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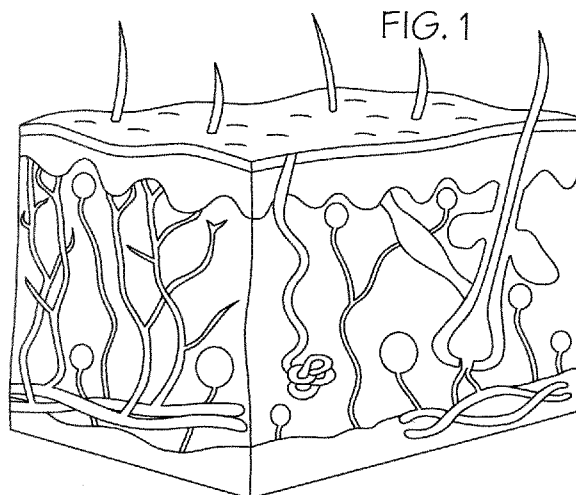
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(54) Title: METHODS FOR IDENTIFYING COSMETIC AGENTS FOR SKIN CARE COMPOSITIONS



(57) Abstract: Provided are methods for determining functional relationships between a cosmetic agent and a skin tissue condition of interest. Also provided are methods for identifying cosmetic agents that affect a skin aging tissue condition, as well as the use of agents identified by such methods for the preparation of cosmetic compositions, personal care products, or both.

METHODS FOR IDENTIFYING COSMETIC AGENTS FOR SKIN CARE COMPOSITIONS

BACKGROUND OF THE INVENTION

Connectivity mapping is a well-known hypothesis generating and testing tool having
5 successful application in the fields of operations research, computer networking and
telecommunications. The undertaking and completion of the Human Genome Project, and the
parallel development of very high throughput high-density DNA microarray technologies
enabling rapid and simultaneous quantization of cellular mRNA expression levels, resulted in the
10 generation of an enormous genetic database. At the same time, the search for new
pharmaceutical actives via *in silico* methods such as molecular modeling and docking studies
stimulated the generation of vast libraries of potential small molecule actives. The amount of
information linking disease to genetic profile, genetic profile to drugs, and disease to drugs grew
exponentially, and application of connectivity mapping as a hypothesis testing tool in the
medicinal sciences ripened.

15 The general notion that functionality could be accurately determined for previously
uncharacterized genes, and that potential targets of drug agents could be identified by mapping
connections in a data base of gene expression profiles for drug-treated cells, was spearheaded in
2000 with publication of a seminal paper by T.R. Hughes et al. ["Functional discovery via a
compendium of expression profiles" *Cell* 102, 109-126 (2000)], followed shortly thereafter with
20 the launch of The Connectivity Map (-map Project by Justin Lamb and researchers at MIT
("Connectivity Map: Gene Expression Signatures to Connect Small Molecules, Genes, and
Disease", *Science*, Vol 313, 2006.) In 2006, Lamb's group began publishing a detailed synopsis
of the mechanics of C-map construction and installments of the reference collection of gene
expression profiles used to create the first generation C-map and the initiation of an on-going
25 large scale community C-map project, which is available under the "supporting materials"
hyperlink at <http://www.sciencemag.org/content/313/5795/1929/suppl/DC1>.

The basic paradigm of predicting novel relationships between disease, disease phenotype,
and drugs employed to modify the disease phenotype, by comparison to known relationships has
been practiced for centuries as an intuitive science by medical clinicians. Modern connectivity
30 mapping, with its rigorous mathematical underpinnings and aided by modern computational
power, has resulted in confirmed medical successes with identification of new agents for the
treatment of various diseases including cancer. Nonetheless, certain limiting presumptions
challenge application of C-map with respect to diseases of polygenic origin or syndromic
conditions characterized by diverse and often apparently unrelated cellular phenotypic

manifestations. According to Lamb, the challenge to constructing a useful C-map is in the selection of input reference data which permit generation of clinically salient and useful output upon query. For the drug-related C-map of Lamb, strong associations comprise the reference associations, and strong associations are the desired output identified as hits.

5 Noting the benefit of high-throughput, high density profiling platforms which permit automated amplification, labeling hybridization and scanning of 96 samples in parallel a day, Lamb nonetheless cautioned: “[e]ven this much firepower is insufficient to enable the analysis of every one of the estimated 200 different cell types exposed to every known perturbagen at every possible concentration for every possible duration...compromises are therefore required” (page 10 54, column 3, last paragraph). Hence, Lamb confined his C-map to data from a very small number of established cell lines. This leads to heightened potential for *in vitro* to *in vivo* mismatch, and limits information to the context of a particular cell line. Selection of cell line, therefore, may be critical to the utility of a resulting C-map.

 Lamb stresses that particular difficulty is encountered if reference connections are 15 extremely sensitive and at the same time difficult to detect (weak), and Lamb adopted compromises aimed at minimizing numerous, diffuse associations. Since the regulatory scheme for drug products requires high degrees of specificity between a purported drug agent and disease state, and modulation of disease by impacting a single protein with a minimum of tangential associations is desired in development of pharmaceutical actives, the Lamb C-map is well-suited 20 for screening for potential pharmaceutical agents despite the Lamb compromises.

 The connectivity mapping protocols of Lamb would not be predicted, therefore, to have utility for hypothesis testing/generating in the field of cosmetics. Cosmetic formulators seek agents or compositions of agents capable of modulating multiple targets and having effects across complex phenotypes and conditions. Further, the phenotypic impact of a cosmetic agent must be 25 relatively low by definition, so that the agent avoids being subject to the regulatory scheme for pharmaceutical actives. Nonetheless, the impact must be perceptible to the consumer and preferably empirically confirmable by scientific methods. Gene transcription/expression profiles for cosmetic conditions are generally diffuse, comprising many genes with low to moderate fold differentials. Cosmetic agents, therefore, provide more diverse and less acute effects on cellular 30 phenotype and generate the sort of associations expressly taught by Lamb as unsuitable for generating connectivity maps useful for confident hypothesis testing.

 Contrary to the teachings of Lamb and the prior art in general, the present inventors surprisingly discovered that useful connectivity maps could be developed from cosmetic active – cellular phenotype – gene expression data associations in particular with respect to skin care

cosmetics. Specifically, certain aspects of the present invention are based on the surprising discovery that selection of human dermal fibroblast cells as the relevant cell line resulted in construction of connectivity maps useful for hypothesis generating and testing relating to cosmetic agents in treatment of photo-damaged/photo-aged skin, while a combination of fibroblast and keratinocyte cells appeared most suitable for intrinsically aged skin. Skin is a highly complex system, and the effects of aging conditions, whether intrinsic or photo-induced, on skin are diffuse and not fully understood. Therefore, it could not be predicted that a fibroblast cell or a keratinocyte cell, or any combination thereof, could be used to construct a connectivity map effective for generating and testing hypotheses relating to cosmetic actives and genes associated with skin aging.

Skin is a complex, multi-layered and dynamic system that provides a protective covering defining the interactive boundary between an organism and the environment. It is the largest organ of the body and is vitally important to both our health and our self image. As shown in **Fig. 1**, skin comprises three principal layers, the epidermis, the dermis, and a layer of subcutaneous fat. The majority of cells in the epidermis are keratinocytes that produce a family of proteins called keratins. Keratins contribute to the strength of the epidermis. The epidermis itself may be divided into multiple layers with the outermost layer referred to as the stratum corneum, and the innermost layer referred to as the basal layer. All epidermal cells originate from the basal layer and undergo a process known as differentiation as they gradually displace outward to the stratum corneum, where they fuse into squamous sheets and are eventually shed. In healthy, normal skin, the rate of production equals the rate of shedding (desquamation).

The differentiating epidermal cells form distinct though naturally blended layers. As the cells displace outward, they flatten and become joined by spiny processes forming the stratum spinosum, or spinous layer. The cells manufacture specialized fats called sphingolipids, and begin to express keratins associated with terminal differentiation. As keratin is produced, it is incorporated into the cellular matrix, strengthening the skin and providing structural support to the outer layers. As the cells migrate further outward and develop characteristic granules that contain proteins which contribute to the aggregation of keratins; they now form part of the granular layer. Cells lose their nuclei in the outer part of this layer, and the granules release their contents contributing to cornification. Vesicles containing lipids discharge into the spaces between the cells, creating a barrier structure that has been suggested to function like bricks (cells) and mortar (lipids). As the cells rise into the outermost layer of the epidermis - the stratum corneum, sometimes called the horny layer or the cornified layer - they take the form of flattened discs, tightly packed together. These flattened cells, called corneocytes, are effectively dead. The

lipids of the epidermis play an important role in maintaining skin health, as they help the stratum corneum to regulate water loss while providing a virtually impermeable hydrophobic barrier to the environment. Fully mature keratinocytes function to protect the skin from UV light damage, and help effectuate immune response to environmental stimuli.

5 The dermis, which lies just beneath the epidermis, is composed largely of the protein collagen. Most of the collagen is organized in bundles which run horizontally through the dermis and which are buried in a jelly-like material called the ground substance. Collagen accounts for up to 75% of the weight of the dermis, and is responsible for the resilience and elasticity of skin. The collagen bundles are held together by elastic fibers running through the dermis. The fibers
10 are comprised of a protein called elastin, and make up less than 5% of the weight of the dermis. Fibroblasts function to synthesize collagen and the dermis ground substance, including components glycoproteins and glycosaminoglycans such as hyaluronic acid (which is able to bind water). The junction between the epidermis and the dermis is not straight but undulates - more markedly so in some areas of the body than others. A series of finger-like structures called rete
15 pegs project up from the dermis, and similar structures project down from the epidermis. These projections increase the area of contact between the layers of skin, and help to prevent the epidermis from being sheared off. As skin ages, the projections get smaller and flatter. Networks of tiny blood vessels run through the rete pegs, bringing nutrients, vitamins and oxygen to the epidermis, although the epidermis itself is avascular and nourished by diffusion from the
20 rete pegs. The dermis also contains the pilosebaceous units comprising hair follicles and sebaceous glands, apocrine and eccrine sweat glands, lymphatic vessels, nerves, and various sensory structures, including the mechano-sensing Pacinian and Meissner's corpuscles.

Beneath the dermis lies the hypodermis, which comprises subcutaneous fat that cushions the dermis from underlying tissues such as muscle and bones. The fat is contained in adipose
25 cells embedded in a connective tissue matrix. This layer may also house the hair follicles when they are in the growing phase.

Thus, skin is a multilayered complex organ comprising a wide variety of cellular types and structures, including epidermal and dermal connective tissue with blood and lymphatic vessels, the pilosebaceous units, glands, nerves, various sensory structures, the hypodermal
30 adipose tissue, and the elastic fascia beneath the hypodermis. In turn, these structures are composed of a number of different cell types including keratinocytes, melanocytes, neuroendocrine Merkel cells, sebocytes, fibroblasts, endothelial cells, pericytes, neurons, adipocytes, myocytes and resident immunocytes including Langerhans cells, other dendritic cells, T cells and mast cells. Two of the main cell lineages in the skin are epithelial cells, which in

general form the linings of the body and the parenchyma of many organs and glands, and mesenchymal cells, which form connective tissue, blood vessels and muscle. Dermal fibroblasts are mesenchymal cells, and keratinocytes are epithelial cells, which comprise most of the structure of the epidermis.

5 Skin aging is likewise a complex multi-factorial process that results from unrepaired cellular and tissue damage leading to impaired functional capacity. The aging process in skin is the result of both intrinsic and extrinsic factors occurring over decades. Skin is subject to many of the same intrinsic aging processes as other organs, but is also exposed to solar radiation, an important extrinsic factor that contributes to premature skin aging or photo-aging. Another
10 important extrinsic factor potentially contributing to skin aging is smoking. There have been major advances in the understanding of the aging process with the identification of cellular pathways and genes associated with longevity and aging. Several theories have been proposed to explain intrinsic aging, including cellular senescence resulting from telomere shortening, mutations in nuclear and mitochondrial DNA, hormonal insufficiency and oxidative stress.
15 Reactive active oxygen species and the direct effects of ultraviolet radiation (UVR) appear to play major roles in photo-aging. As is the case for aging in general, an integrated understanding of skin aging has not been developed.

Skin researchers have categorized age-inducing factors as either intrinsic or extrinsic, although these are interdependent, reflected for example by the fact that extrinsic factors may
20 accelerate intrinsic aging. One example of the complex interplay of factors involves free radicals, which are both generated internally through normal metabolic processes and produced as a consequence of external factors, including UVR exposure. As a result of the age-associated decline in protective internal antioxidant mechanisms, free radicals can reach higher and sustained levels in cells and alter both proteins and DNA in skin. Levels of altered protein and
25 DNA may accumulate causing damage. In addition, ongoing accumulation of damage secondary to internally-generated free radicals combined with those generated from UVR and other external assaults (surfactants, allergens, and other irritants) can promote a chronic inflammatory state. This chronic inflammation compromises skin health and may accelerate the aging process; for example, proteolytic enzymes are produced, resulting in collagen degradation. Activated
30 inflammatory cells resulting from elevations in circulating pro-inflammatory mediators (e.g., prostaglandins, cytokines, histamines) produce reactive oxygen species that can cause oxidative damage to nucleic acids, cellular proteins and lipids. Accumulated damage caused by reactive oxygen species may stimulate a host of cytokine cascades that results in photo-aging and photo-carcinogenesis. These changes may be tied to the appearance of aging skin.

Other changes resulting from the complex interplay between intrinsic and extrinsic factors that may impact the appearance of fine lines, wrinkles and texture include the following:

- Epidermal thickness and cellular turnover rate of both the epidermis and the stratum corneum declines and epidermal differentiation is altered.
- 5 • The dermis becomes thinner as major structural molecules including collagen, elastin and glycosaminoglycans decrease in amount. The elastic network in photo-damaged skin becomes disorganized and aggregated and the various structural proteins may be modified by glycation. Metalloproteinase activity increases in photo-damaged skin, contributing to the degradation of collagen and elastin.
- 10 • Convolution of dermal-epidermal junction (rete ridges) flattens with age, resulting in a loss of mechanical strength. This also leads to decreased microcirculation to the upper dermis and, thus, decreased nourishment to the epidermis.
- Age-related changes in inter- and intra-cellular signaling lead to decreases in collagen synthesis.
- 15 • Changes in hyaluronic acid content within the skin occur with age. Hyaluronic acid is a natural moisturizer within the skin, binding up to 1000 times its weight in water. Age-related declines result in compromised moisturization and firmness.
- Decreased intracellular energy sources including ATP and NADH lead to an inability of skin cells to sustain youthful skin biochemistry, thereby reducing the skin's ability to maintain and restore youthful skin structure.
- 20 • In the epidermis, a lack of estrogen slows the activity of the basal keratinocytes, and consequently leads to epidermal atrophy. This atrophic, fragile skin is less well protected by the normal surface film of lipids, because of the slow decline in sebum secretion experienced by everyone as they age. The stratum corneum barrier is less effective, and the skin may develop reactions to irritants, particularly if skin care has been inadequate or too aggressive.
- 25 • The time necessary to repair the stratum corneum barrier increases considerably with age: the replacement of skin cells takes about twice as long for people over 75 as for those around 30.

30 These changes may compromise skin's elasticity, firmness and structure - contributing to areas of collapse and irregularity and ultimately manifesting as fine lines, wrinkles and texture problems.

There are many skin care products available to consumers which are directed to improving the health and/or physical appearance of skin tissue, such as keratinous tissue. Many of such products are directed to delaying, minimizing or even eliminating changes typically associated with one or both of aging and environmental damage to skin. Such products may include one or more of the numerous cosmetic agents known to be useful in improving the health and/or appearance of keratinous tissue. Although many such agents are known, an ongoing need exists to identify cosmetic agents that can provide new or improved benefits to skin tissue. There is also a need to identify additional cosmetic agents that provide similar or improved benefits as compared to existing products but which are easier to formulate, produce, and/or market.

Successful identification of anti-aging cosmetic agents has proven to be difficult due to the multi-cellular, multi-factorial processes that occur in skin over the course of decades. In addition, many desirable cosmetic agents may comprise a mixture of compounds with effects and interactions that may not be fully understood. This is often the case with a botanical or other natural extract that may affect many cellular/pathways. An additional challenge for cosmetic formulators is that cosmetics must be very safe and adverse effects generally are not acceptable. Further, while much is known about skin aging, there is much that is still poorly understood or unknown. Conventional *in vitro* studies of biological responses to potential cosmetic agents involve testing hundreds or thousands of potential agents in various cell types before an agent that gives the desired result can be identified and moved into a next stage of testing. However, such studies can be hindered by the complex or weakly detectable responses typically induced and/or caused by cosmetic agents. Such weak responses arise, in part, due to the great number of genes and gene products involved, and cosmetic agents may affect multiple genes in multiple ways. Moreover, the degree of bioactivity of cosmetic agents may differ for each gene and be difficult to quantify.

For example, niacinamide is a well-known cosmetic agent producing skin benefits such as improved barrier function and anti-inflammatory activity. Niacinamide is a precursor of NADH, which is involved in more than 100 reactions in cellular metabolism. In contrast to drug agents, which are selected for specificity and which are intended to have measurable effects on structure and function of the body, cosmetic agents are selected for effect on appearance and may not effect structure and function of the body to a measurable degree. Cosmetic agents tend to be non-specific with respect to effect on cellular phenotype, and administration to the body is generally limited to application on or close to the body surface.

The value of a connectivity map approach to discover functional connections among cosmetic phenotypes such as aged skin, gene expression perturbation, and cosmetic agent action

is counter-indicated by the progenors of the drug-based C-map. The relevant phenotypes are very complex, the genetic perturbations are numerous and weak, and cosmetic agent action is likewise diffuse and by definition, relatively weak. It is unclear whether statistically valid data may be generated from cosmetic C-maps and it is further unclear whether a cell line exists which may provide salient or detectable cosmetic data.

Surprisingly, the present inventors have provided a C-map approach that is generalizable and biologically relevant for identification of potential cosmetic actives, and demonstrate that the C-map concept is viable by use of benchmark cosmetic actives to query the reference data and by identification of new cosmetic actives.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel methods useful for generating potential new actives for the treatment of aged and photo-damaged skin. In particular, by careful selection of cell type, and by generation of a reference collection of gene-expression profiles for known cosmetic actives, the present inventors were surprisingly able to create a connectivity map useful for testing and generating hypotheses about cosmetic actives and cosmetic conditions. The present investigators confirmed the validity of connectivity mapping as a tool for identifying cosmetic agents efficacious in the treatment of aged and photo-damaged skin. Potentially efficacious cosmetic agents were identified using gene expression signatures derived from multi-cellular, full thickness human skin biopsies that were compared to short term *in vitro* experiments of simple cell culture systems. Based on the counter-intuitive and surprising discovery that a fibroblast cell line appears particularly predicative for use with some skin aging gene expression signatures (e.g., a photo-aging gene expression signature), while a combination of fibroblast and keratinocyte cell lines appears more predictive for other skin aging conditions (e.g., intrinsically aged skin), the invention provides methods and systems uniquely suited for desired treatment targets.

The present inventors discovered that it is possible to derive unique photo-aging and intrinsic aging gene expression signatures for use in a connectivity map, particularly where the photo-aging gene expression signature is derived from a full thickness biopsy of skin that was chronologically or intrinsically aged. The present inventors have also surprisingly discovered methods that utilize a plurality of unique skin aging gene expression signatures in a connectivity map to identify useful cosmetic skin care agents.

The present invention provides embodiments which broadly include methods and systems for determining relationships between a skin aging tissue condition of interest and one or more

cosmetic agents, one or more genes associated with the skin aging tissue condition, and one or more cells associated with the skin aging tissue condition. Such methods may be used to identify cosmetic agents without detailed knowledge of the mechanisms of biological processes associated with a skin aging condition of interest, all of the genes associated with such a condition, or the cell types associated with such a condition.

According to one embodiment of the invention, a method for constructing a data architecture for use in identifying connections between perturbagens and genes associated with one or more skin aging conditions is provided. The method comprises: (a) providing a gene expression profile for a control human dermal fibroblast cell; (b) generating a gene expression profile for a human dermal fibroblast cell exposed to at least one perturbagen; (c) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (a) and (b); (d) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes; (e) storing the ordered list as a fibroblast instance on at least one computer readable medium; and (f) constructing a data architecture of stored fibroblast instances by repeating (a) through (e), wherein the at least one perturbagen of step (a) is different for each fibroblast instance. In another embodiment, the method further requires (g) providing a gene expression profile for a control human keratinocyte cell; (h) generating a gene expression profile for a human keratinocyte cell exposed to at least one perturbagen; (i) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (g) and (h); (j) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes identified in (i); (k) storing the ordered list created in step (j) as a keratinocyte instance on the at least one computer readable medium; and (l) constructing a data architecture of stored keratinocyte instances by repeating (g) through (k), wherein the at least one perturbagen of step (h) is different for each keratinocyte instance.

Other embodiments provide that the inventive methods are implemented to generate connections useful for identifying cosmetic agents effective for treating aged skin. According to one embodiment, the method comprises querying the data architecture with at least one skin aging gene expression signature, wherein querying comprises comparison of at least one skin aging gene expression signature to each instance in a data architecture of stored instances, wherein the skin aging gene expression signature represents genes differentially expressed in association with at least one skin aging condition. Examples of skin aging conditions include

intrinsic skin aging conditions, which are generally age-dependent, and photo-aged skin conditions, which are a form of extrinsic skin aging where the skin is exposed to UV radiation.

Additional embodiments provide methods for formulating a skin care composition by identifying connections between perturbagens and genes associated with one or more skin aging conditions. The methods comprise: (a) accessing a plurality of instances stored in a data architecture, wherein each instance is associated with a perturbagen and a skin cell type and wherein each instance comprises an ordered list comprising a plurality of identifiers representing a plurality of up-regulated and a plurality of down-regulated genes; (b) accessing at least one skin aging gene expression signature stored in a data architecture, wherein the at least one skin aging gene expression signature comprises one or more lists comprising a plurality of identifiers representing a plurality of up-regulated genes and a plurality of down-regulated genes associated with a skin aging condition. According to one embodiment, a skin aging gene expression signature is selected from up-regulated genes set forth in **Tables A and C**, and down-regulated genes set forth in **Tables B and D**. In more specific embodiments, about 25-100 percent of the up-regulated genes are selected from the genes set forth in **Tables A or C**, and about 25-100 percent of the down-regulated genes are selected from the genes set forth in **Tables B and D**; (c) comparing the at least one skin aging gene expression signature to the plurality of the instances, wherein the comparison comprises comparing each identifier in the gene expression signature list(s) with the position of the same identifier in the ordered lists for each of the plurality of instances; (d) assigning a connectivity score to each of the plurality of instances, wherein the connectivity score of each instance represents how strongly the gene expression profile represented by the ordered list of an instance correlates to the skin aging gene expression signature; and (e) formulating a skin care composition comprising a dermatologically acceptable carrier and at least one perturbagen, wherein the connectivity score of the instance associated with the at least one perturbagen has a negative correlation or connectivity score.

In other embodiments, methods for generating a gene expression signature for use in identifying connections between perturbagens and genes associated with one or more skin aging conditions are provided. In a specific embodiment, the method comprises: (a) providing a gene expression profile for a reference sample of human skin cells; (b) generating a gene expression profile for at least one sample of human skin cells from a subject exhibiting at least one skin aging condition, (c) comparing the expression profiles of (a) and (b) to determine a gene expression signature comprising a set of genes differentially expressed in (a) and (b); (d) assigning an identifier to each gene constituting the gene expression signature and ordering the identifiers according to magnitude of differential expression to create one or more gene

expression signature lists; and (e) storing the gene expression signature list(s) in a data architecture.

Systems useful for identifying connections between perturbagens and genes associated with one or more skin aging conditions are also provided. According to one embodiment, the system comprises (a) a data architecture having stored therein a plurality of instances, and at least one skin aging gene expression signature, wherein the instances and the gene expression signature are derived from a human dermal fibroblast cell, wherein each instance comprises an instance list of rank-ordered identifiers of differentially expressed genes, and wherein the at least one skin aging gene expression signature comprises one or more gene expression signature lists of identifiers representing differentially expressed genes associated with a skin aging condition; (b) a programmable computer comprising computer-readable instructions that cause the programmable computer to execute one or more of the following: (i) accessing the plurality of instances and the at least one skin aging gene expression signature stored in the data architecture; (ii) comparing the at least one skin aging gene expression signature to the plurality of the instances, wherein the comparison comprises comparing the each identifier in the gene expression signature list(s) with the position of the same identifier in the instance list for each of the plurality of instances; and (iii) assigning a connectivity score to each of the plurality of instances, wherein the connectivity score of each instance represents how strongly the gene expression profile represented by the ordered list of an instance correlates to the skin aging gene expression signature. In other embodiments, the system may comprise a microarray scanner for receiving a sample comprising human dermal fibroblast cells and/or human keratinocyte cells; and a second programmable computer for transmitting gene expression data from the scanner to the first programmable computer.

In other aspects, the invention provides inventive gene expression signatures which may exist tangibly in various forms known in the art. For example, a gene expression signature may exist as a set of immobilized oligonucleotides wherein each oligonucleotide uniquely hybridizes to a nucleotide sequence identifying a region of a gene in the signature. In a specific embodiment, a gene expression signature for intrinsically aged skin consisting of genes selected from the genes set forth in **Table E** is provided. In another specific embodiment, a gene expression signature for photoaged skin consisting of genes selected from the genes set forth in **Table F** is provided. It is understood that the "genes set forth" in a table refers to gene identifiers designating the genes, and that a genetic signature as set forth herein is set forth according to a gene identifier.

According to yet another embodiment, a computer readable medium comprising the inventive data architecture is provided. The computer readable medium comprises a first digital file stored in a spreadsheet file format, a word processing file format, or a database file format suitable to be read by a respective spreadsheet, word processing, or database computer program, the first digital file comprising data arranged to provide one or more gene expression signature lists comprising a plurality of identifiers when read by the respective spreadsheet, word processing, or database computer program; and wherein each identifier is selected from the group consisting of a microarray probe set ID, a human gene name, a human gene symbol, and combinations thereof representing a gene set forth in Table E and wherein the gene expression signature list comprises between about 50 and about 600 identifiers.

These and additional objects, embodiments, and aspects of the invention will become apparent by reference to the Figures and Detailed Description below.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic illustration of the epidermal, dermal, and subcutaneous skin layers;

Figure 2 is a schematic illustration of a computer system suitable for use with the present invention;

Figure 3 is a schematic illustration of an instance associated with a computer readable medium of the computer system of Figure 2;

Figure 4 is a schematic illustration of a programmable computer suitable for use with the present invention;

Figure 5 is a schematic illustration of an exemplary system for generating an instance;

Figure 6 is a schematic illustration of a comparison between a gene expression signature and an instance, wherein there is a positive correlation between the lists;

Figure 7 is a schematic illustration of a comparison between a gene expression signature and an instance, wherein there is a negative correlation between the lists; and

Figure 8 is a schematic illustration of a comparison between a gene expression signature and an instance, wherein there is a neutral correlation between the lists.

Figure 9 illustrates morphology of **A**: telomerized-keratinocytes treated with 0.1% DMSO for 6 hr (vehicle control); **B**: telomerized-keratinocytes treated with 10 μ M all-*trans*-retinoic acid (tRA) in DMSO for 6 hr; **C**: BJ fibroblasts treated with 0.1% DMSO for 6 hr

(vehicle control); and **D**: BJ fibroblasts treated with 10 μ M tRA in DMSO for 6 hr; wherein the control keratinocytes are observed to have a cobblestone-like morphology, the control fibroblasts are observed to have a spindly morphology; and wherein treatment with 10 μ M tRA caused dramatic morphologic changes in the keratinocytes (**B** compared to **A**) but had no apparent morphologic effect on the fibroblasts (**D** compared to **C**).

DETAILED DESCRIPTION

The present invention will now be described with occasional reference to the specific embodiments of the invention. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these

Tables A through J are submitted herewith as .txt files in accordance with large tabled data submission guidelines. **Tables A through J** in the .txt file format are incorporated herein, in their entirety, by this reference. **Table A** is a table of 300 identifiers for genes up-regulated in response to skin intrinsic aging conditions. **Table B** is a table of 300 identifiers for genes down-regulated in response to skin intrinsic aging conditions. **Table C** is a table of 300 identifiers for genes up-regulated in response to skin photo-aging conditions. **Table D** is a table of 300 identifiers for genes down-regulated in response to skin photo-aging conditions. **Table E** reflects an exemplary instance according to certain embodiments of the invention and includes a rank-ordered list of identifiers (chip probe set ID) for an illustrative number of high, middle and low ranked genes profiled by the 22,214 probe sets on Affymetrix chip model HG-U133A2.0 in response to exposure of human dermal fibroblast cells to the perturbagen *Cynara scolymus* (artichoke) leaf extract (instance CMP_62_13). **Table F** reflects an exemplary instance according to certain embodiments of the invention and includes a rank-ordered list of the identifiers (chip probe set ID) for an illustrative number of high, middle and low ranked genes profiled by the 22,214 probe sets on Affymetrix chip model HG-U133A2.0 in response to exposure of human keratinocyte cells to the perturbagen artichoke leaf extract (instance CMP_62_13). **Table G** reflects an exemplary instance according to certain embodiments of the invention and includes a rank-ordered list of the identifiers (chip probe et ID) for an illustrative number of high, middle and low ranked genes profiled by the 22,214 probe sets on Affymetrix chip model HG-U133A2.0 in response to exposure of human dermal fibroblast cells to the perturbagen carob leaf extract (instance CMP_62_24). **Table H** reflects an exemplary instance according to certain embodiments of the invention and includes a rank-ordered list of the identifiers (chip probe set ID) for an illustrative number of high, middle and low ranked genes

profiled by the 22,214 probe sets on Affymetrix chip model HG-U133A2.0 in response to exposure of human keratinocyte cells to the perturbagen carob leaf extract (instance CMP_61_23). **Table I** is a list of identifiers for up-regulated Signature 3, a set of genes up-regulated under photo-aging conditions, optimized for fibroblasts. **Table J** is a list of identifiers for down-regulated Signature 3, a set of genes down-regulated under photo-aging conditions, optimized for fibroblasts.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. The terminology used in the description of the invention herein is for describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a," "an," and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

As used interchangeably herein, the terms "connectivity map" and "C-map" refer broadly to devices, systems, articles of manufacture, and methodologies for identifying relationships between cellular phenotypes or cosmetic conditions, gene expression, and perturbagens, such as cosmetic actives.

As used herein, the term "cosmetic agent" means any substance, as well any component thereof, intended to be rubbed, poured, sprinkled, sprayed, introduced into, or otherwise applied to a mammalian body or any part thereof. Cosmetic agents may include substances that are Generally Recognized as Safe (GRAS) by the US Food and Drug Administration, food additives, and materials used in non-cosmetic consumer products including over-the-counter medications. In some embodiments, cosmetic agents may be incorporated in a cosmetic composition comprising a dermatologically acceptable carrier suitable for topical application to skin. A cosmetic agent includes, but is not limited to, (i) chemicals, compounds, small or large molecules, extracts, formulations, or combinations thereof that are known to induce or cause at least one effect (positive or negative) on skin tissue; (ii) chemicals, compounds, small molecules, extracts, formulations, or combinations thereof that are known to induce or cause at least one effect (positive or negative) on skin tissue and are discovered, using the provided methods and systems, to induce or cause at least one previously unknown effect (positive or negative) on the skin tissue; and (iii) chemicals, compounds, small molecules, extracts, formulations, or combinations thereof that are not known have an effect on skin tissue and are discovered, using the provided methods and systems, to induce or cause an effect on skin tissue.

Some examples of cosmetic agents or cosmetically actionable materials can be found in: the PubChem database associated with the National Institutes of Health, USA

(<http://pubchem.ncbi.nlm.nih.gov>); the Ingredient Database of the Personal Care Products Council (<http://online.personalcarecouncil.org/jsp/Home.jsp>); and the 2010 International Cosmetic Ingredient Dictionary and Handbook, 13th Edition, published by The Personal Care Products Council; the EU Cosmetic Ingredients and Substances list; the Japan Cosmetic
5 Ingredients List; the Personal Care Products Council, the SkinDeep database (URL: <http://www.cosmeticsdatabase.com>); the FDA Approved Excipients List; the FDA OTC List; the Japan Quasi Drug List; the US FDA Everything Added to Food database; EU Food Additive list; Japan Existing Food Additives, Flavor GRAS list; US FDA Select Committee on GRAS Substances; US Household Products Database; the Global New Products Database (GNPD)
10 Personal Care, Health Care, Food/Drink/Pet and Household database (URL: <http://www.gnpd.com>); and from suppliers of cosmetic ingredients and botanicals.

Other non-limiting examples of cosmetic agents include botanicals (which may be derived from one or more of a root, stem bark, leaf, seed or fruit of a plant). Some botanicals may be extracted from a plant biomass (e.g., root, stem, bark, leaf, etc.) using one more solvents.
15 Botanicals may comprise a complex mixture of compounds and lack a distinct active ingredient. Another category of cosmetic agents are vitamin compounds and derivatives and combinations thereof, such as a vitamin B3 compound, a vitamin B5 compound, a vitamin B6 compound, a vitamin B9 compound, a vitamin A compound, a vitamin C compound, a vitamin E compound, and derivatives and combinations thereof (e.g., retinol, retinyl esters, niacinamide, folic acid,
20 panthenol, ascorbic acid, tocopherol, and tocopherol acetate). Other non-limiting examples of cosmetic agents include sugar amines, phytosterols, hexamidine, hydroxy acids, ceramides, amino acids, and polyols.

The terms "gene expression signature," and "gene-expression signature" refer to a rationally derived list, or plurality of lists, of genes representative of a skin tissue condition or a
25 skin agent. In specific contexts, the skin agent may be a benchmark skin agent or a potential skin agent. Thus, the gene expression signature may serve as a proxy for a phenotype of interest for skin tissue. A gene expression signature may comprise genes whose expression, relative to a normal or control state, is increased (up-regulated), whose expression is decreased (down-regulated), and combinations thereof. Generally, a gene expression signature for a modified
30 cellular phenotype may be described as a set of genes differentially expressed in the modified cellular phenotype over the cellular phenotype. A gene expression signature can be derived from various sources of data, including but not limited to, from *in vitro* testing, *in vivo* testing and combinations thereof. In some embodiments, a gene expression signature may comprise a first

list representative of a plurality of up-regulated genes of the condition of interest and a second list representative of a plurality of down-regulated genes of the condition of interest.

As used herein, the term "benchmark skin agent" refers to any chemical, compound, small or large molecule, extract, formulation, or combinations thereof that is known to induce or cause a superior effect (positive or negative) on skin tissue. Non-limiting examples of benchmark skin agents include niacinamide, trans-retinoic acid, and hexamidine.

As used herein, the term "query" refers to data that is used as an input to a Connectivity Map and against which a plurality of instances are compared. A query may include a gene expression signature associated with one or both of a skin aging condition and a benchmark skin agent.

The term "instance," as used herein, refers to data from a gene expression profiling experiment in which skin cells are dosed with a perturbagen. In some embodiments, the data comprises a list of identifiers representing the genes that are part of the gene expression profiling experiment. The identifiers may include gene names, gene symbols, microarray probe set IDs, or any other identifier. In some embodiments, an instance may comprise data from a microarray experiment and comprises a list of probe set IDs of the microarray ordered by their extent of differential expression relative to a control. The data may also comprise metadata, including but not limited to data relating to one or more of the perturbagen, the gene expression profiling test conditions, the skin cells, and the microarray.

The term "keratinous tissue," as used herein, refers to keratin-containing layers disposed as the outermost protective covering of mammals which includes, but is not limited to, skin, hair, nails, cuticles, horns, claws, beaks, and hooves. With respect to skin, the term refers to one or all of the dermal, hypodermal, and epidermal layers, which includes, in part, keratinous tissue.

As used herein, the term "skin aging" refers to a human skin tissue condition resulting from the expression or repression of genes, environmental factors (e.g., sun exposure, UVA and/or UVB exposure, smoking), intrinsic factors (e.g. endogenous free radical production or cellular senescence) or interactions there between that produces one or more of fine lines and/or wrinkles, dry skin, inflamed skin, rough skin, sallowness, telangiectasia, sagging skin, enlarged pores, and combinations thereof.

The term "perturbagen," as used herein, means anything used as a challenge in a gene expression profiling experiment to generate gene expression data for use in the present invention. In some embodiments, the perturbagen is applied to fibroblast and/or keratinocyte cells and the gene expression data derived from the gene expression profiling experiment may be stored as an instance in a data architecture. Any substance, chemical, compound, active, natural product,

extract, drug [e.g. Sigma-Aldrich LOPAC (Library of Pharmacologically Active Compounds) collection], small molecule, and combinations thereof used as to generate gene expression data can be a perturbagen. A perturbagen can also be any other stimulus used to generate differential gene expression data. For example, a perturbagen may also be UV radiation, heat, osmotic stress, pH, a microbe, a virus, and small interfering RNA. A perturbagen may be, but is not required to be, any cosmetic agent.

The term “dermatologically acceptable,” as used herein, means that the compositions or components described are suitable for use in contact with human skin tissue.

As used herein, the term “computer readable medium” refers to any electronic storage medium and includes but is not limited to any volatile, nonvolatile, removable, and non-removable media implemented in any method or technology for storage of information such as computer readable instructions, data and data structures, digital files, software programs and applications, or other digital information. Computer readable media includes, but are not limited to, application-specific integrated circuit (ASIC), a compact disk (CD), a digital versatile disk (DVD), a random access memory (RAM), a synchronous RAM (SRAM), a dynamic RAM (DRAM), a synchronous DRAM (SDRAM), double data rate SDRAM (DDR SDRAM), a direct RAM bus RAM (DRRAM), a read only memory (ROM), a programmable read only memory (PROM), an electronically erasable programmable read only memory (EEPROM), a disk, a carrier wave, and a memory stick. Examples of volatile memory include, but are not limited to, random access memory (RAM), synchronous RAM (SRAM), dynamic RAM (DRAM), synchronous DRAM (SDRAM), double data rate SDRAM (DDR SDRAM), and direct RAM bus RAM (DRRAM). Examples of non-volatile memory include, but are not limited to, read only memory (ROM), programmable read only memory (PROM), erasable programmable read only memory (EPROM), and electrically erasable programmable read only memory (EEPROM). A memory can store processes and/or data. Still other computer readable media include any suitable disk media, including but not limited to, magnetic disk drives, floppy disk drives, tape drives, Zip drives, flash memory cards, memory sticks, compact disk ROM (CD-ROM), CD recordable drive (CD-R drive), CD rewriteable drive (CD-RW drive), and digital versatile ROM drive (DVD ROM).

As used herein, the terms “software” and “software application” refer to one or more computer readable and/or executable instructions that cause a computing device or other electronic device to perform functions, actions, and/or behave in a desired manner. The instructions may be embodied in one or more various forms like routines, algorithms, modules, libraries, methods, and/or programs. Software may be implemented in a variety of executable

and/or loadable forms and can be located in one computer component and/or distributed between two or more communicating, co-operating, and/or parallel processing computer components and thus can be loaded and/or executed in serial, parallel, and other manners. Software can be stored on one or more computer readable medium and may implement, in whole or part, the methods and functionalities of the present invention.

As used herein, the term “intrinsic aging gene expression signature” refers to a gene expression signature derived from gene expression profiling of an intrinsic aging skin condition.

As used herein, the term “intrinsic aging skin condition” refers to a skin aging condition that derives, in whole or part, from chronological aging of the skin.

As used herein, the term “photo-aging skin condition” refers to a skin aging condition that derives, in whole or part, from exposure to sunlight and/or ultraviolet light (e.g., UVR, UVA, UVB, and/or UVC).

As used herein, the term “photo-aging gene expression signature” refers to a gene expression signature derived from gene expression profiling of a photo-aging skin condition.

As used herein, the term “connectivity score” refers to a derived value representing the degree to which an instance correlates to a query.

As used herein, the term “data architecture” refers generally to one or more digital data structures comprising an organized collection of data. In some embodiments, the digital data structures can be stored as a digital file (e.g., a spreadsheet file, a text file, a word processing file, a database file, etc.) on a computer readable medium. In some embodiments, the data architecture is provided in the form of a database that may be managed by a database management system (DBMS) that is be used to access, organize, and select data (e.g., instances and gene expression signatures) stored in a database.

As used herein, the terms “gene expression profiling” and “gene expression profiling experiment” refer to the measurement of the expression of multiple genes in a biological sample using any suitable profiling technology. For example, the mRNA expression of thousands of genes may be determined using microarray techniques. Other emerging technologies that may be used include RNA-Seq or whole transcriptome sequencing using NextGen sequencing techniques.

As used herein, the term “microarray” refers broadly to any ordered array of nucleic acids, oligonucleotides, proteins, small molecules, large molecules, and/or combinations thereof on a substrate that enables gene expression profiling of a biological sample. Non-limiting examples of microarrays are available from Affymetrix, Inc.; Agilent Technologies, Inc.; Illumina (two “I”s?), Inc.; GE Healthcare, Inc.; Applied Biosystems, Inc.; Beckman Coulter, Inc.; etc.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth as used in the specification and claims are to be understood as being modified in all instances by the term “about”. Additionally, the disclosure of any ranges in the specification and claims are to be understood as including the
5 range itself and also anything subsumed therein, as well as endpoints. All numeric ranges are inclusive of narrower ranges; delineated upper and lower range limits are interchangeable to create further ranges not explicitly delineated. Unless otherwise indicated, the numerical properties set forth in the specification and claims are approximations that may vary depending on the desired properties sought to be obtained in embodiments of the present invention.
10 Notwithstanding that numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical values, however, inherently contain certain errors necessarily resulting from error found in their respective measurements.

In accordance with one aspect of the present invention, provided are devices, systems and
15 methods for implementing a connectivity map utilizing one or more query signatures associated with a skin aging condition. The query signatures may be derived in variety of ways. In some embodiments, the query signatures may be gene expression signatures derived from gene expression profiling of full thickness skin biopsies of skin exhibiting a skin aging condition of interest compared to a control (e.g., photo-damaged skin compared to sun protected skin). The
20 gene expression profiling can be carried out using any suitable technology, including but not limited to microarray analysis or NextGen sequencing. Some examples of gene expression signatures include a photo-aging gene expression signature and an intrinsic aging gene expression signature, examples of which are described more fully hereafter. In other embodiments, the query signature may be derived from benchmark agents known to positively affect, treat, or
25 reverse a skin aging condition, wherein the query signature is derived from a fibroblast and/or keratinocyte cell line exposed to the benchmark skin agent. These query signatures may be used singularly or in combination.

In accordance with another aspect of the present invention, provided are devices, systems, and methods for implementing a connectivity map utilizing one or more instances derived from a
30 perturbagen, such as a cosmetic agent, exposed to a fibroblast (e.g., BJ fibroblasts) and/or keratinocyte (e.g., telomerized human keratinocytes) skin cell line. Instances from more complex cell culture systems may also be used, such as skin organotypic cultures containing both keratinocytes and fibroblasts or *ex vivo* human skin. Instances from a plurality of cell lines may be used with the present invention.

