggcg  cagggcacca
601  cacacccctt  gagggagctg  gaggagcttc  tgcgagctca  atcacctaag  aagaccaaag

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661 aaaaatcccc tgcaaagagg atcatcatctt ccttgaagat caatgaccca ctggctacta
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 781 aagacctact gggagtgtctg gcttccgccc acatcctcca gttcagtggc ctgtttcaaa
 841 ggtgcgtgga tgtgatgata gccagactca agccaagcac catcaagaaa ttctacgagg
 901 ccggctgcaa gtacaaggaa gagcagctca ccaccggctg cgagaagtgg ctggaaatga
 961 acttggttcc tctagggggg acgcagatcc acctccacaa aatcccacag gacctgtcc
 1021 acaaagtgtc gaagtcccc aggttattta cctttagtga attccatctt ctgaaaacaa
 1081 tgcttttgtg ggtcttcttg caactgaact acaagattca ggcaattccg acttatgaaa
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 1201 gacggagctt gaggcgctc ttcctctgct tgctgtctgca cggcatcacc aaaggcaagg
 1261 atctggaggt gctgcggcac cttaacttct tcccagagtc atggctcgac caggttacag
 1321 tcaaccatta ccacgcactg gagaatgggg gcgacatggc ccacctgaaa gatcttaaca
 1381 cccaggtgtg gagatttggg ctgctcttta accaggagaa tacaacttat tcgaaaacga
 1441 ttgctctata tggattcttc ttttaagataa agggactcaa acatgatact acctcttata
 1501 gtttttacat gcagagaata aagcacacag acctggaatc tccctctgcg gtctacgagc
 1561 acaaccacgt cagcctgcga gcggcacgcc tgggtgaagta tgagatcaga gcagaggccc
 1621 tgggtgacgg caagtggcag gaggttcagga caaaccagat caagcagaag tttgggttga
 1681 ccacgtcatc ctgcaaaagc cataccttga aaatccaaac tgtgggcac ccaatctatg
 1741 taagttttgc attcatcttc ccagcatctt gacagtttcc agaagaatct atgggatttt
 1801 cccccactg gtctgcataa aagaaaataa aatgacataa aagggagc

SEQ ID NO. 23

Homo sapiens stratifin (SFN), NM_006142.3

1 gagagacaca gagtccggca ttgggtcccag gcagcagtta gcccgcggcc cgctgtgtg
 61 tccccagagc catggagaga gccagtctga tccagaaggc caagctggca gagcaggccc
 121 aacgtatga ggacatggca gccttcatga aaggcgccgt ggagaagggc gaggagctct
 181 cctgcgaaga gcgaaacctg ctctcagtag cctataagaa cgtgggtgggc ggccagaggg
 241 ctgcctggag ggtgctgtcc agtattgagc agaaaagcaa cgaggagggc tcggaggaga
 301 aggggcccga ggtgcgtgag taccgggaga aggtggagac tgagctccag ggcgtgtgcg
 361 acaccgtgtc gggcctgtctg gacagccacc tcatcaagga ggccggggac gccgagagcc
 421 gggctctcta cctgaagatg aagggtgact actaccgcta cctggccgag gtggccaccg
 481 gtgacgacaa gaagcgcac attgactcag cccggtcagc ctaccaggag gccatggaca
 541 tcagcaagaa ggagatgccg cccaccaacc ccatccgcct gggcctggcc ctgaactttt
 601 ccgtcttcca ctacgagatc gccaacagcc ccgaggaggc catctctctg gccaaagacca
 661 ctttcgacga ggccatggct gatctgcaca ccctcagcga ggactcctac aaagacagca
 721 ccctcatcat gcagctgtctg cgagacaacc tgacactgtg gacggccgac aacgccgggg
 781 aagagggggg cgaggctccc caggagcccc agagctgagt gttgcccgc accgccccgc
 841 cctgccccct ccagtcccc accctgccga gaggactagt atgggggtggg agggccccacc
 901 cttctcccct aggcgtgtt cttgtctcaa agggctccgt ggagagggac tggcagagct
 961 gaggccacct ggggctgggg atcccactct tcttgagct gttgagcgca cctaaccact
 1021 ggtcatgccc ccacccctgc tctccgcacc cgcttctctc cgaccccagg accaggctac
 1081 ttctcccctc ctcttgctc cctcctgccc ctgctgcctc tgatcgtagg aattgaggag
 1141 tgtcccgctc tgtggctgag aactggacag tggcaggggc tggagatggg tgtgtgtgtg
 1201 tgtgtgtgtg tgtgtgtgtg tgtgcgcgcg cgccagtga agaccgagat tgagggaaa

1261 catgtctgct ggggtgtgacc atgtttcctc tcaataaagt tccccgtgta cactcaaaaa
 1321 aaaaaaaaaa aaaaaa

SEQ ID NO. 24

Homo sapiens misc_RNA (KRT17P3), XR_015626.2

1 gcgtgtgaac ccccacagcc ctacacaact tggggccctt ctctcccca gcccttctcc
 61 tgtgtgcctg cctcctgccg ccgccaccat gaccaccacc atccaccagt tcacctctc
 121 cagctccatc aagggtcctt ccggcctggg agtggctcat cccgcacctc ctgccggctg
 181 tctggcggcc tgggtgccgg ctctgcagg ctgggatctg ctgggtggct gggcagtgcc
 241 ctccggggtg gcagctattc cagctgctac tgctttggct ctggcgggtg ctatggcagc
 301 agctttgggg gcgttgatgg gctgctggcc ggaggtgaga aggccaccat gcagaacctc
 361 aatgaccgcc tggcctccta cctggacaag atgcgcgccc tggaggaggc caacactgag
 421 ctggaggtga agatccgtga ctggtaccag aggcaggccc cggggcccgcc cctgtactac
 481 agccagtact acaggacaat cgaggagctg cagaacaaga tcctcacagc caccttgaaac
 541 aatgccaaca tcctgctaca gattgacaat gcccatctgg ctgctgctga cttctgcacc
 601 aagtttgaga cagagcaggc cctgcgcctg agtgtggagg ccgccatcaa tggcctgcgc
 661 aggtgtctgg atgggctgac cttggccaga gccgacctgg agatgcagat tgagaacctc
 721 aaggaggagc tggcctacct gaagaagaac cagcaggagg agataaacgc cctgcgaggc
 781 caggtgggcg gtgagatcaa tgtggagatg gacgctgccc caggcatgga cctgagccgc
 841 atcctgaacg agatgcatga gtagtacgag aagatggcag agaagaaccg caaggatgcc
 901 aaggattggt tcttcagcaa gacagaggaa ctgaaacgcg aggtggctac caacagcgaa
 961 ctggtccaga ggggcaagag caagatttcg gagctctggc gcaccatgca ggccttgag
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 1081 gagagccgct actgcatgca gctgtcccag atccaggggc tgatcggcag tgtggaggag
 1141 cagctggccc agcttcgctg cgagacggag cagcagaacc agcagtacaa gatcctgctg
 1201 gacgtgaaga cgcggctgga gcaggagatc gccacctacc accgcctgct agagggcgag
 1261 gatgcccacc tgactcagta caagaaagaa cataagcatc ttcgtggctg a

SEQ ID NO. 25

Homo sapiens vestigial like 1 (Drosophila) (VGLL1), NM_016267.2

1 ctagaggggc ggaaagtaac aaggaggtgg ggggtacaaat cctcagctcc tgcttccgca
 61 agcactaacc tgctctgaag tgagccaggc agctctggcc atcttttccc agccacagaa
 121 tcaggtgatg gtccagaatt aagagctgtc acctgtgtca ttcactcaca atggaagaaa
 181 tgaagaagac tgccatccgg ctgccccaaag gcaaacagaa gcctataaag acggaatgga
 241 attcccgggtg tgtccttttc acctacttcc aaggggacat cagcagcgta gtggatgaac
 301 acttctccag agctctgagc aatatcaaga gccccagga attgaccccc tcgagtcaga
 361 gtgaaggtgt gatgctgaaa aacgatgata gcatgtctcc aaatcagtgg cgttactcgt
 421 ctccatggac aaagccacaa ccagaagtac ctgtcacaaa ccgtgccgcc aactgcaact
 481 tgcatgtgcc tgggtcccatg gctgtgaatc agttctcacc gtccctggct aggagggcct
 541 ctgttcggcc tggggagctg tggcatttct cctccctggc gggcaccagc tccttagagc
 601 ctggctactc tcaccccttc cccgctcggc acctggttcc agagccccag cctgatggga
 661 aacgtgagcc tctcctaagt ctctccagc aagacagatg cctagcccggt cctcaggaat
 721 ctgccgccag ggagaatggc aaccctggcc agatagctgg aagcacaggg ttgctcttca

781 acctgcctcc eggctcagtt cactataaga aactatatgt atctcgtgga tctgccagta
 841 ccagccttcc aaatgaaact ctttcagagt tagagacacc tgggaaatac tcacttacac
 901 caccaaacca ctggggccac ccacatcgat acctgcagca tcttttagtca agttggagga
 961 gaaagacaac acttggtcta agacacggca gcaagacatc cctgcatatt gttccagata
 1021 aaaatgaaag ctgctcacac ccacttgctt cccaatctg ttaaacagct tcgtgtctag
 1081 tatgagctca gtacttgccc tgtgaaaatc ccagaagccc ccgctgtcaa tgttccccat
 1141 ccacaccctg cttgctcctg tgtaacagct cagatgatga ataataataa aactgtactt
 1201 ttttggatgg tgaaaaaaaa aaaaaaaaaa aa

SEQ ID NO. 26

Homo sapiens cadherin 3, type 1, P-cadherin (placental) (CDH3), NM_001793.3

1 ccgctgtag ccgctgttgaggagcgac gggcctgctt caaagctttg ggataacagc
 61 gcctccgggg gataatgaat gcggagcctc cgttttcagt cgacttcaga tgtgtctcca
 121 cttttttccg ctgtagccgc aaggcaagga aacattttctc ttcccgtaact gaggaggctg
 181 aggagtgcac tgggtgttct tttctcctct aaccagaaac tgcgagacag aggctgagtc
 241 cctgtaaaga acagctccag aaaagccagg agagcgcagg agggcatccg ggaggccagg
 301 aggggttcgc tggggcctca accgcaccca catcggtccc acctgcgagg gggcgggacc
 361 tcgtggcgct ggaccaatca gcacccacct gcgctcacct ggctcctcc cgctggctcc
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 541 ctctttctcc aggtttgctg gctgcagtgc gcggcctccg agccgtgcgc ggcggtcttc
 601 agggaggctg aagtgcactt ggaggcggga ggcgcggagc aggagcccg ccaggcgctg
 661 gggaaagtat tcatgggctg ccctgggcaa gagccagctc tgtttagcac tgataatgat
 721 gacttcaactg tgcggaatgg cgagacagtc caggaaagaa ggtcactgaa ggaaaggaat
 781 ccattgaaga tcttcccatc caaacgtatc ttacgaagac acaagagaga ttgggtggtt
 841 gctccaatat ctgtccctga aaatggcaag ggtcccttcc ccagagact gaatcagctc
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 1441 gcagtggcag tagtgagat ccttgatgcc aatgacaatg ctcccatgtt tgacccccag
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 1561 actgatctgg acgcccccaa ctcaccagcg tggcgtgcca cctaccttat catgggcggt
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 1681 accaggaagg gtttggtttt tgaggccaaa aaccagcaca cctgtacgt tgaagtgacc
 1741 aacgaggccc cttttgtgct gaagctccca acctccacag ccaccatagt ggtccacgtg
 1801 gaggatgtga atgaggcacc tgtgtttgtc ccacctcca aagtgcgttg ggtccaggag
 1861 ggcacccca ctggggagcc tgtgtgtgtc tacactgcag aagacctga caaggagaat
 1921 caaaagatca gctaccgcat cctgagagac ccagcagggt ggctagccat ggaccagac

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1981 agtgggcagg tcacagctgt gggcaccctc gaccgtgagg atgagcagtt tgtgaggaac
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2221 ctgtctcccc acacctcccc tttccaggcc cagctcacag atgactcaga catctactgg
2281 acggcagagg tcaacgagga aggtgacaca gtggtcttgt ccctgaagaa gttcctgaag
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2401 gtgatcaggg ccactgtgtg cgactgccat ggccatgtcg aaacctgccc tggacctggg
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2641 gactatgaca tcaccagct ccaccgaggt ctggaggcca ggccggaggt ggttctccgc
2701 aatgacgtgg caccaaccat catcccgaca cccatgtacc gtccctcgcc agccaacca
2761 gatgaaatcg gcaactttat aattgagaac ctgaaggcgg ctaacacaga cccacagcc
2821 ccgcctacg acacctctt ggtgttcgac tatgagggca gcggtccga cgccgctcc
2881 ctgagctccc tcacctctc cgctccgac caagaccaag attacgatta tctgaacgag
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3301 gcctgctgtg actgacctac agtggacttt ctctctggaa tggaaccttc ttaggcctcc
3361 tgggtgcaact taattttttt ttttaatgct atcttcaaaa cgttagagaa agttcttcaa
3421 aagtgcagcc cagagctgct gggccactg gccgtcctgc atttctgggt tccagacccc
3481 aatgcctccc attcgatgg atctctgctg ttttatactg agtgtgecta ggttgccctc
3541 tattttttat tttccctgtt gcgttgctat agatgaaggg tgaggacaat cgtgtatatg
3601 tactagaact tttttattaa agaaactttt cccagaaaaa aaaaaaaaa

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SEQ ID NO. 27

Homo sapiens chemokine (C-X-C motif) ligand 10 (CXCL10), NM_001565.2

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1 ggggggagaca ttctcaatt gcttagacat attctgagcc tacagcagag gaacctccag
61 tctcagcacc atgaatcaaa ctgccattct gatttgctgc cttatcttcc tgactctaag
121 tggcattcaa ggagtacctc tctctagaac tgtacgtgt acctgcatca gcattagtaa
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601 gtaagctcta ctgaggtgct atgttcttag tggatgttct gacctgctt caaatatttc
661 cctcaccttt cccatcttcc aagggtacta aggaatcttt ctgctttggg gtttatcaga
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781 ctttacttca tggacttcca ctgccatcct cccaaggggc ccaaattctt tcagtggcta
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901 tattcttatt taatgaaaga ctgtacaaag tagaagtctt agatgtatat atttcctata
961 ttgttttcag tgtacatgga ataacatgta attaagtact atgtatcaat gagtaacagg
1021 aaaattttta aaatacagat agatatatgc tctgcatgtt acataagata aatgtgctga
1081 atggttttca aaataaaaat gaggtactct cctggaaata ttaagaaaga ctatctaaat
1141 gttgaaagat caaaagggtta ataaagtaat tataactaaa aaaa

SEQ ID NO. 28

Homo sapiens S100 calcium binding protein A9 (calgranulin B) (S100A9), NM_002965.2

1 aaacactctg tgtggctcct cggctttggg acagagtgca agacgatgac ttgcaaaatg
61 tcgcagctgg aacgcaacat agagaccatc atcaacacct tccaccaata ctctgtgaag
121 ctggggcacc cagacaccct gaaccagggg gaattcaaag agctgggtgcg aaaagatctg
181 caaaattttc tcaagaagga gaataagaat gaaaagggtca tagaacacat catggaggac
241 ctggacacaa atgcagacaa gcagctgagc ttcgaggagt tcatcatgct gatggcgagg
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481 cctgcctcta cccaaccagg gccccggggc ctgttatgtc aaactgtctt ggctgtgggg
541 ctaggggctg gggccaaata aagtctcttc ctccaa

SEQ ID NO. 29

Homo sapiens gap junction protein, beta 2, 26kDa (GJB2), NM_004004.4

1 ggggtgctgt taaaaggcgc cagggcggga gacaggtgtt gcggccccgc agcgccccgc
61 cgctcctctc cccgactcgg agccccctcg cggcgccccg cccaggaccc gcctaggagc
121 gcaggagccc cagcgcagag accccaacgc cgagaccccc gccccggccc cgccgcgctt
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841 aattgtgtta tttgctaatt agatattgtt ctgggaagtc aaaaaagcca gtttaacgca
901 ttgccaggtt gtttagattaa gaaatagaca gcatgagagg gatgaggcaa cccgtgctca
961 gctgtcaagg ctcatctgct agcatttccc aacacaaaga ttctgacctt aatgcaacc
1021 atttgaacc cctgtaggcc tcagggtgaa ctccagatgc cacaatggag ctctgctccc
1081 ctaaagcctc aaaacaaagg cctaattcta tgccctgtctt aattttcttt cacttaagtt
1141 agttccactg agaccccagg ctgttagggg ttattgggtg aaggtacttt catattttaa

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1201 acagaggata tcggcatttg tttctttctc tgaggacaag agaaaaaagc caggttccac
1261 agaggacaca gagaagggtt gggtgtcctc ctgggggttct ttttgccaac tttccccacg
1321 ttaaagggtga acattgggttc tttcatttgc tttggaagtt ttaatctcta acagtggaca
1381 aagttaccag tgccttaaac tctgttacac tttttggaag tgaaaacttt gtagtatgat
1441 aggttatttt gatgtaaaga tgttctggat accattatat gtccccctg tttcagaggc
1501 tcagattgta atatgtaaat ggtatgtcat tcgctactat gatttaattt gaaatatggt
1561 cttttggtta tgaatacttt gcagcacagc tgagaggctg tctgttgtat tcattgtggt
1621 catagcacct aacaacattg tagcctcaat cgagtgagac agactagaag ttcctagtga
1681 tggcttatga tagcaaatgg cctcatgtca aatattttaga tgtaattttg tgtaagaaat
1741 acagactgga tgtaccacca actactacct gtaatgacag gcctgtccaa cacatctccc
1801 ttttccatga ctgtggtagc cagcatcgga aagaacgctg atttaaagag gtcgcttggg
1861 aattttattg acacagtacc atttaatggg gaggacaaaa tggggcaggg gagggagaag
1921 tttctgtcgt taaaaacaga tttgaaaga ctggactcta aagtctgttg attaaagatg
1981 agctttgtct acttcaaaag tttgtttgct tacccttca gcctccaatt ttttaagtga
2041 aaatatagct aataacatgt gaaaagaata gaagctaagg tttagataaa tattgagcag
2101 atctatagga agattgaacc tgaatattgc cattatgctt gacatggttt ccaaaaaatg
2161 gtactccaca tatttcagtg agggtaagta ttttctgtt gtcaagaata gcattgtaaa
2221 agcattttgt aataataaag aatagcttta atgatatgct tgtaactaaa ataattttgt
2281 aatgtatcaa atacatttaa aacattaaaa tataatctct ataataattt a

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SEQ ID NO. 30

Homo sapiens tyrosine hydroxylase (TH), transcript variant 2, NM_000360.3

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1 cggacctcca cactgagcca tgcccacccc cgacgccacc acgccacagg ccaagggtctt
61 ccgcagggcc gtgtctgagc tggacgccaa gcaggcagag gccatcatgt ccccgcggtt
121 cattgggcgc aggcagagcc tcatcgagga cgcccgaag gagcgggagg cggcggtggc
181 agcagcggcc gctgcagtcc cctcggagcc cggggacccc ctggaggctg tggcctttga
241 ggagaaggag gggaaggccg tgctaaacct gctcttctcc ccgagggcca ccaagccctc
301 ggcgtgttcc cgagctgtga aggtgtttga gacgtttgaa gccaaaatcc accatctaga
361 gaccgcggcc gccagaggc cgcgagctgg gggcccccac ctggagtact tcgtgcgcct
421 cgaggtgcgc cgaggggacc tggccgcctt gctcagtggg gtgcgccagg tgtcagagga
481 cgtgcgcagc ccgcggggc ccaaggctcc ctggttccca agaaaagtggt cagagctgga
541 caagtgtcat cacctgggtca ccaagttcga ccctgacctg gacttggacc acccgggtctt
601 ctcgaccag gtgtaccgcc agcgcaggaa gctgattgct gagatcgctt tccagtacag
661 gcacggcgac ccgattcccc gtgtggagta caccgccgag gagattgcca cctggaagga
721 ggtctacacc acgctgaagg gcctctacgc cacgcacgcc tgcggggagc acctggaggc
781 ctttgctttg ctggagcgct tcagcggcta ccggaagac aatatcccc agctggagga
841 cgtctccgc ttcctgaagg agcgacggg cttccagctg cggcctgtgg ccggcctgct
901 gtcgcgccgg gacttcctgg ccagcctggc cttccgcgtg ttccagtga cccagtatat
961 ccgccacgg tctctgccc tgcactcccc tgagccggac tgctgccacg agctgctggg
1021 gcacgtgccc atgtggccg accgcacctt cgcgcagttc tcgcaggaca ttggcctggc
1081 gtcctgggg gctcggatg aggaaattga gaagctgtcc acgctgtact ggttcacggt
1141 ggagttcggg ctgtgtaagc agaacgggga ggtgaaggcc tatggtgccg ggctgctgtc
1201 ctctacggg gagctcctgc actgcctgtc tgaggagcct gagattcggg ctttcgaccc
1261 tgaggctgcg gccgtgcagc cctaccaaga ccagacgtac cagtcagtct acttcgtgtc

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1321 tgagagcttc agtgacgcca aggacaagct caggagctat gcctcacgca tccagcgcgc
 1381 cttctccgtg aagttcgacc cgtacacgct ggccatcgac gtgctggaca gccccaggc
 1441 cgtgcggcgc tccctggagg gtgtccagga tgagctggac acccttgccc atgcgctgag
 1501 tgccattggc taggtgcacg gcgtccctga gggcccttcc caacctcccc tggctcctgca
 1561 ctgtcccgga gctcaggccc tggtaggggg ctgggtcccg ggtgcccccc atgccctccc
 1621 tgctgccagg ctcccactgc ccctgcacct gcttctcagc gcaacagctg tgtgtgccccg
 1681 tggtagagggt gtgctgcctg tggtagaggtc ctgtcctggc tcccagggtc ctgggggctg
 1741 ctgcaactgcc ctccgccctt ccctgacact gtctgctgcc ccaatcacccg tcacaataaa
 1801 agaaactgtg gtctcta

SEQ ID NO. 31

Homo sapiens glutathione S-transferase M1 (GSTM1), transcript variant 1, NM_000561.2

1 ctctgagccc tgctcgggtt aggctgtct gcggaatccg caccaaccag caccatgccc
 61 atgatactgg ggtactggga catccgcggg ctggcccacg ccatccgcct gctcctggaa
 121 tacacagact caagctatga ggaaaagaag tacacgatgg gggacgctcc tgattatgac
 181 agaagccagt ggctgaatga aaaattcaag ctgggcctgg actttcccaa tctgccctac
 241 ttgattgatg gggctcacaa gatcacccag agcaacgcca tcttgtgcta cattgccgc
 301 aagcacaacc tgtgtgggga gacagaagag gagaagattc gtgtggacat tttggagaac
 361 cagaccatgg acaaccatat gcagctgggc atgatctgct acaatccaga atttgagaaa
 421 ctgaagccaa agtacttgga ggaactccct gaaaagctaa agctctactc agagtttctg
 481 gggaaagcggc catggtttgc aggaacaag atcacttttg tagattttct cgtctatgat
 541 gtccttgacc tccaccgtat atttgagccc aagtgccttg acgccttccc aaatctgaag
 601 gacttcatct cccgctttga gggcttgag aagatctctg cctacatgaa gtccagccgc
 661 ttctctccaa gacctgtgtt ctcaaagatg gctgtctggg gcaacaagta gggccttgaa
 721 ggccaggagg tgggagttag gagcccatat tcagcctgct gcccaggctg tgcagcgcag
 781 ctggactctg catcccagca cctgcctcct cgttcctttc tctgtttat tcccatcttt
 841 actccaaga cttcattgtc cctcttact cccctaaac cctgtccca tgcaggccct
 901 ttgaagcctc agctaccac tatccttctg gaacatcccc tcccatcatt acccttccct
 961 gcactaaagc cagcctgacc ttccttctct ttagtggttg tgtctgcttt aaagggcctg
 1021 cctggccctc cgctgtgga gctcagcccc gagctgtccc cgtgttgcat gaaggagcag
 1081 cattgactgg tttacaggcc ctgtcctgc agcatggtcc ctgccttagg cctacctgat
 1141 ggaagtaaa cctcaaccac a

SEQ ID NO. 32

Homo sapiens absent in melanoma 2 (AIM2), NM_004833.1

1 tcagccaatt agagctccag ttgtcactcc taccacact gggcctgggg gtgaagggaa
 61 gtgtttatta ggggtacatg tgaagccgtc cagaagtgtc agagtctttg tagctttgaa
 121 agtcacctag gttatattggg catgctctcc tgagtcctct gctagttaag ctctctgaaa
 181 agaaggtggc agaccgggtt tgctgatcgc cccagggatc aggaggctga tcccaaagtt
 241 gtcagatgga gagtaaatac aaggagatac tcttgctaac aggctggat aacatcactg
 301 atgaggaact ggataggttt aagtcttttc tttcagacga gtttaatat gccacaggca
 361 aactacatac tgcaaacaga atacaagtag ctaccttgat gattcaaaat gctggggcgg
 421 tgtctgcagt gatgaagacc attcgtattt ttcagaagtt gaattatatg cttttggcaa

