METHODS AND REAGENTS FOR DETECTION AND TREATMENT OF ESOPHAGEAL METAPLASIA

RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 61/388,394, Attorney Docket No. ET9-001-1, filed September 30, 2010, entitled "METHODS AND REAGENTS FOR DETECTION AND TREATMENT OF ESOPHAGEAL METAPLASIA". The contents of any patents, patent applications, and references cited throughout this specification are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The invention described herein relates to the treatment, detection, and diagnosis of various cancers, including esophageal or gastric adenocarcinoma and related metaplasias.

GOVERNMENTAL FUNDING

The invention described herein was supported, in part, by grants from the National Institutes of Health (R01 GM 083348). The United States government may have certain rights in the invention.

BACKGROUND OF THE INVENTION

Esophageal and gastric adenocarcinoma together kill more than one million people each year worldwide and represent the 2nd leading cause of death from cancer. Both cancers arise in association with chronic inflammation and are preceded by robust metaplasia with intestinal characteristics. In fact, the patient population with precancerous lesions is estimated to be significantly larger – in the range of 100 million people in size – all at substantial risk of developing cancer in their lifetimes. Current treatments for both cancer and precancerous patients have an exceptionally high degree of relapse, with the 5 year survival rate for patients developing cancer being marginal.

Gastric intestinal metaplasia can be triggered by gastritis involving *H. pylori* infections, while Barrett's metaplasia of the esophagus is linked to gastroesophageal reflux disease (GERD). While *H. pylori* suppression therapies have contributed to the recent decline of gastric adenocarcinoma, the incidence of esophageal adenocarcinoma, especially in the West, has increased dramatically in the past several decades (Spechler *et al.* N Engl J Med. 1986; 315:362-71; Blot *et al.* JAMA 1991; 265:1287-9; Raskin *et al.* Cancer Res 1992; 52:2946-50; Jankowski *et al.* Am J Pathol 1999;154:965-973; and Reid *et al.* Nat Rev Cancer 2010; 10:87-101). Treatments for late stages of these diseases are challenging and largely palliative, and therefore considerable efforts have focused on understanding the earlier, premalignant stages of these diseases for therapeutic opportunities.

The prevailing theory for the development of metaplasia has been that the abnormal cells seen in Barrett's esophagus arise as the normal squamous cells "transcommit" in response to inflammation (such as acid-reflux) to a new, intestine-like fate. Intestine-like metaplasia is a columnar epithelium marked by prominent goblet cells and intestinal markers such as villin and trefoil factors 1, 2, and 3, and, once established, appears to be irreversible (Sagar *et al.* Br J Surg. 1995; 82:806-10; Barr *et al.* Lancet 1996; 348:584-5; and Watari *et al.* Clin Gastroenterol Hepatol 2008; 6:409-17). There is compelling evidence for a dynamic competition among clones of cells within Barrett's metaplasia that almost certainly contributes to its premalignant progression. Cancers arise from this metaplasia via stereotypic genetic and cytologic changes that present as dysplasia, high-grade dysplasia, and finally invasive adenocarcinoma (Raskin *et al.*, *supra*; Jankowski *et al.*, *supra*; Haggitt. Hum Pathol 1994; 25:982-93; Schlemper *et al.* Gut 2000;47:251-5; and Correa *et al.* Am J Gastroenterol 2010;105:493-8).

SUMMARY OF THE INVENTION

An understanding of the ontogeny of gastric intestinal metaplasia would allow for the development of compositions and methods for the early detection and treatment of gastric intestinal metaplasia prior to progression to adenocarcinoma. As described in greater detail herein, the inventors have replaced the old paradigm of transcommittment of cell fate with a new understanding of the origins of esophageal and gastric metaplasias in which stem cells of embryonic origin – left behind during organogenesis of the alimentary canal - give rise to the precancerous diseases and ultimately to esophageal and gastric adenocarcinoma. The inventors have shown that this discrete population stem cells persist in humans at the squamocolumnar junction, the source of Barrett's metaplasia. The inventors have also shown that upon damage to the squamous epithelium, these stem cell are activated and proliferate in the development of the precancerous lesions. The findings presented in this application demonstrate that gastric intestinal and Barrett's metaplasias initiate not from genetic alterations or transcommittment of differentiated tissue, but rather from competitive interactions between cell lineages driven by opportunity. Targeting these precancerous lesions by preventing growth and/or differentiation of these vestigial stem cells, which have proven to be resistant to physical ablation and other therapies directed to the resulting metaplasias, offers a unique opportunity to prevent progression to cancer in a very large patient population.

As described in further detail in this application, the inventors have isolated these cancer stem cells, as well as normal epithelial stem cells for the esophagus, stomach and intestines, and through gene expression profiling have identified a number of targets for development of antibodies, RNAi and small therapeutics that may be selectively lethal to the cancer stem cell relative to rest of the alimentary canal. With the isolated cells in hand, there is not the opportunity to rapidly develop drug candidates with selectivity and in vitro efficacy. Coupled with animal models for these diseases presented herein and others available in the art, there is a clear preclinical and clinical path to providing effective therapies. While it is expected that systemic delivery of

therapeutic agents is an option, the fact of the matter is that the sites of treatment lend themselves well to oral or endoscopic depot delivery. The dim prognosis for gastric intestinal and esophageal adenocarcinoma argues for therapies directed at preventing even the initiation of the precancerous metaplasia. For these precancerous metaplasia patients again numbering in the tens of millions - this provides a ten to twenty year window for treatment before cancer would typically develop.

Accordingly, a salient feature to the current application is the discovery that a unique population of primitive epithelial stem cells give rise to the metaplasia underlying esophageal and gastric adenocarcinoma and that these primitive epithelial stem cells have a distinct molecular signature that can be exploited for diagnostic and therapeutic targeting. For instance, these discoveries allow for the therapeutic targeting of the population of stem cells responsible for the metaplasia using cytotoxic and/or growth inhibitory and/or differentiation inhibitory agents, particularly agents selective for the stem cell relative to normal squamous cells or regenerative stem cells of the esophagus or stomach, thus facilitating the treatment of metaplasia and prevention of its progression to adenocarcinoma. Likewise, the use of agents directed to gene products unique to the stem cell, particularly cell surface markers that can be detected with antibodies, the present invention provides reagents and methods for detecting the stem cell in tissue biopsy samples as well as in vivo (i.e., for imaging or detection using endoscopic visualization). Given the accessibility of these tissues through non-invasive and minimally invasive techniques , in certain preferred embodiments the therapeutic agents or imaging agents are delivered by direct injection, such as by endoscopic injection.

The following are merely illustrative. In the case of a gene encoding a cell surface protein, the therapeutic agent can be an antibody or antibody mimetic, i.e., one which inhibits growth or differentiation by inhibiting the function of the cell surface protein, or one which is cytotoxic to the cell as a consequence to invoking an immunological response (i.e., ADCC) against the targeted stem cell. In the case of a gene encoding an enzyme, the therapeutic may be a small molecule inhibitor of the enzymatic activity, or a prodrug including a substrate for

the enzyme such that the prodrug is converted to an activate agent upon cleavage of the substrate portion. In the case of transcription factors, the therapeutic agent may be a decoy nucleic acid that competes with the genomic regulatory elements for binding to the transcription factor; or in the case of ligand-mediated transcription factors (such as PPARγ), may be an agonist or antagonist ligand of the transcription factor. In instances where the viability, growth or differentiation of the target stem cell is dependent on the level of expression of the gene, then use of antisense, RNAi or other inhibitory nucleic acid therapeutics can be considered.

In one aspect, the invention provides a method for treating or preventing esophageal metaplasia, comprising administering to a subject a therapeutic amount of an agent that decreases the expression and/or biological activity of one or more of the genes set forth in Tables 1-5 and Figures 9-11, such that the metaplasia is treated or prevented. In certain embodiments, the agent is an antibody, antibody-like molecule, antisense oligonucleotide, small molecule or RNAi agent.

In another aspect, the invention provides a method for treating or preventing esophageal metaplasia, comprising administering a therapeutic amount of an agent that specifically binds to a cell surface polypeptide encoded by one of the genes set forth in Tables 1-5 and Figures 9-11, wherein said agent is linked to one or more cytotoxic moiety. In certain embodiments, the agent is an antibody, antibody-like molecule or cell surface receptor ligand. The cytotoxic moiety can be, for example, a radioactive isotope, chemotoxin, or toxin protein. In certain embodiments, the cytotoxic moiety is encapsulated in a biocompatible delivery vehicle including, without limitation, microcapsules, microparticles, nanoparticles, and liposomes. In some embodiments, the agent is directly linked to the cytotoxic moiety.

In another aspect, the invention provides a method of imaging esophageal metaplasia, the method comprising administering to a subject an effective amount of an agent that specifically binds to a cell surface polypeptide encoded by one of the genes set forth in Tables 1-5 and Figures 9-11, and visualizing the agent. In certain embodiments, the agent is an antibody,

antibody-like molecule or cell surface receptor ligand. In certain embodiments, the agent is linked to an imaging moiety. The imaging moiety can be, for example, a positron-emitter, nuclear magnetic resonance spin probe, an optically visible dye, or an optically visible particle. The imaging agent may be one which permits non-invasive imaging, such as by MRI, PET or the like. In other embodiments, the imaging moiety can be a fluorescent probe or other optically active probe which can be visualized, e.g., through an endoscope.

According to the methods of the invention, a therapeutic and/or imaging agent can be administered by any suitable route and/or means including, without limitation, orally and/or parenterally. In a preferred embodiment, the agent is administered endoscopically to the esophageal squamocolumnar junction or a site of esophageal metaplasia.

In another aspect, the invention provides a method of detecting the presence or absence of the target stem cell in a tissue biopsy. Such detection agents can include antibodies and nucleic acids which bind to a gene or gene product unique to the stem cell relative to other normal or diseased esophageal tissue.

In another aspect, the invention provides a method of diagnosing, or predicting the future development or risk of development of, esophageal metaplasia or adenocarcinoma, comprising measuring the expression level of one or more of the genes set forth in Tables 1-5 and Figures 9-11 in an epithelial tissue sample from a subject, wherein an increase in the expression level relative to a suitable control indicates that the subject has, or has a future risk of developing, metaplasia. In some embodiments, mRNA levels of the gene are measured. In other embodiments, the levels of the protein product of the gene are measured. Such methods can be performed *in vivo* or *in vitro*.

In another aspect, the invention provides a method of identifying a compound useful for treating or preventing esophageal metaplasia, the method comprising administering a test compound to p63 null mouse and determining the amount of epithelial metaplasia in the presence and absence of the test

compound, wherein a decrease in the amount of epithelial metaplasia identifies a compound useful for treating esophageal metaplasia.

In another aspect, the invention provides a method of identifying a compound useful for treating or preventing esophageal metaplasia, the method comprising administering a test compound to a mouse, wherein the mouse comprises stratified epithelial tissue in which basal cells have been ablated, and determining the amount of epithelial metaplasia in said epithelial tissue in the presence and absence of the test compound, wherein a decrease in the amount of epithelial metaplasia identifies a compound useful for treating esophageal metaplasia.

The invention further provides a composition comprising a clonal population of Barrett's Esophagus (BE) stem cells, such as may be isolated from an esophagus of a subject or generated from ES cells or iPS cells, wherein the stem cells differentiate into Barrett's epithelium (i.e., columnar epithelium). Preferably the composition, with respect to the cellular component, is at least 50 percent BE stem cell, more preferably at least 75, 80, 85, 90, 95 or even 99 percent BE stem cell. The BE stem cells can be pluripotent, multipotent or oligopotent. In certain preferred embodiments, the BE stem cells are characterized as having an mRNA profile can further include a profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA in the clonal cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the clonal cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the mRNA transcript profile for the BE cells will also be characterized by detectable levels of BICC1 and NTS. In certain embodiments, the BE cells will also be characterized by non-detectable levels of SOX2, p63, Krt20, GKN1/2, FABP1/2, Krt14, CXCL17, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA.

In an additional embodiment, the BE stem cells are characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining. For instance, levels of Krt20, Sox2 and p63 are less than 10

percent of the level of CEACAM6, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

The invention further provides a composition comprising a population of cells enriched in a clonal subpopulation of BE stem cells from an esophagus of a subject, wherein the clonal subpopulation of cells differentiates into Barrett's epithelium (i.e., columnar epithelium). The BE stem cells can be pluripotent, multipotent or oligopotent.

Another aspect of the invention provides a clonal population of Barrett's Esophagus (BE) stem cells, derived from human or stem cell or iPS cell sources, characterized as having an mRNA profile can further include a profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA in the stem cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the clonal cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the mRNA transcript profile for the BE cells will also be characterized by detectable levels of BICC1 and NTS. In certain embodiments, the BE cells will also be characterized by non-detectable levels of SOX2, p63, Krt20, GKN1/2, FABP1/2, Krt14, CXCL17, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA. The clonal population of BE stem cells may also be characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining. For instance, levels of Krt20, Sox2 and p63 are less than 10 percent of the level of CEACAM6, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

The invention further provides a method of screening for an agent effective in the treatment or prevention of Barrett's esophagus including the steps of providing a population of BE stem cells, wherein the BE stem cells are able to differentiate into Barrett's epithelium; providing a test agent; and exposing the BE stem cells to the test agent; wherein if the test agent is cytotoxic, cytostatic and/or able to inhibit the differentiation of the BE stem cells

to columnar epithelial cells, the test agent is an agent effective in the treatment or prevention of Barrett's esophagus.

In certain embodiments, the BE stem cells are mammalian BE stem cells, such as human BE stem cells.

In certain embodiments, candidate therapeutic agents reduce the viability, growth or ability to differentiation by 70, 80, 90, 95, 96, 97, 98, 99 or even 100%.

The BE stem cells can be clonal, and can be pluripotent, multipotent or oligopotent. In certain preferred embodiments, the BE stem cells are characterized as having an mRNA profile can further include a profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA in the stem cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the mRNA transcript profile for the BE cells will also be characterized by detectable levels of BICC1 and NTS. In certain embodiments, the BE cells will also be characterized by non-detectable levels of SOX2, p63, Krt20, GKN1/2, FABP1/2, Krt14, CXCL17, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA. The clonal population of BE stem cells may also be characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining. For instance, levels of Krt20, Sox2 and p63 are less than 10 percent of the level of CEACAM6, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

The invention further provides a method of screening for an agent effective in the detection of Barrett's esophagus including the steps of providing BE stem cells; providing a test agent; and exposing the BE stem cells to the test agent; wherein if the test agent specifically binds to the BE stem cells, i.e., relative to normal squamous cells or intestinal cells or Barrett's epithelial cells, the test agent is an agent effective in the detection of stem cells giving rise to Barrett's esophagus.

In certain embodiments, the BE stem cells are mammalian, and more preferably are human.

In certain embodiments, the test agent specifically binds to a cell surface protein on the stem cells. Cell surface proteins include CEACAM6, MMP1, SLC26A3, TSPAN8, LYZ and SPINK1. Specifically, the test agent can be an antibody. Optionally, the antibody can be a monoclonal antibody.

The invention further provides a method of detecting the presence of Barrett's esophagus in a subject including the steps of providing a detection agent that specifically binds to BE stem cells; administering the detection agent to a subject; and detecting whether the detection agent specifically binds to a BE stem cell in the esophagus of the subject, wherein, if the detection agent specifically binds to a cell in the esophagus of the subject to a higher degree than the average non-Barrett's esophagus patient , the subject is diagnosed with Barrett's esophagus or as having a risk of developing Barrett's esophagus.

The invention further provides a method of for treating or preventing Barrett's esophagus and/or esophageal metaplasia in a subject in need thereof comprising administering to subject an effective amount of an agent that is cytotoxic or cytostatic for Barrett's Esophagus stem cells in the esophagus of the subject, or inhibits differentiation of the Barrett's Esophagus stem cells to columnar epithelium.

In certain embodiments, the subject is a mammal. In a preferred embodiment, the mammal is human.

In certain embodiments, candidate therapeutic agents reduce the viability, growth or ability to differentiation by 70, 80, 90, 95, 96, 97, 98, 99 or even 100%.

The targeted BE stem cells can characterized as having an mRNA profile that can further include a profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA in the stem cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the mRNA transcript profile for the BE cells will also be

characterized by detectable levels of BICC1 and NTS. In certain embodiments, the BE cells will also be characterized by non-detectable levels of SOX2, p63, Krt20, GKN1/2, FABP1/2, Krt14, CXCL17, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA. The stem population of BE stem cells may also be characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining. For instance, levels of Krt20, Sox2 and p63 are less than 10 percent of the level of CEACAM6, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

In certain embodiments, the therapeutic agent specifically binds to a cell surface protein on the BE stem cells. Cell surface proteins include CEACAM6, MMP1, SLC26A3, TSPAN8, LYZ and SPINK1. Specifically, the therapeutic agent can be an antibody. Optionally, the antibody can be a monoclonal antibody. The antibody can be conjugated to a cytotoxic or cytostatic moiety.

The therapeutic agent can be selected from the group consisting of produgs comprising a medoximil moiety, PPARγ inhibitors and NR5A2 activity modulators. The test agent can also be an RNAi or antisense composition. The RNAi or antisense composition can reduce the amount of mRNA in the targeted BE stem cells of a member of the group consisting of GSTM4, SLC16A4, CMBL, CEACAM6, NR5A2, CFTR, GCNT3 and PPARγ.

The invention further provides a composition comprising a population of squamous stem cells isolated from an esophagus of a subject, wherein the squamous stem cells differentiate into normal squamous epithelial cells of the esophagus, i.e., the squamous stem cells are regenerative. The squamous stem cells can be clonal, and can be pluripotent, multipotent or oligopotent. In certain preferred embodiments, the squamous stem cells are characterized as having an mRNA profile can further include a profile wherein the amount of one or more of S100A8, Krt14, SPRR1A or CSTA mRNA in the stem cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the squamous cells will also be characterized by non-detectable levels of SOX2,

Krt20, CXCL17, CEACAM6 or NR5A2, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA. The clonal population of squamous stem cells may also be characterized as p63 positive, and CEACAM6 negative, as detected by standard antibody staining. For instance, levels of CEACAM6 are less than 10 percent of the level of p63, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

The invention further provides a composition comprising a clonal population of gastric cardia (GC) stem cells isolated from gastric cardia or esophagus of a subject, wherein the GC stem cells differentiates into gastric cardia cells of the stomach. The gastric cardia stem cells can be clonal, and can be pluripotent, multipotent or oligopotent. In certain preferred embodiments, the gastric cardia stem cells are characterized as having an mRNA profile can further include a profile wherein the amount of one or more of CXCL17, CAPN6, PSCA, GKN1, GKN2 or MT1G mRNA in the stem cell population are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell population, more preferably in the range of 10-25 percent. Preferably all seven genes have an mRNA profile in that range. In certain embodiments, the gastric cardia cells will also be characterized by non-detectable levels of CEACAM6, p63, FABP1, FABP2, Krt14 or Krt20, i.e., less than 0.1 percent the level of actin, and even more preferably less than 0.01 or even 0.001 percent the level of actin mRNA. The clonal population of gastric cardia stem cells may also be characterized as CEACAM6 negative, as detected by standard antibody staining. For instance, levels of CEACAM6 are less than 10 percent of the level of CXCL17, and more preferably less than 5 percent, 1 percent, and even less than 0.1 percent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Metaplasia in the Proximal Stomach of p63 Null Embryos. Panel A shows a section through the stomach of an E18 wild type mouse highlighting the p63-positive squamous epithelia of the proximal stomach (PS) and the glandular epithelium of the distal stomach (DS). Panel B are immunofluorescence images of E17 wild type (WT) and p63 null (KO) sections of epidermis showing the intermittent staining for basal (anti-keratin 5) and differentiated (anti-loricrin) markers reflecting the degradation of the p63 null epidermis due to loss of epidermal stem cells. Panel C shows a comparison of H&E stained sections through stomachs of E18 wild type and p63 null embryos.

FIG. 2. Gene Expression of Metaplasia in p63 Null Embryos. Panels A and B show Principle Component Analysis and heat maps of expression microarray data comparisons between E18 wild type (WT) and p63 null (KO) proximal stomachs and other indicated gastrointestinal tissues from these embryos. PS, proximal stomach; DS, distal stomach; LI, large intestine; SI, small intestine. "Intestine-like" box are genes in common with lower portions of the gastrointestinal tract; "Unique" box contains genes specific to the metaplasia. Panel C shows gene expression heat maps comparing genes high and low in wild type and p63 null proximal stomach and compares these to gene expression patterns preformed on datasets comparing normal human esophagus and Barrett's metaplasia. Panels D and E show the relative expression of known Barrett's metaplasia biomarkers in the metaplasia of the E18 p63 null embryos compared to wild type proximal stomach ($p<10^{-7}$ for all), and the validation of several markers by immunohistochemistry on sections of wild type and mutant proximal stomach.

FIG. 3. Retrospective Tracing of Metaplasia through Embryogenesis. Panel A shows a series of immunofluorescence images using antibodies against claudin 3 (Cnd3), keratin 7 (Krt7), and Car4/Cnd3 on sections of E18 metaplasia in p63 null embryos. These markers were used to track the metaplasia back through timed embryos to E14, where the metaplasia labels with Car4, Krt7, and is highly proliferative as judged by Ki67 staining in Panel B. Panel C shows that one day earlier, at E13, both wild type and p63 null proximal stomachs display a

similar layer of Car4-positive cells in the proximal stomach. Panel D shows sections though wild type E13 (left) and E14 (right) proximal stomachs probed with antibodies to Car4 and p63. Arrow depicts an anterior-to-posterior gradient of p63 positive cells from esophagus to proximal stomach.

FIG. 4. Persistence of Embryonic Epithelium at the Squamocolumnar Junction. Panels A-C show the distribution of the keratin 7 (Krt7, green)-expressing cells in wild type embryos from its suprasquamous position at E17, its disintegration at E18, and its remnant population residing at the squamocolumnar junction of the stomach in E19 embryos and three-week-old mice. The basal cells of the squamous epithelium of the proximal stomach are labeled with antibodies to keratin 5 (Krt5, red). Panel E shows a gene expression analysis of the residual embryonic epithelium of three-week-old mice.

FIG. 5. Upregulation of Muc4 in epithelium at the Squamocolumnar Junction, Panel A shows immunofluorescence images using antibodies against Muc4. Panel B depicts a schematic for the ontogeny of Barrett's metaplasia from residual embryonic cells at the squamocolumnar junction in response to epithelial damage.

FIG. 6. Histological Analysis of Car4-Expressing and p63-Expressing Cells During the Development of the Squamocolumnar Junction in Mice.

FIG. 7. Histological Analysis of the Squamocolumnar Junction in Wild-type (Panel A) and p63 Null Mice (Panel B) at E17 to E19.

FIG. 8. Histological Analysis of Squamocolumnar Junctional Markers identified by Gene Expression Profiling in Wild-type and p63 Null Mice at E18.

FIG 9. Novel Biomarkers of Barrett's Metaplasia Identified by Gene Expression Profiling of Barrett's-like Metaplasia in the p63 null mice

FIG 10. Cell Surface Markers Genes of Barrett's Metaplasia Identified by Gene Expression Profiling of Barrett's-like Metaplasia in the p63 null mice.

FIG 11. Genes Upregulated in both the cells of Squamocolumnar Junction of the Stomach and in the Barrett's-like Metaplasia in the p63 null mice.

FIG. 12. Gene Expression of Barrett's Esophagus Progenitor Cells Compared to Gene Expression in Squamous Cell Progenitor Cells.

FIG. 13. Protein expression in Barrett's Esophagus Progenitor Cells Compared to Protein Expression in Squamous and Gastric Cardia Progenitor Cells.

FIG. 14. Protein expression in Barrett's Esophagus Progenitor Cells Compared to Protein Expression in Gastric Cardia Progenitor Cells.

FIG. 15 is a schematic showing ligands of NR5A2.

DETAILED DESCRIPTION OF INVENTION

I. Overview

The present invention is based, in part, on the discovery that a unique population of primitive epithelial cells give rise to the metaplasia underlying esophageal and gastric adenocarcinoma and that these cells have a distinct molecular signature.

Specifically, Applicants have demonstrated that during murine embryogenesis, squamous stem cells displace a primitive epithelium in the proximal stomach from the basement membrane to a proliferatively dormant, suprasquamous position. However, in mice lacking p63 (a protein that is essential for the self-renewal of stem cells of all stratified epithelial tissues, including mammary and prostate glands as well as all squamous epithelial), these squamous stem cells fail to supplant the primitive epithelium, which then rapidly emerges into a columnar metaplasia with gene expression profiles similar to Barrett's metaplasia but unique to the gastrointestinal tract. Moreover, in adults, a discrete population of these primitive epithelial cells survives embryonic development and resides at the squamocolumnar junction. Upon diptheria toxin-mediated ablation of squamous epithelial stem cells, these residual embryonic cells begin to invade vacated regions of basement membrane originating a highly proliferative metaplasia. Applicants have further performed histological and gene expression analyses of the metaplasia evident

in mouse models of extreme GERD during embryogenesis and in adults to assemble a relative genetic signature of these metaplasias and to define the mechanism of their evolution.

Applicants have also isolated a human Barrett's esophagus progenitor cell. This progenitor cell differentiates into Barrett's esophagus tissue and has a unique mRNA expression profile described below. Together, the clonal population of this Barrett's esophageal progenitor cell allows for the detection and direct therapeutic targeting of the population of cells responsible for the metaplasia by cytotoxic or and/or growth inhibitory agents, thus facilitating the treatment of metaplasia and prevention of its progression to adenocarcinoma. This human Barrett's esophagus progenitor cell can be isolated from human Barrett's metaplasia tissue by dissociating the cells in the tissue and isolating the progenitor cells via FACS using any of the cell surface proteins described in Table YY, below.

Applicants have also isolated human squamous cell and gastric cardia progenitor cells. Applicants have characterized the mRNA and protein expression of these cells to define these cells and to differentiate their expression profiles from Barrett's esophagus progenitor cells. This allows for the ablation of Barrett's esophagus progenitor cells without reducing the viability of nearby squamous cell or gastric cardia progenitor cells.

Accordingly, the present invention provides methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). The present invention also provides methods identifying compounds useful for treating esophageal metaplasia.

II. Definitions

The term "agent" includes any substance, molecule, element, compound, entity, or a combination thereof. It includes, but is not limited to, *e.g.,* protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, and the like. It can be a natural product, a synthetic compound, or a chemical compound, or a combination of two or more substances

As used herein, the term "RNAi agent" refers to an agent, such as a nucleic acid molecule, that mediates gene-silencing by RNA interference, including, without limitation, small interfering siRNAs, small hairpin RNA (shRNA), and microRNA (miRNA).

The term "cell surface receptor ligand", as used herein, refers to any natural ligand for a cell surface receptor.

The term "antibody" encompasses any antibody (both polyclonal and monoclonal), or fragment thereof, from any animal species. Suitable antibody fragments include, without limitation, single chain antibodies (see *e.g.,* Bird *et al.* (1988) Science 242:423-426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. U.S.A 85:5879-5883, each of which is herein incorporated by reference in its entirety), domain antibodies (see, e.g., U.S. Patent 6,291,158; 6,582,915; 6,593,081; 6,172,197; 6,696,245, each of which is herein incorporated by reference in its entirety), Nanobodies (see, *e.g.,* U.S. 6,765,087, which is herein incorporated by reference in its entirety), and UniBodies (see, *e.g.,* W02007/059782, which is herein incorporated by reference in its entirety

The term "antibody-like molecule", as used herein, refers to a non-immunoglobulin protein that has been engineered to bind to a desired antigen. Examples of antibody-like molecules include, without limitation, Adnectins (see, e.g., WO 2009/083804, which is herein incorporated by reference in its entirety), Affibodies (see, e.g., U.S. Patent No. 5,831,012, which is herein incorporated by reference in its entirety), DARPins (see, e.g., U.S. Patent Application Publication No. 2004/0132028, which is herein incorporated by reference in its entirety), Anticalins (see, e.g., U.S. Patent No. 7,250,297, which is herein incorporated by reference in its entirety), Avimers (see, e.g., U.S. Patent Application Publication Nos. 200610286603, which is herein incorporated by reference in its entirety), and Versabodies (see, e.g., U.S. Patent Application Publication No. 2007/0191272, which is hereby incorporated by reference in its entirety).

The term "cytotoxic moiety", as used herein, refers to any agent that is detrimental to *(e.g.,* kills) cells.

The term "chemotoxin", as used herein, refers to any small molecule

cytotoxic moiety that is detrimental to *(e.g.,* kills) cells.

The term "biological activity" of a gene, as used herein, refers to a functional activity of the gene or its protein product in a biological system, e.g., enzymatic activity and transcriptional activity.

The term "p63 null mouse", as used herein, refers to a mouse in which the p63 gene (NCBI Reference Sequence: NM_011641.2) has been deleted or downregulated in one or more tissue (e.g., epithelial tissue).

The term "biocompatible delivery vehicle", as used herein, refers to any phyioslogically compatible compound that can carry a drug payload, including, without limitation, microcapsules, microparticles, nanoparticles, and liposomes.

The term "imaging moiety", as used herein, refers to an agent that can be detected and used to image tissue *in vivo.*

The term "ablated" or "ablation", as used herein, refers to the functional removal of cells, e.g., the basal cells of the mouse stratified epithelial tissue, using any art-recognized means. In one embodiment, cells are ablated by treatment with a cytotoxic moiety, e.g., using Cre-mediated expression of diphtheria toxin fragment A as described in Ivanova *et al.* Genesis. 2005; 43:129-35. In other embodiments, cells are chemically or physically ablated, e.g., by endoscopy-assisted ablation, radiofrequency ablation, laser ablation, microwave ablation, cryogenic ablation, thermal ablation, chemical ablation, and the like. In one exemplary embodiment, the ablation energy is radio frequency electrical current applied to conductive needle. The electrical current may be selected to provide pulsed or sinusoidal waveforms, cutting waves, or blended waveforms. In addition, the electrical current may include ablation current followed by current sufficient to cauterize any blood vessels that may be compromised during the ablation process. Alternatively, in some embodiments, ablation probe may take the form of a bipolar probe that carries two or more electrodes, in which case the current flows between the electrodes.

The term "suitable control", as used herein, refers to a measured mRNA or protein level (e.g. from a tissue sample not subject to treatment by an agent), or a reference value that has previously been established.

The term "pluripotent" as used herein, refers to a stem or progenitor cell that is capable of differentiating into any of the three germ layers endoderm, mesoderm or ectoderm.

The term "multipotent", as used herein, refers to a stem or progenitor cell that is capable of differentiating into multiple lineages, but not all lineages. Often, multipotent cells can differentiate into most of the cells of a particular lineage, for example, hematopoietic stem cells.

The term "oligopotent", as used herein, refers to a stem or progenitor cell that can differentiate into two to five cell types, for example, lymphoid or myeloid stem cells.

The term "positive", as used herein, refers to the expression of an mRNA or protein in a cell, wherein the expression is at least 5 percent of the expression of actin in the cell.

The term "negative", as used herein, refers to the expression of an mRNA or protein in a cell, wherein the expression is less than 1 percent of the expression of actin in the cell.

III. Exemplary Embodiments

A. Molecular Signature of Cells Responsible for the Esophageal Metaplasia.

The present invention is based, in part, on the discovery that a unique population of primitive epithelial cells give rise to the metaplasia underlying esophageal and gastric adenocarcinoma. Transcriptome analysis of RNA derived by microdissection from this population of cells led to the remarkable discovery that these cells have a distinct molecular signature. In particular, a number of genes were identified as being upregulated in these cells. Moreover, a subset of these genes (set forth below in Tables 1-5, 15 and 16 and Figures 9-11, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers) were determined to be useful diagnostically for the identification of these primitive epithelial cells

and/or as target molecules for therapeutics designed to kill or inhibit growth of these cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 1. Genes upregulated in Barrett's-like metaplasia in p63 null mice

Gene Symbol	Gene Title	RefSeq Transcript ID
Foxi1	forkhead box I1	NM_023907
6430514M23Rik	RIKEN cDNA 6430514M23 gene	---
Tcerg1l	transcription elongation regulator 1-like	NM_183289 /// XM_916561
Akr1c18	aldo-keto reductase family 1, member C18	NM_134066
Gad1	glutamic acid decarboxylase 1	NM_008077
BC048546	cDNA sequence BC048546	NM_001001179
Slc14a1	solute carrier family 14 (urea transporter), member 1	NM_028122
LOC100047091 /// Tmem163	hypothetical protein LOC100047091 /// transmembrane protein 163	NM_028135 /// XM_001477366
Tcerg1l	transcription elongation regulator 1-like	NM_183289 /// XM_916561

Aox3	aldehyde oxidase 3	NM_023617
Slc14a1	solute carrier family 14 (urea transporter), member 1	NM_028122
Upk2	uroplakin 2	NM_009476
Gm3515	predicted gene 3515	XM_001477025
Pkib	protein kinase inhibitor beta, cAMP dependent, testis specific	NM_001039050 /// NM_001039051 /// NM_001039052 /// NM_001039053 /// NM_008863
Inhbb /// LOC100046802	inhibin beta-B /// similar to Inhbb protein	NM_008381 /// XM_001476835
Cnpy1	canopy 1 homolog (zebrafish)	NM_175651
Pkib	protein kinase inhibitor beta, cAMP dependent, testis specific	NM_001039050 /// NM_001039051 /// NM_001039052 /// NM_001039053 /// NM_008863
6430514M23Rik	RIKEN cDNA 6430514M23 gene	---
Dnajc12	DnaJ (Hsp40) homolog, subfamily C, member 12	NM_013888
Pcsk1	proprotein convertase subtilisin/kexin type 1	NM_013628
Calca	calcitonin/calcitonin-related polypeptide, alpha	NM_001033954 /// NM_007587
Slc38a5	solute carrier family 38, member 5	NM_172479
Lemd1	LEM domain containing 1	NM_001033250
Wif1	Wnt inhibitory factor 1	NM_011915
Vtcn1	V-set domain containing T cell activation inhibitor 1	NM_178594
B630019K06Rik	RIKEN cDNA B630019K06 gene	NM_175327
Adh7	alcohol dehydrogenase 7 (class IV), mu or	NM_009626

	sigma polypeptide	
Sox1	SRY-box containing gene 1	NM_009233
Cnpy1	canopy 1 homolog (zebrafish)	NM_175651
Nrip3	nuclear receptor interacting protein 3	NM_020610
Adh7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	NM_009626
Slc35d3	solute carrier family 35, member D3	NM_029529
Cnpy1	canopy 1 homolog (zebrafish)	NM_175651
Tnfsf12 /// Tnfsf12-tnfsf13 /// Tnfsf13	tumor necrosis factor (ligand) superfamily, member 12 /// tumor necrosis factor	NM_001034097 /// NM_001034098 /// NM_001159503 /// NM_001159505 /// NM_011614 //
Eya2	eyes absent 2 homolog (Drosophila)	NM_010165
Fxyd2	FXYD domain-containing ion transport regulator 2	NM_007503 /// NM_052823
Bik	BCL2-interacting killer	NM_007546
Krt31	keratin 31	NM_010659
Calcb	calcitonin-related polypeptide, beta	NM_054084
Neto1	neuropilin (NRP) and tolloid (TLL)-like 1	NM_144946
Pion	pigeon homolog (Drosophila)	NM_175437
Myof	myoferlin	NM_001099634 /// XM_001480162 /// XM_001480167 /// XM_283556
Lrig1	leucine-rich repeats and immunoglobulin-like domains 1	NM_008377
Fgf1	fibroblast growth factor 1	NM_010197
Hivep3	human	NM_010657

	immunodeficiency virus type I enhancer binding protein 3	
Insrr	insulin receptor-related receptor	NM_011832
Neto1	neuropilin (NRP) and tolloid (TLL)-like 1	NM_144946
Cldn10	claudin 10	NM_001160096 /// NM_001160097 /// NM_001160098 /// NM_001160099 /// NM_021386 //
Gad1	glutamic acid decarboxylase 1	NM_008077
Cib3	calcium and integrin binding family member 3	NM_001080812 /// XM_356089 /// XM_904518
Capsl	calcyphosine-like	NM_029341
---	---	---
Nptx1	neuronal pentraxin 1	NM_008730
Muc4	mucin 4	NM_080457
Calca	calcitonin/calcitonin-related polypeptide, alpha	NM_001033954 /// NM_007587
Lrig1	leucine-rich repeats and immunoglobulin-like domains 1	NM_008377
Gabrp	gamma-aminobutyric acid (GABA) A receptor, pi	NM_146017
Cxcl17	chemokine (C-X-C motif) ligand 17	NM_153576
Lrrc26	leucine rich repeat containing 26	NM_146117
LOC100047840 /// Stap1	similar to stem cell adaptor protein STAP-1 /// signal transducing adaptor famil	NM_019992 /// XM_001479407 /// XM_001479415
Msln	mesothelin	NM_018857
5730414M22Rik	RIKEN cDNA 5730414M22 gene	---
Aspa	aspartoacylase	NM_023113

Gng13	guanine nucleotide binding protein (G protein), gamma 13	NM_022422
Muc4	mucin 4	NM_080457
Car4	carbonic anhydrase 4	NM_007607
A430071A18Rik	RIKEN cDNA A430071A18 gene	---
C130021I20Rik	Riken cDNA C130021I20 gene	NM_177842
Cplx2	complexin 2	NM_009946
Runx2	runt related transcription factor 2	NM_001145920 /// NM_001146038 /// NM_009820
Dcxr	dicarbonyl L-xylulose reductase	NM_026428
1700061J05Rik	RIKEN cDNA 1700061J05 gene	NM_001163612 /// NM_001163613 /// NM_028522 /// XM_181371 /// XM_911673
Fam46c	family with sequence similarity 46, member C	NM_001142952 /// XR_001536 /// XR_002338 /// XR_005163
Muc16	mucin 16	XM_001476091 /// XM_911929
Cplx2	complexin 2	NM_009946
5830428M24Rik	RIKEN cDNA 5830428M24 gene	---
Kcnj1	potassium inwardly-rectifying channel, subfamily J, member 1	NM_019659
Gabrp	gamma-aminobutyric acid (GABA) A receptor, pi	NM_146017
Car4	carbonic anhydrase 4	NM_007607
Kcnma1	Potassium large conductance calcium-activated channel, subfamily M, alpha member	NM_010610
Otop1	otopetrin 1	NM_172709

Prox1	prospero-related homeobox 1	NM_008937
Abcc4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	NM_001033336 /// NM_001163675 /// NM_001163676
BC064078	cDNA sequence BC064078	NR_015455 /// XR_034925 /// XR_035011
Fgf1	fibroblast growth factor 1	NM_010197
Tst	thiosulfate sulfurtransferase, mitochondrial	NM_009437
Rshl2a	radial spokehead-like 2A	NM_025789
Muc20	mucin 20	NM_001145874 /// NM_146071
4922501L14Rik	RIKEN cDNA 4922501L14 gene	NM_175176 /// XM_001481326 /// XR_032207
Ropn1l	ropporin 1-like	NM_145852
Slfn4	schlafen 4	NM_011410

Table 2. Cell surface marker genes upregulated in Barrett's like metaplasia.