In accordance with yet another aspect of the present invention, provided are devices, systems and methods for identification of relationships between a skin aging query signature and a plurality of instances. For example, it may be possible to ascertain perturbagens that give rise to a statistically significant activity on a statistically significant number of genes associated with a skin aging tissue condition of interest, leading to the identification of new cosmetic agents for treating a skin condition or new uses of known cosmetic agents.

I. Systems and Devices

Referring to **FIGS. 2, 4 and 5**, some examples of systems and devices in accordance with the present invention for use in identifying relationships between perturbagens, skin aging tissue conditions, and genes associated with the skin aging tissue condition will now be described. System 10 comprises one or more of computing devices 12, 14, a computer readable medium 16 associated with the computing device 12, and communication network 18.

The computer readable medium 16, which may be provided as a hard disk drive, comprises a digital file 20, such as a database file, comprising a plurality of instances 22, 24, and 26 stored in a data structure associated with the digital file 20. The plurality of instances may be stored in relational tables and indexes or in other types of computer readable media. The instances 22, 24, and 26 may also be distributed across a plurality of digital files, a single digital file 20 being described herein however for simplicity.

The digital file 20 can be provided in wide variety of formats, including but not limited to a word processing file format (e.g., Microsoft Word), a spreadsheet file format (e.g., Microsoft Excel), and a database file format. Some common examples of suitable file formats include, but are not limited to, those associated with file extensions such as *.xls, *.xld, *.xlk, *.xll, *.xlt, *.xlxs, *.dif, *.db, *.dbf, *.accdb, *.mdb, *.mdf, *.cdb, *.fdb, *.csv, *.sql, *.xml, *.doc, *.txt, *.rtf, *.log, *.docx, *.ans, *.pages, *.wps, etc.

Referring to **FIG. 3**, in some embodiments the instance 22 may comprise an ordered listing of microarray probe set IDs, wherein the value of N is equal to the total number of probes on the microarray used in analysis. Common microarrays include Affymetrix GeneChips and Illumina BeadChips, both of which comprise probe sets and custom probe sets. To generate the reference gene profiles according to the invention, preferred chips are those designed for profiling the human genome. Examples of Affymetrix chips with utility in the instant invention include model Human Genome (HG)-U133 Plus 2.0. A specific Affymetrix chip employed by the instant investigators is HG-U133A2.0, however it will be understood by a person of ordinary skill in the art that any chip or microarray, regardless of proprietary origin, is suitable so long as the probe

sets of the chips used to construct a data architecture according to the invention are substantially similar.

Instances derived from microarray analyses utilizing Affymetrix GeneChips may comprise an ordered listing of gene probe set IDs where the list comprises 22,000+ IDs. The
5 ordered listing may be stored in a data structure of the digital file 20 and the data arranged so that, when the digital file is read by the software application 28, a plurality of character strings are reproduced representing the ordered listing of probe set IDs. An example of an ordered listing of probe set IDs for a perturbagen having the INCI name *Cynara scolymus* (artichoke leaf extract) is set forth in **Table E**, which specifically includes an ordered list derived from a microarray
10 analysis of fibroblast cells dosed with *Cynara scolymus*. **Table F** is a table of rank-ordered identifiers in association with the rank as derived from a microarray analysis of keratinocyte cells dosed with *Cynara scolymus*. While it is preferred that each instance comprise a full list of the probe set IDs, it is contemplated that one or more of the instances may comprise less than all of the probe set IDs of a microarray. It is also contemplated that the instances may include other
15 data in addition to or in place of the ordered listing of probe set IDs. For example, an ordered listing of equivalent gene names and/or gene symbols may be substituted for the ordered listing of probe set IDs. Additional data may be stored with an instance and/or the digital file 20. In some embodiments, the additional data is referred to as metadata and can include one or more of cell line identification, batch number, exposure duration, and other empirical data, as well as any
20 other descriptive material associated with an instance ID. The ordered list may also comprise a numeric value associated with each identifier that represents the ranked position of that identifier in the ordered list.

Referring again to **FIGS. 2, 3 and 4**, the computer readable medium 16 may also have a second digital file 30 stored thereon. The second digital file 30 comprises one or more lists 32 of
25 microarray probe set IDs associated with one or more skin aging gene expression signatures. The listing 32 of microarray probe set IDs typically comprises a much smaller list of probe set IDs than the instances of the first digital file 20. In some embodiments, the list comprises between 2 and 1000 probe set IDs. In other embodiments the list comprises greater than 10, 50, 100, 200, or 300 and/or less than about 800, 600, or about 400 probe set IDs. The listing 32 of probe set IDs
30 of the second digital file 30 comprises a list of probe set IDs representing up, and/or down-regulated genes selected to represent a skin aging condition of interest. In some embodiments, a first list may represent the up-regulated genes and a second list may represent the down-regulated genes of the gene expression signature. The listing(s) may be stored in a data structure of the digital file 30 and the data arranged so that, when the digital file is read by the software

application 28, a plurality of character strings are reproduced representing the list of probe set IDs. Instead of probe set IDs, equivalent gene names and/or gene symbols (or another nomenclature) may be substituted for a list of probe set IDs. Additional data may be stored with the gene expression signature and/or the digital file 30 and this is commonly referred to as metadata, which may include any associated information, for example, cell line or sample source, and microarray identification. Examples of listings of probe set IDs for intrinsic aging gene expression signatures are set forth in **Tables A** (up-regulated) and **B** (down-regulated), and an example of listings of probe set IDs for photo-aging gene expression signatures are set forth in **Tables C** (up-regulated) and **D**(down-regulated). In some embodiments, one or more skin aging gene expression signatures may be stored in a plurality of digital files and/or stored on a plurality of computer readable media. In other embodiments, a plurality of gene expression signatures (e.g., 32, 34) may be stored in the same digital file (e.g., 30) or stored in the same digital file or database that comprises the instances 22, 24, and 26.

As previously described, the data stored in the first and second digital files may be stored in a wide variety of data structures and/or formats. In some embodiments, the data is stored in one or more searchable databases, such as free databases, commercial databases, or a company's internal proprietary database. The database may be provided or structured according to any model known in the art, such as for example and without limitation, a flat model, a hierarchical model, a network model, a relational model, a dimensional model, or an object-oriented model. In some embodiments, at least one searchable database is a company's internal proprietary database. A user of the system 10 may use a graphical user interface associated with a database management system to access and retrieve data from the one or more databases or other data sources to which the system is operably connected. In some embodiments, the first digital file 20 is provided in the form of a first database and the second digital file 30 is provided in the form of a second database. In other embodiments, the first and second digital files may be combined and provided in the form of a single file.

In some embodiments, the first digital file 20 may include data that is transmitted across the communication network 18 from a digital file 36 stored on the computer readable medium 38. In one embodiment, the first digital file 20 may comprise gene expression data obtained from a cell line (e.g., a fibroblast cell line and/or a keratinocyte cell line) as well as data from the digital file 36, such as gene expression data from other cell lines or cell types, gene expression signatures, perturbagen information, clinical trial data, scientific literature, chemical databases, pharmaceutical databases, and other such data and metadata. The digital file 36 may be provided

in the form of a database, including but not limited to Sigma-Aldrich LOPAC collection, Broad Institute C-MAP collection, GEO collection, and Chemical Abstracts Service (CAS) databases.

The computer readable medium 16 (or another computer readable media, such as 16) may also have stored thereon one or more digital files 28 comprising computer readable instructions or software for reading, writing to, or otherwise managing and/or accessing the digital files 20, 30. The computer readable medium 16 may also comprise software or computer readable and/or executable instructions that cause the computing device 12 to perform one or more steps of the methods of the present invention, including for example and without limitation, the step(s) associated with comparing a gene expression signature stored in digital file 30 to instances 22, 24, and 26 stored in digital file 20. In some embodiments, the one or more digital files 28 may form part of a database management system for managing the digital files 20, 28. Non-limiting examples of database management systems are described in United States Patent Serial Nos. 4,967,341 and 5,297,279.

The computer readable medium 16 may form part of or otherwise be connected to the computing device 12. The computing device 12 can be provided in a wide variety of forms, including but not limited to any general or special purpose computer such as a server, a desktop computer, a laptop computer, a tower computer, a microcomputer, a mini computer, and a mainframe computer. While various computing devices may be suitable for use with the present invention, a generic computing device 12 is illustrated in **FIG. 4**. The computing device 12 may comprise one or more components selected from a processor 40, system memory 42, and a system bus 44. The system bus 44 provides an interface for system components including but not limited to the system memory 42 and processor 40. The system bus 36 can be any of several types of bus structures that may further interconnect to a memory bus (with or without a memory controller), a peripheral bus, and a local bus using any of a variety of commercially available bus architectures. Examples of a local bus include an industrial standard architecture (ISA) bus, a microchannel architecture (MSA) bus, an extended ISA (EISA) bus, a peripheral component interconnect (PCI) bus, a universal serial (USB) bus, and a small computer systems interface (SCSI) bus. The processor 40 may be selected from any suitable processor, including but not limited to, dual microprocessor and other multi-processor architectures. The processor executes a set of stored instructions associated with one or more program applications or software.

The system memory 42 can include non-volatile memory 46 (e.g., read only memory (ROM), erasable programmable read only memory (EPROM), electrically erasable programmable read only memory (EEPROM), etc.) and/or volatile memory 48 (e.g., random access memory (RAM)). A basic input/output system (BIOS) can be stored in the non-volatile

memory 38, and can include the basic routines that help to transfer information between elements within the computing device 12. The volatile memory 48 can also include a high-speed RAM such as static RAM for caching data.

5 The computing device 12 may further include a storage 44, which may comprise, for example, an internal hard disk drive [HDD, e.g., enhanced integrated drive electronics (EIDE) or serial advanced technology attachment (SATA)] for storage. The computing device 12 may further include an optical disk drive 46 (e.g., for reading a CD-ROM or DVD-ROM 48). The drives and associated computer-readable media provide non-volatile storage of data, data structures and the data architecture of the present invention, computer-executable instructions, and so forth. For the computing device 12, the drives and media accommodate the storage of any data in a suitable digital format. Although the description of computer-readable media above refers to an HDD and optical media such as a CD-ROM or DVD-ROM, it should be appreciated by those skilled in the art that other types of media which are readable by a computer, such as Zip disks, magnetic cassettes, flash memory cards, cartridges, and the like may also be used, and further, that any such media may contain computer-executable instructions for performing the methods of the present invention.

A number of software applications can be stored on the drives 44 and volatile memory 48, including an operating system and one or more software applications, which implement, in whole or part, the functionality and/or methods described herein. It is to be appreciated that the embodiments can be implemented with various commercially available operating systems or combinations of operating systems. The central processing unit 40, in conjunction with the software applications in the volatile memory 48, may serve as a control system for the computing device 12 that is configured to, or adapted to, implement the functionality described herein.

25 A user may be able to enter commands and information into the computing device 12 through one or more wired or wireless input devices 50, for example, a keyboard, a pointing device, such as a mouse (not illustrated), or a touch screen. These and other input devices are often connected to the central processing unit 40 through an input device interface 52 that is coupled to the system bus 44 but can be connected by other interfaces, such as a parallel port, an IEEE 1394 serial port, a game port, a universal serial bus (USB) port, an IR interface, etc. The computing device 12 may drive a separate or integral display device 54, which may also be connected to the system bus 44 via an interface, such as a video port 56.

The computing devices 12, 14 may operate in a networked environment across network 18 using a wired and/or wireless network communications interface 58. The network interface port 58 can facilitate wired and/or wireless communications. The network interface port can be

part of a network interface card, network interface controller (NIC), network adapter, or LAN adapter. The communication network 18 can be a wide area network (WAN) such as the Internet, or a local area network (LAN). The communication network 18 can comprise a fiber optic network, a twisted-pair network, a T1/E1 line-based network or other links of the T-carrier/E
5 carrier protocol, or a wireless local area or wide area network (operating through multiple protocols such as ultra-mobile band (UMB), long term evolution (LTE), etc.). Additionally, communication network 18 can comprise base stations for wireless communications, which include transceivers, associated electronic devices for modulation/demodulation, and switches and ports to connect to a backbone network for backhaul communication such as in the case of
10 packet-switched communications.

II. Methods for Creating a Plurality of Instances

In some embodiments, the methods of the present invention may comprise populating at least the first digital file 20 with a plurality of instances (e.g., 22, 24, 26) comprising data derived from a plurality of gene expression profiling experiments, wherein one or more of the
15 experiments comprise exposing dermal fibroblast cells and/or keratinocyte cells (or other skin cells such as human skin equivalent cultures or *ex vivo* cultured human skin) to at least one perturbagen. For simplicity of discussion, the gene expression profiling discussed hereafter will be in the context of a microarray experiment.

Referring to **FIG. 5**, one embodiment of a method of the present invention is illustrated.
20 The method 58 comprises exposing a fibroblast cells 60 and/or keratinocyte cells 62 to a perturbagen 64. The perturbagen may be dissolved in a carrier, such as dimethyl sulfoxide (DMSO). After exposure, mRNA is extracted from the cells exposed to the perturbagen and reference cells 66 (e.g., fibroblast or keratinocyte cells) which are exposed to only the carrier. The mRNA 68, 70, 72 may be reverse transcribed to cDNA 64, 76, 78 and marked with different
25 fluorescent dyes (e.g., red and green) if a two color microarray analysis is to be performed. Alternatively, the samples may be prepped for a one color microarray analysis as described in Example 1, and further a plurality of replicates may be processed if desired. The cDNA samples may be co-hybridized to the microarray 80 comprising a plurality of probes 82. The microarray may comprise thousands of probes 82. In some embodiments, there are between 10,000 and
30 50,000 gene probes 82 present on the microarray 80. The microarray is scanned by a scanner 84, which excites the dyes and measures the amount fluorescence. A computing device 86 may be used to analyze the raw images to determine the expression levels of a gene in the cells 60, 62 relative to the reference cells 66. The scanner 84 may incorporate the functionality of the computing device 86. The expression levels include: i) up-regulation [e.g., greater binding of

the test material (e.g., cDNA 74, 76) to the probe than the reference material (e.g., cDNA 78)], or ii) down-regulation [e.g., greater binding of the reference material (e.g., cDNA 78) to the probe than the test material (e.g., cDNA 74, 76)], iii) expressed but not differentially [e.g., similar binding of the reference material (e.g., cDNA 78) to the probe than the test material (e.g., cDNA 74, 76)], and iv) no detectable signal or noise. The up- and down-regulated genes are referred to as differentially expressed. Microarrays and microarray analysis techniques are well known in the art, and it is contemplated that other microarray techniques may be used with the methods, devices and systems of the present invention. For example, any suitable commercial or non-commercial microarray technology and associated techniques may be used. Good results have been obtained with Affymetrix GeneChip® technology and Illumina BeadChip™ technology. One illustrative technique is described in **Example 1**. However, one of skill in the art will appreciate that the present invention is not limited to the methodology of the example and that other methods and techniques are also contemplated to be within its scope.

In a very specific embodiment, an instance consists of the rank ordered data for all of the probe sets on the Affymetrix HG-U133A2.0 GeneChip wherein each probe on the chip has a unique probe set IDentifier. The probe sets are rank ordered by the fold change relative to the controls in the same C-map batch (single instance/average of controls). The probe set IDentifiers are rank-ordered to reflect the most up-regulated to the most down-regulated.

Notably, even for the non-differentially regulated genes the signal values for a particular probe set are unlikely to be identical for the instance and control so a fold change different from 1 will be calculated that can be used for comprehensive rank ordering. In accordance with methods disclosed by Lamb *et al.* (2006), data are adjusted using 2 thresholds to minimize the effects of genes that may have very low noisy signal values, which can lead to spurious large fold changes. The thresholding is preferably done before the rank ordering. An example for illustrative purposes includes a process wherein a first threshold is set at 20. If the signal for a probe set is below 20, it is adjusted to 20. Ties for ranking are broken with a second threshold wherein the fold changes are recalculated and any values less than 2 are set to 2. For any remaining ties the order depends on the specific sorting algorithm used but is essentially random. The probe sets in the middle of the list do not meaningfully contribute to an actual connectivity score.

The rank ordered data are stored as an instance. The probes may be sorted into a list according to the level of gene expression regulation detected, wherein the list progresses from up-regulated to marginal or no regulation to down-regulated, and this rank ordered listing of probe IDs is stored as an instance (e.g., 22) in the first digital file 20. Referring to **FIG. 3**, the data associated with an instance comprises the probe ID 80 and a value 82 representing its ranking in

the list (e.g., 1, 2, 3, 4 . . . N, where N represents the total number of probes on the microarray).

The ordered list 84 may generally comprise approximately three groupings of probe IDs: a first

grouping 86 of probe IDs associated with up-regulated genes, a second group 88 of probe IDs

associated with genes with marginal regulation or no detectable signal or noise, and a third group

90 of probe IDs associated with down-regulated genes. The most up regulated genes are at or

near the top of the list 84 and the most down-regulated genes are at or near the bottom of the list

84. The groupings are shown for illustration, but the lists for each instance may be continuous

and the number of regulated genes will depend on the strength of the effect of the perturbagen

associated with the instance. Other arrangements within the list 84 may be provided. For

example, the probe IDs associated with the down-regulated genes may be arranged at the top of

the list 84. This instance data may also further comprise metadata such as perturbagen

identification, perturbagen concentration, cell line or sample source, and microarray

identification.

In some embodiments, one or more instances comprise at least about 1,000, 2,500, 5,000,

10,000, or 20,000 identifiers and/or less than about 30,000, 25,000, or 20,000 identifiers. In some

embodiments, the database comprises at least about 50, 100, 250, 500, or 1,000 instances and/or

less than about 50,000, 20,000, 15,000, 10,000, 7,500, 5,000, or 2,500 instances. Replicates of an

instance may created, and the same perturbagen may be used to derive a first instance from

fibroblast cells and a second instance from keratinocyte cells and a third instance from another

skin cell type, such as melanocytes or complex tissue, for example *ex vivo* human skin.

The present inventors have surprisingly discovered that instances derived from fibroblast

cells appear to be more predictive than other cell types when used in combination with a photo-

aging gene expression signature. As described more fully hereafter in Example 6, the present

inventors compared instances derived from BJ fibroblast cells and keratinocyte cells with a

photo-aging gene expression signature and found that instances derived from the fibroblast cells

were dramatically over represented in the highest ranking results (the higher the ranking, the

more likely the perturbagen is to have a beneficial affect upon the photo aging condition)

compared to keratinocyte cells. The inventors also discovered that the up-regulated genes of a

photo-aging gene expression signature most closely correlated with instances derived from

fibroblast cells. In comparison, the present inventors discovered that a combination of instances

derived from fibroblast cells and keratinocyte cells using the same set of perturbagens correlated

more closely with an intrinsic aging gene expression signature, with the instances derived from

the fibroblast cells being slightly more preferential. The inventors were surprised to find that

instances derived from keratinocyte cells were under represented in the top ranking results of the

photo-aging gene expression signature, while more equal representation was observed with respect to an intrinsic aging gene expression signature. Still further, both results are surprising considering that the gene expression signatures were derived from full thickness biopsies representing complex, multi-factorial skin aging conditions and further that the photo-aging gene expression signature was derived from a full thickness skin biopsy that was also intrinsically aged. In other words, a photo-aging gene expression signature could be differentiated from biopsy samples containing both intrinsic aging and photo aging phenotypes.

III. Methods for Deriving Skin Aging Gene expression signatures

Some methods of the present invention comprise identifying a gene expression signature that represents the up-regulated and down-regulated genes associated with a skin aging condition of interest. A skin aging condition typically involves complex processes involving numerous known and unknown extrinsic and intrinsic factors, as well as responses to such factors that are subtle over a relatively short period of time but non-subtle over a longer period of time. This is in contrast to what is typically observed in drug screening methods, wherein a specific target, gene, or mechanism of action is of interest. Due to the unique screening challenges associated with a skin aging condition, the quality of the gene expression signature representing the condition of interest can be important for distinguishing between the gene expression data actually associated with a response to a perturbagen from the background expression data. One challenge in developing skin aging gene expression signatures is that the number of genes selected needs to be adequate to reflect the dominant and key biology but not so large as to include many genes that have achieved a level of statistical significance by random chance and are non-informative. Thus, query signatures should be carefully derived since the predictive value may be dependent upon the quality of the gene expression signature.

One factor that can impact the quality of the query signature is the number of genes included in the signature. The present inventors have found that, with respect to a cosmetic data architecture and connectivity map, too few genes can result in a signature that is unstable with regard to the highest scoring instances. In other words, small changes to the gene expression signature can result significant differences in the highest scoring instance. Conversely, too many genes may tend to partially mask the dominant biological responses and will include a higher fraction of genes meeting statistical cutoffs by random chance - thereby adding undesirable noise to the signature. The inventors have found that the number of genes desirable in a gene expression signature is also a function of the strength of the biological response associated with the condition and the number of genes needed to meet minimal values (e.g., a p-value less than about 0.05) for statistical significance. When the biology is weaker, such as is the case typically

with cosmetic condition phenotypes, fewer genes than those which may meet the statistical requisite for inclusion in the prior art, may be used to avoid adding noisy genes. For example, the gene expression profiling analysis of a photo aging skin condition yielded approximately 4000 genes having a statistical p-value of less than 0.05 and approximately 1000 genes having a p-value of less than 0.001, which could be considered a very strong biological response. The gene expression profiling analysis of an intrinsic aging skin condition yielded approximately 1000 genes have a statistical p-value of less than 0.05 and approximately 400 genes have a p-value of less than 0.001, which could be considered a moderately strong biological response. In these cases, a gene expression signature comprises between about 100 and about 600 genes. Weaker biology may be better represented by a gene expression signature comprising fewer genes.

While a gene expression signature may represent all significantly regulated genes associated with skin aging condition of interest; typically it represents a subset of such genes. The present inventors have discovered that skin aging gene expression signatures comprising between about 200 and about 800 genes of approximately equal numbers of up-regulated and/or down-regulated genes are stable, reliable, and can provide predictive results. For example, a suitable gene expression signature may have from about 200-250 genes, 250-300 genes, 300-350 genes, 350-400 genes, 400-450 genes, 450-500 genes, 500-550 genes, 550-600 genes, 600-650 genes, 650-700 genes, 700-750 genes, and 750-800 genes. However, one of skill in the art will appreciate that gene expression signatures comprising fewer or more genes are also within the scope of the various embodiments of the invention. For purposes of depicting a gene expression signature, the probe set IDs associated with the genes are preferably separated into a first list comprising the most up-regulated genes and a second list comprising the most down-regulated.

Gene expression signatures may be generated from full thickness skin biopsies from skin having the skin aging condition of interest compared to a control. Two gene expression signature types for skin aging can include an intrinsic aging gene expression signature and a photo-aging gene expression signature, which may be derived by comparing gene expression data from a full thickness skin biopsy from skin having the condition of interest and a control. Examples 2 and 3 below describe in greater detail non-limiting methods for deriving these gene expression signatures. Generally, for a photo-aging gene expression signature, biopsies may be taken from sun exposed skin (e.g., extensor forearm) and sun protected skin (e.g., buttocks) of a plurality of older subjects. The subjects may vary in age, but one age range is between about 45 years of age and 70 years of age. A gene expression profiling analysis of the biopsy samples may be performed and one or more photo-aging gene expression signatures derived from a statistical analysis of the results. In some embodiments, the photo-aging gene expression signature

comprises about equal numbers of up-regulated and down-regulated genes. In an alternate embodiment, a photo-aging gene expression signature may be derived by comparing a sun exposed site of an older individual (e.g., 45 to 80 y.o.) to a sun exposed site of a younger individual (e.g., 18 to 25 y.o.)

5 Generally, for an intrinsic aging gene expression signature, biopsies may be taken from sun protected sites (e.g., buttocks) of a plurality of older and younger subjects. The subjects may vary in age, but one age range is between about 45 years of age and 80 years of age for the older subjects and 18 years of age and 25 years of age for the younger subjects. A gene expression profiling analysis of the biopsy samples may be performed and one or more intrinsic aging gene
10 expression signatures derived from a statistical analysis of the microarray results. In some embodiments, the intrinsic aging gene expression signature comprises about equal numbers of up-regulated and down-regulated genes.

In some embodiments, the photo-aging and intrinsic aging gene expression signatures have fewer than 20% of their genes in common, and they reflect different aspects of the biology
15 of aging skin as described. The intrinsic aging gene expression signatures may capture decreased expression of epidermal differentiation markers and down-regulation of pathways involved in the synthesis of lipids important in epidermal barrier function as well as changes related to the dermis, while the photo-aging signatures may be much more reflective of modified biology of the dermis and fibroblasts. Therefore, both photo-aging and intrinsic aging gene expression
20 signatures are useful for identification of cosmetic agents to improve the appearance of aging skin and allow identification of potential perturbagens with differing biological activities.

In other embodiments of the present invention, a gene expression signature may be derived from a gene expression profiling analysis of fibroblast and/or keratinocyte cells treated with a benchmark skin agent to represent cellular perturbations leading to improvement in the
25 skin tissue condition treated with that benchmark skin agent, said signature comprising a plurality of genes up-regulated and down-regulated by the benchmark skin agent in cells *in vitro*. As one illustrative example, microarray gene expression profile data where the perturbagen is the known skin anti-aging agent all *trans*-retinoic acid (tRA) may be analyzed using the present invention to determine from the rank-ordered instances in the query results, the genes associated with the
30 highest scoring instances. Thus, a list of genes strongly up-regulated and strongly down-regulated in response to challenge with tRA can be derived, and said list of genes (a proxy for skin anti-aging) can be used as a query signature to screen for skin anti-aging agents. In another embodiment, a signature may be derived to represent more than one aspect of the condition of interest.

IV. Methods for Comparing a Plurality of Instances to One or More Skin Aging Gene expression signatures

Referring to **FIG. 6** and **FIG. 7**, a method for querying a plurality of instances with one or more skin aging gene signatures will now be described. Broadly, the method comprises querying a plurality of instances with one or more skin aging gene signatures and applying a statistical method to determine how strongly the signature genes match the regulated genes in an instance. Positive connectivity occurs when the genes in the up-regulated signature list are enriched among the up-regulated genes in an instance and the genes in the down-regulated signature list are enriched among the down-regulated genes in an instance. On the other hand, if the up-regulated genes of the signature are predominantly found among the down-regulated genes of the instance, and vice versa, this is scored as negative connectivity. **FIG. 6** schematically illustrates an extreme example of a positive connectivity between signature 90 and the instance 104 comprising the probe IDs 102, wherein the probe IDs of the instance are ordered from most up-regulated to most down-regulated. In this example, the probe IDs 100 (e.g., X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈) of the gene signature 90, comprising an up list 97 and a down list 99, have a one to one positive correspondence with the most up-regulated and down-regulated probe IDs 102 of the instance 104, respectively. Similarly, **FIG. 7** schematically illustrates an extreme example of a negative connectivity between signature 94 and the instance 88 comprising the probe IDs 90, wherein the probe IDs of the instance are ordered from most up-regulated to most down-regulated. In this example, the probe IDs of the up list 93 (e.g., X₁, X₂, X₃, X₄) correspond exactly with the most down-regulated genes of the instance 88, and the probe IDs of the down list 95 (e.g., X₅, X₆, X₇, X₈) correspond exactly to the most up-regulated probe IDs of the instance 88. **FIG. 8** schematically illustrates an extreme example of neutral connectivity, wherein there is no consistent enrichment of the up- and down-regulated genes of the signature among the up- and down-regulated genes of the instance, either positive or negative. Hence the probe IDs 106 (e.g., X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈) of a gene signature 108 (comprising an up list 107 and a down list 109) are scattered with respect to rank with the probe IDs 110 of the instance 112, wherein the probe IDs of the instance are ordered from most up-regulated to most down-regulated. While the above embodiments illustrate process where the gene signature comprises a both an up list and a down list representative of the most significantly up- and down-regulated genes of a skin condition, it is contemplated that the gene signature may comprise only an up list or a down list when the dominant biology associated with a condition of interest shows gene regulation in predominantly one direction.

In some embodiments, the connectivity score can be a combination of an up-score and a down score, wherein the up-score represents the correlation between the up-regulated genes of a gene signature and an instance and the down-score represents the correlation between the down-regulated genes of a gene signature and an instance. The up score and down score may have values between +1 and -1. For an up score (and down score) a high positive value indicates that the corresponding perturbagen of an instance induced the expression of the microarray probes of the up-regulated (or down-regulated) genes of the gene signature, and a high negative value indicates that the corresponding perturbagen associated with the instance repressed the expression of the microarray probes of the up-regulated (or down-regulated) genes of the gene signature.

The up-score can be calculated by comparing each identifier of an up list of a gene signature comprising the up-regulated genes (e.g., Tables **A, C, I** and lists 93, 97, and 107) to an ordered instance list (e.g., Tables **E, F, G, H**) while the down-score can be calculated by comparing each identifier of a down list of a gene signature comprising the down-regulated genes (see, e.g., Tables **B, D, J** and down lists 95, 99, and 109) to an ordered instance list (e.g., Tables **E, F, G, H**). In these embodiments, the gene signature comprises the combination of the up list and the down list.

In some embodiments, the connectivity score value may range from +2 (greatest positive connectivity) to -2 (greatest negative connectivity), wherein the connectivity score (e.g., 101, 103, and 105) is the combination of the up score (e.g., 111, 113, 115) and the down score (e.g., 117, 119, 121) derived by comparing each identifier of a gene signature to the identifiers of an ordered instance list. In other embodiments the connectivity range may be between +1 and -1. Examples of the scores are illustrated in **FIGS. 6, 7 and 8** as reference numerals 101, 103, 105, 111, 113, 115, 117, 119, and 121. The strength of matching between a signature and an instance represented by the up scores and down scores and/or the connectivity score may be derived by one or more approaches known in the art and include, but are not limited to, parametric and non-parametric approaches. Examples of parametric approaches include Pearson correlation (or Pearson *r*) and cosine correlation. Examples of non-parametric approaches include Spearman's Rank (or rank-order) correlation, Kendall's Tau correlation, and the Gamma statistic. Generally, in order to eliminate a requirement that all profiles be generated on the same microarray platform, a non-parametric, rank-based pattern matching strategy based on the Kolmogorov-Smirnov statistic (see M. Hollander et al. "*Nonparametric Statistical Methods*"; Wiley, New York, ed. 2, 1999)(see, e.g., pp. 178-185). It is noted, however, that where all expression profiles are derived from a single technology platform, similar results may be obtained using conventional measures of correlation, for example, the Pearson correlation coefficient.

In specific embodiments, the methods and systems of the present invention employ the nonparametric, rank-based pattern-matching strategy based on the Kolmogorov-Smirnov statistic, which has been refined for gene profiling data by Lamb's group, commonly known in the art as Gene Set Enrichment Analysis (GSEA) (see, e.g., Lamb *et al.* 2006 and Subramanian, A. *et al.* (2005) *Proc.Natl.Acad Sci U.S.A.*, 102, 15545-15550). For each instance, a down score is calculated to reflect the match between the down-regulated genes of the query and the instance, and an up score is calculated to reflect the correlation between the up-regulated genes of the query and the instance. In certain embodiments the down score and up score each may range between -1 and +1. The combination represents the strength of the overall match between the query signature and the instance.

The combination of the up score and down score is used to calculate an overall connectivity score for each instance, and in embodiments where up and down score ranges are set between -1 and +1, the connectivity score ranges from -2 to +2, and represents the strength of match between a query signature and the instance. The sign of the overall score is determined by whether the instance links positivity or negatively to the signature. Positive connectivity occurs when the perturbagen associated with an instance tends to up-regulate the genes in the up list of the signature and down-regulate the genes in the down list. Conversely, negative connectivity occurs when the perturbagen tends to reverse the up and down signature gene expression changes. The magnitude of the connectivity score is the sum of the absolute values of the up and down scores when the up and down scores have different signs. A high positive connectivity score predicts that the perturbagen will tend to induce the condition that was used to generate the query signature, and a high negative connectivity score predicts that the perturbagen will tend to reverse the condition associated with the query signature. A zero score is assigned where the the up and down scores have the same sign, indicating that a perturbagen did not have a consistent impact the condition signature (e.g., up-regulating both the up and down lists).

According to Lamb *et al.* (2006), there is no standard for estimating statistical significance of connections observed. Lamb teaches that the power to detect connections may be greater for compounds with many replicates. Replicating in this context means that the same perturbagen is profiled multiple times. Where batch to batch variation must be avoided, a perturbagen should be profiled multiple times in each batch. However, since microarray experiments tend to have strong batch effects it is desirable to replicate instances in different batches (i.e., experiments) to have the highest confidence that connectivity scores are meaningful and reproducible.

Each instance may be rank ordered according to its connectivity score to the query signature and the resulting rank ordered list displayed to a user using any suitable software and computer hardware allowing for visualization of data.

In some embodiments, the methods may comprise identifying from the displayed rank-ordered list of instances (i) the one or more perturbagens associated with the instances of interest (thereby correlating activation or inhibition of a plurality of genes listed in the query signature to the one or more perturbagens); (ii) the differentially expressed genes associated with any instances of interest (thereby correlating such genes with the one or more perturbagens, the skin tissue condition of interest, or both); (iii) the cells associated with any instance of interest (thereby correlating such cells with one or more of the differentially expressed genes, the one or more perturbagens, and the skin tissue condition of interest); or (iv) combinations thereof. The one or more perturbagens associated with an instance may be identified from the metadata stored in the database for that instance. However, one of skill in the art will appreciate that perturbagen data for an instance may be retrievably stored in and by other means. Because the identified perturbagens statistically correlate to activation or inhibition of genes listed in the query signature, and because the query signature is a proxy for a skin tissue condition of interest, the identified perturbagens may be candidates for new cosmetic agents, new uses of known cosmetic agents, or to validate known agents for known uses.

In some embodiments, the methods of the present invention may further comprise testing the selected candidate cosmetic agent, using *in vitro* assays and/or *in vivo* testing, to validate the activity of the agent and usefulness as a cosmetic agent. Any suitable *in vitro* test method can be used, including those known in the art, and most preferably *in vitro* models having an established nexus to the desired *in vivo* result. For example, MatTek human skin equivalent cultures and skin biopsy assays may be used to evaluate candidate cosmetic agents. In some embodiments, evaluation of selected agents using *in vitro* assays may reveal, confirm, or both, that one or more new candidate cosmetic agents may be used in conjunction with a known cosmetic agent (or a combination of known cosmetic agents) to regulate a skin aging tissue condition of interest.

V. Cosmetic Compositions and Personal Care Products

Because of the desirability of providing various cosmetic skin anti-aging benefits to a consumer, it may be beneficial to incorporate test agents or compounds identified by one or more of the screening methods described herein into a cosmetic composition suitable for topical application to skin. That is, it may be desirable to include the test agent as an ingredient in the cosmetic composition. In certain embodiments, the cosmetic composition may include a

dermatological acceptable carrier, the test agent, and one or more optional ingredients of the kind commonly included in the particular cosmetic compositing being provided.

5 Dermatologically acceptable carriers should be safe for use in contact with human skin tissue. Suitable carriers may include water and/or water miscible solvents. The cosmetic skin care composition may comprise from about 1% to about 95 % by weight of water and/or water miscible solvent. The composition may comprise from about 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% to about 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10% , or 5% water and/or water miscible solvents. Suitable water miscible solvents include monohydric alcohols, 10 dihydric alcohols, polyhydric alcohols, glycerol, glycols, polyalkylene glycols such as polyethylene glycol, and mixtures thereof. When the skin care composition is in the form of an emulsion, water and/or water miscible solvents are carriers typically associated with the aqueous phase.

Suitable carriers also include oils. The skin care composition may comprise from about 15 1% to about 95 % by weight of one or more oils. The composition may comprise from about 0.1%, 0.5%, 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% to about 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 5%, or 3% of one or more oils. Oils may be used to solubilize, disperse, or carry materials that are not suitable for water or water soluble solvents. 20 Suitable oils include silicones, hydrocarbons, esters, amides, ethers, and mixtures thereof. The oils may be volatile or nonvolatile.

Suitable silicone oils include polysiloxanes. Commercially available polysiloxanes include the polydimethylsiloxanes, which are also known as dimethicones, examples of which include the DM-Fluid series from Shin-Etsu, the Vicasil[®] series sold by Momentive Performance 25 Materials Inc., and the Dow Corning[®] 200 series sold by Dow Corning Corporation. Specific examples of suitable polydimethylsiloxanes include Dow Corning[®] 200 fluids (also sold as Xiameter[®] PMX-200 Silicone Fluids) having viscosities of 0.65, 1.5, 50, 100, 350, 10,000, 12,500 100,000, and 300,000 centistokes.

Suitable hydrocarbon oils include straight, branched, or cyclic alkanes and alkenes. The 30 chain length may be selected based on desired functional characteristics such as volatility. Suitable volatile hydrocarbons may have between 5-20 carbon atoms or, alternately, between 8-16 carbon atoms.

Other suitable oils include esters. The suitable esters typically contained at least 10 carbon atoms. These esters include esters with hydrocarbyl chains derived from fatty acids or

alcohols (*e.g.*, mono-esters, polyhydric alcohol esters, and di- and tri-carboxylic acid esters). The hydrocarbyl radicals of the esters hereof may include or have covalently bonded thereto other compatible functionalities, such as amides and alkoxy moieties (*e.g.*, ethoxy or ether linkages, etc.).

5 Other suitable oils include amides. Amides include compounds having an amide functional group while being liquid at 25 °C and insoluble in water. Suitable amides include N-acetyl-N-butylaminopropionate, isopropyl N-lauroylsarcosinate, and N,N-diethyltoluamide. Other suitable amides are disclosed in U.S. Patent No. 6,872,401.

10 Other suitable oils include ethers. Suitable ethers include saturated and unsaturated fatty ethers of a polyhydric alcohol, and alkoxyated derivatives thereof. Exemplary ethers include C₄-20 alkyl ethers of polypropylene glycols, and di-C₈₋₃₀ alkyl ethers. Suitable examples of these materials include PPG-14 butyl ether, PPG-15 stearyl ether, dioctyl ether, dodecyl octyl ether, and mixtures thereof.

15 The skin care composition may comprise an emulsifier. An emulsifier is particularly suitable when the composition is in the form of an emulsion or if immiscible materials are being combined. The skin care composition may comprise from about 0.05%, 0.1%, 0.2%, 0.3%, 0.5%, or 1% to about 20%, 10%, 5%, 3%, 2%, or 1% emulsifier. Emulsifiers may be nonionic, anionic or cationic. Non-limiting examples of emulsifiers are disclosed in U.S. Patent 3,755,560, U.S. Patent 4,421,769, and McCutcheon's, *Emulsifiers and Detergents*, 2010 Annual Ed.,
20 published by M. C. Publishing Co.. Other suitable emulsifiers are further described in the Personal Care Product Council's *International Cosmetic Ingredient Dictionary and Handbook*, Thirteenth Edition, 2006, under the functional category of "Surfactants - Emulsifying Agents."

Linear or branched type silicone emulsifiers may also be used. Particularly useful polyether modified silicones include KF-6011, KF-6012, KF-6013, KF-6015, KF-6015, KF-25 6017, KF-6043, KF-6028, and KF-6038 from Shin Etsu. Also particularly useful are the polyglycerolated linear or branched siloxane emulsifiers including KF-6100, KF-6104, and KF-6105 from Shin Etsu. Emulsifiers also include emulsifying silicone elastomers. Suitable silicone elastomers may be in the powder form, or dispersed or solubilized in solvents such as volatile or nonvolatile silicones, or silicone compatible vehicles such as paraffinic hydrocarbons or esters.
30 Suitable emulsifying silicone elastomers may include at least one polyalkyl ether or polyglycerolated unit.

Structuring agents may be used to increase viscosity, thicken, solidify, or provide solid or crystalline structure to the skin care composition. Structuring agents are typically grouped based on solubility, dispersibility, or phase compatibility. Examples of aqueous or water structuring

agents include polymeric agents, natural or synthetic gums, polysaccharides, and the like. In one embodiment, the composition may comprises from about 0.0001%, 0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 5% to about 25%, 20%, 10%, 7%, 5%, 4%, or 2%, by weight of the composition, of one or more structuring agents.

5 Polysaccharides and gums may be suitable aqueous phase thickening agents. Suitable classes of polymeric structuring agents include but are not limited to carboxylic acid polymers, polyacrylamide polymers, sulfonated polymers, high molecular weight polyalkylglycols or polyglycerins, copolymers thereof, hydrophobically modified derivatives thereof, and mixtures thereof. Silicone gums are another oil phase structuring agent. Another type of oily phase
10 structuring agent includes silicone waxes. Silicone waxes may be referred to as alkyl silicone waxes which and are semi-solids or solids at room temperature. Other oil phase structuring agents may be one or more natural or synthetic waxes such as animal, vegetable, or mineral waxes.

The skin care compositions may be generally prepared by conventional methods such as
15 known in the art of making compositions and topical compositions. Such methods typically involve mixing of ingredients in or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like. Typically, emulsions are prepared by first mixing the aqueous phase materials separately from the fatty phase materials and then combining the two phases as appropriate to yield the desired continuous phase. The compositions are
20 preferably prepared such as to optimize stability (physical stability, chemical stability, photostability, etc.) and/or delivery of active materials. The composition may be provided in a package sized to store a sufficient amount of the composition for a treatment period. The size, shape, and design of the package may vary widely. Certain package examples are described in USPNs D570,707; D391,162; D516,436; D535,191; D542,660; D547,193; D547,661; D558,591;
25 D563,221; 2009/0017080; 2007/0205226; and 2007/0040306.

EXAMPLES

The present invention will be better understood by reference to the following examples which are offered by way of illustration not limitation.

Example 1

30 Generating Instances

Individual experiments (referred to as batches) generally comprise 30 to 96 samples analyzed using Affymetrix GeneChip® technology platforms, containing 6 replicates of the vehicle control (e.g., DMSO), 2 replicate samples of a positive control that gives a strong reproducible effect in the cell type used (e.g., all *trans*-retinoic acid for fibroblast cells), and

samples of the test material/perturbagen. Replication of the test material is done in separate batches due to batch effects. *In vitro* testing was performed in 6-well plates to provide sufficient RNA for GeneChip® analysis (2-4 µg total RNA yield/well).

Human telomerized keratinocytes (tKC) were obtained from the University of Texas,
5 Southwestern Medical Center, Dallas, TX. tKC cells were grown in EpiLife® media with 1X Human Keratinocyte Growth Supplement (Invitrogen, Carlsbad, CA) on collagen I coated cell culture flasks and plates (Becton Dickinson, Franklin Lakes, NJ). Keratinocytes were seeded into 6-well plates at 20,000 cells /cm² 24 hours before chemical exposure. Human skin fibroblasts (BJ cell line from ATCC, Manassas, VA) were grown in Eagle's Minimal Essential
10 Medium (ATCC) supplemented with 10% fetal bovine serum (HyClone, Logan, UT) in normal cell culture flasks and plates (Corning, Lowell, MA). BJ fibroblasts were seeded into 6-well plates at 12,000 cells/cm² 24 hours before chemical exposure.