481 aacgtcttca ggaggagaag gagaaagttg ataagcaata caaatcggt acaaaaccaa
 541 agccactaag tcaagctgaa atgagtcctg ctgcatctgc agccatcaga aatgatgtcg
 601 caaagcaacg tgctgcacca aaagtctctc ctcatgttaa gcctgaacag aaacagatgg
 661 tggcccagca ggaatctatc agagaagggt ttcagaagcg ctgtttgcc aattatggtag
 721 tgaaagcaaa gaagcccttc acgtttgaga cccaagaagg caagcaggag atgtttcatg
 781 ctacagtggc tacagaaaag gaattcttct ttgtaaaagt ttttaataca ctgctgaaag
 841 ataaattcat tccaaagaga ataattataa tagcaagata ttatcggcac agtggtttct
 901 tagaggtaaa tagcgctca cgtgtgtag atgctgaatc tgacaaaaag gttaatgtcc
 961 cgctgaacat tatcagaaaa gctggtgaaa cccgaagat caacacgctt caaactcagc
 1021 cccttggaac aattgtgaat ggtttgtttg tagtccagaa ggtaacagaa aagaagaaaa
 1081 acatattatt tgacctagt gacaacactg ggaaaatgga agtactgggg gttagaaacg
 1141 aggacacaat gaaatgtaag gaaggagata aggttcgact tacattcttc aactgtcaa
 1201 aaaatggaga aaaactacag ctgacatctg gagttcatag caccataaag gttattaag
 1261 ccaaaaaaaaa aacatagaga agtaaaaagg accaattcaa gccactgggt ctaagcagca
 1321 ttttaattgaa gaatatgtga tacagcctct tcaatcagat tgtaagttac ctgaaagctg
 1381 cagttcacag gctcctctct ccaccaaatt aggatagaat aattgctgga taaacaaatt
 1441 cagaatatca acagatgatc acaataaaca tctgtttctc attcc

SEQ ID NO. 33

Homo sapiens neuromedin U (NMU), NM_006681.1

1 agtcctgcgt cggggcccg aggcgcagca gggcaccagg tggagacca gctacgcgtg
 61 gcgcagcgca ggcgcctag caccgagcct cccgcagccg ccgagatgct gcgaacagag
 121 agctgccgcc ccaggtcgcc cgccggacag gtggccgcgg cgccccgct cctgctgctg
 181 ctgctgctgc tcgcctggtg cgcgggcgcc tgccgaggtg ctccaatatt acctcaagga
 241 ttacagcctg aacaacagct acagttgtgg aatgagatag atgatacttg ttcgtctttt
 301 ctgtccattg attctcagcc tcaggcatcc aacgcactgg aggagctttg ctttatgatt
 361 atgggaatgc taccaaagcc tcaggaacaa gatgaaaaag ataatactaa aaggttctta
 421 tttcattatt cgaagacaca gaagttgggc aagtcaaatg ttgtgtcgtc agttgtgcat
 481 ccgttgctgc agctcgttcc tcacctgcat gagagaagaa tgaagagatt cagagtggac
 541 gaagaattcc aaagtcctt tgcaagtcaa agtcgaggat attttttatt caggccacgg
 601 aatggaagaa ggtcagcagg gttcatttaa aatggatgcc agctaatttt ccacagagca
 661 atgctatgga atacaaaatg tactgacatt ttgttttctt ctgaaaaaaaa tccttgctaa
 721 atgtactctg ttgaaaatcc ctgtgttgtc aatgttctca gttgtaacaa tgttgtaaat
 781 gttcaatttg ttgaaaatta aaaaatctaa aaataaa

SEQ ID NO. 34

Homo sapiens melanoma antigen family A, 10 (MAGEA10), transcript variant 2, NM_021048.3

1 gagaagcgag gttctcgttc tgagggacag gcttgagatc ggctgaagag agcggggcca
 61 ggctctgtga ggaggcaagg gaggtgagaa ccttgctctc agagggtgac tcaagtcaac
 121 acagggaacc cctcttttct acagacacag tgggtcgcag gatctgacaa gagtccaggt
 181 tctcagggga caggagagc aagaggtcaa gagctgtggg acaccacaga gcagcactga
 241 aggagaagac ctgcctgtgg gtccccatcg cccaagtcct gccacactc ccacctgcta

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301 ccctgatcag agtcatcatg cctcgagetc caaagcgtca gcgctgcatg cctgaagaag
361 atcttcaatc ccaaagttag acacagggcc tcgagggtgc acaggctccc ctggctgtgg
421 aggaggatgc ttcatcatcc acttccacca gtcctctctt tccatcctct tttccctcct
481 cctcctcttc ctcctcctcc tctgctatc ctctaatacc aagcacccca gaggaggttt
541 ctgctgatga tgagacacca aatcctcccc agagtgtcga gatagcctgc tctccccct
601 cggctgttgc ttcctttcca ttagatcaat ctgatgaggg ctccagcagc caaaaggagg
661 agagtccaag caccctacag gtctgtccag acagtgagtc tttaccaga agtgagatag
721 atgaaaagg gactgatttg gtgcagtttc tgctcttcaa gtatcaaatg aaggagccga
781 tcacaaaggc agaaatactg gagagtgtca taaaaaatta tgaagaccac ttcctttgt
841 tgttttagtga agcctccgag tgcagtgtgc tggctcttgg cattgatgta aaggaagtgg
901 atcccactgg ccactccttt gtctgtgca cctccctggg cctcacctat gatgggatgc
961 tgagtgatgt ccagagcatg cccaagactg gcattctcat acttacctta agcataatct
1021 tcatagaggg ctactgcacc cctgaggagg tcatctggga agcactgaat atgatggggc
1081 tgtatgatgg gatggagcac ctcatttatg gggagcccag gaagctgctc acccaagatt
1141 ggggtgcagga aaactacctg gagtaccggc aggtgcctgg cagtgatect gcacggtatg
1201 agtttctgtg ggggtccaagg gctcatgctg aaattaggaa gatgagtctc ctgaaatttt
1261 tggccaagg aaatgggagt gatccaagat cttcccact gtggtatgag gaggctttga
1321 aagatgagga agagagagcc caggacagaa ttgccaccac agatgatact actgccatgg
1381 ccagtgcagg ttctagcgtc acaggtagct tctcctacce tgaataaagt aagacagatt
1441 cttactgtg ttttaaaagg caagtcaa ataccatgat tttactcata tgtggaatct
1501 aaaaaaaaa aaaaaaaaa

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SEQ ID NO. 35

Homo sapiens Down syndrome critical region gene 8 (DSCR8), transcript variant 2,
NM_203428.1

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1 accccaccct aatcttggtt tgcaaatagg cttcccactt ggcagggggc gtcttgtcca
61 ctcgtttctg taaacatggg tggcaaaaag agaagatgga gctgccattt agaacatgcc
121 taatcccagc ttcatcttgc tgagcaaaaa tgaaggagcc tggacccaac tttgttactg
181 tgagaaaggg tcttcattca ttcaagatgg catttggtta gcacctacta caaaccttgg
241 aaatcaagaa agttctggaa tgatgaagct gttcatgcca agaccgaaag tgctggccca
301 gtatgagtcc attcagttca tgccgtgaca attttcttgg aactcctttt tattgttagt
361 tctcacttgt ttccatattt agtgaatgta catttaattg caaagctgtc attaataaaa
421 attcttatag tacctcaaaa a

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SEQ ID NO. 36

Homo sapiens gametocyte specific factor 1 (GTSF1), NM_144594.1

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1 agcggagggg tgtgtccacc gagcacttgg attcagcttc ttcatttcca acatggaaga
61 aacttacacc gactccctgg accctgagaa gctattgcaa tgcccctatg aaaaaacca
121 tcaaatcagg gcttgcagg ttccttatca tcttatcaag tgcagaaaga atcatcctga
181 tgttgcaagc aaattggcta cttgtccctt caatgctcgc caccaggttc ctcgagctga
241 aattagtcat catatctcaa gctgtgatga cagaagttgt attgagcaag atgttgtcaa
301 ccaaaccagg agccttagac aagagactct ggctgagagc acttggcagt gccctccttg
361 cgatgaagac tgggataaag atttgtggga gcagaccagc accccatttg cctggggcac

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421 aactcactac tctgacaaca acagccctgc gagcaacata gttacagaac ataagaataa
481 cctggcttca ggcatgagag ttcccaaatc tctgccgtat gttctgccat ggaaaaacaa
541 tggaaatgca cagtaactga atacctatct catcaaagtc cagaccctag aagactgttg
601 cttcttcttc taccagtggg ttctcatttt cctcctaate taattataga atagtaaact
661 cctgtgact ttccaaactg acaagcacac ttttttcctc ccccttgaa tctctattta
721 atgcaagaac cctcactc agaagcttcc aaataaacct ttgatacaga aaaaaaaaaa
781 aaaaa

SEQ ID NO. 37

Homo sapiens keratin 6A (KRT6A), NM_005554.3

1 atatttcata ctttctaga aactgggtgt gatctcactg ttggtaaagc ccagcccttc
61 ccaacctgca agctcacctt ccaggactgg gccagccca tgctctccat atataagctg
121 ctgccccgag cctgattcct agtcctgctt ctcttccctc tctcctccag cctctcacac
181 tctctcagc tctctcatct cctggaaaca tggccagcac atccaccacc atcaggagcc
241 acagcagcag ccgccggggt ttcagtgcc aactcagccag gctccctggg gtcagccgct
301 ctggcttcag cagcgtctcc gtgtcccgct ccaggggcag tgggtggctg ggtggtgcat
361 gtggaggagc tggctttggc agccgcagtc tgtatggcct ggggggctcc aagaggatct
421 ccattggagg gggcagctgt gccatcagtg gcggctatgg cagcagagcc ggaggcagct
481 atggctttgg tggcgccggg agtggatttg gtttcgggtg tggagccggc attggctttg
541 gtctgggtgg tggagccggc ctgtctggtg gctttggggg ccctggcttc cctgtgtgcc
601 cccctggagg catccaagag gtcaccgta accagagtct cctgactccc ctcaacctgc
661 aaatcgatcc caccatccag cgggtgcggg ctgaggagcg tgaacagatc aagaccctca
721 acaacaagtt tgctccttc atcgacaagg tgcggttcct ggagcagcag aacaaggttc
781 tggaaacaaa gtggaccctg ctgcaggagc agggcaccaa gactgtgagg cagaacctgg
841 agccgttggt cgagcagtac atcaacaacc tcaggaggca gctggacagc attgtcgggg
901 aacggggccg cctggactca gagctcagag gcatgcagga cctggtggag gacttcaaga
961 aaaaatatga ggatgaaatc aacaagcgca cagcagcaga gaatgaattt gtgactctga
1021 agaaggatgt ggatgctgcc tacatgaaca aggttgaact gcaagccaa gacagacctc
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1141 cccacatctc agacacatct gtggtgctgt ccatggacaa caaccgcaac ctggacctgg
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1261 aggctgagtc ctggtaccag accaagtaag aggagctgca ggtcacagca ggcagacatg
1321 gggacgacct gcgcaacacc aagcaggaga ttgctgagat caaccgcatg atccagaggc
1381 tgagatctga gatcgaccac gtcaagaagc agtgcgcaa cctgcaggcc gccattgctg
1441 atgctgagca gcgtggggag atggccctca aggatgcaa gaacaagctg gaagggtg
1501 aggatgccct gcagaaggcc aagcaggacc tggcccggct gctgaaggag taccaggagc
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1621 gtgaggagtg caggctgaat ggcaaggcg ttggacaagt caacatctct gtggtgcagt
1681 ccaccgtctc cagtggctat ggcggtgcca gtggtgtcgg cagtggctta ggcctgggtg
1741 gaggaagcag ctactcctat ggcagtggtc ttggcggttg aggtggcttc agttccagca
1801 gtggcagagc cattgggggt ggcctcagct ctggtggagg cggcagttcc accatcaagt
1861 acaccaccac ctctcctcc agcaggaaga gctataagca ctaaagtgcg tctgctagct
1921 ctcggtccca cagtctcag gccctctct ggctgcagag cctctctctc aggttgctt
1981 tctctcctg gcctccagtc tcccctgctg tcccaggtag agctgggtat ggatgcttag

2041 tgcctcact tttctctct ctctctatac catctgagca cccattgctc accatcagat
2101 caacctctga ttttacatca tgatgtaatc accactggag cttcactggt actaaattat
2161 taattttcttg cctccagtgt tctatctctg aggctgagca ttataagaaa atgacctctg
2221 ctctttttca ttgcagaaaa ttgccagggg cttattttcag aacaacttcc acttactttc
2281 cactggctct caaactctct aacttataag tgttgatgaac cccaccacag gcagtatcca
2341 tgaaagcaca agtgactagt cctatgatgt acaaagcctg tatctctgtg atgattttctg
2401 tgctcttcgc tgtttgcaat tgctaaataa agcagattta taatacaata

SEQ ID NO. 38

Homo sapiens chemokine (C-X-C motif) ligand 9 (CXCL9), NM_002416.1

1 atccaatata ggagtgactt ggaactccat tctatcacta tgaagaaaag tgggtgttctt
61 ttctctcttg gcatcatctt gctggttctg attggagtgc aagggaacccc agtagtgaga
121 aagggtcgct gttcctgcat cagcaccaac caagggacta tccacctaca atccttgaaa
181 gaccttaaac aatttgcccc aagcccttcc tgcgagaaaa ttgaaatcat tgctacactg
241 aagaatggag ttcaaacatg tctaaacca gattcagcag atgtgaagga actgattaaa
301 aagtgggaga aacaggtcag ccaaaaagaa aagcaaaaaga atgggaaaaa acatcaaaaa
361 aagaaagttc tgaaagtctg aaaatctcaa cgttctcgtc aaaagaagac tacataagag
421 accacttcac caataagtat tctgtgttaa aaatgttcta ttttaattat accgctatca
481 ttccaaagga ggatggcata taatacaaag gcttattaat ttgactagaa aatttaaaac
541 attactctga aattgtaact aaagttagaa agttgatttt aagaatccaa acgttaagaa
601 ttgttaaagg ctatgattgt ctttgttctt ctaccacca ccagttgaat ttcacatgc
661 ttaaggccat gattttagca ataccatgt ctacacagat gttcacccaa ccacatccca
721 ctcaaacag ctgcttgga gagcagccct aggttccac gtactgcagc ctccagagag
781 tatctgaggc acatgtcagc aagtccaaag cctgttagca tgctgggtgag ccaagcagtt
841 tgaaattgag ctggacctca ccaagctgct gtggccatca acctctgtat ttgaatcagc
901 ctacaggcct cacacacaat gtgtctgaga gattcatgct gattgttatt gggatcacc
961 actggagatc accagtgtgt ggctttcaga gcctccttcc tggctttgga agccatgtga
1021 ttccatcttg cccgctcagg ctgaccaact tatttctttt tgttccccct tgcttcattc
1081 aagtcagctc ttctccatcc taccacaatg cagtgccttt cttctctcca gtgcacctgt
1141 catatgctct gatttatctg agtcaaactc tttctcatct tgtcccaaac accccacaga
1201 agtgctttct tctcccaatt catcctcact cagtccagct tagttcaagt cctgcctctt
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CLAIMS

1. A method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of a panel of markers encoded by the gene WDR72 and one or more genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, or a complement thereof; c) contacting a non-cancerous cell, with the one or more agents from b); and d) comparing the expression level of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6, or a complement thereof in the sample obtained from the subject with the expression level of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof, in the non-cancerous cell, wherein a higher level of expression of the panel of markers encoded by the gene WDR72 and one or more markers encoded for by the genes chosen from LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the sample compared to the non-cancerous cell indicates that the subject has bladder cancer.

2. The method of claim 1, wherein the subject is a human.
3. The method of claim 1, wherein the sample is a bodily fluid.
4. The method of claim 3, wherein the bodily fluid is blood.
5. The method of claim 3, wherein the bodily fluid is serum.
6. The method of claim 3, wherein the bodily fluid is urine.
7. The method of claim 1, wherein the sample is a tissue sample.
8. The method of claim 1, wherein the sample is comprised of cells.
9. The method of claim 1, wherein the one or more agents is a nucleic acid.
10. The method of claim 1, wherein the one or more agents is a protein.
11. The method of claim 10, wherein the protein is an antibody.

12. A method of detecting bladder cancer in a subject comprising a) obtaining a sample from a subject b) contacting the sample obtained from the subject with one or more agents that detect expression of one or more of the markers encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof; c) contacting a non-cancerous cell with the one or more agents from b); and d) comparing the expression level of one or more of the markers encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the non-cancerous cell, wherein a higher level of expression in the sample of one or more of the markers

encoded by genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6 or a complement thereof in the sample obtained from the subject compared to the non-cancerous cell indicates that the subject has bladder cancer.

13. The method of claim 12, wherein the subject is a human.

14. The method of claim 12, wherein the sample is a bodily fluid.

15. The method of claim 14, wherein the bodily fluid is blood.

16. The method of claim 14, wherein the bodily fluid is serum.

17. The method of claim 14, wherein the bodily fluid is urine.

18. The method of claim 12, wherein the sample is a tissue sample.

19. The method of claim 12, wherein the sample is comprised of cells.

20. The method of claim 12, wherein the one or more agents is a nucleic acid.

21. The method of claim 12, wherein the one or more agents is a protein.

22. The method of claim 21, wherein the protein is an antibody.

23. A kit for detecting bladder cancer in sample comprising one or more agents that bind to a marker encoded for by one or more genes chosen from WDR72, LOC650517, FCRLB, IL1A, S100A2, MMP11, S100A7A, UGT1A6, FAM83A, SLC1A6, UPK3B, BX116033, MMP12, KRT16, UBD, UGT1A6, S100A7, WISP3, PTHLH, COL10A1, SERPINB4, UBE2C, BTBD16, SFN, KRT17P3, VGLL1, CDH3, CXCL10, S100A9, GJB2, TH, GSTM1, AIM2, NMU, MAGEA10, DSCR8, GTSF1, KRT6A, CXCL9, SERPINB5, DSCR6.

24. The kit of claim 23, wherein the one or more agents is a nucleic acid.

25. The kit of claim 23, wherein the one or more agents is a protein.

26. The kit of claim 23, wherein the protein is an antibody.

- 27. The kit of claim 23, wherein the sample is obtained from a human.
- 28. The kit of claim 23, wherein the sample is a bodily fluid.
- 29. The kit of claim 23, wherein the bodily fluid is blood.
- 30. The kit of claim 23, wherein the bodily fluid is serum.
- 31. The kit of claim 23, wherein the sample is tissue.
- 32. The kit of claim 23, wherein the sample is comprised of cells.