Gene Symbol	Gene Title
slc6a14	
muc1	mucin 1
MFsd4	
DNER	
Tlr1	
Kcne3	
Cldn3	
Gprc5a	
Ceacam1	
Upk1a	
Steap1	

Muc16	mucin 1
Vtcn1	
Slc38a5	
Muc20	
Abcc4	
Neto1	
Muc4	mucin 4
Slc35d3	
Tmem163	
Car4	
Slc14a1	
Hepacam2	
cd177	
kcnq1	
sgms2	
rab17	

Table 3. Genes upregulated in cells of the squamocolumnar junction of the stomach.

Gene Symbol	Gene Title
LOC632073 /// U46068	similar to long palate, lung and nasal epithelium carcinoma associated 1 isoform
Ltf	lactotransferrin
Defb4	defensin beta 4
Ugt8a	UDP galactosyltransferase 8A
Mcpt2	mast cell protease 2
Onecut2	one cut domain, family member 2
Mcpt1	mast cell protease 1
Gcg	glucagon
Cldn7	claudin 7
Calcb	calcitonin-related polypeptide, beta

Pigr	polymeric immunoglobulin receptor
Gpr120	G protein-coupled receptor 120
Pate4	prostate and testis expressed 4
Wfdc2	WAP four-disulfide core domain 2
Rgs13	regulator of G-protein signaling 13
Muc4	mucin 4
Apob	apolipoprotein B
Gm14446	predicted gene 14446
U46068	cDNA sequence U46068
Cd177	CD177 antigen
Itih2	inter-alpha trypsin inhibitor, heavy chain 2
Spib	Spi-B transcription factor (Spi-1/PU.1 related)
Krt6a	keratin 6A
F5	coagulation factor V
Hamp	hepcidin antimicrobial peptide
Slfn4	schlafen 4
Trpm5	transient receptor potential cation channel, subfamily M, member 5
Spink12	serine peptidase inhibitor, Kazal type 11
Hsd11b2	hydroxysteroid 11-beta dehydrogenase 2
Gabrp	gamma-aminobutyric acid (GABA) A receptor, pi
Ceacam1	carcinoembryonic antigen-related cell adhesion molecule 1
Cldn2	claudin 2
BC100530 /// Stfa1	cDNA sequence BC100530 /// stefin A1
Siglec5	sialic acid binding Ig-like lectin 5
Reg3g	regenerating islet-derived 3 gamma
Gsdmc2 /// LOC100045250	gasdermin C2 /// hypothetical protein LOC100045250
2010205A11Rik /// Gm10883 /// Gm1420 /// Gm7202 /// Igk /// Igk-C /// Igk-V28 ///	RIKEN cDNA 2010205A11 gene /// predicted gene 10883 /// predicted gene 1420 ///

LOC100047628	
Ppbp	pro-platelet basic protein
Expi	extracellular proteinase inhibitor
2310038E17Rik	RIKEN cDNA 2310038E17 gene
Slc6a14	solute carrier family 6 (neurotransmitter transporter), member 14
Fcgbp	Fc fragment of IgG binding protein
Aqp5 /// LOC100046616	aquaporin 5 /// similar to aquaporin 5
Naip5	NLR family, apoptosis inhibitory protein 5
Gm10883 /// Gm1420 /// Gm7202 /// Igk /// Igk-C /// Igk-V28 /// LOC100047628	predicted gene 10883 /// predicted gene 1420 /// predicted gene 7202 /// immunog
Dclk1	doublecortin-like kinase 1
Stfa2l1	stefin A2 like 1
Kcne3	potassium voltage-gated channel, Isk-related subfamily, gene 3
Pcdh24	protocadherin 24
Igh /// Igh-2 /// Igh-VJ558 /// LOC544903	immunoglobulin heavy chain complex /// immunoglobulin heavy chain 2 (serum IgA)
Stfa3	stefin A3
Trpm5	transient receptor potential cation channel, subfamily M, member 5
Igh /// Igh-2 /// Igh-VJ558 /// LOC544903	immunoglobulin heavy chain complex /// immunoglobulin heavy chain 2 (serum IgA)
Igj	immunoglobulin joining chain
Gpa33	glycoprotein A33 (transmembrane)

Also provided is a subset of genes from the human isolated clonal population of Barrett's esophagus progenitor cells (set forth below in Table 4, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). Each of these genes is expressed at, at least, 10% of the expression of actin in these cells. These genes were determined to be useful diagnostically for the identification of these cells and/or as target molecules for therapeutics designed to kill or inhibit growth

of these cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 4

Gene Symbol	Accession No.
GSTM4	NM_000850
SLC16A4	NM_004696
CMBL	NM_138809.3
CEACAM6	NM_002483
NR5A2	NM_205860
CFTR	NM_000492
GCNT3	NM_004751

Also provided is a subset of genes from the human isolated clonal population of Barrett's esophagus progenitor cells (set forth below in Table 5, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). These genes are upregulated in Barrett's esophagus progenitor cells when compared to their expression in squamous cell and gastric cardia progenitor cells. These genes were also determined to be useful diagnostically for the identification of these cells and/or

as target molecules for therapeutics designed to kill or inhibit growth of these cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 5

Gene Symbol	RefSeq
ODAM	NM_017855
GSTM4	NM_000850
BICC1	NM_001080512
SLC16A4	NM_004696
NTS	NM_006183
BAAT	NM_001701
DDX43	NM_018665
MXRA5	NM_015419
FGF2	NM_002006
AK5	NM_174858
CCL28	NM_148672
HLA-DMB	NM_002118
TNFRSF10C	NM_003841
HS3ST5	NM_153612
CTH	NM_001902
TGFB2	NM_001135599
CLDN10	NM_182848
SLC15A1	NM_005073
CYP2E1	NM_000773
GSTM2	NM_000848
LRRC6	NM_012472
CCBE1	NM_133459
STC2	NM_003714
NKX6-3	NM_152568
MATN2	NM_002380
USP44	NM_032147

In certain embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of mRNA of any one or more of the genes shown in Table 6, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 6

Negatively expressing genes

Gene Symbol	RefSeq
SOX2	NM_003106
TP63	NM_003722
KRT20	NM_019010
GKN1	NM_019617
GKN2	NM_182536
FABP1	NM_001443
FABP2	NM_000134
Krt14	NM_000526
CXCL17	NM_198477

In certain specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of Krt20, Sox2 and p63 mRNA. In other specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of SOX2, p63, KRT20, GKN1, GKN2, FABP1, FABP2, KRT14 and CXCL17.

In certain embodiments, the isolated Barrett's esophagus progenitor cells described herein are positive for the expression of any one or more mRNA of any one or more of the genes shown in Table 7, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 7

Positively expressing genes

Gene Symbol	RefSeq
GSTM4	NM_000850
SLC16A4	NM_004696
CMBL	NM_138809
CEACAM6	NM_002483
NR5pA2	NM_205860
CFTR	NM_000492
GCNT3	NM_004751
BICC1	NM_001080512
NTS	NM_006183

In certain specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are positive for the expression of CEACAM6

mRNA. In other specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of CEACAM6, GSTM4, SLC16A4, CMBL, NR5A2, CFTR, GCNT3, BICC1 and NTS mRNA.

In other embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of any one or more of Sox2, p63, Krt20, GKN1/2, FABP1/2, KRT14 or CXCL17 mRNA and positive for the expression of any one or more of CEACAM6, GSTM4, SLC16A4, CMBL, NR5A2, CFTR, GCNT3, BICC1 or NTS mRNA. In certain specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are positive for the expression of CEACAM6 mRNA and negative for the expression of Krt20, Sox2 and p63. In other specific embodiments, the isolated Barrett's esophagus progenitor cells described herein are negative for the expression of Sox2, p63, Krt20, GKN1/2, FABP1/2, KRT14 and CXCL17 mRNA and positive for the expression of CEACAM6, GSTM4, SLC16A4, CMBL, NR5A2, CFTR, GCNT3, BICC1 and NTS mRNA.

In certain embodiments, the human isolated clonal population of Barrett's esophagus progenitor cells disclosed herein are cultured with 5 mg/ml insulin, 10 ng/ml EGF, $2x10^{-9}$ M 3,3',5-triiodo-L-thyronine, 0.4 mg/ml hydrocortisone, 24 mg/ml adenine, $1x10^{-10}$ M cholera toxin, 1µM Jagged 1, 100ng/ml Noggin, 125ng/ml R Spondin 1, 2.5 µM Rock inhibitor in DMEM/Ham's F12 3:1 medium with 10% fetal bovine serum when the mRNA expression analysis is performed.

Also provided is a subset of genes from a human isolated clonal population of squamous progenitor cells (set forth below in Table 8, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). Each of these genes is expressed at, at least, 10% of the expression of actin in these cells. These genes were determined to be useful diagnostically for the identification of these cells and/or to distinguish these cells from Barrett's esophagus progenitor cells, so that the Barrett's esophagus progenitor cells can be selectively ablated without damaging squamous progenitor cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal

metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 8

Gene Symbol	Accession No.
S100A8	NM_002964
Krt14	NM_000526
SPRR1A	NM_005987
CSTA	NM_005213

Also provided is a subset of genes from the human isolated clonal population of squamous progenitor cells (set forth below in Table 9, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). These genes are upregulated in squamous progenitor cells when compared to their expression in Barrett's esophagus and gastric cardia progenitor cells. These genes were determined to be useful diagnostically for the identification of these cells and/or differentiation of these cells from Barrett's esophagus progenitor cells, so that the Barrett's esophagus progenitor cells can be selectively ablated without damaging squamous progenitor cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used

more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 9

Gene Symbol	RefSeq
S100A8	NM_002964
DSG1	NM_001942
SPINK6	NM_205841
SPRR1B	NM_003125
SERPINB13	NM_012397
DSC3	NM_024423
KRT14	NM_000526
KRT17	NM_000422
SPRR2D	NM_006945
DSG3	NM_001944
A2ML1	NM_144670
TMEM45A	NM_018004
SBSN	NM_198538
KRT5	NM_000424
SPRR1A	NM_005987
SERPINB7	NM_003784
TFPI2	NM_006528
IVL	NM_005547
CAPNS2	NM_032330
DSC1	NM_004948
TP63	NM_003722

In certain embodiments, the isolated squamous progenitor cells described herein are negative for the expression of any one or more of mRNA of any one or more of the genes shown in Table 10, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 10

Negatively expressing genes

Gene Symbol	RefSeq
SOX2	NM_003106
Krt20	NM_019010
CXCL17	NM_198477
CEACAM6	NM_002483
NR5A2	NM_205860

In certain specific embodiments, the isolated squamous progenitor cells described herein are negative for the expression of CEACAM6 mRNA. In other specific embodiments, the isolated squamous progenitor cells described herein are negative for the expression of Sox2, Krt20, CXCL17 and CEACAM6 mRNA.

In certain embodiments, the isolated squamous progenitor cells described herein are positive for the expression of any one or more mRNA of any one or more of the genes shown in Table 11, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 11

Positively expressing genes

Gene Symbol	RefSeq
S100A8	NM_002964
Krt14	NM_000526
SPRR1A	NM_005987
CSTA	NM_005213
TP63	NM_003722

In certain specific embodiments, the isolated squamous progenitor cells described herein are positive for the expression of p63 mRNA. In other specific embodiments, the isolated squamous progenitor cells described herein are negative for the expression of S100A8, Krt14, SPRR1A, CSTA and p63 mRNA.

In other embodiments, the isolated squamous progenitor cells described herein are negative for the expression of any one or more of Sox2, Krt20, GKN1/2, FABP1/2, CXCL17 or CEACAM6 mRNA and positive for the expression of any one or more of S100A8, Krt14, SPRR1A, CSTA or p63

mRNA. In certain specific embodiments, the isolated squamous progenitor cells described herein are positive for the expression of p63 mRNA and negative for the expression of CEACAM6. In other specific embodiments, the isolated squamous progenitor cells described herein are negative for the expression of Sox2, Krt20, GKN1/2, FABP1/2, CXCL17 and CEACAM6 mRNA and positive for the expression of S100A8, Krt14, SPRR1A, CSTA and p63 mRNA.

Also provided is a subset of genes from a human isolated clonal population of gastric cardia progenitor cells (set forth below in Table 12, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). Each of these genes is expressed at, at least, 10% of the expression of actin in these cells. These genes were determined to be useful diagnostically for the identification of these cells and/or to distinguish these cells from Barrett's esophagus progenitor cells, so that the Barrett's esophagus progenitor cells can be selectively ablated without damaging gastric cardia progenitor cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 12

Gene Symbol	Accession No.
CXCL17	NM_198477
CAPN6	NM_014289

PSCA	NM_005672
GKN1	NM_019617
GKN2	NM_182536
MT1G	NM_005950
SPINK4	NM_014471

Also provided is a subset of genes from the human isolated clonal population of gastric cardia progenitor cells (set forth below in Table 13, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers). These genes are upregulated in gastric cardia progenitor cells when compared to their expression in Barrett's esophagus and squamous progenitor cells. These genes were determined to be useful diagnostically for the identification of these cells and/or to distinguish these cells from Barrett's esophagus progenitor cells, so that the Barrett's esophagus progenitor cells can be selectively ablated without damaging squamous progenitor cells. Accordingly, the present invention makes use of the identified genes to provide methods and compositions for diagnosing, imaging, treating or preventing metaplasia (e.g., esophageal metaplasia). However, it should be appreciated that such methods and compositions are not limited to diagnosing, imaging, treating or preventing metaplasia, but can be can be used more generally for diagnosing, imaging, treating or preventing any disease arising from or containing cells that share the molecular signature disclosed herein. Such diseases include, without limitation, dysplasia (e.g., esophageal and gastric dysplasia), adenocarcinoma (e.g., esophageal, gastric and pancreatic adenocarcinoma), pancreatic intraepithelial neoplasia, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), and micropapillary carcinoma.

Table 13

Gene Symbol	RefSeq
CXCL17	NM_198477
LOC84740	NR_026892
KIAA1324	NM_020775
MT1M	NM_176870
C20orf114	NM_033197
MT1A	NM_005946
ORM2	NM_000608
CAPN6	NM_014289
CAPN9	NM_006615
PSCA	NM_005672
SLC26A9	NM_052934
SOX2OT	NR_004053
GABRP	NM_014211
UGT2B15	NM_001076
ITGBL1	NM_004791
UGT1A9	NM_021027
PIK3C2G	NM_004570
GKN1	NM_019617
SCGB2A1	NM_002407
PTER	NM_030664
GPR64	NM_001079858
LUM	NM_002345
HRASLS2	NM_017878
GKN2	NM_182536
MRAP2	NM_138409
MAL	NM_002371
SIM2	NM_009586
ORM1	NM_000607
FBP2	NM_003837
ALDH3A1	NM_000691
C11orf92	NM_207429
NPSR1	NM_207172
ARL14	NM_025047
CAPN13	NM_144575
RAB37	NM_175738
CYP4F12	NM_023944
PCDHB2	NM_018936
MGAM	NM_004668
TCEA3	NM_003196

In certain embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of any one or more mRNA of any one or more of the genes shown in Table 14, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 14

Negatively expressing genes

Gene Symbol	RefSeq
CEACAM6	NM_002483
TP63	NM_003722
FABP1	NM_001443
FABP2	NM_000134
Krt14	NM_000526
Krt20	NM_019010

In certain specific embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of CEACAM6 mRNA. In other specific embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of CEACAM6, p63, FABP1/2, Krt14 and Krt20 mRNA.

In certain embodiments, the isolated gastric cardia progenitor cells described herein are positive for the expression of any one or more mRNA of any one or more of the genes shown in Table 15, the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers.

Table 14

Positively expressing genes

Gene Symbol	RefSeq
CXCL17	NM_198477
CAPN6	NM_014289
CAPN9	NM_006615
PSCA	NM_005672
SOX2	NM_003106
GKN1	NM_019617
GKN2	NM_182536
MT1G	NM_005950
SPINK4	NM_014471

In other specific embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of CXCL17, CAPN6, CAPN9, PSCA, GKN1, GKN2, MT1G, SPINK4 and SOX2 mRNA.

In other embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of any one or more of CEACAM6, p63, FABP1/2, Krt14 or Krt20 mRNA and positive for the expression of any one or more of CXCL17, CAPN6, CAPN9, PSCA, GKN1, GKN2, MT1G, SPINK4 or SOX2 mRNA. In other specific embodiments, the isolated gastric cardia progenitor cells described herein are negative for the expression of CEACAM6, p63, FABP1/2, Krt14 and Krt20 mRNA and positive for the expression of CXCL17, CAPN6, CAPN9, PSCA, GKN1, GKN2, MT1G, SPINK4 and SOX2 mRNA.

B. Methods of Treatment

In one aspect, the invention provides methods for treating or preventing metaplasia (e.g., esophageal metaplasia). The methods of the invention generally comprise administering to a subject a therapeutic amount of an agent that decreases the expression and/or biological activity of one or more of the genes set forth in Tables 1-5 and Figures 9-11.

Any agent that causes a decrease in the expression and/or biological activity of the desired gene(s) is suitable for use in the methods of the invention. Suitable agents include, without limitation, antibodies, antibody-like molecules, aptamers, peptides, antisense oligonucleotides, small molecules or RNAi agents. In some embodiments, the agent decreases the amount of mRNA of the target gene. In other embodiments the agent decreases the expression of the protein product of the targeted gene. In other embodiments, the agent inhibits the biological activity of the protein product of the targeted gene (e.g., enzymatic activity or transcriptional activity). Such agents can be identified, for example, using the screening assays described herein.

In another aspect, the invention provides methods for treating or preventing metaplasia (e.g., esophageal metaplasia). The methods of the invention generally comprise administering a therapeutic amount of an agent that specifically binds to a cell surface polypeptide encoded by one of the genes set forth in Tables 1-5, 15 and 16 and Figures 9-11, wherein said agent is linked to one or more cytotoxic moiety.

Any agent that binds to the desired cell surface polypeptide is suitable for use in the methods of the invention. Suitable agents include, without limitation, antibodies, antibody-like molecules, aptamers, peptides, cell surface receptor ligand, or small molecules. In a preferred embodiment, the agent is an antibody, antibody-like molecule or cell surface receptor ligand.

In certain embodiments, cell surface polypeptides are targeted that are highly expressed in the Barrett's Esophagus progenitor cell but not in squamous cell progenitor cells that may be located nearby. The squamous cell progenitor cell described above and its mRNA expression profile compared to the profile of the clonal population of Barrett's Esophagus progenitor cells. Table 15 shows the mRNA from gene that were most highly expressed in clonal population of Barrett's Esophagus progenitor cells compared to the isolated squamous cell progenitor cell the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers. Shaded genes in Table 15 are cell surface proteins.

Table 15

GO_cellular_component	Gene Symbol
NM_004616 // GO:0005764 // lysosome // traceable author statement /// NM_004616	TSPAN8
NM_000239 // GO:0005576 // extracellular region // inferred from electronic anno	LYZ
NM_003122 // GO:0005576 // extracellular region // inferred from electronic anno	SPINK1
NM_080870 // GO:0016020 // membrane // inferred from electronic annotation ///	DPCR1
NM_003225 // GO:0005576 // extracellular region // inferred from electronic anno	TFF1
NM_002443 // GO:0005576 // extracellular region // inferred from electronic anno	MSMB
NM_000689 // GO:0005634 // nucleus // inferred from direct assay /// NM_000689	ALDH1A1
NM_001056 // GO:0005737 // cytoplasm // traceable author statement /// NM_00105	SULT1C2
NM_033049 // GO:0005576 // extracellular region // inferred from electronic anno	MUC13
NM_007193 // GO:0005634 // nucleus // inferred from direct assay /// NM_007193	ANXA10
NM_006149 // GO:0005829 // cytosol // traceable author statement /// NM_006149	LGALS4
NM_005423 // GO:0005576 // extracellular region // inferred from electronic anno	TFF2
NM_006408 // GO:0005576 // extracellular region // inferred from electronic anno	AGR2
NM_182536 // GO:0005576 // extracellular region // inferred from electronic anno	GKN2
NM_000669 // GO:0005737 // cytoplasm // non-traceable author statement /// NM_0	ADH1C
NM_182607 // GO:0016020 // membrane // inferred from electronic annotation ///	VSIG1
NM_005472 // GO:0016020 // membrane // inferred from electronic annotation ///	KCNE3
NM_019617 // GO:0005576 // extracellular region // inferred from electronic anno	GKN1
NM_006633 // GO:0005622 // intracellular // inferred from electronic annotation	IQGAP2
NM_003561 // GO:0005576 // extracellular region // traceable author statement /	PLA2G10
NM_002630 // GO:0005576 // extracellular region // inferred from electronic anno	PGC
NM_000492 // GO:0016020 // membrane // inferred from electronic annotation ///	CFTR
NM_176813 // GO:0005576 // extracellular region // inferred from electronic anno	AGR3
NM_003048 // GO:0016020 // membrane // inferred from electronic annotation ///	SLC9A2
NM_019844 // GO:0005886 // plasma membrane // not recorded /// NM_019844 // GO:	SLCO1B3
NM_001039724 // GO:0005737 // cytoplasm // inferred from electronic annotation	NOSTRIN
NM_058186 // GO:0005576 // extracellular region // non-traceable author statemen	FAM3B
NM_018728 // GO:0016459 // myosin complex // inferred from electronic annotation	MYO5C
NM_001002026 // GO:0005886 // plasma membrane // inferred from electronic annota	CLDN18
NM_017625 // GO:0005576 // extracellular region // inferred from electronic anno	ITLN1
NM_025257 // GO:0016020 // membrane // inferred from electronic annotation ///	SLC44A4
NM_016234 // GO:0005739 // mitochondrion // inferred from electronic annotation	ACSL5
NM_002083 // GO:0005737 // cytoplasm // traceable author statement /// AK225871	GPX2
NM_004447 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_00444	EPS8
NM_020873 // GO:0016020 // membrane // inferred from electronic annotation ///	LRRN1
NM_015480 // GO:0005886 // plasma membrane // inferred from sequence or structur	PVRL3
NM_007069 // GO:0005575 // cellular_component // no biological data available /	PLA2G16
NM_001098484 // GO:0005886 // plasma membrane // inferred from electronic annota	SLC4A4
NM_001145847 // GO:0005615 // extracellular space // inferred from electronic an	PROM1
NM_017855 // GO:0005576 // extracellular region // inferred from electronic anno	ODAM
NM_004363 // GO:0005886 // plasma membrane // inferred from electronic annotatio	CEACAM5
---	PLAC8
NM_001105078 // GO:0005622 // intracellular // inferred from electronic annotati	EVI1
NM_014585 // GO:0005737 // cytoplasm // traceable author statement /// NM_01458	SLC40A1
NM_017899 // GO:0001726 // ruffle // inferred from sequence or structural simila	TESC
NM_006252 // GO:0005634 // nucleus // inferred from electronic annotation /// N	PRKAA2
NM_032148 // GO:0005886 // plasma membrane // inferred from electronic annotatio	SLC41A2
NM_205860 // GO:0005634 // nucleus // traceable author statement /// NM_003822	NR5A2
NM_000111 // GO:0005624 // membrane fraction // traceable author statement ///	SLC26A3
NM_000850 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GSTM4

NM_001003954 // GO:0005886 // plasma membrane // non-traceable author statement_	ANXA13
NM_001024465 // GO:0005739 // mitochondrion // inferred from electronic annotati	FAM177B
NM_006418 // GO:0005576 // extracellular region // inferred from electronic anno	OLFM4
NM_001002236 // GO:0005576 // extracellular region // not recorded /// NM_00100	SERPINA1
---	BICC1
NM_001482 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GATM
NM_194463 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	RNF128
NM_003657 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	BCAS1
NM_004617 // GO:0005624 // membrane fraction // traceable author statement ///	TM4SF4
NM_145740 // GO:0005737 // cytoplasm // non-traceable author statement /// NM_0	GSTA1
NM_016548 // GO:0005794 // Golgi apparatus // traceable author statement /// NM	GOLM1
NM_000772 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	CYP2C18
NM_001135099 // GO:0005576 // extracellular region // inferred from electronic a	TMPRSS2
NM_003982 // GO:0005886 // plasma membrane // inferred from electronic annotatio	SLC7A7
NM_001311 // GO:0005737 // cytoplasm // traceable author statement /// ENST0000	CRIP1
NM_002423 // GO:0005576 // extracellular region // inferred from electronic anno	MMP7
NM_014312 // GO:0005624 // membrane fraction // traceable author statement ///	VSIG2
NM_014265 // GO:0005576 // extracellular region // inferred from electronic anno	ADAM28
NM_003558 // GO:0005575 // cellular_component // no biological data available /	PIP5K1B
NM_016235 // GO:0005886 // plasma membrane // inferred from electronic annotatio	GPRC5B
NM_000898 // GO:0005739 // mitochondrion // inferred from electronic annotation	MAOB
NM_152311 // GO:0016020 // membrane // inferred from electronic annotation ///	CLRN3
NM_004133 // GO:0005634 // nucleus // inferred from electronic annotation /// N	HNF4G
NM_001159352 // GO:0005576 // extracellular region // inferred from electronic a	REG4
NM_002276 // GO:0005882 // intermediate filament // traceable author statement	KRT19
NM_001461 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	FMO5
---	SLAIN1
NM_022129 // GO:0005575 // cellular_component // no biological data available /	PBLD
NM_004696 // GO:0005624 // membrane fraction // traceable author statement ///	SLC16A4
NM_002354 // GO:0005886 // plasma membrane // traceable author statement /// NM	EPCAM
NM_014391 // GO:0005634 // nucleus // traceable author statement /// NM_014391	ANKRD1
NM_001105248 // GO:0016020 // membrane // inferred from electronic annotation /	TMC5
NM_012339 // GO:0005624 // membrane fraction // traceable author statement ///	TSPAN15
NM_080860 // GO:0005634 // nucleus // inferred from direct assay /// NM_080860	RSPH1
NM_000166 // GO:0005789 // endoplasmic reticulum membrane // not recorded /// N	GJB1
NM_025047 // GO:0005622 // intracellular // inferred from electronic annotation	ARL14
NM_052854 // GO:0005634 // nucleus // inferred from electronic annotation /// N	CREB3L1
---	C14orf105
NM_145343 // GO:0005576 // extracellular region // inferred from electronic anno	APOL1
NM_004079 // GO:0005576 // extracellular region // non-traceable author statemen	CTSS
NM_016341 // GO:0000139 // Golgi membrane // inferred from electronic annotation	PLCE1
NM_001083926 // GO:0005737 // cytoplasm // inferred from sequence or structural	ASRGL1
NM_005556 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_00555	KRT7
NM_004063 // GO:0005886 // plasma membrane // inferred from electronic annotatio	CDH17
NM_000769 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	CYP2C19
NM_004751 // GO:0000139 // Golgi membrane // inferred from electronic annotation	GCNT3
NM_004132 // GO:0005576 // extracellular region // non-traceable author statemen	HABP2
NM_006183 // GO:0005576 // extracellular region // inferred from electronic anno	NTS
NM_000561 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GSTM1
NM_003963 // GO:0005886 // plasma membrane // traceable author statement /// NM	TM4SF5
---	C5orf32

---	CCDC68
NM_002153 // GO:0005789 // endoplasmic reticulum membrane // traceable author st	HSD17B2
NM_001500 // GO:0005622 // intracellular // inferred from electronic annotation	GMDS
NM_012137 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	DDAH1
NM_000716 // GO:0005576 // extracellular region // non-traceable author statemen	C4BPB
NM_006424 // GO:0005624 // membrane fraction // traceable author statement ///	SLC34A2
NM_001042471 // GO:0005737 // cytoplasm // inferred from electronic annotation	GSDMB
NM_003979 // GO:0005783 // endoplasmic reticulum // inferred from direct assay	GPRC5A
NM_002483 // GO:0005886 // plasma membrane // not recorded /// NM_002483 // GO:	CEACAM6
NM_001025159 // GO:0005622 // intracellular // traceable author statement /// N	CD74
NR_027332 // GO:0005634 // nucleus // inferred from direct assay /// NR_027332	HPGD
NM_001100619 // GO:0005634 // nucleus // inferred from electronic annotation //	CABLES1
NM_032918 // GO:0005622 // intracellular // inferred from electronic annotation	RERG
NM_017700 // GO:0005622 // intracellular // inferred from electronic annotation	FLJ20184
NM_138712 // GO:0005634 // nucleus // inferred from electronic annotation /// N	PPARG
NM_004726 // GO:0005634 // nucleus // inferred from direct assay /// NM_004726	REPS2
NM_003739 // GO:0005622 // intracellular // inferred from direct assay /// NM_0	AKR1C3
NM_001128174 // GO:0016020 // membrane // inferred from electronic annotation /	UGT8
NM_002644 // GO:0005576 // extracellular region // inferred from electronic anno	PIGR
NM_020384 // GO:0005886 // plasma membrane // inferred from electronic annotatio	CLDN2
NM_017655 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GIPC2
NM_198232 // GO:0005576 // extracellular region // inferred from electronic anno	RNASE1
NM_013261 // GO:0005634 // nucleus // traceable author statement /// NM_013261	PPARGC1A
NM_017954 // GO:0016020 // membrane // inferred from electronic annotation ///	CADPS2
---	CMBL
NM_206927 // GO:0005624 // membrane fraction // inferred from sequence or struct	SYTL2
---	BANK1
---	HIST1H4B
NM_003937 // GO:0005625 // soluble fraction // inferred from direct assay /// N	KYNU
NM_001216 // GO:0005634 // nucleus // inferred from electronic annotation /// N	CA9
NM_004293 // GO:0005622 // intracellular // traceable author statement /// NM_0	GDA
NM_015184 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	PLCL2
NM_205854 // GO:0005576 // extracellular region // inferred from electronic anno	SFTA2
NM_002843 // GO:0005634 // nucleus // inferred from direct assay /// NM_002843	PTPRJ
NM_004170 // GO:0005624 // membrane fraction // traceable author statement ///	SLC1A1
NM_002456 // GO:0005576 // extracellular region // inferred from electronic anno	MUC1
---	FSIP2
NM_001128424 // GO:0000139 // Golgi membrane // inferred from electronic annotat	C4orf18
NM_000667 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	ADH1A
NR_024010 // GO:0016020 // membrane // inferred from electronic annotation ///	UGT2A3
---	FAM107B
NM_001114086 // GO:0005626 // insoluble fraction // inferred from direct assay	CLIC5
NM_005379 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_00537	MYO1A
NM_007127 // GO:0005634 // nucleus // inferred from direct assay /// NM_007127	VIL1
---	LCE1D
NM_001701 // GO:0005737 // cytoplasm // traceable author statement /// NM_00170	BAAT
NM_000130 // GO:0005576 // extracellular region // not recorded /// NM_000130 /	F5
NM_178155 // GO:0005794 // Golgi apparatus // non-traceable author statement //	FUT8
NM_006287 // GO:0005576 // extracellular region // not recorded /// NM_006287 /	TFPI
NM_003226 // GO:0005576 // extracellular region // traceable author statement /	TFF3
NM_024022 // GO:0005783 // endoplasmic reticulum // inferred from direct assay	TMPRSS3

NM_053277 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	CLIC6
NM_138342 // GO:0005576 // extracellular region // inferred from electronic anno	GLB1L2
NM_021255 // GO:0005829 // cytosol // inferred from electronic annotation /// N	PELI2
NM_001651 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	AQP5
NM_012338 // GO:0005624 // membrane fraction // traceable author statement ///	TSPAN12
NM_020299 // GO:0005575 // cellular_component // no biological data available /	tcag7.1260
---	C8orf54
---	ATAD4
NM_001025616 // GO:0005622 // intracellular // inferred from electronic annotati	ARHGAP24
NM_007011 // GO:0005634 // nucleus // inferred from direct assay /// NM_007011	ABHD2
---	LRRC31
NM_002994 // GO:0005576 // extracellular region // inferred from electronic anno	CXCL5
NM_181337 // GO:0005575 // cellular_component // no biological data available /	DCDC2
NM_007011 // GO:0005634 // nucleus // inferred from direct assay /// NM_007011	ABHD2
NM_020826 // GO:0005887 // integral to plasma membrane // inferred from electron	SYT13
---	HKDC1
NM_018414 // GO:0000139 // Golgi membrane // inferred from electronic annotation	ST6GALNAC
NM_000507 // GO:0005739 // mitochondrion // inferred from direct assay /// NM_0	FBP1
NM_002310 // GO:0005576 // extracellular region // inferred from electronic anno	LIFR
NM_033103 // GO:0005622 // intracellular // inferred from electronic annotation	RHPN2
NM_003816 // GO:0005576 // extracellular region // inferred from electronic anno	ADAM9
NM_006200 // GO:0005576 // extracellular region // inferred from electronic anno	PCSK5
NM_139053 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	EPS8L3
---	PLCB4
NM_004055 // GO:0005622 // intracellular // inferred from electronic annotation	CAPN5
NM_213599 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	ANO5
BC008502 // GO:0016020 // membrane // inferred from electronic annotation /// B	C4orf34
NM_001097634 // GO:0000139 // Golgi membrane // inferred from electronic annotat	GCNT1
NM_000624 // GO:0005576 // extracellular region // non-traceable author statemen	SERPINA5
NM_001112706 // GO:0005737 // cytoplasm // inferred from sequence or structural	SCIN
---	PAPSS2
NM_004968 // GO:0000139 // Golgi membrane // inferred from direct assay /// NM_	ICA1
NM_020716 // GO:0016020 // membrane // inferred from electronic annotation ///	GRAMD1B
NM_015028 // GO:0005575 // cellular_component // no biological data available /	TNIK
NM_138573 // GO:0005576 // extracellular region // inferred from electronic anno	NRG4
NM_003280 // GO:0005861 // troponin complex // inferred from direct assay /// E	TNNC1
NM_007072 // GO:0005575 // cellular_component // no biological data available /	HHLA2
NM_001145319 // GO:0005737 // cytoplasm // inferred from electronic annotation	PLS1
NM_016315 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GULP1
NM_016132 // GO:0005634 // nucleus // inferred from electronic annotation /// N	MYEF2
NM_015993 // GO:0016020 // membrane // inferred from electronic annotation ///	PLLP
---	C12orf36
NM_001040105 // GO:0005576 // extracellular region // inferred from electronic a	MUC17
NM_002349 // GO:0005887 // integral to plasma membrane // traceable author state	LY75
NM_018665 // GO:0005622 // intracellular // inferred from direct assay /// ENST	DDX43
NM_015419 // GO:0005576 // extracellular region // inferred from electronic anno	MXRA5
NM_002867 // GO:0005886 // plasma membrane // inferred from electronic annotatio	RAB3B
NM_002163 // GO:0005634 // nucleus // inferred from electronic annotation /// E	IRF8
NM_002006 // GO:0005576 // extracellular region // not recorded /// NM_002006 /	FGF2
NM_020167 // GO:0005886 // plasma membrane // inferred from electronic annotatio	NMUR2
---	METTL7A

NM_006095 // GO:0016020 // membrane // inferred from electronic annotation ///	ATP8A1
NM_000170 // GO:0005739 // mitochondrion // inferred from electronic annotation	GLDC
NM_001146274 // GO:0005634 // nucleus // inferred from electronic annotation //	TCF7L2
NM_004932 // GO:0005634 // nucleus // inferred from direct assay /// NM_004932	CDH6
NM_003774 // GO:0000139 // Golgi membrane // inferred from electronic annotation	GALNT4
NM_017549 // GO:0005576 // extracellular region // inferred from electronic anno	EPDR1
---	HIST1H4C

NM_174858 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	AK5
NM_000691 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	ALDH3A1
NM_019111 // GO:0005764 // lysosome // inferred from direct assay /// NM_019111	HLA-DRA
NM_014936 // GO:0016020 // membrane // inferred from electronic annotation ///	ENPP4
NM_030622 // GO:0005783 // endoplasmic reticulum // non-traceable author stateme	CYP2S1
NM_000584 // GO:0005576 // extracellular region // inferred from electronic anno	IL8
NM_006208 // GO:0005615 // extracellular space // inferred from direct assay //	ENPP1
NM_016276 // GO:0005575 // cellular_component // no biological data available /	SGK2
NM_019053 // GO:0000145 // exocyst // inferred from electronic annotation /// N	EXOC6
NM_000777 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	CYP3A5
NM_207361 // GO:0005604 // basement membrane // inferred from electronic annotat	FREM2
NM_001307 // GO:0005886 // plasma membrane // inferred from electronic annotatio	CLDN7
NM_006615 // GO:0005575 // cellular_component // no biological data available /	CAPN9
NM_054024 // GO:0005576 // extracellular region // inferred from electronic anno	MIA2
NM_153676 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_15367	USH1C
NM_003551 // GO:0005575 // cellular_component // no biological data available /	NME5
---	RARRES3
NM_207015 // GO:0016020 // membrane // inferred from electronic annotation ///	NAALADL2
NM_001142393 // GO:0005634 // nucleus // traceable author statement /// NM_0011	NEDD9
NM_021069 // GO:0005634 // nucleus // non-traceable author statement /// NM_021	SORBS2
NM_144682 // GO:0005622 // intracellular // inferred from direct assay /// NM_0	SLFN13
NM_030923 // GO:0016020 // membrane // inferred from electronic annotation ///	TMEM163
NM_138780 // GO:0016020 // membrane // inferred from electronic annotation ///	SYTL5
NM_000458 // GO:0005634 // nucleus // inferred from electronic annotation /// N	HNF1B

NM_000511 // GO:0005794 // Golgi apparatus // traceable author statement /// NM	FUT2
NM_001145 // GO:0005576 // extracellular region // inferred from electronic anno	ANG
NM_024101 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	MLPH
---	TEX15
NM_148672 // GO:0005576 // extracellular region // traceable author statement /	CCL28
NM_002118 // GO:0005765 // lysosomal membrane // inferred from electronic annota	HLA-DMB
NM_005727 // GO:0016020 // membrane // inferred from electronic annotation ///	TSPAN1
NM_016245 // GO:0005576 // extracellular region // inferred from electronic anno	HSD17B11
NM_014646 // GO:0005634 // nucleus // inferred from electronic annotation /// N	LPIN2
NM_012156 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	EPB41L1
NM_000771 // GO:0005783 // endoplasmic reticulum // non-traceable author stateme	CYP2C9
NM_004864 // GO:0005576 // extracellular region // traceable author statement /	GDF15
NM_024642 // GO:0000139 // Golgi membrane // inferred from electronic annotation	GALNT12
NM_001086 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_00108	AADAC
NM_003513 // GO:0000786 // nucleosome // non-traceable author statement /// NM_	HIST1H2AB
NM_018043 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	ANO1
NM_020770 // GO:0005923 // tight junction // non-traceable author statement ///	CGN
NM_003786 // GO:0005624 // membrane fraction // traceable author statement ///	ABCC3

In certain embodiments, cell surface polypeptides are targeted that are highly expressed in the Barrett's Esophagus progenitor cell but not in gastric cardia cell progenitor cells that may be located nearby. The gastric cardia cell progenitor cell described above and its mRNA expression profile compared to the profile of the clonal population of Barrett's Esophagus progenitor cells. Table 16 shows the mRNA from gene that were most highly expressed in clonal

population of Barrett's Esophagus progenitor cells compared to the isolated squamous cell progenitor cell the sequences of which are each specifically incorporated herein by reference to their respective RefSeq Transcript ID numbers. Shaded genes in Table 16 are cell surface proteins.