All cells were incubated at 37°C in a humidified incubator with 5% CO₂. At t= -24 hours cells were trypsinized from T-75 flasks and plated into 6-well plates in basal growth medium. At
15 t=0 media was removed and replaced with the appropriate dosing solution as per the experimental design. Dosing solutions were prepared the previous day in sterile 4 ml Falcon snap cap tubes. Pure test materials may be prepared at a concentration of 1-200 µM, and botanical extracts may be prepared at a concentration of 0.001 to 1% by weight of the dosing solution. After 6 to 24 hours of chemical exposure, cells were viewed and imaged. The wells were examined with a
20 microscope before cell lysis and RNA isolation to evaluate for morphologic evidence of toxicity. If morphological changes were sufficient to suggest cytotoxicity, a lower concentration of the perturbagen was tested. Cells were then lysed with 350ul/well of RLT buffer containing β-mercaptoethanol (Qiagen, Valencia, CA), transferred to a 96-well plate, and stored at -20° C.

RNA from cell culture batches was isolated from the RLT buffer using Agencourt®
25 RNAdvance Tissue-Bind magnetic beads (Beckman Coulter) according to manufacturer's instructions. 1 µg of total RNA per sample was labeled using Ambion Message Amp™ II Biotin Enhanced kit (Applied Biosystems Incorporated) according to manufacturer's instructions. The resultant biotin labeled and fragmented cRNA was hybridized to an Affymetrix HG-U133A 2.0 GeneChip®, which was then washed, stained and scanned using the protocol provided by
30 Affymetrix.

In one embodiment, an exemplary test perturbagen was *Cynara scolymus* (artichoke) leaf extract obtained from Ichimaru Pharcos, JP. Following generally the procedure described above, a resultant rank-ordered listing of 22,214 probe set IDs (e.g., an instance) for the artichoke leaf perturbagen applied to fibroblast cells was generated and are set forth in **Table E**. Following

generally the procedure described above, a resultant rank-ordered listing of 22,214 probe set IDs (e.g., an instance) for the artichoke leaf extract perturbagen applied to keratinocyte cells was generated and illustrative portions are set forth in **Table F**. In another aspect, an exemplary test perturbagen was Hydrolyzed *Ceratonia siliqua* (carob) seed extract. Following generally the procedure described above, a resultant rank-ordered listing of 22,214 probe set IDs (e.g., an instance) for the carob seed extract perturbagen applied to fibroblast cells was generated and illustrative portions are set forth in **Table G**. Following generally the procedure described above, a resultant rank-ordered listing of 22,214 probe set IDs (e.g., an instance) for the carob seed extract perturbagen applied to keratinocyte cells was generated and illustrative portions are set forth in **Table H**.

Example 2

Deriving a Photo-Aging Gene expression signature

A clinical survey study to obtain biopsy specimens for use in the investigation of gene expression patterns associated with sun light-mediated skin aging (photo-aging) was performed. Baseline gene expression patterns were examined in sun-protected and sun-exposed skin from young and aged women to examine gene expression profiles associated with photo-aging. A total of 3 full thickness skin biopsies (~4mm) were taken from sun-protected (buttocks) and sun-exposed (extensor forearm) body sites from each of 10 young women (aged 18 to 20 years) and 10 older women (aged 60 to 67 years). The older women were selected to have moderate to severe forearm photo-damage. Biopsies were flash frozen in liquid nitrogen and stored at -80°C until RNA isolation.

Frozen skin biopsies were homogenized in Trizol (Invitrogen) and RNA extracted using the protocol provided by Invitrogen. Since the tissue samples were from full thickness biopsies, RNA was extracted from a variety of cell types within the full-thickness skin sample, including keratinocytes, fibroblasts, melanocytes, endothelial cells, pericytes, nerves, smooth muscle, sebocytes, adipocytes, and immunocytes). RNA was further purified using RNEasy spin columns (Qiagen). Total RNA was quantified using a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA) and quality was confirmed using an Agilent (Santa Clara, CA) 2100 BioAnalyzer. Total RNA (5 µg) was converted to GeneChip targets using the Enzo BioArray labeling procedure (Enzo Life Sciences, Farmingdale, NY) and protocol provided. All biotin-labeled GeneChip targets were hybridized to Affymetrix Human Genome HG-U133 Plus 2.0 GeneChips overnight, which were then washed, stained and scanned using the protocol provided by Affymetrix. Forearm and buttock samples were processed on the same day using the same manufacturing lot of GeneChips.

The samples were analyzed on the Affymetrix HG-U133 Plus 2.0 GeneChips, which contain 54,613 probe sets complementary to the transcripts of more than 20,000 genes. However, instances in the provided database used were derived from gene expression profiling experiments using Affymetrix HG-U133A 2.0 GeneChips, containing 22,214 probe sets, which are a subset of those present on the Plus 2.0 GeneChip. Therefore, in developing gene expression signatures from the clinical data, the probe sets were filtered for those included in the HG-U133A 2.0 gene chips.

Using, generally the following selection process, a statistical analysis of the microarray data was performed to derive a plurality of photo-aging gene expression signatures comprising between about 200 and about 600 up-regulated and down-regulated genes.

a. Filtering based on Absent/Margin/Present Calls. This filter creates a list of potential genes for inclusion in the gene expression signature. For example, a suitable filter may be that at least 50% of the samples in one treatment group must have a Present call for each probe set. Present calls are derived from processing the raw GeneChip data and provide evidence that the gene transcript complementary to a probe set that is actually expressed in the biological sample. The probes that are absent from all samples are likely to be just noisy measurements. This step is important to filter out probe sets that do not contribute meaningful data to the signature. For both photo-aging and intrinsic aging gene expression signatures, the data was filtered for probe sets with at least 10% Present calls provided by the Affymetrix MAS 5 software.

b. Filtering According to a Statistical Measure. For example, a suitable statistical measure may be p-values from a t-test, ANOVA, correlation coefficient, or other model-based analysis. As one example, p-values may be chosen as the statistical measure and a cutoff value of $p=0.05$ may be chosen. Limiting the signature list to genes that meet some reasonable cutoff for statistical significance compared to an appropriate control is important to allow selection of genes that are characteristic of the biological state of interest. This is preferable to using a fold change value, which does not take into account the noise around the measurements. The t-statistic was used to select the probe sets in the signatures because it is signed and provides an indication of the directionality of the gene expression changes (i.e. up- or down-regulated) as well as statistical significance.

c. Sorting the Probe Sets. All the probe sets are sorted into sets of up-regulated and down-regulated sets using the statistical measure. For example, if a t-test was used to compute p-values, the values (positive and negative) of the t-statistic are used to sort the list since p-values are always positive. The sorted t-statistics will place the sets with the

most significant p-values at the top and bottom of the list with the non-significant ones near the middle.

d. Creation of the Gene expression signature. Using the filtered and sorted list created, a suitable number of probe sets from the top and bottom are selected to create a gene expression signature that preferably has approximately the same number of sets chosen from the top as chosen from the bottom. For example, the gene expression signature created may have at least about 10, 50, 100, 200, or 300 and/or less than about 800, 600, or about 400 genes corresponding to a probe set on the chip. The number of probe sets approximately corresponds to the number of genes, but a single gene may be represented by more than one probe set. It is understood that the phrase "number of genes" as used herein, corresponds generally with the phrase "number of probe sets." The number of genes included in the signature was based upon the observations in preliminary studies that indicated signatures with from 200 to 800 probe sets equally divided between up- and down-regulated genes provide stable results with regard to the top scoring chemical instances when using the signature to query the provided database.

For photo-aging, three gene expression signatures were selected as follows:

(i) "Photo-aging 200" signature (P200), which comprises 100 most significant up- and 100 most significant down-regulated probe sets comparing older arm to younger arm as set forth in **Tables C and D**, respectively;

(ii) "Photo-aging 400" signature (P400), which comprises 200 most significant up- and 200 most significant down-regulated probe sets comparing older arm to younger arm as set forth in **Tables C and D**, respectively; and

(iii) "Photo-aging 600" signature (P600), which comprises 300 most significant up- and 300 most significant down-regulated probe sets comparing older arm to younger arm as set forth in **Tables C and D**, respectively.

Example 3

Deriving an Intrinsic Aging Gene expression signature

A clinical survey study to obtain biopsy specimens for use in the investigation of gene expression patterns associated with chronological (intrinsic) skin aging was performed. Baseline gene expression patterns were examined in sun-protected skin from young and aged women to examine gene expression profiles associated with intrinsic aging. A total of 3 full thickness skin biopsies (~4mm) were taken from sun-protected (buttocks) body sites from each of 10 young

women (aged 18 to 20 years) and 10 older women (aged 60 to 67 years). Biopsies were flash frozen in liquid nitrogen and stored at -80°C until RNA isolation.

Frozen skin biopsies were homogenized in Trizol (Invitrogen) and RNA extracted using the protocol provided by Invitrogen. Since the tissue samples were from full thickness biopsies,

RNA was extracted from a variety of cell types within the full-thickness skin sample, including keratinocytes, fibroblasts, melanocytes, endothelial cells, pericytes, nerves, smooth muscle, sebocytes, adipocytes, and immunocytes). RNA was further purified using RNEasy spin columns (Qiagen). Total RNA was quantified using a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA) and quality was confirmed using an Agilent (Santa Clara, CA) 2100 BioAnalyzer. Total RNA (5 µg) was converted to GeneChip targets using the Enzo BioArray labeling procedure (Enzo Life Sciences, Farmingdale, NY) and protocol provided. All biotin-labeled GeneChip targets were hybridized to Affymetrix Human Genome HG-U133 Plus 2.0 gene chips overnight, which were then washed, stained and scanned using the protocol provided by Affymetrix. Samples were processed on the same day using the same manufacturing lot of gene chips.

Using, generally the same sorting process as set forth in Example 2, a statistical analysis of the microarray data was performed to derive intrinsic aging gene expression signatures comprising between about 200 genes and about 600 genes.

(i) "Intrinsic Aging 200" signature (I200), which comprises 100 most significant up- and 100 most significant down-regulated probe sets comparing older buttock to younger buttock as set forth in **Table A** and **B**, respectively.

(ii) "Intrinsic Aging 400" signature (I400), which comprises 200 most significant up- and 200 most significant down-regulated probe sets older buttock to younger buttock as set forth in **Table A** and **B**, respectively.

(iii) "Intrinsic Aging 600" signature (I600), which comprises 300 most significant up- and 300 most significant down-regulated probe sets older buttock to younger buttock as set forth in **Table A** and **B**, respectively.

The photo-aging gene expression signatures and the intrinsic aging gene expression signatures may be used in whole or part, or they may be used in combination as a query in the present invention. In some embodiments, the gene expression signature comprises the set of most up-regulated or most down-regulated genes. In some embodiments, the photo-aging gene expression signature and intrinsic aging gene expression signature may have between about 10% and 50% of their probe set IDs in common. In other embodiments, the photo-aging gene

expression signature and the intrinsic aging gene expression signature may have between about 20% and 30% of their probe set IDs in common. Some materials tested in C-map link to only to gene expression signatures developed for one of the types of skin aging because these agents may be affecting different biology. For example, the inventors have found that the photo-aging gene expression signatures show strong preferential linkage to perturbation instances tested in fibroblasts and the gene expression changes are more reflective of changes in the dermal connective tissue. In contrast, the intrinsic aging gene expression signatures reflect changes in both the epidermis and dermis that occur with aging. Therefore, it is useful to query the connectivity map with separate signatures derived for both intrinsic aging and photo-aging. Also, it is desirable to use signatures with different numbers of genes. Predictions of biological activity based on multiple signatures are more likely to be correct.

Example 4

Photo-Aging Gene expression signature and Intrinsic Aging Gene expression signature Comparison to Fibroblast and Keratinocyte Instances

The inventors observed that photo-aging gene signatures (e.g., Example 2) have a strong preferential connectivity to perturbation instances tested in BJ fibroblasts. In other words, among the top ranked instances (i.e., with high connectivity scores) resulting from queries with photo-aging signatures BJ fibroblast instances were strongly over-represented. This effect was most dramatic when the genes up-regulated in photoaged skin were used as the query signatures. A similar result, but less strong, was obtained with the intrinsic aging signatures (e.g., Example 3). A summary of the results of comparing a plurality of instances with the Photo-aging 600 signature is shown in Table 1. These results are completely unpredicted and surprising considering that: i) the gene signatures derived from full thickness biopsies comprising a variety of cell types expected to contribute to the skin aging phenotype, and ii) skin aging is a complex multi-factorial condition involving changes in most of the tissues and structures of skin,

Table 1.

Distribution of fibroblast (BJ and keratinocyte (tKC) instances in the top ranked instances from a C-map query with the Photo-aging 600 signature¹

Rank ²	Chemical instances tested in each cell type					
	Complete signature		Up list ³		Down list ³	
	BJ	tKC	BJ	tKC	BJ	tKC
1-100	79	21	100	0	36	64
101-200	60	40	100	0	36	64
201-300	57	43	100	0	41	59

301-400	51	49	96	4	34	66
401-500	38	62	85	15	15	72

¹This signature comprises the 300 most statistically significant up-regulated and the 300 most significant down-regulated Affymetrix probe sets in the older arm to younger arm comparison described in Example 2, above.

²Instances were ranked from the most negatively scoring to most positive (i.e., 1 was the most negatively scoring instance). Chemicals scoring negatively are predicted to have beneficial effects on photo-aging.

³The up list results are from querying a database of instances with only up-regulated probe sets in the gene expression signature. Similarly, the down list results are from querying with a gene expression signature comprising only probe sets that are down-regulated.

Among the top 300 ranked instances linking to the complete photo-aging signature, 196 (65.3%) were with respect to BJ fibroblasts and only 34.7% were with respect to keratinocytes. This was more than a 2-fold over-representation of fibroblasts, since they comprised only 31% of the instances in the database. The preferential connectivity of fibroblasts to the photo-aging signature was much more dramatic when only the up list was used for the query. Remarkably, in that case all of the top 300 instances were in fibroblasts. The up signature contribution accounted for the preferential connectivity of fibroblasts to the complete photo-aging signature, because querying with the down signature alone gave a distribution of top scoring instances more proportional to the percentages of the two cell lines instances in the database. Similar results were obtained with the Photo-aging P200 and P400 signatures described in Example 2. Overall, the strong preferential connectivity of fibroblast instances to the photo-aging signatures is surprising because keratinocytes are expected to contribute to the photo-aging phenotype and all of the materials tested in BJ fibroblasts were also tested in keratinocytes (i.e., the effect is not due to any chemical specificity).

A similar but subtly different pattern was observed when the provided database was queried with intrinsic aging gene expression signatures. Table 2 shows results obtained with the Intrinsic Aging 600 signature (Example 3). Again there was an over-representation of fibroblasts among the top ranked instances with the complete signature, and this effect was due to the up-regulated probe sets in the signature, but the effect was not as strong as with the photo-aging signatures. Furthermore, the top ranking instances connecting to the down list showed some over-representation of keratinocytes relative to their proportion of the samples tested (Table 2).

Table 2

Distribution of fibroblast (BJ) and keratinocyte (tKC) instances in the top ranked instances from a C-map query with the Intrinsic Aging 600 signature. ¹

Rank ²	Chemical instances tested in each cell type		
	Complete	Up list ³	Down list ³

	signature					
	BJ	tKC	BJ	tKC	BJ	tKC
1-100	68	32	95	5	13	87
101-200	55	45	84	16	17	83
201-300	38	62	72	28	17	83
301-400	37	63	67	33	21	79
401-500	31	69	57	43	26	74

¹ This signature comprises the 300 most statistically significant up- and 300 most significant down-regulated Affymetrix probe sets in the older buttock to younger buttock comparison in the clinical study described in Example 3.

² Instances were ranked as in Table 1.

5 ³ The up list results are from querying the C-Map database with only the up-regulated probe sets in the signature. Similarly, the down list results are from querying only with the down list.

Unexpectedly, the gene expression signatures generated from clinical samples of photo-aged skin show very strong preferential connectivity to chemical instances tested in dermal fibroblasts compared to epidermal keratinocytes. Furthermore, this preferential connectivity was
 10 observed with signatures generated from gene expression profiling done on RNA extracted from full thickness biopsies of skin, which comprise a composite sample of all of the cell types within the complex structure of skin. Analysis of the biological processes associated with the genes differentially expressed in photo-aged skin indicated that many of the processes were related to the dermis and fibroblasts including wound healing (see Theme Analysis, Example 5). These
 15 results support the hypothesis that the dominant gene expression changes in photo-aged skin occur in dermal fibroblasts. Furthermore, in clinical testing statistically significant anti-wrinkle results were obtained with two botanical extracts predicted to have skin anti-aging activity based on C-Map queries of fibroblast instances (e.g. Examples 6 and 7). In contrast, the keratinocytes instances of these materials did not predict their anti-aging activities.

20 These differences between the photo-aging and intrinsic aging signatures may be accounted for by the fact that they represent overlapping but different biological changes in aging skin (see Theme Analysis, Example 5). Photo-aging is due to a combination of the effects of UV radiation exposure and intrinsic factors, while intrinsic aging lacks the solar/UV component. Fewer than 20% of the genes in the photo-aging and intrinsic aging signatures were observed to
 25 be in common. These results point to the value of using both photo-aging and intrinsic aging signatures when applying C-map to identify cosmetic agents to improve aging skin, because the signatures will allow detection of materials that affect different aspects of the complex aging process.

The under-representation of telomerized keratinocytes in the top ranked C-map instances with queries using the complete photo-aging and intrinsic aging gene expression signatures was not due to a lack of responsiveness of the cells under the conditions of testing. **Table 3** sets forth gene expression outlier numbers for 493 chemicals that were tested in both BJ fibroblasts and telomerized keratinocytes using the same stock solutions. Outlier numbers were calculated for each singleton C-map instance and are a measure of the number of probe sets regulated by treatment. In this probe set-by-probe set analysis, the 6 vehicle control samples in a C-map batch are used to form a prediction interval for each probe set, and then for each chemical instance in the batch the probe sets falling outside the interval are counted. This statistic is used because chemical replication is usually done in different C-map batches due to batch effects on the scoring.

Table 3.

Gene expression outlier numbers for 493 materials tested in both BJ fibroblasts and telomerized keratinocytes.¹

Range of outliers	Number of C-MAP instances	
	BJ fibroblasts	Telomerized-keratinocytes
≥ 2000	123	245
1000 – 1999	711	725
<1000	292	234
Totals:	1126	1204

¹Materials from the same stock tubes were tested in both types of cells. Outlier numbers were calculated for each singleton C-map instance and are a measure of the number of probe sets regulated by treatment. In this probe set-by-probe set analysis, the 6 vehicle control samples in a C-map batch are used to form a prediction interval for each probe set, and then for each chemical instance in the batch the probe sets falling outside the interval are counted. This statistic is used because chemical replication is usually done in different C-map batches due to batch effects on the scoring.

Based on outlier numbers, the keratinocytes tended to be more responsive to treatment than fibroblasts and there were about twice as many keratinocyte instances with high outlier numbers (≥2,000) compared to those with fibroblasts. Additional indications of cellular responsiveness to treatment are morphologic changes. Altered morphology in telomerized keratinocytes treated with various chemicals has been observed. In contrast, morphologic changes in BJ fibroblasts have rarely been observed under the same conditions. A fairly dramatic comparative example is shown in **Figure 9**, which documents the morphology of cells treated

Table 4.
Theme analysis of genes regulated in photo-aging.

5

Gene Ontology Biological Process Terms	Old Arm to Young Arm Comparison ¹		Terms related to dermis
	Up	Down	
. . . GO:0006956 complement activation	*		
. GO:0032501 multicellular organismal process	*****		
. . GO:0007275 multicellular organismal development	****		
. . . GO:0035295 tube development	*		
. . . . GO:0030323 respiratory tube development	*		
. GO:0048754 branching morphogenesis of a tube	*		
. . . GO:0048731 system development	****		
. . . . GO:0048513 organ development	*		
. GO:0048568 embryonic organ development	*		
. GO:0009887 organ morphogenesis	*		
. GO:0009888 tissue development	*		
. . . . GO:0007399 nervous system development	**		
. . . . GO:0001501 skeletal system development	**		X
. GO:0048706 embryonic skeletal system development	*		X
. . . GO:0048736 appendage development	**		X
. . . . GO:0035107 appendage morphogenesis	*		X
. . . . GO:0060173 limb development	*		X
. . . GO:0007389 pattern specification process	*		
. GO:0032502 developmental process	****		
. . GO:0048856 anatomical structure development	****		
. . . GO:0009653 anatomical structure morphogenesis	****		
. . . GO:0016477 cell migration	*		
. GO:0002541 activation of plasma proteins involved in acute inflammat...	*		
. . . GO:0009611 response to wounding	*****		X
. . . . GO:0042060 wound healing	*****		X
. . GO:0009605 response to external stimulus	*****		
. . . GO:0019222 regulation of metabolic process		*	
. GO:0045941 positive regulation of transcription		*	
. GO:0045893 positive regulation of transcription,		*	

DNA-dependent			
..... GO:0045944 positive regulation of transcription from RNA polym...		*	
..... GO:0006355 regulation of transcription, DNA-dependent		*	
..... GO:0045892 negative regulation of transcription, DNA-dependent		*	
..... GO:0000122 negative regulation of transcription from RNA polym...		**	
..... GO:0006357 regulation of transcription from RNA polymerase II pr...		**	
..... GO:0016481 negative regulation of transcription		*	
..... GO:0051253 negative regulation of RNA metabolic process		*	
..... GO:0051252 regulation of RNA metabolic process		*	
..... GO:0051254 positive regulation of RNA metabolic process		*	
..... GO:0045935 positive regulation of nucleobase, nucleoside, nucleotide...		**	
..... GO:0031324 negative regulation of cellular metabolic process		*	
..... GO:0031327 negative regulation of cellular biosynthetic process		**	
..... GO:0031325 positive regulation of cellular metabolic process		*	
..... GO:0031328 positive regulation of cellular biosynthetic process		*	
..... GO:0051173 positive regulation of nitrogen compound metabolic process		**	
..... GO:0060255 regulation of macromolecule metabolic process		*	
..... GO:0010628 positive regulation of gene expression		*	
..... GO:0010629 negative regulation of gene expression		*	
..... GO:0010557 positive regulation of macromolecule biosynthetic process		*	
..... GO:0010558 negative regulation of macromolecule biosynthetic process		*	
..... GO:0010604 positive regulation of macromolecule metabolic process		*	
..... GO:0010605 negative regulation of macromolecule metabolic process		*	
..... GO:0009890 negative regulation of biosynthetic		**	

process			
. GO:0009891 positive regulation of biosynthetic process		*	
. . . . GO:0009892 negative regulation of metabolic process		*	
. . . . GO:0048522 positive regulation of cellular process		*	
. GO:0002053 positive regulation of mesenchymal cell proliferation	*		X
. . . . GO:0048634 regulation of muscle organ development	*		X
. GO:0016202 regulation of striated muscle tissue development	*		X
. GO:0010464 regulation of mesenchymal cell proliferation	**		X
. . . . GO:0007165 signal transduction	*	*	
. GO:0009966 regulation of signal transduction		*	
. . GO:0043062 extracellular structure organization	*		
. . . GO:0030198 extracellular matrix organization	**		X
. GO:0006350 transcription		*	
. . GO:0006928 cellular component movement	*		
. . . . GO:0006325 chromatin organization		*	
. GO:0016568 chromatin modification		**	
. . GO:0007154 cell communication	*		
. GO:0016485 protein processing	*		
. GO:0051605 protein maturation by peptide bond cleavage	*		

¹ Statistical significance is as follows.

P-Value Legend			
1.00E-4 <	p		
1.00E-5 <	p	<= 1.00E-4	*
1.00E-6 <	p	<= 1.00E-5	**
1.00E-7 <	p	<= 1.00E-6	***
	p	<= 1.00E-7	****

This analysis revealed that up- and down-regulated genes in photo-aging were associated with quite distinct biological processes. A number of biological processes closely associated with fibroblasts and connective tissue were up-regulated in photo-aging. It is notable that the Gene Ontology terms “**response to wounding**” and “**wound healing**” were among the most statistically significant terms ($p \leq 1 \times 10^{-7}$) for the up-regulated gene list. Other terms clearly associated with fibroblasts or mesenchymal cells are marked in **Table 4** and these all were significant for the up list. Most of these other terms associated with the up-regulated list relate to developmental processes in which mesenchymal cells play important roles. The genes down-regulated in photo-aging were associated with more general processes such as gene transcription and various aspects of metabolism and signal transduction that relate to various cell types.

The Photo-aging 600 signature gene lists (see Example 2) were also subject to theme analysis (not shown), which revealed a pattern of significant terms quite similar to that obtained with the entire photo-aging data set. The up-regulated gene list contains genes involved in biological processes closely associated with fibroblasts or mesenchymal cells. Again among the most significant terms for the up list included “**response to wounding**” and “**wound healing**” ($P \leq 1 \times 10^{-5}$). The results of these theme analyses provide a clear rationale for the specific linkage of fibroblasts to the photo-aging up-regulated gene expression signature and the strong linkage to the overall signature. It appears that the dominant processes that are up-regulated in photo-aging involve the dermis and fibroblasts. Overall, the photo-aging gene signatures reflect this dominant biology observed in the gene expression profiling of the photo-aging skin condition.

Theme analysis was also performed on the genes regulated in intrinsic aging, which involved approximately 12,500 expressed genes. **Table 5** shows GO Biological Process terms that are significantly enriched in the comparison of the older buttock to younger buttock (intrinsic aging) from the clinical gene expression study described in Example 3. Similarly with respect to **Table 4**, only the most highly significant themes are shown ($p \leq 1 \times 10^{-4}$) to keep the size of this table manageable.

Table 5
Theme analysis of genes regulated in intrinsic aging

Gene Ontology Biological Process Terms	Old Buttock to Young Buttock Comparison ¹		Terms related to epidermis
	Up	Down	
. GO:0032501 multicellular organismal process	*		

. . . GO:0022600 digestive system process		*	
. . . GO:0003012 muscle system process	*		
. . GO:0007275 multicellular organismal development	*		
. . . GO:0048731 system development	***		
. . . . GO:0048513 organ development	***		
. GO:0007398 ectoderm development		*	X
. GO:0021846 cell proliferation in forebrain		*	
. . . . GO:0007399 nervous system development		*	
. GO:0007417 central nervous system development		**	
. . GO:0007586 digestion		*	
. . GO:0001503 ossification	*		
. GO:0032502 developmental process	*		
. . GO:0048856 anatomical structure development	**		
. . . GO:0060021 palate development	*		
. . . GO:0061061 muscle structure development	*		
. GO:0043434 response to peptide hormone stimulus		**	
. . . . GO:0042127 regulation of cell proliferation	*		
. . . GO:0042180 cellular ketone metabolic process		*	
. . . . GO:0043436 oxoacid metabolic process		*	X
. GO:0019752 carboxylic acid metabolic process		*	X
. GO:0006631 fatty acid metabolic process		*	X
. GO:0006633 fatty acid biosynthetic process		*	X
. GO:0046394 carboxylic acid biosynthetic process		*	X
. . . . GO:0042438 melanin biosynthetic process		*	
. . . . GO:0051188 cofactor biosynthetic		*	

process			
.... GO:0016053 organic acid biosynthetic process		*	X
... GO:0044255 cellular lipid metabolic process		***	X
... GO:0051186 cofactor metabolic process		**	
.... GO:0006732 coenzyme metabolic process		*	
... GO:0006082 organic acid metabolic process		*	X
.. GO:0019748 secondary metabolic process		*	
... GO:0006582 melanin metabolic process		*	X
... GO:0006629 lipid metabolic process		****	X
.... GO:0008202 steroid metabolic process		*	X
..... GO:0006694 steroid biosynthetic process		**	X
..... GO:0016126 sterol biosynthetic process		**	X
..... GO:0006695 cholesterol biosynthetic process		**	X
..... GO:0016125 sterol metabolic process		*	X
.... GO:0008610 lipid biosynthetic process		****	X
.. GO:0044281 small molecule metabolic process		****	
... GO:0044283 small molecule biosynthetic process		*	
... GO:0006066 alcohol metabolic process		*	
.. GO:0055114 oxidation reduction		**	

¹ Statistical significance is as described in **Table 4**.

The theme analysis of the genes regulated in intrinsic aging, like that for photo-aging, revealed that the up- and down-regulated genes were associated with very different processes. The down-regulated genes in intrinsic skin aging were associated with a number of processes related to the epidermis and keratinocytes. Most dominant were terms related to lipid biosynthetic pathways that are involved in the synthesis of lipids important in epidermal barrier

function. A more specific term related to epithelial biology, “**ectoderm development**,” was associated with the down-regulated genes. The related term “**epidermal development**” ($p < 0.001$) was not included in the table because it did not make the p value cutoff, but it was also associated with the down-regulated genes. Terms related to regulation of pigmentation (melanogenesis), which is an epidermal function, were also significant for the down list analysis. As seen in the analysis of photo-aging, up-regulated themes included various developmental processes related to mesenchymal cells. The appearance of terms such as “ossification,” which may seem irrelevant to skin, was due to the fact that various regulatory pathways and related genes are involved in a number of processes associated with cell lineages. Bone matrix cells are of mesenchymal origin. The term “**regulation of mesenchymal cell proliferation**” (highly significant in the photo-aging analysis) was not included in the table because it did not make the p value cutoff, but was significant at $p < 0.001$ for the up list in intrinsic aging.

The Intrinsic Aging 600 signature gene lists (described in Example 3 and defined as the top 300 up- and down-regulated genes set forth in **Tables A and B**) were also subjected to theme analysis (not shown), which revealed a pattern of significant terms similar to that obtained with the entire intrinsic aging data set. The up-regulated gene list contains genes involved in biological processes associated with fibroblasts or mesenchymal cells, and the down-regulated list contained genes more closely associated with epidermal processes and keratinocytes. The results of these theme analyses suggest a rationale for the strong connectivity of fibroblasts to the intrinsic aging up-regulated gene expression signature and their preferential linkage to the overall signature, as well as the preferential connectivity of keratinocyte instances to the down-regulated gene expression signature. Overall, the intrinsic aging signatures reflect the biology in intrinsic aging.

The biological theme analyses performed on the genes regulated in photo-aging and intrinsic aging demonstrate differences in the dominant biology in these two aspects of skin aging. The major differences related to an apparently greater down-regulation of processes associated with keratinocyte differentiation in intrinsic aging. These analyses further support the value of using signatures for both photo-aging and intrinsic aging in querying the C-map database to identify cosmetic materials to treat aging skin. These analyses also further support the non-intuitive finding that fibroblasts cell lines are more useful than keratinocyte cell lines for identifying cosmetic agents to improve photo-aged skin. The studies described herein also demonstrate that cell type-specific signals can be detected from full thickness biopsies using the C-map method and system.

Example 6

Connectivity Map Results for Artichoke Leaf Extract and Carob Seed Extract

In this example, 20 materials that were candidates for an anti-aging facial benefit study were tested in fibroblasts and keratinocytes. A microarray analysis was conducted for each sample compound and ordered lists of the probe set IDs were stored as instances in a database. Photo-aging and intrinsic aging gene expression signatures were compared against the instances and connectivity scores were derived.

Of the 20 candidates screened, 2 showed consistent connections to the photo-aging gene expression signatures when tested in BJ fibroblasts. The detailed results for these materials, artichoke leaf extract and carob seed extract, are shown in **Table 6**. Since both intrinsic aging and photo-aging are considered adverse conditions, it is preferential to find materials that tend to reverse one or both of the gene expression signatures. Such materials will have negative connectivity score, and the more negative the score the stronger the negative connection. It can be seen in **Table 6** that all fibroblast instances of artichoke leaf extract consistently linked negatively to the 3 photo-aging gene expression signatures. Artichoke leaf extract also consistently scored negatively with the intrinsic aging signatures when tested in fibroblasts, but the scores were weaker and there were some null or zero scores. Null scores are not considered inconsistent with other scores all showing the same directionality. When tested in keratinocytes, artichoke leaf extract showed generally weak positive connections to both the photo-aging and intrinsic aging gene expression signatures. Therefore, the testing in fibroblasts and keratinocytes gave inconsistent results. Similarly, carob seed extract fibroblast instances showed a pattern of negative connections to the photo-aging gene expression signatures and inconsistent results were obtained with keratiocyte instances with both sets of gene signatures.

Table 6.

C-MAP scores for two cosmetic supplier materials, Biobenefit™ and Glyco-repair™, tested in fibroblasts and keratinocytes.

GeneChip ID	Material ¹	Cell Line Utilized for Instance Data	Intrinsic Aging Clinical Signatures			Photo-aging Clinical Signatures		
			Intrinsic 200	Intrinsic 400	Intrinsic 600	Photo-aging 200	Photo-aging 400	Photo-aging 600
CMP_62_13	Artichoke Leaf Extract ²	BJ fibroblasts	-0.403	0	-0.333	-0.551	-0.553	-0.547
CMP_62_14			-0.211	-0.198	-0.235	-0.251	-0.298	-0.299
CMP_65_51			0	-0.222	0	-0.31	-0.264	-0.295
CMP_61_13		Telomerized-keratinocytes	0	0	0	0	0	0.19
CMP_61_14			0.401	0.346	0.316	0.293	0.268	0.284

CMP_68A_27			-0.251	0	0.137	0.209	0.156	0.149
CMP_62_23	Carob Seed Extract ³	BJ fibroblasts	0	0	0	-0.342	-0.288	-0.325
CMP_62_24			0	0	0	-0.41	-0.327	-0.325
CMP_65_55			0	0	0.151	0	0	0
CMP_61_23		Telomerized-keratinocytes	-0.321	-0.286	-0.248	-0.44	-0.438	-0.404
CMP_61_24			0.27	0.25	0.226	-0.374	-0.349	0
CMP_68A_31			0.287	0.263	0.268	0.347	0.348	0.346

¹ Test compositions were prepared using a concentration of 0.01% of one of artichoke leaf extract or carob seed extract.

² One example of Artichoke leaf extract is available from Ichimaru Pharcos, Japan under the tradename Biobenifity™

5 ³ One example of carob seed extract is available from Silab, France under the tradename Glyco-Repair™

In view of the discovery that there is a strong preferential linkage of the skin aging gene expression signatures to instances derived from fibroblasts, additional gene expression signatures optimized for the fibroblast linkage were also generated to screen the cosmetic materials. Only the photo-aging data from the aging skin genomics study in Example 2 were used because the fibroblast linkage to the photo-aging gene expression signature was stronger than that to intrinsic aging gene expression signature. The modified gene expression signatures were generated similarly to the photo-aging signatures in Example 3, except that the microarray probe sets were also filtered for genes selected from a microarray analysis of BJ fibroblast cells that had $\geq 10\%$ Present calls, wherein the microarray analysis of the BJ fibroblast cells was derived from data from 30 control and chemically-treated cultures. This filter was added so that the modified gene expression signature would only contain probes complementary to genes actually expressed in the fibroblasts. Additionally, the probes used in the modified gene expression signature were identified using the following filters.

- 20 (i) **“Signature 1”** Filtered on log t-test rank; best ranked 100 up-regulated and 100 down-regulated probe sets in the arm old to young comparison.
- (ii) **“Signature 2”** Filtered on log t-test rank; best ranked 150 up-regulated and 150 down-regulated probe sets in the arm old to young comparison.
- 25 (iii) **“Signature 3”** (identifiers set forth in **Table I**) Filtered on log t-test rank; best ranked 200 up-regulated and 200 down-regulated probe sets in the arm old to young comparison.

Table 7

Connectivity scores derived from a comparison of artichoke leaf extract and carob seed extract instances tested in fibroblast cells compared to the fibroblast-optimized photo-aging signatures.

GeneChip ID	Material ¹	Cell Line	Photo-aging signatures optimized for fibroblasts		
			Signature 1	Signature 2	Signature 3
CMP_62_13	Artichoke leaf extract	BJ fibroblasts	-0.721	-0.707	-0.684
CMP_62_14			-0.341	-0.366	-0.375
CMP_65_51			-0.417	-0.38	-0.365
CMP_62_23	Carob seed extract	BJ fibroblasts	-0.482	-0.43	-0.415
CMP_62_24			-0.48	-0.41	-0.416
CMP_65_55			0	0	0

¹ The C-map instances are the same as in Table 6. Only results with fibroblasts are shown.

5 The results set forth in **Table 7** are similar to those for the photo-aging signatures shown in **Table 6** except that the scores are stronger.

10 An overall weighting of the C-map scores was used to determine whether the materials tested were considered hits against the gene expression signatures. For each signature in a category (e.g. photo-aging or intrinsic aging), the hits were identified and given a weight using the criteria in **Table 8**. The desired directionality of the scores depends on whether the analysis is intended to identify materials that will ameliorate a condition like photo-aging (negative scores) or that are similar to a known benefit agent (positive scores). This heuristic approach was applied because of the limited number of replicates available for the materials in the C-map database.

Table 8

Weight	Criteria
3	At least 2 instances in the top 5% of all C-map instances ¹ based on C-map score, all instances with correct directionality or null. Non-null instances >50%.
2	At least 1 instance in the top 5% of all C-map instances based on C-map score, all instances with correct directionality or null. Non-null instances >50%.
2	At least 2 instances in the top 10% of all C-map instances based on C-map score, all instances with correct directionality or null. Non-null instances >50%.
1	1 instance in the top 5% of all C-map instances, all instances with correct directionality or null. Non-null instances ≥40% AND ≤50%..

15 ¹ There were more than 4000 chemical instances in the C-map database when these analyses were done.

The average weight was calculated for each set of signatures (e.g. the 3 photo-aging signatures described in Example 2 and derived from **Tables C** and **D**). Materials were considered a hit if their average weights across signatures were as described in **Table 9**.

Table 9

Weighting of hits	Average hit weigh
Strong hit	value = 3
Hit	$2 \leq \text{value} < 3$
Weak hit	$1 < \text{value} < 2$
Weak linkage	$0 < \text{value} \leq 1$

The results of the weighted analysis for artichoke leaf extract and carob seed extract are shown in **Table 10**. Based on the average hit weights artichoke leaf extract was considered an overall negative hit against the photo-aging signatures and a weak negative hit against the intrinsic aging signatures when tested in fibroblasts. Carob seed extract was a weak negative hit against the photo-aging signatures optimized for fibroblasts. Considering the strong preferential linkage of the photo-aging signatures to instances derived from fibroblasts (described above), the keratinocyte data were discounted and only the fibroblast data were used as part of the weight of evidence to determine whether artichoke leaf extract and carob seed extract should be advanced to *in vivo* testing.

Table 10.

Weighting of the C-map scores from Table 6 and Table 7 to determine hits.

Material	Cell Line	Average hit weights		
		Intrinsic Aging Signatures (I200, I 400, I600)	Photo-aging Signatures (P200, P400, P600)	Fibroblast Optimized Photo-aging Signatures (Signatures 1-3)
Artichoke leaf extract	BJ fibroblasts	1.33	2	2
	Telomerized-keratinocytes	0	0	0
Carob seed extract	BJ fibroblasts	0	0	1.33
	Telomerized-keratinocytes	0	0	0

Example 7

In vitro and *In vivo* Results for Artichoke Leaf Extract and Carob Seed Extract

C-map is a hypothesis-generating tool whose predictiveness for identifying agents that can improve aging skin should be validated through clinical testing. Artichoke leaf extract and carob seed extract were subjected to *in vitro* testing to establish a weight of evidence before

submitting them for clinical tests. Skin equivalent cultures were treated with the materials as described below and assayed for endpoints related to cosmetic benefits including: procollagen, hyaluronic acid, fibronectin, and inhibition of matrix metalloprotease 1 (MMP1) activity.

5 *In vitro* Testing Procedures:

Human skin equivalent cultures (EFT-400 Full-Thickness Skin Model, MatTek Corporation, Ashland MA) were equilibrated overnight at 37°C and 5% CO₂. Cultures were treated topically with 40 µl of test material for 24 hours. The test materials evaluated were aqueous solutions of 3.0% of a commercial preparation of hydrolyzed carob seed extract or 3.5%
10 of a commercial preparation of artichoke leaf extract. Control cultures were treated with water vehicle alone. After treatment with test material, the cultures were rinsed with PBS. A 5-mm punch biopsy sample was taken for procollagen and hyaluronic acid measurements and the remaining quantities of each culture were used for cell viability (MTT) analysis.

Cultures to be tested for cell viability were transferred to new six-well plates containing 2
15 ml of MTT solution (MTT kit, MatTek Corporation) in each well and incubated for 3 hours. Cultures were then removed from wells, blotted dry, and transferred to new six-well plates containing 3 ml of extraction solution in each well. One ml of extraction solution was added topically to each culture, and the plates were placed on a shaker for 2 hours at room temperature. An aliquot (200 µl) of extraction solution was removed from each culture well, transferred to a
20 96-well flat bottom plate, and read at A₅₇₀.

Culture samples for procollagen and hyaluronic acid analysis were incubated with 1 ml of mild protein extraction reagent (T-per, Pierce Protein Research Products, Thermo Fisher Scientific Inc., Rockford, IL), then homogenized with a mixer mill (Model MM 300, Qiagen Inc., Valencia, CA) for 6 minutes. Samples were then centrifuged at 10,000 rpm for 15 minutes at 4°C
25 and the soluble fractions collected. Supernatants were analyzed with a Micro BCA Protein Assay Kit (Pierce Protein Research Products, Thermo Fisher Scientific Inc., Rockford, IL) to quantify protein concentrations. For analysis of procollagen 1, supernatant samples were diluted 1:5 in assay buffer and analyzed with a commercially available ELISA kit (Takara Bio Inc., Shiga, Japan). For hyaluronic acid analysis, supernatant samples were diluted 1:300 in assay buffer and
30 analyzed with a commercially available ELISA kit (Corgenix, Broomfield CO). Procollagen and hyaluronic acid were normalized to protein levels for each culture, and expressed as a % of the vehicle control. Statistical comparisons to vehicle control were made using the Students *t*-test.

In vitro Testing Results:

In vitro Skin Biomarker Responses

Compound	Level (%)	Hyaluronic Acid (% control)	Procollagen (% control)	Other (% control)
Carob Seed Extract	3.0	139*	354*	-
Artichoke Leaf Extract	3.5	160*	270*	MMP-1: 64*

* indicates $p < 0.05$; nc = no change vs Control

These results indicate that human skin cultures treated with 3.0% of a commercial preparation of hydrolyzed carob seed extract significantly ($p < 0.05$) increased expression of procollagen (the precursor of dermal matrix collagens) and hyaluronic acid (a matrix component that binds water and hydrates the skin). Cultures treated with 3.5% of a commercial preparation of artichoke leaf extract produced significantly increased expression of procollagen and hyaluronic acid, and also significantly reduced MMP-1 expression (an enzyme increased in skin aging and inflammation that damages dermal matrix).

