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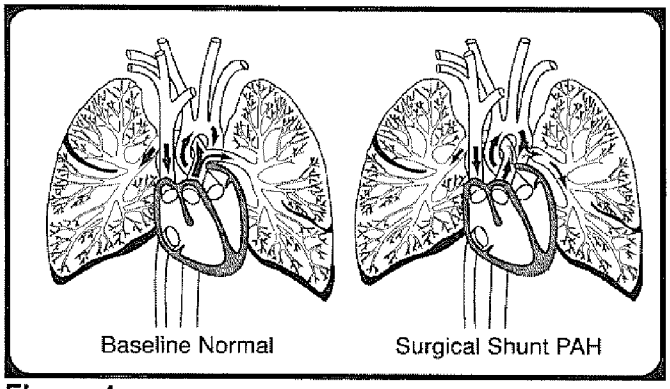

Figure 1

(57) Abstract: The present invention discloses multiple treatment regimens for vascular-related diseases and disorders. The present invention provides for methods of treating vascular-related disorders based on gene expression studies from samples collected from individuals having symptoms of vascular-related disorders. Additionally, methods are disclosed involving diagnostic techniques to focus treatment regimens. Finally, methods of treating vascular-related disorder involving targeting microRNAs are also disclosed.

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METHODS OF NOVEL THERAPEUTIC CANDIDATE IDENTIFICATION THROUGH GENE EXPRESSION ANALYSIS IN VASCULAR-RELATED DISEASES

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CROSS-REFERENCES

This application claims the benefit of priority of U.S. Provisional Application Ser. No. 61/040,065, filed on March 27, 2008, the disclosure of which is hereby incorporated by referenced in its entirety.

FIELD OF THE INVENTION

The present invention relates to assessment and identification of expression of genes related to vascular-related diseases. The present invention also includes methods of comparing gene expression patterns with respect to various disease states.

BACKGROUND OF THE INVENTION

Pulmonary arterial hypertension (PAH) is an occlusive disease of the pulmonary arteries leading to serious hemodynamic abnormality, right heart failure, and premature death. The molecular mechanisms behind PAH are still unclear. Without a more complete understanding of PAH and how its complex vascular dysfunctions relate to one another, patients will suffer from imprecise diagnosis and drug therapy that may be less than optimal. Despite recent advances and introduction of new clinically approved drugs, the 5-year survival from pulmonary hypertension remains an estimated 50% (Archer and Rich, 2000). Consequently, treatment for PAH, while recently improved, still offers significant and long-lasting improvement in only a minority of patients. A methodology to elucidate the molecular

pathways associated with PAH could guide the development of new therapies for this disease.

Though platelets and other cells may have a role in PAH, pulmonary endothelial cells and pulmonary smooth muscle cells appear to be the primary sites of disease progression (Humbert et al 2004). Molecular pathways that show abnormality in pulmonary endothelial cells and pulmonary smooth muscle cells during PAH include endothelin-1 (Giaid et al 1993), serotonin & serotonin transporter (Marcos et al 2003), thromboxane (Walmrath et al 1997), nitric oxide synthase (Kobs and Chesler 2006), prostacyclins (Gailes, et al 2001), potassium channels (Mandegar et al 2002), BMP signaling (Eddahibi et al 2002), and survivin (McMurtry et al 2005). PAH impairs normal signaling and growth in both pulmonary endothelial and pulmonary smooth muscle cells, yet the cellular abnormalities seem to shift over time in unpredictable patterns that has thus far escaped concise definition (Michelakis, 2006).

PAH may be understood as proceeding in phases. In early PAH, endothelial apoptosis occurs, probably resulting in pulmonary arteriole plugging and an increase in pulmonary vascular pressure (Michelakis, 2006). In late PAH, chronic exposure to elevated pulmonary artery pressure together with dysfunctional endothelial signaling initiates hyperproliferation of smooth muscle cells (McMurtry et al 2005). Increased concentric pulmonary smooth muscle cell proliferation leads to ever increasing pulmonary artery pressure, right ventricular failure, and death.

Lung pathology in all PAH patients show thickening throughout the arterial wall of the pulmonary vascular bed. In

some forms of the disease, the pulmonary vascular lesions are reversible (e.g. in newborns with congenital heart defects). In other patients, such as those with the idiopathic form, the lesions are irreversible. It is unknown how these variations in PAH relate to one another on a molecular basis (Pearl et al 2002).

Current therapies for PAH patients primarily target vascular tone. Treatments that aim at correcting potassium channel dysfunction (Machado et al 2001), nitric oxide impairment (Humbert et al 2004), prostacyclin impairment (Tuder et al 1999, Christman et al 1992), and endothelin-1 expression (Giaid et al 1993) have all been clinically available for several years. These therapies offer some relief from hemodynamic symptoms, but most patients show only a transient response. The proliferative disease continues to progress in most PAH patients, resulting in a five year mortality rate that remains at around 50% (Newman et al 2004).

Currently, there are no clinically available routine means to obtain endothelial and smooth muscle samples from the pulmonary arteries of pulmonary hypertension patients for diagnosis, disease staging or drug discovery. Applicant's earlier invention, described in US Patent No. 5,406,959, describes an endoarterial biopsy catheter that has demonstrated its safety and effectiveness in normal canines (Rothman, Mann et al., 1996), canines with experimentally-induced pulmonary hypertension (Rothman, Mann et al., 1998), and canines with single-sided lung transplant rejection (Rothman, Mann et al., 2003). Preliminary studies have also demonstrated the safety and efficacy of a catheter-based method to obtain endovascular samples from a porcine model of PAH.

Percutaneously-obtained pulmonary endoarterial biopsy samples were found to be of sufficient quantity and quality for porcine whole genome mRNA microarray analysis and microRNA analysis. Whole genome microarray analysis revealed time-sensitive variations in gene expression values as PAH progressed in the subject animal model. Genes previously shown to be associated with PAH displayed changes characteristic of the disease, and genes previously unassociated with PAH also displayed expression level dysregulation. These findings raise the possibility that the endoarterial biopsy catheter combined with microarray analysis may provide a valuable platform for the discovery of novel drug and biomarker targets in pulmonary hypertension and a platform to deliver individualized pharmacotranscriptomics.

MicroRNA analysis revealed pressure sensitive changes in microRNA expression. As our surgical shunt model of pulmonary hypertension progressed from a high flow low pressure (HFLP) manifestation to a high flow high pressure (HFHP) manifestation, different microRNAs became dysregulated either increasing or decreasing in expression relative to our baseline normal values.

Most new therapies promise to focus on arresting either the endothelial apoptosis that characterizes early PAH (angiopoetin-1 & endothelial nitric oxide synthase cell-base gene transfer (Zhao et al 2003; 2005), caspase inhibitors (Taraseviciene-Stewart et al 2001)) or the smooth muscle cell proliferation typical of late PAH (dichloroacetate (McMurtry et al 2004), simvastatin (Nishimura et al 2003), sidenafil (Wharton et al 2005), imatinib (Schermuly et al 2005), anti-survivin (McMurtry

et al 2005), K+ channel replacement gene therapy (Pozeg et al 2003)).

Before administering therapies, however, it would be extremely valuable to determine which genes are dysregulated in each PAH patient at any stage of their individual disease progression. Without knowing what genes are aberrant during any point in the patient's disease course, targeted therapies may miss the mark in some patients. Life threatening side effects may emerge if the wrong cells, at the wrong time, are encouraged to die or proliferate in patients with compromised pulmonary vascular health.

A powerful method for determining the gene expression levels of thousands of genes simultaneously are DNA microarrays. Initially used for the classification of cancers that were difficult to discriminate histologically (Golub et al 1999, Bhattacharjee et al 2001, and Ramaswamy et al 2001), microarrays have been more recently applied to PAH (Geraci et al 2001). PAH microarray studies have been performed on whole lung homogenates in humans (Fantozzi et al 2005) and rats (Hoshikawa et al 2003), surgically-dissected pulmonary arteries in pigs (Medhora et al 2002), laser-microdissected pulmonary arteries in rats (Kwapiszewska et al 2005), and mononuclear peripheral blood in humans (Bull et al 2004). These studies have been performed to discover potentially novel PAH disease pathways, biomarkers, therapeutic targets and patient classification gene expression profiles.

To advance PAH microarray studies into practical clinical use, tissue procurement methodologies are required that do not require surgical explant or postmortem procurement, and

peripheral blood has thus far proven to be inadequate to discriminate gene expression signatures between subgroups of PAH patients (Bull et al 2004; Bull et al 2007). To take advantage of the full power of microarray technologies in PAH patients, a safe and effective minimally invasive means for the repeat procurement of endovascular samples from living PAH patients is required.

The present invention provides for the use of a novel interventional catheter, an endoarterial biopsy catheter, to obtain serial biopsy specimens from hypertensive pulmonary vessels for analysis. The ability to procure endothelial and smooth muscle samples in a minimally invasive manner will allow physicians to use microarray profiling and other techniques to classify patients upon initial presentation according to their gene expression signatures, prescribe therapies that target genes empirically found to be dysregulated in each individual patient, and monitor and adjust PAH patient therapy according to subsequent biopsy findings. A greater understanding of the complex molecular pathways underlying each patient's PAH should enable more precise diagnosis and the delivery of more effective therapies. Also of importance is the ability to discover new uses for existing drugs as well as discovering new drug targets.

Individualized pharmacotranscriptomics based on endoarterial biopsy and microarray analysis represents a reasonable choice for researchers struggling with the complexities and contradictions of PAH and other vascular diseases. The huge literature generated from in vitro and animal studies falls short, at times, in addressing the actual facts of patient health. Many commentators describe this dilemma as the "bench-to-bedside gap", where in vitro and animal

laboratory data fails to model human disease circumstances (Aird, 2004). Bridging that gap through catheter-based access to the vasculature in a model that recapitulates the clinical and histopathological manifestations of a form of human pulmonary hypertension will likely enable closer correlations between animal studies and patient care, and serve as a model for other vascular-based diseases such as atherosclerosis, congestive heart failure, sickle cell disease, organ transplant rejection, connective tissue diseases, chronic obstructive pulmonary disease, pulmonary embolism, asthma, systemic inflammatory response, battlefield trauma, cancer, sepsis and acute respiratory distress syndrome. There is a need in the art to provide data from gene expression analyses in order to target novel candidates for use in treating or preventing PAH.

SUMMARY OF THE INVENTION

One aspect of the present invention provides for methods of treating an individual suffering from a vascular-related disease comprising the steps of:

a) obtaining a biopsy sample from the individual's pulmonary artery;

b) analyzing gene expression levels of the biopsy sample from the pulmonary artery of the individual and a non-diseased control;

c) comparing the gene expression levels between the biopsy sample from the pulmonary artery of the individual and the non-diseased control;

d) identifying at least one gene from step c) that is upregulated or downregulated in the biopsy sample based on the non-diseased control;

e) obtaining gene products from the genes identified in step c); and

f) selecting pharmaceutical agents which are known inhibitors of the gene products from the at least one upregulated gene or known promoters of the gene products from the at least one downregulated gene. An additional aspect to the present invention provides for the pharmaceutical agents selected for administration to the individual suffering from the vascular-related disease. In yet another aspect, the individual is categorized based on progression of the vascular-related disease, with the treatment being based on the timing of the disease.

Another aspect of the present invention provides for a means of comparing varying levels of gene expression based on an animal model for pulmonary arterial hypertension. In a preferred embodiment, the genes expressed in the animal model are genes found to be either upregulated or downregulated. In a more preferred embodiment, the upregulated or downregulated genes are time-dependent based on the time after exposure to the PAH.

Another aspect of the present invention provides for methods of identifying genes involved in the pathway of PAH based on differential gene expression studies in a time-dependent animal model for PAH. In one embodiment, the genes are compared to other known genes which are upregulated or downregulated in the known PAH pathway.

Yet another aspect of the present invention provides for methods of diagnosing a vascular-related disease in an individual comprising the steps of:

a) identifying at least one gene that is upregulated or downregulated in the vascular-related disease comprising the steps of:

1) obtaining a biopsy sample from the individual's pulmonary artery during progression of the vascular-related disease;

2) obtaining a pulmonary artery sample from a non-diseased control;

3) extracting RNA from the samples in steps 1) and 2);

4) obtaining gene products from the RNA extracted in step 3); and

5) comparing gene expression levels from the biopsy sample with the non-diseased control, and

b) associating the genes upregulated in the biopsy sample with an inhibitor of the gene products for administration to the individual and genes downregulated in the biopsy sample with a promoter of the gene products for administration to the individual.

Another aspect of the present invention provides for methods of treating an individual having a vascular-related disease by targeting microRNAs comprising the following steps:

a) assessing a stage of the vascular-related disease in the individual;

b) identifying whether microRNAs are upregulated or downregulated;

c) selecting the microRNAs to target based on the stage of the vascular-related disease and whether the microRNAs are upregulated or downregulated; and

d) administering an agent known to inhibit an upregulated microRNA or an agent known to promote a downregulated microRNA

to the individual. A variation of this embodiment provides for the stage of the vascular-related disease being based on flow rates and blood pressure within an artery of the individual.

Another aspect of the present invention provides for methods of therapeutically targeting microRNA dysregulated in PAH comprising the steps of:

(a) obtaining a biopsy sample from the pulmonary artery during the progression of PAH;
(b) obtaining a pulmonary artery sample from a non-diseased control;
(c) extracting RNA from the artery samples;
(d) converting the RNA to cDNA;
(e) comparing levels of microRNA expression at the two differing times;
(f) identifying microRNA dysregulated in PAH relative to baseline; and
(g) inhibiting upregulated microRNA or promoting downregulated microRNA identified in PAH biopsies.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a surgical shunt model of PAH and its association with congenital heart disease (CHD).

Figure 2 depicts the endoarterial biopsy procedural configuration.

Figure 3 depicts biopsies: normal vessels at baseline, hypertensive LPA at 7, 21, 60 and 180 days post shunt.

Figure 4 depicts GeneSpring downstream analysis of microarray data.

DETAILED DESCRIPTION OF THE INVENTION

The model described in the present invention is surgically-induced PAH in pigs. Our model mimics human Eisenmenger syndrome (a form of PAH related to congenital heart malformation) in both symptoms and pathology (Corno et al 2003). The size of the animals makes the pulmonary vessels available to the catheter, providing a ready transition to human clinical use. And finally, the commercial availability of whole genome porcine microarrays (Bai et al 2003) makes the species ideal for our purposes in the study, and renders the use of cross species microarrays unnecessary (Medhora et al 2002).

By obtaining pulmonary endovascular samples at early, intermediate and late time points in PAH progression, and analyzing these samples using porcine whole genome microarrays, a time-sensitive microarray based map of the underlying molecular biology of PAH may be obtained. Improved knowledge of the molecular mechanisms underlying PAH progression can lead to the identification of stage-specific biomarkers, new therapeutic targets for drug intervention, and novel signaling pathways involved in the pathogenesis of PAH. These novel target genes can then be validated using quantitative PCR and immunohistochemical stains on porcine endoarterial biopsy samples procured concurrently. At the same time, the combination of minimally invasive endoarterial biopsy and whole genome microarray analysis can serve as an animal model for subsequent studies in PAH patients.

The following examples provided in this disclosure provide a profile gene expression in pulmonary hypertensive pigs by surgical anastomosis of the left pulmonary artery to the descending aorta. Endoarterial biopsy samples are collected from animals with a surgical shunt model of pulmonary hypertension at multiple time points over a 6-month time course. Gene expression analysis of the biopsy samples was performed on porcine microarrays. Microarray analysis was performed to detect dysregulated genes previously unassociated with PAH, discover novel biomarkers of pulmonary hypertension and novel targets for therapeutic intervention and advance knowledge of the molecular mechanisms of pulmonary hypertension. These studies will also help validate a new platform for PAH diagnosis and drug discovery, endoarterial biopsy and microarray analysis, for eventual clinical practice.

EXAMPLES

Example I: Construction of a microarray-based map of changes in gene expression during the progression of PAH and the identification of novel therapeutic candidates

In an animal model of PAH created by Antonio Corno and colleagues, pigs undergo surgery that redirects systemic circulation into the left pulmonary artery mimicking pulmonary hypertension secondary to congenital heart disease. The surgery elevates PA pressure and creates the same hemodynamic conditions that PAH patients experience. The present study investigates how the elevated pressure remodels the pulmonary vasculature. In Corno's studies, histology on necropsy confirmed intimal hyperplasia in the pulmonary arteries, evidence that the surgical shunt surgery described will cause endovascular remodeling (Corno et al 2003).

Biopsy Extraction and Surgery Protocol

20-30 kg Yucatan Micropigs (*Sus scrofa*, Yucatan micro breed) underwent surgical anastomosis of the left pulmonary artery to the descending aorta, resulting in left pulmonary arterial hypertension of at least ½ systemic levels. Animals are penned in the laboratory for no less than one week prior to surgery and fed normal chow. On surgery day, animals were premedicated with 20mg/kg intramuscular ketamine and 0.1 mg/kg intramuscular midazolam. After 0.25 mg of intramuscular atropine, anesthesia was induced with 1 mg/kg intravenous midazolam and 0.1 mg/kg intravenous fentanyl and maintained with 0.1 mg/kg/hr intravenous pancuronium bromide. Pigs were ventilated with an inspired oxygen fraction (FiO2) of 0.4, a tidal volume of 15 ml/kg, and a respiratory rate of 12 breaths/minute. One gram of intravenous cefazolin was given before and 2 hours after the surgical procedure. Surgical and catheter procedures were performed under general anesthesia with endo-tracheal intubation. Sedation medications and anesthetics were administered by an anesthesiologist. Intra-cardiac and intravascular pressures, EKG, and blood oxygen saturations were monitored continuously.

Under sterile conditions (the thoracic area was shaved and prepared with betadine, a left thoracotomy was performed through the fourth intercostal space, about 5 centimeters, to expose the great arteries. The main pulmonary artery (MPA) and its branches were identified and freed from surrounding tissue. Two clamps were placed on the proximal left pulmonary artery (LPA). The proximal LPA was sutured closed, using prolene, and the distal LPA was sutured end to side in a clamped region in the descending aorta (Figure 1), using cardiovascular prolene.

Pieces of LPA endoarterial tissue were taken for histology. The clamps were removed and an IV dose of 1 mg/kg Furosemide immediately given. Hemostasis was obtained with sutures and cautery. Direct needle blood pressures were recorded in the main pulmonary artery and in the newly anastomosed left pulmonary artery. The chest was closed with sutures, both subcutaneous and cutaneous layers, using prolene and surgical wire. The animals then were weaned from anesthesia and mechanical ventilation. Postoperative analgesia was provided with morphine four times a day and a 1-2 mg/kg dose from 0.25% solution of IV Bupivacaine, a local anesthetic. A circulating warming blanket was used during surgery and recovery.

Endoarterial biopsies were performed at baseline prior to surgery to obtain unaffected tissue, and at post-shunt timepoints to obtain hypertensive biopsy samples (Figure 2). Follow up endoarterial biopsy procedures were scheduled 7, 21, 60 and 180 days after surgery. On each catheterization day, animals were premedicated with 10 mg/kg of IV propofol, were intubated and ventilated at a rate of 12 breaths/min and were maintained under anesthesia with 1.5% halpthane. A femoral artery line was placed for monitoring. To obtain biopsies from the hypertensive left lung, an 8F introducer is placed in a carotid artery, and a 7F endhole catheter is advanced into the aorta. An angiogram is performed to visualize the LPA- aortic anastomosis. The 7F endhole catheter is then threaded through the anastomosis with X-ray fluroscopic guidance. An angiogram of the hypertensive left pulmonary vascular tree is then performed, and the catheter is advanced to the distal pulmonary artery selected for biopsy. A 0.038 in, 260 cm extra stiff Amplatz exchange guide wire will then be passed through the end-hole catheter. The end-hole catheter was exchanged for a long

flexible 8F introducer sheath that is adapted with a radio opaque band at the distal end and shaped to conform to the vascular pathway. A 7F angiographic catheter was advanced through the sheath in to a 2.5 mm to 3.0 mm distal pulmonary artery branch, where an angiogram was obtained. The angiographic catheter will serve as a guide to advance the stiff sheath into a small vessel targeted for biopsy and will then be exchanged for the endoarterial biopsy catheter.

The endoarterial biopsy catheter has an external diameter of 2.5 mm and is composed of two flexible polymeric tubes that slide relative to each other. The inner tube has a stainless steel distal end with a beveled opening that is designed to accommodate arterial tissue. A vacuum is coupled to the inner tube and channeled to the beveled opening. The outer tube terminates in a stainless steel cutting tube. The proximal ends of the two tubes are with a spring powered operating mechanism. To obtain the biopsy sample a vacuum is transmitted to the beveled opening of the inner tube, causing a tissue sample to be drawn in. The outer tube is then advanced over the inner tube, severing the tissue sample. With this design, the area of artery contacted by the outer periphery of the beveled opening is larger than the inner aperture connected to the vacuum, this maintaining the tissue sample with its orientation preserved. After each biopsy, the catheter was removed and the tissue sample was placed in the appropriate solution for further processing and analysis. After the biopsy procedures were completed, repeated angiograms were obtained to assess the degree of vascular injury. At the end of the procedure, the biopsy catheter and introducer sheath were removed and hemostasis was obtained by surgical repair of the carotid artery. The animals will then be weaned from anesthesia and

mechanical ventilation. Postoperative analgesia was provided with morphine four times a day and or fentanyl patches and non-steroidal anti-inflammatory drugs four times a day.

Tissue processing

For microarray analysis, biopsy samples are placed in a test tube containing RNAlater (Qiagen), flash frozen in dry ice, and kept frozen until RNA extraction. Additional samples are preserved in formalin, OCT freezing solution, or Bouin's solution for subsequent immunohistochemical and quantitative PCR analysis.

Porcine Genome Arrays

The Affymetrix GeneChip® Porcine Genome Array provides comprehensive coverage of the *Sus scrofa* transcriptome. The array contains 23,937 probe sets that interrogate approximately 23,256 transcripts from 20,201 *Sus scrofa* genes.