Table 16

GO_cellular_component	Gene Symbol
NM_002421 // GO:0005576 // extracellular region // inferred from electronic anno	MMP1
NM_000111 // GO:0005624 // membrane fraction // traceable author statement ///	SLC26A3
NM_004696 // GO:0005624 // membrane fraction // traceable author statement ///	SLC16A4
NM_001003954 // GO:0005886 // plasma membrane // non-traceable author statement	ANXA13
NM_002483 // GO:0005886 // plasma membrane // not recorded /// NM_002483 // GO:	CEACAM6
NM_006418 // GO:0005576 // extracellular region // inferred from electronic anno	OLFM4
---	GMBL
NM_000492 // GO:0016020 // membrane // inferred from electronic annotation ///	CFTR
NM_021814 // GO:0005783 // endoplasmic reticulum // inferred from electronic ann	ELOVL5
NM_004063 // GO:0005886 // plasma membrane // inferred from electronic annotatio	CDH17
NM_001130992 // GO:0005737 // cytoplasm // inferred from electronic annotation	RBP1
NM_152311 // GO:0016020 // membrane // inferred from electronic annotation ///	CLRN3
NM_003930 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	SKAP2
NM_205860 // GO:0005634 // nucleus // traceable author statement /// NM_003822	NR5A2
---	BICC1
NR_024010 // GO:0016020 // membrane // inferred from electronic annotation ///	UGT2A3
NM_006547 // GO:0005634 // nucleus // inferred from electronic annotation /// N	IGF2BP3
NM_000850 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	GSTM4
NM_001040105 // GO:0005576 // extracellular region // inferred from electronic a	MUC17
NM_006111 // GO:0005739 // mitochondrion // non-traceable author statement ///	ACAA2
NM_133459 // GO:0005576 // extracellular region // inferred from electronic anno	CCBE1
NM_018665 // GO:0005622 // intracellular // inferred from direct assay /// ENST	DDX43
NM_006183 // GO:0005576 // extracellular region // inferred from electronic anno	NTS
NM_001128424 // GO:0000139 // Golgi membrane // inferred from electronic annotat	C4orf18
NM_053024 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	PFN2
NM_002380 // GO:0005576 // extracellular region // inferred from electronic anno	MATN2
NM_001114086 // GO:0005626 // insoluble fraction // inferred from direct assay	CLIC5
---	RASSF8
NM_014899 // GO:0005634 // nucleus // inferred from direct assay /// ENST00003	RHOBTB3
NM_015990 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	KLHL5
NM_003841 // GO:0005886 // plasma membrane // inferred from electronic annotatio	TNFRSF10C
NM_000610 // GO:0005737 // cytoplasm // inferred from direct assay /// NM_00061	CD44
NM_015419 // GO:0005576 // extracellular region // inferred from electronic anno	MXRA5
NM_030762 // GO:0005634 // nucleus // non-traceable author statement /// ENST00	BHLHE41
NM_174858 // GO:0005737 // cytoplasm // inferred from electronic annotation ///	AK5
NM_002118 // GO:0005765 // lysosomal membrane // inferred from electronic annota	HLA-DMB
NM_002223 // GO:0005783 // endoplasmic reticulum // traceable author statement	ITPR2
NM_133436 // GO:0005625 // soluble fraction // inferred from direct assay /// N	ASNS
NM_144975 // GO:0005634 // nucleus // inferred from electronic annotation /// E	SLFN5
NM_001964 // GO:0005622 // intracellular // inferred from electronic annotation	EGR1
NM_138933 // GO:0005634 // nucleus // inferred from electronic annotation /// N	A1CF
NM_138737 // GO:0016020 // membrane // inferred from electronic annotation ///	HEPH
NM_000313 // GO:0005576 // extracellular region // non-traceable author statemen	PROS1
NM_001042483 // GO:0005634 // nucleus // inferred from direct assay /// NM_0123	NUPR1

Any cytotoxic moiety is suitable for use in the methods of the invention, including, without limitation, radioactive isotopes, chemotoxins, or toxin proteins. Suitable radioactive isotopes include, without limitation, iodine^{131}, indium^{111}, yttrium^{90}, and lutetium^{177}. Suitable chemotoxins include, without limitation,

anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, l-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, antimetabolites (e.g., 30 methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), anti-mitotic agents (e.g., vincristine and vinblastine), duocarmycins, calicheamicins, maytansines and auristatins, and derivatives thereof. Suitable toxin proteins include, without limitation, bacterial toxins (e.g., diphtheria toxin, and plant toxins (e.g., ricin).

Additional cytotoxic moieties include a medoximil moiety, PPARγ inhibitors and NR5A2 activity modulator.

CMBL (carboxymethylenebutenolidase homolog; NP_620164.1) is highly expressed in Barrett's esophagus progenitor. CMBL is a cysteine hydrolase of the dienelactone hydrolase family that is highly expressed in liver and small intestine. CMBL preferentially cleaves cyclic esters, and it activates medoxomil-ester prodrugs in which the medoxomil moiety is linked to an oxygen atom (Ishizuka et al., 2010, J. Biol. Chem. 285, 11892-11902, incorporated by reference, herein, in its entirety). Thus, in certain embodiments, cytotoxic moieties include prodrug versions of common cytotoxic molecules, such as medoxomil-linked chemotherapeutics, to selectively damage Barrett's esophagus progenitor cells without significantly affecting other cell types of the esophagus or stomach. Alternatively this strategy could be used to introduce any appropriate pro-drug based on medoxomil chemistry to selectively affect the stem cells of IM.

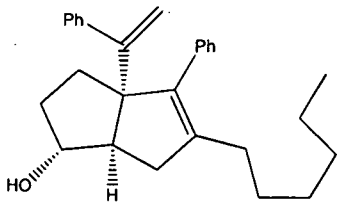
PPARgamma (NM 138712) and PPARgC1A (NM 013261) are highly overexpressed in Barrett's esophagus progenitor cells versus squamous stem

cells that give rise to the esophagus. Therefore, in certain embodiments, the cytotoxic moiety is a modulator of PPARgamma. An example of an irreversible inhibitor of PPARgamma is GW-9662 (2-Chloro-5-nitro-N-phenyl-benzamide), which suppresses PPARgamma with a nanomolar IC50. Modulators of PPARgamma, such as the drug class of thiazolidinediones (TZDs) are used clinically for the treatment of insulin resistance Yki-Järvinen, N Engl J Med. 351, 1106-1118 (2004); Staels and Fruchart Diabetes 54, 2460–2470 (2004).

The liver receptor homolog-1 (LRH-1) also known as NR5A2 (nuclear receptor subfamily 5, group A, member 2; NM 205860) is a protein that in humans is encoded by the NR5A2 gene, plays a critical role in the regulation of development, cholesterol transport, bile acid homeostasis and steroidogenesis. Bernier et al. (1993). Mol. Cell. Biol. 13 (3): 1619; and Galarneau et al. (1998) Cytogenet. Cell Genet. 82 (3-4): 269. NR5A2 is one of 49 "nuclear receptors" in the human genome that together represent ligand-regulated transcription factors. About half of these nuclear receptors have known ligands (estrogen, androgens, thyroid hormone, retinoids, vitamin D, etc.), the other half are orphan receptors.

The inventors have discovered, such as based on gene expression analysis of the cloned stem cells from Barrett's esophagus and gastric intestinal metaplasia, that the expression of NR5A2 is 10-20-fold higher when compared to indigenous stem cells of the esophagus and stomach. Our analysis further suggests that NR5A2 is likely a key stem cell factor required for self-renewal of both of both Barrett's and gastric intestinal metaplasia, and is different from the key self-renewal factors in the esophagus and stomach. Therefore targeting NR5A2 with agents that specifically affect the level of expression and/or functioning of NR5A2 in BE and IM stem cells versus the esophagus or stomach stem cells may be a useful way to inhibit the growth of those target stem cells, and perhaps a means to selectively ablate the BE and/or IM stem cell populations. The modulatory agents can include, for example, nucleic acid therapeutics such as siRNA, antisense, decoys and the like, as well as intracellular antibodies and antibody mimetics, and small molecules.

While NR5A2 is an orphan nuclear receptor, but considerable efforts are underway to drug these orphan receptors using molecular docking into homologous ligand pockets within the NR5A2 structures. In certain embodiments, the NR5A2 modulator is an agonist, such as dilauroyl phosphatidylcholine, or an agonist having the structure



Other natural and synthetic modulators are disclosed in Whitby et al., (2011) J. Mol. Med. 54, 2266, and representative embodiments are shown in Figure 15. Additional compounds can by synthesized from these parent compounds using standard medicinal chemistry.

In certain embodiments the cytotoxic moiety is linked directly (either covalently or non-covalently) to the agent. In other embodiments the cytotoxic moiety is incorporated into a biocompatible delivery vehicle that is in turn linked directly (either covalently or non-covalently) to the agent. Biocompatible delivery vehicles are well known in the art and include, without limitation, microcapsules, microparticles, nanoparticles, liposomes and the like.

Applicants have discovered that it is a primitive cell population residing at the squamocolumnar junction that is responsible for esophageal metaplasia. Accordingly, ablation of this cell population in normal, healthy individuals would protect those individuals from esophageal metaplasia and, in turn, from esophageal adenocarinoma. Thus, the present invention provides for both prophylactic and therapeutic methods of treatment. In some embodiments, the patient to be treated has been diagnosed as having metaplasia. In other embodiments, the patient to be treated does not have metaplasia.

According to the methods of the invention, the agent can be administered via any means appropriate to effect treatment. In some embodiments, the agent

is administered parenterally. In other embodiments, the agent is administered orally. In a preferred embodiment, the agent is administered endoscopically to the esophageal squamocolumnar junction or to a site of esophageal metaplasia. Any endoscopic device or procedure capable of delivering an agent is suitable for use in the methods of the invention.

An agent of the invention typically is administered to the subject in a pharmaceutical composition. The pharmaceutical composition typically includes the agent formulated together with a pharmaceutically acceptable carrier. Pharmaceutical compositions can be administered in combination therapy, *i.e.*, combined with other agents. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for oral, and parenteral administration *(e.g.,* by injection or infusion).

In some embodiments, the expression of genes required for activation, division or growth of the stem cell can reduced or otherwise inhibited using a nucleic acid therapeutic. In preferred embodiments, the nucleic acid therapeutic is selectively cytotoxic or cytotoxic to the stem cell relative to other normal tissue in the alimentary canal, particularly adjacent tissues. In the case of the BE stem cell, preferable nucleic acid therapeutics are selectively cytotoxic or cytotoxic to the BE cell as relative to normal esophageal squamous epithelium and/or esophageal squamous stem cells and/or stomach cardia stem cells.

Exemplary nucleic acid therapeutics include, but are not limited to, antisense oligonucleotides, decoys, siRNAs, miRNAs, shRNAs and ribozymes. These agents can be delivered through a variety of routes of administration, but a preferred route is through local delivery, such as by local injection or endoscopic delivery. Moreover, the nucleic acid therapeutic can be modified with one or more moieties which promote uptake of the polynucleotide by the targeted stem cell. For instance, the modification can be a peptide or a peptidomimetic that enhances cell permeation,or a lipophilic moiety which enhances entrance into a cell. Exemplary lipophilic moieties include those chosen from the group consisting of a lipid, cholesterol, oleyl, retinyl, cholesteryl

residues, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

RNA Interference Nucleic Acids

In particular embodiments, nucleic acid therapeutic is an RNA interference (RNAi) molecule. RNA interference methods using RNAi molecules may be used to disrupt the expression of a gene of interest, such as gene overexpressed by the targeted stem cell. Exemplary genes to be targeted in the case of BE stem cells are provided in Tables 1-5 and Figures 9-11. Small interfering RNA (siRNA) are RNA duplexes normally 21-30 nucleotides long that can associate with a cytoplasmic multi-protein complex known as RNAi-induced silencing complex (RISC). RISC loaded with siRNA mediates the degradation of homologous mRNA transcripts, therefore siRNA can be designed to knock down protein expression with high specificity. A variety of RNAi reagents, including siRNAs targeting clinically relevant targets, are currently under pharmaceutical development, as described, e.g., in de Fougerolles, A. et al., Nature Reviews 6:443-453 (2007).

While the first described RNAi molecules were RNA:RNA hybrids comprising both an RNA sense and an RNA antisense strand, it has now been demonstrated that DNA sense:RNA antisense hybrids, RNA sense:DNA antisense hybrids, and DNA:DNA hybrids are capable of mediating RNAi (Lamberton, J. S. and Christian, A. T., (2003) Molecular Biotechnology 24:111-119). Thus, the invention includes the use of RNAi molecules comprising any of these different types of double-stranded molecules. In addition, it is understood that RNAi molecules may be used and introduced to cells in a variety of forms. Accordingly, as used herein, RNAi molecules encompasses any and all molecules capable of inducing an RNAi response in cells, including, but not limited to, double-stranded polynucleotides comprising two separate strands, i.e.

a sense strand and an antisense strand, e.g., small interfering RNA (siRNA); polynucleotides comprising a hairpin loop of complementary sequences, which forms a double-stranded region, e.g., shRNAi molecules, and expression vectors that express one or more polynucleotides capable of forming a double-stranded polynucleotide alone or in combination with another polynucleotide.

RNA interference (RNAi) may be used to specifically inhibit expression of target genes in the stem cell. Double-stranded RNA-mediated suppression of gene and nucleic acid expression may be accomplished according to the invention by introducing dsRNA, siRNA or shRNA into cells or organisms. SiRNA may be double-stranded RNA, or a hybrid molecule comprising both RNA and DNA, e.g., one RNA strand and one DNA strand. It has been demonstrated that the direct introduction of siRNAs to a cell can trigger RNAi in mammalian cells (Elshabir, S. M., et al. Nature 411:494-498 (2001)). Furthermore, suppression in mammalian cells occurred at the RNA level and was specific for the targeted genes, with a strong correlation between RNA and protein suppression (Caplen, N. et al., Proc. Natl. Acad. Sci. USA 98:9746-9747 (2001)).

RNAi molecules targeting specific genes can be readily prepared according to procedures known in the art. Structural characteristics of effective siRNA molecules have been identified. Elshabir, S. M. et al. (2001) Nature 411:494-498 and Elshabir, S. M. et al. (2001), EMBO 20:6877-6888. Accordingly, one of skill in the art would understand that a wide variety of different siRNA molecules may be used to target a specific gene or transcript. In certain embodiments, siRNA molecules according to the invention are double-stranded and 16-30 or 18-25 nucleotides in length, including each integer in between. In one embodiment, an siRNA is 21 nucleotides in length. In certain embodiments, siRNAs have 0-7 nucleotide 3' overhangs or 0-4 nucleotide 5' overhangs. In one embodiment, an siRNA molecule has a two nucleotide 3' overhang. In one embodiment, an siRNA is 21 nucleotides in length with two nucleotide 3' overhangs (i.e. they contain a 19 nucleotide complementary region between the sense and antisense strands). In certain embodiments, the overhangs are UU or dTdT 3' overhangs.

Generally, siRNA molecules are completely complementary to the target mRNA molecule, since even single base pair mismatches have been shown to reduce silencing. In other embodiments, siRNAs may have a modified backbone composition, such as, for example, 2'-deoxy- or 2'-O-methyl modifications. However, in preferred embodiments, the entire strand of the siRNA is not made with either 2' deoxy or 2'-O-modified bases.

In one embodiment, siRNA target sites are selected by scanning the target mRNA transcript sequence for the occurrence of AA dinucleotide sequences. Each AA dinucleotide sequence in combination with the 3' adjacent approximately 19 nucleotides are potential siRNA target sites. In one embodiment, siRNA target sites are preferentially not located within the 5' and 3' untranslated regions (UTRs) or regions near the start codon (within approximately 75 bases), since proteins that bind regulatory regions may interfere with the binding of the siRNP endonuclease complex (Elshabir, S. et al. Nature 411:494-498 (2001); Elshabir, S. et al. EMBO J. 20:6877-6888 (2001)). In addition, potential target sites may be compared to an appropriate genome database, such as BLASTN 2.0.5, available on the NCBI server at www.ncbi.nlm, and potential target sequences with significant homology to other coding sequences eliminated.

Short Hairpin RNA (shRNA) is a form of hairpin RNA capable of sequence-specifically reducing expression of a target gene. Short hairpin RNAs may offer an advantage over siRNAs in suppressing gene expression, as they are generally more stable and less susceptible to degradation in the cellular environment. It has been established that such short hairpin RNA-mediated gene silencing works in a variety of normal and cancer cell lines, and in mammalian cells, including mouse and human cells. Paddison, P. et al., Genes Dev. 16(8):948-58 (2002). Furthermore, transgenic cell lines bearing chromosomal genes that code for engineered shRNAs have been generated. These cells are able to constitutively synthesize shRNAs, thereby facilitating long-lasting or constitutive gene silencing that may be passed on to progeny cells. Paddison, P. et al., Proc. Natl. Acad. Sci. USA 99(3):1443-1448 (2002).

ShRNAs contain a stem loop structure. In certain embodiments, they may contain variable stem lengths, typically from 19 to 29 nucleotides in length, or any number in between. In certain embodiments, hairpins contain 19 to 21 nucleotide stems, while in other embodiments, hairpins contain 27 to 29 nucleotide stems. In certain embodiments, loop size is between 4 to 23 nucleotides in length, although the loop size may be larger than 23 nucleotides without significantly affecting silencing activity. ShRNA molecules may contain mismatches, for example G-U mismatches between the two strands of the shRNA stem without decreasing potency. In fact, in certain embodiments, shRNAs are designed to include one or several G-U pairings in the hairpin stem to stabilize hairpins during propagation in bacteria, for example. However, complementarity between the portion of the stem that binds to the target mRNA (antisense strand) and the mRNA is typically required, and even a single base pair mismatch is this region may abolish silencing. 5' and 3' overhangs are not required, since they do not appear to be critical for shRNA function, although they may be present (Paddison et al. (2002) Genes & Dev. 16(8):948-58).

MicroRNAs

In other embodiments, the nucleic acid therapeutic is a Micro RNA (miRNA), MicroRNA mimic or an antagonist. Micro RNAs (miRNAs) are a highly conserved class of small RNA molecules that are transcribed from DNA in the genomes of plants and animals, but are not translated into protein. Processed miRNAs are single stranded @17-25 nucleotide (nt) RNA molecules that become incorporated into the RNA-induced silencing complex (RISC) and have been identified as key regulators of development, cell proliferation, apoptosis and differentiation. They are believed to play a role in regulation of gene expression by binding to the 3'-untranslated region of specific mRNAs. RISC mediates down-regulation of gene expression through translational inhibition, transcript cleavage, or both. RISC is also implicated in transcriptional silencing in the nucleus of a wide range of eukaryotes.

The number of miRNA sequences identified to date is large and growing, illustrative examples of which can be found, for example, in: "miRBase: microRNA sequences, targets and gene nomenclature" Griffiths-Jones S, Grocock R J, van Dongen S, Bateman A, Enright A J. NAR, 2006, 34, Database Issue, D140-D144; "The microRNA Registry" Griffiths-Jones S, NAR, 2004, 32, Database Issue, D109-D111; and also at http://microrna.sanger.ac.uk/sequences/. In certain preferred embodiments, the miRNA, miRNA mimic or antagonist is selectively cytotoxic or cytotoxic to BE cell as relative to normal esophageal squamous epithelium and/or esophageal squamous stem cells and/or gastric cardia stem cells.

Antisense Oligonucleotides

In one embodiment, the nucleic acid therapeutic is an antisense oligonucleotide directed to a target gene overexpressed in the stem cell, i.e., the BE stem cell, or for which inhibition of expression is selectively cytotoxic or cytotoxic to the BE cell as relative to normal esophageal squamous epithelium and/or esophageal squamous stem cells and/or stomach cardia stem cells. The term "antisense oligonucleotide" or simply "antisense" is meant to include oligonucleotides that are complementary to a targeted polynucleotide sequence. Antisense oligonucleotides are single strands of DNA or RNA that are complementary to a chosen sequence. In the case of antisense RNA, they prevent translation of complementary RNA strands by binding to it. Antisense DNA can be used to target a specific, complementary (coding or non-coding) RNA. If binding takes places this DNA/RNA hybrid can be degraded by the enzyme RNase H. In particular embodiment, antisense oligonucleotides contain from about 10 to about 50 nucleotides, more preferably about 15 to about 30 nucleotides. The term also encompasses antisense oligonucleotides that may not be exactly complementary to the desired target gene. Thus, the invention can be utilized in instances where non-target specific-activities are found with antisense, or where an antisense sequence containing one or more mismatches with the target sequence is the most preferred for a particular use.

Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, can be used to specifically inhibit protein synthesis by a targeted gene. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. Methods of producing antisense oligonucleotides are known in the art and can be readily adapted to produce an antisense oligonucleotide that targets any polynucleotide sequence. Selection of antisense oligonucleotide sequences specific for a given target sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m, binding energy, and relative stability. Antisense oligonucleotides may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA include those regions at or near the AUG translation initiation codon and those sequences that are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software (Molecular Biology Insights) and/or the BLASTN 2.0.5 algorithm software (Altschul et al., Nucleic Acids Res. 1997, 25(17):3389-402).

Ribozymes

According to another embodiment of the invention, the nucleic acid therapeutic is a ribozyme. Ribozymes are RNA-protein complexes having specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci USA. 1987 December; 84(24):8788-92; Forster and Symons, Cell. 1987 Apr. 24; 49(2):211-20) and can cleave an inactive a target mRNA. For example, a large number of ribozymes accelerate phosphodiester transfer reactions with a high degree of specificity, often cleaving only one of several phosphodiesters in an oligonucleotide substrate (Cech et al., Cell. 1981 December; 27(3 Pt 2):487-96; Michel and Westhof, J Mol. Biol. 1990 Dec. 5; 216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14; 357(6374):173-6). This specificity has been attributed to the requirement that the

substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

At least six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in trans (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis Δvirus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif, for example. Specific examples of hammerhead motifs are described by Rossi et al. Nucleic Acids Res. 1992 Sep. 11; 20(17):4559-65. Examples of hairpin motifs are described by Hampel et al. (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun. 13; 28(12):4929-33; Hampel et al., Nucleic Acids Res. 1990 Jan. 25; 18(2):299-304 and U.S. Pat. No. 5,631,359. An example of the hepatitis □virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec. 1; 31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada et al., Cell. 1983 December; 35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18; 61(4):685-96; Saville and Collins, Proc Natl Acad Sci USA. 1991 Oct. 1; 88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar. 23; 32(11):2795-9); and an example of the Group I intron is described in U.S. Pat. No. 4,987,071. Desirable characteristics of enzymatic nucleic acid molecules used according to the invention are that they have a specific substrate binding site which is

complementary to one or more of the target RNA regions, and that they have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Methods of producing a ribozyme targeted to any polynucleotide sequence are known in the art. Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference, and synthesized to be tested in vitro and in vivo, as described therein.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U.S. Pat. No. 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Cell Penetrating Moieties Attached to the Nucleic Acid Therapeutics

A variety of agents can be associated with the nucleic acid therapeutic, preferably through a reversible covalent linker, in order to enhance the uptake of the therapeutic by cells, particularly the targeted stem cell. These cell penetrating (CP) moieties may be so attached directly or indirectly via a linker. Functionally, the CP moieties may be designed to achieve one or more improved outcomes. As used herein the term "CP moiety" is a compound or molecule or construct which is attached, linked or associated with the nucleic acid therapeutic.

In one embodiment the CP moieties comprise molecules which promote endocytosis of the nucleic acid therapeutic. As such the CP moiety acts as a

"membrane intercalator." For example, the membrane intercalators may comprise C_{10}-C_{18} moieties which may be attached to the 3' end of antisense strand. These moieties may facilitate or result in the nucleic acid therapeutic becoming embedded in the lipid bilayer of a cell. Upon "flipping" of the lipids, the nucleic acid therapeutic would then enter the cell. In these constructs, the linker between the CP moiety and the nucleic acid therapeutic can be selected such that it is sensitive to the physicochemical environment of the cell and/or to be susceptible to or resistant to enzymes present. The end result being the liberation of the nucleic acid therapeutic, with or without a portion of the optional linker. The present invention also contemplates nucleic acid therapeutics that bind to receptors which are internalized.

Furthermore, the nucleic acid therapeutics of the invention itself can have one or more CP moieties which facilitates the active or passive transport, localization, or compartmentalization of the nucleic acid therapeutic.

Conjugates as CP moieties

CP moieties, while attached directly to the nucleic acid therapeutic or to the nucleic acid therapeutic via an optional linker may comprise conjugate groups attached to one or more of the nucleic acid therapeutic termini at selected nucleobase positions, sugar positions or to one of the terminal internucleoside linkages.

There are numerous methods for preparing conjugates of nucleic acid therapeutics. Generally, a nucleic acid therapeutic is attached to a conjugate moiety by contacting a reactive group (e.g., OH, SH, amine, carboxyl, aldehyde, and the like) on the oligomeric compound with a reactive group on the conjugate moiety. In some embodiments, one reactive group is electrophilic and the other is nucleophilic. For example, an electrophilic group can be a carbonyl-containing functionality and a nucleophilic group can be an amine or thiol. Methods for conjugation of nucleic acids and related compounds with and without linking groups are well described in the literature such as, for example, in Manoharan in Antisense Research and Applications, Crooke and LeBleu, eds., CRC Press,

Boca Raton, Fla., 1993, Chapter 17, which is incorporated herein by reference in its entirety.

In some embodiments, conjugate moieties can be attached to the terminus of a nucleic acid therapeutic such as a 5' or 3' terminal residue of either strand. Conjugate moieties can also be attached to internal residues of the oligomeric compounds. For nucleic acid therapeutics, conjugate moieties can be attached to one or both strands. In some embodiments, a double-stranded nucleic acid therapeutic contains a conjugate moiety attached to each end of the sense strand. In other embodiments, a double-stranded nucleic acid therapeutic contains a conjugate moiety attached to both ends of the antisense strand.

In some embodiments, conjugate moieties can be attached to heterocyclic base moieties (e.g., purines and pyrimidines), monomeric subunits (e.g., sugar moieties), or monomeric subunit linkages (e.g., phosphodiester linkages) of nucleic acid molecules. Conjugation to purines or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In some embodiments, the 2-, 6-, 7-, or 8-positions of a purine base are attached to a conjugate moiety. Conjugation to pyrimidines or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine base can be substituted with a conjugate moiety. Conjugation to sugar moieties of nucleosides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a conjugate moiety include the 2', 3', and 5' carbon atoms.

Internucleosidic linkages can also bear conjugate moieties. For phosphorus-containing linkages (e.g., phosphodiester, phosphorothioate, phosphorodithioate, phosphoroamidate, and the like), the conjugate moiety can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleosidic linkages (e.g., PNA), the conjugate moiety can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

These CP moieties act to enhance the properties of the nucleic acid therapeutic or may be used to track the nucleic acid therapeutic or its

metabolites and/or effect the trafficking of the construct. Properties that are typically enhanced include without limitation activity, cellular distribution and cellular uptake. In one embodiment, the nucleic acid therapeutics are prepared by covalently attaching the CP moieties to chemically functional groups available on the nucleic acid therapeutic or linker such as hydroxyl or amino functional groups. Conjugates which may be used as terminal moities include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, and groups that enhance the pharmacodynamic and/or pharmacokinetic properties of the nucleic acid therapeutic.

Typical conjugate groups include cholesterols, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve properties including but not limited to construct uptake, construct resistance to degradation, and/or strengthen sequence-specific hybridization with RNA.

Conjugate groups also include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, an aliphatic chain, a phospholipid, a polyamine or a polyethylene glycol chain or adamantane acetic acid, a palmityl moiety or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

The nucleic acid therapeutics of the invention may also be conjugated to active drug substances. Representative U.S. patents that teach the preparation of such conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941.

The present invention provides, inter alia, nucleic acid therapeutics and compositions containing the same wherein the CP moiety comprises one or more conjugate moieties. The CP moieties (e.g., conjugates) of the present invention can be covalently attached, optionally through one or more linkers, to one or more nucleic acid therapeutics. The resulting constructs can have modified or enhanced pharmacokinetic, pharmacodynamic, and other properties compared with non-conjugated constructs. A conjugate moiety that can modify or enhance the pharmacokinetic properties of a nucleic acid therapeutic can improve cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the nucleic acid therapeutic. A conjugate moiety that can modify or enhance pharmacodynamic properties of a nucleic acid therapeutic can improve activity, resistance to degradation, sequence-specific hybridization, uptake, and the like.

Representative conjugate moieties can include lipophilic molecules (aromatic and non-aromatic) including steroid molecules; proteins (e.g., antibodies, enzymes, serum proteins); peptides; vitamins (water-soluble or lipid-soluble); polymers (water-soluble or lipid-soluble); small molecules including drugs, toxins, reporter molecules, and receptor ligands; carbohydrate complexes; nucleic acid cleaving complexes; metal chelators (e.g., porphyrins, texaphyrins, crown ethers, etc.); intercalators including hybrid photonuclease/intercalators; crosslinking agents (e.g., photoactive, redox active), and combinations and derivatives thereof. Oligonucleotide conjugates and their syntheses are also reported in comprehensive reviews by Manoharan in Antisense Drug Technology, Principles, Strategies, and Applications, S. T. Crooke, ed., Ch. 16, Marcel Dekker, Inc., 2001 and Manoharan, Antisense & Nucleic Acid Drug Development, 2002, 12, 103, each of which is incorporated herein by reference in its entirety.

Lipophilic conjugate moieties can be used, for example, to counter the hydrophilic nature of a nucleic acid therapeutic and enhance cellular penetration. Lipophilic moieties include, for example, steroids and related compounds such as cholesterol (U.S. Pat. No. 4,958,013 and Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553), thiocholesterol (Oberhauser et al., Nuc. Acids Res.,

1992, 20, 533), lanosterol, coprostanol, stigmasterol, ergosterol, calciferol, cholic acid, deoxycholic acid, estrone, estradiol, estratriol, progesterone, stilbestrol, testosterone, androsterone, deoxycorticosterone, cortisone, 17-hydroxycorticosterone, their derivatives, and the like.

Other lipophilic conjugate moieties include aliphatic groups, such as, for example, straight chain, branched, and cyclic alkyls, alkenyls, and alkynyls. The aliphatic groups can have, for example, 5 to about 50, 6 to about 50, 8 to about 50, or 10 to about 50 carbon atoms. Example aliphatic groups include undecyl, dodecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, terpenes, bornyl, adamantyl, derivatives thereof and the like. In some embodiments, one or more carbon atoms in the aliphatic group can be replaced by a heteroatom such as O, S, or N (e.g., geranyloxyhexyl). Further suitable lipophilic conjugate moieties include aliphatic derivatives of glycerols such as alkylglycerols, bis(alkyl)glycerols, tris(alkyl)glycerols, monoglycerides, diglycerides, and triglycerides. Saturated and unsaturated fatty functionalities, such as, for example, fatty acids, fatty alcohols, fatty esters, and fatty amines, can also serve as lipophilic conjugate moieties. In some embodiments, the fatty functionalities can contain from about 6 carbons to about 30 or about 8 to about 22 carbons. Example fatty acids include, capric, caprylic, lauric, palmitic, myristic, stearic, oleic, linoleic, linolenic, arachidonic, eicosanoic acids and the like.

In further embodiments, lipophilic conjugate groups can be polycyclic aromatic groups having from 6 to about 50, 10 to about 50, or 14 to about 40 carbon atoms. Example polycyclic aromatic groups include pyrenes, purines, acridines, xanthenes, fluorenes, phenanthrenes, anthracenes, quinolines, isoquinolines, naphthalenes, derivatives thereof and the like.

Other suitable lipophilic conjugate moieties include menthols, trityls (e.g., dimethoxytrityl (DMT)), phenoxazines, lipoic acid, phospholipids, ethers, thioethers (e.g., hexyl-S-tritylthiol), derivatives thereof and the like. nucleic acid therapeutics containing conjugate moieties with affinity for low density lipoprotein (LDL) can help provide an effective targeted delivery system. High expression levels of receptors for LDL on tumor cells makes LDL an attractive carrier for selective delivery of drugs to these cells (Rump et al., Bioconjugate

Chem. 9: 341, 1998; Firestone, Bioconjugate Chem. 5: 105, 1994; Mishra et al., Biochim. Biophys. Acta 1264: 229, 1995). Moieties having affinity for LDL include many lipophilic groups such as steroids (e.g., cholesterol), fatty acids, derivatives thereof and combinations thereof. In some embodiments, conjugate moieties having LDL affinity can be dioleyl esters of cholic acids such as chenodeoxycholic acid and lithocholic acid.

Conjugate moieties can also include vitamins. Vitamins are known to be transported into cells by numerous cellular transport systems. Typically, vitamins can be classified as water soluble or lipid soluble. Water soluble vitamins include thiamine, riboflavin, nicotinic acid or niacin, the vitamin B_6 pyridoxal group, pantothenic acid, biotin, folic acid, the B_{12} cobamide coenzymes, inositol, choline and ascorbic acid. Lipid soluble vitamins include the vitamin A family, vitamin D, the vitamin E tocopherol family and vitamin K (and phytols).

In some embodiments, the conjugate moiety includes folic acid (folate) and/or one or more of its various forms, such as dihydrofolic acid, tetrahydrofolic acid, folinic acid, pteropolyglutamic acid, dihydrofolates, tetrahydrofolates, tetrahydropterins, 1-deaza, 3-deaza, 5-deaza, 8-deaza, 10-deaza, 1,5-dideaza, 5,10-dideaza, 8,10-dideaza and 5,8-dideaza folate analogs, and antifolates.

Vitamin conjugate moieties include, for example, vitamin A (retinol) and/or related compounds. The vitamin A family (retinoids), including retinoic acid and retinol, are typically absorbed and transported to target tissues through their interaction with specific proteins such as cytosol retinol-binding protein type II (CRBP-II), retinol binding protein (RBP), and cellular retinol-binding protein (CRBP). The vitamin A family of compounds can be attached to a nucleic acid therapeutic via acid or alcohol functionalities found in the various family members. For example, conjugation of an N-hydroxy succinimide ester of an acid moiety of retinoic acid to an amine function on a linker pendant to a nucleic acid therapeutic can result in linkage of vitamin A compound to the nucleic acid therapeutic via an amide bond. Also, retinol can be converted to its phosphoramidite, which is useful for 5' conjugation.

alpha-Tocopherol (vitamin E) and the other tocopherols (beta through zeta) can be conjugated to nucleic acid therapeutics to enhance uptake because of their lipophilic character. Also, vitamin D, and its ergosterol precursors, can be conjugated to nucleic acid therapeutics through their hydroxyl groups by first activating the hydroxyl groups to, for example, hemisuccinate esters. Conjugation can then be effected directly to the nucleic acid therapeutic or to an amino linker pendant from the nucleic acid therapeutic. Other vitamins that can be conjugated to nucleic acid therapeutics in a similar manner on include thiamine, riboflavin, pyridoxine, pyridoxamine, pyridoxal, deoxypyridoxine. Lipid soluble vitamin K's and related quinone-containing compounds can be conjugated via carbonyl groups on the quinone ring. The phytol moiety of vitamin K can also serve to enhance binding of the oligomeric compounds to cells.

Pyridoxal (vitamin B_6) has specific B_6-binding proteins. Other pyridoxal family members include pyridoxine, pyridoxamine, pyridoxal phosphate, and pyridoxic acid. Pyridoxic acid, niacin, pantothenic acid, biotin, folic acid and ascorbic acid can be conjugated to nucleic acid therapeutics, for example, using N-hydroxysuccinimide esters that are reactive with amino linkers located on the nucleic acid therapeutic, as described above for retinoic acid.

Conjugate moieties can also include polymers. Polymers can provide added bulk and various functional groups to affect permeation, cellular transport, and localization of the conjugated nucleic acid therapeutic. For example, increased hydrodynamic radius caused by conjugation of a nucleic acid therapeutic with a polymer can help prevent entry into the nucleus and encourage localization in the cytoplasm. In some embodiments, the polymer does not substantially reduce cellular uptake or interfere with hybridization to a complementary strand or other target. In further embodiments, the conjugate polymer moiety has, for example, a molecular weight of less than about 40, less than about 30, or less than about 20 kDa. Additionally, polymer conjugate moieties can be water-soluble and optionally further comprise other conjugate moieties such as peptides, carbohydrates, drugs, reporter groups, or further conjugate moieties.

