label, for detecting hybridization. A wide variety of appropriate indicators are known in the art including, fluorescent, radioactive, enzymatic or other ligands (*e. g.* avidin/biotin).

Probes typically comprise single-stranded nucleic acids of between 10 to 1000 nucleotides in length, for instance of between 10 and 800, more preferably of between 15 and 700, typically of between 20 and 500. Primers typically are shorter single-stranded nucleic acids, of between 10 to 25 nucleotides in length, designed to perfectly or almost perfectly match a nucleic acid of interest, to be amplified. The probes and primers are "specific" to the nucleic acids they hybridize to, i.e. they preferably hybridize under high stringency hybridization conditions (corresponding to the highest melting temperature Tm, *e.g.,* 50 % formamide, 5x or 6x SCC. SCC is a 0.15 M NaCl, 0.015 M Na-citrate). For instance, the probes and primers can be selected from the Taqman Applied ones cited in the present application.

The nucleic acid primers or probes used herein may be assembled as a kit. Such a kit includes consensus primers and molecular probes. A preferred kit also includes the components necessary to determine if amplification has occurred. The kit may also include, for example, PCR buffers and enzymes; positive control sequences, reaction control primers; and instructions for amplifying and detecting the specific sequences.

In another preferred embodiment, the expression level is determined by DNA chip analysis. Such DNA chip or nucleic acid microarray consists of different nucleic acid probes that are chemically attached to a substrate, which can be a microchip, a glass slide or a microsphere-sized bead. A microchip may be constituted of polymers, plastics, resins, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, or nitrocellulose. Probes comprise nucleic acids such as cDNAs or oligonucleotides that may be about 10 to about 60 base pairs. To determine the expression level, a sample from a test subject, optionally first subjected to a reverse transcription, is labelled and contacted with the microarray in hybridization conditions, leading to the formation of complexes between target nucleic acids that are complementary to probe sequences attached to the microarray surface. The labelled hybridized complexes are then detected and can be quantified or semi-quantified. Labelling may be achieved by various methods, *e.g.* by using radioactive or fluorescent labelling. Many variants of the microarray hybridization technology are available to the man skilled in the art (see e.g. the review by Hoheisel, et 2006)

Other methods for determining the expression level of said genes include the determination of the quantity of proteins encoded by said genes.

Such methods comprise contacting a biological sample with a binding partner capable of selectively interacting with a marker protein present in the sample. The binding partner is generally an antibody that may be polyclonal or monoclonal, preferably monoclonal.

The presence of the protein can be detected using standard electrophoretic and immunodiagnostic techniques, including immunoassays such as competition, direct reaction, or sandwich type assays. Such assays include, but are not limited to, Western blots; agglutination tests; enzyme-labeled and mediated immunoassays, such as ELISAs; biotin/avidin type assays; radioimmunoassays; immunoelectrophoresis; immunoprecipitation, etc. The reactions generally include revealing labels such as fluorescent, chemiluminescent, radioactive, enzymatic labels or dye molecules, or other methods for detecting the formation of a complex between the antigen and the antibody or antibodies reacted therewith.

The aforementioned assays generally involve separation of unbound protein in a liquid phase from a solid phase support to which antigen-antibody complexes are bound. Solid supports which can be used in the practice of the invention include substrates such as nitrocellulose (*e. g.*, in membrane or microtiter well form); polyvinylchloride (*e. g.,* sheets or microtiter wells); polystyrene latex (*e.g.*, beads or microtiter plates); polyvinylidine fluoride; diazotized paper; nylon membranes; activated beads, magnetically responsive beads, and the like.

More particularly, an ELISA method can be used, wherein the wells of a microtiter plate are coated with an antibody against the protein to be tested. A biological sample containing or suspected of containing the marker protein is then added to the coated wells. After a period of incubation sufficient to allow the formation of antibody-antigen complexes, the plate(s) can be washed to remove unbound moieties and a detectably labeled secondary binding molecule added. The secondary binding molecule is allowed to react with any captured sample marker protein, the plate washed and the presence of the secondary binding molecule detected using methods well known in the art.

The invention further provides a tool for implementing said methods, e.g. a DNA chip comprising a solid support which carries nucleic acids that are specific to at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes selected from the group consisting of the genes listed in Tables 1 to 6, optionally Tables 1 and 2. Optionally, the DNA chip further carries nucleic acids that are specific to at least one gene selected from the group consisting of the genes listed in Tables 3 to 6, optionally Tables 3 and 4. In a preferred embodiment, the DNA chip carries nucleic acids that are specific to genes of Table 6, and optionally of one, several or all genes of Table 5. Optionally, the DNA chip may further include nucleic acids specific of additional genes from Tables 1-4.The DNA chip can further comprise

nucleic acids for control gene, for instance a positive and negative control or a nucleic acid for an ubiquitous gene in order to normalize the results. In addition, the present invention also provides a kit for implementing said methods comprising detection means that are specific to at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes selected from the group consisting of the genes listed in Tables 1 to 6, optionally Tables 1 and 2. Optionally, the kit further comprises detection means that are specific to at least one gene selected from the group consisting of the genes listed in Tables 3 to 6, optionally Tables 3 and 4. In a preferred embodiment, the kit carries detection means that are specific to genes of Table 6, and optionally of one, several or all genes of Table 5. Optionally, the kit may further include detection means for additional genes from Tables 1-4. In particular, the detection means can be a pair of primers, a probe or an antibody. The kit can further comprise control reagents and other necessary reagents.

In a particular embodiment, the genes, preferably additional genes are selected for the tool or kit as above detailed for the methods of the invention. Preferably, the at least 5 genes, preferably additional genes, are selected from the group consisting of ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1, RP4-692D3.1, CB985069, ARL14, AY831680, XRN1, THAP5, ZNF248, BC016022, PLAG1, THC2724353, THC2488083, C5orf41, BMS1P5, BMS1, THC2627008, PLA2G4A, DPY19L2, VCX2, PPP1R1C, GLT25D2, KIAA1841, IFIT2, ZNF596, TSPAN19, BC029907, C10orf107, ZNF594, AMPD1, C21orf88, THC2694827, HSPC105, IFI44, THC2662262, FAM84A, DNAH7, KHDRBS2, NANP, AK091357, N4BP2L1, FAM105A, CA941346, CCDC68, CASC1, FAM90A12, PBX1, THC2739159, KCNQ2, ANXA1, AL122040, THC2655194, ENST00000342608, DSC2, ENOX1, IL13, BG571904, BX455216, LOC729085, BG188151, LOC729409, C1orf103, PPP1R14C, NAIP, C13orf31, GOLGA8E, AK022848, CXorf22, KIF5C, LRRCC1, FAM81B, ID2, CMYA5, C1orf194, TTC18, tcag7.1314, ZNF385B, ADAMTS6, RHOU, ENST00000378850, C2orf55, GPR83, LRRIQ1, WDR31, DEFB126, ARMETL1, LOC642826, LOC129881, C2orf13, THC2553512, ACVR1C, ZNF207, ANTXR1, CHD9, THC2526838, ABCA12, TncRNA, FKTN, PTPRG, ZNF233, ENST00000370378, FANK1, PCM1, SERPINI1, ARID4B, KIAA1377, FGF7, CV339166, LINCR, DA834198, CFH, SCG2, ARHGEF10, DA093175, GOLGA8A, AK021467, LOC283666, FLJ35767, THC2725553, ZNF430, CCDC141, MAP3K13, CCDC66, THC2727226, THC2528990, THC2718728, THC2507829, AK123972, EDEM3, DB304731, TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14, CR594735, FLJ11235, C15orf52, LIMCH1, LOH11CR2A, BX281122, GPR110, ARNT2, ATP6V0A4, PDGFRB, ELA3B, NEDD9, MYH6, SLC35F2, HAS3, COLEC12, SLC3A2, AW993939, RUNX2, SUSD3, PLAU, SLC22A3, FCRL4, DOCK2, SOX3, THC2616558, RNASET2, LOC100130360, IL1R2, MGAT5B, TCF7L1, AF222857, AHNAK, HOXB8, S100A16,

INSIG1 and DCDC2. More preferably, the genes are selected from the group consisting of ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1, RP4-692D3.1, CB985069, ARL14, AY831680, XRN1, THAP5, ZNF248, BC016022, PLAG1, THC2724353, THC2488083, C5orf41, BMS1P5, BMS1, THC2627008, PLA2G4A, DPY19L2, VCX2, PPP1R1C, GLT25D2, KIAA1841, IFIT2, ZNF596, TSPAN19, BC029907, C10orf107, ZNF594, AMPD1, C21orf88, THC2694827, HSPC105, IFI44, THC2662262, FAM84A, DNAH7, KHDRBS2, NANP, AK091357, N4BP2L1, FAM105A, CA941346, CCDC68, CASC1, FAM90A12, PBX1, THC2739159, KCNQ2, ANXA1, AL122040, THC2655194, ENST00000342608, DSC2, ENOX1, IL13, BG571904, BX455216, LOC729085, BG188151, LOC729409, C1orf103, PPP1R14C, NAIP, C13orf31, GOLGA8E, AK022848, CXorf22, KIF5C, TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14, CR594735, FLJ11235, C15orf52, LIMCH1, LOH11CR2A, BX281122, GPR110, ARNT2, ATP6V0A4, PDGFRB, ELA3B, NEDD9, MYH6, SLC35F2, HAS3, COLEC12, SLC3A2, AW993939, RUNX2 and SUSD3. Even more preferably, the genes are selected from the group consisting of ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1, RP4-692D3.1, TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14 and CR594735. In the most preferred embodiment, the genes are selected from the group consisting of ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB and CR627122. Optionally, at least one further gene is selected for the tool or kit, said gene being selected from the group consisting of the genes listed in Tables 3 and 4, preferably TFPI2, PCDH7, SMAD9, AK090762, RAB39B, BF831953, AL050204, VCX, ITGA2, CXCR4, SLC16A10, PDE1A, MAL, KRT80, FXYD2 and AK3L1, more preferably TFPI2, PCDH7, SMAD9, AK090762, RAB39B, BF831953, AL050204, VCX, CXCR4, SLC16A10, PDE1A, MAL, and even more preferably TFPI2, PCDH7, SMAD9, CXCR4 and SLC16A10.

The present invention also relates to the use of a DNA chip or a kit of the invention for preparing a kit for predicting or monitoring whether a patient affected by a cancer is responsive to a treatment with a molecule of the taxoid family. Preferably, the cancer is selected from the group consisting of the breast cancer, the lung cancer, the prostate cancer, the gastric cancer and the head and neck cancer. More preferably the cancer is the prostate cancer. In a preferred embodiment, the molecule of the taxoid family is selected from the group consisting of docetaxel, larotaxel, cabazitaxel (XRP6258), BMS-184476, BMS-188797, BMS-275183, ortataxel, RPR 109881A, RPR 116258, NBT-287, PG-paclitaxel, ABRAXANE®, Tesetaxel,

IDN 5390, Taxoprexin, DHA-paclitaxel, and MAC-321. More preferably, the molecule of the taxoid family is docetaxel.

The present invention further concerns methods for screening or identifying a compound suitable for improving the treatment of a cancer with a molecule of the taxoid family or for reducing the resistance development during the treatment of a cancer with a molecule of the taxoid family.

In a first embodiment, the method comprises: 1) providing a cell-line with at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes over-expressed and/or under-expressed respectively selected from the group of over-expressed genes of Tables 1, 3 and 5, optionally of Table 1, and under-expressed genes of Tables 2, 4 and 5, optionally of Table 2; 2) contacting said cell-line with a test compound; 3) determining the expression level of said at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes; and, 4) selecting the compound which decreases the expression level of over-expressed genes and increases the expression level of under-expressed genes. More preferably, the genes are selected from the genes of Tables 5 and 6. Still more preferably, at least the genes of Table 6 are selected, and optionally one, several or all genes of Table 5.

In a second embodiment, the method comprises: 1) providing a cell-line sensitive to the molecule of the taxoid family; 2) contacting said cell-line with a test compound and the molecule of the taxoid family; 3) determining the expression level of said at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes selected from the genes listed in Tables 1 to 6, optionally of Tables 1 and 2; and, 4) selecting the compound which inhibits the appearance of an over-expression and/or an under-expression of at least 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 500 or 1000 genes respectively selected from the group of genes of over-expressed genes of Tables 1, 3 and 5, optionally of Table 1, and under-expressed genes of Tables 2, 4 and 5, optionally of Table 2. More preferably, the genes are selected from the genes of Tables 5 and 6. Still more preferably, at least the genes of Table 6 are selected, and optionally one, several or all genes of Table 5.

In a third embodiment, the method comprises: 1) providing a cell-line with at least one gene over-expressed and/or under-expressed respectively selected from the group consisting of ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1, RP4-692D3.1, CB985069, ARL14, AY831680, XRN1, THAP5, ZNF248, BC016022, PLAG1, THC2724353, THC2488083, C5orf41, BMS1P5, BMS1, THC2627008, PLA2G4A, DPY19L2, VCX2, PPP1R1C, GLT25D2, KIAA1841, IFIT2, ZNF596, TSPAN19,

BC029907, C10orf107, ZNF594, AMPD1, C21orf88, THC2694827, HSPC105, IFI44, THC2662262, FAM84A, DNAH7, KHDRBS2, NANP, AK091357, N4BP2L1, FAM105A, CA941346, CCDC68, CASC1, FAM90A12, PBX1, THC2739159, KCNQ2, ANXA1, AL122040, THC2655194, ENST00000342608, DSC2, ENOX1, IL13, BG571904, BX455216, LOC729085, BG188151, LOC729409, C1orf103, PPP1R14C, NAIP, C13orf31, GOLGA8E, AK022848, CXorf22, KIF5C, LRRCC1, FAM81B, ID2, CMYA5, C1orf194, TTC18, tcag7.1314, ZNF385B, ADAMTS6, RHOU, ENST00000378850, C2orf55, GPR83, LRRIQ1, WDR31, DEFB126, ARMETL1, LOC642826, LOC129881, C2orf13, THC2553512, ACVR1C, ZNF207, ANTXR1, CHD9, THC2526838, ABCA12, TncRNA, FKTN, PTPRG, ZNF233, ENST00000370378, FANK1, PCM1, SERPINI1, ARID4B, KIAA1377, FGF7, CV339166, LINCR, DA834198, CFH, SCG2, ARHGEF10, DA093175, GOLGA8A, AK021467, LOC283666, FLJ35767, THC2725553, ZNF430, CCDC141, MAP3K13, CCDC66, THC2727226, THC2528990, THC2718728, THC2507829, AK123972, EDEM3, DB304731, preferably ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1, RP4-692D3.1, CB985069, ARL14, AY831680, XRN1, THAP5, ZNF248, BC016022, PLAG1, THC2724353, THC2488083, C5orf41, BMS1P5, BMS1, THC2627008, PLA2G4A, DPY19L2, VCX2, PPP1R1C, GLT25D2, KIAA1841, IFIT2, ZNF596, TSPAN19, BC029907, C10orf107, ZNF594, AMPD1, C21orf88, THC2694827, HSPC105, IFI44, THC2662262, FAM84A, DNAH7, KHDRBS2, NANP, AK091357, N4BP2L1, FAM105A, CA941346, CCDC68, CASC1, FAM90A12, PBX1, THC2739159, KCNQ2, ANXA1, AL122040, THC2655194, ENST00000342608, DSC2, ENOX1, IL13, BG571904, BX455216, LOC729085, BG188151, LOC729409, C1orf103, PPP1R14C, NAIP, C13orf31, GOLGA8E, AK022848, CXorf22 and KIF5C, more preferably ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6, BC044624, AY358241, ZNF251, ST6GAL2, LOC643401, NOV, CLGN, PROM1, SPEF2, FLRT2, RGS2, FOXP2, TRIM55, PKD2L1 and RP4-692D3.1, even more preferably ENST00000399723, BI836406, C10orf79, AK022962, TMTC1, LOC728295, SUSD5, WNT6 and BC044624 for the over-expressed genes, and TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14, CR594735, FLJ11235, C15orf52, LIMCH1, LOH11CR2A, BX281122, GPR110, ARNT2, ATP6V0A4, PDGFRB, ELA3B, NEDD9, MYH6, SLC35F2, HAS3, COLEC12, SLC3A2, AW993939, RUNX2, SUSD3, PLAU, SLC22A3, FCRL4, DOCK2, SOX3, THC2616558, RNASET2, LOC100130360, IL1R2, MGAT5B, TCF7L1, AF222857, AHNAK, HOXB8, S100A16, INSIG1 and DCDC2, preferably TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14, CR594735, FLJ11235, C15orf52, LIMCH1, LOH11CR2A, BX281122, GPR110, ARNT2, ATP6V0A4, PDGFRB, ELA3B, NEDD9, MYH6, SLC35F2, HAS3, COLEC12, SLC3A2, AW993939, RUNX2 and SUSD3, more preferably TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB, CR627122, JAM3, CXCL14 and

CR594735, even more preferably TPD52L1, MFAP5, EHF, NCF2, TRIM6, PERLD1, ATXN1, INHBB and CR627122 for the under-expressed genes; 2) contacting said cell-line with a test compound; 3) determining the expression level of said at least one gene; and, 4) selecting the compound which decreases the expression level of over-expressed genes and increases the expression level of under-expressed genes.

In a fourth embodiment, the method comprises 1) providing a cell-line with the genes PCDH7, KHDRBS2, AUTS2, and C2orf55 being over-expressed and the genes JAM3, DCDC2, MFAP5, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3 being under-expressed; 2) contacting said cell-line with a test compound; 3) determining the expression level of said genes; and, 4) selecting the compound which decreases the expression level of one or several of the over-expressed genes and increases the expression level of one or several of the under-expressed genes.

In a fifth embodiment, the method comprises 1) providing a cell-line sensitive to the molecule of the taxoid family; 2) contacting said cell-line with a test compound and the molecule of the taxoid family; 3) determining the expression level of the genes JAM3, PCDH7, DCDC2, KHDRBS2, MFAP5, AUTS2, C2orf55, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3; and, 4) selecting the compound which inhibits the appearance of an over-expression of the genes PCDH7, KHDRBS2, AUTS2, and C2orf55 and/or an under-expression of the genes JAM3, DCDC2, MFAP5, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3.

Preferably, the cell-line is a cancer cell-line. In particular, the cancer cell-line is specific of the targeted cancer. For instance, if the prostate cancer is to be treated, then the cell-line is a prostate cancer cell-line.

In a preferred embodiment, the molecule of the taxoid family is selected from the group consisting of docetaxel, larotaxel, cabazitaxel (XRP6258), BMS-184476, BMS-188797, BMS-275183, ortataxel, RPR 109881A, RPR 116258, NBT-287, PG-paclitaxel, ABRAXANE®, Tesetaxel, IDN 5390, Taxoprexin, DHA-paclitaxel, and MAC-321. More preferably, the molecule of the taxoid family is docetaxel. Preferably, the cancer is selected from the group consisting of the breast cancer, the lung cancer, the prostate cancer, the gastric cancer and the head and neck cancer. More preferably the cancer is the prostate cancer.

The example illustrates the invention without limiting its scope.

EXAMPLE

Methods

Cell culture and selection of docetaxel-resistant clones

The human androgen-independent IGR-CaP1 cell line recently obtained for a localized prostate cancer was maintained in RPMI medium complemented with 10% FBS and antibiotics. Docetaxel-resistant clones were selected by culturing the cells in docetaxel in a dose-escalation manner. Initial culture was done in 5nM docetaxel. Cellular clones surviving in the presence of 5nM docetaxel were maintained in culture during four passages, and then the concentration of docetaxel in the medium was increased to 12nM, 25nM, 50nM, 100nM and 200nM. The same selection methodology was followed with each increase in docetaxel concentration. Once cells were freely dividing in each dose of docetaxel mediums, they were considered as resistant and labelled IGR-CaP1-R. Cell cultures were maintained at 70% confluency and medium was changed every 48 h.

Total RNA Preparation and Reverse Transcription

Total RNA from parental and docetaxel-resistant IGR-CaP1 cells was isolated using TriReagent (Sigma-Aldrich) and purified with RNeasy Micro Kit (Qiagen) according to manufacturer's protocols. Quality of RNA preparation, based on the RNA Integrity Number (RIN), was assessed using the Agilent RNA 6000 Nano Kit as developed on the Agilent 2100 Bioanalyzer device (Agilent Technologies, Palo Alto, CA). All specimens included in this study displayed a RIN of 10. RNA samples were frozen in nuclease-free water (Qiagen).

Oligo Microarray Technology

Parental and resistant-cell line total RNAs were directly compared by using Agilent oligonucleotide dual-color technology, running dye-swap and duplicate experiments. Total RNA from the parental IGR-CaP1 cell line without treatment was used as the RNA reference. Total RNA from IGR-CaP1 cells resistant to treatment with 5nM, 12nM, 25nM, 50nM, 100nM and 200nM of docetaxel respectively, were used as samples. Probe synthesis and labeling were performed by Agilent's Low Fluorescent Low input Linear Amplification Kit. Hybridization was performed on the Agilent 4x44K Human 1A (G4112F) long (60-bp) oligonucleotide microarrays (Agilent Technologies) by using reagents and protocols provided by the manufacturer. Feature extraction software provided by Agilent (Version A.9.5.3.1) was used to quantify the intensity of fluorescent images and to normalize results using the linear and lowess subtraction method.

The methodology described below is based on a dose-dependent gene expression changes:

Under the hypothesis of a clone enrichment, and/or a biological effect due to drug increasing, monotonically increasing or decreasing expression profiles were identified by using a 5-parameters logistic regression model: $y_g = B + \frac{(T-B)}{\left[1+10^{(x_c-x)*s}\right]^p}$

where y_g is the log.ratio of treatment vs. reference for the gene g, x is the drug-dose in Log_{10}[nM], and B, T, x_c, p are, respectively, the estimated minimal value, the estimated maximal value, the slope at the inflexion point, and the asymmetric parameter.

For each probe, parameters were first initialized with the observed values, and then optimized by an iterative method of gradient (the Newton-Raphson method). The aim of this iterative algorithm is to minimize the weighted quadratic sum of residuals:

$$S = \Sigma_i w_i (y_i.fit - y_i.obs)^2 \quad \text{where} \quad w_i = \frac{1}{|y_i.fit - y_i.obs|}$$

The performance of the fitting was measured, for each probe, by a robust linear regression (RLR) of the fitted values against the observed values.

Probes potentially associated with the drug increasing were selected on the 2 following criterion:

RLRp-value $\leq$ 1e-5, and |fold change| $\geq$ 2 between the first and the last dose (resp: 5 and 200nM), considering the fold change estimated by the 5-parameters logistic regression model.

Calculations and graphic visualizations were performed in R (free software version 2.6.2), by using the package "MASS" (version 7.2-40), and supplemental scripts, in R language, written in the lab (F. Commo).

RESULTS

Generation of acquired resistance to Docetaxel *in vitro*. Prostate cancer IGR-CaP1 cells were used to generate successive docetaxel-resistant cell lines. The addition of docetaxel induced a selection process, whereby a large majority of cells initially underwent cell death until the ability to proliferate was regained. The inventors obtained IGR-CaP1 resistant (IGR-CaP1-R) clones which survived in medium containing respectively 5nM, 12nM, 25nM, 50nM, 100nM and 200nM of docetaxel. Cell cycle analysis was done to show acquired resistance to drug. The resistant cell lines showed cell cycle similar to the parental IGR-CaP1 cells, suggesting that acquired resistance had been gained (not shown).

Genome-wide analysis of IGR-CaP1 docetaxel-resistant lines using microarray. Human genome-wide analysis of gene expression changes was realized in order to stringently

identify human genes that might represent the molecular signature of resistance or sensitivity to docetaxel in prostate cancer. Untreated IGR-CaP1 parental cell lines were used as baseline. Such genes were those for which expression changes (at least one probe in case of multiple probe sets per gene) appeared as drug-dependent, in the sense of criterion described above.

In the first analysis, 772 genes were over-expressed (Tables 1 and 3) and 309 were down-regulated (Tables 2 and 4) in docetaxel-resistant cells. These genes were sorted out by the mean of the fold change observed between the first and the last doses of docetaxel (between 5 and 200 nM).

A second analysis was performed from biological duplicates to confirm the first data set. In the second analysis, only the irreversible resistance mechanisms were retained by using resistant cells cultured in the absence of drug during two passages before the microarray analysis. The second analysis generated a list of 486 genes in which 44 genes were already observed in the first analysis. In the list of 44 genes commons in the two analyses, 17 genes were over-expressed and 27 genes were down-regulated in docetaxel-resistance cells (Table 5). These genes were sorted out by the mean of the fold change observed between the first and the last doses of docetaxel (between 5 and 200 nM).

Among these genes, a subset of 17 genes was selected containing 4 over-expressed genes and 13 under-expressed genes in docetaxel-resistance cells (Table 6). This set of genes has been selected by the following method.

Table 1: First list of the over-expressed genes

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
ENST00000399723	AK090412	Hs.656011	hs|1q12	-0,532	0,134	-0,173	-0,222	0,451	0,773	20,197	2,20E-06
BI836406	BI836406	Hs.1302203	hs|4q22.1	-0,285	0,130	0,601	0,857	1,070	0,984	18,566	1,61E-10
C10orf79	NM_025145	Hs.288927	hs|10q25.1	-0,498	0,030	0,049	0,449	0,347	0,766	18,347	5,60E-04
AK022962	AK022962	Hs.654412	hs|1q23.3	0,000	0,046	0,780	1,186	1,188	1,118	15,444	2,64E-12
TMTC1	NM_175861	Hs.401954	hs|12p11.22	-0,321	-0,077	0,643	0,839	0,981	0,820	15,296	7,16E-12
LOC728295	XR_015377	Hs.636711	hs|1q12	-0,490	0,017	-0,233	-0,459	0,354	0,680	14,803	8,14E-08
SUSD5	AB011099	Hs.196647	hs|3p22.3	-0,568	-0,260	-0,364	-0,179	0,398	0,554	13,302	7,36E-04
WNT6	NM_006522	Hs.29764	hs|2q35	0,165	0,593	0,914	1,045	1,170	1,304	12,542	1,08E-05
BC044624	BC044624	Hs.654412	hs|1q23.3	0,325	0,756	1,134	1,226	1,389	1,334	10,428	5,01E-05
AY358241	AY358241	Hs.626042	hs|12q23.3	-0,170	0,637	0,980	0,826	0,827	0,876	9,965	7,40E-07
ZNF251	BC006258	Hs.534516	hs|8q24.3	-0,365	0,089	0,042	0,278	0,077	0,624	9,730	2,11E-05
ST6GAL2	AB058780	Hs.98265	hs|2q12.3	-0,599	-0,541	-0,040	-0,067	0,403	0,393	9,586	7,95E-05
LOC643401	BC039509	Hs.533212	hs|5p14.1	0,111	0,333	0,137	0,165	0,981	1,118	9,578	6,61E-14
NOV	NM_002514	Hs.235935	hs|8q24.12	-0,304	0,024	0,568	0,436	0,590	0,677	9,304	2,21E-05
CLGN	NM_004362	Hs.86368	hs|4q31.1	-0,214	0,064	0,256	0,241	0,765	0,743	9,045	7,64E-04
PROM1	NM_006017	Hs.614734	hs|4p15.32	-0,640	-0,574	0,286	0,333	0,225	0,311	8,952	2,30E-15
SPEF2	NM_024867	Hs.298863	hs|5p13.2	-0,304	0,000	0,156	0,337	0,551	0,644	8,861	4,78E-05
FLRT2	NM_013231	Hs.533710	hs|14q31.3	-0,690	-0,382	0,040	0,180	0,113	0,284	8,564	3,90E-05
RGS2	NM_002923	Hs.78944	hs|1q31.2	-0,032	0,048	0,417	0,368	0,723	0,893	8,426	2,12E-04
FOXP2			hs|7q31.1	0,063	0,265	0,717	0,781	0,546	0,987	8,291	7,83E-06
TRIM55	NM_184086	Hs.85524	hs|8q13.1	-0,382	-0,104	0,582	0,576	0,147	0,523	8,181	5,17E-04
PKD2L1	NM_033215	Hs.433652	hs|Xp11.23	0,353	0,056	0,071	0,409	0,461	0,965	8,134	1,80E-05
RP4-692D3.1	NM_001080850	Hs.473495	hs|1p34.2	0,235	0,481	0,692	0,649	0,892	1,272	8,036	4,13E-04
CB985069			hs|4q22.1	-0,976	-0,365	-0,860	-0,627	-0,356	-0,077	7,853	4,41E-06
ARL14	NM_025047	Hs.287702	hs|3q26.1	-0,437	-0,545	-0,408	-0,525	-0,009	0,452	7,749	3,74E-04
AY831680	AY831680	Hs.526752	hs|3q13.12	0,181	0,386	0,913	1,091	1,033	1,058	7,541	6,17E-10
XRN1	NM_019001	Hs.435103	hs|3q23	0,005	0,078	0,084	0,109	0,318	0,379	7,483	2,62E-12
THAP5	NM_182529	Hs.650237	hs|7q31.1	0,103	0,133	0,117	0,131	0,387	0,499	7,368	3,83E-05
ZNF248	NM_021045	Hs.572001	hs|10p11.21	-0,123	0,326	-0,062	-0,037	0,391	0,742	7,332	8,55E-04
BC016022	BC016022	Hs.679496		-0,098	0,398	0,160	0,227	0,590	0,767	7,315	3,75E-04
PLAG1	NM_002655	Hs.14968	hs|8q12.1	-0,353	-0,429	-0,074	-0,175	0,268	0,505	7,207	7,04E-04
THC2724353			hs|15q11.2	0,186	0,317	0,216	0,357	0,696	1,032	7,024	5,20E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
THC2488083			hs|17p11.2	-0,038	0,000	-0,011	-0,005	0,514	0,829	6,932	8,84E-08
C5orf41	NM_153607	Hs.484195	hs|5q35.2	0,059	0,425	0,254	0,416	0,618	1,010	6,865	1,02E-04
BMS1P5	AL833330	Hs.652959	hs|10q11.22	-0,013	0,270	0,525	0,675	0,793	0,824	6,850	4,34E-08
BMS1	NM_014753	Hs.10848	hs|10q11.21	-0,043	0,276	0,457	0,656	0,801	0,654	6,701	1,04E-04
THC2627008			hs|4q24	-0,500	-0,162	-0,038	0,227	0,267	0,324	6,668	1,34E-05
PLA2G4A	NM_024420	Hs.497200	hs|1q31.1	-0,526	-0,241	-0,434	-0,267	0,158	0,375	6,580	8,10E-12
DPY19L2	NM_173812	Hs.533644	hs|12q14.2	0,157	0,309	0,303	0,659	0,708	0,787	6,543	3,18E-05
VCX2	NM_016378	Hs.279737	hs|Xp22.31	0,421	0,441	0,602	0,451	0,877	1,223	6,329	1,77E-07
PPP1R1C	NM_001080545	Hs.10941	hs|2q31.3	-0,431	-0,367	-0,349	-0,704	0,096	0,364	6,244	3,36E-05
GLT25D2	NM_015101	Hs.387995	hs|1q25.3	-0,557	-0,383	0,233	0,284	0,112	0,143	6,207	1,85E-04
KIAA1841	BC039298	Hs.468653	hs|2p15	-0,347	0,132	-0,135	-0,012	0,311	0,445	6,191	6,70E-04
IFIT2	NM_001547	Hs.437609	hs|10q23.31	0,181	0,194	0,031	0,613	0,586	0,974	6,185	6,76E-05
ZNF596	NM_173539	Hs.591388	hs|8p23.3	-0,058	0,000	0,066	-0,051	0,419	0,781	6,175	1,94E-04
TSPAN19	NM_001924	Hs.80409	hs|1p31.3	0,000	0,068	0,405	0,491	0,607	0,789	6,155	1,68E-04
BC029907	BC029907	Hs.405427	hs|1p22.1	0,022	0,174	0,251	0,478	0,628	0,811	6,131	5,50E-06
C10orf107	NM_173554	Hs.673160	hs|10q21.2	0,508	0,660	1,258	1,312	1,232	1,294	6,106	3,87E-12
ZNF594	AB058774	Hs.658402	hs|17p13.2	-0,050	0,212	-0,099	-0,037	0,391	0,732	6,100	4,14E-06
AMPD1	NM_000036	Hs.89570	hs|1p13.2	-0,338	0,000	-0,180	-0,261	0,060	0,668	6,082	9,22E-04
C21orf88	BC080530	Hs.375120	hs|21q22.2	0,077	0,271	0,783	0,940	0,855	0,642	6,007	3,23E-12
THC2694827			hs|Xq22.1	-0,035	0,284	-0,078	0,202	0,440	0,742	5,999	1,56E-05
HSPC105	NM_145168	Hs.87779	hs|16q23.3	0,000	-0,008	-0,421	0,000	0,478	0,764	5,976	4,68E-05
IFI44	NM_006417	Hs.82316	hs|1p31.1	-0,039	0,217	0,475	0,248	0,686	0,735	5,948	2,49E-06
THC2662262			hs|14q32.32	-0,646	-0,243	-0,458	-0,263	-0,178	0,130	5,940	9,66E-04
FAM84A	NM_145175	Hs.260855	hs|2p24.3	0,485	0,175	0,418	0,711	1,062	1,146	5,923	2,19E-09
DNAH7	NM_018897	Hs.97403	hs|2q32.3	-0,145	0,079	0,243	0,356	0,373	0,653	5,856	9,23E-05
KHDRBS2	NM_152688	Hs.519794	hs|6q11.1	-0,433	-0,171	0,316	0,587	0,210	0,330	5,791	8,68E-12
NANP	AK074335	Hs.666255	hs|20p11.21	-0,507	-0,097	-0,185	0,083	0,237	0,253	5,704	3,94E-04
AK091357	BC036917	Hs.485528	hs|6p12.3	0,149	0,006	0,093	0,072	0,567	0,822	5,626	4,35E-05
N4BP2L1	NM_052818	Hs.161220	hs|13q13.1	0,041	0,204	0,110	0,144	0,492	0,795	5,548	5,93E-05
FAM105A	NM_019018	Hs.591751	hs|5p15.2	-0,404	-0,095	-0,078	-0,209	0,201	0,352	5,537	2,43E-04
CA941346	CA941346		hs|15q11.2	-0,666	0,120	-0,415	-0,207	-0,126	0,110	5,522	3,90E-04
CCDC68	NM_025214	Hs.120790	hs|18q21.2	-0,069	0,000	0,248	0,445	0,446	0,668	5,448	1,72E-08

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
CASC1	NM_018272	Hs.407771	hs|12p12.1	0,073	0,384	0,774	1,070	0,808	0,760	5,439	2,61E-07
FAM90A12	XM_496857	Hs.694406	hs|8p23.1	0,277	0,349	0,420	0,186	0,718	1,013	5,435	2,07E-04
PBX1	NM_002585	Hs.654412	hs|1q23.3	0,099	0,250	0,602	0,979	0,827	0,824	5,428	4,16E-07
THC2739159			hs|9q12	-0,115	0,034	0,573	0,587	0,482	0,574	5,381	8,89E-05
KCNQ2	NM_172109	Hs.161851	hs|20q13.33	-0,345	-0,015	0,466	0,327	0,341	0,385	5,348	2,52E-06
ANXA1	NM_000700	Hs.494173	hs|9q21.13	0,130	0,078	0,350	0,398	0,713	0,856	5,329	4,80E-04
AL122040	AL122040	Hs.594784	hs|15q21.2	0,168	0,000	0,389	0,518	0,805	0,894	5,326	6,86E-04
THC2655194			hs|8q11.23	-0,122	0,320	0,129	0,290	0,291	0,604	5,321	2,72E-05
ENST00000342608	NM_001013675	Hs.291198	hs|22q11.21	0,031	0,000	0,038	0,751	0,732	0,860	5,301	1,29E-05
DSC2	NM_025004	Hs.287555	hs|11q24.2	-0,956	-0,615	-0,148	-0,188	-0,302	-0,235	5,248	9,74E-04
ENOX1	NM_017993	Hs.128258	hs|13q14.11	-0,535	-0,492	-0,165	-0,386	0,121	0,184	5,231	2,00E-04
IL13	NM_002188	Hs.845	hs|5q31.1	0,305	0,276	0,355	0,648	0,810	0,978	5,230	8,80E-07
BG571904	BG571904	Hs.660990	hs|10q22.2	-0,033	0,157	0,445	0,616	0,668	0,492	5,151	7,70E-09
BX455216	N52197	Hs.300701	hs|2q33.3	-0,514	-0,306	0,029	0,486	0,195	0,135	5,141	5,12E-08
LOC729085	AL117530	Hs.646840	hs|3p22.1	-0,801	-1,033	-0,260	-0,124	0,023	-0,093	5,116	2,51E-04
BG188151	BG188151	Hs.71944	hs|5q14.2	0,159	0,224	0,513	0,480	0,808	0,868	5,114	8,26E-04
LOC729409	XR_015594	Hs.587721	hs|12q15	-0,023	0,028	0,197	0,321	0,486	0,684	5,093	1,37E-06
C1orf103	NM_018372	Hs.25245	hs|1p13.3	0,018	0,155	0,213	0,273	0,619	0,725	5,077	2,08E-04
PPP1R14C	NM_030949	Hs.486798	hs|6q25.1	-0,212	0,256	0,054	-0,074	0,378	0,492	5,061	2,52E-04
NAIP	NM_004536	Hs.654500	hs|5q13.2	-0,017	0,370	0,145	0,231	0,518	0,687	5,056	2,09E-05
C13orf31	NM_153218	Hs.210586	hs|13q14.11	-0,227	-0,175	0,005	-0,140	0,382	0,477	5,056	6,87E-06
GOLGA8E	NM_001012423	Hs.454647	hs|15q11.2	0,009	0,360	0,119	0,144	0,453	0,712	5,051	1,35E-10
AK022848	AK022848	Hs.112482	hs|11q14.3	0,027	0,099	-0,026	-0,109	0,207	0,850	5,049	3,49E-04
CXorf22	NM_152632	Hs.680415	hs|Xp21.1	-0,667	-0,354	-0,432	-0,776	-0,077	0,035	5,033	4,89E-04
KIF5C	NM_004522	Hs.660699	hs|2q23.1	-0,173	-0,142	0,013	0,007	0,476	0,528	5,024	5,08E-04
LRRCC1	NM_033402	Hs.193115	hs|8q21.2	-0,084	0,040	0,125	0,212	0,634	0,613	4,985	2,78E-04
FAM81B	NM_152548	Hs.276287	hs|5q15	0,486	0,685	1,083	1,506	1,152	1,125	4,929	7,09E-04
ID2	NM_002166	Hs.180919	hs|2p25.1	-0,446	-0,253	-0,153	-0,356	0,100	0,279	4,928	2,33E-04
CMYA5	NM_153610	Hs.482625	hs|5q14.1	0,000	0,082	0,052	0,046	0,181	0,728	4,899	1,91E-04
C1orf194	BC127905	Hs.446962	hs|1p13.3	0,145	0,337	0,549	0,971	0,626	0,833	4,874	4,56E-10
TTC18	NM_145170	Hs.591367	hs|10q22.2	0,004	0,274	0,386	0,469	0,603	0,706	4,849	1,66E-05
tcag7.1314	AK126364	Hs.186649	hs|7q11.23	0,229	0,442	0,554	0,723	0,862	0,913	4,832	9,08E-07

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
ZNF385B	NM_152520	Hs.655005	hs|2q31.2	-0,525	-0,088	0,315	0,147	0,299	0,406	4,799	4,16E-04
ADAMTS6	NM_197941	Hs.482291	hs|5q12.3	-0,037	0,225	-0,181	0,083	0,287	0,645	4,793	6,71E-04
RHOU	NM_021205	Hs.647774	hs|1q42.13	0,352	0,367	0,554	0,734	0,736	1,030	4,767	1,07E-07
ENST00000378850	BC127739	Hs.549398	hs|4q35.1	-0,429	-0,199	0,001	0,103	0,140	0,249	4,762	3,02E-07
C2orf55	NM_207362	Hs.658091	hs|2q11.2	0,459	0,649	1,123	1,227	1,137	1,030	4,756	6,90E-08
GPR83	NM_016540	Hs.272385	hs|11q21	0,221	0,166	0,385	0,417	0,785	0,898	4,755	2,91E-04
LRRIQ1	NM_032165	Hs.402200	hs|12q21.31	0,008	0,144	0,331	0,463	0,718	0,683	4,736	5,64E-09
WDR31	NM_001012361	Hs.133331	hs|9q32	-0,436	-0,054	0,222	0,311	0,229	0,142	4,726	9,33E-04
DEFB126	NM_178001	Hs.400740	hs|9q34.11	-0,263	-0,147	0,448	0,355	0,407	0,437	4,690	4,25E-05
ARMETL1	NM_001029954	Hs.559067	hs|10p13	-0,147	-0,102	-0,092	0,118	0,157	0,571	4,686	5,83E-06
LOC642826	BC019715	Hs.680765	hs|10q22.2	-0,178	0,049	0,342	0,464	0,501	0,478	4,678	8,50E-12
LOC129881	BC117445	Hs.370111	hs|2q31.1	0,000	0,000	0,369	0,867	0,670	0,590	4,677	1,44E-12
C2orf13	NM_173545	Hs.258941	hs|2p14	-0,172	-0,113	0,180	0,121	0,305	0,495	4,646	8,01E-11
THC2553512			hs|1q42.11	-0,053	0,614	-0,137	0,094	0,401	0,616	4,621	4,30E-04
ACVR1C	NM_145259	Hs.352338	hs|2q24.1	-0,390	-0,198	-0,182	-0,211	-0,009	0,070	4,611	5,20E-06
ZNF207	AL834501	Hs.500775	hs|17q11.2	-0,067	0,242	0,013	0,130	0,439	0,600	4,600	2,04E-04
ANTXR1	NM_032208	Hs.165859	hs|2p14	0,344	0,341	0,727	0,739	0,920	1,007	4,595	8,65E-04
CHD9	NM_025134	Hs.59159	hs|16q12.2	0,091	0,246	0,222	0,301	0,583	0,751	4,575	2,29E-04
THC2526838			hs|1q23.3	0,030	0,111	0,305	0,339	0,378	0,688	4,547	2,57E-05
ABCA12	NM_173076	Hs.134585	hs|2q35	-0,320	0,372	-0,327	-0,615	0,167	0,336	4,536	4,34E-05
TncRNA	U60873	Hs.648467	hs|11q13.1	0,087	0,572	0,252	0,195	0,531	0,754	4,532	2,42E-04
FKTN	NM_006731	Hs.55777	hs|9q31.2	0,048	-0,013	-0,044	0,041	0,410	0,518	4,506	2,78E-04
PTPRG	BC036018	Hs.654488	hs|3p14.2	-0,253	0,048	0,230	0,442	0,381	0,000	4,502	8,40E-05
ZNF233	NM_181756	Hs.466891	hs|19q13.31	0,117	0,093	0,261	0,229	0,395	0,784	4,492	7,07E-05
ENST00000370378	AB029030	Hs.21554	hs|1p22.1	-0,318	0,222	-0,180	-0,196	0,138	0,396	4,450	8,81E-04
FANK1	NM_145235	Hs.352591	hs|10q26.2	-0,604	-0,263	0,100	0,034	-0,019	0,054	4,378	3,62E-04
PCM1	NM_006197	Hs.491148	hs|8p22	-0,047	-0,007	0,122	0,209	0,390	0,481	4,371	5,67E-04
SERPINI1	NM_005025	Hs.478153	hs|3q26.1	-0,040	0,236	0,123	0,088	0,463	0,599	4,362	6,27E-04
ARID4B	NM_016374	Hs.575782	hs|1q42.3	0,023	0,213	0,151	0,202	0,517	0,662	4,352	4,67E-04
KIAA1377	NM_020802	Hs.156352	hs|11q22.1	-0,342	0,256	-0,004	0,127	0,177	0,295	4,326	2,06E-05
FGF7	NM_014379	Hs.13285	hs|8q23.2	-0,117	-0,039	-0,021	-0,026	0,224	0,591	4,320	8,18E-05
CV339166	CV339166	Hs.694226	hs|1q41	0,078	0,183	0,131	0,162	0,507	0,713	4,300	1,10E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
LINCR	NM_001080535	Hs.149219	hs|2q11.2	-0,002	0,646	0,116	0,236	0,220	0,635	4,278	3,20E-05
DA834198	DA834198	Hs.491872	hs|8q13.1	-0,040	-0,090	0,088	0,234	0,454	0,591	4,272	2,13E-06
CFH	NM_002113	Hs.363396	hs|1q31.3	0,050	-0,092	0,080	0,173	0,369	0,677	4,271	2,32E-07
SCG2	NM_003469	Hs.516726	hs|2q36.1	-0,155	0,000	-0,154	-0,059	0,210	0,474	4,258	1,52E-10
ARHGEF10	BC026965	Hs.98594	hs|8p23.3	-0,184	0,148	0,004	0,154	0,309	0,443	4,233	1,71E-06
DA093175			hs|9p12	-0,275	-0,037	0,164	0,365	0,337	0,239	4,229	3,32E-04
GOLGA8A	NM_032632	Hs.253726	hs|14q32.2	-0,122	0,014	0,041	0,135	0,318	0,369	4,225	8,36E-06
AK021467	AK021467	Hs.661311	hs|1q23.3	-0,529	0,000	-0,280	-0,144	-0,029	0,146	4,217	2,14E-04
LOC283666	BC035094	Hs.655155	hs|15q22.2	0,103	0,222	0,508	0,328	0,582	0,817	4,217	6,08E-04
FLJ35767	NM_207459	Hs.231897	hs|17q25.3	-0,165	0,068	0,148	0,365	0,365	0,462	4,209	1,84E-04
THC2725553			hs|21q21.1	-0,354	0,048	-0,087	0,055	0,171	-0,055	4,194	1,20E-04
ZNF430	NM_025189	Hs.466289	hs|19p12	0,057	-0,130	-0,054	0,053	0,454	0,565	4,162	4,12E-08
CCDC141	AK096821	Hs.324341	hs|2q31.2	-1,010	-0,339	-0,967	-0,874	-0,337	-0,374	4,151	2,35E-04
MAP3K13	NM_004721	Hs.656069	hs|3q27.2	-0,532	0,051	-0,354	-0,181	-0,009	0,086	4,150	3,08E-04
CCDC66	NM_001012506	Hs.476399	hs|3p14.3	-0,069	0,105	0,004	0,090	0,436	0,555	4,143	2,33E-04
THC2727226			hs|3q13.31	-0,061	0,163	0,511	0,757	0,558	0,529	4,140	5,58E-06
THC2528990			hs|10q11.22	-0,146	0,244	0,285	0,431	0,537	0,471	4,132	1,23E-04
THC2718728			hs|9p12	-0,279	-0,002	0,186	0,335	0,319	0,203	4,103	4,60E-09
THC2507829			hs|5q13.2	0,101	0,345	0,339	0,402	0,655	0,714	4,103	1,56E-04
AK123972	AK123972	Hs.435458	hs|18q12.3	0,309	0,261	0,737	0,700	0,975	0,912	4,073	3,45E-04
EDEM3	NM_025191	Hs.523811	hs|1q25.3	0,091	0,088	0,227	0,235	0,554	0,694	4,023	2,59E-04
DB304731	BX111927	Hs.659410	hs|2q24.2	-0,066	0,131	0,287	0,150	0,505	0,538	4,015	3,14E-09
MNS1	NM_018365	Hs.444483	hs|15q21.3	-0,109	-0,140	0,100	0,321	0,386	0,302	3,976	1,70E-05
AK022443	AK022443	Hs.656237	hs|3p14.1	-0,146	0,221	0,352	0,431	0,528	0,407	3,970	1,17E-04
PHF21B	NM_138415	Hs.254097	hs|22q13.31	-0,245	-0,061	0,316	0,353	0,408	0,347	3,970	1,31E-11
CPE	NM_001873	Hs.75360	hs|4q32.3	-0,529	-0,304	-0,070	-0,188	-0,044	0,071	3,970	7,37E-04
BDH2	NM_020139	Hs.124696	hs|4q24	-0,159	-0,209	-0,049	-0,065	0,184	0,439	3,964	1,56E-04
CP110	NM_014711	Hs.279912	hs|16p12.3	0,023	0,007	0,054	0,105	0,356	0,382	3,952	9,22E-06
TRIP11	NM_004239	Hs.654511	hs|14q32.12	-0,066	0,171	-0,028	-0,013	0,363	0,567	3,948	1,51E-07
DMXL2	NM_015263	Hs.511386	hs|15q21.2	-0,092	0,039	0,118	0,262	0,424	0,499	3,904	1,09E-07
THC2673918			hs|3q13.31	-0,243	0,059	0,361	0,307	0,447	0,348	3,888	7,97E-04
LRRC6	NM_012472	Hs.591865	hs|8q24.22	0,074	0,091	0,637	0,709	0,544	0,610	3,883	3,50E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
FAM90A1	NM_018088	Hs.196086	hs|12p13.31	0,255	0,358	0,242	0,304	0,597	0,843	3,870	1,08E-04
BX538272	BX538272	Hs.567380	hs|1p31.1	0,081	-0,008	0,188	0,252	0,399	0,669	3,867	2,41E-04
BRWD1	NM_018963	Hs.654740	hs|21q22.2	-0,051	0,304	0,021	0,122	0,560	0,612	3,831	2,58E-04
CROP	NM_016424	Hs.130293	hs|17q21.33	-0,052	0,078	0,140	0,312	0,404	0,531	3,825	2,76E-06
BI771054	BI771054	Hs.341729	hs|3p22.2	0,078	0,423	0,101	0,305	0,463	0,660	3,811	6,44E-04
C2orf63	NM_152385	Hs.468590	hs|2p16.1	-0,203	0,069	-0,133	0,008	0,221	0,378	3,810	2,29E-04
THC2679528			hs|9p12	-0,314	0,067	0,285	0,289	0,264	0,234	3,804	3,51E-05
CAMK2N1	NM_018584	Hs.197922	hs|1p36.12	0,000	0,117	0,725	0,210	0,470	0,580	3,803	3,46E-10
RELN	NM_005045	Hs.655654	hs|7q22.1	0,000	0,000	0,148	0,155	0,321	0,580	3,800	6,98E-06
ANKRD12	NM_015208	Hs.464585	hs|18p11.22	-0,027	0,086	0,176	0,281	0,341	0,379	3,789	2,02E-04
ZBTB1	NM_014950	Hs.655536	hs|14q23.3	0,086	0,161	0,162	0,278	0,510	0,663	3,781	2,68E-04
BU928689			hs|8q21.3	-0,157	0,157	-0,123	-0,006	0,192	0,420	3,780	3,82E-04
XRCC4	NM_022550	Hs.567359	hs|5q14.2	0,049	0,136	0,280	0,229	0,565	0,625	3,773	9,41E-05
GEN1	NM_182625	Hs.467793	hs|2p24.2	-0,027	0,052	0,047	0,212	0,586	0,577	3,766	7,46E-05
IL1RAPL1	NM_014271	Hs.658912	hs|Xp21.2	0,000	0,043	0,308	0,773	0,565	0,576	3,763	2,34E-08
ZNF493	NM_175910	Hs.656558	hs|19p12	0,013	0,091	-0,018	-0,089	0,276	0,588	3,759	6,14E-04
AK026718	AK026718	Hs.125352	hs|5q23.2	0,142	0,128	0,237	0,354	0,555	0,715	3,756	1,11E-05
TSPAN5	AK055659	Hs.591706	hs|4q23	0,035	0,320	0,521	0,531	0,463	0,390	3,720	6,68E-05
AK127804	AK127804	Hs.438858	hs|9p24.2	-0,204	0,040	0,174	0,389	0,285	0,365	3,709	2,12E-04
DCLRE1C	BC022254	Hs.656065	hs|10p13	-0,025	0,145	0,157	0,321	0,522	0,545	3,708	2,67E-04
RIMS4	NM_182970	Hs.517065	hs|20q13.12	-0,216	0,019	0,402	0,466	0,341	0,312	3,701	3,03E-04
BC009228	BC009228	Hs.633824	hs|1q24.1	-0,076	0,390	0,023	0,174	0,304	0,493	3,691	7,04E-05
AA861995	AA861995	Hs.153521	hs|1p13.3	-0,693	-0,340	-0,462	-0,699	-0,244	-0,105	3,685	5,47E-04
AMY1C	NM_001008219	Hs.655232	hs|1p21.1	0,154	0,345	0,418	0,563	0,655	0,721	3,683	6,03E-06
STK31	NM_032944	Hs.309767	hs|7p15.3	0,137	0,220	0,289	0,286	0,582	0,702	3,678	5,89E-05
TPRG1	NM_198485	Hs.338851	hs|3q28	-0,302	0,000	0,210	0,340	-0,002	0,264	3,673	5,40E-07
GCC2	NM_181453	Hs.436505	hs|2q12.3	0,097	0,276	0,069	0,087	0,257	0,507	3,673	1,26E-04
BC062758	BC062758	Hs.571424	hs|8q21.11	-0,275	-0,025	0,146	-0,123	0,286	0,290	3,667	2,94E-08
ZBBX	NM_024687	Hs.478143	hs|3q26.1	0,106	0,330	0,691	0,607	0,617	0,701	3,663	1,88E-04
TMEM67	NM_153704	Hs.116240	hs|8q22.1	-0,236	-0,134	0,033	0,202	0,074	0,327	3,657	5,56E-04
FLJ32679	NM_001012452	Hs.510812		-0,102	0,046	0,087	0,201	0,338	0,461	3,656	4,42E-08
CA2	NM_000067	Hs.155097	hs|8q21.2	-0,566	-0,372	-0,388	-0,473	-0,143	-0,005	3,635	3,35E-07