10 *In vivo* Testing Procedures

The study design was a 13-week, randomized, double-blinded, vehicle controlled, split-face study to evaluate fine lines and wrinkles in 40 to 65 year old women, Fitzpatrick skin type I to III, with moderate to moderately-severe photo-aged facial skin. The duration of the study included 1-week preconditioning with vehicle product, followed by 12 weeks of test product application to the facial skin twice each day. High density digital images of subject facial skin were captured with a Fuji S2 Pro digital SLR camera with a 60mm Nikon lens. Images were taken at baseline, 4, 8 and 12 weeks. Coded images were evaluated on a 0 to 8 grading scale by expert graders to determine the degree of change in eye area fine lines and wrinkles at 4, 8 or 12 weeks as compared to the matching baseline image for each subject.

The test products used by the panelists contained a commercial preparation of 3.0% hydrolyzed carob seed extract or 3.5% artichoke leaf extract, each prepared in an oil-in-water formulation. The control was the oil-in-water formulation alone.

In vivo Test Results:

Table 12.

25 Eye Area Fine Lines & Wrinkle Grades at 4, 8 and 12 Weeks of Test Product Use

		8 Weeks			12 Weeks		
Facial Product	Level (%)	FLW Grade	Statistical Grouping	p value vs Vehicle	FLW Grade	Statistical Grouping	p value vs Vehicle
Vehicle	-	0.137	a	-	0.230	a	-

Carob Seed extract	3.0%	0.741	bc	0.0302	0.799	bc	0.0213
Artichoke Leaf extract	3.5%	0.503	ab	0.1207	0.924	c	0.0059

These results indicate that test product containing 3.0% of a commercial preparation of carob seed extract produced a significant ($p < 0.05$) improvement in eye area fine lines and wrinkles as compared to the concurrent vehicle control product at 4, 8 and 12 weeks. Test product containing 3.5% of a commercial preparation of artichoke leaf extract produced a significant improvement in eye area fine lines and wrinkles as compared to the concurrent vehicle control product at 12 weeks. Overall, the *in vivo* test results demonstrate the predictiveness of the methods described here to identify skin anti-aging agents.

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The values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such value is intended to mean both the recited value and a functionally equivalent range surrounding that value.

The present invention should not be considered limited to the specific examples described herein, but rather should be understood to cover all aspects of the invention. Various modifications, equivalent processes, as well as numerous structures and devices to which the present invention may be applicable will be readily apparent to those of skill in the art. Those skilled in the art will understand that various changes may be made without departing from the scope of the invention, which is not to be considered limited to what is described in the specification. Some examples of the invention are described in the following clauses:

1. A method for constructing a data architecture for use in identifying connections between perturbagens and genes associated with one or more skin aging conditions, comprising:
 - (a) providing a gene expression profile for a control human dermal fibroblast cell;
 - (b) generating a gene expression profile for a human dermal fibroblast cell exposed to at least one perturbagen;
 - (c) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (a) and (b);

- (d) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes;
 - (e) storing the ordered list as a fibroblast instance on at least one computer readable medium; and
 - (f) constructing a data architecture of stored fibroblast instances by repeating (a) through (e), wherein the at least one perturbation of step (a) is different for each fibroblast instance.
2. A method according to clause 1, comprising using a programmable computer to perform one or more of steps (c), (d), (e) and (f).
 3. A method according to clause 1, wherein the ordered list comprises the ordered list of identifiers in association with a numerical ranking for the identifier corresponding to its rank in the ordered list.
 4. A method according to clause 1, wherein the step of generating is performed by extracting a biological sample from the treated cell and subjecting the biological sample to microarray analysis.
 5. A method according to clause 1, wherein the biological sample comprises mRNA.
 6. A method according to clause 1, wherein the microarray is a global microarray or a specific microarray, wherein the specific microarray comprises oligonucleotides which hybridize to genes corresponding to a gene expression signature for a cellular phenotype.
 7. A method according to clause 1, wherein the step of constructing the data architecture of stored instances by repeating steps (a) through (e) comprises repeating steps (a) through (e) for between about 50 and about 50,000 instances.
 8. A method according to clause 7, wherein the step of constructing a gene expression data bases of stored instances comprises repeating steps (a) through (e) for between about 1000 and about 20,000 instances.
 9. A method according to clause 1, wherein the at least one perturbation is a cosmetic agent.
 10. A method according to clause 1, wherein each of the different perturbations is a cosmetic agent.

11. A method according to clause 1, wherein the identifiers are selected from the group consisting of gene names, gene symbols, microarray probe set ID values, and combinations thereof.
12. A method according to clause 1, wherein the ordered list is arranged so that an identifier associated with a most up-regulated gene is positioned at the top of the ordered list and an identifier associated with a most down-regulated gene is positioned at the bottom of the ordered list.
13. A method according to clause 12, wherein the ordered list of each instance is arranged so that an identifier associated with each gene that is not differentially expressed is positioned between the identifier associated with the most up-regulated gene and the identifier associated with the most down-regulated gene.
14. A method according to clause 1, wherein each instance comprises between about 1,000 and about 50,000 identifiers.
15. A method according to clause 1, wherein each instance comprises metadata for the at least one perturbagen associated with the instance.
16. A method according to clause 1, further comprising:
 - (a) providing a gene expression profile for a control human keratinocyte cell;
 - (b) generating a gene expression profile for a human keratinocyte cell exposed to at least one perturbagen;
 - (c) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (g) and (h);
 - (d) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes identified in (i);
 - (e) storing the ordered list created in step (j) as a keratinocyte instance on the at least one computer readable medium; and
 - (f) constructing a data base of stored keratinocyte instances by repeating (g) through (k), wherein the at least one perturbagen of step (h) is different for each keratinocyte instance.
17. A method according to clause 16, wherein the at least one perturbagen of step (a) is the same as the at least one perturbagen of step (g).

18. A method according to clause 1, wherein the at least one perturbagen is a botanical.
19. A method according to clause 18, wherein the botanical is derived from one or more of a root, stem, bark, leaf, seed, or fruit of a plant.
20. A method according to clause 1, wherein the at least one perturbagen is selected from the group consisting of a vitamin compound, a sugar amine, a phytosterol, hexamidine, a hydroxy acid, a ceramide, an amino acid, and a polyol.
21. A method according to clause 20, wherein the vitamin compound is selected from the group consisting of a vitamin B3 compound, a vitamin B5 compound, a vitamin B6 compound, a vitamin B9 compound, a vitamin A compound, a vitamin C compound, a vitamin E compound, and derivatives and combinations thereof.
22. A method according to clause 20, wherein the vitamin compound is selected from the group consisting of retinol, retinyl esters, niacinamide, folic acid, panthenol, ascorbic acid, tocopherol, and tocopherol acetate.
23. A method for implementing the data architecture according to claim 1 to generate connections useful for identifying cosmetic agents effective for treating aged skin, the method comprising querying the data architecture with at least one skin aging gene expression signature, wherein querying comprises comparing the at least one skin aging gene expression signature to each stored fibroblast instance, wherein the skin aging gene expression signature represents genes differentially expressed in association with at least one skin aging condition.
24. A method according to clause 23, wherein the comparison of the at least one skin aging gene expression signature to each stored fibroblast instance is performed by a programmable computer.
25. A method according to clause 23, wherein the at least one skin aging condition is selected from intrinsic skin aging conditions; photo-aging skin conditions; and combinations thereof.
26. A method according to clause 23, wherein the at least one skin aging gene expression signature is constructed by a method comprising (i) identifying genes having up-regulated expression in the at least one skin aging condition when compared to a control; (ii) identifying genes having down-regulated expression in the at least one skin aging

condition when compared to a control; (iii) creating one or more gene expression signature lists associated with the at least one skin aging gene expression signature comprising identifiers corresponding to a plurality of the genes identified in (i) and (ii); and storing the one or more gene expression signature lists on the at least one computer readable medium.

27. A method according to clause 26, wherein the number of genes having up-regulated expression in the at least one skin aging condition is between about 10 and about 400, and the number of genes down-regulated in the at least one skin aging condition is between about 10 and about 400.
28. A method according to clause 27 wherein the identifiers for from between about 80% and about 100% of the up-regulated genes are set forth as in Table C and wherein identifiers for from between about 80% and about 100% of the down-regulated genes are set forth in Table D.
29. A method according to clause 23, wherein the identifiers representing the genes identified in (i) and (ii) are selected from the group consisting of gene names, gene symbols, and microarray probe set ID values.
30. A method according to clause 26, wherein the one or more gene expression signature lists comprises a first list representing a plurality of the up-regulated genes identified in (i) and a second list representing a plurality of down-regulated genes identified in (ii).
31. A method according to clause 26, wherein at least one skin sample is taken from a human subject exhibiting the at least one skin condition, a biological sample is extracted from the skin sample, and a gene expression profile of the at least one skin sample is generated prior to at least one of the steps (i) and (ii).
32. A method according to clause clause 31, wherein the at least one human subject is between the ages of about 18 and about 80.
33. A method according to clause 31, wherein the skin sample comprises cells from epidermal and dermal layers of the human subject.
34. A method according to clause 23, wherein the comparison further comprises assigning a connectivity score to each of plurality of instances.

35. A method according to clause 34, wherein a plurality of connectivity scores represents a positive correlation and a plurality of the connectivity scores represents a negative correlation.
36. A method according to clause 34, wherein the connectivity score has a value between +2 and -2.
37. A method for formulating a skin care composition by identifying connections between perturbagens and genes associated with one or more skin aging conditions, comprising:
 - (a) accessing a plurality of instances stored on at least one computer readable medium, wherein each instance is associated with a perturbagen and a skin cell type and wherein each instance comprises an ordered list comprising a plurality of identifiers representing a plurality of up-regulated and a plurality of down regulated genes;
 - (b) accessing at least one skin aging gene expression signature stored on the at least one computer readable medium, wherein the at least one skin aging gene expression signature comprises one or more lists comprising a plurality of identifiers representing a plurality of up-regulated genes and a plurality of down-regulated genes associated with a skin aging condition;
 - c) comparing the at least one skin aging gene expression signature to the plurality of the instances, wherein the comparison comprises comparing each identifier in the one or more gene expression signature lists with the position of the same identifier in the ordered lists for each of the plurality of instances;
 - (d) assigning a connectivity score to each of the plurality of instances; and
 - (e) formulating a skin care composition comprising a dermatologically acceptable carrier and at least one perturbagen, wherein the connectivity score of the instance associated with the at least one perturbagen has a negative correlation.
38. A method according to clause 37, further comprising applying the skin care composition to a plurality of human subjects having the skin aging condition.

39. A method according to clause 38, wherein the skin care composition improves the appearance of facial fine lines or wrinkles of one or more of the plurality of human subjects.
40. A method according to clause 37, wherein the identifiers are selected from the group consisting of gene names, gene symbols, and microarray probe set ID values.
41. A method according to clause 37, wherein each instance comprises between about 50 and about 400 identifiers.
42. A method according to clause 37, wherein the plurality of instances comprises between about 50 and about 50,000 instances.
43. A method according to clause 37, wherein the plurality of instances comprises between about 1000 and about 20,000 instances.
44. A method according to clause 37, wherein the at least one perturbagen is a cosmetic agent.
45. A method according to clause 37, wherein the at least one perturbagen is a botanical.
46. A method according to clause 45, wherein the botanical is derived from one or more of a root, stem, bark, leaf, seed, or fruit of a plant.
47. A method according to clause 37 wherein one or more of steps (a), (b), (c), and (d) are performed by a programmable computer.
48. A method according to clause 37, wherein the at least one skin aging gene expression signature comprises a plurality of skin aging gene expression signatures and each of the plurality of instances has a connectivity score assigned thereto for each of the plurality of skin aging gene expression signatures.
49. A method according to clause 48, wherein the connectivity score for each of the plurality of instances is a combination of the connectivity scores assigned to each instance for each of the plurality of skin aging gene expression signatures.
50. A method according to clause 49, wherein the plurality of skin aging gene expression signatures comprises a plurality of photo-aging gene expression signatures.

51. A method according to clause 49, wherein the plurality of skin aging gene expression signatures comprises a plurality of intrinsic aging gene expression signatures.
52. A method according to clause 49, wherein the plurality of skin aging gene expression signatures comprises a plurality of photo-aging gene expression signatures and a plurality of intrinsic aging gene expression signatures.
53. A method according to clause 52, wherein each of the plurality of the intrinsic aging gene expression signatures comprises one or more gene expression signature lists comprising a plurality of identifiers representing a plurality of up-regulated genes and a plurality of down-regulated genes, wherein an identifier for between about 80% and about 100% of the up-regulated genes are set forth in **Table A** and wherein an identifier for between about 80% and about 100% of the down-regulated genes are set forth in **Table B**.
54. A method according to clause 49, wherein each connectivity score assigned to the instance associated with the at least one perturbagen of the skin care composition has a negative correlation.
55. A method according to clause 37, wherein the plurality of instances are stored in a database on the at least one computer readable medium.
56. A method according to clause 55, wherein the plurality of instances comprises a plurality of instances associated with a first skin cell type and a plurality of instances associated with a second skin cell type.
57. A method according to clause 56, wherein the first skin cell type is a human dermal fibroblast and the second skin cell type is a human keratinocyte.
58. A method according to clause 55, wherein each of the plurality of instances further comprises metadata associated with the skin cell type and the perturbagen associated therewith.
59. A method according to clause 58, wherein the metadata comprises a name for the skin cell type and a name for the perturbagen.
60. A method according to clause 37, wherein the plurality of instances are stored in a first digital file and the at least one skin aging gene expression signature is stored in a second digital file.

61. A skin care composition formulated according to the method of clause 37.
62. A method for generating a gene expression signature for use in identifying connections between perturbagens and genes associated with one or more skin aging conditions, comprising:
 - (a) providing a gene expression profile for a reference sample of human skin cells;
 - (b) generating a gene expression profile for at least one sample of human skin cells from a subject exhibiting at least one skin aging condition,
 - (c) comparing the expression profiles of (a) and (b) to determine a gene expression signature comprising a set of genes differentially expressed in (a) and (b);
 - (d) assigning an identifier to each gene constituting the gene expression signature and ordering the identifiers according to the direction of differential expression to create one or more gene expression signature lists;
 - (e) storing the one or more gene expression signature lists on at least one computer readable medium.
63. The method according to clause 62, wherein the human skin cells derive from either an epidermal or dermal layer of skin and the human subject is between the age of about 18 to about 80 years.
64. A gene expression signature determined according to clause 62 having from about 50 to about 400 genes differentially up-regulated in the at least one skin aging condition and about 50 to about 400 differentially down-regulated in the at least one skin aging condition.
65. A method according to clause 62, wherein the identifiers are selected from the group consisting of gene names, gene symbols, and microarray probe set IDs.
66. A method according to clause 62, wherein the at least one sample of human skin cells comprises a plurality of samples and wherein one of the plurality of skin samples is taken from a sun exposed location and one of the plurality of skin samples is taken from sun protected location.

67. A method according to clause 66, wherein the sun exposed location is a on a forearm and the sun protected location is on a buttock.
68. A system for identifying connections between perturbagens and genes associated with one or more skin aging conditions, comprising:
- (a) at least one computer readable medium having stored thereon a plurality of instances, and at least one skin aging gene expression signature, wherein the instances and the gene expression signature are derived from a human dermal fibroblast cell, wherein each instance comprises an instance list of rank-ordered identifiers of differentially expressed genes, and wherein the at least one skin aging gene expression signature comprises one or more gene expression signature lists of identifiers representing differentially expressed genes associated with a skin aging condition;
 - (b) a programmable computer comprising computer-readable instructions that cause the programmable computer to execute one or more of the following:
 - (i) accessing the plurality of instances and the at least one skin aging gene expression signature stored on the computer readable medium;
 - (ii) comparing the at least one skin aging gene expression signature to the plurality of the instances, wherein the comparison comprises comparing each identifier in the gene expression signature list with the position of the same identifier in the instance list for each of the plurality of instances; and
 - (iii) assigning a connectivity score to each of the plurality of instances.
69. A system according to clause 68, further comprising a plurality of instances and at least one gene expression signature derived from a human keratinocyte cell.
70. A system according to clause 68, further comprising: a microarray scanner for receiving a sample comprising human dermal fibroblast cells and/or human keratinocyte cells; and a second programmable computer for transmitting gene expression data from the scanner to the first programmable computer.
71. A system according to clause 70, further comprising an array of perturbagens for application to the dermal fibroblast cells and the keratinocyte cells.

72. A system according to clause 68, wherein the plurality of instances comprises between about 50 and about 50,000 instances.
73. A system according to clause 68, wherein the plurality of instances comprises between about 1,000 and about 20,000 instances.
74. A gene expression signature for intrinsically aged skin consisting of genes selected from the genes set forth in **Tables A and B**.
75. An immobilized array of oligonucleotides which hybridize to the genes selected for the gene expression signature according to clause 74.
76. A gene expression signature according to clause 74 stored on a memory device accessible by a programmable computer.
77. A gene expression signature according to clause 74, comprising from 50-300 genes identified to be up-regulated in **Table A**.
78. A gene expression signature according to clause 74, comprising from 50-300 genes identified to be down-regulated in **Table B**.
79. A gene expression signature according to clause 74, comprising a set of genes identified to be up-regulated and a set of genes identified to be down-regulated.
80. A gene expression signature for photo-aged skin consisting of genes selected from the genes set forth in **Tables C and D**.
81. An immobilized array of oligonucleotides which hybridize to the genes selected for the gene expression signature according to clause 80.
82. A gene expression signature according to clause 80 stored on a memory device accessible by a programmable computer.
83. A gene expression signature according to clause 80, comprising from 50-300 genes identified to be up-regulated in **Table C**.
84. A gene expression signature according to clause 80, comprising from 50-300 genes identified to be down-regulated in **Table D**.

85. A gene expression signature according to clause 80, comprising a set of genes identified to be up-regulated and a set of genes identified to be down-regulated.
86. A computer readable medium, comprising:
- a data architecture comprising a digital file stored in a spreadsheet file format, a word processing file format, or a database file format suitable to be read by a respective spreadsheet, word processing, or database computer program, the first digital file comprising data arranged to provide one or more gene expression signature lists comprising a plurality of identifiers when read by the respective spreadsheet, word processing, or database computer program; and
- wherein each identifier is selected from the group consisting of a microarray probe set ID, a human gene name, a human gene symbol, and combinations thereof representing a gene set forth in any of **Tables A-D** wherein each of the one or more gene expression signature lists comprises between about 50 and about 600 identifiers.
87. The computer readable medium of clause 86, further comprising computer readable instructions for reading the digital file.

Probe Set ID	Gene Symbol	Gene Name	Table_A	Representative Public ID	p
value					
212134_at	PHLDB1	pleckstrin homology-like domain family B member 1			
AB014538		2.5989E-07			
203384_s_at	GOLGA1	golgi autoantigen golgin subfamily a 1		NM_002077	
8.8180E-07					
203812_at		null	AB011538	2.6720E-06	
218418_s_at	KANK2	KN motif and ankyrin repeat domains 2		NM_015493	
2.9847E-06					
210619_s_at	HYAL1	hyaluronoglucosaminidase 1	AF173154	4.4879E-06	
213891_s_at	TCF4	transcription factor 4	AI927067	7.1351E-06	
40665_at	FMO3	flavin containing monooxygenase 3	M83772	7.4313E-06	
218007_s_at	RPS27L	ribosomal protein S27-like	NM_015920	9.9049E-06	
218986_s_at	DDX60	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60		NM_017631	
1.3762E-05					
204112_s_at	HNMT	histamine N-methyltransferase	NM_006895	1.5543E-05	
202510_s_at	TNFAIP2	tumor necrosis factor alpha-induced protein 2		NM_006291	
1.5736E-05					
205236_x_at	SOD3	superoxide dismutase 3 extracellular		NM_003102	
2.1085E-05					
204940_at	PLN	phospholamban	NM_002667	2.4429E-05	
204742_s_at	PDS5B	PDS5 regulator of cohesion maintenance homolog B (S.			
cerevisiae)	NM_015032	3.5542E-05			
217721_at		null	BE551361	3.9171E-05	
61732_r_at	IFT74	intraflagellar transport 74 homolog (Chlamydomonas)			
AI610355		4.0031E-05			
220276_at	RERGL	RERG/RAS-like	NM_024730	4.0141E-05	
210147_at	ART3	ADP-ribosyltransferase 3	U47054	4.0793E-05	
203874_s_at	SMARCA1	SWI/SNF related matrix associated actin dependent regulator			
of chromatin subfamily a member 1		NM_003069	4.2533E-05		
218718_at	PDGFC	platelet derived growth factor C		NM_016205	
4.7811E-05					
216321_s_at	NR3C1	nuclear receptor subfamily 3 group C member 1			
(glucocorticoid receptor)		X03348	4.8089E-05		
203083_at	THBS2	thrombospondin 2	NM_003247	4.9034E-05	
212798_s_at	ANKMY2	ankyrin repeat and MYND domain containing 2		AK001389	
4.9281E-05					
213435_at	SATB2	SATB homeobox 2	AB028957	5.2665E-05	
212796_s_at	TBC1D2B	TBC1 domain family member 2B	BF195608	5.3819E-05	
218901_at	PLSCR4	phospholipid scramblase 4	NM_020353	5.3859E-05	
208792_s_at	CLU	clusterin	M25915	5.5727E-05	
204457_s_at	GAS1	growth arrest-specific 1	NM_002048	5.9563E-05	
203906_at	IQSEC1	IQ motif and Sec7 domain 1	AI652645	6.1904E-05	
204963_at	SSPN	sarcospan (Kras oncogene-associated gene)		AL136756	
6.1925E-05					
218854_at	DSE	dermatan sulfate epimerase	NM_013352	6.4684E-05	
200771_at	LAMC1	laminin gamma 1 (formerly LAMB2)		NM_002293	
6.7641E-05					
212195_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M			
receptor)	AL049265	6.9132E-05			
212914_at	CBX7	chromobox homolog 7	AV648364	7.2463E-05	
204719_at	ABCA8	ATP-binding cassette sub-family A (ABC1) member 8			
NM_007168		7.2719E-05			
213397_x_at	RNASE4	ribonuclease RNase A family 4	AI761728	7.3945E-05	
209613_s_at	ADH1B	alcohol dehydrogenase 1B (class I) beta polypeptide			
M21692		7.4466E-05			
205361_s_at	PFDN4	prefoldin subunit 4	AI718295	7.5317E-05	
212713_at	MFAP4	microfibrillar-associated protein 4	R72286	7.6567E-05	
218285_s_at	BDH2	3-hydroxybutyrate dehydrogenase type 2	NM_020139		
7.8227E-05					
65472_at	c2orf68	chromosome 2 open reading frame 68		AI161338	
8.0285E-05					
221747_at	TNS1	tensin 1	AL046979	8.1012E-05	

Table_A

204944_at 8.5062E-05	PTPRG	protein tyrosine phosphatase receptor type G	NM_002841
205803_s_at member 1	TRPC1 NM_003304	transient receptor potential cation channel subfamily C	9.1121E-05
202664_at 9.5200E-05	WIPF1	WAS/WASL interacting protein family member 1	AW058622
212386_at 202598_at 9.9951E-05	TCF4 S100A13	transcription factor 4 S100 calcium binding protein A13	BF592782 9.6608E-05 NM_005979
209375_at 1.0203E-04	XPC	xeroderma pigmentosum complementation group C	D21089
221611_s_at 203638_s_at 1.1006E-04	PHF7 FGFR2	PHD finger protein 7 fibroblast growth factor receptor 2	AY014283 1.0523E-04 NM_022969
209990_s_at 1.1153E-04	GABBR2	gamma-aminobutyric acid (GABA) B receptor 2	AF056085
204446_s_at 212530_at 1.2283E-04	ALOX5 NEK7	arachidonate 5-lipoxygenase NIMA (never in mitosis gene a)-related kinase 7	NM_000698 1.1577E-04 AL080111
211675_s_at 1.3221E-04	MDFIC	MyoD family inhibitor domain containing	AF054589
222103_at 1.3421E-04	ATF1	activating transcription factor 1	AI434345
209763_at 216840_s_at 210664_s_at coagulation inhibitor)	CHRD1 LAMA2 TFPI	chordin-like 1 laminin alpha 2 tissue factor pathway inhibitor (lipoprotein-associated	AL049176 1.3715E-04 AK026829 1.3816E-04 AF021834 1.3910E-04
222043_at 208747_s_at 210129_s_at 1.6579E-04	CLU C1S TTL3	clusterin complement component 1 s subcomponent tubulin tyrosine ligase-like family member 3	AI982754 1.5732E-04 M18767 1.6336E-04 AF078842
204136_at 218168_s_at NM_020247	COL7A1 CABC1	collagen type VII alpha 1 chaperone ABC1 activity of bc1 complex homolog (S. pombe)	NM_000094 1.6678E-04 1.6820E-04
212690_at 203799_at 209086_x_at 206227_at	DDHD2 CD302 MCAM CILP	DDHD domain containing 2 CD302 molecule melanoma cell adhesion molecule cartilage intermediate layer protein nucleotide	AB018268 1.6898E-04 NM_014880 1.7414E-04 BE964361 1.7613E-04 NM_003613 1.7709E-04
pyrophosphohydrolyase 205498_at 204939_s_at 209737_at containing 2 207606_s_at 1.9567E-04	GHR PLN MAGI2 AB014605 ARHGAP12	growth hormone receptor phospholamban membrane associated guanylate kinase ww and PDZ domain Rho GTPase activating protein 12	NM_000163 1.8023E-04 NM_002667 1.8529E-04 1.9535E-04 NM_018287
206502_s_at 201811_x_at 2.0465E-04	INSM1 SH3BP5	insulinoma-associated 1 SH3-domain binding protein 5 (BTK-associated)	NM_002196 2.0132E-04 NM_004844
221530_s_at 2.0872E-04	BHLHE41	basic helix-loop-helix family member e41	BE857425
203177_x_at 2.1048E-04	TFAM	transcription factor A mitochondrial	NM_003201
202142_at (Arabidopsis)	COPS8 BC003090	COP9 constitutive photomorphogenic homolog subunit 8	2.1440E-04
221950_at 205116_at 218456_at 211340_s_at 213247_at containing 1 209210_s_at 201313_at 203884_s_at	EMX2 LAMA2 CAPRIN2 MCAM SVEP1 AA716107 FERMT2 ENO2 RAB11FIP2	empty spiracles homeobox 2 laminin alpha 2 caprin family member 2 melanoma cell adhesion molecule sushi von willebrand factor type A EGF and pentraxin domain fermitin family homolog 2 (Drosophila) enolase 2 (gamma neuronal) RAB11 family interacting protein 2 (class I)	AI478455 2.1866E-04 NM_000426 2.2469E-04 NM_023925 2.2868E-04 M28882 2.3165E-04 2.3856E-04 Z24725 2.4012E-04 NM_001975 2.4732E-04

Table_A

NM_014904	2.6635E-04		
204853_at	ORC2L	origin recognition complex subunit 2-like (yeast)	
NM_006190	2.6654E-04		
221230_s_at	ARID4B	AT rich interactive domain 4B (RBP1-like)	NM_016374
2.6997E-04			
212970_at	APBB2	amyloid beta (A4) precursor protein-binding family B member	
2	AI694303	3.0394E-04	
203446_s_at	OCRL	oculocerebrorenal syndrome of Lowe	NM_000276
3.0709E-04			
203217_s_at	ST3GAL5	ST3 beta-galactoside alpha-23-sialyltransferase 5	
NM_003896	3.1215E-04		
221748_s_at	TNS1	tensin 1	AL046979 3.1441E-04
218087_s_at	SORBS1	sorbin and SH3 domain containing 1	NM_015385
3.1579E-04			
203689_s_at	FMR1	fragile X mental retardation 1	AI743037 3.1785E-04
221218_s_at	TPK1	thiamin pyrophosphokinase 1	NM_022445 3.2805E-04
208669_s_at	EID1	EP300 interacting inhibitor of differentiation 1	
AF109873	3.6197E-04		
212736_at	C16orf45	chromosome 16 open reading frame 45	BE299456
3.6201E-04			
218204_s_at	FYCO1	FYVE and coiled-coil domain containing 1	NM_024513
3.8403E-04			
213373_s_at	CASP8	caspase 8 apoptosis-related cysteine peptidase	BF439983
3.8971E-04			
218625_at	NRN1	neuritin 1	NM_016588 4.0450E-04
210788_s_at	DHRS7	dehydrogenase/reductase (SDR family) member 7	AF126782
4.1440E-04			
205612_at	MMRN1	multimerin 1	NM_007351 4.1487E-04
209335_at	DCN	decorin	AI281593 4.1933E-04
213519_s_at	LAMA2	laminin alpha 2	AI078169 4.2572E-04
217504_at	ABCA6	ATP-binding cassette sub-family A (ABC1) member 6	
AA099357	4.3088E-04		
203983_at	TSNAX	translin-associated factor X	NM_005999 4.3798E-04
202979_s_at	CREBZF	CREB/ATF bZIP transcription factor	NM_021212
4.3846E-04			
207317_s_at	CASQ2	calsequestrin 2 (cardiac muscle)	NM_001232
4.4266E-04			
213480_at	VAMP4	vesicle-associated membrane protein 4	AF052100
4.4528E-04			
203661_s_at	TMOD1	tropomodulin 1	BC002660 4.4930E-04
212764_at	ZEB1	zinc finger E-box binding homeobox 1	AI806174
4.5363E-04			
209332_s_at	MAX	MYC associated factor X	BC003525 4.6003E-04
209732_at	CLEC2B	C-type lectin domain family 2 member B	BC005254
4.7151E-04			
201648_at	JAK1	Janus kinase 1 (a protein tyrosine kinase)	AL039831
4.7270E-04			
214151_s_at	CCPG1	cell cycle progression 1	AU144243 4.8468E-04
221958_s_at	GPR177	G protein-coupled receptor 177	AA775681 4.9941E-04
212805_at	PRUNE2	prune homolog 2 (Drosophila)	AB002365 5.0295E-04
213415_at	CLIC2	chloride intracellular channel 2	AI768628
5.1005E-04			
213262_at	SACS	spastic ataxia of Charlevoix-Saguenay (sacsin)	AI932370
5.1009E-04			
39582_at	CYLD	cylindromatosis (turban tumor syndrome)	AL050166
5.1801E-04			
209265_s_at	METTL3	methyltransferase like 3	BC001650 5.2345E-04
201581_at	TMX4	thioredoxin domain containing 13	BF572868
5.3682E-04			
213429_at	BICC1	bicaudal C homolog 1 (Drosophila)	AW025579
5.4069E-04			
203662_s_at	TMOD1	tropomodulin 1	NM_003275 5.4629E-04
206496_at	FMO3	flavin containing monooxygenase 3	NM_006894

Table_A

5.4990E-04				
40446_at	PHF1	PHD finger protein 1	AL021366	5.5428E-04
209467_s_at	MKNK1	MAP kinase interacting serine/threonine kinase 1		
BC002755		5.5795E-04		
219949_at	LRRC2	leucine rich repeat containing 2		NM_024512
5.6098E-04				
218957_s_at	PAAF1	proteasomal ATPase-associated factor 1		NM_025155
5.6482E-04				
201237_at	CAPZA2	capping protein (actin filament) muscle Z-line alpha 2		
AV685920		5.9285E-04		
209568_s_at	RGL1	ral guanine nucleotide dissociation stimulator-like 1		
AF186779		5.9347E-04		
212163_at	KIDINS220	kinase D-interacting substrate 220kDa		AB033076
5.9605E-04				
221757_at	PIK3IP1	phosphoinositide-3-kinase interacting protein 1		BE042976
6.0094E-04				
204779_s_at	HOXB7	homeobox B7	NM_004502	6.0694E-04
221139_s_at	CSAD	cysteine sulfinic acid decarboxylase		NM_015989
6.1189E-04				
218946_at	NFU1	NFU1 iron-sulfur cluster scaffold homolog (S. cerevisiae)		
NM_015700		6.2140E-04		
201753_s_at	ADD3	adducin 3 (gamma)	NM_019903	6.2561E-04
219895_at	FAM70A	family with sequence similarity 70 member A		NM_017938
6.2596E-04				
202074_s_at	OPTN	optineurin	NM_021980	6.2626E-04
221556_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)		
BF792631		6.3179E-04		
213194_at	ROBO1	roundabout axon guidance receptor homolog 1 (Drosophila)		
BF059159		6.3295E-04		
205986_at	AATK	apoptosis-associated tyrosine kinase		NM_004920
6.4921E-04				
212558_at	SPRY1	sprouty homolog 1 antagonist of FGF signaling (Drosophila)		
BF508662		6.5829E-04		
209787_s_at	HMGN4	high mobility group nucleosomal binding domain 4		
BC001282		6.6274E-04		
205083_at	AOX1	aldehyde oxidase 1	NM_001159	6.6633E-04
203427_at	ASF1A	ASF1 anti-silencing function 1 homolog A (S. cerevisiae)		
NM_014034		6.6918E-04		
209822_s_at	VLDLR	very low density lipoprotein receptor	L22431	6.7088E-04
217967_s_at	FAM129A	family with sequence similarity 129 member A		AF288391
6.7923E-04				
203131_at	PDGFRA	platelet-derived growth factor receptor alpha polypeptide		
NM_006206		6.9010E-04		
210150_s_at	LAMA5	laminin alpha 5	BC003355	6.9685E-04
212675_s_at	CEP68	centrosomal protein 68kDa	AB011154	6.9915E-04
219700_at	PLXDC1	plexin domain containing 1	NM_020405	7.0728E-04
47608_at	TJAP1	tight junction associated protein 1 (peripheral)		
AI697401		7.1269E-04		
218288_s_at	CCDC90B	coiled-coil domain containing 90B		NM_021825
7.1308E-04				
209285_s_at	C3orf63	chromosome 3 open reading frame 63	N38985	7.1497E-04
215245_x_at	FMR1	fragile X mental retardation 1	AA830884	7.1688E-04
212913_at	C6orf26	chromosome 6 open reading frame 26		BE674960
7.3457E-04				
214086_s_at	PARP2	poly (ADP-ribose) polymerase 2	AK001980	7.4675E-04
218656_s_at	LHFP	lipoma HMGIC fusion partner	NM_005780	7.5779E-04
213800_at	CFH	complement factor H	X04697	7.6114E-04
212126_at	CBX5	chromobox homolog 5 (HP1 alpha homolog Drosophila)		
BG391282		7.6440E-04		
206958_s_at	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)		
AF318575		7.6790E-04		
219848_s_at	ZNF432	zinc finger protein 432	NM_014650	7.6977E-04
212653_s_at	EHBP1	EH domain binding protein 1	AB020710	7.7156E-04

Table_A

216044_x_at 7.7784E-04	FAM69A	family with sequence similarity 69 member A		AK027146
219161_s_at 210102_at 7.9257E-04	CKLF VWA5A	chemokine-like factor von willebrand factor A domain containing 5A	NM_016951 7.8299E-04	BC001234
210155_at response 202409_at 8.0081E-04	MYOC D88214 IGF2	myocilin trabecular meshwork inducible glucocorticoid 7.9752E-04 insulin-like growth factor 2 (somatomedin A)		x07868
218501_at 8.2089E-04	ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3		NM_019555
212535_at 214453_s_at 212368_at 205011_at 8.5033E-04	MEF2A IFI44 ZNF292 VWA5A	myocyte enhancer factor 2A interferon-induced protein 44 zinc finger protein 292 von willebrand factor A domain containing 5A	AA142929 NM_006417 8.4711E-04	8.2429E-04 8.4432E-04
214684_at 208683_at 205547_s_at 218303_x_at 201384_s_at 8.8284E-04	MEF2A CAPN2 TAGLN KRCC1 LOC100133166	myocyte enhancer factor 2A calpain 2 (m/II) large subunit transgelin lysine-rich coiled-coil 1 similar to neighbor of BRCA1 gene 1	X63381 M23254 NM_003186 NM_016618	8.5065E-04 8.5570E-04 8.6781E-04 8.7453E-04 NM_005899
212589_at 8.8349E-04	RRAS2	related RAS viral (r-ras) oncogene homolog 2		AI753792
201034_at 205158_at 204793_at NM_014710 202928_s_at 203717_at 206157_at NM_002852 219355_at 9.2632E-04	ADD3 RNASE4 GPRASP1 PHF1 DPP4 PTX3 CXorf57	adducin 3 (gamma) ribonuclease RNase A family 4 G protein-coupled receptor associated sorting protein 1 PHD finger protein 1 dipeptidyl-peptidase 4 pentraxin-related gene rapidly induced by IL-1 beta chromosome X open reading frame 57	BE545756 NM_002937 8.9876E-04 NM_024165 NM_001935 9.1050E-04 NM_018015	8.8904E-04 8.9603E-04
204070_at NM_004585 204428_s_at 9.4980E-04 204897_at 9.5926E-04	RARRES3 LCAT	retinoic acid receptor responder (tazarotene induced) 3 lecithin-cholesterol acyltransferase		9.2641E-04 NM_000229
209612_s_at M24317 9.7983E-04	PTGER4 ADH1B	prostaglandin E receptor 4 (subtype EP4) alcohol dehydrogenase 1B (class I) beta polypeptide		AA897516
222001_x_at 218486_at 217816_s_at NM_020357 209780_at 1.0108E-03	LOC728855 KLF11 PCNP PHTF2	hypothetical LOC728855 Kruppel-like factor 11 PEST proteolytic signal containing nuclear protein putative homeodomain transcription factor 2	AI160126 AA149594 9.9522E-04	9.8111E-04 9.8974E-04
214683_s_at 216620_s_at AF009205 213158_at 210273_at 212793_at BF513244 205545_x_at 1.0523E-03	CLK1 ARHGEF10 null PCDH7 DAAM2 DNAJC8	CDC-like kinase 1 Rho guanine nucleotide exchange factor (GEF) 10 AA045174 protocadherin 7 dishevelled associated activator of morphogenesis 2 DnaJ (Hsp40) homolog subfamily C member 8	AI251890 1.0113E-03 1.0352E-03 AB006757 1.0391E-03 1.0515E-03	1.0113E-03 1.0523E-03
204310_s_at (atri)natriuretic 216250_s_at 202748_at NM_004120 208248_x_at	NPR2 LPXN GBP2 APLP2	natriuretic peptide receptor B/guanylate cyclase B leupaxin guanylate binding protein 2 interferon-inducible amyloid beta (A4) precursor-like protein 2	NM_003995 X77598 1.0558E-03	1.0523E-03 1.0523E-03 NM_001642

Table_A

1.0602E-03					
216973_s_at	HOXB7	homeobox B7	S49765	1.0759E-03	
221044_s_at	TRIM6	tripartite motif-containing 34	NM_021616		1.0950E-03
217853_at	TNS3	tensin 3	NM_022748	1.0951E-03	
209009_at	ESD	esterase D/formylglutathione hydrolase	BC001169		
1.0953E-03					
220127_s_at	FBXL12	F-box and leucine-rich repeat protein 12			NM_017703
1.0997E-03					
218196_at	OSTM1	osteopetrosis associated transmembrane protein 1			
NM_014028					
200986_at	SERPING1	serpin peptidase inhibitor clade G (C1 inhibitor)			
member 1	NM_000062		1.1056E-03		
214044_at	RYR2	ryanodine receptor 2 (cardiac)	BE968750		1.1145E-03
205549_at	PCP4	Purkinje cell protein 4	NM_006198	1.1168E-03	
212761_at	TCF7L2	transcription factor 7-like 2 (T-cell specific HMG-box)			
AI949687					
204994_at	MX2	myxovirus (influenza virus) resistance 2 (mouse)			
NM_002463					
218919_at	ZFAND1	zinc finger AN1-type domain 1	NM_024699		1.1391E-03
204438_at	MRC1L1	mannose receptor C type 1	NM_002438		1.1392E-03
218146_at	GLT8D1	glycosyltransferase 8 domain containing 1			NM_018446
1.1414E-03					
222229_x_at	RPL26P37	60S ribosomal protein L26 pseudogene			AL121871
1.1749E-03					
212509_s_at	MXRA7	matrix-remodelling associated 7	BF968134		1.1781E-03
204938_s_at	PLN	phospholamban	M60411	1.1841E-03	
216241_s_at	TCEA1	transcription elongation factor A (SII)	1		x57198
1.1997E-03					
214703_s_at	MAN2B2	mannosidase alpha class 2B member 2			AW954107
1.2028E-03					
203336_s_at	ITGB1BP1	integrin beta 1 binding protein 1			AL548363
1.2099E-03					
65718_at	GPR124	G protein-coupled receptor 124	AI655903		1.2271E-03
211679_x_at	GABBR2	gamma-aminobutyric acid (GABA) B receptor 2			AF095784
1.2692E-03					
202552_s_at	CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin-like)			
NM_016441					
202853_s_at	RYK	RYK receptor-like tyrosine kinase			NM_002958
1.3008E-03					
213703_at	LOC150759	hypothetical protein LOC150759	W95043	1.3148E-03	
206167_s_at	ARHGAP6	Rho GTPase activating protein 6	NM_001174		1.3166E-03
213294_at	EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2			
AV755522					
212343_at	YIPF6	Yip1 domain family member 6	AL117461		1.3337E-03
212586_at	CAST	calpastatin	AA195244	1.3533E-03	
212077_at	CALD1	caldesmon 1	AL583520	1.3697E-03	
213309_at	PLCL2	phospholipase C-like 2	AL117515	1.3761E-03	
203774_at	MTR	5-methyltetrahydrofolate-homocysteine methyltransferase			
NM_000254					
209621_s_at	PDLIM3	PDZ and LIM domain 3	AF002280	1.4120E-03	
203249_at	EZH1	enhancer of zeste homolog 1 (Drosophila)			AB002386
1.4127E-03					
201784_s_at	C11orf58	chromosome 11 open reading frame 58			NM_014267
1.4222E-03					
203156_at	AKAP11	A kinase (PRKA) anchor protein 11			NM_016248
1.4238E-03					
213165_at	CEP350	centrosomal protein 350kDa	AI041204		1.4348E-03
212984_at	ATF2	activating transcription factor 2	BE786164		
1.4415E-03					
202907_s_at	NBN	nibrin	NM_002485	1.4488E-03	
205260_s_at	ACYP1	acylphosphatase 1 erythrocyte (common) type			NM_001107
1.4518E-03					
206332_s_at	IFI16	interferon gamma-inducible protein 16			NM_005531