In some embodiments, polymer conjugates include polyethylene glycol (PEG) and copolymers and derivatives thereof. Conjugation to PEG has been shown to increase nuclease stability of nucleic acid based compounds. PEG conjugate moieties can be of any molecular weight including for example, about 100, about 500, about 1000, about 2000, about 5000, about 10,000 and higher. In some embodiments, the PEG conjugate moieties contains at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, or at least 25 ethylene glycol residues. In further embodiments, the PEG conjugate moiety contains from about 4 to about 10, about 4 to about 8, about 5 to about 7, or about 6 ethylene glycol residues. The PEG conjugate moiety can also be modified such that a terminal hydroxyl is replaced by alkoxy, carboxy, acyl, amido, or other functionality. Other conjugate moieties, such as reporter groups including, for example, biotin or fluorescein can also be attached to a PEG conjugate moiety. Copolymers of PEG are also suitable as conjugate moieties. Preparation and biological activity of polyethylene glycol conjugates of oligonucleotides are described, for example, in Bonora et al., Nucleosides Nucleotides 18: 1723, 1999; Bonora et al., Farmaco 53: 634, 1998; Efimov, Bioorg. Khim. 19: 800, 1993; and Jaschke et al., Nucleic Acids Res. 22: 4810, 1994. Further example PEG conjugate moieties and preparation of corresponding conjugated oligomeric compounds is described in, for example, U.S. Pat. Nos. 4,904,582 and 5,672,662, each of which is incorporated by reference herein in its entirety. Nucleic acid compounds conjugated to one or more PEG moieties are available commercially.

Other polymers suitable as conjugate moieties include polyamines, polypeptides, polymethacrylates (e.g., hydroxylpropyl methacrylate (HPMA)), poly(L-lactide), poly(DL lactide-co-glycolide (PGLA), polyacrylic acids, polyethylenimines (PEI), polyalkylacrylic acids, polyurethanes, polyacrylamides, N-alkylacrylamides, polyspermine (PSP), polyethers, cyclodextrins, derivatives thereof and co-polymers thereof. Many polymers, such as PEG and polyamines have receptors present in certain cells, thereby facilitating cellular uptake. Polyamines and other amine-containing polymers can exist in protonated form at physiological pH, effectively countering an anionic backbone of some oligomeric compounds, effectively enhancing cellular permeation. Some example

polyamines include polypeptides (e.g., polylysine, polyomithine, polyhistadine, polyarginine, and copolymers thereof), triethylenetetramine, spermine, polyspermine, spermidine, synnorspermidine, C-branched spermidine, and derivatives thereof. Other amine-containing moieties can also serve as suitable conjugate moieties due to, for example, the formation of cationic species at physiological conditions. Example amine-containing moieties include 3-aminopropyl, 3-(N,N-dimethylamino)propyl, 2-(2-(N,N-dimethylamino)ethoxy)ethyl, 2-N-(2-aminoethyl)-N-methylaminooxy)ethyl, 2-(1-imidazolyl)ethyl, and the like.

Conjugate moieties can also include peptides. Suitable peptides can have from 2 to about 30, 2 to about 20, 2 to about 15, or 2 to about 10 amino acid residues. Amino acid residues can be naturally or non-naturally occurring, including both D and L isomers.

In some embodiments, peptide conjugate moieties are pH sensitive peptides such as fusogenic peptides. Fusogenic peptides can facilitate endosomal release of agents such as nucleic acid therapeutics to the cytoplasm. It is believed that fusogenic peptides change conformation in acidic pH, effectively destabilizing the endosomal membrane thereby enhancing cytoplasmic delivery of endosomal contents. Example fusogenic peptides include peptides derived from polymyxin B, influenza HA2, GALA, KALA, EALA, melittin-derived peptide, .alpha.-helical peptide or Alzheimer .beta.-amyloid peptide, and the like. Preparation and biological activity of oligonucleotides conjugated to fusogenic peptides are described in, for example, Bongartz et al., Nucleic Acids Res. 22: 4681, 1994, and U.S. Pat. Nos. 6,559,279 and 6,344,436.

Other peptides that can serve as conjugate moieties include delivery peptides which have the ability to transport relatively large, polar molecules (including peptides, oligonucleotides, and proteins) across cell membranes. Example delivery peptides include Tat peptide from HIV Tat protein and Ant peptide from Drosophila antenna protein. Conjugation of Tat and Ant with oligonucleotides is described in, for example, Astriab-Fisher et al., Biochem. Pharmacol. 60: 83, 2000.

Conjugated delivery peptides can help control localization of nucleic acid therapeutics and constructs to specific regions of a cell, including, for example, the cytoplasm, nucleus, nucleolus, and endoplasmic reticulum (ER). Nuclear localization can be effected by conjugation of a nuclear localization signal (NLS). In contrast, cytoplasmic localization can be facilitated by conjugation of a nuclear export signal (NES). Methods for conjugating peptides to oligomeric compounds such as oligonucleotides is described in, for example, U.S. Pat. No. 6,559,279, which is incorporated herein by reference in its entirety.

Many drugs, receptor ligands, toxins, reporter molecules, and other small molecules can serve as conjugate moieties. Small molecule conjugate moieties often have specific interactions with certain receptors or other biomolecules, thereby allowing targeting of conjugated nucleic acid therapeutics to specific cells or tissues.

Other conjugate moieties can include proteins, subunits, or fragments thereof. Proteins include, for example, enzymes, reporter enzymes, antibodies, receptors, and the like. In some embodiments, protein conjugate moieties can be antibodies or fragments. Antibodies can be designed to bind to desired targets such as tumor and other disease-related antigens. In further embodiments, protein conjugate moieties can be serum proteins. In yet further embodiments, nucleic acid therapeutics can be conjugated to RNAi-related proteins, RNAi-related protein complexes, subunits, and fragments thereof. For example, oligomeric compounds can be conjugated to Dicer or RISC or fragments thereof. RISC is a ribonucleoprotein complex that contains an oligonucleotide component and proteins of the Argonaute family of proteins, among others. Argonaute proteins make up a highly conserved family whose members have been implicated in RNA interference and the regulation of related phenomena. Members of this family have been shown to possess the canonical PAZ and Piwi domains, thought to be a region of protein-protein interaction. Other proteins containing these domains have been shown to effect target cleavage, including the RNAse, Dicer.

Other conjugate moieties can include, for example, oligosaccharides and carbohydrate clusters; a glycotripeptide that binds to Gal/GalNAc receptors on

hepatocytes, lysine-based galactose clusters; and cholane-based galactose clusters (e.g., carbohydrate recognition motif for asialoglycoprotein receptor). Further suitable conjugates can include oligosaccharides that can bind to carbohydrate recognition domains (CRD) found on the asialoglycoprotein-receptor (ASGP-R).

A wide variety of linker groups are known in the art that can be useful in the attachment of CP moieties to nucleic acid therapeutics. A review of many of the useful linker groups can be found in, for example, Antisense Research and Applications, S. T. Crooke and B. Lebleu, Eds., CRC Press, Boca Raton, Fla., 1993, p. 303-350. Any of the reported groups can be used as a single linker or in combination with one or more further linkers.

Linkers and their use in preparation of conjugates of oligonucleotides are provided throughout the art. For example, see U.S. Pat. Nos. 4,948,882; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,580,731; 5,486,603; 5,608,046; 4,587,044; 4,667,025; 5,254,469; 5,245,022; 5,112,963; 5,391,723; 5,510,475; 5,512,667; 5,574,142; 5,684,142; 5,770,716; 6,096,875; 6,335,432; and 6,335,437.

In one embodiment, the linker may comprise a nucleic acid hairpin which links the 5' end of one strand

The term "linking moiety," or "linker" as used herein is generally a bi-functional group, molecule or compound. It may covalently or non-covalently bind the nucleic acid therapeutic to the CP moiety. The covalent binding may be at both or only one end of the linker. Whether the nature of binding to the nucleic acid therapeutic and CP moiety is either covalent or noncovalent, the linker itself may be labile. As used herein the term "labile" as it applies to linkers means that the linker is either temporally or spatially stable for only a definite period or under certain environmental conditions. For example, a labile linker may lose integrity at a certain, time, temperature, pH, pressure, or under a certain magnetic field or electric field. The result of lost integrity being the severance of the connection between the nucleic acid therapeutic and one or more CP moieties.

Suitable linking moieties or linkers include, but are not limited to, divalent group such as alkylene, cycloalkylene, arylene, heterocyclyl, heteroarylene, and the other variables are as described herein.

C. Imaging Methods

In another aspect, the invention provides methods for imaging metaplasia (e.g., esophageal metaplasia). The methods of the invention generally comprise administering to a subject an effective amount of an agent that specifically binds to a cell surface polypeptide encoded by one of the genes set forth in Tables 1-5, 15 and 16 and Figures 9-11, and visualizing the agent. In a preferred embodiment, cell surface proteins are used that are differentially expressed in Barrett's esophagus progenitor cells and squamous cell progenitor cells and/or gastric cardia progenitor cells.

Any agent that binds to the desired cell surface polypeptide is suitable for use in the methods of the invention. Suitable agents include, without limitation, antibodies, aptamers, peptides, cell surface receptor ligands, or small molecules. In a preferred embodiment, the agent is an antibody, antibody-like molecule or cell surface receptor ligand.

In some embodiments, the agent is linked (covalently or non-covalently) to an imaging moiety to facilitate detection of the agent. Any imaging moiety is suitable for use in the methods of the invention, including, without limitation, positron-emitters, nuclear magnetic resonance spin probes, an optically visible dye, or an optically visible particle. Suitable positron-emitters include, without limitation, positron emitters of oxygen, nitrogen, iron, carbon, or gallium, ^{43}K, ^{52}Fe, ^{57}Co, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{123}I, ^{125}I, ^{131}I, ^{132}I,.or ^{99}Tc. Suitable nuclear magnetic resonance spin probes include, without limitation, iron chelates and radioactive chelates of gadolinium or manganese.

In certain embodiments, abalation techniques are used in conjunction with imaging methods disclosed herein. For example, the expression markers described herein may improve the ability to image or otherwise visualize metaplastic cells and facilitate their ablation. The types of ablation technique

that techniques that be used in conjunction with imaging or other visualization of markers described herein include radiofrequency, laser, microwave, cryogenic, thermal, chemical, and the like. The ablation probe may conform to the ablation energy source. For example, an endoscope with fiber optics can be used to view the operation field, and to help select the areas for ablation based on the detection of one or more markers described here.

D. Diagnostic Methods

In another aspect, the invention provides methods for diagnosing, or predicting the future development of metaplasia (e.g., esophageal metaplasia). The methods of the invention generally comprise measuring the expression level of one or more of the genes set forth in Tables 1-5, 15 and 16 and Figures 9-11 in an epithelial tissue sample from a subject, wherein an increase in the expression level relative to a suitable control indicates that the subject has, or has a future risk of developing, metaplasia. In a preferred embodiment, cell surface proteins are used that are differentially expressed in Barrett's esophagus progenitor cells and squamous cell progenitor cells.

Any means for measuring the expression level of a gene is suitable for use in the methods of the invention. Exemplary, art recognized, methods include, without limitation, gene expression profiling using gene chips to detect mRNA levels or antibody-based binding assays (e.g. ELISA) to detect the protein-product of a gene.

The epithelial tissue sample can be obtained by any means, including biopsy or by scraping or swabbing an area or by using a needle to aspirate. Methods for collecting various body samples are well known in the art, including, without limitation, endoscopic biopsy. Tissue samples may be fresh, frozen, or fixed according to methods known to one of skill in the art.

The diagnostic methods of the invention are generally performed *in vitro*. However, in certain embodiments, the tissue sample is not excised, but instead, assayed *in vivo*, for example, by using agents that can measure the real-time levels of a gene or gene product in the patient's tissue.

In certain embodiments, those patients that have been determined to be at risk of developing metaplasia and are at high degree of risk of developing cancer can then be selected for prophylactic treatment. In exemplary embodiments, the epithelial stem cell crypts that give rise to the metaplasia can be proactively and selectively ablated, such as using techniques described above, before any occurrence of transformed cells or development of esophageal or other cancers.

E. Screening Methods

In another aspect, the invention provides methods of identifying a compound useful for treating esophageal metaplasia (e.g., esophageal metaplasia).

In one embodiment, the method generally comprises administering a test compound to a p63 null mouse and determining the amount of epithelial metaplasia in the presence and absence of the test compound, wherein a decrease in the amount of epithelial metaplasia identifies a compound useful for treating esophageal metaplasia.

Suitable p63 null mice include mice with complete germ-line deletion of the p63 gene (see e.g., Yang *et al.* Nature 1999; 398: 714-8), mice in which the p63 gene has been conditionally deleted in one or more epithelial tissue, and mice in which the cellular levels of p63 protein have been reduced (e.g., by RNAi-mediated gene silencing).

In another embodiment, the method generally comprises administering a test compound to a mouse, wherein the mouse comprises stratified epithelial tissue in which basal cells have been ablated, and determining the amount of epithelial metaplasia in said epithelial tissue in the presence and absence of the test compound, wherein a decrease in the amount of epithelial metaplasia identifies a compound useful for treating esophageal metaplasia.

The basal cells of the mouse stratified epithelial tissue can be ablated using any art-recognized means. In a preferred embodiment, basal cells are

ablated using Cre-mediated expression of diphtheria toxin fragment A as described in Ivanova *et al.* Genesis. 2005; 43:129-35.

The amount of epithelial metaplasia can be determined by any means, including by the examination of pathological specimens obtained from sacrificed mice.

The test compound can be administered to the mice by any route and means that will achieve delivery of the test compound to the requisite location.

In another embodiment, the method generally comprises administering a test compound to a Barrett's esophagus progenitor cell, wherein in the presence and absence of the test compound, wherein a decrease in the viability of the Barrett's esophagus progenitor cell identifies a compound useful for treating esophageal metaplasia. The reduction in viability can be a 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99 or 100% reduction in viability.

IV. Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

General Methods

In general, the practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, recombinant DNA technology, immunology (especially, e.g., immunoglobulin technology), and animal husbandry. See, e.g., Sambrook, Fritsch and Maniatis, Molecular Cloning: Cold Spring Harbor Laboratory Press (1989); Antibody Engineering Protocols (Methods in Molecular Biology), 510, Paul, S., Humana Pr (1996); Antibody Engineering: A Practical Approach (Practical Approach Series, 169), McCafferty, Ed., Irl Pr (1996); Antibodies: A Laboratory Manual,

Harlow et al, C.S.H.L. Press, Pub. (1999); Current Protocols in Molecular Biology, eds. Ausubel *et al.*, John Wiley & Sons (1992).

Animal Models

p63-/- mice used in this study were backcrossed 10-12 times on a BALB/c background (Yang *et al.*, 1999 *supra*). Wild type controls were derived from littermates. To obtain staged embryos, heterozygotes were crossed and the presence of vaginal plugs set the timing at E0.5. The heterozygous DTA-Krt14-Cre strain was generated by crossing the homozygous Gt(ROSA)26Sor<tm1(DTA)Jpmb>/J stain (Ivanova *et al.* Genesis. 2005; 43:129-35. (Jackson Laboratory) with the homozygous Tg(KRT14-cre/Esr1)20Efu/J (see Vasioukhin *et al.* Proc Natl Acad Sci U S A. 1999; 96:8551-6) (Jackson laboratory). Diptheria toxin A was transcriptionally activated in basal cells of stratified epithelia via intraperitoneal injection of Tamoxifen in corn oil (100mg/kg) one to three weeks prior to analysis. Porcine gastroesophageal junctions of three-month-old pigs were obtained from a local abattoir in Strasbourg. Human gastrointestinal junctions were obtained from autopsies at the Brigham and Women's Hospital under IRB approval.

Expression Microarrays and Bioinformatics

All Cel files were processed using GeneChip Operating Software to calculate probeset intensity values, and probe hybridization ratios were calculated using Affymetrix Expression Console Software to valid sample quality. These intensity values were log2 transformed and then imported into Partek Genomics Suite 6.5 (beta). A 1-way ANOVA was performed to identify differentially expressed genes. For each analysis, fold-changes and p-values for probesets were calculated. Principal component analysis (PCA) was carried out using all probesets, and heatmaps were generated using sorted datasets based on Euclidean distance and average linkage methods.

Gene expression datasets from normal and Barrett's esophagus were downloaded from the Gene Expression Omnibus (GEO) Genesets of the NCBI (Stairs *et al.* PLoS One. 2008;3:e3534). Barrett's metaplasia datasets containing considerable squamous gene expression were excluded from the analysis.

Histology and Immunofluorescence

Histology, immunohistochemistry, and immunofluorescence were performed using standard techniques. Details on the primary and secondary antibodies employed in these studies are detailed in the Appendix.

Example 1. Gastric and esophageal metaplasia in the p63 Null Mouse is similar to that seen in Barrett's metaplasia.

The squamocolumnar junction present at the distal esophagus in humans is shifted posteriorly in mice due to an extension of squamous epithelium to the gastric midline (Fig. 1a). As with all stratified epithelia, the p63 gene is expressed in the basal cells of the esophageal and gastric squamous epithelia (Yang *et al.* Mol. Cell 1998; 2:305-16) (Fig. 1a). In p63 null mice, embryos develop to term but are born without an epidermis, mammary or prostate glands, and virtually all other stratified epithelial are either absent or highly deranged (Yang *et al.*1999, *supra*). The epidermis, for instance, begins its normal stratification from a single layer of ectoderm at embryonic day 13-14 (E13-14) and by E17 is a squamous epithelium with suprabasal expression of differentiation markers such as loricrin (Fig. 1b). However, the p63 null epidermis begins to degrade from that point on as evidenced by discontinuous loricrin and keratin 5 staining (Fig. 1b) in a process of non-regenerative differentiation due to the depletion of stem cells (Senoo *et al.* Cell. 2007; 129:523-36). To determine if similar events occur in the squamous epithelia of the esophagus and proximal stomach of p63 null embryos, these regions were examined by histologically. Although the wild type E18 embryo shows a mature squamous epithelium in the proximal stomach (Fig. 1c), the p63 null embryo

showed a remarkably well-developed columnar epithelium marked by hobnail apical projections (Fig. 1d). Taken together these data demonstrate that gastric and esophageal metaplasia in the p63 Null Mouse is similar to that seen in Barrett's metaplasia.

Example 2. Gene expression of metaplasia the in p63 null mouse is similar to that seen in Barrett's metaplasia.

To more fully characterize the metaplasia in the proximal stomach of the p63 null embryo, its gene expression profile was compared with those of specific regions of the gastrointestinal tract in mutant and wild type animals. In brief, RNA was extracted from microdissected tissues and used to probe expression microarray chips (Mouse Genome 430 2.0 Array, Affymetrix). Unsupervised principal component analysis of these data revealed that the wild type and p63 null colon, small intestine, and distal stomach formed concordant pairs of overall gene expression (Fig. 2a, 2b). In contrast, the comparisons of gene expression between wild type and p63 null proximal stomach revealed stark differences, thus the observed metaplasia was clearly distinct from the indigenous squamous epithelia at this site. Moreover, a broad comparison of the gene expression profiles of the metaplasia in the p63 null embryos indicated only passing relationships with either the small or large intestines (Fig. 2b, "intestine-like" box), demonstrating that this metaplasia is much more an entity unto itself rather than of other major tissues of the gastrointestinal tract. The gene expression profile of the metaplasia in the p63 null embryo was then compared with available datasets (Stairs *et al.* 2008 *supra*) from the intestinal metaplasia of human Barrett's esophagus (Fig. 2c). Within the top fifty genes overrepresented in the metaplasia of the p63 null embryos were many of the markers established for Barrett's and gastric intestinal metaplasia (Wang *et al.* J Gastroenterol 2009; 44:897-911), including mucin 4 (73x), keratin 20 (61x), trefoil factor 2 (49x), claudin 3 (46x), Agr2 (120x), and villin (27x; $p< 10^{-7}$ for all) (Fig. 2d). Moreover, antibodies to multiple markers, including Adh7 and *Agr2*, showed robust staining of the proximal stomach of the mutant embryos (Fig. 2e), validating the relevance of these expression datasets to the observed metaplasia. Taken

together these data demonstrate that gene expression of metaplasia the in p63 null mouse is similar to that seen in Barrett's metaplasia

Example 3. Metaplasia evolves from a Car4-positive, primitive embryonic epithelium.

To identify the source of the metaplasia evident in the p63 null proximal stomach, known biomarkers of Barrett's metaplasia were used to perform a retrospective analysis of embryological development. Using antibodies to claudin 3 (Cdn3), keratin 7 (Krt7), and carbonic anhydrase 4 (Car4) that show robust staining of E18 metaplasia (Fig. 3a), it was demonstrated that metaplasia was present as early as E14, when the metaplastic tissue in the stomach presents as a highly proliferative columnar epithelium marked by Car4, Cdn3, and Ki67 expression (Fig. 3b). One day earlier in development, at E13, Car4-positive cells were detected in a single layer in the stomach of the mutant embryos on an extended region of basement membrane of the proximal stomach (Fig. 3c). Significantly, the wild type E13 embryos also showed a similar population of Car4-positive cells at the basement membrane of the proximal stomach (Fig. 3c), demonstrating that this cell population is the origin of the observed metaplasia in the mutants, and that at E13, the evolution of the metaplasia had not been initiated. Given the both the p63 null and the wild type embryos displayed an apparently similar layer of Car4-positive cells on the basement membrane of the proximal stomach at E13, it was unclear why the p63 null embryos went on to develop a Barrett's-like metaplasia while the wild type embryos did not. p63 is a transcription factor required for long-term self-renewal of stem cells of stratified epithelia but is not required for their commitment to stem cells nor for their differentiation (Yang *et al.*, 1999; Senoo *et al.*, 2007 *supra*). Strong p63 expression was first detected at E13 in a population of cells at the esophageal gastric junction and this expression is notably weaker in cells that extended distally to the junction of Car4 cells (Fig. 3d). By E14, this population of p63-positive cells appears to extend to and actually among and under the population of Car4/Cdn3 positive cells in an anterior-posterior gradient (Fig. 3d), such that many of the Car4/Cdn3 cells are

displaced from the basement membrane to an apical position about the p63-expressing cells. Remarkably, whereas the Car4 expressing cells positioned on the basement membrane at the posterior end of this gradient are highly proliferative, those undermined by p63-expressing cells show significantly reduced cell cycle activity as judged by decreased Ki67 expression (Fig. 6). In the p63 null embryo, the Car4 cells are not undermined by epithelial cells at E14 and instead appear to rapidly propagate to a columnar epithelium. This lack of epithelial cells is due to the absence of p63 and their loss of self-renewal capacity, as has been demonstrated for stem cells of other squamous epithelia including the epidermis and thymic epithelial cells (Senoo *et al.*, 2007 *supra*). It was also noted that both the epidermal and thymic epithelial stem cells still undergo complete differentiation programs in the absence of p63, no evidence of squamous differentiation at any stage of the metaplasia was found in the p63 null embryos (Fig. 7). These data demonstrate that the Car4 cells that nucleate the metaplasia in the p63 null embryos lack inherent squamous differentiation programs.

Example 4. Undermined embryonic epithelium is retained at the squamocolumnar junction in adult mammals

To determine the ultimate fate of the Car4/Cdn3-expressing cells undermined by the p63-positive cells at E14, their fate was followed from E14 through to adulthood in wild type mice. By E15, these cells cease expression of Car4 but retain Cdn3 expression and assume expression of keratin 7 (not shown). At E17, these cells maintain their apical position above the stratifying squamous epithelia in the proximal stomach (Fig. 4a), but at E18 undergo a wholesale detachment from the underlying epithelia in large sheets (Fig. 4b). By E19, the Krt7-expressing cells have exfoliated from the entire proximal stomach with the exception of a discrete population of cells (numbering approximately 30 cells in cross-section) remaining precisely at the squamocolumnar junction (Fig. 4c). A similar population of Krt7-positive cells was observed in mice at three weeks of age (Fig. 4d) and as late as one year (not shown). Transcriptome analysis of RNA derived by microdissection of the squamocolumnar junction and

compared with adjacent squamous and columnar regions of the three-week-old mouse stomach revealed a distinct junctional signature marked by carcinoembryonic antigen (CEACAM1), Muc4, and Gabrp, all of which were significantly elevated (11-40x) in metaplasia from E18 p63 knockout embros (Fig. 8). The similarity between the persistent embryonic cells at this junction in wild type mice and the embryonic metaplasia in the p63 null embryos are further links to their common origins in the Car4-positive cells observed at E13. These data were directly supported by laser capture microdissection (LCM) of the junction Krt7-positive cells from three-week only mice compared with epithelial regions of the proximal and distal stomach (Fig. 4e). Lastly, it was determined if gastroesophageal junction tissues obtained from autopsies of humans without overt Barrett's also possessed cells similar to those described in mice. Antibodies to keratin 7, CEACAM1, and mucin 4 all revealed a discrete population of positive cells at the human gastroesophageal junction (Fig. 4e). These data demonstrate that the retention of embryonic epithelia at the squamocolumnar junction in the gastrointestinal tract is a common feature of adult mammals.

Example 5. Retained embryonic epithelia nucleate Barrett's-like metaplasia.

The persistence of a discrete population of cells having a lineage relation to an embryonic version of Barrett's metaplasia raised the possibility that they might spawn similar metaplasias in the adult. To test this hypothesis, mice were generated in which diptheria toxin A was conditionally expressed in basal cells of stratified epithelia by crossing the ROSA26-tm-DTA mouse (see Ivanova *et al.* 2005 *supra*) with one having a Tamoxifen-dependent Cre recombinase under the control of the Krt14 promoter Vasioukhin *et al.* (hereafter the DTA-Krt14Cre mouse). Treatment of three-week-old DTA-Krt14Cre mice with Tamoxifen resulted in a rapid expansion of the Krt7-expressing cells from their original site at the squamocolumnar junction to more anterior regions of the proximal stomach (Fig. 5a). Significantly, accompanying the expansion of these Krt7-expressing cells was their intimate association with the basement membrane that was presumably vacated by basal cells weakened or killed as a

consequence of Cre-mediated diptheria toxin A expression (Fig. 5b). In accord with their rapid expansion, these cells also show high levels of Ki67 indicative of cell cycle progression (Fig. 5c). Overall, the progression of this Barrett's-like metaplasia in the DTA-Krt14Cre mouse underscores the need of these retained embryonic cells to access the basement membrane for expansion, in turn, made possible by damage to the resident squamous epithelia. Taken together these data demonstrate that retained embryonic epithelia nucleate Barrett's-like metaplasia.

Example 6. Gene expression of Barrett's Esophagus Progenitor Cell Comapred to Squamous and Gastric Cardia Progenitor Cells.

Expression microarrays were used to compare the mRNA expression of an isolated clonal population of Barrett's esophagus progenitor cells and a clonal population of squamous progenitor cells. The results of this comparison are shown in Table ZZ, below.

Table ZZ

Gene Symbol	RefSeq No.	p-value (Attribute)	p-value (Barrett's vs. Squamous)	Ratio(Barrett's vs. Squamous)	Fold-Change (Barrett's vs. Squamous)
FABP1	NM_001443	2.34E-09	0.085908	1.47483	1.47483
CPS1	NM_001122633	2.60E-07	0.010034	0.434438	-2.30182
FABP2	NM_000134	5.39E-08	0.386115	1.19002	1.19002
PRSS2	NM_002770	2.27E-05	0.566736	0.808094	-1.23748
KRT20	NM_019010	5.33E-07	0.149126	1.44708	1.44708
DMBT1	NM_007329	7.79E-09	0.774347	1.03935	1.03935
SI	NM_001041	8.23E-09	0.022277	1.43479	1.43479
MTTP	NM_000253	2.97E-09	0.003091	1.54794	1.54794
RBP2	NM_004164	2.08E-07	0.080011	1.42961	1.42961
MT1H	NM_005951	2.21E-06	0.833756	0.952728	-1.04962
CLCA1	NM_001285	1.94E-07	0.284001	1.20283	1.20283
KGFLP2	NR_003670	7.43E-06	0.685646	0.906698	-1.1029

GUCY2C	NM_004963	3.89E-09	0.002247	1.56122	1.56122
GSTA2	NM_000846	0.000164	0.018224	4.07423	4.07423
CDH17	NM_004063	3.78E-09	5.02E-07	9.55456	9.55456
C17orf78	NM_173625	0.00023	0.780594	0.905833	-1.10396
GPR128	NM_032787	3.01E-08	0.009887	1.4728	1.4728
TM4SF4	NM_004617	1.49E-08	2.71E-07	14.0435	14.0435
GJA1	NM_000165	0.000666	0.000192	0.04303	-23.2396
OTC	NM_000531	1.40E-07	0.000185	2.93928	2.93928
BEX1	NM_018476	3.43E-05	0.947974	0.983379	-1.0169
HIST1H1A	NM_005325	1.95E-07	0.00842	1.65384	1.65384
OLFM4	NM_006418	1.75E-10	4.36E-09	15.251	15.251
LOC29034	NR_002763	1.07E-07	0.167948	1.18132	1.18132
BTNL3	NM_197975	4.86E-06	0.027782	1.68628	1.68628
DPY19L2P2	NR_003561	0.000999	0.228149	1.64931	1.64931
CPE	NM_001873	1.65E-06	0.001361	0.513199	-1.94856
RGS5	NM_003617	1.02E-05	0.025869	1.76086	1.76086
CPVL	NM_019029	1.05E-06	0.005975	0.643632	-1.55368
DSG3	NM_001944	7.14E-10	2.84E-10	0.01217	-82.1708
TM4SF20	NM_024795	3.07E-07	0.20159	1.17546	1.17546
SLC38A11	NM_173512	2.05E-06	0.431078	1.12989	1.12989
ADH4	NM_000670	2.50E-07	0.005823	1.58646	1.58646
CEACAM6	NM_002483	3.08E-05	0.001177	8.35385	8.35385
SYNPR	NM_001130003	2.23E-05	0.348375	1.22134	1.22134
ALDOB	NM_000035	2.00E-07	2.93E-05	3.90662	3.90662
FAM13A	NM_001015045	2.05E-05	0.471827	1.15247	1.15247
SLC17A4	NM_005495	4.81E-06	0.237349	1.23116	1.23116
CACNA2D1	NM_000722	9.75E-08	0.00453	1.50218	1.50218
ATF7IP2	NM_024997	2.12E-05	0.759455	0.946229	-1.05683
MEP1A	NM_005588	1.31E-06	0.075815	1.32331	1.32331
RBM46	NM_144979	7.01E-05	0.19628	0.748349	-1.33628
ZG16	NM_152338	8.01E-05	0.648568	1.11182	1.11182
REG4	NM_00115935	2.83E-08	2.50E-07	11.2549	11.2549

	2				
MUC17	NM_001040105	1.67E-06	8.78E-05	5.67432	5.67432
LGR5	NM_003667	3.55E-07	0.000603	2.01122	2.01122
PRSS1	NM_002769	8.44E-05	0.161547	1.42939	1.42939
SLC2A2	NM_000340	3.42E-06	0.079066	1.35541	1.35541
PHYHIPL	NM_032439	1.38E-05	0.065554	1.46452	1.46452
ACE2	NM_021804	1.43E-07	0.000437	1.8846	1.8846
CCND2	NM_001759	5.19E-05	2.30E-05	0.091416	-10.939
SULT1E1	NM_005420	3.45E-07	1.97E-07	0.063952	-15.6367
SLC5A1	NM_000343	8.44E-06	0.001409	2.71989	2.71989
SEMA6A	NM_020796	7.77E-07	0.00025	2.72895	2.72895
MT1L	NR_001447	0.004952	0.000668	0.044037	-22.7081
HMGCS2	NM_005518	3.07E-07	1.87E-05	3.67728	3.67728
MGAT4A	NM_012214	6.97E-06	0.000308	3.50807	3.50807
UGT2B17	NM_001077	5.68E-06	0.001365	2.32882	2.32882
C15orf48	NM_032413	1.19E-08	5.90E-06	2.33056	2.33056
CISD2	NM_001008388	0.000711	0.031534	0.574783	-1.73979
SST	NM_001048	0.000975	0.565834	1.17549	1.17549
SPC25	NM_020675	0.033633	0.373577	0.690568	-1.44808
PLA2G12B	NM_032562	1.29E-05	0.415062	1.12817	1.12817
LGALS2	NM_006498	1.72E-08	3.07E-06	2.57988	2.57988
NR1H4	NM_005123	5.91E-06	0.0257	1.45199	1.45199
UGT3A1	NM_152404	1.50E-05	0.184394	1.22895	1.22895
GIP	NM_004123	0.066104	0.751954	1.19265	1.19265
LOC147727	NR_024333	1.58E-05	0.188258	0.831438	-1.20274
ABCG2	NM_004827	0.000813	0.013104	0.524561	-1.90636
OCR1	AF314543	0.024574	0.808636	1.12556	1.12556
LMBR1	NM_022458	0.008559	0.00191	0.095088	-10.5166
A1CF	NM_138933	7.40E-07	4.35E-05	3.6505	3.6505
IGF2BP1	NM_006546	1.50E-07	0.001471	1.46936	1.46936
TSPAN7	NM_004615	0.000601	0.978363	1.00601	1.00601
CEACAM7	NM_006890	3.74E-06	0.064122	1.28262	1.28262

MYB	NM_001130173	4.65E-06	0.000341	2.52787	2.52787
CFI	NM_000204	8.87E-06	0.000331	3.21941	3.21941
SLC10A2	NM_000452	6.69E-05	0.141134	1.31867	1.31867
UGT2A3	NR_024010	1.48E-07	2.25E-06	7.27273	7.27273
IFITM1	NM_003641	6.18E-05	6.04E-05	0.139414	-7.17288
TMEM20	NM_001134658	0.000102	0.498743	1.12714	1.12714
TNFRSF11B	NM_002546	1.34E-05	0.000327	3.09331	3.09331
SMOC2	NM_022138	8.35E-05	0.047803	1.51645	1.51645
TGFBI	NM_000358	0.000306	8.74E-05	0.107698	-9.28521
GPA33	NM_005814	0.00014	0.144044	1.33829	1.33829
NELL2	NM_001145108	4.57E-05	0.158833	1.26394	1.26394
ATP1B3	NM_001679	7.11E-07	1.23E-07	0.100257	-9.97437
FGF9	NM_002010	2.98E-05	0.295931	1.16051	1.16051
FOLH1	NM_004476	1.41E-05	0.014508	1.5141	1.5141
RGS2	NM_002923	7.55E-06	0.460428	0.886527	-1.128
NAT2	NM_000015	4.42E-05	0.003952	2.07047	2.07047
CCL25	NM_005624	8.63E-05	0.142099	1.28954	1.28954
SEMA6D	NM_153618	1.55E-05	0.147042	0.838921	-1.19201
ANXA13	NM_001003954	2.27E-08	1.51E-07	15.5115	15.5115
KLHL23	ENST00000392647	8.54E-06	0.00107	2.12725	2.12725
GSTA1	NM_145740	1.25E-06	3.65E-06	13.4613	13.4613
S100G	NM_004057	6.67E-05	0.082683	1.37934	1.37934
LCT	NM_002299	1.06E-05	0.047808	1.31511	1.31511
FAM5C	NM_199051	4.88E-06	0.405939	1.08729	1.08729
ANPEP	NM_001150	3.32E-06	0.005603	1.68274	1.68274
HIST1H2AE	NM_021052	0.001216	0.2424	1.31829	1.31829
SLC11A2	NM_000617	1.91E-06	0.002027	1.56795	1.56795
LRRC19	NM_022901	4.02E-06	0.001068	1.87406	1.87406
SLC27A2	NM_003645	1.60E-05	0.000193	3.33023	3.33023
LDHC	NM_002301	5.51E-06	0.128855	1.17817	1.17817

SCGN	NM_006998	0.000129	0.105465	1.31481	1.31481
GPR160	NM_014373	2.16E-05	0.000152	3.88993	3.88993
SLC16A10	NM_018593	0.000465	0.188271	1.30369	1.30369
CLRN3	NM_152311	4.69E-08	2.24E-07	11.4491	11.4491
C12orf28	BC143553	1.27E-05	0.269447	1.18243	1.18243
SATB1	NM_002971	0.000101	6.00E-05	0.132514	-7.54637
GOLT1A	NM_198447	4.68E-07	5.93E-05	1.92107	1.92107
UFM1	NM_016617	1.64E-05	0.140695	0.862813	-1.159
HIBCH	NM_014362	0.011898	0.480496	0.835616	-1.19672
L1TD1	NM_019079	0.000304	0.000105	0.145075	-6.89301
HOXA9	NM_152739	2.96E-05	1.09E-05	0.090174	-11.0897
TPH1	NM_004179	0.000951	0.822371	1.04004	1.04004
HEPH	NM_138737	7.75E-08	1.80E-06	3.68292	3.68292
BMS1P5	NR_003611	0.240068	0.968687	1.02442	1.02442
ASAH2	NM_019893	7.62E-05	0.145436	1.23563	1.23563
KIAA1324	NM_020775	3.22E-08	0.00884	1.48311	1.48311
ALDOC	NM_005165	2.49E-06	0.330685	1.10185	1.10185
KPNA2	NM_002266	0.022754	0.772384	1.09878	1.09878
NEUROD1	NM_002500	0.06316	0.666654	1.17268	1.17268
MS4A8B	NM_031457	5.65E-06	0.003764	1.48823	1.48823
EPHB2	NM_017449	0.001129	0.180313	0.805308	-1.24176
MSI1	NM_002442	9.22E-06	0.012047	1.38697	1.38697
IFNK	NM_020124	0.002165	0.001768	0.168645	-5.92962
FGFBP1	NM_005130	1.79E-08	2.67E-09	0.032053	-31.1981
CDKN1B	NM_004064	3.54E-05	0.900479	0.985955	-1.01425
TFPI	NM_006287	1.26E-05	2.84E-05	7.05765	7.05765
STAMBPL1	NM_020799	4.70E-06	0.109009	0.878368	-1.13848
NLGN4Y	NM_014893	4.39E-05	2.77E-05	0.185298	-5.39672
PLD1	NM_002662	0.000446	0.701913	0.934448	-1.07015
APOBEC3B	NM_004900	0.001419	0.321714	1.22865	1.22865
MEP1B	NM_005925	5.41E-05	0.120667	1.21259	1.21259
	---	0.001183	0.000292	0.157535	-6.34781
EPHX2	NM_001979	1.10E-06	0.122339	0.898451	-1.11303