Figure 2

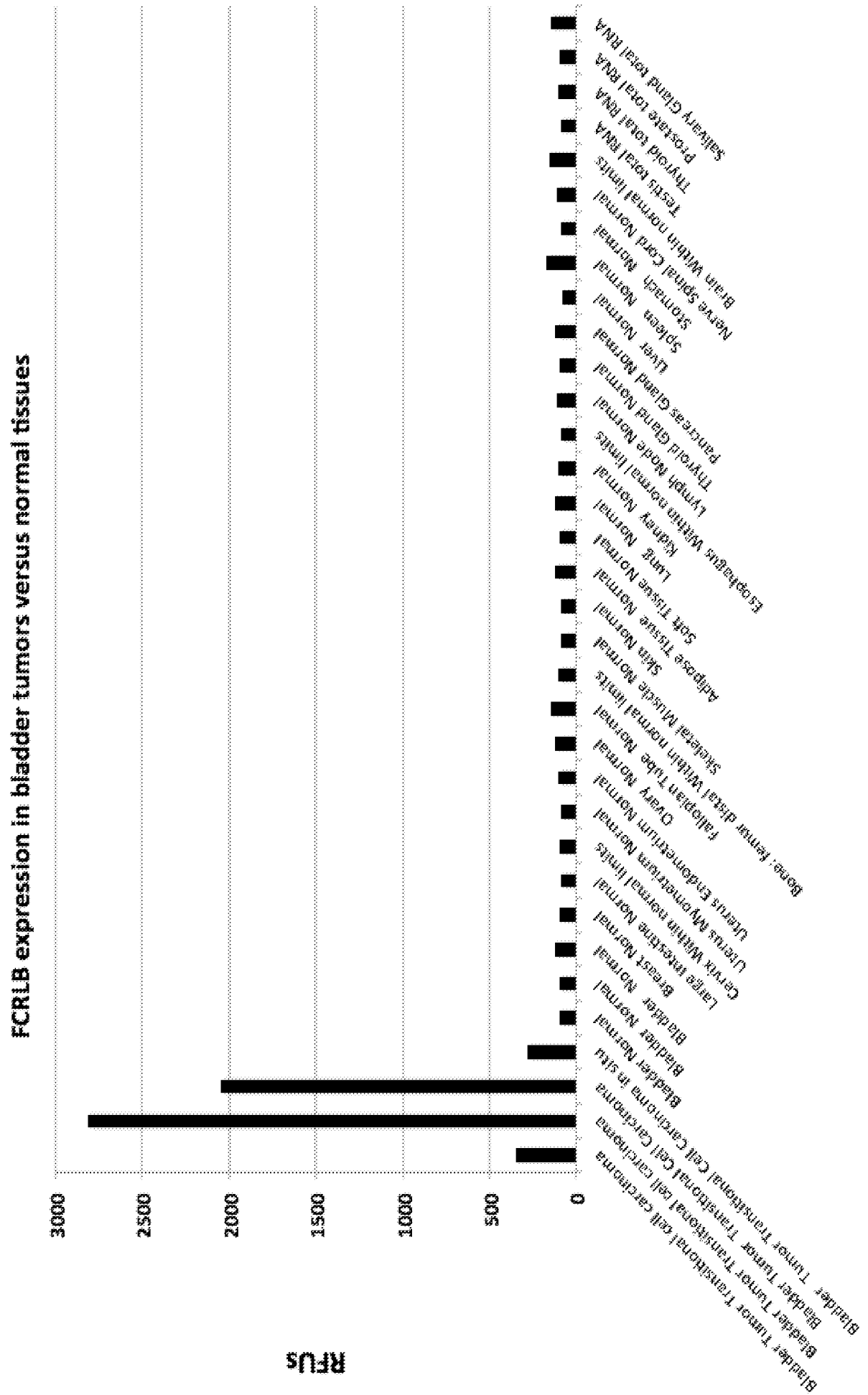


Figure 3
IL1A expression in Bladder tumors versus normal tissues

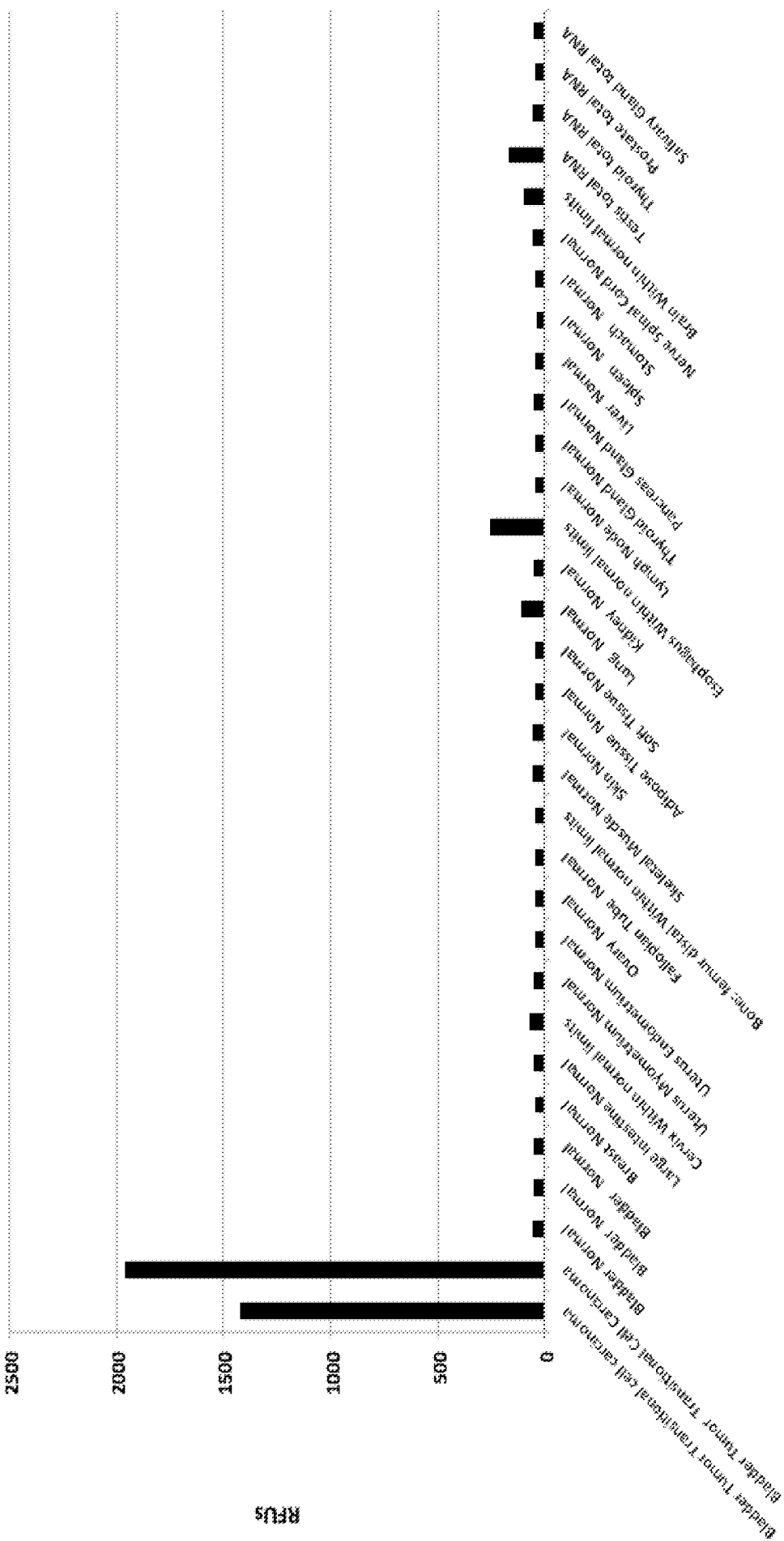


Figure 4

S100A2 expression in Bladder tumors versus normal tissues

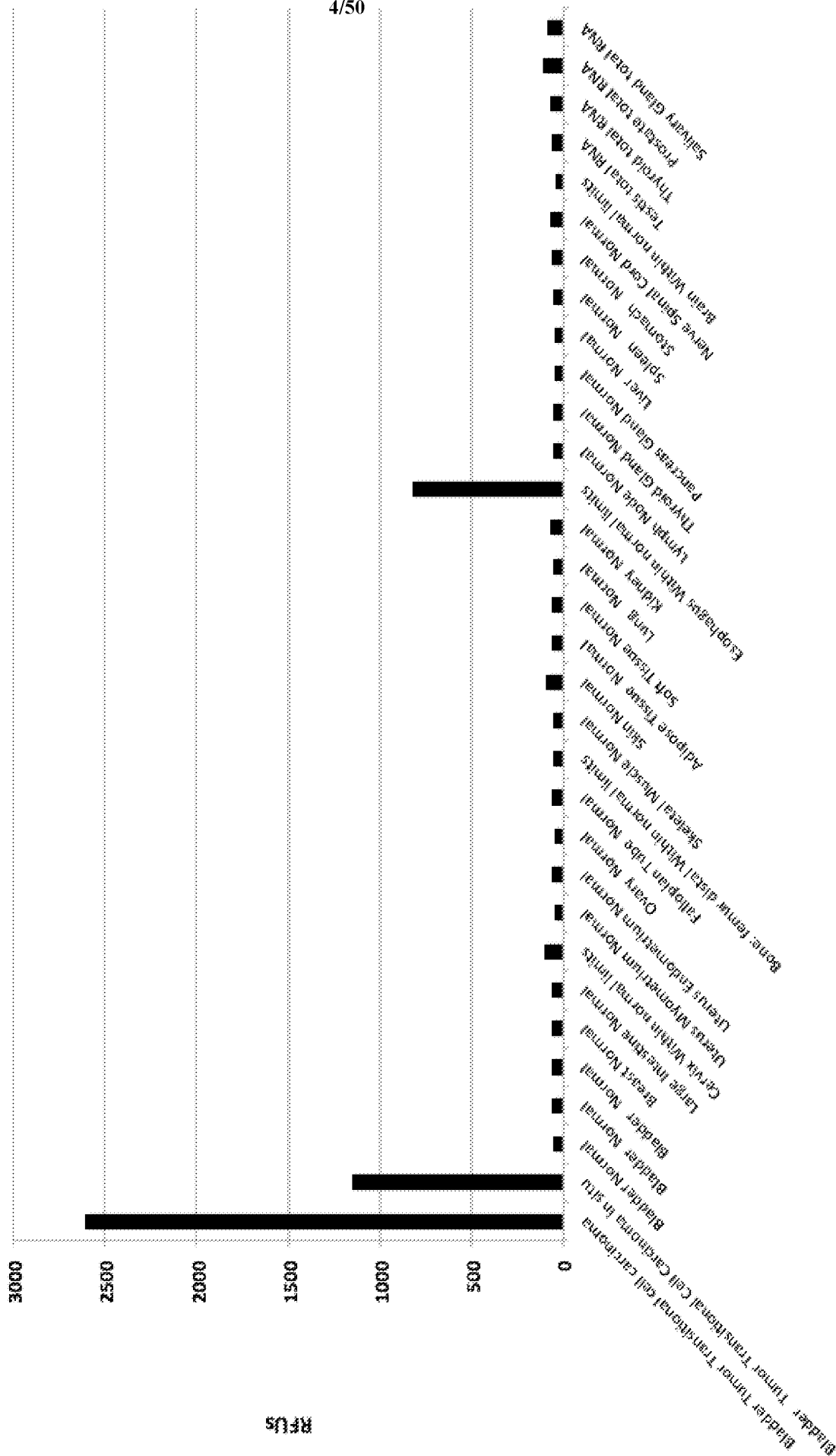


Figure 5
MMP11 expression in bladder tumors versus normal tissues

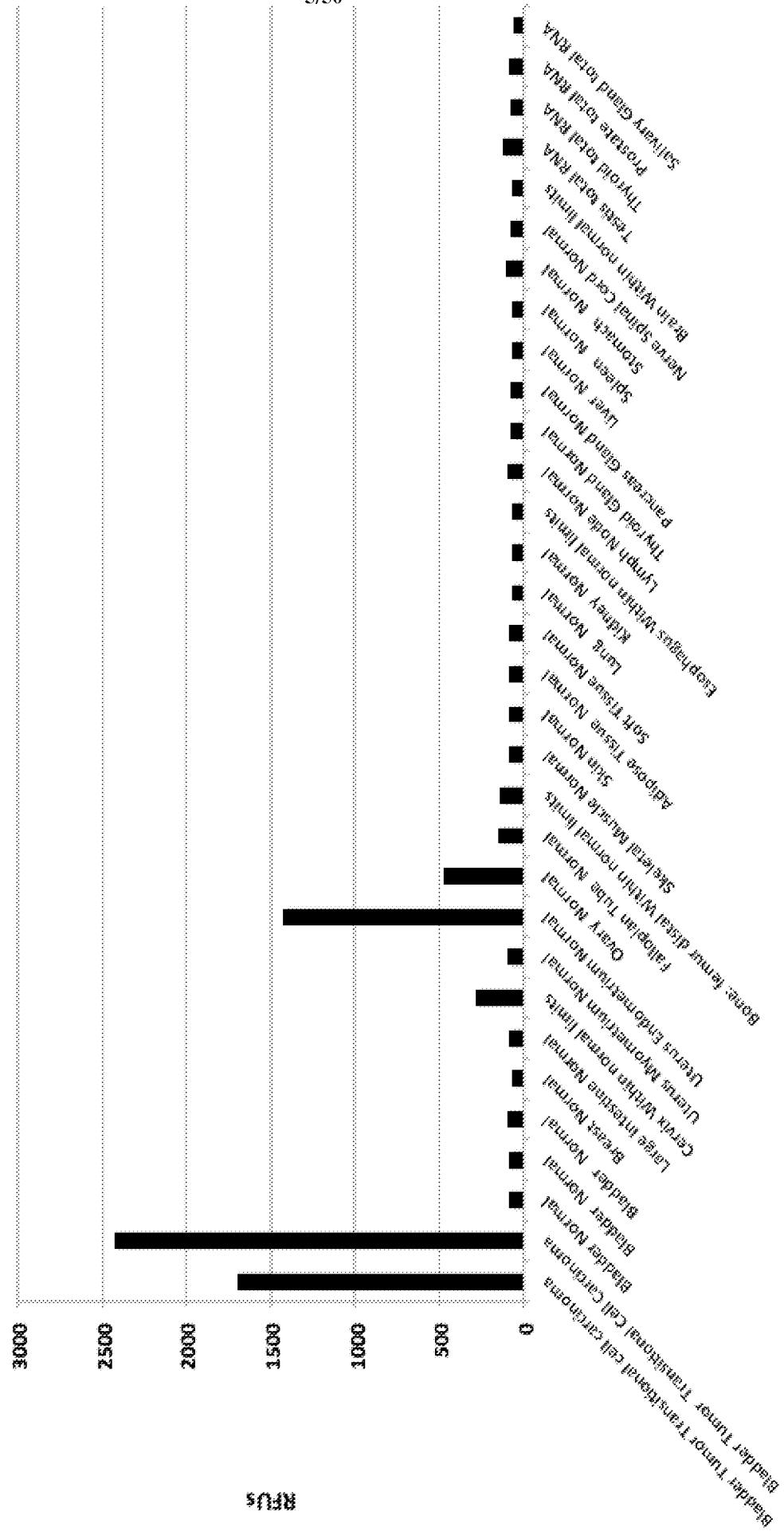


Figure 6

S100A7A expression in Bladder tumors versus normal tissues



Figure 7

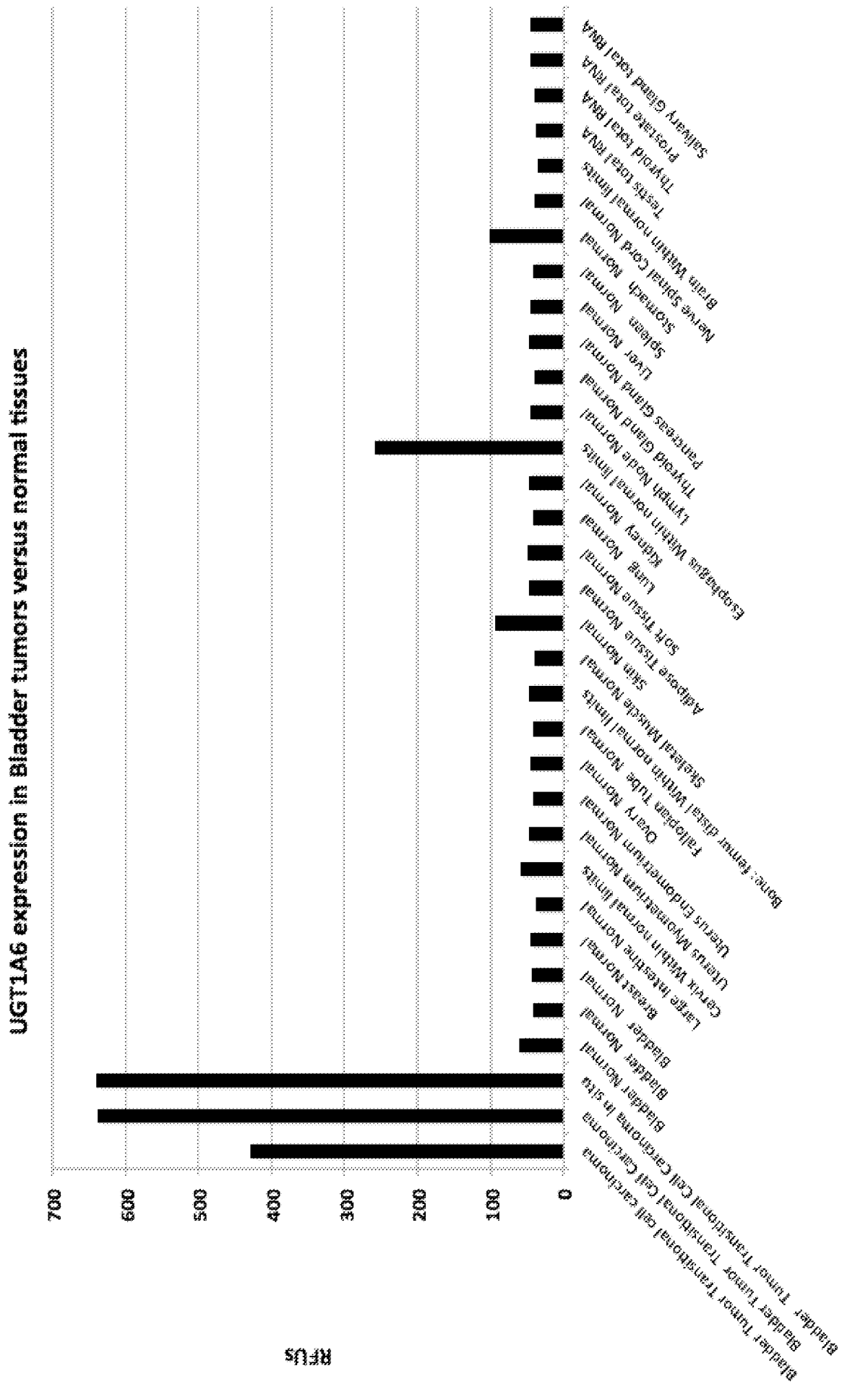


Figure 8

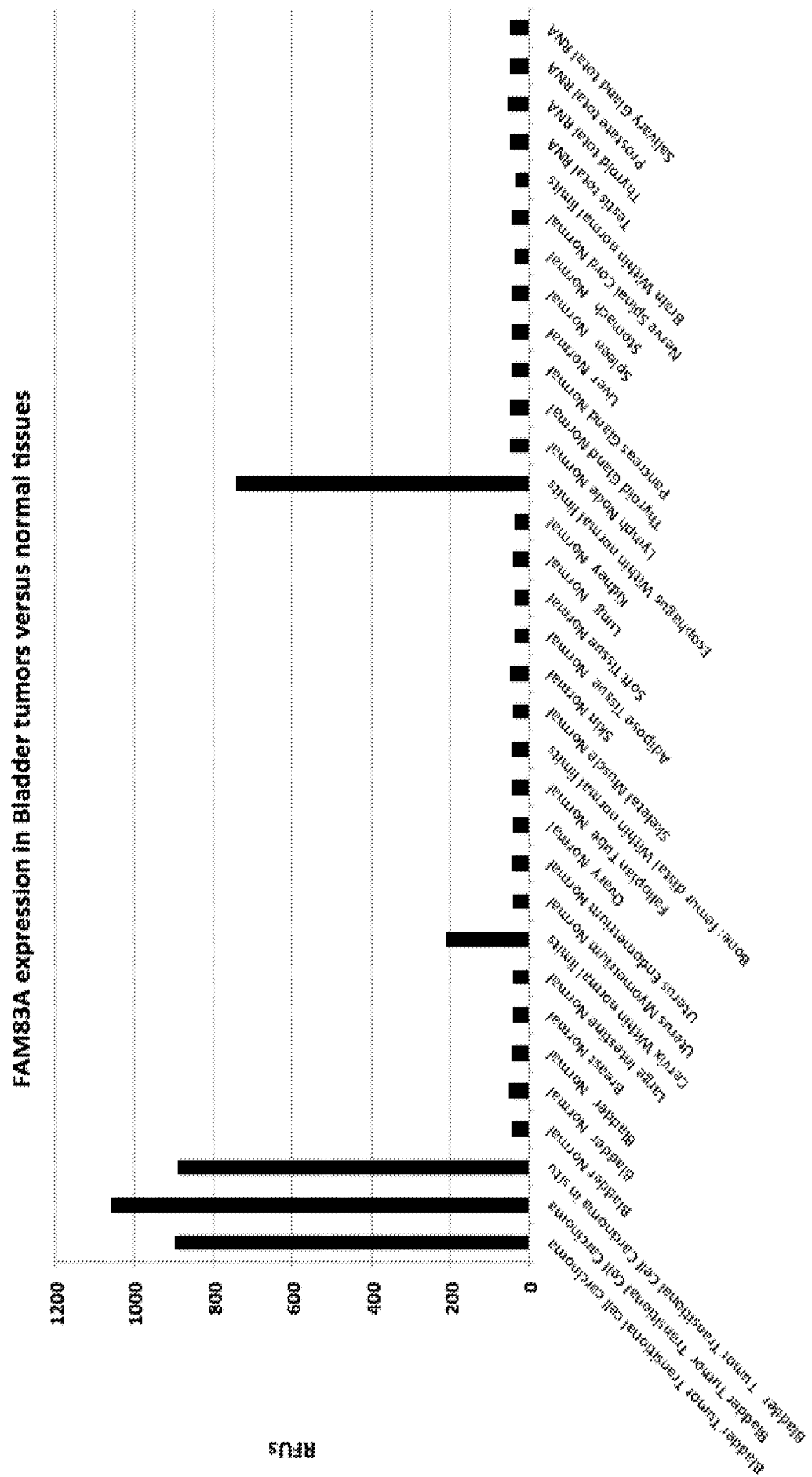


Figure 9

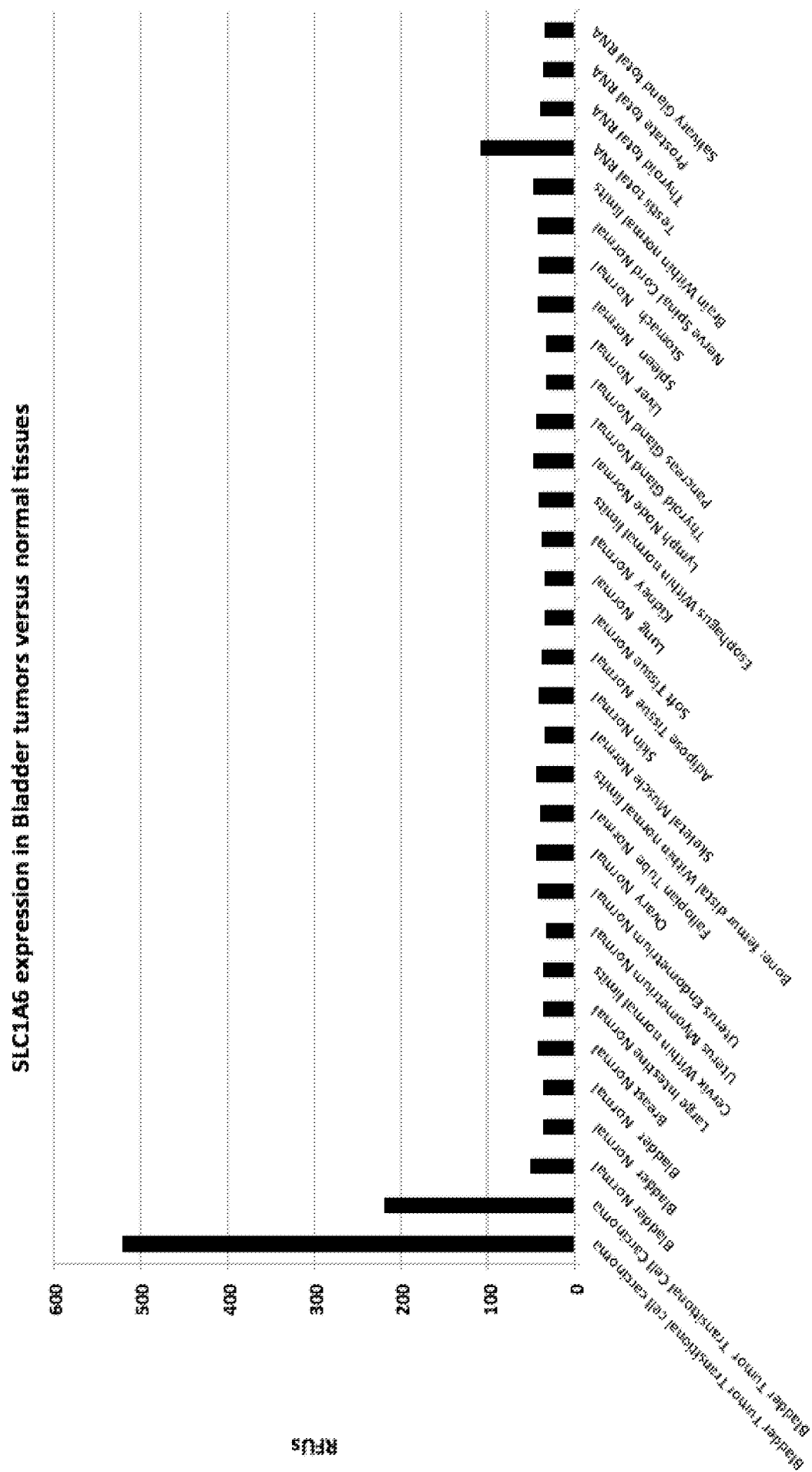


Figure 12