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
C1orf63	AK027318	Hs.259412	hs|1p36.11	-0,151	0,131	0,012	0,134	0,248	0,409	3,631	1,21E-05
FGF12	NM_004113	Hs.584758	hs|3q28	-0,151	-0,089	0,044	0,009	0,321	0,406	3,615	5,55E-05
C10orf118	NM_018017	Hs.159066	hs|10q25.3	-0,072	0,143	-0,128	-0,145	0,273	0,484	3,612	2,78E-04
THC2491396	CB133932	Hs.558671	hs|14q31.3	-0,061	-0,156	-0,097	0,033	0,309	0,377	3,601	3,37E-04
THC2606490			hs|3q13.31	-0,253	0,084	0,298	0,282	0,334	0,253	3,599	4,21E-05
ZNF708	NM_021269	Hs.466296	hs|19p12	-0,009	0,143	-0,089	0,042	0,344	0,552	3,588	4,78E-05
CCNA1	NM_003914	Hs.417050	hs|13q13.3	-0,589	-0,032	-0,220	-0,350	-0,057	-0,035	3,580	2,16E-04
ROCK2	NM_004850	Hs.591600	hs|2p25.1	-0,111	-0,126	-0,149	-0,123	0,338	0,427	3,579	6,17E-04
NEFH	NM_021076	Hs.198760	hs|22q12.2	-0,507	-0,104	-0,262	-0,035	-0,032	0,049	3,572	6,61E-04
CEP110	NM_007018	Hs.653263	hs|9q33.2	-0,186	-0,060	0,074	0,160	0,327	0,367	3,570	4,18E-05
THC2642866			hs|12p13.2	-0,266	0,055	-0,194	-0,051	0,192	0,291	3,568	9,35E-04
THC2697162			hs|3q13.31	-0,076	0,203	0,528	0,452	0,475	0,366	3,551	1,15E-05
ZFP2	NM_030613	Hs.654533	hs|5q35.3	-0,099	-0,100	0,155	0,156	0,075	0,457	3,528	7,79E-04
IPMK	NM_152230	Hs.499690	hs|10q21.1	-0,113	0,043	0,058	0,041	0,349	0,451	3,524	7,24E-04
AV707343	AV707343	Hs.595279	hs|3q28	-0,215	-0,122	0,074	0,002	0,300	0,331	3,522	6,79E-04
THC2701431			hs|1p13.3	-0,223	0,118	-0,036	-0,274	0,194	0,342	3,516	1,14E-04
SDCBP	AK128645	Hs.200804	hs|8q12.1	-0,079	0,123	0,062	0,070	0,373	0,470	3,511	1,76E-04
ZNF813	NM_001004301	Hs.433293	hs|19q13.41	0,111	-0,016	0,120	0,068	0,340	0,443	3,505	5,46E-04
ODF3L1	NM_175881	Hs.144348	hs|15q24.2	0,000	0,000	0,204	0,743	0,614	0,393	3,505	8,61E-04
WBSCR19	NM_175064	Hs.645483	hs|7p13	0,106	0,304	0,271	0,412	0,452	0,795	3,495	2,76E-04
CTGLF4	NM_133446	Hs.656384	hs|10q11.21	0,003	0,208	0,348	0,482	0,540	0,467	3,492	3,25E-06
ATM	NM_000051	Hs.367437	hs|11q22.3	-0,153	0,301	-0,096	0,036	0,214	0,389	3,479	7,46E-07
CB850583	CB850583	Hs.625122	hs|9p24.2	-0,147	0,082	0,174	0,406	0,361	0,395	3,479	3,80E-04
NBEA	NM_015678	Hs.491172	hs|13q13.3	-0,001	-0,065	0,054	0,055	0,385	0,537	3,477	2,76E-04
ITLN1	NM_017625	Hs.50813	hs|1q23.3	-0,004	0,000	0,066	0,386	0,436	0,544	3,473	2,29E-07
THC2750782			hs|19p13.11	0,011	0,109	0,048	0,122	0,303	0,597	3,471	6,13E-05
IQCG	NM_032263	Hs.591675	hs|3q29	-0,082	-0,083	0,197	0,362	0,285	0,248	3,466	3,91E-04
ARID4A	NM_002892	Hs.161000	hs|14q23.1	-0,181	-0,011	-0,068	-0,030	0,211	0,359	3,462	1,23E-04
FANCF	NM_022725	Hs.632151	hs|11p14.3	-0,426	-0,203	-0,493	-0,046	0,008	0,114	3,460	6,58E-04
C7orf53	NM_182597	Hs.396189	hs|7q31.1	0,170	0,187	0,176	0,259	0,432	0,707	3,455	7,95E-06
THC2551948				-0,080	0,069	0,273	0,366	0,489	0,440	3,431	2,00E-04
ZDHHC21	NM_178566	Hs.649522	hs|9p22.3	0,080	-0,068	0,035	0,108	0,534	0,567	3,428	1,42E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
THC2691405			hs|15q21.1	-0,048	0,178	0,095	0,105	0,350	0,466	3,419	1,20E-04
C8orf46	NM_152765	Hs.268869	hs|8q13.1	0,000	0,084	0,180	0,495	0,196	0,534	3,418	5,92E-07
AIFM2	NM_032797	Hs.655377	hs|10q22.1	0,080	0,314	0,123	0,234	0,449	0,622	3,416	4,89E-04
DNAJC21	NM_194283	Hs.131887	hs|5p13.2	-0,153	-0,441	-0,160	-0,064	0,283	0,359	3,412	4,94E-06
AK096154	AK096154	Hs.594968	hs|5q22.3	0,131	0,106	0,252	0,284	0,453	0,566	3,395	1,44E-04
PLGLB1	NM_001032392	Hs.652174	hs|2p11.2	-0,121	0,057	0,147	0,243	0,238	0,419	3,392	2,47E-07
RNF6	NM_005977	Hs.136885	hs|13q12.13	-0,022	-0,036	-0,004	-0,004	0,284	0,486	3,379	6,04E-05
CAV1	NM_001753	Hs.74034	hs|7q31.2	0,208	0,105	0,708	0,844	0,745	0,734	3,374	3,85E-04
EFCAB7	NM_032437	Hs.652324	hs|1p31.3	0,057	0,268	0,218	0,257	0,484	0,585	3,373	7,53E-05
THC2735960			hs|9q31.2	0,078	0,000	-0,065	-0,036	0,482	0,525	3,366	1,48E-04
TEX14	NM_198393	Hs.390221	hs|17q22	0,387	0,299	0,315	0,255	0,518	0,843	3,364	3,43E-04
IFI16	NM_005531	Hs.380250	hs|1q23.1	0,000	0,146	0,014	0,000	0,172	0,546	3,364	3,70E-04
ABCC2	NM_000392	Hs.368243	hs|10q24.2	-0,001	0,139	0,513	0,552	0,421	0,526	3,361	5,14E-12
ZNF429	NM_001001415	Hs.656558	hs|19p12	-0,290	0,002	-0,215	-0,195	0,041	0,237	3,358	7,10E-04
CHURC1	NM_145165	Hs.325531	hs|14q23.3	-0,197	-0,269	-0,133	-0,096	0,195	0,329	3,352	5,34E-04
IFT80	NM_020800	Hs.478095	hs|3q26.1	-0,028	0,081	0,156	0,277	0,413	0,495	3,335	1,87E-05
ENST00000315707	BC113564	Hs.121692	hs|17p13.1	-0,047	-0,009	0,207	0,362	0,297	0,476	3,334	4,28E-04
N4BP2L2	U50529	Hs.507680	hs|13q13.1	-0,094	0,161	-0,029	0,103	0,409	0,486	3,324	7,58E-12
ZFP37	NM_003408	Hs.150406	hs|9q32	-0,029	0,040	0,154	0,123	0,409	0,492	3,319	3,89E-09
AREG	NM_001657	Hs.270833	hs|4q13.3	0,268	0,548	0,555	0,596	0,739	0,835	3,316	4,65E-04
C1orf118	AK075118	Hs.632414	hs|1p31.1	0,019	0,091	0,197	0,322	0,572	0,540	3,314	7,35E-10
ENST00000290943			hs|9p13.3	-0,002	0,231	0,340	0,470	0,547	0,504	3,313	2,86E-04
GIGYF2	BC012484		hs|2q37.1	-0,029	0,164	0,019	0,130	0,388	0,491	3,303	3,57E-04
SUV39H2	NM_024670	Hs.554883	hs|10p13	-0,051	-0,340	-0,238	-0,171	0,174	0,276	3,271	1,13E-10
CPNE8	NM_153634	Hs.40910	hs|12q12	-0,187	-0,081	-0,013	-0,115	0,254	0,334	3,265	1,57E-04
ZNF25	NM_145011	Hs.499429	hs|10p11.21	0,099	0,152	0,334	0,399	0,327	0,670	3,264	7,44E-04
THC2695576	BF735554		hs|3q13.31	-0,104	0,043	0,306	0,361	0,371	0,477	3,263	5,31E-05
SRI	NM_003130	Hs.489040	hs|7q21.12	0,322	0,264	0,784	0,835	0,865	0,726	3,261	2,00E-04
EFHB	NM_144715	Hs.670883	hs|3p24.3	-0,158	0,000	0,276	0,251	0,400	0,356	3,260	6,17E-04
SEL1L	NM_005065	Hs.181300	hs|14q31.1	0,116	-0,023	0,256	0,200	0,401	0,629	3,255	3,13E-04
CEP350	NM_014810	Hs.413045	hs|1q25.2	0,084	0,163	0,202	0,288	0,497	0,596	3,247	6,38E-05
THAP2	NM_031435	Hs.245798	hs|12q21.1	0,053	0,159	0,275	0,220	0,476	0,652	3,241	6,67E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
THAP6	NM_144721	Hs.479971	hs|4q21.1	0,086	0,090	-0,037	0,038	0,345	0,598	3,237	8,56E-04
ZNF582	NM_144690	Hs.244391	hs|19q13.43	0,107	-0,140	-0,091	0,024	0,280	0,405	3,228	5,33E-11
ABHD13	NM_032859	Hs.183528	hs|13q33.3	-0,007	0,000	-0,059	0,036	0,191	0,500	3,222	1,47E-05
GOLGB1	NM_004487	Hs.213389	hs|3q13.33	0,055	0,231	0,076	0,142	0,376	0,561	3,218	1,95E-04
ZNF571	NM_016536	Hs.590944	hs|19q13.12	0,037	0,120	0,059	0,056	0,293	0,544	3,216	3,57E-09
ASPM	NM_018136	Hs.121028	hs|1q31.3	-0,014	0,037	0,084	0,183	0,484	0,494	3,215	1,59E-06
LOC100129397	AK095841	Hs.683848	hs|15q21.1	0,238	0,000	0,525	0,589	0,522	0,536	3,213	2,24E-04
MTHFD2L	NM_001004346	Hs.479954	hs|4q13.3	0,004	0,000	0,132	0,078	0,501	0,511	3,209	7,50E-04
LOC729806	XM_001131376	Hs.635482	hs|1q44	0,061	0,138	0,280	0,330	0,441	0,567	3,208	5,72E-07
SUSD4	NM_017982	Hs.497841	hs|1q41	0,477	0,630	0,667	1,038	0,947	0,981	3,192	2,93E-05
ZNF224			hs|19q13.31	0,026	0,158	0,194	0,229	0,432	0,528	3,180	3,19E-04
RB1CC1	NM_014781	Hs.196102	hs|8q11.23	-0,129	0,006	-0,102	-0,071	0,232	0,404	3,170	7,37E-06
THC2659095			hs|9q12	0,030	-0,165	0,525	0,503	0,464	0,435	3,160	5,50E-04
SLC27A2	NM_003645	Hs.11729	hs|15q21.2	-0,364	-0,339	-0,180	-0,371	0,074	0,135	3,158	7,59E-04
RPGR	NM_000328	Hs.61438	hs|Xp11.4	0,076	0,084	0,310	0,465	0,553	0,576	3,146	4,81E-06
AF237700	AF237700		hs|2p11.2	0,020	0,273	0,135	0,212	0,376	0,516	3,135	6,03E-05
AVIL	NM_006576	Hs.584854	hs|12q14.1	0,123	0,152	0,373	0,397	0,477	0,619	3,132	1,32E-04
JMJD1C	NM_004241	Hs.413416	hs|10q21.2	-0,037	0,052	0,023	0,105	0,310	0,458	3,131	9,69E-05
KIF27	NM_017576	Hs.546403	hs|9q21.32	-0,008	0,165	0,159	0,274	0,449	0,488	3,127	1,36E-06
ACE2	NM_021804	Hs.178098	hs|Xp22.2	-0,372	-0,285	-0,187	-0,215	0,028	0,123	3,126	4,62E-08
C10orf28	NM_014472	Hs.419800	hs|10q24.2	0,040	0,017	0,047	0,019	0,270	0,352	3,119	6,87E-04
AK124263	AK124263	Hs.649522	hs|9p22.3	0,097	0,170	0,200	0,238	0,520	0,591	3,118	5,02E-04
ZNF181	NM_001029997	Hs.659191	hs|19q13.11	0,043	0,160	0,120	0,158	0,316	0,542	3,118	2,46E-05
PIK3C2A	NM_002645	Hs.175343	hs|11p15.1	-0,015	0,006	-0,062	-0,082	0,242	0,478	3,113	2,33E-04
ZNF449	NM_152695	Hs.28780	hs|Xq26.3	0,107	0,320	0,062	0,129	0,432	0,592	3,112	7,26E-05
hCG_23177			hs|1p34.2	-0,049	0,064	0,262	0,242	0,329	0,445	3,111	8,59E-05
CSPP1	NM_024790	Hs.370147	hs|8q13.2	-0,111	0,045	0,058	0,137	0,308	0,381	3,107	7,06E-05
THC2635591			hs|12q14.3	0,206	0,049	0,117	0,175	0,496	0,607	3,100	7,21E-11
ZNF721	NM_133474	Hs.428360	hs|4p16.3	-0,053	0,147	-0,175	-0,146	0,322	0,437	3,092	6,82E-04
KIAA1466	AB040899	Hs.147710	hs|7q33	-0,008	0,035	0,124	0,307	0,419	0,482	3,091	1,85E-08
INTU	NM_015693	Hs.391481	hs|4q28.1	-0,220	-0,023	-0,052	0,098	0,164	0,271	3,090	2,93E-04
KIAA1009	NM_014895	Hs.485865	hs|6q14.3	-0,043	0,034	-0,026	0,012	0,244	0,458	3,080	5,72E-11

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
THC2647962			hs|2p22.2	0,122	0,140	0,316	0,406	0,540	0,611	3,079	5,24E-05
THC2652887			hs|15q21.3	0,015	0,183	0,255	0,343	0,456	0,503	3,077	4,41E-05
GOLGA4	NM_002078	Hs.344151	hs|3p22.2	-0,061	0,168	-0,109	-0,104	0,330	0,439	3,069	2,47E-04
SLU7	NM_006425	Hs.435342	hs|5q33.3	0,084	0,150	0,165	0,192	0,424	0,543	3,064	1,07E-04
BX090520	BX090520	Hs.574305	hs|16q12.2	0,202	0,372	0,587	0,666	0,764	0,571	3,063	4,24E-04
ZNF658B	NM_033160	Hs.522147	hs|9p12	0,104	0,130	0,213	0,277	0,509	0,590	3,062	2,57E-09
IFT81	NM_014055	Hs.528382	hs|12q24.11	-0,015	0,123	0,215	0,317	0,437	0,470	3,054	7,38E-07
DMXL1	NM_005509	Hs.181042	hs|5q23.1	0,153	0,268	0,226	0,351	0,516	0,636	3,043	2,68E-06
WDR33	AK002156	Hs.620490	hs|2q14.3	-0,149	-0,116	-0,129	-0,088	0,079	0,336	3,035	3,54E-05
VCPIP1	AF088033	Hs.632066	hs|8q13.1	0,020	0,035	0,115	0,148	0,412	0,497	3,034	4,35E-04
SFRS12	NM_139168	Hs.519347	hs|5q12.3	0,051	0,113	0,134	0,185	0,417	0,540	3,033	5,16E-04
XR_018765	XR_018765	Hs.647996	hs|4q32.3	-0,044	-0,028	-0,056	-0,048	0,399	0,437	3,032	1,01E-07
THC2612020			hs|Xq22.3	-0,016	0,197	-0,084	0,006	0,373	0,465	3,025	5,70E-12
RBP4	NM_006744	Hs.50223	hs|10q23.33	-0,002	0,000	0,322	0,409	0,492	0,436	3,014	7,78E-04
RECK	NM_021111	Hs.388918	hs|9p13.3	-0,067	0,252	0,316	0,430	0,442	0,504	3,000	5,28E-05
ZNF84	NM_003428	Hs.654730	hs|12q24.33	-0,007	0,066	0,060	0,071	0,297	0,470	3,000	2,26E-05
ZNF14	NM_021030	Hs.659932	hs|19p13.11	0,064	0,120	0,089	0,143	0,443	0,542	2,999	2,38E-05
TUG1	NR_002323	Hs.554829	hs|22q12.2	0,250	0,159	0,429	0,590	0,640	0,726	2,996	8,71E-06
AK022299	AK022299	Hs.565253	hs|19q12	0,033	0,257	0,009	0,067	0,485	0,503	2,994	5,02E-05
ZNF471	AB037817	Hs.590979	hs|19q13.43	0,088	0,178	0,112	0,001	0,333	0,565	2,994	4,04E-04
ZNF397OS	AK001503	Hs.464896	hs|18q12.2	-0,360	-0,350	0,003	0,067	0,106	0,033	2,985	7,28E-05
THC2646608			hs|18q23	-0,090	0,008	0,176	0,216	0,224	0,409	2,983	6,84E-04
AK098220	AK098220	Hs.664334	hs|5q13.2	0,096	0,339	0,310	0,419	0,588	0,570	2,980	3,92E-04
THC2620401	AV696077	Hs.645617	hs|5q22.3	0,152	-0,050	-0,005	0,053	0,354	0,469	2,975	8,91E-13
ENST00000342314	XM_001126928	Hs.568189	hs|15q13.3	-0,107	0,028	0,072	0,183	0,294	0,366	2,975	1,59E-05
F13B	NM_001994	Hs.435782	hs|1q31.3	0,000	-0,053	0,007	0,364	0,447	0,433	2,974	1,70E-05
THC2769342			hs|5q23.2	0,112	0,058	-0,023	0,101	0,419	0,529	2,961	4,02E-08
ZNF789	AK131429	Hs.440384	hs|7q22.1	0,156	0,225	0,294	0,320	0,589	0,626	2,957	2,67E-04
FANCM	NM_020937	Hs.509229	hs|14q21.3	-0,102	-0,054	-0,079	0,013	0,356	0,338	2,955	3,05E-05
C17orf67	BC041467	Hs.658949	hs|17q22	0,008	0,184	0,266	0,397	0,369	0,476	2,944	2,06E-04
FAM80B	AB033064	Hs.504670	hs|12p13.31	0,114	0,157	0,166	0,190	0,469	0,578	2,942	8,33E-04
FAM91A1	NM_144963	Hs.459174	hs|8q24.13	-0,045	0,001	0,110	0,156	0,384	0,422	2,940	9,35E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
ZC3H6	NM_198581	Hs.190477	hs|2q13	0,080	0,173	0,477	0,329	0,407	0,637	2,932	6,48E-04
IQGAP2	NM_006633	Hs.291030	hs|5q13.3	-0,124	-0,001	-0,124	-0,153	0,141	0,342	2,922	6,94E-04
APC2	NM_005883	Hs.446376	hs|19p13.3	0,172	0,255	0,558	0,632	0,645	0,616	2,919	3,69E-13
HERC2P2	NM_199045	Hs.531509	hs|15q13.1	-0,073	0,247	0,100	0,163	0,286	0,404	2,909	5,52E-05
TTC9	D86980	Hs.79170	hs|14q24.2	-0,047	-0,041	0,239	0,581	0,330	0,416	2,905	1,33E-08
LZTFL1	NM_020347	Hs.30824	hs|3p21.31	0,093	0,142	0,340	0,432	0,417	0,556	2,903	3,75E-05
ACOX1	NM_004035	Hs.464137	hs|17q25.1	-0,644	-0,021	-0,644	-0,513	-0,278	-0,182	2,901	1,52E-11
SPDYA	NM_001008779	Hs.511956	hs|2p23.2	0,130	0,211	0,171	0,196	0,391	0,591	2,896	2,35E-04
BAZ2B	NM_013450	Hs.470369	hs|2q24.2	-0,015	0,088	0,016	0,044	0,252	0,447	2,892	2,59E-04
OXTR	NM_000916	Hs.2820	hs|3p25.3	-0,021	0,125	-0,025	-0,004	0,392	0,440	2,888	2,91E-11
MXRA8	NM_032348	Hs.558570	hs|1p36.33	-0,116	-0,100	0,361	0,513	0,320	0,301	2,887	3,01E-04
ZBTB41	NM_194314	Hs.529439	hs|1q31.3	0,139	0,169	0,269	0,299	0,437	0,600	2,886	1,65E-06
BX329117	BX329117	Hs.499925	hs|10q21.3	0,107	-0,010	-0,096	-0,045	0,339	0,431	2,885	6,16E-04
UNC13A	NM_001080421	Hs.164502	hs|19p13.11	-0,077	0,115	0,279	0,385	0,332	0,383	2,880	1,56E-04
LOC220594	NM_145809	Hs.234573	hs|17p11.2	-0,083	0,119	0,018	0,123	0,239	0,375	2,876	1,79E-06
BF575152	BF575152	Hs.403246	hs|20p12.1	0,001	0,162	0,059	0,125	0,290	0,475	2,875	1,71E-05
ENST00000356354	AK127179		hs|14q32.13	-0,298	-0,148	0,168	0,398	-0,011	0,157	2,859	2,11E-04
LOC149134	AK022825	Hs.677168	hs|1q44	0,006	0,128	0,387	0,559	0,448	0,461	2,854	2,98E-04
CCDC132	NM_017667	Hs.222282	hs|7q21.3	0,163	0,191	0,210	0,238	0,507	0,620	2,853	6,18E-04
TIGD7	NM_033208	Hs.653195	hs|16p13.3	0,085	0,165	0,073	0,080	0,296	0,540	2,851	2,59E-04
PNN	NM_002687	Hs.409965	hs|14q21.1	-0,107	-0,050	-0,098	-0,029	0,247	0,348	2,851	2,38E-04
ABCC8	NM_000352	Hs.54470	hs|11p15.1	-0,124	0,074	0,394	0,350	0,319	0,204	2,851	1,64E-04
SH3GL2	NM_003026	Hs.75149	hs|9p22.2	-0,272	-0,177	0,090	-0,122	0,103	0,182	2,839	4,41E-12
AY358681	AY358681	Hs.661469	hs|11q24.2	0,029	0,401	0,000	0,220	0,358	0,482	2,837	7,37E-06
LOC653071	BC068588	Hs.626311		0,172	0,000	0,131	0,176	0,396	0,581	2,831	7,29E-09
ENST00000355232	AK160375	Hs.645346	hs|10q11.22	0,040	0,133	0,351	0,459	0,484	0,319	2,828	5,32E-06
SEC62	NM_003262	Hs.592561	hs|3q26.2	0,148	0,009	0,168	0,231	0,584	0,598	2,818	4,14E-11
AK022030	AK022030	Hs.288178	hs|1q31.2	0,022	0,099	0,136	0,179	0,367	0,470	2,809	1,14E-04
ENST00000378250	AK090824	Hs.653118	hs|12q23.1	-0,464	0,010	-0,267	-0,154	-0,078	-0,071	2,806	9,73E-04
FLJ37035	AK094354	Hs.652548	hs|10q26.13	-0,094	-0,042	0,468	0,295	0,415	0,353	2,800	6,34E-04
HFM1	NM_001017975	Hs.454818	hs|1p22.2	-0,183	-0,237	0,091	0,198	0,436	0,264	2,800	9,78E-04
SBNO1	AK074256	Hs.577403	hs|12q24.31	-0,050	0,027	-0,122	-0,100	0,295	0,383	2,798	2,19E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
LNX1	NM_032622	Hs.655269	hs|4q12	-0,863	-0,656	-0,908	-0,762	-0,625	-0,418	2,789	2,59E-07
BC006271	BC006271		hs|17q21.31	0,032	0,135	0,238	0,166	0,336	0,479	2,783	5,20E-04
IFT74	NM_025103	Hs.145402	hs|9p21.2	-0,133	0,033	0,058	0,070	0,218	0,312	2,780	8,07E-04
SIX4	NM_017420	Hs.97849	hs|14q23.1	-0,235	0,005	-0,295	-0,324	0,072	0,207	2,780	8,94E-04
PLCL1	NM_006226	Hs.153322	hs|2q33.1	0,123	0,592	0,469	0,396	0,470	0,565	2,769	5,05E-04
ATRX	BC002521	Hs.533526	hs|Xq21.1	0,009	0,188	0,036	0,036	0,389	0,450	2,763	7,82E-04
SOCS4	NM_199421	Hs.532610	hs|14q22.3	-0,042	-0,107	-0,100	-0,120	0,307	0,340	2,762	2,88E-06
C14orf45	NM_025057	Hs.644621	hs|14q24.3	-0,123	0,005	0,296	0,359	0,122	0,284	2,758	3,54E-04
CEP170	NM_014812	Hs.533635	hs|1q43	0,076	0,152	0,172	0,216	0,380	0,515	2,748	2,60E-04
THC2657781			hs|8q21.13	0,189	0,134	0,089	0,319	0,464	0,559	2,743	8,29E-04
TMEM27	NM_020665	Hs.129614	hs|Xp22.2	-0,473	-0,416	-0,168	-0,203	-0,181	0,008	2,735	6,60E-04
HIST2H2AA4	NM_003516	Hs.530461	hs|1q21.2	0,312	0,440	0,503	0,486	0,573	0,894	2,735	7,15E-04
ROCK1	NM_005406	Hs.306307	hs|18q11.1	-0,074	-0,003	0,068	0,097	0,228	0,323	2,735	8,17E-04
DNAH5	NM_001369	Hs.212360	hs|5p15.2	0,000	0,000	0,563	0,408	0,414	0,165	2,733	1,42E-12
LOC439949	AY007155	Hs.590987	hs|10p15.1	-0,126	-0,066	-0,031	-0,017	0,198	0,310	2,732	1,05E-04
AK123861	AK123861	Hs.658919	hs|3q25.1	0,094	0,172	0,125	0,149	0,222	0,589	2,727	7,57E-04
C1orf25	NM_030934	Hs.591488	hs|1q25.3	0,034	0,273	-0,042	0,049	0,412	0,470	2,725	2,87E-10
LCOR	NM_032440	Hs.500695	hs|10q24.1	0,048	0,013	-0,053	0,060	0,307	0,399	2,719	1,52E-04
OXR1	NM_181354	Hs.148778	hs|8q23.1	-0,125	-0,082	0,063	0,069	0,163	0,237	2,715	7,41E-06
IBSP	NM_004967	Hs.518726	hs|4q22.1	-0,401	-0,222	-0,430	-0,083	-0,019	0,034	2,715	5,50E-05
TROVE2	NM_004600	Hs.288178	hs|1q31.2	0,028	0,127	0,131	0,183	0,370	0,462	2,713	2,38E-04
CD1D	NM_014034	Hs.292316	hs|6q22.31	0,334	0,133	0,367	0,346	0,504	0,786	2,707	3,93E-04
BE612504	BE612504	Hs.618649	hs|6q25.3	0,009	0,105	0,205	0,318	-0,097	0,441	2,705	9,73E-13
TRPM7	NM_017672	Hs.512894	hs|15q21.2	0,052	0,100	0,086	0,139	0,354	0,484	2,704	2,66E-04
NHLRC3	AL833329	Hs.507783	hs|13q13.3	-0,222	-0,213	-0,125	0,084	0,055	0,210	2,701	1,85E-04
THC2548755	BE091362	Hs.533222	hs|5q12.1	0,002	0,048	0,275	0,366	0,432	0,425	2,697	3,93E-06
GPATCH2	NM_018040	Hs.420757	hs|1q41	-0,012	0,068	0,183	0,252	0,336	0,418	2,695	6,85E-07
THC2660448			hs|1q21.1	0,327	0,334	0,403	0,492	0,485	0,757	2,693	1,12E-04
ZNF12	NM_016265	Hs.431471	hs|7p22.1	0,109	0,120	0,158	0,187	0,390	0,536	2,693	8,24E-06
CCDC144B	NM_182568	Hs.531547	hs|17p11.2	-0,052	0,133	0,084	0,153	0,213	0,353	2,689	4,88E-06
ANXA10	NM_007193	Hs.188401	hs|4q32.3	0,000	0,014	-0,030	0,373	0,435	0,228	2,683	7,23E-05
KIAA1109	BC108274	Hs.408142	hs|4q27	-0,052	0,129	-0,031	0,008	0,201	0,376	2,678	5,00E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
LRRC58	AK056809	Hs.518084	hs|3q13.33	0,094	-0,065	0,104	0,157	0,352	0,440	2,676	4,45E-04
PRDM13	NM_021620	Hs.287386	hs|6q16.3	-0,147	-0,166	-0,200	-0,426	0,106	0,267	2,671	2,68E-04
SPINK2	NM_021114	Hs.98243	hs|4q12	-0,502	-0,310	-0,256	-0,333	-0,108	-0,075	2,671	1,04E-04
CR617033	CR617033	Hs.624529	hs|2p22.3	0,042	0,206	0,284	0,361	0,473	0,532	2,671	8,27E-05
THC2651395			hs|16q24.3	0,253	0,344	0,358	0,541	0,555	0,679	2,669	5,92E-05
KIF18A	NM_031217	Hs.301052	hs|11p14.1	-0,145	-0,092	-0,103	-0,129	0,317	0,281	2,667	9,49E-04
RAB3GAP2	NM_012414	Hs.654849	hs|1q41	0,070	0,138	0,133	0,110	0,403	0,498	2,665	2,08E-04
PLCB1	NM_182734	Hs.431173	hs|20p12.3	0,110	0,182	0,342	0,433	0,433	0,536	2,662	3,50E-07
TBK1	NM_013254	Hs.505874	hs|12q14.2	0,066	0,094	0,066	0,095	0,404	0,491	2,660	3,80E-04
ZNF10	NM_015394	Hs.507355	hs|12q24.33	0,037	0,006	0,208	0,296	0,289	0,462	2,660	1,45E-05
THAP10	NM_020147	Hs.591123	hs|15q23	0,225	0,213	0,315	0,332	0,524	0,651	2,659	1,39E-04
ZNF808	CR749856		hs|19q13.41	0,036	0,012	0,065	0,018	0,266	0,460	2,655	2,51E-08
BC040982	BC040982	Hs.656958	hs|18q12.3	-0,197	-0,219	0,000	0,084	0,248	0,227	2,654	6,10E-04
DYNC2H1	NM_001080463	Hs.503721	hs|11q22.3	-0,136	-0,064	0,028	-0,100	0,266	0,287	2,650	8,22E-04
DIS3	NM_014953	Hs.643464	hs|13q22.1	-0,028	-0,025	0,001	0,045	0,345	0,398	2,648	5,69E-05
ZNF546	NM_178544	Hs.693657	hs|19q13.2	-0,022	0,141	-0,030	0,079	0,226	0,401	2,647	4,23E-04
ZNF254	NM_203282	Hs.434406	hs|19p12	-0,004	0,053	-0,003	0,029	0,289	0,418	2,644	4,39E-05
ZNF559	NM_032497	Hs.655107	hs|19p13.2	0,044	0,055	0,160	0,185	0,390	0,430	2,643	7,73E-04
DZIP3	NM_014648	Hs.409210	hs|3q13.13	-0,038	0,074	-0,013	0,025	0,255	0,342	2,637	6,76E-04
BLZF1	U79751	Hs.130746	hs|1q24.2	0,131	0,195	0,131	0,092	0,399	0,556	2,625	2,36E-05
THC2642409			hs|19q13.31	0,023	0,237	0,018	0,020	0,350	0,441	2,624	1,79E-07
THC2688475			hs|1q44	0,084	0,093	0,347	0,620	0,502	0,411	2,619	1,18E-10
CCDC148	NM_138803	Hs.668597	hs|2q24.1	0,224	0,625	0,409	0,536	0,605	0,658	2,615	1,34E-04
ZNF655	NM_001009956	Hs.521064	hs|7q22.1	0,220	0,146	0,231	0,305	0,469	0,617	2,612	1,30E-04
RABGAP1L	NM_014857	Hs.585378	hs|1q25.1	-0,225	-0,129	-0,010	-0,006	0,086	0,084	2,611	9,51E-05
SETBP1	NM_013239	Hs.124942	hs|Yp11.32	0,323	0,166	0,731	0,783	0,739	0,695	2,610	4,77E-04
KRIT1	NM_194455	Hs.531987	hs|7q21.2	0,150	0,198	0,145	0,184	0,452	0,566	2,609	2,78E-04
ZFYVE16	NM_014733	Hs.482660	hs|5q14.1	0,159	0,292	0,269	0,260	0,436	0,575	2,607	6,56E-04
ZNF765	NM_001008401	Hs.433293	hs|19q13.41	0,068	0,069	0,093	0,059	0,321	0,478	2,604	4,62E-04
ZMYM6	NM_007167	Hs.533986	hs|1p34.3	0,027	0,143	0,179	0,193	0,378	0,443	2,602	3,01E-04
FBXO15	NM_152676	Hs.664011	hs|18q22.3	-0,191	0,044	0,129	0,187	0,172	0,232	2,599	9,29E-05
MYO1B	NM_012223	Hs.439620	hs|2q32.3	-0,020	-0,007	-0,077	-0,027	0,196	0,423	2,594	4,73E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
FGFR1OP2	NM_015633	Hs.591162	hs|12p11.23	0,048	0,074	0,121	0,152	0,386	0,467	2,592	1,51E-04
THC2610657			hs|7q31.33	-0,011	0,070	0,070	0,083	0,353	0,408	2,590	3,35E-04
ENST00000305570	XR_015683	Hs.650957	hs|21q11.2	-0,030	0,021	-0,032	-0,009	0,272	0,383	2,588	5,91E-04
ZNF567	NM_152603	Hs.412517	hs|19q13.12	0,046	0,048	0,006	-0,020	0,342	0,423	2,586	8,99E-05
ZNF479	AF277624	Hs.616660	hs|7p11.2	0,030	0,000	0,051	0,006	0,174	0,442	2,584	8,09E-05
ANGPT2	NM_001147	Hs.583870	hs|8p23.1	-0,185	0,084	-0,013	0,191	0,145	0,227	2,582	1,26E-04
ENST00000397141	XR_015756		hs|19p12	0,002	0,038	0,015	0,040	0,286	0,409	2,582	6,03E-04
DMTF1	NM_021145	Hs.654981	hs|7q21.12	0,130	0,120	0,214	0,273	0,450	0,510	2,580	3,56E-04
BX393727	BX393727	Hs.440088	hs|5q22.3	0,094	0,087	0,209	0,268	0,447	0,506	2,580	2,42E-04
H2AFJ	NM_177925	Hs.524280	hs|12p12.3	-0,121	0,124	0,025	-0,023	0,182	0,290	2,579	4,35E-04
LOC346887	BC040619	Hs.127286	hs|8q23.1	-0,179	0,084	0,073	0,111	0,191	0,294	2,578	7,01E-05
ZNF141	NM_003441	Hs.654355	hs|4p16.3	-0,014	-0,054	0,021	0,019	0,195	0,253	2,575	9,55E-04
SDCCAG8	NM_006642	Hs.591530	hs|1q43	-0,020	0,178	0,164	0,148	0,367	0,456	2,572	1,73E-06
ANKRD26	NM_014915	Hs.361041	hs|10p12.1	-0,083	0,128	0,187	0,188	0,348	0,345	2,571	4,97E-04
SMCHD1	AK126324	Hs.8118	hs|18p11.32	-0,002	-0,017	0,059	0,106	0,371	0,406	2,569	2,57E-04
RWDD2B	NM_016940	Hs.34136	hs|21q21.3	-0,257	-0,143	0,156	0,087	0,093	0,153	2,565	6,28E-04
AW365443	AW365443	Hs.568356	hs|12p11.21	-0,166	0,000	-0,172	-0,295	0,000	0,243	2,564	5,15E-04
THC2606573	AW974708	Hs.657348	hs|3p24.1	0,103	-0,061	0,031	0,122	0,228	0,336	2,561	2,49E-04
PER2	NM_022817	Hs.58756	hs|2q37.3	-0,007	-0,016	0,152	0,303	0,449	0,402	2,561	1,85E-04
MED28	AF321617	Hs.644788	hs|1q32.1	0,219	0,172	0,408	0,473	0,559	0,626	2,557	4,98E-12
WBP4	XR_016161	Hs.648272	hs|22q13.31	-0,096	-0,109	-0,058	-0,066	0,172	0,257	2,556	6,35E-04
THC2641587	BQ719988	Hs.660796	hs|5q13.2	0,222	0,352	0,513	0,597	0,708	0,594	2,556	8,54E-11
FAM76B	NM_144664	Hs.288304	hs|11q21	0,111	0,063	0,213	0,201	0,407	0,467	2,552	9,47E-04
MREG	NM_018000	Hs.281680	hs|2q35	-0,345	-0,068	-0,414	-0,354	-0,032	0,060	2,550	1,57E-04
WDR63	NM_145172	Hs.97933	hs|1p22.3	0,050	0,224	0,344	0,391	0,255	0,472	2,550	3,68E-05
AF086375	AF086375	Hs.264606	hs|8q21.13	0,001	-0,035	0,104	0,107	0,249	0,407	2,549	7,78E-04
BE780682	BE780682	Hs.355684	hs|5p13.2	-0,052	-0,005	-0,083	0,001	0,272	0,365	2,548	9,95E-05
CD250950	CD250950	Hs.658688	hs|3q26.33	-0,163	-0,163	-0,162	-0,166	0,229	0,242	2,545	5,47E-09
AK023131	AK023131	Hs.648372	hs|1q25.3	-0,110	-0,066	0,058	0,124	0,221	0,296	2,545	1,30E-05
MALAT1	NR_002819	Hs.642877	hs|11q13.1	0,162	0,434	0,377	0,500	0,547	0,567	2,542	3,29E-08
TUBB2B	NM_178012	Hs.300701	hs|6p25.2	-0,231	-0,111	0,206	0,275	0,135	0,151	2,539	8,29E-04
MKLN1	NM_013255	Hs.44693	hs|7q32.3	-0,051	0,128	0,003	0,072	0,242	0,353	2,531	7,54E-06

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
SETX	NM_015046	Hs.460317	hs|9q34.13	-0,023	0,010	0,059	0,094	0,348	0,369	2,529	7,60E-07
ZBTB20	BC010934	Hs.693802	hs|3q13.31	-0,108	0,092	0,321	0,256	0,331	0,161	2,524	9,25E-04
DYX1C1	NM_130810	Hs.126403	hs|15q21.3	0,076	0,252	0,305	0,376	0,475	0,539	2,520	4,73E-05
CLK1	NM_004071	Hs.433732	hs|2q33.1	-0,118	0,089	0,030	0,066	0,185	0,301	2,515	5,36E-05
HMCN1	NM_031935	Hs.58877	hs|1q31.1	0,002	-0,011	0,061	-0,124	0,327	0,401	2,511	3,53E-05
ARL13B	NM_182896	Hs.533086	hs|3q11.2	-0,080	-0,104	0,041	0,068	0,225	0,324	2,503	5,62E-04
F2R	NM_001992	Hs.482562	hs|5q13.3	0,136	0,191	0,140	0,177	0,367	0,535	2,502	2,45E-04
EPRS	NM_004446	Hs.497788	hs|1q41	0,098	0,133	0,148	0,232	0,477	0,506	2,502	3,16E-05
FNDC3A	NM_017416	Hs.675519	hs|Xq22.3	-0,274	-0,286	-0,224	-0,158	-0,003	0,097	2,502	1,40E-06
PCDHB14	NM_018934	Hs.658497	hs|5q31.3	0,141	0,165	0,237	0,380	0,293	0,510	2,498	6,46E-04
HIST1H2BH	NM_003524	Hs.247815	hs|6p22.1	0,139	0,247	0,182	0,153	0,366	0,536	2,497	1,15E-06
SFRS18	AL080186	Hs.520287	hs|6q16.3	-0,012	-0,019	-0,052	0,047	0,294	0,375	2,493	2,98E-04
TSNAX	NM_005999	Hs.96247	hs|1q42.2	0,088	0,031	0,095	0,078	0,402	0,448	2,493	6,95E-04
DNAJC13	NM_015268	Hs.12707	hs|3q22.1	-0,100	-0,058	0,063	0,093	0,216	0,296	2,491	7,59E-05
NOP5/NOP58	NM_015934	Hs.471104	hs|2q33.1	-0,033	-0,099	-0,114	-0,104	0,298	0,276	2,490	3,59E-05
NIN	NM_182944	Hs.310429	hs|14q22.1	-0,001	-0,019	-0,001	0,039	0,257	0,374	2,490	6,34E-05
ZC3H11A	NM_014827	Hs.532399	hs|1q32.1	0,055	0,086	0,181	0,268	0,291	0,417	2,488	5,58E-04
C21orf71	AF086441	Hs.597706	hs|21q21.3	-0,019	-0,085	0,114	0,205	0,187	0,376	2,482	6,85E-05
BF984502	BF984502	Hs.445603	hs|2q31.1	0,056	0,186	0,293	0,461	0,422	0,431	2,477	3,59E-05
BC034623	BC034623	Hs.568682	hs|1p12	-0,252	-0,130	0,000	0,188	-0,015	0,141	2,472	3,24E-11
BNIP3L	NM_004331	Hs.131226	hs|8p21.2	-0,336	-0,314	-0,235	-0,181	-0,090	0,056	2,470	3,86E-06
AK021664	AK021664	Hs.653123	hs|15q21.1	0,197	0,236	0,282	0,369	0,529	0,576	2,469	8,83E-05
DHX36	NM_020865	Hs.446270	hs|3q25.2	-0,063	0,006	0,035	0,075	0,286	0,337	2,467	6,76E-04
WDR5B	NM_019069	Hs.567513	hs|3q21.1	0,071	0,233	0,077	0,131	0,392	0,463	2,464	2,38E-04
H1F0	NM_005318	Hs.226117	hs|22q13.1	-0,078	0,163	0,174	0,299	0,338	0,312	2,461	1,29E-04
ZNF121	NM_001008727	Hs.501537	hs|19p13.2	0,053	-0,122	0,016	0,041	0,294	0,407	2,460	4,10E-11
STXBP3	NM_007269	Hs.530436	hs|1p13.3	0,016	0,093	0,080	0,082	0,331	0,391	2,456	4,10E-04
CCDC88A	NM_019858	Hs.631654	hs|12p13.31	-0,134	-0,076	-0,071	-0,026	0,188	0,256	2,454	6,92E-04
ARNTL	NM_001178	Hs.65734	hs|11p15.2	-0,120	0,137	0,061	0,097	0,226	0,269	2,453	5,86E-05
SLC30A5	BX537394	Hs.631975	hs|5q13.2	0,147	0,170	0,211	0,217	0,410	0,536	2,449	5,93E-05
THC2550620			hs|17q23.1	-0,215	0,045	0,096	0,162	0,167	0,173	2,448	2,18E-05
DENND4C	NM_017925	Hs.249591	hs|9p22.1	-0,055	0,047	0,035	0,100	0,247	0,285	2,447	1,95E-06

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
THC2694186			hs|3p24.3	-0,050	0,009	0,167	0,187	0,307	0,322	2,442	4,47E-04
BM690036	BM690036	Hs.121667	hs|10q25.2	-0,007	-0,029	0,052	0,169	0,232	0,379	2,441	7,34E-07
ICA1L	NM_138468	Hs.516629	hs|2q33.1	-0,019	0,062	0,234	0,217	0,291	0,367	2,431	4,88E-09
ZNF28	NM_006969	Hs.554778	hs|19q13.41	0,108	0,069	0,058	-0,009	0,278	0,451	2,429	4,31E-04
TXNDC10	NM_019022	Hs.440534	hs|18q22.1	-0,013	-0,044	0,030	0,008	0,269	0,290	2,428	4,83E-04
BBS10	NM_024685	Hs.96322	hs|12q21.2	0,190	0,168	0,262	0,401	0,565	0,575	2,425	4,54E-05
KIF2A	NM_004520	Hs.558351	hs|5q12.1	-0,065	0,058	0,097	0,136	0,305	0,319	2,422	7,31E-04
THC2654993			hs|8q12.1	0,118	-0,012	0,071	0,044	0,245	0,327	2,421	7,73E-04
TGM1	NM_000359	Hs.508950	hs|14q12	-0,037	-0,245	-0,301	-0,348	0,121	0,049	2,421	7,02E-04
SCN2A	NM_021007	Hs.93485	hs|2q24.3	-0,304	-0,001	-0,022	-0,077	0,013	0,082	2,418	7,22E-04
ATG4C	AK027773	Hs.7353	hs|1p31.3	-0,030	0,041	-0,019	0,010	0,237	0,353	2,417	3,46E-04
MBTD1	AL133577	Hs.656803	hs|17q21.33	-0,104	-0,125	-0,015	0,019	0,206	0,279	2,414	3,65E-04
ENST00000377525	BC119676	Hs.567050	hs|9q12	-0,036	0,292	0,149	0,227	0,273	0,348	2,411	1,60E-05
C21orf91	NM_017447	Hs.293811	hs|21q21.1	0,168	-0,027	0,040	0,066	0,289	0,400	2,409	9,64E-04
ANKRD32	NM_032290	Hs.657315	hs|5q15	0,108	0,183	0,144	0,168	0,566	0,518	2,408	2,52E-04
ENST00000381298	AB074172	Hs.532082	hs|5q11.2	0,216	0,199	0,273	0,316	0,432	0,598	2,407	7,12E-05
SR140	NM_001080415	Hs.596572	hs|3q23	-0,141	-0,156	-0,090	-0,096	0,338	0,250	2,407	5,28E-04
KGFLP1	AY098593	Hs.439341	hs|9p11.2	-0,140	-0,070	0,014	-0,059	0,157	0,419	2,406	8,43E-04
UBLCP1	NM_145049	Hs.591733	hs|5q33.3	0,062	0,101	0,137	0,202	0,337	0,463	2,404	2,38E-05
NPDC1	NM_015392	Hs.105547	hs|9q34.3	-0,054	0,275	0,207	0,246	0,371	0,425	2,403	8,12E-04
BX641014	BX641014	Hs.648609	hs|9p11.2	-0,144	0,151	-0,275	-0,216	0,347	0,547	2,403	6,15E-04
ZNF75A	NM_153028	Hs.513292	hs|16p13.3	-0,063	0,036	0,131	0,116	0,243	0,393	2,402	4,13E-04
SENP7	NM_020654	Hs.529551	hs|3q12.3	0,017	0,032	0,094	0,064	0,216	0,409	2,400	2,86E-05
C3orf63	NM_015224	Hs.116877	hs|3p14.3	0,011	0,051	0,081	0,129	0,295	0,370	2,397	6,66E-04
PDE5A	NM_001083	Hs.647971	hs|4q27	-0,527	-0,423	-0,280	-0,218	-0,257	-0,147	2,395	1,54E-04
LOC644192	AK000872	Hs.58690	hs|15q26.2	0,056	0,154	0,259	0,405	0,425	0,259	2,393	2,86E-05
THC2693401			hs|11q22.3	0,033	0,129	0,102	0,175	0,304	0,411	2,391	1,42E-04
XR_018202	XR_018202	Hs.567832	hs|Xq13.3	-0,028	0,113	0,020	0,094	0,311	0,350	2,390	4,49E-04
ATF7IP2	NM_024997	Hs.513343	hs|16p13.13	-0,092	0,154	-0,038	0,046	0,181	0,285	2,383	1,73E-04
ZBTB10	NM_023929	Hs.591868	hs|8q21.13	-0,236	-0,054	-0,131	-0,176	0,086	0,141	2,382	9,24E-04
IQCH	NM_022784	Hs.657894	hs|15q23	-0,056	0,068	0,230	0,291	0,402	0,320	2,382	2,75E-04
ZNF624	NM_020787	Hs.128078	hs|17p11.2	0,015	0,094	0,108	0,194	0,330	0,394	2,382	1,96E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
C14orf115	NM_018228	Hs.578167	hs|14q24.3	-0,367	-0,033	-0,147	-0,102	-0,034	0,010	2,381	9,05E-06
ZNF347	NM_032584	Hs.467239	hs|19q13.41	0,013	-0,072	0,027	0,019	0,247	0,369	2,381	1,18E-04
HES1	NM_005524	Hs.250666	hs|3q29	0,140	0,630	0,323	0,358	0,434	0,534	2,380	9,79E-04
AV714556	AV714556	Hs.459174	hs|8q24.13	0,005	0,040	0,109	0,151	0,377	0,382	2,380	1,19E-04
ZNF345	NM_003419	Hs.362324	hs|19q13.12	0,246	0,155	0,196	0,290	0,503	0,571	2,378	2,78E-11
THC2676741			hs|7q32.2	0,073	0,181	0,214	0,304	0,390	0,449	2,378	3,36E-05
AI206757	AI206757	Hs.227777	hs|6q12	0,241	0,680	0,330	0,379	0,539	0,617	2,378	8,99E-04
RND3	NM_005168	Hs.6838	hs|2q23.3	0,223	0,075	0,212	0,219	0,357	0,581	2,368	1,32E-04
UCP3	NM_003356	Hs.101337	hs|11q13.4	0,042	0,154	0,246	0,276	0,325	0,422	2,365	2,22E-04
FAM29A	NM_017645	Hs.533468	hs|9p22.1	-0,089	-0,109	-0,064	-0,044	0,258	0,274	2,365	4,73E-04
BX648207	BX648207	Hs.23554	hs|12q12	0,079	0,098	0,087	0,106	0,445	0,451	2,364	1,03E-04
ABCA5	NM_018672	Hs.421474	hs|17q24.3	0,131	0,111	0,184	0,242	0,466	0,507	2,363	3,60E-05
ENST00000369158	BC015544		hs|1q21.2	0,201	0,089	0,145	0,248	0,350	0,429	2,362	1,54E-04
MGEA5	AF307332	Hs.500842	hs|10q24.32	0,053	0,060	0,135	0,219	0,431	0,419	2,362	1,04E-04
VAMP4	AK056124	Hs.6651	hs|1q24.3	0,095	0,121	0,210	0,303	0,341	0,468	2,361	3,02E-05
CCDC11	NM_145020	Hs.658630	hs|18q21.1	0,000	-0,071	0,000	0,397	0,296	0,342	2,360	4,36E-04
OSBPL8	NM_020841	Hs.430849	hs|12q21.2	0,110	0,077	0,090	0,151	0,353	0,447	2,360	3,35E-05
THC2641484			hs|22q11.1	-0,372	-0,170	0,000	0,000	0,119	-0,177	2,360	8,47E-04
SCYL1BP1	NM_152281	Hs.183702	hs|1q24.2	0,038	0,081	0,219	0,236	0,345	0,477	2,358	6,04E-04
UTP15	NM_032175	Hs.406703	hs|5q13.2	0,055	-0,041	-0,047	-0,064	0,309	0,326	2,352	5,25E-05
RRAD	NM_004165	Hs.1027	hs|16q22.1	0,039	0,199	0,179	0,239	0,388	0,411	2,351	2,65E-04
ZNF675	NM_138330	Hs.264345	hs|19p12	-0,004	0,027	0,010	0,031	0,284	0,368	2,349	2,72E-04
AK309617			hs|9q22.31	-0,075	-0,058	-0,001	0,009	0,218	0,295	2,346	2,88E-04
RP5-1022P6.2	NM_019593	Hs.636359	hs|20p12.3	0,065	0,053	0,076	0,198	0,485	0,435	2,343	1,35E-04
LOC442590	NM_175064	Hs.645483	hs|7p13	0,055	0,198	0,271	0,541	0,370	0,427	2,343	2,92E-04
CR622342	AK057480	Hs.527105	hs|4q21.22	-0,106	0,094	0,034	0,107	0,215	0,264	2,342	3,42E-04
ZNF227	NM_182490	Hs.371335	hs|19q13.31	0,009	0,072	0,005	0,021	0,280	0,378	2,340	8,06E-11
LOC440295	NM_198181	Hs.660597		-0,073	0,076	-0,022	0,022	0,168	0,296	2,339	5,68E-05
MIA3	NM_198551	Hs.118474	hs|1q41	0,100	0,107	0,182	0,242	0,392	0,468	2,337	3,83E-05
KRR1	NM_007043	Hs.645517	hs|12q21.2	0,112	0,059	0,059	0,096	0,423	0,427	2,334	1,98E-04
TIA1	NM_022173	Hs.516075	hs|2p14	-0,102	-0,075	0,073	0,115	0,221	0,265	2,326	1,27E-04
CCT6AP1	AK092180		hs|7q11.21	0,065	0,084	0,163	0,207	0,350	0,431	2,325	4,76E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
ZDHHC11	NM_024786	Hs.659832	hs|5p15.33	-0,019	0,163	0,119	0,222	0,248	0,347	2,323	6,15E-04
CCDC150	NM_001080539	Hs.132519	hs|2q33.1	-0,069	-0,096	0,049	0,216	0,211	0,187	2,323	9,23E-04
POLQ	NM_199420	Hs.241517	hs|3q13.33	-0,085	-0,103	0,036	0,179	0,346	0,264	2,323	5,57E-04
VPS37A	AL834189	Hs.343873	hs|8p22	0,006	-0,003	0,026	0,030	0,233	0,337	2,323	2,55E-04
LARP2	NM_004208	Hs.424932	hs|Xq25	0,141	0,159	0,334	0,356	0,434	0,530	2,320	6,11E-04
ZNF177	NM_003451	Hs.172979	hs|19p13.2	0,038	0,314	0,082	0,082	0,230	0,442	2,315	3,05E-04
C11orf47	NM_173589	Hs.377188	hs|11p15.4	-0,299	-0,043	0,000	0,053	0,110	-0,021	2,314	6,77E-04
THC2730719			hs|12p13.2	0,124	-0,043	-0,080	-0,022	0,292	0,321	2,313	4,71E-12
AGGF1	NM_018046	Hs.634849	hs|5q13.3	0,113	0,137	0,210	0,252	0,344	0,471	2,312	2,96E-05
BIVM	NM_017693	Hs.288809	hs|13q33.1	-0,141	-0,116	-0,065	0,090	0,137	0,222	2,308	1,35E-09
DQ786252	DQ786252	Hs.645142	hs|10q26.11	-0,094	-0,054	-0,111	-0,069	0,196	0,267	2,306	9,51E-04
ATG2B	NM_018036	Hs.168241	hs|14q32.2	-0,063	-0,043	-0,037	0,065	0,149	0,299	2,303	2,11E-05
CRYGS	NM_017541	Hs.376209	hs|3q27.3	0,026	0,102	0,193	0,330	0,278	0,388	2,303	5,18E-04
CR617865	BQ018421	Hs.525163	hs|13q34	-0,074	-0,014	0,028	0,095	0,266	0,288	2,302	7,94E-05
CRH	NM_000756	Hs.75294	hs|8q13.1	0,000	0,027	0,000	0,312	0,234	0,366	2,300	3,82E-04
ZFAND1	NM_024699	Hs.655453	hs|8q21.13	-0,038	-0,053	0,066	0,126	0,272	0,324	2,299	1,76E-04
TMEM68	NM_152417	Hs.420076	hs|8q12.1	-0,095	0,002	-0,023	0,000	0,166	0,266	2,296	4,58E-04
SNX2	NM_003100	Hs.134822	hs|5q23.2	0,086	0,161	0,126	0,166	0,343	0,451	2,295	2,67E-04
FUSIP1	NM_054016	Hs.3530	hs|1p36.11	0,004	-0,084	0,022	0,051	0,325	0,364	2,294	3,16E-06
MORC4	NM_024657	Hs.496544	hs|Xq22.3	0,099	0,076	0,110	0,228	0,330	0,431	2,294	1,97E-05
AK091904	AK091904	Hs.202577	hs|3q13.31	0,018	0,205	0,269	0,214	0,389	0,446	2,293	7,75E-04
JHDM1D	NM_030647	Hs.308710	hs|7q34	0,015	0,194	0,082	0,110	0,252	0,374	2,289	7,52E-05
DPY19L4	NM_181787	Hs.567828	hs|8q22.1	-0,130	-0,104	0,073	0,124	0,194	0,229	2,286	2,55E-05
BU173515	BU173515	Hs.655113	hs|11p15.1	0,000	0,012	0,062	0,053	0,200	0,359	2,285	1,36E-06
NAT12			hs|7p12.1	-0,140	-0,109	-0,145	-0,143	0,141	0,218	2,284	6,58E-05
TMTC3	NM_181783	Hs.331268	hs|12q21.32	0,031	0,040	0,013	0,018	0,286	0,376	2,284	2,76E-06
LACTB2	NM_016027	Hs.118554	hs|8q13.3	-0,053	0,018	0,093	0,092	0,285	0,305	2,278	3,68E-04
C1orf181	NM_017953	Hs.5111	hs|1p22.3	0,087	0,119	0,146	0,198	0,347	0,423	2,274	7,66E-04
FLJ11292	AK023417	Hs.694230	hs|5q14.3	-0,004	0,000	0,091	0,119	0,299	0,352	2,272	3,19E-05
ZEB1	NM_030751	Hs.124503	hs|10p11.22	-0,128	-0,095	-0,099	-0,037	0,131	0,227	2,271	2,91E-05
UFM1	NM_016617	Hs.693686	hs|13q13.3	0,005	-0,110	0,007	0,035	0,245	0,359	2,271	1,01E-07
LOC728927	XM_001128828	Hs.670568	hs|7q11.21	0,024	-0,172	0,029	0,025	0,312	0,371	2,270	7,70E-06