XRCC4	NM_022550	0.001579	0.024582	2.32654	2.32654
GAS2	NM_005256	3.49E-05	0.022857	1.37523	1.37523
DPP10	NM_020868	0.000864	0.293544	1.1938	1.1938
TLR4	NR_024168	9.63E-05	0.007119	1.66233	1.66233
LSAMP	NM_002338	2.16E-05	0.002367	1.65097	1.65097
SEPT7	NM_001788	0.01691	0.003851	0.18092	-5.52729
CCNB2	NM_004701	0.009939	0.814129	0.952239	-1.05016
MT1A	NM_005946	1.80E-05	0.000411	0.439688	-2.27434
C2orf43	BC017473	0.002035	0.506445	1.12716	1.12716
EML4	NM_019063	0.003235	0.085036	1.55247	1.55247
CKS2	NM_001827	2.48E-05	0.183434	1.13856	1.13856
CYP2B6	NM_000767	0.000209	0.002722	2.38855	2.38855
CCDC34	NM_030771	4.73E-05	0.48388	0.934202	-1.07043
ADH6	NM_001102470	2.18E-06	3.67E-05	2.77804	2.77804
ATP8A1	NM_006095	9.35E-06	2.53E-05	5.38379	5.38379
FAR2	NM_018099	3.78E-07	0.066621	1.16312	1.16312
TF	NM_001063	7.43E-06	0.63424	1.03621	1.03621
MYO1B	NM_001130158	1.47E-06	9.52E-07	0.114773	-8.71287
SLC35D1	NM_015139	0.066551	0.909823	0.965605	-1.03562
CXorf52	AY168775	0.026084	0.012721	0.219586	-4.55402
PCDH11Y	NM_032971	0.368856	0.665542	1.29083	1.29083
SERPINE2	NM_001136529	2.73E-07	9.54E-08	0.032271	-30.9872
ERP27	NM_152321	0.002033	0.712918	1.07767	1.07767
DNAJC2	NM_014377	0.000601	0.000118	0.173456	-5.76516
PCDH20	NM_022843	0.000951	0.136199	1.2937	1.2937
HNF4G	NM_004133	3.36E-07	5.08E-07	11.2611	11.2611
HIST1H3G	NM_003534	7.92E-05	0.010087	1.48882	1.48882
HPDL	NM_032756	0.001394	0.024925	1.72923	1.72923
SH3PXD2A	NM_014631	2.02E-05	3.22E-06	0.052282	-19.1269
COX18	NM_173827	0.001081	0.111706	1.32598	1.32598
HHLA2	NM_007072	1.26E-05	2.55E-05	5.74993	5.74993

ZNF770	NM_014106	2.22E-05	5.56E-06	0.155206	-6.44304
LYPLA1	NM_006330	5.75E-05	1.43E-05	0.112802	-8.86512
DHRS11	NM_024308	0.000217	0.016866	1.61863	1.61863
EPB41L2	NM_001431	0.003371	0.07753	1.57053	1.57053
EXOC3	AK074086	1.49E-06	0.003021	1.31235	1.31235
GHRL	NR_024138	0.027865	0.649993	1.11777	1.11777
DACH1	NM_080759	0.000217	0.135116	1.21114	1.21114
SPARC	NM_003118	1.66E-06	6.35E-07	0.131619	-7.5977
SLCO4C1	NM_180991	3.06E-05	0.010122	1.40569	1.40569
KLHL23	NM_144711	0.000249	0.00203	2.3695	2.3695
KRT6B	NM_005555	9.83E-11	3.36E-11	0.019068	-52.4439
EPCAM	NM_002354	1.17E-07	1.65E-07	10.5781	10.5781
IL20RB	NM_144717	7.88E-07	2.82E-07	0.024169	-41.3761
MEIS2	NM_172316	5.41E-06	0.00904	1.34573	1.34573
MMP12	NM_002426	0.003373	0.379449	1.17563	1.17563
ACPL2	NM_152282	8.11E-06	0.006848	1.32703	1.32703
TIMP3	NM_000362	3.21E-07	9.08E-08	0.107177	-9.33032
CXCL14	NM_004887	0.000211	0.000136	0.225227	-4.43996
METTL6	NM_152396	0.001275	0.000276	0.240784	-4.15311
ZNF770	NM_014106	1.21E-06	4.25E-07	0.259739	-3.85002
CLDND1	NM_001040199	0.000346	6.39E-05	0.254923	-3.92275
RAET1L	NM_130900	5.71E-06	1.04E-06	0.040894	-24.4532
SDAD1	NM_018115	0.022444	0.003522	0.263153	-3.80007
PLEKHF2	NM_024613	0.005965	0.001481	0.20412	-4.89908
TMEM117	NM_032256	0.000172	3.16E-05	0.205018	-4.87762
RASA1	NM_002890	0.000185	5.26E-05	0.246229	-4.06126
S100A16	NM_080388	2.27E-05	4.60E-06	0.177264	-5.64132
KCTD9	NM_017634	0.000344	5.35E-05	0.225387	-4.4368
GRHL1	NM_014552	2.68E-07	1.05E-07	0.12599	-7.93715
ARHGAP29	NM_004815	8.76E-05	3.38E-05	0.137068	-7.29567
BNIP2	NM_004330	4.25E-05	2.47E-05	0.19726	-5.06945
MARCH7	NM_022826	0.017224	0.00286	0.282151	-3.5442

RAB23	NM_016277	0.001104	0.000412	0.293115	-3.41163
STK17A	NM_004760	0.001954	0.000537	0.142798	-7.00291
REEP3	ENST00000298249	0.000142	4.20E-05	0.194872	-5.13157
ATL2	NM_022374	0.002578	0.000458	0.253567	-3.94373
MALT1	NM_006785	3.81E-07	8.68E-08	0.216331	-4.62254
LOC554203	NR_024582	0.005588	0.002116	0.264831	-3.776
DUSP11	NM_003584	8.27E-05	2.00E-05	0.230212	-4.34382
IGF2BP2	NM_006548	0.00154	0.001246	0.314178	-3.18291
SEPT10	NM_144710	0.005078	0.000948	0.278222	-3.59426
REPS1	NM_031922	0.001111	0.000185	0.275492	-3.62987
C3orf14	AF236158	0.000139	0.000224	0.201203	-4.9701
ADK	NM_006721	6.58E-05	2.37E-05	0.293314	-3.40932
SSR3	NM_007107	0.010975	0.001855	0.262664	-3.80714
PRRG4	NM_024081	3.02E-05	5.11E-06	0.279794	-3.57406
PDPN	NM_006474	8.09E-07	3.12E-07	0.113888	-8.78052
KIAA1586	NM_020931	1.65E-05	6.29E-06	0.20561	-4.86357
PEX3	NM_003630	1.98E-05	7.68E-06	0.169278	-5.90744
	---	0.000761	0.000453	0.290274	-3.44502
EIF2AK2	NM_002759	0.012021	0.00241	0.265477	-3.76681
GTF2F2	NM_004128	0.000579	0.000127	0.319385	-3.13102
SMYD2	NM_020197	7.87E-05	1.92E-05	0.332855	-3.00431
CTSC	NM_001814	1.37E-07	4.24E-08	0.142682	-7.0086
MPP7	NM_173496	1.95E-07	5.74E-07	0.291796	-3.42705
GDAP1	NM_018972	1.52E-06	2.78E-06	0.317421	-3.15039
FN1	NM_212482	0.000112	0.0001	0.165688	-6.03545
TROVE2	NM_004600	0.004196	0.001181	0.324991	-3.07701
C1orf149	NM_022756	0.000508	0.000104	0.338246	-2.95643
CLEC2B	NM_005127	0.003209	0.001006	0.197704	-5.05808
ALS2CR4	NM_001044385	1.40E-06	7.40E-07	0.270404	-3.69817
PTPN12	NM_002835	0.001268	0.000833	0.298352	-3.35175
BOD1L	NM_148894	0.007872	0.001731	0.31122	-3.21316
TNNT1	NM_003283	3.38E-06	1.81E-06	0.202203	-4.94552

FABP7	NM_001446	0.012746	0.00318	0.349501	-2.86123
HDGFRP3	NM_016073	5.09E-07	4.68E-07	0.26362	-3.79334
SPRR2D	NM_006945	1.59E-06	8.94E-07	0.012125	-82.4744
FJX1	NM_014344	4.64E-06	1.75E-06	0.175931	-5.68403
S100A14	NM_020672	9.03E-05	2.19E-05	0.16304	-6.13347
MT1M	NM_176870	6.30E-07	0.004867	1.8299	1.8299
LRRC37B2	NR_015341	0.000454	0.000132	0.296469	-3.37303
IL18	NM_001562	2.33E-06	1.26E-06	0.142113	-7.03667
GABRE	NM_004961	5.51E-05	2.97E-05	0.34087	-2.93367
GNPDA2	NM_138335	5.96E-05	3.00E-05	0.334367	-2.99073
ELOVL4	NM_022726	2.26E-07	9.97E-08	0.050865	-19.6597
WASF1	NM_003931	4.90E-05	3.01E-05	0.218251	-4.58189
PIK3CA	NM_006218	0.000544	0.000205	0.296013	-3.37823
MBOAT2	NM_138799	0.000192	4.28E-05	0.116684	-8.57019
PAR1	AF019616	0.000965	0.000672	0.341623	-2.92721
IVNS1ABP	NM_006469	0.006048	0.001203	0.34905	-2.86492
CHIC2	NM_012110	0.000122	2.47E-05	0.3046	-3.283
VSNL1	NM_003385	3.02E-08	7.56E-08	0.103554	-9.65682
LRRC37A3	NM_199340	0.00638	0.001372	0.365782	-2.73387
FYTTD1	NM_001011537	0.004033	0.000927	0.34136	-2.92946
RNF217	NM_152553	1.89E-10	1.33E-10	0.109281	-9.1507
PLA2G4A	NM_024420	0.006562	0.001299	0.326068	-3.06685
P2RY5	NM_005767	2.90E-06	1.24E-06	0.185982	-5.37686
NT5E	NM_002526	2.00E-07	6.50E-08	0.078079	-12.8076
CTSL2	NM_001333	1.96E-05	6.68E-06	0.138232	-7.23424
ZNF354A	NM_005649	0.006993	0.001288	0.36314	-2.75376
KIFAP3	NM_014970	2.61E-06	1.91E-06	0.217485	-4.59801
RAB18	NM_021252	4.91E-05	9.69E-06	0.26303	-3.80185
C1orf74	BC039719	7.17E-05	2.99E-05	0.315305	-3.17153
RB1	NM_000321	0.000478	8.36E-05	0.331091	-3.02032
CEP170	NM_014812	3.10E-05	2.97E-05	0.172938	-5.78243
KIF13A	NM_022113	7.87E-06	2.98E-06	0.248976	-4.01645

PRKCQ	NM_006257	5.36E-06	1.90E-06	0.29012	-3.44685
C6orf105	NM_001143948	9.93E-05	1.94E-05	0.187106	-5.34455
KRT23	NM_015515	5.21E-08	5.19E-08	0.139057	-7.19128
C10orf55	NM_001001791	0.004044	0.00097	0.269528	-3.71019
EFTUD1	NM_024580	5.31E-05	1.74E-05	0.328301	-3.04598
EDNRA	NM_001957	0.00118	0.000393	0.308992	-3.23633
TMTC1	NM_175861	8.69E-08	2.91E-08	0.146925	-6.80621
DUSP14	NM_007026	3.77E-06	1.88E-06	0.261097	-3.82999
GPNMB	NM_001005340	1.01E-06	4.60E-07	0.072804	-13.7356
PRSS3	NM_007343	0.001276	0.000294	0.339983	-2.94132
EMB	NM_198449	2.20E-07	1.33E-07	0.200409	-4.9898
SLC1A3	NM_004172	3.98E-07	8.12E-08	0.19971	-5.00727
TCTEX1D2	NM_152773	5.43E-08	2.37E-08	0.326036	-3.06715
NUDT11	NM_018159	0.000877	0.000344	0.119	-8.40337
AIG1	NM_016108	4.81E-05	4.03E-05	0.351938	-2.84141
NEDD4	NM_006154	6.37E-05	1.52E-05	0.348084	-2.87287
MMP10	NM_002425	0.005493	0.001812	0.110691	-9.03418
NDFIP2	NM_019080	9.17E-05	4.06E-05	0.298297	-3.35236
D4S234E	NM_014392	2.06E-05	8.81E-06	0.140193	-7.13301
PCTK2	NM_002595	8.48E-06	4.13E-06	0.310024	-3.22556
KIAA0922	NM_001131007	5.88E-07	2.22E-07	0.19079	-5.24136
EFCAB2	NR_026588	0.023377	0.006229	0.32682	-3.05979
RABGEF1	NM_014504	0.002164	0.000498	0.369088	-2.70938
MCART1	NR_024873	0.056152	0.013192	0.258038	-3.8754
IGFL3	NM_207393	9.80E-08	2.73E-08	0.251981	-3.96855
ANTXR2	NM_058172	5.41E-06	1.99E-06	0.242524	-4.12331
FBN2	NM_001999	2.36E-07	1.18E-07	0.102509	-9.75528
SCFD1	NM_016106	0.008561	0.00178	0.362447	-2.75903
C11orf60	NM_020153	2.60E-06	6.09E-07	0.300207	-3.33103
UNQ1887	NM_139015	6.66E-07	6.29E-07	0.394384	-2.5356
HOMER1	NM_004272	0.001456	0.000418	0.265524	-3.76614

LPAR3	NM_012152	1.27E-07	5.44E-08	0.116731	-8.56672
LRRC42	NM_052940	0.000315	8.76E-05	0.385761	-2.59228
GOLGA8B	NR_027410	3.19E-05	0.000633	0.364663	-2.74226
CYB5R2	NM_016229	0.000242	5.19E-05	0.251877	-3.97019
UBE2F	NM_080678	0.0049	0.001097	0.367286	-2.72267
TMTC3	NM_181783	2.84E-05	9.59E-06	0.327532	-3.05314
ZCCHC11	NM_001009881	0.000345	0.000248	0.29348	-3.40739
PPP3CC	NM_005605	0.000139	3.95E-05	0.301889	-3.31247
SESN3	NM_144665	1.87E-05	6.52E-06	0.25186	-3.97047
C14orf149	NM_144581	5.47E-05	1.51E-05	0.359233	-2.78371
PTPLA	NM_014241	9.50E-07	3.15E-07	0.308401	-3.24253
ODF2L	NM_020729	5.20E-05	0.000116	0.359137	-2.78445
FAM174A	NM_198507	0.001283	0.000276	0.267556	-3.73754
CBL	NM_005188	4.47E-06	1.54E-06	0.379841	-2.63268
PDCD1LG2	NM_025239	0.000571	0.000181	0.25123	-3.98041
PMAIP1	NM_021127	1.14E-05	3.36E-05	0.314938	-3.17523
SACS	NM_014363	9.98E-06	1.22E-05	0.223218	-4.47992
FKBP14	NM_017946	0.000421	0.000142	0.318607	-3.13866
ROBO1	NM_133631	5.83E-07	2.71E-07	0.096517	-10.3609
QPCT	NM_012413	0.000184	9.96E-05	0.282185	-3.54378
ZFP42	NM_174900	0.048358	0.018558	0.330818	-3.02281
DSP	NM_004415	2.60E-05	9.56E-06	0.278281	-3.59349
SPRR1A	NM_005987	1.72E-08	5.55E-09	0.022361	-44.7214
IL1A	NM_000575	8.93E-10	3.70E-10	0.013557	-73.7616
LOC654433	NR_015377	0.146494	0.039079	0.328085	-3.04799
EPS15	NM_001981	0.013543	0.003282	0.416586	-2.40046
S100A11	NM_005620	0.000261	6.90E-05	0.335729	-2.97859
SLC36A4	NM_152313	3.46E-05	8.13E-06	0.21093	-4.74091
RRAGC	NM_022157	0.000313	8.26E-05	0.418533	-2.3893
DOCK11	NM_144658	8.05E-07	2.49E-07	0.122978	-8.1315
KDSR	NM_002035	5.66E-08	3.70E-08	0.305384	-3.27456
ERGIC2	NM_016570	0.000598	0.000175	0.383298	-2.60894

CSGALNACT2	NM_018590	0.000202	0.000104	0.376549	-2.65569
LOC554202	NR_027054	1.47E-07	9.82E-08	0.19967	-5.00826
WFDC5	NM_145652	7.11E-06	2.73E-06	0.119263	-8.38481
PLXDC2	NM_032812	1.91E-08	8.73E-09	0.085799	-11.6551
FBXW7	NM_033632	0.001172	0.000341	0.377776	-2.64707
TMEM69	NM_016486	0.000973	0.00066	0.413698	-2.41722
TMEM45A	NM_018004	1.87E-11	8.63E-12	0.012327	-81.123
BBS10	NM_024685	0.001013	0.000372	0.392586	-2.54721
SOX2OT	NR_004053	0.003922	0.723792	0.901073	-1.10979
KDM5B	NM_006618	0.00124	0.000431	0.408709	-2.44673
CDA	NM_001785	7.22E-05	3.37E-05	0.17196	-5.8153
IFIT5	NM_012420	0.001922	0.000722	0.353867	-2.82592
GTF2H1	NM_001142307	0.000615	0.000174	0.396649	-2.52112
NEFM	NM_005382	0.000894	0.000569	0.197269	-5.06923
SGCE	NM_001099401	3.31E-05	0.00013	0.41879	-2.38783
DIRC2	NM_032839	3.81E-05	9.74E-05	0.431249	-2.31885
ITGA1	NM_181501	3.45E-05	2.15E-05	0.419243	-2.38525
RSAD2	NM_080657	0.014966	0.007299	0.275054	-3.63566
SLFN5	NM_144975	2.52E-05	0.000539	0.334263	-2.99166
SLC2A3	NM_006931	1.19E-05	5.47E-06	0.107329	-9.31717
ADAMTS1	NM_006988	8.15E-06	6.46E-06	0.30871	-3.23929
ZBTB1	NM_001123329	0.00013	3.70E-05	0.433489	-2.30686
PIP5K1A	NM_001135638	0.026998	0.007491	0.363813	-2.74867
DFNA5	NM_004403	2.70E-06	4.22E-06	0.205887	-4.85704
DMKN	NM_033317	4.50E-07	2.82E-07	0.236827	-4.22248
FLRT3	NM_198391	7.17E-07	2.66E-06	0.175075	-5.71182
SPRR3	NM_005416	1.85E-07	8.19E-08	0.066713	-14.9897
TTPAL	NM_024331	2.86E-06	1.31E-06	0.264339	-3.78302
RPS6KA5	NM_004755	4.57E-05	1.78E-05	0.432782	-2.31063
CLN5	NM_006493	0.000897	0.000251	0.442076	-2.26206

EFEMP1	NM_004105	2.65E-08	1.20E-08	0.037632	-26.5735
SLC20A1	NM_005415	6.24E-06	2.49E-06	0.1965	-5.08907
GNAI1	NM_002069	0.000112	0.000636	0.315859	-3.16597
FERMT1	NM_017671	0.000364	0.000113	0.412809	-2.42243
FN1	NM_212482	9.48E-07	5.86E-07	0.040084	-24.9475
GJB6	NM_001110219	1.86E-06	1.22E-06	0.038268	-26.1318
GPR1	NM_005279	6.76E-05	2.62E-05	0.430078	-2.32516
GPR115	NM_153838	1.43E-05	6.36E-06	0.170203	-5.87533
ZNF607	NM_032689	4.95E-06	1.90E-06	0.403938	-2.47563
MTHFD2L	NM_001144978	2.12E-06	9.60E-07	0.349225	-2.86348
LRAT	NM_004744	1.74E-05	8.62E-06	0.210638	-4.74749
C3orf64	NM_173654	0.000232	6.09E-05	0.290622	-3.4409
ALDH3B2	NM_000695	0.000138	0.000102	0.417624	-2.3945
MT1X	NM_005952	0.002024	0.000961	0.250085	-3.99863
USP25	NM_013396	0.000737	0.0002	0.422213	-2.36847
USP53	NM_019050	0.007056	0.002821	0.441503	-2.26499
DUSP6	NM_001946	0.00301	0.001557	0.414692	-2.41143
TLE4	NM_007005	5.00E-05	0.000131	0.426477	-2.34479
INHBA	NM_002192	0.000639	0.000228	0.283392	-3.52868
COL12A1	NM_004370	3.22E-07	1.88E-07	0.089012	-11.2344
SLIT2	NM_004787	8.48E-06	3.43E-06	0.316361	-3.16095
KLF8	NM_007250	1.93E-05	6.92E-06	0.309101	-3.23519
IQCA1	NM_024726	3.76E-08	1.67E-08	0.105066	-9.5178
BNC1	NM_001717	2.55E-08	1.17E-08	0.083375	-11.9941
TCFL5	NM_006602	4.73E-05	4.71E-05	0.435426	-2.2966
S100A7	NM_002963	8.46E-06	4.68E-06	0.015904	-62.876
EMP3	NM_001425	0.000135	7.01E-05	0.145977	-6.85038
DEGS1	NM_003676	0.000529	0.00038	0.161454	-6.19372
SPG20	NM_001142295	0.000483	0.000236	0.383804	-2.60549
TPD52L1	NM_001003395	1.12E-05	5.47E-06	0.32833	-3.04572
GPR137B	NM_003272	1.43E-05	6.28E-06	0.31312	-3.19367

NIACR2	NM_006018	2.84E-05	1.54E-05	0.16667	-5.99987
RBMS3	NM_001003793	0.000283	0.000104	0.430427	-2.32327
MUC15	NM_001135091	2.23E-07	1.01E-07	0.062663	-15.9583
PPP4R1	NM_001042388	6.81E-05	2.25E-05	0.376984	-2.65263
FCHO2	NM_138782	0.041643	0.012552	0.361248	-2.76818
LEF1	NM_016269	0.01014	0.003991	0.394152	-2.53709
CLASP1	NM_015282	0.000646	0.000217	0.38302	-2.61083
TMEM154	NM_152680	3.06E-07	1.60E-07	0.091846	-10.8879
IKIP	NM_153687	2.32E-08	9.14E-09	0.100386	-9.96159
HIVEP2	NM_006734	4.23E-07	6.58E-07	0.200746	-4.98141
DSC3	NM_024423	1.04E-10	5.14E-11	0.01042	-95.9707
CLDN1	NM_021101	1.30E-06	1.03E-05	0.383847	-2.60521
GJB2	NM_004004	3.20E-09	1.78E-09	0.088101	-11.3506
WDR47	NM_001142550	5.48E-05	2.11E-05	0.218538	-4.57587
SPINK5	NM_001127698	4.21E-06	1.42E-06	0.061908	-16.1529
S1PR1	NM_001400	2.02E-06	8.79E-07	0.194019	-5.15413
IL1RAP	NM_002182	2.28E-07	1.32E-07	0.17259	-5.79408
VEGFC	NM_005429	2.82E-05	1.50E-05	0.274021	-3.64935
AHSA2	NM_152392	0.007404	0.007981	0.405076	-2.46867
FBXO3	NM_033406	8.51E-05	3.64E-05	0.400594	-2.49629
SRY	NM_003140	0.000306	0.00011	0.25687	-3.89302
RPSAP52	NR_026825	5.72E-06	3.46E-06	0.283622	-3.52582
TAGLN3	NM_013259	7.20E-06	4.26E-06	0.268918	-3.71861
BACH1	NM_206866	3.25E-07	1.18E-07	0.421982	-2.36977
LY6G6C	NM_025261	0.000167	6.47E-05	0.356472	-2.80527
ARL17P1	NM_001113738	0.065934	0.028718	0.39738	-2.51648
PTGS1	NM_000962	0.000309	0.000142	0.327626	-3.05226
NRG1	NM_013960	1.99E-06	9.51E-07	0.216476	-4.61945
TCF4	NM_001083962	1.44E-05	8.70E-06	0.4601	-2.17344

ZFYVE9	NM_004799	0.00013	6.39E-05	0.390789	-2.55892
FAM83A	NM_032899	3.35E-06	1.35E-06	0.291145	-3.43472
ITGA2	NM_002203	0.000116	4.76E-05	0.337958	-2.95894
HERC6	NM_017912	0.000901	0.000419	0.222522	-4.49394
FHL1	NM_001159704	2.69E-05	1.99E-05	0.315264	-3.17194
USP9Y	NM_004654	2.78E-05	3.05E-05	0.348306	-2.87103
PLAU	NM_002658	0.000318	0.000278	0.360965	-2.77035
FGF11	NM_004112	0.000923	0.000345	0.456957	-2.18839
CYP4F12	NM_023944	2.48E-06	1.28E-05	3.4983	3.4983
BCAT1	NM_005504	2.88E-05	1.70E-05	0.225882	-4.42708
KLK8	NM_144505	3.28E-08	1.77E-08	0.088545	-11.2937
BPIL2	NM_174932	3.22E-07	1.47E-07	0.207224	-4.8257
GLI3	NM_000168	1.10E-05	5.21E-06	0.247333	-4.04314
ZBED2	NM_024508	1.18E-06	5.68E-07	0.063856	-15.6602
AADACL2	NM_207365	8.51E-05	4.51E-05	0.24326	-4.11083
RHCG	NM_016321	0.001734	0.000868	0.202579	-4.93635
CCNA1	NM_003914	3.86E-06	2.36E-06	0.11351	-8.80982
CA12	NM_001218	8.75E-06	2.92E-06	0.270851	-3.69207
S100A12	NM_005621	5.41E-05	3.26E-05	0.158186	-6.32166
TP53AIP1	NM_022112	2.01E-06	9.95E-07	0.270922	-3.6911
IFNA1	NM_024013	0.00099	0.00061	0.395885	-2.52599
DENND2C	NM_198459	1.87E-08	8.23E-09	0.266934	-3.74625
DSE	NM_013352	2.20E-07	1.72E-07	0.078935	-12.6686
SLC26A2	NM_000112	0.000313	0.000135	0.405488	-2.46616
RECQL	NM_002907	0.022406	0.009808	0.479229	-2.08668
SERPINB4	NM_002974	1.08E-05	5.21E-06	0.053201	-18.7968
UPP1	NM_003364	5.20E-06	4.01E-06	0.427104	-2.34135
PTER	NM_030664	2.00E-06	0.000123	2.40143	2.40143
IVL	NM_005547	1.03E-07	4.73E-08	0.027985	-35.7334
GJC1	NM_005497	5.99E-05	0.002915	0.470474	-2.12552
SLC2A1	NM_006516	1.53E-07	6.53E-08	0.257368	-3.88548
SLC10A6	NM_197965	2.31E-06	1.37E-06	0.192929	-5.18324

CLIP1	NM_002956	1.41E-05	5.67E-06	0.331249	-3.01888
TPM2	NM_003289	3.73E-05	5.11E-05	0.264382	-3.78241
CNTN1	NM_001843	2.39E-09	1.41E-09	0.043076	-23.2147
SLC7A5	NM_003486	1.38E-05	9.46E-05	0.434743	-2.30021
PAQR7	NM_178422	0.000521	0.000873	0.4232	-2.36295
FBLN1	NM_006486	0.000326	0.00016	0.467469	-2.13918
SEMA3D	NM_152754	0.002343	0.000797	0.20209	-4.94828
CCDC3	NM_031455	0.000571	0.000331	0.264646	-3.77864
TRAF3IP3	NM_025228	0.000398	0.000202	0.329368	-3.03612
NETO1	NM_138966	0.10033	0.042964	0.478779	-2.08865
BCO2	NM_031938	6.33E-06	3.89E-06	0.224959	-4.44525
AMIGO2	NM_001143668	4.45E-08	3.42E-08	0.090723	-11.0225
KRT4	NM_002272	6.63E-07	3.56E-07	0.078699	-12.7067
AKTIP	NM_001012398	0.006513	0.005756	0.413823	-2.41649
SP100	NM_001080391	0.000455	0.000268	0.261235	-3.82797
THSD1P	NR_002816	0.002072	0.001556	0.46573	-2.14717
TMEM136	NM_174926	8.25E-06	3.86E-06	0.31672	-3.15736
TTLL7	NM_024686	0.000107	4.68E-05	0.299448	-3.33948
RND3	NM_005168	7.33E-05	4.65E-05	0.434314	-2.30248
TACSTD2	NM_002353	1.62E-06	8.66E-07	0.446874	-2.23777
RBP7	NM_052960	2.56E-05	1.85E-05	0.148066	-6.75377
OR10A3	NM_001003745	3.64E-05	1.46E-05	0.227959	-4.38675
PLA2R1	NM_007366	2.45E-07	2.75E-07	0.16495	-6.06243
KRTDAP	NM_207392	1.02E-08	6.43E-09	0.010491	-95.3198
PRNP	NM_000311	2.18E-06	1.34E-06	0.274292	-3.64575
SLC9A9	NM_173653	0.000842	0.000526	0.428703	-2.33262
CDC42SE1	NM_001038707	1.84E-05	1.06E-05	0.366331	-2.72977
KLK5	NM_012427	9.59E-07	5.02E-07	0.06538	-15.2951
KTN1	NM_182926	0.001011	0.00053	0.462558	-2.16189
KRT1	NM_006121	6.75E-07	3.49E-07	0.054981	-18.1883

RGS20	NM_170587	6.81E-05	7.00E-05	0.403782	-2.47659
LHFP	NM_005780	9.78E-05	5.16E-05	0.343621	-2.91019
C21orf91	NM_001100420	3.26E-05	1.17E-05	0.193793	-5.16014
ST3GAL5	NM_003896	1.62E-05	7.91E-06	0.222702	-4.49031
KRT24	NM_019016	8.72E-06	4.87E-06	0.252014	-3.96804
DSG1	NM_001942	1.97E-11	1.13E-11	0.006685	-149.599
PLAT	NM_000930	0.001276	0.000698	0.482639	-2.07194
THBS2	NM_003247	4.78E-07	2.87E-07	0.153925	-6.49666
NIACR1	NM_177551	1.23E-05	7.06E-06	0.164225	-6.08919
DSC1	NM_004948	1.38E-08	7.85E-09	0.031029	-32.2285
AQP9	NM_020980	0.001541	0.000661	0.33178	-3.01404
BNIPL	NM_001159642	5.78E-06	3.38E-06	0.299299	-3.34114
TNFAIP3	NM_006290	9.56E-05	6.56E-05	0.495565	-2.0179
LASS3	NM_178842	3.98E-09	2.52E-09	0.061733	-16.1989
RUFY2	NM_017987	3.06E-05	2.21E-05	0.377722	-2.64745
SLC26A9	NM_052934	5.61E-07	0.000865	1.76058	1.76058
RORA	NM_134260	0.0006	0.000263	0.452926	-2.20787
AMOTL1	NM_130847	2.34E-07	2.26E-07	0.222749	-4.48937
CARD18	NM_021571	1.65E-06	9.58E-07	0.101109	-9.89028
C20orf197	NM_173644	0.012273	0.006479	0.450831	-2.21813
CAPN6	NM_014289	1.50E-06	0.001521	1.97105	1.97105
TUBB6	NM_032525	2.26E-06	6.75E-06	0.365262	-2.73776
CCDC80	NM_199511	5.69E-06	3.25E-06	0.178956	-5.58798
TEX2	NM_018469	1.14E-06	5.04E-07	0.401033	-2.49356
EEA1	NM_003566	0.000621	0.000249	0.391432	-2.55472
RAET1G	NM_001001788	7.86E-06	4.61E-06	0.111441	-8.97337
NR3C1	NM_000176	3.04E-05	1.74E-05	0.432923	-2.30988
NCF2	NM_000433	4.35E-06	2.50E-06	0.294316	-3.39771
TRIML2	NM_173553	0.035133	0.018707	0.417187	-2.39701
SLC31A2	NM_001860	7.56E-07	3.48E-07	0.206476	-4.84317
ANO4	NM_178826	0.137128	0.060183	0.449205	-2.22616

SBSN	NM_198538	1.23E-09	7.37E-10	0.020168	-49.5844
ELAVL2	NM_004432	4.22E-06	2.42E-06	0.329714	-3.03293
BIVM	NM_017693	0.000217	0.000141	0.452207	-2.21138
LAMC2	NM_005562	1.16E-06	6.74E-07	0.180854	-5.52931
PHLDB2	NM_001134438	9.26E-06	5.98E-06	0.220681	-4.53142
SFRS12IP1	NM_173829	0.001825	0.001164	0.429242	-2.32969
SYT14	NM_001146261	1.09E-07	7.04E-08	0.084672	-11.8103
DGKH	NM_178009	6.27E-06	4.49E-06	0.427725	-2.33795
KRT10	NM_000421	1.21E-09	6.90E-10	0.02733	-36.5893
ULK2	NM_014683	3.67E-07	3.23E-07	0.481301	-2.0777
DOCK4	NM_014705	1.38E-09	8.71E-10	0.161512	-6.1915
CSRNP2	NM_030809	0.00012	0.000104	0.498398	-2.00643
LOC284033	AK095052	0.00016	7.84E-05	0.306697	-3.26055
DAAM1	NM_014992	6.72E-05	3.06E-05	0.333974	-2.99425
HERC5	NM_016323	8.63E-05	5.19E-05	0.154135	-6.48784
FGD6	NM_018351	5.97E-06	1.78E-05	0.33315	-3.00165
C17orf39	NM_024052	5.60E-05	5.97E-05	0.463506	-2.15747
TIPARP	NM_015508	7.04E-06	7.05E-06	0.331273	-3.01865
ADARB1	NM_001033049	0.000101	6.75E-05	0.434436	-2.30183
TLL1	NM_012464	0.000226	0.000137	0.339309	-2.94717
EFCAB1	NM_024593	1.04E-07	6.34E-08	0.23938	-4.17746
CAMSAP1L1	NM_203459	6.46E-06	3.14E-06	0.187895	-5.32212
BMPR2	NM_001204	0.000242	0.000155	0.359176	-2.78415
CPA4	NM_016352	9.48E-07	5.95E-07	0.09492	-10.5351
UBE2Q2	NM_173469	0.001354	0.000658	0.439636	-2.27461
CAB39L	NM_030925	1.27E-06	7.97E-07	0.340316	-2.93844
TUBA1A	NM_006009	0.07469	0.032673	0.437043	-2.2881
ORM2	NM_000608	6.33E-06	0.073705	1.39226	1.39226
CLCA2	NM_006536	8.01E-11	4.51E-11	0.013943	-71.7201
NIN	NM_020921	4.70E-08	3.06E-08	0.144863	-6.90308
EML1	NM_00100870	2.17E-06	9.65E-07	0.330429	-3.02637

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MYO3B	NM_138995	0.000197	0.000141	0.45953	-2.17613
BBOX1	NM_003986	3.51E-10	2.00E-10	0.043911	-22.7735
ZFP36L1	NM_004926	1.83E-05	1.81E-05	0.456181	-2.19211
KRT17	NM_000422	5.11E-07	2.90E-07	0.011104	-90.0602
EPHA4	NM_004438	6.81E-06	2.90E-06	0.259308	-3.85641
ASAP1	NM_018482	5.27E-05	3.37E-05	0.361779	-2.76412
PARD6G	NM_032510	3.74E-05	1.95E-05	0.346776	-2.88371
TUBA4A	NM_006000	3.89E-08	1.67E-08	0.273785	-3.6525
LOC84740	NR_026892	6.94E-08	0.740089	1.04468	1.04468
TMEM40	NM_018306	9.61E-06	6.85E-06	0.154403	-6.47655
ARL14	NM_025047	3.77E-07	6.60E-07	9.80972	9.80972
BTBD11	NM_001018072	2.57E-06	1.75E-06	0.230868	-4.33147
SPRR1B	NM_003125	6.11E-09	2.83E-09	0.007571	-132.083
HIPK3	NM_005734	0.000546	0.000271	0.414886	-2.4103
PLS3	NM_005032	1.43E-05	7.64E-06	0.353785	-2.82658
SULF2	NM_018837	8.04E-05	5.16E-05	0.402102	-2.48693
IGFL2	NM_001002915	1.96E-08	1.39E-08	0.057	-17.544
SNAPC1	NM_003082	0.000251	0.000323	0.441525	-2.26488
MYO9A	NM_006901	0.000169	9.69E-05	0.466126	-2.14534
CASP14	NM_012114	6.22E-07	3.53E-07	0.096227	-10.3921
LOC100131726	NR_024479	7.07E-07	3.36E-07	0.142613	-7.012
TSHZ3	NM_020856	7.41E-06	3.91E-06	0.096776	-10.3332
FBXO27	NM_178820	5.13E-05	4.66E-05	0.424143	-2.35769
DDX26B	NM_182540	2.10E-07	2.14E-07	0.435689	-2.29521
IL1F9	NM_019618	0.005257	0.003634	0.347607	-2.87682
CSDA	NM_003651	6.66E-05	0.00011	0.473359	-2.11256
SLC30A4	NM_013309	7.96E-06	6.10E-06	0.43967	-2.27443
RAB9A	NM_004251	0.000183	0.00012	0.468324	-2.13527
DSG4	NM_001134453	2.29E-05	1.53E-05	0.35497	-2.81714
MYCBP2	NM_015057	0.000554	0.000367	0.493869	-2.02483