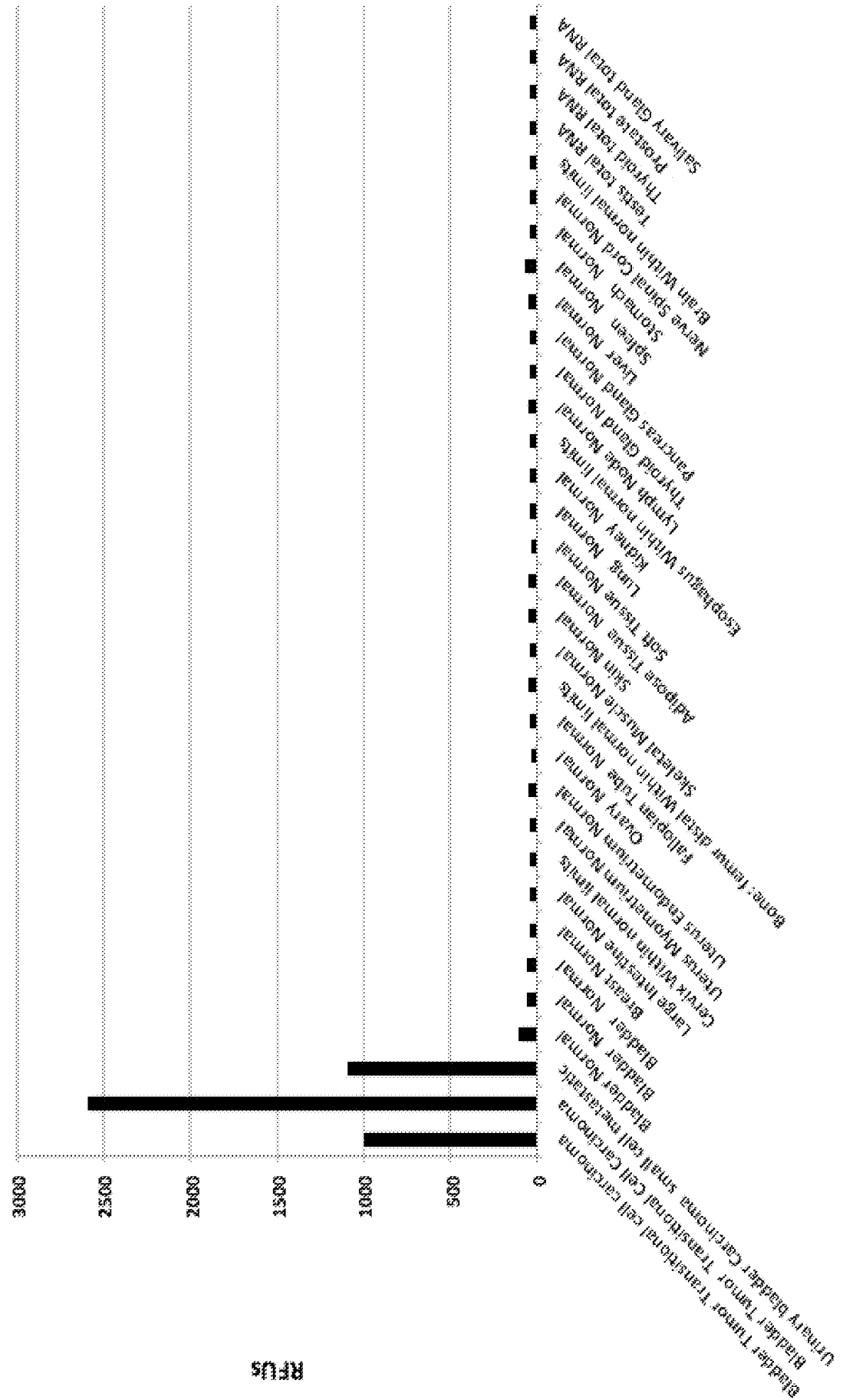


Figure 13
KRT16 expression in Bladder tumors versus normal tissues

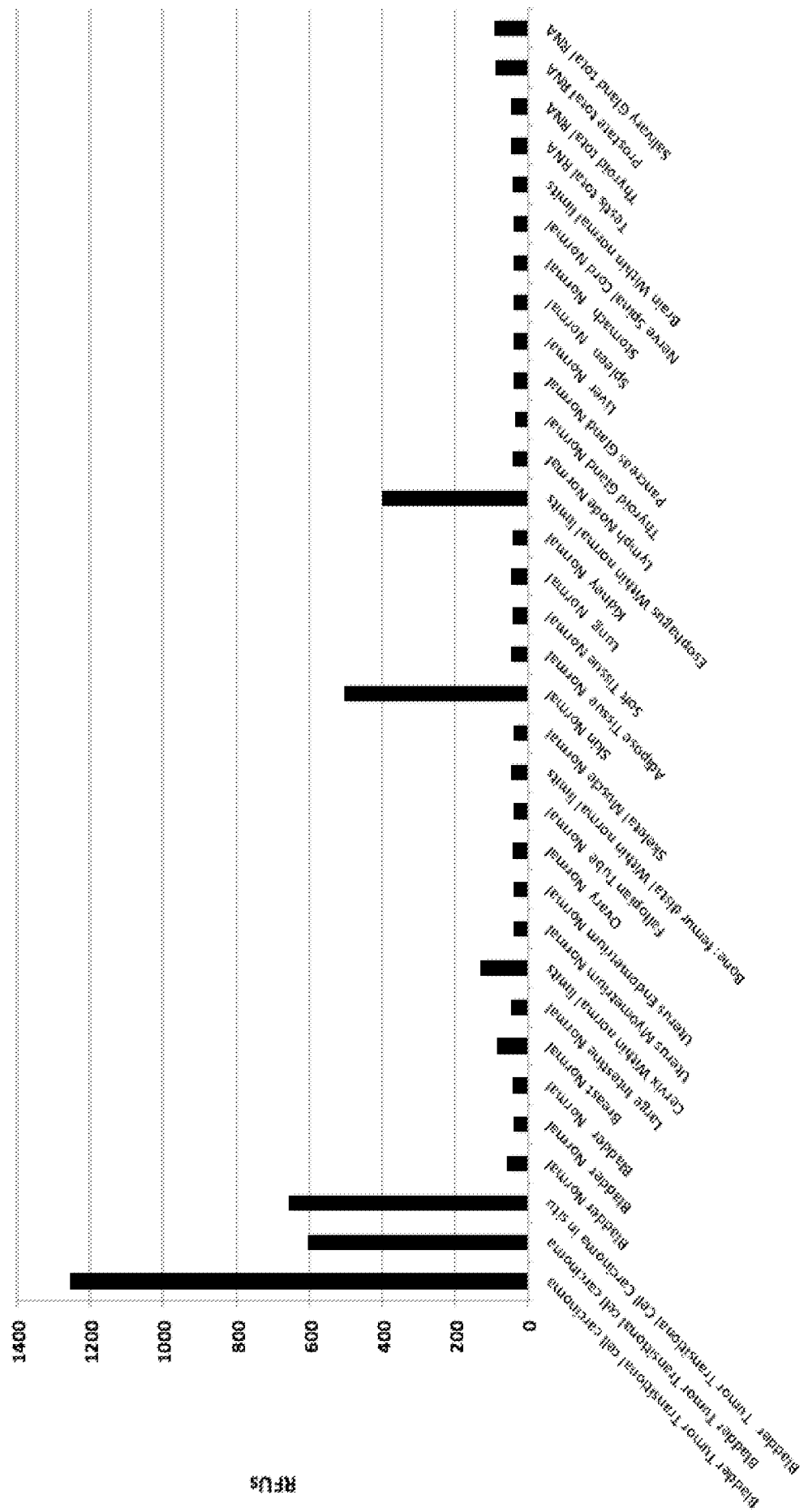


Figure 14

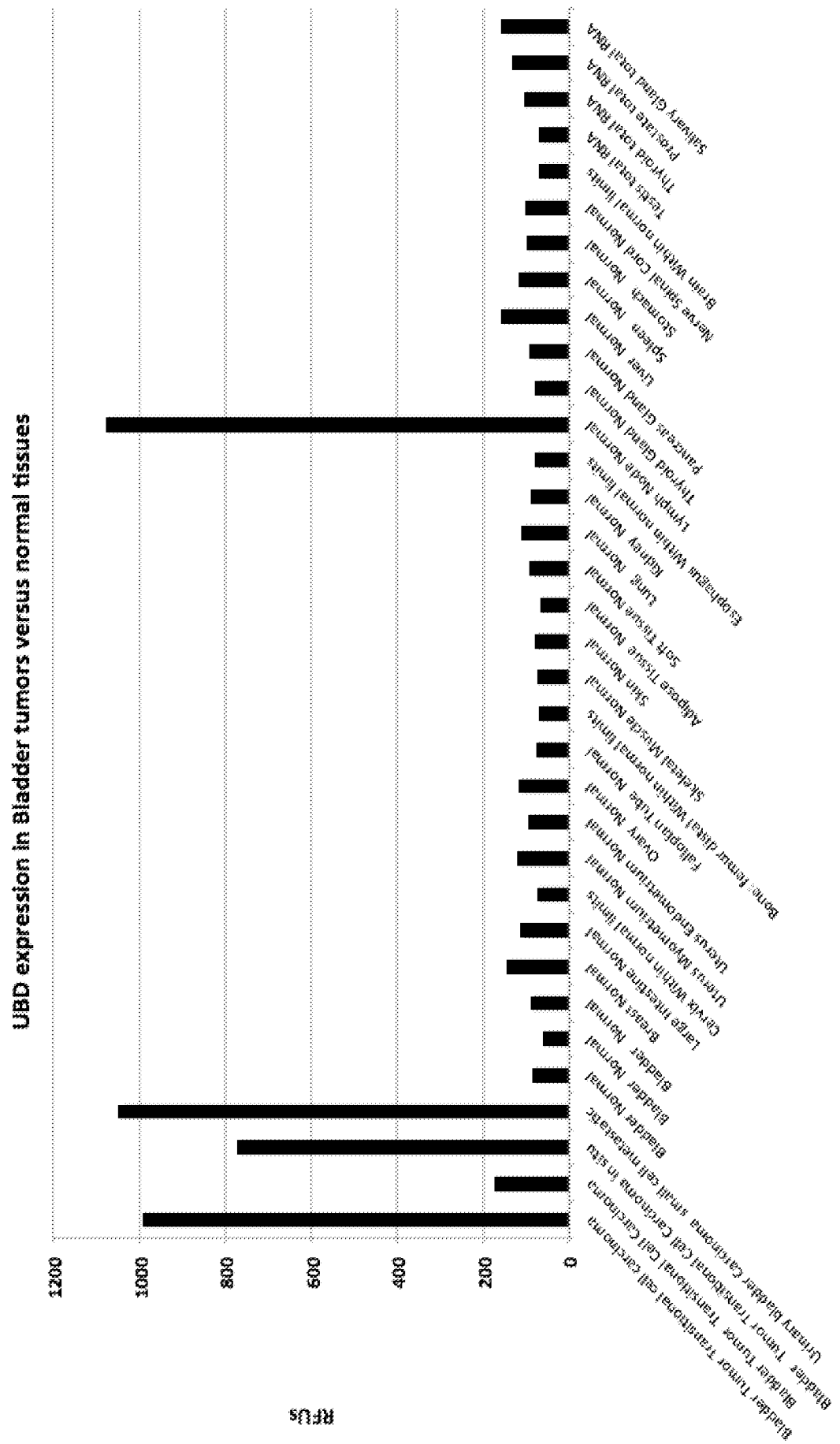


Figure 15
UGT1A6 expression in bladder tumors versus normal tissues

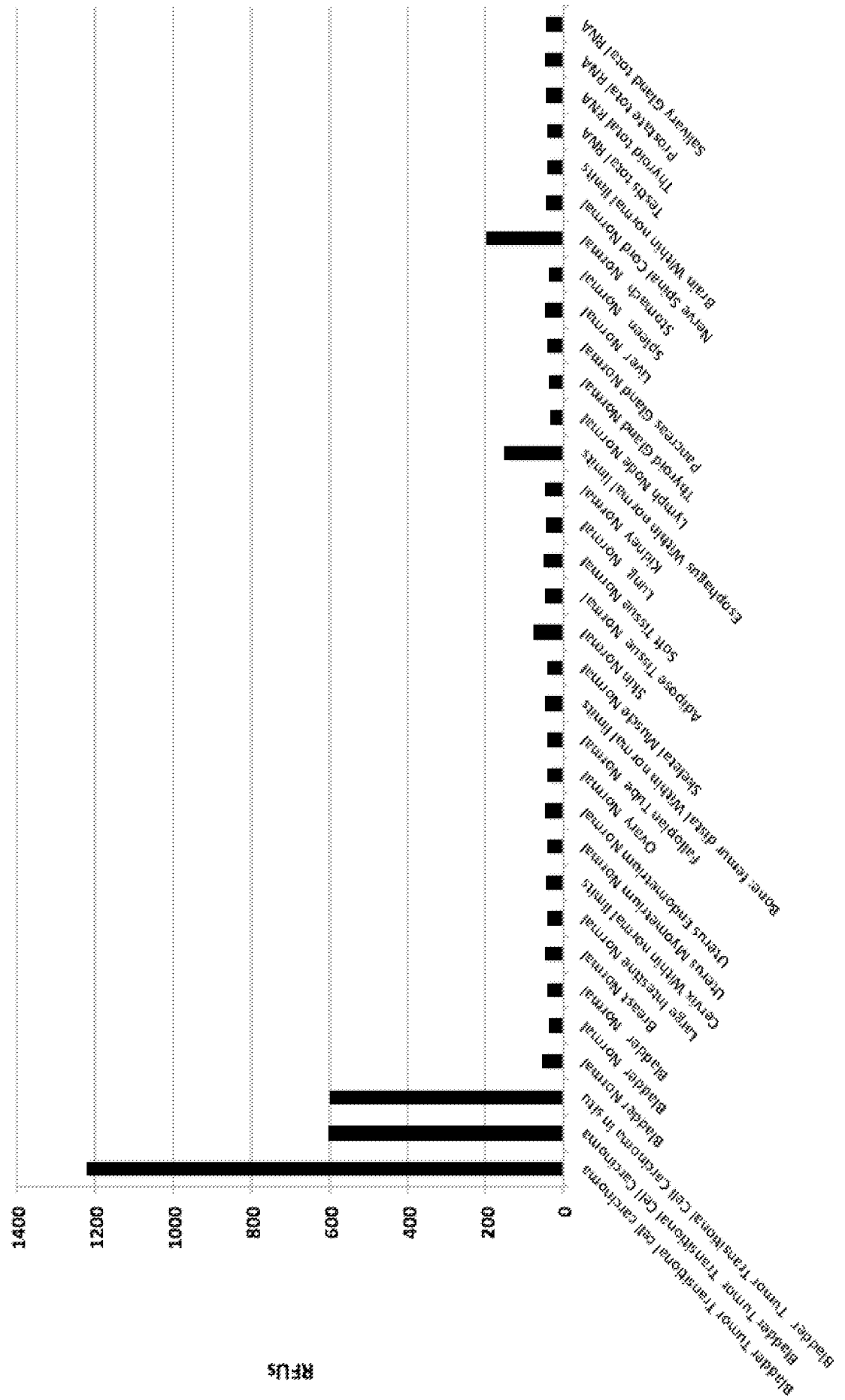


Figure 17

WISP3 expression in Bladder tumors versus normal tissues

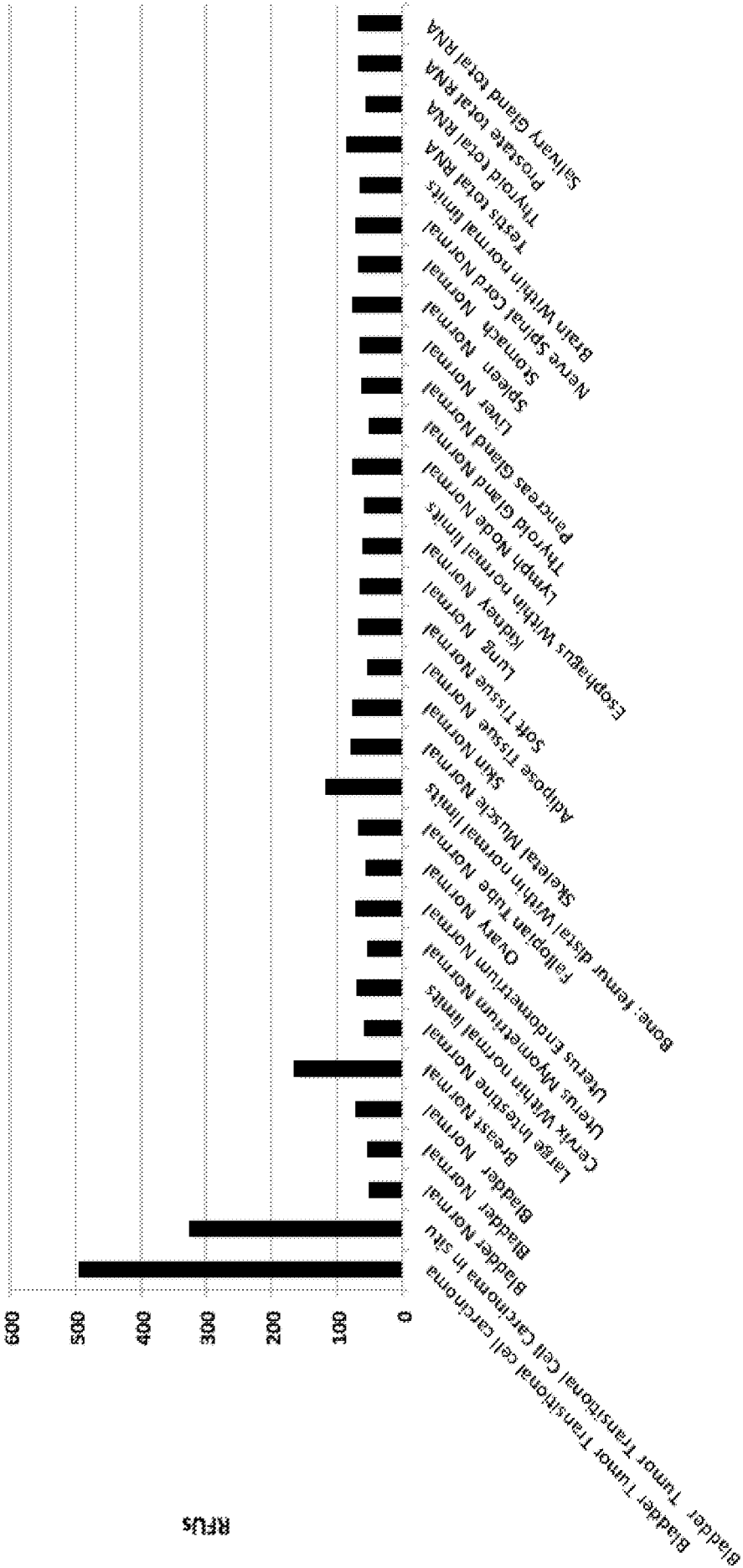


Figure 19

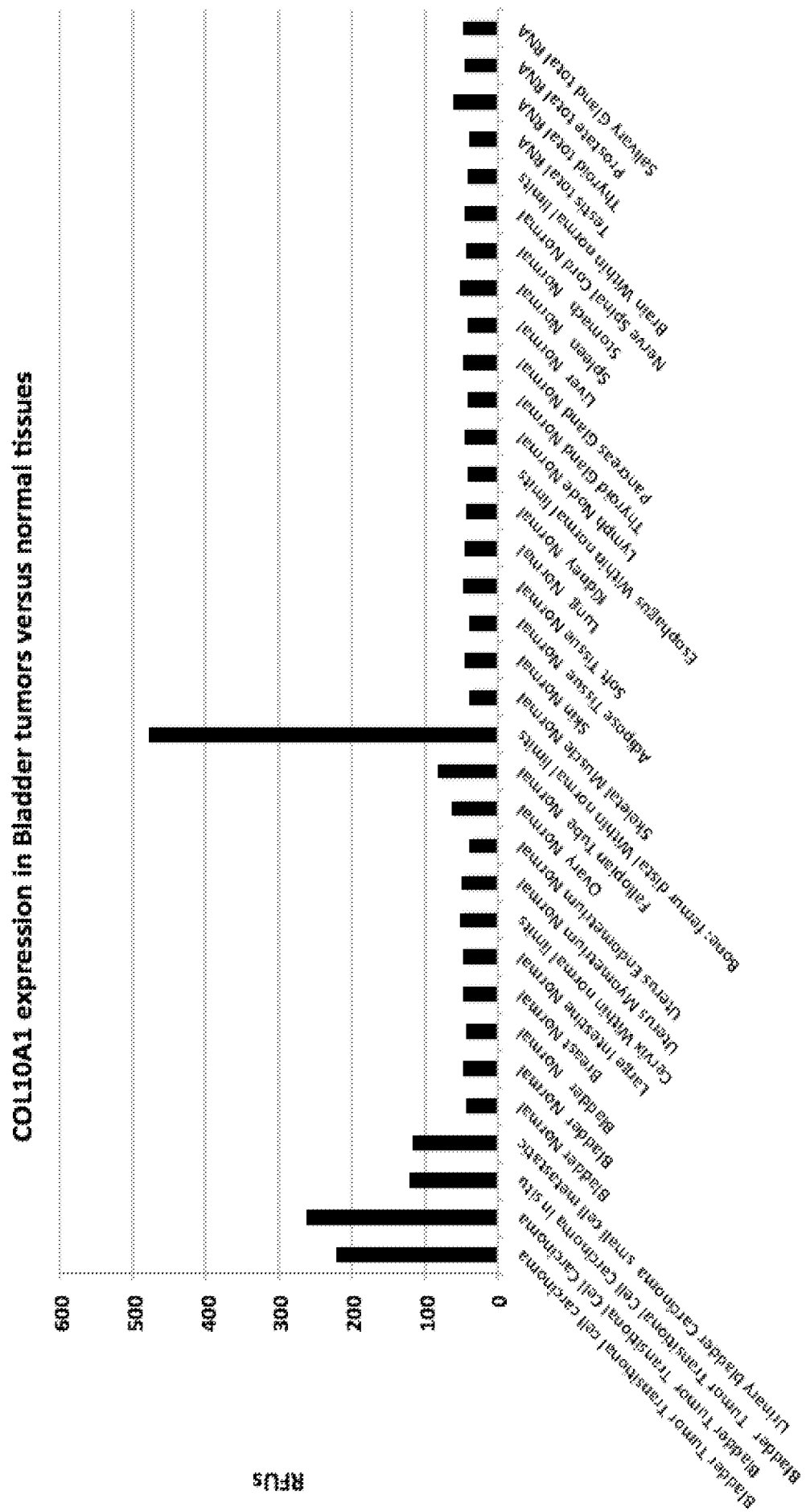


Figure 20

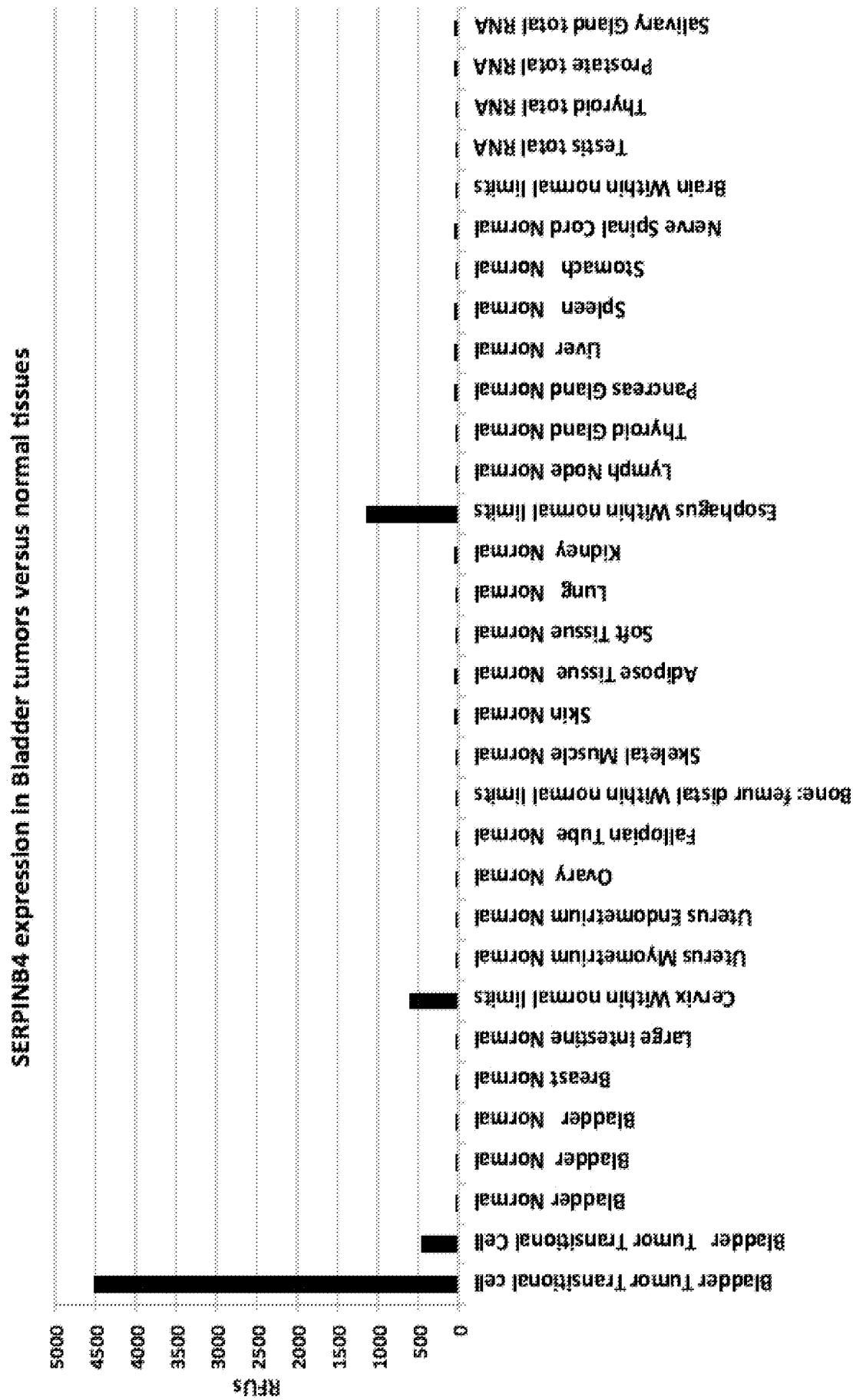


Figure 21

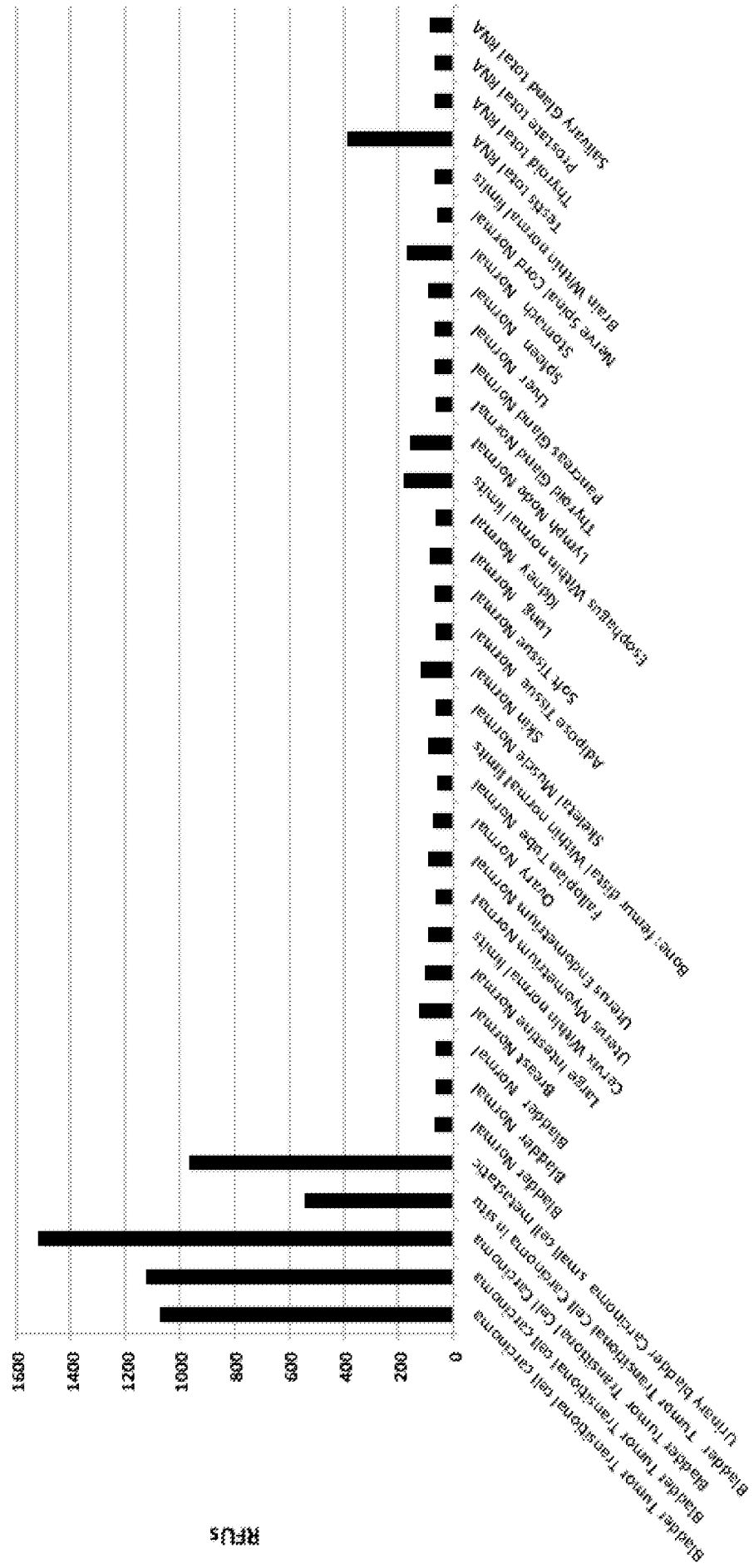
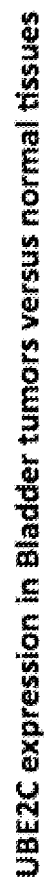