The sequence information for this array was selected from public data sources including UniGene Build 28 (August 2004), GenBank® mRNAs up to August 24, 2004, and GenBank® porcine mitochondrial and rRNA sequences. Probe sets consist of up to eleven probe pairs. The array format consists of eleven micron features synthesized on the 100 format.

RNA Extraction from Endoarterial Biopsy Samples

RNA was prepared from fresh frozen endoarterial biopsy samples in a segregated laboratory, specially prepared and cleaned regularly to destroy nucleases. Specimens were homogenized using QIAshredder columns (Qiagen, Valencia, CA) utilized in a FastPrep FP120 Homogenizer (Thermo Electron Corporation, Waltham, MA). RNA was isolated using RNeasy Mini

columns (Qiagen, Valencia, CA) as per manufacturer's protocol. All total RNA was eluted in nuclease free water, and quantity was established by UV spectrophotometer. Final RNA integrity was evaluated by capillary electrophoresis on the Agilent 2100 Bioanalyzer (Agilent, Palo Alto, CA).

Gene Expression

Before target production, the quality and quantity of each RNA sample was assessed using a 2100 BioAnalyzer (Agilent). Target was prepared and hybridized according to the "Affymetrix Technical Manual". Total RNA (ug) was converted into cDNA using Reverse Transcriptase (Invitrogen) and a modified oligo (dT)24 primer that contains T7 promoter sequences (GenSet). After first strand synthesis, residual RNA was degraded by the addition of RNaseH and a double-stranded cDNA molecule was generated using DNA Polymerase I and DNA Ligase. The cDNA will then be purified and concentrated using a phenol:chloroform extraction followed by ethanol precipitation. The cDNA products will then be incubated with T7 RNA Polymerase and biotinylated ribonucleotides using an In Vitro Transcription kit (Enzo Diagnostics). One-half of the cRNA product was purified using an RNeasy column (Qiagen) and quantified with a spectrophotometer. The cRNA target (20ug) was incubated at 94°C for 35 minutes in fragmentation buffer (Tris, MgOAc, KOAc). The fragmented cRNA was diluted in hybridization buffer (MES, NaCl, EDTA, Tween 20, Herring Sperm DNA, Acetylated BSA) containing biotin-labeled OligoB2 and Eukaryotic Hybridization Controls (Affymetrix). The hybridization cocktail was denatured at 99°C for 5 minutes, incubated at 45°C for 5 minutes and then injected into a GeneChip® cartridge. The GeneChip® array was incubated at 42°C for at least 16 hours in a rotating oven at 60 rpm. GeneChips® were washed with a series of nonstringent (25°C) and stringent

(50°C) solutions containing variable amounts of MES, Tween20 and SSPE. The microarrays will then be stained with Streptavidin Phycoerythrin and the fluorescent signal was amplified using a biotinylated antibody solution. Fluorescent images were detected in a GeneChip® Scanner 3000 and expression data was extracted using the GeneChip® Operating System v 1.1 (Affymetrix). All GeneChips® were scaled to a median intensity setting of 500. Gene expression levels were compared between biopsy samples taken from the control distal pulmonary vasculature (baseline LPA and RPA) and PAH distal pulmonary arteries (surgical shunt LPA).

Gene Expression Analysis

After RNA preparation, array hybridization and scanning of the Porcine GeneChips® exactly as recommended by Affymetrix, the data produced are processed using the Affymetrix tools in the R-Bioconductor package called /Affy/. This tool set allows for various probe level analyses of the data as well as probe level quality control. The MAS5 algorithm was used, taking into account both the MM and PM probe data, and generating "Present" or "Absent" calls for each gene on each chip. If boxplots of the porcine probe level data reveal that any of the hybridizations are of low quality, the data from these chips was removed from any downstream analysis. MAS5 with the non-linear Quantiles normalization (Affy package /normalize.quantiles)/ was used with this data set to produce data almost free of artificial correlations. The Present/Absent calls are also used to remove from the analysis the genes that were never expressed in any of the samples examined (this is analogous to using a P-value for gauging a gene's data quality on a chip, and then filtering).

Based on the first dozen chips processed, after normalization and quality control ~19,000 genes were moved on to the next stage of the analysis. The commercial package GeneSpring was used to assess differential gene expression and perform tests using clustering algorithms. Thus far, hierarchical clustering has revealed that the time-point replicates have the greatest similarity to one another.

Gene expression fold changes for 7, 21 60 and 180 days post-surgery relative to baseline were then loaded into GSEA (gene set enrichment analysis) or specially written PERL scripts which carry out KS (Kolmogorov-Smirnov) statistical analysis in order to identify novel therapeutic candidates.

Novel Therapeutic Identification

During PAH the best therapeutic targets are those which are upregulated as the disease state progresses. Thus drugs which are known to counter the action of any upregulated genes and their products would be of the greatest potential therapeutic value. Therefore, lists of upregulated genes were then matched to drugs which target their gene products.

In addition, many drugs interact with multiple targets in the body's tissues. Lists of the targets (called genesets) for each of ~2000 characterized drugs were obtained from the literature and online databases. These genesets were then used to search for drugs which would be most likely to have therapeutic value in PAH.

This was done by using KS statistics which computes the Kolmogorov-Smirnov score for a geneset for a particular drug within an ordered list. The *KSscore* task is used to examine the

enrichment of a set of genes at the top of an ordered list. The KS score is high when the tags appear early (*i.e.* near the top) of the ordered list. The significance of the KS score for a particular test may be examined by computing KS scores for multiple sets of *X* query genes selected at random from the dataset (note that the KS score is not independent of the number of members of the query gene set). Using this approach we were able to identify in our messenger RNA expression dataset drugs which are currently used as therapeutics for PAH (see Fig 1A). Importantly, using the same approach we were also able to identify additional potential therapeutics, within the existing pool of characterized drugs. This process identified existing drugs as novel therapeutics for PAH.

Example II: Gene expression analysis from porcine animal model data

Gene Expression Analysis

The porcine studies indicate that single endoarterial biopsy samples obtained in the porcine model of surgical shunt PAH contain sufficient RNA for microarray analysis, as we were able to analyze the mRNAs in whole genome porcine microarrays. We obtained endoarterial biopsies and measured pulmonary arterial pressure (PAP) at baseline prior to surgery, and at approximately 7, 21, 60 and 180 days post-PAH surgery from several animals. Porcine whole genome expression values were obtained for biological replicates with 2 samples from each time point. These replicates produced 5 sets of high quality replicated expression data (baseline, day 7, day 21, day 60 and day 180; see Table 1 for PAP data). Downstream data analysis was carried out using commercial (Ingenuity; GeneSpring) and free/open source software (R; Bioconductor; GSEA).

Mean expression values were obtained for each gene by averaging the gene expression values of the two biopsies at each timepoint. The resulting gene expression mean values were used to calculate fold changes between day 7, 21, 60 and day 180 gene expression relative to baseline.

Validity of the model was confirmed by examining the gene expression changes for selected genes previously found to be dysregulated in PAH (Table 2). Endothelin 1 and protein-tyrosine kinase Tie2 both displayed upregulation in accordance with explanted tissue from IPAH transplant recipients (Dewatcher et al 2006), and platelet-derived growth factor receptor alpha, serotonin receptors 2B and 1D, calmodulin, transcription factor STAT5b, voltage-dependent anion channels 1,2 and 3, and RAS p21 protein activator 1 also increased in our model while tumor necrosis factor and plasminogen activator inhibitor-1 were found to be downregulated in our model in a similar fashion with IPAH explant tissue results (Fantozzi et al 2005). Survivin was upregulated in our model in a similar fashion to published findings (McMurtry et al 2005), and FYN and VAV-1 oncogenes, requiem homolog, inward rectifier K + channel, and chloride channel 1 also increased while DEAD/H box polypeptide 3 and angiopoietin 1 displayed decreased expression in agreement with patient findings (Geraci et al 2001). We also observed decreased expression of peroxisome proliferator-activated receptor gamma (Ameshima et al 2003), and downregulated vascular endothelial growth factor B (Louzier et al 2003) in correspondence with previous results. The concordance between genes previously found to be aberrant in published PAH studies and altered gene expression in our model attest to the validity and potential usefulness of gene expression data derived from endoarterial

biopsies. The time dependent nature of gene expression dysregulation found in our model further demonstrates the utility of obtaining endoarterial biopsies at multiple time points in PAH progression.

While several of these genes have been previously associated with PAH (for example, KCBN1, CASP3, TLR4, IL1B, IL6, HMGCR, TOP1, FYN, PRKCA, EDNRB, PDGFRA, and HRT2B), several have not (for example, HSPE, YES1, CFTR, MAOA, MAOB, and CACND21), raising the intriguing possibility that known existing drugs that target upregulated genes previously unassociated with PAH may be effective in treatment of the disease.

Example III: Identification of dysregulated microRNA during the progression of PAH

Endoarterial biopsy samples percutaneously obtained during the progression of PAH were analyzed to correlate changes in microRNA expression to disease progression.

microRNA Expression data analysis

Data analysis was done in three stages. First, expression intensities were calculated for each miRNA probed on the array for all hybridizations (12 in total) using illumina's Beadstudio Version 3.0 software. Second, intensity values were quality controlled and normalized: quality control was carried out by using the illumina Beadstudio detection P-value set to <0.05 as a cutoff. This removed miRNAs which were effectively absent from the arrays (that is, were never detected). After this step, the initial 1145 miRNAs were reduced to 1094. All the arrays were then normalized using the *normalize.quantiles* routine from the

Affy package in Bioconductor. This procedure accounted for any variation in hybridization intensity between the individual arrays

Finally, these normalized data were imported into GeneSpring and analysed for differentially expressed miRNAs. The groups of biological replicates were described to the software and significantly differentially expressed genes determined on the basis of Welch t-tests and fold difference changes in expression level. The determination of miRNA targets genes was done using a publicly available database of miRNA target sequences and a specially written PERL programming script.

miRNA Pressure Related Analysis

The data was also looked at to reflect the stages of the disease (based on blood pressure and flow rates), as opposed to the time point or the individual pigs. Three groups were defined (1) Normal (baseline); (2) High Flow Low Pressure 'HFLP' and (3) High Flow High Pressure 'HFHP' (see Table 11). The groups were compared back to the baseline and the statistically significantly differentially regulated miRNAs determined (Tables 12, 13, 14 & 15).

Using illumina microRNA expression microarrays, fluctuations in the level of expression of ~1200 microRNAs were determined during the onset and progression of PAH. Porcine and Homo sapiens miRNA sequences are very often highly conserved. Expression comparisons were done on a timepoint basis, taking in account the available replicates and the statistical significance of the expression changes. The data was also looked at to reflect the stages of the disease (based on blood pressure and flow rates), as opposed to the time point or the individual

pigs. Three groups were defined (1) Normal (baseline); (2) High Flow Low Pressure 'HFLP' and (3) High Flow High Pressure 'HFHP'. The groups were compared back to the baseline and the statistically significantly differentially regulated miRNAs determined.

Finding micro RNAs with potential as therapeutic targets

The messenger RNA expression data set was analysed looking for expression changes in sets of genes with known target sites for particular miRNAs. miRNAs are known to negatively regulate gene expression at the level of translation by binding to upstream regions of mRNA and blocking events required for translation of the mRNA into protein. This was again done using Gene Set Enrichment Analysis (GSEA) and the publicly available miRNA genesets. "Cross-talk" is seen between the messenger RNA gene expression changes and the microRNA expression changes. The messenger RNA expression analysis directly revealed the differential expression of groups of genes competent to be regulated by these miRNA.

Example IV: Personalizing Therapeutic Regimens for Vascular-based Diseases

The use of gene expression data to shape individual drug therapies has been postulated as the next phase in personalized medicine. The bioinformatic processing of an individual's gene expression data can be used to generate a ranked list of therapies suitable for that individual. PAH disease pathology varies greatly over time, and is also likely to be specific for particular individuals. The analysis of the RNA in the PAH biopsy samples allows therapies to be tailored to the individual at that particular stage of the diseases progression.

The genes and biochemical pathways changing the most at the level of gene expression can be determined by comparing the PAH biopsy samples to a baseline control of normal healthy vasculature tissue. Observations show time-dependent extensive changes in gene expression with the progression of PAH. Known targets for approved PAH therapeutics can be seen Up-regulated in the diseased state.

Drug therapies can be ranked by using the known targets of drugs as genesets. These drug signature lists can then be used in a process such as Gene Set Enrichment Analysis, or KS statistics. KS Statistics returns a score for how well ranked a particular drug would be for a particular patient.

A drug is represented as the set of its known target genes; this can be in the dozens for some bioactive compounds. Genesets for ~2000 drugs were assembled. KS Statistics yields a value ('KS score') representing the positional distribution of the set of query genes (here, the drug targets) within an ordered list of genes (genes induced in PAH). The ordered list is produced by looking at the fold change in a mRNAs expression between time X and the baseline, and sorting on this value. The gene with the greatest fold change is ranked as #1, second greatest fold change is ranked as #2, etc. KS score is computed in accordance with the Kolmogorov-Smirnov non-parametric rank statistic where X is the number of genes in the query gene set, Z is the number of genes in the ordered list, and Y = Z - X. A suitable baseline is generated using gene expression from artery samples from non-diseased controls. These samples can be obtained surgically, percutaneously or post-mortem.

This process can be repeated for all the PAH time points and the resulting table of KS scores for each drug hierarchically clustered. This reveals which drugs are potentially of the greatest therapeutic value for a patient.

This supports the idea of achieving personalized treatments for vascular-based diseases by generating individualized drug prescriptions based on the bioinformatic processing of gene expression data from endoarterial biopsy samples obtained from diseased arteries. Similarly, this enables personalized treatments for vascular-based diseases by generating lists of dysregulated microRNA from the bioinformatic processing of microRNA expression data from endoarterial biopsy samples from diseased arteries.

Table 1

Pulmonary arterial pressures obtained during endoarterial biopsy catheterization for biopsy samples used in microarray analysis.

	Pulmonary Arterial Pressure mmHg		
Biopsy Sample	Systolic	Diastolic	Mean
Baseline Pig #9	22	11	17
Baseline Pig #10	25	16	18
Day 21 Pig #2	95	66	82
Day 21 Pig #6	41	26	33
Day 60 Pig #6	87	59	74
Day 60 Pig #5	49	27	38

TABLE 2

Selected genes previously associated with PAH similarly dysregulated in the porcine model.

Gene Symbol	Name	Baseline	Day 7	Day 21	Day 60	Day 180	Fold Change Day 7/Base	Fold Change Day 21/Base	Fold Change Day 60/Base	Fold Change Day 180/Base
VAV1	vav 1 oncogene	32.56	21.65	237.16	138.29	15.39	-1.50	7.28	4.25	-2.12
RASA1	RAS p21 protein activator 1	73.23	388.68	280.27	704.56	361.25	5.31	3.83	9.62	4.93
TIE2	protein-tyrosine kinase Tie2	20.92	2.59	32.46	702.68	218.34	-8.08	1.55	33.59	10.44
FYN	fyn proto-oncogene	43.33	180.38	404.77	531.03	166.17	4.16	9.34	12.26	3.83
VDAC1	voltage-dependent anion channel 1	1176.57	2350.33	6629.76	3144.14	2277.10	2.00	5.63	2.67	1.94
PDGFRA	platelet-derived growth factor receptor alpha	69.46	152.75	10.45	611.81	18.80	2.20	-6.64	8.81	-3.69
5-HT2B	serotonin 2B receptor	49.96	19.03	166.45	142.91	488.77	-2.63	3.33	2.86	9.78
KCNJ2	inwardly rectifying potassium channel KIR6.1	389.66	83.23	1059.11	212.29	84.28	-4.68	2.72	-1.84	-4.62
5-HT1D	serotonin 1D receptor	14.17	42.48	8.32	61.48	4.95	3.00	-1.70	4.34	-2.86
DPF2	requiem, apoptosis response zinc finger gene	140.95	123.89	140.90	195.55	93.92	-1.14	-1.00	1.39	-1.50
VDAC2	Voltage-dependent anion channel 2	5683.09	2665.62	1620.37	4940.32	3643.38	-2.13	-3.51	-1.15	-1.56
STAT5B	signal transducer and activator of transcription 5b	469.40	571.47	1327.53	808.09	626.07	1.22	2.83	1.72	1.33
AGPT	angiopoietin 1	17.825026	50.240685	11.806807	70.12715	3.4479218	2.82	-1.51	3.93	-5.17

BIRC5	apoptosis inhibitor survivin	169.33	751.37	140.45	31.26	44.69	4.44	-1.21	-5.42	-3.79
VDAC3	voltage-dependent anion channel 3	4092.99	750.86	5013.26	959.72	2018.55	-5.45	1.22	-4.26	-2.03
PLANH1	plasminogen activator inhibitor I	27760.742	43007.71	23685.375	28771.838	36086.305	1.55	-1.17	1.04	1.30
PPARG	peroxisome proliferator-activated receptor gamma 2	177.80	12.86	18.96	194.20	62.40	-13.83	-9.38	1.09	-2.85
CALM1	Calmodulin	3092.78	2436.23	867.25	1401.38	2252.81	-1.27	-3.57	-2.21	-1.37
APOE	apolipoprotein E	358.91	206.34	94.35	129.60	288.79	-1.74	-3.80	-2.77	-1.24

TABLE 3

Day 7 prescription.

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.11018.1.A1_at	Mitogen-activated protein kinase 14	39.80	-5.02	-17.27	-20.43	MAPK14	SCIO-469, RO-3201195
Ssc.15986.1.S1_at	Insulin receptor	29.28	-16.85	-17.70	-19.01	INSR	insulin, insulin aspart, insulin glulisine, insulin lispro, insulin glargine
Ssc.873.1.S1_at	Cell division control protein 2	27.38	-2.37	-4.66	-7.76	CDC2	flavopiridol
Ssc.29928.1.A1_at	Histone deacetylase 11 (HD11)	21.56	-3.17	-2.91	-10.50	HDAC11	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.100.1.S1_at	Tumor necrosis factor precursor (TNF-alpha)	18.41	-1.70	-9.62	-3.15	TNF	adalimumab, etanercept, infliximab, CDP870, golimumab, thalidomide
Ssc.19672.1.S1_at	RAC-alpha serine/threonine-protein kinase	17.77	1.25	-19.82	-2.11	AKT1	enzastaurin
Ssc.14475.3.S1_a_at	Peroxisome proliferator activated receptor gamma (PPAR-gamma)	13.83	-9.38	1.09	-2.85	PPARG	rosiglitazone, GI262570, pioglitazone, tesaglitazar, troglitazone
Ssc.14326.1.A1_at	Mitogen-activated protein kinase 13	12.63	1.56	-1.80	-7.24	MAPK13	SCIO-469
Ssc.25843.1.S1_at	Chloride channel protein 2 (ClC-2	11.77	-17.04	-21.97	-9.92	CLCN2	lubiprostone
Ssc.16201.1.A1_at	Metabotropic glutamate receptor	10.79	-35.68	-33.34	-47.92	GRM7	fasoracetam
Ssc.11381.1.S1_at	Interferon-alpha/beta receptor alpha chain	10.45	8.08	2.61	-1.30	IFNAR1	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							IFNA2A
Ssc.5371.1.S1_a_at	DNA polymerase epsilon subunit B (DNA polymerase II subunit B)	10.16	1.68	-1.37	-3.14	POLE2	gemcitabine
Ssc.14471.1.S1_at	B-lymphocyte antigen CD19	9.54	3.30	-10.32	3.04	CD19	combotox, HD37-dgRTA, MT103
Ssc.24856.1.A1_at	phosphodiesterase 11A; cyclic nucleotide phosphodiesterase 11A1	9.36	-2.70	-3.68	-2.68	PDE11A	dyphylline, nitroglycerin, aminophylline, dipyridamole, tolbutamide, tadalafil, theophylline, pentoxifylline
Ssc.189.1.S1_at	Diacylglycerol O-acyltransferase 1	9.16	-4.21	-36.07	-24.06	DGAT1	omacor
Ssc.16186.1.S1_at	T-cell surface glycoprotein CD3 epsilon	9.00	3.12	2.12	-5.66	CD3E	visilizumab, MT103, muromonab-CD3
Ssc.15601.1.A1_s_at	Interleukin-1 beta precursor (IL-1 beta)	8.18	4.65	-14.71	-2.84	IL1B	IL-1 trap
Ssc.5538.1.S1_at	Carbonic anhydrase II (Carbonate dehydratase II) (CA-II) (Carbonic anhydrase C)]	8.09	1.39	-2.25	-1.35	CA2	methazolamide, hydrochlorothiazide, acetazolamide, trichloromethiazide, dorzolamide, chlorothiazide, dorzolamide/timolol, brinzolamide, chlorthalidone, benzthiazide, sulfacetamide, topiramate
Ssc.113.1.S1_at	Interleukin-1 alpha (IL-1 alpha)	8.01	-2.65	-1.59	-7.73	IL1A	IL-1 trap
Ssc.2895.1.S1_at	Serine/threonine-protein kinase	7.48	-2.02	-2.45	-1.81	AURKB	AZD-1152
Ssc.8219.1.A1_at	Histone deacetylase 8 (HD8)	7.21	-2.18	-12.09	-29.63	HDAC8	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.13473.1.A1_at	Ceramide glucosyltransferase	7.13	-2.88	-4.17	-6.14	UGCG	N-