STK3	NM_006281	1.09E-05	1.22E-05	0.341489	-2.92835
GABRP	NM_014211	0.013059	0.600955	1.24205	1.24205
SLC6A11	NM_014229	1.84E-05	1.33E-05	0.34986	-2.85829
KRT5	NM_000424	3.19E-09	2.07E-09	0.021941	-45.5779
CCL27	NM_006664	0.001975	0.001156	0.457267	-2.1869
PTPN14	NM_005401	1.54E-05	1.60E-05	0.356726	-2.80327
C3orf34	NM_032898	1.69E-08	1.77E-08	0.212946	-4.69603
LAYN	NM_178834	1.42E-06	1.38E-06	0.233102	-4.28997
NEK1	NM_012224	0.002354	0.001458	0.381839	-2.6189
LY6K	NM_017527	4.86E-05	3.34E-05	0.220512	-4.53491
ULBP1	NM_025218	0.004888	0.002621	0.240299	-4.16148
TMPRSS11F	NM_207407	4.77E-06	2.85E-06	0.16775	-5.96125
GADD45A	NM_001924	0.00014	0.000159	0.413059	-2.42096
PPP1R14C	NM_030949	2.91E-05	2.49E-05	0.262596	-3.80814
NAV3	NM_014903	8.29E-06	5.74E-06	0.326906	-3.05898
TFPI2	NM_006528	2.13E-11	1.56E-11	0.027611	-36.217
SPRR2A	NM_005988	3.49E-08	1.85E-08	0.11895	-8.40688
CYYR1	NM_052954	0.000156	0.000109	0.33116	-3.01969
AQP3	NM_004925	1.81E-08	1.03E-08	0.19219	-5.20318
SNCA	NM_000345	1.06E-07	8.88E-08	0.204606	-4.88745
MORC3	NM_015358	9.63E-06	6.22E-06	0.417415	-2.3957
FAT2	NM_001447	2.37E-07	1.62E-07	0.153144	-6.5298
PKP1	NM_000299	2.05E-07	1.40E-07	0.131756	-7.58976
FEZ1	NM_005103	8.18E-08	4.85E-08	0.10453	-9.56661
SFRP1	NM_003012	3.17E-05	2.21E-05	0.286746	-3.48741
TGM1	NM_000359	3.34E-07	2.70E-07	0.157519	-6.34845
LYST	NM_000081	0.006956	0.003186	0.383653	-2.60652
HOXC9	NM_006897	8.36E-05	6.27E-05	0.327183	-3.05639
SHC1	NM_183001	3.06E-05	2.84E-05	0.488294	-2.04795
S100A8	NM_002964	5.73E-10	3.66E-10	0.004813	-207.77
GSDMC	NM_031415	3.72E-09	2.21E-09	0.07223	-13.8447
RAB38	NM_022337	5.10E-09	3.71E-09	0.165795	-6.03155

SAA1	NM_000331	0.003802	0.003989	0.213549	-4.68277
HERC3	NM_014606	0.000663	0.000421	0.362275	-2.76033
FAM127A	NM_001078171	1.05E-05	6.75E-06	0.117546	-8.50732
FLRT2	NM_013231	7.17E-08	5.06E-08	0.072015	-13.8859
PPP4R4	NM_058237	0.000209	0.000185	0.497693	-2.00927
INTS6	NM_012141	0.0002	0.000152	0.423852	-2.35931
CRCT1	NM_019060	0.000408	0.000238	0.322439	-3.10136
DNAJB4	NM_007034	0.000509	0.000531	0.316077	-3.16378
ZNF750	NM_024702	3.22E-08	2.04E-08	0.09617	-10.3982
HTR7	NM_019859	0.004453	0.004553	0.497268	-2.01099
FABP4	NM_001442	0.097674	0.056799	0.482036	-2.07453
TNNT2	NM_000364	4.41E-05	2.85E-05	0.193259	-5.17441
FER	NM_005246	0.000641	0.000443	0.323276	-3.09333
GJB4	NM_153212	0.001835	0.002072	0.499175	-2.0033
STARD5	NM_181900	4.65E-06	3.04E-06	0.302556	-3.30518
DUOXA1	NM_144565	0.000575	0.000451	0.418438	-2.38984
SERPINB3	NM_006919	2.94E-08	2.00E-08	0.012711	-78.6698
HIAT1	NM_033055	0.01459	0.007654	0.422788	-2.36525
MAL	NM_002371	7.23E-05	0.39336	0.893702	-1.11894
MMP9	NM_004994	0.000388	0.000361	0.364991	-2.73979
CD86	NM_175862	0.006281	0.006303	0.488157	-2.04852
GM2A	NM_000405	8.00E-07	6.52E-07	0.230115	-4.34565
NFAT5	NM_138714	3.81E-06	5.42E-06	0.454936	-2.19811
AJAP1	NM_018836	1.05E-05	9.40E-06	0.401521	-2.49053
CNGA1	NM_001142564	0.045943	0.065021	0.452679	-2.20907
OSBPL6	NM_032523	6.84E-08	5.06E-08	0.167078	-5.98522
MTSS1	NM_014751	1.35E-08	8.38E-09	0.207966	-4.80847
TRIM23	NM_001656	6.72E-06	5.22E-06	0.393904	-2.53869
COPZ2	NM_016429	0.000202	0.000108	0.347427	-2.87831
C20orf114	NM_033197	1.48E-08	0.025151	1.28715	1.28715
SGTB	NM_019072	8.79E-05	6.25E-05	0.448303	-2.23063
LYPD3	NM_014400	1.84E-07	1.38E-07	0.121182	-8.25202

ALOX15B	NM_001141	3.55E-07	2.58E-07	0.235379	-4.24847
SLC6A15	NM_182767	2.71E-08	1.70E-08	0.023514	-42.5281
MARK3	NM_001128918	1.02E-05	1.05E-05	0.483147	-2.06976
BICD2	NM_001003800	6.95E-05	5.18E-05	0.333536	-2.99818
PTHLH	NM_198965	5.00E-08	3.20E-08	0.063055	-15.8592
TPRG1	NM_198485	1.20E-06	9.21E-07	0.197023	-5.07554
CYP4F11	NM_021187	5.46E-05	4.85E-05	0.243507	-4.10666
PARP9	NM_001146106	0.011648	0.007957	0.337264	-2.96504
ITGA5	NM_002205	0.000201	0.000206	0.452953	-2.20774
CTSL1	NM_001912	1.13E-05	8.72E-06	0.289579	-3.45329
SFN	NM_006142	7.85E-09	5.23E-09	0.273003	-3.66297
ETNK2	NM_018208	0.000167	0.000131	0.336163	-2.97475
SPINK6	NM_205841	1.67E-10	9.48E-11	0.007065	-141.545
TFAP2A	NM_003220.	1.99E-07	1.01E-07	0.203498	-4.91405
EMR2	NM_013447	0.00025	0.000274	0.490212	-2.03993
CLCA4	NM_012128	1.90E-07	1.20E-07	0.041414	-24.1466
S100A9	NM_002965	4.79E-07	2.96E-07	0.032138	-31.1161
EPGN	NM_001013442	2.48E-08	1.59E-08	0.024427	-40.9378
GJB5	NM_005268	1.40E-06	6.39E-07	0.113731	-8.79268
MPZL2	NM_144765	8.50E-07	5.95E-07	0.365191	-2.7383
NOTCH2	NM_024408	2.38E-06	5.20E-06	0.456723	-2.18951
PTPRZ1	NM_002851	1.89E-09	1.20E-09	0.041355	-24.1807
KRT14	NM_000526	7.05E-10	4.13E-10	0.011096	-90.1236
FAP	NM_004460	0.000184	0.00014	0.249611	-4.00624
SLC39A2	NM_014579	1.02E-06	7.37E-07	0.227705	-4.39164
TMPRSS11E	NM_014058	2.32E-05	1.49E-05	0.068107	-14.6828
KCNQ5	NM_019842	0.002317	0.001959	0.467845	-2.13746
ARL4D	NM_001661	1.68E-05	1.48E-05	0.206539	-4.84169
PTGS2	NM_000963	0.00066	0.000381	0.241888	-4.13415
SIM2	NM_009586	1.67E-06	0.10316	1.16053	1.16053

CDH13	NM_001257	6.12E-08	4.66E-08	0.073861	-13.5389
RAB37	NM_175738	4.76E-06	0.002977	1.43301	1.43301
NUAK1	NM_014840	0.001449	0.00114	0.474631	-2.1069
ST6GALNAC2	NM_006456	9.39E-08	5.37E-08	0.172351	-5.80212
NTM	NM_001144058	9.37E-05	0.000142	0.386502	-2.58731
PTPRE	NM_006504	5.05E-07	6.26E-07	0.301006	-3.3222
EMP1	NM_001423	8.78E-06	9.68E-06	0.264861	-3.77557
PLD5	NM_152666	1.99E-05	1.77E-05	0.168198	-5.94536
GBP6	NM_198460	5.06E-05	3.77E-05	0.304061	-3.28882
LAMP2	NM_002294	0.000116	0.000115	0.340154	-2.93984
F2R	NM_001992	0.000105	0.000565	0.40176	-2.48905
PYGL	NM_002863	1.53E-08	3.26E-08	0.167494	-5.97036
PGLYRP3	NM_052891	0.001406	0.001542	0.452129	-2.21176
ORM1	NM_000607	0.000765	0.437758	1.16127	1.16127
LPCAT2	NM_017839	0.00011	7.07E-05	0.312527	-3.19972
HOXC10	NM_017409	7.80E-05	6.97E-05	0.31526	-3.17198
PLA2G4E	NM_001080490	4.00E-08	3.36E-08	0.177956	-5.61936
NEBL	NM_006393	9.72E-05	5.95E-05	0.282602	-3.53855
PCDH21	NM_033100	5.93E-05	6.57E-05	0.434091	-2.30367
CALB2	NM_001740	0.000121	8.20E-05	0.183533	-5.44861
FSCN1	NM_003088	0.000138	0.000192	0.465068	-2.15022
SWAP70	NM_015055	2.00E-07	2.12E-07	0.371359	-2.69281
MARK1	NM_018650	1.32E-07	1.18E-07	0.265896	-3.76087
IGFL1	NM_198541	4.72E-06	3.02E-06	0.12375	-8.0808
KRT77	NM_175078	1.52E-05	1.36E-05	0.274278	-3.64593
ERC1	NM_178037	6.44E-06	9.84E-06	0.49748	-2.01013
GNAL	NM_182978	7.49E-05	6.78E-05	0.44032	-2.27108
SERPING1	NM_000062	2.86E-05	3.83E-05	0.253286	-3.94811
ATP12A	NM_001676	0.000248	0.00019	0.306484	-3.26281
LAMP3	NM_014398	0.028786	0.019166	0.470295	-2.12632
FST	NM_006350	5.16E-07	3.36E-07	0.124071	-8.05989

DUOX1	NM_017434	5.36E-05	5.29E-05	0.396325	-2.52318
CYP1B1	NM_000104	0.001671	0.001644	0.398847	-2.50723
ERCC6	NM_000124	1.12E-08	9.06E-09	0.241083	-4.14795
ABCA12	NM_173076	4.61E-09	2.31E-09	0.019165	-52.1794
ERCC1	NM_202001	4.26E-05	4.26E-05	0.362622	-2.75769
CCDC109B	NM_017918	0.002651	0.001655	0.34527	-2.89628
TMEM86A	NM_153347	5.02E-05	6.66E-05	0.423458	-2.36151
KCTD1	NM_001142730	2.89E-07	2.43E-07	0.354433	-2.82141
FLJ21511	NM_025087	2.01E-08	1.40E-08	0.024546	-40.7406
MSRB3	NM_001031679	0.000156	0.00024	0.457294	-2.18678
GATA3	NM_001002295	1.57E-06	1.52E-06	0.307929	-3.2475
ETS1	NM_001143820	3.08E-08	4.67E-08	0.340598	-2.93602
JUP	NM_002230	2.79E-06	2.68E-06	0.366333	-2.72976
TAGLN	NM_001001522	0.002535	0.002146	0.44908	-2.22677
SLC7A1	NM_003045	2.99E-05	3.58E-05	0.462538	-2.16198
QKI	NM_206855	0.000221	0.000276	0.446033	-2.24199
XG	NM_001141919	5.23E-06	2.82E-06	0.147072	-6.79939
FERMT2	NM_006832	7.03E-07	1.34E-06	0.243822	-4.10136
MACF1	NM_012090	3.54E-05	3.46E-05	0.333934	-2.9946
OSMR	NM_003999	0.000719	0.000927	0.448172	-2.23129
GNA15	NM_002068	2.27E-06	1.29E-06	0.160651	-6.22468
IFNE	NM_176891	1.48E-08	9.98E-09	0.088706	-11.2732
AMZ2	NM_016627	5.92E-05	9.02E-05	0.459625	-2.17569
TBC1D19	NM_018317	1.69E-05	1.96E-05	0.431646	-2.31671
CRIM1	NM_016441	4.50E-07	4.71E-07	0.312858	-3.19634
CALML5	NM_017422	2.24E-05	2.14E-05	0.269774	-3.7068
GPR64	NM_001079858	3.59E-05	0.061676	1.38514	1.38514
SNX24	NM_014035	0.00317	0.002572	0.404827	-2.47019
SERPINB13	NM_012397	2.87E-11	1.85E-11	0.010222	-97.826

KRT15	NM_002275	1.07E-09	6.99E-10	0.035418	-28.2344
MCC	NM_001085377	5.92E-06	7.10E-06	0.337538	-2.96263
TP63	NM_003722	1.98E-09	1.32E-09	0.060277	-16.59
CYB5R1	NM_016243	8.18E-08	5.36E-08	0.196948	-5.07747
SERPINB2	NM_001143818	0.000522	0.000316	0.130409	-7.66815
MARVELD1	NR_026753	0.000246	0.001632	0.499073	-2.00371
ERRFI1	NM_018948	4.24E-05	0.00015	0.461638	-2.1662
SLCO3A1	NM_013272	3.37E-06	8.70E-06	0.475199	-2.10438
TIMP1	NM_003254	7.98E-06	5.22E-06	0.177266	-5.64125
CAPRIN2	NM_001002259	0.000102	0.000198	0.43531	-2.29721
PLTP	NM_006227	0.000998	0.001704	0.473561	-2.11166
CALCRL	NM_005795	7.23E-07	2.74E-06	0.465558	-2.14796
IFIH1	NM_022168	0.015725	0.0111	0.37925	-2.63678
CLIC4	NM_013943	0.001914	0.002345	0.482499	-2.07254
IRF6	NM_006147	2.28E-07	2.73E-07	0.274871	-3.63807
A2ML1	NM_144670	7.47E-08	4.30E-08	0.012286	-81.3962
FCHSD2	NM_014824	3.04E-05	2.74E-05	0.342655	-2.91839
DNAJB5	NM_001135005	0.0014	0.002946	0.450186	-2.2213
TIAM1	NM_003253	1.18E-06	1.01E-06	0.280659	-3.56304
CAPNS2	NM_032330	1.59E-07	1.38E-07	0.028316	-35.3156
KATNAL1	NM_001014380	1.94E-06	2.23E-06	0.220371	-4.53781
GRHL3	NM_198173	3.64E-09	3.70E-09	0.247268	-4.04419
MAP2	NM_002374	1.28E-07	1.26E-07	0.251667	-3.97351
SMARCA1	NM_003069	3.35E-05	0.00021	0.459756	-2.17507
C9orf95	NR_023352	0.00091	0.001364	0.477435	-2.09453
LUM	NM_002345	0.00038	0.0381	1.75631	1.75631
MLF1	NM_001130157	0.000152	0.000314	0.434315	-2.30248
RPE65	NM_000329	0.004304	0.009863	0.482605	-2.07209
KLF7	NM_003709	3.34E-07	3.44E-07	0.281847	-3.54802
STEAP4	NM_024636	4.23E-09	3.62E-09	0.067452	-14.8253

ARSJ	NM_024590	3.70E-05	6.21E-05	0.408595	-2.44741
FGF5	NM_004464	0.000358	0.000318	0.281323	-3.55463
IFI44L	NM_006820	0.001777	0.001409	0.093098	-10.7414
TNC	NM_002160	3.71E-06	3.69E-06	0.229225	-4.36253
LY6D	NM_003695	0.00028	0.00047	0.391998	-2.55103
SLITRK6	NM_032229	0.00074	0.000631	0.266593	-3.75104
RAET1E	NM_139165	3.95E-06	4.49E-06	0.217168	-4.60473
SEC14L2	NM_012429	2.11E-06	3.38E-06	0.399713	-2.5018
DUSP7	NM_001947	3.65E-06	8.31E-06	0.46662	-2.14307
ELK3	NM_005230	1.44E-06	2.42E-06	0.300748	-3.32504
SMURF2	NM_022739	8.79E-06	2.18E-05	0.451238	-2.21612
TRIM29	NM_012101	1.30E-08	9.48E-09	0.137993	-7.24674
UGT1A9	NM_021027	3.69E-06	0.008457	0.673124	-1.48561
	---	0.017796	0.034272	0.41183	-2.42819
SERPINE1	NM_000602	0.000464	0.000338	0.187171	-5.3427
MYO5A	NM_000259	6.81E-10	6.71E-10	0.098157	-10.1878
	---	1.57E-06	1.47E-06	0.184668	-5.41512
EGFR	NM_005228	7.76E-08	1.17E-07	0.289142	-3.45851
SLC38A2	NM_018976	7.02E-08	7.65E-08	0.288013	-3.47207
HAS2	NM_005328	0.004297	0.007023	0.488528	-2.04697
LRRC8C	NM_032270	1.86E-05	4.09E-05	0.253481	-3.94506
MPDZ	NM_003829	0.001944	0.006307	0.455314	-2.19629
DDX60	NM_017631	0.006426	0.009508	0.325216	-3.07488
PCDHB2	NM_018936	0.000695	0.175936	1.2872	1.2872
IL1B	NM_000576	5.25E-07	3.89E-07	0.10028	-9.97204
BBS9	NM_198428	0.003029	0.00491	0.471346	-2.12158
STEAP1	NM_012449	0.135915	0.156455	0.419955	-2.38121
CD274	NM_014143	5.19E-05	7.83E-05	0.361298	-2.7678
SLC39A6	NM_012319	3.85E-07	4.72E-07	0.255285	-3.91719
MGAM	NM_004668	1.99E-07	0.000115	1.54142	1.54142
SEMA3C	NM_006379	0.000153	0.000259	0.394099	-2.53744
WDFY2	NM_052950	2.45E-08	6.49E-08	0.38159	-2.62061
LDOC1	NM_012317	1.18E-05	2.88E-05	0.374132	-2.67285

GLTP	NM_016433	0.000199	0.000481	0.429942	-2.3259
CAPN13	NM_144575	1.06E-07	7.76E-06	1.96105	1.96105
IKZF2	NM_001079526	1.78E-06	2.80E-06	0.309067	-3.23554
RBP1	NM_001130992	1.32E-06	0.001574	0.470568	-2.12509
SCGB2A1	NM_002407	4.48E-06	0.059586	1.31277	1.31277
IGFBP6	NM_002178	6.93E-06	1.33E-05	0.219911	-4.54729
C7orf10	NM_024728	1.87E-07	8.84E-07	0.437612	-2.28513
SLPI	NM_003064	1.62E-06	1.44E-06	0.127431	-7.84737
CD109	NM_133493	9.85E-09	7.72E-09	0.072182	-13.8539
SP110	NM_080424	0.002794	0.005834	0.475861	-2.10145
VGLL1	NM_016267	0.000107	0.00025	0.261018	-3.83115
LRP12	NM_013437	1.05E-06	2.43E-06	0.334472	-2.98979
PRB4	NM_002723	0.023507	0.028814	0.366051	-2.73186
OPTN	NM_001008211	1.79E-05	6.64E-05	0.471762	-2.11971
YPEL5	NM_001127401	0.000254	0.000762	0.476714	-2.09769
SULT2B1	NM_004605	7.72E-05	0.000455	0.474461	-2.10766
CDH3	NM_001793	7.22E-06	3.22E-05	0.412099	-2.4266
MLLT11	NM_006818	7.84E-05	0.00014	0.167583	-5.9672
DRAP1	NM_006442	0.000223	0.000666	0.465382	-2.14877
CASP1	NM_033292	1.68E-06	6.26E-06	0.197904	-5.05296
TFAP2C	NM_003222	7.94E-06	2.51E-05	0.434692	-2.30048
EREG	NM_001432	0.000459	0.00082	0.215688	-4.63633
CAV1	NM_001753	3.96E-08	5.88E-08	0.095451	-10.4766
OGFRL1	NM_024576	8.46E-06	1.81E-05	0.240403	-4.15968
DEFB1	NM_005218	1.17E-05	1.07E-05	0.125584	-7.96278
MRAP2	NM_138409	1.35E-07	5.55E-06	2.6499	2.6499
KRT6A	NM_005554	9.88E-08	6.23E-08	0.019287	-51.8491
FDXACB1	NM_138378	5.58E-06	4.87E-06	0.058653	-17.0494
PI3	NM_002638	2.91E-05	0.000337	0.324725	-3.07953
FZD6	NM_003506	0.00022	0.001103	0.488675	-2.04635
SPTLC3	NM_018327	1.08E-05	5.58E-05	0.396875	-2.51968

CLIP4	NM_024692	1.46E-05	5.76E-05	0.307238	-3.2548
RAB31	NM_006868	1.73E-06	4.05E-06	0.201838	-4.95448
KLK13	NM_015596	2.92E-05	7.82E-05	0.365322	-2.73731
CD44	NM_000610	6.59E-06	0.000944	0.464831	-2.15132
DZIP1	NM_198968	3.02E-06	4.18E-05	0.436947	-2.28861
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CALD1	NM_033138	1.59E-05	6.56E-05	0.290067	-3.44748
TUBG2	NM_016437	7.33E-06	6.60E-05	0.471308	-2.12176
PRKCH	NM_006255	2.73E-05	0.000208	0.477771	-2.09305
KRT16	NM_005557	3.75E-08	2.92E-08	0.016898	-59.18
FAM63B	NM_001040450	1.96E-05	6.06E-05	0.274221	-3.64669
C3orf67	BC132815	3.15E-07	2.16E-06	0.426573	-2.34426
RIMKLB	NM_020734	1.58E-05	3.10E-05	0.275478	-3.63005
ATP10D	NM_020453	1.04E-06	1.38E-06	0.156271	-6.39915
ARL4C	NM_005737	8.07E-07	1.61E-06	0.264687	-3.77805
FRMD6	NM_001042481	5.92E-07	8.16E-07	0.15212	-6.57374
KRT13	NM_153490	2.54E-07	2.72E-07	0.039864	-25.0852
KIF3A	NM_007054	0.006094	0.01185	0.360572	-2.77337
FBP2	NM_003837	6.19E-06	0.000707	2.038	2.038
PHLDB2	NM_001134438	2.38E-06	4.18E-06	0.181124	-5.52107
SNAI2	NM_003068	4.56E-08	7.90E-08	0.039535	-25.2942
IFIT1	NM_001548	0.000118	0.000184	0.078991	-12.6596
SCEL	NM_144777	7.26E-07	1.49E-06	0.135947	-7.3558
PITPNC1	NM_181671	4.67E-08	2.43E-07	0.337134	-2.96618
DDX58	NM_014314	1.91E-05	5.21E-05	0.265773	-3.76262
ITGBL1	NM_004791	1.75E-05	0.003058	2.23812	2.23812
PYGB	NM_002862	7.79E-06	9.30E-05	0.48814	-2.04859
CAV2	NM_001233	2.37E-05	0.000191	0.353143	-2.83172
DCBLD2	NM_080927	1.79E-07	5.13E-07	0.261835	-3.8192
PALMD	NM_017734	8.09E-09	2.20E-08	0.191061	-5.23394
EPHX3	NM_024794	0.007575	0.044958	0.495538	-2.01801

UGT2B15	NM_001076	8.86E-05	0.001024	4.48116	4.48116
CYBRD1	NM_024843	7.67E-07	1.17E-06	0.143509	-6.96818
STXBP1	NM_003165	1.67E-06	2.62E-05	0.408365	-2.44879
IFIT3	NM_001031683	0.012789	0.047085	0.401431	-2.49109
PLK2	NM_006622	4.19E-06	3.34E-05	0.314953	-3.17508
ATP2B4	NM_001001396	2.62E-06	1.20E-05	0.316108	-3.16347
MID2	NM_012216	1.44E-07	1.55E-06	0.396467	-2.52228
CCL28	NM_148672	9.94E-05	1.19E-05	4.73086	4.73086
ZNF185	NM_007150	9.88E-08	8.44E-07	0.370874	-2.69634
USP44	NM_032147	3.67E-05	1.13E-05	2.46786	2.46786
STC2	NM_003714	0.007593	0.001551	2.71205	2.71205
ANXA1	NM_000700	1.81E-05	0.000396	0.496828	-2.01277
DAPP1	NM_014395	6.66E-07	4.14E-06	0.334232	-2.99194
TCP11L1	NM_018393	1.16E-07	1.36E-06	0.398607	-2.50873
PIK3C2G	NM_004570	1.19E-05	0.005384	1.97156	1.97156
ITGB6	NM_000888	1.44E-05	0.000105	0.35966	-2.7804
IFI6	NM_002038	0.000558	0.002824	0.370478	-2.69922
AREG	NM_001657	9.80E-08	2.46E-07	0.147063	-6.79982
TCEA3	NM_003196	6.03E-05	0.004343	1.89648	1.89648
NKX6-3	NM_152568	0.000222	4.36E-05	2.62399	2.62399
CRABP2	NM_001878	1.24E-09	1.60E-09	0.070954	-14.0936
NEXN	NM_144573	0.000501	0.010025	0.433806	-2.30518
HSPC159	NM_014181	7.31E-08	5.29E-07	0.320174	-3.1233
SAMD9L	NM_152703	0.002066	0.020527	0.481049	-2.07879
TNS4	NM_032865	1.33E-06	1.11E-05	0.309366	-3.23242
PTPN13	NM_080683	2.15E-06	5.85E-06	0.143409	-6.97308
SERPINB7	NM_003784	5.70E-08	7.81E-08	0.027398	-36.4991
PSCA	NM_005672	6.84E-07	0.000149	2.73319	2.73319
NPSR1	NM_207172	2.73E-06	3.99E-05	3.10457	3.10457
CTH	NM_001902	0.000612	8.41E-05	3.8776	3.8776
MX1	NM_001144925	0.000642	0.004132	0.296965	-3.3674

LRRC6	NM_012472	0.002159	0.000568	3.03333	3.03333
TNFRSF10C	NM_003841	7.46E-05	1.74E-05	4.07284	4.07284
CYR61	NM_001554	4.65E-05	0.002536	0.486456	-2.05568
CXCL17	NM_198477	1.48E-06	0.686453	1.10161	1.10161
ANKRD50	NM_020337	1.33E-05	0.000643	0.479385	-2.08601
GSTM4	NM_000850	1.62E-06	2.29E-07	15.5494	15.5494
GSTM2	NM_000848	0.000898	0.000207	3.39662	3.39662
HRASLS2	NM_017878	0.000251	0.009109	2.71842	2.71842
C11orf92	NM_207429	9.79E-08	8.14E-07	4.28703	4.28703
ODAM	NM_017855	6.17E-06	9.19E-07	21.2503	21.2503
AHNAK2	NM_138420	8.07E-08	6.68E-07	0.20488	-4.88091
DDX43	NM_018665	0.000328	6.84E-05	5.61594	5.61594
IFI16	NM_005531	1.79E-06	5.60E-06	0.106816	-9.36187
SLC16A4	NM_004696	0.000184	0.00011	10.6066	10.6066
AK5	NM_174858	0.000101	1.64E-05	5.2323	5.2323
FKBP5	NM_001145775	8.41E-05	0.001373	0.314812	-3.1765
THBS1	NM_003246	6.21E-05	0.000356	0.188047	-5.31782
KCNJ15	NM_002243	5.99E-07	0.000208	0.498867	-2.00454
LCN2	NM_005564	4.89E-05	0.000961	0.309656	-3.22939
HS3ST5	NM_153612	7.36E-05	1.83E-05	3.97874	3.97874
CAPN9	NM_006615	1.80E-09	9.82E-08	4.95981	4.95981
CLDN10	NM_182848	1.13E-06	4.61E-07	3.6212	3.6212
KLK10	NM_002776	2.17E-06	0.000336	0.448689	-2.22871
SAMD9	NM_017654	8.12E-06	4.59E-05	0.138963	-7.19618
HLA-DMB	NM_002118	0.000348	8.26E-05	4.70494	4.70494
KLK7	NM_139277	5.21E-07	8.75E-06	0.190983	-5.23607
NTS	NM_006183	0.018973	0.0031	9.28925	9.28925
TGFB2	NM_001135599	0.001966	0.000761	3.65589	3.65589
CYP2E1	NM_000773	3.35E-05	1.79E-05	3.40286	3.40286
ALDH3A1	NM_000691	1.89E-08	1.95E-07	5.15825	5.15825
CCBE1	NM_133459	4.81E-06	1.96E-05	2.82626	2.82626

MATN2	NM_002380	6.77E-06	3.60E-05	2.61679	2.61679
MFAP5	NM_003480	3.58E-05	0.000104	0.059705	-16.7491
BAAT	NM_001701	5.52E-08	9.52E-09	7.07911	7.07911
SLC15A1	NM_005073	4.59E-06	3.94E-06	3.51845	3.51845
MXRA5	NM_015419	0.000382	0.0001	5.60412	5.60412
FGF2	NM_002006	4.92E-06	1.56E-06	5.5274	5.5274
IFI44	NM_006417	0.000107	0.000873	0.128059	-7.80893
CSTA	NM_005213	2.09E-07	7.47E-07	0.024791	-40.3374
SERPINB5	NM_002639	1.66E-09	7.33E-08	0.136954	-7.30173
GPR87	NM_023915	1.16E-07	4.53E-06	0.135101	-7.40189
BICC1	NM_001080512	2.71E-06	6.08E-07	14.6863	14.6863
MSN	NM_002444	2.62E-07	0.000796	0.429086	-2.33053
GKN1	NM_019617	1.12E-07	6.54E-07	37.4703	37.4703
GKN2	NM_182536	1.22E-08	4.25E-08	53.4059	53.4059

Expression microarrays were used to compare the mRNA expression of an isolated clonal population of Barrett's esophagus progenitor cells and a clonal population of gastric cardia progenitor cells. The results of this comparison are shown in Table YY, below.

Table YY

Gene Symbol	RefSeq	p-value (Attribute)	p-value (Barrett's vs. Cardia)	Ratio (Barrett's vs. Cardia)	Fold-Change (Barrett's vs. Cardia)
FABP1	NM_001443	2.34E-09	0.443141	1.1736	1.1736
CPS1	NM_001122633	2.60E-07	0.721073	1.09633	1.09633
FABP2	NM_000134	5.39E-08	0.915975	0.979547	-1.02088
PRSS2	NM_002770	2.27E-05	0.122173	0.53986	-1.85233
KRT20	NM_019010	5.33E-07	0.135603	0.680989	-1.46845
DMBT1	NM_007329	7.79E-09	0.927446	0.987845	-1.0123
SI	NM_001041	8.23E-09	0.863031	1.02302	1.02302
MTTP	NM_000253	2.97E-09	0.39728	1.09805	1.09805

RBP2	NM_004164	2.08E-07	0.364822	1.18689	1.18689
MT1H	NM_005951	2.21E-06	1.31E-05	0.121771	-8.21216
CLCA1	NM_001285	1.94E-07	0.674392	0.932292	-1.07263
KGFLP2	NR_003670	7.43E-06	0.122882	0.668756	-1.49531
GUCY2C	NM_004963	3.89E-09	0.289294	1.12138	1.12138
GSTA2	NM_000846	0.000164	0.651187	1.24989	1.24989
CDH17	NM_004063	3.78E-09	1.82E-06	6.74546	6.74546
C17orf78	NM_173625	0.00023	0.348551	0.710482	-1.40749
GPR128	NM_032787	3.01E-08	0.20003	1.17444	1.17444
TM4SF4	NM_004617	1.49E-08	0.005923	1.86836	1.86836
GJA1	NM_000165	0.000666	0.195597	0.503858	-1.98469
OTC	NM_000531	1.40E-07	0.001647	2.15821	2.15821
BEX1	NM_018476	3.43E-05	0.912943	0.972302	-1.02849
HIST1H1A	NM_005325	1.95E-07	0.041247	1.42195	1.42195
OLFM4	NM_006418	1.75E-10	2.00E-08	9.46554	9.46554
LOC29034	NR_002763	1.07E-07	0.973418	1.00379	1.00379
BTNL3	NM_197975	4.86E-06	0.389088	1.19403	1.19403
DPY19L2P2	NR_003561	0.000999	0.326134	0.669634	-1.49335
CPE	NM_001873	1.65E-06	0.936389	0.988612	-1.01152
RGS5	NM_003617	1.02E-05	0.010102	0.499497	-2.00202
CPVL	NM_019029	1.05E-06	0.006054	0.644326	-1.55201
DSG3	NM_001944	7.14E-10	0.468093	1.09383	1.09383
TM4SF20	NM_024795	3.07E-07	0.964612	1.00533	1.00533
SLC38A11	NM_173512	2.05E-06	0.498316	1.11012	1.11012
ADH4	NM_000670	2.50E-07	0.054095	1.32233	1.32233
CEACAM6	NM_002483	3.08E-05	0.000582	10.7156	10.7156
SYNPR	NM_001130003	2.23E-05	0.877069	1.03258	1.03258
ALDOB	NM_000035	2.00E-07	0.000338	2.61325	2.61325
FAM13A	NM_001015045	2.05E-05	0.250942	0.792478	-1.26186
SLC17A4	NM_005495	4.81E-06	0.740182	1.0575	1.0575
CACNA2D1	NM_000722	9.75E-08	0.203122	1.15551	1.15551

ATF7IP2	NM_024997	2.12E-05	0.002184	0.461398	-2.16733
MEP1A	NM_005588	1.31E-06	0.680298	1.0605	1.0605
RBM46	NM_144979	7.01E-05	0.895065	0.972392	-1.02839
ZG16	NM_152338	8.01E-05	0.802539	1.05959	1.05959
REG4	NM_001159352	2.83E-08	0.15174	0.785147	-1.27365
MUC17	NM_001040105	1.67E-06	0.000237	4.49768	4.49768
LGR5	NM_003667	3.55E-07	0.413975	1.11663	1.11663
PRSS1	NM_002769	8.44E-05	0.006798	0.43254	-2.31192
SLC2A2	NM_000340	3.42E-06	0.644334	1.07519	1.07519
PHYHIPL	NM_032439	1.38E-05	0.779037	0.949399	-1.0533
ACE2	NM_021804	1.43E-07	0.026458	1.34995	1.34995
CCND2	NM_001759	5.19E-05	0.627003	0.870802	-1.14837
SULT1E1	NM_005420	3.45E-07	0.484764	1.13106	1.13106
SLC5A1	NM_000343	8.44E-06	0.063502	1.57083	1.57083
SEMA6A	NM_020796	7.77E-07	0.001034	2.24175	2.24175
MT1L	NR_001447	0.004952	0.030826	0.218511	-4.57642
HMGCS2	NM_005518	3.07E-07	0.004662	0.569986	-1.75443
MGAT4A	NM_012214	6.97E-06	0.241395	0.76894	-1.30049
UGT2B17	NM_001077	5.68E-06	0.509228	1.12953	1.12953
C15orf48	NM_032413	1.19E-08	0.048232	1.20649	1.20649
CISD2	NM_001008388	0.000711	0.120867	0.691153	-1.44686
SST	NM_001048	0.000975	0.862	1.04966	1.04966
SPC25	NM_020675	0.033633	0.163262	0.547071	-1.82792
PLA2G12B	NM_032562	1.29E-05	0.818515	0.967277	-1.03383
LGALS2	NM_006498	1.72E-08	0.002572	1.42912	1.42912
NR1H4	NM_005123	5.91E-06	0.994737	1.00093	1.00093
UGT3A1	NM_152404	1.50E-05	0.373038	0.874674	-1.14328
GIP	NM_004123	0.066104	0.974579	1.01786	1.01786
LOC147727	NR_024333	1.58E-05	0.819467	0.970185	-1.03073
ABCG2	NM_004827	0.000813	0.308928	0.801872	-1.24708
OCR1	AF314543	0.024574	0.35436	1.59119	1.59119

LMBR1	NM_022458	0.008559	0.417077	0.641549	-1.55873
A1CF	NM_138933	7.40E-07	0.000107	3.13037	3.13037
IGF2BP1	NM_006546	1.50E-07	0.643519	1.03984	1.03984
TSPAN7	NM_004615	0.000601	0.992739	1.00201	1.00201
CEACAM7	NM_006890	3.74E-06	0.853763	1.02232	1.02232
MYB	NM_001130173	4.65E-06	0.040136	0.683024	-1.46408
CFI	NM_000204	8.87E-06	0.01031	1.91938	1.91938
SLC10A2	NM_000452	6.69E-05	0.836931	1.03668	1.03668
UGT2A3	NR_024010	1.48E-07	6.93E-06	5.52838	5.52838
IFITM1	NM_003641	6.18E-05	0.237116	1.39004	1.39004
TMEM20	NM_001134658	0.000102	0.600376	1.0965	1.0965
TNFRSF11B	NM_002546	1.34E-05	0.396002	1.18421	1.18421
SMOC2	NM_022138	8.35E-05	0.680888	1.07905	1.07905
TGFBI	NM_000358	0.000306	0.525043	0.81542	-1.22636
GPA33	NM_005814	0.00014	0.753218	1.06031	1.06031
NELL2	NM_001145108	4.57E-05	0.587981	1.0888	1.0888
ATP1B3	NM_001679	7.11E-07	0.004315	0.593605	-1.68462
FGF9	NM_002010	2.98E-05	0.821578	0.969452	-1.03151
FOLH1	NM_004476	1.41E-05	0.817179	0.968607	-1.03241
RGS2	NM_002923	7.55E-06	0.000328	2.53448	2.53448
NAT2	NM_000015	4.42E-05	0.292778	1.22741	1.22741
CCL25	NM_005624	8.63E-05	0.690336	0.937517	-1.06665
SEMA6D	NM_153618	1.55E-05	0.945868	0.992365	-1.00769
ANXA13	NM_001003954	2.27E-08	3.99E-07	11.2408	11.2408
KLHL23	ENST00000392647	8.54E-06	0.023326	1.52693	1.52693
GSTA1	NM_145740	1.25E-06	0.154535	0.693914	-1.4411
S100G	NM_004057	6.67E-05	0.166669	1.27986	1.27986
LCT	NM_002299	1.06E-05	0.997468	1.00038	1.00038
FAM5C	NM_199051	4.88E-06	0.38727	0.91647	-1.09114
ANPEP	NM_001150	3.32E-06	0.000306	2.31363	2.31363
HIST1H2AE	NM_021052	0.001216	0.592642	0.885169	-1.12973