Figure 22

SFN expression in Bladder tumors versus normal tissues

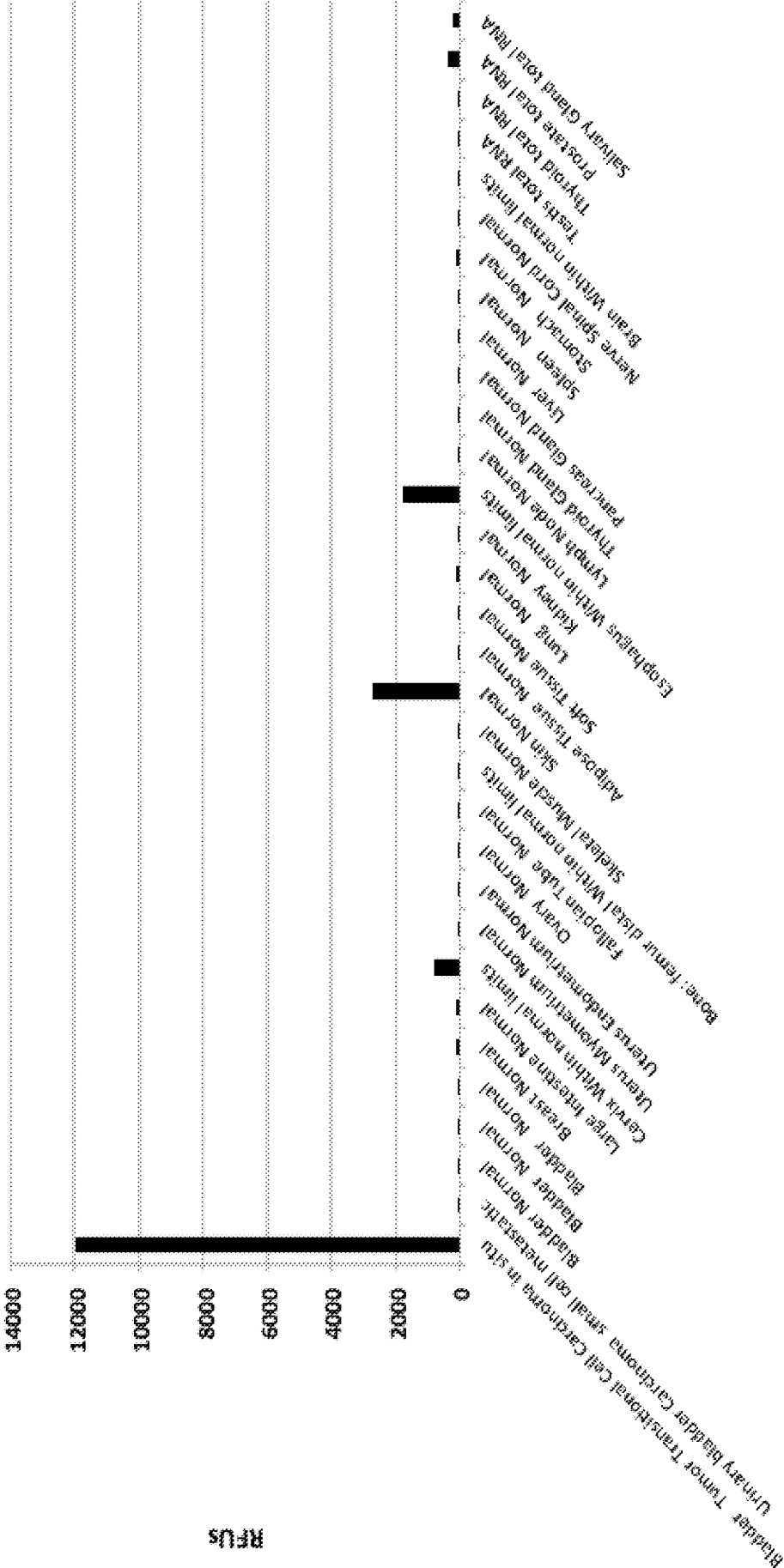


Figure 23
KRT17P3 expression in Bladder tumors versus normal tissues

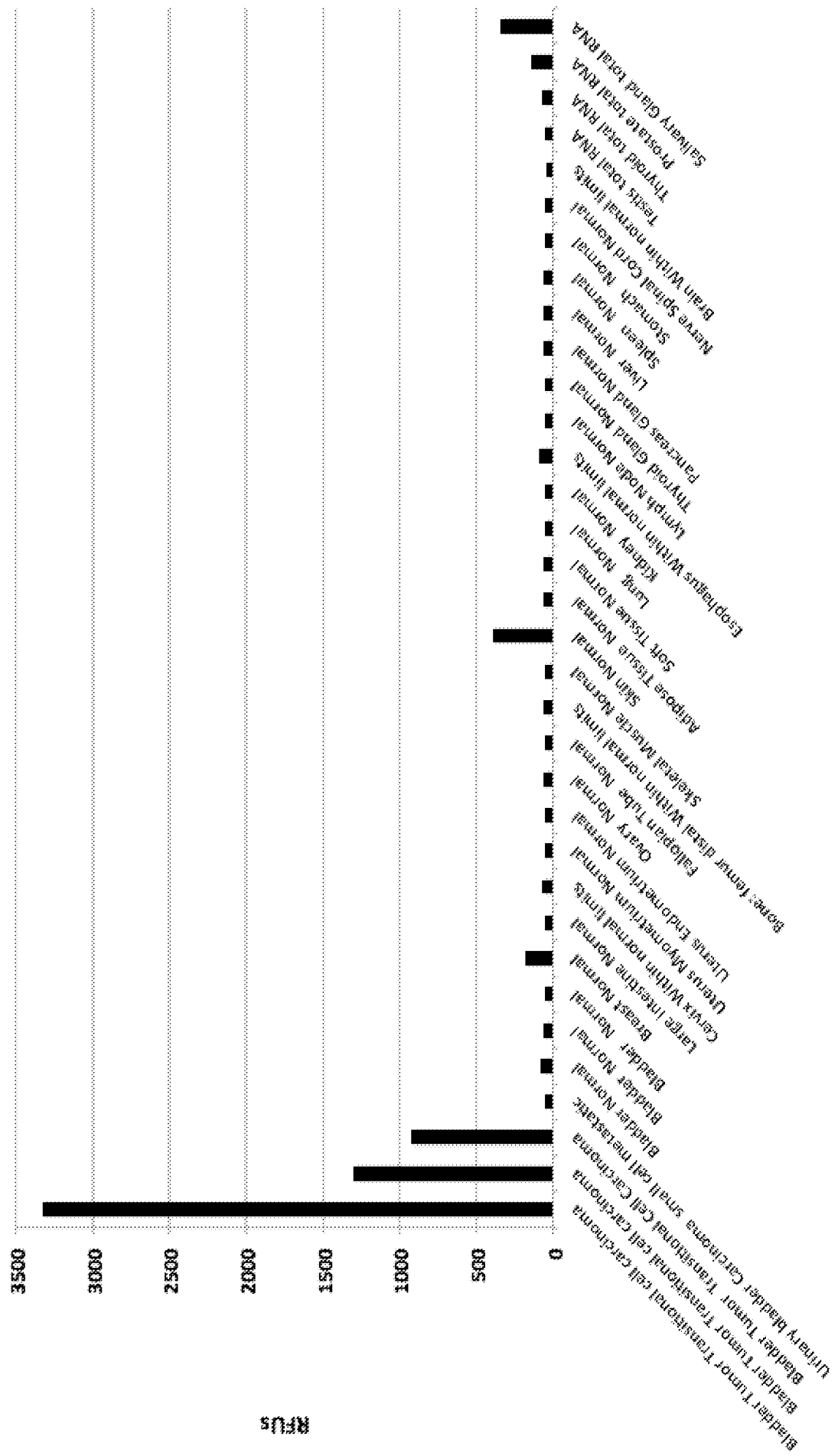


Figure 24

MMP11

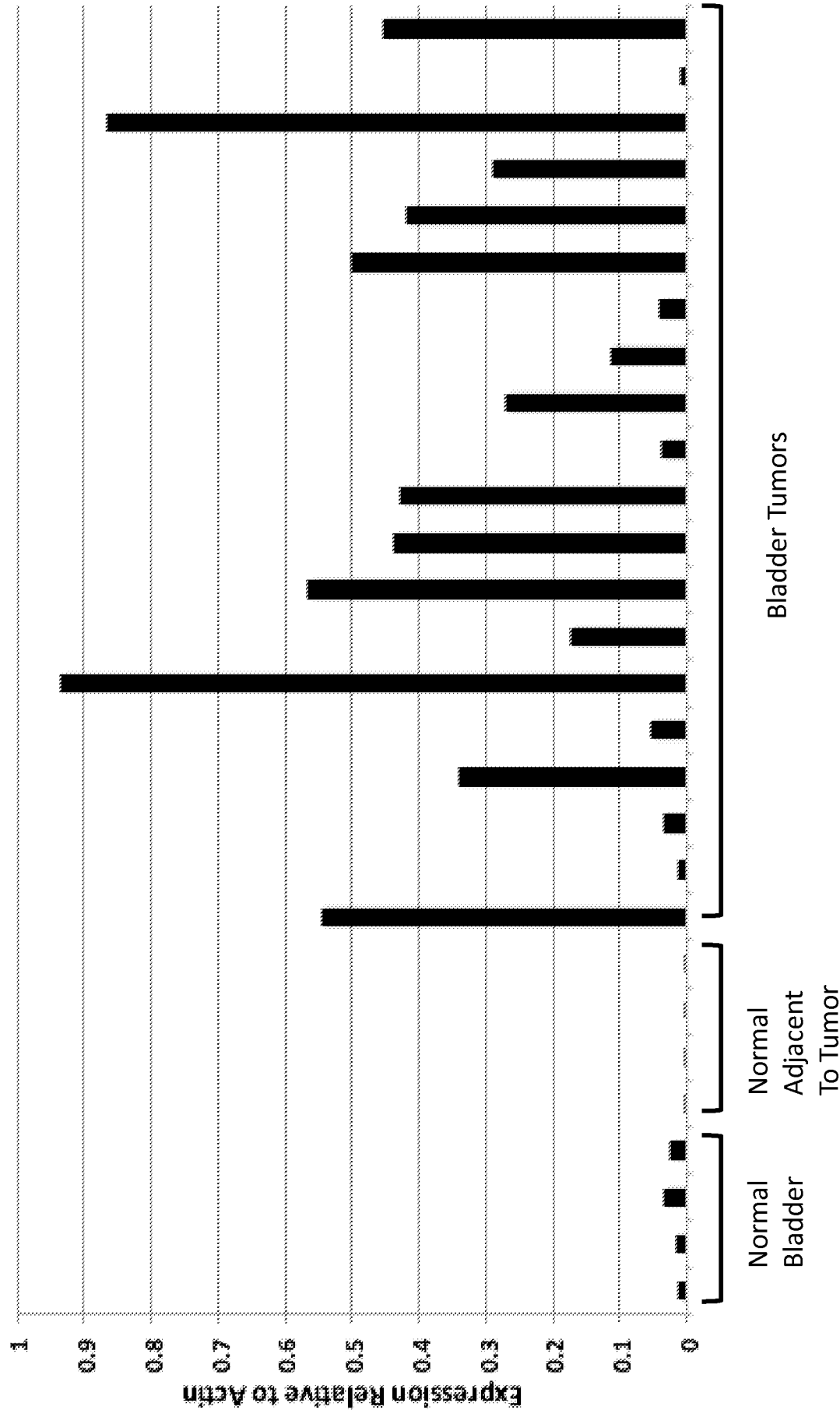


Figure 25

MMP12

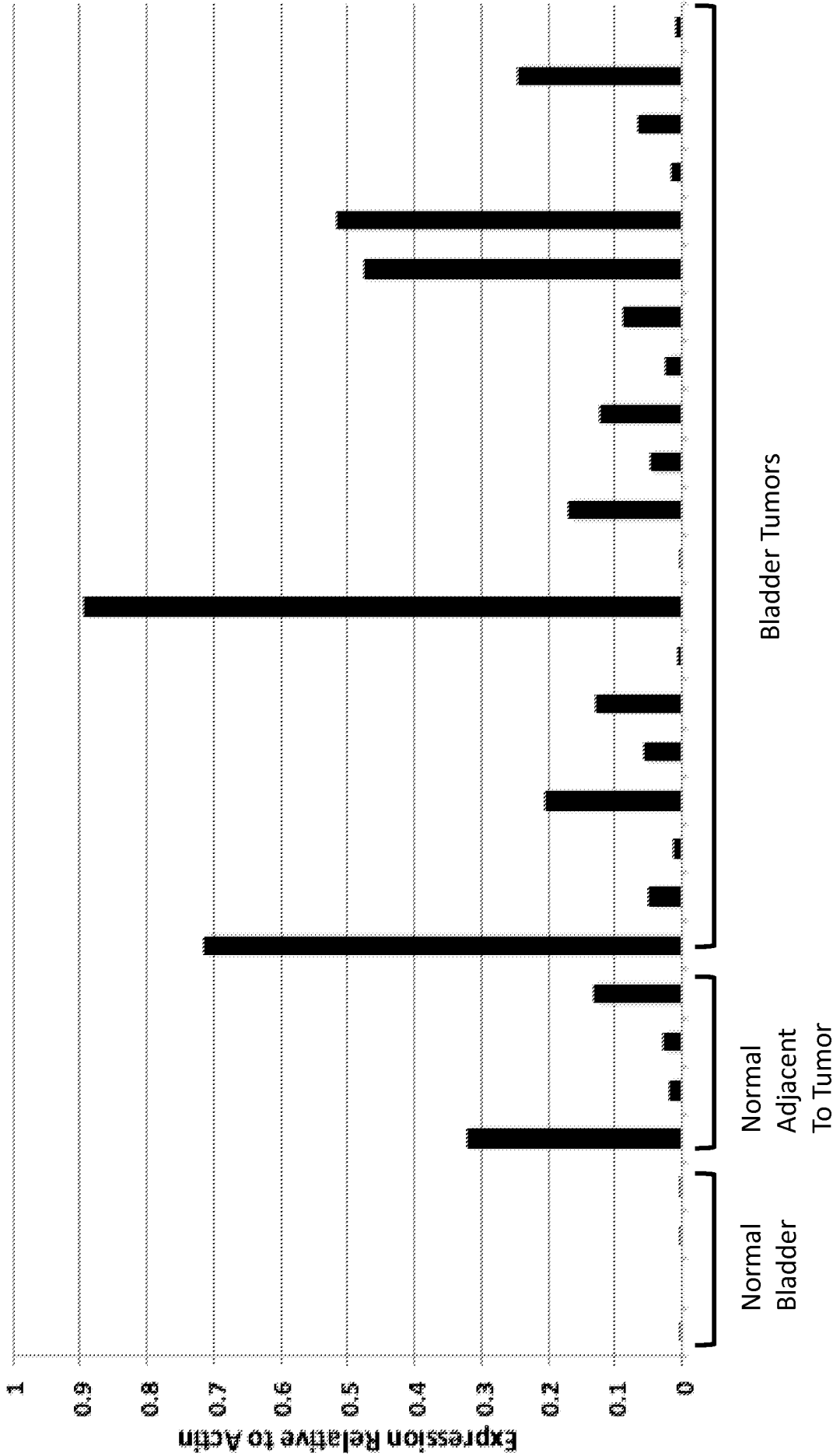


Figure 26

COL10A1

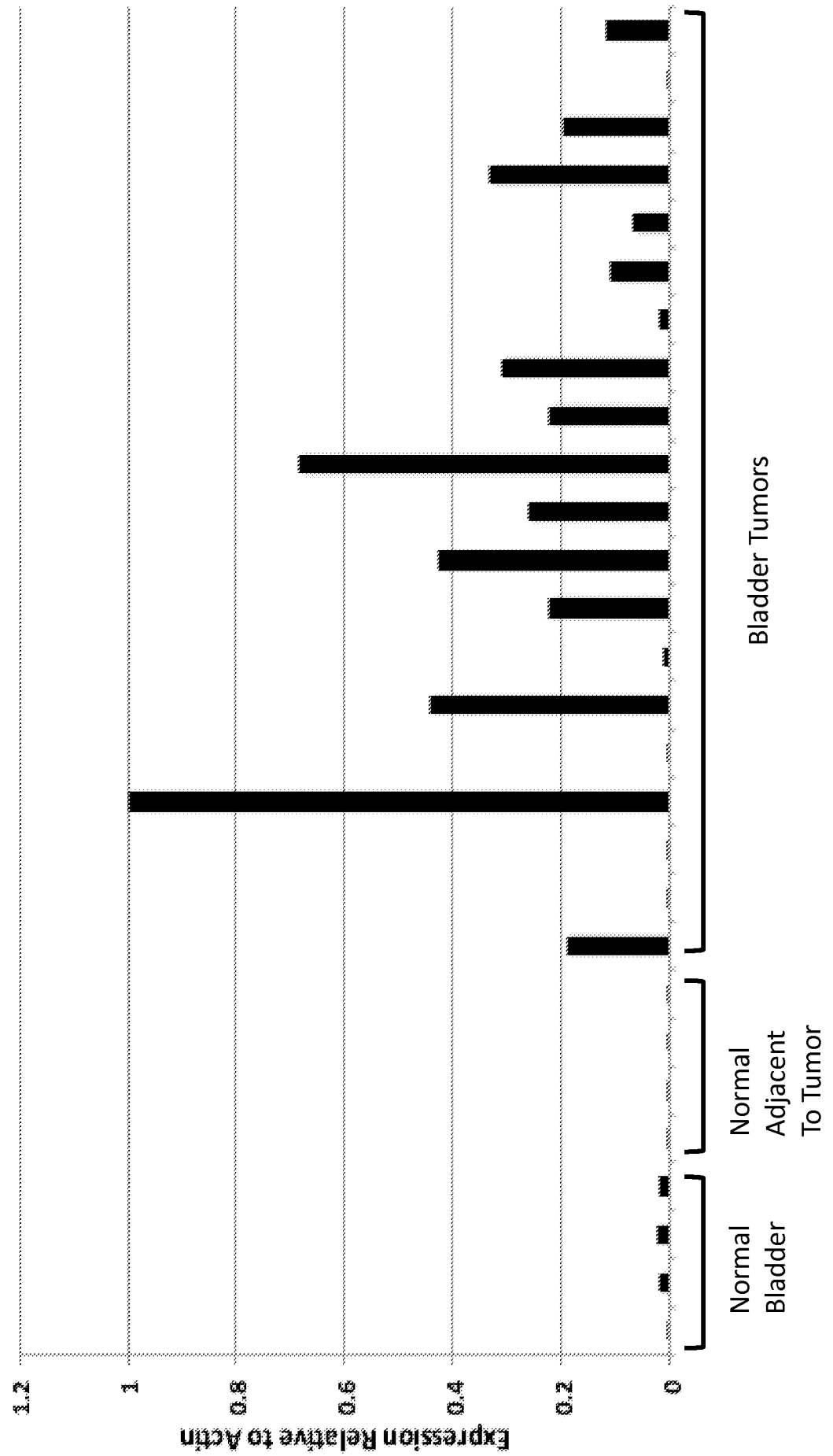


Figure 27

KRT6A

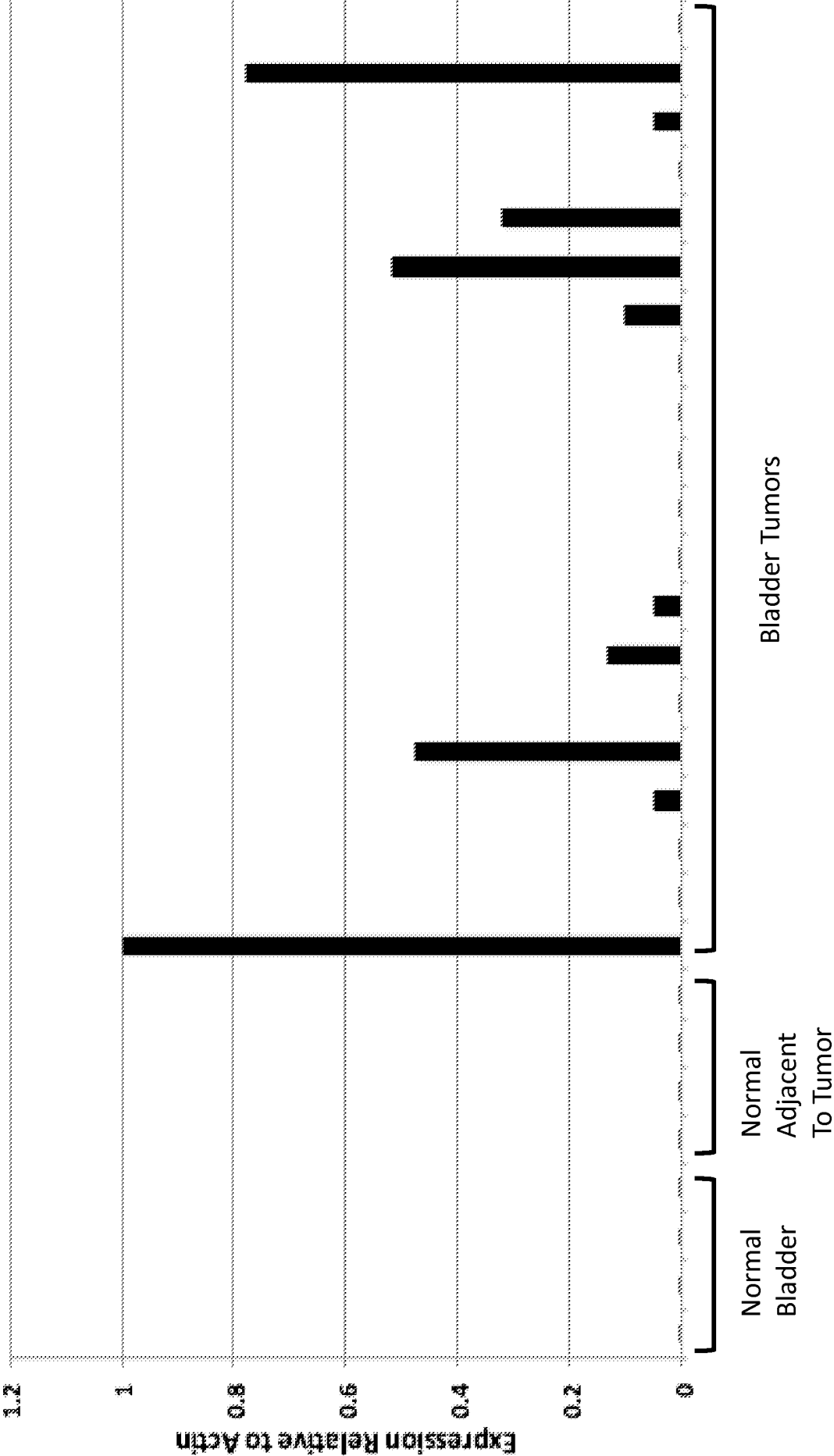


Figure 28

SFN