Table_A

1.4578E-03	LOC727893	similar to phosphodiesterase 4D interacting protein	
212390_at	AB007923	1.4580E-03	
(myomegalin)			
212455_at	YTHDC1	YTH domain containing 1	N36997 1.4597E-03
209337_at	PSIP1	PC4 and SFRS1 interacting protein 1	AF063020
1.4630E-03			
213375_s_at	N4BP2L1	NEDD4 binding protein 2-like 1	N80918 1.4697E-03
34031_i_at	KRIT1	KRIT1 ankyrin repeat containing	U90269 1.4716E-03
210538_s_at	BIRC3	baculoviral IAP repeat-containing 3	U37546 1.4849E-03
216949_s_at	PKD1	polycystic kidney disease 1 (autosomal dominant)	
L39891			1.4913E-03
219778_at	ZFPM2	zinc finger protein multitype 2	NM_012082 1.4980E-03
203505_at	ABCA1	ATP-binding cassette sub-family A (ABC1) member 1	
AF285167			1.4984E-03
202328_s_at	PKD1	polycystic kidney disease 1 (autosomal dominant)	
NM_000296			1.5072E-03
219820_at	SLC6A16	solute carrier family 6 member 16	NM_014037
1.5190E-03			
207558_s_at	PITX2	paired-like homeodomain 2	NM_000325 1.5248E-03
209236_at	SLC23A2	solute carrier family 23 (nucleobase transporters) member 2	
AL389886			1.5384E-03
201038_s_at	ANP32A	Cerebellar leucine rich acidic nuclear protein (LANP)	
T67821			1.5626E-03
205407_at	RECK	reversion-inducing-cysteine-rich protein with kazal motifs	
NM_021111			1.5697E-03
203281_s_at	UBA7	ubiquitin-like modifier activating enzyme 7	NM_003335
1.5792E-03			
206201_s_at	MEOX2	mesenchyme homeobox 2	NM_005924 1.5832E-03
209815_at	PTCH1	patched homolog 1 (Drosophila)	BG054916 1.5922E-03
213295_at	CYLD	cylindromatosis (turban tumor syndrome)	AA555096
1.6088E-03			
211742_s_at	EVI2B	ecotropic viral integration site 2B	BC005926
1.6282E-03			
203035_s_at	PIAS3	protein inhibitor of activated STAT 3	NM_006099
1.6319E-03			
212233_at	MAP1B	microtubule-associated protein 1B	AL523076
1.6369E-03			
211743_s_at	PRG2	proteoglycan 2 bone marrow (natural killer cell activator	
eosinophil granule		major basic protein)	BC005929 1.6770E-03
213388_at	PDE4DIP	phosphodiesterase 4D interacting protein	H15535
1.6837E-03			
206159_at	GDF10	growth differentiation factor 10	NM_004962
1.6866E-03			
219654_at	PTPLA	protein tyrosine phosphatase-like (proline instead of	
catalytic arginine)		member A	NM_014241 1.6959E-03
210312_s_at	IFT20	intraflagellar transport 20 homolog (Chlamydomonas)	
BC002640			1.7097E-03
210794_s_at	MEG3	maternally expressed 3 (non-protein coding)	AF119863
1.7106E-03			
202136_at	ZMYND11	zinc finger MYND domain containing 11	BE250417
1.7169E-03			
201395_at	RBM5	RNA binding motif protein 5	NM_005778 1.7384E-03
203881_s_at	DMD	dystrophin	NM_004010 1.7474E-03
208861_s_at	ATRX	alpha thalassemia/mental retardation syndrome x-linked	
(RAD54 homolog s. cerevisiae)			U72937 1.7816E-03
202104_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal	
recessive)			NM_003119 1.7951E-03
209656_s_at	TMEM47	transmembrane protein 47	AL136550 1.7975E-03
210644_s_at	LAIR1	leukocyte-associated immunoglobulin-like receptor 1	
AF109683			1.8453E-03
213849_s_at	PPP2R2B	protein phosphatase 2 (formerly 2A) regulatory subunit B	
beta isoform			AA974416 1.8555E-03
212547_at	BRD3	bromodomain containing 3	N34842 1.8672E-03

Table_A

213880_at	LGR5	leucine-rich repeat-containing G protein-coupled receptor 5		
AL524520		1.8699E-03		
212698_s_at	SEPT10	septin 10	BF966021	1.8766E-03
204215_at	C7orf23	chromosome 7 open reading frame 23		NM_024315
1.8796E-03				
204277_s_at	TK2	thymidine kinase 2 mitochondrial		BE895437
1.8964E-03				
217954_s_at	PHF3	PHD finger protein 3	NM_015153	1.9020E-03
207845_s_at	ANAPC10	anaphase promoting complex subunit 10		NM_014885
1.9148E-03				
213071_at	DPT	dermatopontin	AL049798	1.9353E-03
210829_s_at	SSBP2	single-stranded DNA binding protein 2		AF077048
1.9382E-03				
217989_at	HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11		
NM_016245		1.9516E-03		
219862_s_at	NARF	nuclear prelamin A recognition factor		NM_012336
1.9592E-03				
212726_at	PHF2	PHD finger protein 2	AB014562	1.9691E-03
205933_at	SETBP1	SET binding protein 1	NM_015559	1.9781E-03
204894_s_at	AOC3	amine oxidase copper containing 3 (vascular adhesion protein 1)		
1) NM_003734		1.9794E-03		
209894_at	LEPR	leptin receptor	U50748	1.9798E-03
202363_at	SPOCK1	sparc/osteonectin cwcx and kazal-like domains proteoglycan		
(testican) 1	AF231124	1.9920E-03		
202265_at	BMI1	BMI1 polycomb ring finger oncogene		NM_005180
1.9971E-03				
214494_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal recessive)		
recessive)	NM_005200	2.0054E-03		
218518_at	FAM13B	family with sequence similarity 13 member B1		NM_016603
2.0060E-03				
210105_s_at	FYN	FYN oncogene related to SRC FGR YES	M14333	2.0099E-03

Probe Set ID value	Gene Symbol	Gene Name	Table_B Representative Public ID	p
213330_s_at	STIP1	stress-induced-phosphoprotein 1	BE886580	1.9219E-07
213887_s_at	POLR2E	polymerase (RNA) II (DNA directed) polypeptide E 25kDa		
AI554759			5.9774E-07	
201631_s_at	IER3	immediate early response 3	NM_003897	8.6381E-07
221610_s_at	STAP2	signal transducing adaptor family member 2		BC000795
3.7342E-06				
205847_at	PRSS22	protease serine 22	NM_022119	4.7883E-06
208928_at	POR	P450 (cytochrome) oxidoreductase	AF258341	
5.1845E-06				
201530_x_at	EIF4A1	eukaryotic translation initiation factor 4A isoform 1		
NM_001416			1.0859E-05	
217835_x_at	C20orf24	chromosome 20 open reading frame 24		NM_018840
1.0871E-05				
222231_s_at	LRRC59	leucine rich repeat containing 59	AK025328	
1.1501E-05				
201118_at	PGD	phosphogluconate dehydrogenase	NM_002631	1.1705E-05
206426_at	MLANA	melan-A	NM_005511	1.4820E-05
210719_s_at	HMG20B	high-mobility group 20B	BC002552	1.5452E-05
208909_at	UQCRCF1	ubiquinol-cytochrome c reductase Rieske iron-sulfur		
polypeptide 1	BC000649		1.8592E-05	
208336_s_at	GPSN2	glycoprotein synaptic 2	NM_004868	2.3068E-05
201195_s_at	SLC7A5	solute carrier family 7 (cationic amino acid transporter y+		
system) member 5	AB018009		2.3348E-05	
211787_s_at	EIF4A1	eukaryotic translation initiation factor 4A isoform 1		
BC006210			2.8418E-05	
202435_s_at	CYP1B1	cytochrome P450 family 1 subfamily B polypeptide 1		
AU154504			2.9878E-05	
204039_at	CEBPA	CCAAT/enhancer binding protein (C/EBP) alpha		NM_004364
3.0309E-05				
212070_at	GPR56	G protein-coupled receptor 56	AL554008	3.6504E-05
209126_x_at	KRT6B	keratin 6B	L42612	3.7302E-05
220174_at	LRRC8E	leucine rich repeat containing 8 family member E		
NM_025061			4.2418E-05	
219402_s_at	DERL1	Der1-like domain family member 1		NM_024295
5.1192E-05				
212858_at	PAQR4	progesterin and adipoQ receptor family member IV	AL520675	
5.2306E-05				
203702_s_at	TTLL4	tubulin tyrosine ligase-like family member 4	AL043927	
5.8383E-05				
217854_s_at	POLR2E	polymerase (RNA) II (DNA directed) polypeptide E 25kDa		
NM_002695			5.8400E-05	
201287_s_at	SDC1	syndecan 1	NM_002997	5.8419E-05
212041_at	ATP6V0D1	ATPase H+ transporting lysosomal 38kDa v0 subunit d1		
AL566172			6.4338E-05	
212531_at	LCN2	lipocalin 2	NM_005564	6.5499E-05
220013_at	ABHD9	abhydrolase domain containing 9	NM_024794	6.8876E-05
209792_s_at	KLK10	kallikrein-related peptidase 10	BC002710	6.9165E-05
212085_at	SLC25A6	solute carrier family 25 (mitochondrial carrier; adenine		
nucleotide translocator) member 6	AA916851		7.4951E-05	
213680_at	KRT6B	keratin 6B	AI831452	7.5036E-05
210020_x_at	CALML3	calmodulin-like 3	M58026	7.9243E-05
208002_s_at	ACOT7	acyl-CoA thioesterase 7	NM_007274	8.1836E-05
216607_s_at	CYP51A1	cytochrome P450 family 51 subfamily A polypeptide 1		
U40053			8.3548E-05	
202005_at	ST14	suppression of tumorigenicity 14 (colon carcinoma)		
NM_021978			8.4956E-05	
216512_s_at	DCT	dopachrome tautomerase (dopachrome delta-isomerase		
tyrosine-related protein 2)	AL139318		9.5957E-05	
204331_s_at	MRPS12	mitochondrial ribosomal protein S12		NM_021107
1.0048E-04				
213571_s_at	EIF4E2	eukaryotic translation initiation factor 4E family member 2		

Table_B

BF516289	1.0230E-04			
212075_s_at	CSNK2A1	casein kinase 2 alpha 1 polypeptide	AI161318	
1.1634E-04				
212501_at	CEBPB	CCAAT/enhancer binding protein (C/EBP) beta	AL564683	
1.1968E-04				
203663_s_at	COX5A	cytochrome c oxidase subunit Va	NM_004255	1.2510E-04
36994_at	ATP6V0C	ATPase H+ transporting lysosomal 16kDa V0 subunit c		
M62762	1.2780E-04			
201976_s_at	MYO10	myosin X	NM_012334	1.3176E-04
209502_s_at	BAIAP2	BAI1-associated protein 2	BC002495	1.4026E-04
200658_s_at	PHB	prohibitin	AL560017	1.4366E-04
206630_at	TYR	tyrosinase (oculocutaneous albinism IA)	NM_000372	
1.4525E-04				
200895_s_at	FKBP4	FK506 binding protein 4 59kDa	NM_002014	1.4549E-04
204532_x_at	UGT1A10	UDP glucuronosyltransferase 1 family polypeptide A1		
NM_021027	1.5004E-04			
221676_s_at	CORO1C	coronin actin binding protein 1C	BC002342	
1.5064E-04				
204132_s_at	FOXO3	forkhead box O3	NM_001455	1.5795E-04
217999_s_at	PHLDA1	pleckstrin homology-like domain family A member 1		
NM_007350	1.6252E-04			
206498_at	OCA2	oculocutaneous albinism II	NM_000275	1.6286E-04
201310_s_at	C5orf13	chromosome 5 open reading frame 13	NM_004772	
1.6328E-04				
209125_at	KRT6A	keratin 6A	J00269	1.6608E-04
209149_s_at	TM9SF1	transmembrane 9 superfamily member 1	BE899402	
1.6635E-04				
206427_s_at	MLANA	melan-A	U06654	1.6829E-04
219752_at	RASAL1	RAS protein activator like 1 (GAP1 like)		NM_004658
1.7105E-04				
201322_at	ATP5B	ATP synthase H+ transporting mitochondrial F1 complex beta		
polypeptide	NM_001686		1.7170E-04	
208918_s_at	NADK	NAD kinase	AI334128	1.7531E-04
218548_x_at	TEX264	testis expressed 264	NM_015926	1.7787E-04
206595_at	CST6	cystatin E/M	NM_001323	1.8189E-04
217947_at	CMTM6	CKLF-like MARVEL transmembrane domain containing 6		
NM_017801	1.9994E-04			
218028_at	ELOVL1	elongation of very long chain fatty acids (FEN1/Elo2		
SUR4/Elo3 yeast)-like 1	NM_016031		2.0196E-04	
202068_s_at	LDLR	low density lipoprotein receptor		NM_000527
2.1143E-04				
221295_at	CIDEA	cell death-inducing DFFA-like effector a		NM_001279
2.1176E-04				
209482_at	POP7	processing of precursor 7 ribonuclease P/MRP subunit (S.		
cerevisiae)	BC001430		2.1329E-04	
214580_x_at	KRT6C	keratin 6A	AL569511	2.1776E-04
201131_s_at	CDH1	cadherin 1 type 1 E-cadherin (epithelial)		NM_004360
2.2275E-04				
206094_x_at	UGT1A10	UDP glucuronosyltransferase 1 family polypeptide A1		
NM_001072	2.2335E-04			
208906_at	BSCL2	Bernardinelli-Seip congenital lipodystrophy 2 (seipin)		
BC004911	2.2965E-04			
207986_x_at	CYB561	cytochrome b-561	NM_001915	2.3248E-04
222138_s_at	WDR13	WD repeat domain 13	AF158978	2.5149E-04
201577_at	NME1	non-metastatic cells 1 protein (NM23A) expressed in		
NM_000269	2.5496E-04			
210613_s_at	SYNGR1	synaptogyrin 1	BC000731	2.5878E-04
206445_s_at	PRMT1	protein arginine methyltransferase 1		NM_001536
2.6001E-04				
57163_at	ELOVL1	elongation of very long chain fatty acids (FEN1/Elo2		
SUR4/Elo3 yeast)-like 1	H93026		2.6427E-04	
218368_s_at	TNFRSF12A	tumor necrosis factor receptor superfamily member		
12A	NM_016639		2.7727E-04	

Table_B

218897_at	TMEM177	transmembrane protein 177	NM_030577	2.7927E-04
205749_at	CYP1A1	cytochrome P450 family 1 subfamily A polypeptide 1		
NM_000499				2.8164E-04
203287_at	LAD1	ladinin 1	NM_005558	2.9269E-04
218189_s_at	NANS	N-acetylneuraminic acid synthase	NM_018946	
2.9981E-04				
201489_at	PPIF	peptidylprolyl isomerase F	BC005020	3.0445E-04
202799_at	CLPP	ClpP caseinolytic peptidase ATP-dependent proteolytic		
subunit homolog (E. coli)			NM_006012	3.1644E-04
215206_at		null	AK025143	3.1867E-04
208700_s_at	TKT	transketolase	L12711	3.2294E-04
207126_x_at	UGT1A10	UDP glucuronosyltransferase 1 family polypeptide A1		
NM_000463				3.2300E-04
204941_s_at	ALDH3B2	aldehyde dehydrogenase 3 family member B2		AA071510
3.2381E-04				
212826_s_at	SLC25A6	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator) member 6	AI961224	3.2556E-04
218739_at	ABHD5	abhydrolase domain containing 5	NM_016006	3.2819E-04
209208_at	MPDU1	mannose-P-dolichol utilization defect 1	AF059752	
3.3424E-04				
200846_s_at	PPP1CA	protein phosphatase 1 catalytic subunit alpha isoform		
NM_002708				3.5337E-04
200750_s_at	RAN	RAN member RAS oncogene family	AF054183	3.5383E-04
201739_at	SGK1	serum/glucocorticoid regulated kinase 1	NM_005627	
3.5459E-04				
212165_at	TMEM183B	transmembrane protein 183A		AF070537
3.5638E-04				
218756_s_at	DHRS11	dehydrogenase/reductase (SDR family) member 11		NM_024308
3.6110E-04				
204733_at	KLK6	kallikrein-related peptidase 6	NM_002774	3.8374E-04
213726_x_at	TUBB2C	tubulin beta 2C	AA515698	3.9114E-04
214549_x_at	SPRR1A	small proline-rich protein 1A	NM_005987	3.9410E-04
211800_s_at	USP4	ubiquitin specific peptidase 4 (proto-oncogene)		AF017306
4.0198E-04				
202712_s_at	LOC100133623	creatine kinase mitochondrial 1A		NM_020990
4.0457E-04				
213796_at	SPRR1A	small proline-rich protein 1A	AI923984	4.1153E-04
209036_s_at	MDH2	malate dehydrogenase 2 NAD (mitochondrial)		BC001917
4.1608E-04				
31846_at	RHOD	ras homolog gene family member D		AW003733
4.1843E-04				
217140_s_at	LOC100133724	similar to voltage-dependent anion-selective channel protein 1 (VDAC-1) (hVDAC1) (Outer mitochondrial membrane protein porin 1) (Plasmalemmal porin) (Porin 31HL) (Porin 31HM)	AJ002428	4.1935E-04
207367_at	ATP12A	ATPase H+/K+ transporting nongastric alpha polypeptide		
NM_001676				4.1960E-04
203109_at	UBE2M	ubiquitin-conjugating enzyme E2M (UBC12 homolog yeast)		
NM_003969				4.2473E-04
202421_at	IGSF3	immunoglobulin superfamily member 3		AB007935
4.2745E-04				
208977_x_at	TUBB2C	tubulin beta 2C	BC004188	4.2872E-04
201231_s_at	ENO1	enolase 1 (alpha)	NM_001428	4.3258E-04
207507_s_at	ATP5G3	ATP synthase H+ transporting mitochondrial F0 complex subunit C3 (subunit 9)	NM_001689	4.3401E-04
217973_at	DCXR	dicarbonyl/L-xylulose reductase	NM_016286	4.3576E-04
213132_s_at	MCAT	malonyl CoA:ACP acyltransferase (mitochondrial)		AL022237
4.3749E-04				
212236_x_at	KRT17	keratin 17	Z19574	4.3848E-04
207192_at	DNASE1L2	deoxyribonuclease I-like 2		NM_001374
4.4267E-04				
202376_at	SERPINA3	serpin peptidase inhibitor clade A (alpha-1 antitrypsin) member 3	NM_001085	4.4762E-04
antiproteinase				
208813_at	GOT1	glutamic-oxaloacetic transaminase 1 soluble (aspartate		

Table_B				
aminotransferase 1)	BC000498	4.5160E-04		
205157_s_at	KRT17	keratin 17	NM_000422	4.5700E-04
200862_at	DHCR24	24-dehydrocholesterol reductase	NM_014762	4.6729E-04
205293_x_at	BAIAP2	BAI1-associated protein 2	AB017120	4.6882E-04
202436_s_at	CYP1B1	cytochrome P450 family 1 subfamily B polypeptide 1		
AU144855		4.7083E-04		
220994_s_at	STXBP6	syntaxin binding protein 6 (amisyn)	NM_014178	
4.7382E-04				
216475_at		null	AL133269	4.8343E-04
204341_at	TRIM16	tripartite motif-containing 16	NM_006470	4.8792E-04
201175_at	TMX2	thioredoxin domain containing 14	NM_015959	
5.0497E-04				
203462_x_at	EIF3B	eukaryotic translation initiation factor 3 subunit B		
NM_003751		5.1683E-04		
205064_at	SPRR1B	small proline-rich protein 1B (cornifin)	NM_003125	
5.3559E-04				
210959_s_at	SRD5A1	steroid-5-alpha-reductase alpha polypeptide 1 (3-oxo-5		
alpha-steroid delta 4-dehydrogenase alpha 1)		AF113128	5.3596E-04	
220976_s_at	LOC728946	keratin associated protein 1-1	NM_030967	
5.3814E-04				
215626_at		null	AU144887	5.4582E-04
209800_at	KRT16	keratin 16	AF061812	5.4918E-04
206714_at	ALOX15B	arachidonate 15-lipoxygenase type B	NM_001141	
5.5543E-04				
206302_s_at	NUDT4	nudix (nucleoside diphosphate linked moiety X)-type motif 4		
NM_019094		5.6492E-04		
212861_at	MFS5	major facilitator superfamily domain containing 5		
BF690150		5.7171E-04		
208756_at	EIF3I	eukaryotic translation initiation factor 3 subunit I		
U36764		5.8834E-04		
205338_s_at	DCT	dopachrome tautomerase (dopachrome delta-isomerase		
tyrosine-related protein 2)		NM_001922	5.9284E-04	
205436_s_at	H2AFX	H2A histone family member X	NM_002105	5.9320E-04
215952_s_at	OAZ1	ornithine decarboxylase antizyme 1	AF090094	
5.9942E-04				
210130_s_at	TM7SF2	transmembrane 7 superfamily member 2	AF096304	
6.0308E-04				
215100_at	C6orf105	chromosome 6 open reading frame 105	AL022724	
6.1457E-04				
205417_s_at	DAG1	dystroglycan 1 (dystrophin-associated glycoprotein 1)		
NM_004393		6.2276E-04		
216237_s_at	MCM5	minichromosome maintenance complex component 5	AA807529	
6.2290E-04				
201113_at	TUFM	Tu translation elongation factor mitochondrial	NM_003321	
6.2822E-04				
205694_at	TYRP1	tyrosinase-related protein 1	NM_000550	6.3022E-04
202315_s_at	BCR	breakpoint cluster region	NM_004327	6.3140E-04
203391_at	FKBP2	FK506 binding protein 2 13kDa	NM_004470	6.3385E-04
218880_at	FOSL2	FOS-like antigen 2	N36408	6.3536E-04
220978_at	LOC728951	keratin associated protein 1-3	NM_030966	
6.3713E-04				
207670_at	KRT85	keratin 85	NM_002283	6.4259E-04
201463_s_at	LOC100133665	similar to transaldolase	NM_006755	
6.4937E-04				
210589_s_at	GBA	glucosidase beta; acid (includes glucosylceramidase)		
D13287		6.6217E-04		
219395_at	ESRP2	RNA binding motif protein 35B	NM_024939	6.6704E-04
204675_at	SRD5A1	steroid-5-alpha-reductase alpha polypeptide 1 (3-oxo-5		
alpha-steroid delta 4-dehydrogenase alpha 1)		NM_001047	6.6827E-04	
215808_at	KLK10	kallikrein-related peptidase 10	AK026045	6.7220E-04
33646_g_at	GM2A	GM2 ganglioside activator	X61094	6.8424E-04
207508_at	ATP5G3	ATP synthase H+ transporting mitochondrial F0 complex		
subunit C3 (subunit 9)		NM_001689	6.8567E-04	

Table_B

214370_at	S100A8	calcium-binding protein in macrophages (MRP-8)	macrophage	
migration inhibitory factor (MIF)-related protein			AW238654	6.8779E-04
200803_s_at	TMBIM6	transmembrane BAX inhibitor motif containing 6		AF033095
6.8912E-04				
221872_at	RARRES1	retinoic acid receptor responder (tazarotene induced)	1	
AI669229				6.9158E-04
207088_s_at	SLC25A11	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier) member 11	NM_003562	6.9700E-04
219412_at	RAB38	RAB38 member RAS oncogene family		NM_022337
7.0409E-04				
218893_at	ISOC2	isochorismatase domain containing 2		NM_024710
7.1390E-04				
202917_s_at	S100A8	S100 calcium binding protein A8	NM_002964	7.1637E-04
220970_s_at	LOC644350	keratin associated protein 2.1B	NM_030977	
7.2209E-04				
219911_s_at	LOC100134295	similar to Solute carrier organic anion transporter family member 4A1		
family member 4A1			NM_016354	7.2592E-04
200894_s_at	FKBP4	FK506 binding protein 4 59kDa	AA894574	7.3446E-04
206709_x_at	GPT	glutamic-pyruvate transaminase (alanine aminotransferase)		
NM_005309				7.3607E-04
219723_x_at	AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3		NM_020132
7.4330E-04				
209372_x_at	TUBB2B	tubulin beta 2A	BF971587	7.4649E-04
203535_at	S100A9	S100 calcium binding protein A9	NM_002965	7.6032E-04
218214_at	C12orf44	chromosome 12 open reading frame 44		NM_021934
7.6225E-04				
206391_at	RARRES1	retinoic acid receptor responder (tazarotene induced)	1	
NM_002888				7.6289E-04
206605_at	P11	26 serine protease	NM_006025	7.7125E-04
201490_s_at	PPIF	peptidylprolyl isomerase F	NM_005729	7.7571E-04
219850_s_at	EHF	ets homologous factor	NM_012153	7.7583E-04
221256_s_at	HDHD3	haloacid dehalogenase-like hydrolase domain containing 3		
NM_031219				7.7612E-04
218105_s_at	MRPL4	mitochondrial ribosomal protein L4		NM_015956
7.8720E-04				
216810_at	KRTAP4-7	keratin associated protein 4-7		AJ406939
7.9938E-04				
218556_at	ORMDL2	ORM1-like 2 (S. cerevisiae)	NM_014182	8.2452E-04
201286_at	SDC1	syndecan 1	Z48199	8.2815E-04
211715_s_at	BDH1	3-hydroxybutyrate dehydrogenase type 1		BC005844
8.2925E-04				
220189_s_at	MGAT4B	mannosyl (alpha-13-)-glycoprotein		
beta-14-N-acetylglucosaminyltransferase isozyme B			NM_014275	8.3956E-04
217208_s_at	DLG1	discs large homolog 1 (Drosophila)		AL121981
8.4322E-04				
208653_s_at	CD164	CD164 molecule sialomucin	AF263279	8.4956E-04
207065_at	KRT75	keratin 75	NM_004693	8.5476E-04
202122_s_at	M6PRBP1	mannose-6-phosphate receptor binding protein 1		NM_005817
8.6534E-04				
221561_at	SOAT1	sterol O-acyltransferase 1	L21934	8.6953E-04
203119_at	CCDC86	coiled-coil domain containing 86		NM_024098
8.7851E-04				
203431_s_at	RICS	Rho GTPase-activating protein	NM_014715	8.7902E-04
208699_x_at	TKT	transketolase	BF696840	8.8246E-04
206392_s_at	RARRES1	retinoic acid receptor responder (tazarotene induced)	1	
NM_002888				8.8393E-04
210715_s_at	SPINT2	serine peptidase inhibitor Kunitz type 2		AF027205
8.9891E-04				
200837_at	BCAP31	B-cell receptor-associated protein 31		NM_005745
9.0194E-04				
209025_s_at	SYNCRIP	synaptotagmin binding cytoplasmic RNA interacting protein		
AF037448				9.0260E-04
211047_x_at	AP2S1	adaptor-related protein complex 2 sigma 1 subunit		

Table_B

BC006337	9.0723E-04			
204942_s_at	ALDH3B2	aldehyde dehydrogenase 3 family member B2		NM_000695
9.1058E-04				
208919_s_at	NADK	NAD kinase	BC001709	9.1552E-04
210074_at	CTSL2	cathepsin L2	AF070448	9.3602E-04
208963_x_at	FADS1	fatty acid desaturase 1	BG165833	9.5738E-04
208799_at	PSMB5	proteasome (prosome macropain) subunit beta type 5		
BC004146	9.6091E-04			
219429_at	FA2H	fatty acid 2-hydroxylase	NM_024306	9.6450E-04
36475_at	GCAT	glycine C-acetyltransferase (2-amino-3-ketobutyrate coenzyme		
A ligase)	Z97630	9.6676E-04		
215093_at	NSDHL	NAD(P) dependent steroid dehydrogenase-like		U82671
9.6805E-04				
215189_at	LOC100134394	keratin 86	X99142	9.7401E-04
209078_s_at	TXN2	thioredoxin 2	AF276920	9.7751E-04
208852_s_at	CANX	calnexin	AI761759	9.7992E-04
204253_s_at	VDR	vitamin D (125- dihydroxyvitamin D3) receptor		AA454701
9.8319E-04				
209457_at	DUSP5	dual specificity phosphatase 5	U16996	9.9441E-04
207595_s_at	BMP1	bone morphogenetic protein 1	NM_006132	1.0199E-03
211752_s_at	NDUFS7	NADH dehydrogenase (ubiquinone) Fe-S protein 7 20kDa		
(NADH-coenzyme Q reductase)	BC005954	1.0313E-03		
219843_at	IPP	intracisternal A particle-promoted polypeptide		NM_005897
1.0419E-03				
218582_at	MARCH5	membrane-associated ring finger (C3HC4) 5		NM_017824
1.0479E-03				
201119_s_at	COX8A	cytochrome c oxidase subunit 8A (ubiquitous)		NM_004074
1.0583E-03				
210334_x_at	BIRC5	baculoviral IAP repeat-containing 5		AB028869
1.0585E-03				
201201_at	CSTB	cystatin B (stefin B)	NM_000100	1.0624E-03
207787_at	KRT33B	keratin 33B	NM_002279	1.0655E-03
208688_x_at	EIF3B	eukaryotic translation initiation factor 3 subunit B		
U78525	1.1028E-03			
201433_s_at	PTDSS1	phosphatidylserine synthase 1	NM_014754	1.1096E-03
91684_g_at	EXOSC4	exosome component 4	AI571298	1.1230E-03
213288_at	MBOAT2	membrane bound O-acyltransferase domain containing 2		
AI761250	1.1339E-03			
206074_s_at	HMGAL	high mobility group AT-hook 1	NM_002131	1.1423E-03
220486_x_at	LOC100130886	hypothetical protein LOC100130886		NM_017698
1.1621E-03				
200734_s_at	ARF3	ADP-ribosylation factor 3	BG341906	1.1713E-03
203971_at	SLC31A1	solute carrier family 31 (copper transporters) member 1		
NM_001859	1.1747E-03			
201284_s_at	APEH	N-acylaminoacyl-peptide hydrolase		NM_001640
1.1833E-03				
204014_at	DUSP4	dual specificity phosphatase 4	NM_001394	1.1864E-03
217806_s_at	POLDIP2	polymerase (DNA-directed) delta interacting protein 2		
NM_015584	1.1923E-03			
210236_at	PPFIA1	protein tyrosine phosphatase receptor type f polypeptide		
(PTPRF) interacting				
208527_x_at	HIST1H2BG	histone cluster 1 H2bc	NM_003523	1.2099E-03
208962_s_at	FADS1	fatty acid desaturase 1	BE540552	1.2236E-03
206873_at	CA6	carbonic anhydrase VI	NM_001215	1.2902E-03
212048_s_at	YARS	tyrosyl-tRNA synthetase	AW245400	1.3124E-03
205916_at	S100A7	S100 calcium binding protein A7	NM_002963	1.3187E-03
210655_s_at	FOXO3	forkhead box O3	AF041336	1.3616E-03
220163_s_at	HR	hairless homolog (mouse)	NM_018411	1.3692E-03
204836_at	GLDC	glycine dehydrogenase (decarboxylating)	NM_000170	
1.4104E-03				
202218_s_at	FADS2	fatty acid desaturase 2	NM_004265	1.4192E-03
214786_at	MAP3K1	mitogen-activated protein kinase kinase kinase 1		
AA361361	1.4341E-03			

Table_B

211906_s_at member 4	SERPINB4	serpin peptidase inhibitor clade B (ovalbumin)	
220615_s_at	ABO46400		1.4392E-03
205759_s_at	FAR2	fatty acyl CoA reductase 2	NM_018099 1.4407E-03
1.4410E-03	SULT2B1	sulfotransferase family cytosolic 2B member 1	NM_004605
209605_at	TST	thiosulfate sulfurtransferase (rhodanese)	D87292
1.4493E-03			
212218_s_at	FASN	fatty acid synthase	AI954041 1.4565E-03
206465_at	ACSBG1	acyl-CoA synthetase bubblegum family member 1	BE856376
1.4571E-03			
205661_s_at cerevisiae)	FLAD1	FAD1 flavin adenine dinucleotide synthetase homolog (S.	
218062_x_at	NM_025207		1.4794E-03
NM_012121	CDC42EP4	CDC42 effector protein (Rho GTPase binding) 4	
205783_at	KLK13	kallikrein-related peptidase 13	NM_015596 1.4883E-03
212807_s_at	SORT1	sortilin 1	BF447105 1.5110E-03
210816_s_at	CYB561	cytochrome b-561	BC000021 1.5129E-03
205856_at blood group)	SLC14A1	solute carrier family 14 (urea transporter) member 1 (Kidd	
204471_at	NM_015865		1.5262E-03
208708_x_at	GAP43	growth associated protein 43	NM_002045 1.5287E-03
1.5349E-03	EIF5	eukaryotic translation initiation factor 5	AL080102
202826_at	SPINT1	serine peptidase inhibitor Kunitz type 1	NM_003710
1.5419E-03			
200971_s_at	SERP1	stress-associated endoplasmic reticulum protein 1	
NM_014445			1.5589E-03
201695_s_at	NP	nucleoside phosphorylase	NM_000270 1.5658E-03
201760_s_at	WSB2	WD repeat and SOCS box-containing 2	NM_018639
1.5795E-03			
209624_s_at	MCCC2	methylcrotonoyl-Coenzyme A carboxylase 2 (beta)	AB050049
1.6326E-03			
216396_s_at	EI24	etoposide induced 2.4 mRNA	AF131850 1.6335E-03
209832_s_at	CDT1	chromatin licensing and DNA replication factor 1	
AF321125			1.6426E-03
215066_at	PTPRF	protein tyrosine phosphatase receptor type F	AU158443
1.6528E-03			
207114_at	LY6G6C	lymphocyte antigen 6 complex locus G6C	NM_025261
1.6553E-03			
202671_s_at	PDXK	pyridoxal (pyridoxine vitamin B6) kinase	NM_003681
1.6560E-03			
214665_s_at	CHP	calcium binding protein P22	AK000095 1.6605E-03
219369_s_at	OTUB2	OTU domain ubiquitin aldehyde binding 2	NM_023112
1.6717E-03			
219272_at	TRIM62	tripartite motif-containing 62	NM_018207 1.6780E-03
209093_s_at	GBA	glucosidase beta; acid (includes glucosylceramidase)	
K02920 1.6857E-03			
212088_at	PMPCA	peptidase (mitochondrial processing) alpha	BF570122
1.6997E-03			
218580_x_at	AURKAIP1	aurora kinase A interacting protein 1	NM_017900
1.7063E-03			
220972_s_at	KRTAP9-9	keratin associated protein 9-4	NM_030975
1.7166E-03			
201274_at	PSMA5	proteasome (prosome macropain) subunit alpha type 5	
NM_002790			1.7264E-03
202788_at	MAPKAPK3	mitogen-activated protein kinase-activated protein	
kinase 3	NM_004635		1.7807E-03
216641_s_at	LAD1	ladinin 1	U58994 1.7904E-03
201277_s_at	HNRNPAB	heterogeneous nuclear ribonucleoprotein A/B	NM_004499
1.7905E-03			
205942_s_at	ACSM3	acyl-CoA synthetase medium-chain family member 3	
NM_005622			1.7973E-03
217188_s_at	C14orf1	chromosome 14 open reading frame 1	AC007182
1.8045E-03			

Table_B

201879_at	ARIH1	ariadne homolog ubiquitin-conjugating enzyme E2 binding	
protein 1 (Drosophila)	AI694332	1.8359E-03	
200890_s_at	SSR1	signal sequence receptor alpha	AW006345 1.8454E-03
210337_s_at	ACLY	ATP citrate lyase	U18197 1.8472E-03
208301_at		null	NM_025033 1.8565E-03
202831_at	GPX2	glutathione peroxidase 2 (gastrointestinal)	NM_002083
1.8811E-03			
208351_s_at	MAPK1	mitogen-activated protein kinase 1	NM_002745
1.8879E-03			
202418_at	YIF1A	Yip1 interacting factor homolog A (S. cerevisiae)	
NM_020470			1.9069E-03
216979_at	NR4A3	nuclear receptor subfamily 4 group A member 3	x89894
1.9090E-03			
219980_at	C4orf29	chromosome 4 open reading frame 29	NM_025097
1.9117E-03			
207457_s_at	LY6G6D	lymphocyte antigen 6 complex locus G6D	NM_021246
1.9129E-03			
209885_at	RHOD	ras homolog gene family member D	BC001338
1.9191E-03			
220431_at	TMPRSS11E	transmembrane protease serine 11E	NM_014058
1.9354E-03			
213553_x_at	APOC1	apolipoprotein C-I	w79394 1.9760E-03
200824_at	GSTP1	glutathione S-transferase pi 1	NM_000852 1.9764E-03
221934_s_at	LOC100133719	DALR anticodon binding domain containing 3	
BF941492			1.9812E-03
206969_at	KRT34	keratin 34	NM_021013 1.9840E-03
213059_at	CREB3L1	CAMP responsive element binding protein 3-like 1	
AF055009			1.9924E-03
218951_s_at	PLCXD1	phosphatidylinositol-specific phospholipase C x domain	
containing 1			NM_018390 1.9969E-03
219131_at	UBIAD1	UbiA prenyltransferase domain containing 1	NM_013319
2.0022E-03			
39729_at	PRDX2	peroxiredoxin 2	L19185 2.0334E-03
220675_s_at	PNPLA3	patatin-like phospholipase domain containing 3	NM_025225
2.0480E-03			
211695_x_at	MUC1	mucin 1 cell surface associated	AF348143 2.0496E-03
206027_at	S100A3	S100 calcium binding protein A3	NM_002960 2.0599E-03
208660_at	CS	citrate synthase	BC000105 2.0731E-03
218018_at	PDXK	pyridoxal (pyridoxine vitamin B6) kinase	AW449022
2.0955E-03			

Probe set ID value	Gene Symbol	Gene Name	Table_C Representative Public ID	p
205236_x_at 4.1207E-10	SOD3	superoxide dismutase 3 extracellular	NM_003102	
213247_at containing 1	SVEP1	sushi von willebrand factor type A EGF and pentraxin domain		
212796_s_at	AA716107	5.1550E-10		
213113_s_at 1.0187E-08	TBC1D2B	TBC1 domain family member 2B	BF195608	3.6373E-09
202510_s_at 2.4861E-08	SLC43A3	solute carrier family 43 member 3	AI630178	
213364_s_at	TNFAIP2	tumor necrosis factor alpha-induced protein 2	NM_006291	
202291_s_at	SNX1	sorting nexin 1	AI052536	2.7627E-08
219304_s_at 7.2053E-08	MGP	matrix Gla protein	NM_000900	6.9902E-08
213258_at	PDGFD	platelet derived growth factor D	NM_025208	
213071_at	TFPI	tissue factor pathway inhibitor (lipoprotein-associated		
202912_at	coagulation inhibitor)	BF511231	7.6953E-08	
202363_at	DPT	dermatopontin	AL049798	8.6564E-08
(testican) 1	ADM	adrenomedullin	NM_001124	1.1154E-07
212067_s_at 1.7318E-07	SPOCK1	sparc/osteonectin cwcw and kazal-like domains proteoglycan		
203088_at	AF231124	1.3816E-07		
212589_at 2.0143E-07	CLR	complement component 1 r subcomponent	AL573058	
202994_s_at	FBLN5	fibulin 5	NM_006329	1.8181E-07
213164_at	RRAS2	related RAS viral (r-ras) oncogene homolog 2		AI753792
member 3	FBLN1	fibulin 1	Z95331	2.4381E-07
212761_at	SLC5A3	solute carrier family 5 (sodium/myo-inositol cotransporter)		
AI949687	AI867198	3.0577E-07		
216620_s_at AF009205	TCF7L2	transcription factor 7-like 2 (T-cell specific HMG-box)		
217800_s_at 3.8336E-07	ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10		
206157_at	NDFIP1	Nedd4 family interacting protein 1	NM_030571	
NM_002852	PTX3	pentraxin-related gene rapidly induced by IL-1 beta		
209763_at	CHRD1	chordin-like 1	AL049176	4.1288E-07
207606_s_at 4.3253E-07	ARHGAP12	Rho GTPase activating protein 12		NM_018287
213348_at 4.6161E-07	CDKN1C	cyclin-dependent kinase inhibitor 1C (p57 Kip2)	N33167	
208747_s_at	C1s	complement component 1 s subcomponent	M18767	4.8744E-07
213150_at	HOXA10	homeobox A10	BF792917	4.9645E-07
210155_at	MYOC	myocilin trabecular meshwork inducible glucocorticoid		
response	D88214	5.0664E-07		
212558_at	SPRY1	sprouty homolog 1 antagonist of FGF signaling (Drosophila)		
BF508662		5.2222E-07		
205794_s_at 5.5567E-07	NOVA1	neuro-oncological ventral antigen 1	NM_002515	
200785_s_at	LOC100134190	similar to low density lipoprotein-related protein 1		
(alpha-2-macroglobulin receptor)		NM_002332		6.7345E-07
205422_s_at	ITGBL1	integrin beta-like 1 (with EGF-like repeat domains)		
NM_004791		6.8540E-07		
204749_at 7.3357E-07	NAP1L3	nucleosome assembly protein 1-like 3	NM_004538	
204963_at 7.4308E-07	SSPN	sarcospan (Kras oncogene-associated gene)		AL136756
220327_at	VGLL3	vestigial like 3 (Drosophila)	NM_016206	9.2218E-07
217853_at	TNS3	tensin 3	NM_022748	9.6113E-07
213068_at	DPT	dermatopontin	AI146848	9.9396E-07
212944_at	SLC5A3	solute carrier family 5 (sodium/myo-inositol cotransporter)		
member 3	AK024896	1.0012E-06		