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							butyldeoxygalactonojirimycin, N-butyldeoxynojirimycin
Ssc.14129.1.A1_at	4-aminobutyrate aminotransferase, mitochondrial (GABA transaminase)	6.91	2.56	-21.17	-3.35	ABAT	valproic acid
Ssc.15379.1.S1_at	diacylglycerol O-acyltransferase homolog 2; GS1999full	6.60	-1.51	-3.49	-2.13	DGAT2	omacor
Ssc.15830.1.A1_at	Retinoic acid receptor beta	6.60	-3.28	-1.83	-1.10	RARB	etretinate, adapalene, 13-cis-retinoic acid, tazarotene, acitretin, retinoic acid, 9-cis-retinoic acid, fenretinide
Ssc.17928.1.A1_at	helicase (DNA) B; helicase B	6.40	-2.65	-4.38	-1.06	HELB	epirubicin
Ssc.19673.1.S1_at	T-cell surface glycoprotein CD3 delta	6.40	2.70	2.03	-11.77	CD3D	visilizumab, MT103
Ssc.17222.1.A1_at	mucin 1, transmembrane;	6.31	-6.10	-5.94	-13.48	MUC1	HuHMFG1
Ssc.55.1.S1_at	Epidermal growth factor receptor	6.09	-5.46	-4.68	-4.52	EGFR	cetuximab, AEE 788, panitumumab, BMS-599626, ARRY-334543, XL647, canertinib, gefitinib, HKI-272, PD 153035, lapatinib, vandetanib, erlotinib
Ssc.19059.1.A1_at	Type-1 angiotensin II receptor (AT1) (AT1AR	5.57	-2.57	1.50	-11.08	AGTR1	amlodipine/olmesartan medoxomil, losartan/hydrochlorothiazide, valsartan/hydrochlorothiazide, candesartan cilexetil, olmesartan medoxomil, irbesartan, losartan potassium, telmisartan, eprosartan, candesartan

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							cilexetil/hydrochlorothiazide, hydrochlorothiazide/irbesartan, eprosartan/hydrochlorothiazide, hydrochlorothiazide/telmisartan , hydrochlorothiazide/olmesartan medoxomil, valsartan
Ssc.16162.1.S1_at	4-hydroxyphenylpyruvate dioxygenase	5.43	-8.93	-8.65	-3.84	HPD	nitisinone
Ssc.27603.1.S1_at	Endothelin B receptor	5.30	-3.27	15.99	1.23	EDNRB	bosentan, sitaxsentan, atrasentan
Ssc.16333.1.A1_at	Multidrug resistance protein 1	4.94	-2.99	-3.50	-22.89	ABCB1	XR9576, OC 144-093, valspodar
Ssc.12769.1.A1_at	Amiloride-sensitive cation channel 1, neuronal	4.82	-13.74	-9.59	-10.72	ACCN1	amiloride, amiloride/hydrochlorothiazide
Ssc.17155.1.A1_at	heparanase; heparanase-1	4.81	5.38	2.98	-1.83	HPSE	heparanase inhibitor PI-88
Ssc.15933.1.S1_s_at	Cytotoxic T-lymphocyte protein 4 (Cytotoxic T-lymphocyte-associated antigen 4) (CTLA-4) (CD152 antigen)	4.76	-5.14	-6.63	-26.39	CTLA4	ipilimumab, ticilimumab
Ssc.15965.1.S1_at	Inward rectifier potassium channel 2 (IRK1)	4.68	2.72	-1.84	-4.62	KCNJ2	nicorandil, amiodarone
Ssc.26351.1.S1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4D	4.67	4.99	3.61	-1.15	PDE4D	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.15990.1.A1_at	Retinoic acid receptor RXR-alpha	4.42	-4.18	-18.45	-24.58	RXRA	bexarotene, retinoic acid, 9-cis-retinoic acid

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.2605.1.A1_at	Protein farnesyltransferase beta	4.39	-2.62	-7.00	-2.74	FNTB	lonafarnib, tipifarnib
Ssc.30373.1.A1_at	cGMP-specific 3',5'-cyclic phosphodiesterase	4.27	1.52	2.34	4.09	PDE5A	dyphylline, nitroglycerin, DA-8159, aminophylline, sildenafil, dipyridamole, aspirin/dipyridamole, vardenafil, tolbutamide, tadalafil, theophylline, pentoxifylline
Ssc.19233.1.S1_at	Collagen alpha 2(IX) chain	4.23	-1.14	-22.83	-2.12	COL9A2	collagenase
Ssc.1147.1.A1_at	Lipoprotein lipase	4.05	-5.49	3.78	-8.08	LPL	nicotinic acid, lovastatin/niacin
Ssc.13160.1.A1_at	Voltage-dependent L-type calcium channel alpha-1F subunit	4.03	-4.75	-1.11	-2.77	CACNA1F	MEM-1003, mibefradil, bepridil, nisoldipine, isradipine, nicardipine
Ssc.12748.1.A1_at	Catechol O-methyltransferase, membrane-bound form	4.03	-3.20	-5.82	-21.93	COMT	carbidopa/entacapone/levodopa, BIA-3-202, tolcapone, entacapone
Ssc.24986.1.S1_at	Aldehyde dehydrogenase 1A1	4.00	-3.76	-2.17	-9.20	ALDH1A1	disulfiram, chlorpropamide
Ssc.15972.1.S1_at	Peroxisome proliferator activated receptor delta (PPAR-delta)	3.83	-1.07	-2.73	-1.60	PPARD	GW501516
Ssc.24509.1.A1_at	Gamma-aminobutyric-acid receptor pi subunit	3.76	-1.28	-1.98	-1.23	GABRP	alphadolone, sevoflurane, isoflurane, isoniazid, felbamate, etomidate, halothane, fluoxetine/olanzapine, eszopiclone, zolpidem, lorazepam, olanzapine, zaleplon, secobarbital, phenobarbital, pentobarbital, desflurane, methoxyflurane,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							enflurane
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (	3.74	10.91	9.15	1.68	CXCR4	JM 3100
Ssc.6570.1.S1_at	Delta-aminolevulinic acid dehydratase]	3.71	-3.43	-3.05	-1.66	ALAD	delta-aminolevulinic acid
Ssc.17485.1.S1_at	Guanylate cyclase soluble, alpha-2 chain	3.57	-38.82	-1.77	-7.04	GUCY1A2	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.26200.1.S1_at	Thyroid hormone receptor beta-1	3.49	-1.56	7.96	2.52	THRB	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.9595.1.S1_at	Beta platelet-derived growth factor receptor	3.48	-3.60	1.40	1.65	PDGFRB	dasatinib, sunitinib, axitinib, KRN-951, imatinib, sorafenib, becaplermin
Ssc.108.1.S1_at	Oxytocin receptor (OT-R)	3.44	-8.53	-16.69	-4.47	OXTR	TT-235
Ssc.15801.1.A1_at	Protein kinase C, beta	3.36	6.36	3.53	-4.98	PRKCB1	enzastaurin, ruboxistaurin
Ssc.27928.1.S1_at	Opioid growth factor receptor (OGFr)	3.34	-3.33	-2.89	-3.51	OGFR	enkephalin, methionine
Ssc.12791.1.A1_at	3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase	3.27	2.77	1.77	-2.56	HMGCR	aspirin/pravastatin, lovastatin/niacin, ezetimibe/simvastatin, amlodipine/atorvastatin, fluvastatin, cerivastatin, atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin
Ssc.7933.1.A1_at	Cell division protein kinase 8	3.26	-1.63	-1.78	-3.05	CDK8	flavopiridol
Ssc.11147.1.S1_at	Aldehyde dehydrogenase, mitochondrial (ALDH class 2) (ALDHI) (ALDH-E2)	3.18	1.13	2.00	-1.68	ALDH2	disulfiram, chlorpropamide

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.19608.1.S1_at	Retinoic acid receptor RXR-gamma	3.15	-1.39	-1.73	-3.97	RXRG	bexarotene, retinoic acid, 9-cis-retinoic acid
Ssc.29260.1.A1_at	Granulocyte colony stimulating factor receptor (G-CSF-R) [CD114 antigen)]	3.15	-2.50	-4.36	-4.68	CSF3R	pegfilgrastim, filgrastim
Ssc.22797.1.S1_at	DNA topoisomerase II, beta isozyme	3.15	-1.87	1.02	-2.91	TOP2B	novobiocin, etoposide, CPI-0004Na, pixantrone, becatecarin, elsamitrucin, AQ4N, BN 80927, tafluposide, mitoxantrone, norfloxacin, dexrazoxane, tirapazamine, TAS-103, XK469, gatifloxacin, valrubicin, gemifloxacin, moxifloxacin, nemorubicin, nalidixic acid, epirubicin, doxorubicin, daunorubicin
Ssc.16121.1.A1_at	Corticotropin releasing factor receptor 1	3.03	-4.50	-17.00	-4.36	CRHR1	Crh, CRA0165, CRA1001, SSR125543A
Ssc.12630.1.A1_at	Sodium/potassium-transporting ATPase alpha-1 chain	2.97	2.81	-7.30	-2.03	ATP1A1	digoxin, omeprazole, ethacrynic acid, perphenazine
Ssc.13254.1.A1_at	Metabotropic glutamate receptor 8	2.95	-15.40	-9.66	-3.57	GRM8	fasoracetam
Ssc.30888.1.S1_at	Voltage-dependent L-type calcium channel alpha-1D	2.92	-2.72	1.90	-7.82	CACNA1D	MEM-1003, mibefradil, bepridil, nisoldipine, isradipine, nicardipine
Ssc.9565.1.S1_at	Interferon-gamma receptor alpha	2.92	1.63	1.41	-1.23	IFNGR1	interferon gamma-1b
Ssc.15880.1.S1_at	Cysteinyl leukotriene receptor 2 (CysLTR2)	2.86	1.14	-3.12	-3.42	CYSLTR2	montelukast, zafirlukast
Ssc.2753.1.S1_at	Serine/threonine-protein kinase PLK1	2.77	-4.42	-7.50	-4.52	PLK1	BI 2536
Ssc.16123.1.A1_at	cAMP-specific 3',5'-cyclic	2.75	-3.97	-3.49	-1.46	PDE4A	arofylline, tetomilast, L

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	phosphodiesterase 4A						869298, anagrelide, cilomilast, milrinone, rolipram, L-826,141, amrinone, roflumilast, pentoxifylline, caffeine
Ssc.11383.1.A1_at	Glutamate receptor 3	2.61	1.85	-1.87	-2.43	GRIA3	talampanel, Org 24448, LY451395, tezampanel
Ssc.14403.1.S1_at	Sodium/potassium-transporting ATPase alpha-2 chain	2.61	-1.95	-8.51	-6.43	ATP1A2	digoxin, omeprazole, ethacrynic acid, perphenazine
Ssc.21754.1.A1_at	Collagen alpha 1(VI) chain	2.57	-47.00	-5.79	-4.37	COL6A1	collagenase
Ssc.6498.1.A1_at	Mitogen-activated protein kinase 12 (Mitogen-activated protein kinase p38 gamma)	2.41	-10.79	-5.78	-3.26	MAPK12	SCIO-469
Ssc.16167.1.S1_at	Rho-associated protein kinase 1	2.40	2.32	2.83	3.00	ROCK1	fasudil, Y-27632
Ssc.12781.1.A1_at	Toll-like receptor 4	2.39	1.83	-1.52	-6.10	TLR4	TAK-242
Ssc.29366.1.A1_at	DNA topoisomerase I	2.37	-2.30	-2.87	-10.72	TOP1	elsamitrucin, T 0128, CT-2106, BN 80927, tafluposide, TAS-103, beta-lapachone, irinotecan, topotecan, 9-amino-20-camptothecin, rubitecan, gimatecan, karenitecin
Ssc.14485.1.S1_at	Parathyroid hormone/parathyroid hormone-related peptide receptor	2.28	-1.62	-3.40	-6.83	PTHR1	teriparatide
Ssc.12238.1.A1_at	Cysteinyl leukotriene receptor 1 (CysLTR1)	2.28	-1.73	-1.34	-6.96	CYSLTR1	zeneca ZD 3523, montelukast, zafirlukast
Ssc.3607.1.S1_at	Interferon-alpha/beta receptor beta chain	2.28	4.65	1.11	-1.56	IFNAR2	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.2548.1.S1_at	DNA polymerase epsilon p17]	2.27	1.93	-1.67	-1.21	POLE3	gemcitabine
Ssc.19706.1.A1_at	Mitogen-activated protein kinase 8	2.25	-4.27	-2.31	-4.98	MAPK8	aplidine
Ssc.15382.1.S1_at	Cannabinoid receptor 2 (CB2) (CB-2) (CX5)	2.22	3.48	-1.37	-4.69	CNR2	BAY 38-7271, delta-9-tetrahydrocannabinol
Ssc.4756.1.A1_at	Adenosine A3 receptor	2.15	2.10	1.88	-1.81	ADORA3	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine
Ssc.23261.1.A1_at	Trifunctional purine biosynthetic protein adenosine-3	2.15	-3.54	-3.66	-5.67	GART	LY231514
Ssc.27293.1.A1_at	Hypoxanthine-guanine phosphoribosyltransferase	2.15	-1.16	1.63	-7.14	HPRT1	6-mercaptopurine, thioguanine, azathioprine
Ssc.14476.1.S1_at	Interleukin-2 receptor alpha	2.07	-8.52	-8.73	-5.00	IL2RA	LMB-2, daclizumab, basiliximab, aldesleukin, denileukin diftitox
Ssc.27232.1.S1_at	Succinate semialdehyde dehydrogenase, mitochondrial	2.06	1.12	-2.84	-5.73	ALDH5A1	valproic acid
Ssc.10142.1.A1_at	Dihydropyrimidine dehydrogenase [NADP+]	2.06	2.17	1.13	-2.68	DPYD	eniluracil
Ssc.1908.1.S1_at	FKBP-rapamycin associated protein (FRAP)	1.99	1.13	-1.88	-1.46	FRAP1	AP23573, temsirolimus, tacrolimus, everolimus
Ssc.204.1.S1_at	Cytochrome P450 3A4	1.97	-3.35	2.16	-1.42	CYP3A4	ketoconazole
Ssc.18459.1.S1_at	Amiloride-sensitive sodium channel alpha-	1.97	-2.41	1.43	-1.93	SCNN1A	triamterene/hydrochlorothiazide, amiloride, amiloride/hydrochlorothiazide, triamterene
Ssc.24889.1.S1_at	Arachidonate 12-lipoxygenase, 12S-type	1.97	2.83	-1.18	-2.78	ALOX12	sulfasalazine, balsalazide, 5-aminosalicylic acid, masoprocol, verteporfin
Ssc.15748.2.S2_at	T lymphocyte activation	1.95	-1.24	1.54	-3.12	CD80	abatacept

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	antigen CD80						
Ssc.5826.1.A1_at	Macrophage colony stimulating factor I receptor (CD115 antigen)	1.93	-4.97	-13.18	1.61	CSF1R	sunitinib
Ssc.15822.1.S1_at	Coagulation factor V	1.92	3.76	1.89	-1.75	F5	drotrecogin alfa
Ssc.9262.1.A1_at	Histamine H1 receptor	1.91	-4.10	-3.91	-1.86	HRH1	nitisinone
Ssc.62.2.S1_a_at	Interleukin-6 (IL-6) (	1.89	-6.32	2.77	-1.04	IL6	tocilizumab
Ssc.14258.1.S1_at	Amyloid beta A4 protein	1.87	3.33	1.34	-1.02	APP	AAB-001
Ssc.15878.1.S1_at	Serine/threonine protein phosphatase 2B	1.85	3.22	3.62	-1.49	PPP3CA	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.19379.1.A1_at	Voltage-dependent L-type calcium channel alpha-1C subunit	1.83	-1.34	1.07	-3.27	CACNA1C	clevidipine, MEM-1003, amlodipine/olmesartan medoxomil, amlodipine/benazepril, diltiazem, verapamil, mibefradil, bepridil, enalapril/felodipine, amlodipine/atorvastatin, nisoldipine, isradipine, felodipine, nimodipine, nitrendipine, amlodipine, nicardipine, nifedipine, trandolapril/verapamil, diltiazem/enalapril
Ssc.10215.1.A1_at	High-affinity cAMP-specific and IBMX-insensitive 3',5'-cyclic phosphodiesterase 8A	1.83	1.12	-8.48	-15.51	PDE8A	dyphylline, nitroglycerin, aminophylline, anagrelide, milrinone, dipyridamole, tolbutamide, theophylline, pentoxifylline
Ssc.20944.1.S1_at	Carbonic anhydrase XIV	1.82	-3.49	-5.34	-12.64	CA14	methazolamide, hydrochlorothiazide, acetazolamide,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							trichloromethiazide, chlorothiazide, chlorthalidone, benzthiazide, sulfacetamide, topiramate
Ssc.4125.1.A1_at	Histone deacetylase 5 (HD5)	1.82	-4.64	-4.18	-2.74	HDAC5	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.6301.1.S1_at	Aromatic-L-amino-acid decarboxylase	1.76	1.80	-4.91	-1.88	DDC	carbidopa/entacapone/levodopa, carbidopa/levodopa, S(-)-carbidopa, L-dopa
Ssc.15995.1.S1_at	Potassium voltage-gated channel subfamily E member 1	1.74	-26.30	-13.45	-2.79	KCNE1	nicorandil, amiodarone, azimilide
Ssc.7581.1.A1_at	FL cytokine receptor precursor	1.69	1.04	-1.81	1.01	FLT3	CHIR-258, sorafenib, lestaurtinib, CGP 41251
Ssc.26325.1.S1_at	Cystic fibrosis transmembrane conductance regulator (CFTR)	1.60	-5.71	4.77	-8.99	CFTR	SP 303
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase	1.59	1.16	3.01	1.47	PLA2G7	darapladib
Ssc.24714.1.A1_at	Excitatory amino acid transporter 2 (Sodium-dependent glutamate/aspartate transporter 2)	1.58	-2.29	-7.61	-3.45	SLC1A2	riluzole
Ssc.22477.1.S1_at	Collagen alpha 1(IV) chain	1.58	-5.08	-1.78	1.04	CCL4A1	collagenase
Ssc.227.1.S1_at	Potassium-transporting ATPase beta	1.56	-5.89	-51.53	-15.60	ATP4B	ilaprazole, TAK-390MR, tenatoprazole, AGN 201904, AR-H047108, esomeprazole magnesium, omeprazole, lansoprazole, amoxicillin/clarithromycin/lans

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							oprazole, rabeprazole, pantoprazole
Ssc.30147.1.A1_at	Fibroblast growth factor receptor 2	1.56	1.13	-1.05	-1.18	FGFR2	palifermin
Ssc.9523.1.A1_at	Methylated-DNA--protein-cysteine methyltransferase	1.55	-1.17	3.35	1.47	MGMT	O6-benzylguanine
Ssc.26466.1.A1_at	Integrin beta-3 (CD61 antigen	1.55	-1.49	-4.11	-2.73	ITGB3	TP 9201, EMD121974, tirofiban
Ssc.5592.1.S1_at	Protein farnesyltransferase/geranylgeranyltransferase type I alpha	1.49	-3.49	-2.81	-3.68	FNTA	lonafarnib, tipifarnib
Ssc.17986.1.A1_at	Poly [ADP-ribose] polymerase-1	1.47	-6.14	-4.64	-5.80	PARP1	INO-1001
Ssc.11051.1.S1_at	Cell division protein kinase 4	1.44	-7.67	-4.96	23.75	CDK4	PD-0332991, flavopiridol
Ssc.20818.1.S1_at	Interleukin-2 receptor beta chain	1.43	6.35	-1.17	-5.23	IL2RB	humanized MiK-Beta-1, aldesleukin, denileukin diftitox
Ssc.16489.1.S1_at	Interleukin-7 receptor alpha chain	1.42	2.34	1.86	-6.31	IL7R	recombinant human interleukin-7
Ssc.10287.1.A1_at	Transforming growth factor beta 2	1.41	-4.54	1.43	1.67	TGFB2	AP-12009
Ssc.14375.1.A1_at	ribonucleotide reductase M2 B	1.40	-2.19	-5.17	-2.28	RRM2B	triapine, hydroxyurea
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor) (P2Y(ADP))	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140 (Ticagrelor), clopidogrel
Ssc.11164.1.A1_at	DNA polymerase gamma subunit 1	1.37	-1.33	-3.67	-3.60	POLG	stavudine, vidarabine, zalcitabine
Ssc.10219.1.A1_at	Excitatory amino acid transporter 4	1.36	1.24	-3.38	-1.03	SLC1A6	riluzole
Ssc.3815.1.S1_at	RAC-beta serine/threonine-protein kinase	1.35	-3.13	-3.28	-3.19	AKT2	enzastaurin
Ssc.19619.1.S1_at	Proto-oncogene tyrosine-protein kinase LCK	1.35	-1.51	-3.32	-2.41	LCK	dasatinib
Ssc.2926.1.S1_at	Heme oxygenase 2	1.34	-1.43	-4.13	-1.81	HMOX2	tin mesoporphyrin

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.11171.1.S1_at	Adenosine deaminase	1.32	-2.04	-3.23	1.12	ADA	pentostatin, vidarabine
Ssc.16621.1.A1_at	Excitatory amino acid transporter 3	1.27	-7.18	-3.04	-8.29	SLC1A1	riluzole
Ssc.11549.1.A1_at	Dual specificity mitogen-activated protein kinase kinase 1	1.25	-33.67	-11.33	-6.48	MAP2K1	PD 0325901
Ssc.6356.1.S1_at	Ornithine decarboxylase	1.24	-1.36	-1.74	-1.84	ODC1	tazarotene, eflornithine
Ssc.15999.1.A1_at	Vascular endothelial growth factor receptor 2 (VEGFR-2)	1.24	1.24	18.52	-11.02	KDR	AEE 788, sunitinib, AZD 2171, pazopanib, XL647, CEP 7055, BMS-582664, KRN-951, vatalanib, sorafenib, vandetanib, pegaptanib
Ssc.9669.1.S1_at	Cell division protein kinase 5	1.21	-2.68	-17.06	-1.65	CDK5	flavopiridol
Ssc.115.1.S1_s_at	Heme oxygenase 1	1.18	-2.09	-3.40	-3.55	HMOX1	tin mesoporphyrin
Ssc.17224.1.S1_at	Toll-like receptor 8	1.17	6.49	3.13	-1.52	TLR8	resiquimod
Ssc.8046.1.A1_at	peptidylprolyl isomerase A isoform 1	1.16	-1.08	1.39	1.26	PPIA	N-methyl-4-Ile-cyclosporin
Ssc.7297.1.S1_at	Amine oxidase [flavin-containing] B (MAO-B)	1.16	6.42	7.02	-1.13	MAOB	safinamide, ladostigil, rasagiline, selegiline, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.12202.2.S1_at	Farnesyl pyrophosphate synthetase	1.12	-1.26	-2.68	-1.13	FDPS	YM 529, alendronic acid, pamidronic acid
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.8549.1.A1_at	Guanylate cyclase soluble, alpha-3 chain	1.11	1.84	-2.00	-2.59	GUCY1A3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.15374.1.S1_at	COL14A1 protein	1.10	-17.71	3.79	2.24	COL14A1	collagenase
Ssc.15901.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase A	1.10	-13.33	-3.16	-1.41	PDE3A	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole, amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.16000.1.A1_at	Vascular endothelial growth factor receptor 1	1.08	-3.40	3.34	1.72	FLT1	sunitinib, axitinib, CEP 7055
Ssc.20987.1.S1_at	Thrombopoietin receptor]	1.06	-1.58	-3.97	-5.87	MPL	SB-497115
Ssc.11149.1.S1_at	Carbonic anhydrase IX	1.04	-1.91	-1.33	-1.26	CA9	cG250, I 131 chimeric G250, Y 90 chimeric G250, methazolamide, hydrochlorothiazide, acetazolamide, trichloromethiazide, chlorothiazide, chlorthalidone, benzthiazide, sulfacetamide, topiramate
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase	1.03	1.24	4.16	-1.11	PPAT	6-mercaptopurine, thioguanine, azathioprine
Ssc.11406.1.A1_a_at	Interleukin-1 receptor, type I	1.03	2.70	-2.44	1.42	IL1R1	anakinra
Ssc.14506.1.S1_at	DNA topoisomerase II, alpha	1.01	3.80	-1.18	-14.30	TOP2A	novobiocin, etoposide, CPI-0004Na, pixantrone, becatecarin, elsamitrucin, AQ4N, BN 80927, tafluposide, mitoxantrone, norfloxacin,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							dexrazoxane, tirapazamine, TAS-103, gatifloxacin, valrubicin, gemifloxacin, moxifloxacin, nemorubicin, nalidixic acid, epirubicin, doxorubicin, daunorubicin

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Table 4

Day 21 prescription.