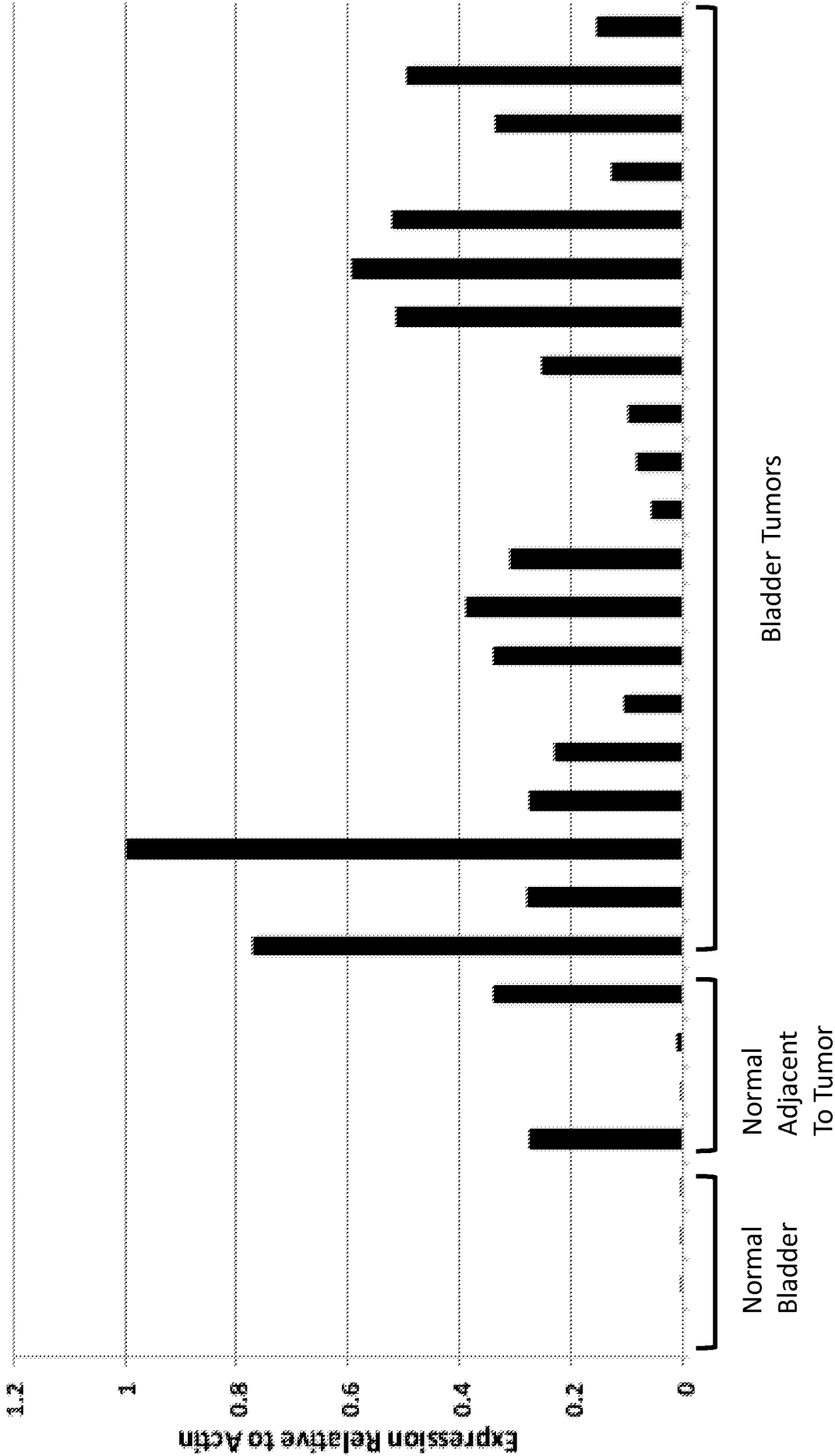


Figure 29

FCRLB

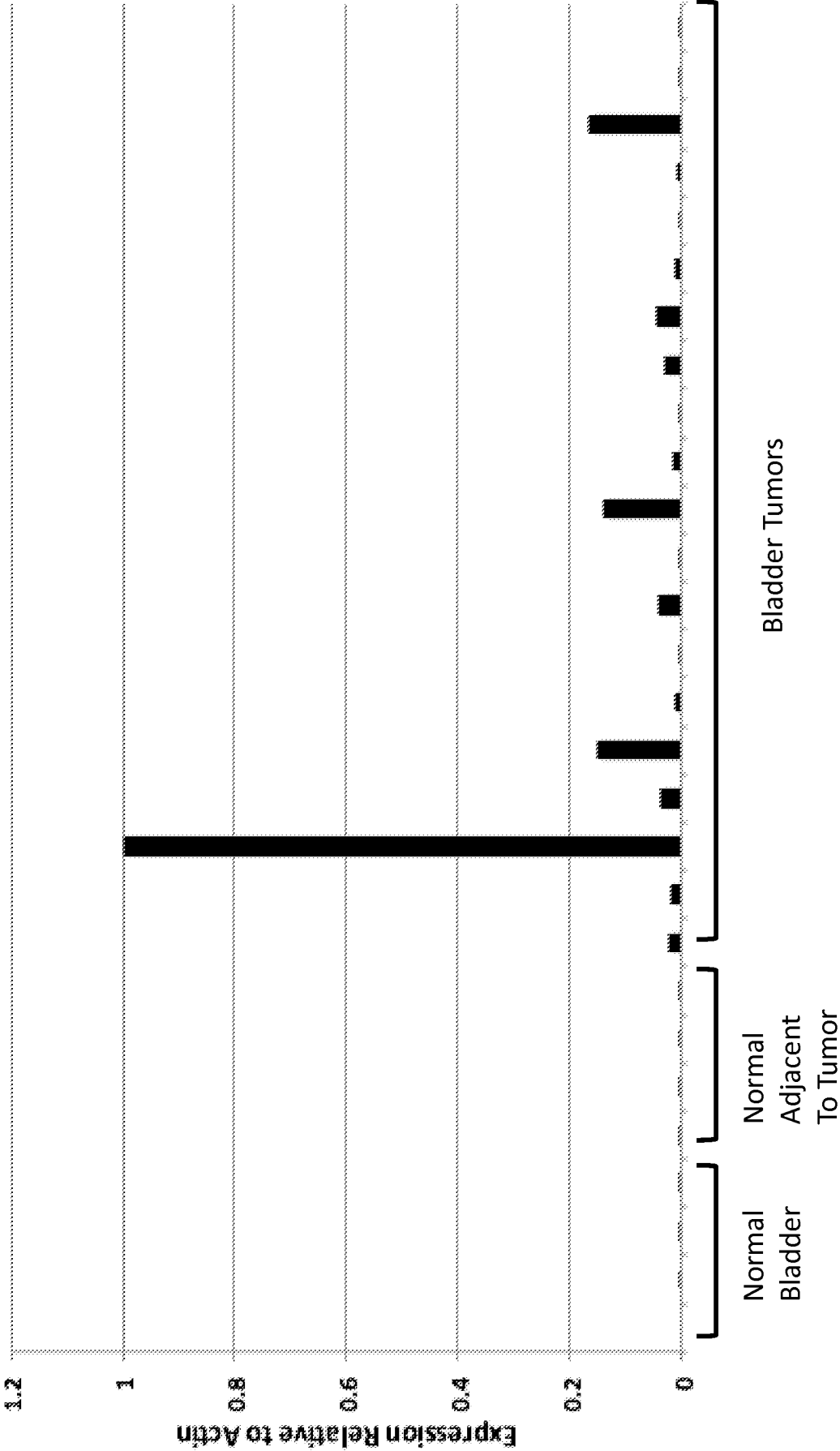


Figure 30
SERPINB5

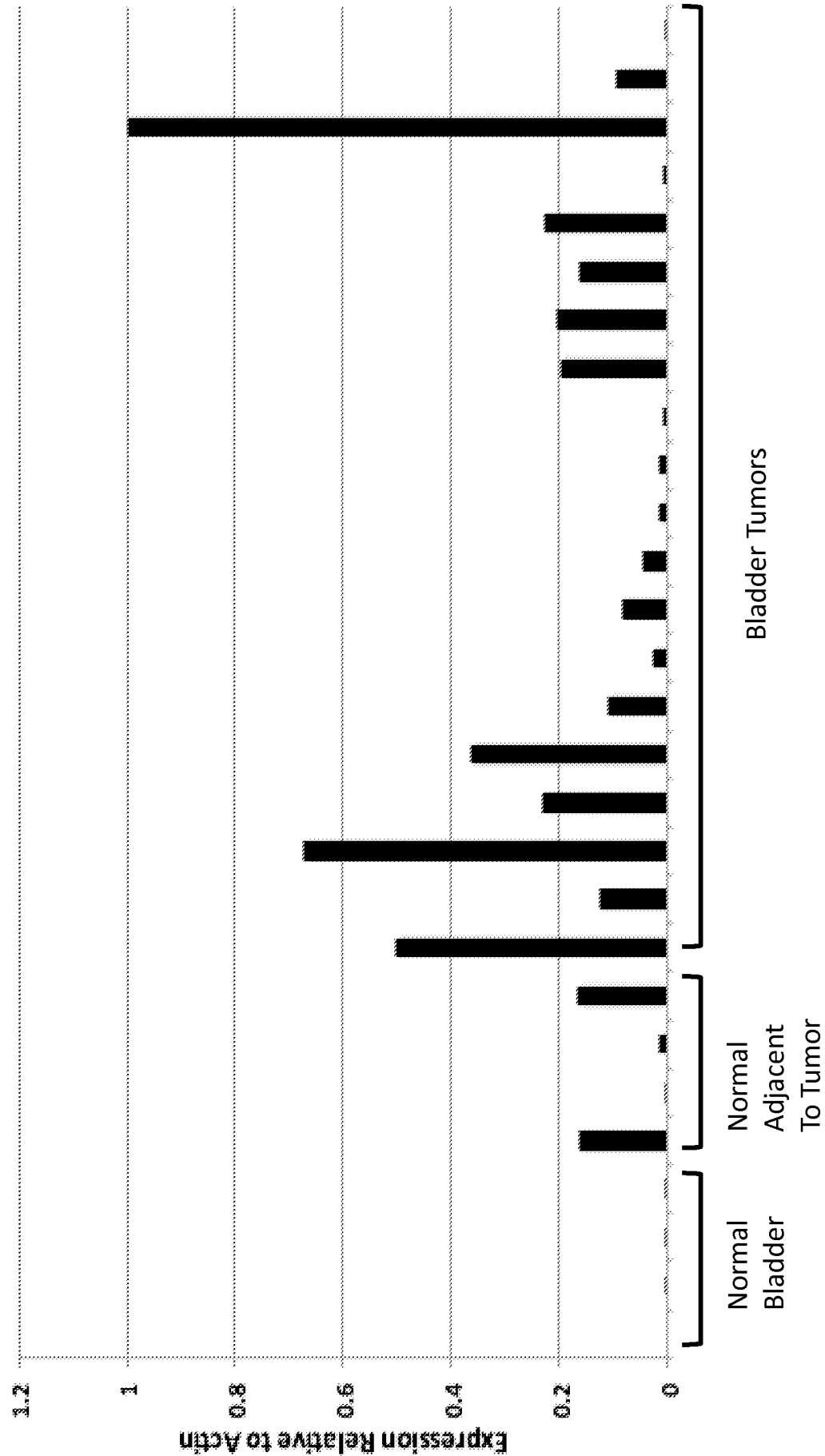


Figure 31

IL1A

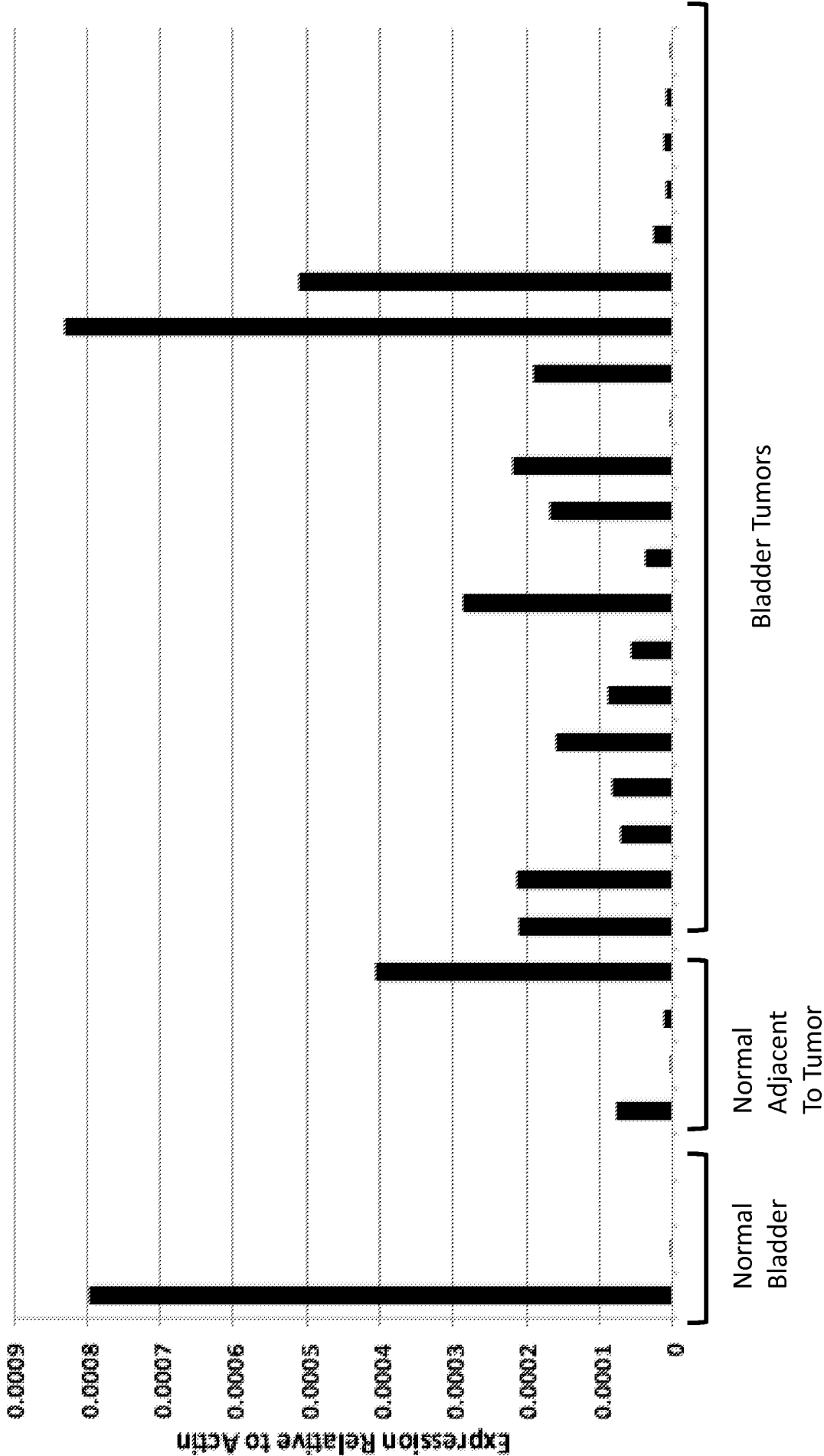


Figure 32
KRT16

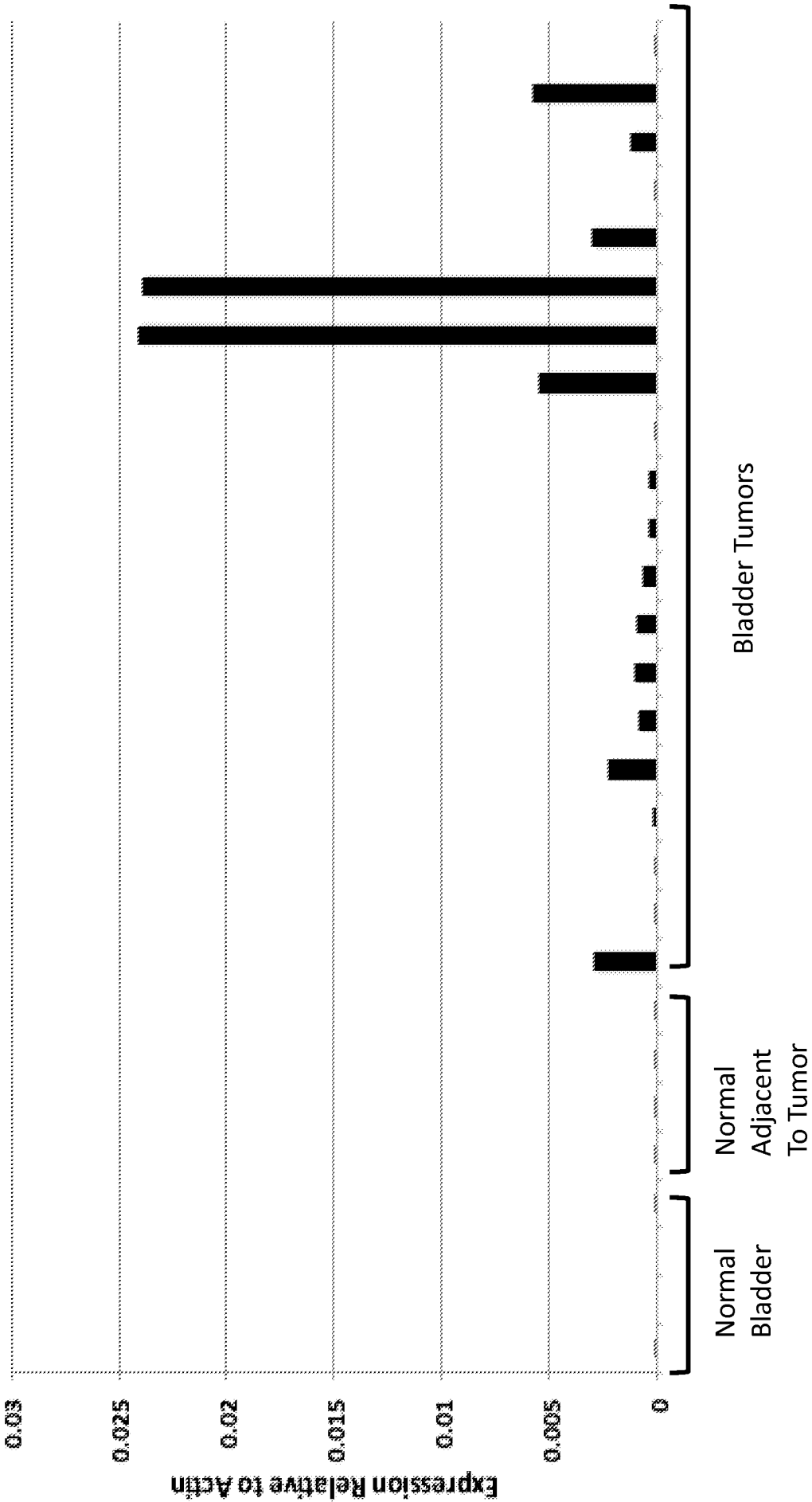


Figure 33

SLC1A6

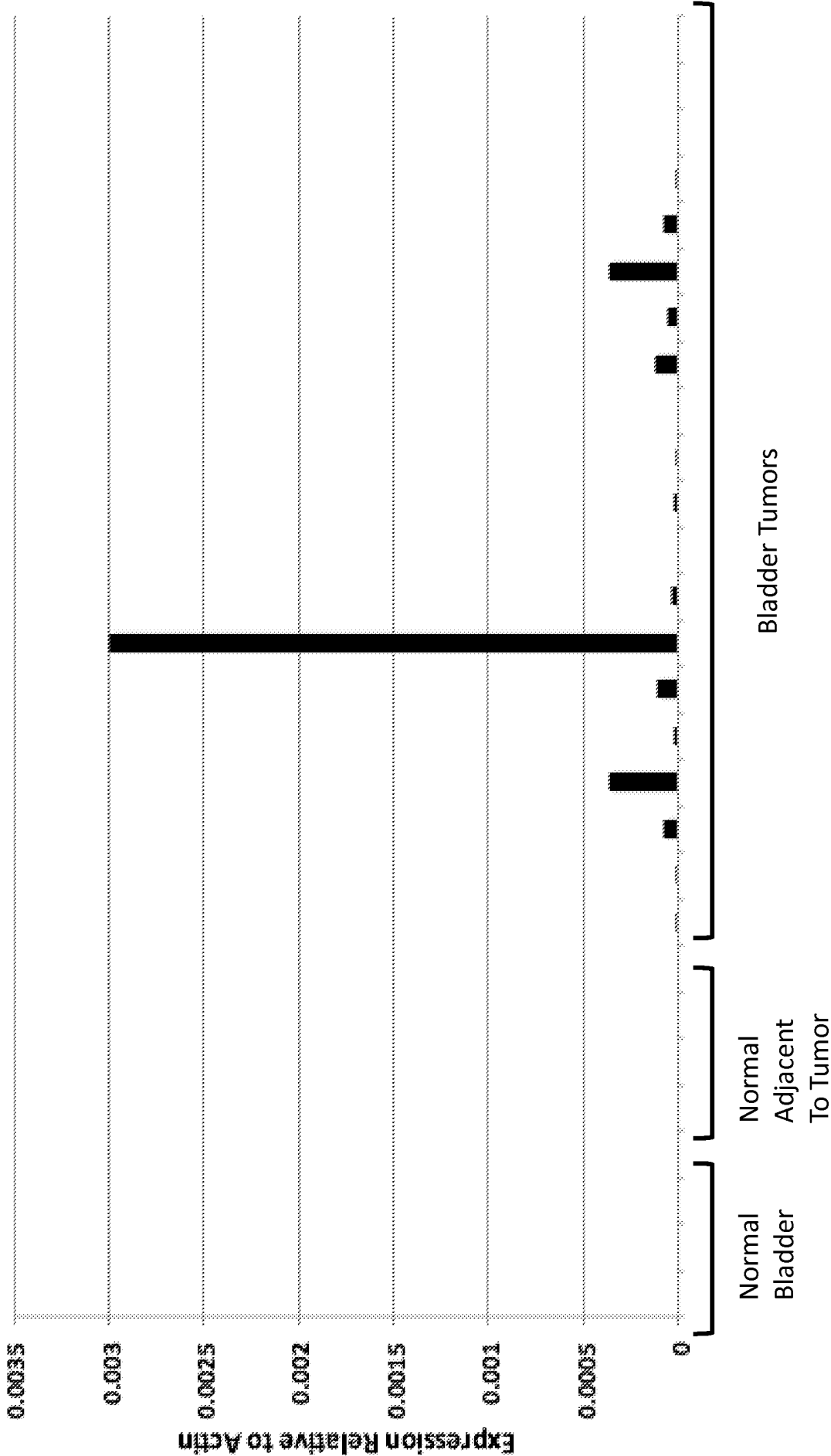


Figure 35
S100A7A Expression in Bladder Cancer

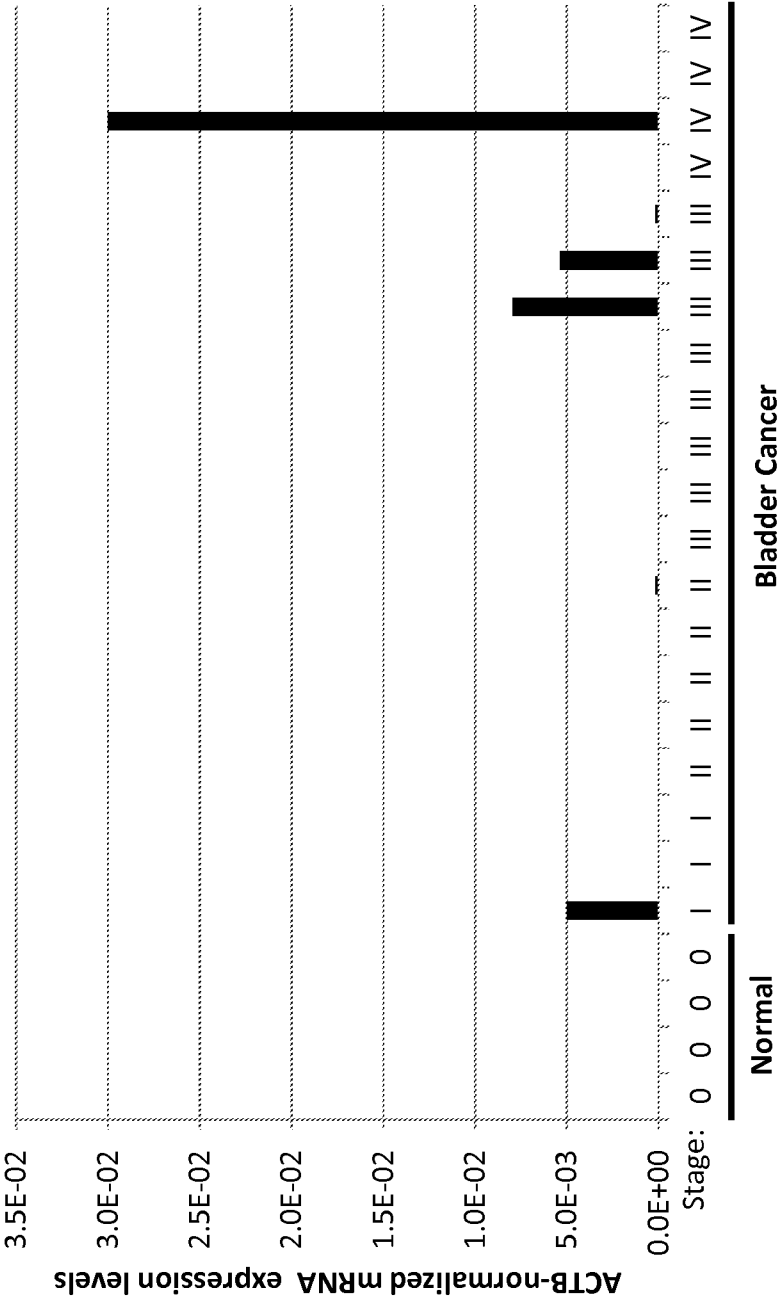
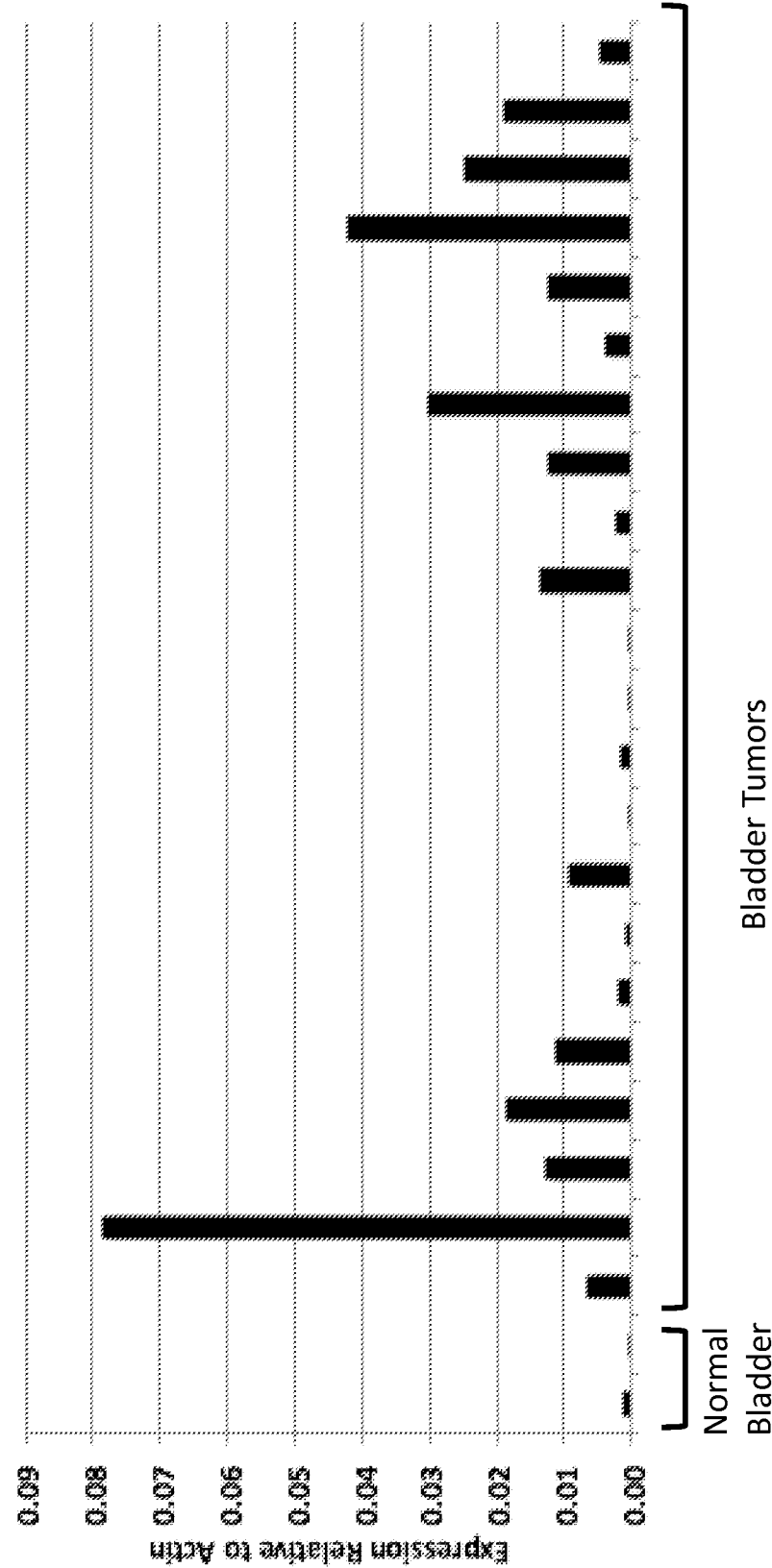