Table_C

209335_at	DCN	decorin	AI281593	1.0494E-06
200986_at	SERPING1	serpin peptidase inhibitor clade G (C1 inhibitor)		
member 1	NM_000062		1.0535E-06	
201842_s_at	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1		
AI826799			1.1054E-06	
212224_at	ALDH1A1	aldehyde dehydrogenase 1 family member A1		NM_000689
1.1206E-06				
221950_at	EMX2	empty spiracles homeobox 2	AI478455	1.1299E-06
203939_at	NT5E	5'-nucleotidase ecto (CD73)	NM_002526	1.1852E-06
217904_s_at	BACE1	beta-site APP-cleaving enzyme 1	NM_012104	1.2008E-06
213568_at	OSR2	odd-skipped related 2 (Drosophila)	AI811298	
1.2131E-06				
212419_at	ZCCHC24	zinc finger CCHC domain containing 24	AA131324	
1.2940E-06				
204846_at	CP	ceruloplasmin (ferroxidase)	NM_000096	1.3807E-06
203217_s_at	ST3GAL5	ST3 beta-galactoside alpha-23-sialyltransferase 5		
NM_003896			1.4759E-06	
206373_at	ZIC1	Zic family member 1 (odd-paired homolog Drosophila)		
NM_003412			1.4967E-06	
202897_at	SIRPA	signal-regulatory protein alpha	AB023430	1.6045E-06
201787_at	LOC10013843	fibulin 1	NM_001996	1.6142E-06
218505_at	WDR59	WD repeat domain 59	NM_024673	1.6525E-06
221019_s_at	COLEC12	collectin sub-family member 12	NM_030781	1.6596E-06
201744_s_at	LUM	lumican	NM_002345	1.7389E-06
220037_s_at	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1		
NM_016164			1.7506E-06	
213429_at	BICC1	bicaudal C homolog 1 (Drosophila)	AW025579	
1.7710E-06				
218901_at	PLSCR4	phospholipid scramblase 4	NM_020353	1.8289E-06
221016_s_at	TCF7L1	transcription factor 7-like 1 (T-cell specific HMG-box)		
NM_031283			1.8590E-06	
213800_at	CFH	complement factor H	X04697	2.0989E-06
202995_s_at	FBLN1	fibulin 1	NM_006486	2.1038E-06
207977_s_at	DPT	dermatopontin	NM_001937	2.1423E-06
205612_at	MMRN1	multimerin 1	NM_007351	2.1544E-06
201811_x_at	SH3BP5	SH3-domain binding protein 5 (BTK-associated)		NM_004844
2.2599E-06				
201792_at	AEBP1	AE binding protein 1	NM_001129	2.2845E-06
202664_at	WIPF1	WAS/WASL interacting protein family member 1	AW058622	
2.3077E-06				
214494_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal recessive)		
recessive)	NM_005200		2.3371E-06	
202729_s_at	LTBP1	latent transforming growth factor beta binding protein 1		
NM_000627			2.3760E-06	
201843_s_at	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1		
NM_004105			2.4011E-06	
218418_s_at	KANK2	KN motif and ankyrin repeat domains 2	NM_015493	
2.4190E-06				
205407_at	RECK	reversion-inducing-cysteine-rich protein with kazal motifs		
NM_021111			2.4567E-06	
210135_s_at	SHOX2	short stature homeobox 2	AF022654	2.4688E-06
215116_s_at	DNM1	dynamitin 1	AF035321	2.5340E-06
221556_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)		
BF792631			2.5893E-06	
205011_at	VWA5A	von willebrand factor A domain containing 5A		NM_014622
2.6449E-06				
200771_at	LAMC1	laminin gamma 1 (formerly LAMB2)		NM_002293
2.6594E-06				
203083_at	THBS2	thrombospondin 2	NM_003247	2.7220E-06
201116_s_at	CPE	carboxypeptidase E	AI922855	2.7262E-06
205802_at	TRPC1	transient receptor potential cation channel subfamily C		
member 1	NM_003304		2.7777E-06	
200945_s_at	SEC31A	SEC31 homolog A (S. cerevisiae)	NM_014933	2.8298E-06

Table_C				
203813_s_at	SLIT3	slit homolog 3 (Drosophila)	NM_003062	2.9973E-06
200784_s_at	LOC100134190	similar to low density lipoprotein-related protein 1 (alpha-2-macroglobulin receptor)	BF304759	3.1301E-06
201818_at	LPCAT1	lysophosphatidylcholine acyltransferase 1		NM_024830
3.1321E-06				
205382_s_at	CFD	complement factor D (adipsin)	NM_001928	3.3053E-06
210105_s_at	FYN	FYN oncogene related to SRC FGR YES	M14333	3.3891E-06
221796_at	NTRK2	neurotrophic tyrosine kinase receptor type 2		AA707199
3.4378E-06				
219173_at	MYO15B	myosin XVB pseudogene	NM_024957	3.4389E-06
218276_s_at	SAV1	salvador homolog 1 (Drosophila)	NM_021818	3.5175E-06
211743_s_at	PRG2	proteoglycan 2 bone marrow (natural killer cell activator		
eosinophil granule major		basic protein)	BC005929	3.5818E-06
218162_at	OLFML3	olfactomedin-like 3	NM_020190	3.6798E-06
202202_s_at	LAMA4	laminin alpha 4	NM_002290	3.6835E-06
213249_at	FBXL7	F-box and leucine-rich repeat protein 7	AU145127	
3.7131E-06				
202220_at	KIAA0907	KIAA0907	NM_014949	3.8586E-06
212736_at	C16orf45	chromosome 16 open reading frame 45		BE299456
3.9881E-06				
209550_at	NDN	necdin homolog (mouse)	U35139	4.0364E-06
213422_s_at	MXRA8	matrix-remodelling associated 8	AW888223	4.0854E-06
209568_s_at	RGL1	ral guanine nucleotide dissociation stimulator-like 1		
AF186779				4.1032E-06
212713_at	MFAP4	microfibrillar-associated protein 4	R72286	4.2791E-06
203131_at	PDGFRA	platelet-derived growth factor receptor alpha polypeptide		
NM_006206				4.2993E-06
204140_at	TPST1	tyrosylprotein sulfotransferase 1		NM_003596
4.4001E-06				
209265_s_at	METTL3	methyltransferase like 3	BC001650	4.6265E-06
218715_at	UTP6	UTP6 small subunit (SSU) processome component homolog		
(yeast) NM_018428				4.6383E-06
204671_s_at	ANKRD6	ankyrin repeat domain 6	BE677131	4.7769E-06
201535_at	UBL3	ubiquitin-like 3	NM_007106	4.8034E-06
218146_at	GLT8D1	glycosyltransferase 8 domain containing 1		NM_018446
4.8282E-06				
204042_at	WASF3	WAS protein family member 3	AB020707	4.8795E-06
204345_at	COL16A1	collagen type XVI alpha 1	NM_001856	4.9731E-06
216033_s_at	FYN	FYN oncogene related to SRC FGR YES	S74774	5.0274E-06
36030_at	IFFO1	intermediate filament family orphan 1	AL080214	
5.0956E-06				
218718_at	PDGFC	platelet derived growth factor C		NM_016205
5.1266E-06				
203706_s_at	FZD7	frizzled homolog 7 (Drosophila)	NM_003507	5.4817E-06
219093_at	PID1	phosphotyrosine interaction domain containing 1		NM_017933
5.7633E-06				
203583_at	UNC50	unc-50 homolog (C. elegans)	NM_014044	5.7712E-06
205609_at	ANGPT1	angiopoietin 1	NM_001146	5.7795E-06
204457_s_at	GAS1	growth arrest-specific 1	NM_002048	5.7891E-06
205083_at	AOX1	aldehyde oxidase 1	NM_001159	5.9671E-06
203812_at		null	AB011538	6.2204E-06
212621_at	TMEM194A	transmembrane protein 194A		AB006624
6.3362E-06				
206404_at	FGF9	fibroblast growth factor 9 (glia-activating factor)		
NM_002010				6.5054E-06
204606_at	CCL21	chemokine (C-C motif) ligand 21	NM_002989	6.5807E-06
201117_s_at	CPE	carboxypeptidase E	NM_001873	6.8179E-06
213802_at		null	AI810767	7.0439E-06
212486_s_at	FYN	FYN oncogene related to SRC FGR YES	N20923	7.2524E-06
201278_at	DAB2	disabled homolog 2 mitogen-responsive phosphoprotein		
(Drosophila)	N21202			7.7092E-06
218656_s_at	LHFP	lipoma HMGIC fusion partner	NM_005780	7.9930E-06
212230_at	PPAP2B	phosphatidic acid phosphatase type 2B	AV725664	

Table_C

8.1114E-06					
221760_at	MAN1A1	CDNA: FLJ21946 fis clone HEP04860 highly similar to HSHUMM9			
Homo sapiens	HUMM9 mRNA	BG287153	8.1833E-06		
210139_s_at	PMP22	peripheral myelin protein 22	L03203	8.8249E-06	
212877_at	KLC1	kinesin light chain 1	AA284075	9.1329E-06	
217767_at	C3	complement component 3	NM_000064	9.1495E-06	
212503_s_at	DIP2C	DIP2 disco-interacting protein 2 homolog C (Drosophila)			
N22859					
218204_s_at	FYCO1	FYVE and coiled-coil domain containing 1		NM_024513	
9.6526E-06					
212793_at	DAAM2	dishevelled associated activator of morphogenesis 2			
BF513244			1.0235E-05		
202920_at	ANK2	ankyrin 2 neuronal	BF726212	1.0636E-05	
203476_at	TPBG	trophoblast glycoprotein	NM_006670	1.0681E-05	
217122_s_at	LOC728661	similar to solute carrier family 35 member E2			
AL031282			1.0828E-05		
211896_s_at	DCN	decorin AF138302	1.0835E-05		
204453_at	ZNF84	zinc finger protein 84	NM_003428	1.0897E-05	
211535_s_at	FGFR1	fibroblast growth factor receptor 1	M60485	1.1017E-05	
211548_s_at	HPGD	hydroxyprostaglandin dehydrogenase 15-(NAD)	J05594		
1.1089E-05					
213880_at	LGR5	leucine-rich repeat-containing G protein-coupled receptor 5			
AL524520			1.1094E-05		
202273_at	PDGFRB	platelet-derived growth factor receptor beta polypeptide			
NM_002609			1.1180E-05		
207808_s_at	PROS1	protein S (alpha)	NM_000313	1.1272E-05	
220744_s_at	IFT122	intraflagellar transport 122 homolog (Chlamydomonas)			
NM_018262			1.2426E-05		
205542_at	STEAP1	six transmembrane epithelial antigen of the prostate 1			
NM_012449			1.2639E-05		
205933_at	SETBP1	SET binding protein 1	NM_015559	1.2646E-05	
214323_s_at	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)			
N36842			1.2818E-05		
212597_s_at	HMGXB4	HMG box domain containing 4	AL079310	1.2979E-05	
204112_s_at	HNMT	histamine N-methyltransferase	NM_006895	1.3109E-05	
213652_at	PCSK5	Protease PC6 isoform A (PCSK5)	AU152579	1.3167E-05	
215388_s_at	CFH	complement factor H	X56210	1.3176E-05	
204036_at	LPAR1	lysophosphatidic acid receptor 1		AW269335	
1.3211E-05					
209884_s_at	SLC4A7	solute carrier family 4 sodium bicarbonate cotransporter			
member 7	AF047033		1.4144E-05		
205452_at	PIGB	phosphatidylinositol glycan anchor biosynthesis class B			
NM_004855			1.4354E-05		
207177_at	PTGFR	prostaglandin F receptor (FP)	NM_000959	1.4808E-05	
219059_s_at	LYVE1	lymphatic vessel endothelial hyaluronan receptor 1			
AL574194			1.4902E-05		
201150_s_at	TIMP3	TIMP metalloproteinase inhibitor 3		NM_000362	
1.4957E-05					
200770_s_at	LAMC1	laminin gamma 1 (formerly LAMB2)	J03202	1.5246E-05	
212327_at	LIMCH1	LIM and calponin homology domains 1		AK026815	
1.6143E-05					
206958_s_at	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)			
AF318575			1.6235E-05		
39650_s_at	PCNXL2	pecanex-like 2 (Drosophila)	AB007895	1.6512E-05	
207417_s_at	ZNF177	zinc finger protein 177	NM_003451	1.6676E-05	
213293_s_at	TRIM22	tripartite motif-containing 22	AA083478	1.6798E-05	
218686_s_at	RHBDF1	rhomboid 5 homolog 1 (Drosophila)		NM_022450	
1.7255E-05					
212195_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M			
receptor)	AL049265		1.7471E-05		
202598_at	S100A13	S100 calcium binding protein A13		NM_005979	
1.7872E-05					
203893_at	TAF9	TAF9 RNA polymerase II TATA box binding protein			

Table_C				
(TBP)-associated factor 32kDa	NM_016283	1.7916E-05		
218093_s_at	ANKRD10	ankyrin repeat domain 10	NM_017664	1.8440E-05
216840_s_at	LAMA2	laminin alpha 2 AK026829	1.8901E-05	
219552_at	SVEP1	sushi von willebrand factor type A EGF and pentraxin domain		
containing 1	NM_024500	1.9057E-05		
203914_x_at	HPGD	hydroxyprostaglandin dehydrogenase 15-(NAD)	NM_000860	
1.9929E-05				
218793_s_at	SCML1	sex comb on midleg-like 1 (Drosophila)	NM_006746	
2.0086E-05				
209612_s_at	ADH1B	alcohol dehydrogenase 1B (class I) beta polypeptide		
M24317	2.0211E-05			
209580_s_at	MBD4	methyl-CpG binding domain protein 4	AF114784	
2.0320E-05				
221897_at	TRIM52	tripartite motif-containing 52	AA205660	2.0818E-05
219283_at	C1GALT1C1	C1GALT1-specific chaperone 1	NM_014158	
2.1265E-05				
202478_at	TRIB2	tribbles homolog 2 (Drosophila)	NM_021643	2.1280E-05
214703_s_at	MAN2B2	mannosidase alpha class 2B member 2	AW954107	
2.1437E-05				
59375_at	MYO15B	myosin XVB pseudogene	AI825877	2.1605E-05
204719_at	ABCA8	ATP-binding cassette sub-family A (ABCI) member 8		
NM_007168	2.1721E-05			
211675_s_at	MDFIC	MyoD family inhibitor domain containing	AF054589	
2.1807E-05				
213161_at	C9orf97	chromosome 9 open reading frame 97	AI583393	
2.2081E-05				
202951_at	STK38	serine/threonine kinase 38	BE048506	2.2195E-05
213519_s_at	LAMA2	laminin alpha 2 AI078169	2.2351E-05	
209409_at	GRB10	growth factor receptor-bound protein 10	D86962	2.2881E-05
201034_at	ADD3	adducin 3 (gamma)	BE545756	2.3091E-05
206227_at	CILP	cartilage intermediate layer protein nucleotide		
pyrophosphohydrolyase	NM_003613	2.3220E-05		
212651_at	RHOBTB1	Rho-related BTB domain containing 1	AB018283	
2.3246E-05				
215016_x_at	DST	dystonin	BC004912	2.3884E-05
212958_x_at	PAM	peptidylglycine alpha-amidating monooxygenase	AI022882	
2.4348E-05				
219949_at	LRRC2	leucine rich repeat containing 2	NM_024512	
2.4451E-05				
219639_x_at	PARP6	poly (ADP-ribose) polymerase family member 6	NM_020213	
2.4585E-05				
220992_s_at	C1orf25	chromosome 1 open reading frame 25	NM_030934	
2.4860E-05				
203600_s_at	C4orf8	chromosome 4 open reading frame 8	NM_003704	
2.5273E-05				
219729_at	PRRX2	paired related homeobox 2	NM_016307	2.5432E-05
212855_at	DCUN1D4	DCN1 defective in cullin neddylation 1 domain containing 4		
(S. cerevisiae)	D87466	2.5564E-05		
212328_at	LIMCH1	LIM and calponin homology domains 1	AB029025	
2.6031E-05				
201395_at	RBM5	RNA binding motif protein 5	NM_005778	2.6282E-05
203139_at	DAPK1	death-associated protein kinase 1	NM_004938	
2.6335E-05				
222043_at	CLU	clusterin	AI982754	2.6684E-05
203886_s_at	FBLN2	fibulin 2	NM_001998	2.7202E-05
212979_s_at	FAM115A	family with sequence similarity 115 member A	AW293343	
2.7293E-05				
209220_at	GPC3	glypican 3	L47125	2.7421E-05
212148_at	PBX1	pre-B-cell leukemia homeobox 1	AL049381	2.7560E-05
202142_at	COPS8	COP9 constitutive photomorphogenic homolog subunit 8		
(Arabidopsis)	BC003090	2.7754E-05		
222235_s_at	CSGALNACT2	chondroitin sulfate		
N-acetylgalactosaminyltransferase 2	AL139812	2.8031E-05		

Table_C

212764_at 2.8104E-05	ZEB1	zinc finger E-box binding homeobox 1	AI806174
214749_s_at 2.8574E-05	ARMCX6	armadillo repeat containing x-linked 6	AK000818
201944_at 2.8860E-05	HEXB	hexosaminidase B (beta polypeptide)	NM_000521
205515_at 2.8866E-05	PRSS12	protease serine 12 (neurotrypsin motopsin)	NM_003619
213698_at 2.8874E-05	LOC100130633	similar to ZMYM6 protein	AI805560
203824_at 203117_s_at cerevisiae)	TSPAN8 PAN2	tetraspanin 8 PAN2 poly(A) specific ribonuclease subunit homolog (S.	NM_004616 2.9175E-05
204605_at 3.0162E-05	NM_014871 CGRRF1	3.0053E-05 cell growth regulator with ring finger domain 1	NM_006568
219778_at 217892_s_at	ZFPM2 LIMA1	zinc finger protein multitype 2 LIM domain and actin binding 1	NM_012082 3.0400E-05
212681_at 3.0884E-05	EPB41L3	erythrocyte membrane protein band 4.1-like 3	NM_016357 3.0815E-05
204085_s_at 3.0907E-05	CLN5	ceroid-lipofuscinosis neuronal 5	AI770004
210102_at 3.0936E-05	VWA5A	von willebrand factor A domain containing 5A	NM_006493
220351_at 3.1140E-05	CCRL1	chemokine (C-C motif) receptor-like 1	BC001234
210406_s_at 3.1167E-05	RAB6A	RAB6A member RAS oncogene family	NM_016557
221569_at 3.1574E-05	AHI1	Abelson helper integration site 1	AL136727
219550_at NM_022370	ROBO3	roundabout axon guidance receptor homolog 3 (Drosophila)	AL136797
200762_at 201086_x_at	3.1855E-05 DPYSL2	3.1884E-05 dihydropyrimidinase-like 2	NM_001386
218285_s_at 3.2876E-05	SON BDH2	SON DNA binding protein 3-hydroxybutyrate dehydrogenase type 2	NM_003103 3.2222E-05
213397_x_at 219908_at	RNASE4 DKK2	ribonuclease RNase A family 4 dickkopf homolog 2 (Xenopus laevis)	AI761728 3.3089E-05
3.4237E-05 213262_at	SACS	spastic ataxia of Charlevoix-Saguenay (sacsin)	NM_014421
3.4386E-05 208944_at	TGFB2	transforming growth factor beta receptor II (70/80kDa)	AI932370
D50683 3.4404E-05 209946_at	VEGFC	vascular endothelial growth factor C	U58111 3.4474E-05
219700_at 213737_x_at	PLXDC1 GOLGA9P	plexin domain containing 1 golgi autoantigen golgin subfamily a 9 pseudogene	NM_020405 3.4923E-05
AI620911 201669_s_at	3.5009E-05 MARCKS	3.5037E-05 myristoylated alanine-rich protein kinase C substrate	
NM_002356 204897_at	PTGER4	prostaglandin E receptor 4 (subtype EP4)	AA897516
3.5257E-05 220642_x_at	GPR89B	G protein-coupled receptor 89A	NM_016334 3.5976E-05
206159_at 3.6140E-05	GDF10	growth differentiation factor 10	NM_004962
201798_s_at 215000_s_at	MYOF FEZ2	myoferlin fasciculation and elongation protein zeta 2 (zygin II)	NM_013451 3.7082E-05
AL117593 212985_at	3.7115E-05 APBB2	3.7441E-05 amyloid beta (A4) precursor protein-binding family B member	
2 209101_at	BF115739 CTGF	connective tissue growth factor M92934	3.7465E-05
221447_s_at 3.7495E-05	GLT8D2	glycosyltransferase 8 domain containing 2	NM_031302
218303_x_at 203241_at	KRCC1 UVRAG	lysine-rich coiled-coil 1 UV radiation resistance associated gene	NM_016618 3.7642E-05

Table_C

3.7762E-05				
209659_s_at	CDC16	cell division cycle 16 homolog (S. cerevisiae)	AF164598	
3.8581E-05				
216321_s_at	NR3C1	nuclear receptor subfamily 3 group C member 1		
(glucocorticoid receptor)		X03348	3.8658E-05	
201063_at	RCN1	reticulocalbin 1 EF-hand calcium binding domain	NM_002901	
3.8695E-05				
202304_at	FNDC3A	fibronectin type III domain containing 3A	NM_014923	
3.9178E-05				
206484_s_at	XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P) 2 membrane-bound		
NM_003399			3.9464E-05	
210312_s_at	IFT20	intraflagellar transport 20 homolog (Chlamydomonas)		
BC002640			4.0492E-05	
220065_at	TNMD	tenomodulin	NM_022144	4.0580E-05
209356_x_at	EFEMP2	EGF-containing fibulin-like extracellular matrix protein 2		
AB030655			4.0584E-05	
202336_s_at	PAM	peptidylglycine alpha-amidating monooxygenase	NM_000919	
4.0770E-05				
208669_s_at	EID1	EP300 interacting inhibitor of differentiation 1		
AF109873			4.1682E-05	
202446_s_at	PLSCR1	phospholipid scramblase 1	AI825926	4.1757E-05
209497_s_at	RBM4B	RNA binding motif protein 4B	BC003503	4.1986E-05
201139_s_at	SSB	Sjogren syndrome antigen B (autoantigen La)	NM_003142	
4.2098E-05				
212169_at	FKBP9	FK506 binding protein 9 63 kDa	AL050187	4.2116E-05
201753_s_at	ADD3	adducin 3 (gamma)	NM_019903	4.2645E-05
217525_at	OLFML1	olfactomedin-like 1	AW305097	4.2856E-05
218616_at	INTS12	integrator complex subunit 12	NM_020395	4.3996E-05
205100_at	GFPT2	glutamine-fructose-6-phosphate transaminase 2	NM_005110	
4.4073E-05				
218801_at	UGCGL2	UDP-glucose ceramide glucosyltransferase-like 2	NM_020121	
4.4535E-05				
201398_s_at	TRAM1	translocation associated membrane protein 1	BC000687	
4.4699E-05				
213455_at	FAM114A1	family with sequence similarity 114 member A1		
w87466 4.4874E-05				
219493_at	SHCBP1	SHC SH2-domain binding protein 1	NM_024745	
4.5019E-05				
219073_s_at	OSBPL10	oxysterol binding protein-like 10	NM_017784	
4.5703E-05				
216044_x_at	FAM69A	family with sequence similarity 69 member A	AK027146	
4.6409E-05				
208986_at	TCF12	transcription factor 12	AL559478	4.6942E-05
205792_at	WISP2	WNT1 inducible signaling pathway protein 2	NM_003881	
4.7104E-05				
204735_at	PDE4A	phosphodiesterase 4A CAMP-specific (phosphodiesterase E2		
dunce homolog Drosophila)			NM_006202	4.7153E-05
202382_s_at	GNPDA1	glucosamine-6-phosphate deaminase 1	NM_005471	
4.7273E-05				
214434_at	HSPA12A	heat shock 70kDa protein 12A	AB007877	4.8185E-05
211864_s_at	MYOF	myoferlin	AF207990	4.9709E-05
211719_x_at	FN1	fibronectin 1	BC005858	5.0797E-05
205728_at		nu11	AL022718	5.1523E-05
218885_s_at	GALNT12	UDP-N-acetyl-alpha-D-galactosamine:polypeptide		
N-acetylgalactosaminyltransferase 12 (GalNAc-T12)			NM_024642	5.1829E-05
218076_s_at	ARHGAP17	Rho GTPase activating protein 17	NM_018054	
5.2424E-05				
217792_at	SNX5	sorting nexin 5	NM_014426	5.2561E-05
212779_at	KIAA1109	KIAA1109	AB029032	5.2993E-05
212254_s_at	DST	dystonin	AI798790	5.3772E-05
202863_at	SP100	SP100 nuclear antigen	NM_003113	5.4231E-05
218084_x_at	FXYD5	FXYD domain containing ion transport regulator 5		
NM_014164			5.4271E-05	

Table_C				
205573_s_at	SNX7	sorting nexin 7	NM_015976	5.4748E-05
221020_s_at	SLC25A32	solute carrier family 25 member 32		NM_030780
5.5194E-05				
202104_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal		
recessive)	NM_003119		5.5970E-05	
201780_s_at	RNF13	ring finger protein 13	NM_007282	5.6181E-05
204093_at	CCNH	cyclin H	NM_001239	5.6217E-05
208016_s_at	AGTR1	angiotensin II receptor type 1	NM_004835	5.6967E-05
221773_at	ELK3	ELK3 ETS-domain protein (SRF accessory protein 2) mRNA (cDNA		
clone MGC:13551	IMAGE:4287696)	AW575374	5.7036E-05	
213392_at	IQCK	IQ motif containing K	AW070229	5.7402E-05
212798_s_at	ANKMY2	ankyrin repeat and MYND domain containing 2		AK001389
5.7754E-05				
221645_s_at	ZNF83	zinc finger protein 83	M27877	5.9654E-05
218999_at	TMEM140	transmembrane protein 140	NM_018295	5.9756E-05
203799_at	CD302	CD302 molecule	NM_014880	5.9942E-05
214093_s_at	FUBP1	far upstream element (FUSE) binding protein 1		AA156865
6.0566E-05				
202958_at	PTPN9	protein tyrosine phosphatase non-receptor type 9		
NM_002833	6.1062E-05			
203903_s_at	HEPH	hephaestin	NM_014799	6.1829E-05
210495_x_at	FN1	fibronectin 1	AF130095	6.1983E-05
218007_s_at	RPS27L	ribosomal protein S27-like	NM_015920	6.2147E-05
205139_s_at	UST	uronyl-2-sulfotransferase	NM_005715	6.2337E-05

Probe set ID	Gene Symbol	Gene Name	Table_D Representative Public ID	p
212291_at 1.4712E-08	HIPK1	homeodomain interacting protein kinase 1	AI393355	
205187_at	SMAD5	SMAD family member 5	AF010601	2.3661E-08
216022_at		null AL049278	1.5264E-07	
211074_at	FOLR1	folate receptor 1 (adult)	AF000381	2.3573E-07
208711_s_at	CCND1	cyclin D1	BC000076	2.4510E-07
214265_at	ITGA8	integrin alpha 8	AI193623	3.5683E-07
202102_s_at	BRD4	bromodomain containing 4	BF718610	4.5386E-07
222024_s_at 6.8737E-07	AKAP13	A kinase (PRKA) anchor protein 13	AK022014	
210717_at		null AF116659	8.8389E-07	
211081_s_at	MAP4K5	mitogen-activated protein kinase kinase kinase kinase 5		
225426 1.0560E-06	C7orf28B	chromosome 7 open reading frame 28B		
1.0617E-06			AK000993	
209936_at	RBM5	RNA binding motif protein 5	AF107493	1.2081E-06
206061_s_at	DICER1	dicer 1 ribonuclease type III	NM_030621	1.5719E-06
217649_at	ZFAND5	zinc finger AN1-type domain 5	AV702306	1.6384E-06
216858_x_at		null AL080112	2.8178E-06	
220071_x_at	CEP27	centrosomal protein 27kDa	NM_018097	2.8584E-06
216187_x_at		null AF222691	2.8639E-06	
214041_x_at	RPL37A	Ribosomal protein L37a	BE857772	2.9005E-06
209088_s_at	UBN1	ubiquitin 1	T70262	3.0772E-06
210807_s_at	SLC16A7	solute carrier family 16 member 7 (monocarboxylic acid transporter 2)	AF049608	3.7623E-06
214153_at	ELOVL5	ELOVL family member 5 elongation of long chain fatty acids (FEN1/Elo2 SUR4/Elo3-like yeast)	BE467941	3.8401E-06
212057_at	KIAA0182	KIAA0182	AA206161	3.8589E-06
213718_at	RBM4	RNA binding motif protein 4	BE222257	3.9440E-06
207291_at	PRRG4	proline rich Gla (G-carboxyglutamic acid) 4 (transmembrane)		
NM_024081		4.4222E-06		
203742_s_at 4.5161E-06	LOC645233	thymine-DNA glycosylase pseudogene		BF674842
221943_x_at	RPL38	Ribosomal protein L38 mRNA (cDNA clone MGC:1637		
IMAGE:3346447)	AW303136	4.7760E-06		
204881_s_at	UGCG	UDP-glucose ceramide glucosyltransferase		NM_003358
4.9560E-06				
206036_s_at	REL	v-rel reticuloendotheliosis viral oncogene homolog (avian)		
NM_002908		5.0576E-06		
202940_at	WNK1	KIAA0344 gene	NM_014823	5.0700E-06
217538_at	SGSM2	small G protein signaling modulator 2	BF347113	
5.3480E-06				
212492_s_at	JMJD2B	jumonji domain containing 2B	AW237172	5.3779E-06
211503_s_at	RAB14	RAB14 member RAS oncogene family	AF112206	
6.0532E-06				
203803_at	PCYOX1	prenylcysteine oxidase 1	N45309	6.5416E-06
211993_at	WNK1	WNK lysine deficient protein kinase 1	AI768512	
6.7386E-06				
202040_s_at	JARID1A	jumonji AT rich interactive domain 1A		NM_005056
6.7560E-06				
214807_at		null AI278204	7.1860E-06	
201195_s_at	SLC7A5	solute carrier family 7 (cationic amino acid transporter y+		
system) member 5		AB018009	7.2298E-06	
213517_at	PCBP2	poly(rC) binding protein 2	AW103422	7.3423E-06
201299_s_at	MOBK1B	MOB1 Mps One Binder kinase activator-like 1B (yeast)		
NM_018221		7.3742E-06		
63825_at	ABHD2	abhydrolase domain containing 2	AI557319	7.6414E-06
214902_x_at		null AL080232	7.8481E-06	
221664_s_at	F11R	F11 receptor	AF154005	8.1916E-06
212659_s_at	IL1RN	interleukin 1 receptor antagonist		AW083357
8.3955E-06				

Table_D

219024_at	PLEKHA1	pleckstrin homology domain containing family A (phosphoinositide binding specific) member 1	NM_021622	8.6942E-06
204524_at	PDPK1	3-phosphoinositide dependent protein kinase-1	NM_002613	
9.1327E-06				
203318_s_at	ZNF148	zinc finger protein 148	NM_021964	9.1431E-06
213229_at	DICER1	dicer 1 ribonuclease type III	BF590131	9.7278E-06
214422_at	LOC131185	similar to RAD23B protein	T93562	9.7480E-06
209945_s_at	GSK3B	glycogen synthase kinase 3 beta	BC000251	1.0201E-05
205322_s_at	MTF1	metal-regulatory transcription factor 1	AW182367	
1.0323E-05				
204181_s_at	ZBTB43	zinc finger and BTB domain containing 43		T90308
1.0792E-05				
203321_s_at	ADNP2	ADNP homeobox 2	AK022688	1.1043E-05
201901_s_at	YY1	YY1 transcription factor	Z14077	1.1154E-05
212525_s_at	H2AFX	H2A histone family member X	AA760862	1.1321E-05
201917_s_at	SLC25A36	solute carrier family 25 member 36		AI694452
1.1789E-05				
211337_s_at	TUBGCP4	tubulin gamma complex associated protein 4		BC000966
1.1823E-05				
215179_x_at	PGF	Placenta growth factor 2 (PlGF-2)		AK023843
1.2046E-05				
205967_at	HIST1H4A	histone cluster 1 H4a	NM_003542	1.2155E-05
210943_s_at	LYST	lysosomal trafficking regulator	U84744	1.2287E-05
221753_at	SSH1	slingshot homolog 1 (Drosophila)		AI651213
1.2405E-05				
221705_s_at	SIKE	suppressor of IKK epsilon	BC005934	1.3958E-05
215892_at	ZNF440	zinc finger protein 440 mRNA (cDNA clone MGC:46665		
IMAGE:5556302)	AK021474			1.4065E-05
208624_s_at	EIF4G1	eukaryotic translation initiation factor 4 gamma 1		
BE966878				1.4201E-05
208610_s_at	SRRM2	serine/arginine repetitive matrix 2		AI655799
1.4389E-05				
222366_at		null	W86781	1.4392E-05
220085_at	HELLS	helicase lymphoid-specific	NM_018063	1.4498E-05
207657_x_at	TNPO1	transportin 1	NM_002270	1.4524E-05
214815_at	TRIM33	tripartite motif-containing 33	AU136587	1.5331E-05
212520_s_at	SMARCA4	SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily a member 4	AI684141	1.5496E-05
221986_s_at	KLHL24	kelch-like 24 (Drosophila)	AW006750	1.5586E-05
217007_s_at	ADAM15	ADAM metalloproteinase domain 15	AK000667	1.5851E-05
210479_s_at	RORA	RAR-related orphan receptor A	L14611	1.6006E-05
204021_s_at	PURA	purine-rich element binding protein A	NM_005859	
1.7428E-05				
220572_at	DKFZp547G183	hypothetical LOC55525	NM_018705	1.8600E-05
206462_s_at	NTRK3	neurotrophic tyrosine kinase receptor type 3		NM_002530
1.8602E-05				
207057_at	SLC16A7	solute carrier family 16 member 7 (monocarboxylic acid transporter 2)	NM_004731	1.9146E-05
207911_s_at	TGM5	transglutaminase 5	NM_004245	1.9378E-05
207730_x_at		null	NM_017932	1.9989E-05
217620_s_at	PIK3CB	phosphoinositide-3-kinase catalytic beta polypeptide		
AA805318				2.0764E-05
208345_s_at	POU3F1	POU class 3 homeobox 1	NM_002699	2.1059E-05
220796_x_at	SLC35E1	solute carrier family 35 member E1		NM_024881
2.1364E-05				
210613_s_at	SYNGR1	synaptogyrin 1	BC000731	2.1806E-05
214305_s_at	SF3B1	splicing factor 3b subunit 1 155kDa		AW003030
2.2116E-05				
201867_s_at	TBL1X	transducin (beta)-like 1X-linked		AW968555
2.2119E-05				
213748_at	TRIM66	tripartite motif-containing 66	AW271713	2.2307E-05
220688_s_at	MRT04	mRNA turnover 4 homolog (S. cerevisiae)		NM_016183
2.2339E-05				

Table_D

204180_s_at 2.2691E-05	ZBTB43	zinc finger and BTB domain containing 43	AI745225
202669_s_at	EFNB2	ephrin-B2	U16797 2.2926E-05
208003_s_at NM_006599	NFAT5	nuclear factor of activated T-cells 5	tonicity-responsive
212106_at 2.3380E-05	FAF2	Fas associated factor family member 2	BF116183
211921_x_at	PTMA	prothymosin alpha	AF348514 2.3625E-05
220901_at	GPR157	G protein-coupled receptor 157	NM_024980 2.4153E-05
218930_s_at 2.4608E-05	TMEM106B	transmembrane protein 106B	NM_018374
211992_at 2.4613E-05	WNK1	WNK lysine deficient protein kinase 1	AI445745
215206_at		null	AK025143 2.4978E-05
203181_x_at	SRPK2	SFRS protein kinase 2	AW149364 2.5494E-05
209030_s_at	CADM1	cell adhesion molecule 1	NM_014333 2.5571E-05
211316_x_at 2.6699E-05	CFLAR	CASP8 and FADD-like apoptosis regulator	AF009616
211387_x_at 2.7582E-05	RNGTT	RNA guanylyltransferase and 5'-phosphatase	AB012143
219633_at 2.8430E-05	TTPAL	tocopherol (alpha) transfer protein-like	NM_024331
200637_s_at 2.8541E-05	PTPRF	protein tyrosine phosphatase receptor type F	AI762627
213298_at x12492 2.8753E-05	NFIC	nuclear factor I/C (CCAAT-binding transcription factor)	
212079_s_at	MLL	myeloid/lymphoid or mixed-lineage leukemia (trithorax	
homolog Drosophila)	AA715041		2.9516E-05
219235_s_at 3.0091E-05	PHACTR4	phosphatase and actin regulator 4	NM_023923
212229_s_at	FBXO21	F-box protein 21	AK001699 3.0649E-05
220720_x_at 3.1771E-05	FAM128B	family with sequence similarity 128 member B	NM_025029
219717_at 3.4671E-05	C4orf30	chromosome 4 open reading frame 30	NM_017741
210426_x_at	RORA	RAR-related orphan receptor A	U04897 3.5549E-05
207382_at	TP63	tumor protein p63	NM_003722 3.6289E-05
202082_s_at	SEC14L1	SEC14-like 1 (S. cerevisiae)	AV748469 3.6797E-05
215628_x_at		null	AL049285 3.6881E-05
210057_at (C. elegans)	SMG1	SMG1 homolog phosphatidylinositol 3-kinase-related kinase	
212808_at	U32581		3.7071E-05
calcineurin-dependent 2	NFATC2IP	nuclear factor of activated T-cells cytoplasmic	
215066_at		interacting protein	AI884627 3.9473E-05
3.9879E-05	PTPRF	protein tyrosine phosphatase receptor type F	AU158443
205370_x_at 4.0073E-05	DBT	dihydrolipoamide branched chain transacylase E2	NM_001918
218489_s_at 4.1739E-05	ALAD	aminolevulinate delta- dehydratase	NM_000031
209024_s_at AI472757	SYNCRIP	synaptotagmin binding cytoplasmic RNA interacting protein	
210407_at			4.1961E-05
alpha isoform	PPM1A	protein phosphatase 1A (formerly 2C) magnesium-dependent	
204290_s_at	AF070670		4.2137E-05
4.2320E-05	ALDH6A1	aldehyde dehydrogenase 6 family member A1	NM_005589
33646_g_at	GM2A	GM2 ganglioside activator	X61094 4.2372E-05
201606_s_at	PWP1	PWP1 homolog (S. cerevisiae)	BE796924 4.3138E-05
208485_x_at 4.3820E-05	CFLAR	CASP8 and FADD-like apoptosis regulator	NM_003879
215428_at		null	AL109707 4.4947E-05
201918_at 4.5232E-05	SLC25A36	solute carrier family 25 member 36	AI927944
221416_at	PLA2G2F	phospholipase A2 group IIF	NM_022819 4.5850E-05

Table_D

221006_s_at	SNX27	sorting nexin family member 27	NM_030918	4.6187E-05
209065_at	UQCRB	ubiquinol-cytochrome c reductase binding protein		
BC005230				4.6351E-05
219910_at	FICD	FIC domain containing	NM_007076	4.6518E-05
210130_s_at	TM7SF2	transmembrane 7 superfamily member 2	AF096304	
4.6563E-05				
216189_at		null	BC002465	4.7282E-05
39313_at	WNK1	KIAA0344 gene	AB002342	4.8130E-05
208930_s_at	ILF3	interleukin enhancer binding factor 3 90kDa		BG032366
4.8427E-05				
208549_x_at	PTMAP7	prothymosin alpha pseudogene 7	NM_016171	4.9816E-05
201631_s_at	IER3	immediate early response 3	NM_003897	5.0093E-05
210701_at	CFDP1	craniofacial development protein 1	D85939	5.0154E-05
213998_s_at	DDX17	DEAD (Asp-Glu-Ala-Asp) box polypeptide 17		AW188131
5.0660E-05				
214972_at	MGEA5	Meningioma expressed antigen 5 (hyaluronidase) mRNA (cDNA		
clone MGC:48750	IMAGE:558183)	AU144791		5.0939E-05
220113_x_at	POLR1B	polymerase (RNA) I polypeptide B 128kDa	NM_019014	
5.1800E-05				
209203_s_at	BICD2	bicaudal D homolog 2 (Drosophila)		BC002327
5.2918E-05				
209508_x_at	CFLAR	CASP8 and FADD-like apoptosis regulator	AF005774	
5.4720E-05				
208120_x_at	FKSG49	FKSG49	NM_031221	5.4869E-05
201683_x_at	TOX4	TOX high mobility group box family member 4		BE783632
5.5472E-05				
201548_s_at	JARID1B	jumonji AT rich interactive domain 1B	W02593	5.7057E-05
216175_at		null	AK025276	5.8353E-05
209225_x_at	TNPO1	transportin 1	AI653355	5.8424E-05
212629_s_at	PKN2	protein kinase N2	AI633689	5.8864E-05
214843_s_at	USP33	ubiquitin specific peptidase 33	AK022864	5.8995E-05
212840_at	UBXN7	UBX domain protein 7	BG339560	5.9251E-05
214374_s_at	PPFIBP1	PTPRF interacting protein binding protein 1 (liprin beta 1)		
AI962377				5.9916E-05
212807_s_at	SORT1	sortilin 1	BF447105	6.1077E-05
201879_at	ARIH1	ariadne homolog ubiquitin-conjugating enzyme E2 binding		
protein 1 (Drosophila)			AI694332	6.1735E-05
202844_s_at	RALBP1	ralA binding protein 1	AW025261	6.2362E-05
203176_s_at	TFAM	transcription factor A mitochondrial		BE552470
6.3943E-05				
202867_s_at	DNAJB12	DnaJ (Hsp40) homolog subfamily B member 12		NM_017626
6.5775E-05				
217593_at	ZSCAN18	zinc finger and SCAN domain containing 18		AI375002
6.6413E-05				
201846_s_at	RYBP	RING1 and YY1 binding protein	NM_012234	6.6541E-05
210734_x_at	MAX	MYC associated factor X M64240		6.7154E-05
221985_at	KLHL24	kelch-like 24 (Drosophila)	AW006750	6.8295E-05
213506_at	F2RL1	coagulation factor II (thrombin) receptor-like 1		
BE965369				6.9457E-05
219915_s_at	SLC16A10	solute carrier family 16 member 10 (aromatic amino		
acid transporter)			NM_018593	7.0225E-05
216243_s_at	IL1RN	interleukin 1 receptor antagonist		BE563442
7.0801E-05				
210679_x_at		null	BC002629	7.1307E-05
204863_s_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M		
receptor)	BE856546			7.2636E-05
209750_at	NR1D2	nuclear receptor subfamily 1 group D member 2		N32859
7.4546E-05				
204680_s_at	RAPGEF5	Rap guanine nucleotide exchange factor (GEF) 5		AI263837
7.6949E-05				
205809_s_at	WASL	wiskott-Aldrich syndrome-like	BE504979	7.7732E-05
217370_x_at	FUS	fusion (involved in t(12;16) in malignant liposarcoma)		
S75762				7.8524E-05