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.23793.1.S1_at	T-cell surface antigen CD2	-3.27	79.25	93.34	5.20	CD2	alefacept, siplizumab
SscAffx.20.1.S1_at	T-cell surface glycoprotein CD3 gamma chain	-2.19	14.07	10.96	3.62	CD3G	visilizumab, MT103
Ssc.19532.1.S1_at	Guanylate cyclase soluble, beta-1 chain	-4.28	12.74	3.04	2.13	GUCY1B3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4) (CD184 antigen).	3.74	10.91	8.15	1.68	CXCR4	JM 3100
Ssc.2714.1.S1_a_at	Proto-oncogene tyrosine-protein kinase FYN	-4.26	9.56	12.54	3.93	FYN	dasatinib
Ssc.15739.1.S1_at	Cytokine receptor common gamma chain (Interleukin- 2 receptor gamma chain) (IL-2R gamma chain) (CD132 antigen).	-1.12	9.42	1.90	-1.28	IL2RG	aldesleukin, denileukin diftitox
Ssc.11381.1.S1_at	Interferon-alpha/beta receptor alpha chain	10.45	8.08	2.61	-1.30	IFNAR1	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.10256.1.A1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4B	-1.89	6.74	2.20	2.44	PDE4B	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.17224.1.S1_at	Toll-like receptor 8	1.17	6.49	3.13	-1.52	TLR8	resiquimod
Ssc.7297.1.S1_at	Amine oxidase [flavin-containing] B (Monoamine oxidase) (MAO-B).	1.16	6.42	7.02	-1.13	MAOB	safinamide, ladostigil, rasagiline, selegiline, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine
Ssc.15801.1.A1_at	Protein kinase C, beta	3.36	6.36	3.53	-4.98	PRKCB1	enzastaurin, ruboxistaurin
Ssc.20818.1.S1_at	Interleukin-2 receptor beta chain (IL-2 receptor)	1.43	6.35	-1.17	-5.23	IL2RB	humanized MiK-Beta-1, aldesleukin, denileukin diftitox
Ssc.12937.1.S1_at	Presenilin 1 (PS-1) (S182 protein).	-14.09	6.21	2.48	3.79	PSEN1	(R)-flurbiprofen
Ssc.15932.1.S1_at	Integrin alpha-V	-6.15	5.79	2.94	3.14	ITGAV	abciximab, CNTO 95, EMD121974
Ssc.26328.1.S1_at	C-C chemokine receptor type 5 (CCR5) (CD195 antigen).	-2.53	5.61	3.25	1.29	CCR5	maraviroc, vicriviroc, SCH 351125
Ssc.12845.1.S1_at	Cell division protein kinase 6	-6.56	5.40	4.77	5.13	CDK6	PD-0332991, flavopiridol
Ssc.17155.1.A1_at	heparanase; heparanase-1	4.81	5.38	2.98	-1.83	HPSE	heparanase inhibitor PI-88
Ssc.13460.1.A1_at	Histone deacetylase 9 (HD9) (HD7B) (HD7)	-6.40	5.13	-1.79	5.72	HDAC9	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.24528.1.S1_at	Angiotensin-converting enzyme	-1.61	5.01	2.33	4.76	ACE	pentopril, perindoprilat, amlodipine/benazepril, lisinopril/hydrochlorothiazide, benazepril, enalapril, perindopril, captopril, enalapril/felodipine, hydrochlorothiazide/moexipril,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							benazepril/hydrochlorothiazide, hydrochlorothiazide/quinapril, fosinopril/hydrochlorothiazide, captopril/hydrochlorothiazide, enalapril/hydrochlorothiazide, ramipril, moexipril, quinapril, lisinopril, enalaprilat, trandolapril, trandolapril/verapamil, diltiazem/enalapril, fosinopril
Ssc.26351.1.S1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4D	4.67	4.99	3.61	-1.15	PDE4D	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.15601.1.A1_s_at	Interleukin-1 beta precursor (IL-1 beta)	8.18	4.65	-14.71	-2.84	IL1B	IL-1 trap
Ssc.3607.1.S1_at	Interferon-alpha/beta receptor beta chain	2.28	4.65	1.11	-1.56	IFNAR2	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.20841.1.S1_at	Proto-oncogene tyrosine-protein kinase Src	-1.13	4.37	-2.59	-1.93	SRC	dasatinib, AZM-475271
Ssc.11200.1.S1_a_at	Proto-oncogene tyrosine-protein kinase ABL1	-1.15	4.28	-3.41	-1.18	ABL1	imatinib, temozolomide
Ssc.22974.1.A1_at	Metabotropic glutamate	-1.05	4.28	-2.05	-5.66	GRM1	fasoracetam

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	receptor 1						
Ssc.7111.1.A1_at	Ribonucleoside-diphosphate reductase M2 chain (Ribonucleotide reductase small chain)	-13.13	4.08	1.37	1.67	RRM2	gemcitabine, triapine, hydroxyurea, fludarabine phosphate
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.16160.1.S1_at	T lymphocyte activation antigen CD86	-1.55	3.88	-1.37	1.18	CD86	abatacept
Ssc.14506.1.S1_at	DNA topoisomerase II, alpha isozyme	1.01	3.80	-1.18	-14.30	TOP2A	novobiocin, etoposide, CPI-0004Na, pixantrone, becatecarin, elsamitrucin, AQ4N, BN 80927, tafluposide, mitoxantrone, norfloxacin, dexrazoxane, tirapazamine, TAS-103, gatifloxacin, valrubicin, gemifloxacin, moxifloxacin, nemorubicin, nalidixic acid, epirubicin, doxorubicin, daunorubicin
Ssc.15822.1.S1_at	Coagulation factor V (Activated protein C cofactor).	1.92	3.76	1.89	-1.75	F5	drotrecogin alfa
Ssc.9034.1.A1_at	Proteinase activated receptor 1 precursor (PAR-1) (Thrombin receptor)	-1.29	3.75	-1.40	1.37	F2R	chrysalin, argatroban, bivalirudin
Ssc.15886.1.S1_at	Apopain precursor (Caspase-3) (CASP-3)	-3.02	3.64	2.31	2.29	CASP3	IDN-6556
Ssc.17518.1.S1_at	Adenosine A1 receptor	-3.16	3.44	-1.56	1.58	ADORA1	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							tecadenoson
Ssc.14258.1.S1_at	Amyloid beta A4 protein precursor (APP) (ABPP)	1.87	3.33	1.34	-1.02	APP	AAB-001
Ssc.14471.1.S1_at	B-lymphocyte antigen CD19 precursor (Differentiation antigen CD19	9.54	3.30	-10.32	3.04	CD19	combotox, HD37-dgRTA, MT103
Ssc.15878.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, alpha	1.85	3.22	3.62	-1.49	PPP3CA	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.21108.1.S1_at	Complement C5	-17.35	3.21	618.80	9.28	C5	eculizumab
Ssc.16186.1.S1_at	T-cell surface glycoprotein CD3 epsilon chain (T-cell surface antigen T3/Leu-4 epsilon chain)	9.00	3.12	2.12	-5.66	CD3E	visilizumab, MT103, muromonab-CD3
Ssc.24966.1.S1_at	Purine nucleoside phosphorylase (Inosine phosphorylase) (PNP).	-3.34	3.12	3.46	-1.14	NP	forodesine, 9-deaza-9-(3-thienylmethyl)guanine
Ssc.19873.1.S1_at	Collagen alpha 1(XVII) chain (Bullous pemphigoid antigen 2)	-2.37	3.02	-1.55	2.18	COL17A1	collagenase
Ssc.20904.1.A1_at	RAC-gamma serine/threonine-protein kinase (RAC-PK-gamma) (Protein kinase Akt-3) (Protein kinase B, gamma) (PKB gamma) (STK-2)	-1.34	3.01	-2.18	1.23	AKT3	enzastaurin
Ssc.26646.1.S1_at	Glutamate receptor 1	-1.10	2.91	-5.42	-3.43	GRIA1	talampanel, Org 24448, LY451395, tezampanel
Ssc.15312.1.S1_at	Histone deacetylase 4 (HD4)	-1.93	2.85	-2.41	1.20	HDAC4	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.24889.1.S1_at	Arachidonate 12-lipoxygenase, 12S-type	1.97	2.83	-1.18	-2.78	ALOX12	sulfasalazine, balsalazide, 5-aminosalicylic acid, masoprocol, verteporfin

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.12630.1.A1_at	Sodium/potassium-transporting ATPase alpha-1 chain	2.97	2.81	-7.30	-2.03	ATP1A1	digoxin, omeprazole, ethacrynic acid, perphenazine
Ssc.3040.1.S1_at	Histone deacetylase 2 (HD2)	-3.24	2.79	4.94	4.72	HDAC2	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.12791.1.A1_at	3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase)	3.27	2.77	1.77	-2.56	HMGCR	aspirin/pravastatin, lovastatin/niacin, ezetimibe/simvastatin, amlodipine/atorvastatin, fluvastatin, cerivastatin, atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin
Ssc.20685.1.S1_at	Apoptosis regulator Bcl-2	-2.22	2.77	2.58	3.25	BCL2	oblimersen, (-)-gossypol
Ssc.15965.1.S1_at	Inward rectifier potassium channel 2 (Potassium channel, inwardly rectifying, subfamily J, member 2) (Inward rectifier K+ channel Kir2.1) (Cardiac inward rectifier potassium channel) (IRK1).	4.68	2.72	-1.84	-4.62	KCNJ2	nicorandil, amiodarone
Ssc.19673.1.S1_at	T-cell surface glycoprotein CD3 delta chain precursor (T-cell receptor T3 delta chain)	6.40	2.70	2.03	-11.77	CD3D	visilizumab, MT103
Ssc.16127.1.S1_at	Adrenocorticotropic hormone receptor (ACTH receptor) (ACTH-R)	-1.67	2.70	-2.51	-1.10	MC2R	cosyntropin, ACTH
Ssc.11406.1.A1_a_at	Interleukin-1 receptor, type I precursor (IL-1R-1) (IL-1R-alpha) (P80) (Antigen CD121a)	1.03	2.70	-2.44	1.42	IL1R1	anakinra
Ssc.19937.1.S1_at	Inosine-5'-monophosphate dehydrogenase 2 (IMP	1.00	2.69	-1.47	3.65	IMPDH2	thioguanine, VX-944, interferon alfa-2a/ribavirin,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	dehydrogenase 2)						mycophenolic acid, ribavirin
Ssc.818.1.S1_at	RAF proto-oncogene serine/threonine-protein kinase	-1.40	2.56	1.58	1.98	RAF1	sorafenib
Ssc.14129.1.A1_at	4-aminobutyrate aminotransferase, mitochondrial precursor (Gamma-amino-N-butyrate transaminase) (GABA transaminase)	6.91	2.56	-21.17	-3.35	ABAT	valproic acid
Ssc.13186.1.S1_at	Cell division protein kinase 7	-1.08	2.38	4.34	1.24	CDK7	BMS-387032, flavopiridol
Ssc.16167.1.S1_at	Rho-associated protein kinase 1	2.40	2.32	2.83	3.00	ROCK1	fasudil, Y-27632
Ssc.6418.1.S1_at	Farnesyl-diphosphate farnesyltransferase	-1.25	2.31	1.33	1.08	FDFT1	TAK-475, zoledronic acid
Ssc.15829.1.S1_at	Retinoic acid receptor alpha	-1.73	2.23	-1.33	-1.16	RARA	etretinate, adapalene, arsenic trioxide, 13-cis-retinoic acid, tazarotene, acitretin, retinoic acid, 9-cis-retinoic acid
Ssc.10142.1.A1_at	Dihydropyrimidine dehydrogenase [NADP+] (DPD) (DHPDHase) (Dihydrouracil dehydrogenase) (Dihydrothymine dehydrogenase).	2.06	2.17	1.13	-2.68	DPYD	eniluracil
Ssc.23505.1.S1_at	Amine oxidase [flavin-containing] A (Monoamine oxidase) (MAO-A)	-1.86	2.17	1.08	1.20	MAOA	ladostigil, 1-ethylphenoxathiin 10,10-dioxide, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine, N-(2-indanyl)glycinamide
Ssc.20438.1.S1_at	Prostaglandin F2-alpha	-3.20	2.13	5.28	-38.97	PTGFR	tafluprost, travoprost,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	receptor (Prostanoid FP receptor) (PGF receptor) (PGF2 alpha receptor).						isopropyl unoprostone, bimatoprost, latanoprost
Ssc.4756.1.A1_at	Adenosine A3 receptor	2.15	2.10	1.88	-1.81	ADORA3	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine
Ssc.11302.1.S1_at	Collagen alpha 1(III) chain	-1.80	2.02	2.06	1.26	COL3A1	collagenase
Ssc.19400.2.A1_at	Presenilin 2 (PS-2) (STM-2) (E5-1) (AD3LP) (AD5)	-2.32	1.99	-5.30	-3.44	PSEN2	(R)-flurbiprofen
Ssc.3059.1.S1_at	Aldose reductase (AR) (Aldehyde reductase).	-1.74	1.98	-1.66	2.49	AKR1B1	sorbinil, Zopolrestat (Alond, Pfizer), zenarestat (Fujisawa, Parke-Davis)
Ssc.18051.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase B (Cyclic GMP inhibited phosphodiesterase B) (CGI-PDE B) (CGIPDE1) (CGIP1)	-3.16	1.96	3.41	2.32	PDE3B	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole, amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.2548.1.S1_at	DNA polymerase epsilon p17 subunit (DNA polymerase epsilon subunit 3) (Chromatin accessibility complex 17) (HuCHRAC17) (CHRAC-17).	2.07	1.93	-1.67	-1.21	POLE3	gemcitabine
Ssc.11383.1.A1_at	Glutamate receptor 3 precursor (GluR-3) (GluR-C) (GluR-K3) (Glutamate receptor ionotropic, AMPA 3)	2.61	1.85	-1.87	-2.43	GRIA3	talampanel, Org 24448, LY451395, tezampanel
Ssc.8549.1.A1_at	Guanylate cyclase soluble, alpha-3 chain (GCS-alpha-3) (Soluble guanylate cyclase large subunit) (GCS-alpha-1).	1.11	1.84	-2.00	-2.59	GUCY1A3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.12781.1.A1_at	Toll-like receptor 4	2.39	1.83	-1.52	-6.10	TLR4	TAK-242

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.6301.1.S1_at	Aromatic-L-amino-acid decarboxylase (AADC) (DOPA decarboxylase)	1.76	1.80	-4.91	-1.88	DDC	carbidopa/entacapone/levodopa, carbidopa/levodopa, S(-)-carbidopa, L-dopa
Ssc.6801.1.S1_at	Proto-oncogene tyrosine-protein kinase YES	-1.06	1.69	2.36	-1.82	YES1	dasatinib
Ssc.5371.1.S1_a_at	DNA polymerase epsilon subunit B (DNA polymerase II subunit B).	10.16	1.68	-1.37	-3.14	POLE2	gemcitabine
Ssc.11572.1.A1_at	Histone deacetylase 3 (HD3) (RPD3-2) (SMAP45)	-1.65	1.67	-1.55	2.36	HDAC3	tributyrin, PXD101, pyroxamide, MGCD0103, vorinostat, FR 901228
Ssc.23234.1.S1_at	collagen, type XXIV, alpha 1	-1.43	1.66	1.16	1.76	COL24A1	collagenase
Ssc.9565.1.S1_at	Interferon-gamma receptor alpha chain precursor (IFN-gamma-R1) (CD119 antigen)	2.92	1.63	1.41	-1.23	IFNGR1	interferon gamma-1b
Ssc.5021.1.S1_at	Glutamate decarboxylase, 65 kDa isoform (GAD-65) (65 kDa glutamic acid decarboxylase)	-29.44	1.62	-10.79	-5.61	GAD2	valproic acid
Ssc.14326.1.A1_at	Mitogen-activated protein kinase 13 (Stress-activated protein kinase-4) (Mitogen-activated protein kinase p38 delta) (MAP kinase p38 delta)	12.63	1.56	-1.80	-7.24	MAPK13	SCIO-469
Ssc.10591.1.A1_at	Metabotropic glutamate receptor 5 precursor (mGluR5)	-7.83	1.54	-1.31	1.40	GRM5	fasoracetam
Ssc.30373.1.A1_at	cGMP-specific 3',5'-cyclic phosphodiesterase	4.27	1.52	2.34	4.09	PDE5A	dyphylline, nitroglycerin, DA-8159, aminophylline, sildenafil, dipyridamole, aspirin/dipyridamole, vardenafil, tolbutamide, tadalafil, theophylline, pentoxifylline

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.6710.1.A1_at	Ribonucleoside-diphosphate reductase M1 chain (Ribonucleotide reductase large chain)	-1.90	1.44	2.01	-1.01	RRM1	gemcitabine, clofarabine, fludarabine phosphate
Ssc.7139.1.S1_at	Dihydrofolate reductase	-1.13	1.41	-1.12	2.06	DHFR	pyrimethamine, trimethoprim, iclaprim, methotrexate, sulfisoxazole, triamterene, folic acid, trimetrexate, LY231514, PT 523
Ssc.5538.1.S1_at	Carbonic anhydrase II (Carbonate dehydratase II) (CA-II) (Carbonic anhydrase C)	8.09	1.39	-2.25	-1.35	CA2	methazolamide, hydrochlorothiazide, acetazolamide, trichloromethiazide, dorzolamide, chlorothiazide, dorzolamide/timolol, brinzolamide, chlorthalidone, benzthiazide, sulfacetamide, topiramate
Ssc.5569.1.S1_at	Thyroid hormone receptor alpha (C-erbA-alpha) (c-erbA-1) (EAR-7) (EAR7)	-10.22	1.26	1.26	6.49	THRA	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.10360.1.S1_at	B-Raf proto-oncogene serine/threonine-protein kinase	-2.15	1.26	3.09	1.36	BRAF	sorafenib
Ssc.19672.1.S1_at	RAC-alpha serine/threonine-protein kinase (RAC-PK-alpha) (Protein kinase B) (PKB) (C-AKT)	17.77	1.25	-19.82	-2.11	AKT1	enzastaurin
Ssc.21011.1.S1_at	Collagen alpha 2(I) chain	-2.70	1.24	3.12	-1.01	COL1A2	collagenase
Ssc.5045.1.S1_at	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase (Cholestenol delta-isomerase)	-1.55	1.24	2.19	2.08	EBP	SR 31747