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
C1orf58	NM_144695	Hs.552608	hs|1q41	0,082	0,072	0,211	0,241	0,371	0,437	2,268	5,16E-04
TAF2	NM_003184	Hs.122752	hs|8q24.12	-0,006	0,005	0,030	0,067	0,282	0,355	2,267	1,29E-04
ZNF30	NM_194325	Hs.657402	hs|19q13.11	0,070	0,048	0,087	0,097	0,305	0,419	2,265	8,68E-05
HIST1H2BL	NM_003519	Hs.137594	hs|6p22.1	0,127	0,199	0,167	0,133	0,342	0,513	2,261	2,02E-04
CSNK1G3	NM_004384	Hs.129206	hs|5q23.2	0,108	0,091	0,164	0,213	0,375	0,463	2,260	3,34E-05
PREPL	NM_006036	Hs.444349	hs|2p21	0,031	0,017	0,042	0,040	0,265	0,325	2,258	6,98E-04
ACADM	NM_000016	Hs.445040	hs|1p31.1	-0,076	-0,024	0,023	-0,033	0,183	0,276	2,250	6,88E-06
FLJ39653	AK093550	Hs.445315	hs|4p15.32	-0,008	0,144	0,141	0,265	0,309	0,350	2,249	5,03E-04
MATR3	NM_199189	Hs.268939	hs|5q31.2	-0,041	-0,033	-0,070	-0,068	0,231	0,319	2,247	8,31E-05
KIAA1012	NM_014939	Hs.202001	hs|18q12.1	-0,015	0,047	0,111	0,117	0,265	0,336	2,245	1,27E-07
SYF2	NM_015484	Hs.20013	hs|1p36.11	0,135	0,173	0,266	0,345	0,383	0,478	2,244	2,37E-04
FAM71A	NM_153606	Hs.129293	hs|1q32.3	-0,348	-0,050	-0,172	-0,003	-0,031	0,016	2,243	3,20E-04
RCOR3	NM_018254	Hs.356399	hs|1q32.3	0,100	0,142	0,255	0,285	0,420	0,452	2,242	2,57E-04
HIST1H3F	BC062305	Hs.70937	hs|6p22.1	0,156	0,209	0,154	0,150	0,310	0,506	2,241	2,89E-04
SLC43A2	NM_152346	Hs.160550	hs|17p13.3	0,007	0,171	-0,052	-0,013	0,343	0,357	2,240	2,71E-05
TSEN54	AK094466	Hs.655875	hs|17q25.1	-0,098	0,051	0,134	0,195	0,329	0,260	2,239	9,66E-04
FLJ13611	NM_024941	Hs.591760	hs|5q12.3	0,172	0,069	0,163	0,225	0,304	0,389	2,237	1,25E-04
TWF1	NM_002822	Hs.189075	hs|12q12	0,026	0,004	0,018	0,021	0,296	0,368	2,233	4,11E-05
PTAR1	AL832683	Hs.494100	hs|9q21.11	0,123	0,081	0,070	0,124	0,379	0,429	2,227	9,47E-06
SMAD2	NM_001003652	Hs.12253	hs|18q21.1	-0,005	-0,063	0,145	0,227	0,296	0,278	2,226	4,30E-04
THC2610890			hs|3p14.1	0,105	0,128	0,243	0,310	0,493	0,451	2,225	1,64E-04
ARHGAP12	NM_018287	Hs.499264	hs|10p11.22	-0,019	0,055	0,050	0,069	0,234	0,328	2,225	4,44E-04
LOC727834	XM_926013			-0,170	0,070	-0,058	-0,001	0,087	0,177	2,223	2,62E-07
KLC1	AK092868	Hs.20107	hs|14q32.33	-0,293	-0,178	-0,032	0,074	0,055	0,052	2,222	1,88E-05
UHRF1BP1L	NM_015054	Hs.620701	hs|12q23.1	0,037	0,021	0,093	0,144	0,238	0,247	2,221	2,93E-04
IL6ST	NM_002184	Hs.532082	hs|5q11.2	0,221	0,163	0,220	0,303	0,379	0,550	2,221	1,52E-04
RGS5	NM_003617	Hs.24950	hs|1q23.3	0,421	0,562	0,647	0,740	0,716	0,767	2,220	1,38E-04
PRKAA2	BC043195	Hs.437039	hs|1p32.2	0,113	0,017	0,080	0,155	0,279	0,340	2,220	4,19E-05
CF143262	CF143262	Hs.252387	hs|22q13.31	0,272	0,045	0,140	0,210	0,304	0,425	2,219	1,79E-04
WRN	NM_000553	Hs.632050	hs|8p12	0,191	0,194	0,325	0,450	0,538	0,536	2,217	9,80E-04
THC2585464			hs|11q23.3	-0,162	-0,137	-0,099	-0,020	0,066	0,182	2,211	1,01E-05
DPY19L2P4	AK098759	Hs.406964	hs|7q21.13	0,232	0,340	0,416	0,579	0,613	0,576	2,210	4,52E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
ZNF700	NM_144566	Hs.528486	hs|19p13.2	0,015	0,058	0,083	0,157	0,281	0,374	2,208	2,92E-04
AK026668	AK026668	Hs.693653	hs|1q23.3	0,230	0,205	0,238	0,251	0,539	0,581	2,208	1,95E-04
TRIM36	NM_018700	Hs.519514	hs|5q22.3	0,198	0,027	0,050	0,053	0,286	0,371	2,207	4,74E-04
ZNF146	NM_007145	Hs.643436	hs|19q13.12	-0,060	-0,021	-0,052	-0,040	0,209	0,301	2,205	1,57E-04
ZFP1	NM_152904	Hs.431045	hs|17p11.2	0,038	0,088	0,098	0,145	0,375	0,377	2,203	2,11E-04
AK091744	AK091744	Hs.622771	hs|10q23.2	-0,118	0,099	0,184	0,215	0,223	0,098	2,203	9,19E-07
FLJ13305	BX648834	Hs.440466	hs|2p15	-0,170	-0,179	-0,002	0,089	0,169	0,163	2,200	8,12E-04
GOLGA1	AK021820	Hs.133469	hs|9q33.3	0,068	0,043	0,067	0,287	0,254	0,400	2,199	9,81E-04
CAND1	AK027783	Hs.546407	hs|12q14.3	-0,150	-0,075	0,009	0,214	0,170	0,140	2,199	2,56E-04
ZNF283	AK098175	Hs.652513	hs|19q13.31	0,044	0,069	-0,013	-0,040	0,252	0,337	2,199	1,87E-04
ZZZ3	NM_015534	Hs.480506	hs|1p31.1	0,084	0,120	0,085	0,112	0,388	0,454	2,195	7,21E-04
FAM44A	NM_148894	Hs.444517	hs|4p15.33	-0,164	0,209	-0,265	-0,172	0,140	0,176	2,187	1,46E-04
ZBTB38	NM_001080412	Hs.518301	hs|3q23	-0,003	-0,102	-0,018	-0,008	0,117	0,181	2,187	5,26E-04
ZNF492	BC110575	Hs.232108	hs|19p12	-0,004	0,008	-0,021	0,022	0,247	0,335	2,183	1,38E-04
THC2658030	BX089071	Hs.664834	hs|1p34.2	-0,057	-0,002	0,138	0,212	0,259	0,228	2,177	3,95E-04
MBNL1	NM_021038	Hs.478000	hs|3q25.2	-0,054	-0,012	0,073	0,108	0,255	0,284	2,177	7,04E-05
BC027922	BC027922	Hs.288995	hs|19q13.43	0,239	0,082	0,126	0,210	0,284	0,434	2,176	6,04E-04
AK130891	AK130891	Hs.656546	hs|8q24.13	-0,231	0,013	0,090	0,103	0,223	0,045	2,176	1,27E-04
THUMPD1	NM_017736	Hs.460232	hs|16p12.2	0,045	0,003	-0,021	-0,076	0,324	0,339	2,175	5,93E-05
SUZ12P	CR597846	Hs.628886	hs|17q11.2	-0,200	-0,134	-0,081	0,016	0,070	0,130	2,174	1,11E-05
BC037740	BC037740	Hs.597434	hs|17q11.2	0,033	0,061	0,093	0,116	0,289	0,369	2,172	1,68E-04
EVI1	NM_005241	Hs.656395	hs|3q26.2	0,001	-0,012	0,112	0,196	0,328	0,338	2,172	2,97E-04
CAMTA1			hs|Xq25	-0,062	-0,002	0,170	0,182	0,196	0,275	2,172	9,65E-05
ACTA1	AK095258	Hs.16622	hs|Xq28	0,025	0,057	0,117	0,111	0,251	0,363	2,168	2,29E-04
CTGLF5	NM_133446	Hs.656384	hs|10q11.21	-0,032	0,112	0,212	0,315	0,296	0,240	2,166	1,59E-04
SMC5	AB011166	Hs.534189	hs|9q21.11	0,030	0,047	0,033	0,068	0,383	0,366	2,165	5,06E-05
PIH1D2	NM_138789	Hs.420662	hs|11q23.1	0,022	0,145	0,200	0,189	0,369	0,357	2,163	2,38E-04
SNX16	NM_022133	Hs.492121	hs|8q21.13	-0,053	0,114	0,046	0,068	0,199	0,282	2,162	7,09E-05
ZNF578	AK095562	Hs.676961	hs|19q13.41	0,057	-0,022	0,031	0,001	0,201	0,366	2,161	2,93E-04
THC2611971			hs|7p21.1	0,065	0,064	0,154	0,184	0,349	0,400	2,161	2,53E-04
PNPLA8	NM_015723	Hs.617340	hs|7q31.1	0,122	0,125	0,123	0,070	0,224	0,477	2,160	7,98E-04
ZNF826	NM_001039884	Hs.631635	hs|19p12	0,000	0,023	0,011	0,037	0,244	0,344	2,155	6,88E-10

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
HIST1H2BK	NM_080593	Hs.437275	hs|6p22.1	0,370	0,364	0,432	0,401	0,524	0,706	2,154	3,46E-04
FAM27E3	BC032035	Hs.31240	hs|9q12	0,004	0,298	0,148	0,217	0,277	0,337	2,154	6,39E-07
C1QTNF3	NM_181435	Hs.171929	hs|5p13.3	-0,045	0,084	0,184	0,240	0,304	0,266	2,152	9,71E-05
FBN2	X62009	Hs.519294	hs|5q23.3	-0,351	-0,137	-0,032	0,000	-0,021	-0,019	2,151	3,48E-06
APC	NM_000038	Hs.158932	hs|5q22.2	0,110	0,130	0,114	0,128	0,377	0,446	2,148	2,61E-04
TTC14	NM_133462	Hs.43213	hs|3q26.33	0,038	-0,022	-0,009	0,030	0,264	0,295	2,148	4,46E-04
SPAG1	NM_003114	Hs.591866	hs|8q22.2	0,065	-0,014	0,028	0,072	0,221	0,340	2,148	4,28E-04
TWISTNB	NM_001002926	Hs.353035	hs|7p15.3	0,210	0,122	0,149	0,146	0,444	0,487	2,148	3,26E-04
LOC100132006	AK092846	Hs.593666	hs|16p13.2	-0,050	0,105	0,089	0,164	0,223	0,176	2,146	3,28E-04
DUXAP10	AK056135	Hs.536395	hs|22q11.1	-0,130	0,035	-0,070	0,077	0,152	0,201	2,141	5,07E-04
LMLN	AL832783	Hs.516540	hs|3q29	-0,065	0,171	0,214	0,228	0,308	0,399	2,140	2,42E-04
HLTF	NM_003071	Hs.3068	hs|3q24	-0,070	-0,098	-0,038	0,018	0,224	0,264	2,138	2,76E-04
LOC100132439			hs|9q12	0,011	0,329	0,179	0,242	0,315	0,341	2,135	2,23E-05
TRAM1	NM_014294	Hs.491988	hs|8q13.3	-0,063	-0,007	0,036	0,060	0,186	0,284	2,133	1,10E-04
JMJD1A	NM_018433	Hs.557425	hs|2p11.2	-0,259	-0,212	-0,141	-0,074	-0,092	0,051	2,132	9,80E-05
CCDC144A	BC133019	Hs.531547	hs|17p11.2	-0,086	0,070	0,043	0,114	0,186	0,235	2,131	2,56E-05
RP5-1000E10.4	CR936771	Hs.632428	hs|1p13.2	0,040	0,039	0,048	0,068	0,247	0,366	2,130	3,06E-05
THC2495785	CN284574	Hs.533222	hs|5q12.1	0,019	0,002	0,211	0,289	0,346	0,333	2,129	6,09E-04
ZNF714	NM_182515	Hs.466291	hs|19p12	0,022	0,002	0,006	0,017	0,223	0,334	2,128	1,48E-06
PJA2	NM_014819	Hs.483036	hs|5q21.3	0,167	0,171	0,280	0,342	0,375	0,495	2,125	2,14E-04
ENST00000344759	NM_001001675	Hs.444446	hs|19q13.41	-0,007	0,015	-0,010	-0,155	0,203	0,323	2,124	4,33E-05
ARHGAP18	NM_033515	Hs.486458	hs|6q22.33	0,226	0,193	0,231	0,225	0,451	0,507	2,123	6,60E-04
AF131777	AF131777	Hs.655994	hs|13q34	-0,182	0,039	0,049	0,091	0,168	0,145	2,123	5,81E-04
BX093444	BC047720	Hs.345877	hs|18q21.1	-0,053	0,145	0,091	0,106	0,221	0,269	2,121	1,65E-04
C14orf118	AB032978		hs|14q24.3	-0,252	-0,195	-0,227	-0,121	-0,054	0,075	2,121	1,15E-04
PHF20L1	NM_032205	Hs.304362	hs|8q24.22	-0,055	0,092	0,187	0,240	0,256	0,222	2,120	2,95E-06
DENND1A	NM_024820	Hs.655834	hs|9q33.2	-0,119	-0,026	0,228	0,208	0,251	0,066	2,119	2,59E-04
ZC3H11A	NM_014827	Hs.532399	hs|1q32.1	0,073	0,091	0,203	0,304	0,305	0,412	2,118	4,54E-04
ZC3H8	NM_032494	Hs.418416	hs|2q13	-0,014	-0,008	-0,011	0,031	0,225	0,312	2,114	2,95E-06
ZC3H12C	AB096241	Hs.376289	hs|11q22.3	-0,072	-0,147	0,264	0,256	0,367	0,284	2,111	1,94E-04
BC035156	BC035156	Hs.658127	hs|8q22.3	-0,094	-0,025	0,160	0,229	0,223	0,159	2,111	3,84E-04
ENST00000354519	NR_003246	Hs.534573	hs|15q25.2	-0,204	-0,037	-0,048	0,071	0,096	0,114	2,110	1,66E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
LOC728613	BC014604	Hs.379186	hs|5p15.33	-0,002	0,062	0,226	0,273	0,308	0,279	2,110	2,90E-04
LOC150759	AK057596	Hs.651675	hs|2q11.2	0,040	0,154	0,262	0,352	0,314	0,364	2,108	2,56E-04
CYP2C9	NM_000771	Hs.282624	hs|10q23.33	-0,122	0,157	0,063	0,138	0,200	0,226	2,108	3,08E-05
AL137400	BC002572	Hs.161181	hs|10p13	0,064	0,148	0,273	0,309	0,298	0,402	2,107	6,57E-04
FOXO1	NM_002015	Hs.370666	hs|13q14.11	-0,041	0,147	0,095	0,114	0,236	0,283	2,106	6,95E-04
GPBP1	AL161991	Hs.444279	hs|5q11.2	0,153	0,153	0,161	0,161	0,394	0,470	2,106	3,50E-04
MDM2	NM_002392	Hs.567303	hs|12q15	-0,237	-0,142	-0,263	-0,309	-0,031	0,089	2,106	8,80E-04
R78584	BU928961	Hs.656847	hs|3q13.13	-0,161	-0,173	-0,145	-0,167	-0,017	0,162	2,105	1,02E-05
EG328448	EG328448	Hs.651090	hs|16p11.2	-0,050	0,268	0,044	0,153	0,225	0,272	2,101	4,07E-04
IFT57	NM_018010	Hs.412196	hs|3q13.12	-0,021	-0,028	0,197	0,279	0,372	0,300	2,100	1,12E-04
ZNF354A	NM_005649	Hs.484324	hs|5q35.3	0,043	0,064	0,048	0,114	0,298	0,368	2,099	5,68E-04
LOC342892	CR627133	Hs.406307	hs|19q13.12	0,050	0,113	0,089	0,074	0,290	0,372	2,097	2,26E-04
CLUAP1	NM_024793	Hs.155995	hs|16p13.3	-0,113	-0,016	0,052	0,109	0,269	0,208	2,095	1,67E-05
PDCD4	NM_145341	Hs.232543	hs|10q25.2	0,083	0,114	0,215	0,263	0,203	0,404	2,094	4,58E-04
CR603951	BC032409	Hs.632886	hs|2q11.2	0,024	0,164	0,254	0,310	0,289	0,351	2,094	2,37E-06
SRFBP1	NM_152546	Hs.107622	hs|5q23.1	0,069	0,045	-0,009	0,004	0,277	0,337	2,094	1,89E-04
CCDC131	NM_144982	Hs.527874	hs|12q21.1	0,091	0,150	0,123	0,247	0,329	0,412	2,092	1,13E-04
MAP1B	AK055112	Hs.637017	hs|5q13.2	0,239	-0,161	0,207	0,173	0,331	0,453	2,087	7,31E-04
SNX13	NM_015132	Hs.585343	hs|7p21.1	0,039	0,104	0,114	0,173	0,338	0,358	2,086	3,78E-04
PSIP1	NM_033222	Hs.658434	hs|9p22.3	-0,025	0,011	0,088	0,155	0,349	0,269	2,083	4,02E-04
EPC2	NM_015630	Hs.23270	hs|2q23.1	0,061	0,135	0,118	0,170	0,371	0,380	2,083	2,09E-04
ZNF468	NM_199132	Hs.467223	hs|19q13.41	0,055	0,020	0,076	0,057	0,220	0,368	2,079	2,74E-04
TNNI2	NM_003282	Hs.523403	hs|11p15.5	-0,159	-0,042	-0,148	-0,300	0,164	0,167	2,077	2,66E-04
THC2691276	AI694364	Hs.533936	hs|18q12.3	-0,044	0,044	0,081	0,162	0,220	0,068	2,076	3,20E-04
OSTbeta	NM_178859	Hs.534533	hs|15q22.31	0,556	0,108	0,060	0,097	0,424	0,425	2,075	2,58E-04
ZKSCAN1	NM_003439	Hs.615360	hs|7q22.1	0,186	0,183	0,237	0,283	0,401	0,472	2,073	8,09E-05
PPM1D	NM_003620	Hs.591184	hs|17q23.2	0,148	0,060	0,116	0,126	0,249	0,420	2,073	1,08E-04
LRRC44	BX647210	Hs.644625	hs|1p31.1	-0,177	0,022	-0,386	-0,156	0,139	0,139	2,068	4,16E-06
CLIP1	NM_004168	Hs.440475	hs|5p15.33	-0,075	-0,061	-0,035	0,038	0,120	0,241	2,068	1,46E-07
BM687502			hs|3q21.3	-0,146	-0,058	0,049	0,098	0,095	0,170	2,067	7,42E-05
NACA	NM_005594	Hs.505735	hs|12q13.3	0,092	0,047	0,124	0,153	0,250	0,317	2,066	5,52E-04
ZNF117	NM_024498	Hs.250693	hs|7q11.21	-0,008	0,002	-0,018	-0,001	0,264	0,307	2,066	4,63E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
LYPD1	NM_144586	Hs.656644	hs|2q21.2	-0,204	-0,066	-0,130	-0,193	0,024	0,156	2,065	7,42E-04
MEIG1	NM_001080836	Hs.257249	hs|10p13	0,026	-0,025	0,049	0,154	0,453	0,341	2,064	4,49E-04
MOSPD2	NM_152581	Hs.190043	hs|Xp22.2	0,224	0,136	0,190	0,278	0,283	0,385	2,059	7,73E-04
ZFP62	AK091550	Hs.509227		0,190	0,246	0,278	0,402	0,482	0,503	2,056	2,06E-04
KIAA0265	NM_014997	Hs.520710	hs|7q32.2	-0,215	0,094	-0,191	-0,179	-0,013	0,100	2,056	2,24E-05
ZMYM4	NM_005095	Hs.269211	hs|1p34.3	-0,045	-0,012	0,057	0,059	0,257	0,267	2,053	9,41E-04
C1orf71	NM_152609	Hs.368353	hs|1q44	0,007	0,087	0,137	0,170	0,241	0,358	2,053	2,20E-04
AK095738	CR627188	Hs.666645	hs|8q24.3	0,075	0,101	0,367	0,498	0,367	0,387	2,052	5,10E-11
NPNT	NM_001033047	Hs.518921	hs|4q24	0,080	0,233	0,291	0,333	0,394	0,445	2,051	2,18E-04
PDIA2	NM_006849	Hs.66581	hs|16p13.3	-0,206	-0,038	0,078	0,182	0,107	0,094	2,051	2,11E-04
TRIM24	NM_015905	Hs.490287	hs|7q34	0,105	0,111	0,132	0,187	0,317	0,413	2,049	1,40E-06
HIST2H2BE	NM_003528	Hs.2178	hs|1q21.2	0,295	0,360	0,404	0,494	0,555	0,603	2,047	3,34E-06
MYST4	NM_012330	Hs.35758	hs|10q22.2	0,005	0,019	0,072	0,121	0,283	0,316	2,046	4,60E-05
FAM18B2	NM_145301	Hs.659357	hs|17p12	0,010	0,082	0,096	-0,009	0,240	0,321	2,045	3,46E-04
VPS13B	NM_152564	Hs.191540	hs|8q22.2	0,001	0,083	0,186	0,264	0,268	0,313	2,044	1,53E-05
LOC389634	AK074886	Hs.434403	hs|12p13.31	-0,065	0,070	0,253	0,282	0,245	0,087	2,042	3,34E-04
ZNF43	NM_003423	Hs.534365	hs|19p12	-0,008	0,006	-0,033	-0,014	0,214	0,302	2,042	4,00E-04
PCMTD1	NM_052937	Hs.308480	hs|8q11.23	0,079	0,045	0,371	0,430	0,185	0,379	2,040	6,09E-04
GOLIM4	NM_014498	Hs.143600	hs|3q26.2	-0,084	-0,094	-0,053	-0,086	0,133	0,179	2,037	4,58E-04
THC2672083			hs|3p14.3	-0,259	-0,049	-0,072	-0,219	-0,011	0,050	2,037	7,68E-04
RAB18	NM_021252	Hs.406799	hs|10p12.1	0,060	0,002	0,072	0,047	0,254	0,367	2,037	8,80E-04
KNTC1	NM_014708	Hs.300559	hs|12q24.31	-0,042	-0,036	0,144	0,221	0,408	0,268	2,035	5,22E-04
ZNF197	NM_006991	Hs.157035	hs|3p21.32	-0,040	-0,002	0,011	0,029	0,184	0,250	2,035	3,39E-04
PIK3CA	NM_006218	Hs.85701	hs|3q26.32	0,032	0,112	0,163	0,171	0,285	0,403	2,035	2,20E-04
ENST00000306453			hs|7q31.1	-0,179	-0,094	-0,020	-0,036	0,137	0,129	2,033	7,86E-05
ZNF506	AK074757	Hs.659321	hs|19p12	0,002	0,042	0,138	0,240	0,233	0,310	2,033	4,10E-04
SUGT1L1	BC020814	Hs.442781	hs|13q14.11	-0,058	0,000	0,169	0,131	0,000	0,250	2,031	5,48E-04
NR3C1	NM_000176	Hs.122926	hs|5q31.3	0,096	0,004	0,138	0,194	0,306	0,399	2,028	1,05E-05
ZNF529	NM_020951	Hs.654960	hs|19q13.12	0,100	0,072	0,113	0,123	0,235	0,407	2,028	3,88E-05
THC2508355			hs|9q33.3	0,102	0,094	0,174	0,232	0,351	0,403	2,025	1,15E-04
EID1	NM_014335	Hs.255973	hs|15q21.1	0,022	0,117	0,156	0,227	0,309	0,329	2,025	1,05E-05
CRYZ	NM_001889	Hs.83114	hs|1p31.1	-0,096	-0,060	0,018	0,049	0,133	0,210	2,025	1,31E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
SLC30A7	NM_133496	Hs.533903	hs|1p21.2	0,122	0,031	0,121	0,172	0,237	0,387	2,024	5,12E-04
ALG10B			hs|12q12	0,163	0,121	0,283	0,409	0,472	0,468	2,024	1,14E-06
MAP3K2	NM_006609	Hs.145605	hs|2q14.3	0,167	0,116	0,133	0,193	0,316	0,412	2,023	3,02E-04
AW858928	AW858928	Hs.81848	hs|8q24.11	-0,070	-0,074	-0,020	-0,043	0,122	0,250	2,019	1,31E-04
EHHADH	NM_001966	Hs.429879	hs|3q27.2	-0,197	0,015	-0,166	-0,125	-0,026	0,109	2,019	1,15E-04
SLC12A2	NM_001046	Hs.162585	hs|5q23.3	0,119	0,095	0,153	0,277	0,444	0,420	2,018	7,74E-05
BF207040	BF207040	Hs.353024	hs|22q11.23	0,099	0,056	0,440	0,426	0,400	0,235	2,017	5,37E-04
SS18	NM_001007559	Hs.404263	hs|18q11.2	-0,004	-0,059	0,028	0,044	0,170	0,220	2,016	5,63E-04
C3orf62	NM_198562	Hs.403828	hs|3p21.31	-0,003	0,185	0,146	0,157	0,206	0,308	2,013	8,11E-04
ANKIB1	AL137349	Hs.83293	hs|7q21.2	0,078	0,110	0,153	0,176	0,298	0,362	2,011	7,72E-05
ZNF507	NM_014910	Hs.205392	hs|19q13.11	0,062	-0,008	0,151	0,225	0,327	0,364	2,006	2,35E-04
LOC653080	AK097091	Hs.652798	hs|5q13.2	0,091	0,158	0,249	0,334	0,376	0,393	2,005	9,27E-11
CCDC100	NM_153223	Hs.483209	hs|5q23.2	0,155	0,096	0,233	0,282	0,378	0,454	2,003	7,00E-05

Table 2: First list of the under-expressed genes

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
TPD52L1	NM_001003395	Hs.591347	hs|6q22.31	0,651	0,580	-0,195	-0,884	-0,485	-0,359	-22,779	3,12E-04
MFAP5	NM_003480	Hs.512842	hs|12p13.31	0,004	-0,556	-0,733	-1,273	-1,216	-1,169	-17,382	9,04E-05
EHF	NM_012153	Hs.502306	hs|11p13	1,175	1,108	1,152	-0,130	-0,030	0,067	-16,013	1,82E-05
NCF2	NM_000433	Hs.587558	hs|1q25.3	-0,157	-0,364	-0,773	-1,221	-1,306	-1,162	-14,393	5,23E-06
TRIM6	NM_001003818	Hs.125300	hs|11p15.4	-0,431	-0,359	-0,712	-1,189	-1,188	-1,069	-13,030	2,24E-11
PERLD1	NM_033419	Hs.462971	hs|17q12	0,905	-0,125	0,129	0,017	-0,188	-0,152	-11,387	2,95E-04
ATXN1	NM_000332	Hs.434961	hs|6p22.3	0,292	-0,061	-0,395	-0,802	-0,731	-0,483	-10,898	8,07E-04
INHBB			hs|2q14.2	0,829	0,583	0,328	-0,202	-0,106	-0,200	-10,685	3,66E-06
CR627122	CR627122	Hs.291319	hs|Xq26.2	-0,297	-0,407	-0,848	-1,286	-1,328	-1,116	-10,322	1,10E-05
JAM3	NM_032801	Hs.150718	hs|11q25	-0,316	-0,310	-0,836	-1,349	-0,888	-0,848	-9,234	5,12E-05
CXCL14	NM_004887	Hs.483444	hs|5q31.1	0,283	-0,385	-0,311	-0,599	-0,718	-0,662	-8,802	1,54E-04
CR594735	AK001432	Hs.153408	hs|11p15.2	-0,256	-0,100	-0,701	-1,036	-1,192	-1,181	-8,399	1,13E-07
FLJ11235	AK002097	Hs.591264	hs|5q22.2	0,973	0,474	0,203	0,234	-0,008	0,078	-7,860	3,77E-07
C15orf52	NM_207380	Hs.32433	hs|15q15.1	1,166	0,851	0,498	0,384	0,228	0,441	-7,813	3,20E-04
LIMCH1	NM_014988	Hs.335163	hs|4p13	0,669	0,610	0,158	-0,316	-0,197	-0,061	-7,337	6,57E-11
LOH11CR2A	NM_198315	Hs.152944	hs|11q24.1	0,677	0,255	0,000	-0,151	-0,078	-0,185	-7,274	9,65E-07
BX281122	AW014342	Hs.665091	hs|6q22.31	0,745	0,377	-0,064	-0,450	-0,101	-0,065	-7,023	9,80E-13
GPR110	NM_153840	Hs.256897	hs|6p12.3	0,223	0,742	0,608	0,293	0,133	0,038	-6,872	9,70E-05
ARNT2	NM_014862	Hs.459070	hs|15q25.1	0,161	0,211	0,132	0,048	-0,575	-0,640	-6,432	8,94E-04
ATP6V0A4	NM_020632	Hs.98967	hs|7q34	0,741	0,106	0,477	-0,063	-0,054	0,096	-6,236	8,61E-05
PDGFRB	NM_002609	Hs.509067	hs|5q33.1	0,861	0,308	0,148	0,027	0,078	0,538	-6,068	3,71E-04
ELA3B	NM_007352	Hs.181289	hs|1p36.12	0,165	-0,035	-0,619	-0,773	-0,612	-0,465	-5,997	3,00E-05
NEDD9	NM_006403	Hs.37982	hs|6p24.1	0,053	-0,005	-0,194	-0,571	-0,836	-0,721	-5,995	7,39E-06
MYH6	NM_002471	Hs.278432	hs|14q11.2	0,314	-0,051	0,249	0,015	-0,269	-0,454	-5,863	4,84E-10
SLC35F2	NM_017515	Hs.524014	hs|11q22.3	-0,349	-0,234	-0,644	-1,274	-1,096	-0,848	-5,586	7,46E-04
HAS3	NM_005329	Hs.592069	hs|16q22.1	0,220	0,050	-0,384	-0,510	-0,646	-0,520	-5,496	1,50E-12
COLEC12	NM_130386	Hs.464422	hs|18p11.32	-0,119	-0,280	-0,458	-1,049	-0,938	-0,896	-5,494	3,38E-04
SLC3A2	NM_002394	Hs.502769	hs|11q12.3	0,109	0,021	-0,385	-0,614	-0,696	-0,616	-5,418	2,61E-11
AW993939	AW993939	Hs.520819	hs|7q36.3	-0,080	-0,038	0,006	0,013	-0,714	-0,752	-5,378	2,72E-05
RUNX2	NM_004348	Hs.535845	hs|6p12.3	0,489	0,000	-0,282	-0,349	-0,226	-0,151	-5,217	9,80E-04
SUSD3	NM_145006	Hs.88417	hs|9q22.31	-0,157	-0,288	-0,531	-0,856	-0,891	-0,886	-5,131	2,21E-04
PLAU	NM_002658	Hs.77274	hs|10q22.2	0,351	0,650	0,291	0,083	-0,502	-0,345	-4,969	9,69E-04
SLC22A3	NM_021977	Hs.567337	hs|6q25.3	-0,012	-0,073	-0,331	-0,853	-0,709	-0,677	-4,966	1,05E-04
FCRL4	NM_031282	Hs.120260	hs|1q23.1	0,549	-0,008	0,287	0,000	-0,117	-0,146	-4,954	5,67E-04
DOCK2	NM_004946	Hs.586174	hs|5q35.1	0,545	0,210	-0,055	-0,129	-0,150	-0,038	-4,847	1,38E-12

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
SOX3	NM_005634	Hs.157429	hs|Xq27.1	-0,164	-0,082	-0,543	-0,844	-0,883	-0,769	-4,789	7,72E-05
THC2616558			hs|16q13	-0,598	-0,635	-0,776	-1,120	-1,367	-1,271	-4,716	1,86E-06
RNASET2	NM_003730	Hs.529989	hs|6q27	-0,254	-0,475	-0,595	-0,752	-0,963	-0,926	-4,696	5,13E-05
LOC100130360	BX538057	Hs.408455	hs|6p22.3	0,306	0,232	-0,375	-0,764	-0,353	-0,012	-4,559	2,99E-04
IL1R2	NM_004633	Hs.25333	hs|2q11.2	0,894	0,879	0,742	0,066	0,356	0,386	-4,454	6,06E-04
MGAT5B	NM_144677	Hs.144531	hs|17q25.2	0,230	0,275	0,049	-0,193	-0,411	-0,409	-4,358	5,87E-05
TCF7L1	NM_031283	Hs.516297	hs|2p11.2	0,047	-0,199	-0,093	-0,179	-0,451	-0,592	-4,356	8,41E-04
AF222857	AF222857	Hs.673626	hs|15q21.1	0,333	0,066	0,000	-0,080	-0,195	-0,318	-4,342	1,09E-04
AHNAK	NM_001620	Hs.502756	hs|11q12.3	0,084	-0,067	-0,082	-0,168	-0,178	-0,273	-4,220	2,36E-07
HOXB8	NM_024016	Hs.514292	hs|17q21.32	0,531	0,625	0,489	-0,147	-0,087	0,008	-4,212	1,48E-04
S100A16	NM_080388	Hs.515714	hs|1q21.3	-0,036	0,022	-0,317	-0,736	-0,649	-0,560	-4,132	1,34E-04
INSIG1	NM_198336	Hs.520819	hs|7q36.3	-0,200	-0,042	-0,104	-0,176	-0,711	-0,718	-4,127	1,49E-05
DCDC2	NM_016356	Hs.660365	hs|6p22.2	-0,102	0,022	-0,225	-0,687	-0,777	-0,644	-4,045	3,41E-04
LEMD1	NM_001001552	Hs.655520	hs|1q32.1	-0,214	-0,377	-0,470	-0,668	-1,005	-0,810	-3,945	1,72E-05
HEG1	BQ184357	Hs.619929	hs|3q21.2	0,222	0,015	0,056	-0,051	-0,378	-0,373	-3,936	3,21E-04
AFAP1	NM_021638	Hs.529369	hs|4p16.1	0,075	-0,063	-0,168	-0,171	-0,461	-0,520	-3,929	3,82E-04
PAQR9	NM_198504	Hs.656111	hs|3q23	0,355	-0,208	0,199	0,106	-0,132	-0,236	-3,904	4,69E-04
LOC165186			hs|2p23.2	-0,319	-0,583	-0,746	-0,856	-0,887	-0,663	-3,893	2,47E-07
GUCA2B	NM_007102	Hs.32966	hs|1p34.2	0,527	0,123	0,111	-0,341	-0,055	-0,055	-3,838	2,81E-06
C9orf61	NM_004816	Hs.118003	hs|9q21.11	0,535	0,278	0,302	-0,145	0,051	-0,074	-3,813	1,58E-04
BX415272	BX415272	Hs.681876	hs|11p13	-0,284	-0,495	-0,905	-0,947	-0,849	-0,763	-3,780	5,47E-04
RRAGD	NM_021244	Hs.485938	hs|6q15	-0,250	-0,196	-0,510	-0,903	-0,822	-0,537	-3,768	5,43E-04
FHL2	NM_201555	Hs.443687	hs|2q12.2	-0,092	-0,272	-0,451	-0,554	-0,591	-0,666	-3,750	3,25E-06
MBNL3	NM_133486	Hs.105134	hs|Xq26.2	-0,279	-0,556	-0,762	-1,012	-0,845	-0,694	-3,699	1,26E-08
HIST1H1A	NM_005325	Hs.150206	hs|6p22.1	-0,034	-0,100	-0,241	-0,445	-0,258	-0,608	-3,697	6,29E-05
CPVL	NM_031311	Hs.233389	hs|7p15.1	0,274	0,183	-0,002	-0,142	-0,473	-0,294	-3,696	2,99E-05
SLC16A2	NM_006517	Hs.75317	hs|Xq13.2	-0,294	-0,174	-0,737	-0,808	-0,870	-0,451	-3,630	4,60E-04
SCD5	NM_001037582	Hs.379191	hs|4q21.22	-0,113	-0,392	-0,489	-0,541	-0,657	-0,667	-3,582	4,40E-04
SLC34A2	NM_006424	Hs.479372	hs|4p15.2	-0,024	-0,159	-0,385	-0,537	-0,571	-0,492	-3,578	1,40E-10
CHST1	NM_003654	Hs.104576	hs|11p11.2	0,446	-0,034	0,090	0,170	-0,082	-0,098	-3,574	5,31E-04
CDC14B	AF064105		hs|9q22.33	0,568	0,000	0,598	0,511	0,366	0,008	-3,550	1,76E-04
EGLN3	NM_022073	Hs.135507	hs|14q13.1	0,559	0,243	0,121	-0,245	0,070	0,009	-3,544	2,71E-05
ZFPM2	NM_012082	Hs.431009	hs|8q23.1	0,527	0,091	0,000	0,000	-0,020	-0,031	-3,518	8,46E-08
DLC1	NM_182643	Hs.134296	hs|8p22	0,086	-0,152	-0,255	-0,416	-0,417	-0,516	-3,516	3,41E-06
ZNF649	NM_023074	Hs.567573	hs|19q13.33	0,061	-0,199	-0,440	-0,658	-0,478	-0,328	-3,451	5,84E-07