Figure 36

DSCR6



UBE2C
Multiplex PCR LDA assay

Figure 37

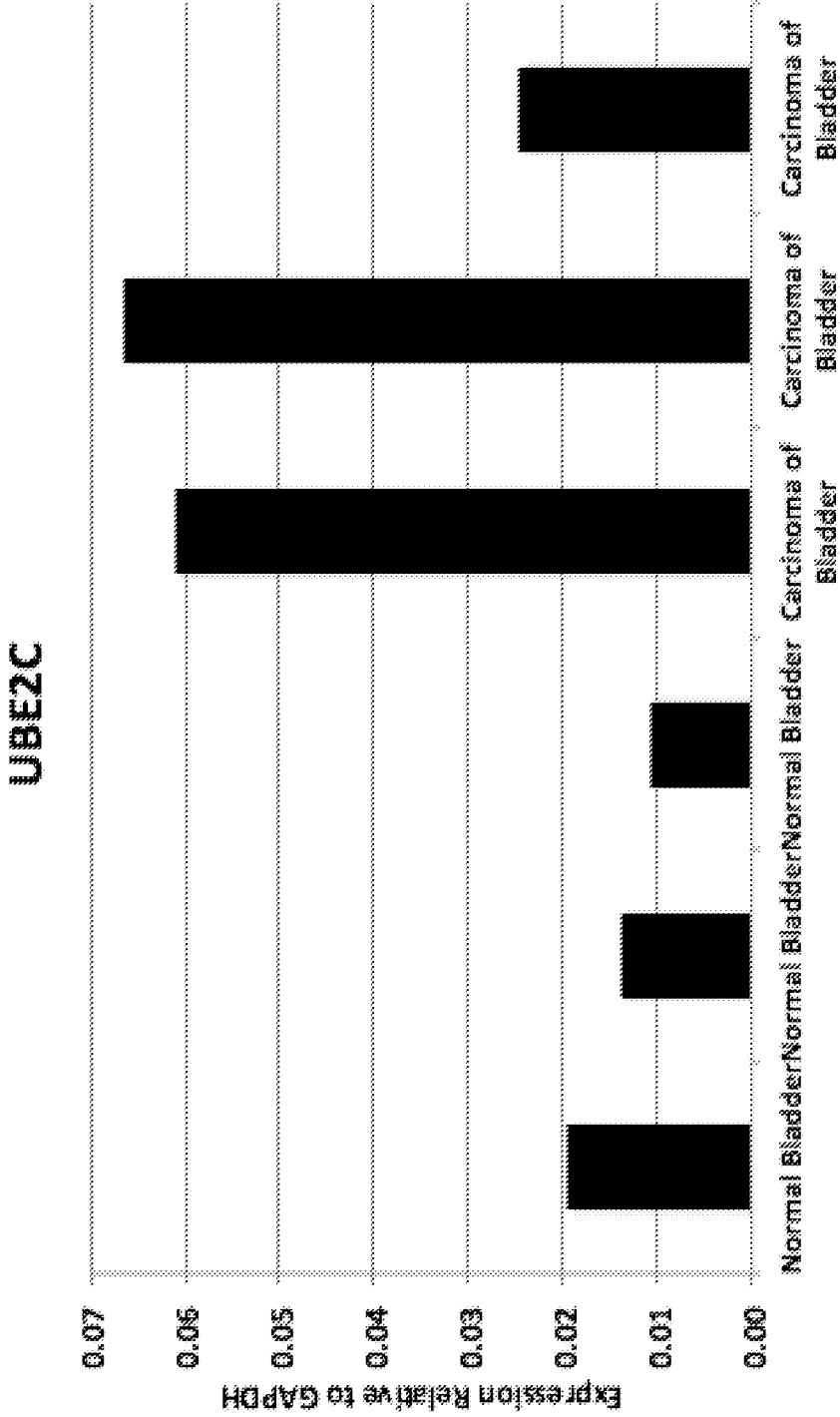
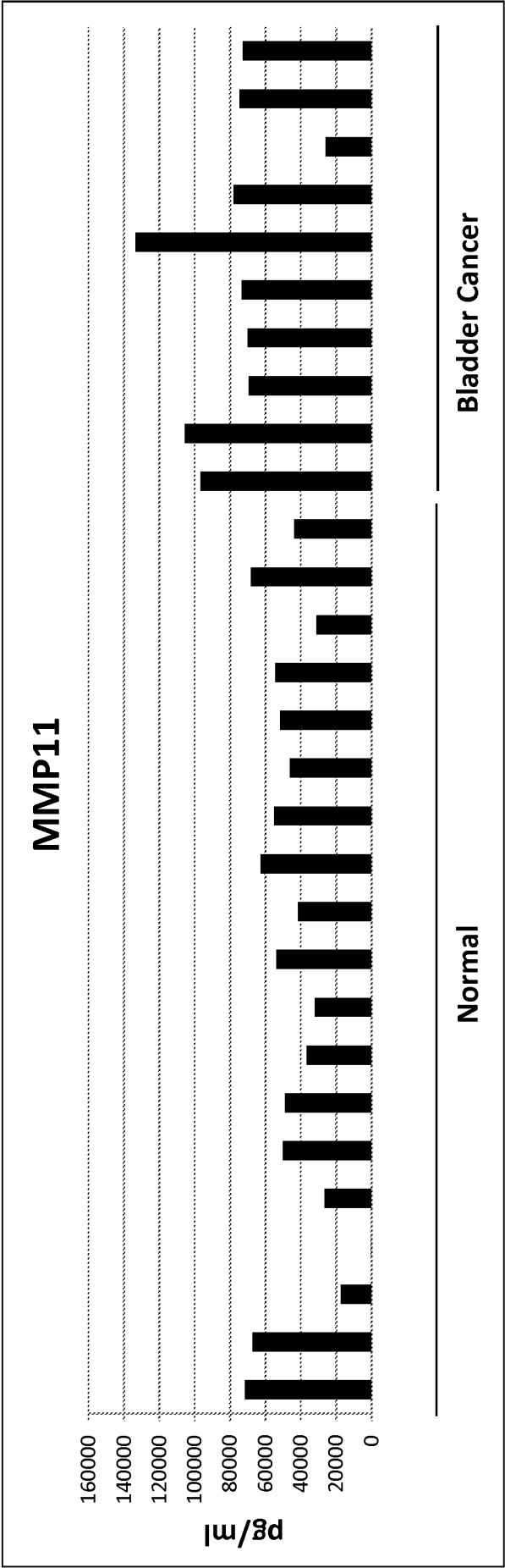