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	(Delta8-delta7 sterol isomerase) (D8-D7 sterol isomerase) (Emopamil-binding protein)						
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase precursor (Glutamine phosphoribosylpyrophosphate amidotransferase) (ATASE) (GPAT)	1.03	1.24	4.16	-1.11	PPAT	6-mercaptopurine, thioguanine, azathioprine
Ssc.10219.1.A1_at	Excitatory amino acid transporter 4 (Sodium-dependent glutamate/aspartate transporter)	1.36	1.24	-3.38	-1.03	SLC1A6	riluzole
Ssc.15999.1.A1_at	Vascular endothelial growth factor receptor 2 precursor (VEGFR-2) (Kinase insert domain receptor) (Protein-tyrosine kinase receptor Flk-1)	1.24	1.24	18.52	-11.02	KDR	AEE 788, sunitinib, AZD 2171, pazopanib, XL647, CEP 7055, BMS-582664, KRN-951, vatalanib, sorafenib, vandetanib, pegaptanib
Ssc.9348.1.S1_at	Peroxisome proliferator activated receptor alpha (PPAR-alpha)	-1.05	1.22	-3.05	-1.52	PPARA	NS-220, tesaglitazar, clofibrate, fenofibrate, docosahexaenoic acid, gemfibrozil
Ssc.1498.1.S1_at	Proteasome subunit beta type 5 precursor (Proteasome epsilon chain) (Macropain epsilon chain) (Multicatalytic endopeptidase complex epsilon chain) (Proteasome subunit X) (Proteasome chain 6) (Proteasome subunit MB1)	-1.81	1.19	1.38	5.94	PSMB5	bortezomib
Ssc.6934.1.A1_at	Thymidylate synthase (EC	-1.13	1.19	-1.11	-2.81	TYMS	flucytosine, 5-fluorouracil,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	2.1.1.45) (TS) (TSase) (OK/SW-cl.39)						plevitrexed, nolatrexed, capecitabine, trifluridine, floxuridine, LY231514
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor) (P2Y(ADP)) (ADP-glucose receptor) (ADPG-R) (P2Y(AC)) (P2Y(cyc)) (P2T(AC)) (SP1999	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140 (Ticagrelor), clopidogrel
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase precursor (EC 3.1.1.47) (PAF acetylhydrolase) (PAF 2-acylhydrolase) (LDL-associated phospholipase A2) (LDL-PLA(2)) (2-acetyl-1-alkylglycerophosphocholine esterase) (1-alkyl-2-acetylglycerophosphocholine esterase)	1.59	1.16	3.01	1.47	PLA2G7	darapladib
Ssc.15880.1.S1_at	Cysteinyl leukotriene receptor 2 (CysLTR2) (PSEC0146) (HG57) (HPN321) (hGPCR21)	2.86	1.14	-2.12	-3.42	CYSLTR2	montelukast, zafirlukast
Ssc.11147.1.S1_at	Aldehyde dehydrogenase, mitochondrial precursor (EC 1.2.1.3) (ALDH class 2) (ALDHI) (ALDH-E2)	3.18	1.13	2.00	-1.68	ALDH2	disulfiram, chlorpropamide
Ssc.1908.1.S1_at	FKBP-rapamycin associated protein (FRAP) (Rapamycin	1.99	1.13	-1.88	-1.46	FRAP1	AP23573, temsirolimus, tacrolimus, everolimus

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	target protein)						
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.30147.1.A1_at	Fibroblast growth factor receptor 2 precursor (FGFR-2) (Keratinocyte growth factor receptor 2)	1.56	1.13	-1.05	-1.18	FGFR2	palifermin
Ssc.27232.1.S1_at	Succinate semialdehyde dehydrogenase, mitochondrial precursor (NAD(+)-dependent succinic semialdehyde dehydrogenase)	2.06	1.12	-2.84	-5.73	ALDH5A1	valproic acid
Ssc.10215.1.A1_at	High-affinity cAMP-specific and IBMX-insensitive 3',5'-cyclic phosphodiesterase 8A	1.83	1.12	-8.48	-15.51	PDE8A	dyphylline, nitroglycerin, aminophylline, anagrelide, milrinone, dipyridamole, tolbutamide, theophylline, pentoxifylline
Ssc.2767.2.S1_a_at	Prostaglandin E2 receptor, EP3 subtype (Prostanoid EP3 receptor) (PGE receptor, EP3 subtype)	2.30	1.12	-1.59	-6.78	PTGER3	prostaglandin E1
Ssc.15955.1.S1_at	Antithrombin-III precursor (ATIII) (PRO0309)	-1.89	1.12	-2.06	-2.42	SERPINC1	enoxaparin, SR-123781A, fondaparinux
Ssc.25040.1.S1_at	Serine/threonine-protein kinase Chk1	-3.75	1.11	1.06	-2.45	CHEK1	UCN-01 (7-hydroxystaurosporine)
Ssc.14488.1.S1_at	Glutamate carboxypeptidase II (Membrane glutamate carboxypeptidase)	-1.04	1.10	1.02	1.69	FOLH1	capromab pendetide
Ssc.1.1.S1_at	3-oxo-5-alpha-steroid 4-dehydrogenase 2 (Steroid 5-alpha-reductase 2) (SR type 2)	-1.77	1.05	-4.11	-1.09	SRD5A2	finasteride, dutasteride

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	(5 alpha-SR2)						
Ssc.7581.1.A1_at	FL cytokine receptor precursor (Tyrosine-protein kinase receptor FLT3) (Stem cell tyrosine kinase 1) (STK-1) (CD135 antigen)	1.69	1.04	-1.81	1.01	FLT3	CHIR-258, sorafenib, lestaurtinib, CGP 41251

Table 5

Day 60 prescription.

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.21108.1.S1_at	Complement C5	-17.35	3.21	618.80	9.28	C5	eculizumab
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.23793.1.S1_at	T-cell surface antigen CD2	-3.27	79.25	93.34	5.20	CD2	alefacept, siplizumab
Ssc.17245.1.S1_at	Interleukin-13 receptor alpha-1 chain	-1.99	23.04	21.92	7.16	IL13RA1	cintredekin besudotox
Ssc.15999.1.A1_at	Vascular endothelial growth factor receptor 2	1.24	1.24	18.52	-11.02	KDR	AEE 788, sunitinib, AZD 2171, pazopanib, XL647, CEP 7055, BMS-582664, KRN-951, vatalanib, sorafenib, vandetanib, pegaptanib
Ssc.27603.1.S1_at	Endothelin B receptor precursor (ET-B) (Endothelin receptor Non- selective type)	5.30	-3.27	15.99	1.23	EDNRB	bosentan, sitaxsentan, atrasentan
Ssc.2714.1.S1_a_at	Proto-oncogene tyrosine-protein kinase FYN	-4.26	9.56	12.54	3.93	FYN	dasatinib
SscAffx.20.1.S1_at	T-cell surface glycoprotein CD3 gamma chain	-2.19	14.07	10.96	3.62	CD3G	visilizumab, MT103
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4)	3.74	10.91	8.15	1.68	CXCR4	JM 3100
Ssc.26200.1.S1_at	Thyroid hormone receptor beta-1	3.49	-1.56	7.96	2.52	THRB	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.7297.1.S1_at	Amine oxidase [flavin-containing] B(Monoamine oxidase) (MAO-B).	1.16	6.42	7.02	-1.13	MAOB	safinamide, ladostigil, rasagiline, selegiline, dextroamphetamine, procainamide,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							tranylcypromine, phenelzine, isocarboxazid, benzphetamine
Ssc.9019.1.A1_at	Atrial natriuretic peptide clearance receptor precursor (ANP-C) (ANPRC)	-1.09	-1.69	5.31	1.18	NPR3	nesiritide
Ssc.20438.1.S1_at	Prostaglandin F2-alpha receptor	-3.20	2.13	5.28	-38.97	PTGFR	tafluprost, travoprost, isopropyl unoprostone, bimatoprost, latanoprost
Ssc.3040.1.S1_at	Histone deacetylase 2 (HD2)	-3.24	2.79	4.94	4.72	HDAC2	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.26325.1.S1_at	Cystic fibrosis transmembrane conductance regulator (CFTR)	1.60	-5.71	4.77	-8.99	CFTR	SP 303
Ssc.12845.1.S1_at	Cell division protein kinase 6	-6.56	5.40	4.77	5.13	CDK6	PD-0332991, flavopiridol
Ssc.13186.1.S1_at	Cell division protein kinase 7	-1.08	2.38	4.34	1.24	CDK7	BMS-387032, flavopiridol
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase	1.03	1.24	4.16	-1.11	PPAT	6-mercaptopurine, thioguanine, azathioprine
Ssc.15374.1.S1_at	COL14A1 protein	1.10	-17.71	3.79	2.24	COL14A1	collagenase
Ssc.1147.1.A1_at	Lipoprotein lipase	4.05	-5.49	3.78	-8.08	LPL	nicotinic acid, lovastatin/niacin
Ssc.15878.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, alpha	1.85	3.22	3.62	-1.49	PPP3CA	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.26351.1.S1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4D	4.67	4.99	3.61	-1.15	PDE4D	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.15801.1.A1_at	Protein kinase C, beta	3.36	6.36	3.53	-4.98	PRKCB1	enzastaurin, ruboxistaurin
Ssc.10055.1.A1_at	Alpha platelet-derived growth factor receptor	-2.14	-1.46	3.52	-1.14	PDGFRA	sunitinib, axitinib, imatinib, becaplermin
Ssc.24966.1.S1_at	Purine nucleoside phosphorylase	-3.34	3.12	3.46	-1.14	NP	forodesine, 9-deaza-9-(3-thienylmethyl)guanine
Ssc.18051.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase B	-3.16	1.96	3.41	2.32	PDE3B	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole, amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.9523.1.A1_at	Methylated-DNA--protein-cysteine methyltransferase	1.55	-1.17	3.35	1.47	MGMT	O6-benzylguanine
Ssc.16000.1.A1_at	Vascular endothelial growth factor receptor 1	1.08	-3.40	3.34	1.72	FLT1	sunitinib, axitinib, CEP 7055
Ssc.26328.1.S1_at	C-C chemokine receptor type 5 (CCR5) (CD195 antigen).	-2.53	5.61	3.25	1.29	CCR5	maraviroc, vicriviroc, SCH 351125
Ssc.17224.1.S1_at	Toll-like receptor 8	1.17	6.49	3.13	-1.52	TLR8	resiquimod
Ssc.21011.1.S1_at	Collagen alpha 2(I) chain	-2.70	1.24	3.12	-1.01	COL1A2	collagenase
Ssc.10360.1.S1_at	B-Raf proto-oncogene serine/threonine-protein kinase	-2.15	1.26	3.09	1.36	BRAF	sorafenib
Ssc.19532.1.S1_at	Guanylate cyclase soluble, beta-1 chain	-4.28	12.74	3.04	2.13	GUCY1B3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase precursor	1.59	1.16	3.01	1.47	PLA2G7	darapladib
Ssc.17155.1.A1_at	heparanase; heparanase-1	4.81	5.38	2.98	-1.83	HPSE	heparanase inhibitor PI-88
Ssc.15932.1.S1_at	Integrin alpha-V precursor	-6.15	5.79	2.94	3.14	ITGAV	abciximab, CNTO 95, EMD121974
Ssc.16167.1.S1_at	Rho-associated protein kinase	2.40	2.32	2.83	3.00	ROCK1	fasudil, Y-27632

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	1						
Ssc.62.2.S1_a_at	Interleukin-6 (IL-6)	1.89	-6.32	2.77	-1.04	IL6	tocilizumab
Ssc.11246.1.A1_at	Protein kinase C, alpha	-5.96	-4.78	2.68	2.46	PRKCA	L-threo-safingol
Ssc.11381.1.S1_at	Interferon-alpha/beta receptor alpha	10.45	8.08	2.61	-1.30	IFNAR1	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.20685.1.S1_at	Apoptosis regulator Bcl-2	-2.22	2.77	2.58	3.25	BCL2	oblimersen, (-)-gossypol
Ssc.12937.1.S1_at	Presenilin 1 (PS-1) (S182 protein)	-14.09	6.21	2.48	3.79	PSEN1	(R)-flurbiprofen
Ssc.8500.1.A1_at	Glutamate receptor 4 precursor (GluR-4) (GluR4) (GluR-D) (Glutamate receptor ionotropic, AMPA 4)	-1.04	-1.13	2.39	-7.80	GRIA4	talampanel, Org 24448, LY451395, tezampanel
Ssc.6801.1.S1_at	Proto-oncogene tyrosine-protein kinase YES	-1.06	1.69	2.36	-1.82	YES1	dasatinib
Ssc.30373.1.A1_at	cGMP-specific 3',5'-cyclic phosphodiesterase	4.27	1.52	2.34	4.09	PDE5A	dyphylline, nitroglycerin, DA-8159, aminophylline, sildenafil, dipyridamole, aspirin/dipyridamole, vardenafil, tolbutamide, tadalafil, theophylline, pentoxifylline
Ssc.15886.1.S1_at	Apopain precursor (Caspase-3) (CASP-3)	-3.02	3.64	2.31	2.29	CASP3	IDN-6556
Ssc.16114.1.S1_at	Dihydropyridine-sensitive L-type, calcium channel alpha-2/delta subunits	-1.96	-4.18	2.24	3.65	CACNA2D1	bepridil, amlodipine, pregabalin
Ssc.10256.1.A1_at	cAMP-specific 3',5'-cyclic	-1.89	6.74	2.20	2.44	PDE4B	dyphylline, nitroglycerin,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	phosphodiesterase 4B (EC 3.1.4.17) (DPDE4) (PDE32)						arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.5045.1.S1_at	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase (Emopamil-binding protein)	-1.55	1.24	2.19	2.08	EBP	SR 31747
Ssc.204.1.S1_at	Cytochrome P450 3A4	1.97	-3.35	2.16	-1.42	CYP3A4	ketoconazole
Ssc.16186.1.S1_at	T-cell surface glycoprotein CD3 epsilon chain	9.00	3.12	2.12	-5.66	CD3E	visilizumab, MT103, muromonab-CD3
Ssc.1091.1.S1_at	Collagen alpha 1(I) chain	-3.27	-17.59	2.07	1.03	COL1A1	collagenase
Ssc.11302.1.S1_at	Collagen alpha 1(III) chain	-1.80	2.02	2.06	1.26	COL3A1	collagenase
Ssc.19673.1.S1_at	T-cell surface glycoprotein CD3 delta chain	6.40	2.70	2.03	-11.77	CD3D	visilizumab, MT103
Ssc.6710.1.A1_at	Ribonucleoside-diphosphate reductase M1 chain (Ribonucleotide reductase large chain)	-1.90	1.44	2.01	-1.01	RRM1	gemcitabine, clofarabine, fludarabine phosphate
Ssc.11147.1.S1_at	Aldehyde dehydrogenase, mitochondrial precursor ((ALDH)	3.18	1.13	2.00	-1.68	ALDH2	disulfiram, chlorpropamide
Ssc.1520.1.A1_at	Proto-oncogene tyrosine-protein kinase receptor ret	-1.05	-1.88	2.00	2.39	RET	sunitinib
Ssc.30888.1.S1_at	Voltage-dependent L-type calcium channel alpha-1D subunit	2.92	-2.72	1.90	-7.82	CACNA1D	MEM-1003, mibefradil, bepridil, nisoldipine, isradipine, nicardipine
Ssc.15739.1.S1_at	Cytokine receptor common gamma	-1.12	9.42	1.90	-1.28	IL2RG	aldesleukin, denileukin diftitox

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	chain (IL-2R gamma chain) (CD132 antigen)						
Ssc.15822.1.S1_at	Coagulation factor V (Activated protein C cofactor)	1.92	3.76	1.89	-1.75	F5	drotrecogin alfa
Ssc.4756.1.A1_at	Adenosine A3 receptor.	2.15	2.10	1.88	-1.81	ADORA3	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine
Ssc.12791.1.A1_at	3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase)	3.27	2.77	1.77	-2.56	HMGCR	aspirin/pravastatin, lovastatin/niacin, ezetimibe/simvastatin, amlodipine/atorvastatin, fluvastatin, cerivastatin, atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin
Ssc.27293.1.A1_at	Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)	2.15	-1.16	1.63	-7.14	HPRT1	6-mercaptopurine, thioguanine, azathioprine
Ssc.16189.1.S1_at	Endothelin-1 receptor (Endothelin A receptor) (ET-A)	-1.11	-2.54	1.58	-2.91	EDNRA	bosentan, avosentan, clazosentan, ambrisentan, sitaxsentan, ZD4054, SB 234551, TBC 3214, BSF 302146, PD 180988, atrasentan
Ssc.818.1.S1_at	RAF proto-oncogene serine/threonine-protein kinase	-1.40	2.56	1.58	1.98	RAF1	sorafenib
Ssc.15748.2.S2_at	T lymphocyte activation antigen CD80	1.95	-1.24	1.54	-3.12	CD80	abatacept
Ssc.19059.1.A1_at	Type-1 angiotensin II receptor (AT1) (AT1AR)	5.57	-2.57	1.50	-11.08	AGTR1	amlodipine/olmesartan medoxomil, losartan/hydrochlorothiazide, valsartan/hydrochlorothiazide,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							candesartan cilexetil, olmesartan medoxomil, irbesartan, losartan potassium, telmisartan, eprosartan, candesartan cilexetil/hydrochlorothiazide, hydrochlorothiazide/irbesartan, eprosartan/hydrochlorothiazide, hydrochlorothiazide/telmisartan, hydrochlorothiazide/olmesartan medoxomil, valsartan
Ssc.18459.1.S1_at	Amiloride-sensitive sodium channel alpha-subunit	1.97	-2.41	1.43	-1.93	SCNN1A	triamterene/hydrochlorothiazide, amiloride, amiloride/hydrochlorothiazide, triamterene
Ssc.10287.1.A1_at	Transforming growth factor beta 2 precursor (TGF-beta 2)	1.41	-4.54	1.43	1.67	TGFB2	AP-12009
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor) (P2Y(ADP))	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140, clopidogrel
Ssc.9565.1.S1_at	Interferon-gamma receptor alpha chain	2.92	1.63	1.41	-1.23	IFNGR1	interferon gamma-1b
Ssc.9595.1.S1_at	Beta platelet-derived growth factor receptor	3.48	-3.60	1.40	1.65	PDGFRB	dasatinib, sunitinib, axitinib, KRN-951, imatinib, sorafenib, becaplermin
Ssc.8046.1.A1_at	peptidylprolyl isomerase A isoform 1; cyclophilin A;	1.16	-1.08	1.39	1.26	PPIA	N-methyl-4-Ile-cyclosporin
Ssc.1498.1.S1_at	Proteasome subunit beta type 5	-1.81	1.19	1.38	5.94	PSMB5	bortezomib
Ssc.7111.1.A1_at	Ribonucleoside-diphosphate reductase M2 chain (Ribonucleotide reductase small chain)	-13.13	4.08	1.37	1.67	RRM2	gemcitabine, triapine, hydroxyurea, fludarabine phosphate

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.14258.1.S1_at	Amyloid beta A4 protein precursor (APP) (ABPP)	1.87	3.33	1.34	-1.02	APP	AAB-001
Ssc.6418.1.S1_at	Farnesyl-diphosphate farnesyltransferase	-1.25	2.31	1.33	1.08	FDFT1	TAK-475, zoledronic acid
Ssc.16096.2.S1_a_at	Mast/stem cell growth factor receptor	-1.28	-2.63	1.30	-4.71	KIT	dasatinib, sunitinib, KRN-951, imatinib, sorafenib
Ssc.29149.1.A1_at	Mineralocorticoid receptor (MR)	-2.18	-2.78	1.28	-11.66	NR3C2	hydrochlorothiazide/spironolactone, fludrocortisone acetate, drospirenone, spironolactone, eplerenone
Ssc.5569.1.S1_at	Thyroid hormone receptor alpha	-10.22	1.26	1.26	6.49	THRA	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.26215.1.S1_at	DNA polymerase epsilon p12 subunit (DNA polymerase epsilon subunit 4)	-1.23	-2.71	1.19	-1.04	POLE4	gemcitabine
Ssc.23234.1.S1_at	collagen, type XXIV, alpha 1	-1.43	1.66	1.16	1.76	COL24A1	collagenase
Ssc.10142.1.A1_at	Dihydropyrimidine dehydrogenase [NADP+]	2.06	2.17	1.13	-2.68	DPYD	eniluracil
Ssc.3607.1.S1_at	Interferon-alpha/beta receptor beta	2.28	4.65	1.11	-1.56	IFNAR2	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.14475.3.S1_a_at	Peroxisome proliferator activated receptor gamma	13.83	-9.38	1.09	-2.85	PPARG	rosiglitazone, GI262570, pioglitazone, tesaglitazar,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
	(PPAR-gamma)						troglitazone
Ssc.5000.1.A1_at	Receptor protein-tyrosine kinase erbB-2	-1.04	-4.15	1.08	2.25	ERBB2	trastuzumab, BMS-599626, ARRY-334543, XL647, CP-724,714, HKI-272, lapatinib, erlotinib
Ssc.23505.1.S1_at	Amine oxidase [flavin-containing] A (Monoamine oxidase) (MAO-A)	-1.86	2.17	1.08	1.20	MAOA	ladostigil, 1-ethylphenoxathiin 10,10-dioxide, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine, N-(2-indanyl)glycinamide
Ssc.19379.1.A1_at	Voltage-dependent L-type calcium channel alpha-1C	1.83	-1.34	1.07	-3.27	CACNA1C	clevidipine, MEM-1003, amlodipine/olmesartan medoxomil, amlodipine/benazepril, diltiazem, verapamil, mibefradil, bepridil, enalapril/felodipine, amlodipine/atorvastatin, nisoldipine, isradipine, felodipine, nimodipine, nitrendipine, amlodipine, nicardipine, nifedipine, trandolapril/verapamil, diltiazem/enalapril
Ssc.6713.1.S1_at	Androgen receptor (Dihydrotestosterone receptor)	-1.47	-11.56	1.07	-2.36	AR	estradiol valerate/testosterone enanthate, estradiol cypionate/testosterone cypionate, bicalutamide, flutamide, nandrolone decanoate, testosterone cypionate, medroxyprogesterone acetate, oxandrolone, danazol, stanozolol, spironolactone, testosterone,

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							oxymetholone, testosterone propionate, testosterone enanthate
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.25040.1.S1_at	Serine/threonine-protein kinase Chk1	-3.75	1.11	1.06	-2.45	CHEK1	UCN-01 (7-hydroxystaurosporine)
Ssc.9781.1.S1_at	Plasminogen activator inhibitor-1 (PAI-1) (Endothelial plasminogen activator inhibitor) (PAI)	-1.55	-1.17	1.04	1.30	SERPINE1	drotrecogin alfa
Ssc.16532.1.S1_at	Cell division protein kinase 2 (p33 protein kinase).	-1.83	-1.51	1.04	1.35	CDK2	BMS-387032, flavopiridol
Ssc.22797.1.S1_at	DNA topoisomerase II, beta	3.15	-1.87	1.02	-2.91	TOP2B	novobiocin, etoposide, CPI-0004Na, pixantrone, becatecarin, elsamitrucin, AQ4N, BN 80927, tafluposide, mitoxantrone, norfloxacin, dexrazoxane, tirapazamine, TAS-103, XK469, gatifloxacin, valrubicin, gemifloxacin, moxifloxacin, nemorubicin, nalidixic acid, epirubicin, doxorubicin, daunorubicin
Ssc.14488.1.S1_at	Glutamate carboxypeptidase II	-1.04	1.10	1.02	1.69	FOLH1	capromab pendetide

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TABLE 6

Day 180 prescription.