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
BM129308	BM129308	Hs.653792	hs|8p21.2	-0,432	-0,331	-0,564	-1,111	-0,968	-0,944	-3,440	6,61E-04
BC043218	BC043218	Hs.220558	hs|22q13.1	0,505	0,164	0,202	0,069	0,016	-0,041	-3,432	6,24E-05
MIRN155	NR_001458	Hs.662258	hs|21q21.3	0,163	0,000	0,138	0,000	-0,121	-0,371	-3,421	3,75E-04
TJP2	NM_201629	Hs.50382	hs|9q21.11	0,068	0,112	-0,344	-0,500	-0,510	-0,418	-3,418	9,88E-11
FOXD1	NM_004472	Hs.519385	hs|5q13.2	-0,098	-0,199	-0,374	-0,540	-0,674	-0,627	-3,413	1,65E-06
L1CAM	NM_000425	Hs.522818	hs|Xq28	0,280	-0,136	0,310	0,170	-0,348	-0,235	-3,370	8,14E-04
LOC388630	XM_371250	Hs.576171	hs|1p33	-0,329	-0,470	-0,730	-0,798	-0,866	-0,854	-3,355	7,64E-05
SMOC2	NM_022138	Hs.487200	hs|6q27	-0,211	-0,219	-0,355	-0,613	-0,731	-0,731	-3,317	1,29E-07
BCMO1	NM_017429	Hs.212172	hs|16q23.2	0,269	0,099	-0,180	-0,247	-0,252	-0,138	-3,297	1,09E-06
LDLR	NM_000527	Hs.213289	hs|19p13.2	-0,068	0,013	-0,177	-0,274	-0,506	-0,517	-3,286	1,93E-06
DLG3	NM_021120	Hs.522680	hs|Xq13.1	0,125	0,076	0,010	-0,042	-0,361	-0,415	-3,279	4,78E-04
BC033829	BC033829	Hs.371240	hs|6q25.1	-0,287	-0,493	-0,618	-0,953	-0,774	-0,723	-3,262	5,23E-04
GSTM1	NM_146421	Hs.301961	hs|1p13.3	0,109	0,069	-0,139	-0,370	-0,443	-0,361	-3,240	2,08E-07
MARCKS	NM_002356	Hs.519909	hs|6q22.1	0,630	0,538	0,427	0,216	0,125	0,187	-3,198	4,47E-05
LOC553137	AK124400	Hs.652438	hs|6q21	-0,324	-0,198	-0,414	-0,736	-0,953	-0,828	-3,193	7,04E-04
SRrp35	NM_080743	Hs.254414	hs|6q15	-0,141	-0,171	-0,572	-0,642	-0,706	-0,642	-3,175	1,58E-12
SEPTIN6	NM_145802	Hs.496666	hs|Xq24	0,285	0,210	-0,059	-0,224	-0,250	-0,212	-3,161	7,28E-07
SPNS2	BC041772	Hs.567664	hs|17p13.2	0,468	0,428	0,238	0,066	-0,163	-0,031	-3,151	6,45E-05
C5orf13	NM_004772	Hs.36053	hs|5q22.1	0,275	0,296	0,243	0,246	-0,138	-0,179	-3,126	5,71E-04
CDKN2A	NM_058197	Hs.512599	hs|9p21.3	0,194	0,019	-0,032	-0,226	-0,270	-0,119	-3,120	3,01E-04
TOM1L2	NM_001082968	Hs.462379	hs|17p11.2	0,074	-0,127	-0,235	-0,296	-0,574	-0,419	-3,109	1,56E-04
FZD4	NM_012193	Hs.591968	hs|11q14.2	-0,176	-0,136	-0,478	-0,677	-0,667	-0,517	-3,092	1,62E-04
GSTM3	NM_000849	Hs.2006	hs|1p13.3	0,114	0,085	-0,141	-0,353	-0,399	-0,324	-3,050	9,13E-13
TMEM16A	BC032907	Hs.98470	hs|5p15.2	0,483	0,213	0,000	-0,045	0,000	0,059	-3,048	5,15E-06
GSTM4	NM_147148	Hs.348387	hs|1p13.3	0,279	0,108	0,014	-0,110	-0,341	-0,262	-3,034	5,52E-05
SLC44A1	NM_080546	Hs.573495	hs|9q31.1	-0,125	-0,131	-0,317	-0,516	-0,505	-0,530	-3,029	2,98E-05
DCLK1	NM_004734	Hs.507755	hs|13q13.3	-0,626	-0,615	-0,840	-1,107	-1,094	-1,002	-3,024	1,34E-05
MGC33846	NM_175885	Hs.448218	hs|11q14.1	0,031	-0,267	-0,338	-0,480	-0,500	-0,433	-3,023	2,39E-04
NKX3-1	NM_006167	Hs.55999	hs|8p21.2	-0,050	-0,021	-0,303	-0,599	-0,515	-0,444	-3,020	6,14E-05
PKP2	NM_004572	Hs.164384	hs|12p11.21	0,290	0,008	-0,138	-0,174	-0,219	-0,155	-3,012	1,03E-04
ENST00000343505	BC020940	Hs.652741	hs|6q23.3	0,216	0,101	-0,021	-0,165	-0,188	-0,262	-3,010	9,85E-06
THC2616992			hs|13q13.1	-0,217	-0,209	-0,687	-0,802	-0,692	-0,404	-3,007	7,44E-05
SH3RF1	NM_020870	Hs.301804	hs|4q32.3	0,422	0,448	0,206	0,014	-0,069	-0,049	-2,966	1,18E-04
LGI2	NM_017688	Hs.632677	hs|9q32	-0,196	-0,255	-0,353	-0,565	-0,700	-0,668	-2,954	5,53E-05
GALM	NM_138801	Hs.435012	hs|2p22.1	-0,062	-0,177	-0,302	-0,312	-0,499	-0,526	-2,928	3,91E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
MAP6	NM_033063	Hs.585540	hs|11q13.5	0,510	0,020	0,502	0,432	0,094	0,042	-2,891	2,88E-07
ROR1	NM_005012	Hs.654491	hs|1p31.3	0,132	0,066	-0,328	-0,418	-0,319	-0,090	-2,888	1,41E-04
FRMD4A	NM_018027	Hs.330463	hs|10p13	-0,095	-0,218	-0,379	-0,351	-0,626	-0,556	-2,886	7,52E-04
MAGEA10	NM_001011543	Hs.18048	hs|Xq28	0,000	-0,069	0,000	-0,081	-0,404	-0,457	-2,865	3,62E-04
UBASH3B	NM_032873	Hs.444075	hs|11q24.1	0,031	-0,070	-0,005	0,004	-0,317	-0,463	-2,858	6,30E-05
BI832578	BI832578	Hs.669408	hs|1p22.2	0,071	-0,033	-0,311	-0,320	-0,307	-0,385	-2,854	2,03E-05
SPON1	NM_006108	Hs.654637	hs|11p15.2	0,342	0,288	0,224	0,166	-0,067	-0,116	-2,849	2,62E-04
THC2533833	AA873311	Hs.693594	hs|6q25.3	0,048	-0,259	-0,248	-0,313	-0,286	-0,410	-2,838	5,51E-04
OGFRL1	NM_024576	Hs.656091	hs|6q13	0,111	-0,187	-0,258	-0,319	-0,366	-0,256	-2,826	9,63E-05
BU943730	BU943730	Hs.636188	hs|12p13.1	0,037	-0,080	-0,013	-0,021	-0,211	-0,367	-2,815	2,38E-04
LOC388610	NM_001013642	Hs.355747	hs|1p36.11	0,387	0,291	0,084	-0,046	-0,067	0,032	-2,806	5,72E-04
SDC1	NM_001006946	Hs.224607	hs|2p24.1	0,398	0,092	0,294	0,159	0,042	-0,049	-2,802	5,22E-04
BF312639	BF312639	Hs.655654	hs|7q22.1	0,221	-0,034	-0,236	-0,210	-0,227	-0,048	-2,795	3,73E-05
FAM83A	NM_032899	Hs.379821	hs|8q24.13	0,321	0,031	-0,167	-0,140	-0,096	-0,125	-2,791	1,96E-04
RCAN3	NM_013441	Hs.656799	hs|1p36.11	0,253	0,051	-0,157	-0,166	-0,222	-0,191	-2,781	5,42E-05
THC2636507			hs|11q23.1	0,382	0,000	0,000	-0,039	-0,106	-0,057	-2,749	2,35E-05
ELK3	NM_005230	Hs.591015	hs|12q23.1	-0,013	-0,030	-0,151	-0,273	-0,562	-0,456	-2,731	6,50E-04
TMEM171	NM_173490	Hs.162246	hs|5q13.2	-0,059	-0,282	-0,207	-0,334	-0,447	-0,473	-2,722	1,41E-04
ENST00000370624	AK092806	Hs.407054	hs|1p22.3	0,085	-0,171	-0,283	-0,392	-0,345	-0,152	-2,704	6,74E-04
LOC440900	AK096065	Hs.592185	hs|7p21.1	0,131	-0,035	-0,188	-0,254	-0,297	-0,110	-2,695	9,07E-06
RAB7B	NM_177403	Hs.534612		0,464	0,162	0,330	0,139	0,019	0,036	-2,689	9,42E-04
ABHD2	NM_007011	Hs.122337	hs|15q26.1	0,352	-0,011	0,191	0,185	0,014	-0,081	-2,685	4,95E-05
PDE6A	NM_000440	Hs.567314	hs|5q33.1	-0,245	-0,309	-0,756	-0,818	-0,736	-0,534	-2,665	4,56E-04
OR2H2	NM_007160	Hs.529493	hs|6p22.1	0,260	-0,038	0,097	-0,009	-0,097	-0,163	-2,664	8,27E-06
GJC1	NM_005497	Hs.659160	hs|17q21.31	-0,795	-0,801	-0,866	-1,177	-1,249	-1,195	-2,660	2,46E-05
AY007156	AY007156	Hs.593067	hs|20p11.23	0,251	0,130	0,031	-0,104	-0,202	-0,139	-2,659	2,71E-04
IL6R	NM_000565	Hs.591492	hs|1q21.3	-0,301	-0,394	-0,523	-0,599	-0,656	-0,557	-2,657	7,80E-04
HUS1B	NM_148959	Hs.669039	hs|6p25.3	0,203	-0,028	-0,188	-0,353	-0,218	-0,192	-2,646	5,83E-04
SOCS1	NM_003745	Hs.50640	hs|16p13.13	0,433	0,211	0,122	0,044	0,001	0,011	-2,645	6,51E-06
DB111455	DB111455	Hs.660706	hs|11q21	0,422	0,105	0,353	0,339	0,131	0,000	-2,643	7,28E-05
AK026194	AK026194	Hs.593067	hs|20p11.23	0,211	0,120	-0,009	-0,128	-0,226	-0,160	-2,640	3,76E-05
WDR40B	NM_178470	Hs.120403	hs|Xq25	0,269	0,148	-0,080	-0,143	0,000	-0,174	-2,607	5,28E-11
THC2707284			hs|11q13.4	-0,044	0,010	-0,350	-0,437	-0,439	-0,460	-2,605	5,74E-05
HSU79275	U79275	Hs.598507	hs|12q13.11	-0,038	-0,169	-0,314	-0,398	-0,476	-0,453	-2,600	6,05E-07
TMEM2	NM_013390	Hs.494146	hs|9q21.13	0,453	0,112	0,115	0,067	0,043	0,002	-2,600	4,51E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
PADI3	NM_016233	Hs.149195	hs|1p36.13	0,291	0,351	0,148	-0,043	-0,115	-0,114	-2,571	1,20E-06
MMAB	NM_052845	Hs.12106	hs|12q24.11	-0,039	-0,121	-0,071	-0,129	-0,363	-0,447	-2,556	6,81E-07
ME1	NM_002395	Hs.21160	hs|6q14.2	0,157	0,008	-0,102	-0,177	-0,230	-0,197	-2,552	1,40E-05
MPP1	NM_002436	Hs.496984	hs|Xq28	0,116	0,031	-0,142	-0,140	-0,194	-0,291	-2,550	3,81E-05
ACSS2	NM_018677	Hs.517034	hs|20q11.22	0,224	0,096	-0,008	-0,070	-0,203	-0,182	-2,547	6,69E-06
ZBTB24	NM_014797	Hs.409876	hs|6q21	-0,017	-0,411	-0,286	-0,386	-0,440	-0,420	-2,531	5,31E-04
DHCR7	NM_001360	Hs.503134	hs|11q13.4	-0,118	-0,136	-0,201	-0,256	-0,533	-0,521	-2,527	6,45E-04
ACAT2	NM_005891	Hs.571037	hs|6q25.3	-0,032	-0,077	-0,078	-0,155	-0,324	-0,425	-2,520	1,82E-04
G6PD	NM_000402	Hs.461047	hs|Xq28	0,218	0,143	-0,061	-0,048	-0,044	-0,106	-2,504	3,02E-04
SEPP1	NM_005410	Hs.275775	hs|5p12	0,455	0,347	0,318	0,188	0,120	0,368	-2,502	2,44E-04
BARX2	NM_003317	Hs.465511	hs|19p13.3	-0,052	-0,186	-0,344	-0,424	-0,541	-0,278	-2,499	4,82E-11
PGC	NM_002630	Hs.1867	hs|6p21.1	0,431	0,419	0,293	0,141	0,031	0,128	-2,497	4,47E-04
ZBED1	NM_004729	Hs.131452	hs|Yp11.31	0,169	-0,092	-0,136	-0,195	-0,263	-0,327	-2,494	5,73E-04
TMCC3	NM_020698	Hs.370410	hs|12q22	0,018	-0,061	-0,084	-0,203	-0,331	-0,379	-2,492	5,20E-04
THC2732364			hs|6q27	0,167	-0,016	0,114	-0,022	-0,107	-0,229	-2,490	9,24E-04
CHRFAM7A	BX395274	Hs.663861	hs|15q13.3	-0,067	-0,209	-0,269	-0,376	-0,568	-0,463	-2,484	3,17E-04
LBH	NM_030915	Hs.567598	hs|2p23.1	-0,192	-0,162	-0,404	-0,550	-0,713	-0,587	-2,483	2,85E-04
RAPGEF3	NM_006105	Hs.8578	hs|12q13.11	-0,086	-0,027	-0,314	-0,404	-0,446	-0,451	-2,477	6,66E-05
SLC18A1	NM_003053	Hs.158322	hs|8p21.3	0,322	0,362	0,000	-0,186	-0,029	-0,006	-2,473	3,97E-04
PRKD1	NM_002742	Hs.508999	hs|14q12	-0,289	-0,218	-0,411	-0,718	-0,711	-0,524	-2,468	9,84E-04
THC2634493			hs|13q13.3	-0,505	-0,624	-0,719	-0,998	-0,864	-0,774	-2,459	2,05E-04
F3	NM_001993	Hs.62192	hs|1p21.3	0,109	-0,160	-0,138	-0,223	-0,263	-0,282	-2,459	3,00E-06
MGC50722	NM_203348	Hs.530383		0,314	-0,081	-0,015	0,032	-0,086	-0,104	-2,454	3,02E-04
B4GALT4	NM_212543	Hs.13225	hs|3q13.32	0,266	0,166	-0,083	-0,211	-0,123	-0,079	-2,453	4,47E-11
SLC12A8	NM_024628	Hs.658514	hs|3q21.2	-0,057	-0,025	-0,264	-0,535	-0,445	-0,402	-2,448	4,13E-04
DMRT3	NM_021240	Hs.189174	hs|9p24.3	-0,564	-0,356	-0,432	-0,608	-0,747	-0,723	-2,446	8,20E-04
TLE6	BC007329	Hs.334507	hs|19p13.3	0,046	0,006	-0,230	-0,162	-0,321	-0,342	-2,440	8,41E-04
MICAL2	NM_014632	Hs.501928	hs|11p15.3	0,010	-0,062	-0,041	-0,050	-0,269	-0,306	-2,424	9,30E-04
ADRA1B	NM_000679	Hs.368632	hs|5q33.3	-0,137	-0,314	-0,471	-0,582	-0,515	-0,521	-2,420	6,83E-11
NDRG2	NM_201535	Hs.525205	hs|14q11.2	-0,048	-0,082	-0,053	-0,206	-0,340	-0,431	-2,417	2,08E-04
CSF2RA	NM_172247	Hs.520937	hs|Yp11.32	0,109	-0,040	-0,104	-0,177	-0,256	-0,240	-2,411	7,43E-06
BG695979	BG695979	Hs.594262	hs|1p36.11	0,390	0,109	0,004	-0,045	-0,172	-0,076	-2,407	9,86E-04
LOC100133991	AK097219	Hs.668927	hs|17q21.31	0,177	-0,096	-0,090	0,000	-0,185	-0,249	-2,404	5,67E-04
LOC389895			hs|Xq27.1	-0,127	-0,221	-0,330	-0,525	-0,440	-0,510	-2,395	6,01E-05
RNF8	NM_003958	Hs.485278	hs|6p21.2	0,013	-0,090	-0,200	-0,264	-0,394	-0,359	-2,377	3,79E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
CTSC	NM_024996	Hs.518355	hs|3q25.32	0,172	0,038	-0,014	-0,035	-0,151	-0,207	-2,375	7,15E-06
RAB3B	NM_002867	Hs.123072	hs|1p32.3	-0,118	-0,350	-0,420	-0,411	-0,524	-0,607	-2,369	8,43E-04
EPB41L2	NM_001431	Hs.486470	hs|6q23.1	0,169	0,196	-0,213	-0,282	-0,167	-0,205	-2,368	4,09E-04
HAVCR1	NM_012206	Hs.129711	hs|5q33.3	0,178	0,038	0,097	-0,122	-0,265	-0,196	-2,367	9,77E-04
MGC3032	AK096306	Hs.568945	hs|11q13.1	0,182	0,096	-0,030	-0,087	-0,148	-0,049	-2,366	3,59E-04
AKAP7	NM_016377	Hs.486483	hs|6q23.2	0,158	0,004	-0,144	-0,206	-0,188	-0,216	-2,364	1,69E-04
CDKAL1	NM_017774	Hs.657604	hs|6p22.3	0,164	0,202	0,005	-0,088	-0,160	-0,165	-2,360	8,77E-04
SLC2A1	NM_003245	Hs.2022	hs|20p13	0,009	-0,197	-0,328	-0,343	-0,367	-0,363	-2,360	1,10E-07
PALLD	NM_016081	Hs.151220	hs|4q32.3	0,052	-0,173	-0,179	-0,268	-0,315	-0,320	-2,352	3,13E-05
BTBD9	NM_152733	Hs.654635	hs|6p21.2	0,174	-0,078	-0,292	-0,202	-0,192	-0,042	-2,347	5,78E-04
C6orf64	NM_018322	Hs.58382	hs|6p21.2	0,176	0,077	0,019	-0,009	-0,131	-0,194	-2,341	2,05E-05
FGFR4	NM_213647	Hs.165950	hs|5q35.2	-0,123	-0,195	-0,291	-0,302	-0,419	-0,500	-2,335	1,78E-04
RBMY1E	NM_001006118	Hs.536001	hs|Yq11.223	0,279	-0,127	0,195	0,109	-0,018	-0,089	-2,332	4,12E-04
RERE	NM_012102	Hs.463041	hs|1p36.23	-0,024	-0,206	-0,330	-0,378	-0,426	-0,208	-2,332	1,31E-10
TINAGL1	NM_022164	Hs.199368	hs|1p35.2	0,372	0,293	0,286	0,116	-0,092	-0,138	-2,327	1,33E-06
THC2722891			hs|6q23.2	0,552	0,402	0,369	0,211	0,203	0,192	-2,323	6,39E-04
KIF13A	NM_022113	Hs.189915	hs|6p22.3	0,010	-0,157	-0,244	-0,331	-0,310	-0,354	-2,314	1,93E-06
LOC440335	BC022385	Hs.390599	hs|16p13.3	0,306	-0,129	0,000	-0,035	-0,073	-0,058	-2,312	3,37E-04
B3GALT5	NM_033173	Hs.655094	hs|21q22.2	-0,112	0,340	0,379	0,367	0,091	-0,023	-2,311	1,27E-04
GNB5	BC011671	Hs.155090	hs|15q21.2	0,110	0,123	-0,151	-0,210	-0,239	-0,199	-2,276	1,05E-05
GALNT6	NM_007210	Hs.505575	hs|12q13.13	0,166	0,051	0,028	-0,147	-0,137	-0,191	-2,276	3,94E-04
THC2608967			hs|15q25.2	0,370	0,045	0,295	0,200	0,092	0,012	-2,276	2,50E-04
HFE	NM_139009	Hs.233325	hs|6p22.1	0,188	0,074	0,051	0,014	-0,148	-0,169	-2,274	9,29E-04
GMDS	NM_001500	Hs.144496	hs|6p25.3	-0,025	-0,080	-0,257	-0,294	-0,375	-0,381	-2,266	2,04E-04
THC2582296	BU194531	Hs.654439	hs|19q13.32	0,123	0,006	-0,049	-0,203	-0,227	0,206	-2,260	3,72E-05
ADAMTS4	BC030812		hs|1q23.3	0,254	0,009	0,085	0,000	-0,060	-0,100	-2,259	5,79E-05
TBC1D1	NM_015173	Hs.176503	hs|4p14	0,052	-0,136	0,060	0,049	-0,134	-0,302	-2,259	3,75E-05
POU5F1	NM_002701	Hs.249184	hs|6p21.33	-0,240	-0,136	-0,225	-0,364	-0,514	-0,457	-2,252	6,40E-05
DNMT3B	NM_175850	Hs.655708	hs|20q11.21	-0,093	-0,015	-0,126	-0,166	-0,284	-0,445	-2,246	2,68E-06
CDH5	NM_001795	Hs.76206	hs|16q21	0,193	0,126	0,119	-0,223	-0,095	-0,157	-2,243	7,32E-11
FLJ22222	BC009297		hs|17q25.3	-0,097	-0,156	-0,180	-0,257	-0,316	-0,483	-2,243	1,37E-04
KIAA1553	NM_001080450	Hs.418045	hs|6q21	-0,073	-0,238	-0,202	-0,223	-0,275	-0,424	-2,240	5,64E-04
XR_018059	XR_018059	Hs.648104	hs|7p13	0,066	-0,050	-0,050	-0,116	-0,136	-0,301	-2,239	2,50E-04
MTA3	AK127245	Hs.435413	hs|2p21	-0,018	-0,121	-0,165	-0,145	-0,342	-0,367	-2,236	5,94E-04
RAB15	NM_198686	Hs.512492	hs|14q23.3	-0,089	-0,195	-0,319	-0,344	-0,406	-0,426	-2,232	5,98E-05

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
XIRP1	NM_194293	Hs.447868	hs|3p22.2	0,221	-0,008	0,000	-0,066	-0,015	-0,127	-2,227	7,11E-04
RAB11FIP4	NM_032932	Hs.406788	hs|17q11.2	-0,067	0,036	0,171	0,189	-0,179	-0,173	-2,220	6,39E-04
LOC100132338	AK074662	Hs.473927	hs|21q22.3	0,250	-0,058	0,062	-0,016	-0,082	-0,095	-2,215	1,67E-04
HLA-DRB4	NM_021983	Hs.654405		0,441	0,008	0,330	0,374	0,169	0,097	-2,211	8,39E-05
FZD5	NM_003468	Hs.17631	hs|2q33.3	-0,018	-0,080	-0,178	-0,284	-0,321	-0,361	-2,199	1,41E-06
PRAGMIN	AF075060	Hs.657673	hs|8p23.1	0,112	-0,031	-0,056	-0,195	-0,227	-0,007	-2,198	1,39E-04
UBE2J1	NM_016021	Hs.163776	hs|6q15	-0,193	-0,244	-0,348	-0,470	-0,556	-0,506	-2,198	7,93E-05
CHRDL2	NM_015424	Hs.432379	hs|11q13.4	0,230	-0,089	0,053	-0,021	-0,020	-0,112	-2,197	3,50E-04
C15orf50	BC031958	Hs.569502	hs|15q23	0,245	-0,046	0,000	0,066	-0,027	-0,099	-2,191	8,28E-04
CLDN4	NM_001305	Hs.647036	hs|7q11.23	0,274	0,006	0,010	-0,014	-0,066	-0,093	-2,189	9,23E-05
IGF2R	NM_000876	Hs.487062	hs|6q25.3	0,054	-0,023	-0,152	-0,205	-0,317	-0,285	-2,187	3,94E-04
GSTM2	NM_000848	Hs.279837	hs|1p13.3	0,292	0,098	0,083	0,015	-0,125	-0,092	-2,182	1,99E-04
RRAS2	NM_012250	Hs.502004	hs|11p15.2	-0,040	-0,098	-0,293	-0,349	-0,366	-0,319	-2,173	2,08E-04
AW268902	AW268902	Hs.29802	hs|4p15.31	0,133	0,054	-0,124	-0,157	-0,192	0,087	-2,169	2,76E-04
HDDC2	NM_016063	Hs.32826	hs|6q22.31	0,183	0,054	-0,123	-0,224	-0,150	-0,158	-2,167	8,89E-06
CDC20B	NM_152623	Hs.669184	hs|5q11.2	0,126	-0,086	0,000	0,000	-0,128	-0,211	-2,161	4,35E-04
PFKL	NM_001002021	Hs.255093	hs|21q22.3	-0,043	-0,124	NA	-0,130	-0,304	-0,378	-2,159	6,84E-05
LRP8	NM_033300	Hs.576154	hs|1p32.3	0,148	0,181	0,122	0,076	-0,019	-0,186	-2,156	7,10E-05
STIM1	NM_003156	Hs.501735	hs|11p15.4	0,029	-0,115	-0,187	-0,226	-0,325	-0,304	-2,151	4,01E-05
KLHL5	NM_015990	Hs.272251	hs|4p14	0,331	0,043	0,175	0,204	0,009	-0,001	-2,147	9,71E-04
TP53INP2	NM_021202	Hs.516994	hs|20q11.22	0,008	-0,018	-0,179	-0,300	-0,457	-0,324	-2,145	4,67E-06
FURIN	NM_002569	Hs.513153	hs|15q26.1	0,038	-0,058	-0,151	-0,045	-0,320	-0,309	-2,144	6,16E-05
TRIB3	NM_021158	Hs.516826	hs|20p13	0,120	0,020	-0,111	-0,099	-0,183	-0,214	-2,139	3,92E-04
ADCY4	NM_139247	Hs.443428	hs|14q12	0,213	-0,045	0,066	0,026	-0,069	-0,117	-2,137	2,06E-04
KANK1	NM_153186	Hs.306764	hs|9p24.3	0,175	-0,036	0,061	0,011	-0,142	-0,154	-2,132	9,75E-04
SH3KBP1	NM_031892	Hs.444770	hs|Xp22.12	0,040	0,010	-0,281	-0,363	-0,236	-0,303	-2,132	7,91E-04
S73202	S73202		hs|9q34.11	0,274	0,340	0,227	-0,034	-0,079	-0,017	-2,130	4,35E-05
CCDC109B	NM_017918	Hs.234149	hs|4q25	0,032	-0,008	-0,072	-0,162	-0,151	-0,265	-2,129	1,66E-04
AGPAT4	NM_020133	Hs.353175	hs|6q26	-0,069	-0,083	-0,190	-0,248	-0,431	-0,397	-2,129	7,92E-04
ACSS1	NM_032501	Hs.529353	hs|20p11.21	0,181	0,013	0,000	0,000	-0,078	-0,147	-2,125	9,18E-04
AK094629	AK094629	Hs.594896	hs|6q26	-0,136	-0,153	-0,476	-0,626	-0,461	-0,281	-2,123	4,79E-04
LRRC31	NM_024727	Hs.411295	hs|3q26.2	0,552	0,383	0,432	0,173	0,289	0,226	-2,118	6,26E-04
AY090769	AY090769	Hs.275865	hs|6p21.32	0,062	0,007	0,004	-0,113	-0,153	-0,263	-2,117	2,63E-04
NSDHL	NM_015922	Hs.57698	hs|Xq28	-0,011	-0,057	-0,128	-0,135	-0,291	-0,335	-2,110	1,24E-05
SLC35B2	NM_178148	Hs.182885	hs|6p21.1	0,062	0,050	-0,062	-0,127	-0,260	-0,264	-2,110	5,86E-04

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
SVIL	NM_021738	Hs.499209	hs|10p11.23	0,203	0,164	0,105	0,029	-0,160	-0,120	-2,104	4,70E-08
THC2569387	AA632084	Hs.159161	hs|17q25.3	0,108	-0,110	-0,009	-0,045	-0,111	-0,228	-2,089	9,93E-04
ENST00000366623	AJ311797	Hs.547779	hs|1q42.2	0,238	0,056	0,129	0,070	0,043	-0,087	-2,089	3,18E-04
RFFL	NM_057178	Hs.13680	hs|17q12	0,134	0,041	-0,040	-0,178	-0,156	-0,098	-2,081	3,08E-04
THC2512502	AW589254	Hs.653501	hs|Xp11.23	0,092	-0,184	-0,131	-0,104	-0,162	-0,229	-2,081	3,34E-04
NQO2	NM_000904	Hs.533050	hs|6p25.2	-0,018	-0,077	-0,048	-0,083	-0,215	-0,337	-2,080	3,42E-05
RHOF	NM_019034	Hs.524804	hs|12q24.31	-0,096	-0,126	-0,239	-0,294	-0,321	-0,413	-2,074	4,10E-04
MLL3	NM_170606	Hs.647120	hs|7q36.1	0,058	-0,024	-0,086	-0,100	-0,274	-0,263	-2,074	3,56E-04
AL522622	AL522622	Hs.432121	hs|19p13.13	-0,062	-0,002	-0,021	-0,097	-0,205	-0,298	-2,072	3,04E-04
FBXO9	NM_033481	Hs.216653	hs|6p12.1	0,046	-0,007	-0,092	-0,164	-0,222	-0,168	-2,070	1,82E-04
MSN	NM_002444	Hs.87752	hs|Xq11.1	0,102	0,019	-0,072	-0,083	-0,149	-0,212	-2,061	1,08E-04
BY798802	BY798802	Hs.598890	hs|15q15.1	0,265	0,068	-0,002	-0,012	-0,046	-0,068	-2,061	1,86E-05
CSPG5	NM_006574	Hs.45127	hs|3p21.31	-0,168	-0,299	-0,433	-0,479	-0,476	-0,377	-2,055	9,65E-04
SHROOM2	NM_001649	Hs.567236	hs|Xp22.2	0,092	0,049	-0,116	-0,116	-0,164	-0,220	-2,053	3,43E-04
C11orf51	NM_014042	Hs.38044	hs|11q13.4	-0,017	-0,093	-0,148	-0,254	-0,236	-0,329	-2,051	5,86E-04
ENST00000399048	BC110641	Hs.572477	hs|17p11.2	0,273	0,277	0,242	-0,058	0,044	-0,040	-2,050	8,29E-04
SUV39H1	NM_003173	Hs.522639	hs|Xp11.23	0,049	-0,116	-0,013	0,015	-0,159	-0,274	-2,049	4,17E-04
CR599788	CF124646	Hs.650678	hs|17q25.3	0,327	0,155	-0,059	-0,025	0,017	0,032	-2,045	6,49E-04
SFTPA1	XM_934590	Hs.523084	hs|10q22.3	0,000	-0,061	0,000	-0,175	-0,178	-0,327	-2,041	7,31E-04
DYNLT1	NM_006519	Hs.445999	hs|6q25.3	-0,023	-0,128	-0,130	-0,216	-0,276	-0,333	-2,041	8,72E-06
ABCD1	NM_000033	Hs.159546	hs|Xq28	0,084	0,038	-0,076	-0,093	-0,225	-0,226	-2,040	6,92E-04
GPNMB	BC011595	Hs.190495	hs|7p15.3	0,738	0,489	0,312	0,366	-0,055	0,388	-2,040	5,90E-04
BOK	NM_032515	Hs.293753	hs|2q37.3	0,058	-0,063	-0,076	-0,129	-0,196	-0,254	-2,039	9,11E-07
TNIP2	NM_024309	Hs.368551	hs|4p16.3	-0,096	-0,028	-0,082	-0,120	-0,221	-0,265	-2,038	1,41E-04
KIFC1	NM_002263	Hs.436912	hs|6p21.32	-0,067	-0,101	-0,160	-0,153	-0,261	-0,402	-2,037	1,33E-04
PRPS1L1	NM_175886	Hs.169284	hs|7p21.1	-0,041	-0,099	-0,238	-0,290	-0,326	-0,346	-2,032	4,51E-06
COQ3	NM_017421	Hs.653253	hs|6q16.3	-0,077	-0,114	-0,216	-0,363	-0,297	-0,385	-2,031	2,23E-04
WASF2	NM_006990	Hs.590909	hs|1p36.11	0,164	0,072	0,029	0,077	-0,099	-0,143	-2,030	1,01E-05
BC040577	BC040577	Hs.563191	hs|4q34.1	0,191	0,155	-0,145	-0,129	-0,116	0,149	-2,029	6,87E-05
LYRM4	NM_020408	Hs.387755	hs|6p25.1	0,047	-0,025	-0,018	-0,008	-0,164	-0,216	-2,024	3,17E-04
CYorf16	NR_001553	Hs.638604	hs|Yp11.2	0,187	-0,022	0,000	-0,135	-0,118	-0,110	-2,022	4,03E-04
SPNS3	NM_182538	Hs.657543	hs|17p13.2	0,183	0,041	0,039	-0,077	-0,084	-0,123	-2,019	4,45E-04
EVL	NM_016337	Hs.125867	hs|14q32.2	-0,116	-0,176	-0,163	-0,149	-0,325	-0,368	-2,012	3,96E-05
HSPA12A	NM_025015	Hs.654682	hs|10q25.3	-0,062	-0,173	-0,242	-0,428	-0,314	-0,366	-2,011	5,29E-04
APH1A	NM_016022	Hs.108408	hs|1q21.2	0,148	0,049	0,118	-0,016	-0,062	-0,155	-2,010	3,81E-04
NR2F6	NM_005234	Hs.466148	hs|19p13.11	-0,025	-0,077	-0,140	-0,144	-0,317	-0,327	-2,006	5,14E-04
CHRNA7	NM_000746	Hs.511772	hs|15q13.3	-0,042	-0,141	-0,175	-0,248	-0,296	-0,276	-2,005	4,62E-05
TAS2R7	NM_023919	Hs.533754	hs|12p13.2	0,223	-0,034	0,385	0,432	-0,027	-0,066	-2,004	4,06E-04

Table 3: Second list of the over-expressed genes

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
TFPI2	AK129833	Hs.438231	hs|7q21.3	0,152	0,549	1,032	1,370	1,482	1,565	25,892	2,88E-09
PCDH7	NM_032456	Hs.570785	hs|4p15.1	-0,038	0,000	0,728	0,931	0,728	0,770	13,584	1,16E-05
SMAD9	BM802662	Hs.586812	hs|13q13.3	-1,698	-1,063	-1,451	-1,366	-1,015	-0,788	8,127	1,71E-07
AK090762	AK090762	Hs.531632	hs|19p12	0,128	0,146	0,468	0,479	0,674	0,981	7,646	4,79E-05
RAB39B	NM_171998	Hs.632832	hs|Xq28	-0,264	0,000	-0,694	-0,226	0,293	0,516	6,031	4,98E-11
BF831953			hs|7q31.1	-0,111	0,000	0,231	0,448	0,658	0,189	5,987	9,33E-05
AL050204	AL050204	Hs.28540	hs|11q22.3	0,110	0,043	0,221	0,351	0,694	0,883	5,922	6,79E-05
VCX	NM_013452	Hs.567503	hs|Xp22.31	0,559	0,486	0,538	0,372	0,883	1,203	5,235	8,85E-05
ITGA2	NM_002203	Hs.482077	hs|5q11.2	-1,460	-0,725	-1,429	-1,566	-0,809	-0,748	4,838	5,20E-04
AKAP9	NM_147171	Hs.651221	hs|7q21.2	0,101	0,299	0,159	0,244	0,502	0,694	3,908	5,59E-05
AUTS2	NM_015570	Hs.654801	hs|7q11.22	-1,021	-0,844	-0,522	-0,587	-0,547	-0,433	3,823	2,33E-05
CEP152	NM_014985	Hs.597323	hs|15q21.1	0,066	0,166	0,311	0,527	0,642	0,592	3,617	2,86E-06
SLITRK6	NM_032229	Hs.525105	hs|13q31.1	-0,617	-0,363	-0,352	-0,370	-0,200	-0,071	3,519	7,87E-04
CCPG1	NM_020739	Hs.612814	hs|15q21.3	0,382	0,542	0,493	0,535	0,767	0,889	3,213	1,72E-04
MANEAL	NM_152496	Hs.534562	hs|1p34.3	0,371	0,580	0,700	0,753	0,940	0,895	2,884	9,37E-04
THC2733296			hs|21q21.1	0,163	0,091	0,289	0,381	0,474	0,578	2,603	1,00E-07
CD55	NM_000574	Hs.527653	hs|1q32.2	0,389	0,306	0,664	0,740	0,785	0,784	2,505	6,48E-04
ANKRD18A	AB095935	Hs.561966	hs|9p13.1	0,354	0,482	0,527	0,655	0,723	0,629	2,340	3,02E-04
LAT2	NM_032463	Hs.647049	hs|7q11.23	-0,058	-0,077	0,005	-0,021	0,200	0,291	2,234	4,54E-04
BRCA2	NM_000059	Hs.34012	hs|13q13.1	-0,101	-0,078	0,010	0,131	0,299	0,244	2,211	3,92E-06
LRP2BP	NM_018409	Hs.558513	hs|4q35.1	-0,236	-0,103	-0,048	0,090	0,008	0,118	2,199	3,45E-04
LPHN2	NM_012302	Hs.24212	hs|1p31.1	0,002	0,170	0,306	0,362	0,333	0,310	2,147	1,95E-11
ITGB8	NM_002214	Hs.592171	hs|7p15.3	0,744	0,834	0,877	0,871	1,028	1,062	2,079	3,14E-04

Table 4 : Second list of the under-expressed genes

Gene Symbol	Genbank Accession#	UniGeneID	Cytoband	5nM	12nM	25nM	50nM	100nM	200nM	FoldChange	p.value
CXCR4	NM_001008540	Hs.593413	hs|2q21.3	-0,410	-0,660	-1,321	-1,590	-1,751	-1,556	-15,696	2,05E-11
SLC16A10	NM_018593	Hs.591327	hs|6q21	-0,491	-0,724	-1,217	-1,186	-1,354	-1,417	-8,417	1,11E-07
PDE1A	AL110263	Hs.191046	hs|2q32.1	-0,383	-0,617	-1,020	-1,000	-1,256	-1,250	-7,360	3,52E-05
MAL	NM_002371	Hs.80395	hs|2q11.1	0,983	1,206	1,000	0,879	0,459	0,253	-5,715	3,35E-08
KRT80	NM_182507	Hs.140978	hs|12q13.13	0,311	-0,060	0,113	-0,055	-0,243	-0,340	-4,483	2,16E-04
FXYD2	AY946020	Hs.413137	hs|11q23.3	0,550	0,262	0,237	0,277	-0,068	-0,070	-4,167	6,81E-04
AK3L1	NM_001002921	Hs.10862	hs|1p31.3	-0,564	-0,781	-0,994	-1,137	-1,012	-0,829	-4,112	7,08E-05
LIN7A	NM_004664	Hs.144333	hs|12q21.31	-0,523	-0,608	-0,593	-0,982	-1,110	-0,778	-3,868	9,34E-07
GPR177	NM_024911	Hs.647659	hs|1p31.3	-0,630	-0,673	-0,891	-1,274	-1,210	-1,100	-3,808	9,54E-05
TNF	NM_000594	Hs.241570	hs|6p21.33	1,035	1,276	1,284	1,222	0,739	0,661	-3,603	2,51E-04
WNT2B	NM_004185	Hs.258575	hs|1p13.2	1,015	0,358	0,964	0,953	0,482	0,420	-3,571	8,91E-05
CGNL1	NM_032866	Hs.148989	hs|15q21.3	-0,727	-0,723	-1,256	-1,397	-1,270	-1,070	-3,530	2,40E-05
RPS6KA2	NM_021135	Hs.655277	hs|6q27	0,621	0,375	0,470	0,387	0,201	0,102	-3,299	3,04E-04
SUNC1	NM_152782	Hs.406741	hs|7p12.3	-0,522	-0,710	-0,790	-0,947	-0,966	-0,657	-2,997	9,40E-04
DIAPH2	NM_006729	Hs.656813	hs|Xq21.33	-0,038	-0,158	-0,416	-0,584	-0,510	-0,436	-2,969	1,90E-06
AKAP12	NM_144497	Hs.371240	hs|6q25.1	-0,434	-0,483	-0,678	-0,942	-0,905	-0,790	-2,958	2,95E-04
NRG1	NM_013959	Hs.453951	hs|8p12	0,334	0,000	0,077	-0,296	-0,095	-0,129	-2,898	5,02E-04
PDE4DIP	NM_022359	Hs.654651	hs|1q21.1	0,515	0,107	0,124	0,018	0,045	0,032	-2,870	2,32E-04
IL1R1	NM_000877	Hs.693591	hs|2q12.1	0,626	0,638	0,618	0,389	0,156	0,206	-2,638	1,16E-07
LZTS1	NM_139201	Hs.434996	hs|12q24.11	-0,455	-0,913	-0,711	-0,811	-0,857	-0,924	-2,603	2,04E-06
SLC3A1	NM_000341	Hs.112916	hs|2p21	-0,507	-0,558	-0,737	-0,869	-0,968	-0,921	-2,594	2,28E-05
MGST1	NM_145791	Hs.389700	hs|12p12.3	-0,583	-0,555	-0,678	-0,977	-0,968	-0,864	-2,335	4,51E-05
ACOT9	NM_001037171	Hs.298885	hs|Xp22.11	0,083	-0,126	-0,097	-0,118	-0,230	-0,272	-2,205	1,95E-04
SLC12A3	NM_000339	Hs.658965	hs|16q13	-0,569	-0,521	-0,673	-0,855	-0,936	-0,833	-2,182	6,59E-04
ASRGL1	BC006267	Hs.535326	hs|11q12.3	-0,038	-0,172	-0,316	-0,299	-0,342	-0,417	-2,053	6,67E-04
HRG	NM_000412	Hs.1498	hs|3q27.3	0,313	0,016	0,179	0,045	-0,018	-0,019	-2,053	6,77E-04

Table 5: List of 44 genes

AccessNum	UniGeneID	Symbol	Gene Name	FC exp1	FC exp2
NM_152688	Hs.519794	KHDRBS2	KH domain containing, RNA binding, signal transduction associated 2	5,79	11,91
NM_015570	Hs.21631	AUTS2	Autism susceptibility candidate 2	3,82	10,44
NM_032456	Hs.479439	PCDH7	Protocadherin 7	13,58	8,19
NM_207362	Hs.469398	C2orf55	Chromosome 2 open reading frame 55	4,76	7,86
NM_001999	Hs.519294	FBN2	Fibrillin 2	2,15	5,51
NM_001040874	Hs.530461	HIST2H2AA4	Histone cluster 2, H2aa4	2,73	5,28
NM_001012361	Hs.133331	WDR31	WD repeat domain 31	4,73	4,62
NM_152676	Hs.664011	FBXO15	F-box protein 15	2,60	3,48
NM_031435	Hs.245798	THAP2	THAP domain containing, apoptosis associated protein 2	3,24	3,46
BF207040	Hs.353024	BF207040	Transcribed locus	2,02	3,12
NM_080593	Hs.437275	HIST1H2BK	Histone cluster 1, H2bk	2,15	3,02
NM_001080421	Hs.164502	UNC13A	Unc-13 homolog A (C. elegans)	2,88	2,84
BC032035	Hs.31240	FAM27E3	Family with sequence similarity 27, member E3	2,15	2,75
NR_003713	Hs. 720393	LOC728613	Programmed cell death 6 pseudogene	2,11	2,69
BC119676	Hs.567050	FAM27E1	Family with sequence similarity 27, member E1	2,41	2,49
NM_015392	Hs.719906	NPDC1	Neural proliferation, differentiation and control, 1	2,40	2,15
NM_003519	Hs.137594	HIST1H2BL	Histone cluster 1, H2bl	2,26	2,02
NM_016021	Hs.163776	UBE2J1	Ubiquitin-conjugating enzyme E2, J1 (UBC6 homolog, yeast)	-2,20	-2,06
NM_201629	Hs.50382	TJP2	Tight junction protein 2 (zona occludens 2)	-3,42	-2,29
NM_012206	Hs.129711	HAVCR1	Hepatitis A virus cellular receptor 1	-2,37	-2,31
NM_014797	Hs.409876	ZBTB24	Zinc finger and BTB domain containing 24	-2,53	-2,39
NM_017774	Hs.657604	CDKAL1	CDK5 regulatory subunit associated protein 1-like 1	-2,36	-2,41
NM_017421	Hs.713623	COQ3	Coenzyme Q3 homolog, methyltransferase (S. cerevisiae)	-2,03	-2,85
NM_020698	Hs.370410	TMCC3	Transmembrane and coiled-coil domain family 3	-2,49	-2,88
NM_012082	Hs.431009	ZFPM2	Zinc finger protein, multitype 2	-3,52	-3,35
NM_000341	Hs.112916	SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	-2,59	-3,42
NM_002394	Hs.502769	SLC3A2	Solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	-5,42	-3,56
NM_014988	Hs.335163	LIMCH1	LIM and calponin homology domains 1	-7,34	-3,71
NM_001431	Hs.486470	EPB41L2	Erythrocyte membrane protein band 4.1-like 2	-2,37	-4,33
NM_212543	Hs.13225	B4GALT4	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 4	-2,45	-4,64
NM_144497	Hs.371240	AKAP12	A kinase (PRKA) anchor protein 12	-2,96	-4,81
NM_016356	Hs.61345	DCDC2	Doublecortin domain containing 2	-4,04	-5,24
AW014342	Hs.665091	BX281122	Transcribed locus	-7,02	-5,45
NM_023074	Hs.148322	ZNF649	Zinc finger protein 649	-3,45	-5,87
NM_001003395	Hs.591347	TPD52L1	Tumor protein D52-like 1	-22,78	-7,30
NM_032801	Hs.150718	JAM3	Junctional adhesion molecule 3	-9,23	-7,37
NM_003730	Hs.529989	RNASET2	Ribonuclease T2	-4,70	-7,43
NM_000433	Hs.587558	NCF2	Neutrophil cytosolic factor 2	-14,39	-7,68
NM_182643	Hs.134296	DLC1	Deleted in liver cancer 1	-3,52	-9,34
NM_001008540	Hs.593413	CXCR4	Chemokine (C-X-C motif) receptor 4	-15,70	-12,23
CR594735	Hs.153408	CR594735	hypothetical LOC100506305 (Homo sapiens)	-8,40	-13,45
NM_001003818	Hs. 729048	TRIM6	Tripartite motif-containing 6	-13,03	-16,24
NM_133486	Hs.105134	MBNL3	Muscleblind-like 3 (Drosophila)	-10,32	-17,16
NM_003480	Hs.512842	MFAP5	Microfibrillar associated protein 5	-17,38	-91,67

Table 6: List of 17 genes.

AccessNum	UniGeneID	Symbol	Gene Name	FC exp1	FC exp2	SEQ ID No
NM_152688	Hs.519794	KHDRBS2	KH domain containing, RNA binding, signal transduction associated 2	5,79	11,91	1
NM_015570	Hs.21631	AUTS2	Autism susceptibility candidate 2	3,82	10,44	2
NM_032456	Hs.479439	PCDH7	Protocadherin 7	13,58	8,19	3
NM_207362	Hs.469398	C2orf55	Chromosome 2 open reading frame 55	4,76	7,86	4
NM_000341	Hs.112916	SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	-2,59	-3,42	5
NM_144497	Hs.371240	AKAP12	A kinase (PRKA) anchor protein 12	-2,96	-4,81	6
NM_016356	Hs.61345	DCDC2	Doublecortin domain containing 2	-4,04	-5,24	7
NM_023074	Hs.148322	ZNF649	Zinc finger protein 649	-3,45	-5,87	8
NM_032801	Hs.150718	JAM3	Junctional adhesion molecule 3	-9,23	-7,37	9
NM_003730	Hs.529989	RNASET2	Ribonuclease T2	-4,70	-7,43	10
NM_000433	Hs.587558	NCF2	Neutrophil cytosolic factor 2	-14,39	-7,68	11
NM_182643	Hs.134296	DLC1	Deleted in liver cancer 1	-3,52	-9,34	12
NM_001008540	Hs.593413	CXCR4	Chemokine (C-X-C motif) receptor 4	-15,70	-12,23	13
CR594735	Hs.153408	CR594735	hypothetical LOC100506305 (Homo sapiens)	-8,40	-13,45	14
NM_001003818	Hs. 729048	TRIM6	Tripartite motif-containing 6	-13,03	-16,24	15
NM_133486	Hs.105134	MBNL3	Muscleblind-like 3 (Drosophila)	-10,32	-17,16	16
NM_003480	Hs.512842	MFAP5	Microfibrillar associated protein 5	-17,38	-91,67	17

CLAIMS

1- An *in vitro* method for predicting or monitoring whether a patient affected by a cancer is responsive to a treatment with a molecule of the taxoid family, wherein the method comprises: 1) providing a biological sample from said subject; 2) determining in the biological sample the expression level of the genes JAM3, PCDH7, DCDC2, KHDRBS2, MFAP5, AUTS2, C2orf55, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3 thereby predicting or monitoring whether a patient affected by a prostate cancer is responsive to a treatment with a molecule of the taxoid family.

2- The method according to claim 1, wherein the method further comprises comparing the expression level of said genes to a reference expression level, the reference expression level being the expression level of the genes in cell-lines or patients sensitive to the treatment by the molecule of the taxoid family.

3- The method according to claim 2, wherein the over-expression of genes PCDH7, KHDRBS2, AUTS2, and C2orf55, and/or the under-expression of genes JAM3, DCDC2, MFAP5, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3 are indicative of a resistance to the treatment by the molecule of the taxoid family.

4- The method according to anyone of claims 1-3, wherein the molecule of the taxoid family is docetaxel, larotaxel, cabazitaxel (XRP6258), BMS-184476, BMS-188797, BMS-275183, ortataxel, RPR 109881A, RPR 116258, NBT-287, PG-paclitaxel, ABRAXANE®, Tesetaxel, IDN 5390, Taxoprexin, DHA-paclitaxel, and MAC-321, more preferably docetaxel.

5- The method according to anyone of claims 1-4, wherein the method further comprises determining the expression level of at least one gene selected from the group consisting of FBN2, HIST2H2AA4, WDR31, FBXO15, THAP2, BF207040, HIST1H2BK, UNC13A, FAM27E3, LOC728613, FAM27E1, NPDC1, HIST1H2BL, UBE2J1, TJP2, HAVCR1, ZBTB24, CDKAL1, COQ3, TMCC3, ZFPM2, SLC3A2, LIMCH1, EPB41L2, B4GALT4, BX281122 and TPD52L1.

6- The method according to anyone of claims 1-5, wherein the method further comprises determining the expression level of the genes FBN2, HIST2H2AA4, WDR31, FBXO15,

THAP2, BF207040, HIST1H2BK, UNC13A, FAM27E3, LOC728613, FAM27E1, NPDC1, HIST1H2BL, UBE2J1, TJP2, HAVCR1, ZBTB24, CDKAL1, COQ3, TMCC3, ZFPM2, SLC3A2, LIMCH1, EPB41L2, B4GALT4, BX281122 and TPD52L1.

7- The method according to anyone of claims 1-6, wherein the method further comprises determining the expression level of at least one gene selected from the group consisting of the genes listed in Tables 1-4.

8- The method according to anyone of claims 1-7, wherein the biological sample is a cancer sample.

9- The method according to anyone of claims 1-8, wherein the cancer is selected from the group consisting of the breast cancer, the lung cancer, the prostate cancer, the gastric cancer and the head and neck cancer, more preferably a prostate cancer.

10- Use of a kit for predicting or monitoring whether a patient affected by a cancer is responsive to a treatment with a molecule of the taxoid family, wherein the kit comprises detection means selected from the group consisting of a pair of primers, a probe and an antibody specific to the genes JAM3, PCDH7, DCDC2, KHDRBS2, MFAP5, AUTS2, C2orf55, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3.

11- Use of DNA chip for predicting or monitoring whether a patient affected by a cancer is responsive to a treatment with a molecule of the taxoid family, wherein the DNA chip comprises a solid support which carries nucleic acids that are specific to the genes JAM3, PCDH7, DCDC2, KHDRBS2, MFAP5, AUTS2, C2orf55, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3.

12- The use according to claim 10 or 11, wherein the kit or DNA chip further comprises detection means for at least one gene selected from the group consisting of FBN2, HIST2H2AA4, WDR31, FBXO15, THAP2, BF207040, HIST1H2BK, UNC13A, FAM27E3, LOC728613, FAM27E1, NPDC1, HIST1H2BL, UBE2J1, TJP2, HAVCR1, ZBTB24, CDKAL1, COQ3, TMCC3, ZFPM2, SLC3A2, LIMCH1, EPB41L2, B4GALT4, BX281122 and TPD52L1.

13- A method for screening or identifying a compound suitable for improving the treatment of a cancer with a molecule of the taxoid family or for reducing the resistance development during the treatment of a cancer with a molecule of the taxoid family, comprising 1) providing a cell-line with the genes PCDH7, KHDRBS2, AUTS2, and C2orf55 being over-expressed and the genes JAM3, DCDC2, MFAP5, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3 being under-expressed; 2) contacting said cell-line with a test compound; 3) determining the expression level of said genes; and, 4) selecting the compound which decreases the expression level of one or several of the over-expressed genes and increases the expression level of one or several of the under-expressed genes.

14- A method for screening or identifying a compound suitable for improving the treatment of a cancer with a molecule of the taxoid family or for reducing the resistance development during the treatment of a cancer with the molecule of the taxoid family, comprising 1) providing a cell-line sensitive to the molecule of the taxoid family; 2) contacting said cell-line with a test compound and the molecule of the taxoid family; 3) determining the expression level of the genes JAM3, PCDH7, DCDC2, KHDRBS2, MFAP5, AUTS2, C2orf55, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3; and, 4) selecting the compound which inhibits the appearance of an over-expression of the genes PCDH7, KHDRBS2, AUTS2, and C2orf55 and/or an under-expression of the genes JAM3, DCDC2, MFAP5, SLC3A1, AKAP12, ZNF649, RNASET2, NCF2, DLC1, CXCR4, CR594735, TRIM6, and MBNL3.

15- The method according to any one of claims 13 to 14, wherein the cell-line is a cancer cell-line.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/055482

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	EP 2 177 630 A1 (ROUSSY INST GUSTAVE [FR]) 21 April 2010 (2010-04-21) the whole document claims 1-5	1-15
Y	WO 2006/062811 A2 (AVENTIS PHARMA INC [US]; GRUENEBERG DORRE [US]; HUANG XI [US]; NATESAN) 15 June 2006 (2006-06-15) the whole document	1-15
Y	WO 2004/035805 A2 (BAYLOR COLLEGE MEDICINE [US]; CHANG JENNY CHEE NING [US]; O'CONNELL PE) 29 April 2004 (2004-04-29) the whole document	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2011	17/06/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gabriels, Jan

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/055482

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/038792 A2 (H LEE MOFFITT CANCER CT [US]; LANCASTER JONATHAN M [US]; NEVINS JOSEPH) 5 April 2007 (2007-04-05) figures 16A-16E,22A-22C; example 5	1-15
Y	WO 2006/060742 A2 (ONCOTECH INC [US]; KERFOOT CHRISTOPHER [US]; RICKETTS WILLIAM A [US];) 8 June 2006 (2006-06-08) claims 1-5	1-15
Y	HUANG CHUNG-YING ET AL: "Molecular alterations in prostate carcinomas that associate with in vivo exposure to chemotherapy: identification of a cytoprotective mechanism involving growth differentiation factor 15.", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 OCT 2007 LNKD-PUBMED:17908975, vol. 13, no. 19, 1 October 2007 (2007-10-01), pages 5825-5833, XP002585628, ISSN: 1078-0432 the whole document	1-15
A	CHANG JENNY C ET AL: "Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer.", LANCET 2 AUG 2003 LNKD- PUBMED:12907009, vol. 362, no. 9381, 2 August 2003 (2003-08-02), pages 362-369, XP002585629, ISSN: 1474-547X the whole document	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/055482

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purpose of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/055482

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2177630 A1	21-04-2010	WO 2010037859 A2	08-04-2010
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(74) Agent: **RUTENBERG, Isaac M.**; BOZICEVIC, FIELD & FRANCIS LLP, 1900 University Avenue, Suite 200, East Palo Alto, California 94303 (US).

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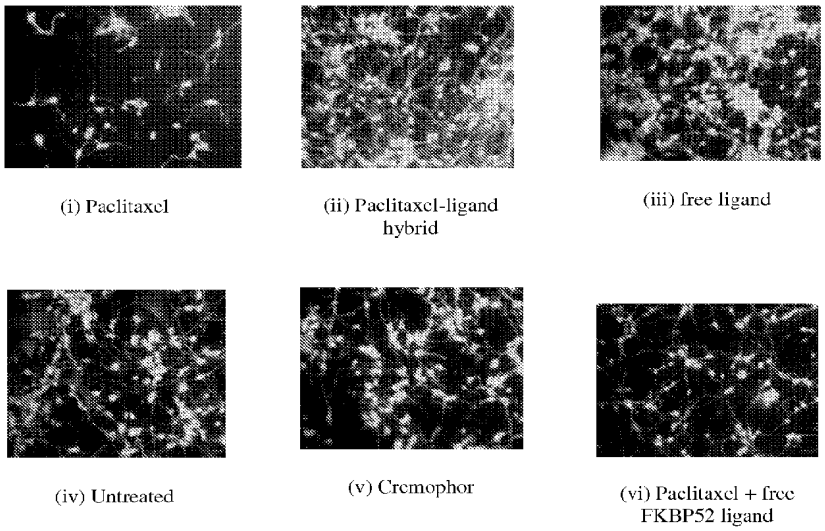
[Continued on next page]

(54) Title: THERAPEUTIC AGENTS HAVING REDUCED TOXICITY

FIG. 5



(57) Abstract: Therapeutic hybrid compounds having an active moiety and a toxicity reducing moiety are provided, as are methods of use of such compounds, methods of preparation of such compounds, and compositions containing such compounds. In some embodiments, the hybrid compounds have lower toxicity (such as lower neurotoxicity) compared with the non-hybridized active moiety.

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— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Therapeutic Agents Having Reduced Toxicity

Cross Reference to Related Applications

[0001] This application claims priority under 35 U.S.C. § 119(e)(1) to United States Provisional Patent Application Serial Nos. 61/323,820, filed April 13, 2010, and 61/324,211, filed April 14, 2010, the contents of which are incorporated herein by reference.

Background

[0002] Chemically induced peripheral neuropathy (CIPN) is an undesirable condition that compromises the use of a number of clinically important therapeutics including paclitaxel, docetaxel, cisplatin, vincristine, and interferon-alpha. Numbness and pain generally appear first in the extremities, followed by more extreme muscle cramps, aching, weakness, and even respiratory dysfunction. The taxanes paclitaxel and docetaxel are mainstay therapeutics for breast cancer and ovarian cancer, and docetaxel is also commonly used to treat androgen refractory prostate cancer. Docetaxel is sold as Taxotere by Sanofi-Aventis and has projected sales of over $1.65 billion in 2010.

[0003] Unfortunately, toxicity often limits dosing courses for taxanes and precludes patient compliance: 33% of patients receiving paclitaxel at 250 mg/m2 experience Grade 3 or 4 neuropathy. CIPN is the most common, non-hematological toxicity for patients undergoing taxane chemotherapy. In spite of various approaches to lowering PNP including co-administering additional therapeutics such as gabapentin and glutamine, altering drug vehicles, changing infusion times, or searching for less neurotoxic taxane derivatives, CIPN remains an important problem for patients undergoing chemotherapy.