Table_D				
201085_s_at	SON	SON DNA binding protein	AA664291	8.0308E-05
217550_at	ATF6	ATF family member ATF6 (ATF6)	AA576497	8.1358E-05
213299_at	ZBTB7A	zinc finger and BTB domain containing 7A		AW027070
8.2767E-05				
217152_at		null	AK024136	8.4186E-05
204358_s_at	FLRT2	fibronectin leucine rich transmembrane protein 2		
AF169676				8.5719E-05
201996_s_at	SPEN	spen homolog transcriptional regulator (Drosophila)		
AL524033				8.8224E-05
213446_s_at	IQGAP1	IQ motif containing GTPase activating protein 1	AI679073	
8.8686E-05				
214001_x_at	RPS10	Ribosomal protein S10	AW302047	8.9790E-05
211317_s_at	CFLAR	CASP8 and FADD-like apoptosis regulator	AF041461	
9.0579E-05				
204131_s_at	FOXO3	forkhead box O3	N25732	9.2446E-05
202971_s_at	DYRK2	dual-specificity tyrosine-(Y)-phosphorylation regulated		
kinase 2			NM_006482	9.2687E-05
209807_s_at	NFIX	nuclear factor I/X (CCAAT-binding transcription factor)		
U18759				9.3413E-05
222180_at		null	AU147889	9.4177E-05
216711_s_at	TAF1	TAF1 RNA polymerase II TATA box binding protein		
(TBP)-associated factor			250kDa M73444	9.4219E-05
214912_at		null	AK022067	9.4601E-05
203899_s_at	CRCP	CGRP receptor component	NM_014478	9.4951E-05
208336_s_at	GPSN2	glycoprotein synaptic 2	NM_004868	9.7951E-05
200616_s_at	MLEC	malectin	BC000371	1.0015E-04
219963_at	DUSP13	dual specificity phosphatase 13	NM_016364	1.0195E-04
222263_at	SLC35E1	solute carrier family 35 member E1		BE904333
1.0454E-04				
202045_s_at	GRLF1	glucocorticoid receptor DNA binding factor 1		AI670100
1.0659E-04				
213650_at	GOLGA8A	golgi autoantigen golgin subfamily a 8A		AW006438
1.0835E-04				
220675_s_at	PNPLA3	patatin-like phospholipase domain containing 3		NM_025225
1.0928E-04				
211000_s_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M		
receptor)				
208114_s_at	AB015706			1.1061E-04
NM_030980	ISG20L2	interferon stimulated exonuclease gene 20kDa-like 2		
203515_s_at	PMVK	phosphomevalonate kinase	NM_006556	1.1168E-04
209890_at	TSPAN5	tetraspanin 5	AF065389	1.1232E-04
203027_s_at	MVD	mevalonate (diphospho) decarboxylase		AI189359
1.1424E-04				
210251_s_at	RUFY3	RUN and FYVE domain containing 3		AF112221
1.1432E-04				
207993_s_at	CHP	calcium binding protein P22	NM_007236	1.1696E-04
212007_at	UBXN4	UBX domain protein 4	AI927512	1.1705E-04
218150_at	ARL5A	ADP-ribosylation factor-like 5A	NM_012097	1.1723E-04
202035_s_at	SFRP1	secreted frizzled-related protein 1		AI332407
1.1931E-04				
221765_at	UGCG	UDP-glucose ceramide glucosyltransferase		AI378044
1.1935E-04				
201183_s_at	CHD4	chromodomain helicase DNA binding protein 4		AI613273
1.2057E-04				
213579_s_at	EP300	E1A binding protein p300	AI459462	1.2148E-04
210598_at		null	AF130051	1.2242E-04
208042_at	AGGF1	angiogenic factor with G patch and FHA domains 1		
NM_013303				1.2329E-04
208699_x_at	TKT	transketolase	BF696840	1.2417E-04
204463_s_at	EDNRA	endothelin receptor type A	AU118882	1.2584E-04
216316_x_at	GK	glycerol kinase x78713		1.2804E-04
203542_s_at	KLF9	Kruppel-like factor 9	AI690205	1.2986E-04
214833_at	TMEM63A	transmembrane protein 63A	AB007958	1.3339E-04

Table_D

201072_s_at	SMARCC1	SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily c member 1	AW152160	1.3391E-04	
217813_s_at	SPIN1	spindlin 1	NM_006717	1.3414E-04	
200635_s_at	PTPRF	protein tyrosine phosphatase receptor type F			AU145351
1.3466E-04					
209069_s_at	H3F3A	H3 histone family 3A	BC001124	1.3652E-04	
35436_at	GOLGA2	golgi autoantigen golgin subfamily a 2	L06147	1.3653E-04	
201287_s_at	SDC1	syndecan 1	NM_002997	1.3732E-04	
214670_at	ZKSCAN1	zinc finger with KRAB and SCAN domains 1			AA653300
1.4190E-04					
222214_at		null	AK024988	1.4292E-04	
219428_s_at	PXMP4	peroxisomal membrane protein 4 24kDa			BF057649
1.4316E-04					
203524_s_at	MPST	mercaptopyruvate sulfurtransferase			NM_021126
1.4351E-04					
213805_at	ABHD5	abhydrolase domain containing 5	AI692428	1.4397E-04	
209193_at	PIM1	pim-1 oncogene	M24779	1.4475E-04	
218724_s_at	TGIF2	TGFB-induced factor homeobox 2	NM_021809	1.4720E-04	
219723_x_at	AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3			NM_020132
1.4809E-04					
220178_at	C19orf28	chromosome 19 open reading frame 28			NM_021731
1.4817E-04					
222036_s_at	MCM4	minichromosome maintenance complex component 4			AI859865
1.4881E-04					
203975_s_at	CHAF1A	chromatin assembly factor 1 subunit A (p150)			BF000239
1.4883E-04					
214352_s_at	KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog			
BF673699					
205783_at	KLK13	kallikrein-related peptidase 13	NM_015596	1.5104E-04	
211040_x_at	GTSE1	G-2 and S-phase expressed 1	BC006325	1.5322E-04	
207700_s_at	NCOA3	nuclear receptor coactivator 3	NM_006534	1.5903E-04	
215986_at		null	AU146999	1.5936E-04	
222284_at		null	AI734111	1.6225E-04	
215355_at	POU2F3	CDNA FLJ61459 complete cds highly similar to POU domain class 2 transcription factor 3	AI686582	1.6659E-04	
204712_at	WIF1	WNT inhibitory factor 1	NM_007191	1.6699E-04	
204074_s_at	KIAA0562	KIAA0562	AI936976	1.6713E-04	
204710_s_at	WIPI2	WD repeat domain phosphoinositide interacting 2			NM_016003
1.6842E-04					
203007_x_at	LYPLA1	lysophospholipase I	AF077198	1.6870E-04	
218155_x_at	TSR1	TSR1 20S rRNA accumulation homolog (S. cerevisiae)			
AK026565					
204941_s_at	ALDH3B2	aldehyde dehydrogenase 3 family member B2			AA071510
1.7220E-04					
213936_x_at	SFTPB	surfactant protein B	AW276646	1.7285E-04	
217713_x_at		null	AA126763	1.7423E-04	
91920_at	BCAN	brevican	AI205180	1.7852E-04	
216641_s_at	LAD1	ladinin 1	U58994	1.7900E-04	
202028_s_at	RPL38	ribosomal protein L38	BC000603	1.8201E-04	
200842_s_at	EPRS	glutamyl-prolyl-tRNA synthetase	AI475965	1.8206E-04	
215032_at	RREB1	ras responsive element binding protein 1			AK022442
1.8444E-04					
211944_at	BAT2D1	BAT2 domain containing 1	BE729523	1.8445E-04	
215780_s_at	SET	SET translocation (myeloid leukemia-associated)			pseudogene
Z95126					
209136_s_at	USP10	ubiquitin specific peptidase 10	BG390445	1.8544E-04	
201035_s_at	HADH	hydroxyacyl-Coenzyme A dehydrogenase			BC000306
1.8556E-04					
205338_s_at	DCT	dopachrome tautomerase (dopachrome delta-isomerase tyrosine-related protein 2)	NM_001922	1.8660E-04	
219392_x_at	PRR11	proline rich 11	NM_018304	1.8715E-04	
214682_at	LOC399491	LOC399491 protein			AK023376
221419_s_at		null	NM_013307	1.8781E-04	

Table_D

201411_s_at member 2	PLEKHB2	pleckstrin homology domain containing family B (evectins)		
202053_s_at	NM_017958		1.9071E-04	
1.9195E-04	ALDH3A2	aldehyde dehydrogenase 3 family member A2		L47162
215029_at		null	AL117451	1.9204E-04
217482_at		null	AK021987	1.9253E-04
218521_s_at	UBE2W	ubiquitin-conjugating enzyme E2W (putative)		NM_018299
1.9276E-04				
208200_at	IL1A	interleukin 1 alpha	NM_000575	1.9377E-04
200727_s_at	ACTR2	ARP2 actin-related protein 2 homolog (yeast)		AA699583
1.9730E-04				
215069_at	NMT2	N-myristoyltransferase 2	AK025065	1.9771E-04
215067_x_at	PRDX2	peroxiredoxin 2	AU147942	2.0142E-04
201294_s_at	WSB1	WD repeat and SOCS box-containing 1	N24643	2.0215E-04
201205_at		null	AF006751	2.0372E-04
214734_at	EXPH5	exophilin 5	AB014524	2.0781E-04
210513_s_at	VEGFA	vascular endothelial growth factor A	AF091352	
2.0886E-04				
209167_at	GPM6B	glycoprotein M6B	AI419030	2.1021E-04
206551_x_at	KLHL24	kelch-like 24 (Drosophila)	NM_017644	2.1048E-04
221830_at	RAP2A	RAP2A member of RAS oncogene family	AI302106	
2.1126E-04				
204675_at	SRD5A1	steroid-5-alpha-reductase alpha polypeptide 1 (3-oxo-5		
alpha-steroid delta 4-dehydrogenase alpha 1)			NM_001047	2.1270E-04
212468_at	SPAG9	sperm associated antigen 9	AK023512	2.1355E-04
213228_at	PDE8B	phosphodiesterase 8B	AK023913	2.1410E-04
206929_s_at	NFIC	nuclear factor I/C (CCAAT-binding transcription factor)		
NM_005597				2.1412E-04
204347_at	AK3L1	adenylate kinase 3-like 1	AI653169	2.1420E-04
204387_x_at	MRP63	mitochondrial ribosomal protein 63	NM_024026	
2.1456E-04				
212290_at	SLC7A1	solute carrier family 7 (cationic amino acid transporter y+		
system) member 1			AA527433	2.1475E-04
210282_at	ZMYM2	zinc finger MYM-type 2	AL136621	2.1681E-04
216503_s_at	MLLT10	myeloid/lymphoid or mixed-lineage leukemia (trithorax		
homolog Drosophila); translocated to 10			AF060927	2.1739E-04
216512_s_at	DCT	dopachrome tautomerase (dopachrome delta-isomerase		
tyrosine-related protein 2)			AL139318	2.2002E-04
220011_at	Clorf135	chromosome 1 open reading frame 135		NM_024037
2.2283E-04				
217703_x_at		null	AA401963	2.2444E-04
202122_s_at	M6PRBP1	mannose-6-phosphate receptor binding protein 1		NM_005817
2.2502E-04				
219789_at	NPR3	natriuretic peptide receptor C/guanylate cyclase C		
(atrionatriuretic peptide receptor C)			AI628360	2.2627E-04
208615_s_at	PTP4A2	protein tyrosine phosphatase type IVA member 2		BF795101
2.2678E-04				
219341_at	CLN8	ceroid-lipofuscinosis neuronal 8 (epilepsy progressive with		
mental retardation)			NM_018941	2.3705E-04
33148_at	ZFR	zinc finger RNA binding protein	AI459274	2.3899E-04
214383_x_at	KLHDC3	kelch domain containing 3	BF063121	2.3941E-04
1053_at RFC2		replication factor C (activator 1) 2 40kDa	M87338	2.4024E-04
215620_at	RREB1	ras responsive element binding protein 1		AU147182
2.4784E-04				
214715_x_at	ZNF160	zinc finger protein 160	AK024789	2.5344E-04
205538_at	CORO2A	coronin actin binding protein 2A		NM_003389
2.5574E-04				
202975_s_at	RHOBTB3	Rho-related BTB domain containing 3	N21138	2.5588E-04
221479_s_at	BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like		
AF060922				2.5978E-04
215600_x_at	FBXW12	CDNA FLJ40275 fis clone TESTI2027185	AK022174	
2.6324E-04				
204375_at	CLSTN3	calsyntenin 3	NM_014718	2.6950E-04

Table_D				
217862_at	PIAS1	protein inhibitor of activated STAT 1	N24868	2.6992E-04
215604_x_at		null AK023783		2.7098E-04
213209_at	TAF6L	TAF6-like RNA polymerase II p300/CBP-associated factor		
(PCAF)-associated factor	65kDa	BF058726		2.7694E-04

Table_E

Probe Set ID	CMP_62_13	CMapRank
33579_i_at	1	
205182_s_at	2	
216001_at	3	
222160_at	4	
202005_at	5	
211197_s_at	6	
209325_s_at	7	
208725_at	8	
207675_x_at	9	
204397_at	10	
217516_x_at	11	
207136_at	12	
204466_s_at	13	
212823_s_at	14	
202616_s_at	15	
219853_at	16	
217171_at	17	
221176_x_at	18	
208349_at	19	
215292_s_at	20	
208340_at	10100	
214046_at	10101	
219159_s_at	10102	
207402_at	10103	
215757_at	10104	
217026_at	10105	
210163_at	10106	
207659_s_at	10107	
214470_at	10108	
203703_s_at	10109	
222114_x_at	10110	
208515_at	10111	
207369_at	10112	
206865_at	10113	
214067_at	10114	
214059_at	10115	
206498_at	10116	
206957_at	10117	
206434_at	10118	
221391_at	10119	
211701_s_at	10120	
213075_at	22193	
219784_at	22194	
214283_at	22195	
215233_at	22196	
219752_at	22197	
208987_s_at	22198	
203836_s_at	22199	
216025_x_at	22200	
220178_at	22201	
210126_at	22202	
216320_x_at	22203	
222015_at	22204	
214372_x_at	22205	
205875_s_at	22206	
218720_x_at	22207	
211573_x_at	22208	
219640_at	22209	
204701_s_at	22210	
204484_at	22211	

Table_E

209547_s_at	22212
209876_at	22213
219664_s_at	22214

Table_F

Probe Set ID	CMP_61_13	CMapRank
216074_x_at	1	
217391_x_at	2	
219807_x_at	3	
220538_at	4	
205654_at	5	
213710_s_at	6	
202099_s_at	7	
204307_at	8	
213141_at	9	
210974_s_at	10	
217723_x_at	11	
202991_at	12	
218272_at	13	
219057_at	14	
212487_at	15	
206485_at	16	
206289_at	17	
202669_s_at	18	
205182_s_at	19	
216472_at	20	
220630_s_at	10100	
211333_s_at	10101	
203547_at	10102	
210889_s_at	10103	
221159_at	10104	
208253_at	10105	
216188_at	10106	
216879_at	10107	
205949_at	10108	
216763_at	10109	
215186_at	10110	
221141_x_at	10111	
209145_s_at	10112	
206731_at	10113	
217514_at	10114	
213162_at	10115	
217429_at	10116	
206645_s_at	10117	
37201_at	10118	
217706_at	10119	
207167_at	10120	
210357_s_at	22194	
222362_at	22195	
213303_x_at	22196	
211112_at	22197	
214879_x_at	22198	
210739_x_at	22199	
216042_at	22200	
209436_at	22201	
206063_x_at	22202	
213521_at	22203	
209926_at	22204	
218965_s_at	22205	
206911_at	22206	
222167_at	22207	
221061_at	22208	
214893_x_at	22209	
202685_s_at	22210	
218599_at	22211	
215595_x_at	22212	

221992_at
215015_at

22213
22214

Table_F

Table_G

Probe Set ID	CMP_62_24	CMapRank
212925_at	1	
214542_x_at	2	
206739_at	3	
214223_at	4	
222013_x_at	5	
221010_s_at	6	
205648_at	7	
207346_at	8	
208040_s_at	9	
214054_at	10	
204776_at	11	
205950_s_at	12	
221270_s_at	13	
216293_at	14	
206994_at	15	
222210_at	16	
216940_x_at	17	
215736_at	18	
205275_at	19	
222375_at	20	
217583_at	11000	
214025_at	11001	
210392_x_at	11002	
216673_at	11003	
220911_s_at	11004	
207873_x_at	11005	
219572_at	11006	
214329_x_at	11007	
213683_at	11008	
208385_at	11009	
211336_x_at	11010	
205380_at	11011	
204855_at	11012	
208593_x_at	11013	
214952_at	11014	
220893_at	11015	
215228_at	11016	
205814_at	11017	
210121_at	11018	
208208_at	11019	
215465_at	11020	
209794_at	22194	
221810_at	22195	
217107_at	22196	
212611_at	22197	
217135_x_at	22198	
221077_at	22199	
211241_at	22200	
212153_at	22201	
210126_at	22202	
212475_at	22203	
209547_s_at	22204	
208987_s_at	22205	
216320_x_at	22206	
212713_at	22207	
204484_at	22208	
214880_x_at	22209	
206764_x_at	22210	
219636_s_at	22211	
210933_s_at	22212	

219664_s_at	22213
219018_s_at	22214

Table_G

Table_H

Probe Set ID	CMP_61_23 CMapRank
209547_s_at	1
210974_s_at	2
210348_at	3
219807_x_at	4
205743_at	5
216243_s_at	6
215195_at	7
214320_x_at	8
220940_at	9
220694_at	10
210325_at	11
205950_s_at	12
201808_s_at	13
220319_s_at	14
220243_at	15
220028_at	16
336_at	17
215757_at	18
207670_at	19
211304_x_at	20
221866_at	11000
208534_s_at	11001
211643_x_at	11002
219890_at	11003
216655_s_at	11004
216065_at	11005
213945_s_at	11006
215048_at	11007
211232_x_at	11008
220687_at	11009
215770_at	11010
204915_s_at	11011
203325_s_at	11012
212706_at	11013
205948_at	11014
205852_at	11015
205155_s_at	11016
222089_s_at	11017
203071_at	11018
221784_at	11019
210794_s_at	11020
205918_at	22194
208347_at	22195
215845_x_at	22196
205662_at	22197
208301_at	22198
212559_at	22199
211088_s_at	22200
209031_at	22201
216532_x_at	22202
213755_s_at	22203
211112_at	22204
207953_at	22205
202497_x_at	22206
209035_at	22207
215849_x_at	22208
210201_x_at	22209
219847_at	22210
202328_s_at	22211
219664_s_at	22212

204757_s_at	22213
216822_x_at	22214

Table_H

Probe set ID	Gene Symbol	Gene Name	Table_I Representative Public ID	Log
t-ttestRank				
205236_x_at	SOD3	superoxide dismutase 3 extracellular	NM_003102	1
213113_s_at	SLC43A3	solute carrier family 43 member 3	AI630178	3
212796_s_at	TBC1D2B	TBC1 domain family member 2B	BF195608	4
213364_s_at	SNX1	sorting nexin 1	AI052536	7
202510_s_at	TNFAIP2	tumor necrosis factor alpha-induced protein 2	NM_006291	8
213258_at	TFPI	tissue factor pathway inhibitor (lipoprotein-associated		
coagulation inhibitor)	BF511231		9	
202291_s_at	MGP	matrix Gla protein	NM_000900	13
219304_s_at	PDGFD	platelet derived growth factor D	NM_025208	14
202994_s_at	FBLN1	fibulin 1	Z95331	15
212589_at	RRAS2	related RAS viral (r-ras) oncogene homolog 2	AI753792	16
202912_at	ADM	adrenomedullin	NM_001124	17
203088_at	FBLN5	fibulin 5	NM_006329	20
216620_s_at	ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10		
AF009205	21			
212067_s_at	C1R	complement component 1 r subcomponent	AL573058	22
202363_at	SPOCK1	sparc/osteonectin cwcw and kazal-like domains proteoglycan		
(testican) 1	AF231124		23	
206157_at	PTX3	pentraxin-related gene rapidly induced by IL-1 beta		
NM_002852	24			
208747_s_at	C1S	complement component 1 s subcomponent	M18767	29
209763_at	CHRD1	chordin-like 1	AL049176	30
200785_s_at	LOC100134190	similar to low density lipoprotein-related protein 1		
(alpha-2-macroglobulin receptor)			NM_002332	31
206373_at	ZIC1	Zic family member 1 (odd-paired homolog Drosophila)		
NM_003412	33			
213164_at	SLC5A3	solute carrier family 5 (sodium/myo-inositol cotransporter)		
member 3	AI867198		34	
202897_at	SIRPA	signal-regulatory protein alpha	AB023430	36
201787_at	LOC100133843	fibulin 1	NM_001996	37
213348_at	CDKN1C	cyclin-dependent kinase inhibitor 1C (p57 Kip2)	N33167	38
201842_s_at	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1		
AI826799	39			
217800_s_at	NDFIP1	Nedd4 family interacting protein 1	NM_030571	40
212761_at	TCF7L2	transcription factor 7-like 2 (T-cell specific HMG-box)		
AI949687	41			
212944_at	SLC5A3	solute carrier family 5 (sodium/myo-inositol cotransporter)		
member 3	AK024896		43	
217904_s_at	BACE1	beta-site APP-cleaving enzyme 1	NM_012104	44
209335_at	DCN	decorin	AI281593	45
213568_at	OSR2	odd-skipped related 2 (Drosophila)	AI811298	49
205422_s_at	ITGBL1	integrin beta-like 1 (with EGF-like repeat domains)		
NM_004791	50			
200771_at	LAMC1	laminin gamma 1 (formerly LAMB2)	NM_002293	51
207606_s_at	ARHGAP12	Rho GTPase activating protein 12	NM_018287	
52				
213150_at	HOXA10	homeobox A10	BF792917	53
214494_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal		
recessive)	NM_005200		54	
205802_at	TRPC1	transient receptor potential cation channel subfamily c		
member 1	NM_003304		55	
212558_at	SPRY1	sprouty homolog 1 antagonist of FGF signaling (Drosophila)		
BF508662	57			
218901_at	PLSCR4	phospholipid scramblase 4	NM_020353	58
200986_at	SERPING1	serpin peptidase inhibitor clade G (C1 inhibitor)		
member 1	NM_000062		59	
204963_at	SSPN	sarcospan (Kras oncogene-associated gene)	AL136756	
60				
203939_at	NTSE	5'-nucleotidase ecto (CD73)	NM_002526	63

Table_I

201843_s_at NM_004105	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	64	
202995_s_at	FBLN1	fibulin 1	NM_006486	65
204749_at	NAP1L3	nucleosome assembly protein 1-like 3	NM_004538	66
212419_at	ZCCHC24	zinc finger CCHC domain containing 24	AA131324	67
203217_s_at NM_003896	ST3GAL5	ST3 beta-galactoside alpha-23-sialyltransferase 5		68
218418_s_at	KANK2	KN motif and ankyrin repeat domains 2	NM_015493	69
220327_at	VGLL3	vestigial like 3 (Drosophila)	NM_016206	72
205612_at	MMRN1	multimerin 1	NM_007351	73
218276_s_at	SAV1	salvador homolog 1 (Drosophila)	NM_021818	76
212224_at 78	ALDH1A1	aldehyde dehydrogenase 1 family member A1	NM_000689	
221950_at	EMX2	empty spiracles homeobox 2	AI478455	79
205407_at	RECK	reversion-inducing-cysteine-rich protein with kazal motifs		80
NM_021111	TCF7L1	transcription factor 7-like 1 (T-cell specific HMG-box)		83
221016_s_at NM_031283	UBL3	ubiquitin-like 3	NM_007106	87
201535_at	BICC1	bicaudal C homolog 1 (Drosophila)	AW025579	88
213429_at	TNS3	tensin 3	NM_022748	90
217853_at	SH3BP5	SH3-domain binding protein 5 (BTK-associated)		NM_004844
201811_x_at 91	VWA5A	von willebrand factor A domain containing 5A		NM_014622
205011_at 92	KIAA0907	KIAA0907	NM_014949	95
221019_s_at	COLEC12	collectin sub-family member 12	NM_030781	97
218162_at	OLFML3	olfactomedin-like 3	NM_020190	98
201744_s_at	LUM	lumican	NM_002345	99
202664_at 101	WIPF1	WAS/WASL interacting protein family member 1		AW058622
210135_s_at	SHOX2	short stature homeobox 2	AF022654	102
203083_at	THBS2	thrombospondin 2	NM_003247	104
201792_at	AEBP1	AE binding protein 1	NM_001129	105
209265_s_at	METTL3	methyltransferase like 3	BC001650	106
204457_s_at	GAS1	growth arrest-specific 1	NM_002048	109
213249_at	FBXL7	F-box and leucine-rich repeat protein 7	AU145127	111
201818_at 112	LPCAT1	lysophosphatidylcholine acyltransferase 1		NM_024830
203583_at	UNC50	unc-50 homolog (C. elegans)	NM_014044	113
212486_s_at	FYN	FYN oncogene related to SRC FGR YES	N20923	114
205609_at	ANGPT1	angiopoietin 1	NM_001146	117
202729_s_at NM_000627	LTBP1	latent transforming growth factor beta binding protein 1		119
36030_at	IFFO1	intermediate filament family orphan 1	AL080214	123
204140_at	TPST1	tyrosylprotein sulfotransferase 1	NM_003596	124
217122_s_at AL031282	LOC728661	similar to solute carrier family 35 member E2		125
200945_s_at	SEC31A	SEC31 homolog A (S. cerevisiae)	NM_014933	126
212621_at	TMEM194A	transmembrane protein 194A	AB006624	127
203131_at NM_006206	PDGFRA	platelet-derived growth factor receptor alpha polypeptide		129
218715_at (yeast) NM_018428	UTP6	UTP6 small subunit (SSU) processome component homolog		132
212877_at	KLC1	kinesin light chain 1	AA284075	134
218204_s_at 138	FYCO1	FYVE and coiled-coil domain containing 1		NM_024513
203812_at		null	AB011538	140
213422_s_at	MXRA8	matrix-remodelling associated 8	Aw888223	141
212736_at 142	C16orf45	chromosome 16 open reading frame 45		BE299456
212230_at	PPAP2B	phosphatidic acid phosphatase type 2B	AV725664	146
209550_at	NDN	necdin homolog (mouse)	U35139	147

Table_I

221556_at	CDC14B	CDC14 cell division cycle 14 homolog B (S. cerevisiae)		
BF792631	148			
213802_at		null	AI810767	149
218718_at	PDGFC	platelet derived growth factor C	NM_016205	150
218146_at	GLT8D1	glycosyltransferase 8 domain containing 1	NM_018446	
153				
205083_at	AOX1	aldehyde oxidase 1	NM_001159	154
213161_at	C9orf97	chromosome 9 open reading frame 97	AI583393	155
212597_s_at	HMGXB4	HMG box domain containing 4	AL079310	159
210105_s_at	FYN	FYN oncogene related to SRC FGR YES	M14333	160
203706_s_at	FZD7	frizzled homolog 7 (Drosophila)	NM_003507	163
202202_s_at	LAMA4	laminin alpha 4	NM_002290	165
216033_s_at	FYN	FYN oncogene related to SRC FGR YES	S74774	167
221897_at	TRIM52	tripartite motif-containing 52	AA205660	169
218656_s_at	LHFP	lipoma HMGIC fusion partner	NM_005780	173
204112_s_at	HNMT	histamine N-methyltransferase	NM_006895	175
204042_at	WASF3	WAS protein family member 3	AB020707	177
209568_s_at	RGL1	ral guanine nucleotide dissociation stimulator-like 1		
AF186779	179			
209884_s_at	SLC4A7	solute carrier family 4 sodium bicarbonate cotransporter		
member 7	AF047033		180	
201395_at	RBM5	RNA binding motif protein 5	NM_005778	185
219552_at	SVEP1	sushi von Willebrand factor type A EGF and pentraxin domain		
containing 1	NM_024500		188	
214323_s_at	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)		
N36842	189			
219093_at	PID1	phosphotyrosine interaction domain containing 1	NM_017933	
191				
204345_at	COL16A1	collagen type XVI alpha 1	NM_001856	198
203476_at	TPBG	trophoblast glycoprotein	NM_006670	202
203117_s_at	PAN2	PAN2 poly(A) specific ribonuclease subunit homolog (S.		
cerevisiae)	NM_014871		208	
204453_at	ZNF84	zinc finger protein 84	NM_003428	209
203600_s_at	C4orf8	chromosome 4 open reading frame 8	NM_003704	210
221760_at	MAN1A1	CDNA: FLJ21946 fis clone HEP04860 highly similar to HSHUMM9		
Homo sapiens	HUMM9 mRNA	BG287153	211	
218793_s_at	SCML1	sex comb on midleg-like 1 (Drosophila)	NM_006746	213
205542_at	STEAP1	six transmembrane epithelial antigen of the prostate 1		
NM_012449	215			
215388_s_at	CFH	complement factor H	X56210	217
201278_at	DAB2	disabled homolog 2 mitogen-responsive phosphoprotein		
(Drosophila)	N21202		218	
206958_s_at	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)		
AF318575	219			
202273_at	PDGFRB	platelet-derived growth factor receptor beta polypeptide		
NM_002609	224			
218686_s_at	RHBDL1	rhomboid 5 homolog 1 (Drosophila)	NM_022450	227
39650_s_at	PCNXL2	pecanex-like 2 (Drosophila)	AB007895	228
219639_x_at	PARP6	poly (ADP-ribose) polymerase family member 6	NM_020213	
231				
222235_s_at	CSGALNACT2	chondroitin sulfate		
N-acetylgalactosaminyltransferase 2	AL139812		232	
209580_s_at	MBD4	methyl-CpG binding domain protein 4	AF114784	234
212651_at	RHOBTB1	Rho-related BTB domain containing 1	AB018283	236
207177_at	PTGFR	prostaglandin F receptor (FP)	NM_000959	239
205452_at	PIGB	phosphatidylinositol glycan anchor biosynthesis class B		
NM_004855	241			
212195_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M		
receptor)	AL049265		242	
220351_at	CCRL1	chemokine (C-C motif) receptor-like 1	NM_016557	243
212503_s_at	DIP2C	DIP2 disco-interacting protein 2 homolog C (Drosophila)		
N22859	246			
218093_s_at	ANKRD10	ankyrin repeat domain 10	NM_017664	248

Table_I

207808_s_at	PROS1	protein S (alpha)	NM_000313	249	
201034_at	ADD3	adducin 3 (gamma)	BE545756	251	
212327_at	LIMCH1	LIM and calponin homology domains 1	AK026815	252	
212979_s_at	FAM115A	family with sequence similarity 115 member A	AW293343		
253					
212855_at	DCUN1D4	DCN1 defective in cullin neddylation 1 domain containing 4			
(S. cerevisiae)	D87466	257			
219283_at	C1GALT1C1	C1GALT1-specific chaperone 1	NM_014158	259	
211896_s_at	DCN	decorin	AF138302	260	
210139_s_at	PMP22	peripheral myelin protein 22	L03203	263	
207417_s_at	ZNF177	zinc finger protein 177	NM_003451	265	
200770_s_at	LAMC1	laminin gamma 1 (formerly LAMB2)	J03202	266	
202920_at	ANK2	ankyrin 2 neuronal	BF726212	267	
221569_at	AHL1	Abelson helper integration site 1	AL136797	268	
213737_x_at	GOLGA9P	golgi autoantigen golgin subfamily a 9 pseudogene			
AI620911		269			
202142_at	COPS8	COP9 constitutive photomorphogenic homolog subunit 8			
(Arabidopsis)	BC003090	270			
202951_at	STK38	serine/threonine kinase 38	BE048506	272	
201139_s_at	SSB	Sjogren syndrome antigen B (autoantigen La)	NM_003142		
274					
213293_s_at	TRIM22	tripartite motif-containing 22	AA083478	276	
218285_s_at	BDH2	3-hydroxybutyrate dehydrogenase type 2	NM_020139	278	
213262_at	SACS	spastic ataxia of Charlevoix-Saguenay (sacsin)	AI932370		
281					
203893_at	TAF9	TAF9 RNA polymerase II TATA box binding protein			
(TBP)-associated factor		32kDa	NM_016283	282	
201086_x_at	SON	SON DNA binding protein	NM_003103	283	
204085_s_at	CLN5	ceroid-lipofuscinosis neuronal 5	NM_006493	287	
204897_at	PTGER4	prostaglandin E receptor 4 (subtype EP4)	AA897516		
288					
212793_at	DAAM2	dishevelled associated activator of morphogenesis 2			
BF513244	289				
204036_at	LPAR1	lysophosphatidic acid receptor 1	AW269335	291	
212958_x_at	PAM	peptidylglycine alpha-amidating monooxygenase	AI022882		
292					
211535_s_at	FGFR1	fibroblast growth factor receptor 1	M60485	295	
212764_at	ZEB1	zinc finger E-box binding homeobox 1	AI806174	298	
221645_s_at	ZNF83	zinc finger protein 83	M27877	300	
208922_s_at	NXF1	nuclear RNA export factor 1	BC004904	301	
203139_at	DAPK1	death-associated protein kinase 1	NM_004938	302	
220992_s_at	C1orf25	chromosome 1 open reading frame 25	NM_030934	306	
214703_s_at	MAN2B2	mannosidase alpha class 2B member 2	AW954107	307	
214749_s_at	ARMCX6	armadillo repeat containing X-linked 6	AK000818	308	
201150_s_at	TIMP3	TIMP metalloproteinase inhibitor 3	NM_000362	309	
213455_at	FAM114A1	family with sequence similarity 114 member A1			
W87466	310				
203886_s_at	FBLN2	fibulin 2	NM_001998	313	
202104_s_at	SPG7	spastic paraplegia 7 (pure and complicated autosomal			
recessive)	NM_003119	316			
201669_s_at	MARCKS	myristoylated alanine-rich protein kinase C substrate			
NM_002356	318				
217792_at	SNX5	sorting nexin 5	NM_014426	319	
204093_at	CCNH	cyclin H	NM_001239	320	
208669_s_at	EID1	EP300 interacting inhibitor of differentiation 1			
AF109873	326				
204605_at	CGRFR1	cell growth regulator with ring finger domain 1	NM_006568		
328					
211675_s_at	MDFIC	MyoD family inhibitor domain containing	AF054589	331	
209101_at	CTGF	connective tissue growth factor	M92934	332	
201798_s_at	MYOF	myoferlin	NM_013451	334	
206876_at	SIM1	single-minded homolog 1 (Drosophila)	AL121948	338	
209946_at	VEGFC	vascular endothelial growth factor C	U58111	339	

Table_I				
216840_s_at	LAMA2	laminin alpha 2 AK026829	340	
208848_at	ADH5	alcohol dehydrogenase 5 (class III) chi polypeptide		
M30471 343				
218014_at	NUP85	nucleoporin 85kDa NM_024844	345	
202478_at	TRIB2	tribbles homolog 2 (Drosophila) NM_021643	346	
201063_at	RCN1	reticulocalbin 1 EF-hand calcium binding domain NM_002901		
347				
209409_at	GRB10	growth factor receptor-bound protein 10 D86962	348	
212681_at	EPB41L3	erythrocyte membrane protein band 4.1-like 3 AI770004		
349				
202598_at	S100A13	S100 calcium binding protein A13 NM_005979	351	
209497_s_at	RBM4B	RNA binding motif protein 4B BC003503	352	
219949_at	LRRC2	leucine rich repeat containing 2 NM_024512	353	
210312_s_at	IFT20	intraflagellar transport 20 homolog (Chlamydomonas)		
BC002640	354			
213266_at	TUBGCP4	Tubulin gamma complex associated protein 4 mRNA (cDNA clone		
MGC:2720 IMAGE:2821891)	BF592982	355		
219778_at	ZFPM2	zinc finger protein multitype 2 NM_012082	357	
210406_s_at	RAB6A	RAB6A member RAS oncogene family AL136727	358	
212148_at	PBX1	pre-B-cell leukemia homeobox 1 AL049381	359	
203241_at	UVRAG	UV radiation resistance associated gene NM_003369	360	
218076_s_at	ARHGAP17	Rho GTPase activating protein 17 NM_018054		
361				

Probe set ID	Gene Symbol	Gene Name	Table_J Representative Public ID	Log
t-testRank				
205187_at	SMAD5	SMAD family member 5	AF010601 6	
201702_s_at	PPP1R10	protein phosphatase 1 regulatory (inhibitor) subunit 10		
AI492873	11			
211074_at	FOLR1	folate receptor 1 (adult)	AF000381 19	
202102_s_at	BRD4	bromodomain containing 4	BF718610 25	
214265_at	ITGA8	integrin alpha 8	AI193623 26	
208711_s_at	CCND1	cyclin D1	BC000076 27	
222024_s_at	AKAP13	A kinase (PRKA) anchor protein 13	AK022014 28	
210717_at	null	AF116659 35		
206061_s_at	DICER1	dicer 1 ribonuclease type III	NM_030621 42	
209936_at	RBM5	RNA binding motif protein 5	AF107493 46	
211081_s_at	MAP4K5	mitogen-activated protein kinase kinase kinase 5		
225426 56				
217649_at	ZFAND5	zinc finger AN1-type domain 5	AV702306 70	
209088_s_at	UBN1	ubiquitin 1	T70262 81	
210807_s_at	SLC16A7	solute carrier family 16 member 7 (monocarboxylic acid		
transporter 2)	AF049608	84		
220071_x_at	CEP27	centrosomal protein 27kDa	NM_018097 85	
214153_at	ELOVL5	ELOVL family member 5 elongation of long chain fatty acids		
(FEN1/Elo2 SUR4/Elo3-like yeast)	BE467941	89		
211993_at	WNK1	WNK lysine deficient protein kinase 1	AI768512 100	
213718_at	RBM4	RNA binding motif protein 4	BE222257 103	
216858_x_at	null	AL080112 116		
212057_at	KIAA0182	KIAA0182	AA206161 121	
214041_x_at	RPL37A	Ribosomal protein L37a	BE857772 130	
209945_s_at	GSK3B	glycogen synthase kinase 3 beta	BC000251 131	
216187_x_at	null	AF222691 133		
221943_x_at	RPL38	Ribosomal protein L38 mRNA (cDNA clone MGC:1637		
IMAGE:3346447)	AW303136	136		
217538_at	SGSM2	small G protein signaling modulator 2	BF347113 137	
203803_at	PCYOX1	prenylcysteine oxidase 1	N45309 139	
202040_s_at	JARID1A	jumonji AT rich interactive domain 1A	NM_005056 143	
211503_s_at	RAB14	RAB14 member RAS oncogene family	AF112206 145	
210479_s_at	RORA	RAR-related orphan receptor A	L14611 151	
205967_at	HIST1H4A	histone cluster 1 H4a	NM_003542 156	
201195_s_at	SLC7A5	solute carrier family 7 (cationic amino acid transporter y+		
system) member 5	AB018009	158		
204881_s_at	UGCG	UDP-glucose ceramide glucosyltransferase	NM_003358	
161				
201867_s_at	TBL1X	transducin (beta)-like 1X-linked	AW968555 162	
201901_s_at	YY1	YY1 transcription factor	Z14077 164	
211337_s_at	TUBGCP4	tubulin gamma complex associated protein 4	BC000966	
166				
214422_at	LOC131185	similar to RAD23B protein	T93562 168	
206036_s_at	REL	v-rel reticuloendotheliosis viral oncogene homolog (avian)		
NM_002908	170			
203742_s_at	LOC645233	thymine-DNA glycosylase pseudogene	BF674842	
171				
213517_at	PCBP2	poly(rc) binding protein 2	AW103422 174	
203318_s_at	ZNF148	zinc finger protein 148	NM_021964 176	
214815_at	TRIM33	tripartite motif-containing 33	AU136587 178	
212492_s_at	JMJD2B	jumonji domain containing 2B	AW237172 181	
207657_x_at	TNPO1	transportin 1	NM_002270 184	
213229_at	DICER1	dicer 1 ribonuclease type III	BF590131 186	
221705_s_at	SIKE	suppressor of IKK epsilon	BC005934 187	
210943_s_at	LYST	lysosomal trafficking regulator	U84744 190	
212525_s_at	H2AFX	H2A histone family member x	AA760862 194	
208624_s_at	EIF4G1	eukaryotic translation initiation factor 4 gamma 1		
BE966878	196			
201917_s_at	SLC25A36	solute carrier family 25 member 36	AI694452	
197				

Table_J

212229_s_at	FBX021	F-box protein 21	AK001699	199	
204181_s_at	ZBTB43	zinc finger and BTB domain containing 43		T90308	200
204524_at	PDPK1	3-phosphoinositide dependent protein kinase-1		NM_002613	
201					
63825_at	ABHD2	abhydrolase domain containing 2	AI557319		203
221753_at	SSH1	slingshot homolog 1 (Drosophila)	AI651213		204
214902_x_at		null	AL080232	207	
211387_x_at	RNGTT	RNA guanylyltransferase and 5'-phosphatase		AB012143	
212					
201299_s_at	MOBK1B	MOB1 Mps One Binder kinase activator-like 1B (yeast)			
NM_018221					
205322_s_at	MTF1	metal-regulatory transcription factor 1	AW182367		216
215892_at	ZNF440	Zinc finger protein 440 mRNA (cDNA clone MGC:46665			
IMAGE:5556302)	AK021474		220		
220085_at	HELLS	helicase lymphoid-specific	NM_018063		223
212520_s_at	SMARCA4	SWI/SNF related matrix associated actin dependent regulator			
of chromatin subfamily a member 4			AI684141	226	
202940_at	WNK1	KIAA0344 gene	NM_014823	233	
222366_at		null	w86781	238	
210426_x_at	RORA	RAR-related orphan receptor A	U04897	240	
215179_x_at	PGF	Placenta growth factor 2 (PlGF-2)	AK023843		244
221986_s_at	KLHL24	kelch-like 24 (Drosophila)	AW006750		245
207057_at	SLC16A7	solute carrier family 16 member 7 (monocarboxylic acid			
transporter 2)	NM_004731		247		
203321_s_at	ADNP2	ADNP homeobox 2	AK022688	250	
204021_s_at	PURA	purine-rich element binding protein A	NM_005859		254
220901_at	GPR157	G protein-coupled receptor 157	NM_024980	255	
218930_s_at	TMEM106B	transmembrane protein 106B	NM_018374		258
207730_x_at		null	NM_017932	261	
211316_x_at	CFLAR	CASP8 and FADD-like apoptosis regulator	AF009616		262
208610_s_at	SRRM2	serine/arginine repetitive matrix 2	AI655799		264
219024_at	PLEKHA1	pleckstrin homology domain containing family A			
(phosphoinositide binding specific) member 1			NM_021622	271	
212079_s_at	MLL	myeloid/lymphoid or mixed-lineage leukemia (trithorax			
homolog Drosophila)	AA715041		273		
210613_s_at	SYNGR1	synaptogyrin 1	BC000731	280	
219235_s_at	PHACTR4	phosphatase and actin regulator 4		NM_023923	284
220688_s_at	MRT04	mRNA turnover 4 homolog (S. cerevisiae)		NM_016183	290
212106_at	FAF2	Fas associated factor family member 2	BF116183		293
201606_s_at	PWP1	PWP1 homolog (S. cerevisiae)	BE796924		294
211992_at	WNK1	WNK lysine deficient protein kinase 1	AI445745		296
208003_s_at	NFAT5	nuclear factor of activated T-cells 5 tonicity-responsive			
NM_006599			297		
220572_at	DKFZp547G183	hypothetical LOC55525	NM_018705		303
211921_x_at	PTMA	prothymosin alpha	AF348514		304
209065_at	UQCRB	ubiquinol-cytochrome c reductase binding protein			
BC005230			305		
213998_s_at	DDX17	DEAD (Asp-Glu-Ala-Asp) box polypeptide 17		AW188131	
311					
213298_at	NFIC	nuclear factor I/C (CCAAT-binding transcription factor)			
x12492 312					
209030_s_at	CADM1	cell adhesion molecule 1	NM_014333		315
214305_s_at	SF3B1	splicing factor 3b subunit 1 155kDa	AW003030		317
219910_at	FICD	FIC domain containing	NM_007076	322	
201631_s_at	IER3	immediate early response 3	NM_003897		323
208120_x_at	FKSG49	FKSG49	NM_031221	327	
204180_s_at	ZBTB43	zinc finger and BTB domain containing 43		AI745225	
330					
210057_at	SMG1	SMG1 homolog phosphatidylinositol 3-kinase-related kinase			
(C. elegans)	U32581		335		
219717_at	C4orf30	chromosome 4 open reading frame 30		NM_017741	336
203181_x_at	SRPK2	SFRS protein kinase 2	AW149364	337	
216175_at		null	AK025276	341	