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.11051.1.S1_at	Cell division protein kinase 4	1.44	-7.67	-4.96	23.75	CDK4	PD-0332991, flavopiridol
Ssc.28690.1.A1_at	Histone deacetylase 6 (HD6)	-1.92	-1.57	-3.58	20.60	HDAC6	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.21108.1.S1_at	Complement C5	-17.35	3.21	618.80	9.28	C5	eculizumab
Ssc.5569.1.S1_at	Thyroid hormone receptor alpha	-10.22	1.26	1.26	6.49	THRA	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.1498.1.S1_at	Proteasome subunit beta type 5	-1.81	1.19	1.38	5.94	PSMB5	bortezomib
Ssc.13460.1.A1_at	Histone deacetylase 9 (HD9) (HD7B) (HD7).	-6.40	5.13	-1.79	5.72	HDAC9	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.23793.1.S1_at	T-cell surface antigen CD2	-3.27	79.25	93.34	5.20	CD2	alefacept, siplizumab
Ssc.12845.1.S1_at	Cell division protein kinase 6	-6.56	5.40	4.77	5.13	CDK6	PD-0332991, flavopiridol
Ssc.24528.1.S1_at	Angiotensin-converting enzyme	-1.61	5.01	2.33	4.76	ACE	pentopril, perindoprilat, amlodipine/benazepril, lisinopril/hydrochlorothiazide, benazepril, enalapril, perindopril, captopril, enalapril/felodipine, hydrochlorothiazide/moexipril, benazepril/hydrochlorothiazide, hydrochlorothiazide/quinapril, fosinopril/hydrochlorothiazide,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							captopril/hydrochlorothiazide, enalapril/hydrochlorothiazide, ramipril, moexipril, quinapril, lisinopril, enalaprilat, trandolapril, trandolapril/verapamil, diltiazem/enalapril, fosinopril
Ssc.3040.1.S1_at	Histone deacetylase 2 (HD2)	-3.24	2.79	4.94	4.72	HDAC2	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.30373.1.A1_at	cGMP-specific 3',5'-cyclic phosphodiesterase	4.27	1.52	2.34	4.09	PDE5A	dyphylline, nitroglycerin, DA-8159, aminophylline, sildenafil, dipyridamole, aspirin/dipyridamole, vardenafil, tolbutamide, tadalafil, theophylline, pentoxifylline
Ssc.2714.1.S1_a_at	Proto-oncogene tyrosine-protein kinase FYN	-4.26	9.56	12.54	3.93	FYN	dasatinib
Ssc.12937.1.S1_at	Presenilin 1 (PS-1) (S182 protein).	-14.09	6.21	2.48	3.79	PSEN1	(R)-flurbiprofen
Ssc.19937.1.S1_at	Inosine-5'-monophosphate dehydrogenase 2	1.00	2.69	-1.47	3.65	IMPDH2	thioguanine, VX-944, interferon alfa-2a/ribavirin, mycophenolic acid, ribavirin
Ssc.16114.1.S1_at	Dihydropyridine-sensitive L-type, calcium channel alpha-2/delta	-1.96	-4.18	2.24	3.65	CACNA2D1	bepridil, amlodipine, pregabalin
SscAffx.20.1.S1_at	T-cell surface glycoprotein CD3 gamma chain	-2.19	14.07	10.96	3.62	CD3G	visilizumab, MT103
Ssc.20685.1.S1_at	Apoptosis regulator Bcl-2	-2.22	2.77	2.58	3.25	BCL2	oblimersen, (-)-gossypol
Ssc.11443.1.A1_at	Transcription factor p65	-1.43	-2.45	-3.96	3.24	RELA	NF-kappaB decoy

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.26290.1.S1_at	Integrin beta-5	-1.06	-1.51	-5.43	3.24	ITGB5	EMD121974
Ssc.15932.1.S1_at	Integrin alpha-V	-6.15	5.79	2.94	3.14	ITGAV	abciximab, CNTO 95, EMD121974
Ssc.14471.1.S1_at	B-lymphocyte antigen CD19	9.54	3.30	-10.32	3.04	CD19	combotox, HD37-dgRTA, MT103
Ssc.16167.1.S1_at	Rho-associated protein kinase 1	2.40	2.32	2.83	3.00	ROCK1	fasudil, Y-27632
Ssc.26200.1.S1_at	Thyroid hormone receptor beta-1.	3.49	-1.56	7.96	2.52	THRB	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.3059.1.S1_at	Aldose reductase (Aldehyde reductase).	-1.74	1.98	-1.66	2.49	AKR1B1	sorbinil, Zopolrestat (Alond, Pfizer), zenarestat (Fujisawa, Parke-Davis)
Ssc.11246.1.A1_at	Protein kinase C, alpha	-5.96	-4.78	2.68	2.46	PRKCA	L-threo-safingol
Ssc.10256.1.A1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4B	-1.89	6.74	2.20	2.44	PDE4B	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.1598.1.S1_at	Retinoic acid receptor RXR-beta	-2.21	-1.13	-4.20	2.42	RXRB	bexarotene, retinoic acid, 9-cis-retinoic acid
Ssc.1520.1.A1_at	Proto-oncogene tyrosine-protein kinase receptor ret	-1.05	-1.88	2.00	2.39	RET	sunitinib
Ssc.11572.1.A1_at	Histone deacetylase 3 (HD3) (RPD3-2) (SMAP45).	-1.65	1.67	-1.55	2.36	HDAC3	tributyrin, PXD101, pyroxamide, MGCD0103, vorinostat, FR 901228
Ssc.18051.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase B	-3.16	1.96	3.41	2.32	PDE3B	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.15886.1.S1_at	Apopain precursor (Caspase-3) (CASP-3)	-3.02	3.64	2.31	2.29	CASP3	IDN-6556
Ssc.5000.1.A1_at	Receptor protein-tyrosine kinase erbB-2	-1.04	-4.15	1.08	2.25	ERBB2	trastuzumab, BMS-599626, ARRY-334543, XL647, CP-724,714, HKI-272, lapatinib, erlotinib
Ssc.15374.1.S1_at	COL14A1 protein	1.10	-17.71	3.79	2.24	COL14A1	collagenase
Ssc.19873.1.S1_at	Collagen alpha 1(XVII) chain	-2.37	3.02	-1.55	2.18	COL17A1	collagenase
Ssc.19532.1.S1_at	Guanylate cyclase soluble, beta-1 chain	-4.28	12.74	3.04	2.13	GUCY1B3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.5045.1.S1_at	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase (EC 5.3.3.5) (Cholestenol delta-isomerase) (Emopamil-binding protein).	-1.55	1.24	2.19	2.08	EBP	SR 31747
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.7139.1.S1_at	Dihydrofolate reductase	-1.13	1.41	-1.12	2.06	DHFR	pyrimethamine, trimethoprim, iclaprim, methotrexate, sulfisoxazole, triamterene, folic acid, trimetrexate, LY231514, PT 523
Ssc.818.1.S1_at	RAF proto-oncogene serine/threonine-protein kinase	-1.40	2.56	1.58	1.98	RAF1	sorafenib
Ssc.25168.1.S1_a_at	Collagen alpha 1(XVI) chain	-7.23	-3.61	-4.45	1.87	COL16A1	collagenase

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.3737.1.S1_at	Tubulin gamma-1 chain (Gamma-1 tubulin) (	-1.24	-1.88	-1.29	1.82	TUBG1	epothilone B, ixabepilone, colchicine/probenecid, XRP9881, E7389, AL 108, EC145, NPI-2358, milataxel, TPI 287, TTI-237, docetaxel, vinflunine, vincrelbine, vincristine, vinblastine, paclitaxel, podophyllotoxin, colchicine
Ssc.23234.1.S1_at	collagen, type XXIV, alpha 1	-1.43	1.66	1.16	1.76	COL24A1	collagenase
Ssc.16000.1.A1_at	Vascular endothelial growth factor receptor 1	1.08	-3.40	3.34	1.72	FLT1	sunitinib, axitinib, CEP 7055
Ssc.14488.1.S1_at	Glutamate carboxypeptidase II	-1.04	1.10	1.02	1.69	FOLH1	capromab pendetide
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4)	3.74	10.91	8.15	1.68	CXCR4	JM 3100
Ssc.10287.1.A1_at	Transforming growth factor beta 2	1.41	-4.54	1.43	1.67	TGFB2	AP-12009
Ssc.7111.1.A1_at	Ribonucleoside-diphosphate reductase M2 chain	-13.13	4.08	1.37	1.67	RRM2	gemcitabine, triapine, hydroxyurea, fludarabine phosphate
Ssc.9595.1.S1_at	Beta platelet-derived growth factor receptor	3.48	-3.60	1.40	1.65	PDGFRB	dasatinib, sunitinib, axitinib, KRN-951, imatinib, sorafenib, becaplermin
Ssc.5826.1.A1_at	Macrophage colony stimulating factor I receptor	1.93	-4.97	-13.18	1.61	CSF1R	sunitinib
Ssc.17518.1.S1_at	Adenosine A1 receptor	-3.16	3.44	-1.56	1.58	ADORA1	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine, tecadenoson
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase	1.59	1.16	3.01	1.47	PLA2G7	darapladib

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
Ssc.9523.1.A1_at	Methylated-DNA--protein-cysteine methyltransferase	1.55	-1.17	3.35	1.47	MGMT	O6-benzylguanine
Ssc.11406.1.A1_a_at	Interleukin-1 receptor, type I	1.03	2.70	-2.44	1.42	IL1R1	anakinra
Ssc.11085.1.S1_at	Glucagon-like peptide 2 receptor	-1.08	-1.17	-1.26	1.40	GLP2R	teduglutide
Ssc.10591.1.A1_at	Metabotropic glutamate receptor 5	-7.83	1.54	-1.31	1.40	GRM5	fasoracetam
Ssc.9034.1.A1_at	Proteinase activated receptor 1	-1.29	3.75	-1.40	1.37	F2R	chrysalin, argatroban, bivalirudin
Ssc.10360.1.S1_at	B-Raf proto-oncogene serine/threonine-protein kinase	-2.15	1.26	3.09	1.36	BRAF	sorafenib
Ssc.16532.1.S1_at	Cell division protein kinase 2	-1.83	-1.51	1.04	1.35	CDK2	BMS-387032, flavopiridol
Ssc.9781.1.S1_at	Plasminogen activator inhibitor-1 precursor (PAI-1) (Endothelial plasminogen activator inhibitor) (PAI)	-1.55	-1.17	1.04	1.30	SERPINE 1	drotrecogin alfa
Ssc.26328.1.S1_at	C-C chemokine receptor type 5 (CCR5) (CD195 antigen)	-2.53	5.61	3.25	1.29	CCR5	maraviroc, vicriviroc, SCH 351125
Ssc.8046.1.A1_at	peptidylprolyl isomerase A isoform 1; cyclophilin A;	1.16	-1.08	1.39	1.26	PPIA	N-methyl-4-Ile-cyclosporin
Ssc.11302.1.S1_at	Collagen alpha 1(III) chain	-1.80	2.02	2.06	1.26	COL3A1	collagenase
Ssc.13186.1.S1_at	Cell division protein kinase 7	-1.08	2.38	4.34	1.24	CDK7	BMS-387032, flavopiridol
Ssc.27603.1.S1_at	Endothelin B receptor	5.30	-3.27	15.99	1.23	EDNRB	bosentan, sitaxsentan, atrasentan
Ssc.27093.1.A1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4C	-6.34	-2.27	-7.97	1.23	PDE4C	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.20904.1.A1_at	RAC-gamma serine/threonine-protein kinase	-1.34	3.01	-2.18	1.23	AKT3	enzastaurin
Ssc.23505.1.S1_at	Amine oxidase (flavin-containing) A (Monoamine oxidase) (MAO-A)	-1.86	2.17	1.08	1.20	MAOA	ladostigil, 1-ethylphenoxathiin 10,10-dioxide, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine, N-(2-indanyl)glycinamide
Ssc.15312.1.S1_at	Histone deacetylase 4 (HD4)	-1.93	2.85	-2.41	1.20	HDAC4	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.9019.1.A1_at	Atrial natriuretic peptide clearance receptor	-1.09	-1.69	5.31	1.18	NPR3	nesiritide
Ssc.16160.1.S1_at	T lymphocyte activation antigen CD86	-1.55	3.88	-1.37	1.18	CD86	abatacept
Ssc.1844.1.S1_at	Atrial natriuretic peptide receptor B	-1.94	-1.06	-1.63	1.13	NPR2	nesiritide
Ssc.11171.1.S1_at	Adenosine deaminase	1.32	-2.04	-3.23	1.12	ADA	pentostatin, vidarabine
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor)	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140, clopidogrel
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.26752.1.S1_at	5-hydroxytryptamine (serotonin) receptor 3B	-3.57	1.22	1.60	1.08	HTR3B	cisapride, granisetron, ondansetron, fenfluramine, palonosetron, mirtazapine, alosetron, D-tubocurarine,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	DRUGS
							ergotamine, dolasetron
Ssc.6418.1.S1_at	Farnesyl-diphosphate farnesyltransferase	-1.25	2.31	1.33	1.08	FDFT1	TAK-475, zoledronic acid
Ssc.22477.1.S1_at	Collagen alpha 1(IV) chain	1.58	-5.08	-1.78	1.04	COL4A1	collagenase
Ssc.31192.1.S1_at	Collagen alpha 1(XVIII) chain	-1.89	-1.36	-19.06	1.03	COL18A1	collagenase
Ssc.1091.1.S1_at	Collagen alpha 1(I) chain	-3.27	-17.59	2.07	1.03	COL1A1	collagenase
Ssc.7581.1.A1_at	FL cytokine receptor	1.69	1.04	-1.81	1.01	FLT3	CHIR-258, sorafenib, lestaurtinib, CGP 41251

Table 7

Upregulated gene targets at all timepoints (Days 7, 21, 60, and 180 relative to baseline) of PAH progression with available drugs

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4) (CD184 antigen)	3.74	10.91	8.15	1.68	CXCR4	JM 3100 (1,1'-(1,4-phenylenebis(methylene))bis(1,4,8,11-tetraazacyclotetradecane)octahydrochloride dihydrate)
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase	1.59	1.16	3.01	1.47	PLA2G7	darapladib
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12)	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140 (**Ticagrelor**), clopidogrel
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta isoform	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.14258.1.S1_at	Amyloid beta A4 protein	1.87	3.33	1.34	-1.02	APP	Bapineuzumab (AAB-001)
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase	1.03	1.24	4.16	-1.11	PPAT	thioguanine, azathioprine, 6-mercaptopurine,

Table 8

Upregulated gene targets at Days 21 and 60 (relative to baseline) of PAH progression with available drugs

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.21108.1.S1_at	Complement C5	-17.35	3.21	618.80	9.28	C5	eculizumab
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.23793.1.S1_at	T-cell surface antigen CD2	-3.27	79.25	93.34	5.20	CD2	alefacept, siplizumab
Ssc.17245.1.S1_at	Interleukin-13 receptor alpha-1 chain	-1.99	23.04	21.92	7.16	IL13RA1	cintredekin besudotox
Ssc.15999.1.A1_at	Vascular endothelial growth factor receptor 2	1.24	1.24	18.52	-11.02	KDR	AEE 788, sunitinib, AZD 2171, pazopanib, XL647, CEP 7055, BMS-582664, KRN-951, vatalanib, sorafenib, vandetanib, pegaptanib
Ssc.2714.1.S1_a_at	Proto-oncogene tyrosine-protein kinase FYN	-4.26	9.56	12.54	3.93	FYN	dasatinib
SscAffx.20.1.S1_at	T-cell surface glycoprotein CD3 gamma chain	-2.19	14.07	10.96	3.62	CD3G	visilizumab, MT103
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4) (	3.74	10.91	8.15	1.68	CXCR4	JM 3100
Ssc.7297.1.S1_at	Amine oxidase [flavin-containing] B (EC 1.4.3.4) (Monoamine oxidase) (MAO-B).	1.16	6.42	7.02	-1.13	MAOB	safinamide, ladostigil, rasagiline, selegiline, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.20438.1.S1_at	Prostaglandin F2-alpha receptor (PGF2 alpha receptor).	-3.20	2.13	5.28	-38.97	PTGFR	tafluprost, travoprost, isopropyl unoprostone, bimatoprost, latanoprost
Ssc.3040.1.S1_at	Histone deacetylase 2 (HD2).	-3.24	2.79	4.94	4.72	HDAC2	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.12845.1.S1_at	Cell division protein kinase 6 (E	-6.56	5.40	4.77	5.13	CDK6	PD-0332991, flavopiridol
Ssc.13186.1.S1_at	Cell division protein kinase 7	-1.08	2.38	4.34	1.24	CDK7	BMS-387032, flavopiridol
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase	1.03	1.24	4.16	-1.11	PPAT	6-mercaptopurine, thioguanine, azathioprine
Ssc.15878.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, alpha isoform	1.85	3.22	3.62	-1.49	PPP3CA	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.26351.1.S1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4D (EC 3.1.4.17) (DPDE3) (PDE43). [Source:Uniprot/SWISSPROT;Acc:Q08499]	4.67	4.99	3.61	-1.15	PDE4D	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.15801.1.A1_at	Protein kinase C, beta type (EC 2.7.1.37) (PKC-beta) (PKC-B). [Source:Uniprot/SWISSPROT;Acc:P05771]	3.36	6.36	3.53	-4.98	PRKCB1	enzastaurin, ruboxistaurin
Ssc.24966.1.S1_at	Purine nucleoside phosphorylase	-3.34	3.12	3.46	-1.14	NP	forodesine, 9-deaza-9-(3-thienylmethyl)guanine

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.18051.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase B	-3.16	1.96	3.41	2.32	PDE3B	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole, amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.26328.1.S1_at	C-C chemokine receptor type 5 (C-C CKR-5) (CC-CKR-5) (CCR-5) (CCR5) (HIV-1 fusion coreceptor) (CHEMR13) (CD195 antigen). [Source:Uniprot/SWISSPROT;Acc:P51681]	-2.53	5.61	3.25	1.29	CCR5	maraviroc, vicriviroc, SCH 351125
Ssc.17224.1.S1_at	Toll-like receptor 8 precursor. [Source:Uniprot/SWISSPROT;Acc:Q9NR97]	1.17	6.49	3.13	-1.52	TLR8	resiquimod
Ssc.21011.1.S1_at	Collagen alpha 2(I) chain precursor. [Source:Uniprot/SWISSPROT;Acc:P08123]	-2.70	1.24	3.12	-1.01	COL1A2	collagenase
Ssc.10360.1.S1_at	B-Raf proto-oncogene serine/threonine-protein kinase (v-Raf murine sarcoma viral oncogene homolog B1).	-2.15	1.26	3.09	1.36	BRAF	sorafenib
Ssc.19532.1.S1_at	Guanylate cyclase soluble, beta-1	-4.28	12.74	3.04	2.13	GUCY1B3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.19691.1.S1_at	Platelet-activating	1.59	1.16	3.01	1.47	PLA2G7	darapladib

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Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	factor acetylhydrolase						
Ssc.17155.1.A1_at	heparanase; heparanase-1	4.81	5.38	2.98	-1.83	HPSE	heparanase inhibitor PI-88
Ssc.15932.1.S1_at	Integrin alpha-V	-6.15	5.79	2.94	3.14	ITGAV	abciximab, CNTO 95, EMD121974 (Cilengitide)
Ssc.11381.1.S1_at	Interferon-alpha/beta receptor alpha chain precursor (IFN-alpha-REC). [Source:Uniprot/SWISSPROT;Acc:P17181]	10.45	8.08	2.61	-1.30	IFNAR1	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.20685.1.S1_at	Apoptosis regulator Bcl-2. [Source:Uniprot/SWISSPROT;Acc:P10415]	-2.22	2.77	2.58	3.25	BCL2	Oblimersen (Augmerosen),
Ssc.12937.1.S1_at	Presenilin 1 (PS-1) (S182 protein).	-14.09	6.21	2.48	3.79	PSEN1	(R)-flurbiprofen (Tarenflurbil)
Ssc.6801.1.S1_at	Proto-oncogene tyrosine-protein kinase YES	-1.06	1.69	2.36	-1.82	YES1	dasatinib
Ssc.24528.1.S1_at	Angiotensin-converting enzyme	-1.61	5.01	2.33	4.76	ACE	pentopril, perindoprilat, amlodipine/benazepril, lisinopril/hydrochlorothiazide, benazepril, enalapril, perindopril, captopril, enalapril/felodipine, hydrochlorothiazide/moexipril, benazepril/hydrochlorothiazide, hydrochlorothiazide/quinapril, fosinopril/hydrochlorothiazide,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							captopril/hydrochlorothiazide, enalapril/hydrochlorothiazide, ramipril, moexipril, quinapril, lisinopril, enalaprilat, trandolapril, trandolapril/verapamil, diltiazem/enalapril, fosinopril
Ssc.15886.1.S1_at	Apopain (Caspase-3) (CASP-3	-3.02	3.64	2.31	2.29	CASP3	IDN-6556
Ssc.10256.1.A1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4B	-1.89	6.74	2.20	2.44	PDE4B	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.5045.1.S1_at	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase	-1.55	1.24	2.19	2.08	EBP	SR 31747
Ssc.16145.1.A1_at	5-hydroxytryptamine 2B receptor (5-HT-2B) (Serotonin receptor 2B).	1.08	2.10	2.15	5.45	HTR2B	risperidone, buspirone, blonanserin, asenapine, eletriptan, epinastine, fenfluramine, quetiapine, nefazodone, mirtazapine, dihydroergotamine, apomorphine, ergotamine
Ssc.16186.1.S1_at	T-cell surface glycoprotein CD3 epsilon chain	9.00	3.12	2.12	-5.66	CD3E	visilizumab, MT103, muromonab-CD3
Ssc.11302.1.S1_at	Collagen alpha 1(III) chain precursor.	-1.80	2.02	2.06	1.26	COL3A1	collagenase
Ssc.19673.1.S1_at	T-cell surface glycoprotein CD3	6.40	2.70	2.03	-11.77	CD3D	visilizumab, MT103