[0004] For taxanes, CIPN is the most common cause of dose-limiting toxicity, apart from neutropenia. A patient's inability to maintain a therapeutic regimen due to toxicity limits optimal treatment for taxanes. Neurotoxicity is evident in a number of other important therapeutics (bortezomib, vinblastine, gemcitabine, e.g.). For many years, it was hypothesized that the solvent CremophorEL was primarily responsible for dose-limiting neurotoxicity in treatment regimens including paclitaxel. However, newer paclitaxel formulations which do not include CremophorEL such as Abraxane, as well as the chemically related docetaxel, also exhibit chemically induced peripheral neuropathy (CIPN). Although a

vast number of taxane derivatives have been synthesized and tested, no FDA-approved taxanes have significantly reduced CIPN. Accordingly, there remains a need in the art to develop new anticancer pharmaceuticals (and other pharmaceuticals) that lack or have substantially reduced neurotoxicity.

[0005] In addition to the problem of neurotoxicity of known anti-cancer pharmaceuticals, some anticancer agents are difficult to prepare, are expensive to obtain, have a poor pharmacokinetic profile (which may be reflected in a shorter than desirable half-life), and/or have significant adverse side effects; all of these drawbacks may result in lower patient compliance and/or less effective treatment.

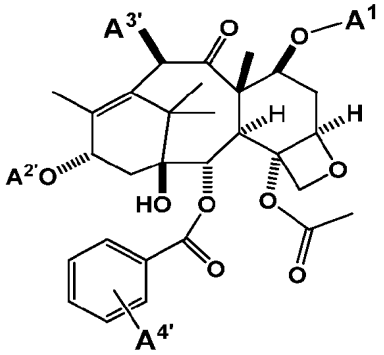
Summary

[0006] In one aspect, there is provided herein a method for lowering the neurotoxic effects of a neurotoxicity producing therapeutic active moiety upon administration to a host, the method comprising: administering to the host an effective amount of a hybrid compound of less than about 15000 Daltons comprising the therapeutic active moiety or an active derivative, fragment or analog thereof and a neurotoxicity lowering moiety, wherein the neurotoxicity lowering moiety binds to at least one neurotoxicity lowering biomoiety and substantially reduces at least one neurotoxicity symptom.

[0007] In another aspect there is provided herein a method for reducing the neurotoxicity of a taxane compound, the method comprising covalently bonding the taxane to a neurotoxicity-lowering moiety either directly or through an optional linking moiety to form a hybrid compound.

[0008] In yet another aspect, there is provided herein a compound comprising a taxane moiety covalently attached either directly or through an optional linking moiety to a neurotoxicity lowering moiety. For example, in some embodiments of this aspect, there is provided compounds having the structure of formula (I)

(I)



wherein the variables A^1, $A^{2'}$, $A^{3'}$, and $A^{4'}$ are as described herein.

[0009] These and other aspects of interest are described in more detail below.

Brief Description of the Figures

[00010] Figure 1 provides blood permeability data showing a comparison between non-hybridized paclitaxel and a hybrid paclitaxel-ligand.

[00011] Figure 2 provides metabolic stability data, and also shows a comparison between non-hybridized paclitaxel and a hybrid paclitaxel-ligand.

[00012] Figure 3 provides tumor volume measurement data over a 46 day period, and compares non-hybridized paclitaxel and a hybrid paclitaxel-ligand.

[00013] Figure 4 provides total neurite outgrowth measurement data for a paclitaxel-ligand hybrid, and compares the data to paclitaxel and control data.

[00014] Figure 5 provides images of primary cortical neuron (PCN) growth after exposure to a paclitaxel-ligand hybrid, and compares the data to paclitaxel data.

[00015] Figure 6 provides cell number data, which were recorded for PCNs untreated (first column) or PCNs treated with: (i) CremophorEL vehicle; (ii) paclitaxel; (iii) a paclitaxel-ligand hybrid; (iv) free FK506; (v) a paclitaxel-FK506 hybrid.

[00016] Figure 7 provides cytotoxicity data for Paclitaxel and Compound **(2)** (a compound prepared according to the disclosure) against SKOV3 cells.

[00017] Figure 8 provides average neurite outgrowth for samples treated with Compound **(2)** and compares the data with paclitaxel and control samples.

[00018] Figure 9 provides cell counts for viable cells after treatment with Compound **(2)**, and compares the data with paclitaxel and control samples.

[00019] Figure 10 provides data for an in vivo study using Compound **(1)**.

Definitions

[00020] Unless otherwise indicated, the disclosure is not limited to specific procedures, starting materials, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[00021] As used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a reactant" includes not only a single reactant but also a combination or mixture of two or more different reactant, reference to "a substituent" includes a single substituent as well as two or more substituents, and the like.

[00022] In describing and claiming the present invention, certain terminology will be used in accordance with the definitions set out below. It will be appreciated that the definitions provided herein are not intended to be mutually exclusive. Accordingly, some chemical moieties may fall within the definition of more than one term.

[00023] As used herein, the phrases "for example," "for instance," "such as," or "including" are meant to introduce examples that further clarify more general subject matter. These examples are provided only as an aid for understanding the disclosure, and are not meant to be limiting in any fashion.

[00024] As used herein, the phrase "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used. The term "independently selected from" is used herein to indicate that the recited elements, e.g., R groups or the like, can be identical or different.

[00025] As used herein, the terms "may," "optional," "optionally," or "may optionally" mean that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not. For example, the phrase "optionally substituted" means that a non-hydrogen substituent may or may not be present on a given atom, and, thus, the description includes structures wherein a non-hydrogen substituent is present and structures wherein a non-hydrogen substituent is not present.

[00026] The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group (i.e., a mono-radical) typically although not necessarily containing 1 to about 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopentyl, cyclohexyl and the like. Generally, although not necessarily, alkyl groups herein may contain 1 to about 18 carbon atoms, and such groups may contain 1 to about 12 carbon atoms. The term "lower alkyl" intends an alkyl group of 1 to 6 carbon atoms. "Substituted alkyl" refers to alkyl substituted with one or more substituent groups, and this includes instances wherein two hydrogen atoms from the same carbon atom in an alkyl substituent are replaced, such as in a carbonyl group (i.e., a substituted alkyl group may include a -C(=O)- moiety). The terms

"heteroatom-containing alkyl" and "heteroalkyl" refer to an alkyl substituent in which at least one carbon atom is replaced with a heteroatom, as described in further detail infra. If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl, respectively.

[00027] The term "alkenyl" as used herein refers to a linear, branched or cyclic hydrocarbon group of 2 to about 24 carbon atoms containing at least one double bond, such as ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, isobutenyl, octenyl, decenyl, tetradecenyl, hexadecenyl, eicosenyl, tetracosenyl, and the like. Generally, although again not necessarily, alkenyl groups herein may contain 2 to about 18 carbon atoms, and for example may contain 2 to 12 carbon atoms. The term "lower alkenyl" intends an alkenyl group of 2 to 6 carbon atoms. The term "substituted alkenyl" refers to alkenyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkenyl" and "heteroalkenyl" refer to alkenyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkenyl" and "lower alkenyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkenyl and lower alkenyl, respectively.

[00028] The term "alkynyl" as used herein refers to a linear or branched hydrocarbon group of 2 to 24 carbon atoms containing at least one triple bond, such as ethynyl, *n*-propynyl, and the like. Generally, although again not necessarily, alkynyl groups herein may contain 2 to about 18 carbon atoms, and such groups may further contain 2 to 12 carbon atoms. The term "lower alkynyl" intends an alkynyl group of 2 to 6 carbon atoms. The term "substituted alkynyl" refers to alkynyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkynyl" and "heteroalkynyl" refer to alkynyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkynyl" and "lower alkynyl" include linear, branched, unsubstituted, substituted, and/or heteroatom-containing alkynyl and lower alkynyl, respectively.

[00029] The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be represented as -O-alkyl where alkyl is as defined above. A "lower alkoxy" group intends an alkoxy group containing 1 to 6 carbon atoms, and includes, for example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *t*-butyloxy, etc. Substituents identified as "C_1-C_6 alkoxy" or "lower alkoxy" herein may, for example, may contain 1 to 3 carbon atoms, and as a further example, such substituents may contain 1 or 2 carbon atoms (i.e., methoxy and ethoxy).

[00030] The term "aryl" as used herein, and unless otherwise specified, refers to an aromatic substituent generally, although not necessarily, containing 5 to 30 carbon atoms and containing a single aromatic ring or multiple aromatic rings that are fused together, directly linked, or indirectly linked (such that the different aromatic rings are bound to a common group such as a methylene or ethylene moiety). Aryl groups may, for example, contain 5 to 20 carbon atoms, and as a further example, aryl groups may contain 5 to 12 carbon atoms. For example, aryl groups may contain one aromatic ring or two or more fused or linked aromatic rings (i.e., biaryl, aryl-substituted aryl, etc.). Examples include phenyl, naphthyl, biphenyl, diphenylether, diphenylamine, benzophenone, and the like. "Substituted aryl" refers to an aryl moiety substituted with one or more substituent groups, and the terms "heteroatom-containing aryl" and "heteroaryl" refer to aryl substituent, in which at least one carbon atom is replaced with a heteroatom, as will be described in further detail infra. If not otherwise indicated, the term "aryl" includes unsubstituted, substituted, and/or heteroatom-containing aromatic substituents.

[00031] The term "aralkyl" refers to an alkyl group with an aryl substituent, and the term "alkaryl" refers to an aryl group with an alkyl substituent, wherein "alkyl" and "aryl" are as defined above. In general, aralkyl and alkaryl groups herein contain 6 to 30 carbon atoms. Aralkyl and alkaryl groups may, for example, contain 6 to 20 carbon atoms, and as a further example, such groups may contain 6 to 12 carbon atoms.

[00032] The term "alkylene" as used herein refers to a di-radical alkyl group. Unless otherwise indicated, such groups include saturated hydrocarbon chains containing from 1 to 24 carbon atoms, which may be substituted or unsubstituted, may contain one or more alicyclic groups, and may be heteroatom-containing. "Lower alkylene" refers to alkylene linkages containing from 1 to 6 carbon atoms. Examples include, methylene (--CH_2--), ethylene (--CH_2CH_2--), propylene (--$CH_2CH_2CH_2$--), 2-methylpropylene (--CH_2--$CH(CH_3)$--CH_2--), hexylene (--$(CH_2)_6$--) and the like.

[00033] Similarly, the terms "alkenylene," "alkynylene," "arylene," "aralkylene," and "alkarylene" as used herein refer to di-radical alkenyl, alkynyl, aryl, aralkyl, and alkaryl groups, respectively.

[00034] The term "amino" is used herein to refer to the group $-NZ^1Z^2$ wherein Z^1 and Z^2 are hydrogen or nonhydrogen substituents, with nonhydrogen substituents including, for example, alkyl, aryl, alkenyl, aralkyl, and substituted and/or heteroatom-containing variants thereof.

[00035] The terms "halo" and "halogen" are used in the conventional sense to refer to a chloro, bromo, fluoro or iodo substituent.

[00036] The term "heteroatom-containing" as in a "heteroatom-containing alkyl group" (also termed a "heteroalkyl" group) or a "heteroatom-containing aryl group" (also termed a "heteroaryl" group) refers to a molecule, linkage or substituent in which one or more carbon atoms are replaced with an atom other than carbon, e.g., nitrogen, oxygen, sulfur, phosphorus or silicon, typically nitrogen, oxygen or sulfur. Similarly, the term "heteroalkyl" refers to an alkyl substituent that is heteroatom-containing, the term "heterocyclic" refers to a cyclic substituent that is heteroatom-containing, the terms "heteroaryl" and "heteroaromatic" respectively refer to "aryl" and "aromatic" substituents that are heteroatom-containing, and the like. Examples of heteroalkyl groups include alkoxyaryl, alkylsulfanyl-substituted alkyl, N-alkylated amino alkyl, and the like. Examples of heteroaryl substituents include pyrrolyl, pyrrolidinyl, pyridinyl, quinolinyl, indolyl, furyl, pyrimidinyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, etc., and examples of heteroatom-containing alicyclic groups are pyrrolidino, morpholino, piperazino, piperidino, tetrahydrofuranyl, etc.

[00037] "Hydrocarbyl" refers to univalent hydrocarbyl radicals containing 1 to about 30 carbon atoms, including 1 to about 24 carbon atoms, further including 1 to about 18 carbon atoms, and further including about 1 to 12 carbon atoms, including linear, branched, cyclic, saturated and unsaturated species, such as alkyl groups, alkenyl groups, aryl groups, and the like. "Substituted hydrocarbyl" refers to hydrocarbyl substituted with one or more substituent groups, and the term "heteroatom-containing hydrocarbyl" refers to hydrocarbyl in which at least one carbon atom is replaced with a heteroatom. Unless otherwise indicated, the term "hydrocarbyl" is to be interpreted as including substituted and/or heteroatom-containing hydrocarbyl moieties.

[00038] By "substituted" as in "substituted hydrocarbyl," "substituted alkyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the hydrocarbyl, alkyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon (or other) atom is replaced with one or more non-hydrogen substituents. Examples of such substituents include, without limitation, functional groups, and the hydrocarbyl moieties C_1-C_{24} alkyl (including C_1-C_{18} alkyl, further including C_1-C_{12} alkyl, and further including C_1-C_6 alkyl), C_2-C_{24} alkenyl (including C_2-C_{18} alkenyl, further including C_2-C_{12} alkenyl, and further including C_2-C_6 alkenyl), C_2-C_{24} alkynyl (including C_2-C_{18} alkynyl, further including C_2-C_{12} alkynyl, and further including C_2-C_6 alkynyl), C_5-C_{30} aryl (including C_5-C_{20} aryl, and further including C_5-C_{12} aryl), and C_6-C_{30} aralkyl (including C_6-C_{20} aralkyl,

and further including C_6-C_{12} aralkyl). The above-mentioned hydrocarbyl moieties may be further substituted with one or more functional groups or additional hydrocarbyl moieties such as those specifically enumerated.

[00039] By the term "functional groups" is meant chemical groups such as halo, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (-CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), halocarbonyl (-CO)-X where X is halo), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), mono-substituted C_1-C_{24} alkylcarbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), di-substituted alkylcarbamoyl (-(CO)-N(C_1-C_{24} alkyl)$_2$), mono-substituted arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano (-C≡N), isocyano (-N^+≡C^-), cyanato (-O-C≡N), isocyanato (-O-N^+≡C^-), isothiocyanato (-S-C≡N), azido (-N=N^+=N^-), formyl (-(CO)-H), thioformyl (-(CS)-H), amino (-NH_2), mono- and di-(C_1-C_{24} alkyl)-substituted amino, mono- and di-(C_5-C_{20} aryl)-substituted amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_5-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R = hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{20} alkaryl, C_6-C_{20} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), arylimino (-CR=N(aryl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), and phosphino (-PH_2), mono- and di-(C_1-C_{24} alkyl)-substituted phosphino, mono- and di-(C_5-C_{20} aryl)-substituted phosphine. In addition, the aforementioned functional groups may, if a particular group permits, be further substituted with one or more additional functional groups or with one or more hydrocarbyl moieties such as those specifically enumerated above.

[00040] By "linking" or "linker" as in "linking group," "linker moiety," etc., is meant a bivalent radical moiety. Examples of such linking groups include alkylene, alkenylene, alkynylene, arylene, alkarylene, aralkylene, and linking moieties containing functional groups including, without limitation: amido (-NH-CO-), ureylene (-NH-CO-NH-), imide (-CO-NH-CO-) , epoxy (-O-), epithio (-S-), epidioxy (-O-O-), carbonyldioxy (-O-CO-O-), alkyldioxy (-O-(CH_2)$_n$-O-), epoxyimino (-O-NH-), epimino (-NH-), carbonyl (-CO-), etc.

[00041] When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group. For example, the phrase "substituted alkyl and aryl" is to be interpreted as "substituted alkyl and substituted aryl."

[00042] Unless otherwise specified, reference to an atom is meant to include isotopes of that atom. For example, reference to H is meant to include ^{1}H, ^{2}H (i.e., D) and ^{3}H (i.e., T), and reference to C is meant to include ^{12}C and all isotopes of carbon (such as ^{13}C).

[00043] The term "hybrid compound" as used herein refers to a drug moiety (also referred to herein as a "first active moiety") and neurotoxicity lowering moiety (also referred to herein as a "second active moiety") that are linked by covalent bonds. The covalent linkage may be via a linking moiety or via a direct covalent bond between the two moieties.

[00044] Unless otherwise indicated, the terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, the terms include prophylactic use of active agents. "Preventing" a disorder or unwanted physiological event in a patient refers specifically to the prevention of the occurrence of symptoms and/or their underlying cause, wherein the patient may or may not exhibit heightened susceptibility to the disorder or event.

[00045] By the term "effective amount" of a therapeutic agent is meant a nontoxic but sufficient amount of a beneficial agent to provide a desirable effect.

[00046] As used herein, and unless specifically stated otherwise, an "effective amount" of a beneficial refers to an amount covering both therapeutically effective amounts and prophylactically effective amounts.

[00047] As used herein, a "therapeutically effective amount" of an active agent refers to an amount that is effective to achieve a desirable therapeutic result, and a "prophylactically effective amount" of an active agent refers to an amount that is effective to prevent or lessen the severity of an unwanted physiological condition.

[00048] By a "pharmaceutically acceptable" component is meant a component that is not biologically or otherwise undesirable, i.e., the component may be incorporated into a pharmaceutical formulation of the disclosure and administered to a patient as described herein without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the formulation in which it is contained. When the term "pharmaceutically acceptable" is used to refer to an excipient, it is generally implied that the component has met the required standards of toxicological and

manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration.

[00049] The term "pharmacologically active" (or simply "active"), as in a "pharmacologically active" derivative or analog, refers to a derivative or analog (e.g., a salt, ester, amide, conjugate, metabolite, isomer, fragment, etc.) having the same type of pharmacological activity as the parent compound and approximately equivalent in degree.

[00050] The term "controlled release" refers to a formulation, dosage form, or region thereof from which release of a beneficial agent is not immediate, i.e., with a "controlled release" dosage form, administration does not result in immediate release of the beneficial agent in an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed. (Easton, PA: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release and delayed release formulations.

[00051] The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a formulation, dosage form, or region thereof that provides for gradual release of a beneficial agent over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of the agent over an extended time period.

[00052] The term "neurotoxicity lowering biomoiety" may refer to proteins, nucleic acids, carbohydrates, lipid, or any naturally occurring moiety in an organism that interacts with the neurotoxicity lowering moiety to produce a neurotoxicity lowering effect.

[00053] The term "naturally occurring" refers to a compound or composition that occurs in nature, regardless of whether the compound or composition has been isolated from a natural source or chemically synthesized.

Detailed Description

[00054] In some embodiments, then, there is disclosed herein hybrid compounds comprising an active moiety and a toxicity reducing moiety. The two moieties are covalently linked, wherein such linkage may be a direct bond or may be via an optional linker moiety that is covalently bonded to each of the active moiety and the toxicity reducing moiety. For example, the active moiety is an anticancer moiety, and the toxicity lowering moiety is a neurotoxicity lowering moiety. Also for example, the toxicity reducing moiety is a neurotoxicity lowering moiety and is a neurotrophic ligand. In some embodiments, the

neurotrophic ligand specifically targets neurotoxicity lowering biomoieties including FKBP proteins such as FKBP52 and FKBP38, or heat shock proteins.

[00055] In some embodiments, the hybrids compounds (also referred to herein as "conjugates," "hybrid compounds," "hybrids," or simply as "compounds") of interest are at least equipotent with the active moiety in non-hybridized form. In addition to being at least equipotent, the compounds of interest are also substantially less neurotoxic compared with the active moiety in non-hybridized form. For example, a paclitaxel-neurotrophic ligand hybrid compound according to the disclosure is at least equipotent with paclitaxel alone, but exhibits substantially reduced neurotoxicity when administered to a patient.

[00056] Although equipotency is preferred, in some embodiments the compounds of the invention exhibit somewhat reduced potency compared with the active moiety in non-hybridized form. In some embodiments, such reduced potency is no more than 10% reduced, or 20% reduced, or 25% reduced, or 30% reduced, or 40% reduced, or 50% reduced.

[00057] The compounds of interest have reduced toxicity compared with the non-hybridized active compound. For example, by one method of measure, a compound of interest is substantially less neurotoxic than the native (non-hybridized) active moiety, wherein "substantially less neurotoxic" occurs when a statistically significant portion of patients receiving treatment with the hybridized compound exhibit reduced symptoms of a neurologic side effect (such as CIPN). By "reduced symptoms" is meant that the symptoms may be reduced by at least 10%, reduced by at least 20%, reduced by at least 25%, reduced by at least 30%, reduced by at least 40%, reduced by at least 50%, reduced by at least 75%, or reduced by 100% (i.e., the patient exhibits no neurotoxic symptoms).

[00058] In some embodiments, the compounds of interest are conjugates of an anticancer moiety and a neurotoxicity lowering moiety, both of which are covalently bound either directly to each other or via an optional linker moiety. In some such embodiments, the neurotoxicity lowering moiety has a dissociation constant of less than 10 μM, or less than 9000 nM, or less than 8000 nM, or less than 7000 nM, or less than 6000 nM, or less than 5000 nM, or less than 4000 nM, or less than 3000 nM, or less than 2000 nM, or less than 1000 nM with an FKBP protein (such as, for example, FKBP52 or FKBP38) or a heat shock protein. In some such embodiments, the neurotoxicity lowering moiety's dissociation constant for FKBP52 divided by the neurotoxicity lowering moiety's dissociation constant for FKBP12 is greater than 0.1, or greater than 0.2, or greater than 0.3, or greater than 0.4, or greater than 0.5.

[00059] In some embodiments, the compounds of the invention achieve reduced neurotoxicity (e.g., reduced CINP) by incorporating into a single compound both a neurotrophic moiety having nanomolar affinity for one or more FKBP proteins and an active moiety such as a taxane moiety. In some embodiments, the toxicity-reducing moiety is a neuroimmunophilin moiety.

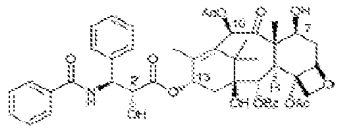
[00060] In some embodiments, the disclosure provides compounds having two or three components: a first active moiety, a second active moiety, and an optional linker moiety that links the first active moiety with the second active moiety. In some embodiments the three components are linked via covalent bonds. In other words, the first and second active moieties are each linked to the linking moiety via one (or more) covalent bond(s). In some embodiments, the linker moiety is absent, such that the first and second active moieties are directly connected via a covalent bond. As described herein, in some embodiments the linkage between the first and second active moieties may be labile such that the moieties are only transiently linked.

[00061] In some embodiments, the compounds have a total molecular weight of less than about 15000 D, or less than about 12500 D, or less than about 10000 D, or less than about 7500 D, or less than about 5000 D, or less than about 4000 D, or less than about 3000 D, or less than about 2000 D, or less than about 1500 D, or less than about 1000 D.

[00062] In some embodiments, the first active moiety is a therapeutically active moiety, derivative, fragment, or analog thereof (collectively referred to herein as a "therapeutically active moiety" or "therapeutic"), wherein such therapeutically active moiety is useful in the treatment of an undesirable medical condition in a patient. For example, in some embodiments, the first active moiety is an anti-cancer moiety, derivative, fragment, or analog thereof (collectively referred to herein as an "anti-cancer moiety"). More specifically, in some embodiments, the first active moiety is a taxane moiety, or a derivative, fragment, or analog thereof (collectively referred to herein as a "taxane moiety"). Examples of suitable taxane moieties include paclitaxel, docetaxel, and cabazitaxel. It will be appreciated that, for the moiety used as the first active moiety, at least one of the atoms (e.g. a hydrogen atom) will be replaced to accommodate a covalent linkage between the first active moiety and the linking moiety or the second active moiety. For example, when the first active moiety is said herein to be "paclitaxel," it will be appreciated that the moiety is in fact the paclitaxel structure having at least one atom replaced with a covalent bond to the linking compound or second active moiety. In other words, the "paclitaxel" moiety used as the first active moiety is not, in fact, the complete paclitaxel structure, but rather is the paclitaxel structure modified

(by replacement of at least one atom) to accommodate a covalent linkage to the linking moiety or second active moiety. This convention applies throughout the instant disclosure wherever a molecule, moiety, or fragment is described as being covalently attached to another molecule, moiety, or fragment.

[00063] Where the first active moiety is a taxane moiety, it may connect to the second active moiety or the linker moiety through any of the oxygen groups at the C-2', C-7, or C-10 positions (taxane structures typically have hydroxyl groups at the C-2' and C-7 positions, and an acetyloxy group at the C-10 position – see the structure and numbering scheme of Paclitaxel below).

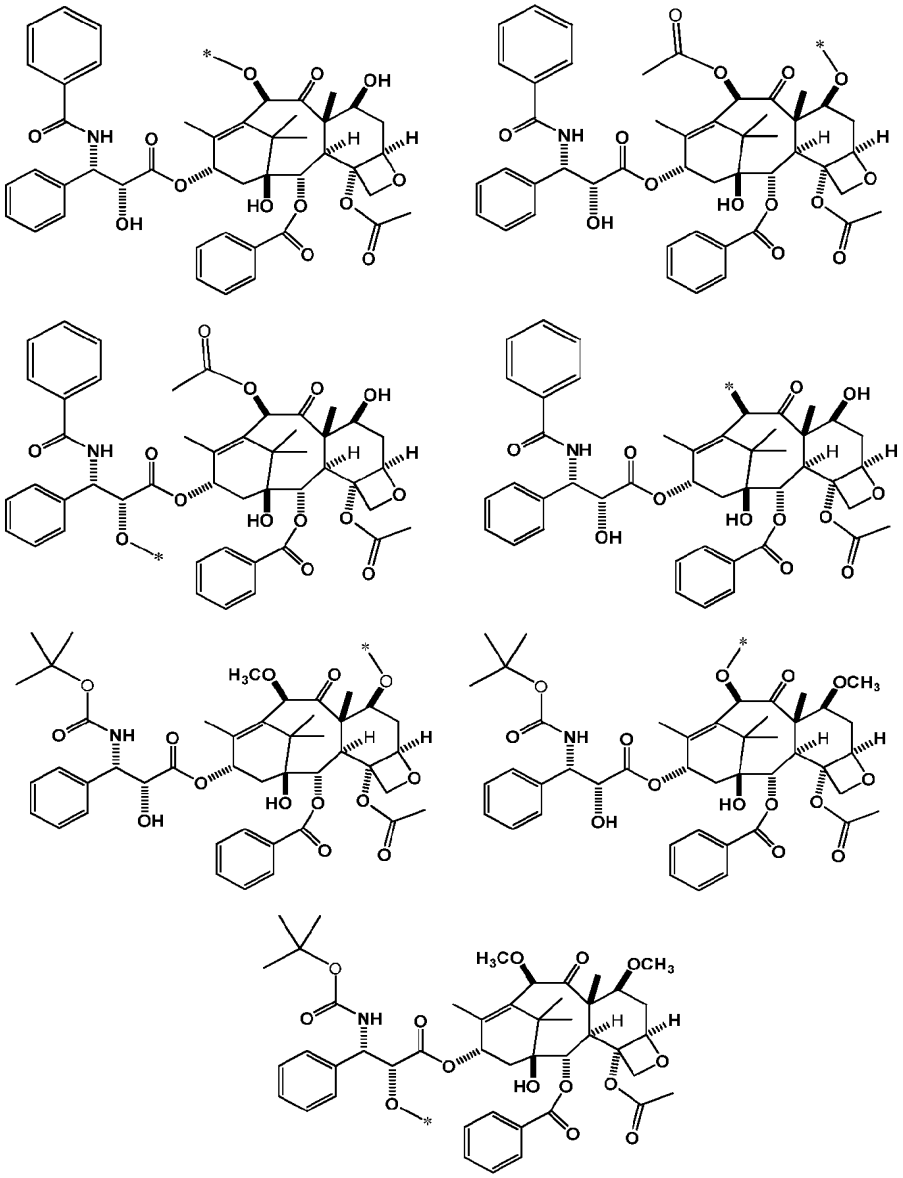


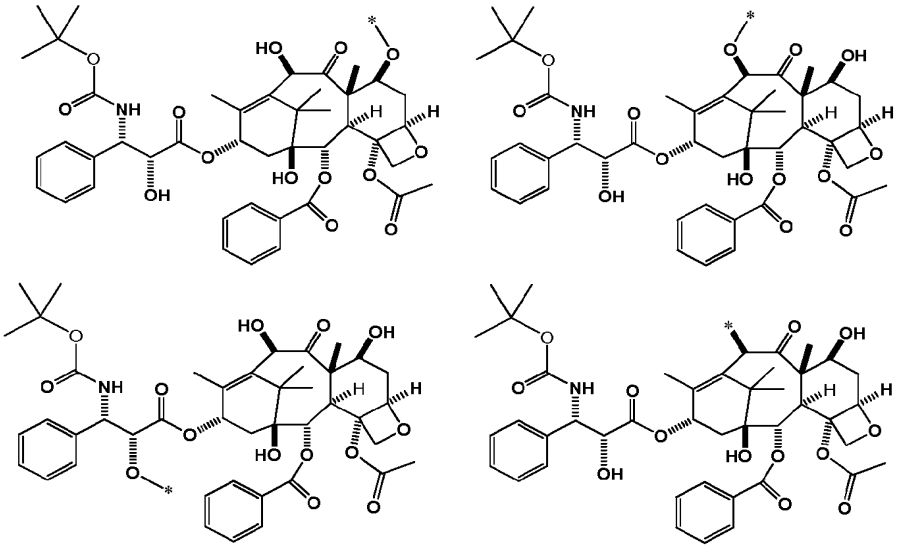
Paclitaxel

[00064] In some embodiments, the acetyloxy group at the C-10 position is not present, as described and shown in the structures below.

[00065] Although the C-2', C-7, and C-10 positions are specifically mentioned here, it will be appreciated that connections through other positions of the taxane moiety are within the scope of interest.

[00066] Some examples of first active moieties, wherein the stars indicate their points of attachment to the linker moiety or the second active moiety, are shown below:

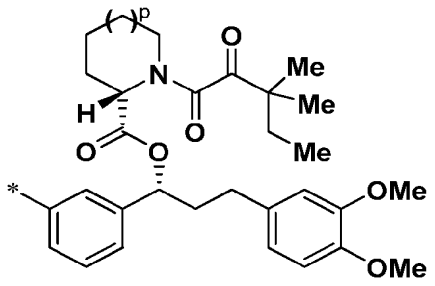




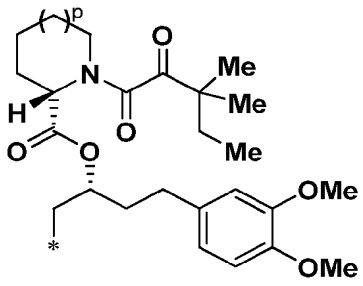
[00067] In some embodiments, the first active moiety is attached to a linker in two locations, such that the linker and first active moiety create a cyclic structure. For example, the linker may attach to the first active moiety at two positions selected from the C-2', C-7, and C-10 positions. In such embodiments, the linker comprises a branch point where the second active moiety attaches. For example, in some embodiments the second active moiety attaches to a position on an aryl ring of the linking moiety.

[00068] The second active moiety is a toxicity lowering moiety, and in some embodiments, the second active moiety is a neurotoxicity lowering moiety. In some embodiments, the second active moiety is a ligand for FKBP protein. In some embodiments, the second active moiety is a ligand for FKBP52 or FKBP38. In some embodiments, the second active moiety is a ligand for a heat shock protein. For example, in some embodiments, the neurotoxicity lowering moiety has a dissociation constant of less than 10 μM with an FKBP protein, or less than 9000 nm with an FKBP protein (e.g. FKBP52 or FKBP38). In some such embodiments, the neurotoxicity lowering moiety has a dissociation constant of less than 10 μM with a heat shock protein, or less than 9000 nm with a heat shock protein. In some embodiments, the second active moiety is a neuroimmunophilin ligand. Examples of suitable second active moieties are provided in the following paragraphs as well as the examples provided herein.

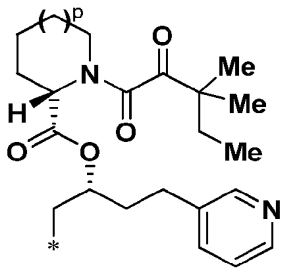
[00069] The second active moiety may be selected from Units A, B, C, D, E, and F:



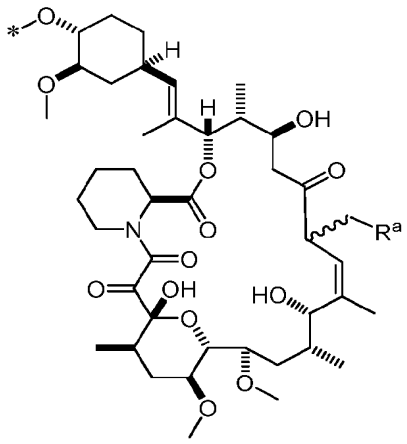
Unit A



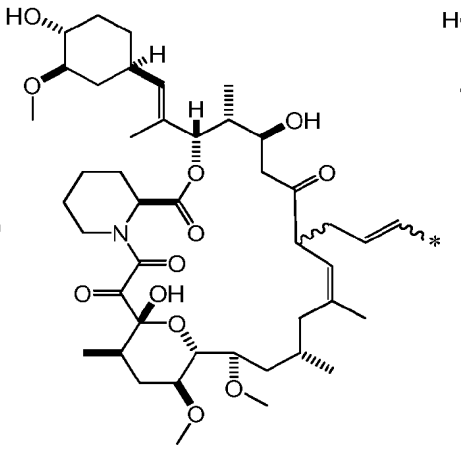
Unit B



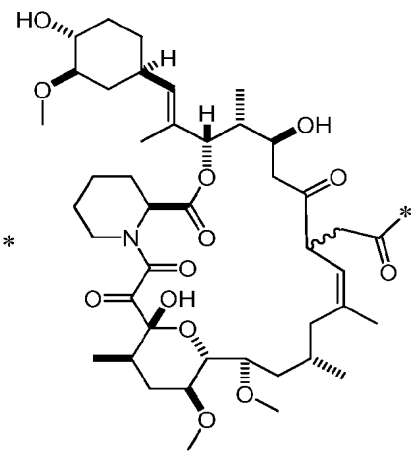
Unit C



Unit D



Unit E



Unit F

[00070] wherein:

[00071] p represents an integer from 0 to 2;

[00072] R^a is selected from hydrocarbyl groups; and

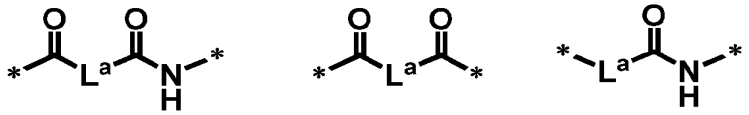
[00073] the stars represent the point of connection to the first active moiety or, when present, the linking moiety as described herein.

[00074] For example, in some embodiments, R^a is an alkyl group such as a methyl, ethyl, or propyl group. For example, R^a is methyl.

[00075] The linker component is an optional moiety that, when present, covalently links the two active moieties. Thus, in some embodiments, the linking moiety links the therapeutic active moiety with the neurotoxicity lowering moiety. When the linker is not present, the two active moieties may be linked via a direct covalent bond. Some embodiments of the linker affect the potency of the overall compound and/or can also be used to optimize

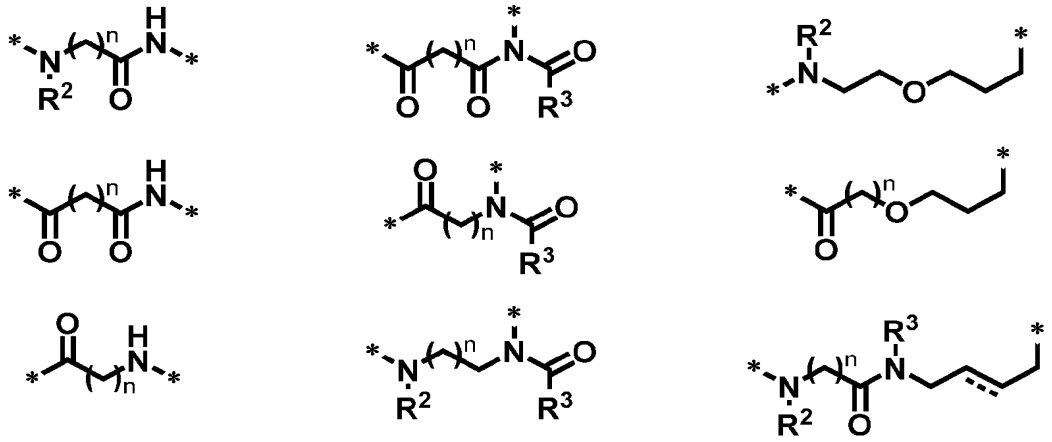
solubility of the overall compound. The linker can also be varied in order to modify the pharmacological and/or chemical properties of the conjugate compound.

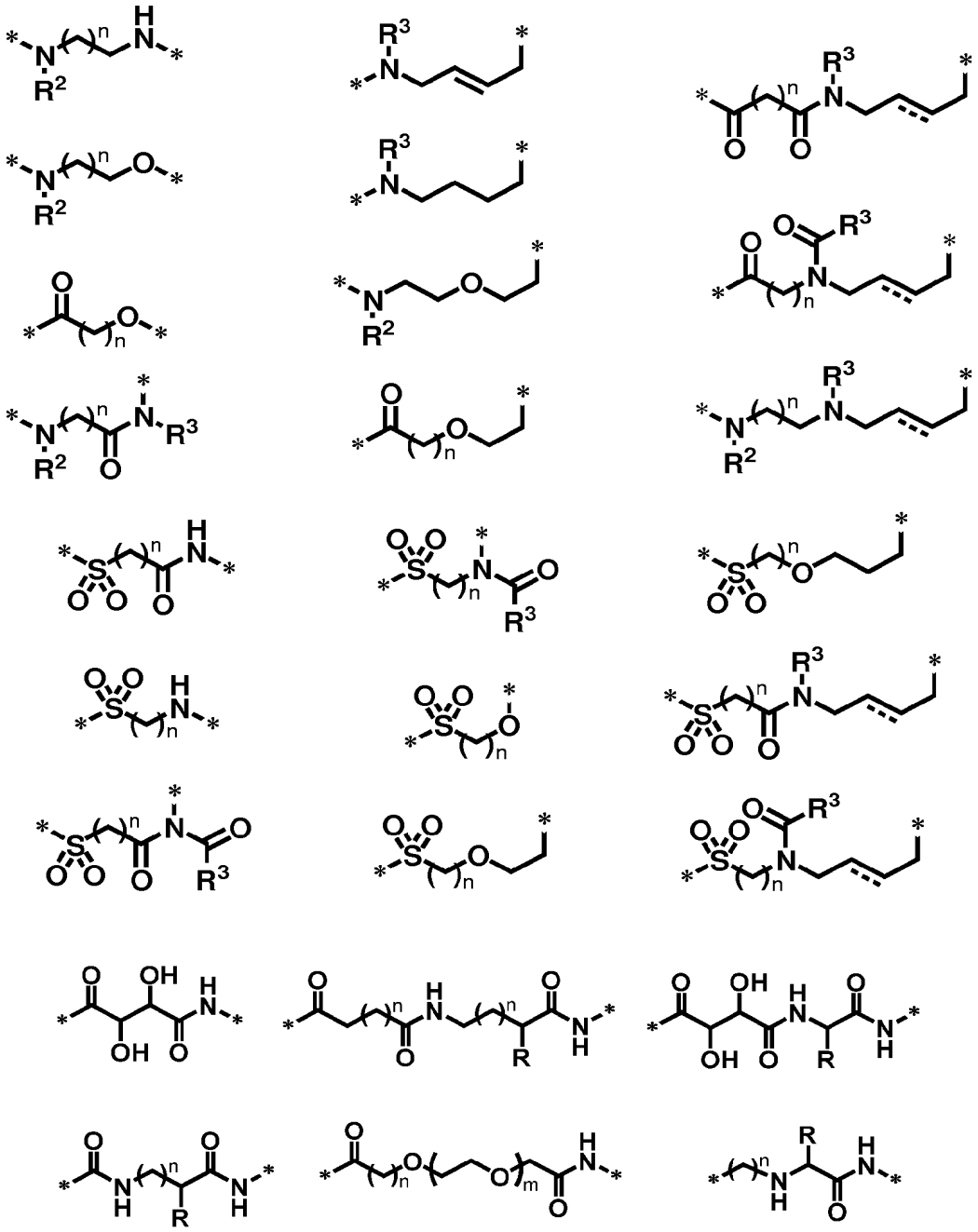
[00076] Some examples of linking moieties include alkylene linkers, amides, ureas, sulfoxides, sulfonamides, amines (including polyamines), carbonyls, ethers (including polyethers), and combinations thereof. For example, some combinations include amide/urea combinations, amide/amide combinations, sulfoxide/ether combinations, amide/ether combinations, amine/ether combinations, amide/amine combinations, carbonyl/amide combinations, and other combinations as appropriate. Such linkers may include unsaturated or saturated segments. Some examples of linking moieties include the following structures:

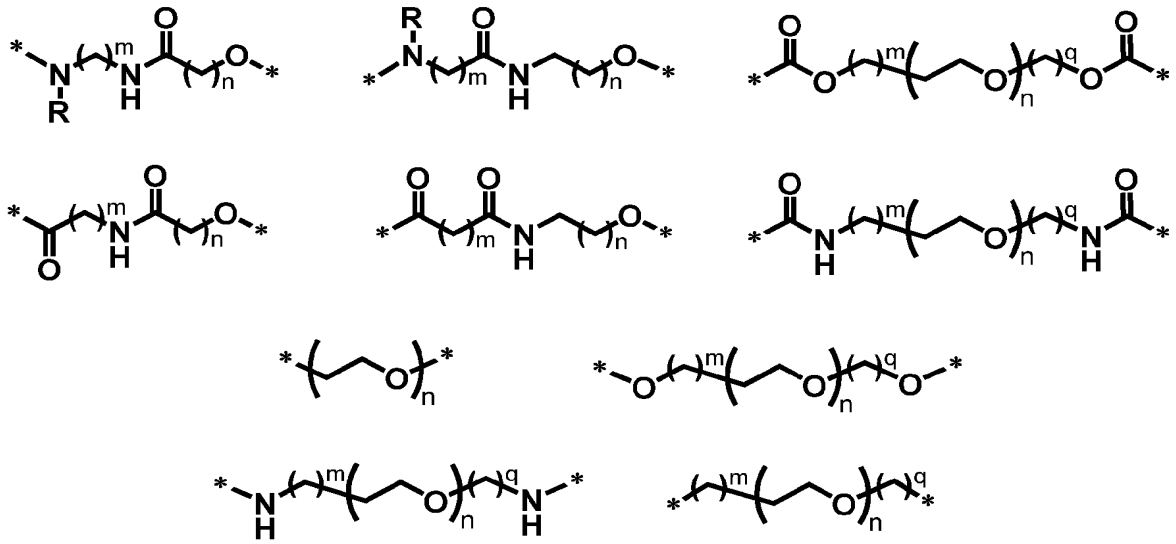


wherein L^a is a linking moieties selected from hydrocarbyl, substituted hydrocarbyl, heteroatom-containing hydrocarbyl, and substituted heteroatom-containing hydrocarbyl.

[00077] Further examples of linking moieties include the structures shown below.







[00078] wherein:

[00079] R, R^2, and R^3 are selected from H, hydrocarbyl, and functional groups;

[00080] the stars (which may be alternatively and equivalently represented herein by wavy lines) represent attachment points to the remainder of the compound; and

[00081] m, n, and q represent independently selected integers.

[00082] For example, the integer values for m, n, and q may, for example, be 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or greater than 10.

[00083] Also for example, R, R^2, and R^3 may be selected from alkyl, aryl, substituted alkyl, substituted aryl, heteroatom containing alkyl, heteroaryl, and functional groups such as hydroxyl, amino, carboxyl, and the like as defined above.

[00084] Protected versions of any of the abovementioned linkers (e.g. a linker having a hydroxyl group protected by a protecting group) are also within the scope of the linkers of interest. Furthermore, it will be appreciated that the linkers may be attached to the first and second active moieties in either "direction" (i.e. as written above or in reverse orientation).

[00085] In some embodiments, the linking moiety is a flexible polymeric linker. By "polymeric" is meant that the linker contains a unit that is repeated two or more times. For example, a polyalkylene oxide or polyethyleneamine linker provides increased water solubility and increased flexibility between the first and second moieties. In some embodiments, the flexible polymeric unit results in a slight decrease in efficacy of the first active moiety (i.e. relative to the parent, non-hybridized active compound). In some embodiments, however, the hybrid compound retains some efficacy, and in some embodiments, the hybrid compound is equipotent compared with the parent non-hybridized compound. In some embodiments, the polymeric linker does not affect cell permeability of

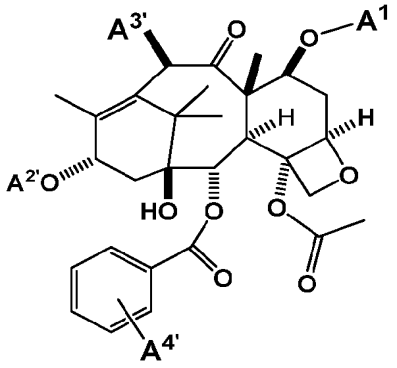
the hybrid compound, and in some embodiments the polymeric linker reduces cell permeability slightly but not to the point that the hybrid compound loses all efficacy.

[00086] In some embodiments, the linker comprises a polyethylene oxide moiety having 2, 3, 4, 5, 6, or more ethylene oxide repeat units. Such linkers may further contain alkylene portions and/or functional groups (e.g., amide groups, amine groups, carbonyl groups, ester groups, additional ether groups, and combinations thereof) between the polyethylene oxide moiety and the first and/or second active moieties.

[00087] The linker moiety may be, in some embodiments, a labile moiety such that the first and second active moieties are only transiently linked. Thus, in some embodiments, the linker moiety is labile *in vivo* such that, when administered to the patient, the compound degrades to produce a neurotoxicity-reducing moiety and an active moiety (e.g., an anti-cancer moiety) that are no longer linked. It will be appreciated that such degradation can be designed to occur under desirable conditions (e.g., when the compound reaches cancerous cells). For example, the compound may be administered as a formulation wherein the compound is contained within a liposome, and the compound degrades when it leaves the liposome environment.

[00088] In some embodiments, the disclosure provides compounds having the structure of formula (I)

(I)



[00089] wherein:

[00090] $A^{2'}$ is selected from H, hydrocarbyl, substituted hydrocarbyl, heteroatom-containing hydrocarbyl, and substituted heteroatom-containing hydrocarbyl, provided that $A^{2'}$ optionally comprises the moiety A^2;

[00091] $A^{3'}$ is selected from $-O-A^3$ and $-A^3$;

[00092] one of A^1, A^2, A^3, and A^4 is selected from –U and –L–U, and the others are selected from H, and alkyl, provided that A^4 may be taken together with A^2 to form a cycle;

[00093] L is a linking moiety; and

[00094] U is a toxicity lowering moiety.

[00095] For example, in various embodiments, L is selected from any of the linking moieties described herein, and U is selected from any of the second active moieties described herein.

[00096] Also for example, in some embodiments, A^1 is selected from –U, –L–U, acetyl, methyl, and H. In some embodiments, A^1 is selected from H or methyl.

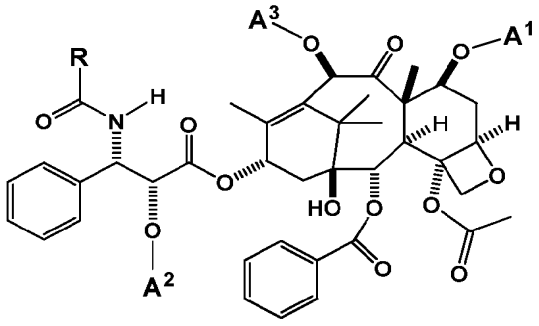
[00097] Also for example, in some embodiments, $A^{2'}$ is a carbonyl-containing moiety that further contains the moiety A^2. For example, $A^{2'}$ is an acetyl moiety. In some embodiments, $A^{2'}$ is an isoserine residue such as a phenylisoserine residue or a derivative thereof.

[00098] Also for example, in some embodiments, A^2 is selected from –U, –L–U, acetyl, methyl, and H. In some embodiments, A^2 is H.

[00099] Also for example, in some embodiments, A^3 is selected from –U, –L–U, acetyl, methyl, and H. In some embodiments, A3 is –L–U or acetyl.

[000100] In certain embodiments, the disclosure provides compounds having the structure of formula (Ia)

(Ia)



[000101] wherein:

[000102] R is selected from hydrocarbyl, substituted hydrocarbyl, heteroatom-containing hydrocarbyl, and substituted heteroatom-containing hydrocarbyl; and

[000103] A^1, A^2, and A^3 are as defined above for formula (I).

[000104] For example, in some embodiments, R is selected from alkyl, alkoxy, aryl, and aryloxy. In some embodiments, R is phenyl, and in other embodiments, R is tert-butoxyl.

[000105] Some embodiments include compounds having the structure of formula (I), wherein the core structure is that of paclitaxel, docetaxel, or carbazitaxel except that one of A^1, A^2, or A^3 is –U or –L–U.

[000106] In some embodiments, the neurotoxicity of the compound when administered to a patient is lower than the neurotoxicity of a compound having the same structure but lacking a –U or –L–U moiety (e.g. having H or alkyl in place of –U or –L–U).

[000107] As described herein in the examples and accompanying disclosure, the relative toxicity of the compounds of interest compared with the parent (non-hybridized) anti-cancer compound may be measured by the normal methods for measuring toxicity of such compounds. In some embodiments, the compounds of interest produce fewer and/or less intense symptoms of chemically induced peripheral neuropathy (CIPN) in patients receiving the compound as compared with patients receiving the parent (non-hybridized) anti-cancer compound.

[000108] It will be appreciated that, for a compound comprising a first active moiety and a second active moiety, the "parent anti-cancer compound" refers to the first active moiety without having been hybridized by linking to the second active moiety. For example, for a paclitaxel-FK506 hybrid compound, the parent anti-cancer compound is non-hybridized paclitaxel.

[000109] A selection of example compounds of interest is shown in the Schemes and Figures set forth herein.

[000110] Any of the compounds of the disclosure may be administered in the form of a salt, ester, amide, prodrug, active metabolite, analog, or the like, provided that the salt, ester, amide, prodrug, active metabolite or analog is pharmaceutically acceptable and pharmacologically active in the present context. Salts, esters, amides, prodrugs, active metabolites, analogs, and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th Ed. (New York: Wiley-Interscience, 2001). Furthermore, where appropriate, functional groups on the compounds of the disclosure may be protected from undesired reactions during preparation or administration using protecting group chemistry. Suitable protecting groups are described, for example, in Green, *Protective Groups in Organic Synthesis*, 3rd Ed. (New York: Wiley-Interscience, 1999).

[000111] For example, where appropriate, any of the compounds described herein may be in the form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt may be prepared from any pharmaceutically acceptable organic acid or base, any pharmaceutically acceptable inorganic acid or base, or combinations thereof. The acid or base used to prepare the salt may be naturally occurring.

[000112] Suitable organic acids for preparing acid addition salts include, e.g., C_1-C_6 alkyl and C_6-C_{12} aryl carboxylic acids, di-carboxylic acids, and tri-carboxylic acids such as acetic acid, propionic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, glycolic acid, citric acid, pyruvic acid, oxalic acid, malic acid, malonic acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, phthalic acid, and terephthalic acid, and aryl and alkyl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, and p-toluenesulfonic acid, and the like. Suitable inorganic acids for preparing acid addition salts include, e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base.

[000113] Suitable organic bases for preparing basic addition salts include, e.g., primary, secondary and tertiary amines, such as trimethylamine, triethylamine, tripropylamine, N,N-dibenzylethylenediamine, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, glucamine, glucosamine, histidine, and polyamine resins, cyclic amines such as caffeine, N-ethylmorpholine, N-ethylpiperidine, and purine, and salts of amines such as betaine, choline, and procaine, and the like. Suitable inorganic bases for preparing basic addition salts include, e.g., salts derived from sodium, potassium, ammonium, calcium, ferric, ferrous, aluminum, lithium, magnesium, or zinc such as sodium hydroxide, potassium hydroxide, calcium carbonate, sodium carbonate, and potassium carbonate, and the like. A basic addition salt may be reconverted to the free acid by treatment with a suitable acid.