SLC11A2	NM_000617	1.91E-06	0.192241	1.15331	1.15331
LRRC19	NM_022901	4.02E-06	0.009847	1.52777	1.52777
SLC27A2	NM_003645	1.60E-05	0.241477	1.265	1.265
LDHC	NM_002301	5.51E-06	0.881698	0.985233	-1.01499
SCGN	NM_006998	0.000129	0.294288	0.845082	-1.18332
GPR160	NM_014373	2.16E-05	0.934977	1.01721	1.01721
SLC16A10	NM_018593	0.000465	0.54731	1.12282	1.12282
CLRN3	NM_152311	4.69E-08	1.73E-06	6.49979	6.49979
C12orf28	BC143553	1.27E-05	0.000652	2.14142	2.14142
SATB1	NM_002971	0.000101	0.405523	1.26097	1.26097
GOLT1A	NM_198447	4.68E-07	0.367544	1.08473	1.08473
UFM1	NM_016617	1.64E-05	0.381874	0.919883	-1.08709
HIBCH	NM_014362	0.011898	0.985899	0.995584	-1.00444
L1TD1	NM_019079	0.000304	0.87407	0.956311	-1.04568
HOXA9	NM_152739	2.96E-05	0.904783	1.0312	1.0312
TPH1	NM_004179	0.000951	0.843169	0.96601	-1.03519
HEPH	NM_138737	7.75E-08	5.35E-06	3.09377	3.09377
BMS1P5	NR_003611	0.240068	0.609905	1.37201	1.37201
ASAH2	NM_019893	7.62E-05	0.547895	1.08578	1.08578
KIAA1324	NM_020775	3.22E-08	2.29E-08	0.084891	-11.7798
ALDOC	NM_005165	2.49E-06	0.001135	1.58838	1.58838
KPNA2	NM_002266	0.022754	0.49921	1.24956	1.24956
NEUROD1	NM_002500	0.06316	0.67004	0.854231	-1.17064
MS4A8B	NM_031457	5.65E-06	0.538728	1.06533	1.06533
EPHB2	NM_017449	0.001129	0.354389	0.865019	-1.15604
MSI1	NM_002442	9.22E-06	0.406005	1.09288	1.09288
IFNK	NM_020124	0.002165	0.348535	1.47073	1.47073
FGFBP1	NM_005130	1.79E-08	2.67E-06	0.241632	-4.13853
CDKN1B	NM_004064	3.54E-05	0.080701	1.24482	1.24482
TFPI	NM_006287	1.26E-05	0.119822	1.49285	1.49285
STAMBPL1	NM_020799	4.70E-06	0.902034	0.990904	-1.00918

NLGN4Y	NM_014893	4.39E-05	0.374066	1.20471	1.20471
PLD1	NM_002662	0.000446	0.042352	1.51016	1.51016
APOBEC3B	NM_004900	0.001419	0.288154	1.24833	1.24833
MEP1B	NM_005925	5.41E-05	0.61469	0.943529	-1.05985
	---	0.001183	0.524315	0.817098	-1.22384
EPHX2	NM_001979	1.10E-06	0.097773	1.12319	1.12319
XRCC4	NM_022550	0.001579	0.028941	2.25274	2.25274
GAS2	NM_005256	3.49E-05	0.391309	1.10823	1.10823
DPP10	NM_020868	0.000864	0.827068	0.965055	-1.03621
TLR4	NR_024168	9.63E-05	0.960524	1.00726	1.00726
LSAMP	NM_002338	2.16E-05	0.478213	0.918271	-1.089
SEPT7	NM_001788	0.01691	0.535765	0.759353	-1.31691
CCNB2	NM_004701	0.009939	0.652125	0.910009	-1.09889
MT1A	NM_005946	1.80E-05	2.09E-06	0.181046	-5.52346
C2orf43	BC017473	0.002035	0.907738	1.0208	1.0208
EML4	NM_019063	0.003235	0.874733	1.03711	1.03711
CKS2	NM_001827	2.48E-05	0.253809	0.896221	-1.1158
CYP2B6	NM_000767	0.000209	0.052391	1.5905	1.5905
CCDC34	NM_030771	4.73E-05	0.58764	1.05377	1.05377
ADH6	NM_001102470	2.18E-06	0.000522	2.005	2.005
ATP8A1	NM_006095	9.35E-06	0.919121	0.979759	-1.02066
FAR2	NM_018099	3.78E-07	3.34E-05	1.80602	1.80602
TF	NM_001063	7.43E-06	0.733031	0.974911	-1.02574
MYO1B	NM_001130158	1.47E-06	0.085899	1.37399	1.37399
SLC35D1	NM_015139	0.066551	0.848775	1.06074	1.06074
CXorf52	AY168775	0.026084	0.737231	1.17926	1.17926
PCDH11Y	NM_032971	0.368856	0.94435	0.959851	-1.04183
SERPINE2	NM_001136529	2.73E-07	0.798267	0.95069	-1.05187
ERP27	NM_152321	0.002033	0.06942	1.50846	1.50846
DNAJC2	NM_014377	0.000601	0.248587	0.730929	-1.36812
PCDH20	NM_022843	0.000951	0.938596	1.01243	1.01243

HNF4G	NM_004133	3.36E-07	0.789701	1.04722	1.04722
HIST1H3G	NM_003534	7.92E-05	0.642299	0.944271	-1.05902
HPDL	NM_032756	0.001394	0.85299	0.962647	-1.0388
SH3PXD2A	NM_014631	2.02E-05	0.003589	0.34797	-2.87381
COX18	NM_173827	0.001081	0.986366	1.00279	1.00279
HHLA2	NM_007072	1.26E-05	0.062731	1.5504	1.5504
ZNF770	NM_014106	2.22E-05	0.36345	0.843946	-1.18491
LYPLA1	NM_006330	5.75E-05	0.408349	0.815345	-1.22648
DHRS11	NM_024308	0.000217	0.026583	1.54368	1.54368
EPB41L2	NM_001431	0.003371	0.243803	1.32387	1.32387
EXOC3	AK074086	1.49E-06	0.140389	1.11189	1.11189
GHRL	NR_024138	0.027865	0.917204	0.974975	-1.02567
DACH1	NM_080759	0.000217	0.930392	1.01044	1.01044
SPARC	NM_003118	1.66E-06	0.745461	1.04966	1.04966
SLCO4C1	NM_180991	3.06E-05	0.128833	1.18801	1.18801
KLHL23	NM_144711	0.000249	0.113175	1.40747	1.40747
KRT6B	NM_005555	9.83E-11	0.091889	0.85651	-1.16753
EPCAM	NM_002354	1.17E-07	0.395177	1.13504	1.13504
IL20RB	NM_144717	7.88E-07	0.782018	0.934046	-1.07061
MEIS2	NM_172316	5.41E-06	0.001467	1.50829	1.50829
MMP12	NM_002426	0.003373	0.45577	1.14604	1.14604
ACPL2	NM_152282	8.11E-06	0.30308	1.09	1.09
TIMP3	NM_000362	3.21E-07	0.325432	0.878479	-1.13833
CXCL14	NM_004887	0.000211	0.329507	1.25497	1.25497
METTL6	NM_152396	0.001275	0.389509	0.809846	-1.2348
ZNF770	NM_014106	1.21E-06	0.825134	0.979436	-1.021
CLDND1	NM_001040199	0.000346	0.168171	0.76108	-1.31392
RAET1L	NM_130900	5.71E-06	0.000821	0.283356	-3.52913
SDAD1	NM_018115	0.022444	0.149688	0.593853	-1.68392
PLEKHF2	NM_024613	0.005965	0.648635	0.853017	-1.17231
TMEM117	NM_032256	0.000172	0.139495	0.732889	-1.36446

RASA1	NM_002890	0.000185	0.674089	0.924542	-1.08162
S100A16	NM_080388	2.27E-05	0.117999	0.756328	-1.32218
KCTD9	NM_017634	0.000344	0.058892	0.655909	-1.5246
GRHL1	NM_014552	2.68E-07	0.670364	1.05302	1.05302
ARHGAP29	NM_004815	8.76E-05	0.827322	1.05553	1.05553
BNIP2	NM_004330	4.25E-05	0.276324	1.24493	1.24493
MARCH7	NM_022826	0.017224	0.205183	0.662246	-1.51001
RAB23	NM_016277	0.001104	0.884425	1.03235	1.03235
STK17A	NM_004760	0.001954	0.683331	0.862241	-1.15977
REEP3	ENST00000298249	0.000142	0.740284	0.932601	-1.07227
ATL2	NM_022374	0.002578	0.213772	0.722131	-1.38479
MALT1	NM_006785	3.81E-07	0.056831	0.829054	-1.20619
LOC554203	NR_024582	0.005588	0.849364	1.06021	1.06021
DUSP11	NM_003584	8.27E-05	0.380791	0.85819	-1.16524
IGF2BP2	NM_006548	0.00154	0.276382	1.32037	1.32037
SEPT10	NM_144710	0.005078	0.295213	0.754419	-1.32552
REPS1	NM_031922	0.001111	0.130513	0.716519	-1.39564
C3orf14	AF236158	0.000139	0.036881	1.883	1.883
ADK	NM_006721	6.58E-05	0.918164	1.01505	1.01505
SSR3	NM_007107	0.010975	0.187956	0.655579	-1.52537
PRRG4	NM_024081	3.02E-05	0.040066	0.74722	-1.33829
PDPN	NM_006474	8.09E-07	0.908853	1.01679	1.01679
KIAA1586	NM_020931	1.65E-05	0.815177	1.0374	1.0374
PEX3	NM_003630	1.98E-05	0.82392	1.04112	1.04112
	---	0.000761	0.393051	1.21631	1.21631
EIF2AK2	NM_002759	0.012021	0.374086	0.751052	-1.33147
GTF2F2	NM_004128	0.000579	0.377913	0.856518	-1.16752
SMYD2	NM_020197	7.87E-05	0.407177	0.898136	-1.11342
CTSC	NM_001814	1.37E-07	0.278963	0.892579	-1.12035
MPP7	NM_173496	1.95E-07	0.000139	1.79904	1.79904
GDAP1	NM_018972	1.52E-06	0.00234	1.54283	1.54283

FN1	NM_212482	0.000112	0.117263	1.55772	1.55772
TROVE2	NM_004600	0.004196	0.795748	0.940558	-1.0632
C1orf149	NM_022756	0.000508	0.277797	0.836815	-1.19501
CLEC2B	NM_005127	0.003209	0.86596	0.945449	-1.0577
ALS2CR4	NM_001044385	1.40E-06	0.189331	1.14579	1.14579
PTPN12	NM_002835	0.001268	0.344662	1.26374	1.26374
BOD1L	NM_148894	0.007872	0.484484	0.83063	-1.20391
TNNT1	NM_003283	3.38E-06	0.23944	1.18015	1.18015
FABP7	NM_001446	0.012746	0.674857	0.895753	-1.11638
HDGFRP3	NM_016073	5.09E-07	0.009735	1.35995	1.35995
SPRR2D	NM_006945	1.59E-06	0.384946	1.35186	1.35186
FJX1	NM_014344	4.64E-06	0.973508	1.00484	1.00484
S100A14	NM_020672	9.03E-05	0.19977	0.749712	-1.33385
MT1M	NM_176870	6.30E-07	7.31E-07	0.114584	-8.72719
LRRC37B2	NR_015341	0.000454	0.741343	0.94108	-1.06261
IL18	NM_001562	2.33E-06	0.261551	1.20103	1.20103
GABRE	NM_004961	5.51E-05	0.348973	1.13527	1.13527
GNPDA2	NM_138335	5.96E-05	0.419588	1.11695	1.11695
ELOVL4	NM_022726	2.26E-07	0.904397	1.02091	1.02091
WASF1	NM_003931	4.90E-05	0.254721	1.24822	1.24822
PIK3CA	NM_006218	0.000544	0.862504	1.03449	1.03449
MBOAT2	NM_138799	0.000192	0.004061	0.34441	-2.90351
PAR1	AF019616	0.000965	0.300889	1.24773	1.24773
IVNS1ABP	NM_006469	0.006048	0.335337	0.80216	-1.24663
CHIC2	NM_012110	0.000122	0.140178	0.798603	-1.25219
VSNL1	NM_003385	3.02E-08	3.48E-05	2.75331	2.75331
LRRC37A3	NM_199340	0.00638	0.446635	0.845344	-1.18295
FYTTD1	NM_001011537	0.004033	0.498991	0.861433	-1.16086
RNF217	NM_152553	1.89E-10	0.000313	1.38293	1.38293
PLA2G4A	NM_024420	0.006562	0.304921	0.775583	-1.28935
P2RY5	NM_005767	2.90E-06	0.68288	1.05684	1.05684

NT5E	NM_002526	2.00E-07	0.114638	0.786981	-1.27068
CTSL2	NM_001333	1.96E-05	0.629843	0.908449	-1.10078
ZNF354A	NM_005649	0.006993	0.240775	0.767069	-1.30366
KIFAP3	NM_014970	2.61E-06	0.06349	1.30939	1.30939
RAB18	NM_021252	4.91E-05	0.049838	0.730702	-1.36855
C1orf74	BC039719	7.17E-05	0.688993	1.05848	1.05848
RB1	NM_000321	0.000478	0.076805	0.735413	-1.35978
CEP170	NM_014812	3.10E-05	0.067147	1.55308	1.55308
KIF13A	NM_022113	7.87E-06	0.933653	1.01045	1.01045
PRKCQ	NM_006257	5.36E-06	0.942759	0.992509	-1.00755
C6orf105	NM_001143948	9.93E-05	0.007267	0.51191	-1.95347
KRT23	NM_015515	5.21E-08	0.00182	1.59222	1.59222
C10orf55	NM_001001791	0.004044	0.453532	0.815553	-1.22616
EFTUD1	NM_024580	5.31E-05	0.855198	0.977134	-1.0234
EDNRA	NM_001957	0.00118	0.939445	0.984322	-1.01593
TMTC1	NM_175861	8.69E-08	0.211894	0.882779	-1.13279
DUSP14	NM_007026	3.77E-06	0.3473	1.11611	1.11611
GPNMB	NM_001005340	1.01E-06	0.850774	1.03534	1.03534
PRSS3	NM_007343	0.001276	0.384432	0.84951	-1.17715
EMB	NM_198449	2.20E-07	0.075382	1.21044	1.21044
SLC1A3	NM_004172	3.98E-07	2.90E-05	0.475033	-2.10512
TCTEX1D2	NM_152773	5.43E-08	0.347454	1.05358	1.05358
NUDT11	NM_018159	0.000877	0.980617	0.991066	-1.00901
AIG1	NM_016108	4.81E-05	0.104716	1.26639	1.26639
NEDD4	NM_006154	6.37E-05	0.261659	0.871193	-1.14785
MMP10	NM_002425	0.005493	0.737511	0.846256	-1.18167
NDFIP2	NM_019080	9.17E-05	0.664582	1.06969	1.06969
D4S234E	NM_014392	2.06E-05	0.917355	1.02137	1.02137
PCTK2	NM_002595	8.48E-06	0.424519	1.09366	1.09366
KIAA0922	NM_001131007	5.88E-07	0.692272	0.958666	-1.04312
EFCAB2	NR_026588	0.023377	0.665681	0.872544	-1.14607

RABGEF1	NM_014504	0.002164	0.389878	0.851125	-1.17492
MCART1	NR_024873	0.056152	0.185878	0.538811	-1.85594
IGFL3	NM_207393	9.80E-08	0.036733	0.848766	-1.17818
ANTXR2	NM_058172	5.41E-06	0.801006	0.969992	-1.03094
FBN2	NM_001999	2.36E-07	0.532557	1.08876	1.08876
SCFD1	NM_016106	0.008561	0.269726	0.769348	-1.2998
C11orf60	NM_020153	2.60E-06	0.032384	0.802562	-1.24601
UNQ1887	NM_139015	6.66E-07	0.010253	1.24687	1.24687
HOMER1	NM_004272	0.001456	0.563836	0.870836	-1.14832
LPAR3	NM_012152	1.27E-07	0.819446	0.974058	-1.02663
LRRC42	NM_052940	0.000315	0.553792	0.922073	-1.08451
GOLGA8B	NR_027410	3.19E-05	0.000483	2.86234	2.86234
CYB5R2	NM_016229	0.000242	0.033137	0.635253	-1.57418
UBE2F	NM_080678	0.0049	0.324724	0.809307	-1.23562
TMTC3	NM_181783	2.84E-05	0.718184	0.958463	-1.04334
ZCCHC11	NM_001009881	0.000345	0.259485	1.26918	1.26918
PPP3CC	NM_005605	0.000139	0.40974	0.879464	-1.13706
SESN3	NM_144665	1.87E-05	0.644605	0.938198	-1.06587
C14orf149	NM_144581	5.47E-05	0.365414	0.899314	-1.11196
PTPLA	NM_014241	9.50E-07	0.419147	0.937001	-1.06723
ODF2L	NM_020729	5.20E-05	0.01168	1.61203	1.61203
FAM174A	NM_198507	0.001283	0.049476	0.608776	-1.64264
CBL	NM_005188	4.47E-06	0.736706	0.973469	-1.02725
PDCD1LG2	NM_025239	0.000571	0.603517	0.892033	-1.12103
PMAIP1	NM_021127	1.14E-05	0.002687	1.81509	1.81509
SACS	NM_014363	9.98E-06	0.02187	1.56338	1.56338
FKBP14	NM_017946	0.000421	0.78068	0.952519	-1.04985
ROBO1	NM_133631	5.83E-07	0.960284	1.00768	1.00768
QPCT	NM_012413	0.000184	0.486296	1.13839	1.13839
ZFP42	NM_174900	0.048358	0.907614	1.04601	1.04601
DSP	NM_004415	2.60E-05	0.777212	0.962674	-1.03877

SPRR1A	NM_005987	1.72E-08	0.000821	0.464088	-2.15476
IL1A	NM_000575	8.93E-10	0.025527	0.7224	-1.38428
LOC654433	NR_015377	0.146494	0.503143	0.728255	-1.37315
EPS15	NM_001981	0.013543	0.49308	0.85887	-1.16432
S100A11	NM_005620	0.000261	0.315911	0.855889	-1.16838
SLC36A4	NM_152313	3.46E-05	0.011347	0.602895	-1.65866
RRAGC	NM_022157	0.000313	0.423692	0.904501	-1.10558
DOCK11	NM_144658	8.05E-07	0.035947	0.717119	-1.39447
KDSR	NM_002035	5.66E-08	0.028676	1.16883	1.16883
ERGIC2	NM_016570	0.000598	0.595637	0.922475	-1.08404
CSGALNACT2	NM_018590	0.000202	0.509818	1.09982	1.09982
LOC554202	NR_027054	1.47E-07	0.056703	1.22206	1.22206
WFDC5	NM_145652	7.11E-06	0.50016	0.878851	-1.13785
PLXDC2	NM_032812	1.91E-08	0.777947	0.970972	-1.0299
FBXW7	NM_033632	0.001172	0.587438	0.911701	-1.09685
TMEM69	NM_016486	0.000973	0.328165	1.1862	1.1862
TMEM45A	NM_018004	1.87E-11	0.057522	0.845463	-1.18278
BBS10	NM_024685	0.001013	0.986878	0.997303	-1.0027
SOX2OT	NR_004053	0.003922	0.001297	0.252645	-3.95812
KDM5B	NM_006618	0.00124	0.8956	0.979129	-1.02132
CDA	NM_001785	7.22E-05	0.853675	1.04127	1.04127
IFIT5	NM_012420	0.001922	0.985909	0.99644	-1.00357
GTF2H1	NM_001142307	0.000615	0.471872	0.899256	-1.11203
NEFM	NM_005382	0.000894	0.435712	1.27359	1.27359
SGCE	NM_001099401	3.31E-05	0.00329	1.68958	1.68958
DIRC2	NM_032839	3.81E-05	0.00751	1.51859	1.51859
ITGA1	NM_181501	3.45E-05	0.254011	1.12878	1.12878
RSAD2	NM_080657	0.014966	0.706236	1.15174	1.15174
SLFN5	NM_144975	2.52E-05	0.000355	3.21394	3.21394
SLC2A3	NM_006931	1.19E-05	0.971294	0.992216	-1.00784
ADAMTS1	NM_006988	8.15E-06	0.091202	1.24299	1.24299

ZBTB1	NM_001123329	0.00013	0.407351	0.914589	-1.09339
PIP5K1A	NM_001135638	0.026998	0.589881	0.852287	-1.17331
DFNA5	NM_004403	2.70E-06	0.005366	1.72407	1.72407
DMKN	NM_033317	4.50E-07	0.141932	1.16214	1.16214
FLRT3	NM_198391	7.17E-07	0.000218	2.58604	2.58604
SPRR3	NM_005416	1.85E-07	0.490821	0.898669	-1.11276
TTPAL	NM_024331	2.86E-06	0.868857	1.01788	1.01788
RPS6KA5	NM_004755	4.57E-05	0.967021	0.996061	-1.00395
CLN5	NM_006493	0.000897	0.458264	0.902943	-1.10749
EFEMP1	NM_004105	2.65E-08	0.342209	0.86779	-1.15235
SLC20A1	NM_005415	6.24E-06	0.559718	0.919276	-1.08781
GNAI1	NM_002069	0.000112	0.004161	2.32485	2.32485
FERMT1	NM_017671	0.000364	0.51844	0.918142	-1.08916
FN1	NM_212482	9.48E-07	0.344093	1.25565	1.25565
GJB6	NM_001110219	1.86E-06	0.280012	1.33981	1.33981
GPR1	NM_005279	6.76E-05	0.920185	0.989886	-1.01022
GPR115	NM_153838	1.43E-05	0.875384	0.972789	-1.02797
ZNF607	NM_032689	4.95E-06	0.742897	0.975057	-1.02558
MTHFD2L	NM_001144978	2.12E-06	0.857342	1.01476	1.01476
LRAT	NM_004744	1.74E-05	0.802563	1.04117	1.04117
C3orf64	NM_173654	0.000232	0.065142	0.707731	-1.41297
ALDH3B2	NM_000695	0.000138	0.226623	1.17486	1.17486
MT1X	NM_005952	0.002024	0.813716	1.06879	1.06879
USP25	NM_013396	0.000737	0.269933	0.853343	-1.17186
USP53	NM_019050	0.007056	0.936263	1.01602	1.01602
DUSP6	NM_001946	0.00301	0.639665	1.09556	1.09556
TLE4	NM_007005	5.00E-05	0.008608	1.53717	1.53717
INHBA	NM_002192	0.000639	0.631387	0.905254	-1.10466
COL12A1	NM_004370	3.22E-07	0.409874	1.13641	1.13641
SLIT2	NM_004787	8.48E-06	0.680656	0.957377	-1.04452
KLF8	NM_007250	1.93E-05	0.394299	0.902273	-1.10831

IQCA1	NM_024726	3.76E-08	0.315482	0.89791	-1.1137
BNC1	NM_001717	2.55E-08	0.37964	0.906132	-1.10359
TCFL5	NM_006602	4.73E-05	0.07954	1.23475	1.23475
S100A7	NM_002963	8.46E-06	0.764639	1.12581	1.12581
EMP3	NM_001425	0.000135	0.782887	1.07599	1.07599
DEGS1	NM_003676	0.000529	0.364489	1.34899	1.34899
SPG20	NM_001142295	0.000483	0.741705	1.05335	1.05335
TPD52L1	NM_001003395	1.12E-05	0.787244	1.02975	1.02975
GPR137B	NM_003272	1.43E-05	0.891138	0.984364	-1.01588
NIACR2	NM_006018	2.84E-05	0.685785	1.08487	1.08487
RBMS3	NM_001003793	0.000283	0.732447	0.958713	-1.04307
MUC15	NM_001135091	2.23E-07	0.423441	0.877041	-1.1402
PPP4R1	NM_001042388	6.81E-05	0.325871	0.890068	-1.12351
FCHO2	NM_138782	0.041643	0.577163	0.831338	-1.20288
LEF1	NM_016269	0.01014	0.975765	0.992718	-1.00733
CLASP1	NM_015282	0.000646	0.506131	0.900357	-1.11067
TMEM154	NM_152680	3.06E-07	0.906144	1.01745	1.01745
IKIP	NM_153687	2.32E-08	0.02648	0.77252	-1.29446
HIVEP2	NM_006734	4.23E-07	0.001835	1.68848	1.68848
DSC3	NM_024423	1.04E-10	0.148326	0.85442	-1.17039
CLDN1	NM_021101	1.30E-06	9.63E-05	2.02073	2.02073
GJB2	NM_004004	3.20E-09	0.511514	1.05777	1.05777
WDR47	NM_001142550	5.48E-05	0.430766	0.867016	-1.15338
SPINK5	NM_001127698	4.21E-06	0.019621	0.527906	-1.89428
S1PR1	NM_001400	2.02E-06	0.479086	0.913656	-1.0945
IL1RAP	NM_002182	2.28E-07	0.468287	1.08077	1.08077
VEGFC	NM_005429	2.82E-05	0.731719	1.05089	1.05089
AHSA2	NM_152392	0.007404	0.225778	1.40222	1.40222
FBXO3	NM_033406	8.51E-05	0.807121	0.972252	-1.02854
SRY	NM_003140	0.000306	0.385178	0.837197	-1.19446
RPSAP52	NR_026825	5.72E-06	0.451358	1.09257	1.09257

TAGLN3	NM_013259	7.20E-06	0.515786	1.08487	1.08487
BACH1	NM_206866	3.25E-07	0.070202	0.901991	-1.10866
LY6G6C	NM_025261	0.000167	0.516811	0.911763	-1.09678
ARL17P1	NM_001113738	0.065934	0.896144	1.04782	1.04782
PTGS1	NM_000962	0.000309	0.92096	0.983269	-1.01702
NRG1	NM_013960	1.99E-06	0.700954	0.955373	-1.04671
TCF4	NM_001083962	1.44E-05	0.465419	1.06152	1.06152
ZFYVE9	NM_004799	0.00013	0.933287	1.01076	1.01076
FAM83A	NM_032899	3.35E-06	0.237368	0.883703	-1.1316
ITGA2	NM_002203	0.000116	0.559486	0.919839	-1.08715
HERC6	NM_017912	0.000901	0.954878	0.984915	-1.01532
FHL1	NM_001159704	2.69E-05	0.266689	1.1672	1.1672
USP9Y	NM_004654	2.78E-05	0.066875	1.30466	1.30466
PLAU	NM_002658	0.000318	0.2318	1.23969	1.23969
FGF11	NM_004112	0.000923	0.559071	0.922811	-1.08365
CYP4F12	NM_023944	2.48E-06	0.000355	0.457181	-2.18732
BCAT1	NM_005504	2.88E-05	0.640106	1.08261	1.08261
KLK8	NM_144505	3.28E-08	0.948291	0.992733	-1.00732
BPIL2	NM_174932	3.22E-07	0.324773	0.907337	-1.10213
GLI3	NM_000168	1.10E-05	0.70959	0.950737	-1.05182
ZBED2	NM_024508	1.18E-06	0.533492	0.882086	-1.13368
AADACL2	NM_207365	8.51E-05	0.878873	1.02832	1.02832
RHCG	NM_016321	0.001734	0.897862	1.04188	1.04188
CCNA1	NM_003914	3.86E-06	0.551723	1.12086	1.12086
CA12	NM_001218	8.75E-06	0.001318	0.578875	-1.72749
S100A12	NM_005621	5.41E-05	0.62284	1.11988	1.11988
TP53AIP1	NM_022112	2.01E-06	0.780029	0.971965	-1.02884
IFNA1	NM_024013	0.00099	0.576181	1.10418	1.10418
DENND2C	NM_198459	1.87E-08	0.080943	0.897954	-1.11364
DSE	NM_013352	2.20E-07	0.073832	1.36852	1.36852
SLC26A2	NM_000112	0.000313	0.721084	0.95225	-1.05014

RECQL	NM_002907	0.022406	0.952671	1.01346	1.01346
SERPINB4	NM_002974	1.08E-05	0.69221	0.893295	-1.11945
UPP1	NM_003364	5.20E-06	0.169556	1.12327	1.12327
PTER	NM_030664	2.00E-06	1.74E-05	0.316463	-3.15992
IVL	NM_005547	1.03E-07	0.187625	0.769062	-1.30028
GJC1	NM_005497	5.99E-05	0.000343	2.89407	2.89407
SLC2A1	NM_006516	1.53E-07	0.104053	0.876208	-1.14128
SLC10A6	NM_197965	2.31E-06	0.62639	1.06766	1.06766
CLIP1	NM_002956	1.41E-05	0.254683	0.879449	-1.13708
TPM2	NM_003289	3.73E-05	0.040905	1.51262	1.51262
CNTN1	NM_001843	2.39E-09	0.517092	1.07211	1.07211
SLC7A5	NM_003486	1.38E-05	0.00079	1.83556	1.83556
PAQR7	NM_178422	0.000521	0.065449	1.42775	1.42775
FBLN1	NM_006486	0.000326	0.980281	0.997089	-1.00292
SEMA3D	NM_152754	0.002343	0.261945	0.691205	-1.44675
CCDC3	NM_031455	0.000571	0.712647	1.08856	1.08856
TRAF3IP3	NM_025228	0.000398	0.973547	1.00592	1.00592
NETO1	NM_138966	0.10033	0.961758	1.01528	1.01528
BCO2	NM_031938	6.33E-06	0.606651	1.07471	1.07471
AMIGO2	NM_001143668	4.45E-08	0.053988	1.3033	1.3033
KRT4	NM_002272	6.63E-07	0.884442	0.975147	-1.02549
AKTIP	NM_001012398	0.006513	0.332753	1.27583	1.27583
SP100	NM_001080391	0.000455	0.710058	1.08744	1.08744
THSD1P	NR_002816	0.002072	0.423221	1.14732	1.14732
TMEM136	NM_174926	8.25E-06	0.501499	0.929729	-1.07558
TTLL7	NM_024686	0.000107	0.525888	0.904002	-1.10619
RND3	NM_005168	7.33E-05	0.588714	1.06102	1.06102
TACSTD2	NM_002353	1.62E-06	0.851125	0.988506	-1.01163
RBP7	NM_052960	2.56E-05	0.351309	1.23374	1.23374
OR10A3	NM_001003745	3.64E-05	0.219649	0.809049	-1.23602
PLA2R1	NM_007366	2.45E-07	0.008386	1.49126	1.49126

KRTDAP	NM_207392	1.02E-08	0.321868	1.20972	1.20972
PRNP	NM_000311	2.18E-06	0.640739	1.05036	1.05036
SLC9A9	NM_173653	0.000842	0.639565	1.07675	1.07675
CDC42SE1	NM_001038707	1.84E-05	0.837519	1.02216	1.02216
KLK5	NM_012427	9.59E-07	0.750788	0.940019	-1.06381
KTN1	NM_182926	0.001011	0.939355	1.01093	1.01093
KRT1	NM_006121	6.75E-07	0.670907	0.919253	-1.08784
RGS20	NM_170587	6.81E-05	0.132416	1.22492	1.22492
LHFP	NM_005780	9.78E-05	0.948746	0.990977	-1.00911
C21orf91	NM_001100420	3.26E-05	0.022371	0.616613	-1.62176
ST3GAL5	NM_003896	1.62E-05	0.616866	0.925493	-1.08051
KRT24	NM_019016	8.72E-06	0.981304	1.0031	1.0031
DSG1	NM_001942	1.97E-11	0.720834	1.03361	1.03361
PLAT	NM_000930	0.001276	0.899146	1.01802	1.01802
THBS2	NM_003247	4.78E-07	0.736915	1.04266	1.04266
NIACR1	NM_177551	1.23E-05	0.889664	1.02556	1.02556
DSC1	NM_004948	1.38E-08	0.969036	1.00566	1.00566
AQP9	NM_020980	0.001541	0.630912	0.902674	-1.10782
BNIPL	NM_001159642	5.78E-06	0.885151	1.01605	1.01605
TNFAIP3	NM_006290	9.56E-05	0.559051	1.05827	1.05827
LASS3	NM_178842	3.98E-09	0.314531	1.11074	1.11074
RUFY2	NM_017987	3.06E-05	0.429326	1.0966	1.0966
SLC26A9	NM_052934	5.61E-07	1.24E-06	0.243313	-4.10993
RORA	NM_134260	0.0006	0.512618	0.916029	-1.09167
AMOTL1	NM_130847	2.34E-07	0.024114	1.29608	1.29608
CARD18	NM_021571	1.65E-06	0.866603	1.03026	1.03026
C20orf197	NM_173644	0.012273	0.852902	1.04266	1.04266
CAPN6	NM_014289	1.50E-06	3.49E-06	0.197617	-5.06028
TUBB6	NM_032525	2.26E-06	0.001073	1.62731	1.62731
CCDC80	NM_199511	5.69E-06	0.952031	1.00945	1.00945
TEX2	NM_018469	1.14E-06	0.063031	0.872803	-1.14573

EEA1	NM_003566	0.000621	0.286705	0.842252	-1.18729
RAET1G	NM_001001788	7.86E-06	0.839722	1.04317	1.04317
NR3C1	NM_000176	3.04E-05	0.940111	0.992877	-1.00717
NCF2	NM_000433	4.35E-06	0.972574	0.996317	-1.0037
TRIML2	NM_173553	0.035133	0.791454	1.0847	1.0847
SLC31A2	NM_001860	7.56E-07	0.146444	0.84624	-1.1817
ANO4	NM_178826	0.137128	0.998072	1.00091	1.00091
SBSN	NM_198538	1.23E-09	0.588773	1.06842	1.06842
ELAVL2	NM_004432	4.22E-06	0.923808	0.99077	-1.00932
BIVM	NM_017693	0.000217	0.701966	1.04755	1.04755
LAMC2	NM_005562	1.16E-06	0.968733	1.00497	1.00497
PHLDB2	NM_001134438	9.26E-06	0.635598	1.07359	1.07359
SFRS12IP1	NM_173829	0.001825	0.694847	1.07242	1.07242
SYT14	NM_001146261	1.09E-07	0.451118	1.11055	1.11055
DGKH	NM_178009	6.27E-06	0.520206	1.05387	1.05387
KRT10	NM_000421	1.21E-09	0.842741	0.978212	-1.02227
ULK2	NM_014683	3.67E-07	0.114604	1.08802	1.08802
DOCK4	NM_014705	1.38E-09	0.493932	1.041	1.041
CSRNP2	NM_030809	0.00012	0.359696	1.10028	1.10028
LOC284033	AK095052	0.00016	0.570407	0.909486	-1.09952
DAAM1	NM_014992	6.72E-05	0.251365	0.851003	-1.17508
HERC5	NM_016323	8.63E-05	0.819443	1.0581	1.0581
FGD6	NM_018351	5.97E-06	0.002279	1.70722	1.70722
C17orf39	NM_024052	5.60E-05	0.161354	1.16761	1.16761
TIPARP	NM_015508	7.04E-06	0.107258	1.21591	1.21591
ADARB1	NM_001033049	0.000101	0.777626	1.03288	1.03288
TLL1	NM_012464	0.000226	0.898293	1.02117	1.02117
EFCAB1	NM_024593	1.04E-07	0.950193	0.995138	-1.00489
CAMSAP1L1	NM_203459	6.46E-06	0.324162	0.857355	-1.16638
BMPR2	NM_001204	0.000242	0.784615	1.04425	1.04425
CPA4	NM_016352	9.48E-07	0.699415	1.06872	1.06872

UBE2Q2	NM_173469	0.001354	0.604512	0.921019	-1.08575
CAB39L	NM_030925	1.27E-06	0.966734	0.996609	-1.0034
TUBA1A	NM_006009	0.07469	0.880957	0.951587	-1.05088
ORM2	NM_000608	6.33E-06	6.64E-06	0.18966	-5.27259
CLCA2	NM_006536	8.01E-11	0.54187	0.943932	-1.0594
NIN	NM_020921	4.70E-08	0.563194	1.05777	1.05777
EML1	NM_001008707	2.17E-06	0.018105	0.781747	-1.27919
MYO3B	NM_138995	0.000197	0.693778	1.04793	1.04793
BBOX1	NM_003986	3.51E-10	0.578459	0.954801	-1.04734
ZFP36L1	NM_004926	1.83E-05	0.189293	1.13282	1.13282
KRT17	NM_000422	5.11E-07	0.968239	0.988188	-1.01195
EPHA4	NM_004438	6.81E-06	0.028544	0.731987	-1.36615
ASAP1	NM_018482	5.27E-05	0.908222	1.01469	1.01469
PARD6G	NM_032510	3.74E-05	0.442029	0.908643	-1.10054
TUBA4A	NM_006000	3.89E-08	4.59E-05	0.631549	-1.58341
LOC84740	NR_026892	6.94E-08	4.32E-08	0.079982	-12.5028
TMEM40	NM_018306	9.61E-06	0.477775	1.14474	1.14474
ARL14	NM_025047	3.77E-07	0.001152	0.447393	-2.23517
BTBD11	NM_001018072	2.57E-06	0.6461	1.05836	1.05836
SPRR1B	NM_003125	6.11E-09	0.023005	0.613446	-1.63014
HIPK3	NM_005734	0.000546	0.455342	0.894018	-1.11855
PLS3	NM_005032	1.43E-05	0.369579	0.907194	-1.1023
SULF2	NM_018837	8.04E-05	0.978442	1.00325	1.00325
IGFL2	NM_001002915	1.96E-08	0.18195	1.20035	1.20035
SNAPC1	NM_003082	0.000251	0.134936	1.25428	1.25428
MYO9A	NM_006901	0.000169	0.6042	0.944044	-1.05927
CASP14	NM_012114	6.22E-07	0.74079	0.948526	-1.05427
LOC100131726	NR_024479	7.07E-07	0.098444	0.787812	-1.26934
TSHZ3	NM_020856	7.41E-06	0.613753	0.895285	-1.11696
FBXO27	NM_178820	5.13E-05	0.329511	1.11889	1.11889
DDX26B	NM_182540	2.10E-07	0.062861	1.11723	1.11723