Table_J					
202669_s_at	EFNB2	ephrin-B2	U16797	344	
220720_x_at	FAM128B	family with sequence similarity 128 member B			NM_025029
350					
212807_s_at	SORT1	sortilin 1	BF447105	356	
201918_at	SLC25A36	solute carrier family 25 member 36			AI927944
368					
204290_s_at	ALDH6A1	aldehyde dehydrogenase 6 family member A1			NM_005589
369					
200637_s_at	PTPRF	protein tyrosine phosphatase receptor type F			AI762627
371					
33646_g_at	GM2A	GM2 ganglioside activator	X61094	381	
220796_x_at	SLC35E1	solute carrier family 35 member E1			NM_024881
212808_at	NFATC2IP	nuclear factor of activated T-cells cytoplasmic			386
calcineurin-dependent 2		interacting protein	AI884627	389	
219633_at	TTPAL	tocopherol (alpha) transfer protein-like			NM_024331
395					
215628_x_at		null	AL049285	399	
221006_s_at	SNX27	sorting nexin family member 27			NM_030918
214972_at	MGEA5	Meningioma expressed antigen 5 (hyaluronidase) mRNA (cDNA			400
clone MGC:48750	IMAGE:5558183)	AU144791			403
209203_s_at	BICD2	bicaudal D homolog 2 (Drosophila)			BC002327
217620_s_at	PIK3CB	phosphoinositide-3-kinase catalytic beta polypeptide			405
AA805318	407				
200616_s_at	MLEC	malectin	BC000371	411	
215206_at		null	AK025143	414	
212629_s_at	PKN2	protein kinase N2	AI633689	417	
214374_s_at	PPFIBP1	PTPRF interacting protein binding protein 1 (liprin beta 1)			418
AI962377	418				
202867_s_at	DNAJB12	DnaJ (Hsp40) homolog subfamily B member 12			NM_017626
423					
210407_at	PPM1A	protein phosphatase 1A (formerly 2C) magnesium-dependent			
alpha isoform	AF070670	427			
201846_s_at	RYBP	RING1 and YY1 binding protein	NM_012234	428	
204131_s_at	FOXO3	forkhead box O3 N25732	429		
213748_at	TRIM66	tripartite motif-containing 66	AW271713	431	
210130_s_at	TM7SF2	transmembrane 7 superfamily member 2	AF096304	436	
204863_s_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M			
receptor)	BE856546	440			
201879_at	ARIH1	ariadne homolog ubiquitin-conjugating enzyme E2 binding			
protein 1 (Drosophila)	AI694332	442			
209225_x_at	TNPO1	transportin 1	AI653355	446	
209750_at	NR1D2	nuclear receptor subfamily 1 group D member 2			N32859
205370_x_at	DBT	dihydrolipoamide branched chain transacylase E2			NM_001918
449					
209024_s_at	SYNCRIP	synaptotagmin binding cytoplasmic RNA interacting protein			451
AI472757	451				
201548_s_at	JARID1B	jumonji AT rich interactive domain 1B	W02593	452	
216315_x_at	LOC100133558	similar to hCG1642170	AL121873	454	
210701_at	CFDP1	craniofacial development protein 1	D85939	462	
202844_s_at	RALBP1	ralA binding protein 1	AW025261	466	
208930_s_at	ILF3	interleukin enhancer binding factor 3 90kDa			BG032366
467					
212840_at	UBXN7	UBX domain protein 7	BG339560	473	
220113_x_at	POLR1B	polymerase (RNA) I polypeptide B 128kDa	NM_019014	477	
207993_s_at	CHP	calcium binding protein P22	NM_007236	484	
201085_s_at	SON	SON DNA binding protein	AA664291	489	
200727_s_at	ACTR2	ARP2 actin-related protein 2 homolog (yeast)			AA699583
498					
209508_x_at	CFLAR	CASP8 and FADD-like apoptosis regulator	AF005774	502	
214843_s_at	USP33	ubiquitin specific peptidase 33	AK022864	503	
201183_s_at	CHD4	chromodomain helicase DNA binding protein 4			AI613273
504					
221985_at	KLHL24	kelch-like 24 (Drosophila)	AW006750	509	

Table_J

217370_x_at	FUS	fusion (involved in t(12;16) in malignant liposarcoma)		
S75762_511				
219428_s_at	PXMP4	peroxisomal membrane protein 4 24kDa	BF057649	522
208485_x_at	CFLAR	CASP8 and FADD-like apoptosis regulator	NM_003879	523
203515_s_at	PMVK	phosphomevalonate kinase	NM_006556	532
208549_x_at	PTMAP7	prothymosin alpha pseudogene 7	NM_016171	535
205809_s_at	WASL	wiskott-Aldrich syndrome-like	BE504979	543
217152_at		null	AK024136	551
214001_x_at	RPS10	Ribosomal protein s10	AW302047	555
202035_s_at	SFRP1	secreted frizzled-related protein 1	AI332407	556
202082_s_at	SEC14L1	SEC14-like 1 (S. cerevisiae)	AV748469	565
219723_x_at	AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	NM_020132	
569				
201072_s_at	SMARCC1	SWI/SNF related matrix associated actin dependent regulator		
of chromatin subfamily c member 1			AW152160	570
203176_s_at	TFAM	transcription factor A mitochondrial	BE552470	575
217550_at	ATF6	ATF family member ATF6 (ATF6)	AA576497	576
204358_s_at	FLRT2	fibronectin leucine rich transmembrane protein 2		
AF169676				
204074_s_at	KIAA0562		AI936976	578
201035_s_at	HADH	hydroxyacyl-Coenzyme A dehydrogenase	BC000306	579
210679_x_at		null	BC002629	580
201683_x_at	TOX4	TOX high mobility group box family member 4		BE783632
587				
222284_at		null	AI734111	591
221765_at	UGCG	UDP-glucose ceramide glucosyltransferase		AI378044
596				
210251_s_at	RUFY3	RUN and FYVE domain containing 3	AF112221	600
218150_at	ARL5A	ADP-ribosylation factor-like 5A	NM_012097	604
201294_s_at	WSB1	WD repeat and SOCS box-containing 1	N24643	609
35436_at	GOLGA2	golgi autoantigen golgin subfamily a 2	L06147	610
201996_s_at	SPEN	spen homolog transcriptional regulator (Drosophila)		
AL524033				
210734_x_at	MAX	MYC associated factor X	M64240	615
203542_s_at	KLF9	Kruppel-like factor 9	AI690205	621
214670_at	ZKSCAN1	zinc finger with KRAB and SCAN domains 1		AA653300
626				
208699_x_at	TKT	transketolase	BF696840	627
217703_x_at		null	AA401963	628
222214_at		null	AK024988	630
212007_at	UBXN4	UBX domain protein 4	AI927512	631
209890_at	TSPAN5	tetraspanin 5	AF065389	634
208200_at	IL1A	interleukin 1 alpha	NM_000575	637
213579_s_at	EP300	E1A binding protein p300	AI459462	641
213650_at	GOLGA8A	golgi autoantigen golgin subfamily a 8A	AW006438	644
203975_s_at	CHAF1A	chromatin assembly factor 1 subunit A (p150)		BF000239
647				
39313_at	WNK1	KIAA0344 gene	AB002342	650
215069_at	NMT2	N-myristoyltransferase 2	AK025065	652
219392_x_at	PRR11	proline rich 11	NM_018304	653
213506_at	F2RL1	coagulation factor II (thrombin) receptor-like 1		
BE965369				
211000_s_at	IL6ST	interleukin 6 signal transducer (gp130 oncostatin M		
receptor)	AB015706			660
222036_s_at	MCM4	minichromosome maintenance complex component 4		AI859865
662				
218155_x_at	TSR1	TSR1 20S rRNA accumulation homolog (S. cerevisiae)		
AK026565				
200635_s_at	PTPRF	protein tyrosine phosphatase receptor type F		AU145351
674				
210686_x_at	SLC25A16	solute carrier family 25 (mitochondrial carrier;		
Graves disease autoantigen) member 16			BC001407	678
66053_at	HNRNPUL2	heterogeneous nuclear ribonucleoprotein U-like 2		

Table_J

AI738452	693				
213299_at	ZBTB7A	zinc finger and BTB domain containing 7A		AW027070	
696					
208336_s_at	GPSN2	glycoprotein synaptic 2	NM_004868	698	
218521_s_at	UBE2W	ubiquitin-conjugating enzyme E2W (putative)		NM_018299	
700					
1053_at	RFC2	replication factor C (activator 1) 2	40kDa	M87338	702
211317_s_at	CFLAR	CASP8 and FADD-like apoptosis regulator	AF041461		705
201205_at		null	AF006751		706
222180_at		null	AU147889		707
221419_s_at		null	NM_013307		709
217813_s_at	SPIN1	spindlin 1	NM_006717		710

CLAIMS

What is claimed is:

1. A method for constructing a data architecture for use in identifying connections between perturbagens and genes associated with one or more skin aging conditions, comprising:
 - (a) providing a gene expression profile for a control human dermal fibroblast cell;
 - (b) generating a gene expression profile for a human dermal fibroblast cell exposed to at least one perturbagen;
 - (c) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (a) and (b);
 - (d) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes;
 - (e) storing the ordered list as a fibroblast instance on at least one computer readable medium; and
 - (f) constructing a data architecture of stored fibroblast instances by repeating (a) through (e), wherein the at least one perturbagen of step (a) is different for each fibroblast instance.
2. The method according to claim 1, further comprising:
 - (a) providing a gene expression profile for a control human keratinocyte cell;
 - (b) generating a gene expression profile for a human keratinocyte cell exposed to at least one perturbagen;
 - (c) identifying genes differentially expressed in response to the at least one perturbagen by comparing the gene expression profiles of (g) and (h);
 - (d) creating an ordered list comprising identifiers representing the differentially expressed genes, wherein the identifiers are ordered according to the differential expression of the genes identified in (i);
 - (e) storing the ordered list created in step (j) as a keratinocyte instance on the at least one computer readable medium; and
 - (f) constructing a data base of stored keratinocyte instances by repeating (g) through (k), wherein the at least one perturbagen of step (h) is different for each keratinocyte instance.

3. The method according to claim 1 or claim 2, comprising using a programmable computer to perform one or more of steps (c), (d), (e), (f), (i), (j), (k) and (l).
4. The method according to any of claims 1 to 3, wherein the step of generating is performed by extracting a biological sample from the treated cell and subjecting the biological sample to microarray analysis.
5. The method according to claim 4, wherein the microarray analysis comprises a global microarray or a specific microarray, wherein the specific microarray comprises oligonucleotides which hybridize to genes corresponding to a gene expression signature for a cellular phenotype.
6. A method for implementing the data architecture according to any of claims 1 to 5, to generate connections useful for identifying cosmetic agents effective for treating aged skin, the method comprising querying the data architecture with at least one skin aging gene expression signature, wherein querying comprises comparing the at least one skin aging gene expression signature to each stored fibroblast instance, wherein the skin aging gene expression signature represents genes differentially expressed in association with at least one skin aging condition.
7. The method according to claim 6, wherein the at least one skin aging gene expression signature is constructed by a method comprising (i) identifying genes having up-regulated expression in the at least one skin aging condition when compared to a control; (ii) identifying genes having down-regulated expression in the at least one skin aging condition when compared to a control; (iii) creating one or more gene expression signature lists associated with the at least one skin aging gene expression signature comprising identifiers corresponding to a plurality of the genes identified in (i) and (ii); and storing the one or more gene expression signature lists on the at least one computer readable medium.
8. The method according to claim 7, wherein at least one skin sample is taken from a human subject exhibiting the at least one skin condition, a biological sample is extracted from the skin sample, and a gene expression profile of the at least one skin sample is generated prior to at least one of the steps (i) and (ii).
9. A method according to claim 8, wherein the skin sample comprises cells from epidermal and dermal layers of the human subject.

10. The method according to any of claims 6 to 9, wherein the comparison further comprises assigning a connectivity score to each of a plurality of instances.
11. The method according to claim 10 further comprising formulating a skin care composition comprising a dermatologically acceptable carrier and at least one perturbagen, wherein the connectivity score of the instance associated with the at least one perturbagen has a negative correlation.
12. The method according to any of claims 1 to 5, further comprising: providing a microarray scanner for receiving a sample comprising human dermal fibroblast cells and/or human keratinocyte cells; and configuring a first programmable computer for transmitting gene expression data from the scanner to a second programmable computer containing the at least one computer readable medium.
13. The method of any of claims 6 to 11 wherein the at least one skin aging gene expression signature consists of genes selected from the genes set forth in **Tables A and B**.
14. The method of any of claims 6 to 11 wherein the at least one skin aging gene expression signature consists of genes selected from the genes set forth in **Tables C and D**.
15. The method of any of claims 1 to 14 wherein each identifier is selected from the group consisting of a microarray probe set ID, a human gene name, a human gene symbol, and combinations thereof representing a gene set forth in any of **Tables A-D** wherein each of the one or more gene expression signature lists comprises between about 50 and about 600 identifiers.

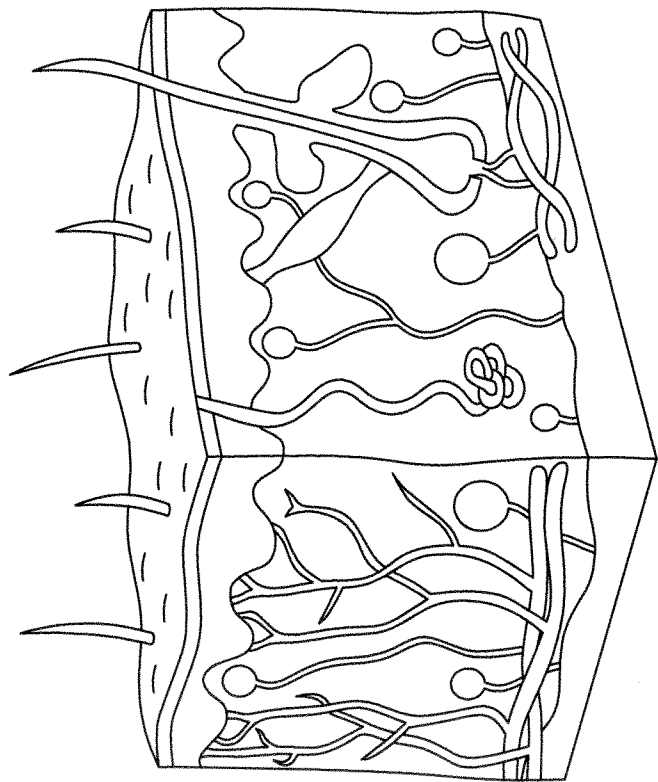


FIG. 1

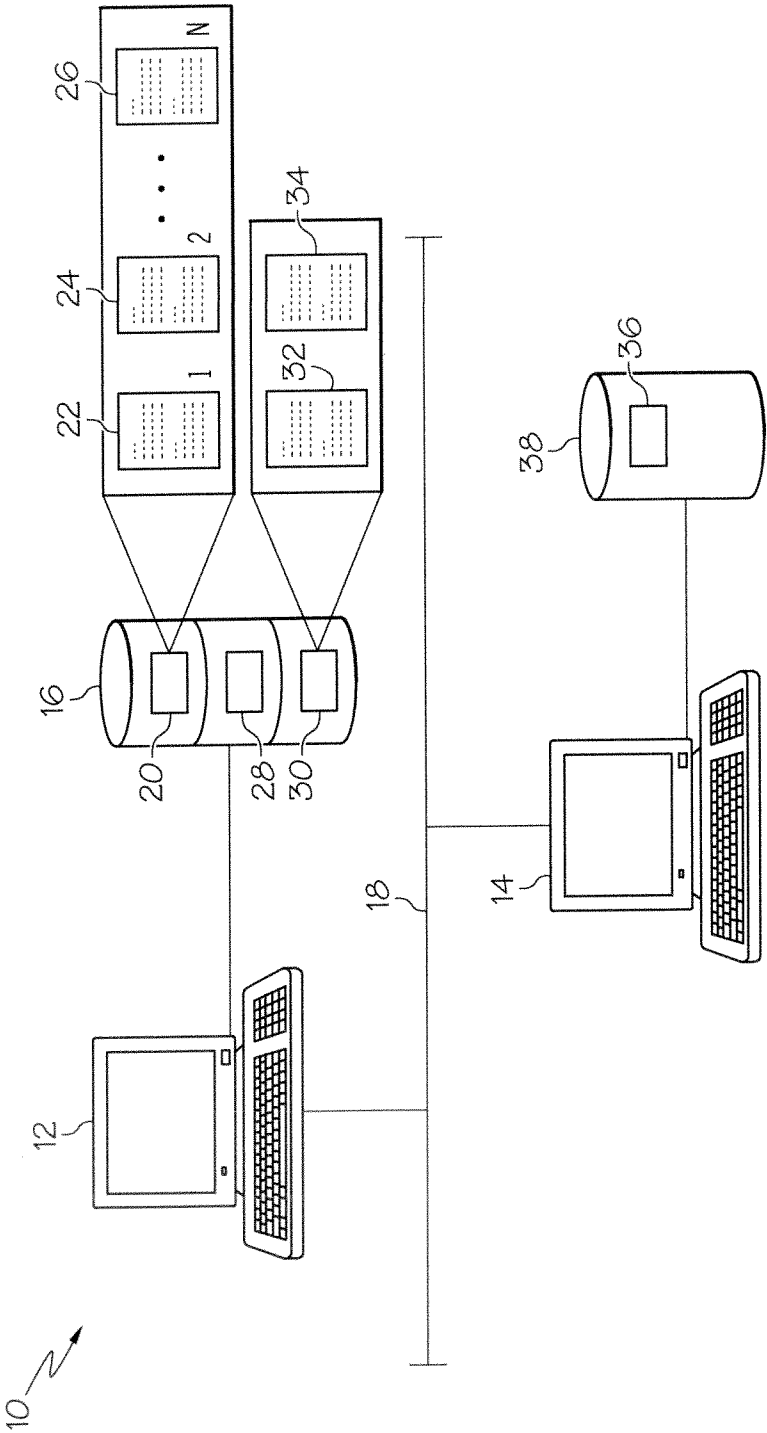


FIG. 2

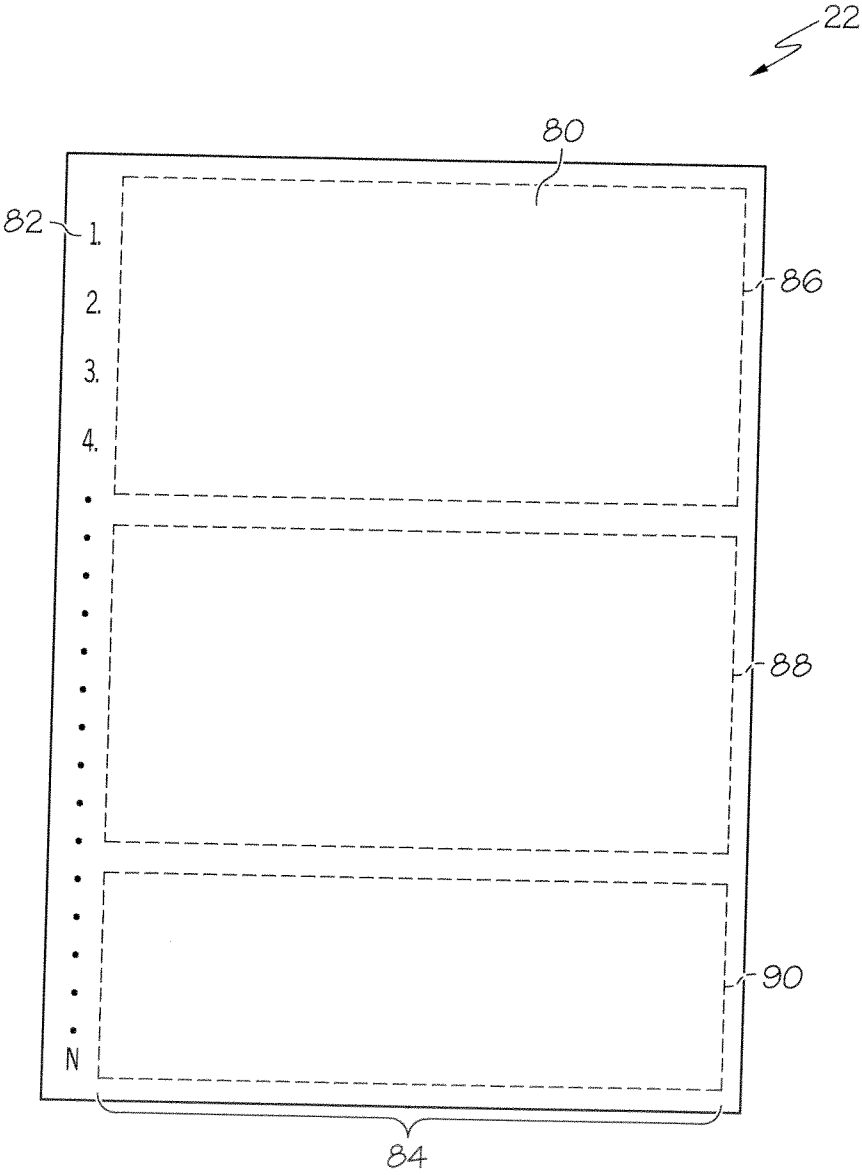


FIG. 3

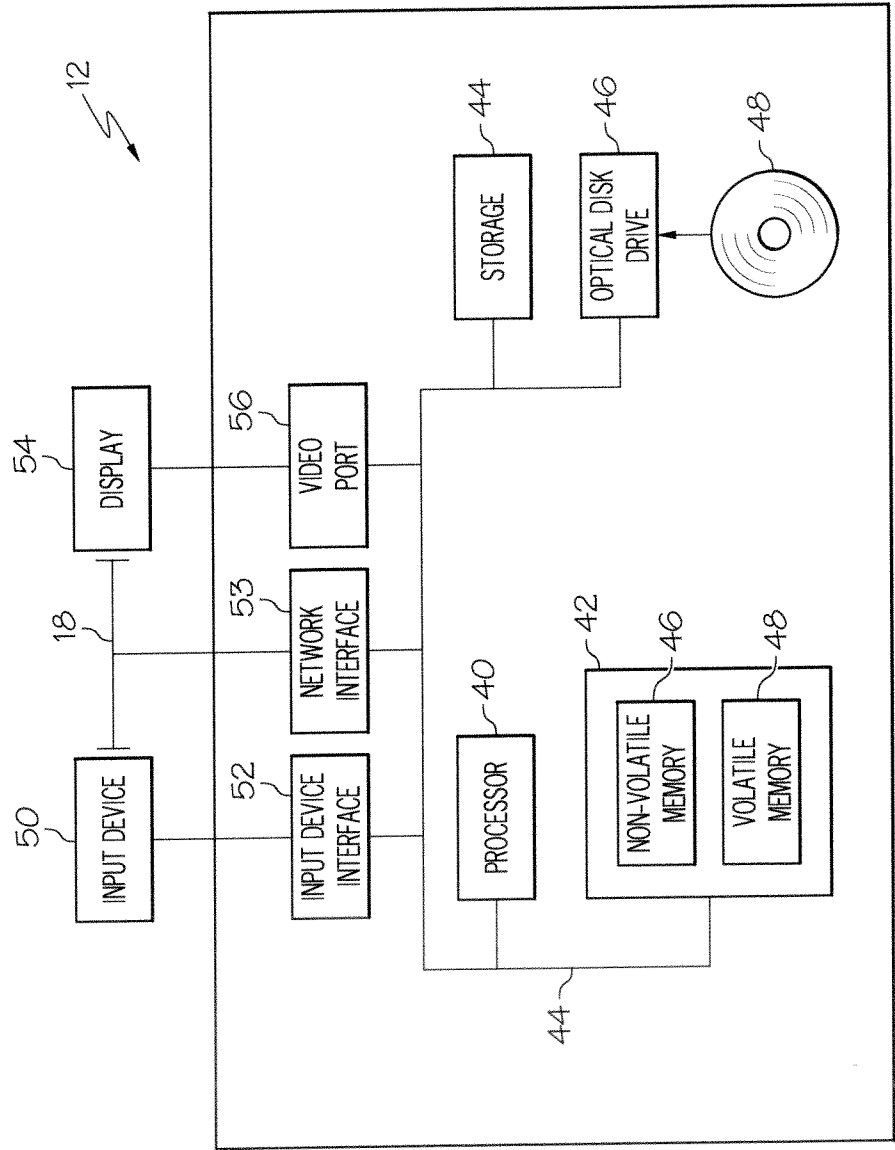


FIG. 4

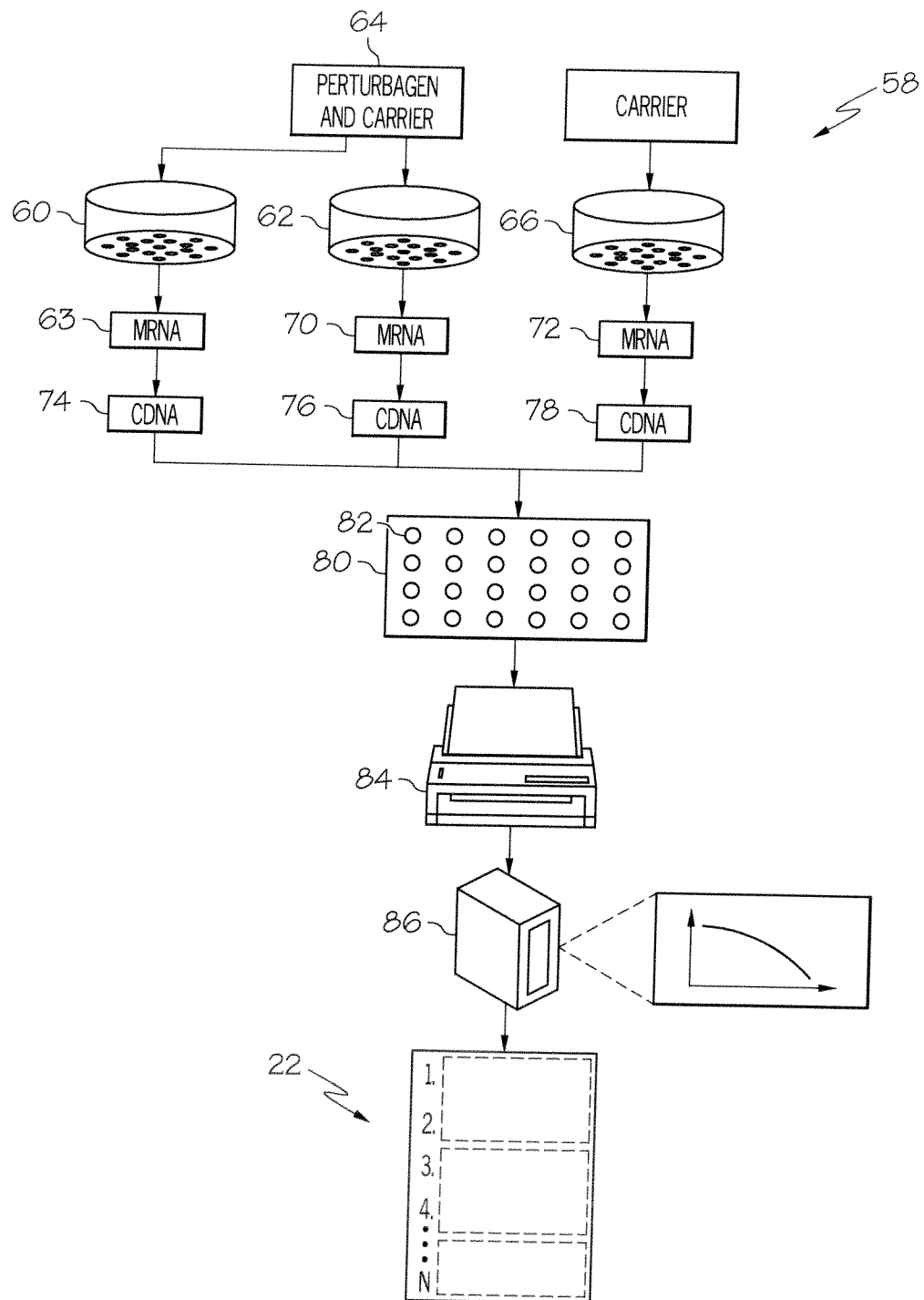


FIG. 5

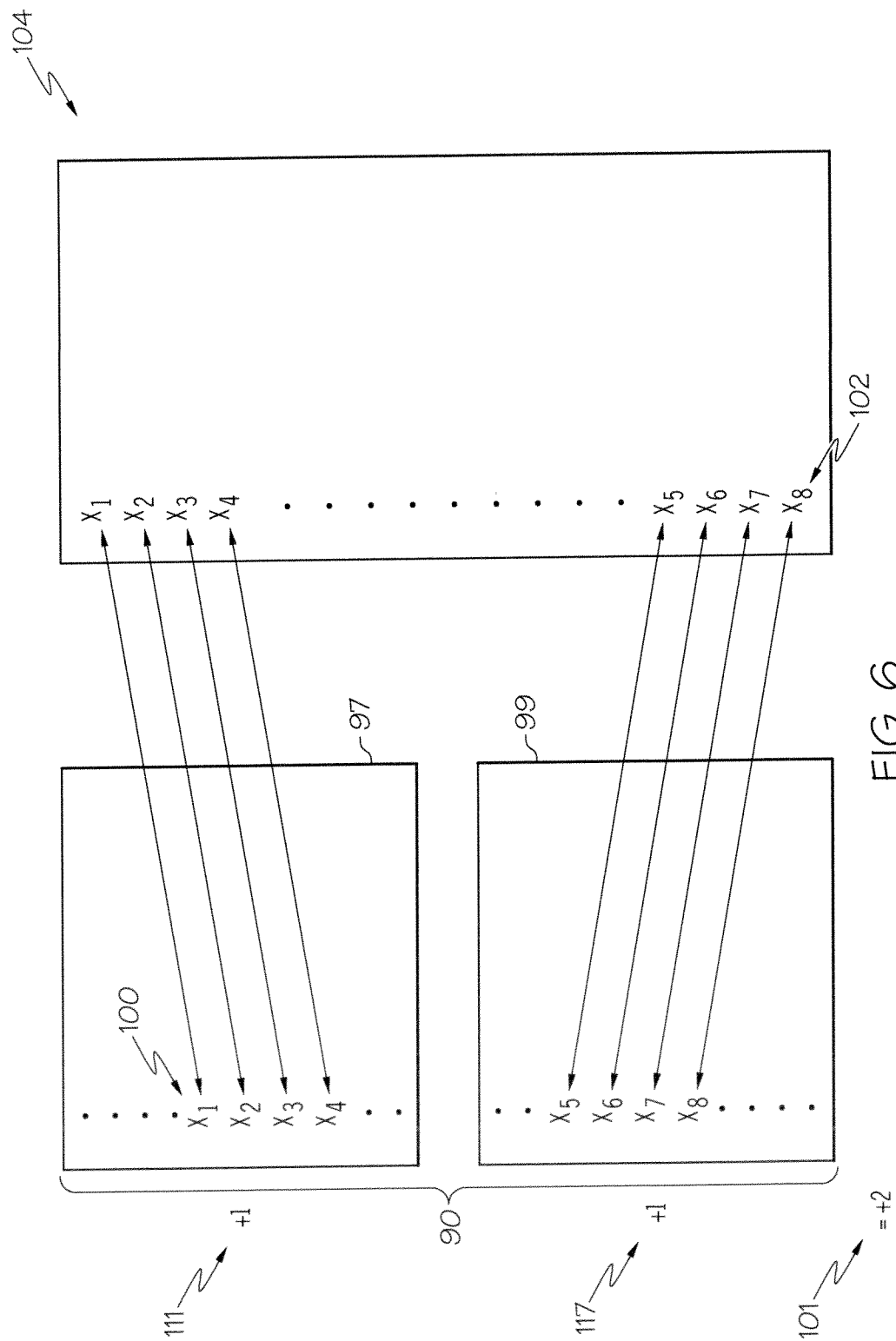


FIG. 6

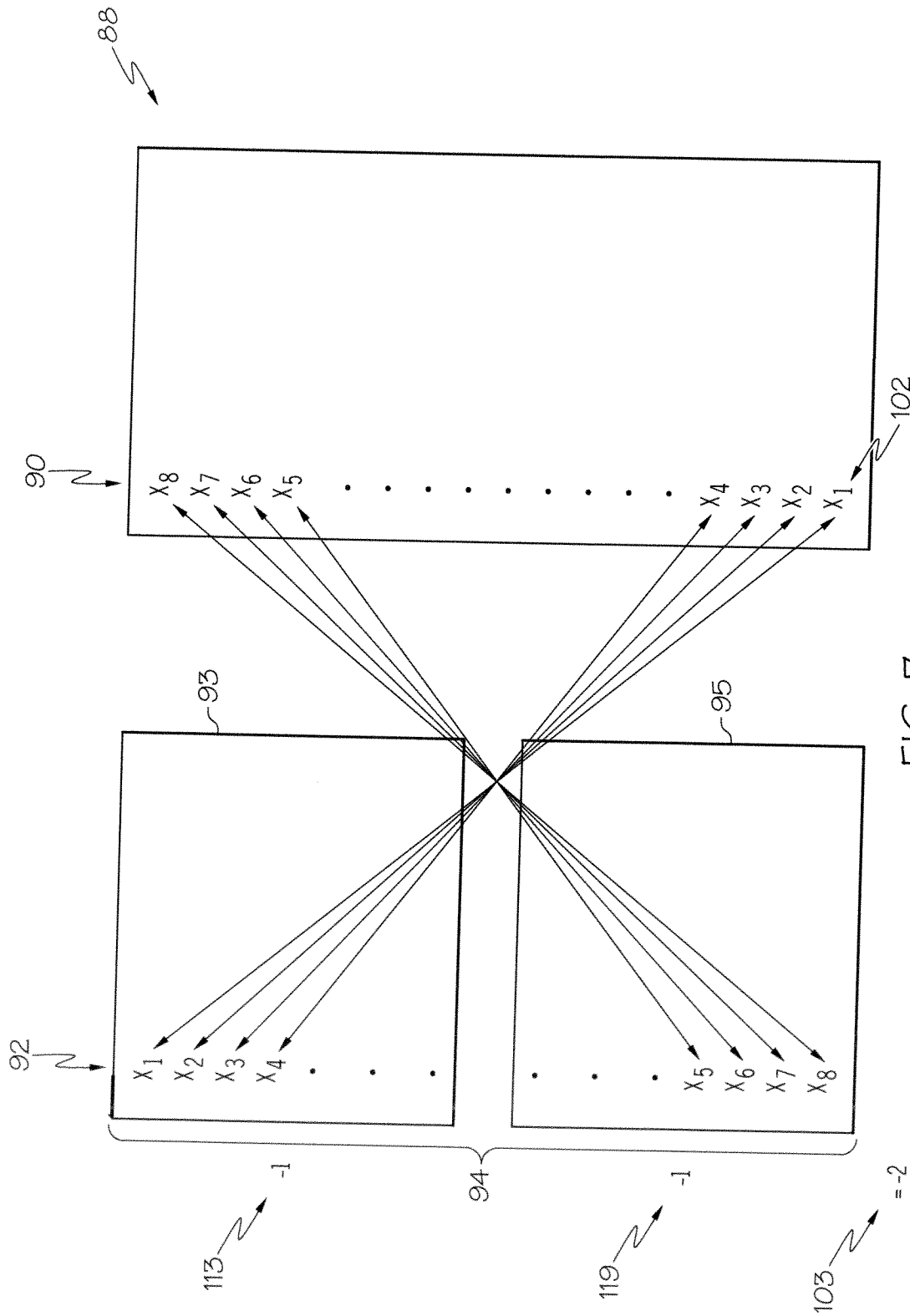


FIG. 7

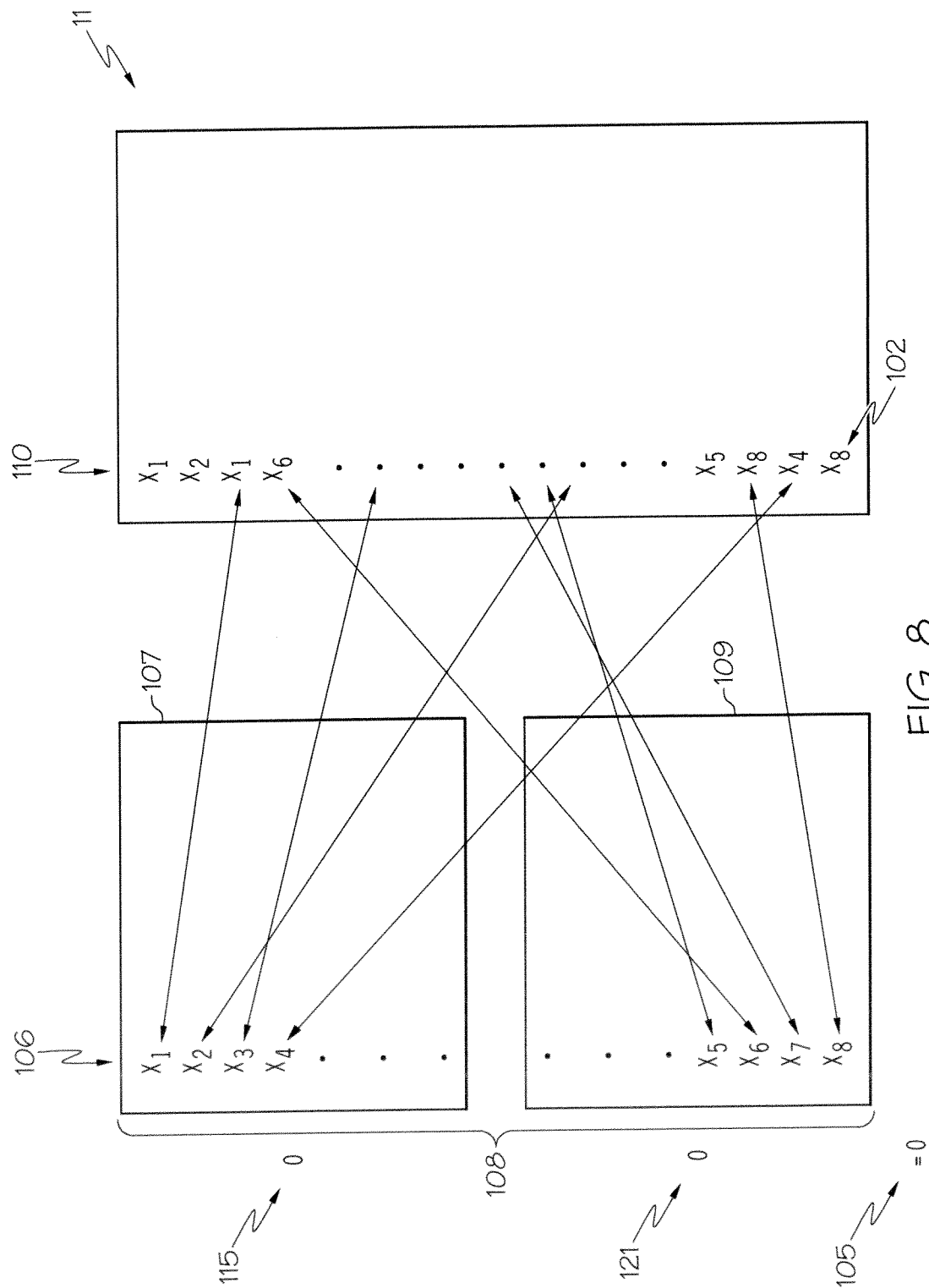


FIG. 8

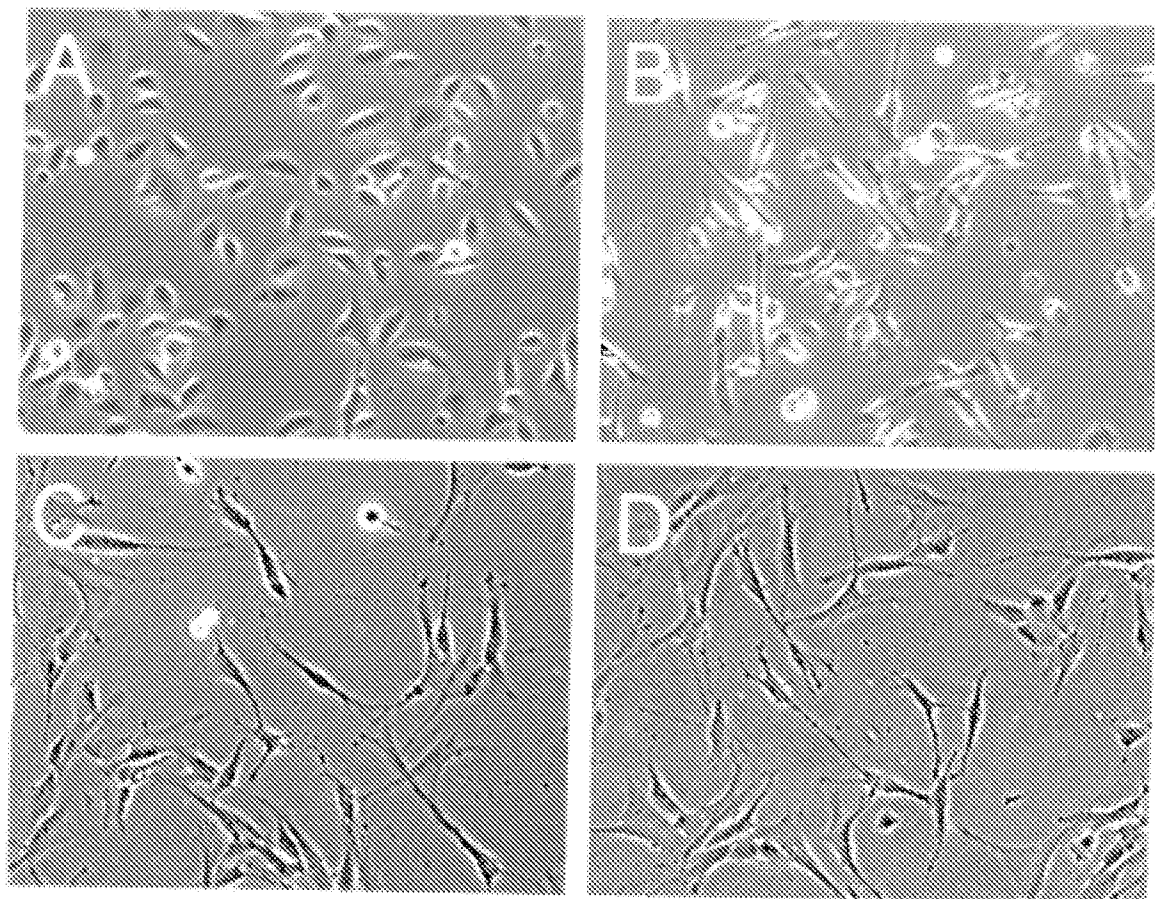


FIG. 9