[000114] Preparation of esters involves transformation of a carboxylic acid group via a conventional esterification reaction involving nucleophilic attack of an RO^- moiety at the carbonyl carbon. Esterification may also be carried out by reaction of a hydroxyl group with an esterification reagent such as an acid chloride. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs and active metabolites may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. Prodrugs are typically prepared by covalent

attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

[000115] Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature. In addition, chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers.

[000116] Any of the compounds of the disclosure may be the active agent in a formulation as described herein. Formulations containing the compounds of the disclosure may include 1, 2, 3 or more of the compounds described herein, and may also include one or more additional active agents such as analgesics and other antibiotics.

[000117] The amount of active agent in the formulation typically ranges from about 0.05 wt% to about 95 wt% based on the total weight of the formulation. For example, the amount of active agent may range from about 0.05 wt% to about 50 wt%, or from about 0.1 wt% to about 25 wt%. Alternatively, the amount of active agent in the formulation may be measured so as to achieve a desired dose.

[000118] Formulations containing the compounds of the disclosure may be presented in unit dose form or in multi-dose containers with an optional preservative to increase shelf life.

[000119] The compositions of the disclosure may be administered to the patient by any appropriate method. In general, both systemic and localized methods of administration are acceptable. It will be obvious to those skilled in the art that the selection of a method of administration will be influenced by a number of factors, such as the condition being treated, frequency of administration, dosage level, and the wants and needs of the patient. For example, certain methods may be better suited for rapid delivery of high doses of active agent, while other methods may be better suited for slow, steady delivery of active agent. Examples of methods of administration that are suitable for delivery of the compounds of the disclosure include parental and transmembrane absorption (including delivery via the digestive and respiratory tracts). Formulations suitable for delivery via these methods are well known in the art.

[000120] For example, formulations containing the compounds of the disclosure may be administered parenterally, such as via intravenous, subcutaneous, intraperitoneal, or intramuscular injection, using bolus injection and/or continuous infusion. Generally, parenteral administration employs liquid formulations.

[000121] The compositions may also be administered via the digestive tract, including orally and rectally. Examples of formulations that are appropriate for administration via the

digestive tract include tablets, capsules, pastilles, chewing gum, aqueous solutions, and suppositories.

[000122] The formulations may also be administered via transmucosal administration. Transmucosal delivery includes delivery via the oral (including buccal and sublingual), nasal, vaginal, and rectal mucosal membranes. Formulations suitable for transmucosal deliver are well known in the art and include tablets, chewing gums, mouthwashes, lozenges, suppositories, gels, creams, liquids, and pastes.

[000123] The formulations may also be administered transdermally. Transdermal delivery may be accomplished using, for example, topically applied creams, liquids, pastes, gels and the like as well as what is often referred to as transdermal "patches."

[000124] The formulations may also be administered via the respiratory tract. Pulmonary delivery may be accomplished via oral or nasal inhalation, using aerosols, dry powders, liquid formulations, or the like. Aerosol inhalers and imitation cigarettes are examples of pulmonary dosage forms.

[000125] Liquid formulations include solutions, suspensions, and emulsions. For example, solutions may be aqueous solutions of the active agent and may include one or more of propylene glycol, polyethylene glycol, and the like. Aqueous suspensions can be made by dispersing the finely divided active agent in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents. Also included are formulations of solid form which are intended to be converted, shortly before use, to liquid form.

[000126] Tablets and lozenges may comprise, for example, a flavored base such as compressed lactose, sucrose and acacia or tragacanth and an effective amount of an active agent. Pastilles generally comprise the active agent in an inert base such as gelatin and glycerine or sucrose and acacia. Mouthwashes generally comprise the active agent in a suitable liquid carrier.

[000127] For topical administration to the epidermis the chemical compound according to the disclosure may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

[000128] Transdermal patches typically comprise: (1) a impermeable backing layer which may be made up of any of a wide variety of plastics or resins, e.g. aluminized polyester or polyester alone or other impermeable films; and (2) a reservoir layer comprising, for example, a compound of the disclosure in combination with mineral oil, polyisobutylene, and alcohols gelled with USP hydroxymethylcellulose. As another example, the reservoir layer may comprise acrylic-based polymer adhesives with resinous crosslinking agents which provide for diffusion of the active agent from the reservoir layer to the surface of the skin. The transdermal patch may also have a delivery rate-controlling membrane such as a microporous polypropylene disposed between the reservoir and the skin. Ethylene-vinyl acetate copolymers and other microporous membranes may also be used. Typically, an adhesive layer is provided which may comprise an adhesive formulation such as mineral oil and polyisobutylene combined with the active agent.

[000129] Other typical transdermal patches may comprise three layers: (1) an outer layer comprising a laminated polyester film; (2) a middle layer containing a rate-controlling adhesive, a structural non-woven material and the active agent; and (3) a disposable liner that must be removed prior to use. Transdermal delivery systems may also involve incorporation of highly lipid soluble carrier compounds such as dimethyl sulfoxide (DMSO), to facilitate penetration of the skin. Other carrier compounds include lanolin and glycerin.

[000130] Rectal or vaginal suppositories comprise, for example, an active agent in combination with glycerin, glycerol monopalmitate, glycerol, monostearate, hydrogenated palm kernel oil and fatty acids. Another example of a suppository formulation includes ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter in combination with an effective amount of an active agent.

[000131] Nasal spray formulations may comprise a solution of active agent in physiologic saline or other pharmaceutically suitable carder liquids. Nasal spray compression pumps are also well known in the art and can be calibrated to deliver a predetermined dose of the solution.

[000132] Aerosol formulations suitable for pulmonary administration include, for example, formulations wherein the active agent is provided in a pressurized pack with a suitable propellant. Suitable propellants include chlorofluorocarbons (CFCs) such as dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gases. The aerosol may also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

[000133] Dry powder suitable for pulmonary administration include, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. Unit doses for dry powder formulations may be, for example, in the form of capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

[000134] In addition to the foregoing components, it may be necessary or desirable in some cases (depending, for instance, on the particular composition or method of administration) to incorporate any of a variety of additives, e.g., components that improve drug delivery, shelf-life, patient acceptance, etc. Suitable additives include acids, antioxidants, antimicrobials, buffers, colorants, crystal growth inhibitors, defoaming agents, diluents, emollients, fillers, flavorings, gelling agents, fragrances, lubricants, propellants, thickeners, salts, solvents, surfactants, other chemical stabilizers, or mixtures thereof. Examples of these additives can be found, for example, in M. Ash and I. Ash, *Handbook of Pharmaceutical Additives* (Hampshire, England: Gower Publishing, 1995), the contents of which are herein incorporated by reference.

[000135] In some embodiments of the invention, the compounds of the invention are administered in the form of a composition comprising one or more additives. In some embodiments, the composition does not comprise CremophorEL (i.e., the polyethoxylated caster oil produced by BASF®). In some such embodiments, the composition consists essentially of a compound of the invention and a pharmaceutically acceptable carrier that is not CremophorEL. In other such embodiments, the compositions consist essentially of a compound of the invention and one or more pharmaceutically acceptable additives that are not CremophorEL.

[000136] In some embodiments, the compounds of the invention are administered in the form of a composition that further comprises a nonionic surfactant other than CremophorEL. In some embodiments, the compositions according to the invention comprise albumin.

[000137] In some embodiments, the compounds of the invention are administered in the form of a composition, wherein the composition comprises liposomes containing one or more of the compounds of the invention. Formation of liposomes for encapsulation of the compounds of the invention may be accomplished in the normal way.

[000138] Appropriate dose and regimen schedules will be apparent based on the present disclosure and on information generally available to the skilled artisan. Administration may be carried out over weeks, months, or years. In some embodiments, controlled, low-level

dosages are provided over a long period of time, whereas in some embodiments, higher level dosages are administered for a short period of time. Other dosage regimens, including less frequent or one-time administration of high-intensity dosages, are also within the scope of the disclosure.

[000139] The amount of active agent in formulations that contain the compounds of the disclosure may be calculated to achieve a specific dose (i.e., unit weight of active agent per unit weight of patient) of active agent. Furthermore, the treatment regimen may be designed to sustain a predetermined systemic level of active agent. For example, formulations and treatment regimen may be designed to provide an amount of active agent that ranges from about 0.001 mg/kg/day to about 100 mg/kg/day for an adult. As a further example, the amount of active agent may range from about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.1mg/kg/day to about 25 mg/kg/day, or about 1mg/kg/day to about 10 mg/kg/day. One of skill in the art will appreciate that dosages may vary depending on a variety of factors, including method and frequency of administration, and physical characteristics of the patient.

[000140] The compounds of the disclosure may be prepared using standard procedures that are known to those skilled in the art of synthetic organic chemistry and used for the preparation of analogous compounds. Appropriate synthetic procedures may be found, for example, in J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th Edition (New York: Wiley-Interscience, 2001). Syntheses of representative compounds are detailed in the Examples below.

[000141] Accordingly, in some embodiments the compounds of interest find utility in treating cancer. In some embodiments, this disclosure provides a method for treating a patient suffering from cancer, the method comprising administering to the patient an effective amount of any of the compounds disclosed herein. This disclosure also provides a method for inhibiting the spread of a cancer (e.g. a cancerous cell or tumor), the method comprising contacting a cancerous cell with an effective amount of any of the compounds disclosed herein. The disclosure also provides a method for inhibiting the spread of a cancer, the method comprising contacting a tissue containing cancerous cells with an effective amount of any of the compounds disclosed herein. As described in more detail herein, in any of the aforementioned methods, the compound may be administered in a composition comprising one or more active agents and one or more additives (such as, for example, a pharmaceutically acceptable carrier).

[000142] In some embodiments, the compounds of interest are used to treat any types of cancer that are normally treated with taxane compounds. Such cancers include, for example,

lung (e.g. non-small cell lung), ovarian, breast cancer, head and neck cancer, and Kaposi's sarcoma. Additionally, such cancers include cancers that may be vulnerable to FKBP inhibition, including chronic lymphocytic leukemia, hepatoma, prostate cancer, glioma, acute lymphoblastic leukemia, melanoma, and glioma. Furthermore, in some embodiments the compounds of interest may be used to treat cancer cells and tumors that have displayed resistance toward unmodified taxanes (e.g. paclitaxel or docetaxel).

[000143] In some embodiments, the disclosure provides a method for lowering the neurotoxic effects of a neurotoxicity producing therapeutic active moiety upon administration to a host. The method includes the step of administering to the host an effective amount of a hybrid compound comprising the therapeutic active moiety, a neurotoxicity lowering moiety, and an optional linker moiety. The hybrid compound has a molecular weight less than about 15,000 Daltons. The neurotoxicity lowering moiety binds to at least one neurotoxicity lowering biomoiety and substantially reduces neurotoxicity symptoms in the host. In this way, the hybrid compound reduces neurotoxicity by activating endogenous neuroprotective pathways (rather than merely preventing or reducing the amount of active agent reaching neurons). In some embodiments, the hybrid compound is administered as a pharmaceutical formulation. In some such embodiments, the pharmaceutical formulation does not contain CremophorEL, and the hybrid compound is not co-administered with CremophorEL. In some embodiments, the pharmaceutical formulations contains albumin. In some embodiments, the hybrid compound is administered in a liposome. In some embodiments, the therapeutic active moiety is an anticancer therapeutic moiety. In some such embodiments, the anticancer therapeutic moiety is a taxane. Examples of taxanes include paclitaxel, docetaxel, and carbazitaxel. In some embodiments, the anticancer therapeutic moiety contains platinum. In some embodiments, the neurotoxicity symptom is chemically induced peripheral neuropathy (CIPN).

[000144] In some embodiments, the disclosure provides a method for preparing a hybrid compound having reduced toxicity, the method comprising covalently bonding an active compound to a toxicity lowering moiety either via a direct covalent bond or via a linking moiety. The hybrid has toxicity that is reduced compared with the active compound in non-hybridized form. In some embodiments, the compound has reduced neurotoxicity. In some embodiments, the active compound is a taxane compound. In some embodiments, the linker is a flexible linker. In some embodiments, the linker is a hydrophilic linker.

[000145] In some embodiments, the disclosure provides compounds comprising a taxane moiety covalently attached either directly or through an optional linking moiety to a

neurotoxicity lowering moiety. In some embodiments, the neurotoxicity lowering moiety is a neurotrophic ligand. In some embodiments, the neurotoxicity lowering moiety targets an FKBP protein (such as FKBP52 or FKBP38) or a heat shock protein. In some embodiments the taxane moiety is selected from paclitaxel, docetaxel, and cabazitaxel. In some embodiments, the taxane moiety is covalently linked through the oxygen at the C-2', C-7, or C-10 position to the neurotoxicity lowering moiety or, when present, to the linking moiety.

[000146] All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entireties. However, where a patent, patent application, or publication containing express definitions is incorporated by reference, those express definitions should be understood to apply to the incorporated patent, patent application, or publication in which they are found, and not to the remainder of the text of this application, in particular the claims of this application.

[000147] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description and the examples that follow are intended to illustrate and not limit the scope of the invention. It will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the invention, and further that other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains.

Examples

Example 1

[000148] Paclitaxel-ligand hybrid compounds of interest were prepared according to the disclosure, and the following observations were noticed:

[000149] 1) Paclitaxel-ligand hybrids achieved high intracellular concentrations;

[000150] 2) Paclitaxel-ligand hybrids were at least equipotent with the parent taxane in vitro in slowing the growth of tumor cell lines;

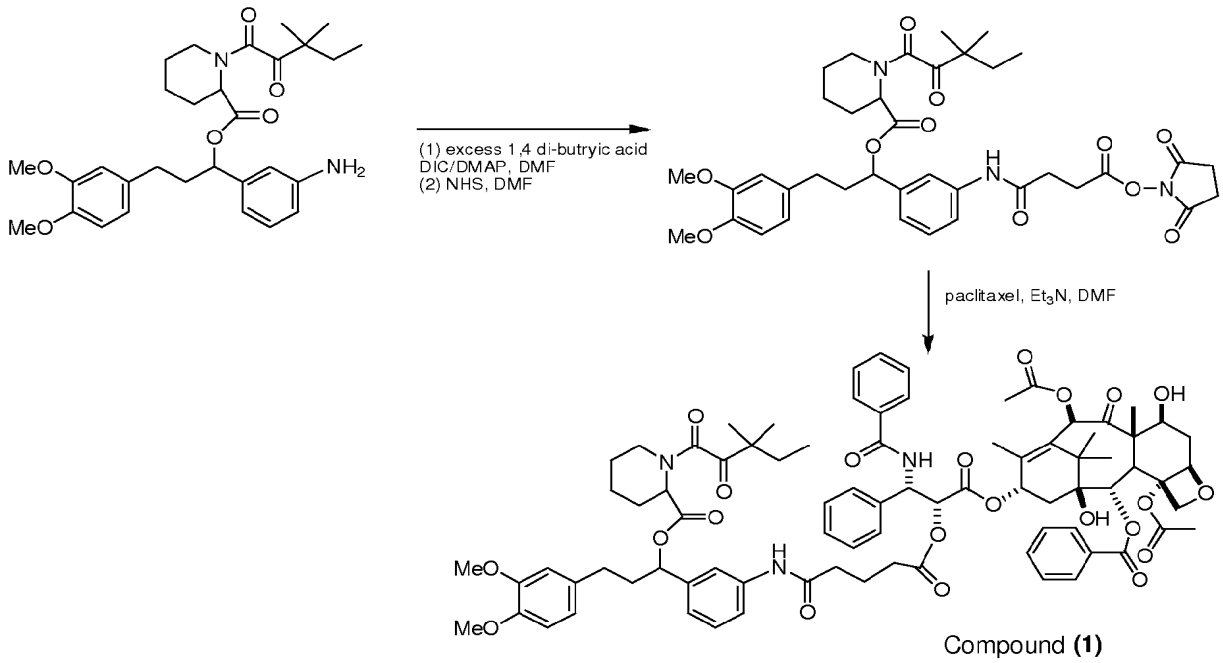
[000151] 3) Paclitaxel-ligand hybrids had good pharmacokinetic properties *in vitro and in vivo* with good metabolic stability;

[000152] 4) Paclitaxel-ligand hybrids were just as efficacious as the parent taxane in reducing tumor size in a xenograft cancer model in mice;

[000153] 5) Paclitaxel-ligand hybrids when administered to mice over a period of 46 days did not produce any greater observable toxicity effects relative to the parent taxane;

[000154] 6) A paclitaxel-ligand hybrid exhibited no detectable neurotoxicity when compared with paclitaxel in a primary cortical neuron outgrowth assay.

[000155] In addition to these observations, Compound (**1**), having paclitaxel (linked at the 2' position) and an FKBP52 ligand linked to a linker moiety, was prepared as shown below in **Scheme 1.** An FKBP52 ligand was employed for this study, as well as unmodified paclitaxel, which is commercially available. An activated succinimidyl ester was created on the FKBP52 ligand and was coupled to the 2' hydroxyl on paclitaxel as shown. The synthesis had a 58% yield after purification by HPLC. The structure was verified by proton NMR and LC-MS.



Scheme 1. Synthesis of Compound (1)

[000156] The resulting paclitaxel-ligand hybrid ("TNL") from Scheme 1 was assessed for its solubility and also permeability into cells. A number of different solvent systems were appropriate for working with the compound, including 0.01% PEG-400 as well as 10% 1-Methyl-2 Pyrrolidinone/30%Labrasol/60%water. Data provided in FIG. 1 shows that the paclitaxel-ligand hybrid is somewhat more permeable into blood cells relative to non-hybridized paclitaxel. To obtain the data in FIG. 1, the paclitaxel-ligand hybrid or paclitaxel were added to a pooled blood sample of human blood and incubated with gentle rocking at 37°C for one hour. Next, samples were centrifuged to separate blood cells and plasma, and then these compounds were subject to organic extraction, and quantities were measured using liquid chromatography-mass spectroscopy employing a standard curve. This data addressed concerns that the larger hybrid might have lower permeability into cells which would lower efficacy since paclitaxel stabilizes tubulin inside cells.

[000157] The paclitaxel-ligand also displayed better metabolic stability compared with paclitaxel in a pharmacokinetic study performed in mice as shown in FIG. 2. To obtain the data in FIG. 2, the paclitaxel-ligand hybrid was injected into mice as shown (4 mice per data point) and the concentration assessed by LC-MS at the time points shown. The area under the curve for the paclitaxel ligand-hybrid was increased relative to paclitaxel, illustrating that it was more stable in the circulation. CremophorEL/Ethanol was used as a solvent (diluted into

normal saline) for both compounds to eliminate pk differences caused by different solvents. Importantly, the paclitaxel-ligand hybrid had comparable potency compared with paclitaxel both *in vitro and in vivo.*

[000158] After verifying comparable *in vitro* activity (data not shown), an *in vivo* study was performed as shown in FIG. 3. The tumor xenograft study established that the paclitaxel-ligand hybrid was equally effective as the parent paclitaxel *in vivo.* Observations of weight loss and behavior showed no increase in toxicity for the hybrid vs. paclitaxel (data not shown). To obtain the data in FIG. 3, an MDA-MB-435 breast cancer cell line was implanted in female athymic Nu/Nu mice. Both compounds and vehicle were dosed every other day at 20 mg/kg. As of day 39, one animal in the Paclitaxel-ligand group had no detectable tumor (N=3) for the remainder of the study.

[000159] FIG. 4 and FIG. 5 show lower axonal injury in primary cortical neurons (PCN) for the paclitaxel-ligand hybrid relative to paclitaxel. Mechanistically, paclitaxel exposure to PCN results in unusual patterns of microtubule assembly which leads to apoptosis. Intriguingly, the exposure of PCN to the paclitaxel-ligand hybrid exhibited no detectable injury to PCN neurons in this assay performed as described. To obtain the data in FIG. 4, primary cortical neurons derived from day 17 Wistar rat fetuses were prepared accordingly to a previously published protocol (Grimaldi, M. *Proc. Natl. Acad. Sci.* 1998, 95, 8268-8273). The neurons were plated in poly-lysine coated 12 well plates and allowed to settle for 48 hours. After that the cells were exposed to PBS, 0.0035% CremophorEL:ethanol (1:1) as vehicle for the other agents, Paclitaxel, and Paclitaxel-ligand. After 72 hours the cells were washed and loaded with the vital staining Calcein-AM for 20 min. Cells were observed under an inverted epifluorescence microscope equipped with a computer operated acquisition system to measure cell size, neurite outgrowth, cell branching, and other parameters as indicators of neurotoxicity. "Ligand" is a neurotoxicity lowering moiety that binds to FKBP52.

[000160] With reference to FIG. 5, images of PCN growth are provided. Images of (i) paclitaxel treated PCN's revealed fewer cell numbers and more morphological abnormalities including sparse, thick, and non-connected prolongments compared with (iv) untreated cells or (v) CremophorEL vehicle**.** In contrast, PCN's treated with a (iii) free FKBP52 ligand or the (ii) paclitaxel-ligand hybrid or (vi) paclitaxel with a non-bound FKBP52 ligand exhibited comparable cell numbers compared with untreated cells or vehicle treated cells and healthy morphology characterized by well interconnected neurite networks between cells and healthy neurite morphology.

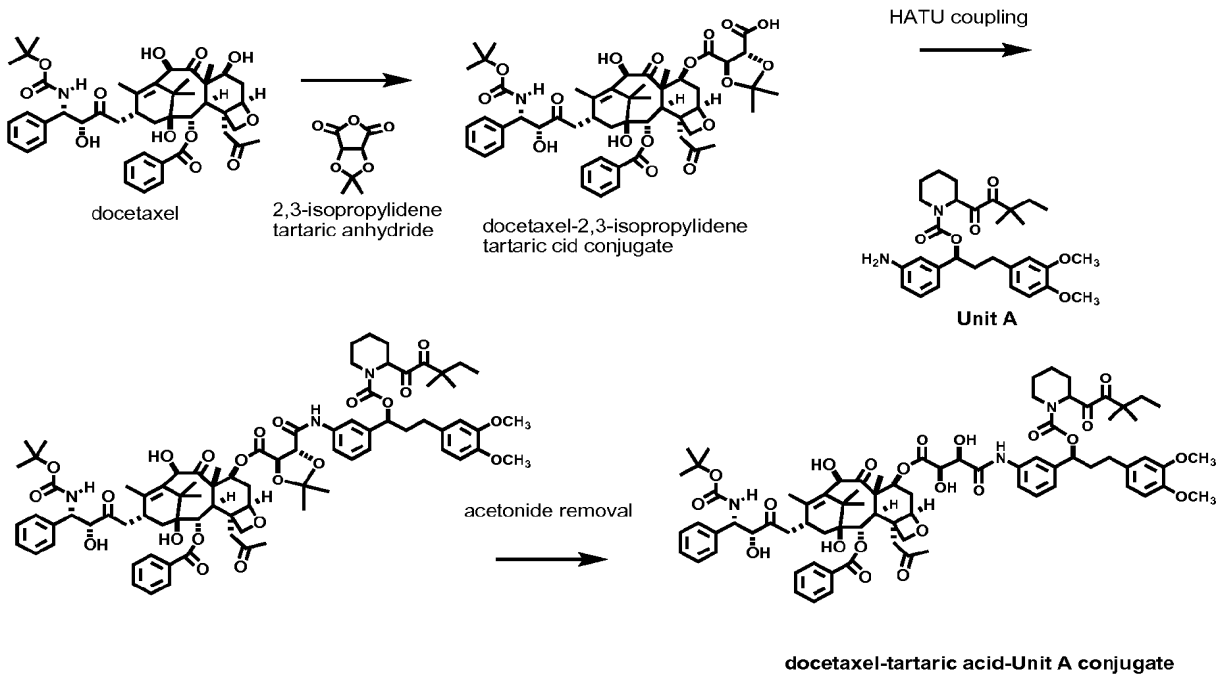
[000161] FIG. 6 shows lower neurotoxicity of the paclitaxel-ligand hybrid compared with paclitaxel as measured by cell number. Cell number data were recorded for PCNs untreated (first column) or PCNs treated with: (i) CremophorEL vehicle; (ii) paclitaxel; (iii) a paclitaxel-ligand hybrid; (iv) free FK506; (v) a paclitaxel-FK506 hybrid. PAC=paclitaxel. PAC-ligand is paclitaxel bound to a neurotoxicity lowering moiety (NLM). The cell numbers were normal for PAC-ligand and low for PAC, indicating protection from neurotoxicity conferred by the ligand, an NLM. The presence of ** indicated $P<0.001$ for the statistical significance of PAC vs. PAC-ligand data.

[000162] As mentioned herein, taxane moieties allow modification (i.e., connection of the second active moiety via a linker, when present) at the C-2, C-7, or C-10 positions. Examples of compounds having a taxane moiety linked at the C-2 position, as well as examples linked at the C-7 position were prepared according to the disclosure, and both were shown to allow good efficacy. Examples having a linkage at the C-10 position were also prepared and are described in Example 5 below.

Example 2

Synthesis of conjugates

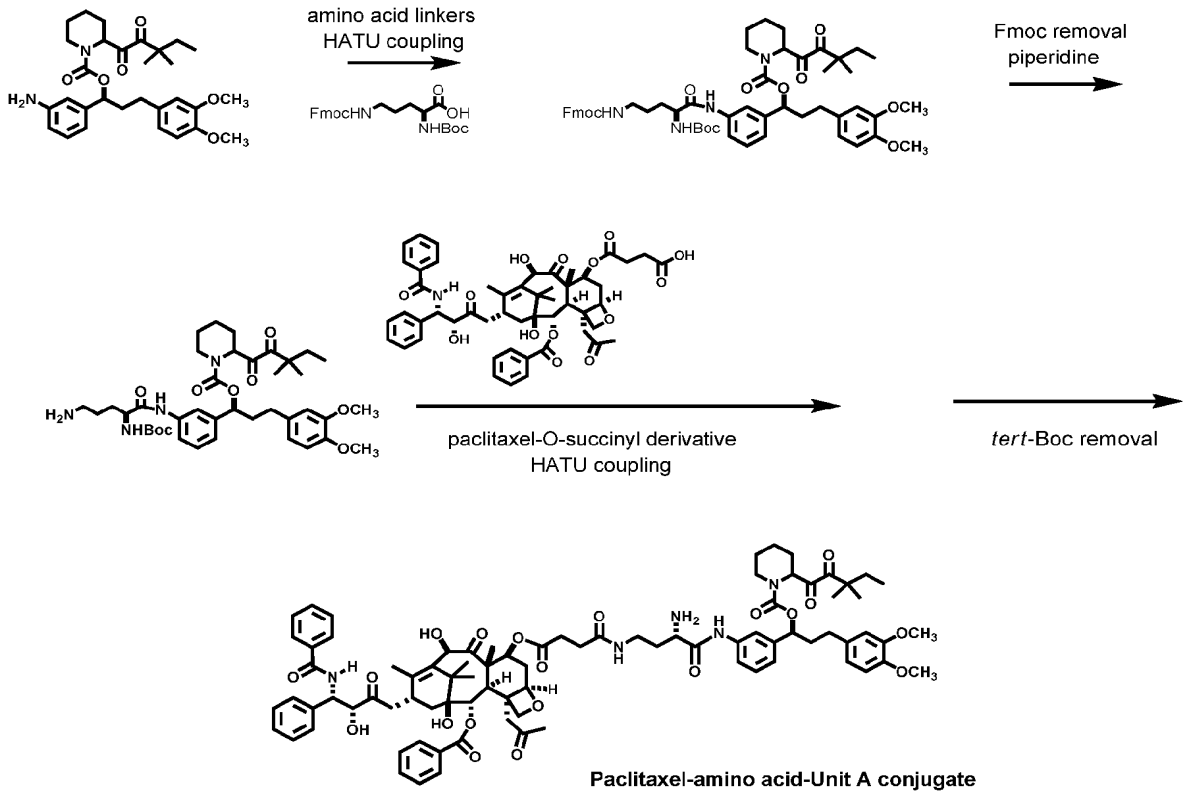
[000163] Docetaxel and docetaxel/palictaxel-related derivates conjugated to known FK506 mimics may be prepared. In one example, a conjugate of docetaxel and Unit A is prepared as shown below (Scheme 2). In the example, docetaxel and Unit A are linked via a tartaric acid linking moiety.



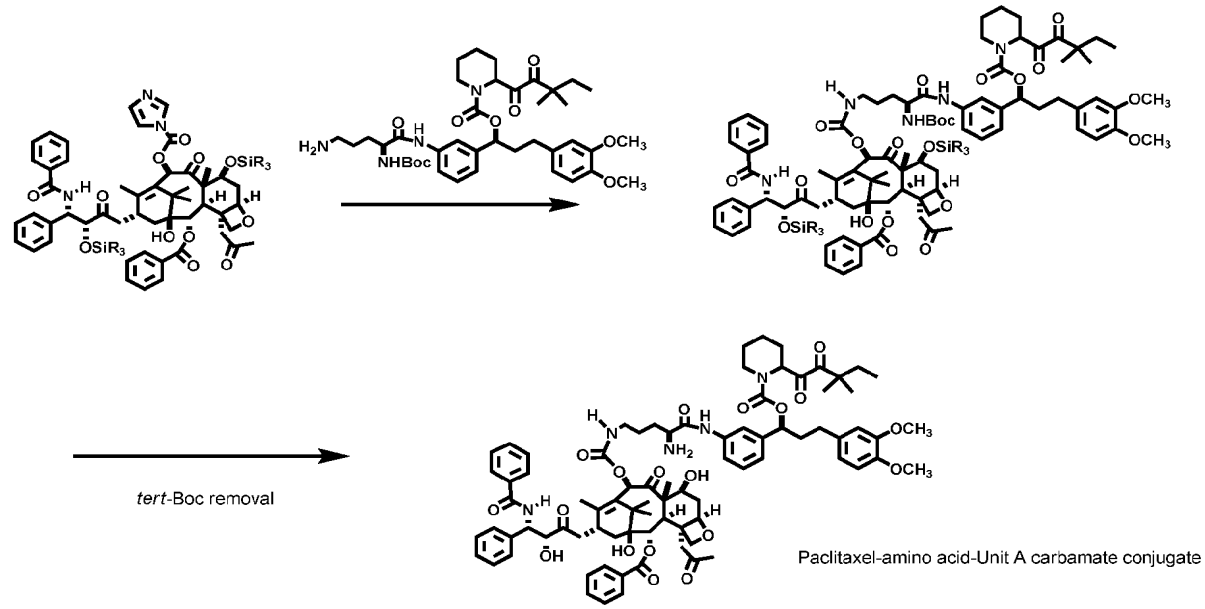
Scheme 2. Synthesis of docetaxel-tartaric acid-Unit A conjugate

[000164] Other neurotoxicity reducing moieties may be used in this chemistry to prepare additional conjugates. Employing the tartaric acid linker moiety is designed to improve the overall solubility of the conjugates, but other linkers as described herein may be used.

[000165] Other docetaxel and docetaxel/palictaxel-related derivates conjugated to known FK506 mimics may also be prepared through the use of solubilizing amino-acid linkers. Examples are shown below in Schemes 3 and 4.



Scheme 3. Synthesis of paclitaxel-amino acid-Unit A conjugate

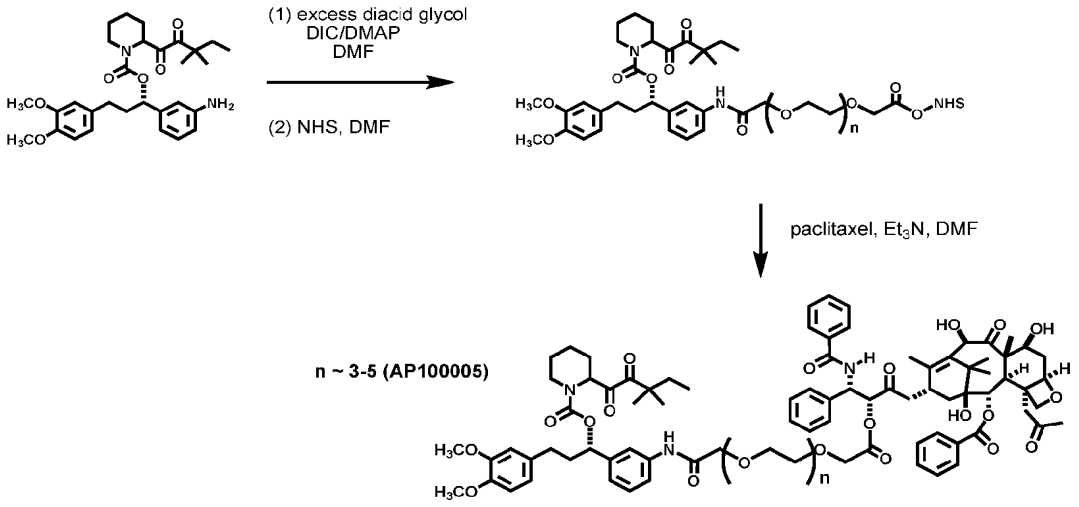


Scheme 4. Synthesis of paclitaxel-amino acid-Unit A conjugate

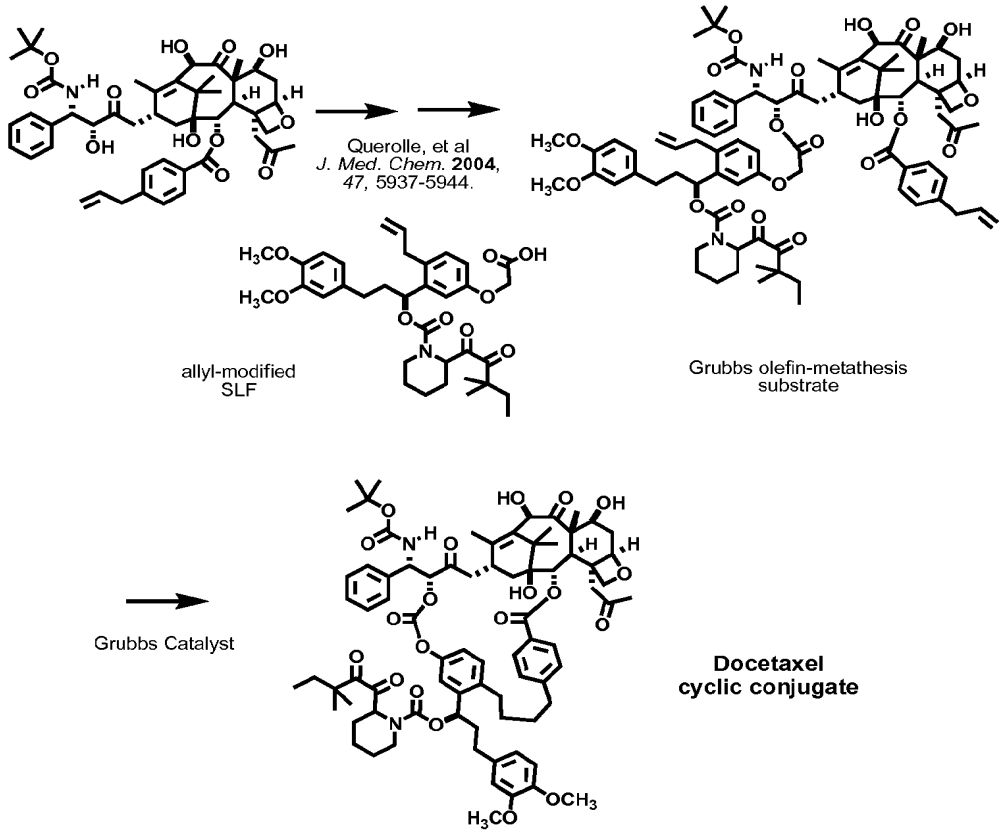
Example 3

Synthesis of conjugates

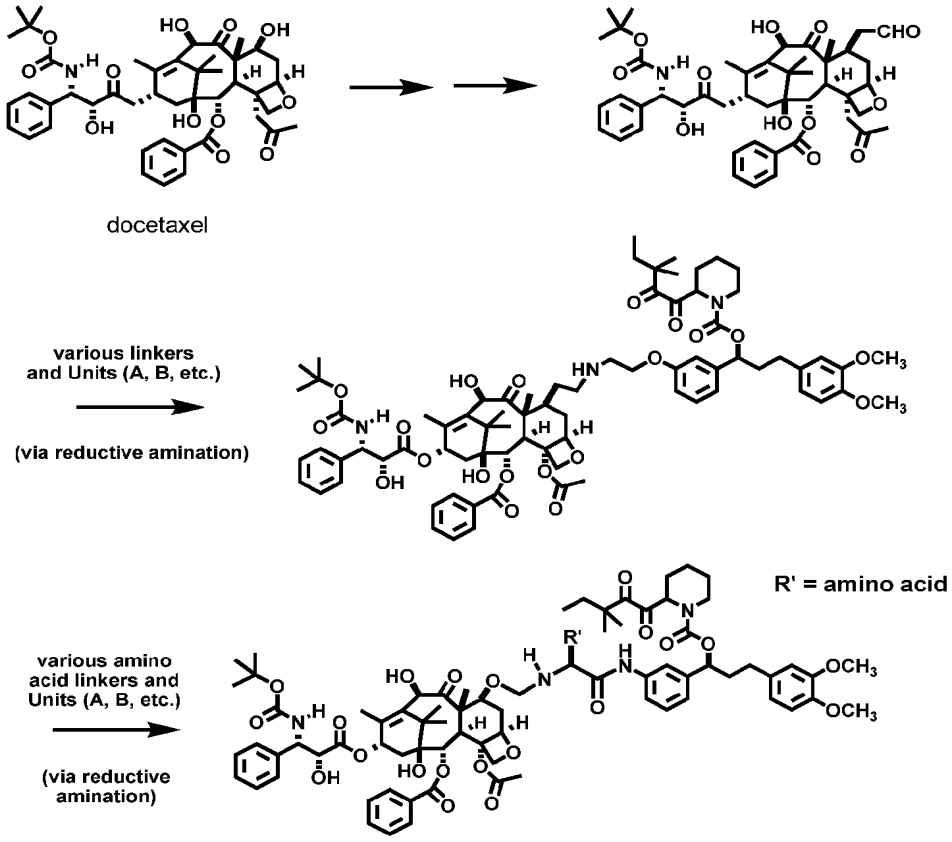
[000166] Further conjugates may be prepared as shown in the following Schemes.



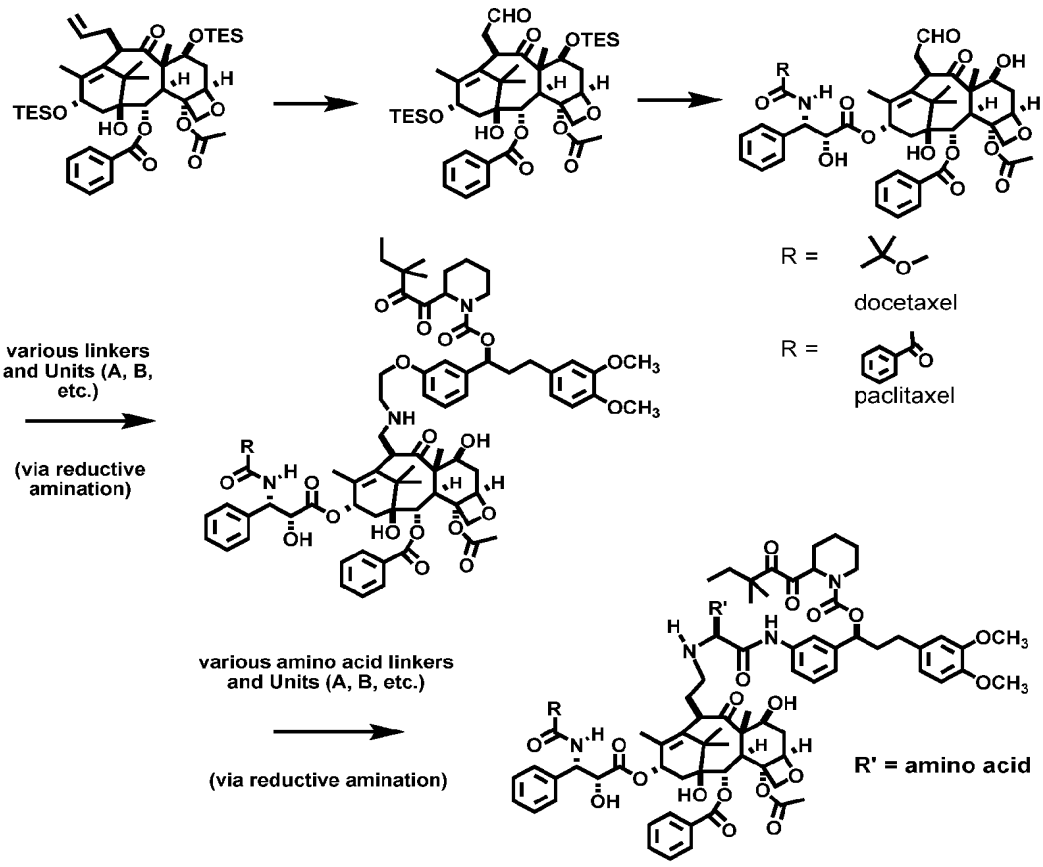
Scheme 5. Synthesis of paclitaxel conjugate



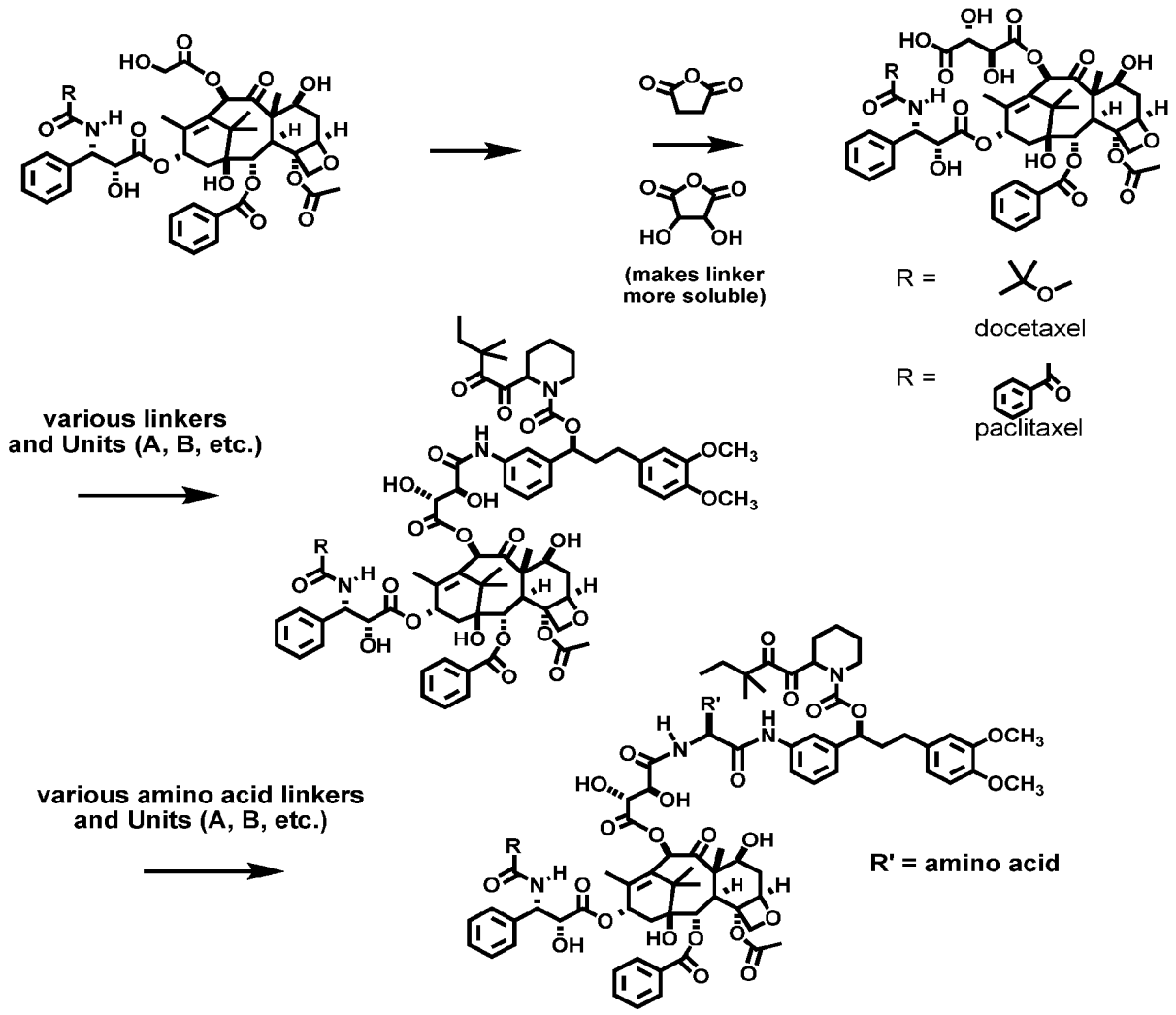
Scheme 6. Synthesis of docetaxel conjugate



Scheme 7. Synthesis of docetaxel conjugate



Scheme 8. Synthesis of taxane conjugates

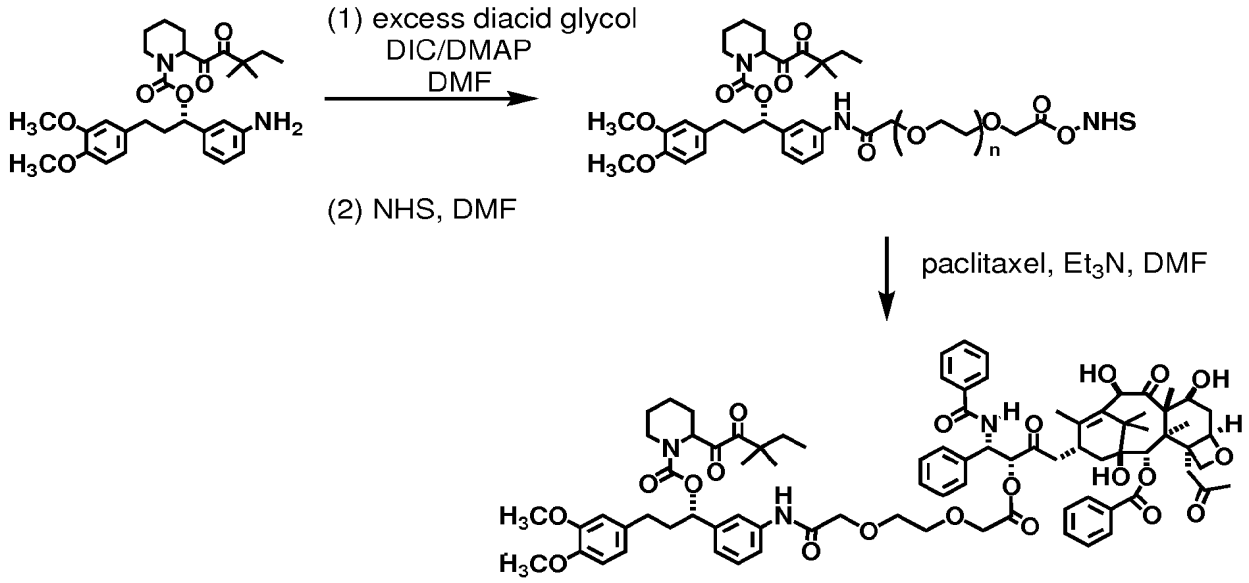


Scheme 9. Synthesis of taxane conjugates

Example 4

Synthesis and efficacy of conjugates

[000167] Further conjugates were prepared and subjected to tests of efficacy. Scheme 10 shows a synthetic route used to prepare one such compound.

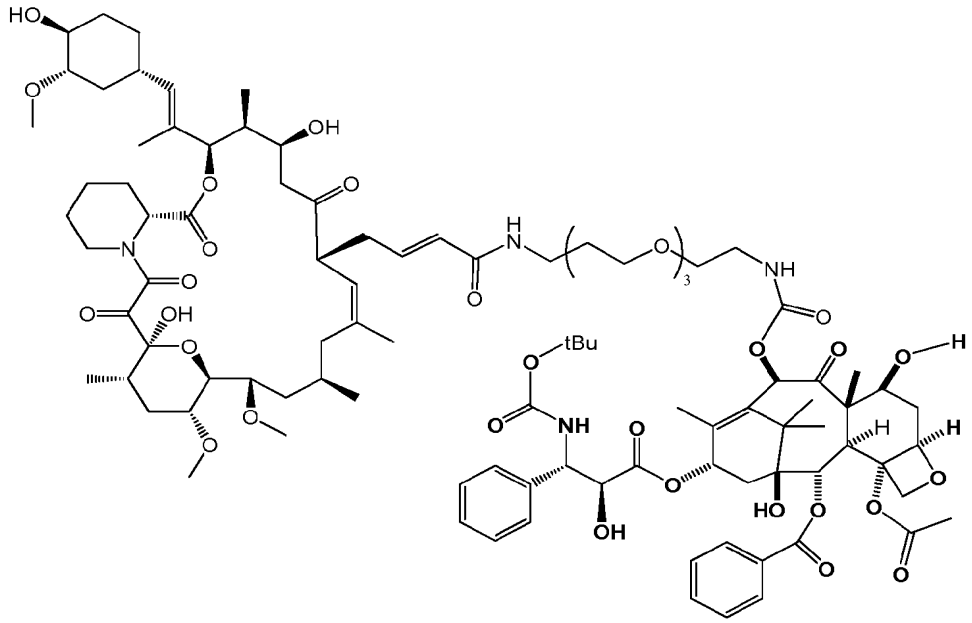


Scheme 10. Synthesis of paclitaxel conjugate

Example 5

Efficacy of conjugates

[000168] Further conjugates were prepared and subjected to tests of efficacy. One such taxane derivative, compound **(2)**, showed remarkable potency and low neurotoxicity in a cell model. The structure of **(2)**, shown below in **Scheme 11**, uses a taxane modified at the 10' position.



Compound **(2)**

Scheme 11.

[000169] This compound represents a departure from prior taxanes in the literature and poses some challenging features. Notable, a very polar linker has been attached to help improve solubility of this notoriously insoluble class of compounds. It would be expected that a bulky, soluble linker would also compromise efficacy due to decreased permeability across cell membranes. Moreover, the large moiety attached to the taxane, an analogue of FK506, would also be expected to pose a challenge in hindering the taxane moiety from interacting with tubulin, the intracellular target.

[000170] Surprisingly, the bulky FK506 analogue and polar linker did not hinder the ability of **(2)** to inhibit the growth of three different cancer cell lines compared to paclitaxel. Data shown in FIG. 7 are a comparison of **(2)** vs. paclitaxel. As can be seen, the activities of paclitaxel and **(2)** are the same vs. the SKOV3 ovarian cancer cell line. The IC_{50} value for Paclitaxel and for **(2)** were both found to be 1 nM. Similar results were obtained from both a lung cancer cell line, PC3, and a breast cancer cell line, MCF7. (Data was obtained by treating cells at the concentrations shown and then assessing viability).

[000171] In contrast with the high potency against this cancer cell line, the observed toxicity when **(2)** is used to treat primary cortical neurons is similar to untreated cells, as shown in FIG. 8. Primary cortical neurons were obtained from fetal rats. Cells were either untreated, exposed to cremophor (vehicle), or treated with 10 nM paclitaxel, 20 nM

compound **(2)**, 20 nM paclitaxel, or 10 nM FK506 for three days prior to assessing neurite outgrowth *via* optical methods or cell viability using a viability fluorescent stain. The data show that at 20 nM compound **(2)**, the neurite outgrowth is equivalent to untreated cells or cells treated with vehicle. However, paclitaxel severely lowers the average neurite outgrowth.

[000172] Similar results are obtained when viable cells are measured, as shown in FIG. 9**.** Cells were treated with compounds as described above with reference to FIG. 8, and viable cells were counted after treatment with a cell viability stain. The number of viable cells treated with **(2)** is similar to untreated cells. However, the cell number of paclitaxel treated cells is 10-fold lower relative to **(2)**-treated cells.

Example 6

In vivo study

[000173] A test compound, "paclitaxel-ligand" (which has the structure of Compound **(1)**), showed evidence of producing significantly less neuropathic pain (NP) *in vivo* in a rat model. Compounds were injected i.p. and animals were evaluated using von Frey filaments for allodynia and heat for thermal hyperalgesia (not shown). The dosage used is at the known LD_{50} for i.p. injected paclitaxel in rats. For the data shown in FIG. 10, *** and ** indicate $p<.001$ and $p< .01$, respectively, for the Bonferroni post-test following RM two-way ANOVA between paclitaxel and vehicle control. Kruskal Wallis analysis between paclitaxel and paclitaxel-ligand gave $p< .005$. The study was perfomed in male Wistar rats and the evaluations used the "up-down" methodology (Chaplan, S. et al. J Neurosci Methods 1994; 53: 55–63) employing 10 animals per group.