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	delta chain precursor (T-cell receptor T3 delta chain).						
Ssc.6710.1.A1_at	Ribonucleoside-diphosphate reductase M1 chain (Ribonucleotide reductase large chain	-1.90	1.44	2.01	-1.01	RRM1	gemcitabine, clofarabine, fludarabine phosphate
Ssc.11147.1.S1_at	Aldehyde dehydrogenase, mitochondrial precursor (ALDH class 2) (ALDHI) (ALDH-E2).	3.18	1.13	2.00	-1.68	ALDH2	disulfiram, chlorpropamide
Ssc.15739.1.S1_at	Cytokine receptor common gamma chain (Interleukin- 2 receptor gamma chain) (IL-2R gamma chain) (CD132 antigen).	-1.12	9.42	1.90	-1.28	IL2RG	aldesleukin, denileukin diftitox
Ssc.15822.1.S1_at	Coagulation factor V precursor (Activated protein C cofactor).	1.92	3.76	1.89	-1.75	F5	drotrecogin alfa
Ssc.4756.1.A1_at	Adenosine A3 receptor.	2.15	2.10	1.88	-1.81	ADORA3	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine
Ssc.12791.1.A1_at	3-hydroxy-3-methylglutaryl-coenzyme A reductase	3.27	2.77	1.77	-2.56	HMGCR	aspirin/pravastatin, lovastatin/niacin, ezetimibe/simvastatin, amlodipine/atorvastatin, fluvastatin,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							cerivastatin, atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin
Ssc.818.1.S1_at	RAF proto-oncogene serine/threonine-protein kinase	-1.40	2.56	1.58	1.98	RAF1	sorafenib
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor)	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140 (Ticagrelor), clopidogrel
Ssc.9565.1.S1_at	Interferon-gamma receptor alpha chain (CD119 antigen)	2.92	1.63	1.41	-1.23	IFNGR1	interferon gamma-1b
Ssc.1498.1.S1_at	Proteasome subunit beta type 5	-1.81	1.19	1.38	5.94	PSMB5	bortezomib
Ssc.7111.1.A1_at	Ribonucleoside-diphosphate reductase M2 chain	-13.13	4.08	1.37	1.67	RRM2	gemcitabine, triapine, hydroxyurea, fludarabine phosphate
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.14258.1.S1_at	Amyloid beta A4 protein	1.87	3.33	1.34	-1.02	APP	AAB-001 (Bapineuzumab)
Ssc.6418.1.S1_at	Farnesyl-diphosphate farnesyltransferase	-1.25	2.31	1.33	1.08	FDFT1	TAK-475, zoledronic acid
Ssc.5569.1.S1_at	Thyroid hormone receptor alpha (C-erbA-alpha) (c-erbA-1)	-10.22	1.26	1.26	6.49	THRA	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.23234.1.S1_at	collagen, type XXIV, alpha 1	-1.43	1.66	1.16	1.76	COL24A1	collagenase

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.10142.1.A1_at	Dihydropyrimidine dehydrogenase [NADP+]	2.06	2.17	1.13	-2.68	DPYD	eniluracil
Ssc.3607.1.S1_at	Interferon-alpha/beta receptor beta chain	2.28	4.65	1.11	-1.56	IFNAR2	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.23505.1.S1_at	Amine oxidase [flavin-containing] A	-1.86	2.17	1.08	1.20	MAOA	ladostigil, 1-ethylphenoxathiin 10,10-dioxide, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine, N-(2-indanyl)glycinamide
Ssc.28329.1.S1_at	DNA polymerase	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.25040.1.S1_at	Serine/threonine-protein kinase Chk1	-3.75	1.11	1.06	-2.45	CHEK1	UCN-01 (7-hydroxystaurosporine)
Ssc.26379.1.S1_at	Glutamate [NMDA] receptor subunit epsilon 3	-1.32	1.37	1.03	-2.59	GRIN2C	dextromethorphan/guaifenesin, morphine/dextromethorphan, neramexane, SPM 927, bicifadine, delucemine, CR 2249, besonprodil, UK-240455, ketamine, felbamate, memantine, orphenadrine, cycloserine, N-(2-indanyl)glycinamide, dextromethorphan, brompheniramine/dextromethorphan/pseudoephedrine, chlorpheniramine/dextromethorphan/phenylephrine, carbinoxamine/dextromethorphan/pseudoephedrine, dextromethorphan/promethazine, 1-aminocyclopropane-1-carboxylic acid

WO 2009/121031
PCT/US2009/038685

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.14488.1.S1_at	Glutamate carboxypeptidase II	-1.04	1.10	1.02	1.69	FOLH1	capromab pendetide

Table 9

Upregulated gene targets at Days 21, 60 and 180 (relative to baseline) of PAH progression with available drugs

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.23793.1.S1_at	T-cell surface antigen CD2	-3.27	79.25	93.34	5.20	CD2	alefacept, siplizumab
SscAffx.20.1.S1_at	T-cell surface glycoprotein CD3 gamma chain	-2.19	14.07	10.96	3.62	CD3G	visilizumab, MT103
Ssc.19532.1.S1_at	Guanylate cyclase soluble, beta-1 chain	-4.28	12.74	3.04	2.13	GUCY1B3	nitroglycerin, isosorbide-5-mononitrate, isosorbide dinitrate, nitroprusside, isosorbide dinitrate/hydralazine
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4)	3.74	10.91	8.15	1.68	CXCR4	JM 3100 (1,1'-(1,4-phenylenebis(methylene))bis(1,4,8,11-tetraazacyclotetradecane)octahydrochloride dihydrate)
Ssc.2714.1.S1_a_at	Proto-oncogene tyrosine-protein kinase FYN	-4.26	9.56	12.54	3.93	FYN	dasatinib
Ssc.10256.1.A1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4B	-1.89	6.74	2.20	2.44	PDE4B	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.12937.1.S1_at	Presenilin 1 (PS-1) (S182 protein).	-14.09	6.21	2.48	3.79	PSEN1	(R)-flurbiprofen
Ssc.15932.1.S1_at	Integrin alpha-V	-6.15	5.79	2.94	3.14	ITGAV	abciximab, CNTO 95, EMD121974 (Cilengitide)
Ssc.26328.1.S1_at	C-C chemokine receptor type 5 (CCR5)	-2.53	5.61	3.25	1.29	CCR5	maraviroc, vicriviroc, SCH 351125

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.12845.1.S1_at	Cell division protein kinase 6	-6.56	5.40	4.77	5.13	CDK6	PD-0332991, flavopiridol
Ssc.24528.1.S1_at	Angiotensin-converting enzyme	-1.61	5.01	2.33	4.76	ACE	pentopril, perindoprilat, amlodipine/benazepril, lisinopril/hydrochlorothiazide, benazepril, enalapril, perindopril, captopril, enalapril/felodipine, hydrochlorothiazide/moexipril, benazepril/hydrochlorothiazide, hydrochlorothiazide/quinapril, fosinopril/hydrochlorothiazide, captopril/hydrochlorothiazide, enalapril/hydrochlorothiazide, ramipril, moexipril, quinapril, lisinopril, enalaprilat, trandolapril, trandolapril/verapamil, diltiazem/enalapril, fosinopril
Ssc.7130.1.S1_at	Phenylalanine-4-hydroxylase	4.70	4.71	11.30	1.48	PAH	(6R)-tetrahydrobiopterin
Ssc.7111.1.A1_at	Ribonucleoside-diphosphate reductase M2 chain (Ribonucleotide reductase small chain).	-13.13	4.08	1.37	1.67	RRM2	gemcitabine, triapine, hydroxyurea, fludarabine phosphate
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.15886.1.S1_at	Apopain (Caspase-3) (CASP-3)	-3.02	3.64	2.31	2.29	CASP3	IDN-6556

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.21108.1.S1_at	Complement C5	-17.35	3.21	618.80	9.28	C5	eculizumab
Ssc.3040.1.S1_at	Histone deacetylase 2 (HD2).	-3.24	2.79	4.94	4.72	HDAC2	tributyrin, PXD101, pyroxamide, vorinostat, FR 901228
Ssc.20685.1.S1_at	Apoptosis regulator Bcl-2	-2.22	2.77	2.58	3.25	BCL2	oblimersen, (-)-gossypol
Ssc.818.1.S1_at	RAF proto-oncogene serine/threonine-protein kinase	-1.40	2.56	1.58	1.98	RAF1	sorafenib
Ssc.13186.1.S1_at	Cell division protein kinase 7	-1.08	2.38	4.34	1.24	CDK7	BMS-387032, flavopiridol
Ssc.6418.1.S1_at	Farnesyl-diphaosphate farnesyltransferase	-1.25	2.31	1.33	1.08	FDFT1	TAR-475, zoledronic acid
Ssc.23505.1.S1_at	Amine oxidase [flavin-containing] A (Monoamine oxidase) (MAO-A).	-1.86	2.17	1.08	1.20	MAOA	ladostigil, 1-ethylphenoxathiin 10,10-dioxide, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine, N-(2-indanyl)glycinamide
Ssc.11302.1.S1_at	Collagen alpha 1(III) chain precursor.	-1.80	2.02	2.06	1.26	COL3A1	collagenase
Ssc.18051.1.S1_at	cGMP-inhibited 3',5'-cyclic phosphodiesterase B	-3.16	1.96	3.41	2.32	PDE3B	dyphylline, nitroglycerin, medorinone, aminophylline, cilostazol, dipyridamole, amrinone, tolbutamide, theophylline, pentoxifylline
Ssc.23234.1.S1_at	collagen, type XXIV, alpha 1	-1.43	1.66	1.16	1.76	COL24A1	collagenase
Ssc.5569.1.S1_at	Thyroid hormone receptor alpha	-10.22	1.26	1.26	6.49	THRA	3,5-diiodothyropropionic acid, amiodarone, thyroxine, L-triiodothyronine
Ssc.10360.1.S1_at	B-Raf proto-oncogene	-2.15	1.26	3.09	1.36	BRAF	sorafenib

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	serine/threonine-protein kinase						
Ssc.5045.1.S1_at	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase	-1.55	1.24	2.19	2.08	EBP	SR 31747
Ssc.1498.1.S1_at	Proteasome subunit beta type 5	-1.81	1.19	1.38	5.94	PSMB5	bortezomib
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor) (P2Y(ADP))	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140, clopidogrel
Ssc.19691.1.S1_at	Platelet-activating factor acetylhydrolase	1.59	1.16	3.01	1.47	PLA2G7	darapladib
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.14488.1.S1_at	Glutamate carboxypeptidase II	-1.04	1.10	1.02	1.69	FOLH1	capromab pendetide

TABLE 10

Upregulated gene targets at both Days 7 and 21 (relative to baseline) of PAH progression with available drugs

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
Ssc.11381.1.S1_at	Interferon-alpha/beta receptor alpha chain	10.45	8.08	2.61	-1.30	IFNAR1	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.16186.1.S1_at	T-cell surface glycoprotein CD3 epsilon chain	9.00	3.12	2.12	-5.66	CD3E	visilizumab, MT103, muromonab-CD3
Ssc.19673.1.S1_at	T-cell surface glycoprotein CD3 delta chain	6.40	2.70	2.03	-11.77	CD3D	visilizumab, MT103
Ssc.17155.1.A1_at	heparanase; heparanase-1	4.81	5.38	2.98	-1.83	HPSE	heparanase inhibitor PI-88
Ssc.7130.1.S1_at	Phenylalanine-4- hydroxylase	4.70	4.71	11.30	1.48	PAH	(6R)-tetrahydrobiopterin
Ssc.26351.1.S1_at	cAMP-specific 3',5'-cyclic phosphodiesterase 4D	4.67	4.99	3.61	-1.15	PDE4D	dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, roflumilast, tolbutamide, theophylline, pentoxifylline, caffeine
Ssc.7176.1.A1_at	C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4)	3.74	10.91	8.15	1.68	CXCR4	JM 3100
Ssc.15801.1.A1_at	Protein kinase C, beta	3.36	6.36	3.53	-4.98	PRKCB1	enzastaurin, ruboxistaurin
Ssc.12791.1.A1_at	3-hydroxy-3-methylglutaryl-coenzyme A reductase	3.27	2.77	1.77	-2.56	HMGCR	aspirin/pravastatin, lovastatin/niacin, ezetimibe/simvastatin,

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
							amlodipine/atorvastatin, fluvastatin, cerivastatin, atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin
Ssc.11147.1.S1_at	Aldehyde dehydrogenase, mitochondrial	3.18	1.13	2.00	-1.68	ALDH2	disulfiram, chlorpropamide
Ssc.9565.1.S1_at	Interferon-gamma receptor alpha chain	2.92	1.63	1.41	-1.23	IFNGR1	interferon gamma-1b
Ssc.3607.1.S1_at	Interferon-alpha/beta receptor beta	2.28	4.65	1.11	-1.56	IFNAR2	interferon beta-1a, interferon alfa-2b, interferon alfacon-1, PEG-interferon alfa-2a, interferon alfa-2a/ribavirin, pegintron, interferon beta-1b, IFNA2A
Ssc.4756.1.A1_at	Adenosine A3 receptor.	2.15	2.10	1.88	-1.81	ADORA3	adenosine, dyphylline, aminophylline, clofarabine, theophylline, caffeine
Ssc.10142.1.A1_at	Dihydropyrimidine dehydrogenase [NADP+]	2.06	2.17	1.13	-2.68	DPYD	eniluracil
Ssc.15822.1.S1_at	Coagulation factor V	1.92	3.76	1.89	-1.75	F5	drotrecogin alfa
Ssc.14258.1.S1_at	Amyloid beta A4 protein precursor (APP) (ABPP)	1.87	3.33	1.34	-1.02	APP	AAB-001
Ssc.15878.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, alpha	1.85	3.22	3.62	-1.49	PPP3CA	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.9272.1.S1_at	Tumor-associated calcium signal transducer 1 (EPCAM antigen)	1.81	3.94	176.50	2.07	TACSTD1	tucotuzumab celmoleukin
Ssc.19691.1.S1_at	Platelet-activating factor	1.59	1.16	3.01	1.47	PLA2G7	darapladib

Probe ID	Name	Fold Change D7/Base	Fold Change D21/Base	Fold Change D60/Base	Fold Change D180 / Base	Gene Symbol	Drugs
	acetylhydrolase						
Ssc.30147.1.A1_at	Fibroblast growth factor receptor 2	1.56	1.13	-1.05	-1.18	FGFR2	palifermin
Ssc.16823.1.S1_at	P2Y purinoceptor 12 (P2Y12) (P2Y12 platelet ADP receptor)	1.38	1.19	1.41	1.11	P2RY12	prasugrel, AZD 6140, clopidogrel
Ssc.15999.1.A1_at	Vascular endothelial growth factor receptor 2	1.24	1.24	18.52	-11.02	KDR	AEE 788, sunitinib, AZD 2171, pazopanib, XL647, CEP 7055, BMS-582664, KRN-951, vatalanib, sorafenib, vandetanib, pegaptanib
Ssc.17224.1.S1_at	Toll-like receptor 8	1.17	6.49	3.13	-1.52	TLR8	resiquimod
Ssc.7297.1.S1_at	Amine oxidase	1.16	6.42	7.02	-1.13	MAOB	safinamide, ladostigil, rasagiline, selegiline, dextroamphetamine, procainamide, tranylcypromine, phenelzine, isocarboxazid, benzphetamine
Ssc.28329.1.S1_at	DNA polymerase beta	1.14	1.19	1.07	5.25	POLB	nelarabine, clofarabine, stavudine, trifluridine, vidarabine, zalcitabine, entecavir
Ssc.19700.1.S1_at	Serine/threonine protein phosphatase 2B catalytic subunit, beta	1.11	1.13	1.34	1.09	PPP3CB	ISAtx-247, tacrolimus, pimecrolimus, cyclosporin A
Ssc.8726.1.A1_at	Amidophosphoribosyltransferase precursor	1.03	1.24	4.16	-1.11	PPAT	6-mercaptopurine, thioguanine, azathioprine

TABLE 11

Animal number, days after post-shunt PAH creation surgery, and pulmonary arterial pressure (PAP).

Pig 19 Timecourse

Animal Day	PAP	PAP mean
P19 Day0	28/1	26
P19 Day10	22/17	19
P19 Day24	76/29	47
P19 Day59	89/50	58
P19 Day94	70/18	54

Pig 20 Timecourse

Animal Day	PAP	PAP mean
P20 Day0	20/11	16
P20 Day6	19/15	16
P20 Day21	20/15	17
P20 Day55	23/15	19
P20 Day83	62/17	45
P20 Day104	116/72	104
P20 Day140	92/40	81

Normal (Normal Pressure & Flow)

Animal Day	PAP	PAP mean
P19 Day0	28/1	26
P20 Day0	20/11	16

HFLP (High Flow Low Pressure)

Animal Day	PAP	PAP mean
P19 Day10	22/17	19
P20 Day6	19/15	16
P20 Day21	20/15	17
P20 Day55	23/15	19

HFHP (High Flow High Pressure)

Animal Day	PAP	PAP mean
P19 Day24	76/29	47
P19 Day59	89/50	58
P19 Day94	70/18	54
P20 Day83	62/17	45
P20 Day104	116/72	104
P20 Day140	92/40	81

TABLE 12

Significantly differently expressed downregulated microRNAs HFHP (High Flow High Pressure) vs. normal.

Downregulated microRNA HFHP vs. Norm (p<.05)				
Illumina ID	Normal	HFHP	HFLP	miRNA Symbol
ILMN_3167128	32.58	-2.36	2.75	solexa-603-1846
ILMN_3167515	4183.74	42.62	142.81	hsa-miR-586
ILMN_3168604	31.83	-2.01	0.90	hsa-miR-1201
ILMN_3167691	127.02	1.76	1358.98	hsa-miR-33a
ILMN_3167249	229.25	18.22	511.84	HS_56
ILMN_3167753	114.97	14.32	66.23	hsa-miR-520d:9.1
ILMN_3168215	37.30	8.98	3110.35	hsa-miR-521
ILMN_3168168	32.58	1.72	28.59	hsa-miR-519a
ILMN_3168054	3916.21	79.38	14.02	HS_134
ILMN_3168235	58.82	6.34	2.94	HS_169
ILMN_3168335	15.54	-2.85	26.65	HS_221
ILMN_3167393	90.38	5.18	5.54	hsa-miR-496
ILMN_3168678	837.14	14.23	777.94	hsa-miR-935
ILMN_3167175	8796.46	1274.47	88.95	hsa-miR-542-5p
ILMN_3168905	92.30	5.07	33.55	solexa-5620-151
ILMN_3168648	593.72	46.29	812.05	hsa-miR-99a
ILMN_3167761	37.30	16.59	0.17	hsa-miR-212
ILMN_3168709	1281.24	218.10	80.10	hsa-let-7f-2
ILMN_3168446	8875.62	343.70	546.81	hsa-miR-494
ILMN_3168663	31.00	3.29	18.23	hsa-miR-1321
ILMN_3168597	99.25	14.28	43.96	hsa-miR-219-2-3p
ILMN_3166971	1310.30	311.18	924.85	hsa-miR-95
ILMN_3167491	3060.68	925.46	1647.50	hsa-miR-128b:9.1
ILMN_3168654	740.78	96.90	957.01	hsa-miR-33a
ILMN_3167052	370.00	45.81	234.11	hsa-miR-495

Downregulated microRNA HFHP vs. Norm (p<.05)				
Illumina ID	Normal	HFHP	HFLP	miRNA Symbol
ILMN_3167337	177.30	43.83	27.93	hsa-miR-1229
ILMN_3168827	569.48	117.37	51.85	hsa-miR-1205
ILMN_3167328	6444.52	2162.76	2119.65	hsa-miR-524-3p
ILMN_3167952	8724.37	2076.18	926.06	HS_150
ILMN_3168798	376.77	151.44	1348.57	hsa-miR-135a
ILMN_3168558	211.48	68.62	28.31	hsa-miR-483-5p
ILMN_3168039	9629.83	3219.90	7248.74	hsa-miR-124a:9.1
ILMN_3168755	233.36	82.45	332.03	hsa-miR-29b-1
ILMN_3168540	493.90	161.33	304.45	hsa-miR-548c-5p
ILMN_3168265	11306.19	5572.32	6108.39	hsa-miR-551a
ILMN_3168481	8687.78	4563.60	5504.04	hsa-miR-377
ILMN_3168882	12023.57	6677.06	8627.69	hsa-miR-1304

TABLE 13

Significantly differently expressed upregulated microRNAs HFHP (High Flow High Pressure) vs. normal.