IL1F9	NM_019618	0.005257	0.63113	1.13872	1.13872
CSDA	NM_003651	6.66E-05	0.05142	1.27608	1.27608
SLC30A4	NM_013309	7.96E-06	0.697786	1.03216	1.03216
RAB9A	NM_004251	0.000183	0.912979	0.987744	-1.01241
DSG4	NM_001134453	2.29E-05	0.937078	1.00917	1.00917
MYCBP2	NM_015057	0.000554	0.98013	0.996926	-1.00308
STK3	NM_006281	1.09E-05	0.098316	1.23481	1.23481
GABRP	NM_014211	0.013059	0.008814	0.254153	-3.93463
SLC6A11	NM_014229	1.84E-05	0.695102	1.0464	1.0464
KRT5	NM_000424	3.19E-09	0.358413	1.1361	1.1361
CCL27	NM_006664	0.001975	0.873923	0.974307	-1.02637
PTPN14	NM_005401	1.54E-05	0.153434	1.19364	1.19364
C3orf34	NM_032898	1.69E-08	0.005592	1.29853	1.29853
LAYN	NM_178834	1.42E-06	0.085162	1.25227	1.25227
NEK1	NM_012224	0.002354	0.892793	1.02864	1.02864
LY6K	NM_017527	4.86E-05	0.681217	1.08069	1.08069
ULBP1	NM_025218	0.004888	0.991583	1.00362	1.00362
TMPRSS11F	NM_207407	4.77E-06	0.854635	0.971205	-1.02965
GADD45A	NM_001924	0.00014	0.192993	1.20764	1.20764
PPP1R14C	NM_030949	2.91E-05	0.329808	1.17407	1.17407
NAV3	NM_014903	8.29E-06	0.896389	1.01437	1.01437
TFPI2	NM_006528	2.13E-11	0.005769	1.28215	1.28215
SPRR2A	NM_005988	3.49E-08	0.119661	0.84558	-1.18262
CYYR1	NM_052954	0.000156	0.805222	1.04086	1.04086
AQP3	NM_004925	1.81E-08	0.155138	0.896981	-1.11485
SNCA	NM_000345	1.06E-07	0.1312	1.15872	1.15872
MORC3	NM_015358	9.63E-06	0.477014	0.939386	-1.06453
FAT2	NM_001447	2.37E-07	0.679351	1.04914	1.04914
PKP1	NM_000299	2.05E-07	0.622854	1.06254	1.06254
FEZ1	NM_005103	8.18E-08	0.654346	0.947736	-1.05515
SFRP1	NM_003012	3.17E-05	0.81695	1.0346	1.0346

TGM1	NM_000359	3.34E-07	0.200733	1.17838	1.17838
LYST	NM_000081	0.006956	0.307764	0.777922	-1.28548
HOXC9	NM_006897	8.36E-05	0.696871	1.06113	1.06113
SHC1	NM_183001	3.06E-05	0.571669	1.05106	1.05106
S100A8	NM_002964	5.73E-10	0.31527	1.17076	1.17076
GSDMC	NM_031415	3.72E-09	0.551774	0.945126	-1.05806
RAB38	NM_022337	5.10E-09	0.32646	1.07178	1.07178
SAA1	NM_000331	0.003802	0.279495	1.56599	1.56599
HERC3	NM_014606	0.000663	0.944061	0.987332	-1.01283
FAM127A	NM_001078171	1.05E-05	0.856793	1.03946	1.03946
FLRT2	NM_013231	7.17E-08	0.369562	1.13719	1.13719
PPP4R4	NM_058237	0.000209	0.672889	1.04805	1.04805
INTS6	NM_012141	0.0002	0.851968	1.02499	1.02499
CRCT1	NM_019060	0.000408	0.723531	0.936078	-1.06829
DNAJB4	NM_007034	0.000509	0.276513	1.27336	1.27336
ZNF750	NM_024702	3.22E-08	0.984116	0.997799	-1.00221
HTR7	NM_019859	0.004453	0.405738	1.1703	1.1703
FABP4	NM_001442	0.097674	0.831132	1.07496	1.07496
TNNT2	NM_000364	4.41E-05	0.947216	1.01332	1.01332
FER	NM_005246	0.000641	0.85206	1.03874	1.03874
GJB4	NM_153212	0.001835	0.345337	1.1685	1.1685
STARD5	NM_181900	4.65E-06	0.563586	0.939106	-1.06484
DUOXA1	NM_144565	0.000575	0.792238	1.04246	1.04246
SERPINB3	NM_006919	2.94E-08	0.330814	1.22933	1.22933
HIAT1	NM_033055	0.01459	0.668688	0.897529	-1.11417
MAL	NM_002371	7.23E-05	4.46E-05	0.370195	-2.70128
MMP9	NM_004994	0.000388	0.439033	1.14921	1.14921
CD86	NM_175862	0.006281	0.433459	1.17482	1.17482
GM2A	NM_000405	8.00E-07	0.399998	1.09767	1.09767
NFAT5	NM_138714	3.81E-06	0.062289	1.17426	1.17426
AJAP1	NM_018836	1.05E-05	0.606008	1.05091	1.05091

CNGA1	NM_001142564	0.045943	0.228827	1.62113	1.62113
OSBPL6	NM_032523	6.84E-08	0.520953	1.06369	1.06369
MTSS1	NM_014751	1.35E-08	0.174182	0.908619	-1.10057
TRIM23	NM_001656	6.72E-06	0.831719	0.981013	-1.01935
COPZ2	NM_016429	0.000202	0.098731	0.755395	-1.32381
C20orf114	NM_033197	1.48E-08	1.36E-08	0.120917	-8.27015
SGTB	NM_019072	8.79E-05	0.451941	0.920019	-1.08693
LYPD3	NM_014400	1.84E-07	0.418123	1.11096	1.11096
ALOX15B	NM_001141	3.55E-07	0.923828	1.00908	1.00908
SLC6A15	NM_182767	2.71E-08	0.858213	1.03144	1.03144
MARK3	NM_001128918	1.02E-05	0.597147	1.04207	1.04207
BICD2	NM_001003800	6.95E-05	0.944173	1.01021	1.01021
PTHLH	NM_198965	5.00E-08	0.972772	1.00473	1.00473
TPRG1	NM_198485	1.20E-06	0.573324	1.07377	1.07377
CYP4F11	NM_021187	5.46E-05	0.399317	1.17296	1.17296
PARP9	NM_001146106	0.011648	0.741725	1.11143	1.11143
ITGA5	NM_002205	0.000201	0.499279	1.09129	1.09129
CTSL1	NM_001912	1.13E-05	0.835256	1.02708	1.02708
SFN	NM_006142	7.85E-09	0.097008	0.910249	-1.0986
ETNK2	NM_018208	0.000167	0.785506	1.04582	1.04582
SPINK6	NM_205841	1.67E-10	0.261146	0.869934	-1.14951
TFAP2A	NM_003220	1.99E-07	0.001986	0.668566	-1.49574
EMR2	NM_013447	0.00025	0.49845	1.08566	1.08566
CLCA4	NM_012128	1.90E-07	0.950937	1.01167	1.01167
S100A9	NM_002965	4.79E-07	0.991769	1.00236	1.00236
EPGN	NM_001013442	2.48E-08	0.788791	1.04667	1.04667
GJB5	NM_005268	1.40E-06	0.004949	0.552073	-1.81136
MPZL2	NM_144765	8.50E-07	0.137208	0.889307	-1.12447
NOTCH2	NM_024408	2.38E-06	0.008463	1.28995	1.28995
PTPRZ1	NM_002851	1.89E-09	0.968372	0.995836	-1.00418
KRT14	NM_000526	7.05E-10	0.522617	0.919211	-1.08789

FAP	NM_004460	0.000184	0.734636	1.07441	1.07441
SLC39A2	NM_014579	1.02E-06	0.940932	0.991832	-1.00824
TMPRSS11E	NM_014058	2.32E-05	0.874615	1.04834	1.04834
KCNQ5	NM_019842	0.002317	0.822837	1.03968	1.03968
ARL4D	NM_001661	1.68E-05	0.378403	1.17177	1.17177
PTGS2	NM_000963	0.00066	0.663103	0.896137	-1.1159
SIM2	NM_009586	1.67E-06	2.08E-06	0.377098	-2.65183
CDH13	NM_001257	6.12E-08	0.281605	1.16533	1.16533
RAB37	NM_175738	4.76E-06	1.60E-05	0.455964	-2.19315
NUAK1	NM_014840	0.001449	0.8209	0.965302	-1.03595
ST6GALNAC2	NM_006456	9.39E-08	0.043628	0.804164	-1.24353
NTM	NM_001144058	9.37E-05	0.11753	1.27909	1.27909
PTPRE	NM_006504	5.05E-07	0.045174	1.22391	1.22391
EMP1	NM_001423	8.78E-06	0.16802	1.22748	1.22748
PLD5	NM_152666	1.99E-05	0.353565	1.21395	1.21395
GBP6	NM_198460	5.06E-05	0.861643	0.974096	-1.02659
LAMP2	NM_002294	0.000116	0.460181	1.12742	1.12742
F2R	NM_001992	0.000105	0.00593	1.84825	1.84825
PYGL	NM_002863	1.53E-08	9.55E-05	1.86349	1.86349
PGLYRP3	NM_052891	0.001406	0.493995	1.12867	1.12867
ORM1	NM_000607	0.000765	0.000815	0.385427	-2.59452
LPCAT2	NM_017839	0.00011	0.306782	0.843871	-1.18502
HOXC10	NM_017409	7.80E-05	0.670233	1.07045	1.07045
PLA2G4E	NM_001080490	4.00E-08	0.343476	1.0885	1.0885
NEBL	NM_006393	9.72E-05	0.013729	0.595382	-1.67959
PCDH21	NM_033100	5.93E-05	0.596516	1.06277	1.06277
CALB2	NM_001740	0.000121	0.946357	0.984058	-1.0162
FSCN1	NM_003088	0.000138	0.308164	1.13718	1.13718
SWAP70	NM_015055	2.00E-07	0.495581	1.04461	1.04461
MARK1	NM_018650	1.32E-07	0.571495	1.04579	1.04579
IGFL1	NM_198541	4.72E-06	0.67711	0.924306	-1.08189

KRT77	NM_175078	1.52E-05	0.635682	1.07023	1.07023
ERC1	NM_178037	6.44E-06	0.268554	1.08836	1.08836
GNAL	NM_182978	7.49E-05	0.538888	0.932404	-1.0725
SERPING1	NM_000062	2.86E-05	0.105436	1.36026	1.36026
ATP12A	NM_001676	0.000248	0.941634	0.986326	-1.01386
LAMP3	NM_014398	0.028786	0.84616	0.949612	-1.05306
FST	NM_006350	5.16E-07	0.528152	0.913803	-1.09433
DUOX1	NM_017434	5.36E-05	0.882588	1.01828	1.01828
CYP1B1	NM_000104	0.001671	0.624845	1.10572	1.10572
ERCC6	NM_000124	1.12E-08	0.551787	0.964147	-1.03719
ABCA12	NM_173076	4.61E-09	0.007414	0.613091	-1.63108
ERCC1	NM_202001	4.26E-05	0.767693	1.03938	1.03938
CCDC109B	NM_017918	0.002651	0.304482	0.777883	-1.28554
TMEM86A	NM_153347	5.02E-05	0.374703	1.11306	1.11306
KCTD1	NM_001142730	2.89E-07	0.056283	0.864729	-1.15643
FLJ21511	NM_025087	2.01E-08	0.517128	1.11595	1.11595
MSRB3	NM_001031679	0.000156	0.27337	1.15808	1.15808
GATA3	NM_001002295	1.57E-06	0.778059	1.02773	1.02773
ETS1	NM_001143820	3.08E-08	0.008698	1.2081	1.2081
JUP	NM_002230	2.79E-06	0.649802	0.960165	-1.04149
TAGLN	NM_001001522	0.002535	0.716696	0.934562	-1.07002
SLC7A1	NM_003045	2.99E-05	0.963659	0.995601	-1.00442
QKI	NM_206855	0.000221	0.586587	1.07727	1.07727
XG	NM_001141919	5.23E-06	0.004947	0.529385	-1.88898
FERMT2	NM_006832	7.03E-07	0.005317	1.52035	1.52035
MACF1	NM_012090	3.54E-05	0.856051	1.02518	1.02518
OSMR	NM_003999	0.000719	0.491391	1.12011	1.12011
GNA15	NM_002068	2.27E-06	0.015346	0.645485	-1.54922
IFNE	NM_176891	1.48E-08	0.451362	0.922917	-1.08352
AMZ2	NM_016627	5.92E-05	0.401675	1.09997	1.09997
TBC1D19	NM_018317	1.69E-05	0.680163	0.960578	-1.04104

CRIM1	NM_016441	4.50E-07	0.803268	1.02068	1.02068
CALML5	NM_017422	2.24E-05	0.723728	1.05588	1.05588
GPR64	NM_001079858	3.59E-05	6.66E-05	0.32254	-3.10039
SNX24	NM_014035	0.00317	0.671286	0.911784	-1.09675
SERPINB13	NM_012397	2.87E-11	0.936936	0.99293	-1.00712
KRT15	NM_002275	1.07E-09	0.510567	0.933518	-1.07122
MCC	NM_001085377	5.92E-06	0.448767	1.08813	1.08813
TP63	NM_003722	1.98E-09	0.410825	0.924053	-1.08219
CYB5R1	NM_016243	8.18E-08	0.004949	0.723942	-1.38133
SERPINB2	NM_001143818	0.000522	0.711281	0.87827	-1.1386
MARVELD1	NR_026753	0.000246	0.009597	1.657	1.657
ERRFI1	NM_018948	4.24E-05	0.017005	1.41294	1.41294
SLCO3A1	NM_013272	3.37E-06	0.028271	1.22074	1.22074
TIMP1	NM_003254	7.98E-06	0.189025	0.79233	-1.2621
CAPRIN2	NM_001002259	0.000102	0.152241	1.22629	1.22629
PLTP	NM_006227	0.000998	0.31831	1.18776	1.18776
CALCRL	NM_005795	7.23E-07	0.001763	1.35315	1.35315
IFIH1	NM_022168	0.015725	0.682984	0.882473	-1.13318
CLIC4	NM_013943	0.001914	0.982278	1.00382	1.00382
IRF6	NM_006147	2.28E-07	0.26013	1.10495	1.10495
A2ML1	NM_144670	7.47E-08	0.278771	0.773098	-1.2935
FCHSD2	NM_014824	3.04E-05	0.065187	0.76483	-1.30748
DNAJB5	NM_001135005	0.0014	0.173331	1.32736	1.32736
TIAM1	NM_003253	1.18E-06	0.077225	0.823143	-1.21486
CAPNS2	NM_032330	1.59E-07	0.142157	1.40374	1.40374
KATNAL1	NM_001014380	1.94E-06	0.254881	1.16813	1.16813
GRHL3	NM_198173	3.64E-09	0.965385	0.997695	-1.00231
MAP2	NM_002374	1.28E-07	0.775196	0.976737	-1.02382
SMARCA1	NM_003069	3.35E-05	0.00418	1.61793	1.61793
C9orf95	NR_023352	0.00091	0.727821	1.05715	1.05715
LUM	NM_002345	0.00038	0.001159	0.326911	-3.05894

MLF1	NM_001130157	0.000152	0.180647	1.22499	1.22499
RPE65	NM_000329	0.004304	0.170309	1.38576	1.38576
KLF7	NM_003709	3.34E-07	0.530485	0.946912	-1.05606
STEAP4	NM_024636	4.23E-09	0.202174	1.14781	1.14781
ARSJ	NM_024590	3.70E-05	0.412978	1.1068	1.1068
FGF5	NM_004464	0.000358	0.815346	0.950385	-1.05221
IFI44L	NM_006820	0.001777	0.615482	1.297	1.297
TNC	NM_002160	3.71E-06	0.913931	1.01482	1.01482
LY6D	NM_003695	0.00028	0.31527	1.19356	1.19356
SLITRK6	NM_032229	0.00074	0.813976	0.942404	-1.06112
RAET1E	NM_139165	3.95E-06	0.457886	1.11564	1.11564
SEC14L2	NM_012429	2.11E-06	0.872635	0.986661	-1.01352
DUSP7	NM_001947	3.65E-06	0.479135	1.05805	1.05805
ELK3	NM_005230	1.44E-06	0.091065	1.21577	1.21577
SMURF2	NM_022739	8.79E-06	0.160301	1.15019	1.15019
TRIM29	NM_012101	1.30E-08	0.01246	0.767939	-1.30219
UGT1A9	NM_021027	3.69E-06	3.62E-06	0.278572	-3.58974
	---	0.017796	0.201567	1.62323	1.62323
SERPINE1	NM_000602	0.000464	0.459577	0.803811	-1.24407
MYO5A	NM_000259	6.81E-10	0.072884	1.15323	1.15323
	---	1.57E-06	0.708859	0.949462	-1.05323
EGFR	NM_005228	7.76E-08	0.207808	1.10214	1.10214
SLC38A2	NM_018976	7.02E-08	0.006881	0.783891	-1.27569
HAS2	NM_005328	0.004297	0.749226	1.06814	1.06814
LRRC8C	NM_032270	1.86E-05	0.03772	1.5262	1.5262
MPDZ	NM_003829	0.001944	0.09554	1.49927	1.49927
DDX60	NM_017631	0.006426	0.31499	1.42656	1.42656
PCDHB2	NM_018936	0.000695	0.00194	0.463338	-2.15825
IL1B	NM_000576	5.25E-07	0.175488	0.795989	-1.2563
BBS9	NM_198428	0.003029	0.779505	0.944932	-1.05828
STEAP1	NM_012449	0.135915	0.392934	1.65021	1.65021

CD274	NM_014143	5.19E-05	0.272787	0.849893	-1.17662
SLC39A6	NM_012319	3.85E-07	0.295822	0.900772	-1.11016
MGAM	NM_004668	1.99E-07	2.04E-06	0.472744	-2.11531
SEMA3C	NM_006379	0.000153	0.339352	0.858519	-1.1648
WDFY2	NM_052950	2.45E-08	0.0586	1.11927	1.11927
LDOC1	NM_012317	1.18E-05	0.219631	1.1671	1.1671
GLTP	NM_016433	0.000199	0.50547	1.10974	1.10974
CAPN13	NM_144575	1.06E-07	2.33E-06	0.454007	-2.20261
IKZF2	NM_001079526	1.78E-06	0.737336	0.965418	-1.03582
RBP1	NM_001130992	1.32E-06	2.52E-06	6.62115	6.62115
SCGB2A1	NM_002407	4.48E-06	1.05E-05	0.299559	-3.33824
IGFBP6	NM_002178	6.93E-06	0.066023	1.40829	1.40829
C7orf10	NM_024728	1.87E-07	0.003813	1.28009	1.28009
SLPI	NM_003064	1.62E-06	0.399929	0.86513	-1.1559
CD109	NM_133493	9.85E-09	0.116094	0.829	-1.20627
SP110	NM_080424	0.002794	0.887726	1.02949	1.02949
VGLL1	NM_016267	0.000107	0.087514	1.52081	1.52081
LRP12	NM_013437	1.05E-06	0.183473	1.14468	1.14468
PRB4	NM_002723	0.023507	0.587484	1.23804	1.23804
OPTN	NM_001008211	1.79E-05	0.563586	1.06182	1.06182
YPEL5	NM_001127401	0.000254	0.896436	1.01909	1.01909
SULT2B1	NM_004605	7.72E-05	0.035154	1.39265	1.39265
CDH3	NM_001793	7.22E-06	0.025863	1.33645	1.33645
MLLT11	NM_006818	7.84E-05	0.116316	1.5896	1.5896
DRAP1	NM_006442	0.000223	0.912902	0.984063	-1.01619
CASP1	NM_033292	1.68E-06	0.001887	2.02769	2.02769
TFAP2C	NM_003222	7.94E-06	0.262607	0.890248	-1.12328
EREG	NM_001432	0.000459	0.212032	1.49169	1.49169
CAV1	NM_001753	3.96E-08	0.011415	1.49491	1.49491
OGFRL1	NM_024576	8.46E-06	0.100833	1.34002	1.34002
DEFB1	NM_005218	1.17E-05	0.375581	0.818125	-1.22231

MRAP2	NM_138409	1.35E-07	3.63E-06	0.356703	-2.80345
KRT6A	NM_005554	9.88E-08	0.048042	0.615147	-1.62563
FDXACB1	NM_138378	5.58E-06	0.986807	0.995518	-1.0045
PI3	NM_002638	2.91E-05	0.001449	2.44838	2.44838
FZD6	NM_003506	0.00022	0.283483	1.18043	1.18043
SPTLC3	NM_018327	1.08E-05	0.024726	1.3906	1.3906
CLIP4	NM_024692	1.46E-05	0.020137	1.55802	1.55802
RAB31	NM_006868	1.73E-06	0.027134	1.47898	1.47898
KLK13	NM_015596	2.92E-05	0.924165	1.01351	1.01351
CD44	NM_000610	6.59E-06	3.45E-05	3.47222	3.47222
DZIP1	NM_198968	3.02E-06	0.000644	1.74329	1.74329
	---	0.010603	0.8323	0.943196	-1.06023
CALD1	NM_033138	1.59E-05	0.016215	1.64354	1.64354
TUBG2	NM_016437	7.33E-06	0.014841	1.36075	1.36075
PRKCH	NM_006255	2.73E-05	0.070199	1.27231	1.27231
KRT16	NM_005557	3.75E-08	0.673889	0.91816	-1.08913
FAM63B	NM_001040450	1.96E-05	0.068358	1.42823	1.42823
C3orf67	BC132815	3.15E-07	0.014819	1.24586	1.24586
RIMKLB	NM_020734	1.58E-05	0.708638	0.942199	-1.06135
ATP10D	NM_020453	1.04E-06	0.710817	0.945438	-1.05771
ARL4C	NM_005737	8.07E-07	0.021078	0.736817	-1.35719
FRMD6	NM_001042481	5.92E-07	0.64632	0.936182	-1.06817
KRT13	NM_153490	2.54E-07	0.343476	1.22976	1.22976
KIF3A	NM_007054	0.006094	0.875752	1.05211	1.05211
FBP2	NM_003837	6.19E-06	0.000103	0.387372	-2.5815
PHLDB2	NM_001134438	2.38E-06	0.800695	1.04141	1.04141
SNAI2	NM_003068	4.56E-08	0.002729	2.11752	2.11752
IFIT1	NM_001548	0.000118	0.197351	1.72857	1.72857
SCEL	NM_144777	7.26E-07	0.053756	1.43077	1.43077
PITPNC1	NM_181671	4.67E-08	0.016814	1.2283	1.2283
DDX58	NM_014314	1.91E-05	0.495801	1.12876	1.12876

ITGBL1	NM_004791	1.75E-05	0.000146	0.272938	-3.66384
PYGB	NM_002862	7.79E-06	0.722711	1.03732	1.03732
CAV2	NM_001233	2.37E-05	0.012178	1.67738	1.67738
DCBLD2	NM_080927	1.79E-07	0.949103	0.993914	-1.00612
PALMD	NM_017734	8.09E-09	0.007945	1.30826	1.30826
EPHX3	NM_024794	0.007575	0.134248	1.6368	1.6368
UGT2B15	NM_001076	8.86E-05	0.00237	0.270879	-3.69168
CYBRD1	NM_024843	7.67E-07	0.102411	0.759074	-1.31739
STXBP1	NM_003165	1.67E-06	0.001928	1.60414	1.60414
IFIT3	NM_001031683	0.012789	0.194776	1.7348	1.7348
PLK2	NM_006622	4.19E-06	0.007484	1.63934	1.63934
ATP2B4	NM_001001396	2.62E-06	0.830052	0.973585	-1.02713
MID2	NM_012216	1.44E-07	0.026004	1.22325	1.22325
CCL28	NM_148672	9.94E-05	0.001755	2.11344	2.11344
ZNF185	NM_007150	9.88E-08	0.165017	1.11833	1.11833
USP44	NM_032147	3.67E-05	1.70E-05	2.35095	2.35095
STC2	NM_003714	0.007593	0.005833	2.20664	2.20664
ANXA1	NM_000700	1.81E-05	0.105435	1.2453	1.2453
DAPP1	NM_014395	6.66E-07	0.875543	1.01624	1.01624
TCP11L1	NM_018393	1.16E-07	0.181957	1.11133	1.11133
PIK3C2G	NM_004570	1.19E-05	0.000104	0.280701	-3.56251
ITGB6	NM_000888	1.44E-05	0.597992	1.08268	1.08268
IFI6	NM_002038	0.000558	0.942851	1.01746	1.01746
AREG	NM_001657	9.80E-08	0.134643	1.22225	1.22225
TCEA3	NM_003196	6.03E-05	0.002289	0.488683	-2.04632
NKX6-3	NM_152568	0.000222	0.000368	2.03266	2.03266
CRABP2	NM_001878	1.24E-09	0.006692	0.727076	-1.37537
NEXN	NM_144573	0.000501	0.013166	2.20289	2.20289
HSPC159	NM_014181	7.31E-08	0.189829	0.89285	-1.12001
SAMD9L	NM_152703	0.002066	0.368463	1.27406	1.27406
TNS4	NM_032865	1.33E-06	0.053027	1.31768	1.31768

PTPN13	NM_080683	2.15E-06	0.229783	1.27158	1.27158
SERPINB7	NM_003784	5.70E-08	0.156301	1.35763	1.35763
PSCA	NM_005672	6.84E-07	1.03E-05	0.232733	-4.29678
NPSR1	NM_207172	2.73E-06	0.000387	0.441786	-2.26354
CTH	NM_001902	0.000612	0.001894	2.32478	2.32478
MX1	NM_001144925	0.000642	0.098969	1.77021	1.77021
LRRC6	NM_012472	0.002159	0.001201	2.68093	2.68093
TNFRSF10C	NM_003841	7.46E-05	4.13E-05	3.48054	3.48054
CYR61	NM_001554	4.65E-05	0.007289	1.81334	1.81334
CXCL17	NM_198477	1.48E-06	2.73E-06	0.068137	-14.6764
ANKRD50	NM_020337	1.33E-05	0.430417	1.1196	1.1196
GSTM4	NM_000850	1.62E-06	1.28E-05	5.0432	5.0432
GSTM2	NM_000848	0.000898	0.00096	2.63294	2.63294
HRASLS2	NM_017878	0.000251	0.005555	0.333009	-3.00292
C11orf92	NM_207429	9.79E-08	5.84E-05	0.439849	-2.27351
ODAM	NM_017855	6.17E-06	0.005289	2.37484	2.37484
AHNAK2	NM_138420	8.07E-08	0.121631	1.21709	1.21709
DDX43	NM_018665	0.000328	0.000219	4.30453	4.30453
IFI16	NM_005531	1.79E-06	0.033083	0.580452	-1.7228
SLC16A4	NM_004696	0.000184	5.26E-05	13.7411	13.7411
AK5	NM_174858	0.000101	0.000176	3.27481	3.27481
FKBP5	NM_001145775	8.41E-05	0.353899	0.788638	-1.26801
THBS1	NM_003246	6.21E-05	0.987229	1.00468	1.00468
KCNJ15	NM_002243	5.99E-07	0.000143	2.08393	2.08393
LCN2	NM_005564	4.89E-05	0.233941	1.34648	1.34648
HS3ST5	NM_153612	7.36E-05	0.000372	2.45858	2.45858
CAPN9	NM_006615	1.80E-09	1.36E-07	0.215242	-4.64593
CLDN10	NM_182848	1.13E-06	2.14E-06	2.86826	2.86826
KLK10	NM_002776	2.17E-06	0.339011	1.14633	1.14633
SAMD9	NM_017654	8.12E-06	0.503399	0.840268	-1.1901
HLA-DMB	NM_002118	0.000348	0.00051	3.27169	3.27169

KLK7	NM_139277	5.21E-07	0.000418	0.383008	-2.61091
NTS	NM_006183	0.018973	0.025816	4.29633	4.29633
TGFB2	NM_001135599	0.001966	0.007631	2.39047	2.39047
CYP2E1	NM_000773	3.35E-05	0.000411	2.1897	2.1897
ALDH3A1	NM_000691	1.89E-08	2.05E-05	0.410963	-2.43331
CCBE1	NM_133459	4.81E-06	1.48E-06	4.33119	4.33119
MATN2	NM_002380	6.77E-06	2.81E-06	3.87824	3.87824
MFAP5	NM_003480	3.58E-05	0.045897	0.390572	-2.56035
BAAT	NM_001701	5.52E-08	1.78E-06	2.7204	2.7204
SLC15A1	NM_005073	4.59E-06	2.83E-05	2.62386	2.62386
MXRA5	NM_015419	0.000382	0.001087	3.33408	3.33408
FGF2	NM_002006	4.92E-06	7.38E-05	2.76247	2.76247
IFI44	NM_006417	0.000107	0.808255	1.10526	1.10526
CSTA	NM_005213	2.09E-07	0.770347	1.08448	1.08448
SERPINB5	NM_002639	1.66E-09	0.001188	0.591351	-1.69104
GPR87	NM_023915	1.16E-07	0.008842	1.88356	1.88356
BICC1	NM_001080512	2.71E-06	1.66E-05	5.66854	5.66854
MSN	NM_002444	2.62E-07	0.016787	1.62807	1.62807
GKN1	NM_019617	1.12E-07	0.001325	0.287564	-3.47749
GKN2	NM_182536	1.22E-08	0.00082	0.353334	-2.83019

The data in Tables ZZ and YY are also summarized in the heat map shown in Figure 12.

Example 7. Differential expression of proteins in Barrett's Esophagus Progenitor Cells Compared to Squamous Progenitor Cells and Gastric Cardia Progenitor Cells.

Cultures of Barrett's Esophagus progenitor cells, squamous progenitor cells and gastric cardia progenitor cells were compared to determine expression of p63, CEACAM6 and Sox2. As shown in FIG. 13, p63 is expressed in squamous progenitor cells, but not in gastric cardia or Barrett's progenitor cells. As shown in FIG. 14, Barrett's esophagus progenitor cells (left panels) lack Sox2

while expressing CEAMCAM6, while gastric cardia progenitor cells (right panels) express Sox2, but lack CEAMCAM6.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A composition comprising a clonal population of stem cells isolated from an esophagus of a subject, wherein the stem cells differentiate into Barrett's epithelium.

2. The composition of claim 1, wherein the stem cells are characterized as having an mRNA profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell.

3. The composition of claim 1, wherein the stem cells are characterized as having an mRNA profile wherein the amount of one or more of GSTM4, SLC16A4, CMBL, CEACAM6, NRFA2, CFTR, GCNT3 mRNA are each at least 10 percent of the amount of actin mRNA in the stem cell.

4. The composition of any of the preceding claims, wherein the stem cells are further characterized as having an mRNA profile wherein mRNA for BICC1 and NTS are present in detectable levels.

5. The composition of any of the preceding claims, wherein the stem cells are further characterized as having an mRNA profile wherein mRNA for SOX2, p63, Krt20, GKN1/2, FABP1/2, Krt14, CXCL17 is present in amounts less than 0.1 percent the level of actin.

6. The composition of any of the preceding claims, wherein the stem cells are further characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining

7. A purified cell preparation comprising a Barrett's esophagus (BE) stem cells, wherein the BE stem cells differentiate into columnar epithelial cells and are characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining.

8. An isolated Barrett's esophagus (BE) stem cell capable of producing columnar epithelial cells, which BE stem cell is characterized as CEACAM6 positive, and Krt20, Sox2 and p63 negative, as detected by standard antibody staining, and having an mRNA profile wherein the amount of one or more of

each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell.

9. A method of screening for an agent which may be used to treat or prevent the occurrence of Barrett's esophagus, comprising

a) providing BE stem cells;

b) contacting the BE stem cells with the test agent;

c) detecting the ability of the test agent to reduce viability, growth or differentiation of the BE stem cells;

wherein if the test agent reduces the viability, growth or differentiation of the BE stem cells than the test agent may be effective in the treatment or prevention of Barrett's esophagus.

10. The method of claim 9, wherein the test agent is also contacted with normal cells or tissue of the alimentary canal, and the differential ability, if any, of the test agent to reduces the viability, growth or differentiation of the normal cells or tissue is compared to that with the BE stem cells.

11. The method of claim 9, wherein the BE stem cells are human BE stem cells.

12. The method of the preceding claims, wherein the test agent is selected for further drug development if the test reduces the viability, growth or ability to differentiation of the BE stem cells is reduced by at least 70%.

13. The method of claim 9, wherein the BE stem cells are provided as a clonal population of cells.

14. The method of claim 9, wherein the test agent is small molecule, carbohydrate, peptide or nucleic acid.

15. The method of claim 9, wherein the test agent specifically binds to a cell surface protein on the clonal population of cells.

antibody mimetic.

17. A method of screening for an agent effective in the detection of Barrett's esophagus comprising

a) providing a BE stem cells;

b) contacting the BE stem cells with the test agent;

c) detecting the ability of the test agent to bind to the BE stem cells;

wherein if the test agent binds to the BE stem cells, the test agent may be an agent effective in the detection of Barrett's esophagus.

18. The method of claim 17, wherein the BE stem cells are human BE stem cells.

19. The method of claim 17, wherein the BE stem cells are provided as a clonal population of cells.

20. The method of claim 17, wherein the test agent is also contacted with normal cells or tissue of the alimentary canal, and the differential ability, if any, of the test agent to bind to the normal cells or tissue is compared to that with the BE stem cells.

21. The method of any of the preceding claims, wherein the test agent is an antibody or antibody mimetic.

22. The method of claim 21, wherein the detection agent is a monoclonal antibody.

23. A method of detecting the presence of esophageal metaplasia, such as associated with Barrett's esophagus, in a patient comprising

a) providing a detection agent that specifically binds to a BE stem cell relative to normal tissue of the esophagus and (optionally) stomach;

b) administering the detection agent to a patient or contacting the detection agent with a biopsy therefrom; and

esophagus of the patient.

24. The method of claim 23, wherein the patient is a human.

25. The method of claim 23, wherein the detection step is performed in vitro on a biopsy sample.

26. The method of claim 23, wherein the detection step is performed in vivo.

27. The method of claim 23, wherein the detection agent is an antibody.

28. The method of claim 27, wherein the detection agent is a monoclonal antibody.

29. The method of claim 23, wherein the detection agent is Positron Emission Tomography (PET) imaging agent or magnetic resonance imaging (MRI) contrast agent.

29. The method of claim 23, wherein the detection agent is radioisotope or contrast enhancing isotope, such as ^{3}H, ^{11}C, ^{177}Lu, ^{111}Indium, ^{67}Cu, ^{99m}Tc, ^{124}I, ^{125}I, ^{131}I and ^{89}Zr.

30. The method of claim 23, wherein the detection agent is detected in the patient by Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Fluorescent Imaging, or Near-infrared (NIR) Emission Spectroscopy.

31. A method for treating or preventing Barrett's esophagus and/or esophageal metaplasia in a subject in need thereof comprising administering to the subject an effective amount of an therapeutic agent that is cytotoxic or cytostatic for Barrett's Esophagus (BE) stem cells in the esophagus of the subject, or inhibits differentiation of the BE stem cells to columnar epithelium.

32. The method of claim 31, wherein the subject is a mammal.

33. The method of claim 32, wherein the mammal is a human.

to columnar epithelium is reduced by 70, 80, 90, 95, 96, 97, 98, 99 or 100% from treatment with the therapeutic agent.

35. The method of claim 31, wherein the therapeutic agent is an antibody or antibody mimetic.

36. The method of claim 35, wherein the therapeutic agent is a monoclonal antibody.

37. The method of claim 35 or 36, wherein the antibody or antibody mimetic is conjugated to a cytotoxic or cytostatic moiety.

38. The method of claim 31, wherein the therapeutic agent is selected from the group consisting of prodrugs comprising a medoximil moiety, PPARγ modulators and NR5A2 activity modulators.

39. The method of claim 31, wherein the therapeutic agent is a nucleic acid or nucleic acid analog.

40. The method of claim 39, wherein the therapeutic agent is an RNAi or antisense composition.

41. The method of claim 40, wherein the RNAi or antisense composition reduces the level of expression of a gene selected from the group consisting of GSTM4, SLC16A4, CMBL, CEACAM6, NR5A2, CFTR, GCNT3 and PPAR γ.

42. A composition comprising a clonal population of stem cells isolated from an esophagus of a subject, wherein the stem cells differentiate into squamous cells.

43. The composition of claim 42, wherein the stem cells are characterized as having an mRNA profile wherein the amount of one or more of S100A8, Krt14, SPRR1A or CSTA mRNA are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cells.

44. The composition of claims 42 or 43, wherein the mRNA profile further comprises a profile wherein the amount of one or more of S100A8, Krt14,

mRNA in the stem cells.

45. The composition of any of claims 42-44, wherein the stem cells are further characterized as having an mRNA profile wherein mRNA for SOX2, Krt20, CXCL17, CEACAM6 or NR5A2 are present in amounts less than 0.1 percent the level of actin.

46. The composition of any of claims 42-45, wherein the stem cells are further characterized as p63 positive, and CEACAM6 negative as detected by standard antibody staining.

47. A purified cell preparation comprising squamous stem cells, wherein the squamous stem cells differentiate into squamous cells and are characterized as p63 positive, and CEACAM6 negative as detected by standard antibody staining.

48. An isolated squamous stem cell capable of producing squamous cells, which squamous stem cell is characterized as p63 positive, and CEACAM6 negative, as detected by standard antibody staining, and having an mRNA profile wherein the amount of one or more of S100A8, Krt14, SPRR1A or CSTA mRNA are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell.

49. A composition comprising a clonal population of stem cells isolated from an esophagus or gastric cardia of a subject, wherein the stem cells differentiate into gastric cardia cells.

50. The composition of claim 49, wherein the stem cells are characterized as having an mRNA profile wherein the amount of one or more of CXCL17, CAPN6, PSCA, GKN1, GKN2 or MT1G mRNA are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cells.

51. The composition of claims 49 or 50, wherein the mRNA profile further comprises a profile wherein the amount of one or more of CXCL17, CAPN6, PSCA, GKN1, GKN2 or MT1G mRNA are each at least 10 percent of the amount of actin mRNA in the stem cells.

further characterized as having an mRNA profile wherein mRNA for CEACAM6, p63, FABP1, FABP2, Krt14 or Krt20 are present in amounts less than 0.1 percent the level of actin.

53. The composition of any of claims 49-52, wherein the stem cells are further characterized as CEACAM6 negative as detected by standard antibody staining.

54. A purified cell preparation comprising gastric cardia stem cells, wherein the gastric cardia stem cells differentiate into gastric cardia cells and are characterized CEACAM6 negative as detected by standard antibody staining.

55. An isolated gastric cardia stem cell capable of producing gastric cardia cells, which gastric cardia stem cell is characterized as CEACAM6 negative, as detected by standard antibody staining, and having an mRNA profile wherein the amount of one or more of CXCL17, CAPN6, PSCA, GKN1, GKN2 or MT1G mRNA are each in the range of 5 to 50 percent of the amount of actin mRNA in the stem cell.