Claims

What is claimed is

1. A method for lowering the neurotoxic effects of a neurotoxicity producing therapeutic active moiety upon administration to a host, the method comprising:

administering to the host an effective amount of a hybrid compound of less than about 15,000 Daltons comprising the therapeutic active moiety or an active derivative, fragment or analog thereof and a neurotoxicity lowering moiety,

wherein the neurotoxicity lowering moiety binds to at least one neurotoxicity lowering biomoiety and substantially reduces at least one neurotoxicity symptom.

2. The method according to claim 1, wherein the compound is administered as a pharmaceutical formulation, and wherein the pharmaceutical formulation does not contain CremophorEL.

3. The method of claim 1, wherein the therapeutic active moiety is an anticancer therapeutic moiety.

4. The method according to claim 3 where the anticancer therapeutic moiety is a taxane analog.

5. The method according to claim 1, wherein the neurotoxicity symptom is chemically induced peripheral neuropathy.

6. The method according to claim 1, wherein the neurotoxicity lowering moiety has a dissociation constant of less than 10 μM with an FKBP protein or with a heat shock protein.

7. The method according to claim 1, wherein the compound further comprises a linking moiety that forms a covalent bond with the therapeutic active moiety and a covalent bond with the neurotoxicity lowering moiety.

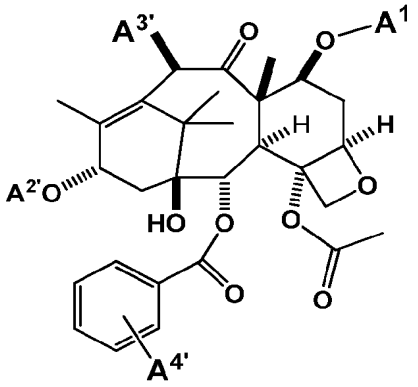
8. A compound comprising a taxane moiety covalently attached either directly or through an optional linking moiety to a neurotoxicity lowering moiety.

9. The compound of claim 8, wherein the neurotoxicity lowering moiety is a neurotrophic ligand and targets an FKBP protein or a heat shock protein.

10. The compound of claim 8, wherein the taxane moiety is covalently linked through the oxygen at the C2, C7, or C10 position to the neurotoxicity lowering moiety or, when present, to the linking moiety.

11. The compound of claim 8, wherein the compound has the structure of formula (I)

(I)



wherein:

$A^{2'}$ is selected from H, hydrocarbyl, substituted hydrocarbyl, heteroatom-containing hydrocarbyl, and substituted heteroatom-containing hydrocarbyl, provided that $A^{2'}$ optionally comprises the moiety A^2;

$A^{3'}$ is selected from $-O-A^3$ and $-A^3$;

one of A^1, A^2, A^3, and A^4 is selected from –U and –L–U, and the others are selected from H, and alkyl, provided that A^4 may be taken together with A^2 to form a cycle;

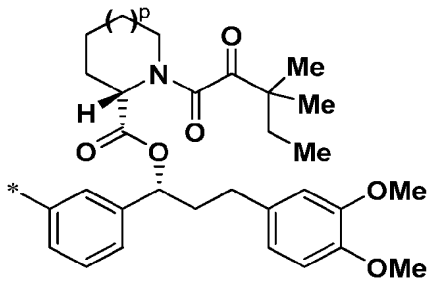
L is the linking moiety; and

U is the neurotoxicity lowering moiety.

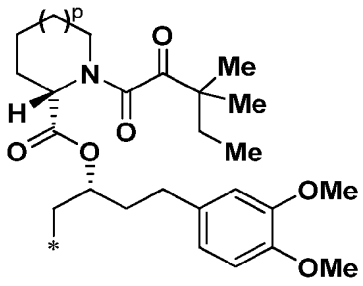
12. The compound of claim 11, wherein R is selected from alkyl, alkoxy, aryl, and aryloxy.

13. The compound of claim 11, wherein A^1 is selected from H and methyl, A^2 is H, and A^4 is H.

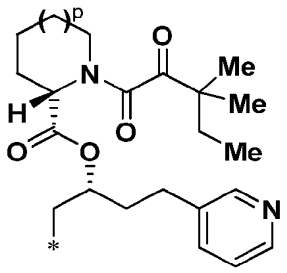
14. The compound of claim 11, wherein U is selected from Units A, B, C, D, E, and F:



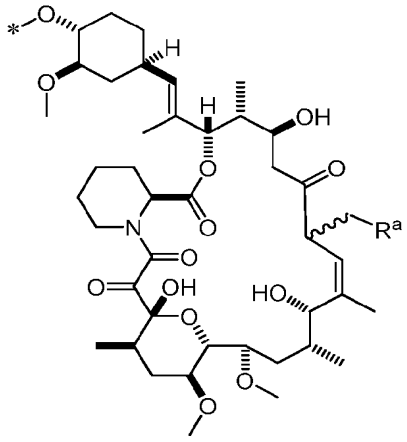
Unit A



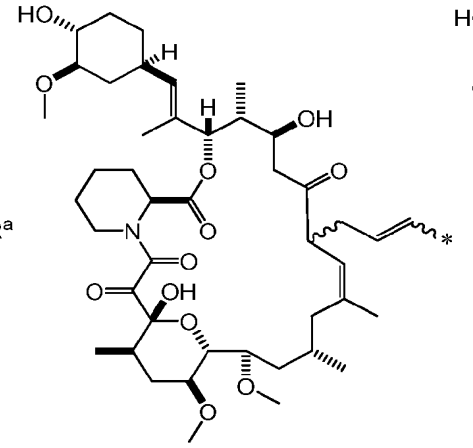
Unit B



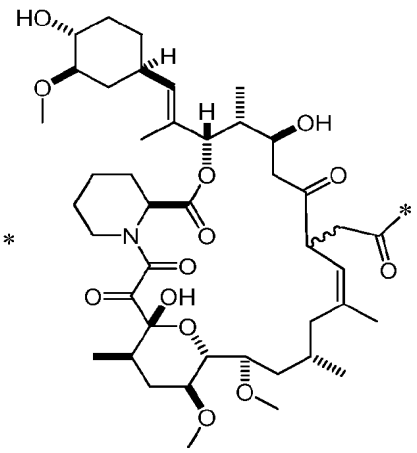
Unit C



Unit D



Unit E



Unit F

wherein:

p represents an integer from 0 to 2;

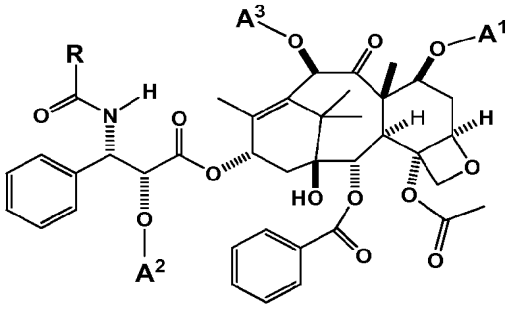
R^a is selected from hydrocarbyl groups; and

the stars represent the point of connection to the first active moiety or, when present, the linking moiety.

15. The compound of claim 11, wherein L is selected from alkylene, amides, ureas, sulfoxides, sulfonamides, amines, carbonyls, ethers, amide/urea combinations, amide/amide combinations, sulfoxide/ether combinations, amide/ether combinations, amine/ether combinations, amide/amine combinations, and carbonyl/amide combinations, any of which may include unsaturated or saturated segments.

16. The compound of claim 11, wherein the compound has the structure of formula (Ia)

(Ia)



wherein

R is selected from hydrocarbyl, substituted hydrocarbyl, heteroatom-containing hydrocarbyl, and substituted heteroatom-containing hydrocarbyl;

one of A^1, A^2, and A^3 is selected from –U and –L–U, and the others are selected from H, and alkyl.

17. A method for reducing the neurotoxicity of a taxane compound, the method comprising covalently bonding the taxane to a neurotoxicity-lowering moiety either directly or through an optional linking moiety to form a hybrid compound.

18. The method of claim 17, wherein the taxane is selected from paclitaxel, docetaxel, and cabazitaxel.

19. The method of claim 18, wherein the optional linker is present and comprises a polyether moiety.

20. The method of claim 17, wherein the hybrid compound exhibits a lower incidence of chemically-induced peripheral neuropathy compared with the taxane compound when administered to a human host.

21. A method for treating cancer in a patient, the method comprising administering to the patient an effective amount of a compound comprising a taxane moiety covalently attached either directly or through an optional linking moiety to a neurotoxicity lowering moiety.

22. The method of claim 21, wherein the cancer is selected from lung, ovarian, breast cancer, head and neck cancer, Kaposi's sarcoma, chronic lymphocytic leukemia, hepatoma, prostate cancer, glioma, acute lymphoblastic leukemia, melanoma, and glioma.

23. The method of claim 22, wherein the cancer is resistant to one or more taxane compounds.

FIG. 1

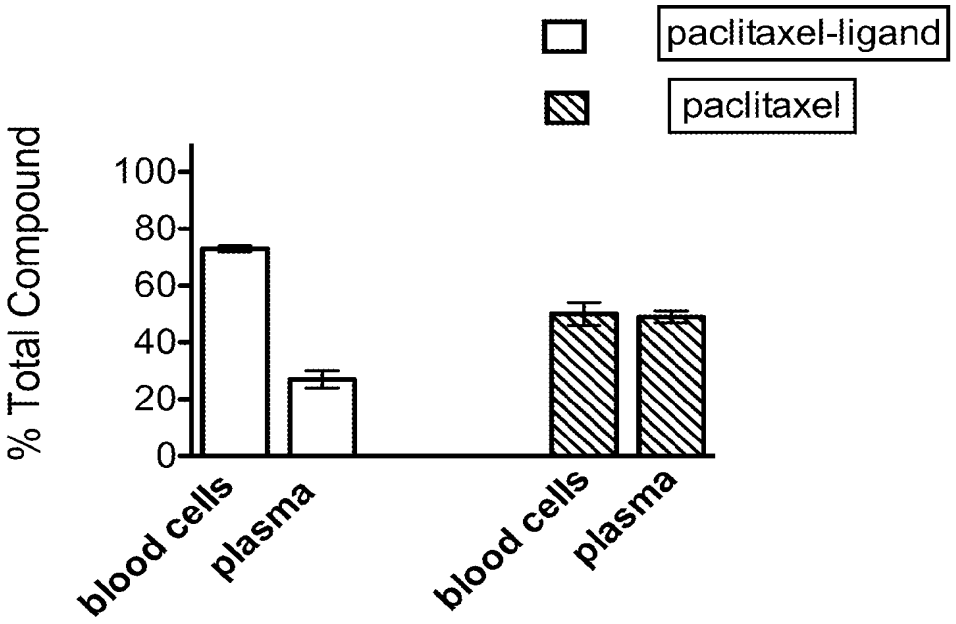

paclitaxel-ligand
paclitaxel
% Total Compound
100
80
60
40
20
0
blood cells
plasma
blood cells
plasma

FIG. 2

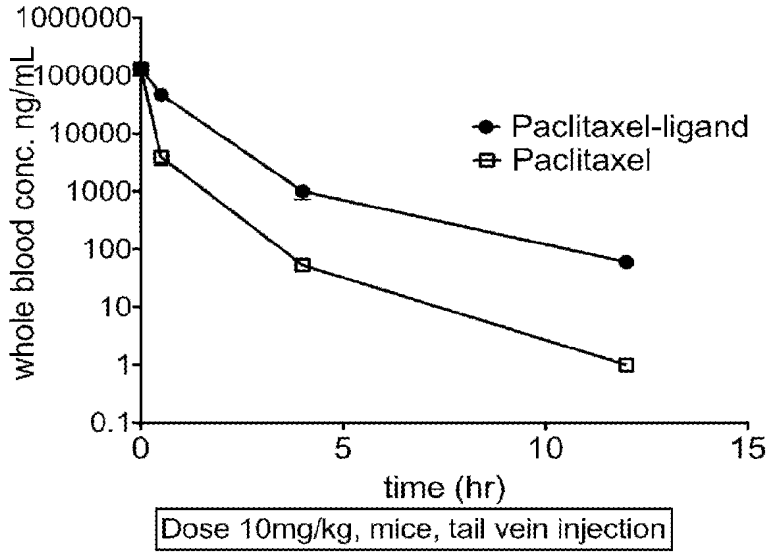

1000000
100000
10000
1000
100
10
1
0.1
whole blood conc. ng/mL
Paclitaxel-ligand
Paclitaxel
0
5
10
15
time (hr)
Dose 10mg/kg, mice, tail vein injection

FIG. 3

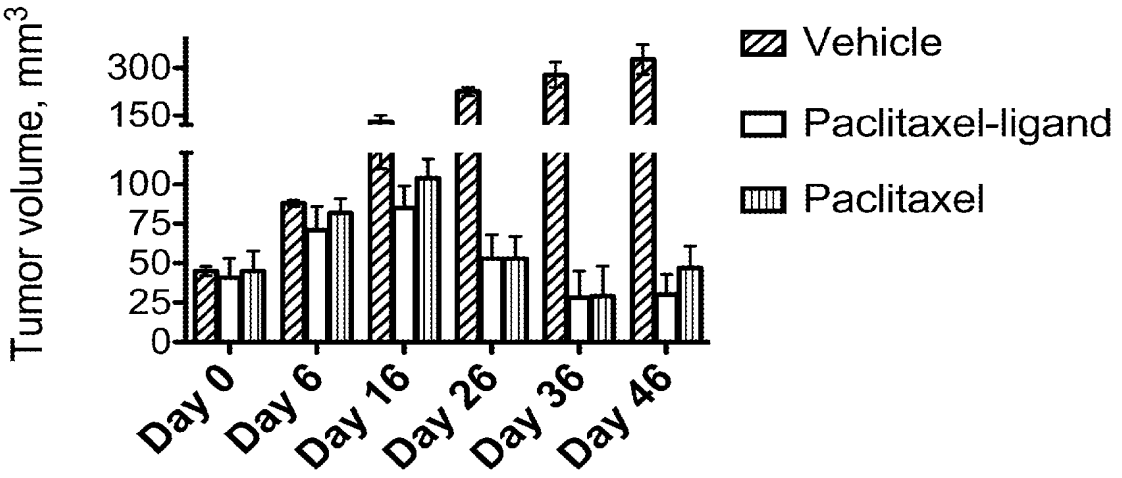

Tumor volume, mm3
300
150
100
75
50
25
0
Day 0
Day 6
Day 16
Day 26
Day 36
Day 46
Vehicle
Paclitaxel-ligand
Paclitaxel

FIG. 4

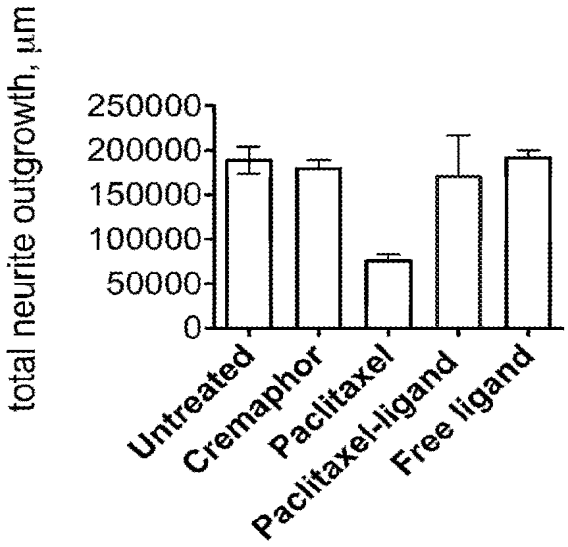
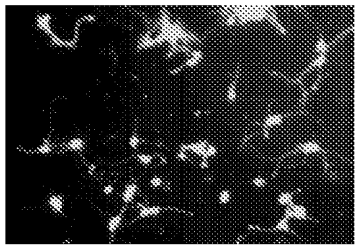
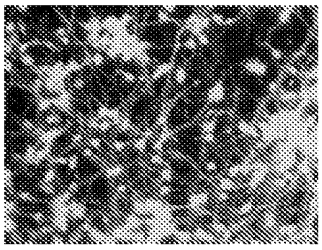

total neurite outgrowth, µm
250000
200000
150000
100000
50000
0
Untreated
Cremaphor
Paclitaxel
Paclitaxel-ligand
Free ligand

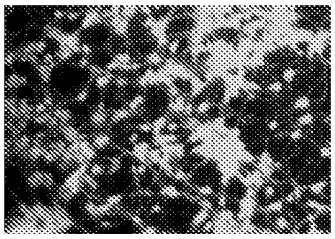
FIG. 5



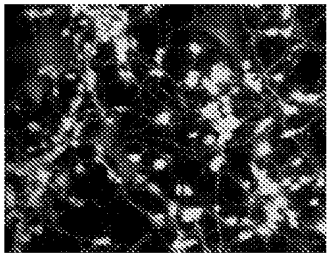
(i) Paclitaxel



(ii) Paclitaxel-ligand hybrid

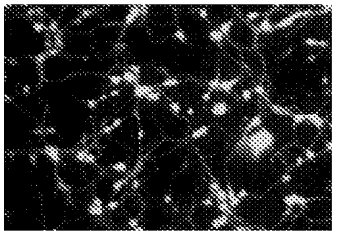


(iii) free ligand



(iv) Untreated

(v) Cremophor



(vi) Paclitaxel + free FKBP52 ligand

FIG. 6

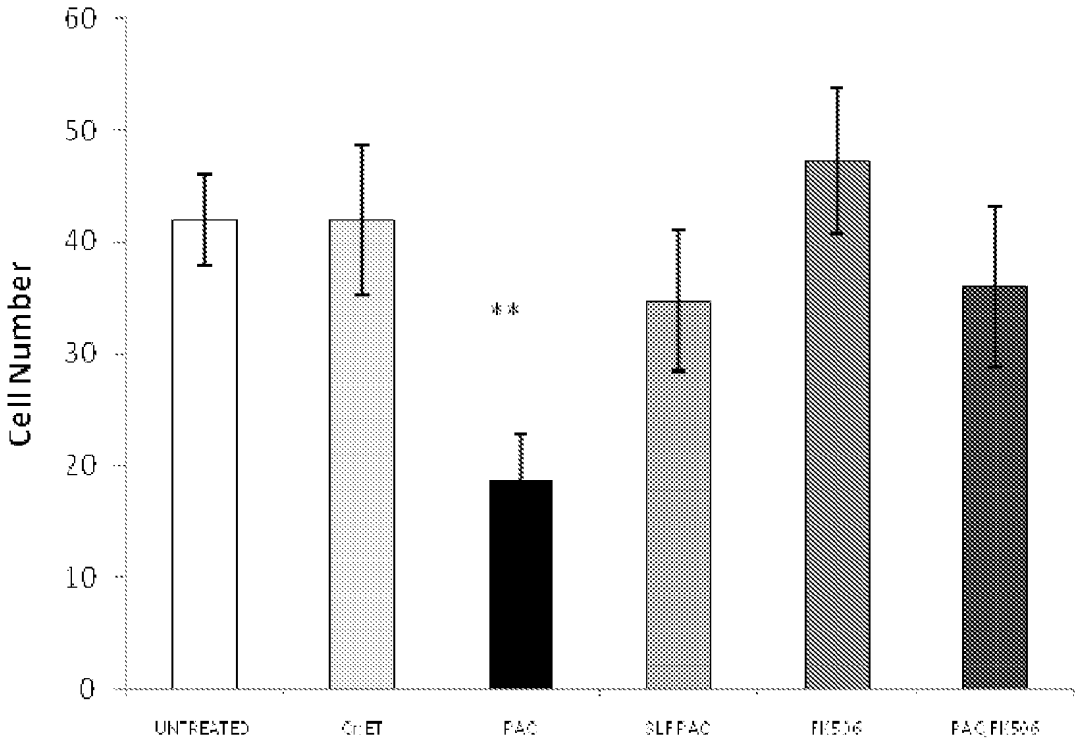

60
50
40
30
20
10
0
Cell Number
**
UNTREATED
CrET
PAC
SLFPAC
FK506
PAC,FK506

FIG. 7

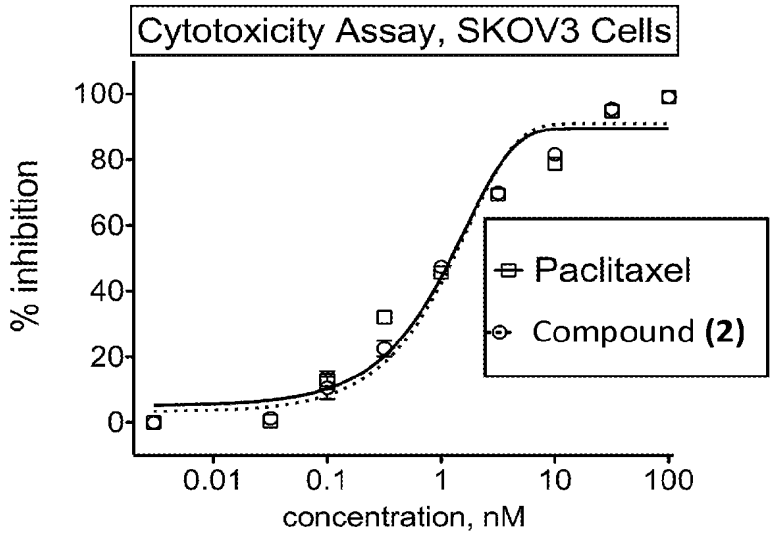

Cytotoxicity Assay, SKOV3 Cells
% inhibition
100
80
60
40
20
0
0.01
0.1
1
10
100
concentration, nM
Paclitaxel
Compound (2)

FIG. 8

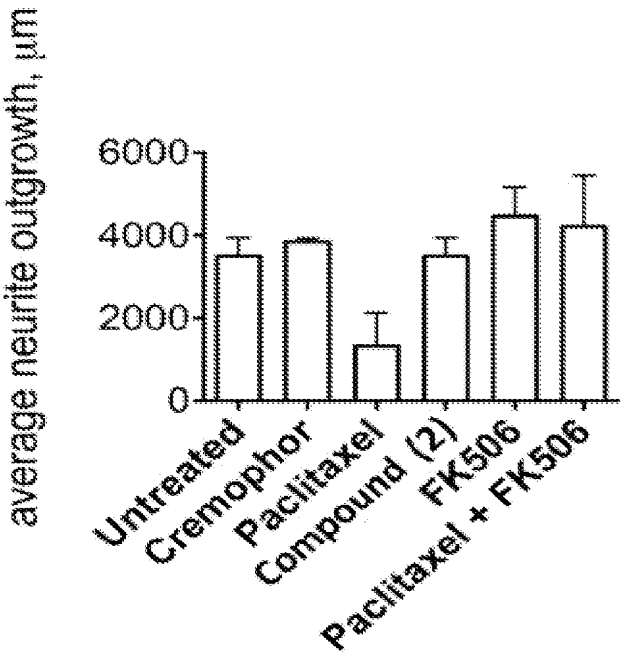

average neurite outgrowth, μm
6000
4000
2000
0
Untreated
Cremophor
Paclitaxel
Compound (2)
FK506
Paclitaxel + FK506

FIG. 9

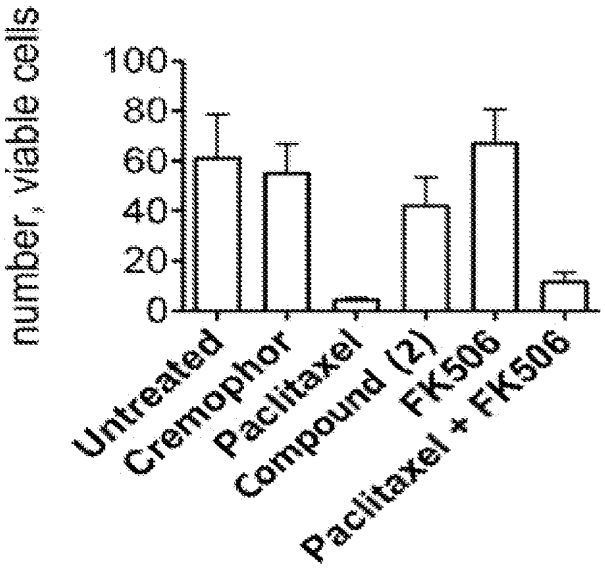
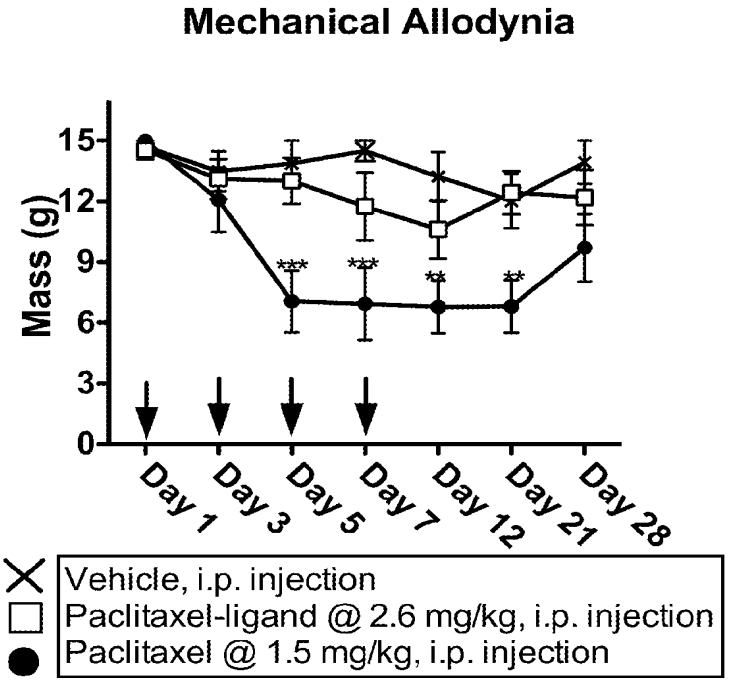

number, viable cells
100
80
60
40
20
0
Untreated
Cremophor
Paclitaxel
Compound (2)
FK506
Paclitaxel + FK506

FIG. 10



*** P<0.001, ** P<0.01 (RM-Two way ANOVA, comparison with vehicle control). Kruskal Wallis analysis between paclitaxel and paclitaxel-ligand gave p< .005.

● 症 例 ●

Docetaxel＋Prednisolone療法が著効し腫瘍熱が軽快したホルモン抵抗性前立腺癌の1例

三浦 徳宣 沼田 幸作 東 浩司 橋根 勝義 住吉 義光*

〔*Jpn J Cancer Chemother* 33(6): 841~844, *June*, 2006〕

A Case of Hormone-Refractory Prostate Cancer (HRPC) with Tumor Fever Responding to Docetaxel Plus Prednisolone Therapy: Noriyoshi Miura, Kosaku Numata, Koji Azuma, Katsuyoshi Hashine and Yoshiteru Sumiyoshi (*Dept. of Urology, Shikoku Cancer Center*)

Summary

We have experienced a patient with tumor fever from hormone-refractory prostate cancer (HRPC) who was treated successfully using docetaxel plus prednisolone therapy.

A 65-year-old male was diagnosed with prostate cancer (T4 N1 M1b). He received androgen-ablation therapy. But six months later he was confirmed to show failure of the previous hormone therapy and disease progression even after anti-androgen withdrawal. Then docetaxel plus prednisolone therapy was started. After two courses of this therapy, the PSA level decreased by 50% or more, and after ten courses an improvement was seen on the bone scan. The patient has survived for twelve months after starting docetaxel plus prednisolone therapy, without serious adverse events. **Key words**: Hormone-refractory prostate cancer (HRPC), Docetaxel, Tumor fever

(*Received Sep. 20, 2005/Accepted Dec. 15, 2005*)

要旨 腫瘍熱を呈したホルモン抵抗性前立腺癌に対し，docetaxel＋prednisolone療法が有効であった症例を経験した。症例は65歳。前立腺癌（T4 N1 M1b）と診断，ホルモン療法（LH-RH agonist単独治療）を開始した。半年後に再燃のため，アンチアンドロゲン剤を追加投与したが効果を認めず，骨転移の増悪，38℃前後の腫瘍熱も出現した。ホルモン抵抗性前立腺癌と診断し，docetaxel＋prednisoloneによる治療を開始した。開始2日目より腫瘍熱は消失し，2コース終了時点でPSAは開始前の50%以上の減少を認め，10コース終了時点で骨転移の改善もみられ効果判定はPRであった。また本治療は，3コース目より外来通院で行うことができており，現在も治療を継続している。

はじめに

前立腺癌Stage D2においてはホルモン治療が選択され，約80%で効果があるといわれている。しかしながら，ホルモン治療も平均2~3年でホルモン抵抗性となるといわれており，このような再燃癌をいかに治療してゆくかが重要な課題となっている[1,2]。

現在，ホルモン抵抗性前立腺癌に対する様々な化学療法の臨床試験が行われており，そのなかでもdocetaxelの有効性が二つの無作為化比較試験で示されている[3,4]。

今回われわれは，docetaxel＋prednisolone療法が奏効したホルモン抵抗性前立腺癌の1例を経験したので報告する。

I. 症 例

症例: 65歳，男性。

主訴: 排尿障害。

家族歴: 兄，前立腺癌。

既往歴: 高血圧，糖尿病。

現病歴: 2002年12月ごろより排尿困難あり，近医を受診した。PSA 179.3 ng/ml と上昇を認め当科紹介され受診した。直腸診では，全体に石様硬，表面不整，前立腺生検で両葉より癌を認めた（グリソンスコア 5＋4＝9）。画像所見より前立腺癌，膀胱浸潤，所属リンパ節転移，骨転移あり（T4 N1 M1b）と診断，2003年5月よりホルモン療法（LH-RH agonist単独治療）を開始した。

連絡先: 〒790-0007 松山市堀之内13 * 国立病院機構四国がんセンター・泌尿器科
三浦 徳宣

0385-0684/06/¥500/論文/JCLS

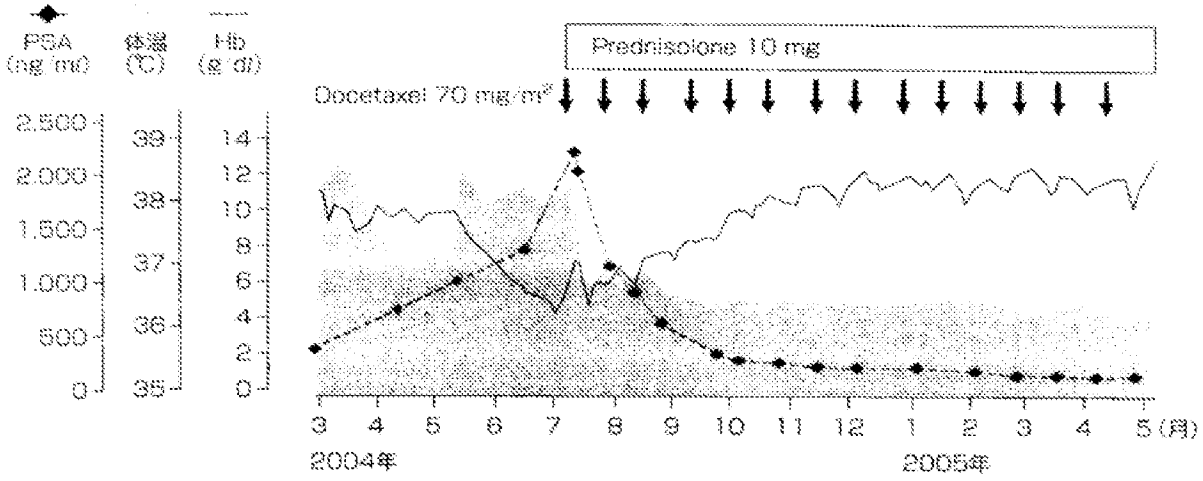


図 1　PSA 再燃後の PSA，体温，Hb の経過

図 2　胸部 CT
a：化学療法前，b：化学療法 10 コース後

2003 年 11 月に PSA 19.3 ng/ml まで低下したが，2004 年 1 月 PSA が 3 回連続上昇し，アンチアンドロゲン剤の追加投与を開始したが効果を認めなかった。同年 3 月ごろより高熱が出現し，インフルエンザとして近医で治療を受けたが軽快なく血液腫瘍の疑いにて当院内科入院した。精査の結果，感染巣はなく，ガリウムシンチグラフィ，骨髄穿刺検査で血液腫瘍疾患も否定され，前立腺癌腫瘍熱と診断，ステロイド内服が開始された（prednisolone 10 mg）。解熱傾向を認めたが糖尿病が悪化し，ステロイドを中止した。中止後より再び 38℃前後の発熱が続くため，2004 年 7 月，docetaxel＋prednisolone 療法目的にて当科入院した。

入院時血液検査所見：WBC 4,400/μl，RBC 226×10⁴/μl，Hb 5.8 g/dl，Hct 19.0%，Plt 21.8×10⁴/μl，分画：St 7.0%，Seg 64.0%，Mono 5.5%，Eos 2.0%，Baso 1.0%，Ly 17.0%，Meta-my 2.0%。

生化学検査：TP 6.5 g/dl，Alb 3.3 g/dl，ALP 1,037 IU/l，LDH 778 IU/l，BUN 24.7 mg/dl，CRE 0.92 mg/dl，血糖値 203 mg/dl，CRP 5.75 mg/dl，PSA 2,100 ng/ml。

入院時画像所見：骨シンチグラムで骨転移の増悪，CT で肋骨転移に伴い腫瘤形成を認めた。

治療経過：docetaxel＋prednisolone 療法は，day 1 に docetaxel 100 mg（70 mg/m²）静注，また同日朝より prednisolone 10 mg 分 2 内服を 21 日間連日投与を 1 コースとし，開始した。続いていた発熱は治療開始翌日より解熱し，以後まったく発熱はなかった。PSA は，治療前 2,100 ng/ml あったものが，1 コース終了時 1,064 ng/ml，2 コース終了時 831.74 ng/ml と 50%以上の減少を認めた。以後 PSA は減少を続け，14 コース終了時点で PSA 77.575 ng/ml まで低下した。また，治療開始後，貧血の著明な改善も認めた。図 1 に本治療開始前後の体温，PSA，Hb の経過を示した。10 コース終了時点での効果判定は，PSA は 94.5%の減少，CT 上肋骨転移に伴い形成されていた軟部腫瘤の 44%の縮小（図 2），骨シンチグラムで改善傾向（図 3）を認め，partial response（PR）と評価した。有害事象は，National Cancer Institute-Common Toxicity Criteria Version 3（NCI-CTC Ver. 3）で評価し，grade 3，4 の好中球減少を認めた。これは，docetaxel 投与 6～10 日後にみられており，G-CSF の投与により速やかに軽快している。その他の有害事象は重篤なものはなく，本治療は 3 コース目より外来

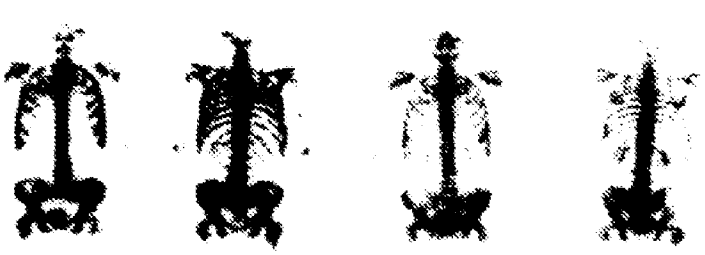


図3　Bone scintigram
a：化学療法前，b：化学療法10コース後

通院にて継続中である。なお，血糖も内服治療で良好にコントロールされている。

II．考　察

ホルモン抵抗性前立腺癌は，一般に再燃後の生存期間の中央値は10～12か月であり，有効な治療は報告されていなかった[1]。そのような状況のなか生存期間には差がなかったものの，mitoxantroneとprednisone併用とprednisone単独治療の無作為化試験において，前者において有意に痛み，QOLの改善を認めたとの報告があった[2,5]。さらに最近QOLの改善に加え，生存期間の延長についてdocetaxelの有効性が二つの無作為化比較試験により示された[3,4]。日本でもdocetaxelを使用した臨床試験が行われており，その有効性が示されてきている[7,8]。

今回，腫瘍熱を有するホルモン抵抗性前立腺癌において，PSA，骨シンチグラフィ，CTにて効果判定でPRを示した。また腫瘍熱と予後の関係については明らかではないが，腫瘍熱，貧血の改善からQOLの改善も認められた。治療開始後約12か月間，再燃の兆候はなく生存期間の延長も期待できると思われる。

効果判定について前立腺癌はその多くは骨転移を来し，広範囲転移を有するホルモン抵抗性前立腺患者できえ実質臓器への転移は10%未満といわれている[9]。したがって測定可能病変が存在する症例が少ないため，化学療法の効果判定についてPSA値により評価していることが多い。このPSAの改善が効果と相関するかという問題について，Kellyらは110例の再燃癌症例の近接効果において，PSA 50%以上低下した症例では生存期間が延長したと報告している[10]。また，Smallらも同様の報告をしており[11]，ホルモン抵抗性前立腺癌の50%以上のPSA低下を治療効果判定で使用することで一致してきている。

有害事象について，Tannockらの報告ではdocetaxel＋prednisone患者で最もみられる有害事象は好中球減少であり，NCI-CTC Ver. 3，grade 3，4の好中球減少が332例中，32%に認められたが，敗血症はまれ(3%)であったと報告している。また，その他の有害事象もそのほとんどが低gradeであったとしている[4]。今回の症例も，grade 3，4の好中球減少がみられたが，nadirの時期がdocetaxel投与後6～10日の間でほぼ一致しており，G-CSFにより容易に改善したため，外来通院にてコントロール可能であった。

docetaxel＋prednisolone療法は，効果判定でPRであり，QOLの改善にも有効であった。有害事象についても重大な副作用も少なく，また外来通院で安全に治療を行うことが可能であった。今後のホルモン抵抗性前立腺癌の治療法として有望であると思われた。

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OPINION

Can the pharmaceutical industry reduce attrition rates?

Ismail Kola and John Landis

The pharmaceutical industry faces considerable challenges, both politically and fiscally. Politically, governments around the world are trying to contain costs and, as health care budgets constitute a very significant part of governmental spending, these costs are the subject of intense scrutiny. In the United States, drug costs are also the subject of intense political discourse. This article deals with the fiscal pressures that face the industry from the perspective of R&D. What impinges on productivity? How can we improve current reduced R&D productivity?

The average life expectancy of humans has gone up from about 45 years of age at the start of the twentieth century to about 77 a century later. This is a consequence of a number of factors, including increased medical knowledge, better technologies and surgical techniques, better health care, better public health and the discovery of drugs such as aspirins, antibiotics, the statins, and numerous other such innovative and crucial medicines from the pharmaceutical industry. However, the current challenges facing the pharmaceutical industry are unprecedented in its history. Perhaps most foremost among these are the industry's lower revenue growth, poor stock performance, the lowest number of new chemical entities (NCE) approvals and the poor late-stage R&D pipelines prevalent throughout the industry.

In 2002, overall top-line revenue growth in the pharmaceutical industry was just 8% and improved only slightly in 2003 to approximately 9%. Similarly, in 2003 large pharma stock prices were among the worst performing sector on the New York Stock Exchange (NYSE), with an average appreciation of 0.3%, compared with the general S&P500 market appreciation of 26%. At present the average price to earnings (P/E) ratio of large pharma stocks is trading at a discount to the entire market. By contrast, this sector has historically traded at a premium to the rest of the market, mainly because of pipeline valuations.

Depressing approval rates

In 2002, the US FDA approvals of NCEs were lower than at any other time in the past decade, and a total of just 17 NCEs were approved; the situation improved marginally in 2003 to 21 approvals. Even if biologics and NCEs are considered together, the number of FDA approvals were at their lowest since 1994. The situation is even bleaker when the number of innovative NCEs approved by regulatory authorities are factored into this performance. Prous Science[1] reported that in the eleven-year period 1990–2000 inclusive, the year with the lowest number of NCEs approved with a novel mechanism of action was 2000. These data are further substantiated by the number of FDA priority reviews of NCEs (an indirect measure of innovativeness or addressing true unmet medical need), in which 2002 and 2003 showed lower numbers of such reviews than any two-year rolling period in the preceding ten years[2].

This lower rate of success in the past few years could be accounted for, in part at least, by a number of explanations: the industry is currently attacking diseases of great complexity; the entry bar for new drugs is higher because they are often competing with enhanced standard of care; and/or the regulatory authorities are more demanding. Whatever the case, these features define the new playing field on which the industry has to compete to produce NCEs that are required to achieve necessary growth; an examination of the factors that impact R&D success is therefore crucial in terms of devising a strategy that can build a pipeline needed to sustain the business case for large pharma.

Defining the business case

A recent survey by Accenture[3] defined the business case for large pharmaceutical companies in terms of NCEs required to remain a growth company on the basis of their current revenues and their desired percentage growth (TABLE 1). On the basis of this calculation, Pfizer, with pharmaceutical revenues in 2003 of approximately US $45 billion, will need to generate approximately nine high-quality NCEs per annum. GlaxoSmithKline, with revenues in excess of £18 billion (~ US$ 32 billion), will need to generate about six high-quality NCEs per annum, and Merck, with US $22.5 billion in revenues, will need approximately 4.5 NCEs. The next tier (in terms of revenues) would need to deliver between three and four NCEs per annum and even the smaller companies in the top ten would need to deliver approximately two NCEs per annum.

Rates of attrition

FIGURE 1 analyses success rates from first-in-man to registration during a ten-year period (1991–2000) for ten big pharma companies in the United States and Europe. The data indicate that the average success rate for all therapeutic areas is approximately 11%; or, put another way, in aggregate only one in nine compounds makes it through development and gets approved by the European and/or the US regulatory authorities. More interestingly,

Table 1 | **NCEs required to achieve specific real growth targets as a function of 2002 revenues***

2002 sales†	Anticipated sales from current products in 2012	Annual real growth target	Sales gap for new products to fill in 2012	Estimated number of NCEs required to fill gap (over ten years)	Year 2012 required NCE output
$45 billion	$30 billion	5%	$43.5 billion	75–90	9.5–11
$30 billion	$20 billion	5%	$29 billion	50–60	6.5–7.5
$20 billion	$13.3 billion	5%	$19.3 billion	33–40	4.3–5
$15 billion	$10 billion	8%	$22 billion	40–45	5.5–6.0
		6%	$17 billion	30–35	4.0–4.5
		5%	$14.5 billion	25–30	3.25–3.75
		4%	$12 billion	20–25	2.5–3.0
$10 billion	$6.67 billion	5%	$9.67 billion	16.5–20	2.15–2.25

*Adapted from REF. 3. †All figures in US $. NCE, New Chemical Entity.

the success rates vary considerably between the different therapeutic areas: cardiovascular, for instance, have a ~20% rate of success, whereas oncology and central nervous system (CNS) disorders have ~5% and ~8% success, respectively. Any R&D portfolio, therefore, would need to aggregate the percent success based on the weight of the various therapeutic areas to calculate how many first-in-man studies are needed to approximate the requisite business case for growth.

The high rate of attrition in drug development and the need for efficiency, both in terms of real and opportunity costs, becomes even more compelling when one considers where most of the attrition occurs in the pipeline. In 2001, the costs of discovering and developing a drug were of the order of US $804 million[4]; current estimates are closer to about US $900 million; considerably more of these costs are incurred later in the pipeline, and the vast majority of attrition occurs in full clinical development (Phases IIb and III).

FIGURE 2 illustrates the top 10 drug companies' success and failure rates from 1991 to 2000 across different therapeutic areas.

The failure rate of compounds even at the registration stage is 23%; that is, roughly one in four compounds fail after all the trials and the documentation for submission have been completed, thereby incurring the full discovery and development costs and the opportunity costs, which, on average, could be as much as 12 years 10 months (the average time taken for the development of all the drugs that gained approval in 2002)[5]. In some therapeutic areas, such as woman's health, the failure rate is as high as 42%, and in oncology it is as high as 30%. Even the rate of failures in Phase III trials — by which stage significant amounts of the costs of discovering and developing a drug would have been incurred — is far too high: approximately 45% of all compounds that enter this phase of full development undergo attrition and in some therapeutic areas, such as oncology, it is as high as 59%. Approximately 62% of all compounds that enter Phase II trials undergo attrition, and again the highest rate of attrition at this phase is in the oncology field: more than 70% of oncology compounds fail in this phase. It is therefore crucial that the industry develop and embrace paradigms (such as obtaining proof of concept in man early in development) and methodologies to identify risk preclinically, and to couple this with experimental medicine procedures to interrogate such risks in man.

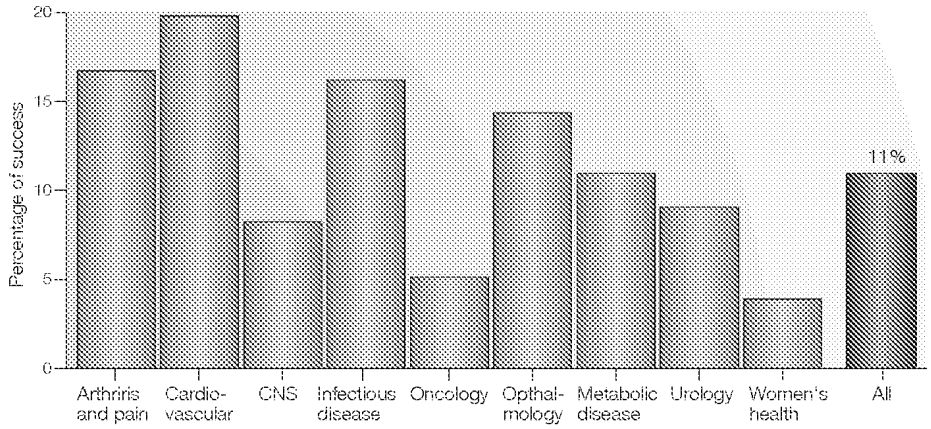


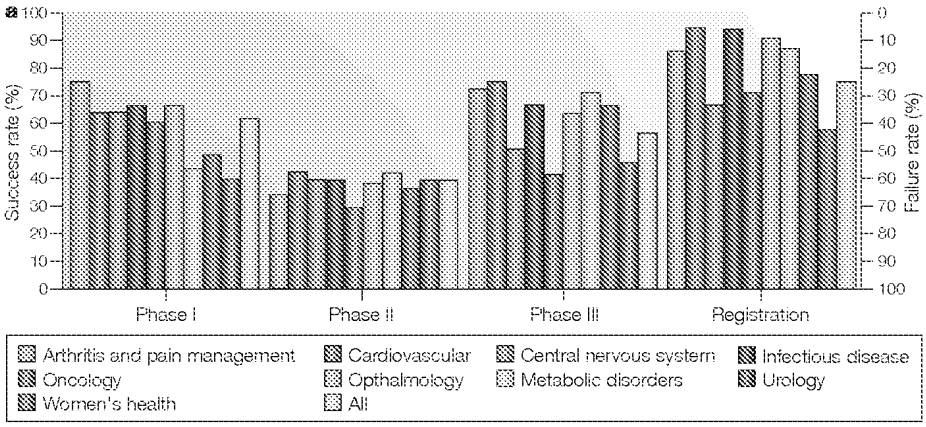
Figure 1 | **Success rates from first-in-man to registration.** The overall clinical success rate is 11%. However, if the analysis is carried out by therapeutic areas, big differences emerge. The data are from the ten biggest drug companies during 1991–2000. (The companies are AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-LaRoche, GlaxoWellcome, Johnson & Johnson, Novartis, Pfizer, Pharmacia, Schering-Plough and SmithKline Beecham; data were obtained by Datamonitor in the Pharmaceutical Benchmarking Study). CNS, central nervous system.

Underlying causes of attrition

An examination of the root causes of why compounds undergo attrition in the clinic is very instructive and helps in the identification of strategies and tactics to reduce these rates and thereby improve the efficiency of drug development. The data in FIG. 3 show the reason why compounds undergo attrition and how this has changed over time. In 1991, adverse pharmacokinetic and bioavailability results were the most significant cause of attrition, and accounted for ~40% of all attrition. By 2000, these factors had dramatically reduced as a cause of attrition in drug development, and contributed less than 10%. These data provide further compelling evidence that the industry can identify and remedy the causes of attrition. It might also, however, be that the solving of this problem has significantly shifted the temporal attrition profiles to later stages, because pharmacokinetic/bioavailability failures would have occurred in Phase I mainly and this might now result in compounds progressing to Phases II and III and failing there for other reasons.

The major causes of attrition in the clinic in 2000 were lack of efficacy (accounting for approximately 30% of failures) and safety (toxicology and clinical safety accounting for a further approximately 30%). The lack of efficacy might be contributing more significantly

to therapeutic areas in which animal models of efficacy are notoriously unpredictive[6], such as CNS and oncology, both of which have relatively higher failure rates in Phase II and III trials. In the case of oncology, small Phase II trials looking at tumour regression in small cohorts of patients with different tumour types does not always translate to outcomes subsequently obtained in larger Phase III trials. Nevertheless, in general, failures due to lack of efficacy and safety demonstrate the need for the development of more predictive animal models where possible and, more importantly, the need to develop experimental medicine paradigms that are more predictive of outcomes and to carry out such proof-of-concept clinical trials much earlier in development.



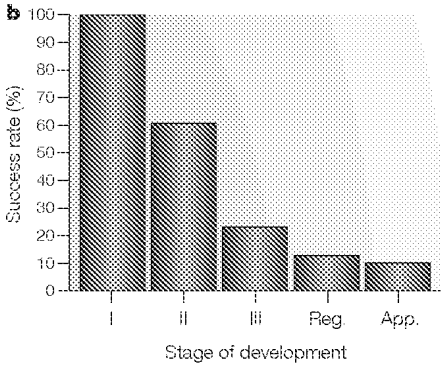


Figure 2 | **Success rate by phase of development and by therapeutic area.** **a** | Data are shown as percent success or percent attrition (second X axes) of compounds entering that particular phase of development by certain therapeutic areas and by the total aggregate for that particular phase of development. The data clearly show that different therapeutic areas have greatly different success or attrition rates, and that significant attrition occurs late in the pipeline. **b** | Shows the percentage rate of success of compounds entering first in man that progress to subsequent development phase. App, approval; Reg, registration.

Can success be increased?

Several strong strands of evidence indicate that it is possible. First is the fact that different therapeutic areas have different rates of success and this implies that if we understood the inherent factors that make one area successful as compared with another, we could then attack such factors.

Second is the finding that biologicals have a higher rate of success from first-in-man to launch — approximately 24%[7]. It is true that most biologicals have been generated in the areas of immunology and cancer, but the average rate of these two therapeutic areas should even out to ~11% (16% for arthritis and pain and 5% for cancer, based on the data in TABLE 1, which averages to ~11% if the two were in equal parts).

Third, licensing-in compounds has a consistently higher probability of success in most studies, at approximately 24%[7]. This is the case even if the compounds are categorized by the stage that the licensing-out company has categorized them. This phenomenon cannot, therefore, be attributed purely to the fact that the licensing-in companies gather more data or because they usually put the compound at an earlier stage in the pipeline.

Fourth, companies with R&D budgets of less than US $400 million also have higher success rates of approximately 18%[7]. This could partly be explained by the possibility that these smaller companies might be more inclined to work on me-too drugs (which should have a higher rate of success), and that their portfolios could be more skewed towards one therapeutic area or another with a greater probability of success. However, if one considers that many of the biotech companies fall into these categories, that many biotech companies are working in high-attrition-rate therapeutic areas such as cancer, and that many of these companies are indeed working on innovative mechanisms of action, then clearly this cannot be the whole explanation. The rate of attrition of compounds with novel mechanisms of action is higher than that of those with previously precedented mechanisms of action (a precedented mechanism of action is defined as one hitting a therapeutic target that a drug in the market place hits, or which has shown proof of concept in late clinical trials).