Upregulated microRNA HFHP vs. Norm (p<.05)				
Illumina ID	Normal	HFHP	HFLP	miRNA Symbol
ILMN_3168350	-6.40	2772.39	12.69	hsa-miR-520g
ILMN_3168706	-3.62	1700.55	8.11	hsa-miR-331-5p
ILMN_3167244	-4.11	1534.57	-4.19	hsa-miR-410
ILMN_3168710	-3.08	1499.40	2147.63	hsa-let-7d
ILMN_3168167	-4.14	1144.02	558.78	hsa-miR-187
ILMN_3168672	-4.20	941.07	162.41	hsa-miR-16-2
ILMN_3168870	-8.25	912.52	8.99	hsa-miR-130a
ILMN_3168639	-4.96	728.32	-3.51	hsa-miR-548n
ILMN_3168719	-1.17	380.69	-2.12	hsa-miR-127-5p
ILMN_3168890	-4.11	343.04	530.05	solexa-2580-353
ILMN_3168217	-5.60	304.34	-1.25	HS_206
ILMN_3167088	-5.06	303.57	-0.34	hsa-miR-663
ILMN_3168911	-1.32	235.62	61.24	solexa-7534-111
ILMN_3168732	-0.63	216.74	12.96	hsa-let-7g
ILMN_3167993	-6.45	192.76	237.96	HS_157
ILMN_3167193	-7.25	151.36	2130.07	hsa-miR-610
ILMN_3167879	-4.09	111.71	11.99	HS_251.1
ILMN_3168031	-4.54	52.02	15.76	hsa-miR-519e
ILMN_3168818	-4.09	20.75	-0.83	hsa-miR-1237
ILMN_3168241	-2.10	18.57	649.52	hsa-miR-1185
ILMN_3167470	-4.18	12.39	7.90	HS_151.1
ILMN_3167512	-1.69	11.79	9.99	HS_135
ILMN_3168895	-2.86	7.81	0.75	solexa-3126-285
ILMN_3167158	-0.63	3.36	739.08	hsa-miR-30a
ILMN_3168722	1.26	529.41	430.69	hsa-miR-192
ILMN_3167039	17.25	1036.96	883.92	hsa-miR-568
ILMN_3168680	2.62	148.59	54.43	hsa-miR-1203
ILMN_3167223	381.67	5756.85	4105.59	hsa-miR-28-5p
ILMN_3167361	21.39	259.94	255.04	HS_262.1

ILMN_3167684	11.78	80.14	21.38	HS_170
ILMN_3168760	11.78	80.09	26.17	hsa-miR-1273
ILMN_3167275	39.19	146.84	1900.87	hsa-miR-602
ILMN_3168240	1613.60	5725.95	4943.62	hsa-miR-374a
ILMN_3168589	597.66	1739.42	928.77	hsa-miR-29a

TABLE 14

Significantly differently expressed downregulated microRNAs HFLP (High Flow Low Pressure) vs. normal.

Downregulated microRNA HFLP vs. Norm (p<.05)				
Illumina ID	Normal	HFLP	HFHP	Gene Symbol
ILMN_3167209	27.46	-3.19	1350.01	HS_104
ILMN_3168537	38.77	-0.76	57.24	hsa-miR-548a-5p
ILMN_3167655	351.30	0.20	74.35	hsa-miR-556-5p
ILMN_3168235	58.82	2.94	6.34	HS_169
ILMN_3167800	13.08	-2.83	1036.31	HS_140
ILMN_3167175	8796.46	88.95	1274.47	hsa-miR-542-5p
ILMN_3168054	3916.21	14.02	79.38	HS_134
ILMN_3167761	37.30	0.17	16.59	hsa-miR-212
ILMN_3167509	17.25	-1.53	17.72	hsa-miR-363
ILMN_3167707	130.17	1.49	42.39	HS_59
ILMN_3167515	4183.74	142.81	42.62	hsa-miR-586
ILMN_3168446	8875.62	546.81	343.70	hsa-miR-494
ILMN_3168827	569.48	51.85	117.37	hsa-miR-1205
ILMN_3168709	1281.24	80.10	218.10	hsa-let-7f-2
ILMN_3168558	211.48	28.31	68.62	hsa-miR-483-5p
ILMN_3167952	8724.37	926.06	2076.18	HS_150
ILMN_3167337	177.30	27.93	43.83	hsa-miR-1229
ILMN_3168305	31.00	5.36	34.52	HS_156
ILMN_3168490	67.94	18.69	106.29	hsa-miR-619
ILMN_3168573	776.09	190.47	805.44	hsa-miR-10b
ILMN_3168586	887.48	304.35	617.25	hsa-miR-371-5p

TABLE 15

Significantly differently expressed upregulated microRNAs HFLP (High Flow Low Pressure) vs. normal.

Upregulated microRNA HFLP vs. Norm (p<.05)				
Illumina ID	Normal	HFLP	HFHP	miRNA Symbol
ILMN_3168010	-9.81	2363.55	689.66	HS_70
ILMN_3168710	-3.08	2147.63	1499.40	hsa-let-7d
ILMN_3168167	-4.14	558.78	1144.02	hsa-miR-187
ILMN_3168890	-4.11	530.05	343.04	solexa-2580-353
ILMN_3167993	-6.45	237.96	192.76	HS_157
ILMN_3168911	-1.32	61.24	235.62	solexa-7534-111
ILMN_3168870	-8.25	8.99	912.52	hsa-miR-130a
ILMN_3167512	-1.69	9.99	11.79	HS_135
ILMN_3168722	1.26	430.69	529.41	hsa-miR-192
ILMN_3167720	2.62	145.01	147.62	hsa-miR-154
ILMN_3167062	78.98	2184.01	1423.21	hsa-miR-151:9.1
ILMN_3168680	2.62	54.43	148.59	hsa-miR-1203
ILMN_3167778	24.39	206.06	81.33	hsa-miR-525-3p
ILMN_3167749	37.30	226.26	272.25	HS_199

TABLE 16

Significantly differently expressed upregulated microRNAs HFHP vs. HFLP.

Upregulated microRNA HFHP vs. HFLP (p<.05)				
Illumina ID	Normal	HFHP	HFLP	miRNA Symbol
ILMN_3167244	-4.11	1534.57	-4.19	has-miR-410
ILMN_3168639	-4.96	728.32	-3.51	has-miR-548n
ILMN_3168537	38.77	57.24	-0.76	has-miR-548a-5p
ILMN_3168613	4.53	18.13	-0.99	has-miR-185
ILMN_3168047	34.59	10.25	-4.94	HS_3
ILMN_3167440	71.49	-0.51	-4.89	HS_67
ILMN_3168585	45.00	97.09	2.43	has-miR-1250
ILMN_3168543	140.56	2778.92	47.17	has-miR-548l
ILMN_3168221	52.52	216.12	13.76	has-miR-548c-3p
ILMN_3167831	31.83	186.98	12.94	has-miR-520d-5p
ILMN_3167105	292.19	174.71	25.34	has-miR-208b
ILMN_3167313	475.92	793.85	135.08	HS_200
ILMN_3168634	892.54	1830.74	479.17	has-miR-218-1
ILMN_3168247	390.00	300.41	111.54	has-miR-643

TABLE 17

Significantly differently expressed downregulated microRNAs HFHP vs. HFLP.

Downregulated microRNA HFHP vs. HFLP (p<.05)				
Illumina ID	Normal	HFHP	HFLP	miRNA Symbol
ILMN_3167778	24.39	81.33	206.06	hsa-miR-525-3p
ILMN_3167052	370.00	45.81	234.11	hsa-miR-495
ILMN_3168052	176.33	116.43	480.71	HS_250
ILMN_3168863	9.59	1.11	46.30	hsa-miR-933
ILMN_3168848	13.53	8.90	475.98	hsa-miR-1287
ILMN_3168750	784.33	2850.15	8118.48	hsa-miR-1308
ILMN_3168348	10.81	9.66	553.87	hsa-miR-133b
ILMN_3166995	1.97	1.33	254.82	HS_215
ILMN_3167545	42.85	10.92	23.89	HS_115
ILMN_3168819	756.53	1345.27	5334.48	hsa-miR-151-5p
ILMN_3167249	229.25	18.22	511.84	HS_56
ILMN_3168010	-9.81	689.66	2363.55	HS_70
ILMN_3168215	37.30	8.98	3110.35	hsa-miR-521

We claim:

1. A method of treating an individual suffering from a vascular-related disease comprising the steps of:

a) obtaining a biopsy sample from the individual's pulmonary artery;

b) analyzing gene expression levels of the biopsy sample from the pulmonary artery of the individual and a non-diseased control;

c) comparing the gene expression levels between the biopsy sample from the pulmonary artery of the individual and the non-diseased control;

d) identifying at least one gene from step c) that is upregulated or downregulated in the biopsy sample based on the non-diseased control;

e) obtaining gene products from the genes identified in step c); and

f) selecting pharmaceutical agents which are known inhibitors of the gene products from the at least one upregulated gene or known promoters of the gene products from the at least one downregulated gene,

wherein the pharmaceutical agents selected are administered to the individual suffering from the vascular-related disease.

2. The method of claim 1, wherein the vascular-related disease is pulmonary arterial hypertension.

3. The method of claim 1, wherein the biopsy sample is extracted using an endoarterial catheter.

4. The method of claim 1, wherein the gene expression levels are analyzed by extracting RNA from the biopsy sample.

5. The method of claim 4, wherein the RNA is converted to cDNA and the cDNA is compared in step c).

6. The method of claim 1, wherein step b) is accomplished using a microarray.

7. The method of claim 1, wherein the vascular-related disease is identified as early, early-mid, late-mid or late stage.

8. The method of claim 1, wherein the analyzing gene expression levels are for genes previously associated with the vascular-related disease.

9. The method of claim 1, wherein the analyzing gene expression levels are for genes not previously associated with the vascular-related disease.

10. A method of diagnosing a vascular-related disease in an individual comprising the steps of:

a) identifying at least one gene that is upregulated or downregulated in the vascular-related disease comprising the steps of:

1) obtaining a biopsy sample from the individual's pulmonary artery during progression of the vascular-related disease;

2) obtaining a pulmonary artery sample from a non-diseased control;

3) extracting RNA from the samples in steps 1) and 2);

4) obtaining gene products from the RNA extracted in step 3); and

5) comparing gene expression levels from the biopsy sample with the non-diseased control, and

b) associating the genes upregulated in the biopsy sample with an inhibitor of the gene products for administration to the individual and genes downregulated in the biopsy sample with a promoter of the gene products for administration to the individual.

11. The method of claim 10, wherein the vascular-related disease is pulmonary arterial hypertension.

12. The method of claim 10, wherein the biopsy sample is extracted using an endoarterial catheter.

13. A method of identifying microRNA dysregulated in an individual having a vascular-related disease comprising the steps of:

a) obtaining a biopsy sample from the individual's pulmonary artery during progression of the vascular-related disease;

b) obtaining a pulmonary artery sample from a non-diseased control;

c) extracting RNA from the samples in steps a) and b);

d) converting the RNA to cDNA;

e) comparing levels of microRNA expression from the biopsy sample with the non-diseased control; and

f) identifying the microRNA dysregulated in the vascular-related disease relative to baseline.

14. The method of claim 13, wherein the vascular-related disease is pulmonary arterial hypertension.

15. The method of claim 13, wherein the microRNA is measured according to stages of progression of the vascular-related disease.

16. A method of treating an individual having a vascular-related disease by targeting microRNAs comprising the following steps:

a) assessing a stage of the vascular-related disease in the individual;

b) identifying whether microRNAs are upregulated or downregulated;

c) selecting the microRNAs to target based on the stage of the vascular-related disease and whether the microRNAs are upregulated or downregulated; and

d) administering an agent known to inhibit an upregulated microRNA or an agent known to promote a downregulated microRNA to the individual,

wherein the stage of the vascular-related disease is based on flow rates and blood pressure within an artery of the individual.

17. The method of claim 16, wherein the vascular-related disease is pulmonary arterial hypertension.

18. The method of claim 16, wherein the microRNAs to target are any microRNAs listed in Tables 12-17.

19. The method of claim 16, wherein the stage of the vascular-related disease is one of high flow and high pressure within the artery of the individual.

20. The method of claim 19, wherein the upregulated microRNAs to inhibit under the stage of high flow and high pressure comprise at least one member selected from the group consisting of hsa-miR-520g, hsa-miR-331-5p, hsa-miR-410, hsa-let-7d, hsa-miR-187, hsa-miR-16-2, hsa-miR-130a, hsa-miR-548n, hsa-miR-127-5p, solexa-2580-353, HS_206, hsa-miR-663, solexa-7534-111, hsa-let-7g, HS_157, hsa-miR-610, HS_251.1, hsa-miR-519e, hsa-miR-1237, hsa-miR-1185, HS_151.1, HS_135, solexa-3126-285, hsa-miR-30a, hsa-miR-192, hsa-miR-568, hsa-miR-1203, hsa-miR-28-5p, HS_262.1, HS_170, hsa-miR-1273, hsa-miR-602, hsa-miR-374a and hsa-miR-29a.

21. The method of claim 16, wherein the stage of the vascular-related disease is one of high flow and low pressure within the artery of the individual.

22. The method of claim 21, wherein the upregulated microRNAs to inhibit under the stage of high flow and low pressure comprise at least one member selected from the group consisting of HS_70, hsa-let-7d, hsa-miR-187, solexa-2580-353, HS_157, solexa-7534-111, hsa-miR-130a, HS_135, hsa-miR-192, hsa-miR-154, hsa-miR-151:9.1, hsa-miR-1203, hsa-miR-525-3p and HS_199.

23. The method of claim 19, wherein the downregulated microRNAs to promote under the stage of high flow and high pressure comprise at least one member selected from the group consisting of solexa-603-1846, hsa-miR-586, hsa-miR-1201, hsa-miR-33a, HS_56, hsa-miR-520d:9.1, hsa-miR-521, hsa-miR-519a, HS_134,

HS_169, HS_221, hsa-miR-496, hsa-miR-935, hsa-miR-542-5p, solexa-5620-151, hsa-miR-99a, hsa-miR-212, hsa-let-7f-2, hsa-miR-494, hsa-miR-1321, hsa-miR-219-2-3p, hsa-miR-95, hsa-miR-128b:9.1, hsa-miR-33a, hsa-miR-495, hsa-miR-1229, hsa-miR-1205, hsa-miR-524-3p, HS_150, hsa-miR-135a, hsa-miR-483-5p, hsa-miR-124a:9.1, hsa-miR-29b-1, hsa-miR-548c-5p, hsa-miR-551a, hsa-miR-377 and hsa-miR-1304.

24. The method of claim 21, wherein the downregulated microRNAs to promote under the stage of high flow and low pressure comprise at least one member selected from the group consisting of HS_104, hsa-miR-548a-5p, hsa-miR-556-5p, HS_169, HS_140, hsa-miR-542-5p, HS_134, hsa-miR-212, hsa-miR-363, HS_59, hsa-miR-586, hsa-miR-494, hsa-miR-1205, hsa-let-7f-2, hsa-miR-483-5p, HS_150, hsa-miR-1229, HS_156, hsa-miR-619, hsa-miR-10b and hsa-miR-371-5p.

25. A method of treating an individual having a vascular-related disease according to claim 1, further wherein the individual is categorized based on progression of the vascular-related disease.

26. The method of claim 25, wherein the progression of the vascular-related disease is selected from the group consisting of early stage, mid stage and late stage.

27. The method of claim 26, wherein the pharmaceutical agent to treat the early stage progression of the vascular-related disease is at least one member selected from the group consisting of the drugs listed in Table 3.

28. The method of claim 26, wherein the pharmaceutical agent to treat the mid stage progression of the vascular-related disease is at least one member selected from the group consisting of the drugs listed in Tables 4 and 5.

29. The method of claim 26, wherein the pharmaceutical agent to treat the late stage progression of the vascular-related disease is at least one member selected from the group consisting of the drugs listed in Table 6.

30. The method of claim 1, wherein the treatment of the individual may be modified over the course of disease progression.

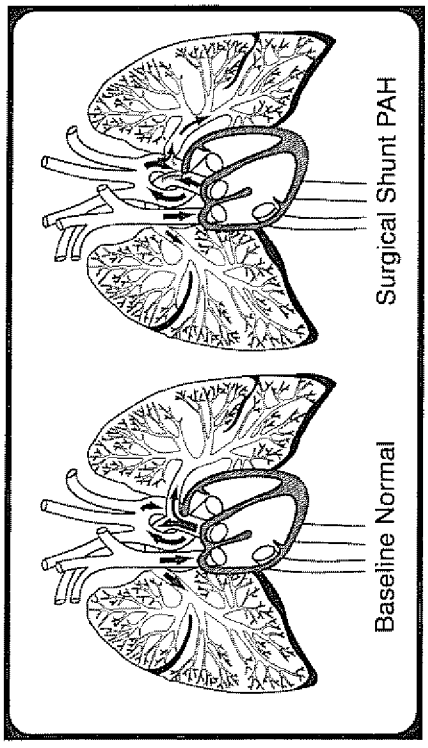

Figure 1

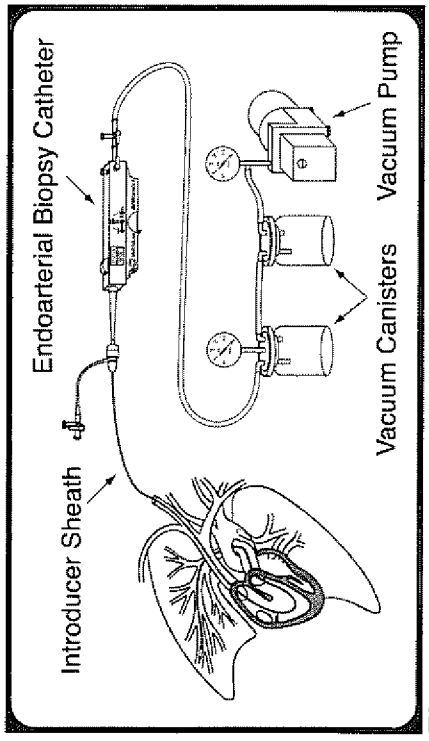

Figure 2

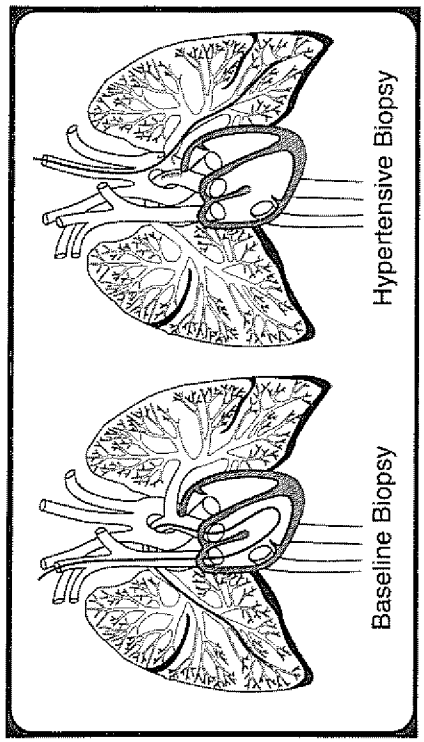

Figure 3

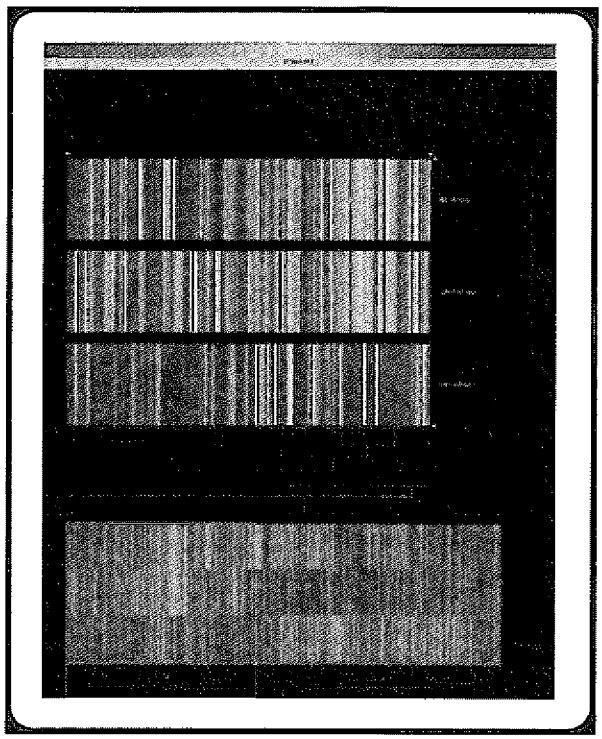

Figure4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038685

A. CLASSIFICATION OF SUBJECT MATTER

C12Q 1/68(2006.01)i, C12N 15/11(2006.01)i, G01N 33/15(2006.01)i

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)

IPC 8: C12Q 1/68, C12Q 1/70, A61K 31/00

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 practicable, search terms used)

eKOMPASS, WPI, USPTO, PAJ "vascular-related disease, pulmonary arterial hypertension, RNA, diagnostic, biomarker, biopsy, etc."

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006-0019272 A1 (MARK W. GERACI et al., US) 26 Jan. 2006 See claims.	10-15
Y	PATRICIA A. THISTLETHWAITE et al. 'Human angiopoietin gene expression is a marker for severity of pulmonary hypertension in patients undergoing pulmonary thromboendarterectomy.' In: The Journal of Thoracic Cardiovascular Surgery. July 2001, Vol.122(1), pp.65-73. See the whole document.	10-15
Y	ABRAHAM ROTHMAN et al. 'Increased expression of endoarterial vascular cell adhesion molecule-1 mRNA in an experimental model of lung transplant rejection: dagnosis by pulmonary arterial biopsy.' In: Transplantation. April 2003, Vol.75(7), pp.1-6. See Figure 2.	10-15
A	FARTOUKH M. et al. 'Chemokine macrophage inflammatory protein-1 alpha mRNA expression in lung biopsy specimens of primary pulmonary hypertension.' In: Chest. July 1998, Vol.114(1), pp.50S-51S. See the whole document.	10-15

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"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
28 AUGUST 2009 (28.08.2009)	**28 AUGUST 2009 (28.08.2009)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
Heo, Joo-Hyung
Telephone No. 82-42-481-8150

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038685

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007-0172856 A1 (CORY M. HOGABOAM and STEVEN L. KUNKEL, US) 26 Jul. 2007 See the whole document.	10-15
A	US 2005-0037946 A1 (NANCY E. STAGLIANO et al., US) 17 Feb. 2005 See the whole document.	10-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038685

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-9, 16-30
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-9 and 16-30 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2009/038685

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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