Figure 38



COL10A1
ELISA data
Serum

Figure 39

COL10A1

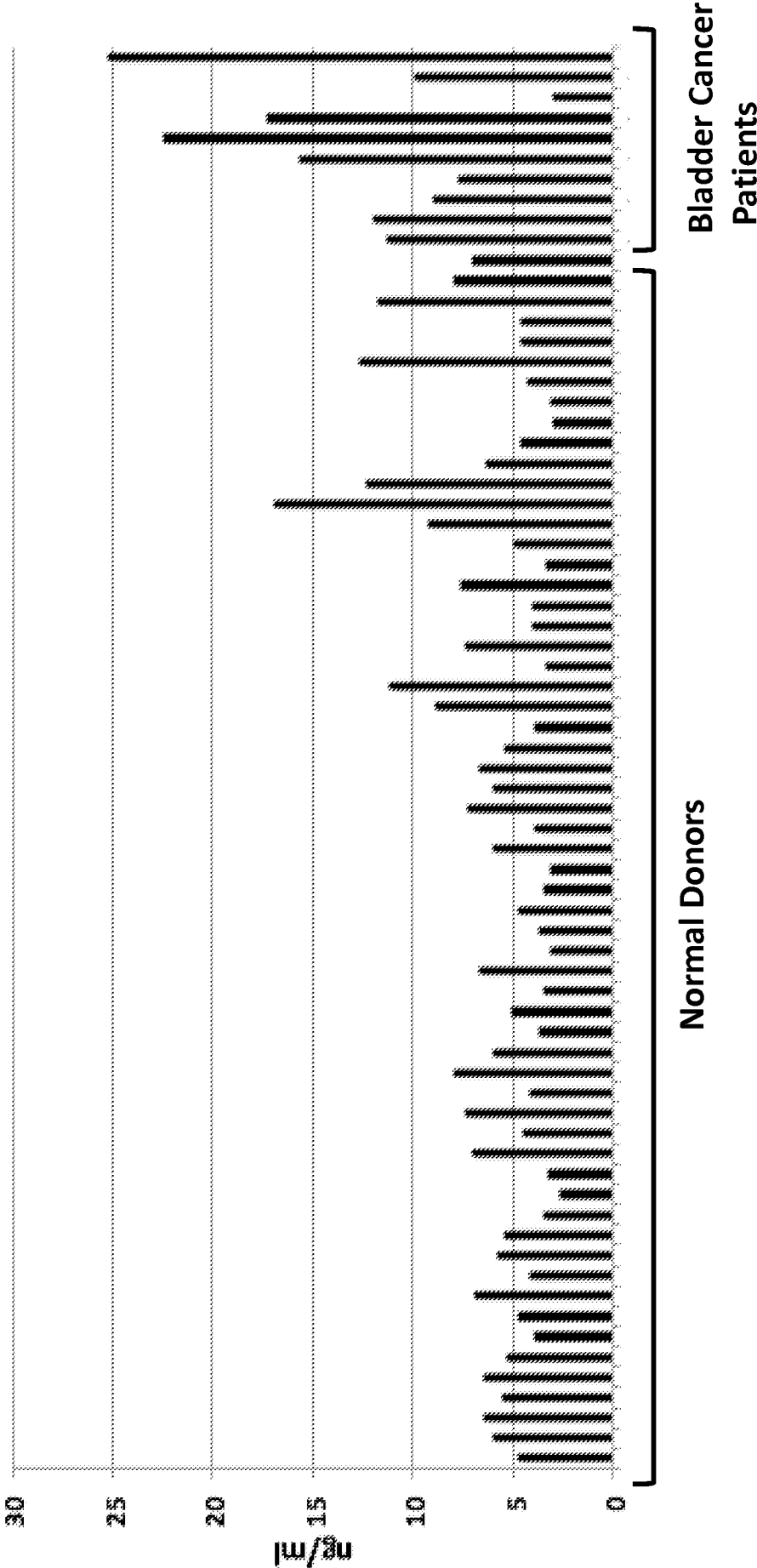


Figure 40

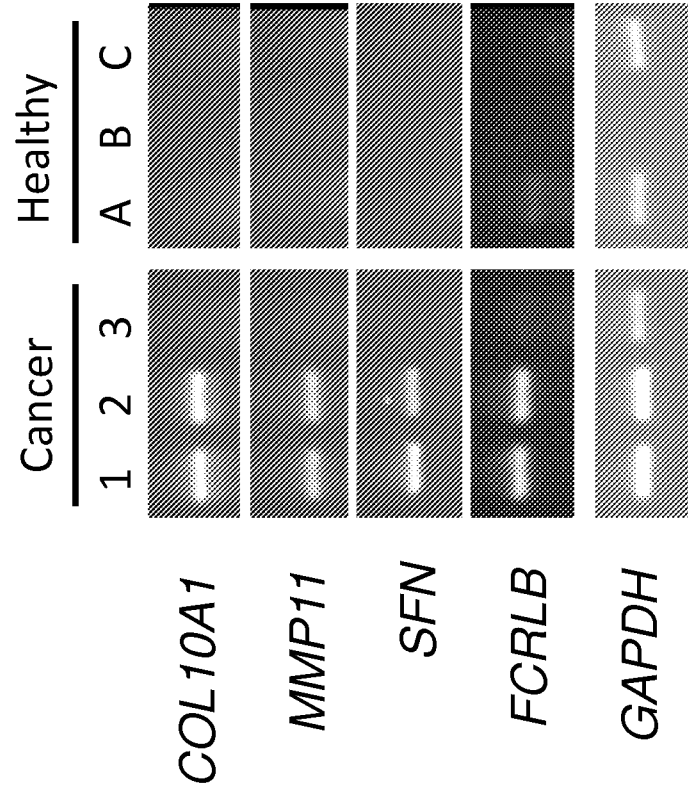


Figure 41

BLADDER CANCER SPECIMEN 1



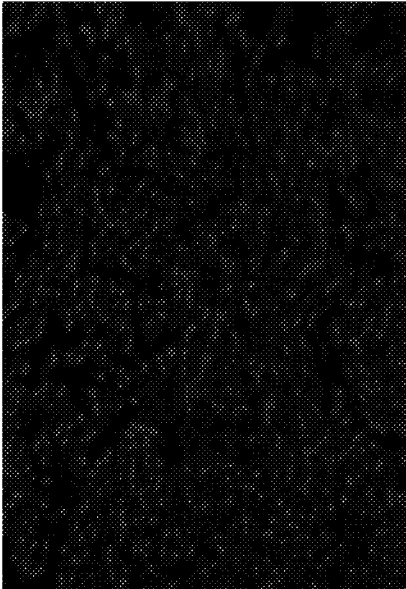
BLADDER CANCER SPECIMEN 2



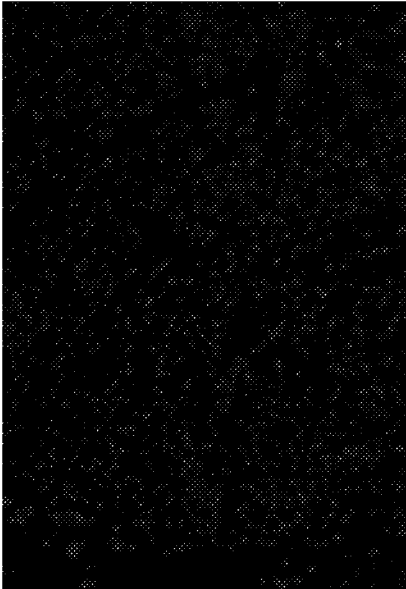
BLADDER CANCER SPECIMEN 3



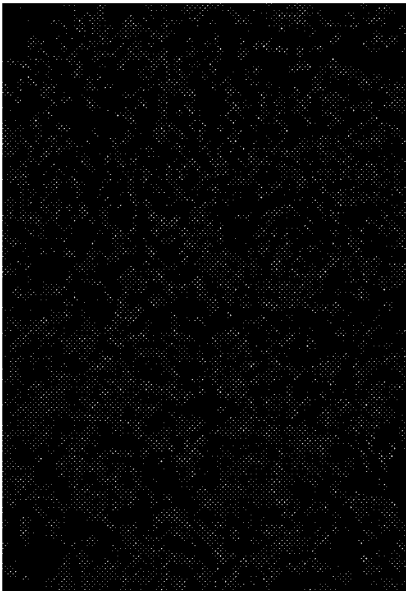
NORMAL BLADDER SECIMEN 1



NORMAL BLADDER SECIMEN 2



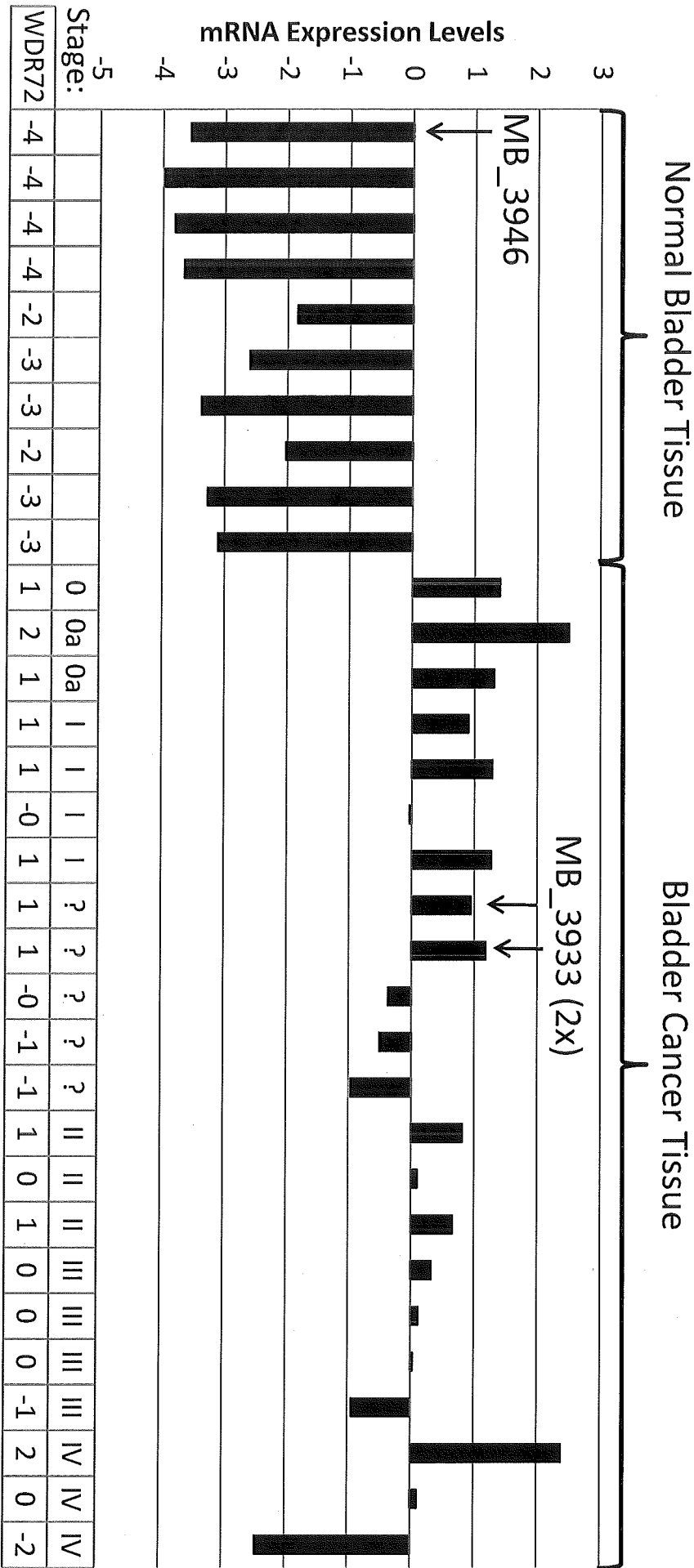
NORMAL BLADDER SECIMEN 3



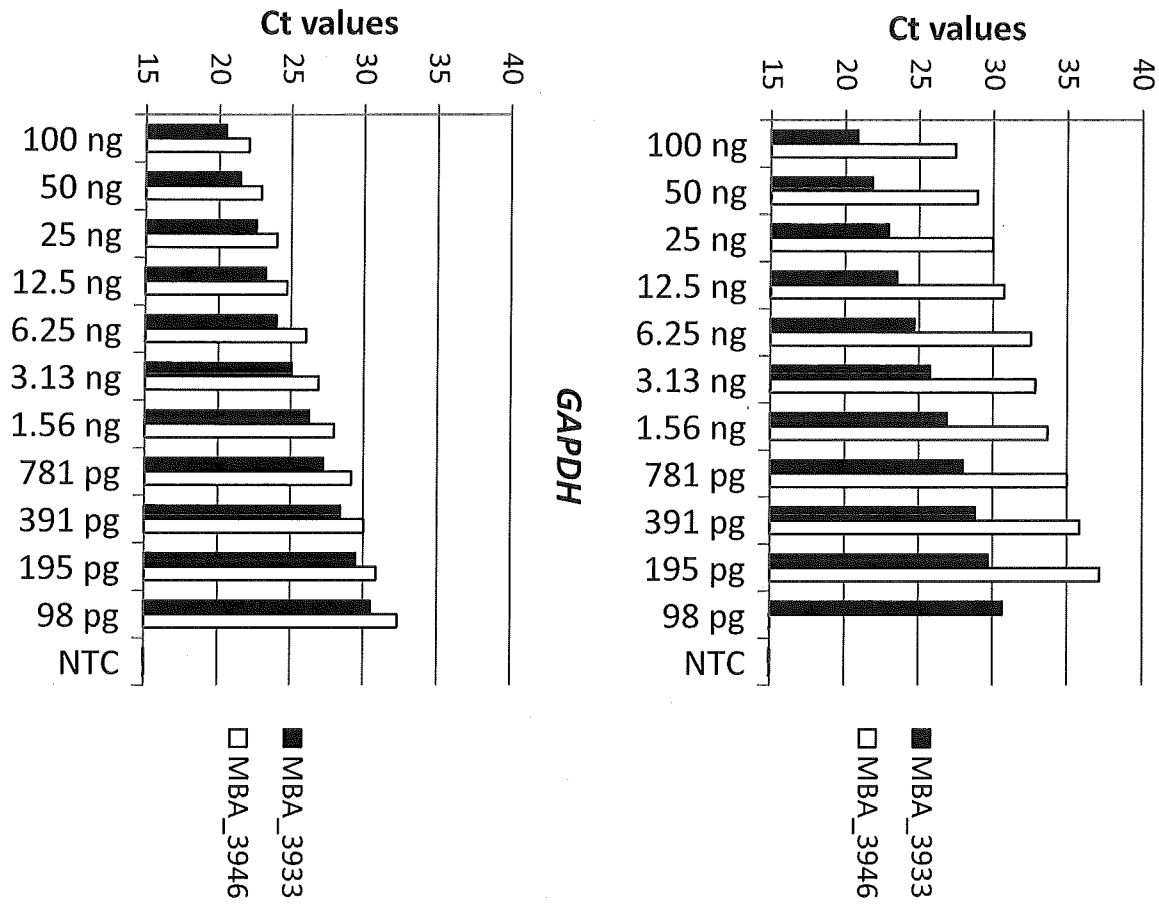
MMP11 IN BLADDER

Fig 42

WDR72 mRNA expression by microarray



A



B

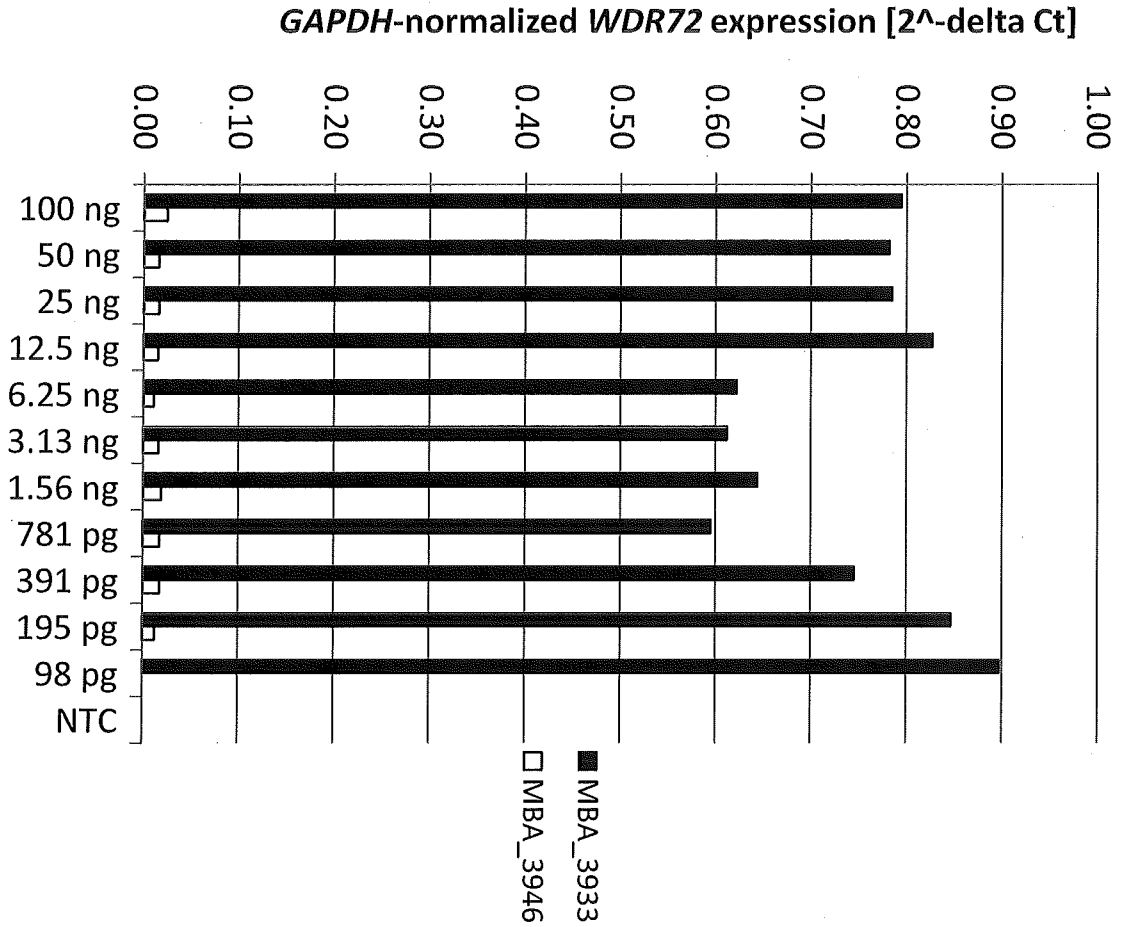


Fig. 43

***GAPDH*-normalized *WDR72* mRNA expression**
(TissueScan Bladder I)

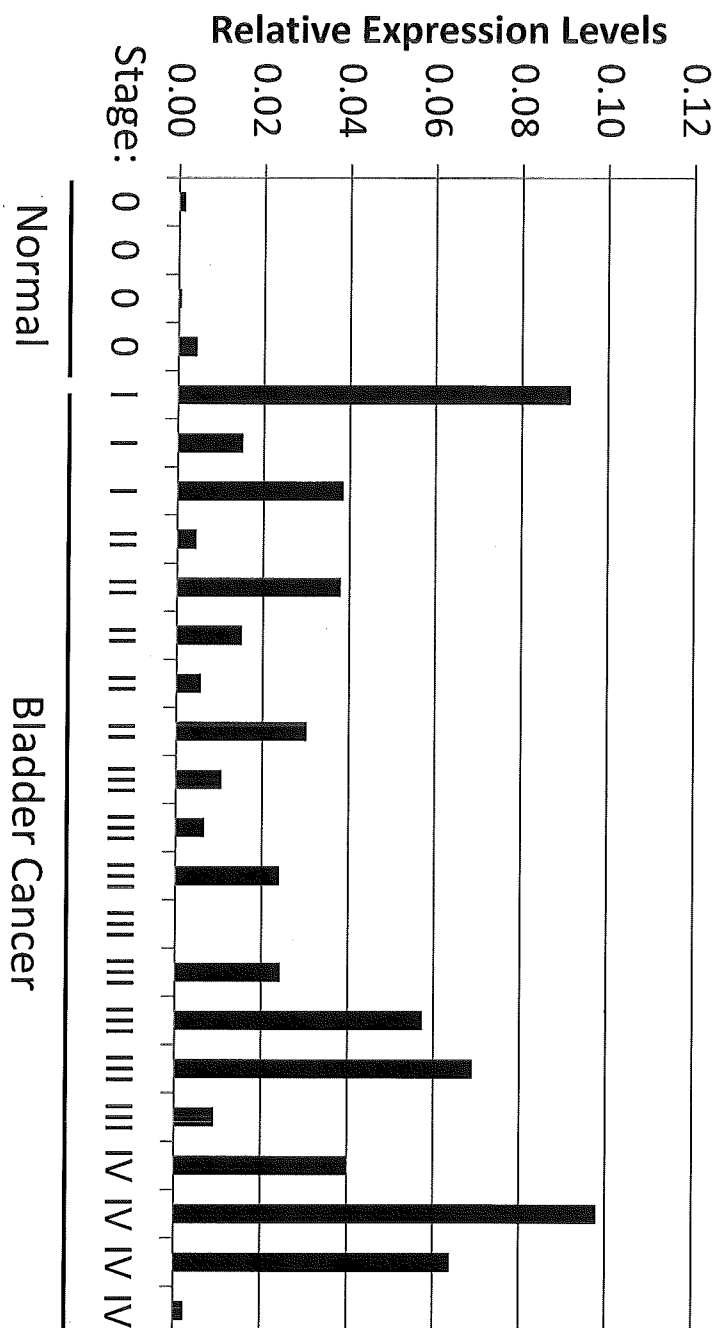


Fig 45

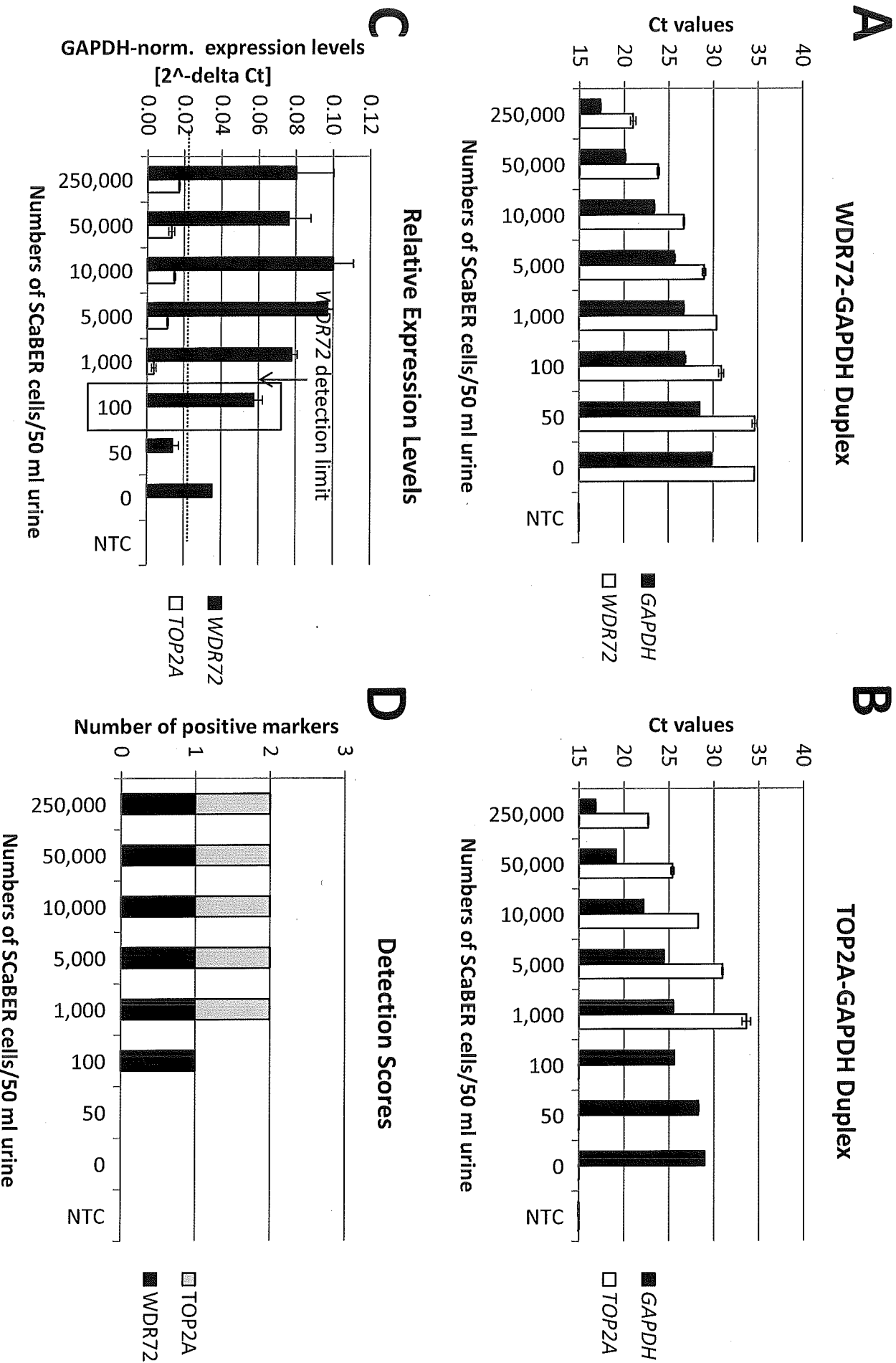


Fig 46

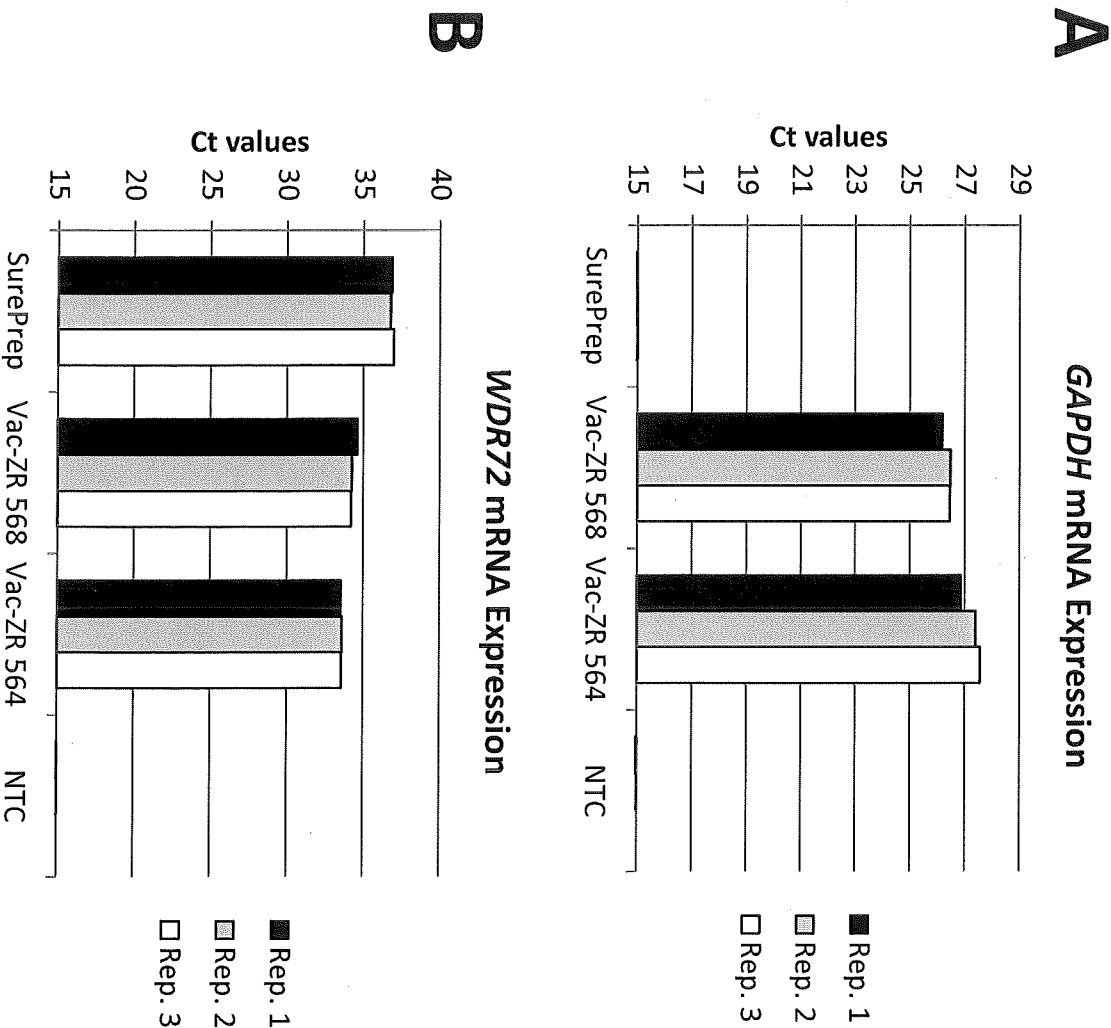


Fig 47

WDR72 Primers (JK1395+JK1416)
with Human Reference RNA Dilutions

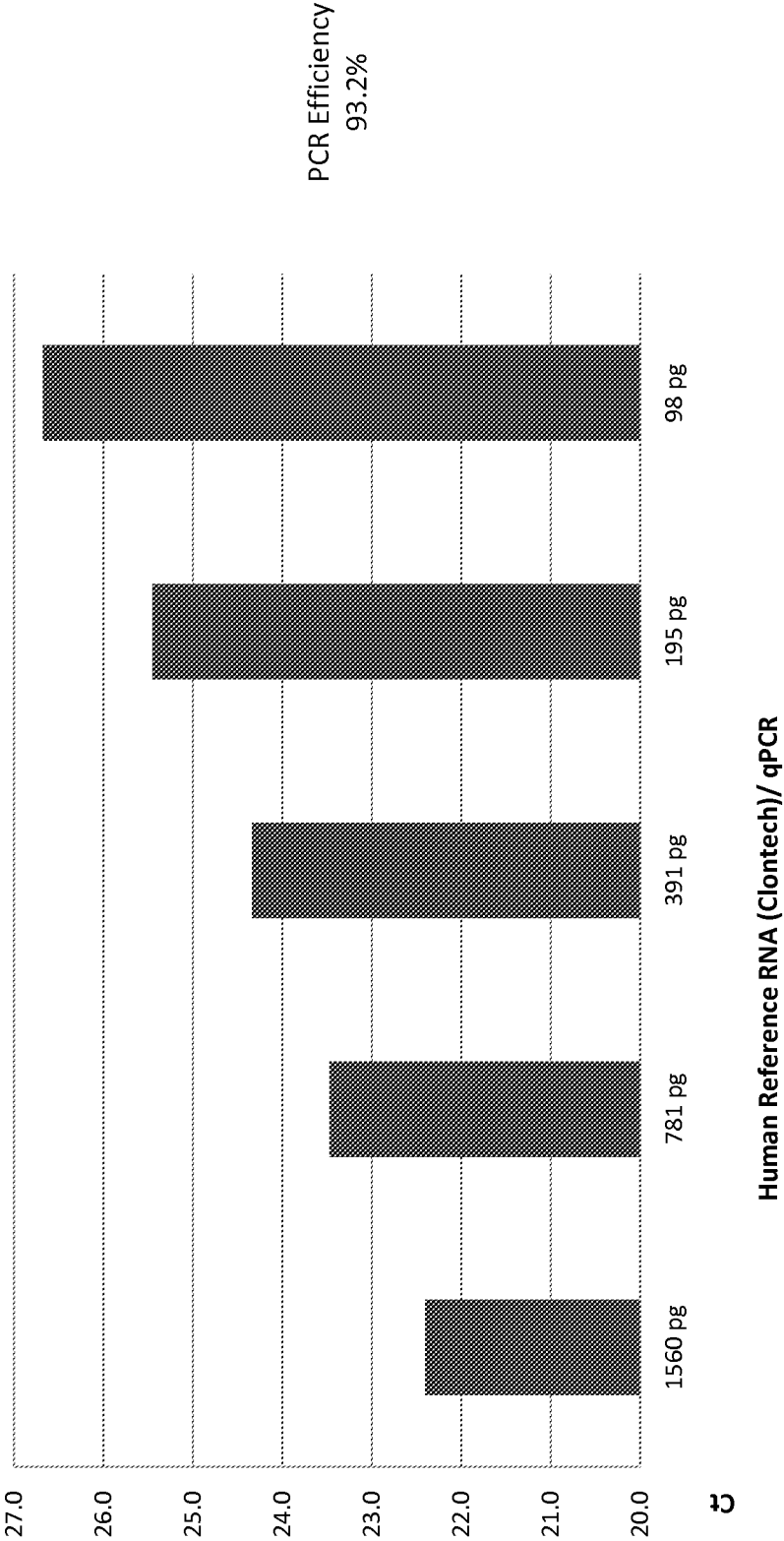


Fig 48

WDR72 Expression in the FlexScript LDA Assay

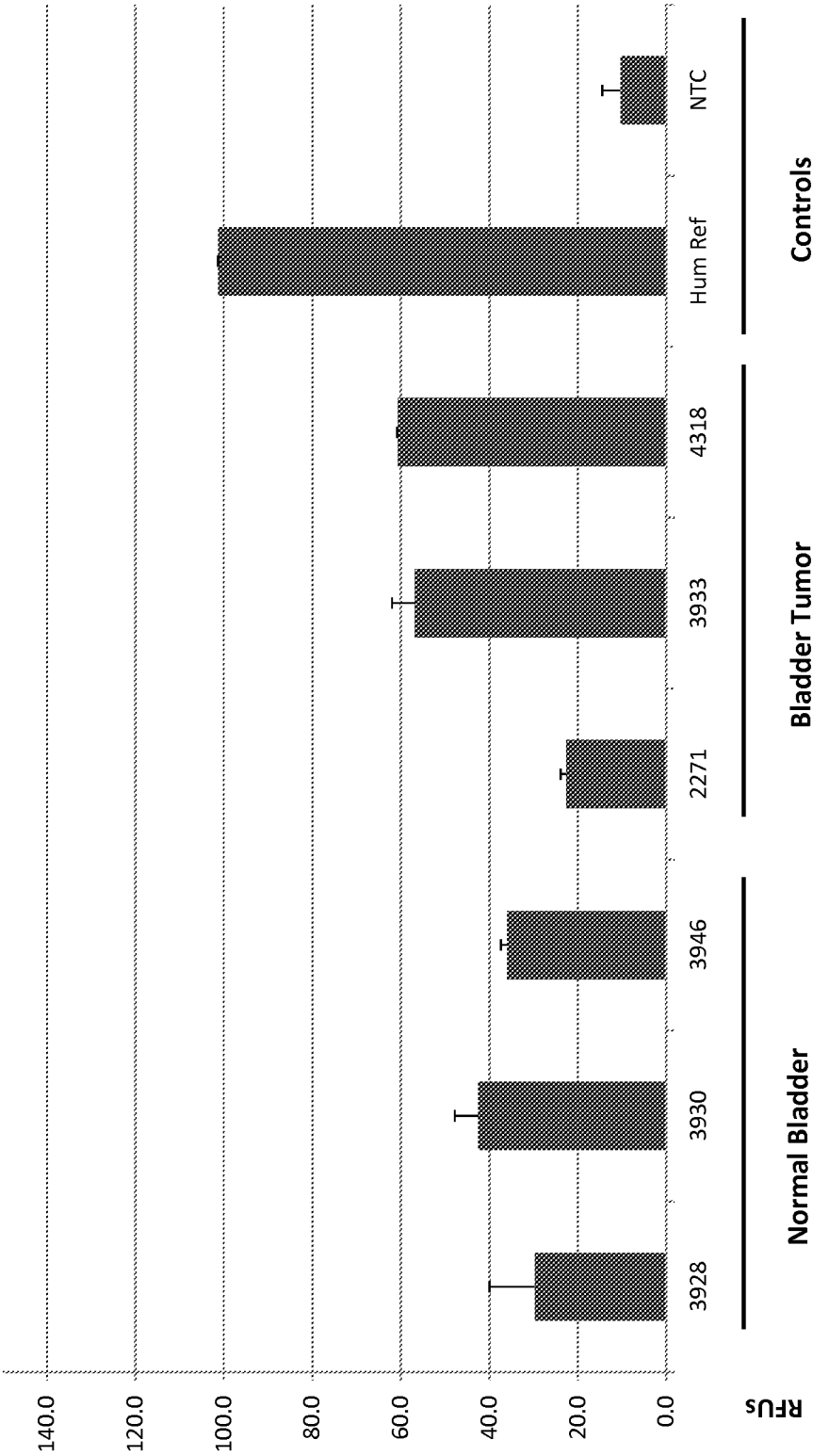


Fig 49
WDR72 (JK1395+JK1416) Expression Relative to GAPDH
in TissueScan Bladder I Array

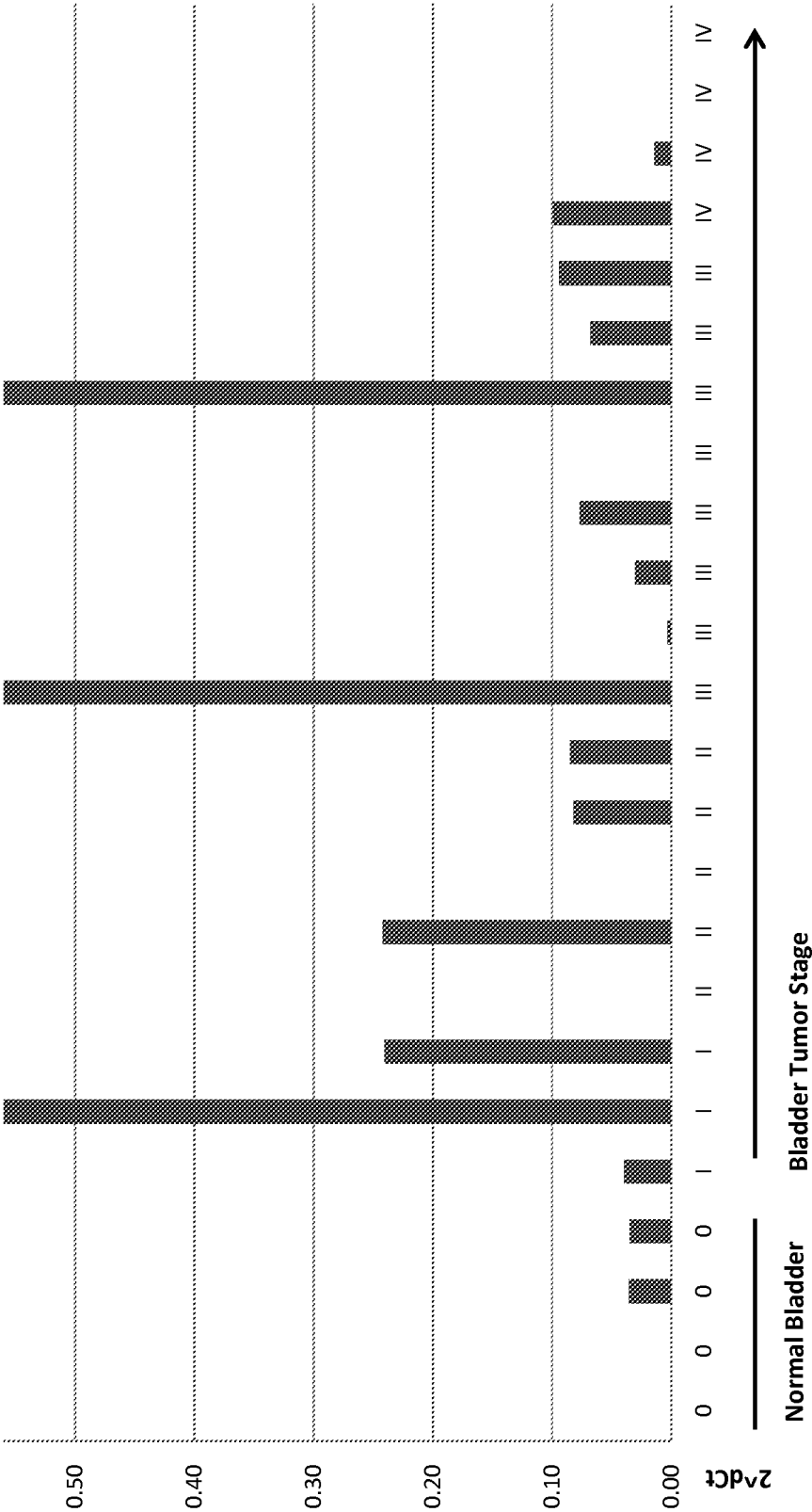


Fig 50

WDR72 Expression (JK1395+JK1416) in Urine
and RNA-Spiked Urine