Last, even comparable large companies with extensive portfolios that would average out the differences in success between different therapeutic areas, and therefore portfolio success, have different probabilities of success. For instance, data from the 2002 Certified Medical Representatives Institute survey shows that the success rate that Merck enjoyed from first human dose to market was approximately twofold greater than the aggregate of the six companies in the same cohort with R&D budgets of >US $2 billion per annum[8]. On the other hand, in a briefing to analysts on 17 June 2003 Pfizer's current President of Research and Development, John La Mattina, was quoted as saying "Right now, only one in 25 early candidates survives to become a prescribed medicine. We think we can improve those odds to one in ten and greatly enhance our ability to bring new medicines to patients around the world."; Pfizer's India Homepage states that "approximately 1 out of every 15 drug candidates entering development completes phase III evaluation and obtains approval," both suggesting that their rate of attrition might be 93–96%. These five factors therefore provide compelling evidence that the rate of attrition could be significantly reduced and that drug development per se does not have this current high attrition rate as an inherent constraint. Indeed, it points to the idea that a systematic evaluation of the science, strategy and processes currently used in drug development merit rigorous evaluation, critical appraisal and modification to fulfil the onerous business case demanded by our patients, shareholders, consumers and governments worldwide.

How can attrition be reduced?

Several companies in the industry are now beginning to take on this problem and are starting to make progress. Below we propose some approaches that are likely to be valuable, but this is clearly not an exhaustive list. It is important that the mindset of reducing attrition in development should be in place from the earliest stages of discovery.

For instance, building the need to get very strong evidence for proof of mechanism into the discovery paradigm is crucial,

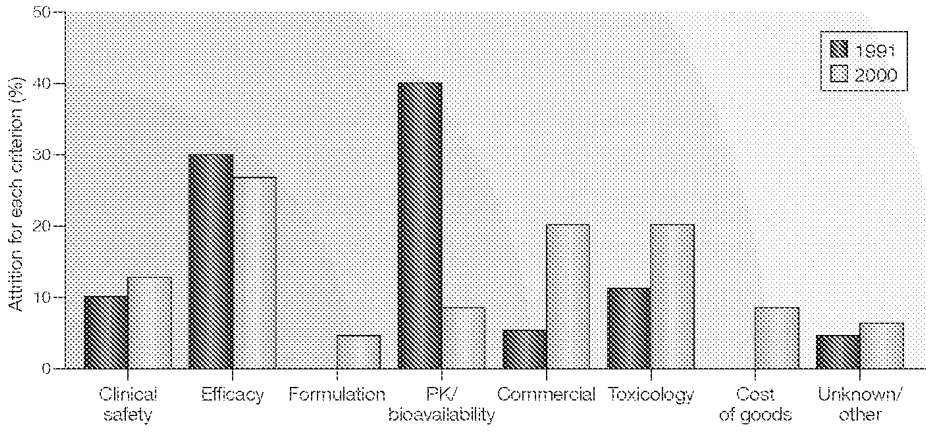


Figure 3 | **Reasons for attrition (1991–2000).** PK, pharmacokinetics.

and therefore showing that modulation of a target in a specific or important disease pathway might reduce the attrition of a large percentage of compounds that fail because of lack of efficacy. The development of imatinib (Gleevec; Novartis), for example, was based on the targeting of a very specific lesion (the BCR-ABL chromosomal translocation protein-product or Philadelphia chromosome) that occurs in chronic myelogenous leukaemia. We have, in a similar manner, provided very strong evidence that inhibition of β-secretase inhibits the production of amyloid-β in knockout mice[9] and that cathepsin K is involved in bone resorption (further compelling proof of mechanism is provided by humans with pycnodysostosis[10,11]). However, we will have to await approval of therapeutics aimed at these latter two mechanisms to see whether drug approvals are eventually obtained — for example, cathepsin K is in Phase II trials and the impact of this approach on attrition is still to early to fully evaluate.

A second method of reducing attrition is to eliminate compounds that have mechanism-based toxicity; this risk can be rigorously interrogated during discovery using tools such as gene knockouts and RNA interference, and, crucially, during preclinical development in toxicity testing. Additional tools such as transcriptional profiling can also affect attrition due to toxicity by giving specific gene-signature readouts that are predictive of toxicities obtained by previous compounds targeting specific molecular targets that have failed, and/or molecular signature algorithms that have been trained from preclinical toxicity studies.

Third, an important clinical tool that can be used is to identify biomarkers that signal correct dosing and whether the specific molecular target has been hit in early proof-of-concept clinical trials.

Fourth, and most important, is the design of proof-of-concept clinical trials during first-in-man studies. This has the distinct advantage of providing evidence in man that the molecular target is being hit and that hitting such a target gives the anticipated physiological response. Appropriately designed proof-of-concept studies (or experimental medicine paradigms) could reduce attrition due to lack of efficacy mostly seen in later development, and also have the distinct advantage of allowing attrition to occur earlier, which is beneficial both in terms of real and opportunity costs. This is likely to be important given that lack of efficacy accounts for about 30% of attrition in this study.

Fifth, another important tool is the use of appropriate animal models for efficacy testing in preclinical studies. It is interesting that oncology and CNS —two therapeutic areas with very high attrition rates in the data provided here — are also the areas in which animal models are not very predictive of the true human pathophysiology. For example, most pharmaceutical companies still use xenograft models for oncology testing, in which a tumour cell line that might have little relevance to the tumour *in vivo* is injected into a nude mouse (which does not resemble the immunology of the host; nor does the artificial location of the tumour significantly resemble what happens *in vivo* during tumorigenesis). The use of appropriate genetic models (for example, transgenic and gene knockout animals) of tumorigenesis might be more pathophysiologically relevant.

Last, another area in which attrition can be reduced is the discontinuation of compounds for commercial reasons either by gaining alignment between the research, development and marketing functions much earlier in the drug discovery process, and/or by better due diligence with respect to competitor development programmes and the likelihood of true differentiation from such drugs that might be ahead in development.

Future perspectives

The demands on pharmaceutical companies to meet their business objectives, as well as the demands of consumers for cost containment of prescription medicines, is forcing the industry to think about ways that efficiencies can be achieved. A particular emphasis is being placed on R&D because of the relatively dry late-phase pipelines, the spiralling costs of drug discovery and drug development, and the patent expirations of major blockbusters innovated in the past two decades. These pressures inevitably lead to a healthy evaluation of the science, strategies and processes involved in drug development, because the rate of attrition in drug development is simply too high, which makes the R&D process inefficient; efficiency and sustained profitability by the pharmaceutical industry are important for reinvestment in further R&D so that therapies for debilitating human diseases can continue to be developed and the price of medications contained.

This inefficiency becomes even more acute when one considers the number of compounds that undergo attrition in preclinical research, and that only three out of every ten drugs that makes it to market recover the original investment made in them. Factors that clearly affect attrition rates will lead to a more efficient industry and will benefit shareholders, and, more importantly, patients and the community. The industry will be forced to focus on attrition rates to balance the costs of drug development, to explore cost containment measures while still investing significantly in R&D, and to continue to generate shareholder value. Scientific and technological innovations that affect efficacy and safety (factors that most significantly contribute to attrition in the clinic) will have to be addressed. These include more appropriate animal models; biomarkers that can report the hitting of the molecular target in dose-ranging, efficacy and toxicity studies; and a new paradigm for drug development that will give early readouts for proof of concept and one that will allow attrition to occur much earlier.

We believe that governments and consumers want to reward truly innovative drugs, and/or those that are genuinely differentiated

from existing drugs and that address a true unmet medical need; this provides a tremendous incentive for the pharma industry to conduct R&D in this arena, and this in itself could affect R&D productivity. Drugs that target novel mechanisms have higher attrition rates[12], but a combination of better-validated preclinical targets that have significant preclinical proof of principal, and the scientific and technological innovations that positively affect efficacy and safety of drugs discussed earlier in this article, can mitigate such attrition risks. It is clear that in the twentieth century the pharmaceutical industry has had significant positive impact on the health and longevity of humans across the globe, but the early twenty-first century will demand both great effectiveness and efficiency from the industry, and it is therefore vital that the industry rapidly gears up to meet these demands.

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Competing interests statement
The authors declare competing financial interests: see Web version for details..

Online links

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Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs

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This study utilizes both public and private data sources to estimate clinical phase transition and clinical approval probabilities for drugs in the development pipelines of the 50 largest pharmaceutical firms (by sales). The study examined the development histories of these investigational compounds from the time point at which they first entered clinical testing (1993–2004) through June 2009. The clinical approval success rate in the United States was 16% for self-originated drugs (originating from the pharmaceutical company itself) during both the 1993–1998 and the 1999–2004 subperiods. For all compounds (including licensed-in and licensed-out drugs in addition to self-originated drugs), the clinical approval success rate for the entire study period was 19%. The estimated clinical approval success rates and phase transition probabilities differed significantly by therapeutic class. The estimated clinical approval success rate for self-originated compounds over the entire study period was 32% for large molecules and 13% for small molecules. The estimated transition probabilities were also higher for all clinical phases with respect to large molecules.

INTRODUCTION

Numerous studies have found that the drug development process is highly expensive and that these costs have trended significantly upward for decades.[1–6] Many factors affect the cost of drug development, but two of the key basic elements are time and risk. Development times increased substantially from the 1960s through the 1980s but overall remained relatively stable during the 1990s.[7,8] Thus, development times did not directly contribute much to the rapid increase in pharmaceutical R&D costs in the past two decades. However, if clinical trials become larger and more complex, and the costs of inputs to the development process increase faster than inflation, the "time costs" associated with the investment of resources in new drug development will increase in absolute terms, even if development times remain the same. Indeed, there is evidence that the clinical trial process has become more extensive and complex in the past few decades.[4,9] The situation is similar for drug development risks. By development risk, we mean the likelihood that development of a drug will be terminated owing to efficacy, safety, or commercial concerns. High drug failure rates contribute substantially to R&D costs, whether or not these costs are otherwise increasing. Thus, the rate at which pharmaceutical firms successfully develop investigational compounds for marketing approval by regulatory agencies is an important indicator of the effectiveness of the drug development process. Processes and technological innovations that can improve the predictability of outcomes for new compounds can therefore significantly increase the productivity of new drug innovation.[10]

The historical literature focusing specifically on the quantification of drug development risks is fairly robust.[11–20] The aforementioned research on drug development costs includes estimates of drug development risks. Early research on development risks suggested that clinical approval rates for self-originated drugs in the 1960s were in the neighborhood of one in eight.[11] Subsequent studies indicated that development risks fell in the 1970s, with approval rates averaging approximately one in five; the risk levels pertaining to the 1970s remained fairly stable to the mid-1990s.[1,3,14,15]

This study provides updated clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by sales). We analyze approval success rates and phase transition rate trends within this period for new compounds as a whole and by therapeutic class. The data are also stratified by product type (large molecule vs. small molecule).

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The results relating to phase transition rates (or their converse, phase attrition rates) allow us to examine whether pharmaceutical firms are "failing" drugs earlier in the development process and thereby (other factors assumed to be equal) potentially reducing overall development costs.

We examined the investigational drug pipelines of the 50 largest pharmaceutical firms as determined on the basis of sales in 2006. Several data sources were consulted, but the core source for the compound list was the IMS R&D Focus investigational drug pipeline database. We supplemented that database with information from two other commercial pipeline databases (iDdb3 and Pharmaprojects), as well as from Tufts CSDD investigational drug, approved drug, and investigational biopharmaceutical databases that were derived, in part, from confidential company surveys, published regulatory agency documents, online company pipeline lists, and Internet searches.

Inclusion criteria

The resulting database contains information on nearly 4,000 drugs and biologics. For the purpose of simplifying the discussion, we refer to all the compounds analyzed as "new drugs." Our analyses are restricted to the new drugs for which the starting dates for phase I testing were available and for which this phase I testing was initiated anywhere in the world from 1993 through 2004. The dataset used for the analysis contains information on the development histories of 1,738 new drugs. For the purposes of this study, the dataset's key elements include information on the drug's therapeutic class (identified by the major indication pursued), the drug type (small molecule, including synthetic peptides and oligonucleotides, or large molecule, including monoclonal antibodies, recombinant proteins, and other biologics), the clinical phases in which the drug has been tested, whether the drug has been approved for marketing in the United States, the latest phase (clinical or regulatory) that the compound had entered (if research on the drug has been terminated), the sponsor company, and the source of the drug (self-originated, licensed-in, or licensed-out). The bulk of the licensed-in compounds were licensed from firms outside the top 50. A compound was considered licensed-out only if it had been licensed from one of the top 50 firms to a firm outside the top 50. We excluded from analysis diagnostics, vaccines, and new formulations and indications for already-approved drugs. We placed drugs in therapeutic categories according to their classification in the IMS R&D Focus database. The database uses the Anatomical Therapeutic Chemical classification system established by the World Health Organization Collaborating Centre for Drug Statistics Methodology for classifying indications.

Clinical approval success rates are defined in terms of US regulatory approval for marketing. Current success rates for the compounds were examined through June 2009. Analyses were conducted for the entire study period (1993–2004) and also separately for two subperiods (1993–1998 and 1999–2004). Data on more recent investigational drugs were available, but, given the length of the new drug development process, we judged them too recent to be included in a comprehensive analysis of success rates.

Calculation of success-rate estimates

The dataset used contains information on the latest phase (development or regulatory) of the abandoned drugs at the time they were terminated. These data allow us to estimate the likelihood that an investigational drug will proceed from one clinical phase to the next as well as the distribution of research terminations by phase. They also, in aggregate, permit us to estimate the probability of approval for new drugs that enter the clinical pipeline. Specifically, we estimate the proportion of new drugs that transition from phase i to phase i + 1 as the ratio:

> No. of new drugs that proceeded to phase i + 1/total no. of new drugs that entered phase i
>
> The denominator in the ratio includes only drugs that either proceeded thereafter to phase i + 1 or were terminated in phase i.

We estimate the clinical approval success rate as the product of the individual phase transition probabilities. These transition probability estimates will be unbiased estimates of the population transition probabilities if the drugs that are still active in a phase are, on average, no different (in terms of the likelihood of proceeding to the next phase) from the set of drugs that either have been terminated in the phase or have moved on to the next phase. There are likely to be variable time lags as to when new information on the status of a drug is available in a database. However, if a database firm has not been able to obtain an update on the status of a drug over a set period of time (e.g., 18 months for R&D Focus), it will show that no development activity has been reported for the drug. For purposes of analysis, we assumed that the drug was discontinued in the latest phase that it had entered if no development activity was subsequently reported. Therefore our transition probability estimates may be underestimated; however, even if this is so, the downward bias is probably small.

As noted above, we utilized information from more than half a dozen databases and other sources. We recognized that, among the databases (pipeline-based or survey-based) and other sources that we used, no single source would have the most recent information for all drugs. For our study, we took the earliest date recorded for the start of phase I testing as the date on which clinical testing of the drug began, and the latest available development or regulatory phase as its current status. For example, if one database had information to the effect that a drug has entered phase III while other databases and sources showed its status at phase II, we assumed that the drug has proceeded to phase III. We thus made use of the most recent information available from the multiple sources regarding the status of an investigational drug.

For the entire study period, 70% of the new drugs in our dataset were self-originated (Table 1). We found that the proportion of all new drugs that were licensed out to firms outside of the top 50 pharmaceutical companies was small. These shares were similar for the 1993–1998 subperiod. For the full study period, we determined a final outcome (success or failure) for 76% of all the drugs analyzed; for self-originated drugs, this figure was 81%. As expected, the percentage of drugs for which a final outcome was available was higher for the earlier period. For example, final outcomes were reported for 88% of all drugs and 92% of

Table 1 Current and maximum-possible success rates by source of molecule for compounds first tested in humans from 1993 to 2004

Source	*n*	Approved molecules	Open molecules[a]	Percentage completed (%)[a]	Current success rate (%)[a]	Maximum-possible success rate (%)[b]
1993–2004						
Self-originated	1,225	87	239	80.5	7.1	26.6
Licensed-in	412	41	141	65.8	10.0	44.2
Licensed-out	101	10	42	58.4	9.9	51.5
All	1,738	138	422	75.7	7.9	32.2
1993–1998						
Self-originated	584	64	48	91.8	11.0	19.2
Licensed-in	180	32	30	83.3	17.8	34.4
Licensed-out	57	9	21	63.2	15.8	52.6
All	821	105	99	87.9	12.8	24.8

[a]Through June 2009. [b]Assumes that all open compounds will eventually be approved.

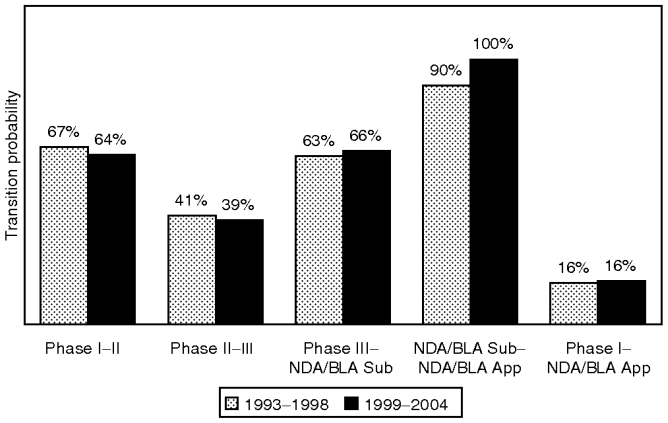

Figure 1 Phase transition probabilities and clinical approval success probabilities for self-originated compounds by period of first-in-human testing. BLA, biologics license application; NDA, new drug application.

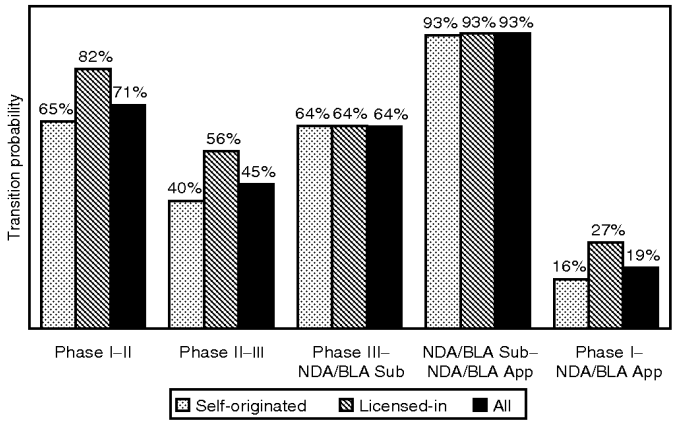

Figure 2 Phase transition probabilities and clinical approval success probabilities by source of compound, for compounds first tested in humans from 1993 to 2004. BLA, biologics license application; NDA, new drug application.

self-originated drugs that commenced clinical trials during the 1993–1998 subperiod. Given that the data are censored (some drugs are still active), we show both the current and maximum-possible US clinical approval success rates. These rates were higher for licensed-in than for self-originated drugs.

Success-rate trends

Figure 1 shows estimated phase transition probabilities and the overall clinical approval success rates for the 1993–1998 and the 1999–2004 subperiods. The results do not suggest any trend in the overall clinical approval success rates for new drugs over this period; estimates showed that approximately one in six new drugs that entered clinical testing during each of these subperiods was eventually approved for marketing. However, there were small differences between the two subperiods with respect to the estimated clinical phase transition rates. The results suggest that the failures occurred somewhat earlier in the clinical trial process (phases I and II) for drugs initiated into clinical trials during the later subperiod.

There are at least two good reasons for the generally higher clinical approval success rates for licensed-in compounds. First, these compounds have generally undergone some screening or testing prior to licensing and have been shown to be promising candidates for marketing approval. Thus, there may be a screening effect for new drugs that are licensed-in. Second, it is likely that many of these licensed-in drugs were acquired after some clinical testing had been done on them. Although drugs may be licensed-in at any point during the development process, including during the preclinical period, later clinical phases are associated with higher approval rates. We do not have data on when in the development process each of the licensed-in drugs was acquired, but if, for example, the average licensed-in drug was acquired at phase II, then we would expect higher clinical approval success rates for the licensed-in group for that reason alone.

Figure 2 shows estimated phase transition probabilities and clinical approval success rates by source of the compound. As expected, the estimated overall clinical approval success rate is substantially higher for the licensed-in drugs than for self-originated drugs (27 vs. 16%). However, the estimated transition probabilities for phase III and regulatory review are identical for licensed-in and self-originated drugs. The higher estimated clinical approval success rate for licensed-in drugs derives from higher transition probabilities at phases I

and II. This suggests that many of the licensed-in drugs were acquired after phase I or phase II testing had already been conducted by the licensor.

Success rates by therapeutic class

Prior research has shown that success rates for new drugs vary by therapeutic class.[3,5,14–16] Table 2 shows current and maximum-possible success rates and the percentage of self-originated drugs that have had a reported final outcome by therapeutic class. Given that the number of compounds available for analysis is greatly reduced when the data are stratified into therapeutic categories, the entire study period (1993–2004) is used. Explicit results are reported for the seven therapeutic classes with the most new drugs taken into clinical testing over the study period (≥80 compounds). These seven classes account for 85% of all self-originated drugs that were included for analysis. The proportion of drugs in these classes that have reached a final outcome varied from 71% for antineoplastic/immunologic drugs to 89% for systemic anti-infectives.

Table 3 shows the estimated phase transition and clinical approval success probabilities for the seven therapeutic classes and one miscellaneous category. There was substantial variability by class for both the phase transition probabilities and the clinical approval success rates. More than 70% of the self-originated drugs in the antineoplastic, musculoskeletal, and respiratory categories moved from phase I testing to phase II testing, whereas fewer than 60% of the self-originated drugs in the systemic anti-infective and central nervous system (CNS) categories did so. One-third or fewer of the self-originated drugs in the respiratory, cardiovascular, and CNS categories proceeded from phase II to phase III testing, but nearly half of the antineoplastic/immunologic drugs moved from phase II trials to much more expensive phase III testing. However, once antineoplastic/immunologic drugs reached phase III, they had a relatively low estimated probability (55%) of having an application for marketing approval submitted to the US Food and Drug Administration. Similarly, only 50% of gastrointestinal/metabolism drugs and 46% of CNS drugs moved from phase III to regulatory review. In contrast, the systemic anti-infective, musculoskeletal, and respiratory drug categories had relatively high estimated probabilities of getting to regulatory review after they had entered phase III (79% or higher).

The estimated clinical approval success rates for self-originated drugs varied substantially by therapeutic class. The CNS (8%), cardiovascular (9%), gastrointestinal/metabolism (9%), and respiratory (10%) categories had relatively low estimated approval

Table 2 Current and maximum-possible success rates by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

Therapeutic class	*n*	Approved molecules	Open molecules[a]	Percentage completed (%)[a]	Current success rate (%)[a]	Maximum-possible success rate (%)[b]
Antineoplastic/immunologic	254	18	75	70.5	7.1	36.6
Cardiovascular	134	4	24	82.1	3.0	20.9
CNS	235	9	40	83.0	3.8	20.9
GI/metabolism	120	4	28	76.7	3.3	26.7
Musculoskeletal	88	8	18	79.5	9.1	29.5
Respiratory	83	4	15	81.9	4.8	22.9
Systemic anti-infective	122	19	14	88.5	15.6	27.0
Miscellaneous	189	21	25	86.8	11.1	24.3

CNS, central nervous system; GI, gastrointestinal.

[a]Through June 2009. [b]Assumes that all open compounds will eventually be approved.

Table 3 Phase transition and clinical approval probabilities by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

Therapeutic class	Phase I–II (%)	Phase II–III (%)	Phase III–RR (%)	RR–approval (%)	Clinical approval success rate (%)
Antineoplastic/immunologic	71.8	49.0	55.3	100	19.4
Cardiovascular	62.9	32.4	64.3	66.7	8.7
CNS	59.6	33.0	46.4	90.0	8.2
GI/metabolism	67.5	34.9	50.0	80.0	9.4
Musculoskeletal	72.4	35.2	80.0	100	20.4
Respiratory	72.5	20.0	85.7	80.0	9.9
Systemic anti-infective	58.2	52.2	78.6	100	23.9
Miscellaneous	62.8	48.7	69.8	91.3	19.5

Through June 2009.

CNS, central nervous system; GI, gastrointestinal; RR, regulatory review.

success rates. In contrast, systemic anti-infectives had a relatively high clinical approval success rate (24%). Although the sample sizes are much smaller, the rankings of approval success rates by therapeutic class were generally similar for the two study subperiods.

Success rates by product type

We also analyzed phase transition probabilities and clinical approval success rates by product type. Specifically, we examined outcomes by grouping drugs into small- and large-molecule categories. Large-molecule compounds comprise a minority of the compounds in the pipelines of the 50 largest pharmaceutical firms, but their number is still significant. For all compounds and for the entire study period, large-molecule compounds constituted 15% of the total number of drugs. There was a slight downward trend in that percentage over time, from 17% for the 1993–1998 period to 13% for the 1999–2004 period. Given that large pharmaceutical firms often seek licensing candidates from small biopharmaceutical firms, the percentage of large-molecule compounds was lower (but not much lower) for self-originated drugs. Of the self-originated drugs over the entire study period, 12% were large-molecule compounds (14% for 1993–1998 and 11% for 1999–2004). The large-molecule category is dominated by monoclonal antibodies and recombinant proteins. For self-originated drugs during the entire study period, 47% of the large molecules were monoclonal antibodies, 43% were recombinant proteins, and 10% were other biologics.

Figure 3 shows our results for estimated transition and clinical approval success probabilities by product type. Estimated transition probabilities for all phases were higher for large molecules. The estimated clinical approval success rate for large molecules (32%) was much higher than for small molecules (13%). Studies have indicated that success rates differ within the monoclonal antibody class by type of antibody (murine, chimeric, human, or humanized).[20] However, overall, the estimated clinical approval success rates for recombinant proteins and monoclonal antibodies did not differ by much (34% for recombinant proteins and 36% for monoclonal antibodies for self-originated drugs). The large-molecule subtypes, however, did vary somewhat in their estimated phase transition probabilities. Specifically, recombinant proteins had higher phase transition rates for the early clinical phases but a lower estimated phase transition probability for phase III to regulatory review (66% for recombinant proteins and 87% for monoclonal antibodies).

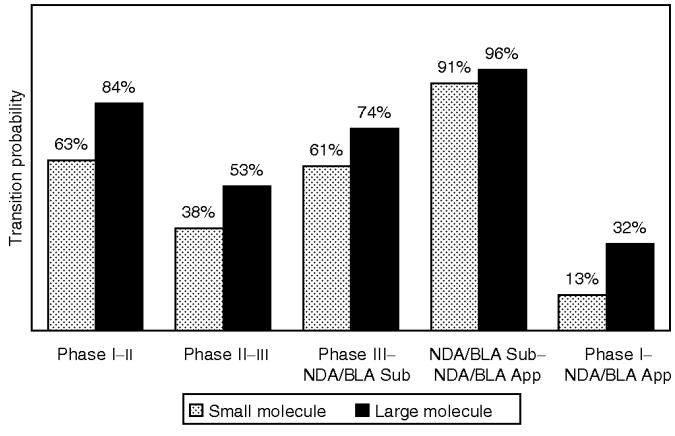

Figure 3 Phase transition probabilities and clinical approval success probabilities by type of compound, for self-originated compounds first tested in humans from 1993 to 2004. BLA, biologics license application; NDA, new drug application.

SUMMARY

We estimated phase transition probabilities and clinical approval success rates for drugs in the pipelines of the 50 largest pharmaceutical firms by sales. These firms are likely to represent very large proportions of the total number of investigational drugs and of aggregate industry R&D expenditures. For self-originated new drugs that first entered clinical testing in 1993–2004 and were observed through mid-2009, the results indicated that approximately one in six drugs that enter the clinical testing pipeline will eventually obtain approval for marketing in the United States. The data did not support the hypothesis of a within-period trend, but the overall estimated clinical approval success rate is lower than it has been for prior periods.[1,4,11–15] Although the overall success rate was fairly constant over the study period, we did find that the failures occurred somewhat earlier in the clinical process for the latter half of the study period. This has implications for the average cost of new drug development.[10] However, the reduction in cost because of a relatively modest improvement in the speed at which firms identify failures may easily be more than offset by increases over time in the out-of-pocket costs of conducting clinical trials. There is evidence to show that clinical trials have become more complex, and therefore probably costlier, in recent years.[9] In addition, when viewed against the background of reported costs of new drug development in earlier periods, the increasing complexity of clinical trials and the overall drop in clinical approval success rates strongly suggest that new drug R&D costs have continued to increase at a high rate in recent years.

We also found, as we have in the past, that clinical approval success rates differ by therapeutic class in any given period. Our analysis of self-originated drugs found estimated clinical approval success rates that varied from 8% for CNS drugs to 24% for systemic anti-infectives. This variability in success rates by therapeutic class might be explained, at least partially, by differences in the uncertainty (inherent in the differing scientific objectives and underlying science knowledge base) about the regulatory standards that must be satisfied for different drug classes. For example, efficacy end points for antibiotics are often clearly defined and can be assessed in a relatively straightforward way. In contrast, it can often be difficult to prove the efficacy of psychotropic compounds, or to establish causal links between these drugs and side effects.

Finally, we did find substantial differences in clinical approval success rates by product type (large vs. small molecules). The success rate for large molecules (nearly one-third) is consistent with the findings from a study of biopharmaceutical R&D costs covering a somewhat earlier period.[6] We also found higher phase transition rates at all phases for large molecules. Although R&D costs should be much lower for large molecules given that success rates in this category are substantially higher, other factors may offset that impact. This appears to be the case for

large-molecule development; the overall projected cost per new small-molecule drug was found to be similar to the reported cost per large-molecule drug.[6]

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CONFLICT OF INTEREST

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Electronic Patent Application Fee Transmittal

Application Number:	13456720
Filing Date:	26-Apr-2012
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL
First Named Inventor/Applicant Name:	Sunil GUPTA
Filer:	Kelly L. Bender
Attorney Docket Number:	FR2009/121 US CNT

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**6740**

Electronic Acknowledgement Receipt

EFS ID:	18492632
Application Number:	13456720
International Application Number:	
Confirmation Number:	1083
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL
First Named Inventor/Applicant Name:	Sunil GUPTA
Customer Number:	5487
Filer:	Kelly L. Bender/Brian Pritchett
Filer Authorized By:	Kelly L. Bender
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	FR2009-121USCNT_20140317_RCE.pdf	186765 87c7bf3ca5ad184178cc30a25ab0995c3253f207	no	3
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		FR2009121USCNT_20140317_RFOA.pdf	207261 270a6d96b5c2c2a95ed67b29aabf7638692f80c2	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	9

Warnings:					
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3	Transmittal Letter	FR2009-121USCNT_20140317_SUPP_IDSL.pdf	121233 bed11aad939d857e291611424dbe5fc560820ddf	no	3
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	FR2009-121USCNT_20140317_COT.pdf	112740 add170ee97942fc56bfcc06968a21d613d4ba4ff	no	1
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Information:					
5	Extension of Time	FR2009-121USCNT_20140317_EOT.pdf	75240 7cb6fd71c261ceb0bc374cec9e7d27a8ef93a7a1	no	2
Warnings:					
Information:					
6	TrackOne Request	FR2009-121USCNT_20140317_REQUESTFORPRIORITIZEDEXAMINATION.pdf	140855 39d387472c302c54e5357a7a5d6171e91ad20c7d	no	2
Warnings:					
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7	Non Patent Literature	FR2009121USCNTSUPPIDSREF1 CISTERNINO.pdf	215161 a06067e0a1d5c202870893f0554065d02d0bb52f	no	9
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8	Non Patent Literature	FR2009121USCNTSUPPIDSREF2 PIVOT.pdf	715221 081891620dd78087a49168db663ae184105bf61c	no	53
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9	Non Patent Literature	FR2009121USCNTSUPPIDSREF3 ATTARD.pdf	216015 045aeced8bc453ffc7535bff3764ec9c1103a822	no	13
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10	Non Patent Literature	FR2009121USCNTSUPPIDSREF5 PIVOT.pdf	137201 ac6da937bb46f0ad50b8f46213febd8172e603a9	no	6
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11	Non Patent Literature	FR2009121USCNTSUPPIDSREF7 NHCS.pdf	886506 c5a38a7e822def8a2bc8b5fd7ac871113b69c3eb	no	6
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Information:					
12	Non Patent Literature	FR2009121USCNTSUPPIDSREF9 DILORENZO.pdf	180680 2641cb18129270ff6236d3b28d938da5430cd94a	no	18
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13	Non Patent Literature	FR2009121USCNTSUPPIDSREF10 YOO.pdf	356522 a9386a691e8ea3bfdcf57b4ed38617217eed9e70	no	6
Warnings:					
Information:					
14	Non Patent Literature	FR2009121USCNTSUPPIDSREF11 SHABAFROUZ.pdf	543494 415d20ddab77fb3fac0545667c4fb607732adb29	no	4
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15	Non Patent Literature	FR2009121USCNTSUPPIDSREF12 DORFF.pdf	336689 ae5cd6a51eb203e1d5a7f7a3a7fee82731bb31d3	no	2

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17	Non Patent Literature	FR2009121USCNTSUPPIDSREF15FIGG.pdf	235031 acbc7dc35fce5bd924d0f17a22a80d6ff21fef11	no	2
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18	Non Patent Literature	FR2009121USCNTSUPPIDSREF16SARTOR.pdf	498578 d4e29a76cbfbd1ded01ac6542e26254da712f6b1	no	6
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22	Non Patent Literature	FR2009121USCNTSUPPIDSREF21LORTHOLARY.pdf	65306 52acbd2a19d448611988d5c35a984d9db3c1cec5	no	2
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25	Non Patent Literature	FR20091210USCNTSUPPIDSREF24ANTIMITOTIC.pdf	108314 b03fcd7691ece1a3bea52323871b513d991d5569	no	2
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27	Foreign Reference	FR20091210USCNTSUPPIDSREF35WO11130566.pdf	12330574 2a6fa27eb71d722282fb8ce321722f00cc369a97	no	267
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28	Foreign Reference	FR20091210USCNTSUPPIDSREF36WO11063421.pdf	13997230 3823b4ed6dbdb8752e4c1ec69b12524207ac799b	no	341
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32	Foreign Reference	FR20091210USCNTSUPPIDSREF40WO0010547.pdf	1029837 73743baecd763db3997e4dea6175d9d3e0429cce	no	25
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34	Foreign Reference	FR2009121USCNTSUPPIDSREF42WO10117668.pdf	22641309 24a4789ac8daacdb663a176ff998e0aaebe2b79a	no	491
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35	Foreign Reference	FR2009121USCNTSUPPIDSREF43WO10128258.pdf	848094 2ebf7fbac76e44d456445bd0436c0c9836e84ee1	no	25
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38	Foreign Reference	FR2009121USCNTSUPPIDSREF46WO11130317.pdf	2440116 ea064cab83acd67f635bacd2ded41355dddcb733	no	58
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39	Foreign Reference	FR2009121USCNTSUPPIDSREF47MIURA.pdf	1580979 da51c9357afaf53bfb50fd0ee16e31ab63e38680	no	4
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Information:					
40	Foreign Reference	FR2009121USCNTSUPPIDSREF49KOLA.pdf	128035 f339cd2a142d9810162faf6df63a1eb8a96a5dad	no	5
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41	Foreign Reference	FR2009121USCNTSUPPIDSREF50DIMASI.pdf	126240 3f4346974b68021c36e155eb8c1f6d5c098d072c	no	6
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42	Non Patent Literature	FR2009121USCNTSUPPIDSREF4BEARDSLEY.pdf	2156233 027c8c372169b189b6b5d386cf1a696efce28fa2	no	6

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43	Non Patent Literature	FR2009121USCNTSUPPIDSREF6PRESS6.pdf	6219480 9c818278ff0489688c0628d4b8ee007f6539d7ba	no	31
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45	Non Patent Literature	FR2009121USCNTSUPPIDSREF13BOUCHET.pdf	2612302 b890f3acac7914799878f94663b326a386513eca	no	8
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47	Non Patent Literature	FR2009121USCNTSUPPIDSREF25CABAZITAXEL.pdf	4018256 0fe0a694161daf0d7a97a96b5934d52a4311de56	no	19
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48	Non Patent Literature	FR2009121USCNTSUPPIDSREF26PRESS1.pdf	6043496 37e8b9029fcfea73c1d70c15b780620445d248de	no	24
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49	Non Patent Literature	FR2009121USCNTSUPPIDSREF27PRESS2.pdf	6231679 af5fd9eb9b90975aab2c445fee903652bcb48921	no	28
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52	Non Patent Literature	FR2009121USCNTSUPPIDSREF30CLINICAL2.pdf	1173024 ec9fc4f1ea89b5a1b9cf3b36cf3a6c266bfa3fd1	no	8
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53	Non Patent Literature	FR2009121USCNTSUPPIDSREF31PRESS4.pdf	7021531 1b0ccac2728cc9d8e9d3a5b575e685e93e64b049	no	26
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54	Non Patent Literature	FR2009121USCNTSUPPIDSREF32CLINICAL3.pdf	1166724 59cf3cba9ce9b6990b3eb875bc9f2cebbafb9458	no	7
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55	Non Patent Literature	FR2009121USCNTSUPPIDSREF33PRESS.pdf	6335507 4515f47a12f02233804b55107a57890b21d3e5cf	no	27
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56	Non Patent Literature	FR2009121USCNTSUPPIDSREF48NUMATA.pdf	2054087 d3ba0c6414fc7695a1e691b4f8c5dd313c855d49	no	7
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57	Fee Worksheet (SB06)	fee-info.pdf	33906 e4fbf7261a9a90cf2dda5a2e4397676189ef2b2d	no	2
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New International Application Filed with the USPTO as a Receiving Office

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/456,720	Filing Date 04/26/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT	03/17/2014	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 33	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***10	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/456,720	04/26/2012	Sunil GUPTA	FR2009/121 US CNT

CONFIRMATION NO. 1083

POA ACCEPTANCE LETTER

5487
ANDREA Q. RYAN
SANOFI
55 Corporate Drive
MAIL CODE: 55A-505A
BRIDGEWATER, NJ 08807

OC000000065404649

Date Mailed: 12/10/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/04/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/sleutchit/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	**Sunil GUPTA**	Examiner:	**James D. Anderson**
Serial No.:	**13/456,720**	Group Art Unit.:	**1629**
Filed:	**April 26, 2012**	Conf. No.	**1083**
Title:	**NOVEL ANTITUMORAL USE OF CABAZITAXEL**		

POWER OF ATTORNEY FOR PATENT APPLICATION

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Josiane MERLIER, an Authorized Signatory of Aventis Pharma S.A., Assignee of the above-identified Application, hereby appoint the attorneys and/or agents associated with the Customer No.(s) provided below as attorneys and/or agents with full power to prosecute this application on behalf of Assignee and to transact all of Assignee's business in connection with the above-identified Application in the Patent and Trademark Office:

Customer No.: 005487

By: Josiane MERLIER

Title: FR Site Head Global Patent Operations

Date: 24th July, 2013

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Telefax (908) 981-7832
Customer No. 005487

Electronic Acknowledgement Receipt

EFS ID:	17559240
Application Number:	13456720
International Application Number:	
Confirmation Number:	1083
Title of Invention:	NOVEL ANTITUMORAL USE OF CABAZITAXEL
First Named Inventor/Applicant Name:	Sunil GUPTA
Customer Number:	5487
Filer:	Kelly L. Bender/Brian Pritchett
Filer Authorized By:	Kelly L. Bender
Attorney Docket Number:	FR2009/121 US CNT
Receipt Date:	04-DEC-2013
Filing Date:	26-APR-2012
Time Stamp:	09:00:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73.	FR2009-121USCNT_20131204_STATEMENT373B.pdf	304681 0a98f80ab51453c3349fcc57f01ea42f0c9fe60d	no	1

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Information:	

2	Power of Attorney	FR2009-121USCNT_20131204_POA.pdf	170472 92fc01ad6e591323c5f966296fdeee42482d7069	no	1

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National Stage of an International Application under 35 U.S.C. 371
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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owners: **Sunil GUPTA**

Application No./Patent No.: **13/456,720** Filed/Issue Date: **April 26, 2012**

Titled: **NOVEL ANTITUMORAL USE OF CABAZITAXEL**

Aventis Pharma S.A. (Name of Assignee) , a **corporation** (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

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2. ☐ an assignee of less than the entire right, title , and interest in
(The extent (by percentage) of its ownership interest is %); or

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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

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[NOTE: A separate copy (i.e., a true copy of the original assignment document (s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature

AVENTIS PHARMA S.A.
20 avenue Raymond Aron
92160 ANTONY - France
R.C.S. Nanterre B 304 403 294

Date 24th July, 2013

Printed or Typed Name: Josiane MERLIER

Title FR Site Head Global Patent Operations

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/456,720	04/26/2012	Sunil GUPTA	FR2009/121 US CNT	1083

5487 7590 09/16/2013

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/16/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi.com
andrea.ryan@sanofi.com

Office Action Summary	Application No. 13/456,720	Applicant(s) GUPTA, SUNIL	
	Examiner JAMES D. ANDERSON	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/16/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,4,6-11,13-19 and 24* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,4,6-11,13-19 and 24* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/2013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 7/16/2013, are acknowledged and entered. Claims 3, 5, 12, 20-23, and 25-33 have been cancelled by Applicant. Claims 1-2, 4, 6-11, 13-19, and 24 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 3, 5, 12, 20-23, and 25-33 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 7/16/2013, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 7/16/2013. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4, 8-12, 13-19, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Mita *et al.*** (Clinical Cancer Research, 2009, vol. 15, pages 723-730) (Published Online January 15, 2009) in view of **Tannock *et al.*** (N. Engl. J. Med., 2004, vol. 351, pages 1502-1512).

Claimed Invention

The amended claims are drawn to treating prostate cancer in a patient comprising administering to said patient cabazitaxel (XRP6258) in combination with prednisone or prednisolone, wherein the patient has hormone refractory prostate cancer and wherein the patient has been previously treated with a docetaxel containing regimen.

Teachings of Mita et al.

Mita *et al.* disclose a Phase I and pharmacokinetic study of cabazitaxel (XRP6258), administered as a 1-hour intravenous infusion every 3 weeks in patients with advanced solid tumors. *See* Abstract.

Mita *et al.* disclose that cabazitaxel (XRP6258) has shown broad spectrum antitumor activity in mice bearing s.c. implanted human xenografts, including Du-145 prostate cancers. *See* page 724, left column, first full paragraph.

Mita *et al.* disclose that the encouraging spectrum of antitumor activity of XRP6258 in experimental tumor models, **particularly its notable activity**

against docetaxel-resistant, Pgp-expressing malignancies, served as a rationale to clinical evaluations. *See* page 724, left column, second full paragraph.

Regarding claims 8-11, Mita *et al.* disclose that XRP6258 was administered as a 1-hour i.v. infusion every 3 weeks at a starting dose of 10 mg/m2, with subsequent incremental increases to 15, 20, and 25 mg/m2 dose levels. *See* page 724, right column, "Drug administration" and "Dose escalation".

Regarding claims 14-16, Mita *et al.* disclose pharmacokinetic variables observed in patients at all tested dose levels, including AUC, Cmax, and clearance falling within the scope of the instant claims. *See* Table 5.

Regarding claims 17-19, Mita *et al.* disclose monitoring blood neutrophil counts, *i.e.*, absolute neutrophil counts (ADC), and that at the highest dose level (25 mg/m2), the ADC was ≤ 1,500 cells/mm3 (990) and at that dose level there were cases of Grade 3 and Grade 4 neutropenia. Mita *et al.* disclose that the rate of dose limiting toxicity (DLT) exceeded the predefined limits of tolerability at the 25 mg/m2 dose level. *See* Table 3; page 726, left column, second full paragraph.

Regarding anticancer activity, Mita et al. disclose that evidence of anticancer activity was observed in a patient with **prostate cancer metastatic to liver and bones** whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone. Further evidence of anticancer activity was observed in a patient with **hormone- and docetaxel-**

refractory prostate cancer metastatic to bone and iliac lymph nodes. *See* page 727, left column, "Anticancer activity".

Mita *et al.* differ from the instant claims in that while Mita *et al.* unequivocally teach, suggest, and motivate the administration of carbazitaxel to treat prostate cancer, including metastatic, hormone- and docetaxel-refractory prostate cancer, Mita *et al.* does not disclose combining carbazitaxel with prednisone.

Teachings of Tannock et al.

Tannock *et al.* disclose that mitoxantrone plus prednisone reduces pain and improves quality of life in men with advanced, hormone-refractory prostate cancer, but it does not improve survival. Tannock *et al.* disclose a study comparing the effects of docetaxel combined with prednisone to mitoxantrone combined with prednisone. *See* Title; Abstract.

Regarding claim 8, Tannock *et al.* disclose that prednisone was administered at a dose of 5 mg twice daily, thus teaching administration of prednisone at a dose of 10 mg/day. *See* Abstract; page 1504, left column, "Randomization and Treatment".

Regarding claims 17-19, Tannock *et al.* disclose that a dose reduction or treatment delay was stipulated for patient who had an absolute neutrophil count of

less than 1500 per cubic millimeter (for those receiving weekly docetaxel). See page 1504, right column, first full paragraph.

Tannock *et al.* disclose that when given with prednisone, treatment with docetaxel every 3 weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared to mitoxantrone plus prednisone, and conclude that **docetaxel plus prednisone is the preferred option for most patients with hormone-refractory prostate cancer**. *See* Abstract; page 1511, right column, last paragraph.

Principles of Law

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v.*

Teleflex Inc., 550 U.S. 398, 416 (2007). "In determining whether obviousness is established by combining the teachings of the prior art, 'the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.'" *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995).

"[I]in a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976).)

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer cabazitaxel in combination with prednisone as taught by Mita et al. in view of the teachings of Tannock et al. to patients with hormone-refractory prostate cancer previously treated with docetaxel.

One would have been motivated to do so because Mita et al. teach that cabazitaxel is effective in treating prostate cancer metastatic to liver and bones whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone and **hormone- and docetaxel-refractory prostate cancer** metastatic to bone and iliac lymph nodes when

administered as a single agent. The motivation to add prednisone to such treatment is clearly seen in Tannock *et al.*, who teach that administration of the taxane, docetaxel, in combination with prednisone is effective in treating hormone-refractory prostate cancer. As such, the skilled artisan would predict that addition of prednisone to the treatment regimen of Mita *et al.* would also be effective in treating hormone-refractory prostate cancer, including prostate cancers refractory to docetaxel therapy.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mita *et al.*** (Clinical Cancer Research, 2009, vol. 15, pages 723-730) (Published Online January 15, 2009) in view of **Tannock *et al.*** (N. Engl. J. Med., 2004, vol. 351, pages 1502-1512) as applied to claims 1-2, 4, 8-12, 13-19, and 24 above, and further in view of **Didier *et al.*** (US 2005/0065138 A1; Published Mar. 24, 2005).

Mita et al. and Tannock et al. teach as applied to claims 1-2, 4, 8-12, 13-19, and 24, supra, which teachings are herein incorporated by reference in their entirety. Claims 6-7 differ from Mita et al. and Tannock et al. in that the references do not disclose an acetone solvate of carbazitaxel.

Teachings of Didier et al.

Didier et al. disclose acetone solvates of carbazitaxel. *See* Abstract; Claims.

Didier et al. disclose acetone solvates containing between 5% and 8% of acetone. *See* page 1, [0020].

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer the acetone solvate of cabazitaxel in combination with prednisone as taught by Mita et al. in view of the teachings of Tannock et al. and Dinier et al.

The skilled artisan would expect that the acetone solvate of carbazitaxel would possess the same anticancer properties as the free base compound. As both carbazitaxel and the acetone solvate thereof were known in the art, selection of either one for use in treating prostate cancer would have been prima facie obvious to the skilled artisan.

Response to Arguments

Applicant submits that the claimed elements of the present invention were not known in the prior art and the combination of Mita and Tannock would not have provided a reasonable expectation of predictable results. Accordingly, Applicant respectfully submits that any presumption of obviousness based on the combination of these references is not warranted. In support of the above, Applicants present the following arguments.

Applicant argues that Mita nowhere suggests that one skilled in the art should use cabazitaxel for the treatment of prostate cancer based on these results, as the efficacy data provided is only "preliminary" evidence. Accordingly, given the extremely limited nature of the patients described in Mita and the complexity of treatment of cancer, Applicant argues that one skilled in the art would not have the requisite reasonable expectation that the results of this phase 1 trial would translate to patients with hormone refractory metastatic prostate cancer, who were previously treated with a docetaxel-containing regimen when evaluated in a statistically relevant setting (such as a Phase III trial).

This is argument is not persuasive because as taught by Mita and admitted by Applicants, Mita indicated that evidence of anticancer activity was noted in two patients, including one patient with "hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes." It is well established in the art that Phase I clinical trials are used as a basis for continuing Phase II and Phase III clinical trials. Given the documented evidence of anti-cancer activity in the Phase I trial taught by Mita against hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes, the skilled artisan would have been imbued with at least a reasonable expectation of success in treating such prostate cancer. This is clearly evidenced by Mita who in fact demonstrate that carbazitaxel is clinically effective in treating hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes. In response to Applicants' assertion that

that Mita nowhere suggests that one skilled in the art should use cabazitaxel for the treatment of prostate cancer based on these results, as the efficacy data provided is only "preliminary" evidence, this is precisely what Mita suggests. Mita in fact explicitly states, "[T]he general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258 [cabazitaxel]". See Abstract.

Applicant next argues that there is nothing in Tannock which would provide one skilled in the art with the reasonable expectation (or even prediction as asserted in the Office Action), that a combination comprising docetaxel would have any similar effectiveness when used in combination with cabazitaxel. Applicants assert that the Office Action provides no evidence or even arguments explaining why one skilled in the art would reasonably have such an expectation, especially in patients with docetaxel-resistant prostate cancer.

In response, the Examiner respectfully submits that Tannock teaches that docetaxel plus prednisone treatment led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared to mitoxantrone plus prednisone, and conclude that **docetaxel plus prednisone is the preferred option for most patients with hormone-refractory prostate cancer**. Based on this teaching, the skilled artisan would clearly and unequivocally be motivated to administer docetaxel plus prednisone to treating hormone-refractory prostate cancer. Taken together with the teachings of Mita, the

skilled artisan would have been motivated to substitute cabazitaxel for docetaxel in such as treatment regimen because Mita teaches that cabazitaxel is superior to docetaxel in many aspects including lower affinity for P-gp, a linear PK profile, and better tolerance and administration profile. Mita further teaches that cabazitaxel is effective in treating hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes. Thus, when viewed in combination, Mita et al. and Tannock et al. teach, suggest, and clearly motivate the administration of cabazitaxel and prednisone to treat patients with hormone- and docetaxel-refractory prostate cancer as presently claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in *ipsis verbis*, clarification on the record may be helpful). Should applicants present new claims, applicants should clearly identify where support can be found in the disclosure

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D. Anderson/

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	11	("20020038038" | "6372780" | "6331635" | "6387946" | "20050065138" | "5438072" | "7241907" | "5847170").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 09:58
L2	39	((SUNIL) near2 (GUPTA)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2013/09/10 09:59
L3	39	L2	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 09:59
L4	1	l3 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
L5	5090	Sanofi-aventis.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
L6	4061	"Aventis Pharma".as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
L7	8681	L5 or L6	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
L8	11	l7 and (cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:00
L9	197	(cabazitaxel or XRP6258)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:01
L10	29	l9 and (@ad<"20101027" or @pd<"20101027")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/09/10 10:01
S1	14	"5847170"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:37
S2	102	cabazitaxel	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:40
S3	21	cabazitaxel.clm.	US-PGPUB; USPAT; USOCR;	OR	ON	2013/01/11 12:40

			EPO; JPO; DERWENT			
S4	12	XRP6258	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 12:42
S5	38	((SUNIL) near2 (GUPTA)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2013/01/11 12:43
S6	4725	Sanofi-aventis.as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:15
S7	38	S6 and taxane	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:15
S8	9	("5229526" | "5319112" | "5486601" | "5739362").PN. OR ("5847170").URPN.	US-PGPUB; USPAT; USOCR	OR	ON	2013/01/11 14:18
S9	4016	"Aventis Pharma".as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:21
S10	67	S9 and taxane	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:21
S11	6	"2005065138"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:31
S12	3	"20050065138"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2013/01/11 14:31

EAST Search History (Interference)

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13456720	GUPTA, SUNIL
	Examiner	Art Unit
	JAMES D ANDERSON	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search	1/11/2013	JDA
EAST Search (see attached)	1/11/2013	JDA
STN Structure Search (see attached)	1/11/2013	JDA
Inventor Name Search	9/10/2013	JDA
EAST Search (see attached)	9/10/2013	JDA
STN Structure Search (see attached)	9/10/2013	JDA

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner